THE CHEMISTRY OF NOVEL DITERPENES FROM

ANDROSTACHYS JOHNSONII PRAIN

A thesis submitted in partial fulfilment of
the requirements for the degree of Doctor of
Philosophy in the Department of Chemistry,
University of Natal.

by

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December 1973.

## DECLARATION

I hereby certify that this research is the result of my own investigation, which has not already been accepted in substance for any degree, and is not being concurrently submitted by me in candidature for any other degree.

Signed: ....~~A. Piacenza~~....

L.P.L. Piacenza

I hereby certify that the above statement is correct.

Signed: ....~~K.H. Pegel~~........

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## ACKNOWLEDGEMENTS

# CONTENTS

# A B B R E V I A T I O N S

| | |
|---|---|
| Ac | acetyl |
| AcO | acetate |
| t-BuO | tertiary butoxide |
| BzO | benzoate |
| b.p. | boiling point |
| c | circa |
| c.d. | circular dichroism |
| d | doublet |
| diglyme | diethylene glycol dimethyl ether |
| e.a. | end absorption |
| Et | ethyl |
| g.l.c. | gas-liquid chromatography |
| hr | hour |
| i.r. | infrared |
| LAH | lithium aluminium hydride |
| m | multiplet |
| Me | methyl |
| MsO or mesylate | methanesulphonate |
| min. | minute |
| m.p. | melting point |
| m.s. | mass spectroscopy |
| $NaBH_4$ | sodium borohydride |
| n.m.r. | nuclear magnetic resonance |
| o.n. | overnight |

| | |
|---|---|
| o.r.d. | optical rotatory dispersion |
| Ph | phenyl |
| q | quartet |
| r.t. | room temperature $(20-24^{\circ})$ |
| s | singlet |
| t | triplet |
| THF | tetrahydrofuran |
| t.l.c. | thin layer chromatography |
| p-tosic acid or tosic acid | p-toluenesulphonic acid |
| TsO or tosylate | p-toluenesulphonate |
| u.v. | ultraviolet |

## NOTES ON NOMENCLATURE

All the diterpenes used in this work have the antipodal stereochemistry, i.e. 5β, 8α, 9β, 10α, 13α and the "ent" nomenclature should be used according to the IUPAC rules[1]. Thus the major diterpene, the α-ketol ( 1), should be correctly named

ent-3β-hydroxybeyer-15-en-2,12-dione.

Since the normal way of drawing the formulae is as follows:



and not

(a)                                    (b)
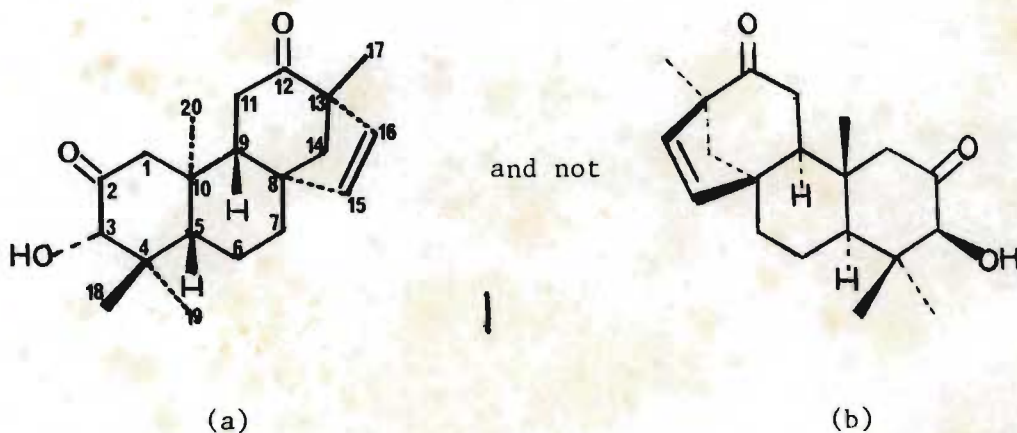
then in stereochemical arguments one should refer to the 3α-hydroxyl function of (a) as ent-3β-hydroxy. Thus all α-configurations become ent-β and all β-configurations become ent-α. This system courts confusion.

One way out of this confusion is to use the parent name "stachane" since this was originally given to ent-beyerane diterpenes isolated from Tambooti wood, Spirostachys africana[2]. However, since the structure of beyerane diterpenes was published first[3], this latter name takes precedence. For the purpose of this thesis

the parent name STACHANE will be used for all the compounds.

Thus the major diterpene (1) will be named 3α-hydroxystach-15-en-2,12-

dione.  However ATISANES prepared in this work will be numbered

in the conventional way:-

e.g.
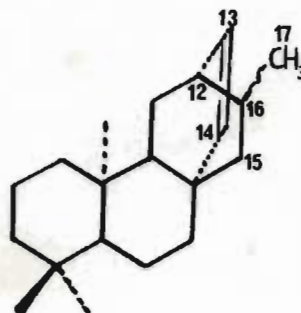


ent-atis-13-ene, whereas as derived from a beyerene the 13(14)-bond

is really 15(16).

Similarly the D-homo-C-nor diterpene is numbered
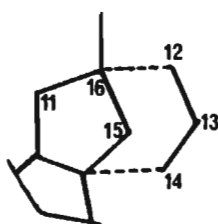


although it is in fact
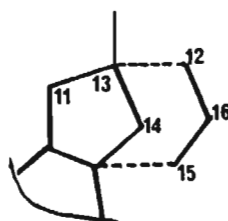
Part of this work has been the subject of 6 preliminary
communications:-

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1973, 26, 2393.

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# ent-3β-Hydroxybeyer-15(16)-ene-2,12-dione from *Androstachys johnsonii* Prain (Euphorbiaceae)

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*Summary* The major heartwood diterpene of *Androstachys johnsonii* presents the first instance of a C-12 oxygenated beyerane-type diterpene and the possible existence of a new type of diterpene skeleton is suggested.

THE major heartwood diterpene of *A. johnsonii* Prain is the tetracyclic ketol (Ia),† $C_{20}H_{28}O_3$, m.p. 163—165·5°, $[\alpha]_D$ — 372° (CHCl$_3$ throughout), $\nu_{max}$ (KBr throughout) 3525 (broad), 1710 (broad), and 767 cm$^{-1}$, $\lambda_{max}$ (EtOH throughout) 296 nm ($\epsilon$ 240); it gives a yellow colour with tetra-



|   | (I) | $R^1$ | | $R^2$ | | $R^3$ | |
|---|---|---|---|---|---|---|---|
|   |   | α | β | α | β | α | β |
| a; |   | O | | OH | H | | O |
| b; |   | H | H | OH | H | H | H |
| c; |   | OH | H | OH | H | OH | H |
| d; |   | H | OH | OH | H | OH | H |
| e; |   | H | OAc | O | | | O |



|   | (II) | $R^1$ | | $R^2$ | | $R^3$ | $R^4$ | |
|---|---|---|---|---|---|---|---|---|
|   |   | α | β | α | β | ξ | α | β |
| a; |   | O | | OH | H | H | | O |
| b; |   | OH | H | OH | H | H | OH | H |
| c; | OAc | H | | O | | H | | O |
| d; |   | O | | OAc | H | Br | | O |
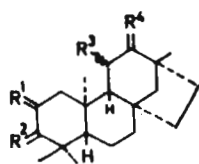


(IV)

(III)

nitromethane and a red colour with alkaline triphenyltetrazolium chloride, but no colour with ferric chloride. The ketol forms a monoacetate, $C_{22}H_{30}O_4$, m.p. 169—170°,

$[\alpha]_D$ — 362°, a dioxime $C_{20}H_{30}N_2O_3$, m.p. 275—277° (dec.), and it is catalytically reduced to the 15,16-dihydroketol (IIa), $C_{20}H_{30}O_3$, m.p. 107—108°, $[\alpha]_D$ — 34°, $\nu_{max}$ no band at 767 cm$^{-1}$, $\lambda_{max}$ 284 nm ($\epsilon$ 71).

The red colour with triphenyltetrazolium chloride indicates the presence of an α-ketol function in (Ia). The formation of *ent*-beyer-15(16)-en-3β-ol (Ib) as one of its Huang–Minlon reduction products, as well as the presence of a singlet at $\tau$ 5·14 in the spectrum of the ketol monoacetate, identifies this function as a 3-hydroxy-2-ketone unit. The hydroxy-group configuration at C-3 was established as 3α-equatorial by preparing (i) the two epimeric C-2 triols (Ic) and (Id) and (ii) the triol (IIb) by two different routes.

Reduction (NaBH$_4$) of the ketol (Ia) gave the triol (Ic), m.p. 223—226° (subl.) which on catalytic reduction was converted into the dihydro-triol (IIb), m.p. 224—227° (subl.). Anhydrous AlCl$_3$ isomerised the parent ketol acetate to the iso-ketol acetate (Ie), m.p. 228—231°, $\tau$ 4·53 (1H, q, C-2 α-proton, *J* 6 and 13 Hz), which on alkaline NaBH$_4$ reduction yielded the triol (Id), m.p. 218—221·5°, dissimilar from (Ic) [i.r. and t.l.c., (Id) having the lower mobility consistent with a 2,3-diequatorial diol structure]. On the other hand, oxidation of the ketol (Ia) with Bi$_2$O$_3$ to the corresponding diosphenol followed by acetylation and catalytic reduction from the β-face[1] finally yielded the dihydro-2α-acetoxy-3,12-dione (IIc), m.p. 156—158°, $\tau$ 4·46 (1H, q, C-2 proton, $J_{boat}$ 8·3 and 11·2 Hz). Reduction (NaBH$_4$) of (IIc), followed by alkaline hydrolysis of the product, resulted in the 2α,3α,12α-dihydro-triol, identical in all respects (m.p., i.r., and t.l.c.) with (IIb). The orientation of the hydroxy-groups in the above products is as indicated since it has been shown[2] that hydride reduction of the C-2 and C-3 *ent*-beyerane carbonyl groups takes place preferentially from the less hindered β-face of the molecule and similar reduction can be expected for the C-12 carbonyl group.

The position of the second carbonyl group at C-12 was established as follows. Formation of the diosphenol from (Ia) and C-2 proton n.m.r. signals of compounds (Ie) and

† The composition of all numbered compounds and their derivatives is based on high-resolution mass spectrometry and/or combustion analysis. Spectroscopic support has been obtained for all structures.

(IIc) excluded C-1, but left C-6 or C-11 and C-7 or C-12 as possible positions. Bromination of the (IIa) acetate furnished a crystalline compound $C_{22}H_{31}O_4Br$ (IId), m.p. 238·5—239·5°, $\tau$ 5·85 (1H, d, $J$ 7 Hz) indicating bromination at C-6 or C-11 next to either a C-7 or C-12 keto-group, respectively. The final choice was provided unequivocally by the rearranged compound (III), m.p. 183—185°, [$\lambda_{max}$(obs) 230, 273, 281, and 300sh. nm ($\epsilon$ 31,530, 1090, 873, and 53, respectively) $\lambda_{max}$(calc) 232³], $\tau$ 4·25 (2H, q, $J_{15,16}$ 9 Hz), 5·44 (1H, s, C-17 $cis$-proton), 5·56 (1H, s, C-17 $trans$-proton), 8·84, 9·00, and 9·24 (3 × 3H, 3 × s, 3 × $CH_3$), obtained by the following reaction sequence. Controlled $NaBH_4$ reduction of the parent ketol benzoate produced the 12α-hydroxy-product which was converted into the corresponding 12α-mesylate (IV). On solvolysis in boiling NaOAc-buffered acetic acid this equatorial 12α-mesylate (IV) underwent in good yield an elimination–rearrangement reaction (IV to III) by a mechanism remini-

scent of the steroidal c-nor–D-homo rearrangement.[4] The absence in (III) of one of the usual four methyl group signals coupled with the obvious presence of a transoid diene system (u.v. and n.m.r.) can be rationalised as due to migration of the C-13 : C-14 $\sigma$-electrons towards the developing carbonium ion at C-12, followed by elimination of a proton from C-17 to establish a C-13 : C-17 double bond.

The above evidence established the structure of the ketol (Ia) as $ent$-3β-hydroxybeyer-15(16)-ene-2,12-dione.‡ The ready formation of the diene (III) from the 12-oxy-beyer-15(16)-ene (IV) suggests that the structure of (III) represents a new type of diterpene skeleton which may eventually be found in Nature.

‡ For the systematic nomenclature of diterpenoids see ref. 5.

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# X-Ray Crystal and Molecular Structure of the Acid-catalysed Rearrangement Product of a Beyer-15(16)-en-12-one System

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*Summary* A double 1,2-rearrangement of a 12-oxo-beyer-15(16)-ene system across the 12,13-single bond, reversible after reduction of the double bond, is confirmed by X-ray crystal structural analysis.

The isolation and identification of a new naturally occurring compound of the beyerane class[1] was recently reported.[2] Dissolution of *ent*-3$\beta$-hydroxybeyer-15(16)-en-2,12-dione (Ia)† in acetic acid–acetic anhydride resulted in its ready acetylation to (Ib): $\lambda_{max}$ (EtOH throughout) 296 nm ($\epsilon$ 233), $\tau$ 9·26 (3H, s, 20-H). Addition of either conc. $H_2SO_4$, 70% $HClO_4$, or $BF_3$-$Et_2O$ to the ice cold solution of either (Ia) or (Ib) induced rearrangement in high yield to the $\alpha\beta$-unsaturated ketone (IIa), m.p. 221—222°, $\lambda_{max}$ 236, 305, and 324 nm ($\epsilon$ 7750, 82, and 92), $\nu_{max}$ (KBr throughout) 1742, 1716, 1665, 1235, and 820 cm$^{-1}$, $\tau$ 3·17 (1H, q, 15-H, $J_{15,16}$ 10 and $J$ 2 Hz), 4·17 (1H, d, 16-H, $J_{16,15}$ 10 Hz), 9·38 (3H, s, 20-H). Compound (IIa) was

† The composition of all numbered compounds is based on high resolution mass spectrometry. Assignment of all structures is supported by spectroscopic evidence.

readily hydrogenated (Pd) at room temperature and atmospheric pressure to give (III), m.p. 213—214°, $\lambda_{max}$ 287 nm ($\epsilon$ 62), $\nu_{max}$ 1750, 1725, 1705, and 1240 cm$^{-1}$, $\tau$ 9·00



(I) a; R = H
b; R = Ac
c; R = p - BrC$_6$H$_4$CO

(II) a; R = Ac
b; R = p - BrC$_6$H$_4$CO

(III)

(IV)
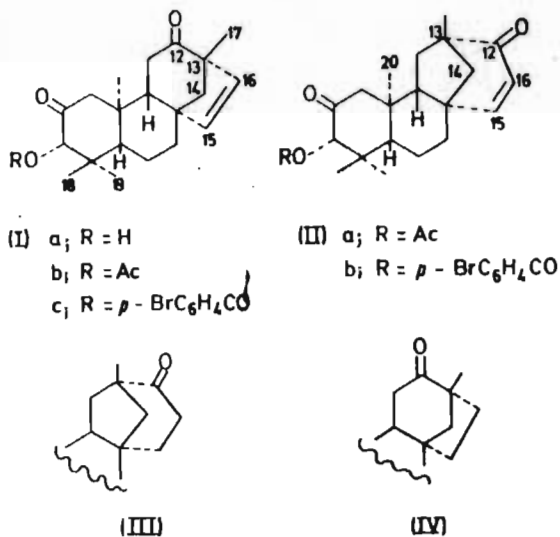
(3H, s, 20-H). Addition of conc. $H_2SO_4$ to an ice-cold acetic acid–acetic anhydride solution of the dihydro-compound (III) afforded an isomer (IV), m.p. 215—216° (subl.), $\lambda_{max}$ 288 nm ($\epsilon$ 59), $\tau$ 9·06 (3H, s, 20-H), identical in all respects to the 15,16-dihydro-derivative of (Ib).

The easy rearrangement of the beyer-15(16)-en-12-one system probably proceeds as indicated in the Scheme, the final product being stabilised by the conjugation of the two unsaturated functions.
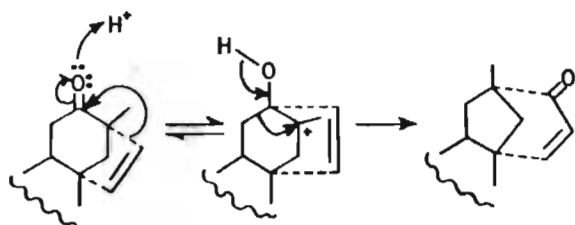


SCHEME

Suitable crystals of the p-bromobenzoate (IIb), $C_{27}H_{31}BrO_4$, m.p. 297—299°, proved to be triclinic: space group P1, $a = 6\cdot35$, $b = 8\cdot71$, $c = 11\cdot93$ ($\pm0\cdot01$ Å), $\alpha = 108\cdot3°$, $\beta = 97\cdot6°$, $\gamma = 102\cdot2°$ ($\pm0\cdot1°$), $U = 598$ Å$^3$, $D_m = 1\cdot37$ g cm$^{-3}$, $Z = 1$, $M = 499$.

Integrated intensity data were collected by the multiple film Weissenberg method with Ni-filtered Cu-$K_\alpha$ radiation and measured with a densitometer. The structure was solved by the usual heavy atom and Fourier methods, and has been refined isotropically by block-diagonal least-squares to $R = 0\cdot17$ for 2430 observed data. (All calcula-

tions were done with the local set of programs;[3] further refinement is continuing.)

The basic stereochemistry of the skeleton is essentially similar to that of *ent*-beyerol,[4] (Figure: a projection down *a*) with all bond lengths within 0·03 Å of the usual values. The geometry of the c and d rings confirms that the re-arrangement took place as suggested. The reason for the large chemical shift of the methyl group C(20) is now quite evident.[5] The distance between the two angular methyl groups C(20) and C(19) is 3·21 Å, while the distance between C(20) and C(15) of the double bond is 3·04 Å. This latter separation is distinctly shorter than the normal value of *ca.* 3·2 Å.[6] The close proximity of the $\pi$-cloud on C(15) to the hydrogen atoms on C(20) causes the marked shielding effect observed in the n.m.r. spectrum. The additional splitting of the n.m.r. signal of the C(15) proton may be due to either long-range coupling with the $\alpha$ axial hydrogen atom on C(6), or possibly coupling with the $\beta$ proton on C(14), with which it forms an M system,[7] albeit not coplanar. As expected, the atoms O, C(12), C(16), and C(15) of the conjugated unsaturated ketone system are coplanar within 0·015 Å.

The large strain experienced by C(20) is reflected in the bond angles: C(9)–C(10)–C(20) 113°, C(5)–C(10)–C(20) 116°, C(1)–C(10)–C(20) 104°, showing that the C(20)–C(10) bond
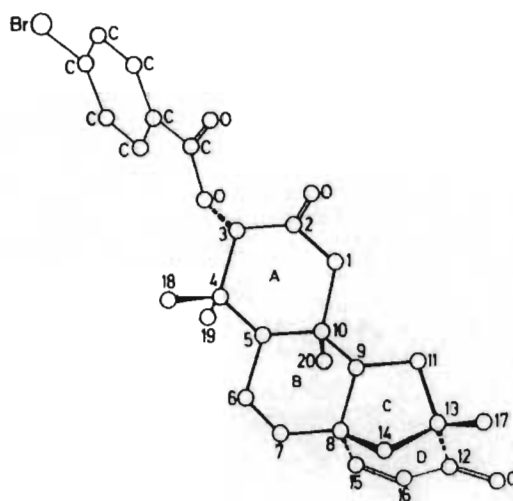


FIGURE

is bent outwards and away from both C(19) and C(15). The angles in the c and d rings show quite large deviations from the usual tetrahedral value. The values of 104° for C(8)–C(9)–C(11) and 99° for C(9)–C(8)–C(14) are not unusual; similar small values have been observed in many other molecules for angles involving atoms in environments analogous to that of C(8).[8] In each case, where one carbon atom at the fusion of the rings of the perhydroindane system carries an angular (axial) carbon atom, the angle at this atom lies between 97 and 100° while that for the other carbon is between 104 and 105°. Distortions caused by variations in the torsion angle at the fusion of the trans fused perhydroindane system have been discussed in detail,[9] but distortions specifically due to one angular methyl group have not.

The ease with which the reverse rearrangement takes place in the dihydro-compound appears to be due to the

increased compression at C(20) and C(15) caused by the additional hydrogen on C(15).[10]

This work was supported in part by grants from the South African Council for Scientific and Industrial Research.

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THE X-RAY CRYSTAL AND MOLECULAR STRUCTURE OF

ent-1α-p-BROMOBENZOYLOXY-16S-ATIS-13-EN-2-ONE

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The marked unreactivity of the ent-16S-atis-13-en system[1] as in compounds (1a-e) and the unusual[2] acetoxylation at C(1) on acetolysis of an ent-3β-tosyloxybeyer-2-ketone system derived from compound (2a), was reported recently. The n.m.r. spectrum of the solvolysis product (2b) of the tosylate of (2a) (broad singlet, $W_{\frac{1}{2}}$ 3 Hz at τ 5.8 due to the H(1α) equatorial proton) suggested that long range ("W rule") coupling takes place between the H(1α) and the H(3α) equatorial protons via the C(2) carbonyl carbon.[3]
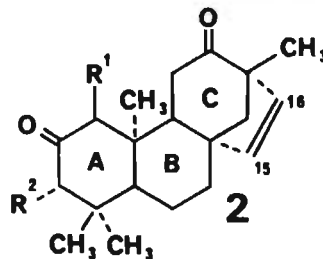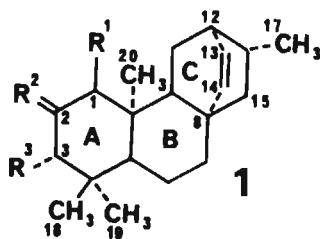


| 1 | R¹ | R² | | R³ | | 2 | R¹ | R² |
|---|---|---|---|---|---|---|---|---|
| | | α | β | | | | | |
| a | p.BrC₆H₄CO₂ | O | | H | | a | H | OH |
| b | H | OH | H | OH | | b | OAc | H |
| c | H | O | | OH | | | | |
| d | OAc | O | | H | | | | |
| e | OH | O | | H | | | | |

These features prompted us to undertake an x-ray structural investigation in order to obtain a detailed picture of the

stereochemical interactions involved and in particular, to deter-
mine the structure of the product of the ring A rearrangement.
We decided to combine the two problems in one molecule suitable
for such a structural investigation and ent-16S-lα-p-bromobenzoyl-
oxyatis-13-en-2-one (1a) was therefore prepared as described
below.

Sodium borohydride reduction of the tosylhydrazone of the
beyerane ketol (2a) gave ent-2β,3β-dihydroxy-16S-atis-13-ene (1b).
The vicinal diol function in (1b) was oxidised within a few
minutes at 80° with silver carbonate on celite in benzene to the
original 3α-hydroxy-2-ketone system to give compound (1c).
Acetolysis of the tosylate of (1c) gave ent-lα-acetoxy-16S-atis-
13-en-2-one (1d), τ 5.63 (1H, broad s, $W_{\frac{1}{2}}$ $3H_z$, H-lα). A methanol
solution of the acetate (1d) on treatment with a few drops of
dilute sodium hydroxide at room temperature rapidly deposited
crystals of the corresponding alcohol (1e) which reluctantly
reacted with p-bromobenzoyl chloride in pyridine to give the
p-bromobenzoate (1a), m.p. 166-170°, τ 5.40 (1H, s, $W_{\frac{1}{2}}$ 3 Hz, H-lα).

Suitable crystals of (1a), $C_{27}H_{33}BrO_3$, obtained from a
mixture of acetone, ethanol and hexane, were triclinic, space
group P1, a=7.34, b=12.47, c=14.38 (± 0.01Å), α=109.3, β=97.6,
γ=92.3 (± 0.01°), U=1227 Å$^3$, $D_m$=1.32 gcm$^{-3}$, Z=2; no required
molecular symmetry. Intensity data were collected on a Philips
four-circle diffractometer with Zr-filtered Mo-Kα radiation. The
structure was solved by the heavy atom and Fourier methods, and
refined isotropically (Br atoms anisotropic) by block diagonal
least-squares to R = 0.09 for 2170 observed data. Further
refinement[4] is continuing.

The two independent molecules in the asymmetric unit are
related by a psuedo two fold axis, and are essentially identical
(Figure: a projection down a). All bond lengths and angles are
normal : Br-C(ph) 1.86 Å, C(13)-C(14) 1.33 Å. The results confirm
that the rearrangement of the C/D ring system has taken place as
proposed. The four atoms of the double bond system,
C(12)-C(13)-C(14)-C(8), are coplanar within 0.01 Å. The extreme
inertness of the C(13)-C(14) double bond is clearly caused by
the close contacts between it and methyl carbons C(17) and C(20),
which must hinder the approach of incoming reactants: C(17)···C(13)
= 3.10 Å, C(20)···C(14) = 3.17 Å. In addition, C(20) is further
buttressed by methyl carbon C(19); C(20)···C(19) = 3.21 Å.
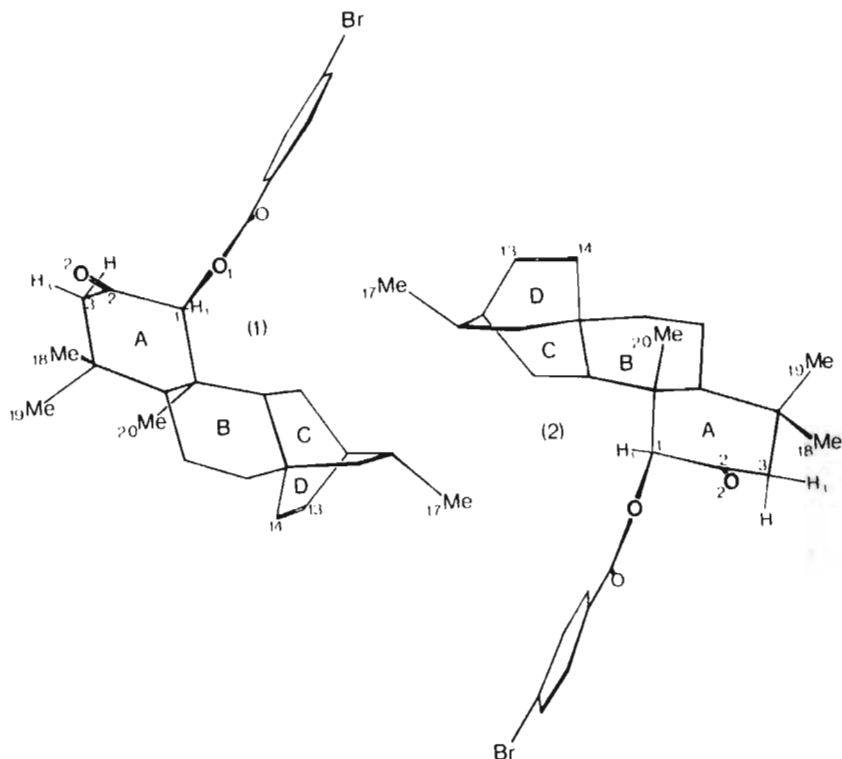
Several aspects of the $H^1$n.m.r. spectrum can now be explained. The short methyl C(17)$\cdots$C(14), and methyl C(20)$\cdots$C(13) separations place these methyl protons in the shielding environment of the C(13)-C(14) double bond $\pi$ cloud and as a consequence of this, their resonances appear at $\tau$ 9.33 and 9.30 respectively. The atoms H(1)-C(1)-C(2)-O(2)-C(3)-H(3) are coplanar within 0.05 $\overset{o}{A}$. The hydrogen atoms H(1) and H(3) are thus part of a W system which is the cause of the broadening of the NMR signal of H(1).[3]

The torsion angle, methyl C(20)-C(10)-C(1)-O(1), is 177°; C(20) and O(1) are almost ideally <u>trans</u> diaxial. The torsion angle O(1)-C(1)-C(2)-O(2) is large, 130°. The low reactivity of the ketol system in (1c) towards T.T.C. reagent is probably caused by the steric hindrance of the equatorial hydrogen atom at C(1) by the hydrogen atoms at C(11). That the solvolysis of the A ring 3α-tosyloxy-2-ketone function, should have yielded the <u>axial</u> product, the 1β-acetoxy-2-ketone function, implies that the approach to C(1) from the α-side of the molecule in the final transition state is considerably hindered, because a regular $S_N2'$ reaction would produce the equatorial isomer.[5] This hindrance is caused by the methyl group C(20).

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# Hydride Induced Conversion of an *ent*-Beyer-15-ene 12-*p*-Tosylhydrazone into the Novel *ent*-16S-Atis-13-ene System

By Karl H. Pegel* and Lorenzo P. L. Piacenza

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*Summary* The hydride induced shift of an *ent*-beyer-15-ene 12-*p*-tosylhydrazone, a bicyclo[3,2,1]octene system, to the hitherto undescribed *ent*-16S-atis-13-ene, a bicyclo-[2,2,2]octene system, is discussed; the extreme unreactivity of the double bond in the product is reported.

Skeletal rearrangements induced by basic decomposition of *p*-tosylhydrazones are well known,[1] whereas reaction with complex hydrides usually accomplishes the reductive elimination of a carbonyl function to the methylene group.[2] We report a stereospecific alkyl group migration during the sodium borohydride decomposition of a *p*-tosylhydrazone.

Treatment of the α-ketol (1a)[3] with *p*-tosylhydrazine in acetic acid at room temperature gave *ent*-3β-hydroxybeyer-15-en-2-one 12-*p*-tosylhydrazone (1b). Reaction of (1b) with $NaBH_4$ in ethanol–dioxan at 0° or reflux temperatures gave as the sole isolable product the novel diol *ent*-16S-2β,-3β-dihydroxyatis-13-ene (2), m.p. 190—192°, in 73% overall yield from (1a). The double bond in the atisane compound (2) is in the 13(14)-position instead of the usual 15(16)- or 16(17)-positions as found in natural or synthetic atisane diterpenes formally derived from a kaurane system. Confirmation of this was obtained from the mass spectrum of (2) where the base peak at 262 ($M - 42$) arises from the

retro-Diels–Alder loss of $C_3H_6$ eliminating C-15, C-16, C-17, and their hydrogen atoms. The stereochemistry at C-16 in the atisane product (2) was deduced from its [1]H n.m.r. spectrum. The C-17 methyl resonance which in beyeranes



a; R = O  (1)

b; R = NNHTs

(2)

is usually[4] one of the downfield methyl group signals now appears as the highest field signal as the expected doublet suggesting that it lies in the shielding region of the double bond and that the configuration at C-16 is therefore *ent*-16S.

The observed alkyl group migration suggested a mechanism involving formation of an incipient positive charge at C-12 with a concerted rearrangement of C-16 from C-13 to

C-12, similar to the first step in the previously reported[5] isomerisation of the beyer-15-en-12-one system.

Similar $NaBH_4$ treatment of the 15,16-dihydro-12-tosylhydrazone analogue of (1b) failed to bring about the rearrangement, but gave instead the known *ent*-2$\beta$,3$\beta$-dihydroxybeyerane.[6] The failure to rearrange may be due in part to the large steric compression that would be incurred by the angular C-20 methyl group and the 13-*endo*- and 14-*endo*-atisane hydrogens[7] in the transition state.

Although the atisene 13(14)-double bond underwent hydrogenation quite readily it was otherwise inert to bromination, acetoxymercuration (*cis* or *trans*),[8] and neutral permanganate oxidation. Attempted epoxidation with *m*-chloroperbenzoic acid gave an as yet unresolved mixture of aromatic acid esters. This inertness of the *ent*-16S-atis-13-ene system must be due to steric crowding of the double bond by the C-20 and C-17 $\alpha$-oriented methyl groups.

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THE X-RAY CRYSTAL AND MOLECULAR STRUCTURE OF A TETRACYCLIC DITERPENOID -
BENZALDEHYDE REACTION PRODUCT AND THE LONG RANGE PROTECTIVE INFLUENCE OF ITS
BENZENE RING

By M. Laing*,  K.H. Pegel*  and  L.P.L. Piacenza
(Chemistry Department, University of Natal, Durban, South Africa)
and L. Phillips and E.S. Waight
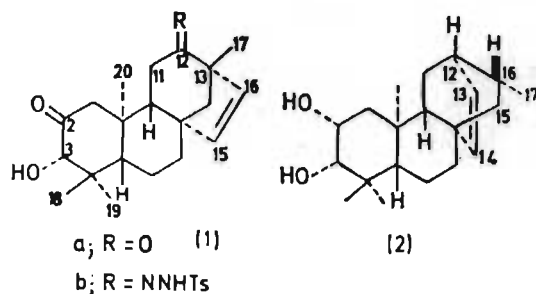(Chemistry Department, Imperial College, London S.W.7 2AY)

Base induced oxidation converts the ketol (1a) in the presence of
oxygen to the 2-hydroxy-1-en-3-one diosphenol which in turn undergoes a
base catalysed aldol condensation with benzaldehyde at C(1) from the β-face
of the molecule.   This is followed by a benzilic acid type ring A
contraction and final esterification to give the lactone (2a), m.p. 267-268°,
$\nu_{max}$ 1750 cm$^{-1}$ and τ 4.83 and 7.31 (each 1H, d, J 9.0 Hz, 1a-H and 1-H
respectively).
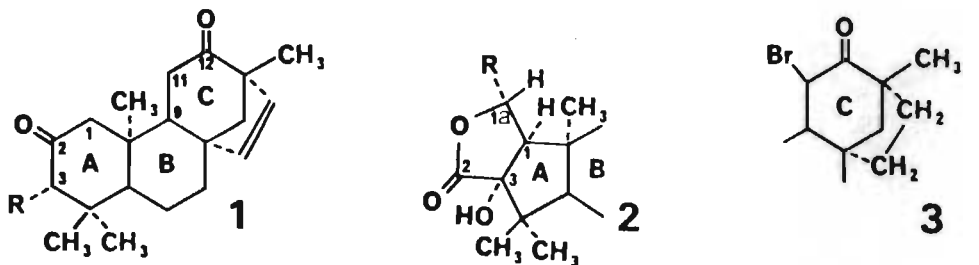


(1) a, R = OH
    b, R = OAc

(2) B/C/D ring system as
    in (1)
    a, R = C$_6$H$_5$
    b, R = H

(3) a, lactone/A/B ring
       system as in (2a)
    b, A/B ring system
       as in (1b)

This lactone is obtained in good yield when a mixture of the ketol (1a)
and benzaldehyde in aq. ethanol is treated with dilute sodium hydroxide in the
presence of oxygen (over 50% crystalline yield from the reaction mixture);
the use of formaldehyde produces an analogous product (2b), m.p. 219-220°,
$\nu_{max}$ 1770 cm$^{-1}$ and τ 5.76 and 6.01 (each 1H, t, J$_{1a\alpha,1a\beta}$ 10.0 Hz)

and 7.43 (1H, d, J 10 Hz, 1-H). A similar stereospecific reaction has been reported[1] for formaldehyde and a steroidal ring D-Homo diosphenol. Since geminal and vicinal electronegative substituents extend the range of proton coupling constants,[2] these values ($J_{1,1a}$ 9.0 Hz in (2a) and 7.2 Hz in (3a)) could not be used to determine the configuration of the nor-ring A/lactone system. However, stereochemical arguments indicated structure (2a).

The two related 11β-bromo compounds (3a), m.p. 270-272° dec., $J_{1,1a}$ 7.2 Hz and $J_{9,11}$ 12.4 Hz, and (3b),[3] $J_{9,11}$ 6.6 Hz, form stable crystals but each readily exchanges its bromine for hydrogen under mild conditions in the presence of proton donating solvents (e.g. acetolysis, base hydrolysis and, for (3a), after a few minutes treatment with boiling methanol) and it has not been possible to effect dehydrobromination.

The decrease in $J_{9,11}$ from 12.4 Hz in (3a) to 6.6 Hz in (3b) reflects the steric interaction between the benzene ring and the 11β-equatorial bromine in (3a) which forces the 9β and the 11α hydrogens into a more perfect transdiaxial conformation. In product (2a), the benzene ring protects the 12-keto group from β-attack. Thus, while NaBH₄ reduction of (1a) resulted in high conversion of the 12-keto group to a 12α-equatorial alcohol,[3] similar reduction of (2a) gave an easily separable mixture of the 12α- and the otherwise not readily accessible 12β-axial alcohol in a 3:2 ratio respectively. This reversal of steric hindrance at C(12) was even more pronounced when the bulkier LiAl(t-BuO)₃H was used; the main reduction product from (2a) was the 12β-axial alcohol (70% crystalline yield). Thus the long range shielding effect of the benzene ring is more effective over the β-face of the molecule than the short range protection afforded by the α-diaxially oriented D-ring towards the α-side of the molecule.

Crystals of the 11β-bromo compound (3a) $C_{27}H_{33}BrO_4$, were orthorhombic, space group P2₁2₁2₁. $a$ = 21.20, $b$ = 11.42, $c$ = 9.84 (±0.01Å), U = 2382 Å³, $D_m$ = 1.31 gcm⁻³, Z = 4.

Intensity data were collected on a Philips four circle diffractometer with Zr-filtered Mo-Kα radiation. The structure was solved by the usual heavy atom and Fourier methods, and refined isotropically (Br anisotropic) by block-diagonal least squares to R = 0.08 for 1230 observed data. (All calculations were done with the local set of programs;[4] further refinement is continuing.)

The stereochemistry of the molecular skeleton confirms that the rearrangements took place as suggested (Figure: a projection down a). The bond lengths and angles are generally normal; Br-C(11) = 1.99 Å.
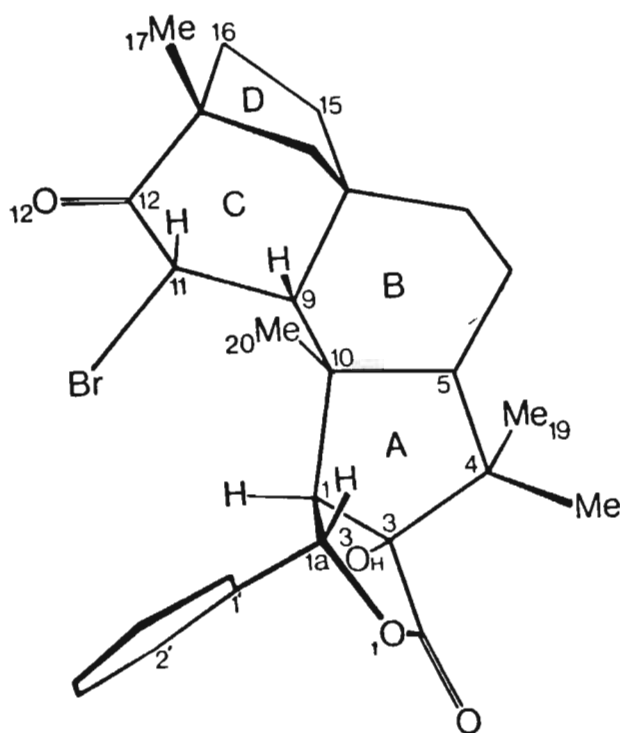


Angle C(4)-C(5)-C(10) = 105°, while angle C(1)-C(10)-C(5) = 99°. Similar distortions at analogous carbon atoms carrying an axial substituent have been observed previously in related compounds.[5] Methyl group C(20) is in close contact with three groups: methyl C(19)-3.33 Å; hydroxyl O(3)-3.25 Å and C(15) of the bridge in the D ring -3.42 Å. The latter separation is distinctly larger than that found for the analogous pair of atoms in a closely related molecule,[5] in which the rings C and D are 5- and 6-membered respectively.

The nor-ring A/lactone system is twisted up and clockwise relative to the average plane of ring C.   This results in the torsion angle between the hydrogen atoms on C(11) and C(9) being 173°, (consistent with the observed coupling constant of 12.4 Hz).   The torsion angle between the hydrogen atoms on C(1) and C(1a) is 124°, again consistent[6] with the observed coupling constant of 7.2 Hz.

The distortions in the skeleton are caused by the short non-bonded distance between the bromine atom and the benzene ring:  Br--C(2') = 3.52, Br--C(1') = 3.46 Å.   The strain is relieved also by angular distortion at C(11) and C(1a) where the internal angles are opened up considerably: C(9)-C(11)-Br = 113°, C(12)-C(11)-Br = 107°, C(1)-C(1a)-C(1') = 120°, O(1)-C(1a)-C(1') = 106°.

It is evident that when the only substituents on C(11) are H atoms, the benzene ring can approach C(11) more closely and hence shield C(12) and O(12) more effectively from above.

<div align="center">*   *   *   *   *</div>

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TERPENOID RING A α-KETOL SULPHONATE ESTER SOLVOLYSIS:   CONVERSION OF

ENT-3β-HYDROXYBEYER-15-EN-2,12-DIONE TO THE ISOMERIC ENT-1α-HYDROXYBEYER-15-EN-2,12-DIONE

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SUMMARY.  Acetolysis of tetracyclic diterpenoid 3-equatorial, 3-axial or 1-axial sulphonate-2-ketones results in attack at the 1-axial position.  Jones oxidation of the derived 1-hydroxy-2-ketone results in an unexpected ring contraction-decarboxylation giving a 2-nor-1-ketone.

Solvolytic reactions of secondary α-ketol sulphonate esters have been scantily documented,[1] although the $S_N2$ reactions of α-halogeno-ketones are well known.[2] Recently Satoh and Takahashi[3] reported a new example of the $S_N2'$ reaction where the incoming nucleophile entered _trans_ to the leaving group instead of the normal _cis_ relationship shown by most $S_N2'$ reactions of allylic halides.[4]  We would like to report an apparently similar exceptional reaction;  however in our case the configuration of the product was always the same irrespective of the initial configuration of the leaving group at the alternate α position.

Tosylation of the tetracyclic diterpene α-ketol, ent-3β-hydroxybeyer-15-en-2, 12-dione (1)[5] with tosyl chloride in pyridine gave the corresponding equatorial tosylate (2), m.p. 202-203°.  Acetolysis of (2) at reflux in sodium acetate buffered acetic acid gave as the major product the axial ent-1α-acetoxybeyer-15-en-2,12-dione (3), m.p. 176-178°, τ 5.8 (1H, broad s, $W_{\frac{1}{2}}$ 3 Hz, H-1 equatorial), accompanied by minor amounts of the ent-3β-acetate (4)[5] and ent-3α-acetate (5),[6] (see Table).  Similar acetolysis of the axial ent-3α-mesylate (6)[7] gave a comparable result (see Table).

The constitution of the major product (3) was deduced as follows. Compound (3) underwent practically instantaneous hydrolysis with dilute base at room temperature to give the corresponding alcohol (7), m.p. 191-193°. Reacetylation of this α'-ketol (7) regenerated the parent acetate (3) showing that during its hydrolysis base induced epimerisation or isomerisation had not taken place. Furthermore sodium borohydride reduction of the 12-dithioethane ketal of (7) gave the diaxial ent-1α,2β-diol which did not form an acetonide (acetone-HClO₄). The recent report by Connolly and Harding[8] that after base equilibration of a 1,2-beyer-15-ene ketol the axial ent-1α-hydroxy-2-ketone was the predominant product of the two possible C-1 epimers, supported our axial ent-1α-acetoxy and hydroxy group assignments to both (3) and (7) respectively.†

The acetolysis of the axial ent-1α-mesylate (8)[7] gave predominantly the ent-1α-acetoxy-2-ketone (3) as before together with minor amounts of the two epimeric 3-acetates (see Table) instead of the expected[9] 20(10→ent-1β)abeobeyerene. This unexpected reaction as well as the product composition suggested the formation of a common intermediate from all three starting sulphonates, possibly the delocalised enol cation (9).
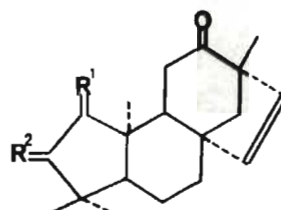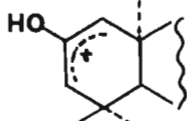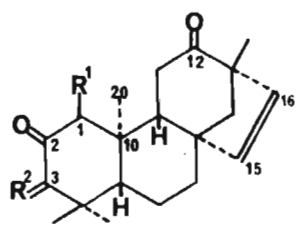


| | R¹ | R² |  |
|---|---|---|---|
| | | α | β |
| (1) | H | OH | H |
| (2) | H | OTs | H |
| (3) | OAc | H | H |
| (4) | H | OAc | H |
| (5) | H | H | OAc |
| (6) | H | H | OMs |
| (7) | OH | H | H |
| (8) | OMs | H | H |

(9)

| | R¹ | R² |
|---|---|---|
| (10) | O | H₂ |
| (11) | H₂ | O |

† An X-ray diffraction study incorporating the ent-1α-hydroxy-2-one moiety has been recently reported.[10]

TABLE

Percentages* of Acetolysis Products

| SUBSTRATE | AXIAL ent-1α-acetate(3) | AXIAL ent-3α-acetate(5) | EQUATORIAL ent-3β-acetate(4) |
|---|---|---|---|
| EQUATORIAL ent-3β-tosylate (2) | 75 | 7.5 | 17.5 |
| AXIAL     ent-3α-mesylate (6) | 71 | 14.5 | 14.5 |
| AXIAL     ent-1α-mesylate (8) | 72 | 14.5 | 13.5 |

*Estimated by n.m.r. of the total crude reaction product - accuracy ± 5%

Jones oxidation with excess reagent at $0°$ of the 1,2-ketol (7) resulted in the evolution of $CO_2$ and the isolation of the 2-nor-1-ketone (10), m.p. 144-146°, in 30% yield, which was different from the isomeric 3-nor-2-ketone (11).[6] This unexpected decarboxylation is tentatively postulated to proceed via a β-hydroxy acid as shown in the SCHEME, although to our knowledge there is no precedent of an acid catalysed aldol type condensation of an aldehyde with the α-carbon of a carboxylic acid under such conditions.
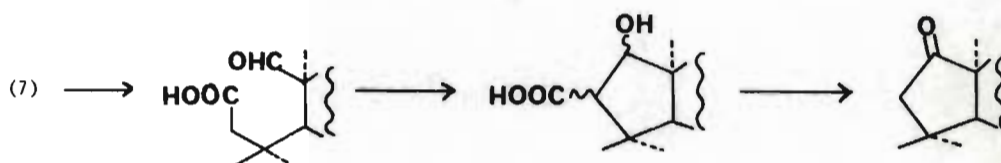


SCHEME

Finally it is noteworthy that Connolly and Harding[8] have recently isolated the ent-2α-hydroxybeyer-15-en-1-one and related C-1 oxygenated diterpenes from an Erythroxylon species and the above reaction is a facile synthetic route to these compounds.

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# INTRODUCTION

Androstachys johnsonii Prain is a large tree found growing
in drier areas in Mocambique, Rhodesia and South Africa.  Locally
it is sometimes known as the Lebombo Ironwood as it is found in the
Lebombo mountain range in the Kruger National Park from where the
specimens used in this work were obtained.  The wood is exceptionally
hard and termite resistant.  For this reason it has been used to
make telegraph poles and railway sleepers as well as fences.  This
dioecious plant had originally been botanically classified as a
Euphorbiaceae but because of anatomical anomalies of its flowers
it was regarded as atypical of that large family and placed in its
own family, the Androstachaceae, of which it is the only known
member.[4]   The botanical taxonomy of this plant was then still in
doubt.

The plant thrives in rocky, dry areas.  Seedlings germinated
from the extremely viable seeds (90% viable) seemed to grow very
slowly and when they were 5 cm tall after about eight months growth
they were transferred to larger pots and found to have a 70 cm long
tap root!  This explained the slow growth of the aerial parts of
the plants.  Obviously the plant establishes itself firmly in the
ground after finding a deep source of water and only then it
grows upwards.

The presence of a dense and dark heartwood is a good
criterion indicating the presence of substantial quantities of
secondary metabolites.  The heartwood of Cleistanthus schlechteri
(Euphorbiaceae) has yielded several new diterpenes[5] as well as
large quantities of (+)-catechin.[6]   An earlier investigation of the

heartwood of the related "Tambooti" Spirostachys africana had yielded three congeneric ent-beyerenes (stachenes).[2]   The heartwood of A. johnsonii was similar to the above two species, all three being dark and heavy.

Light petroleum extraction of the powdered wood gave a bright yellow solution which contained most of the soluble components of the wood.   Later batches of wood gave a dark red liquid instead of yellow.   Concentration of the yellow solution produced a crystalline mass which after repeated crystallisation yielded the pure major component, a novel stachene α-ketol (1), the first compound having this skeleton with a 12-oxygen substituent (see BIOGENESIS SECTION).   Later batches of wood gave the corresponding 12-oxo-diosphenol (18) instead as the main diterpenoid constituent. The remainder of the extract was only partially investigated but furnished several known and some new diterpenes all of the tetracyclic stachene class, as well as a further tetracyclic diterpene probably belonging to the atisene class.

These compounds definitely related A. johnsonii with S. africana from a chemotaxonomic argument, and A. johnsonii is probably best left in the Euphorbiaceae family.
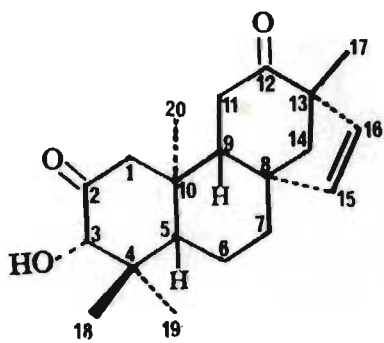
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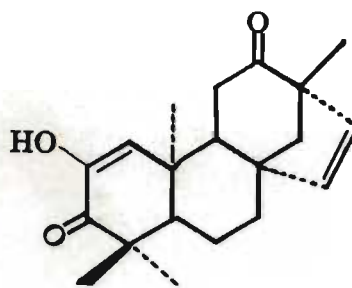
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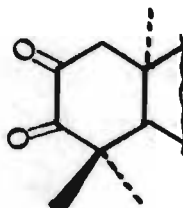
# C H A P T E R   1

## BIOGENESIS OF THE TETRACYCLIC DITERPENES

The cyclisation of geranylgeranylpyrophosphate leads to the group of natural secondary metabolites known as diterpenes. These can be subdivided into bicyclic, tricyclic, tetracyclic and pentacyclic diterpenes. The tetracyclic diterpenes are of prime interest here and will be discussed preferentially. Robinson and West[7] in a series of elegant experiments showed that enzyme preparations from castor oil seedlings (Ricinus communis L) converted geranylgeranyl pyrophosphate into the cyclic diterpenes ent-beyerene, ent-sandaraco-pimaradiene, ent-kaurene and ent-trachylobane as well as the macrocyclic casbene.

## FORMATION OF ENT-BEYERENE
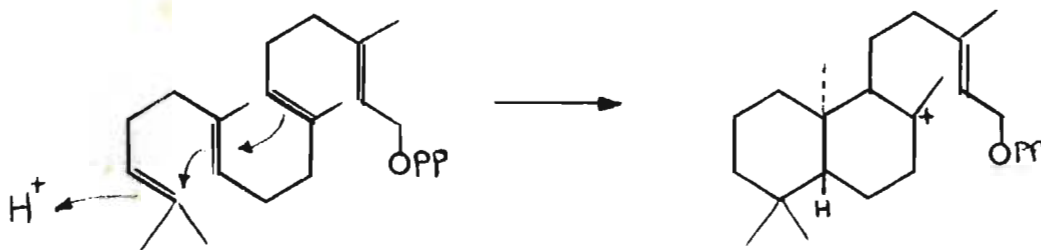


GERANYLGERANYL PYROPHOSPHATE (GGPP)



ent-BEYERENE
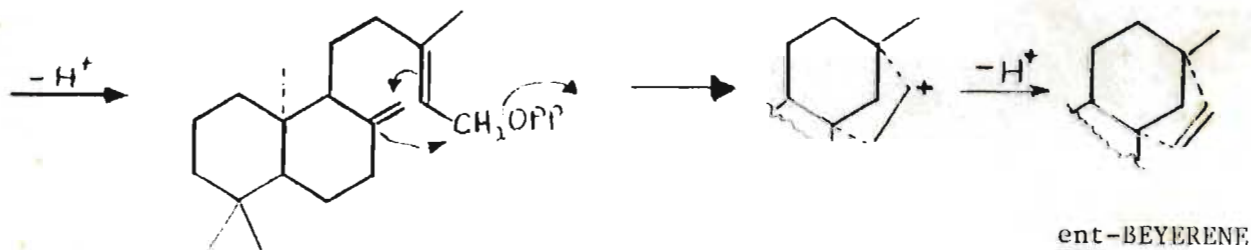
## FORMATION OF ENT-SANDARACOPIMARADIENE
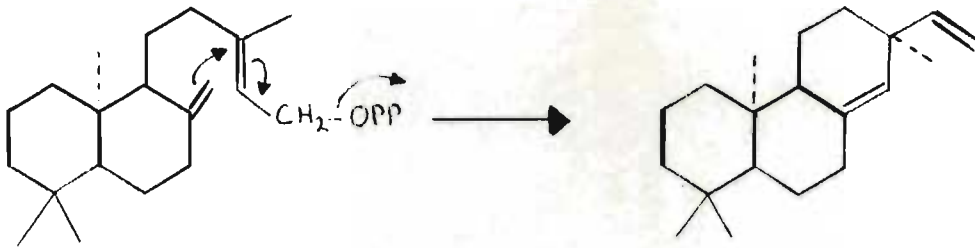


## FORMATION OF ENT-KAURENE AND ENT-TRACHYLOBANE
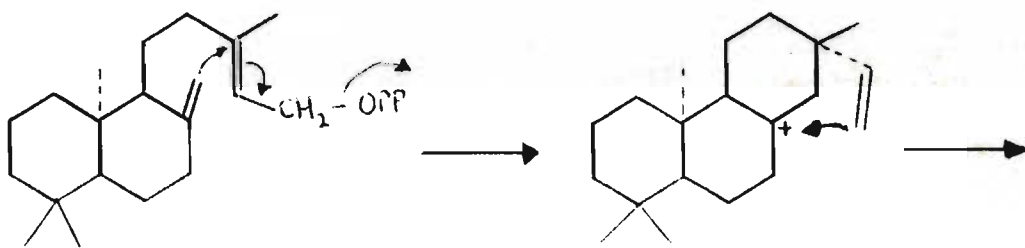


(PIMARADIENE PRECURSOR)
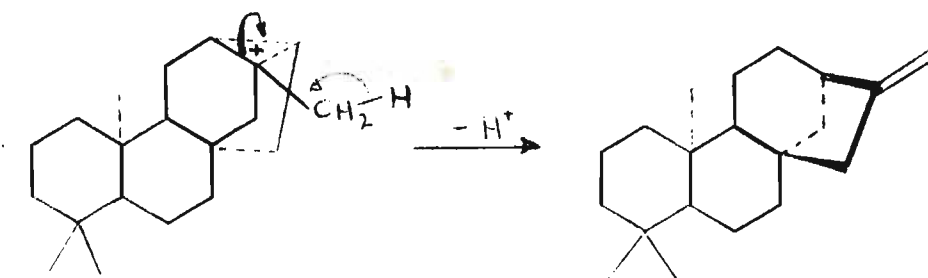


ent-KAURENE
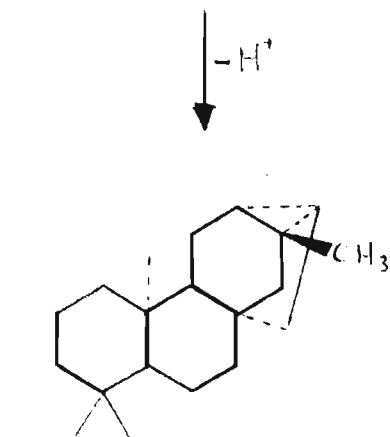
ent-TRACHYLOBANE

However, very recently Hanson[8] showed that in a cell-free

enzyme system of the mould Gibberella fujikuroi, a 'free' pimaradiene

intermediate was not involved in the biosynthesis of ent-kaurene.

Instead the scheme proposed[8] was



ent-KAURENE
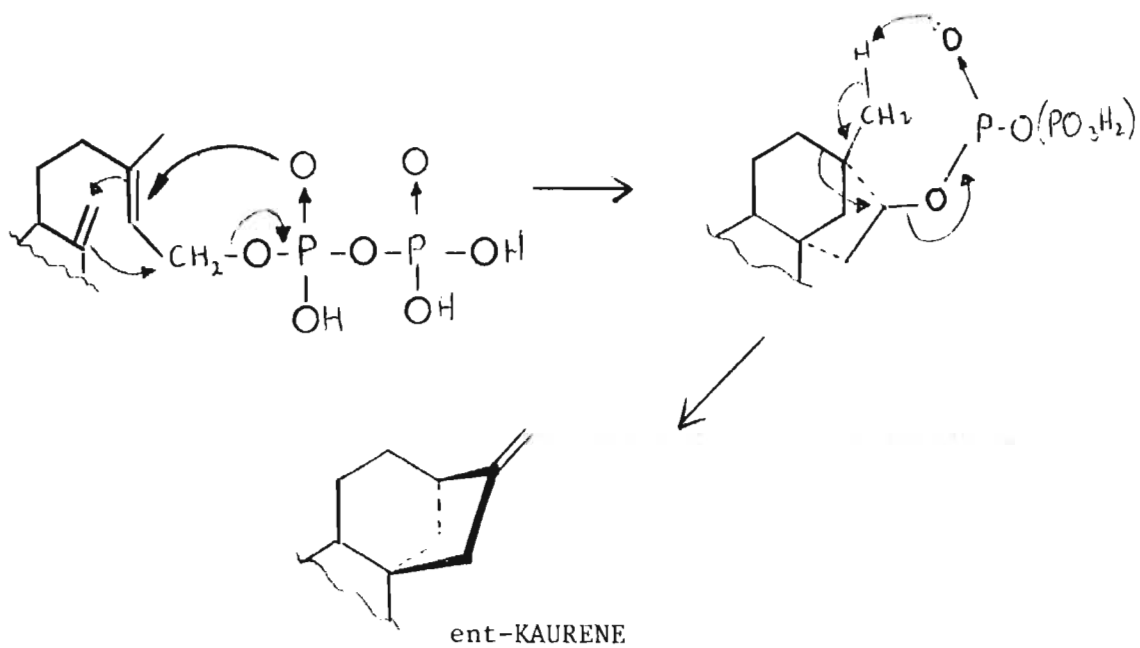
On the other hand, an 'enzyme bound' pimaradiene could not be

excluded as an alternative pathway.

FORMATION OF CASBENE[7]

PPO—CH$_2$

GGPP
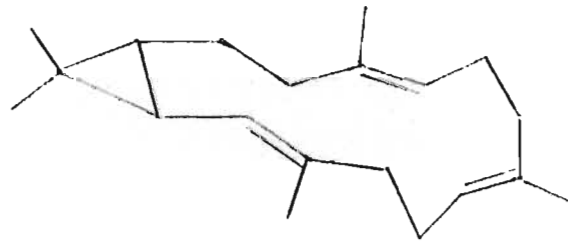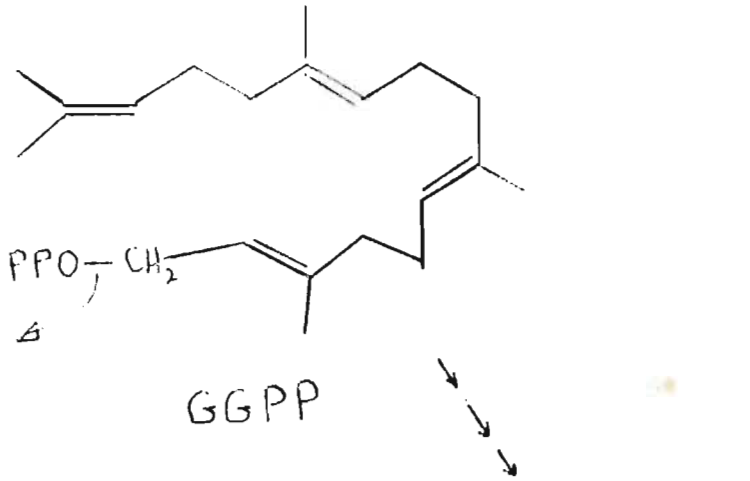
CASBENE

It was noteworthy that no ATISANES were reported to be formed by the _Ricinus_ supernatant,[7] because these should be readily derived from the precursor cation of the pentacyclic trachylobane:

—CH$_3$  ⟶  CH$_3$  —H$^+$
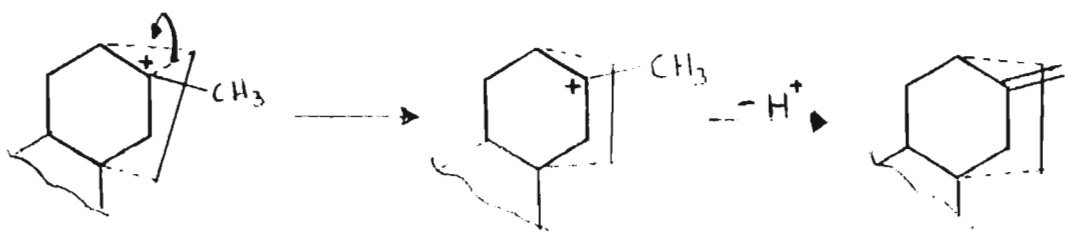
In fact this ion can collapse to give ent-hibaene, ent-trachylobane, ent-beyer-11-ene, ent-kaurene and ent-atiserene as shown in the scheme.[9]



(+)-HIBAENE OR
STACHENE OR
ent-BEYER-15-ENE

ent-TRACHYLOBANE

ent-BEYER-11-ENE

ent-KAURENE

ent-ATISERENE
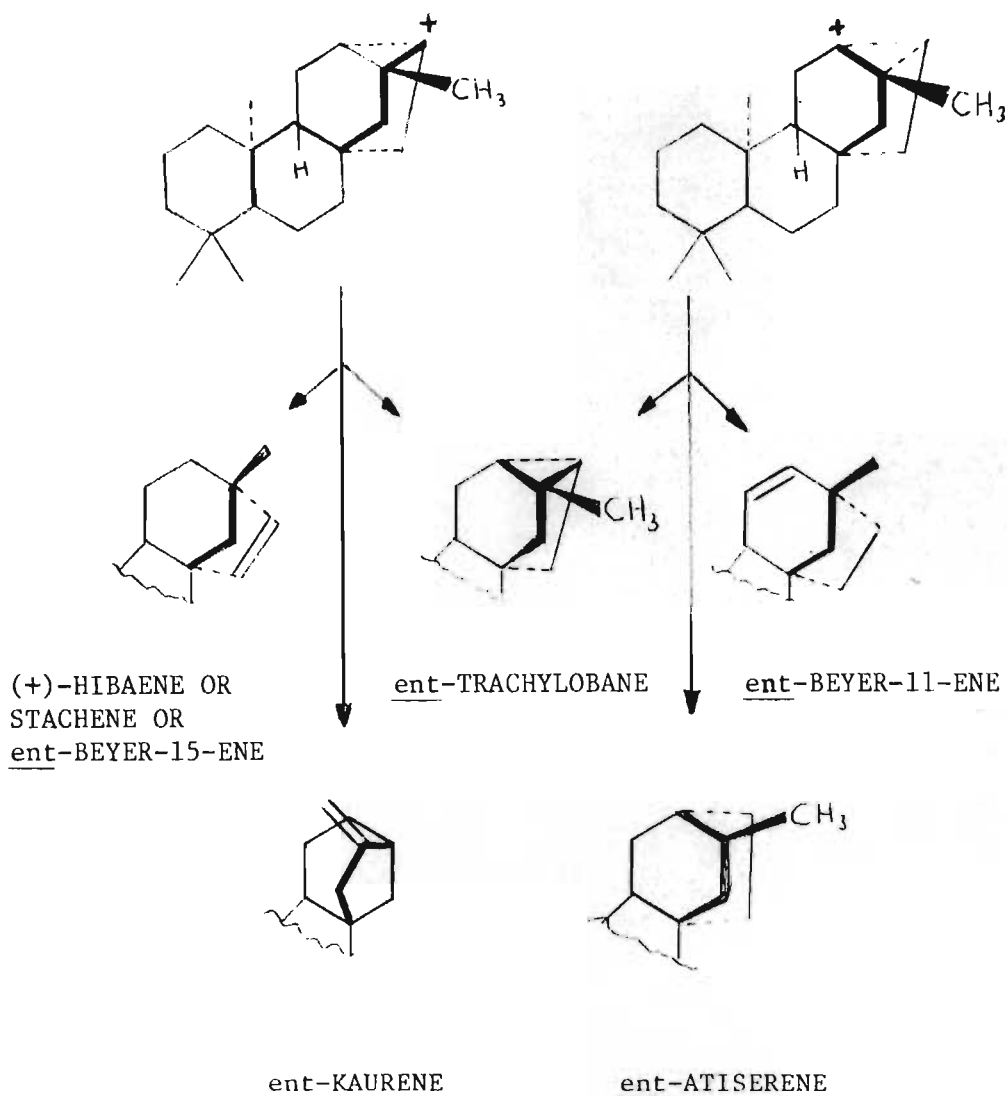
This scheme required the formation of a beyer-11-ene which, the authors[9] mentioned, was unknown from natural sources even as a hydrated equivalent. The 12-ketone function of the Androstachys diterpenes is the hydrated equivalent and these diterpenes then provide the missing link, thus completing the pattern.

The C-3 oxygen function which is found in a variety of diterpenes especially from the Euphorbiaceae,[2,3,5,10] is introduced at a later stage of the biosynthesis, in contrast to the triterpenes which probably arise from protonic opening of squalene epoxide. The opened epoxide function in this way results in the ubiquitous 3-oxygen function of these compounds. However, this function at C-3 is not obligatory in the diterpenoids.

In this work carbonium ion-induced rearrangements converted the stachane (ent-beyerane) skeleton into ent-atisanes and novel D-homo-C-nor diterpenes (see (82, 131, 109, 14, 126)). Biogenetic-like rearrangements of tetracyclic diterpenoids have been carried out extensively by many workers and are well-documented.[9]

The biosynthesis of the diterpenoids has been adequately reviewed.[11]

C H A P T E R   2

OUTLINE OF THE PROJECTS

The initial investigation concerned itself mainly with
the chemical verification of the structure of the main diterpene.
This problem was tackled in part by standard methods (i.e. making
the usual derivatives such as esters, oximes, alcohols) but also
by investigating the possible selective reactivity of the molecule
with various reagents in an attempt to understand the influences
of the stereochemistry of the molecule upon its chemical behaviour.
This method was quite fruitful since not only were some of the
reactions used to establish the structure but many of them led to
unusual or novel rearrangements and compounds which then demanded
further investigation.

Thus three methods were successfully used to prepare all
the three other possible 2,3-ketol acetates from the natural material.
Two of these methods have not previously been reported, whilst the
third was an adaptation from the literature.

An interesting rearrangement of a 3α-sulphonyloxy-2-one to
a 1β-acetoxy-2-one was discovered.  This high yield reaction was
then found to occur with both sulphonate configurations at C-3 (α or β)
and also with a 1β-sulphonate, in all cases with a 2-keto function.
Small amounts of the 3α- and 3β-acetates always accompanied the
major product.   The 1β-hydroxy-2-one system derived from the above
solvolytic rearrangement was then found to undergo a most unusual
oxidative decarboxylation-ring contraction giving the A-nor-1-ketone
with the Jones reagent under extremely mild conditions.

Air mediated alkaline oxidation of the α-ketol function of the major diterpene gave the derived benzilic acid type compound in good yield. The intermediate diketone could be trapped by the addition of benzaldehyde (or formaldehyde) which condensed at C-1. The subsequently formed benzilic acid then lactonised with the benzylic alcohol (or hydroxymethylene) to give a γ-lactone. The aromatic ring of the benzaldehyde derivative was found to unexpectedly shield the 12-carbonyl from β-attack, and also completely inhibited attack at C-11 by selenium dioxide which otherwise occurred quite readily with the natural material to form the 9(11)-en-12-one system.

The lactone function of the above derivative was reduced to a hemiacetal (92) by $LiAlH_4$ in THF. Use of higher reaction temperatures (diglyme) gave the expected triol (84). The interesting stereochemical implications of the hemiacetal and its derived acetals were investigated both by n.m.r. and by X-ray methods.

Attempts to prepare the enol acetate of the 12-carbonyl with the usual acidic reagents (e.g. isopropenyl acetate-acid, acetic anhydride-acid) failed. The systems $BF_3$-acetic anhydride, $H_2SO_4$-$Ac_2O$, $HClO_4$-$Ac_2O$ all resulted instead in a rearrangement in high yield to give the novel skeleton (109). Subsequently the enol acetate was prepared by acetylation of the enolate prepared with the bis-trimethylsilylamide anion. Methylation at C-11 of the same enolate was also successful.

A related rearrangement was observed in an attempt to remove the 12-carbonyl function by hydride reduction of the corresponding p-tosylhydrazone. In this case the intermediate, having carbonium

ion character, was intercepted by hydride giving the atisane

skeleton (131) with the double bond in a hitherto unreported

position. The marked unreactivity of this double bond was

investigated.

The reactivity of the double bond of the stach-15-ene

system was also tested. Halogens and pseudo-halogens added quite

readily and stereospecifically as did mercuric acetate. The Prévost

reaction not unexpectedly failed although the iodide-acetate addition

compounds were obtained readily. These latter compounds were extremely

resistant to acetolysis, $AgNO_3$ in either acetic acid or in ethyl

cellosolve, boiling tri-n-butylamine-tetralin or NaI in acetone.

While catalytic hydrogenation with Pd/C under pressure did not reduce

the iodide-nitrate adduct, mild treatment with zinc in ethanol-acetic

acid gave a quantitative recovery of the regenerated double bond

system thus highlighting the excellent protective properties of the

pseudo-halogen 15-ene adduct. LAH reduction also regenerated the

double bond from the iodide-nitrate.

The epoxide was also found to be resistant to LAH in

boiling THF as well as to Pd/C hydrogenation and Pt/ethyl acetate

hydrogenation under pressure. Furthermore refluxing for prolonged

periods with perchloric acid in aqueous THF gave no reaction.

However, $BF_3$ under anhydrous conditions was quite effective as

previously reported. Epoxidation of the double bond with

m-chloroperbenzoic acid gave excellent yields of the epoxides

provided the 12-carbonyl was protected as its ethanedioxyketal

or reduced to the alcohols. With the free 12-carbonyl the product

was always the epoxide with the carbonyl function having undergone

a Bayer-Villiger oxidation with insertion of oxygen between C-12

and C-13.    However, the presence of a 15β-bromo -16α-acetate

function inhibited the Bayer-Villiger oxidation under mild conditions

such that this method could be used to selectively epoxidize a second

double bond in the molecule without having to mask the carbonyl and

with the certainty of regenerating the 15(16)-double bond easily

in good yield at a later stage.

C H A P T E R   3

THE DETERMINATION OF THE STRUCTURE OF THE MAJOR DITERPENE[85]

3.1.    PRELIMINARY DATA

The major compound isolated (1) was analysed for $C_{20}H_{28}O_3$, thus indicating its diterpenoid nature.   The i.r. spectrum established the presence of both carbonyl and hydroxyl absorption respectively. The n.m.r. spectrum contained an olefinic AB quartet at $\delta$ 6.00 and 5.62 consistent with a disubstituted double bond linked to fully substituted groups.   It was catalytic*ally* hydrogenated under normal conditions readily yielding a dihydro-derivative (2) which gave no colour with tetranitromethane (TNM);   at the same time the AB quartet of (1) had now disappeared in the n.m.r. spectrum of (2) as well as a band at 767 $cm^{-1}$ in the i.r. spectrum of (1) indicating these to be the double bond absorptions.

The formation of a monoacetate (3) and a dioxime (4) from (1) established the presence of one reactive hydroxyl group as well as two carbonyl groups in the original structure of (1).   The i.r. spectrum of the mono acetate derivative (3) lacked hydroxyl absorption in the 3400 $cm^{-1}$ region, thus confirming the presence of a single hydroxyl in (1).  Furthermore the n.m.r. spectrum of (3) had a sharp one proton singlet at $\delta$ 4.90 such that the hydroxyl group in (1) had to be secondary and lacking hydrogens on the adjacent carbon atoms. The i.r. spectrum of the dioxime did not show carbonyl absorption in the 1700 $cm^{-1}$ region and this fact, taken in conjunction with the analytical data, confirmed the presence of only two carbonyl groups.

Thus the three oxygen atoms had been accounted for.

The n.m.r. spectrum of the parent compound (1) had absorptions for four tertiary methyl groups between $\delta$ 0.6 and 1.2. This meant that none of the oxygen functions were contained on pendant carbon atoms, but all were probably on the skeleton. The negative TNM test for the dihydro derivative (2) and the two carbonyl groups indicated the molecule to be tetracyclic (i.e. 7 double bond equivalents = 1 double bond + 2 carbonyls + 4 rings).

### 3.2.    POSITION OF FUNCTIONAL GROUPS

A negative ferric chloride colour test demonstrated the improbability of the two carbonyls being adjacent to one another since an enol would then be most likely to form. However, the ready oxidation of the material (1 and 3) by alkaline triphenyl-tetrazolium chloride solutions (TTC) confirmed the presence of an $\alpha$-ketol grouping. This was suspected from a comparison of the i.r. spectra of (1) and (3). In (1) only one carbonyl absorption at (1705 cm$^{-1}$) was discernible. However, after acetylation three clearly defined peaks were observed at 1740, 1720 and 1692 cm$^{-1}$. The lowering of one of the carbonyl frequencies in (1) was attributed to an intramolecular hydrogen bond between this ketonic function and the hydroxyl group, suggesting a proximal spatial disposition.

The second carbonyl function was present in a six-membered ring or larger and was not directly conjugated with the double bond ($\nu_{max}$ 1705 cm$^{-1}$ only slightly affected by hydrogenation of the double bond) but homoconjugation typical of $\beta,\gamma$-unsaturated ketones was suspected since the molecule showed an abnormally high extinction

coefficient ($\varepsilon$ = 240) and a very large specific optical rotation ($[\alpha]_D$ = -329°), both values falling markedly on hydrogenation ($\varepsilon$ = 71, $[\alpha]_D$ = -33.7°).

## 3.3    THE TETRACYCLIC SKELETON

The skeleton was established as the tetracyclic stachane type from the results of two reduction experiments. Huang-Minlon reduction of the natural material (1) gave as one of the products a monohydroxy compound, stachenol (5) (3α-hydroxystach-15-ene) which was well-known from the work on Tambooti wood[2,12]. Raney nickel hydrogenolysis of the bis-ethanedithioketal (6) gave the 15,16-dihydro alcohol, stachanol (7), since the double bond suffered concomitant hydrogenation. These two results also indicated that C-3 was the position of the hydroxyl group but no definite decision could be made as to the configuration at this carbon since both reactions involved alkaline conditions (albeit only slightly in the Raney nickel desulphurisation), conditions known to isomerise α-ketols with ease[148].

The structure at this stage could then be assigned as 3-hydroxystach-15-en-2,X-dione.

The position of the isolated carbonyl group was inferred initially from bromination studies. Bromination of the 15,16-dihydro-ketol-3α-acetate (8) gave a crystalline monobromide (9) in good yield. The n.m.r. spectrum showed the proton geminal to the halogen as a doublet at δ 4.23, consistent only with a 6-bromo-7-ketone or 11-bromo-12-ketone.

In order to distinguish between these two possibilities,
and since a 12-ketone was strongly suspected, a reaction
characteristic for the 12-position was sought. In the steroid
series solvolysis of 12-equatorial sulphonate esters resulted in
the migration of the C-13 : C-14 bond to C-12 leading to a D-homo-
C-nor structure (10). Molecular models indicated that in the
12-equatorial stachene sulphonates a similar stereochemistry was
present, and an analogous ring contraction reaction should occur.

Selective sodium borohydride reduction of the isolated
carbonyl in the ketol-3α-benzoate (11) gave a mixture of C-12
epimeric alcohols, in which the equatorial isomer (12) predominated
and was separated. Conversion to the 12α-mesylate (13) and its
acetolysis then furnished the expected D-homo-C-nor, exocyclic,
conjugated diene (14) as shown by u.v. and n.m.r. data, thus
establishing C-12 as the locus of the isolated carbonyl group
and thereby confirming the effect on the u.v. and specific rotation
data mentioned earlier.

The remaining structural detail to be established was the
configuration of C-3. This was determined chemically as 3α by
comparing the 15,16-dihydro-2,3,12-triol (15) obtained from (1)
by NaBH$_4$ reduction followed by catalytic hydrogenation, with the
authentic dihydro-2α,3α,12α-triol prepared by a well-defined
route. These two compounds were found to be identical in all respects.
Furthermore, the unsaturated triol (16) prepared by NaBH$_4$ reduction
of (1) was found to be dissimilar to an authentic specimen of the
2β,3α,12α-triol (17) (See Scheme I; page 32).

The structure, stereochemistry and absolute configuration
of the α-ketol (1) was then shown to be 3α-hydroxystach-15-en-2,12-
dione.[85]

The major component of later batches of wood was found
to be a diosphenol, identical in all respects to the diosphenol
prepared by oxidizing the α-ketol (1) hence the structure of this
compound was established as well, and was 2-hydroxystach-1,15(16)-
dien-3,12-dione (18).

2



3



4



5



6



7



8



9

10

11

12

13

14
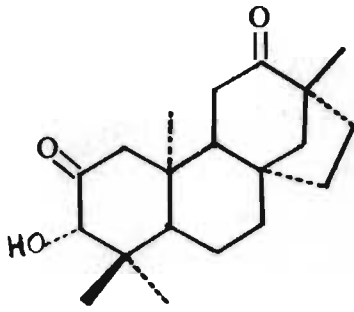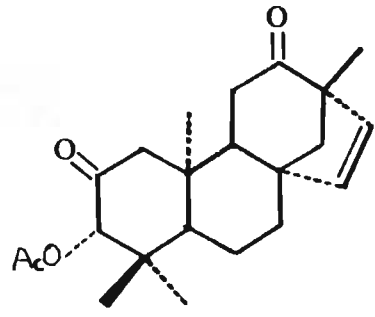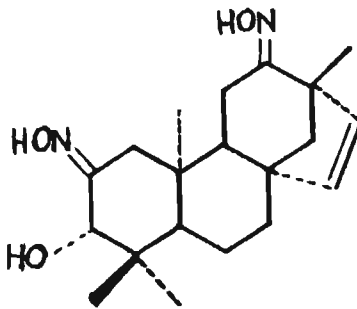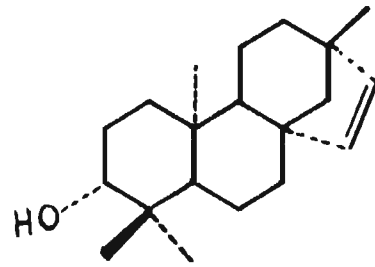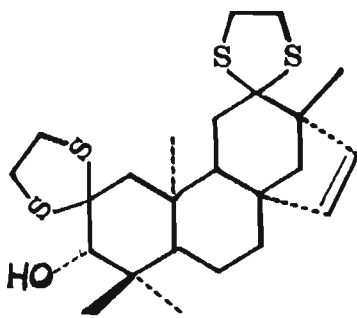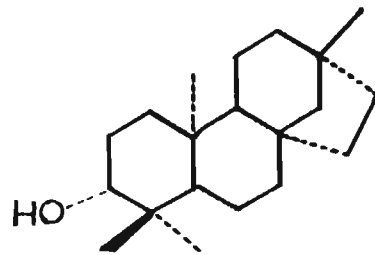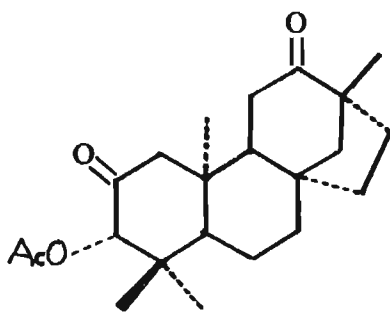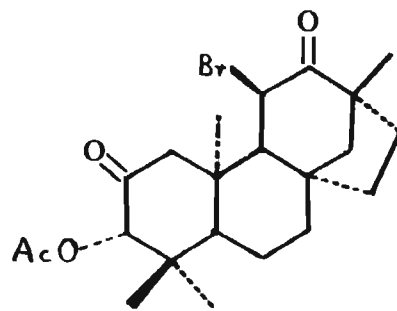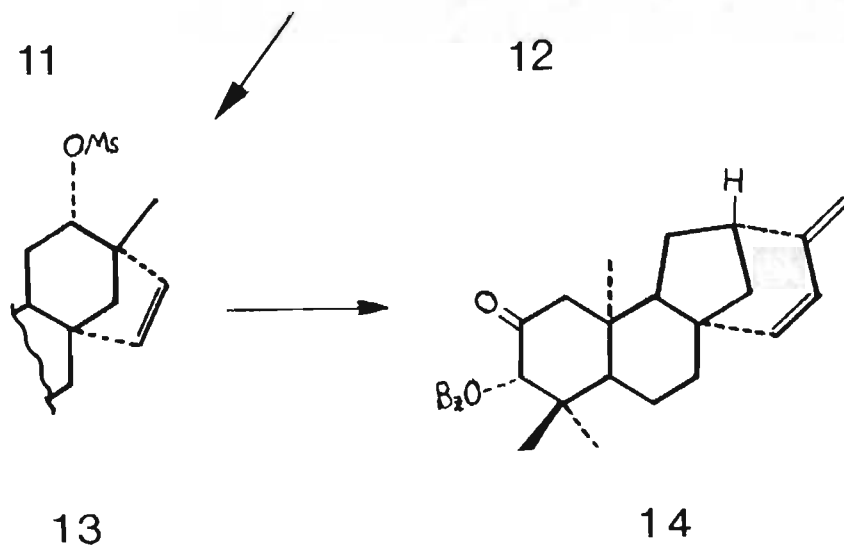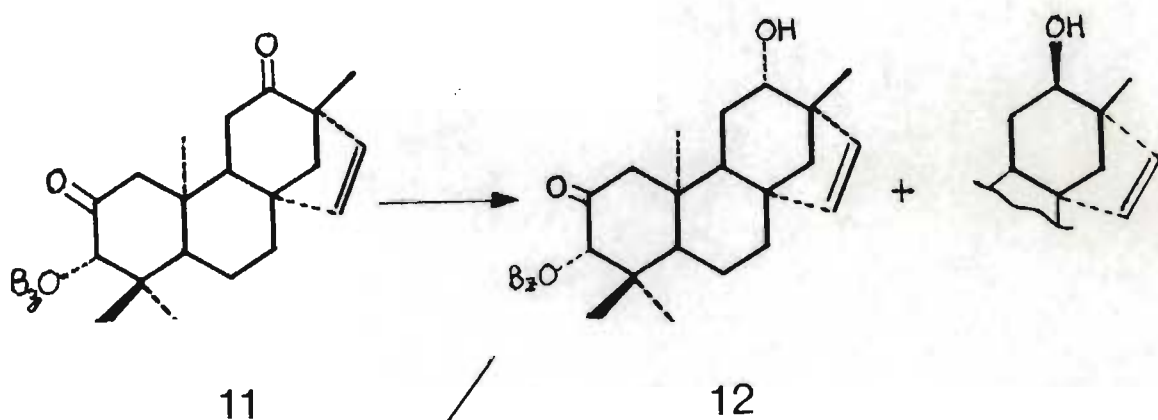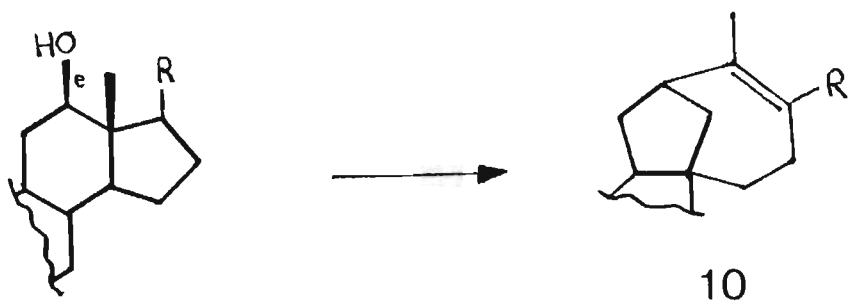
NOTES ON THE REACTIONS USED IN THE STRUCTURE DETERMINATION

3.4.    HUANG-MINLON REDUCTION OF THE α-KETOL (1)

The major product of this reaction was a crystalline hydrocarbon mixture.  N.m.r. analysis indicated that it consisted predominantly of stachene (19) contaminated with traces of other olefinic material.   G.l.c. clearly showed the presence of one major component together with two minor hydrocarbons, one more mobile and one less mobile than the major product.  The mass spectrum had one peak at $M^+_{(Stachene)}$ +2 and one at $M^+_{(Stachene)}$ -2. Wolf-Kisher reduction of α-substituted ketones is known to lead to Kishner elimination[13] and in this case should have furnished a C-2 olefin analogous to the findings of Enzell and Thomas for a pimarane ring A α-ketol.[14]   Those authors obtained evidence for the C-2 olefin by noting prominent peaks in the mass spectrum resulting from retro-Diels-Alder processes of the suspected C-2 olefin.



$$H_2C=CH-CH=C(CH_3)_2$$
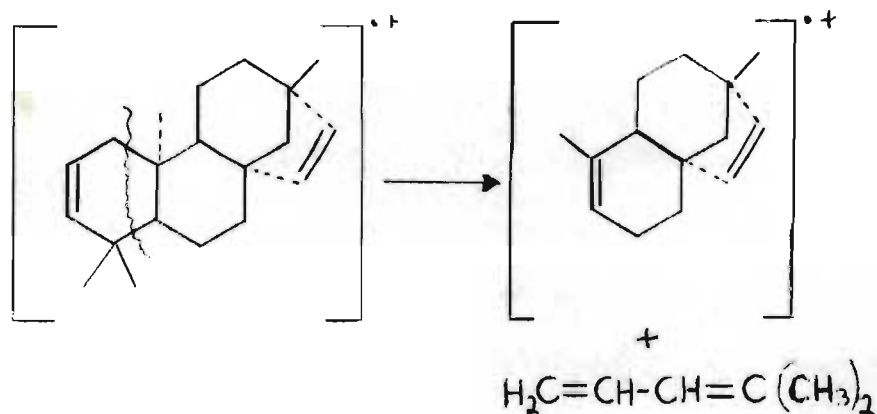
The same loss of 82 m.u. was not observed in the present instance therefore the C-2 alkene structure can be ruled out.  However, the $(M^+-2)$ impurity could instead be a C/D isomeric diene of the type
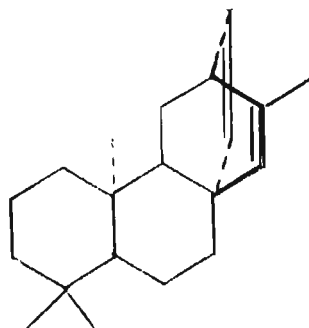
since it will be shown later that the 12-p-tosylhydrazone under-
goes this type of rearrangement with $NaBH_4$ (SECTION 13.1) whilst
it is well known that p-tosylhydrazones undergo the Bamford-Stevens
reaction[15] at high temperature in the presence of base. Reduction
of the ring A double bond resulting from Kishner elimination could
easily occur by diimide generated from the large excess of hydrazine
present. Alternatively the fully saturated ring A could be produced
by the Wolf-Kishner reduction of the "osazone", generated by air
oxidation in the presence of base of the α-ketol to the diosphenol
since this oxidation process was found to occur very readily.

Diimide reduction of the 15(16)-double bond[16] probably
accounted for the $(M^+ + 2)$ ion in the mass spectrum.

The other compound isolated from the reduction in substantial
quantity was the required 3α-hydroxystachene (stachenol, 5). T.l.c.
of the reaction mixture showed the presence of many minor compounds
but these were not further investigated.

### 3.5.     12-SULPHONATE SOLVOLYSIS

The C-12 position with the adjacent quaternary carbon
C-13 forms a typical neopentyl system and consequently is very
prone to rearrangements of the Wagner-Meerwein type.    In
addition due to the disposition of the ethene bridge at C-13,
the type of rearrangement is strictly determined by the stereo-
chemistry of the carbonium ion formed at C-12, that is, it depends
on the orientation of the empty orbital formed by the leaving
group.

The 12α-sulphonate solvolysis is initiated by the loss
of the sulphonate anion leaving an electron deficient orbital
parallel to the C-13 : C-14 σ-orbital, whose electrons can now
effectively overlap with the carbonium ion orbital and thus
reduce the positive charge.    This however allows a small accumula-
tion of positive charge at C-13 and the bond rearrangement goes
to completion when base, in this case acetate ion, abstracts one
of the now more acidic protons from the C-17 methyl group to form
the new double bond.[17]

The presence of the 15(16)-double bond was found to be
immaterial to the outcome of the reaction since the 15-dihydro
derivative (21) underwent the rearrangement just as readily to
give the exocyclic alkene[18] (22).    These rearrangements were also
brought about quite readily by phosphorus oxychloride in pyridine
thus obviating the need to prepare the intermediate sulphonate
esters which were never quite pure, but always contained traces of
their elimination products.[19]    The phosphorus oxychloride reaction
probably proceeded via an intermediate of the type –
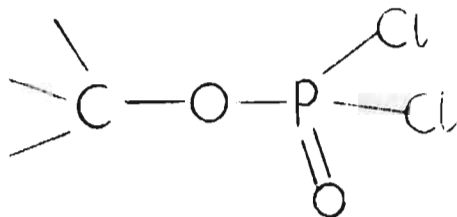
which fragments to give the carbonium ion and a dichlorophosphate
ion.    Thus (23) and (21) gave good yields of the rearrangement
products (24) and (22)    (See however SECTION 18.5.2).

All the above solvolysis reactions are most probably
concerted without the actual intervention of discrete carbonium
ions.

### 3.6.    PREPARATION OF THE 2,3,12-TRIOLS EPIMERIC AT C-2.

Since the configuration at C-3 in the parent ketol (1)
could be either 3α-equatorial or 3β-axial, a chemical proof to
establish this was attempted.

Hanson[12] had shown that metal hydride reduction of a C-2
or C-3 stachene ketone always proceeded mainly by β-face attack of
hydride ion at the carbonyl carbon producing a 2α-axial or a
3α-equatorial alcohol respectively.   Similarly it could be argued
that a 12-ketone should reduce from the β-face to give mainly the
12α-equatorial alcohol, as indicated by the large $W_{\frac{1}{2}}$ of 17 Hz of
the geminal 12β-proton signal which appeared as a quartet (J 6.0
and 8.7 Hz) in the n.m.r. spectrum of (25), as well as by the
stereospecific D-homo-C-nor rearrangement discussed previously.
(see, however, reference 20 for an example of the non-stereospecificity
of this type of reaction).

Reduction of the ketol (1) with $NaBH_4$ gave a triol (16) which was suspected to have the $2\alpha,3\alpha,12\alpha$-trihydroxy structure. This on hydrogenation gave the 15,16-dihydro analogue (15). Both these compounds formed acetonides (23 and 21 respectively) extremely readily, as evidenced by the immediate clarification of a cold suspension of (16) or (15) in acetone on addition of a few drops of perchloric acid. The $2\alpha,3\beta$-dihydroxy isomer was excluded at this stage since even if this were to form an acetonide[21] it should not do so at such a rapid rate because the required distortion of the ring in order for this derivative to form is energetically demanding.

By comparing (16) or (15) with the four possible 2,3-triols the C-3 configuration could then be obtained. However, at first only two triols, the $2\alpha,3\alpha,12\alpha$- and $2\beta,3\alpha,12\alpha$-trihydroxy isomers could be prepared but these sufficed to furnish the required proof (See Scheme I).

19

23      $\xrightarrow{POCl_3}$      24
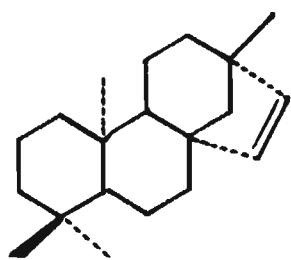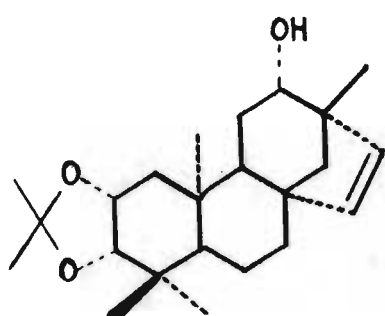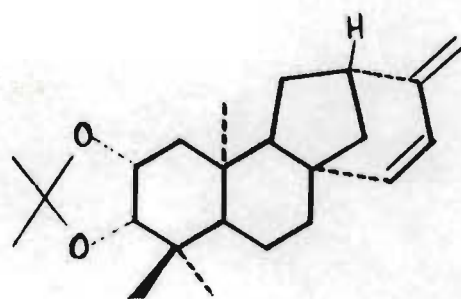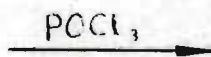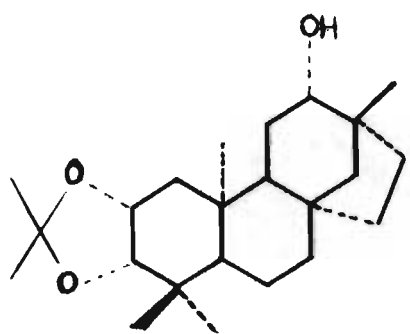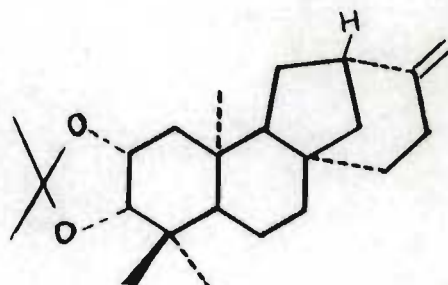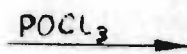
21      $\xrightarrow{POCl_3}$      22

SCHEME I
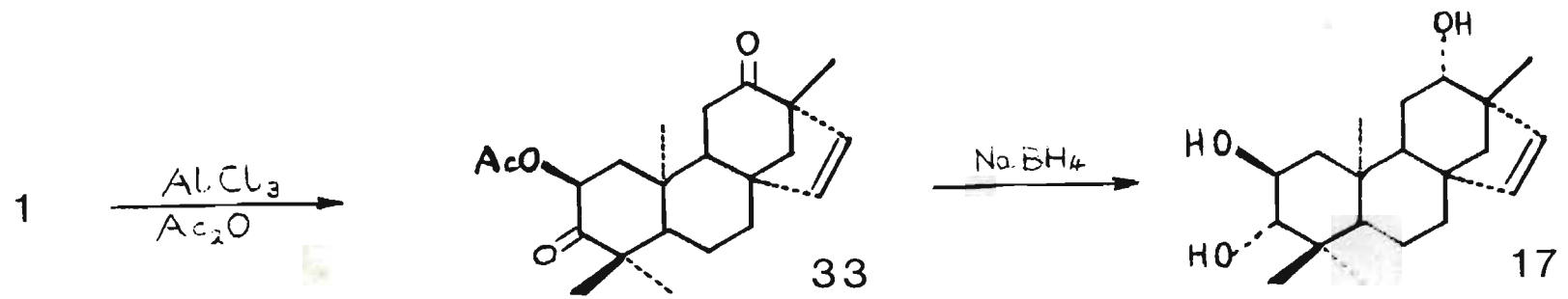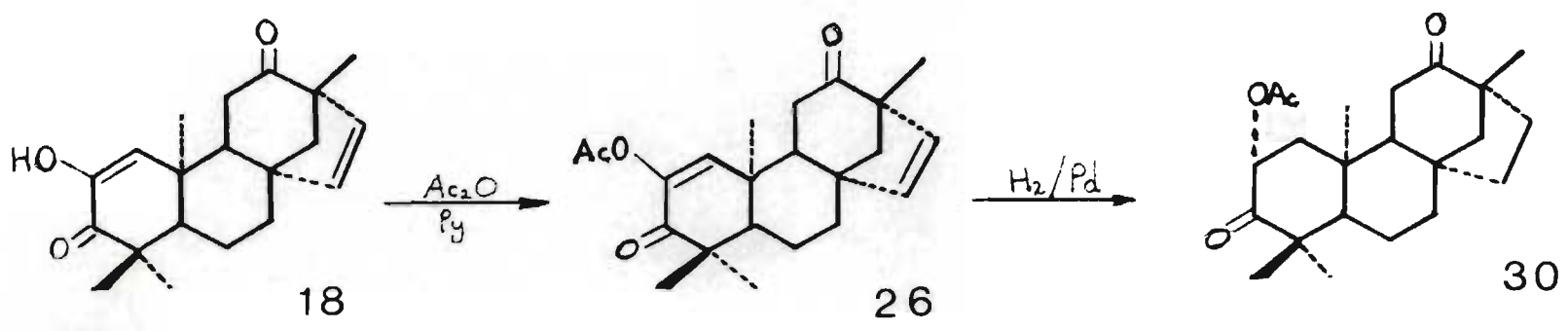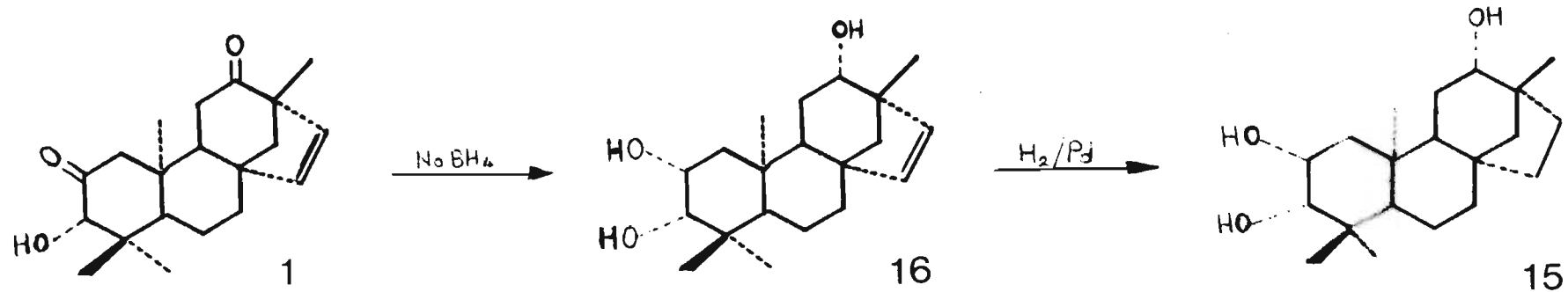
## 3.7.   PREPARATION OF THE $2\alpha,3\alpha,12\alpha$-TRIHYDROXYSTACHANE

3.7.1.   In order to prepare the ring A $2\alpha,3\alpha$-diol the ring A diosphenol acetate (26) was required.  Since initially the diosphenol (18) was not naturally available, it was prepared from the $\alpha$-ketol (1).   $\alpha$-Ketols are readily oxidised to $\alpha$-diketones by a variety of oxidizing agents.  The most commonly used method is that described by Rigby[22] using bismuth trioxide in acetic acid and was used here.   Other methods were tried with less success and these include cupric ion oxidations[23], air oxidation of alkaline alcoholic solutions of (1) and reaction of the $\alpha$-ketol nitrate (27) with sodium acetate in DMSO.[24]   Air oxidation was rather erratic since the best conditions for reproducible results were not determined readily, but on a number of occasions did give a good yield.  In particular the $\alpha$-ketol-12-p-tosylhydrazone (28) in dioxan containing a few drops of dilute alkali gave a consistently fair yield of the corresponding 2,3-diosphenol-12-p-tosylhydrazone (29).  However, often on other occasions the oxidation reaction was followed by benzilic acid rearrangement and ring fission.[25]   If the reaction of (1) with alkali in air was monitored by t.l.c. useful amounts of diosphenol were then obtained.

Rigby's method also gave only a fair yield and the crude product (18) could only be efficiently worked up as the corresponding acetate (26), which fortunately was the material required.   A considerable amount of dark material was found to be the contaminant and could be removed only by repeated crystallisation or chromatography.

Lavie et al[26,156] had shown that in the cucurbitane series, catalytic reduction of the ring A diosphenol acetate enolic double bond proceeds by cis addition from the least hindered side to give α-ketol acetates. In the stachane series the β-face is less hindered and reduction of the diosphenol acetate (26) with palladium was expected to produce the 2α-axial-acetoxy-stachane-3,12-dione (30).

When this reduction was carried out it was observed that after one mole equivalent of hydrogen had been absorbed the solution deposited masses of white needles (31) which when separated from the catalyst by recrystallisation proved to be a 1:1 complex of the 15,16-dihydrodiosphenol acetate (32) and the required tetrahydro compound, the 2α-acetoxystachane-3,12-dione (30). Further hydrogenation resulted in the slow uptake of a second mole of hydrogen to give essentially (30). By using a deactivated catalyst it was also possible to prepare the dihydrodiosphenol acetate (32) selectively.

3.7.2. NaBH$_4$ reduction of (30) in wet ethanol[27] gave a product still containing acetate. Deacetylation gave the expected 2α,3α,12α-trihydroxystachane. This was found to be identical in all respects to the dihydrotriol (15) prepared from the α-ketol (1). The n.m.r. data for the ring A vicinal diol function compared well with that reported for 2α,3α-dihydroxystachene.[12]

3.7.3. At this point it could be argued that during the alkaline NaBH$_4$ treatment of (30), α-ketol isomerisation could have occurred since such ketols isomerise very readily with base.[148] Thus (15) could in fact be, say, the 2β,3α,12α-all equatorial triol!

In order to provide **evidence** for **or against** this alternative structure it was decided to prepare the authentic 2β,3α,12α-triol (17). This required that a 2β-orientated group be present prior to reduction, otherwise the C-2 configuration would be uncertain. The 2β-acetoxy-3-one (33) was available from (1) by $AlCl_3$-acetic anhydride isomerisation. This novel isomerisation reaction resulted in an equilibrium mixture of the parent 2-one-3α-acetate (3) and the isomeric 3-one-2β-acetate (33) in a 7:3 ratio respectively, as estimated from the n.m.r. spectrum of the crude product. Isolation of the less abundant isomer was facilitated by its lower solubility in alcohols, thus making it available by simple crystallisation. Its structure was readily ascertained from its n.m.r. spectrum. The acetoxymethine proton resonance now appeared as a quartet (J 6.0 and 13.0 Hz) consistent with a 2β-equatorial-acetoxy-3-one with ring A in a flattened chair. The isomeric 2α-axial-acetoxy-3-one (30) had J 8.3 and 11.2 Hz. The conformations of these compounds are discussed in Chapter 16.

The isomerisation reaction would be expected to go via an intermediate enediol complex and the thermodynamically more stable equatorial acetate isomers should predominate. Surprisingly, however, when titanium tetrachloride in acetic anhydride was used it also gave an equilibration reaction but the major crystalline product isolated was an inseparable 1:2 mixture of the ring A 2β-acetoxy-3-one (34) and 2α-acetoxy-3-one (35) respectively. This was readily apparent by comparing the n.m.r. of the mixture with the n.m.r. spectrum of the authentic 2β-acetoxy-3-one-C/D-rearranged compound (34) prepared by a different method.
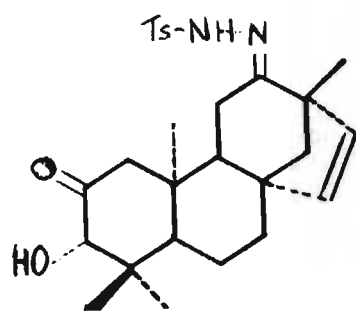
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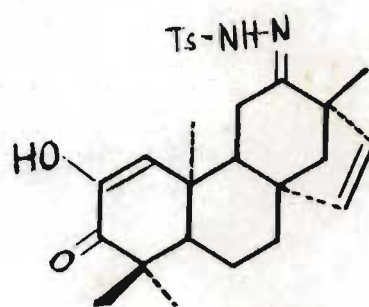
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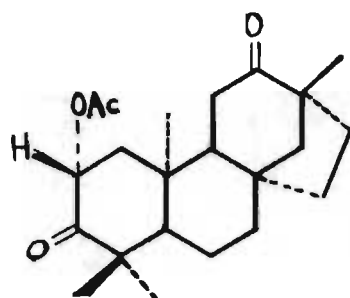
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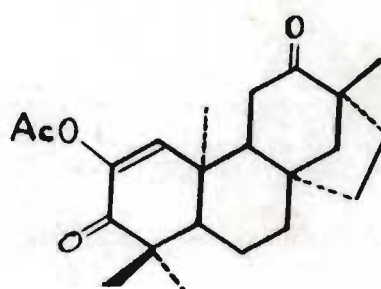
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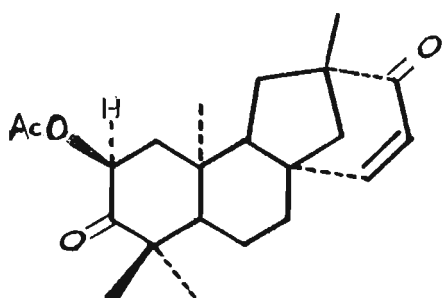
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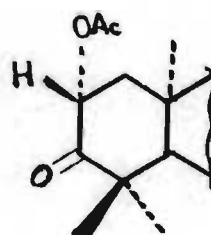
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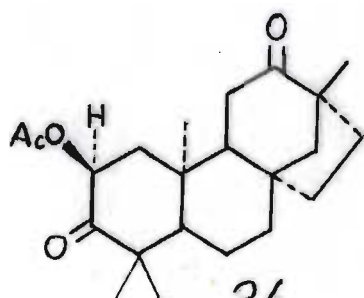
36

The predominance of the 2-axial isomer indicated that the mechanism probably did not resemble that followed by the $AlCl_3$ reaction. Furthermore, a skeletal rearrangement occurred with $TiCl_4$, giving the D-homo-C-nor-$\alpha$,$\beta$-unsaturated ketone. This rearrangement is described later in Chapter 12, Section 12.1.

3.7.4. NaBH$_4$ reduction of (33) gave the 2$\beta$,3$\alpha$,12$\alpha$-triol (17) after brief alkali treatment of the reduction product. This triol was found to be dissimilar to that prepared by simple NaBH$_4$ reduction of the parent ketol (1), confirming that no isomerisation had occurred during the borohydride reduction of the 2$\alpha$-acetoxy-3,12-diketone (30). Since this axial acetate isomer (30) did not epimerise to the equatorial acetate (36) prior to reduction under these mildly alkaline conditions it could be assumed that a 3$\beta$-acetoxy- or 3$\beta$-hydroxy-2-one compound would also not have epimerised to the 3$\alpha$-configuration, and therefore it was reasonable to discard the alternative 3$\beta$-hydroxy-2,12-dione structure for (1).

3.7.5. Thus the structure of the $\alpha$-ketol (1) had been satisfactorily established and its absolute configuration and stereochemistry was defined as 3$\alpha$-hydroxystach-15-en-2,12-dione (1).

3.7.6. In the NaBH$_4$ reduction of the $\alpha$-ketol (1), the major compound (16) was always accompanied by a trace of a less mobile component on t.l.c. which had the same $R_f$ value as (17). This demonstrated that some reduction from the more hindered $\alpha$-side did take place at C-2. Even NaBH$_4$ reduction in ethanol of stachenone (215) gave some 3$\beta$-alcohol. Hanson[12] had prepared this axial C-3 epimer by the Meerwein-Pondorff-Verley reduction

and did not note its formation in the $NaBH_4$ reductions since he
used methanol as a solvent.   In this solvent the reducing species
has a smaller solvation shell and smaller steric demand compared
to that in ethanol solution.

### 3.8.    BROMINATION OF THE 11-POSITION

3.8.1.    Bromination of the 15(16)-dihydroketol acetate gave the
same monobromoketone (9) using a variety of conditions.  The
standard bromination in glacial acetic acid containing a trace of
HBr at room temperature was expected to yield an equatorial 11-
bromide since the enol of the 12-ketone could most easily be
attacked from the β-face.  Any 11-axial product should also be
equilibrated to the thermodynamically more stable equatorial isomer
by the HBr catalyst.

   In the event the product obtained gave an n.m.r. spectrum
showing the bromomethine proton signal as a doublet δ 4.23 with
a coupling constant of 6.5 Hz.

3.8.2.    A comprehensive study of the n.m.r. characteristics of
variously substituted α-bromo-cyclohexanones had been reported[28]
and included were some bicyclo[3.2.1] octanones.  From this work
it was concluded that the configuration of the bromine atom in
α-bromocyclohexanones could be assigned solely from the chemical
shift of the geminal hydrogen.  Thus the axial bromides had proton
resonances in the range 3.96 to 4.18 δ whilst the epimeric equatorial
isomers resonated downfield of this range, in the region 4.68 to
5.21 δ.   The above authors also noted that these values were fairly
insensitive to further alkyl substitution on neighbouring carbon atoms.

Thus a simple comparison to the value obtained for (9), $\delta$ 4.23,
indicated an axial bromine at C-11. However, the coupling constant
of 6.6 Hz did not define the configuration since the axial-
equatorial coupling H-9$\beta$:H-11$\beta$ was expected to be 3-7 Hz whilst
the axial-axial coupling H-9$\beta$:H-11$\alpha$ should have yielded a value
of 8-14 Hz.[29]  When bromination was carried out in hot (100$^\circ$)
acetic acid the identical product, m.p. 238.5 - 239.5$^\circ$ was
obtained. Even bromine in refluxing chloroform gave a compound
m.p. 247 - 249$^\circ$ which however had an identical n.m.r. spectrum
to the lower melting batch (See 230). This data taken as a whole
meant that if the bromine did in fact have an axial configuration,
this configuration was exceptionally stable under forced equilibrating
conditions.  Alternatively one was dealing with an equatorial bromine
having an abnormal n.m.r. characteristic.

3.8.3,  Bromination of the 15,16-dihydrodiosphenol acetate (32)
resulted in bromination at C-11 as well as at C-1, via the enol
acetate dibromide:-



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37
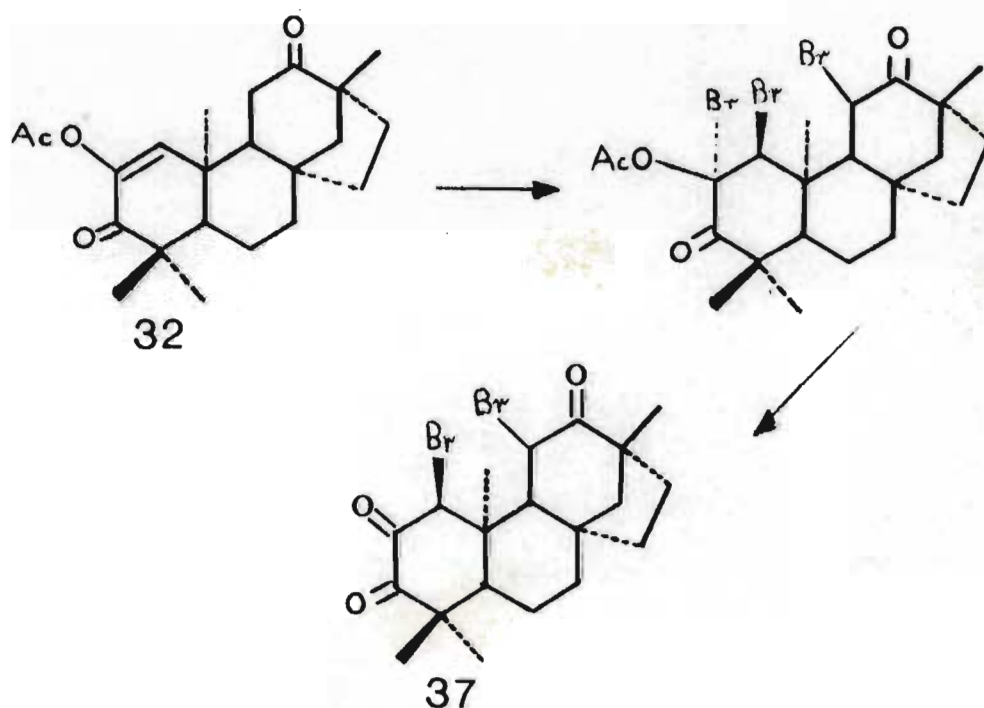
The bright yellow colour of (37) confirmed the presence

of an unenolised 1,2-diketone system.[30]    This type of compound was

known[30] to have an axial bromine at C-1 since even mild base failed

to cause enolisation of the C-2 carbonyl, as this would require the

intermediacy of an equatorial bromine at C-1, a sterically un-

favourable configuration for such a large atom.   The configuration

at C-11 was expected to be the same as in (9).  The n.m.r. of (37)

had a doublet at 4.51 δ for H-11, with a coupling constant of

9.0 Hz.   Although the chemical shift still fell outside the

4.68 - 5.21 δ range for an equatorial bromine, it was much closer

to it.    Furthermore, the coupling constant was now consistent with

an H-9β:H-11α interaction although the dihedral angle between the

protons was not the required 180°.  This has been clearly explained[28]

in terms of the electrostatic repulsion of the C-Br and C=O dipoles,

resulting in the case of (37) in a lessening of the H-9β:H-11α

dihedral angle from the maximum value of 180° as shown.



In (9) this dipolar cancellation would be at a maximum

since no electronegative 1β group is present as in (37) in which the

electrostatic repulsion between the 1β- and 11-β bromines would

lessen the flexing effect.  In this way the small J value of (9)

can be rationalised.  The same torsion of H-11 in (9) explains

the unusual chemical shift value as the H-11 proton is moved closer

to the C-1 methylene group and becomes more shielded by this group

as well as by the $\pi$-orbital of the C-2 carbonyl group.

3.8.4.    Bromination of (38) gave a beautifully crystalline 11β-

equatorial bromide (230) obtained in two crystalline modifications

(compare (9)).   The monoclinic form was metastable and converted

into the stable orthorhombic form within a few days in the absence

of solvent, thereby destroying the crystals.  Crystallisation of

the material from cold methanol gave the orthorhombic form.

However, the n.m.r. was identical for both compounds, with no solvent

peaks, indicating that the phase change was temperature induced and

not caused by loss of solvent of crystallisation.

The n.m.r. spectrum of (230) had a doublet at δ 4.67 with

a coupling constant of 12.5 Hz.   This was now in keeping with the

data of Jefford et al.[28]   The H-9β:H-11α dihedral angle was now

increased as the equatorial bromine atom was forced towards the

α-side, hence the large coupling constant.   The X-ray structure[31]

determined for this compound confirmed the data inferred from the

n.m.r. spectrum.   From the steric point of view it would have been

(230) which should have had an axial bromine, since the equatorial

halogen was shown to be rammed against the aromatic substituent at

C-1.   Since in fact (230) was an equatorial bromoketone it was

then reasonable to assume that the less sterically constrained (9)

also had an equatorial bromine.   However, in the case of (9) the

C ring deviated considerably from the flattened chair of a
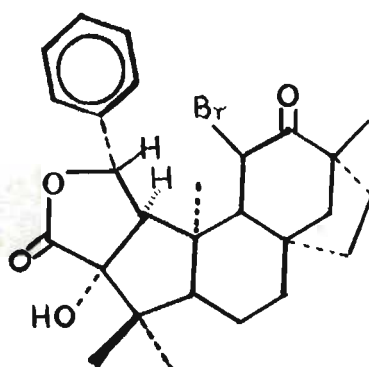
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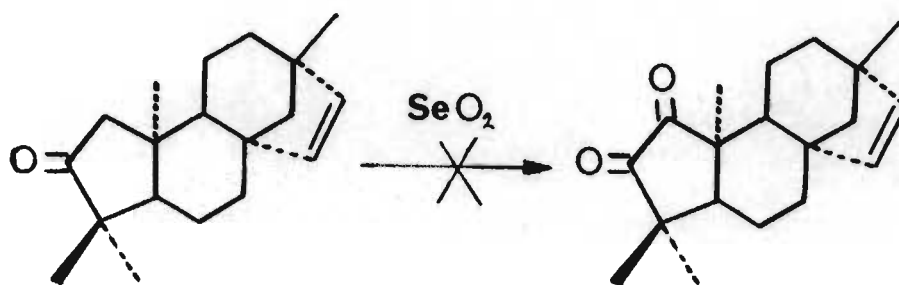


A

cyclohexanone, with C-11 twisted towards the β-face to minimise

the C-Br:C=O electrostatic interaction and this then reduced the

dihedral angle between H-9β and H-11α, resulting in a small

coupling constant of 6.5 Hz.

This configuration was borne out by the dehydrobromination

experiments on (9). Well-established procedures were used, such as

acetolysis, base induced elimination with KOH in methanol and LiBr-

$Li_2CO_3$ in refluxing DMF.[10] In no instance was an α,β-unsaturated

ketone, the 9(11)-en-12-one, formed. Instead a formal reversal

of the bromination reaction occurred and the bromine was replaced

by hydrogen. This was inconsistent with an axial bromine which

would have been ideally placed for an E2 elimination. (230)

was an extreme case of the facile replacement of bromine by hydrogen

since simple heating in methanol for a few minutes achieved this

result. However, cold methanol did not effect the replacement and

was used to grow the orthorhombic form. Nonprotic solvents such

as benzene, chloroform and hexane were without effect even on prolong-

ed boiling and could be used to dissolve the material (230). This

failure to undergo elimination of HBr stands in marked contrast to

the acetolysis of the equatorial 11α- steroidal tosylates which

undergo facile cis-elimination.[187]

3.8.5. The 1-position did not brominate even under forcing conditions

except when activated as in (37). The 1-position was found to be

extremely unreactive, possibly due to steric hindrance from the

11-position. Horn et al[2] failed to oxidize this position in the

A-nor-ketone ( A) although this reaction with $SeO_2$ was successful

in triterpenoid work,[30] and they also concluded that the unreactivity

was possibly due to steric overcrowding.

# C H A P T E R  4

## α-KETOL SULPHONATE ESTER SOLVOLYSIS[71]

4.1.    The ring A contraction of triterpenoid and 4,4-dimethyl steroidal 3-equatorial alcohols is well known (the retropinacolinic rearrangement) and has been extensively studied.[32,33]    The reaction results in a carbonium ion at C-3, followed by nucleophilic attack by the electrons of the C-4:C-5 bond to give the ring contracted C-4 carbonium ion.  Elimination of a proton either from C-5, from one of the geminal methyl groups or attack by water gives the final products which are alkenes or tertiary alcohols respectively.

The steric requirements for this ring contraction reaction are that the four atoms C-5, C-4, C-3 and the leaving group attached to C-3 all lie in a plane, and that the C-3:C-4 bond be trans to the leaving group, that is with an anticoplanar relationship.

4.2.1.    Few studies have concerned themselves with a carbonyl function α to the leaving group.   The documented cases usually contained the leaving group at a tertiary centre[34] but some will be discussed with secondary centres α to the carbonyl function.

4.2.2.    Solvolysis of the 12-equatorial sulphonates of rockogenin (39) resulted in the now classical D-homo-C-nor rearrangement.[19]   However, attempted solvolysis of the 11-keto-12-sulphonate analogue (40) failed to give any rearrangement products presumably because the opposed inductive effect of the carbonyl group was thought to increase the activation energy required for the initial polarisation of the carbon-oxygen bond at the 12-position and this would be sufficient to prevent even the anchimerically assisted[35] D-homo-C-nor

rearrangement reaction observed for rockogenin mesylate.



39



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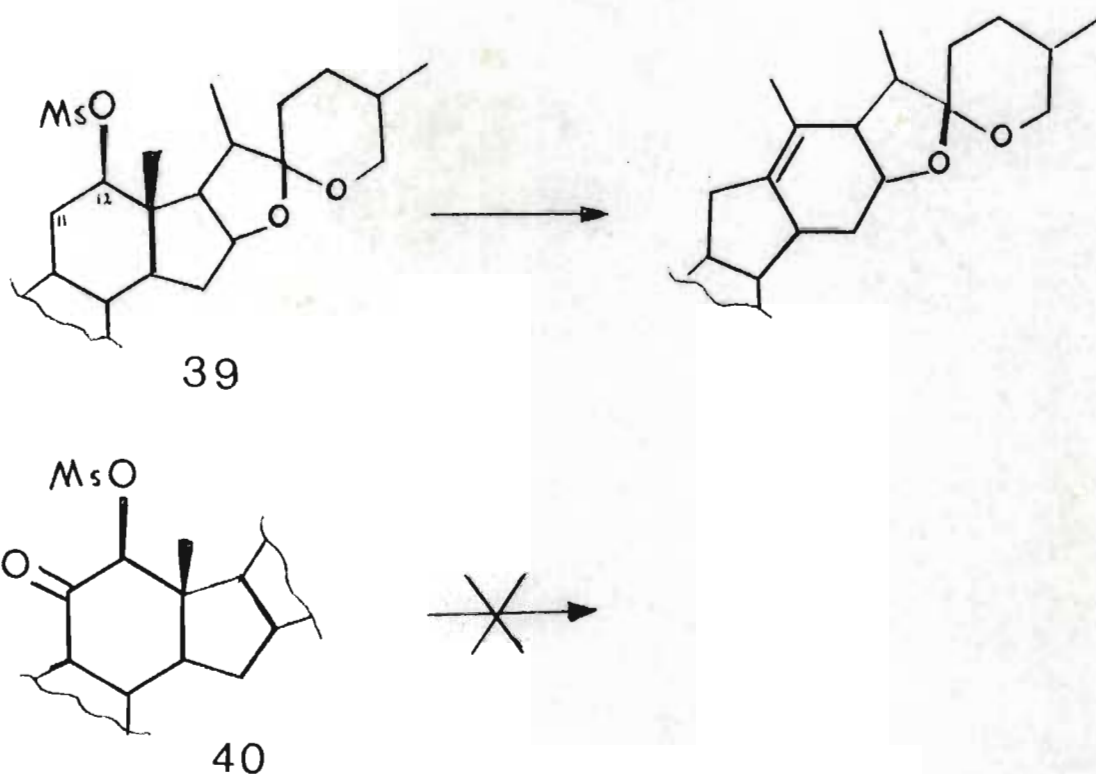
4.2.3.    Overton and Johnson[36] on the other hand successfully
solvolysed a secondary α-ketol sulphonate (41) in the bicyclo
[2.2.2] octane part of the atisane skeleton, converting this
skeleton to an isomeric bicyclo [3.2.1] octane system.



41
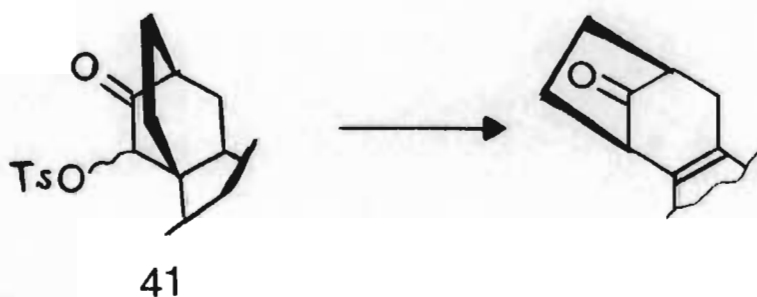
Of interest here was that both epimeric tosylates gave the
same product and this was presumed to occur by prior enolisation or

46.

ion pair return giving the epimer which then underwent solvolysis.
As will be shown later enolisation is an important pathway for
epimerisation of α-ketol esters.

4.3.1.   A reaction common to α-keto halides is the $S_N2'$ reaction[37]
in which the nucleophile has a <u>cis</u> relationship to the leaving
group at the α position when it attacks the α' position.  Recently
Satoh and Takahashi[38] reported a variation of the usual $S_N2'$ reaction
in which the incoming nucleophile entered <u>trans</u> to the leaving group.
Thus acetolysis of the 4β-bromo-5β-cholestan-3-one (42) gave firstly
the 2α-acetoxy-5β-cholestan-3-one (43) which then slowly isomerised
to the 2β-acetoxy-5β-cholestan-3-one isomer (44).

4.3.2.   Using ^{13}C-n.m.r. Stothers <u>et al</u> had established[39] that
heating 2-acetoxycyclohexanone to moderate temperatures resulted in
enolisation and 1,2-group interchange, whilst elevated temperatures
gave 1,3-group interchanges resulting in complete scrambling of
the label:-
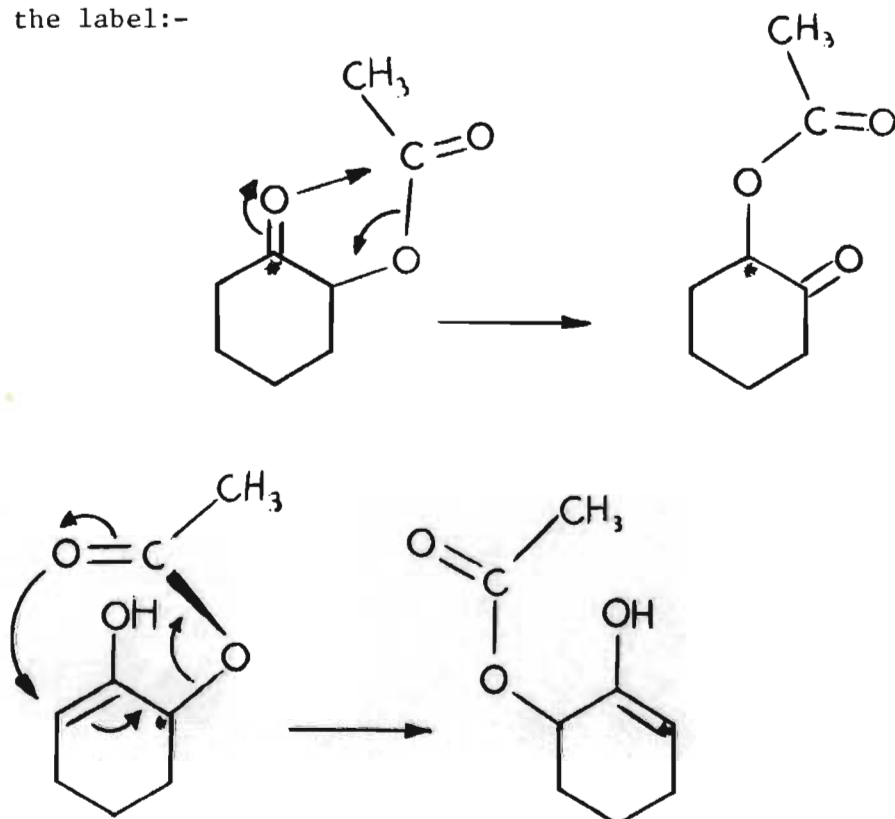
4.3.3. It was then of interest to investigate the acetolysis of the 2-keto-3α-sulphonate system in order to test whether a ring contraction or $S_N2'$ reaction would occur. Finally, it was possible that a simple $S_N2$ substitution reaction would occur to give the 3β-acetate.

4.4.1. In any event acetolysis of the α-ketol-3α-mesylate or tosylate (45 or 46) in glacial acetic acid buffered with anhydrous sodium acetate gave a good yield of the 1β-axial acetoxy-2,12-diketone (47) with some 3α- and 3β-acetates (See TABLE I). The structure of (47) was derived from the following evidence.

4.4.2. The molecular formula $C_{22}H_{30}O_4$ and the presence of the characteristic three hydrogen singlet in the n.m.r. spectrum at δ 2.13 indicated an acetate group. Furthermore, a broad one hydrogen singlet at δ 4.20 ($W_{\frac{1}{2}}$ 3 Hz) indicated that this was a secondary acetoxy group. The broadening was eventually assigned to through-carbonyl coupling of the H-1α and H-3α hydrogens since the system H-1α, C-1, C-2, C-3, H-3α constitutes nearly a perfect plane.[40] The presence of a secondary acetate discounted any retropinacolinic rearrangement products. The i.r. spectrum of (47) had bands at 1755, 1710 and 1705 as well as 1225 $cm^{-1}$, confirming the presence of an acetate and two carbonyl groups. The acetate absorption of α-ketol acetates in the i.r. is raised from the normal value of circa 1730 $cm^{-1}$ for the isolated ester group to circa 1750 $cm^{-1}$ when adjacent to a ketone.[41,42] The value of 1755 $cm^{-1}$ for (47) clearly indicated an α-acetoxyketone.

The acetate grouping of (47) was practically instantaneously hydrolysed by aqueous alkali to give an alcohol (48). Acetylation

of (48) regenerated (47) demonstrating that no epimerisation or

isomerisation had occurred during the alkali treatment. When

the n.m.r. spectrum of (48) was taken in pyridine only one methyl

group was affected on comparison with the spectrum run in $CDCl_3$.

This methyl group was <u>shielded</u> by 0.12 ppm and thus designated

as the 17-methyl group. If the alcohol function had been at C-3

either the 18- or 19- methyl groups, or both, should have been

affected.[12]

### THE 1β,2α-DIOL FUNCTION

<u>4.5.1.</u> The solvolysis reaction was repeated on the α-ketol-3α-

tosylate-12-dithioethane ketal (49) and the acetate product (50)

so obtained displayed similar n.m.r. characteristics to (47).

$NaBH_4$ reduction gave a diol (51) whose n.m.r. spectrum displayed

a one-proton doublet at δ 3.50 (J 4 Hz) and a one-proton quartet

at δ 3.94 (J ∼ 3×4 Hz). Double resonance experiments confirmed

that these two signals were mutually coupled. This then showed the

vicinal nature of the two hydroxymethine protons. The diol failed

to form an acetonide under conditions which were successful for

the 2α,3α-diol function so a <u>trans</u>-diaxial configuration was

expected. Meakins <u>et al</u>[43] had studied the i.r. spectra of twenty-

eight vicinal diols of the cholestane series and observed that at

high dilution the trans-diaxial diols exhibited only one band in

the region 3620 $cm^{-1}$ whereas all the other diols had both this

"free" hydroxyl stretching band as well as a hydrogen-bonded

hydroxyl stretching band at 3580 $cm^{-1}$ (approximate values only).

This would have been the method of choice to determine the relative

disposition of the hydroxyl groups of (51) since Meakins <u>et al</u>[43]

had reported data for the 1,2-diols. However an i.r. solution cell with a one centimetre path length was not available and the experiment could not be carried out. The same workers noted the n.m.r. characteristics of the diacetates and found that equatorial acetoxy groups resonated at δ 1.97 - 2.01 whereas the axial acetoxy groups at δ 2.06 - 2.09. Their data lacked values for the 1,2-diaxial compound, however, so that a direct comparison could not be made.

4.5.2. The diacetate (52) was prepared in the usual way and showed resonances at δ 2.00 and 2.15 for the acetate groupings. These values unfortunately fell outside the two ranges found in the cholestane series and no appropriate comparison could be made. Furthermore, a comparison of authentic 2-axial, 3-equatorial diterpenoid diacetates prepared in this study and also previously reported in the literature,[12] with the values for the corresponding diacetoxy cholestanes indicated a close agreement (See TABLE 1),

TABLE I

NMR DATA FOR SOME 2,3-DISUBSTITUTED DITERPENES AND CHOLESTANES(δ)

| COMPOUND | C-2 | C-3 | LITERATURE REFERENCE |
|---|---|---|---|
| 2α,3α-DIACETOXYSTACH-15-ENE | 5.29 | 4.58 | 12 |
| 2α,3α-DIACETOXYATISENE (231) | 5.27 | 4.59 | |
| 2α,3α-DIACETOXYSTACH-15-EN-12-ONE (232) | 5.33 | 4.59 | |
| 2α,3α-DIACETOXYSTACHANE (233) | 5.30 | 4.65 | |
| 2β,3β-DIACETOXY-5α-CHOLESTANE | 5.25 | 4.85 | 43 |

implying that the data for the 1,2-diacetoxycholestanes should also have been in agreement with 1,2-diterpenoid acetates. However the Oxford group omitted values for these particular pairs, frustrating a possible comparison.

The coupling constants of $3 \times 4$ Hz could not be used for assigning the particular configuration of the diol at C-2 since the conformation of ring A was not known, so the diaxial 1β,2α-diol structural assignment to (51) rests on its failure to form an acetonide.

At this stage the 3β-acetoxy-2,12-dione (53) had been made and shown to be dissimilar to (47). All the 2,3-ketol acetates (3, 30, 33 and 53) gave a positive red colour with alkaline triphenyltetrazolium chloride solutions whereas (47) or (48) only gave a colour on heating, a factor which indicated the more hindered nature of the α-ketol function in (47). Similarly, treatment of (48) with strong alkali for prolonged periods at room temperature gave no reaction, whereas similar treatment of any of the 2,3-ketols listed above resulted in oxidations to the diosphenol, benzilic acid and seco acids.

The structure of (47) was then deduced to be 1β-acetoxystach-15-en-2,12-dione and confirmed by the x-ray structure of the derivative (135), discussed in section 13.5.

|    | R  |
|----|-----|
| 45 | Ms |
| 46 | Ts |

|    | R  |
|----|-----|
| 47 | Ac |
| 48 | H  |
| 56 | Ms |

49

50
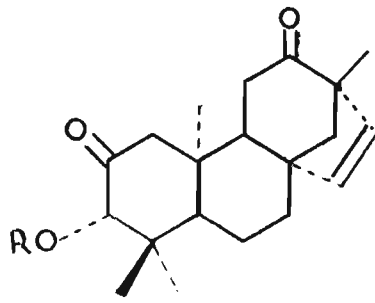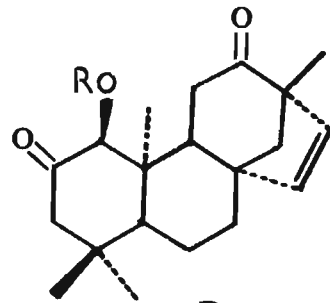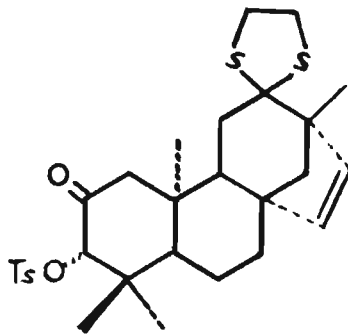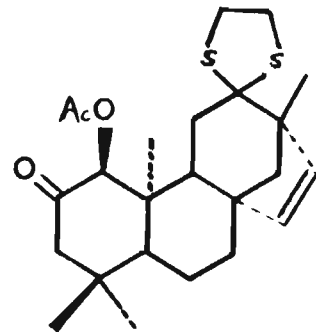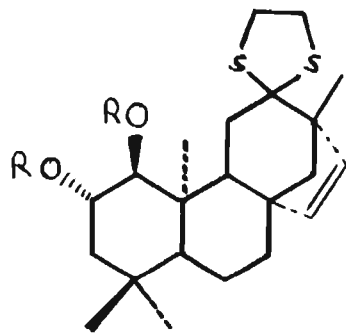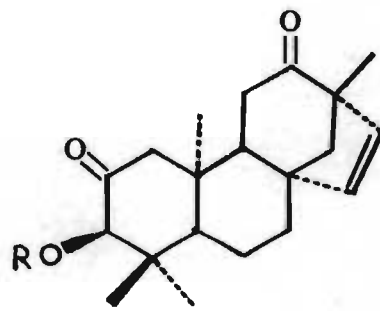
|    | R  |
|----|-----|
| 51 | H  |
| 52 | Ac |

|    | R       |
|----|---------|
| 53 | Ac      |
| 54 | H       |
| 55 | Ms      |
| 57 | $C_2H_5CO$ |

# C H A P T E R  5

## STUDIES TO ELUCIDATE THE MECHANISM

<u>5.1.1</u>    The crude solvolysis mixture was not pure (47) but its n.m.r. spectrum also showed the presence of the 3α-acetoxy-2-one and the 3β-acetoxy-2-one with no trace of any 2-acetoxy-3-ones. The 3β-hydroxy-2,12-dione (54) was prepared from (53) and converted to its mesylate[45] (55).    Acetolysis of this mesylate gave the same mixture as for the equatorial isomer (46) indicating that both compounds were undergoing solvolysis via the same intermediate.    The 1β-mesyloxy-2-one[45] (56) was then prepared from (48) and solvolysed as before.    Surprisingly enough the same mixture of acetates was again obtained, with the 1β-acetoxy-2-one as the major component (see Table II).

## TABLE  II

### PERCENTAGES OF ACETOLYSIS PRODUCTS[46]

| SUBSTRATE | AXIAL 1β-ACETATE | AXIAL 3β-ACETATE | EQUATORIAL 3α-ACETATE |
|---|---|---|---|
| Equatorial-3α-tosylate (46) or Mesylate (45) | 75 | 7.5 | 17.5 |
| Axial-3β-mesylate (55)[45] | 71 | 14.5 | 14.5 |
| Axial-1β-mesylate (56)[45] | 72 | 14.5 | 13.5 |
| Equatorial-3α-acetate (3) | 0 | 11.8 | 88.2 |
| Axial-3β-acetate (53) | 0 | 8 | 9 2 |
| Axial-1β-acetate (47) | 100 | 0 | 0 |

5.2.1    These unexpected results prompted an investigation of

possible enolisation and isomerisation mechanisms.  Acetolysis

of the 3α-acetoxy-2-one (3) resulted in a 12% epimerisation to

the 3β-acetoxy-2-one (53) even after a prolonged reaction time

and therefore this ratio must be the thermodynamic equilibrium

position.  No 1β-acetoxy-2-one (47) was produced during this

equilibration showing that no acyloxy-carbon cleavage occurred,

but to further test this the equatorial 3α-propionoxy-2-one (57)[45]

was also equilibrated in refluxing acetic acid containing sodium

acetate.  In this instance no acetate was produced but again some

equilibration to the axial 3β-propionoxy-2-one occurred.  This

epimerisation then was purely due to enolisation or ion-pair

return.[47,48]

The enolisation pathway was considered more likely by

observing the presence of some diosphenol (18) in the solvolysis

mixture from (46).  This could arise by abstraction of H-3β

by base and expulsion of p-toluenesulphinate ion similar to the

oxidation observed for the α-ketol nitrate (27) (see section 11.1.2).
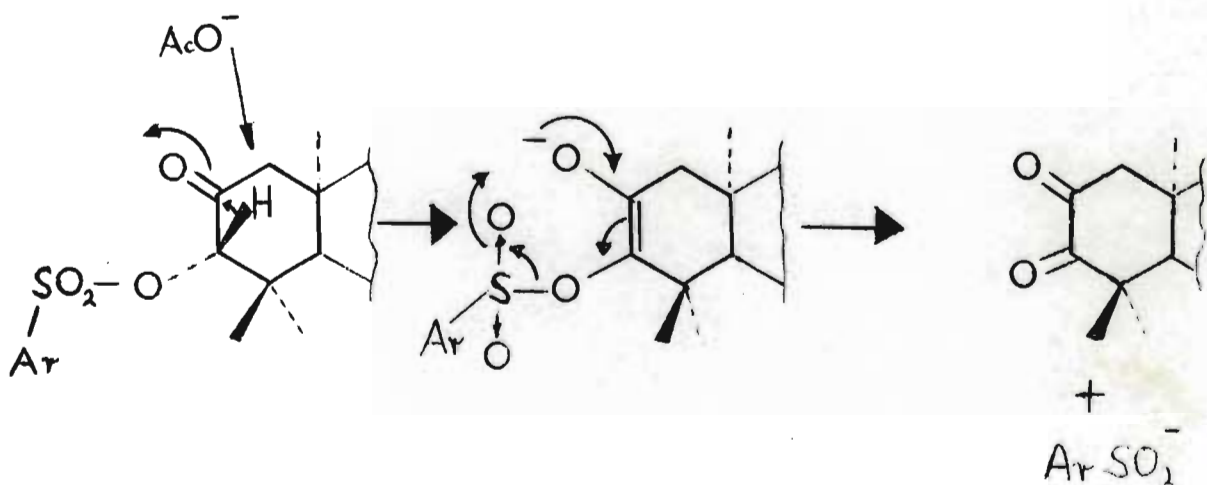
Acetolysis[45] of the 3β-axial acetoxy-2-ketone (53) for

3.5 hours (the usual acetolysis time used) gave 70% of the isomeric

equatorial 3α-acetate, whilst after 3.5 days this had reached 92%.

The amount of 3-axial acetate is similar to that obtained from

the acetolysis of the 3-equatorial sulphonate (46) after 3.5 hours

but the two axial sulphonates differ considerably. This discrepancy

however remains unexplained until a fuller understanding of the

mechanism is obtained.

5.3.1 TEMPERATURE DEPENDENCE OF THE SOLVOLYSIS REACTION

A common mild method of acetolysis is to use sodium acetate

in aqueous acetone at reflux ( 80°). This method was tried but no

reaction was observed even on prolonged heating. A similar solvolysis

using a huge excess of sodium iodide in acetone at reflux for three

months gave only starting material.

Plain glacial acetic acid at reflux over 3.5 hours gave only

a slight amount of acetate, most of the starting material being recovered.

Thus acetate ions from added acetate salt were necessary to effect

conversion. The nature of the salt was important since no reaction

was observed with sodium iodide in refluxing acetic acid, whilst

sodium azide in boiling diglyme achieved conversion to unidentified

products within 1 hour.

Acetolysis in diglyme at steam bath temperature (100°)

although effective, was extremely slow whereas at the reflux point

(about 160°) the reaction proceeded well. In this solvent a greater

proportion of diosphenol was produced probably because of the higher

reaction temperature. Glacial acetic acid was found to be the best

solvent for preparative purposes. The facts noted above indicated

a marked temperature dependence for this reaction to occur such
that a well defined energy barrier had to be surmounted.

## 5.4. MECHANISTIC POSSIBILITIES

Three mechanisms have been put forward to explain these
reactions:

(i)   the classical $S_N2'$ mechanism;

(ii)  reaction via a delocalised enol cation;

(iii) reaction via an intermediate cyclopropanone or
zwitterion.

## 5.4.1. THE $S_N2'$ REACTION

As will be discussed this mechanism satisfactorily explains
the acetolysis of the two epimeric 3-sulphonates (46 and 55) but
is not satisfactory for the 1$\beta$-sulphonate solvolysis. However,
it could be argued that the one anomalous case (56) proceeds via
a different mechanism and the close agreement of its products with
the products obtained from the other two epimers is purely fortuitous,
therefore, for the moment the $S_N2'$ reaction will be discussed only
for the C-3-epimers.

5.4.2.   The classical $S_N2'$ reaction actually involves two nucleophilic
substitutions. Firstly, the $\pi$ electrons of the enol double bond bring
about an internal nucleophilic substitution, displacing the leaving
group;  this is then followed by an external nucleophilic attack
at the $\alpha'$ position:
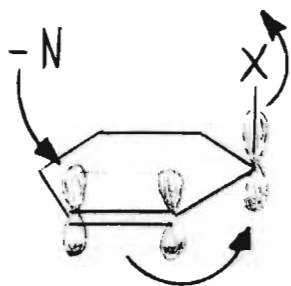
A consequence of this double nucleophilic attack is that the incoming group is on the same side as the leaving group since the internal and external nucleophiles approach from opposite sides.

In the particular instance of the 2-keto-3-sulphonate ester (46) it could be possible that the acetate anion helps to displace the sulphonate anion at C-3 by reducing the positive charge at C-3, whilst simultaneously bonding to C-1
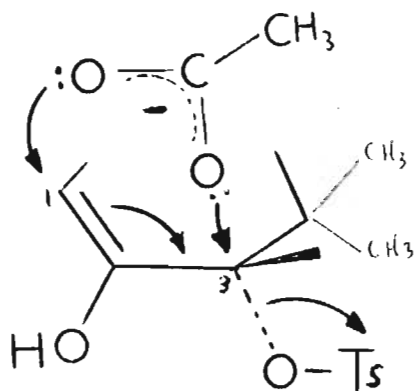


This would explain the anomaly that the 1-acetate in the product (47) is on the opposite side to the leaving group at C-3. However, a further steric reason exists for the 1-axial being preferred to the 1-equatorial position and this may be the overiding effect here. A careful scrutiny of substituent stabilities at C-1 in steroidal or diterpenoid compounds reveals the not unexpected fact that the 1-axial position is much preferred over the epimeric 1-equatorial

orientation. Therefore, any initial 1-equatorial product would be expected to isomerise to the axial isomer. Some pertinent cases will be examined.

5.4.3    Bromination of the 2-acetoxy-1-en-3-one grouping (32) typical of diosphenol acetates leads to the yellow, unenolised 1-axial-bromo-2,3-diketones[32] (e.g. (37), section 3.8.3). The marked instability of the 1-equatorial bromide was shown by the reluctance of the yellow compounds to give the colourless enols even on treatment with base.[32]

5.4.4    NaBH$_4$ reduction of stach-15-en-1-one (58)[49] gave the axial 1β-hydroxystachene (59). This is an excellent example[50] of "product development control" overiding "steric approach control". Steric approach control would require the hydride ion to attack C-1 from the β-face, resulting in a 1-equatorial alcohol. This in fact is not observed. The possible sequence of events is the formation of a solvated -O-BH$_3$ complex with a large steric requirement such that the transition state closely resembles that of the final product, at which stage the hydride ion attacks equatorially.

5.4.5    Equilibration of the 1,2-ketol structure using alkali gave a mixture[49] of three possible 1,2-ketols:   the 2β-hydroxy-1-one (starting material), the 1β-hydroxy-2-one and the 1α-hydroxy-2-one in the following percentages 50, 41 and 9 (with respect to the total α-ketols in the mixture and excluding the major product, the diosphenol).

5.4.6   It is reasonable to propose as an alternative that it is only the 3β-sulphonate which undergoes solvolysis, and since the 3α-acetate did give some 3β-acetate, the same epimerisation could happen to the 3α-sulphonate prior to solvolysis.[36]   Similarly, the case of the 4β-bromo-3-coprostanone (42)[38] could also involve prior enolisation-epimerisation to the 4α-bromide and then acetolysis.   Thus the "anomalous $S_N2'$" would then in fact be a normal $S_N2'$ reaction with the leaving and incoming groups on the same side.

5.4.7   There is a further stereochemical requirement for the $S_N2'$ reaction.   The internal nucleophilic attack by the π-electrons can only occur if maximum overlap is attained between the double bond π-orbital and the developing rear lobe of the p-orbital of the incipient carbonium ion at C-3.   This particular geometry requires ring A to flip from the chair to the boat conformation placing the 3α-sulphonate in a pseudo-axial configuration.   For the 3β-sulphonate case the normal flattened chair allows this same overlap between the π-bond at C-1:C-2 and the p-orbital at C-3, without any change in conformation.

5.4.8   Dreiding models of the 2-enol (60) shows this to have a conformation similar to the keto-tautomer, that is a flattened chair.   However, the 1-enol (61) prefers a boat conformation to a dramatic extent.   This boat form satisfies the orbital overlap requirements discussed above as well as drastically increasing the non-bonded separation of the two axial methyl groups at C-10 and C-4.   In the normal chair form this non-bonded interaction is known to constitute a strain factor since the x-ray structural

investigations of 4,4-dimethyl steroids[51] and diterpenes[52,53,54] have brought to light the tendency of these two pendant groups to repel each other causing ring A to flex slightly. Thus any tendency for this interaction to decrease is of energetic advantage and it seems probable that the 1-enol is more stable than the 2-enol. In addition, it is known from i.r. data[55,56,57,58] that 5α-cholest-1-ene is more stable than 5α-cholest-2-ene since the C=C stretching frequencies are 1644 and 1653 cm$^{-1}$ respectively. This data is further supported by the respective heats of hydrogenation[58,59] of 27.30 and 25.85 kcal/mole and it is then probable that the enols will show the same tendency in stability. The 2-enol does, however, form as indicated by traces of diosphenol in the reaction mixture but the resulting vinyl-sulphonate would not undergo C-3:OSO$_2$R cleavage, therefore only the 1-enol would allow a displacement reaction to occur.

5.4.9    The classical S$_N$2´ reaction was therefore effective in explaining the products from the 3-sulphonate acetolysis but failed when considering the 1β-sulphonate acetolysis.

5.5.1    REACTION VIA THE DELOCALISED ALLYLIC CATION

This mechanism involves the formation of the enol, ion-pair formation and dissociation into a delocalised allylic cation of the structure (62):
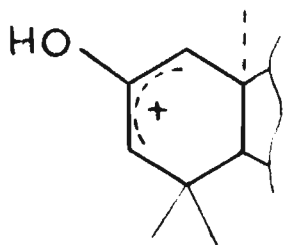


62

A model of this ion indicated no steric preference for attack at C-1 or at C-3, nevertheless the product composition would require the 1-position to bear a positive charge more readily. No reason which explains this preference has been found to date, although this intermediate would be favoured since it would unify the three sulphonate acetolyses.  Note its similarity to the zwitterion discussed next.

## 5.6.1    REACTION VIA THE CYCLOPROPANONE OR ZWITTERION INTERMEDIATE

This could occur by attack of the carbanion at C-1 on the 3-sulphonate (or the carbanion at C-3 on the 1-sulphonate) by the same mechanism as the Favorskii rearrangement.[60]  The sequence of events involves (i) carbanion formation at the unsubstituted methylene group, (ii) loss of sulphonate anion to give the zwitterion (63) and cyclisation by an electrocyclic process according to the Woodward-Hoffman rules[61a] using the same arguments of Kirk & Hartshorn.[60]    The zwitterion has four $\pi$-electrons in the two lowest lying orbitals and a disrotatory process allows cyclisation via the overlapping orbitals, the symmetry of the higher energy occupied orbital determining this ring closure.

ATOMIC P-ORBITALS OF ZWITTERION (63)



LOWER ORBITAL
CONFIGURATION

and

**63**

HIGHER ORBITAL
CONFIGURATION
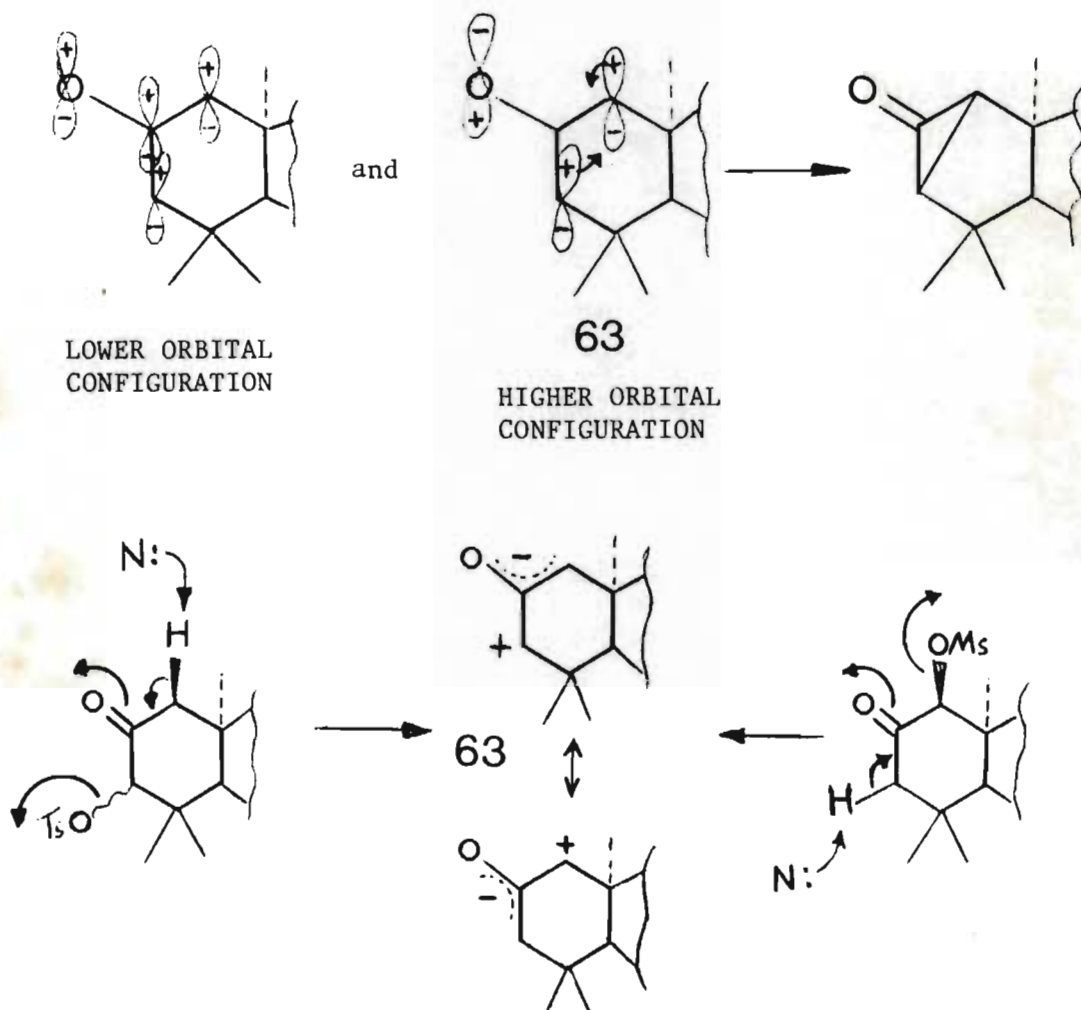


5.6.2    Of interest here is the close similarity between the
zwitterion (63) and the delocalised allylic cation (62).

5.6.3    The 17α-bromo- or 21-halopregnan-20-ones gave the same
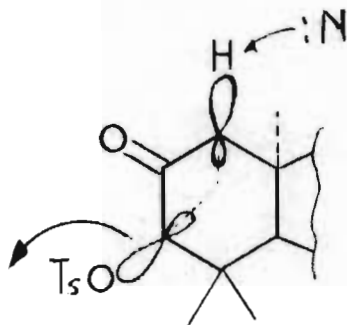etianic acid products under Favorskii conditions[61,62,63,64]
indicating the same intermediate as was the case here.

5.6.4    Some workers considered the ring closure to a cyclopropanone to occur through a direct internal nucleophilic substitution of the leaving group since the orbital orientations would be favourable[65].



This process would be favourable for the equatorial 3α-tosylate and possibly the pseudo-equatorial 3β-mesylate, in a boat conformation, but not when the latter were in a chair conformation, or for the unquestionably axial 1β-mesylate. In these cases the intermediate zwitterion would be preferred since a concerted overlap of the orbitals, the stereo-electronic effect,[66,67] discussed in section 5.4.7 for the first proposed $S_N2'$ mechanism, could be attained.

5.6.5    Attempts at trapping a possible cyclopropanone intermediate as its furan adduct (64)[68] were unsuccessful and t.l.c. of the reaction mixtures failed to show any new compounds when the acetolyses in hot diglyme were performed in the presence of large excesses of furan under nitrogen. This however does not discount the possible occurrence of a cyclopropanone. Nevertheless the most likely mechanism seems to involve the zwitterion intermediate. Although the positive charge is somehow preferentially localised at C-1 rather than C-3, this preference cannot at present be rationalised.

5.7.1    Remote substituents such as the 12-ketone or the 15-double

bond were not critical since this reaction was successfully performed

on the stachene, the ent-16S-atis-13-ene (139) and on the D-homo-

C-nor-α,β-unsaturated ketone (Section 12.1. )

Further experiments with lanostane, cholestane and the ring C

aromatic cleistanthane systems are in progress.

5.7.2    A consequence that can be derived from this reaction is

that the activation energy for a concerted retropinacolinic reaction

must be higher than that required to form the zwitterion intermediate.

Similarly, the nucleophilic attack on this ion has to be concerted

because no products of the 20(10→1α) abeo - rearrangement were formed

from the 1β-mesylate acetolysis.

5.8       SOLVOLYSIS OF THE 2-KETO-3α-SULPHONATE WITH OTHER NUCLEOPHILES

5.8.1    Ethanediol is a good solvent for potassium fluoride and the

reaction of this mixture with primary alkyl halides offers a convenient

preparation of alkyl fluorides[69].  However, the reaction

$R-OH + 2F^- \rightarrow R-O^- + HF_2^-$ is known to occur with ease and in the

case of ethanediol this reaction could lead to the formation of

$^-O-CH_2CH_2-O^-$.  These alkoxide ions are both strong bases and good

nucleophiles.

5.8.2    In an attempt to introduce fluorine into ring A of the

ketol (1) the 2,12-diketo-3α-mesylate (45) was heated in ethanediol

with KF.  The major product of the reaction was derived by attack

of the alkoxide at C-1 giving the α-keto-1β-ethanediol monoether (65)

as an oil.  The structure was deduced from the n.m.r. spectrum

which showed H-1α as a broadened singlet (with a shoulder) at

δ 3.00 indicating the same coupling, through the carbonyl group,

to H-3 . The ethylenedioxy group appeared as an AB quartet between $\delta$ 3.3 - 3.9. (The sample was also contaminated by small amounts of a product containing two ethanedioxy residues, probably the 12-ethanedioxyketal analogue of (65).

5.8.3 The absence of appreciable quantities of "Favorskii" products is peculiar in the light of the mechanisms postulated. Although the acetolysis should not give the Favorskii reaction since acetate is a weak nucleophile and acetic acid is of low polarity, the strong nucleophilicity and basicity of the $HOCH_2CH_2O^-$ anion as well as the highly polar ethanediol solvent should have effected this well known rearrangement.

5.8.4 Repetition of the reaction with KF in hot benzyl alcohol gave in very low yield the analogous benzyl ether (66) with a very similar n.m.r. spectrum. However, the low solubility of KF in benzyl alcohol was probably responsible for the poor yield as the proportion of alkoxy ions would be small.

5.8.5 "Fluorolysis" with KF in sulpholane gave a complex mixture from which was isolated in low yield the 1$\beta$-hydroxy-2,12-dione (48). This probably formed by attack at C-1 by traces of water in the sulpholane as in the case of the acetolysis in acetic acid using hydrated sodium acetate when (48) was the major product.

5.9    SYNTHETIC SCOPE OF THE ACETOLYSIS REACTION

The recent isolation of 1,2-dioxygenated diterpenes (188) of the stachene class from Erythroxylon australe roots[49] made this work important in that this oxygenation pattern can now be readily obtained by a high yield reaction from the readily prepared

2,3-oxygenated diterpenes. Furthermore, it was attractive to
speculate whether the enzyme systems in E. australe also operated
via this "allylic" rearrangement reaction, although no 2,3-oxygenated
diterpenes were reported present. Their apparent absence however
does not invalidate the question since precursor compounds may
not accumulate to any extent.
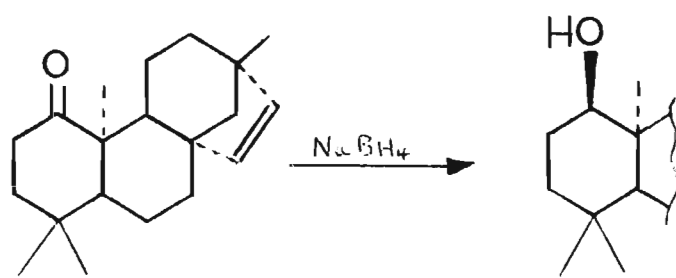


58                                              59
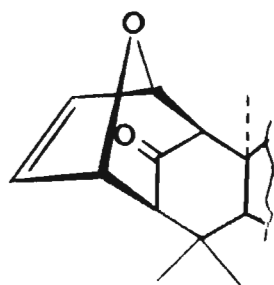


64



65                                              66

C H A P T E R  6

6.1    A Cr(VI)-INDUCED RING CONTRACTION OF AN α-KETOL - A NEW REACTION[71]

6.1.1    This unprecedented reaction occurred when the 1,2-ketol (48) was treated at 0° with the Jones reagent.[70]    Carbon dioxide was evolved and the reaction only went to completion with a large excess of reagent (9-12 equivalents).  Workup afforded a nor-diketone (67) toge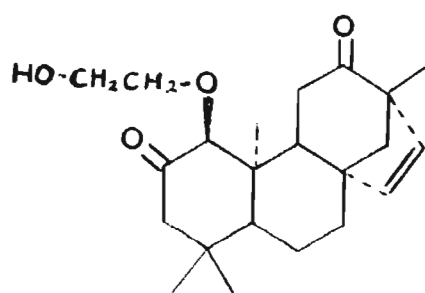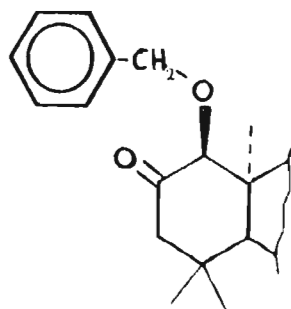ther with uninvestigated acidic material, probably seco-acids. The published mechanism,[71] via an aldol type condensation of an aldehyde with the α-methylene group of the acid, has since been dis-carded as improbable.  A more probable mechanism involves prior oxidation to the α-diketone, enolisation, formation of an enol-chromate ester, cyclisation by attack at the α-position, a second attack by a chromate species, this time at the carbonyl carbon, and a semi-benzilic/*acid* rearrangement.  This would resemble the oxidative ring contraction brought about by hydrogen peroxide-selenium dioxide.[72,73]

6.1.2    INITIALLY PROPOSED MECHANISM



48                    →                                    67
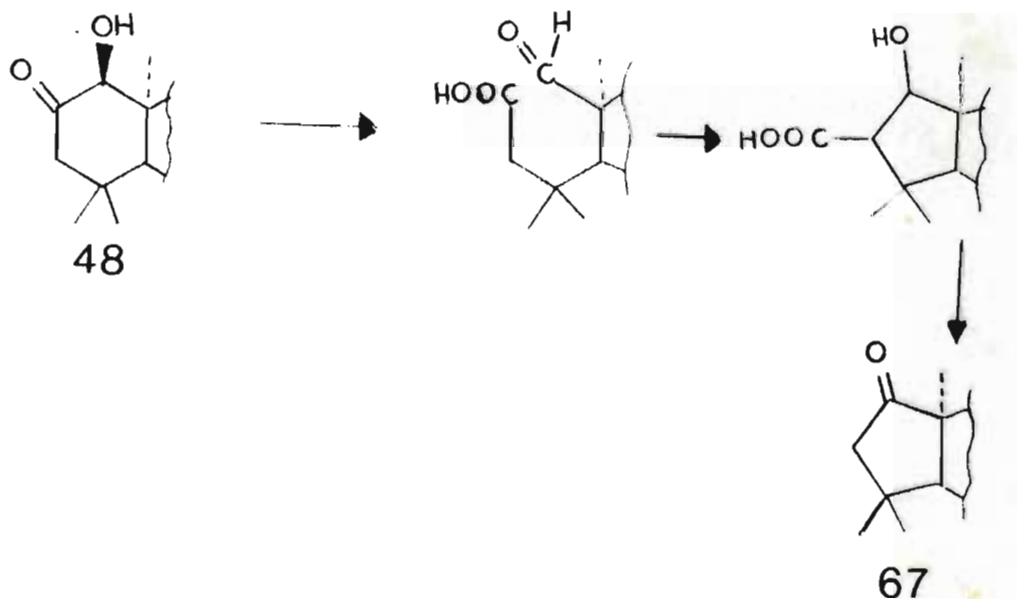
## 6.1.3 REVISED MECHANISM
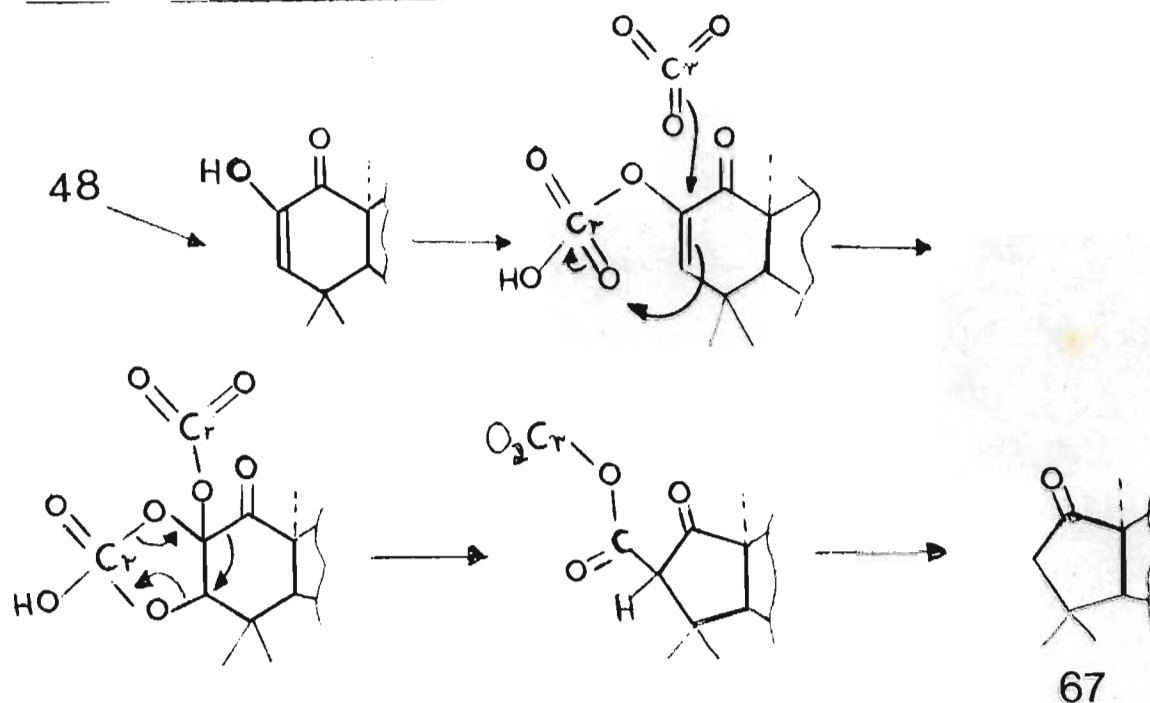


6.1.4 A simple mechanism which however does not explain the *large* excess of Cr(Vl) required would be a typical benzilic acid ring contraction following initial attack at C-1:
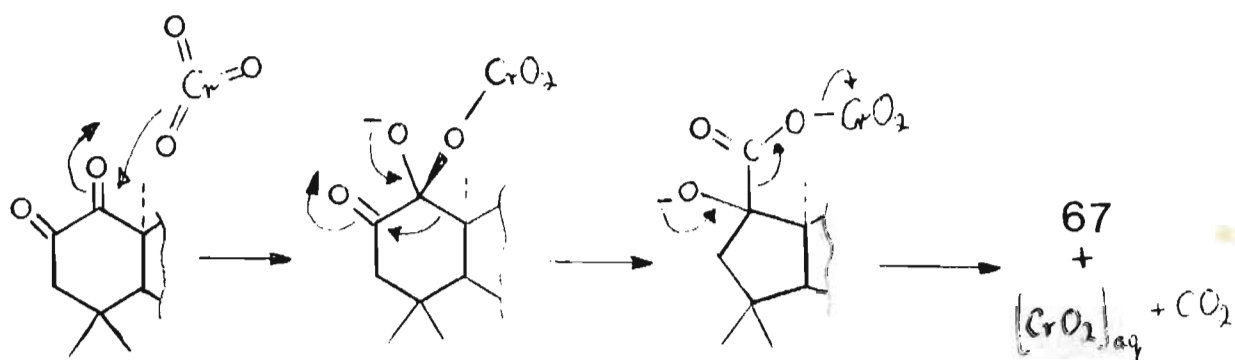


6.2.1 The 2α-hydroxycholestan-1-one was oxidized with $CrO_3$ in acetic acid by Sigg and Tamm[174] to a seco-dicarboxylic acid in 54% yield. The authors did not mention any nor-ketone formation, but

the low yield of acid obtained allows speculation that some material was lost in the neutral fraction as the nor-ketone.

A careful look at the mechanism proposed (6.1.3) allows the prediction to be made that a ketol or diosphenol of the type



should also oxidize faster at the available methylene group (C-2) than at the 3,4-positions, and should also give a nor-ketone. Furthermore a 2-keto-3-ol (such as 1) should undergo bond fission between C-2 and C-3, faster than any possible attack at C-1 which is relatively hindered. When the oxidation of (1) was performed no trace of non-polar products were obtained, instead acidic material was isolated. However, the diosphenol (18) has C-1 activated in an analogous manner to the enol in section 6.1.3 and should undergo reaction at this site to some extent. This was borne out by experiment since on Jones oxidation (18) gave mainly acidic material but also non-polar compounds (t.l.c.), in small quantity, which have not as yet been isolated since this project came to an end before this could be achieved.

6.3     The structure of the A-nor-diketone (67) was deduced initially by n.m.r. and by comparison to the authentic A-nor-2,12-diketone (68) which was dissimilar, and finally established by preparing (67) by a standard route.

<u>6.3.1</u>    Thus the α-ketol (1) or the diosphenol (18) were converted

to the benzilic acid (69) on heating at 100$^O$ in methyl cellosolve

(ethylene-glycol-mono-methylether) with hydrated barium hydroxide

in air.   This method gave a very good yield whereas using potassium

hydroxide in alcohol resulted in partial reduction of the 12-carbonyl

at the same time as the benzilic acid in ring A was formed.[74]   Reaction

of the benzilic acid (69) with lead tetraacetate gave a 97.5% yield

of the A-nor-2,12-diketone (68).

<u>6.3.2</u>    Similar oxidation of the 1β-hydroxy-2,12-dione (48) in

methyl cellosolve at 100$^O$ resulted in only partial conversion to

a mixture of the starting material, diosphenol and benzilic acid.[75]

Refluxing for 20 hours successfully produced the benzilic acid but

this was contaminated once again with the 12α-hydroxy isomer resulting

from hydride transfer from the solvent.   However, the crystalline

mixture gave one compound in excellent yield when reacted with

Jones reagent and this proved to be the same A-nor-1,12-diketone

(67) prepared directly from (48) with the Jones reagent in one step.

In this instance no acidic byproducts  were found.

<u>6.4</u>     THE N.M.R. SPECTRA OF (67) AND (68)

<u>6.4.1</u>    Corroborative evidence for the 1-keto structure of (67) was

obtained by using the n.m.r. shift reagent tris(1,1,1,2,2,3,3-

heptafluoro-7,7-dimethyl-d$_6$-4,6-octanedione-d$_3$)europium, Eu(FOD-d$_9$)$_3$

to simplify the spectra of both diketones.    The 60 MHz spectra

will now be discussed.

6.4.2    THE N.M.R. SPECTRUM OF THE A-NOR-STACH-15-ENE-2,12-DIONE (68)

In the n.m.r. spectrum of this compound in deuterochloroform the signals for the two 11-protons appeared in the region $\delta$ 2.2 - 2.9 as the AB part of an ABC system. Smaller lines were lost under other bands in the spectrum. The two 1-protons were magnetically equivalent and appeared as a singlet at $\delta$ 2.03. These bands all disappeared on deuteration with $CH_3ONa$ - $CH_3OD$.

Addition of the shift reagent $Eu(FOD-d_9)_3$ caused two hydrogens to be mostly affected, the ones appearing as an eight line signal, and also caused only one of the methyl groups, C-17, to be much affected. Furthermore the widely separated AB quartet for the 15-double bond now became much more closely spaced. These facts indicated that only the 12-ketone underwent appreciable complexation with the metal ion and the proximity of the metal to the 17-methyl group and the 11α- and 11β-hydrogens caused these changes. Moreover the homoconjugation of the $\beta,\gamma$-unsaturated ketone system became much weaker and explained the changes in the double bond pattern. The 2-ketone did not complex to an appreciable extent with the europium ion.

6.4.3    THE N.M.R. SPECTRUM OF THE A-NOR-STACH-15-ENE-1,12-DIONE (67)

This spectrum was again run in deuterochloroform. The C-11 protons were found to resonate between $\delta$ 2.60 and 3.20 as six lines, again the smaller lines being lost under other bands. The C-2 protons in this case formed a four line AB quartet at $\delta$ 1.77, 2.10, 2.38 and 2.70.

Addition of the $Eu(FOD-d_9)_3$ complex produced a dramatic change for one hydrogen, the 11β-hydrogen. The ABC spectrum now became an AMX spectrum with the 11β-hydrogen (A) at δ 5.75 as a quartet (J 6 and 16 Hz). The M part, the 11α-hydrogen, at δ 4.40 was also as a quartet (J 10 and 16 Hz). The 9β-hydrogen constituted the X part, a quartet at δ 3.42 (J 6 and 10 Hz). Therefore, the geminal coupling constant for the 11-protons was 16 Hz, the coupling of the two gauche hydrogens, 11β and 9β, was 6 Hz and the trans H-9β to H-11α coupling was 10 Hz.

The C-3 hydrogens resonated as a quartet (20 Hz coupling) at δ 3.73. There is a signal at δ 4.30 integrating for approximately one hydrogen which remains unexplained but may be due to the fortuitous overlapping of the three lines shown in the spectrum.

<u>6.4.4</u>    This data is consistent with the proposed structure since the marked effect on the 11β-hydrogen could only be due to the additive action of complexation at the 1-carbonyl and at the 12-carbonyl groups. Whether the Eu ion was actually bonded to the two ketones simultaneously or whether there existed a competitive equilibrium between the two sites, with both equilibrium constants of comparable magnitude could not be ascertained. However, the geometry of complexation at the 12-carbonyl was quite different in the case of (67) as compared to the strong complex formation with (68), as shown by the remarkably little change in the double bond pattern in the n.m.r. spectrum of (67) even with large amounts of shift reagent added.

The most important difference was the absence of any large deshielding effect on the 17-methyl group in the 1,12-diketone as contrasted to (68). This meant that the metal ion was complexed at an angle to the 12-carbonyl, away from this methyl group and closer to the 1-carbonyl, hence the possibility of chelation by the two sites.



67



68



69
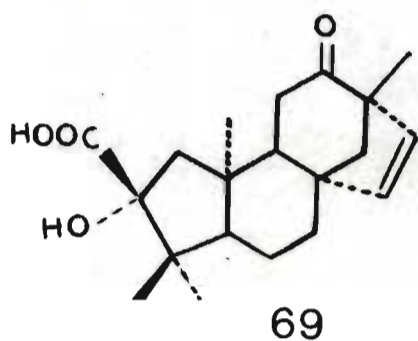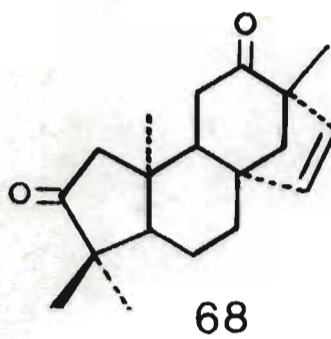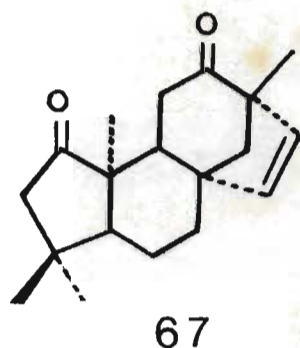
# CHAPTER 7

## 7.1. KETALIZATION REACTIONS

The most common method of protecting carbonyl groups is to convert the carbonyl group to a ketal and various reagents have been used to this effect such as ethylene glycol, β-mercaptoethanol, dithioethane, methanol and benzylmercaptan. Of these the first three form cyclic ketals which are more easily formed, more stable and hence are more useful. The derived ketals are stable to alkaline conditions but are opened up to regenerate the original carbonyl groups on acid treatment. However, the sulphur containing ketals are much more resistant to acid hydrolysis because the weaker nucleophilicity of sulphur compared to oxygen makes it less prone to protonation, the initial step in the hydrolysis. On the other hand the oxygen ketals are stable to the Wolf-Kishner reduction conditions whereas the sulphur containing ketals are reported to be reduced in a similar manner as the original carbonyl group and hence cannot be used under these conditions.

Early on in the investigation it became desirable to be able to selectively block either the 2- or the 12-carbonyl groups in order to carry out reactions at the alternative position, therefore the ability to form ketals by these two groups was investigated.

Refluxing the ketol (1) with ethylene glycol in toluene using p-toluenesulphonic acid as a catalyst gave in good yield the cyclization product (70). The 12-ketal grouping was easily removed

by mild acid treatment to give (71) but the A ring endioxy-ether was remarkably stable even to prolonged refluxing with methanolic HCl. These two compounds were also made in ethylene glycol and toluene containing a large excess of boron trifluoride etherate.

The n.m.r. spectrum of (71) indicated the large mobility of the dioxene ring whose resonance appeared as a sharp four proton singlet, whereas the 12-ketal grouping was more complex in its n.m.r. signal.[76]

Catalytic hydrogenation of the dioxene double bond failed even under conditions in which the 12-ketone was partially reduced to a mixture of 12α- and 12β-alcohols together with starting ketone (the 15-double bond of course being reduced); this mixture surprisingly crystallised very readily! This failure was unexpected since the simple analogue prepared from benzoin (72)[77] was hydrogenated easily.

The dioxene grouping was useful as a blocking group for the A ring as a whole in order to carry out reactions on the 12-ketone, but the ring A ketol was not regenerated by any simple means so that other derivatives were now searched for.

Refluxing the α-ketol tosylate (46) with ethylene glycol in toluene gave exclusively (70).[45] However, reaction with the α-ketol benzoate (11) gave a good yield of the corresponding bis-2,12-ethanedioxyketal (73). Addition of a trace of acid to the n.m.r. sample readily removed the 12-blocking group leaving the 2-group intact. More prolonged acid treatment then removed the 2-group as well. This then constituted a method for selectively modifying the 12-oxygen function (e.g. reduction to the alcohol) keeping the ring A ketol intact as a benzoate ester.

The ketol-3α-tosylate (46) in cold glacial acetic acid
gave an excellent yield of the 12-dithioethane ketal (49) with
ethanedithiol with no elimination of the sulphonate ester as in
the case of the ethanediol reaction as described above.

The reaction of the α-ketol (1) in acetic acid with
ethanedithiol and a small amount of $BF_3$ for a short period gave
the 12-dithioethane ketal (74) in good yield. Reaction for a
longer time using more $BF_3$ gave the 2,12-bis-dithioethane ketal (6).
This constituted the best method for blocking the 12-carbonyl
function exclusively since the 12-dithio ketal was found to be
extremely resistant to most reagents. Similar reaction using
β-mercaptoethanol gave oily mixtures. However, when the 3-hydroxy
group was converted to the acetate or benzoate, good yields of the
12-oxythioketals were obtained. It was interesting to note that
t.l.c. showed the presence of two isomers whenever β-mercaptoethanol
was used, these being the 12-epimeric compounds having the sulphur
β in one and the oxygen β in the other. Using the analogy that an
axial alcohol or ester is more mobile on t.l.c. than the corres-
ponding equatorial isomer, and arguing that oxygen is more polar
than sulphur on t.l.c. (as shown by the greater mobility of the
dithioethane ketals with respect to the dioxyethane ketals), then
the more mobile isomer would be the one with the β oxygen.

Treatment of the ketol-3α-acetate-12-oxythioketal (75)
(as well as the corresponding 12-semicarbazone) with dithioethane
and $BF_3$ under mild conditions resulted in ketal exchange giving
the ketol-3-acetate-12-dithioethane ketal (76) instead of the
expected 2-dithioethane-12-oxythioethane-ketals. This reaction
had been carried out in an attempt to prepare the 3α-acetoxystach-
15-en-12-one from Raney nickel desulphurization of the mixed ketal.

70

71

72

73

74

75　　O

76　　S

X
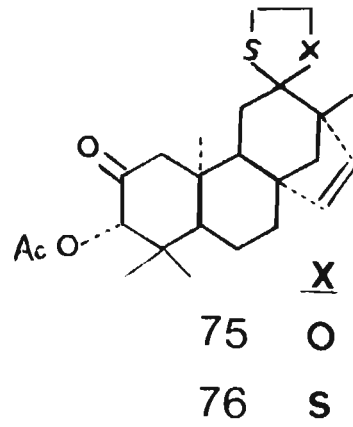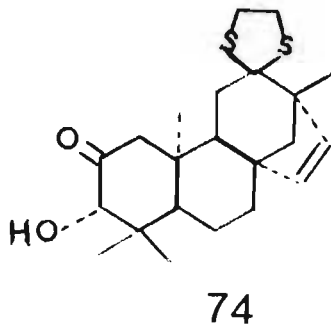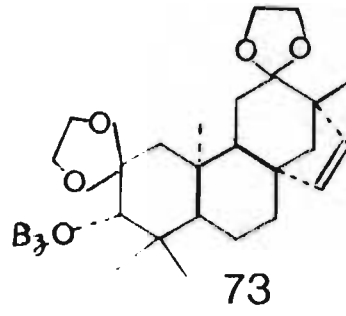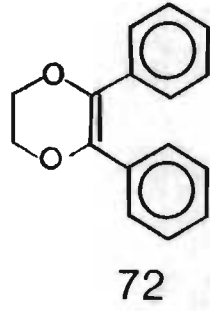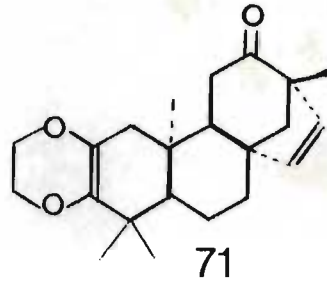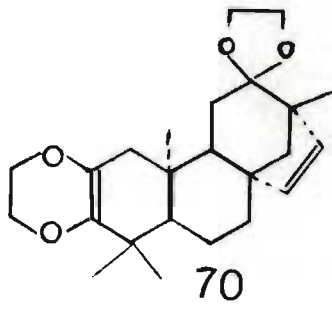
## C H A P T E R 8

### 8.1. ALDEHYDE CONDENSATIONS AND REARRANGEMENTS

The aldol condensation of carbonyl compounds is a well established and useful reaction. Benzaldehyde is frequently used in organic analysis because of its ability to condense with the α-methylene groups of suitable ketones under base catalysis giving the well known benzylidene derivatives which are usually well crystallised.

In the α-ketol (1) there are two carbonyl groups each having one unsubstituted methylene group in a <u>sterically crowded environment</u>; these being the C-1 and C-11 methylenes. It was of practical interest to determine the relative reactivity of these two groups under aldol conditions so as to obtain an insight into the steric effects involved.

Reaction of the α-ketol (1) in ethanol with benzaldehyde and dilute sodium hydroxide gave no benzylidene derivative even after prolonged reaction times. This could be interpreted to mean that even if the initial aldol did form, no elimination of water could take place since this would have placed the aromatic ring and the benzylidene carbon in an extremely crowded environment, this being true at both the C-1 and C-11 positions. Therefore since the first step in the aldol condensation is reversible[78] no net reaction occurred. Attempted reaction of the diosphenol (18) with benzaldehyde and a <u>trace</u> of NaOH failed to give aldol product.[78] After 2 weeks 95% of starting material was recovered from the alkaline solution. However, prolonged (overnight) contact of the basic α-ketol solution containing benzaldehyde with air and subsequent dilution with water precipitated

masses of needles of the compound (77).

The i.r. spectrum had bands at 3400, 1750, 1705 and 760 cm$^{-1}$ indicating the presence of a hydroxyl group, a five-membered ring lactone or ketone, the normal 12-carbonyl absorption, and the stachene double bond. The n.m.r. spectrum had aromatic signals for 5 hydrogens establishing the presence of only one aromatic moiety, the usual double bond AB system, a 1H doublet at $\delta$ 5.17 characteristic for a benzylic proton attached to carbon bearing an oxygen substituent (similar to O-benzylidene sugar acetals) and a higher field 1H doublet at $\delta$ 2.67 obviously coupled to the benzylic hydrogen (J = 9 Hz, evident from double irradiation experiments). Also the sharp resonance of the one hydroxyl proton was shown by its disappearance on deuterium exchange.

The loss of CO and $CO_2$ in the mass spectrum was not very helpful in assigning a structure. The higher field 1H-doublet confirmed that C-1 was involved and not C-11 which would have given a quartet.

Two possible structures (77) and (78) fitted all the above data. The failure of (77) to dissolve in alkali (indeed it crystallised out of even strongly alkaline solutions) seemed at first to refute the real lactone structure (77) and indicated (78) as a possibility. However, (77) was also extremely resistant to acid and even boiling a THF solution of (77) with very strong perchloric acid for 24 hours failed to achieve ring opening of the supposed hemiketal ring. Instead (77) separated in excellent crystals on cooling! The compound was also resistant to periodic acid and lead tetraacetate. Reduction experiments with $NaBH_4$ and $LiAlH_4$

will be discussed further on.

8.2.4    The structure (77) was arrived at by reasoning that since air oxidation of the ketol gave the diosphenol and further reaction gave the benzilic acid, then condensation of the intermediate diosphenol with benzaldehyde would be very efficient as C-1 would now be further activated by the introduction of the conjugated C-3 carbonyl function.    This intermediate aldol could then undergo a benzilic acid type rearrangement and lactonisation to give a very stable γ-lactone.    Furthermore a similar reaction of D-steroidal diosphenols with formaldehyde and alkali had been reported[79] as well as an unusual benzilic acid rearrangement and lactonisation of the C-ring of a steroid with the 17-side chain substituent.[80,81] Thus by analogy, the lactone structure appeared to be the only possibility.    The stereochemistry now presented a problem.    There were two distinct aspects:-    the position of the five-membered lactone ring, that is α or β to the diterpene molecule;    and the configuration at the benzylic carbon, and these will be discussed separately.

8.3.1    STEREOCHEMISTRY OF THE RING A- LACTONE RING FUSION

The o-nitro and p-nitrobenzaldehyde derivatives were prepared.    Molecular models indicated that with an α-lactone ring the o-nitro group on the aromatic ring should affect the C-20 methyl group n.m.r. resonance but the methyl resonances in both the o- and p-nitro derivatives were identical indicating that the lactone ring was probably β-orientated.

8.3.2    The mechanism of the benzilic acid rearrangement was expected to determine the final stereochemistry.    In the cucurbitacin series Lavie et al[82] had found that only one isomer of the two

possible benzilic acid isomers from Ring A diosphenols was formed.

Furthermore, Levisalles and Tkatchenko[83] studied the ring contraction

mechanism in cholestane-2,3-diones by isotopic labelling and con-

cluded that the reaction was stereospecific, where hydroxide ion

attacked that ketone which had the lesser 1,3-diaxial interactions

when it became sp$^3$ hybridized, i.e. C-3.

<u>8.3.3</u>    In alkaline solution the 2,3-diketone must exist largely

in the enolate anion form
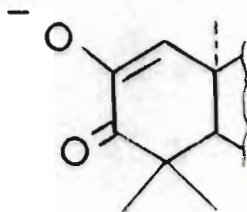
and the initial aldol reaction at the carbanionic centre at C-1

must be from the unhindered β side leaving this benzyl alcohol

substituent β and axial, since no epimerisation was expected to

occur because of the marked reluctance of C-1 to bear a bulky

equatorial substituent (e.g. the yellow 1 -bromo-2,3-diketones[30]

as for (37)).
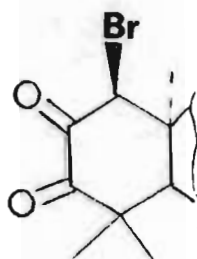
<u>8.3.4</u>    The benzilic acid rearrangement is initiated by hydroxide

ion attacking one of the carbonyl groups.  This attack in cyclic

compounds is expected to occur from the less hindered side (in

this case the β side) and also at the less hindered of the two

carbonyls.  Again, molecular models of the un-enolised 2,3-diketones

show that the A-ring is in a flattened quasi-chair conformation[83]

with C-2 slightly below and C-3 slightly above the plane of the
ring.  Hydroxide attack at C-2 in the unsubstituted C-1 compound
would involve unfavourable interactions with the axial C-1
hydrogen, and in the substituted C-1 compound (where the substituent
is a benzyl alcohol Ph-CHOH-)  this non-bonded interaction would
be prohibitive.

Hydroxide approach to the C-3 carbonyl involved axial
interaction with the C-1 and C-5 axial hydrogens but this would
not be expected to be as sterically demanding as for the C-2
case.   Therefore, the final benzilic acid product would be
expected to have a β-carboxylate and an α-hydroxy group by
extrusion of C-3 towards the β-face.  (See Scheme II).   By
combining this result with the above argument that a C-1 sub-
stituent would be sterically more stable in the β-configuration
(and this can be attained by enolisation of the C-2 carbonyl
regardless of the initial configuration) the result would be that
both the hydroxybenzyl group and the carboxylic acid group would
be on the same β side and hence in a favourable configuration in
order to lactonise.

8.3.5     The possibility of the initial aldol product in the form
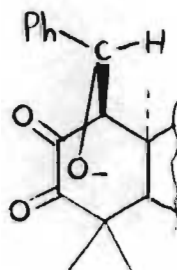


negotiating an internal benzilic acid rearrangement[79] cannot be
excluded and this sequence would then also firmly establish the
observed configuration.

Spectral evidence to be presented in the next section
confirmed the β-configuration assignment to the lactone ring
system.

8.3.6    Having arrived at a reasonable conclusion regarding the
lactone ring configuration there remained the problem of determining
the configuration at the benzylic carbon.

8.4.1    CONFIGURATION AT THE BENZYLIC CARBON

With the benzylic carbon on the β side of the diterpene
molecule two possible configurations at this carbon are formally
possible, that is, with the aromatic ring over the B/C rings or
away from the rest of the diterpene skeleton.    Although Dreiding
molecular models which included van der Waals radii for the hydrogen
atoms indicated that the structure having the phenyl group tucked
over the molecule was untenable on steric grounds, this structure
was not altogether abandoned initially as will be apparent presently.

8.4.2    The coupling constant of 9 Hz between the C-1 hydrogen and
the benzylic hydrogen indicated a dihedral angle of about $20^{\circ}$ or
$140^{\circ}$ using the unmodified Karplus equation.[84]    However, in the
present instance the structure consisted of two cis fused 5-membered
rings and one of the rings carried electronegative substituents
in the form of the lactone grouping as well as the aromatic ring;
the cumulative effect of these groups on the coupling constants
as well as on the angles of the lactone ring bonds invalidated the
use of the unmodified Karplus equation.[84]

8.4.3    Sodium borohydride reduction of (77) left the lactone/
ring A structure intact but reduced the 12-carbonyl giving a mixture

of three alcohols: the 12α- (79), 12β- (80) and a third as yet

un-identified alcohol which is tentatively formulated as the atisane

bridgehead alcohol (81).



79          80          81
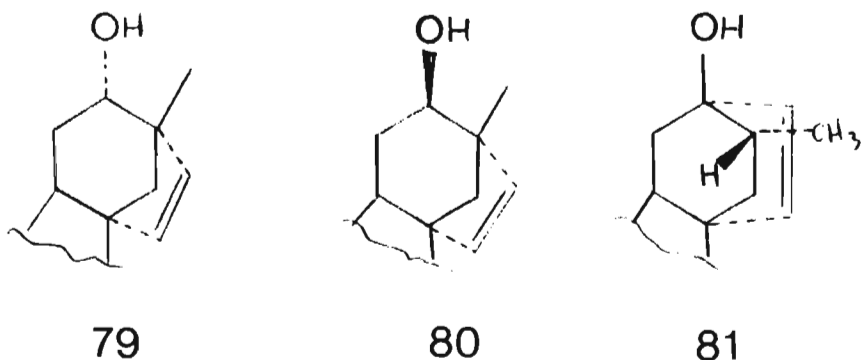
The formation of substantial quantities of the otherwise difficult

to prepare 12β(axial)-alcohol (80) indicated a marked steric hindrance

to reagent approach from the usually sterically unhindered β-face.

Using the bulkier LiAl(t-BuO)$_3$H in THF at low temperatures a 70%

yield of this 12β-axial isomer was obtained together with the other

2 isomers mentioned above. These results implied that the aromatic

ring exerted this protecting effect and this was more consistent

with an endo than an exo configuration for this ring, in spite of

the steric strain involved. If this was the case then the 9β-proton

should experience a large shielding effect by the aromatic ring and

if this proton could be differentiated in the n.m.r. spectrum a

configurational assignment could be possible.

8.4.4    The n.m.r. spectrum of the 3α-acetoxy-stachene-2,12-dione-

11β-bromide[85] (9)  had the 9β-proton as a clearly visible doublet

at δ 2.43 (J 6.5 Hz) therefore the analogous derivative was prepared

by hydrogenating (77) followed by bromination. The resulting

compound (230) proved to have a very interesting though misleading

n.m.r. spectrum. The 9β-proton resonance now appeared as a doublet

at δ 1.94 (J 12.5 Hz). Although the net shielding effect of δ 0.44

compared to (9) could be attributed to the aromatic ring influence,

it was in fact due to the reduced or weakened influence of the

adjacent bromine atom which was forced further towards the α side,

this being evident in the dramatic increase of the H-9 - H-11

coupling constant from 6.5 to 12.5 Hz, reflecting the more perfect

trans disposition of these two hydrogens (SECTION 3.8.3). Although

no change occurred in the resonance position of the benzilic proton

in passing from (38) to the bromo derivative (230), the H-1 resonance

suffered a marked deshielding by the electronegative bromine sub-

stituent, shifting from δ 2.68 in (38) to δ 3.50 in (230), a

downfield shift of δ 0.83. These two changes in the n.m.r. spectra

actually confirmed the assignment of the β-configuration to the

lactone ring.

The apparent "shielding" of the 9β-hydrogen (in fact a

change in torsion angles) demonstrated the ease with which erroneous

conclusions could be drawn from purely spectral evidence.

8.4.5    It was decided that in order to explain the steric shielding

of the 12-carbonyl in this series of compounds an x-ray structural

investigation should be attempted. Various bromine containing

derivatives were prepared with this end in view. The obvious

derivative having a p-bromo-substituent on the aromatic ring was

readily prepared using p-bromobenzaldehyde and reacting it with

the ketol (1) and also the 15-dihydroketol (2). However, these were

unsuitable for x-rays since the well-shaped crystals underwent phase changes or loss of solvent in a few hours and lost their crystallinity. The 11-bromo derivative (230) discussed above was grown in two crystalline modifications, an orthorhombic and a monoclinic form. The monoclinic form also underwent a phase change to the orthorhombic structure but the latter proved to give well-shaped, stable crystals and were used for the x-ray data collecting.

8.4.6    It has already been mentioned (in Section 3.8.4) that (9) readily lost its bromine to regenerate the unbrominated starting material (8) rather than undergoing dehydrobromination. The benzaldehyde-11-bromide adduct (230) provided an extreme example of this facile loss of bromine since dissolution in hot methanol for a few minutes brought about the same result and the orthorhombic crystals required for the x-ray analysis had to be obtained by carefully dissolving the crude material in cold methanol. This marked reactivity was probably caused by the increased steric compression between the bromine and the aromatic ring.

## 8.5. THE X-RAY CRYSTAL AND MOLECULAR STRUCTURE OF (230)

This confirmed the general structure. The torsion angle between H-1α and the benzylic hydrogen was 124°. Using the unmodified Karplus plot[84] this should have given $J_{1, benzylic}$ 3 Hz instead of the observed 7.5 Hz in the 11-bromo derivative (230), demonstrating the inapplicability of this equation to such a system. Thus the observed $J_{9,11}$ 9 Hz for (77) meant that in the latter compound the torsion angle was larger than 124°. The torsion angle between H-9 and H-11 in (230) was found to be 173° and the coupling constant of 12.5 Hz indicated that the steric repulsion between the aromatic ring and the bromine atom (distance between C-1 aromatic and Br = 3.46 Å) causes ring C to flex resulting in a more perfect trans diaxial relationship between H-9 and H-11. The observed coupling constant (12.5 Hz) was as expected, the usual range being 8-14 Hz.[84]

## 8.6. CONVERSION OF THE 12β-ALCOHOL TO THE ATISADIENE SYSTEM

The 12β-alcohol (80) prepared by reducing the 12-ketone of (77) with $LiAl(t-BuO)_3H$ was treated with $POCl_3$ in pyridine and converted to the atisa-13,16-diene system (82). However, this was contaminated with some of the atisa-13,15-diene (83),[9] indicating the small competing loss of the 14-hydrogen instead of a hydrogen from the 17-methyl group.

77

H₂/Pd

78

38

Br₂

230

80

POCl₃

82
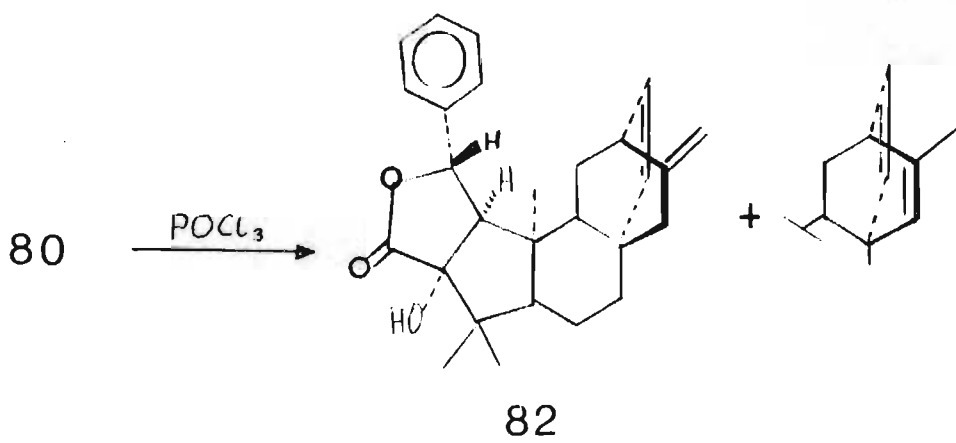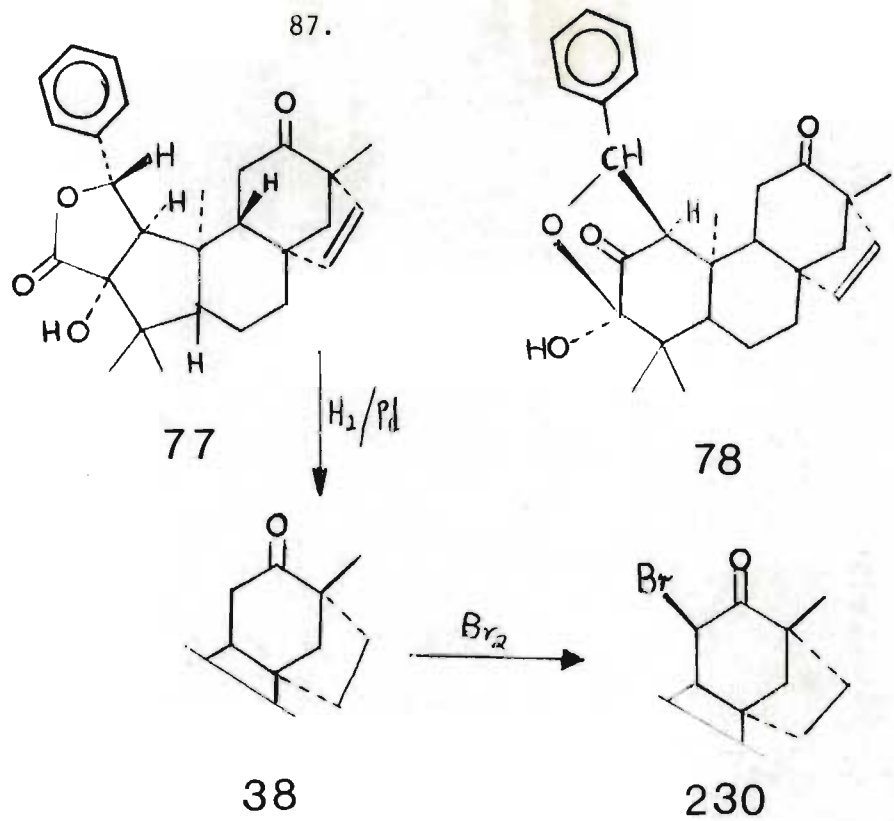
## C H A P T E R   9

9.1.   LITHIUM ALUMINIUM HYDRIDE REDUCTION OF THE LACTONE SYSTEM
       TO AN HEMIACETAL.

9.1.1.   A possible solution to the gross structure of the benzaldehyde
condensation product (77) was envisaged to proceed by LAH reduction
of the lactone system to the triol (84);   periodic acid oxidation
of this would have yielded the 1β-hydroxybenzyl-A-nor-2-ketone (85)
and base treatment should have produced the unsubstituted A-nor-2-
ketone (68) by a retro-aldol step.   The alternative elimination
of water to give (86) would have been very slow since the rate
determining step involving the base abstraction of the 1α-hydrogen
would have been subjected to a marked steric hindrance (See Scheme III).

9.1.2.   A trial run was performed with the 12-oxythioketal derivative
(87) to prevent complications arising from non-stereospecific reduction
of the 12-carbonyl.   The compound (87) was reduced in THF using excess
LAH and then worked up with ethyl acetate, ethanol, then water and
acid.   The crystalline material (88) unexpectedly proved to be non-
polar and could not possibly have been the expected triol!   Further-
more, the i.r. spectrum showed only moderate hydroxyl absorption
without the expected intense hydrogen bonded absorption bands.   No
carbonyl absorption was present.   The starting material (87) had a
molecular formula $C_{29}H_{36}O_4S$ whilst the product (88) was shown by
accurate mass determination to be $C_{31}H_{42}O_4S$ (510 m.u.).   Thus an
additional $C_2H_6$ had to be accounted for.   The n.m.r. spectrum was
interesting.   The aromatic and 15,16-double bond absorptions were
normal and the benzylic proton was still coupled to the C-1 proton

(J $8.0$ Hz) suggesting that the five-membered heterocyclic ring was intact.

A one proton singlet at $\delta$ 4.76 <u>not</u> exchanged with $D_2O$ was attributed to an acetal proton, whilst the exchangeable one proton singlet at $\delta$ 3.47 was assigned to the tertiary hydroxyl group also present in the original compound. Furthermore the oxythioketal grouping was still present, consisting of two sets of complex signals in the regions $\delta$ 2.5 - 3.0 and $\delta$ 3.3 - 4.2 for the $CH_2$-O- and $CH_2$-S- parts respectively. However, the integral trace indicated that two more protons were present in these regions. (With the advantage of hindsight these can be attributed to the methylene group of an ethyl ether. The methyl signal is evident at $\delta$ 1.15 partly overlapped by the tertiary methyl group resonances. Initially, however, the identity of the ethyl group was not established).

9.1.3   The large spread of the 12-oxythioketal signals obviously complicated the spectrum analysis so the 12-dioxyethane ketal of (77) was prepared (89) and reduced with excess LAH in THF. The workup employed sodium hydroxide and tartaric acid and the gummy crude product was deketalised in <u>methanol</u> with a small amount of p-toluenesulphonic acid. The resultant gummy material was chromatogrammed on silica get yielding firstly a small quantity of a crystalline 12-dioxyethane ketal (90). The n.m.r. spectrum again had the acetal proton singlet at $\delta$ 4.63 but the region 3.2 - 3.8 contained eight protons. Four were accounted for by the 12-ketal grouping, one was exchangeable for deuterium and was assigned to

the usual tertiary hydroxy group and the three proton singlet at
$\delta$ 3.40 could be attributed to a methoxy group.

The main eluted fraction consisted of the 12-deketalised
material, obtained as a gum and was converted to the crystalline
12-oxime (91) in the usual fashion. The n.m.r. spectrum was
similar to that of (90) with the acetal proton at $\delta$ 4.65, the
tertiary hydroxyl at 3.40 and the methoxyl at 3.37. The mass
spectrum of the 12-oxime indicated the molecular formula $C_{28}H_{37}O_4N$
such that an extra $CH_4$ had to be fitted in the structure.

9.1.4    The hydride reduction of the 12-dioxyethane derivative
(89) was repeated and worked up with aqueous base and tartaric acid.
This time the material was put directly onto a chromatographic
column without any acid treatment and the product obtained in
excellent yield (80%) was (92). The n.m.r. spectrum of this
compound was very informative. The 12-dioxyethane ketal grouping
was still present, as was the tertiary hydroxyl group at $\delta$ 3.35.
Furthermore, the benzylic proton and the C-1 proton signals were
still doublets (J = 7.5 Hz). However, this compound lacked the
"extra" two or three proton signals in the region $\delta$ 3 - 4 and
instead two one-proton doublets at $\delta$ 4.47 and 5.10 (J = 3.5 Hz) were
evident. These were mutually coupled as shown by spin decoupling
experiments, and furthermore the higher field proton doublet was
completely removed on exchange with $D_2O$ whilst at the same time
the other signal collapsed to a singlet. Therefore, the low field
signal was assigned to a hemiacetal proton and the labile signal
to that of the geminal hydroxy group, that is -O-CH(OH)-.

p-Bromobenzoylation (93) shifted the low field signal from $\delta$ 5.10 to 6.44 and shielded the tertiary hydroxyl which now resonated at $\delta$ 2.58. This shielding may have been due to the ester carbonyl or the new aromatic ring. The aromatic region from $\delta$ 7.2 to 8.1 contained the expected nine protons with extensive overlapping of the two sets of signals for the two aromatic rings. However, the typical pattern for the p-disubstituted aromatic ring was discernible. The structure (92) was assigned to the hemiacetal and (93) to the p-bromobenzoate derivative on the basis of the n.m.r. data although the configuration at the acetal carbon was only later established by analogy to (94) whose molecular structure was solved by x-ray diffraction. This configuration was important in determining the mechanism of reduction.

9.1.5    At this stage it was considered worthwhile to carry out an x-ray diffraction study in order to clarify the above structures, especially the two-proton-multiplet as in (88). The heavy atom technique for diffraction studies simplifies the calculations and correlations required to obtain a molecular structure, thus a suitable heavy atom (Br or I) derivative was sought. (93) proved unsuitable for this work as it always crystallised as twinned crystals. The 15,16-double bond readily adds on halogens or pseudohalogens, and the lactone-12-dioxythane ketal-15β-iodo-16α-nitrate was readily prepared. LAH reduction of this however, not only reduced the lactone system as described above, but completely regenerated the double bond! This sequence therefore had to be abandoned.

9.1.6    Previous experience with the stachene-12-oxime system

(Chapter 10) had shown that this readily esterified giving stable

esters, therefore a p-bromobenzoate of this oxime was envisaged as

being ideally situated for the structural investigation.   (92)

was deketalised in ethanol and converted in situ to the 12-oxime (95).

The n.m.r. spectrum in $CDCl_3$ showed the two proton multiplet after

exchange of the overlapping tertiary hydroxyl signal with $D_2O$.

Repetition of the spectrum in benzene further resolved the complex

multiplet into the expected sixteen line pattern.  The oxime (95)

was p-bromobenzoylated in pyridine but came out as an oil which

spontaneously crystallised in acetone-methanol after a few days.

Product (94) after recrystallisation from the same solvent mixture,

was obtained as excellent monoclinic crystals.  The i.r. spectrum

showed that the ester had indeed formed, but the n.m.r. spectrum

was unexpectedly complex.  The original aromatic ring appeared

as a sharp resonance at δ 7.48 but the characteristic p-disubstituted

aromatic resonance pattern for the p-bromobenzoate ring was not

evident at all!   Instead a one-proton triplet appeared at δ 6.47;

a two proton triplet at δ 7.00 and one further proton was found in

the region δ 7.26 - 7.43, (7.30) overlapped by the chloroform residue

signal and the other aromatic singlet signal.

The x-ray structure clearly explained this oddity.  The

C = N - O - C - ArBr bonds are all virtually in a plane including
               ‖
               O

the p-bromobenzoate ring with the oxime oxygen anti to C-13.  The

other aromatic ring attached to C-1 is orientated perpendicularly

to the bromo-substituted ring, thus shielding the ortho hydrogen

on the same side. The other ortho hydrogen is deshielded by
the ester carbonyl whilst the two meta protons seem to be
magnetically equivalent. This implies that the bromo ring does not rotate.

The complex two-proton multiplet could now be assigned
to the methylene hydrogens of an asymmetric, non-rotating ethyl
group. The methylene group is sterically hindered by the unsub-
stituted aromatic ring and cannot rotate freely about the
$CH_3CH_2$-O- bond. The two hydrogens are magnetically non-equivalent,
coupling with each other as well as with the methyl group and
giving rise to an $ABX_3$ spectrum.[86]

A trace of methanol at $\delta$ 3.30 and acetone at $\delta$ 2.13
were irremovable even by prolonged drying and actually appeared
in the crystal structure where they were probably important in
determining the packing.

9.1.7     Thus the LAH reduction produced the hemiacetal at the
lactone carbonyl carbon instead of the usual ring fission to a
diol. Workup with acid and methanol or ethanol then gave rise to
the methyl or ethyl acetals respectively. This is interesting
since these acetals formed in aqueous solvents where the expected
reaction would have been ring opening to the aldehyde and alcohols,
as evidenced by the ease of removal at the same time of the
12-dioxyethane blocking group. An analogous etherification in
aqueous methanol has been noted below in connection with (106)
formed by periodic acid oxidation.

9.1.8     The reduction to the expected triol (84) was eventually
accomplished using diglyme as a solvent and a higher temperature
of reaction.

9.1.9    The configuration at the acetal carbon was R with the acetal proton $\beta$- and the hydroxyl (or ether) $\alpha$-orientated, neighbouring the original tertiary hydroxyl group.

9.2.1    The postulated mechanism then involved initial reaction of an aluminium species (say $AlH_4^-$) with the tertiary hydroxyl group;  complexation of the lactone carbonyl by this same species forming a bridge between the two oxygens, and hydride transfer from the opposite $\beta$ side to the carbonyl carbon giving the hemiacetal.  The second step which would have resulted in ring-opening giving the triol (84) would have involved either attack by another Al species on the benzylic oxygen followed by a further hydride transfer to the acetal carbon, or with the two steps reversed, hydride displacing the benzylic oxygen at the acetal carbon.  The failure of this second step to occur in tetrahydrofuran may have been due to hindrance to approach of a heavily solvated and bulky aluminium hydride species from the $\beta$ side.

# SOLVENT-INDUCED SHIFTS OF THE AB PROTONS
## OF THE ABX$_3$ SYSTEM OF (95).
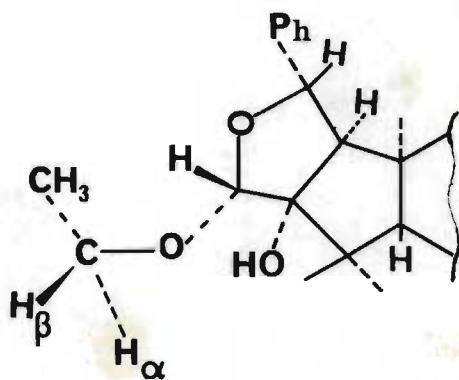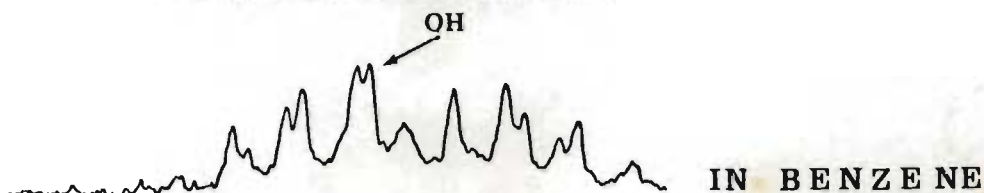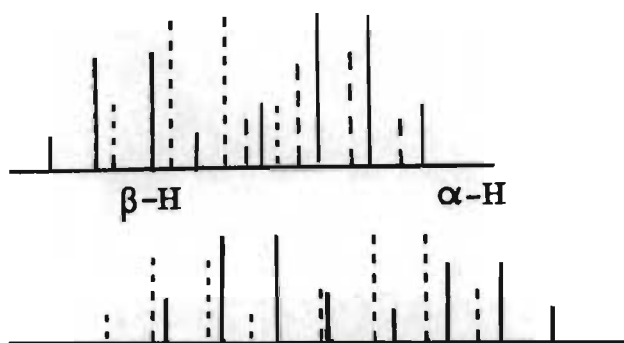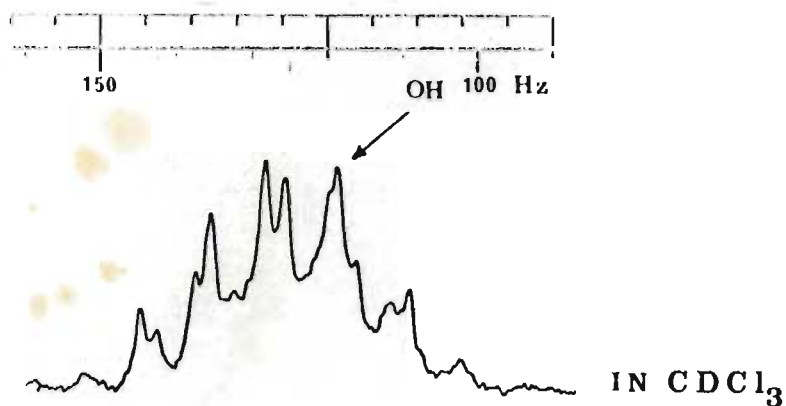


| $\delta$ : | CDCl$_3$ | BENZENE |
|---|---|---|
| $\beta$-H | 3.77 | 3.66 |
| $\alpha$-H | 3.44 | 3.17 |

$J_{AB}$ = 9.5 Hz     $J_{AX}$ = 7.5 Hz     $J_{BX}$ = 7.0 Hz

A = $\beta$-H          B = $\alpha$-H          X$_3$ = CH$_3$

(Chemical Shift ±0.01ppm;   J ±0.5 Hz)
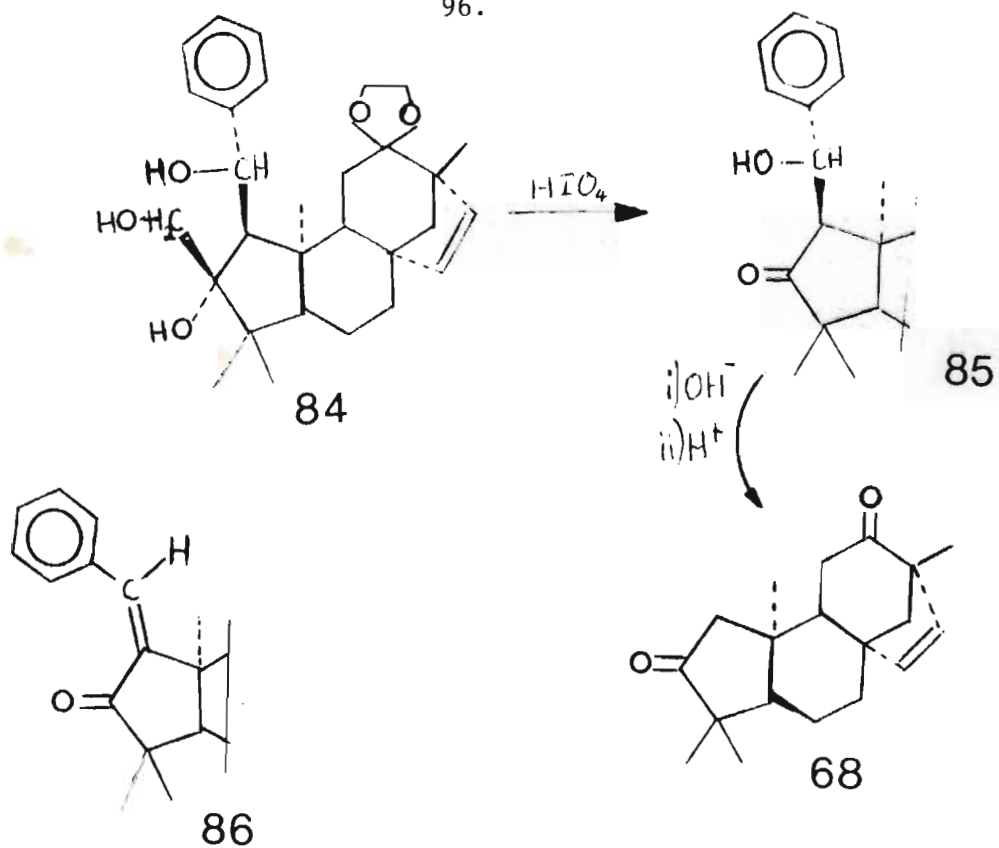
SCHEME III
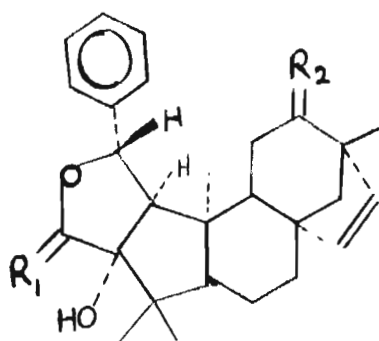
| | R₁ | R₂ |
|------|----|----|
| 87 | O | $OCH_2CH_2S$ |
| 88 | $\alpha\ C_2H_5O,\ \beta H$ | $OCH_2CH_2S$ |
| 89 | O | $OCH_2CH_2O$ |
| 90 | $\alpha\ CH_3O,\ \beta H$ | $OCH_2CH_2O$ |
| 91 | $\alpha\ CH_3O,\ \beta H$ | NOH |
| 92 | $\alpha\ OH,\ \beta H$ | $OCH_2CH_2O$ |
| 93 | $\alpha\ pBrC_6H_4COO, \beta H$ | $OCH_2CH_2O$ |
| 94 | $\alpha\ C_2H_5O,\ \beta H$ | $NOCOC_6H_4Br$ |
| 95 | $\alpha\ C_2H_5O,\ \beta H$ | NOH |

94
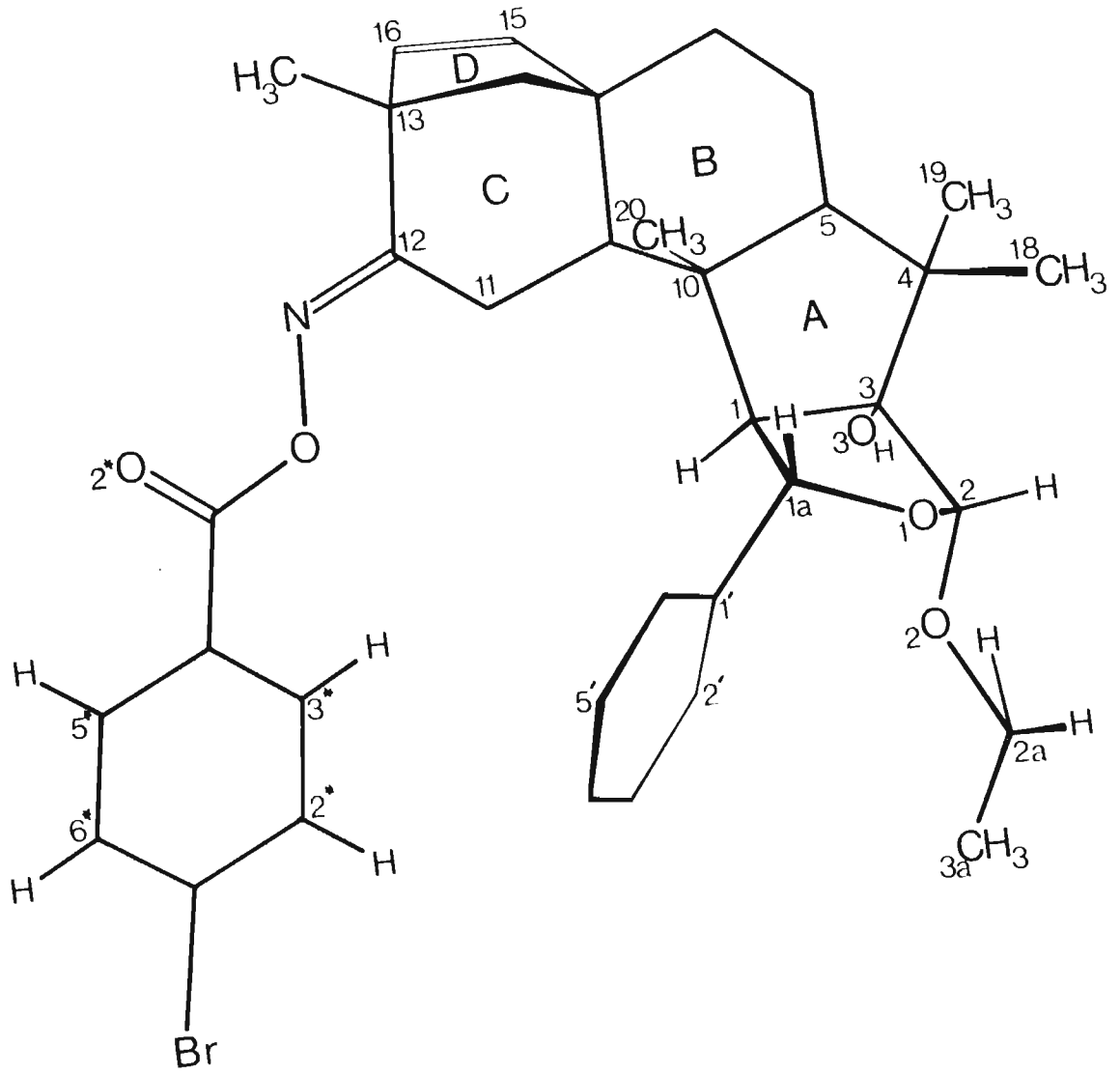
## 9.3 EXPERIMENTS WITH THE RING-OPENED TRIOL (84)

**9.3.1** The <u>vic</u>-glycol system of the triol (84) obtained by reducing (89) in diglyme with LAH, was smoothly cleaved with periodic acid to the nor-ketone (85).[75] Similarly, lead tetraacetate oxidation of the hemiacetal (92) gave the formate derivative of (85), (96).

**9.3.2** Retro aldol loss of the hydroxybenzyl substituent from (85) resulted from base or acid treatment as had been anticipated, to afford the previously prepared nor-diketone (68) and benzaldehyde.[75] No benzylidene derivative was noted.

**9.3.3** This in effect completed the chemical evidence for the structure of (77).

96
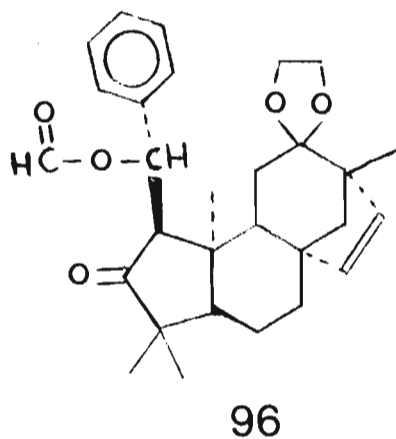
## 9.4    THE FORMALDEHYDE ADDUCTS

9.4.1    The initial conditions used to effect condensation of
the ketol (1)  with benzaldehyde were not successful when using
formaldehyde.  Dissolution of the ketol in ethanol or methanol,
adding formalin and then strong base (  30%), or dilute base
(10%) and heating, resulted in a complex reaction giving a host
of compounds.  The most polar and most insoluble component (97)
was isolated in (33%) yield.  The i.r. spectrum indicated a
polyhydroxy compound with no carbonyl groups.   The double bond
was, however, still present.  No molecular ion was visible but
the fragment $M-(31)_n$ (loss of $CH_2OH$) was mass measured for $C_{21}H_{33}O_4$.
A suspension of this compound in dry acetone when treated with
a drop of perchloric acid rapidly clarified and then masses of
needles appeared.   This compound (98) gave a molecular ion for
$C_{28}H_{44}O_5$, that is, the bis acetonide of $C_{22}H_{36}O_5$, therefore only
one formaldehyde was lost in the mass spectrum of the parent
compound (n=1).   The base-catalysed product is then most probably
a consequence of a Tollen's reaction involving condensation of
the C-1 and C-11 methylene groups with formaldehyde followed by
trans Cannizzarro reactions thus reducing the carbonyl groups.
Although no further work has been carried out to date the compound
is then most likely the 2ξ,3α,12α-trihydroxy-1β,11β-bis-hydroxy-
methyl-stach-15-ene.  No ring contraction has probably occurred
since the diosphenol may not even have formed prior to the
Cannizzarro reaction.

### 9.4.2    THE FORMALDEHYDE ANALOGUE

The formaldehyde analogue (99) was successfully prepared

using sodium bicarbonate and formalin with the ketol (1)

in aqueous methanol.  Over a period of days as the methanol

evaporated, silky needles of (99) were deposited.  10% sodium

hydroxide was successfully employed as a base if the whole process

was carried out at room temperature or below.  Reaction of formalin

in methanol with the diosphenol (18) and dilute $NaHCO_3$ gave (99)

in a few hours.

The i.r. spectrum had hydroxyl absorption at 3516, 3300 $cm^{-1}$

and carbonyl bands at 1770 $cm^{-1}$ ($\gamma$-lactone) and 1690 $cm^{-1}$ (12-carbonyl)

as well as the normal 15(16)-double bond absorption at 760 $cm^{-1}$.

The n.m.r. spectrum indicated one tertiary hydroxy group at $\delta$ 3.39

(exchangeable with $D_2O$), the normal AB double bond pattern and a

pair of triplets at $\delta$ 4.03 and $\delta$ 4.31, each integrating for one

hydrogen and each having a geminal coupling constant of 10 Hz and,

surprisingly, equally coupled to the vicinal proton, J = 10 Hz.

Thus the methylene group at C-1 was equally coupled to the C-1

hydrogen.   The C-1 proton signal was partially overlapped by one

of the C-11 proton signals, probably the 11 -proton signal.

### 9.4.3    Recently[87,88] a manool compound (100) with the exact ring

A structure as (99) was isolated from a conifer <u>Dacrydium colensoi</u>.

It is interesting to speculate that this $C_{21}$ diterpene (100) is

the result of hydroxymethylation at C-1 of the diosphenol system,

a type of Mannich reaction well-known in nature, with subsequent

benzilic acid rearrangement and lactonisation as for (99).

97



98



99



100

# CHAPTER 10

10.1.1   The α-ketol (1) readily gave the dioxime (4) as extremely

insoluble cubes.   However, when this material (4) was suspended in

acetic anhydride and warmed briefly it readily went into solution

and on cooling crystals of the diacetate (101) formed.



101

10.1.2   Similarly the α-ketol benzoate (11) gave a crystalline

12-mono-oxime (102) with ease.   Again this oxime formed the

corresponding acetate (103) when warmed with acetic anhydride.

Refluxing (103) or simply (102) in acetic anhydride converted this

oxime function to the seco-nitrile (104) by a second order

Beckmann rearrangement.



103                              104

10.1.3    This is a well-known reaction especially for oximes of

aldehydes which give the corresponding nitriles with no rearrangement.

Similarly, the second order Beckmann rearrangement of triterpenoid

3-ketoximes is largely stereospecific.[89]    The product (104) actually

consisted of a mixture of the endocyclic cyclopentadiene (major

component) and exocyclic cyclopentadiene (minor component) in

the ratio of 75:25 as estimated from the n.m.r. spectrum.  An attempt

at trapping the endocyclic isomer by a Diels-Alder reaction with

maleic anhydride failed even using AlCl$_3$ catalysis. Models indicated

this diene to be very hindered and in this way explained the lack

of reactivity.

10.1.4    The formation of the seco-nitrile as the sole reaction

product defined the stereochemistry of the oxime such that the

oxime hydroxyl was anti to the C-13 junction.  Otherwise the 11,12-

seco-nitrile should have formed from the syn-isomer.
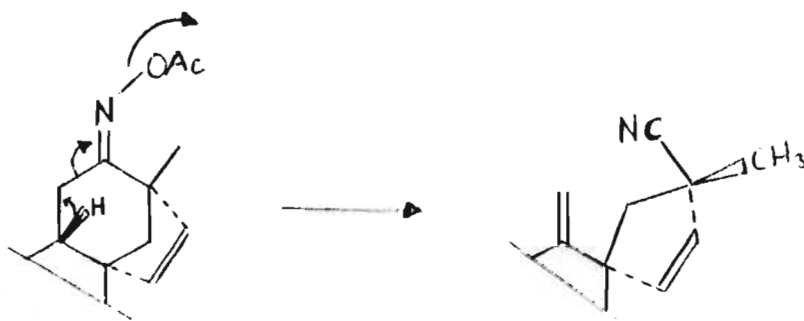


This tertiary nitrile should have readily lost HCN(-27)

in the mass spectrum but no ion corresponding to this type of

fragmentation was observed.  Otherwise the mass spectra of (102),

(103) and (104) were not informative since the ring A substituents

directed the fragmentation of the molecules. For a mass spectral study it would be advantageous to use the simple 12-ketone and its derivatives with no ring A substituents. Finally, the stereochemistry of the 12-oxime was established from the x-ray structural analysis of (94) (Section 9.1.6).

# C H A P T E R   1 1

## 11.1   MISCELLANEOUS RING A REACTIONS

### 11.1.1   PERIODIC ACID OXIDATION

The interesting oxidation of the ring A ketol function
of cucurbitacin D with periodic acid to the seco aldehydic
acid and subsequent cyclization with base to the A-nor ketone
had been reported.[90,91,92]
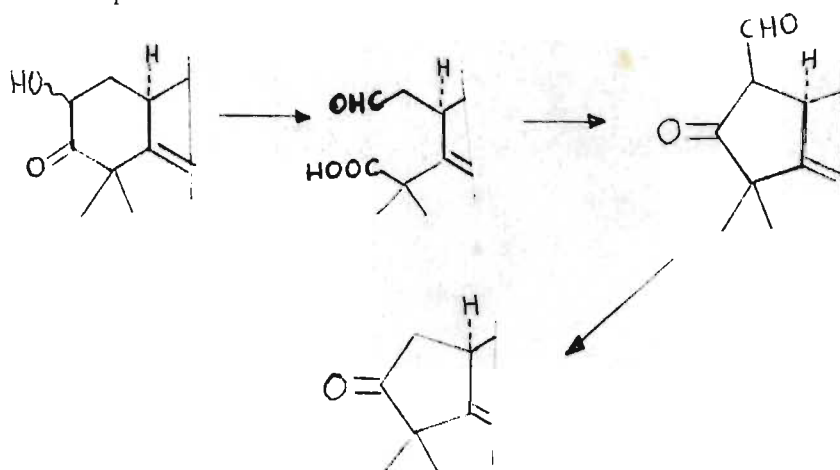
The diterpenoid ketol under investigation possessed the
isomeric 3-equatorial-2-ketone structure and could not cyclize
by the above mechanism.  It was decided to briefly study the
behaviour of the seco-aldehydic  acid (105) (which was never
isolated as such):

**105**
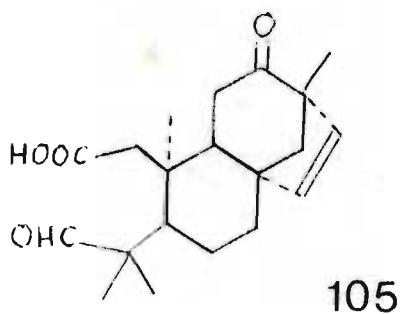
Oxidation of the ketol (1) in dioxan with aqueous periodic acid proceeded readily to polar compounds. After pouring this solution into an excess of water, the suspension was clarified with methanol and left to stand with ready access to air. Several days later the precipitated solid was recrystallised. This compound (106) turned out to be neutral, non-polar; it readily lost $C_3H_4O$ (methanol) in the mass spectrum, had the formula $C_{21}H_{30}O_4$ and possessed no hydroxyl absorption in the i.r. spectrum. The n.m.r. spectrum was instructive since apart from the expected double bond AB quartet and the four angular methyl group signals there was a three hydrogen singlet at $\delta$ 3.52 and a one hydrogen singlet at $\delta$ 4.60. The above results were consistent with the structure put forward, viz.:



106
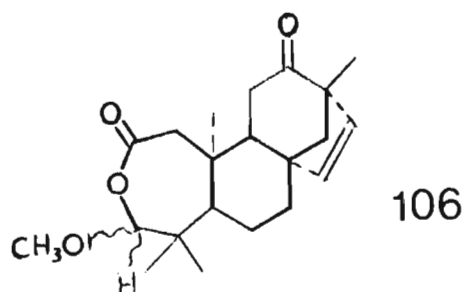
Subsequently, this compound was prepared in reasonable yield by carrying out the oxidation in aqueous methanol, from which the compound crystallized out. The configuration at the acetal carbon is undetermined. Furthermore the sequence of events is also unknown since two mechanisms could be proposed:-

a) <u>HEMIACETAL - LACTONISATION</u>
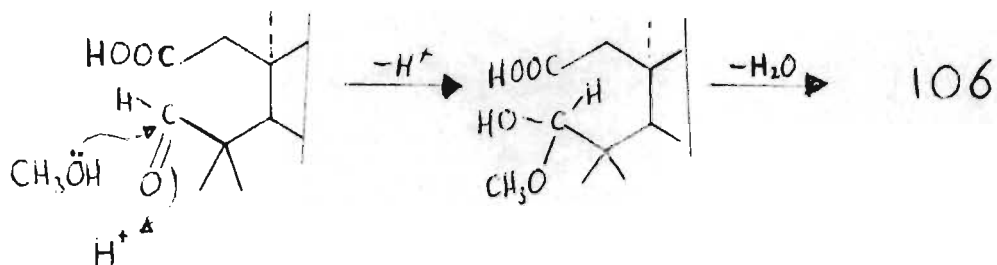


b) <u>LACTONISATION - ACETAL FORMATION</u>
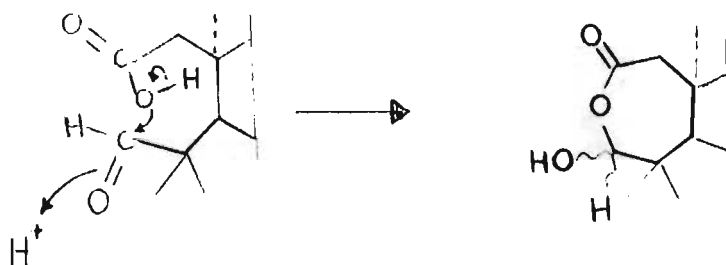


Pathway a) is favoured because of the increased yield when the reaction was carried out in MeOH.

<u>11.1.2</u>    <u>THE α-KETOL-3α-NITRATE (27)</u>

This compound was prepared in excellent yield by treating a cold acetic anhydride solution of the α-ketol (1) with concentrated nitric acid for a few minutes.  The chance occurrence of the equivalence of the chemical shift of three hydrogens (probably H-1α, H-1β and H-11β) at δ 2.27 in the n.m.r. spectrum originally was misleading as this singlet, although rather broad, was mistaken for an acetoxy group, and the compound regarded as the 3α-acetate-2,12-dione-X-nitrostach-15-ene.  Furthermore, the mass spectrum had an ion at 361 mass units as the highest mass peak.  Although this

in fact turned out to be the molecular ion for $C_{20}H_{27}NO_5$, it was

mistaken for $M^+$-ketene (loss of 42 from $C_{22}H_{29}NO_6$) in conjunction

with the n.m.r. data. However, the broadness of the n.m.r. "acetate"

signal, the unusual further loss of $HNO_2$ (typical of a nitrate ester)

instead of the expected loss of $NO_2$ (typical of aliphatic nitro

compounds), the positive colour reaction with the diphenylamine-

sulphuric acid reagent and finally the elemental analysis, were

combined to arrive at the correct structure. Also treating the

compound (27) with acetic anhydride and sulphuric acid rearranged

the C/D rings (Section 12.1. ) but left the nitrate ester intact

(107). The n.m.r. spectrum of (107) now did not have the "acetate"

absorption at δ 2.21. Catalytic hydrogenation of (107) gave the

α-ketol (108).

Reaction of the ketol nitrate (27) with sodium acetate in

DMSO gave the expected diosphenol[93] (18) thus demonstrating a further

method of preparing this compound. Nitrate esters are supposedly

alkali stable groups, for example withstanding Huang-Minlon reaction

conditions,[94,95] but obviously the adjacent carbonyl in the present

instance destroyed this stability by rendering the C-3 proton more

acidic and hence easily abstracted by base:-
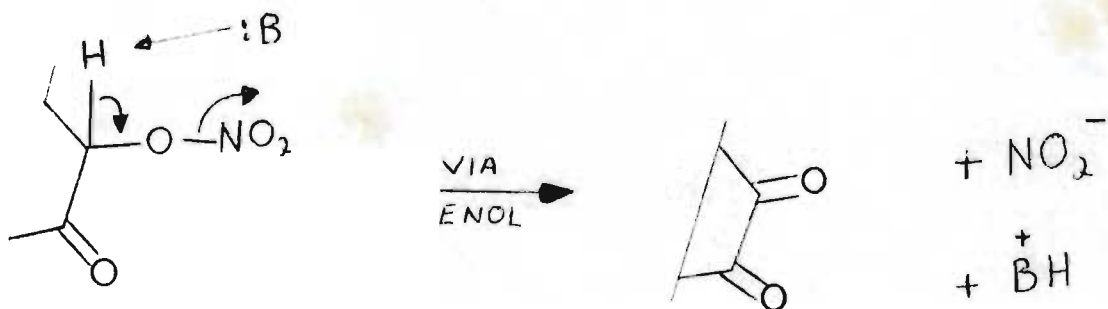
This reaction also took place in methanol and in fact detracted from the yield when initially base was used to remove excess acid from the crude product. Subsequently the acid was found to have no deleterious effect and was not neutralized during crystallisations.



27



107                    108
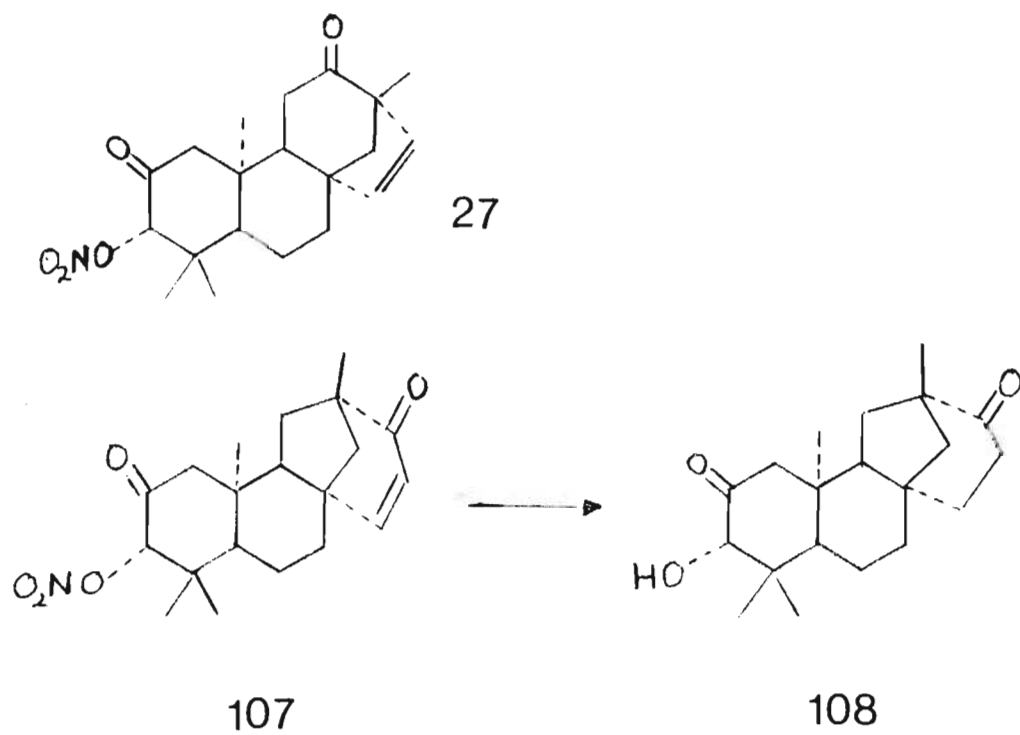
## C H A P T E R   12

<u>12.1</u>   THE ACID-CATALYSED REARRANGEMENT OF THE $\beta,\gamma$-UNSATURATED KETONE SYSTEM.

Conversion of the 12-carbonyl into its enol acetate appeared to be a promising route to an 11-oxygenated system especially in view of the failure of the $\alpha$-bromoketone system to undergo dehydrobromination (Section 3.8.4.).

<u>12.1.1</u>   With this in mind several methods were tried all involving acid-catalysed enolisation.  However, mild reagents such as sodium acetate-acetic anhydride, p-toluenesulphonic acid-acetic anhydride or isopropenylacetate-acid failed to give the required product.

<u>12.1.2</u>   The system $CCl_4$-acetic anhydride-perchloric acid successfully used in the steroid series[96] was tried next but the black tarry material produced was not very inspiring for preparative purposes.  $BF_3$ was known to complex carbonyl oxygen and thus increase the rate of enolisation[97,98] so this reagent was tried on a solution of the $\alpha$-ketol (1) in acetic anhydride.  Workup gave crystalline material in good yield.  Use of sulphuric acid or perchloric acid in acetic anhydride gave the same product and in fact sulphuric acid was found to give the cleanest product, and its use was preferred.  Phosphoric acid and p-tosic acid were ineffective whilst acetic anhydride was absolutely essential in order to provide the "superacid" medium. The sole product so obtained (109) had an i.r. spectrum consistent with an $\alpha,\beta$-unsaturated carbonyl system ($\nu_{max}$ 1665 cm$^{-1}$) as well as an intact ring A ketol acetate function ($\nu_{max}$ 1742 and 1716 cm$^{-1}$). However, the molecular ion at 358 m/u ($C_{22}H_{30}O_4$) indicated that no enol ester was present.

The n.m.r. spectrum was both informative and puzzling.
The presence of only one acetoxy group and the usual H-3 proton
resonance confirmed the intact ketol-3α-acetate ring A structure.
At the same time the α,β-unsaturated ketone structure was evident
since the C-15 proton[99] had shifted downfield by 0.9 ppm when
compared to the parent acetate (3).   However, the doublet signal
for H-15 was further split by 2 Hz through additional coupling.
The 20-methyl group which in stachenes is already substantially
shielded by the 15-double bond, was now even more shielded.

12.1.3   Skeletal rearrangements have been previously reported
for β,γ-unsaturated carbonyl systems involving both strained four-
membered rings[100] or six-membered rings[101,102] as well as for
related systems[103,104] and the predominant products are usually
the fully conjugated systems.   A mechanism following a similar
pattern was envisaged in which the initial protonation or complexation
of the 12-ketone oxygen by the "super-acid" medium[105] was followed
by migration of the etheno bridge and the 11(12)-bonding electrons
to give the final product as shown.   The p-orbital at C-12 and the
C-16:C-13 bond have the requisite coplanarity necessary for optimum
overlap.
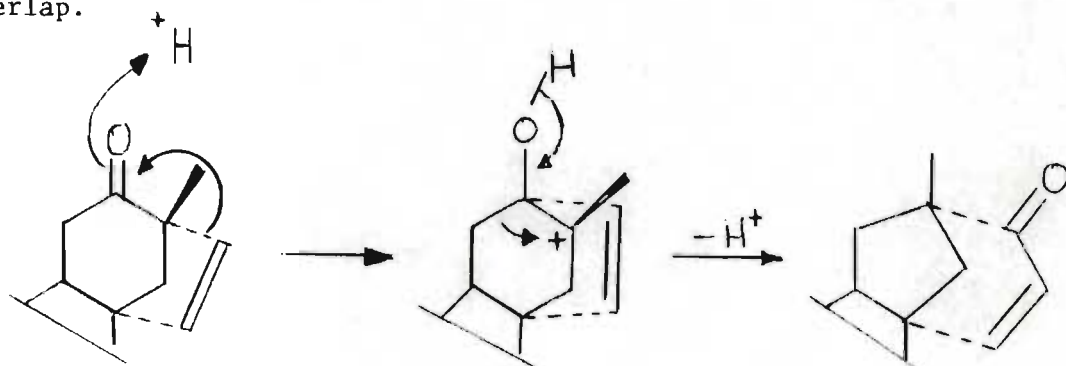
However, the long range coupling between the β-olefinic

proton and some other saturated system seemed to contradict the

postulated structure for this compound.  Long range coupling through

four sigma bonds (W-rule) between H-15 and H14β was thought

improbable because of the non-planarity of the system H14β, C-14,

C-8, C-15, H-15, planarity being a prerequisite for W-coupling in

most systems studied.  The possible alternative involved through

space coupling between H-15 and H-6α which appeared very close on

models.  However, this inter-spatial coupling has no precedent

except for certain fluorine compounds[106], for which no theoretical

explanation has yet been given.   Long range coupling has been

observed in a related structure (110) of the bicyclo [3.3.1] octenone

system[186] and this may be due to the same cause as observed in

(109).

12.1.4   Catalytic reduction of the double bond proceeded very

readily to furnish the saturated six-membered ring ketone compound

(111), $(\nu_{max}$ 1750, 1725, 1705 cm$^{-1}$).  Dissolution of this compound

in acetic anhydride and addition of concentrated sulphuric acid

gave back the stachane compound (8), thus establishing a return

pathway  for the rearrangement.
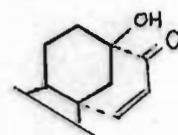
12.1.5   An x-ray structural investigation of the corresponding

p-Br-benzoate (112) was then undertaken to establish the correct

structure rapidly, and hopefully to solve the long range coupling

problem.  The rearrangement was shown to have occurred as indicated

and the closeness of the H-15 and H-6α atoms indicated this to be

a possible cause for the splitting observed whilst the W coupling

was not favoured since the atoms appreciably deviated from the plane.

110

12.1.6    An INDOR experiment is to be carried out to investigate

this through-space long range coupling.[106]    A direct method of

showing whether or not H-6α is responsible would be to functionalise

C-6.  Chemically this would not be easy but microbiological hydroxylation

of stachenes with the fungus Calonectria decora[107] has been reported

to give 50% yield of the 6β-alcohol.  Such a derivative would be

ideal for the n.m.r. observation.   Use of the Eu shift reagents

with (221) failed to give positive results since the responsible

proton signal always appeared under the tertiary methyl signals in

the shifted spectra.

12.1.7    The rearrangement was successful for a number of derivatives

and seemed independent of ring A substituents provided they survived

the reaction conditions.  Thus the α-ketol tosylate (46) gave the

rearranged compound (224), and the benzaldehyde adduct (77) gave

(225) in which the tertiary hydroxy group had acetylated.

12.1.8    The rearranged compound (109) is similar in skeletal structure

to the D-homo-C-nor diene type (14) except for the different positions

of the 17-methyl group.  A Wittig reaction on (109) could convert it

to (116) whilst oxidation of the diene system of (14) would furnish

the 17-nor-(109) type (114).

12.1.9    Since the system  is available from the POCl$_3$
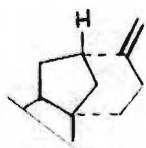
elimination of the 15,16-dihydro-12α-ol system, this could easily be

converted to the ketone (113).

113

115

114

$$\underset{\overline{Br}}{\overset{+}{Ph_3P}=CH_2}$$

116

R

3    Ac

233    p-BrBz

R

109    Ac

112    p-BrBz

H₂/Pd

R
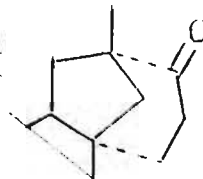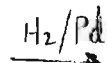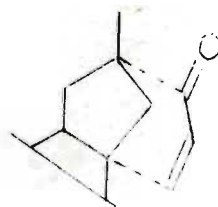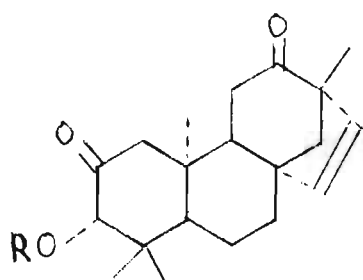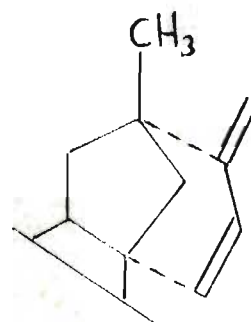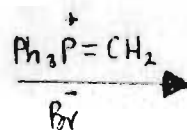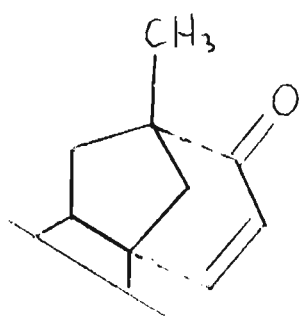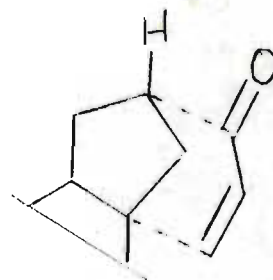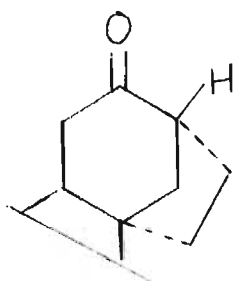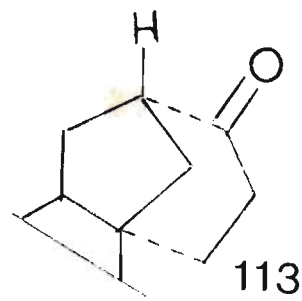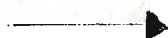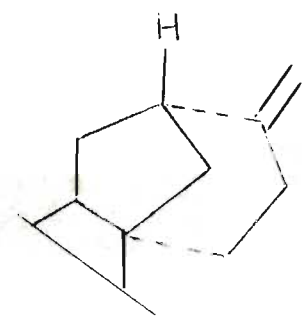
111    Ac

The ketone could then be converted into the $\alpha,\beta$-unsaturated
derivative (114) similar to (109) but in this instance lacking the
bridgehead 17-methyl group. Also the reverse acid-catalyzed
rearrangement as for (111) would then give the useful 17-nor-stachan-
12-one system (115).

## 12.2    OXIDATION OF THE REARRANGEMENT PRODUCT BY ACID-PERMANGANATE

### 12.2.1    Oxidation of the $\alpha,\beta$-unsaturated system in acid medium
with $KMnO_4$ resulted in the isolation of a very small quantity of a
lactonic acid with the ring A ketol still intact. Accurate mass
measurements gave the formula as $C_{22}H_{30}O_7$ which fitted the structure
(117)



117
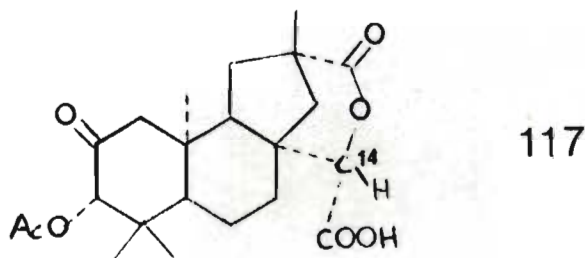
presumably formed from the known attack by $MnO_4^-$ in acid solution
to give ketols from olefins and subsequent cleavage and lactonisation,
thus tentatively defining the stereochemistry at C-14.



117
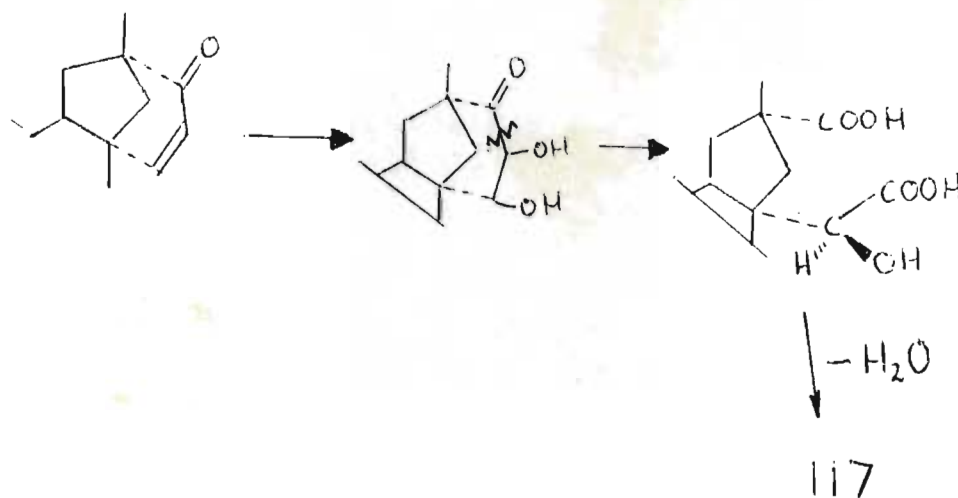
Unfortunately, this reaction could not be repeated and the product
has not been further characterised except for the i.r. and a partial
n.m.r. spectrum run in undeuterated pyridine. A comparison of the
methyl resonances (Table III) shows that the pyridine does not
cause any significant shifts except for the lowest tertiary methyl
signal where the shift may be due to the deshielding influence of
the neighbouring carbonyl.

## TABLE III

COMPARISON OF Me GROUP N.M.R. VALUES ILLUSTRATING THE EFFECTS OF
NEIGHBOURING OXYGEN SUBSTITUENTS.

| | | | | | | |
|------|---------|-------|-------|-------|-------|-------------|
| (3) | 2.13 | 1.10 | 1.10 | 0.85 | 0.75 | } in $CDCl_3$ |
| (109)| 2.16 | 1.20 | 1.13 | 0.88 | 0.62 | } |
| (117)| 2.18 | 1.39 | 1.09 | 0.90 | 0.82* | in PYRIDINE |
| | ACETOXY | 17-Me | 18-Me | 19-Me | 20-Me | |

*Loss of shielding by C=C Oxidation.

12.2.2   The loss of the lactonic acid moiety less one hydrogen,
i.e. $C_3HO_4$ (101 m.u.) is indicated by the ion at m/e 263 (56%)
which probably arises subsequently to the favoured loss of m/e
42 as ketene from the ring A acetate, a permanent feature of the
α-ketol acetate function (i.e. $M^+$ - 42 - 101).

12.3     THE ACID-CATALYSED "REARRANGEMENT" OF THE 15,16-DIHYDRO-
         12-ONE SYSTEM

12.3.1   The interesting and useful rearrangement of the β,γ-
unsaturated system of (3) prompted testing the 15,16-dihydro
derivative (8) under the same conditions with the hope of obtaining
the enol acetate as in this case the absence of the double bond
could possibly prevent the rearrangement. A compound (118) was

obtained which was insoluble in the usual solvents, sparingly soluble in chloroform and soluble in THF. Although no further work has been carried out up to the present, the available data will be discussed here. The mass spectrum gave a weak ion at m/e 482 (probably $C_{27}H_{30}O_8$). The loss of two acetate units (as 2 x ketene) confirmed the presence of two acetates, one of which should be the 3α-acetate. The n.m.r. spectrum in $d_6$-DMSO had signals for the four methyl groups at δ 0.88, 1.12, 1.12 and 1.56. The low field value for this group at δ 1.56 indicated that it was either a vinyl methyl group (δ 1.6) or attached to a carbon bearing oxygen ($CH_3$-C-O-, δ 1.4) such as an alkoxy group, but not an acetyl group ($CH_3C=O$, δ 2.2). The acetyl groups, probably the acetoxy groups, were found at δ 2.10 and 2.16, the latter corresponding to the usual position for the 3-acetate.

A large peak at δ 3.56 integrated for eleven hydrogens, possibly three methyl groups at least. However, this peak may have been due to the DMSO solvent and to check this the spectrum should be rerun in a different solvent such as pyridine. The acetoxymethine proton at C-3 was present at δ 4.92 as well as a doublet at δ 4.25 (J 3 Hz). Comparing this to the authentic C-ring enol acetate (120) the doublet could be assigned to the H-11 vinyl proton except for the large apparent upfield shift since in (120) this vinyl proton resonance appeared at δ 4.95 also with a coupling constant of 3 Hz.

Further work on this problem is contemplated for the future.

## 12.4    FORMATION AND REACTION OF THE ENOLATE OF THE 12-KETONE

12.4.1    Previously it was mentioned that the usual methods for making enol acetates, those using acidic reagents, failed to convert the 12-ketone to the enol acetate but gave instead (109) or starting material (3).

12.4.2  Following a suggestion by Professor Barton, the enolate system was prepared under basic conditions using the extremely powerful and easily prepared sodium bis-trimethylsilylamide (119).[108,109,110] Reaction of this base with (71) and subsequently quenching the reaction with acetic anhydride[109] gave the enol acetate (120), which showed a doublet at $\delta$ 4.95, in the n.m.r. spectrum, for the 11-vinyl proton with a coupling constant of 3 Hz.  Future work on this system using the readily prepared 2,3-diol-12-one (121) and protecting the 15-double bond as the dibromide (Section 14.2.4) should give the corresponding enol acetate which after epoxidation and rearrangement[111,112,113,114] could be converted to the 11,12 -ketol acetates (Scheme IV) since the 11-bromo-12-ketones could not be used to accomplish this by simple acetolysis (Section 3.8.4).

12.4.3  Reaction of the enolate of (71) with methyl iodide gave the 11$\beta$-methyl derivative (122), with the new methyl group at $\delta$ 1.30 as a doublet (J 8 Hz).  The 11$\alpha$-hydrogen appeared as a multiplet centred at $\delta$ 2.37.  Similar treatment of the diosphenol (18) gave the 11$\beta$-methyl-enol methyl ether (123).

12.4.4  The methylation and presumably alkylation in general of C-11 could be done on (121) as well.  The $\alpha$-ketol function in ring A can be regenerated smoothly by silver carbonate on celite.  Then the solvolytic behaviour of the 2,3-$\alpha$-ketol sulphonate esters can be re-investigated using various substituents at C-11, substituents which have different steric demands such as benzyl and ethyl groups. Similarly the tendency towards rearrangement of the 12-carbonyl group can be studied in relation to these substituents, as well as the solvolytic behaviour of the 12$\alpha$- and 12$\beta$-alcohols.  Alkylations

of this type will be useful on the (111) type structure with or without the bridgehead methyl group (124) since acid-catalysed rearrangement would regenerate the 16-methyl (or alkyl)- 12-oxo-stachanes (125), superficially similar to the kauranes which have the 17-methyl group at C-16.

Na⁺ N̄[Si(CH₃)₃]₂

**119**



**120**



SCHEME IV

1) HEAT
2) Zn



**122**

**123**

**124**

**125**

R = H or ALKYL
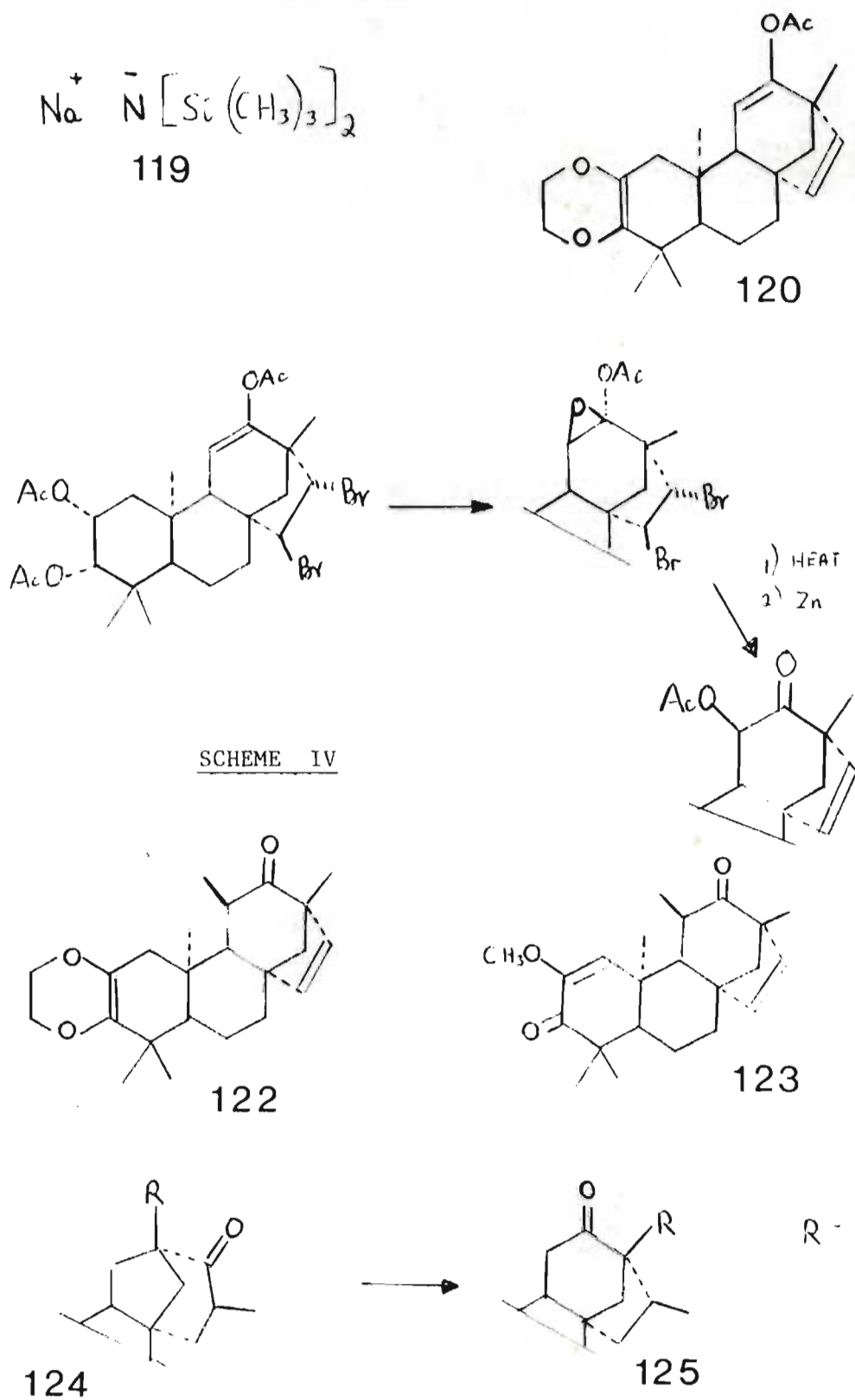
## 12.5   THE PCl$_5$ - INDUCED REARRANGEMENT

12.5.1.   A second superficially similar rearrangement of the
12-carbonyl group occurred during reaction$\overset{\text{of (3)}}{\wedge}$with phosphorus penta-
chloride in benzene.   The isolated crystalline product was never

obtained pure since it was always contaminated by side products

of the same chromatographic polarity and resisted all attempts at

purification.   Nevertheless the rearrangement was interesting

and useful enough to be pursued since the major product was of

the atisane type (126) consisting of the non-conjugated diene

system with a bridgehead chlorine on the bicyclo (2.2.2.) octadiene

structure.   The structure of (126) was deduced as follows.


12.5.2.   Apart from the original double bond quartet there

appeared a broad one-proton signal at $\delta 5.70$ ($W_{\frac{1}{2}}5H_z$).   Only three

tertiary methyl group signals were now present but a three-proton

doublet at $\delta 1.85$ ($J2H_z$) was consistent with a vinyl methyl group

undergoing allylic coupling with the broad olefinic singlet at $\delta$

5.70.   Thus irradiation of the olefinic proton collapsed the

methyl signal into a clean, sharp singlet, whilst similar irra-

diation of the methyl signal caused the broad olefinic proton

singlet to collapse into a sharp singlet.   Since the chemical

shifts of these two mutually coupled signals appeared in identical

regions of the n.m.r. spectrum as for bicyclo (2.2.2.) octenes of

similar structure [115, 116] and the coupling constant also compared

favourably, the part structure shown below was proposed:
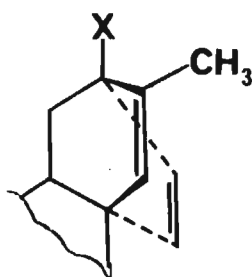
Furthermore the absence of any further splitting of the original
double bond AB quartet indicated that the bridgehead position
was substituted with a group other than hydrogen.  Accurate mass
determination of the molecular ion gave the formula $C_{22}H_{29}O_3Cl$
such that the bridgehead position had to contain halogen since
no protons geminal to halogen were present in the n.m.r. spectrum.

12.5.3.  The immense utility of mass spectroscopy was further
demonstrated during this investigation since it showed that the
impurity or impurities had the formula $C_{22}H_{30}O_3Cl_2$ and could
then be one or more of the examples shown (127, 128, 129, 130).
This information would have been extremely difficult to obtain
otherwise, and allows possible purification schemes to be outlined.
Thus the gem-dichloro derivatives should undergo base hydrolysis
to regenerate the parent ketone or the rearranged ketone as the
case may be and this would then be separable from the diene.

12.5.4. This reaction is thus an alternative route to the atisa-
diene system since the bridgehead halogen should be replaceable
by hydrogen (say with sodium in alcohol) provided the impurities
can be removed at some convenient stage. The overall yields of
atisadienes could then be made more attractive than the indirect
route via the epimeric 12-alcohols and elimination of the 12-
hydroxy group (SECTION 8.6.)
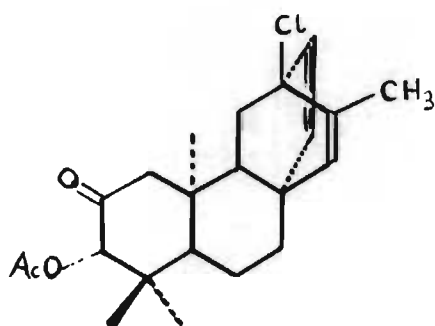


126
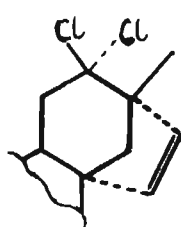


127
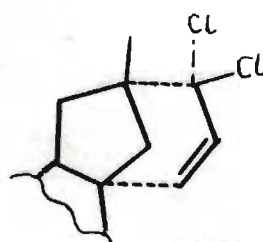


128
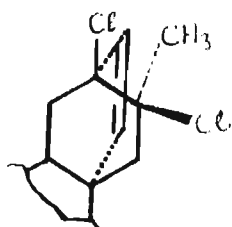


129
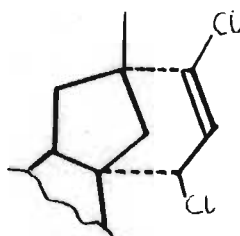


130

C H A P T E R   1 3

13.1    THE 12-TOSYLHYDRAZONE REARRANGEMENT INDUCED BY HYDRIDE

13.1.1.  In 1963 Caglioti and Magi [117] introduced an alternative

sequence to the Wolff-Kishner reduction when they reported the

reductive elimination of tosylhydrazones of aldehydes and ketones

using $LiAlH_4$.  This method was improved in the following year by

Caglioti and Grasselli [118], using $NaBH_4$ is dioxan substituted

for the $LiAlH_4$ making this reaction less demanding since there

was no need for dry solvents.  The yields with steroidal ketones

were especially attractive and the authors remarked on the

apparent absence of olefinic products derived from side reactions.


13.1.2.  Bamford and Stevens in 1952 [15] had used the reaction of

tosylhydrazones with bases at high temperature to produce olefins

in very good yields.


13.1.3.  Two groups [19, 119] reported the reaction of steroidal

12-tosylhydrazones under the Bamford-Stevens conditions, giving

the rearranged C-nor-D-homo ring systems in which the C-13:C-14

bond had migrated, a result similar to the solvolysis of the

equatorial sulphonate esters (SECTION 3.3).
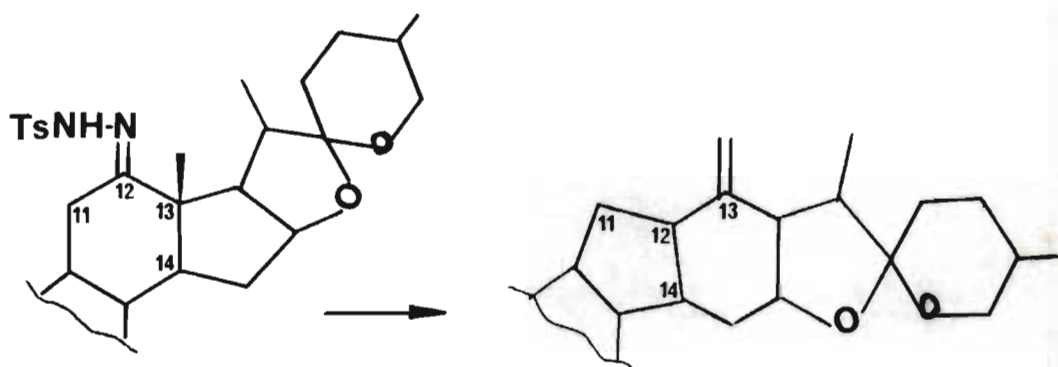
13.2.1. During the structure determination of (1) the configuration of the 3-hydroxy group had to be rigorously proved. Since 2- and 3-hydroxylated stachenes were known [2, 12] removal of the 12-carbonyl by a mild technique could have furnished the 2,3-dihydroxy stachene which could then have been compared to previously reported material.

13.2.2. The $\alpha$-ketol (1) readily gave a crystalline 12-tosylhydrazone (28) in good yield and this was reduced in ethanol-dioxan according to the published method. The crystalline diol so obtained (131, $C_{20}H_{32}O_2$) had a m.p. 190-192°. $2\alpha$, $3\alpha$-dihydroxy stachene (132) melted at 181-182° [2, 12] whilst the $2\beta$, $3\alpha$-isomer (133) [12] had m.p. 146-148° [120].

Since the diol furnished a crystalline acetonide practically instantaneously the diaxial $2\alpha$, $3\beta$-dihydroxy configuration could be discounted even though a report of acetonide formation by a trans-diaxial diol in the lupane series has been published [21], since such a rapid reaction rate would not be consistent with the distortion required to form the cyclic derivative.

The n.m.r. pattern of the diol function and its diacetate (231) were practically identical to those published by Hanson [12] such that the suspected $2\alpha$, $3\alpha$-configuration for ring A was strongly suggested. However a skeletal rearrangement had clearly taken place since the n.m.r. spectrum showed that the double bond was no longer a simple AB quartet. Although the olefinic protons were part of an AB system one of the olefinic protons was further coupled to another proton in the region 2.2 $\delta$ (J=2H$_z$). Furthermore only three tertiary methyl groups were now present, the fourth now appeared as a doublet (J=6.5H$_z$) as the highest field signal. Comparison of the methyl resonances with the literature values for atisenes indicated that this doublet was the C-17 methyl group.

13.2.3. Using a mechanism similar to that postulated for the 12-oxo steroids, [19, 119] mentioned above the product should have been (134)

**134**
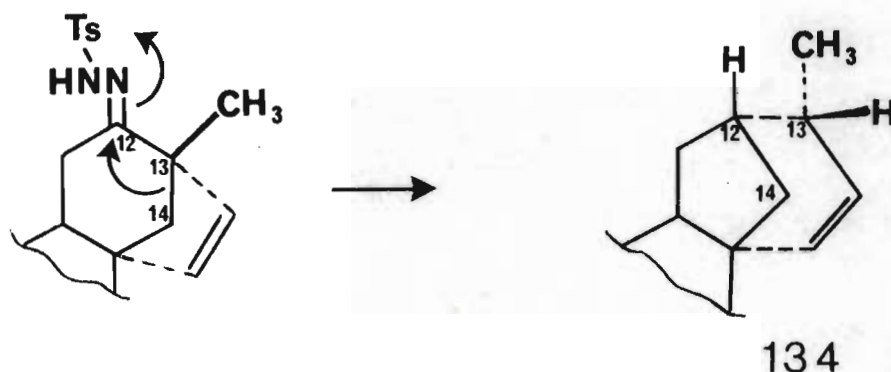
where the C-13:C-14 bond migrated, i.e. a 14(13 ⟶ 12) <u>abeo</u>-rearrangement.

The above structure (134) was not consistent with the n.m.r. data because irradiation of the allylic proton at 2.2 $\delta$ caused a collapse of the one olefinic proton but did not affect the methyl group doublet. Similar irradiation of the methyl group doublet did not affect the allylic signal. This structure (134) however required the allylic proton to be geminal (and hence coupled) to the methyl group. Furthermore the high field value for the 17-methyl resonance could not be explained by such a structure. The double bond was extremely resistant [124] to attack by bromine, permanganate [121] and mercuration [122]. Hydrogenation proceeded quite readily however at normal atmospheric pressure with Pd/C.

13.2.4. A rearrangement similar to that described previously for the acid-catalyzed isomerisation of the 12-carbonyl was found the most promising in that it fitted all required data. Once again the etheno bridge migrated from C-13 to C-12 but now instead of the C-11:C-12 bond migrating to C-13 (as in 109), the "carbonium ion" at C-13 was intercepted by hydride giving the final product.
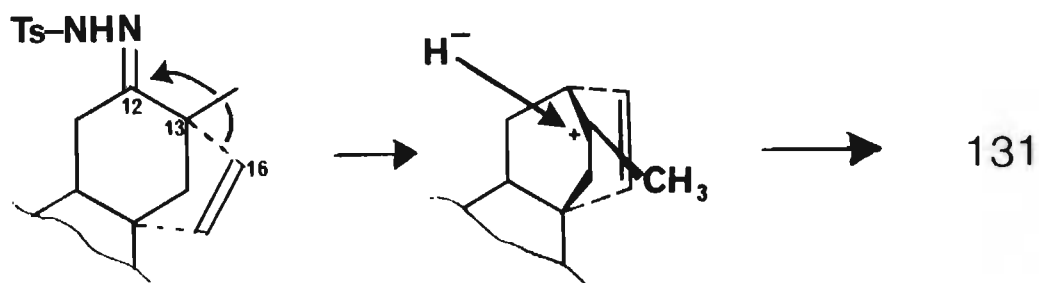
This then was the product of a 16(13 ⟶ 12) abeo-rearrangement.

The structure accounted for the observed n.m.r. data, the high

field value for the 17-CH$_3$ was due to the shielding effect of the

double bond and thus simultaneously defined the stereochemistry at

the secondary carbon.  The marked unreactivity could now be

explained since the olefinic bond was shielded by the 17- and 20-

methyl groups on either side.

The mass spectrum was also consistent with this structure since the

most abundant ion in all the derivatives as well as in the diol

resulted from the retro-Diels-Alder loss of the saturated 12- propano

bridge,  (M-C$_3$H$_6$). [123]

13.2.5.  An X-ray structural determination [53] on the derivative

(135) confirmed the rearrangement and stereochemistry as ent-16 S

(ATISANE NUMBERING).

13.2.6.  The skeleton produced consisted of a novel type of atisane

diterpene since the double bond occurred on the  ethano bridge

lacking the methyl group. [115]
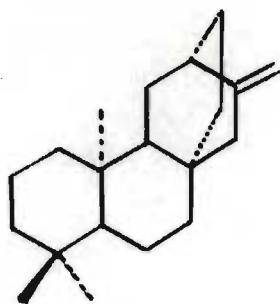
ATISIRENE
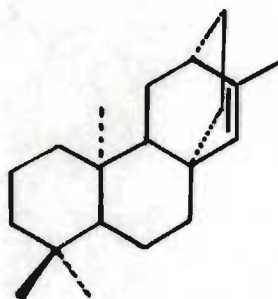
ISO-ATISIRENE
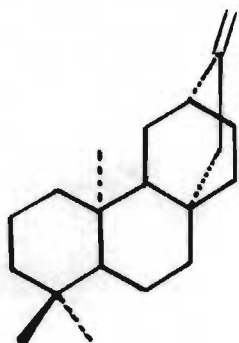
NEO-ATISIRENE
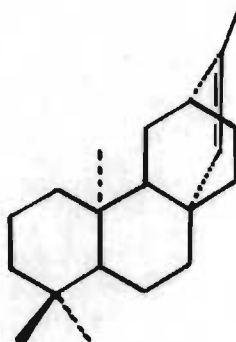
NEO-ISO-ATISIRENE
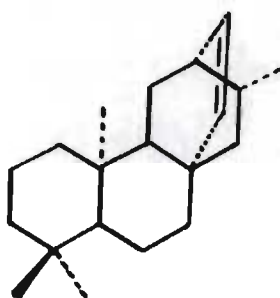
"131"

13.3.1.  The tosylhydrazone function was stable to base.  Thus
treatment of a dioxan solution of the ketol-12-tosylhydrazone (28)
with dilute NaOH in air overnight gave a good yield of the
diosphenol-12-tosylhydrazone (29) also prepared directly from the
diosphenol (18).  Thus the rearrangement is induced by some hydride
species.  Attempts to competetively trap the carbonium ion at C-13
with CN⁻ instead of hydride failed even with large excesses of
CN⁻ and the only product formed was (131).[124]  NaBH₃CN  which has
been used to reduce tosylhydrazones and imines in general [125] also
gave (131).

**13.4.1.** The 15(16)-dihydroketol (2) also gave a 12-tosylhydrazone. The reduction with Na$3H_4$ however proceeded quite normally to give the 2$\alpha$, 3$\alpha$ -dihydroxy-stachane (136).[2]

**13.4.2.** The failure of this dihydro compound to rearrange may be due to the steric repulsion of the _endo_ hydrogens on the 15- and 16-carbon atoms with the 20-methyl group in the transition state [36]. Thus the product obtained depended on the speed of the _abeo_ rearrangement versus that of the incoming hydride such that any hindrance to rearrangement localised the "carbonium ion"at C-12 for sufficient time for the hydride to attack there. Alternatively the rearrangement may be due to overlap of the $\beta$ , $\gamma$-double bond with the C-12 p-orbital system as has been observed for the u.v. and optical absorption noted previously in this discussion. This can be tested by attempting to rearrange the compounds:
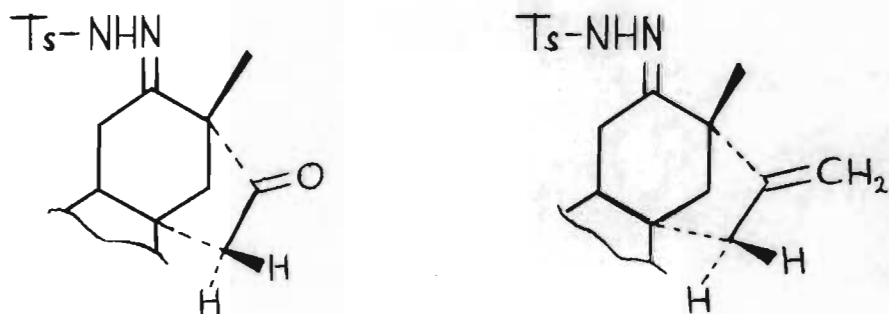


in which a similar degree of homoconjugation should exist but with an endo-hydrogen at C-15.

13.5.1. In order to confirm the 12-tosylhydrazone rearrangement and obtain detailed bond lengths, distances and angles an X-ray structural investigation of a suitable heavy atom derivative was envisaged. At the same time the detailed structure and stereo-chemistry of the product of rearrangement of the 3-tosyloxy-2-ketone system on acetolysis was also required. Thus the two problems could be combined into one structure if a suitable pre-parative route could be found.

13.5.2. Although the ketol-3-mesylate (45) gave practically a quantitative yield of the 12-p-tosylhydrazone derivative, the 12-substituent did not survive the acetolysis conditions and this method was abandoned. Eventually a route to the desired compound (135) was established as follows: the $\alpha$-ketol (1) was converted to the 12-p-tosylhydrazone derivative (28) and reduced with $NaBH_4$ to give the atisene-diol (131) as before. At this stage the $\alpha$-ketol function had to be regenerated. The Fetizon reagent, silver carbonate on celite,[126, 127] had been sucessfully used to convert steroidal alcohols to the corresponding carbonyl compounds. Furthermore the vicinal cyclohexane-1,2-diol was converted to the $\alpha$-ketol in 45% yield. However the stereochemical requirements for this oxidation were not apparent. It was thus tried on (131) with some apprehension. The oxidation in benzene was extremely rapid and was over in a matter of minutes. T.l.c. showed the absence of starting diol and the presence of two less polar compounds. The more mobile compound was present only in minor quantity and gave

an intense blue colour on the silica gel plate when sprayed with methanolic ferro-ferricyanide solution indicating its enolic nature. This was in fact the diosphenol which was not investigated further. The less mobile component was the major material (139) and gave a red colour with an alkaline triphenyltetrazolium solution indicating its $\alpha$-ketolic structure. Changing conditions, such as adding the silver carbonate in small portions, did not reduce the amount of diosphenol produced. Filtration, removal of solvent and recrystallisation from methanol furnished the pure $3\alpha$-hydroxy-2-one (139). This was converted to the tosylate (140) and acetolysed to give the 1-axial-acetoxy-2-ketone (141). This compound was not characterised pure but the crude product gave a satisfactory n.m.r. spectrum, which also showed traces of the epimeric 3-acetates and this observation instigated the more thorough investigation of the solvolysis reported earlier in section 5.1.1. Hydrolysis of this material was instantaneous as indicated by the masses of needles of the alcohol (142) which formed immediately on addition of a few drops of alkali.

13.5.3. Reaction of (142) with p-bromobenzoyl chloride in pyridine was not complete even after several days reaction at room temperature with a large excess of the acyl chloride, followed by a few hours at 80°. This was a clear indication of the hindered nature of the alcohol. Nevertheless chromatography gave the pure p-bromobenzoate ester (135) in reasonable yield. Unfortunately this compound proved to be extremely soluble in all the common solvents such as hexane, alcohol and chloroform and consistently grew in
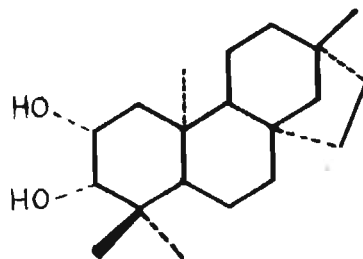
R
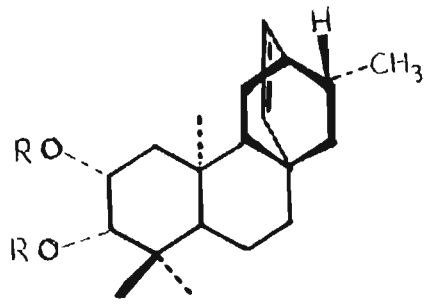
| | R |
|---|---|
| 131 | H |
| 231 | Ac |
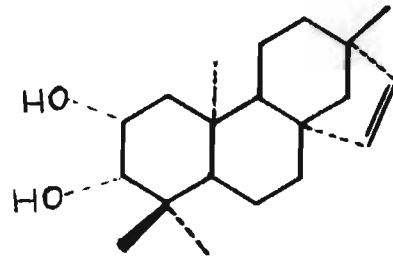
132
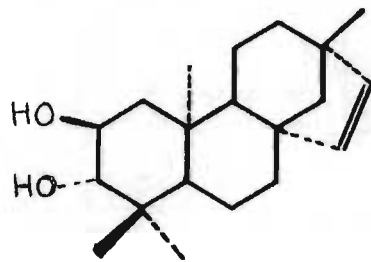
133
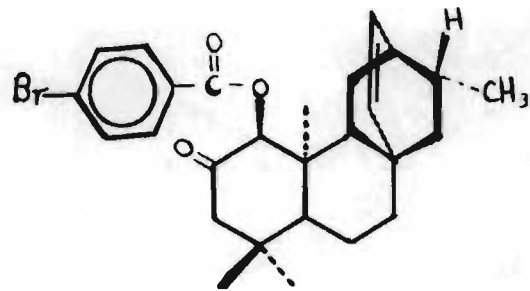
135

136
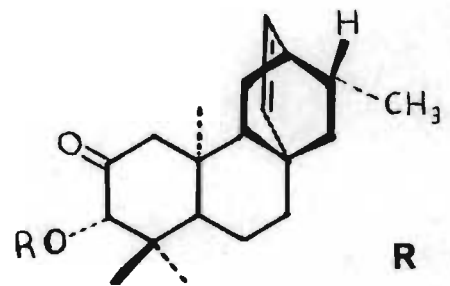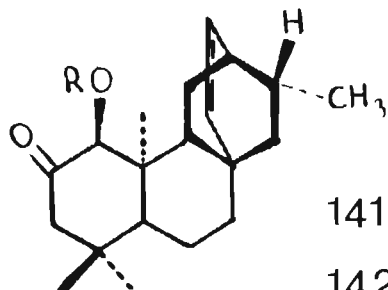
| | R |
|---|---|
| 139 | H |
| 140 | Ts |

| | R |
|---|---|
| 141 | Ac |
| 142 | H |

twinned crystals unsuitable for single crystal X-ray analysis.
Eventually after many trials suitable single crystals formed from
a mixture of acetone, ethanol and hexane.  A discussion of the
structure is found in reference 53.


13.6.   THE FETIZON REAGENT


13.6.1.  The *regioselective* oxidation of the $2\alpha$-axial, $3\alpha$-equa-
torial diol to the $3\alpha$-hydroxy-2-one is probably due to the more
ready availability of the 2-equatorial hydrogen in the reaction.


MECHANISM [129]
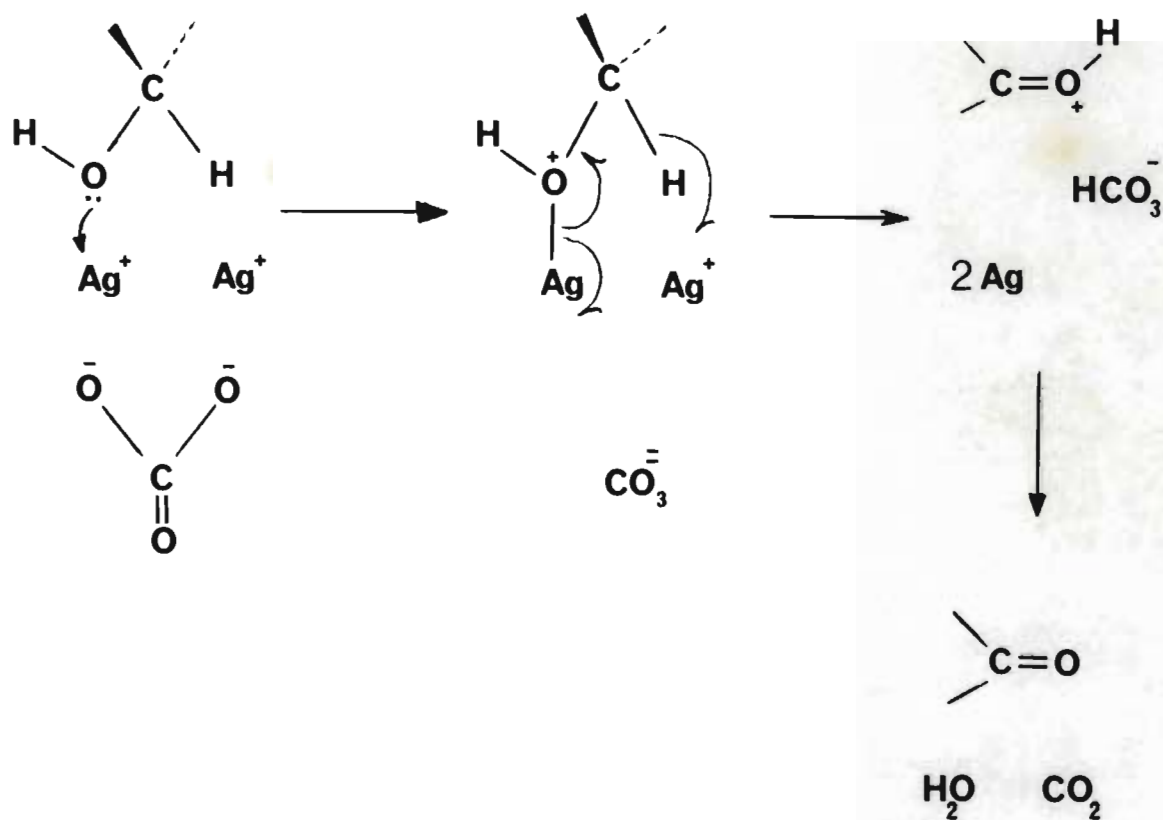
13.6.2    The 2α, 3α-diol function oxidized here appears to be the first example of the use of the Fetizon reagent with a stereo-chemically rigid and defined diol configuration.

Other stereoisomeric vicinal diols have not been tested but since both the _trans_-equatorial 2β, 3α, 12α-triol (17) and the _trans_-diaxial triol (143) as well as the 1,2-diol (51)  are available this should be a fruitful line of study since no stereochemical studies of this oxidation method have been made.  It is noteworthy that the 12-equatorial alcohol is not oxidized even in toluene with a large excess of silver carbonate over a prolonged period of time.
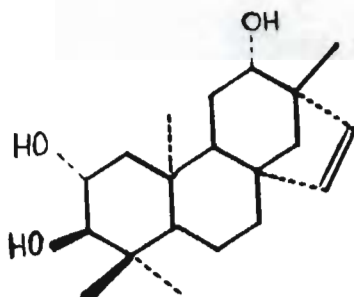


143

CHAPTER 14


ADDITION REACTIONS OF THE 15(16) - DOUBLE BOND


14.1    HYDROGENATION OF THE 15(16) - DOUBLE BOND

Hydrogenation proceeded very readily with Pd or Pt in a variety

of solvents, the uptake of hydrogen being rapid.  The extreme

ease of this grouping towards hydrogenation was noted on several

occasions when Raney nickel desulphurisation of thio-ketals often

gave concomitant double bond hydrogenation, even with deactivated

catalyst.


14.2    HALOGEN, PSEUDO-HALOGEN AND MERCURATION ADDITION REACTIONS


14.2.1.  In all the following reactions the ketol acetate (3) was

used unless stated otherwise.

Dissolution of the ketol acetate (3) in glacial acetic acid

containing 2 equivalents of mercuric acetate in suspension gave no

reaction.  However on  addition of $BF_3$-etherate all the mercury salt

went into solution to provide a yellow solution; no starting

material was detectable on      t.l.c.  Quenching in ice water

usually gave a clear solution which only precipitated material

when the pH was raised to about 6 using solid KOH.  This material

was the mercuric acetate addition product (144).

The assigned stereochemistry will be discussed further on.  It is

noteworthy that this material is highly crystalline as the acetate,

whereas usually a halide is prepared prior to isolation [130] of

organomercurials of this type. Attempts to use this compound to hydroxylate C-16 failed since reduction with alkaline [130] $NaBH_4$ regenerated the double bond and yielded the fully reduced triol (16). Using the H.C. Brown modification[131] (which does not entail isolating the organometallic compound) also failed to produce the desired product.

14.2.2. If the acetic acid reaction mixture used in preparing the oxymercurial was not quenched with water but treated with an excess of anhydrous sodium acetate followed by bromine there was obtained the brom.o-acetoxy-adduct (145).
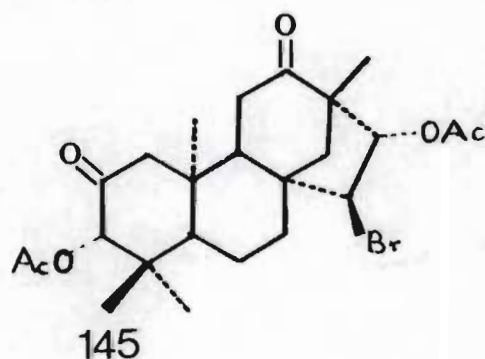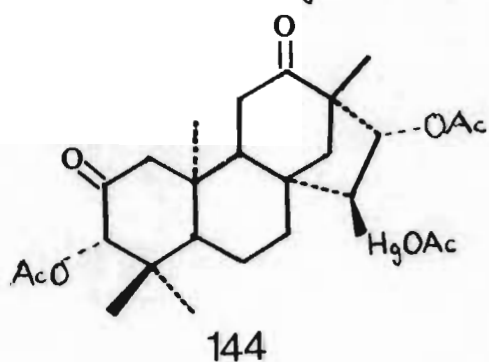


Again the stereochemical assignments will be discussed later.

14.2.3. ADDITION OF IODINE ACETATE AND IODINE NITRATE

The Prévost reaction [132] and its Woodward modification[133,134] are useful reactions in functionalising an olefin. A simplified scheme illustrates this.
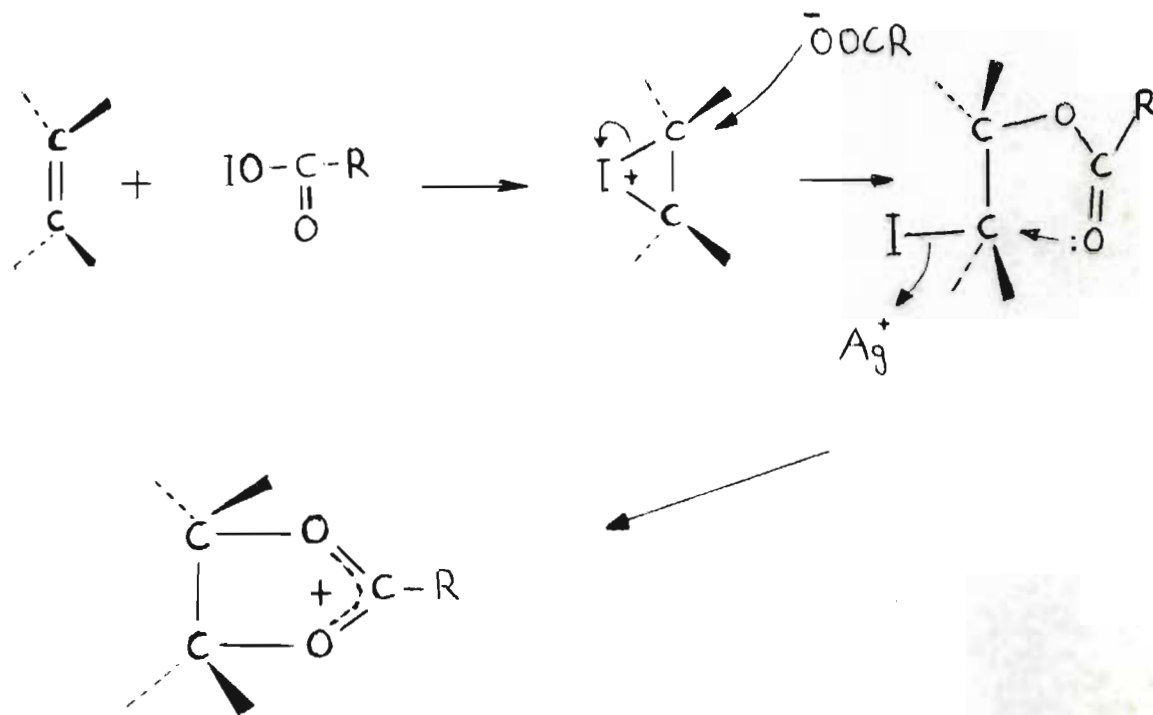
IN THE PRÉVOST REACTION
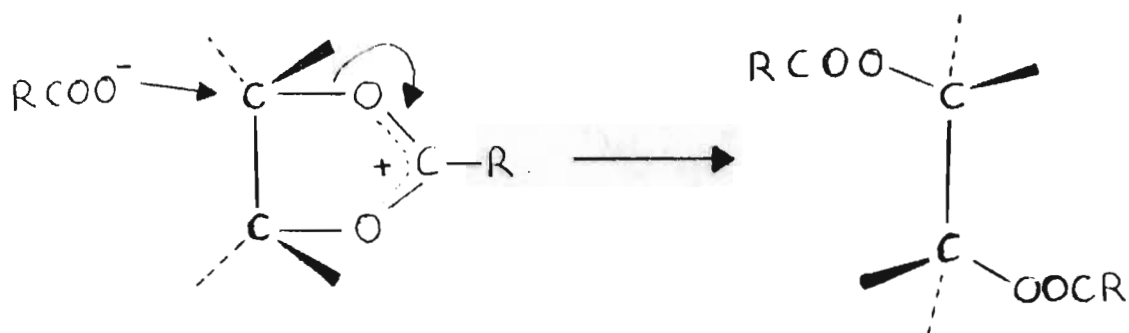


IN THE WOODWARD VARIATION
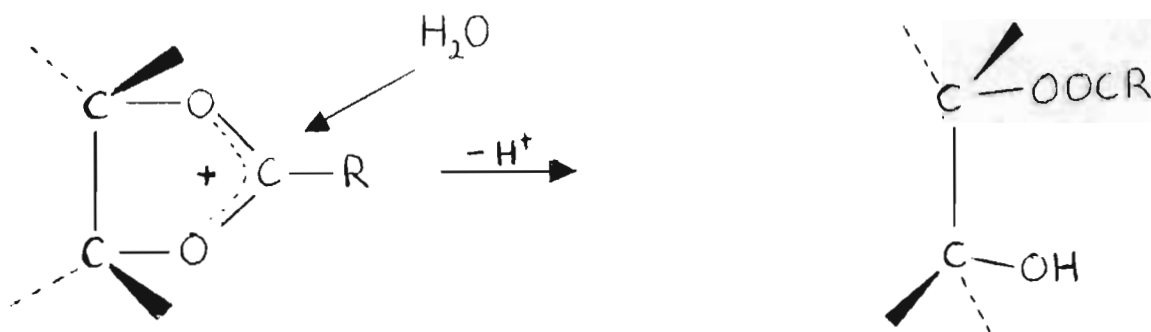
(But see reference 134 for a detailed treatment of by products.)

However in the present instance the geometry and location of the 15(16)-double bond was not suitable for either reaction since the predicted trans ester (15-endo, 16-exo) was sterically improbable as was the formation of the cis hydroxy ester (15-endo, 16-endo).

Meakins [134] had isolated the intermediate iodide-carboxylate adducts as minor products in steroid investigations and these were regarded by us as potentially useful both as protecting groups for the double-bond and to generate the 16-oxygenated compounds.

The reaction of the ketol acetate (3) with silver acetate and iodine in glacial acetic acid with or without the addition of water gave the iodide-acetate adduct (146) in fair yield.



| | R |
|---|---|
| 146 | Ac |
| 147 | $NO_2$ |
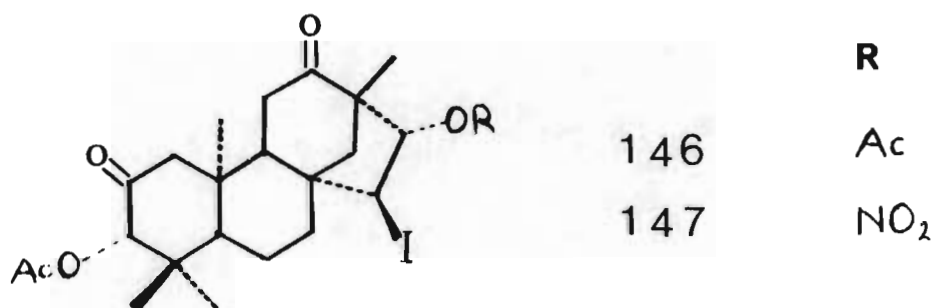
Reaction of (3) with silver nitrate and iodine in acetonitrile rapidly gave the iodide-nitrate adduct (147) in very good yield (77% pure). This reaction proceeded very readily and always worked well with the 15(16)-ene variously substituted in the other rings (148).

14.2.4.  BROMINATION, CHLORINATION AND ATTEMPTS AT PREPARING A
BROMOHYDRIN AT THE 15,16-POSITION

Bromination with molecular bromine in acetic acid or chloroform gave mixtures of products which were not further investigated. Using 2 moles N-bromosuccinimide in chloroform with dibenzoyl peroxide an excellent yield of the 15,16-dibromide (149) contaminated with traces of the 11,15,16-tribromide was obtained. The latter was converted to (149) during the recrystallisation by the addition of a small quantity of sodium acetate (SECTION 3.8.4.) so that over-bromination was of no consequence.

This compound (149) was also prepared on one occasion using a very old batch of N-bromoacetamide which had decomposed to a dark red liquid! Treating a solution of (3) in aqueous acetone, containing sodium acetate, with the aged N-bromoacetamide eventually resulted in the separation of the dibromide in a slightly reduced yield. Since the NBS-CHCl$_3$ method was easy to carry out, this alternative method was not tried with fresh NBA. However replacement of the "old" NBA by bromine gave a mixture as before, indicating that the red liquid contained some brominating species different from molecular bromine.

The 15,16-dichloride (150) was prepared by treating a pyridine solution of (3) with sulphuryl chloride (SO$_2$Cl$_2$). The n.m.r. spectrum was practically superimposable on that of the analogous dibromide (149).

All attempts to isolate a bromohydrin failed. Even the recommended procedure using NBA-aqueous dioxan – $HClO_4$ gave the same complex mixture as all the other molecular bromine methods tried, i.e. molecular bromine in aqueous systems. Although these mixtures were not further investigated at the time since they were of no great preparative value, t.l.c. indicated the presence of the dibromide, material assumed to be the bromohydin(s) from its $R_f$ value and other unidentified compounds. A complication of the 15,16-ene system which could explain this lack of specificity, is the facile rearrangement to a kaurene system [135, 136] on generating a C-16 carbonium ion. Thus opening of the exo-bromonium ion adduct at C-16 could have resulted in skeletal rearrangements which then further brominated. This could be a fruitful line of investigation for future study.

## 14.3. STEREOCHEMISTRY OF THE ADDUCTS

TABLE IV

CHEMICAL SHIFTS OF RELEVANT PROTONS AND THEIR COUPLING CONSTANTS

Note 1. J given in $H_z$ and chemical shifts in $\delta$.

2. The assignments to 17- and 18-methyls are purely arbitrary except for (147).
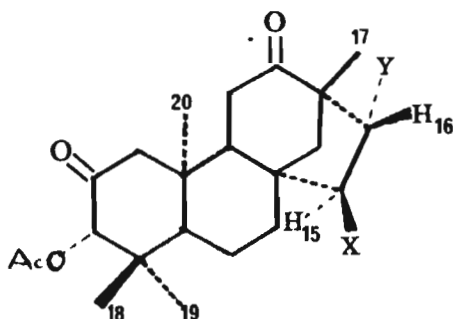
## TABLE IV

### δ VALUES OF RELEVANT PROTONS AND THEIR COUPLING CONSTANTS.

| COMPOUND | X | Y | H-15 | H-16 | $J_{15.16}$ | $J_{15x}$ | Me-17 | Me-18 | Me-19 | Me-20 |
|----------|-----|--------|------|------|------|-----|------|------|------|------|
| 144 | HgOAc | OAc | 2.86 | 5.16 | 5.50 | 2.5 | 1.10 | 1.12 | 0.87 | 0.92 |
| 150 | Cl | Cl | 4.57 | 4.17 | 5.60 | 2.0 | 1.16 | 1.12 | 0.90 | 0.98 |
| 149 | Br | Br | 4.69 | 4.38 | 5.60 | 2.0 | 1.15 | 1.15 | 0.90 | 0.95 |
| 145 | Br | OAc | 4.46 | 5.59 | 4.00 | 2.0 | 1.10 | 1.12 | 0.88 | 0.98 |
| 146 | I | OAc | 4.49 | 5.73 | 4.75 | 2.5 | 1.11 | 1.14 | 0.91 | 0.96 |
| 147 | I | $ONO_2$ | 4.61 | 5.80 | 4.50 | 2.8 | 1.20 | 1.13 | 0.90 | 0.95 |

TABLE V - COUPLING CONSTANTS AND DIHEDRAL ANGLES FOR 15,16-DISUBSTITUTED 13-KAURANES [137].

| COMPOUND | $J_{15,16}$ | CALCULATED $^{\circ}\Theta_{15,16}$ |
|---|---|---|
| 151 a | 11.0 | 0 |
| 151 b | 5.5 | 135 |
| 151 c | 4.0 | 130 |
| 151 d | 8.0 | 30 |
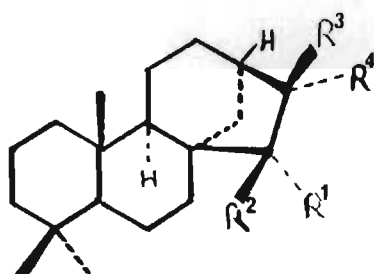


151

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | |
|---|---|---|---|---|---|
| a | OH | H | $CH_3$ | H | (cis) |
| b | OH | H | H | $CH_3$ | (trans) |
| c | H | OH | $CH_3$ | H | (trans) |
| d | H | OH | H | $CH_3$ | (cis) |

14.3.1. A comparison of the observed coupling constants in this halogenated and mercurated series with those for the $13\beta$-kauran-15-ols (151) prepared by MacMillan and Walker [137] (see Tables) allows a trans configurational assignment to be made to the compounds in the present study.

Mechanistically the initial "halogenonium" ion would be expected to form on the exo-side. Backside opening of this ion could only occur at C-16 such that the final product would necessarily be the 15-exo, 16-endo compound.
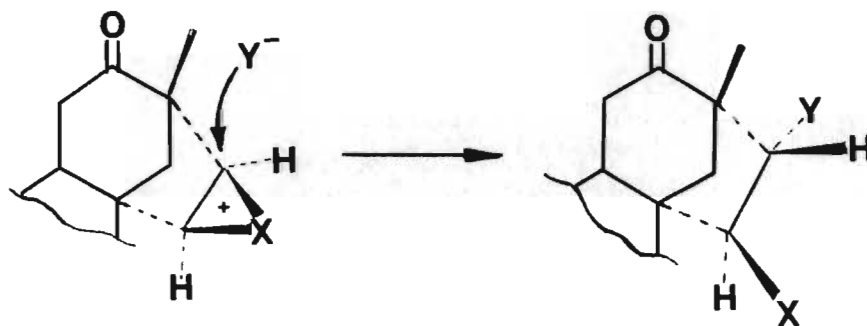


This was further borne out by the fact that the change from iodide-acetate (146) to iodide-nitrate (147) caused very little shift in the n.m.r. resonance positions for the tertiary methyl groups (0.01 p.p.m.) except for the 17-CH$_3$ methyl group (0.09 p.p.m.) implying that the nitrate ester was adjacent to this methyl group.

Furthermore the observed coupling constants confirmed that bromination of the mercuric acetate adduct resulted in replacement of the mercury by bromine with retention of configuration. This can be explained by two mechanisms:-

a) an $S_ni$ type
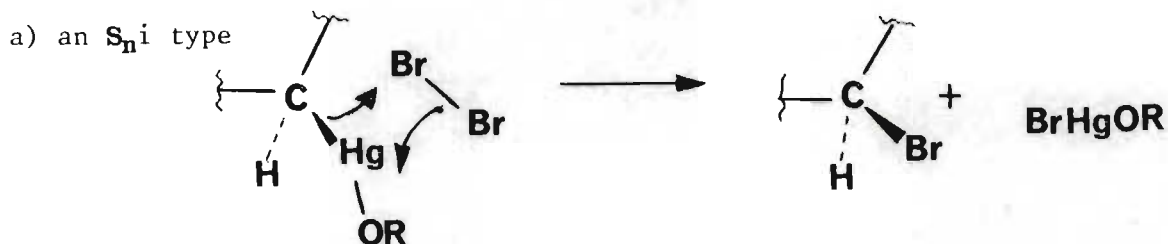


b) Alternatively since the oxymercuration reaction is reversible

in acid medium [138], and the reaction $Hg^{2+} + Br_2 \longrightarrow BrHg^+ + Br^+$

(or as a complex $Br - Hg^{2+} \ldots\ldots Br$) produces a very effective

brominating species, [139,140] then one can envisage the bromination.

of the alkene by a similar system to the first step in the Prévost

reaction discussed previously. A distinction between the two

mechanisms has not been attempted.


## 14.4 REACTION OF THE ADDUCTS

Attempts to utilise these products are now described.


<u>14.4.1.</u> The dibromide (149) was stable to prolonged acetolysis

in refluxing acetic acid. It was hoped that dehydrobromination

would have yielded a vinyl bromide which could then have been

used to further test the electronic and steric requirements of

the various 12-carbonyl rearrangements. Although at the time

the configuration of the dibromide had not been decided upon, it

became apparent later that this dehydrobromination could not take

place with ease since the required <u>trans</u> disposition of the halogen

and the hydrogen (usual for El or E2 mechanisms) was not attainable.

A <u>cis</u> elimination would have been energetically more demanding

and improbable.

14.4.2  Similarly refluxing the dibromide with tri-n-butylamine
in toluene for nine hours gave the starting material with no
other product visible on t.l.c.

14.4.3.  AgNO$_3$ in ethanol did not deiodinate (147) the iodide-
nitrate adduct.  In ethylene glycol monoethyl ether some reaction
occurred as evidenced the precipitation of AgI, however a large
amount of starting material was recovered.  Pyrolysis of the same
compound resulted in tars.

14.4.4.  Catalytic hydrogenolysis of (147) was next attempted
using Pd/C.  The nitrate ester was expected to reduce with or
without the concomitant loss of the iodine.  Thus a 16$\alpha$-alcohol
or the corresponding 15$\beta$-Iodo-16$\alpha$-hydroxy halohydrin was
expected.  However even 50 atmospheres hydrogen pressure for 20
hours resulted in no reaction and the starting material was
recovered unchanged, except for some minor yellowing of the solution.
This was a remarkable "non-reaction" !

14.4.5.  Even the sulphuric acid-acetic anhydride induced rearrange-
ment of the 12-carbonyl [52] failed with (147) which was recovered
unchanged.  Furthermore the Bayer-Villiger oxidation of the 12-ketone
to give the 12,13-oxygen insertion product which occurred with
great ease and rapidity for both the ketol  acetate (3) and its
15,16-dihydro derivative (8) and corresponding epoxide (152) failed
when (145) was used.  This was a blessing in disguise since it

meant that a newly introduced double bond at a remote locus in the molecule could be selectively epoxidized without epoxidizing the protected 15,16 positions nor effecting the Bayer-Villiger oxidation. This became a practical reality when the dibromide adduct (149) (and presumably the others as well) was found to quantitatively regenerate the double bond under the action of Zn in acetic acid. Use of large excesses of sodium iodide in acetone was ineffective.

14.4.6. Thus a convenient blocking group for the 15,16-positions had been found which was even resistant to hydrogenation conditions!

14.4.7. The free radical Cr(II) reduction [141] should remove the 15-subsistent but this procedure was not attempted before termination of the project.

14.4.8. LAH reduction also regenerates the double bond. Thus (89) was converted to the 15,16-iodide-nitrate adduct and reduced, work up with acid and methanol and oximation of the demasked 12-carbonyl gave (91) previously prepared from the 15,16-ene compound. (SEE SECTION 9.1.3. ). Hence both the zinc and the LAH reductions probably proceed via a mechanism of the type:-
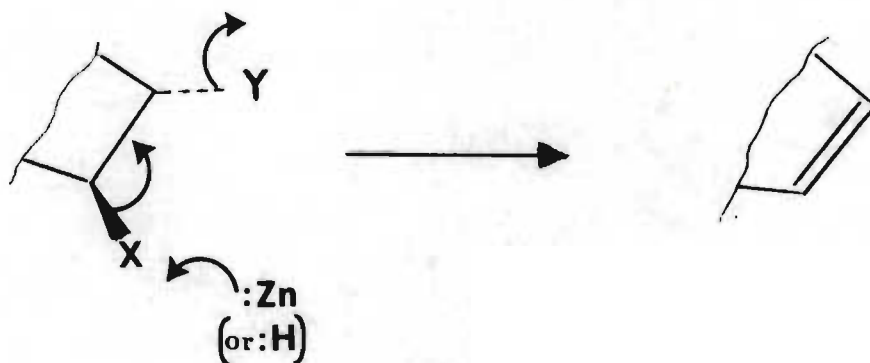
C H A P T E R   1 5

ENAMINE FORMATION AND CONVERSION TO THE 3 $\beta$ -ACETOXYSTACH-15-ENE-
2,12-DIONE SYSTEM $\beta$

Enamines of carbonyl compounds are synthetically useful
and versatile derivatives for organic reactions.  The enhanced
nucleophilicity of the $\alpha$ -carbon allows the alkylation and
acylation of this position as well as attack by other more diverse
and exotic reagents.

15.1.1.  1,2 and 1,3 dicarbonyl compounds give enamines with ease
and these enamines are now much more stable towards hydrolytic
decomposition than those derived from monocarbonyl compounds and
can be isolated in the conventional manner without undue precautions
to exclude moisture.  However most work has been performed on $\beta$-
diketones, especially of the dimedone type [142-146], since these
are easily available from Claisen condensations as an example.
Little is known of $\alpha$ -diketone enamines [147] as well as $\alpha$ -ketol
enamines.

15.1.2.  Reaction in air of the diosphenol (18) in benzene, or more
conveniently in methanol with pyrrolidine and a trace of
-p-toluenesulphonic acid gave an excellent yield of the conjugated
enamine (153).  Attempted reaction of (153) with acetic anhydride
or acetyl chloride gave only starting material, indicating the
decreased nucleophilicity of the 1-position, probably due to a
combination of steric and conjugative effects.

15.1.3. Repetition of the enamine formation in benzene under nitrogen using the α-ketol (1) gave a yellow solution which when quenched with acetic anhydride and poured into water gave a red oil. This oil slowly crystallised into long white needles subsequently found to be the 3β-acetoxy-stach-15-en-2,12-dione (53). The structure of (53) was demonstrated by preparing the 15,16-dihydro-benzaldehyde-lactone (38) from the 15,16-dihydro derivative of (53), thus indicating its 2,3-dioxygenation pattern. Since the three other possible 15,16-dihydro-2, 3-ketol acetates (8,30,36) were known the configuration at C-3 of (53) was unambiguously defined. The analytically pure material isolated in 55% yield meant that all four isomeric 2,3-α-ketol acetates had then been prepared. This method of preparation of (53) however constituted a novel synthetic pathway and attempts to underline the possible mechanism were made.

15.2.1. The reaction could be thought to occur by two possible routes. In one the 2-keto group would form the enamine with the olefinic bond in the 2,3 position (154). Subsequent acetylation and protonation from the α-side would then give ( 53).



154

53
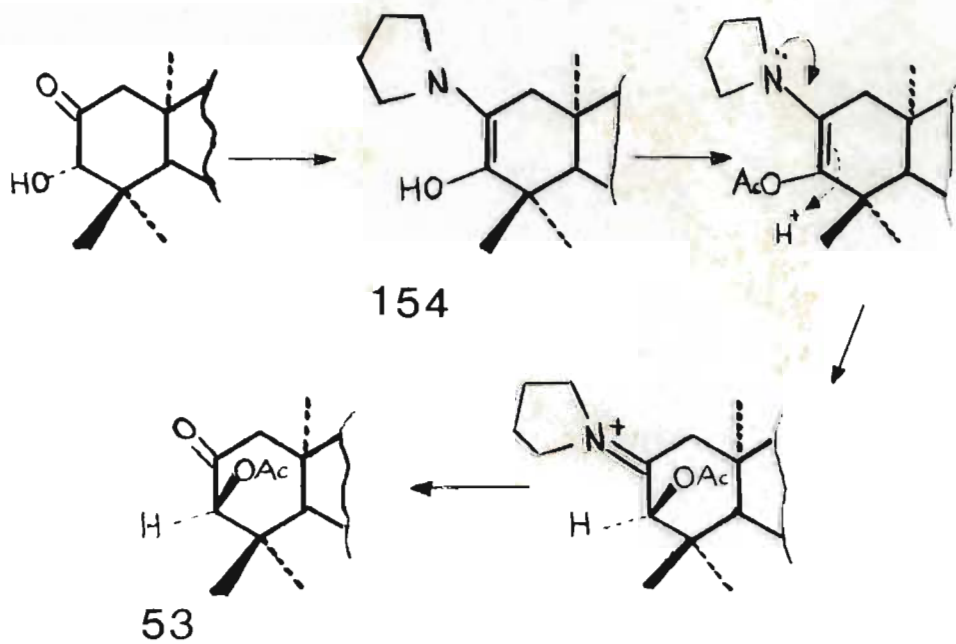
The sterospecific protonation from the usually less common α -side

remains unexplained.


15.2.2. A second possible mechanism would involve the formation

of the enamine with the olefinic grouping in the 1,2-position (155).

This could then be followed by an allylic epimerisation to give

the required compound.



155
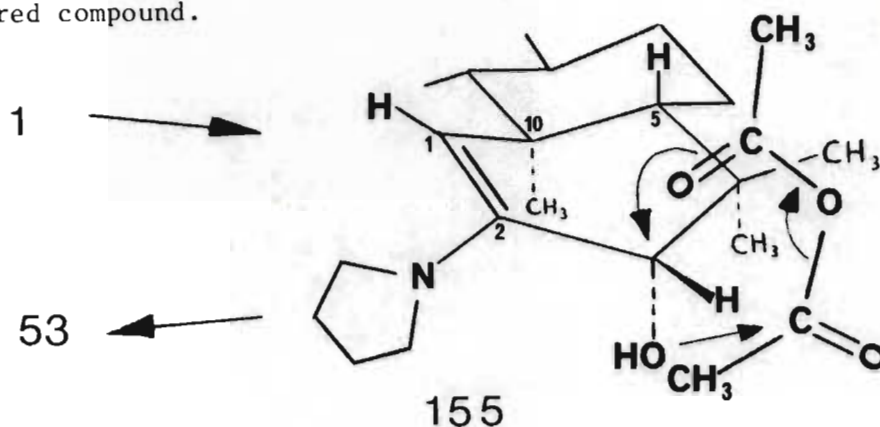
This second mechanism as written requires a six-centre transition

state.


15.2.3. A distinction between intermediates (154) and (155)

should have been possible by n.m.r. since (154) possessed no new

olefinic proton signals whereas (155) should have a definite

signal for the H-1 olefinic hydrogen. Consequently the reaction

was performed in an n.m.r. tube kept spinning in the probe at

$39^{\circ}$ and the progress was follwed over 70 hours by which time no

further reaction occurred and only traces of starting material

showed in the spectrum. At this stage the H-1 signal of the

diosphenol enamine (153) at $\delta$ 5.20 (in benzene) appeared as a very

small bump only, indicating that very little oxidation had occurred.

The results were however conflicting. The H-3 proton signal at $\delta$ 3.77 became progressively weaker until after 70 hours it was very small. This result was consistent with the first mechanism (intermediate 154) but since new signals(not integrating for one full proton) appeared slightly upfield to this original H-3 resonance it could not be excluded that in (155) the chemical shift of H-3 would be slightly different to that in (1).

Furthermore the double bond region $\delta$ 5-6 now showed the presence of three olefinic protons, a new one overlapping the signals due to part of the 15,16-AB quartet at $\delta$ 5.43. This of course would be consistent with the second mechanism (intermediate 155).

Addition of two equivalents of acetic anhydride to the n.m.r. tube reaction resulted in the disappearance of the "extra" olefinic signal and the appearance of a small signal for H-3 of (3) but no trace of the H-3 signal for the expected (53). This result would be in keeping with (154) if the "extra" olefinic signal could be attributed to water perhaps. Finally it could be possible for an equilibrium mixture of both (154) and (155) to form. Intermediate (154) could be expected to tautomerise to form the 2-pyrrolidino-3-one structure to some extent but this was not evident in the n.m.r. spectrum and especially on t.l.c. of the crude material.

No further progress has been made up to the present but future plans are presented. The obvious answer is to try and isolate the intermediate in a pure state and obtain an n.m.r. spectrum of it. One attempt was made earlier in this direction but

the only material isolated was (153) in good yield, indicating that oxidation may have occurred during the isolation. Also the washing process to remove pyrrolidine and acid may have most certainly hydrolysed the ketol enamine. It is then planned to vacuum evaporate all the volatile components from the reaction mixture and to then try and crystallise the enamine under dry conditions in an inert atmosphere.

15.3.1. A second way to obtain some evidence for the reaction intermediate would be to introduce deuterium at C-3 and then check the product (53) for loss or retention of the label. Loss of label would implicate (154) whilst retention would implicate (155).

A workable method of introducing the label at C-3 makes use of the properties and reactions which are known to work for this system. Reaction of the diosphenol (18) with ethylene glycol results in a good conversion to the 12-mono-ketal (156). This on reduction with $NaBD_4$ and deketalisation should yield the 2D,3D-analogue of (121). Silver carbonate oxidation then regenerates the $\alpha$-ketol system with label at C-3. Some labelling at C-1 during the reduction would be expected but would in fact be beneficial rather than a nuisance since if the D-3 atom was found to be retained then the loss or otherwise of label at C-1 could be used as a cross-check (See scheme IV).

15.3.2. Direct deuteration of (1) results in isomerisation to mixtures of ketols and is not recommended. At present NaBD$_4$ is not available however due to paucity of funds, therefore the above project will have to be carried out at some future date.
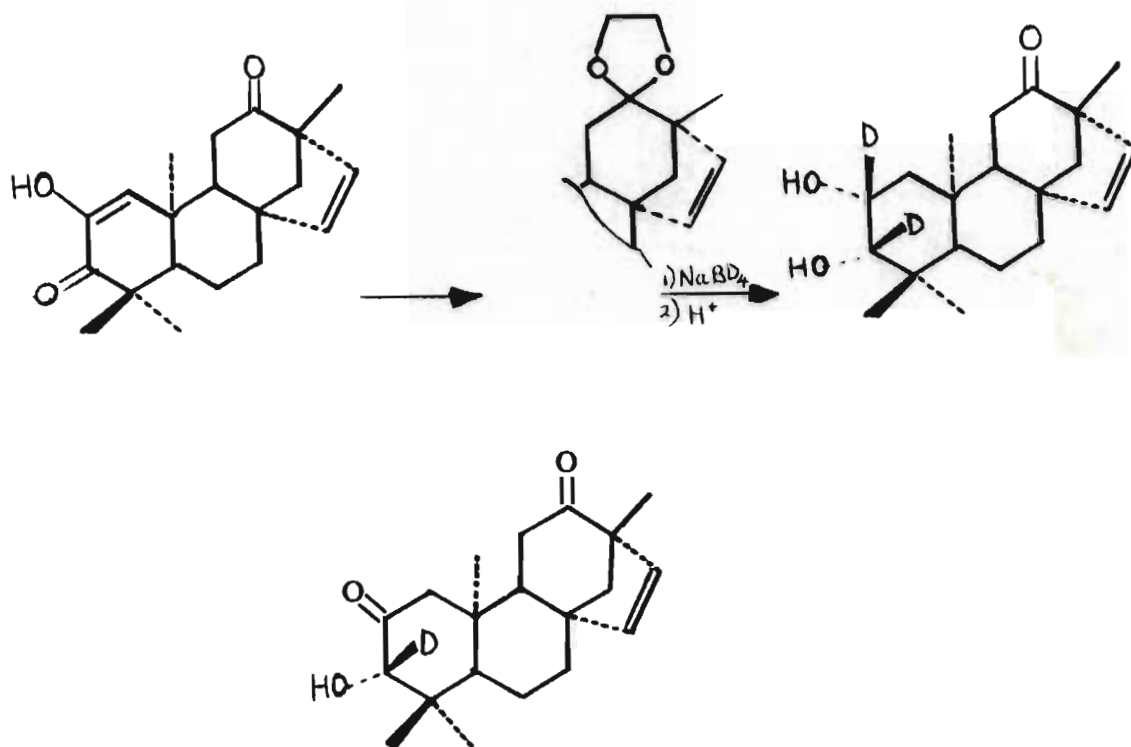


SCHEME IV

15.4.1. NaBH$_4$ reduction of (53) gave an excellent yield of the 2$\alpha$, 3$\beta$, 12$\alpha$-triol (143). Since the 12$\alpha$-hydroxy group is inert to silver carbonate on celite these triol systems (143, 16, 17) can be used to test the stereospecificity of the oxidation of the 2,3-diol groupings by Ag$_2$CO$_3$ to give $\alpha$-ketols as described in section 13.6.2.

15.5.1. The conjugated enamine (153) was conveniently prepared from the mother liquors after recrystallisation of the major diterpenoid constituent, since these were very rich in diosphenol and $\alpha$ -ketol.

15.5.2. Under no conditions was the 12-ketone found to react with pyrrolidine to form an enamine since no products of its supposed reaction with acylating or alkylating agents were ever isolated.

15.5.3. The enamine was exceedingly stable to alkaline conditions. Even refluxing with alkaline methanol for several hours had no effect and in fact such a solution on long standing deposited two huge, well-formed crystals measuring about 1 cm square!

15.5.4. Conjugate addition of HCN to the $\alpha$ , $\beta$ -unsaturated system [149] was also tried with no success except for hydrolysis to the triketone. Acid hydrolysis under mild conditions regenerated the 2,3-dione system as the yellow unenolised 2,3-diketone. Thus when the 12-carbonyl was rearranged to the $\alpha$ , $\beta$ -unsaturated-D-homo-C-nor type and the acetic anhydride-sulphuric acid solution left overnight in water, the corresponding yellow 2,3,12-triketone (157) was obtained in excellent yield. However, even a trace of alkali sufficed to enolise (157) to the colourless diosphenol in contrast to (37). This then offered a method to obtain these unenolised 1,2-diketones in excellent amounts and in a pure form, a hitherto very difficult result to achieve.

15.5.5. (153) did not react with acetic anhydride, acetyl chloride, methyl iodide or benzyl chloride. Attempted benzoylation at C-1 with benzoylperoxide [150] gave some reaction as shown by the disappearence of starting material and marked discolouration. However chromatography gave only benzoic acid. This reaction was only tried once but should be worthwhile repeating.

15.5.6. Attempted generation of the 12-ethylene glycol ketal of (153) gave no reaction under the usual conditions since the p-tosic acid catalyst was removed as the salt of (153). The reaction has not been tried with a slight molar excess of p-tosic acid, but this method should work if it does not first cause hydrolysis of the enamine function.

15.5.7. Finally the conjugated 1-ene bond failed to hydrogenate even under pressure using a palladium catalyst.
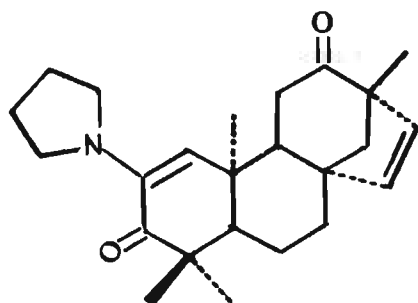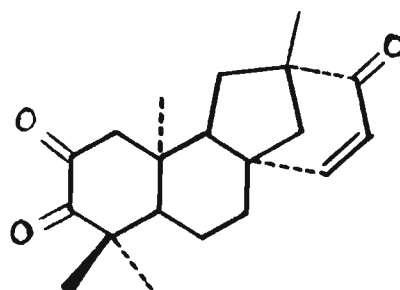
**153**          **157**

# C H A P T E R  1 6

## CONFORMATIONS OF RING A KETOLS AND KETOL ACETATES

16.1.    The occurrence of $\alpha$-ketols in nature (for example

in diterpenoids  and cucurbitacins) and their ease of isomerisation

requires that a reliable system be found which can be used to

determine their configuration and conformations.  O.r.d. and c.d.

measurements have been frequently used tools to determine the

environment of carbonyl groups.  However unless the configurations

are derived by independent means the method is, as yet, not suited

to $\alpha$-oxy and $\alpha$-nitrogen substituted ketones which appear to

show anti-Octant behaviour, [151,152] as established for fluorine

compounds [153].  N.m.r. has also been used in conformational studies

and Williamson and Johnson [113] prepared six isomeric $\alpha$-acetoxyketones

in the cholestane series (the four possible 2,3 and two 3,4 types),

whose n.m.r. characteristics they then studied [154].  Their figures

are collated in TABLE V.  Enslin and coworkers [152,155] tried to

correlate the c.d. data obtained on three isomeric cucurbitacin

ketols (structures 158, 159, 160),



158                159                160
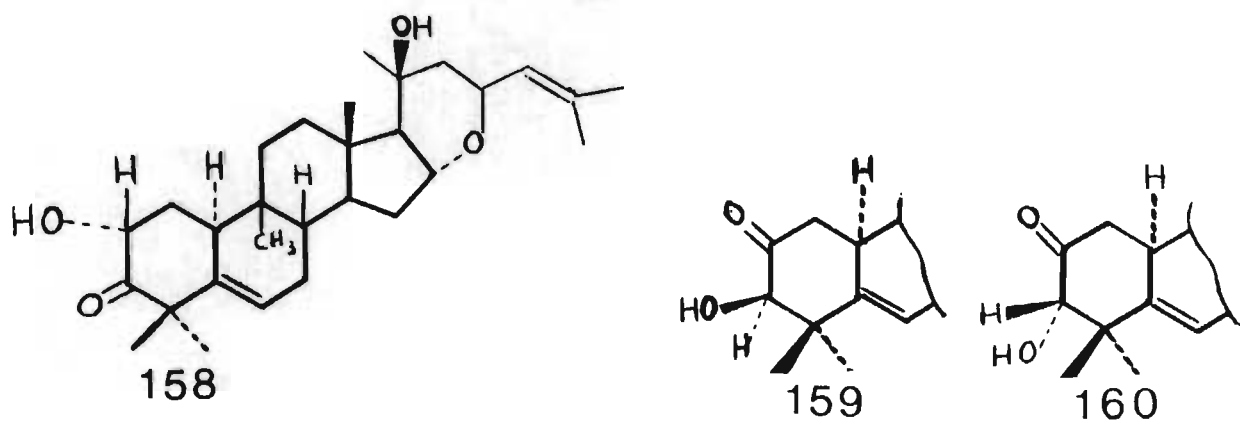
with the n.m.r. data and thus to determine the conformations of the

A-rings.

However uncertainty of the actual configurations did not allow definite conclusions to be made. Thus the configuration at C-2 of (158) had been assigned 2 β -equatorial by n.m.r. [156] but the 2 α-(axial)configuration by c.d. [155]. The 2 β -configuration has been shown to be correct by an X-ray structural analysis of a 2 β -glucoside [157] hence the results of the c.d. experiments must be reinterpreted. The configurational assignments for the cucurbitane 3-acetoxy-2-one pair (159 and 160) were also doubtful.

16.1.1   Of a pair of epimeric alcohols in cyclohexane compounds, that alcohol which is equatorial will have an n.m.r. signal for the methine proton at higher field than for the axial epimer. The axially orientated geminal proton suffers non-bonded 1,3-diaxial interactions with other hydrogens or methyl groups (in steroids and terpenoids) and is therefore more shielded. [158] A similar effect is noted for epimeric halides. However introduction of a keto group adjacent to a halogen atom deshields the axial proton and shields the equatorial proton. [159] This is an unexpected result since an isolated carbonyl group deshields both α -protons of an α- methylene group. Hence some interaction between the carbonyl and the halogen is responsible for this effect. This means that in a large number of cases [28, 159] the equatorial hydrogen atom in an axial α -haloketone resonates at higher field than the corresponding axial hydrogen atom in an equatorial α - haloketone.

16.1.2    An inspection of the n.m.r. data for the six isomeric

cholestane ketol acetates of Williamson and Johnson shows that two

pairs (the 3-acetoxy-2-ketones) (175)and (176) and 4-acetoxy-2-

ketones (182) and (183) follow the same pattern as the $\alpha$ - haloketones

discussed above, in that the equatorial protons of the axial

$\alpha$ -acetoxy ketones resonate at higher field than the respective

axial proton isomers.


16.2.1.    During the present investigation all four possible isomeric

2,3-$\alpha$-ketol acetates were prepared.    The 3-equatorial-2-one (3)

was obtained directly by acetylation of the naturally occurring

$\alpha$ -ketol (1).    The $\alpha$ -ketol on equilibration with anhydrous

aluminium chloride in acetic anhydride gave a mixture (see

SECTION 3.7) from which was isolated the 2-equatorial acetoxy-

3-one   (33).

The 2-axial acetoxy-3-one epimer was obtained as the 15,16-

dihydro derivative (30) by catalytic hydrogenation [26] of the

diosphenol acetate (26).    The final isomer, the 3-axial acetoxy-

2-one (53) was obtained via the pyrrolidine enamine of the ketol

(1) by an unusual reaction which was discussed above (SECTION 15.1.3.)


16.2.2.    Examination of the n.m.r. resonances and coupling constants

for these four compounds shows that the same behaviour is followed

as in the cholestane series.    The chemical shift equivalence of

the 2-acetoxy-3-ones (30 and 36) is explained by deviations from

the normal flattened chair of the 2-equatorial acetoxy-3-one (33

or 36) to a twist conformation for the 2-axial acetoxy-3-one (30).

as indicated by the coupling constants.

**16.2.3.** Connolly and Harding [49] isolated the 2β-hydroxy stach-15-en-1-one ketol (188) and isomerised this to the 1α-and 1β-hydroxy-2-one (186 and 187) derivatives during attempted oxidation to the diosphenol with $Bi_2O_3$. The derived acetates (161 and 162) showed the expected behaviour discussed above with the equatorial proton appearing more shielded ($\delta$4.49) than the axial analogue ($\delta$4.97) by a substantial amount. In the present study the 1β-acetoxy-2, 12-dione (47) was prepared by acetolysis of the 2-keto-3-sulphonate esters (SECTION 4.4.1. ). The 1-equatorial proton for this isomer (47) resonated at $\delta$ 4.22 which is even more shielded than the 12-unsubstituted compound (162). In the novel atisene analogue (141) its resonance appears at $\delta$ 4.37 which is slightly less shielded than the 12-keto stachene.

**16.2.4.** The data for the free ketols follows this exact pattern. Again from Connolly and Harding's work the 1α-equatorial proton geminal to the α-ketol hydroxy group at C-1 resonated 0.3 p.p.m. at higher field than the corresponding axial proton in the 1α-hydroxy isomers, Table V (186 and 187). The only α-ketol in this position prepared in the present study was the 1β-(axial)-hydroxy-2,12-dione (48) and its carbinol proton appeared at $\delta$ 3.33, again slightly shielded with respect to the 12-unsubstituted compounds (186 and 187).
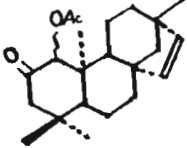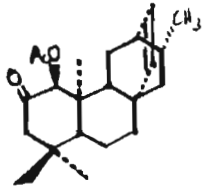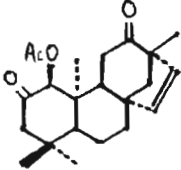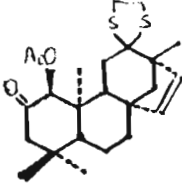
**16.2.5.** The two epimeric 3-hydroxy-2,12-diones (1 and 54) were also studied, the equatorial 3α-isomer being the natural material (1).

Here an apparent reversal to the "normal" sequence has taken place.
However ir the C-ring-aromatic diterpene ring A ketol analogues (196
and 234) the same behaviour as the acetates was observed. This
apparent discrepancy was most probably due to subtle solvation
induced conformational changes since the differences are very
small, of the order of 0.03-0.05 p.p.m. Hydrogenation of (3)
does not materially affect the chemical shift of the 3 $\beta$ -hydrogen.
However hydrogenation of (53) resulted in a downfield shift of
0.07 p.p.m. for the 3 $\alpha$ -hydrogen. This is positive evidence that
the A-ring in (53) exists in a boat or twist conformation such
that the 3 $\alpha$ -hydrogen is tucked on the $\alpha$ -side of the molecule
and is shielded by the 15,16-double bond. Hydrogenation removes
this shielding and consequently the resonance value resembles the
epimer (8) more closely.

For these reasons no definite conclusion can be made in
relation to the epimeric pair of ketol acetates, (159 and 160) in
the cucurbitacin series prepared by Enslin et al[155] since the
difference between them (0.13 p.p.m.) cannot be correlated with
an expected configuration .

# T A B L E  V

## A) THE CHEMICAL SHIFT OF THE ACETOXYMETHINE PROTON OF SECONDARY α-KETOL ACETATES
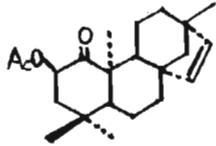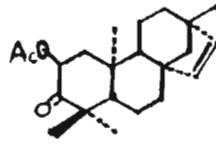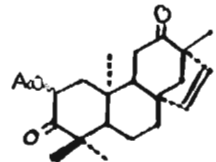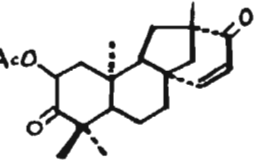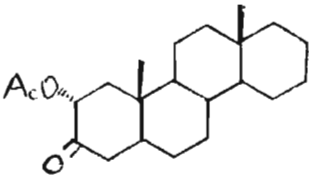
| STRUCTURE | EQ. | AX. | EQUATORIAL ACETATE ≠ | AXIAL ACETATE ≠ | REFERENCE |
|---|---|---|---|---|---|
| | (161)* | (162) | 4.97 | 4.49 | 49 |
| | | (141) | | 4.37** (shoulder) | |
| | | (47) | | 4.22 (shoulder) | |
| | | (50) | | 4.60 (shoulder) | |
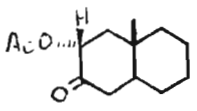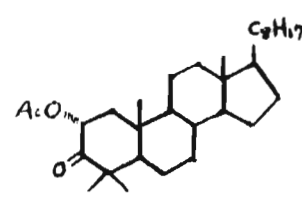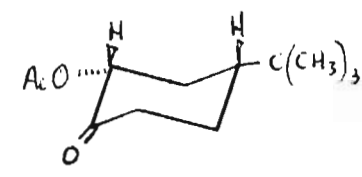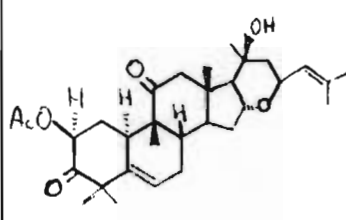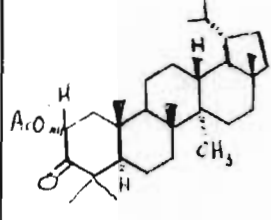
Data refers to CDCl$_3$ solutions unless otherwise stated.
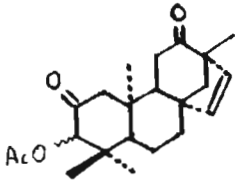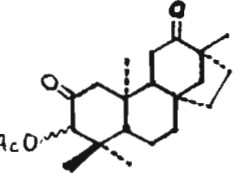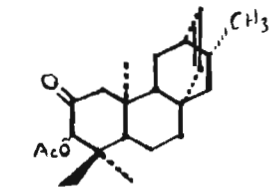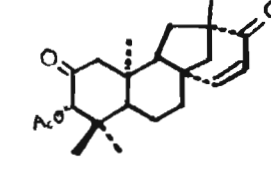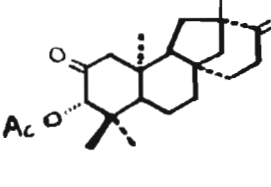
≠ Note: Equatorial and Axial refers to the configuration of the acetate when in the chair form.

\* Compound number in parenthesis     \*\* Coupling constants in Herz in parenthesis.
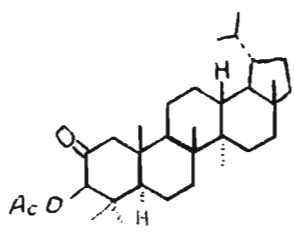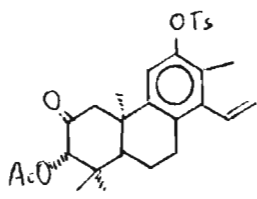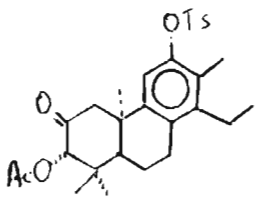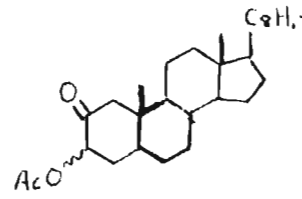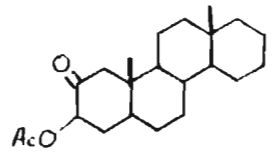
| | | | | |
|---|---|---|---|---|
|  | (163) | 4.2-4.6<br>(overlapped by<br>olefine signal) | | 49 |
|  | (164) | 5.4<br>(6,13)** | | 12 |
|  | (33)<br>(36)    (30) | 5.58<br>(6·0,13·0) | 5.58<br>(8.3, 11.2) | |
|  | (168) | 5.57<br>(6·0,13·0) | | |
|  | (167) | 5.25<br>(7,13) | | 160 |

| | | | |
|---|---|---|---|
|  | (169) | 5.2<br>(6) | 161 |
|  | (170)    (171) | IN CS$_2$<br>5.07        5.12<br>(6.6, 13.1) (7.4, 9.5) | 154 |
|  | (173) | 5.05<br>(6.5, 12) | 162 |
|  | (158) | 5.45<br>(6, 13) | 155 |
|  | (172) | 5.67<br>(5.3, 12.9) | 21 |

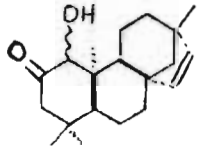| | | | | |
|---|---|---|---|---|
|  | (3) | (53) | 4.90 | 4.70*** |
|  | (8) | DIHYDRO(53) | 4.93 | 4.77*** |
|  | (178) | EPI-(178) | 4.90 | 4.72 |
|  | (109) | | 4.93 | |
|  | (111) | | 4.95 | |
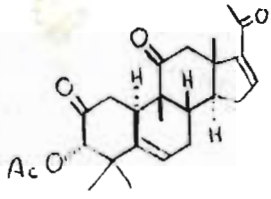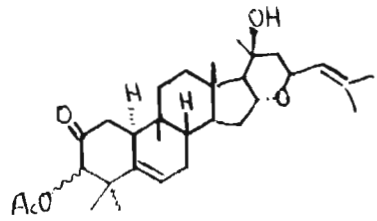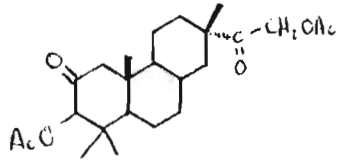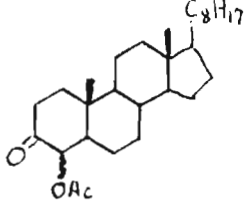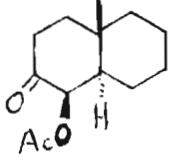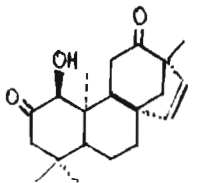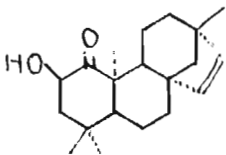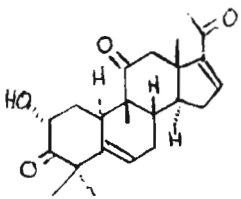
*** Note deshielding on hydrogenation - confirms boat or twist conformation.

| | | IN CS$_2$ | |
|---|---|---|---|
|  | (177) | 4.94 | 21 |
|  | (179) | 4.95 | 45 |
|  | (180) | 4.98 | 45 |
|  | (175)  (176) | 4.98     4.67<br>(6.2, 13.0) (2.5, 2.5) | 154 |
|  | (174) | 5.13<br>(m) | 160 |

| | | | |
|---|---|---|---|
|  | (185) | 4.92 | 163 |
|  | (159)    (160) | 5.08           4.95 | 155 |
|  | | 5.37 | 14 |
|  | (182)     (183) | 4.84 $(CS_2)$ 4.80 | 154 |
| | | 5.0  $(CDCl_3)$ | 147 |
|  | (181) | 4.90 (m) | 161 |
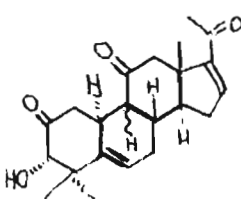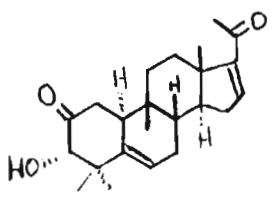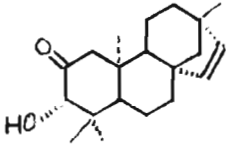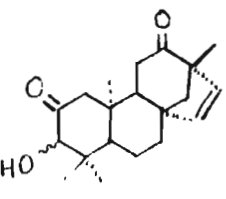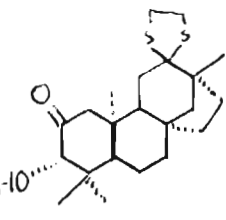
B) <u>THE CHEMICAL SHIFT OF THE HYDROXYMETHINE PROTON OF SECONDARY α-KETOLS.</u>
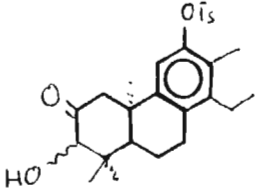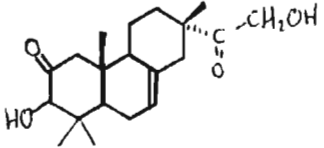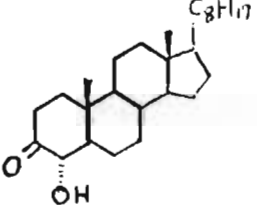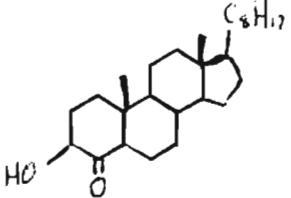
| STRUCTURE | EQUATORIAL≠ | AXIAL≠ | EQUATORIAL | AXIAL | REFERENCE |
|-----------|-------------|--------|------------|-------|-----------|
|  | (186) | (187) | 3.89 | 3.59 | 49 |
|  | (48) | | | 3.33 | |
|  | (188) | | 4.5 (5, 12.5) | | 49 |
|  | (189) | | | 4.39 (6, 13) | 163 |

≠ Equatorial and Axial refers to the configuration of the hydroxyl group when the ring is in the chair form.

**** No shift on hydrogenation.

| | | | |
|---|---|---|---|
|  | (191) | 3.69<br>(1) | 163 |
|  | (190) | 3.86<br>(1) | 163 |
|  | (192) | 3.72 (CCl$_4$) | 2 |
|  | (1)          (54) | 3.90**** 3.93<br>(1) | |
|  | (193) | 3.90 | 45 |

| | | | |
|---|---|---|---|
|  | (108) | 3.90 | |
|  | (139) | 3.87 | |
|  | (194) | 3.91 (CDCl$_3$)<br><br>3.75 (CCl$_4$) | 45<br><br>164 |
|  | (197) | 3.93<br>(2) | 45 |
|  | (195) | 3.93<br>(broad) | 45 |

| | | | | |
|---|---|---|---|---|
|  | (196) | (234) | 3.95 (broad) | 3.90 (broad) | 45 |
|  | (236) | | 4.03 (shoulder) | | 14 |
|  | (198) | | 3.97 | | 147 |
|  | (199) | | 4.08 | | 147 |

**16.3.1.** Inspection of the Table V shows that in fact very little
work has been done on ketols and their acetates since in most
instances only one or at the most two isomers (not always
necessarily epimers) have been prepared, usually in connection
with other work. However if a few complete series could be
added to the list then some definite trends may hopefully emerge
and make future assignments facile. This lack of data only became
apparent at the end of this work, when it was no longer possible
to enlarge on this series.

**16.4.1.** LONG RANGE COUPLING IN THE N.M.R. SPECTRA

The carbinol proton of the ketols and their acetates is not always
a sharp singlet but often shows splitting (1-2 $H_z$) or just broadening
due to long-range coupling. In the case of the 1 $\beta$ -acetoxy-
2,12-dione and its ketol, this was shown to be due to W coupling
to the 3 $\alpha$ -proton as the atoms H-1eq,C-1,C-2,C-3,H-3eq all lie in
a nearly perfect plane, which is a prerequisite for effective
4$\sigma$-bond coupling [165]. However Lacoume [164] reported axial-axial
4$\sigma$-bond coupling through a carbonyl carbon for a series of 3-
substituted-2-ketones in the lanost-8(9)-ene and cholestane systems
thus invalidating any attempts at using the presence or absence
of H-1/H-3 coupling as evidence for a particular conformation in
relation to ambiguous cases such as the 3-axial-acetoxy-2-one
system. The latter is expected to show normal W coupling if in
a chair conformation or $\psi$-axial-$\psi$-axial coupling if in a boat or
twist conformation.

# C H A P T E R   1 7

## SELENIUM DIOXIDE DEHYDROGENATION

17.1.    Selenium dioxide has been widely used to convert ketones
into their $\alpha, \beta$ -unsaturated analogues, especially in the steroid
field. [166]    The 12-ketone in steroids reacts very smoothly giving
the 9(11)-en-12-one chromophore.

17.1.1.   The ready rearrangement of the 12-ketone with acetic
anhydride and strong acids to give the D-homo-C-nor- $\alpha, \beta$ -
unsaturated ketone [52] (SECTION 12.1.) prompted a study of similar
slightly modified systems to test their ease to rearrangement.   The
9(11)-en-12-ketone was an obvious choice since in this case the
12-ketone would be already conjugated and may have been reluctant
to rearrange.   Also the homoconjugation of the 15(16)-double bond
would be altered by the added unsaturation and this was of interest.
Furthermore, reduction of the ketone to an allylic alcohol, as
had been accomplished in the cholane series [20, 168], was a profitable
step since this could then be converted into a good leaving group
(e.g. tosylate or phosphochloridate) and the resulting carbonium ion
could then undergo the previously observed D-homo-C-nor rearrangement
to the transoid diene system [20,85].   Alternatively the 9(11)-
double bond could migrate via an allylic rearrangement, to the 11(12)-
ene system thus causing a backbone rearrangement involving the C-10
methyl group [167] or the etheno-bridge (C-15 from C-8 to C-9).

17.1.2.  The ketol acetate (3) reacted very readily with selenium dioxide in t-butanol to give a quantitative yield of the 9(11)-ene derivative (200) with no trace of any other product (t.l.c.)  It is interesting to note that both the starting material and (200) have the same $R_f$   value on ordinary silica gel used for t.l.c. but a different colour which develops on spraying with acidic anisaldehyde.  The selenium proved very difficult to remove completely, as is usual for this material.  Chromatography gave a product containing only traces of selenium but no further purification could be effected except by sublimation.  Besides this selenium impurity, however, the product proved homogeneous by mass spectroscopy.

17.1.3.  When a solution of this compound (200) in acetic anhydride was treated with a large excess of concentrated sulphuric acid and the mixture set aside for 5-10 minutes before diluting it with water, the starting compound was isolated with no trace of reaction. Thus, as was anticipated, the ketone rearrangement did not take place.

17.1.4.  $NaBH_4$ reduction to yield the 12-allylic alcohols was next attempted.  This reaction however was extremely complex even when carried out under mild conditions and with no acid treatment. The crude product on t.l.c. unexpectedly proved to be a complex mixture of many compounds.  Obviously there were competing reactions. Apart from rearrangement products derived from the reactive allylic alcohols it was also possible that 1,4-hydride addition took place, reducing the 9(11)-double bond and thus giving further complications

in the form of the saturated alcohols. In a recent publication [168]
the aromatisation of the cholane C-ring under mild conditions
has been reported on reaction of the 9(11)-en-12-ols with HCl gas.
It is felt that a related reaction may have occurred in the present
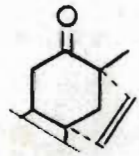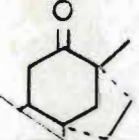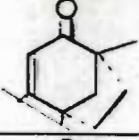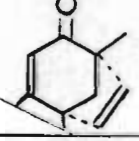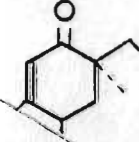investigation. This problem will be the subject of future investi-
gation.


### 17.2.1. HOMOCONJUGATION

Selenium dioxide dehydrogenation of the 15(16)-dihydro
derivative was also carried out giving (201).

Comparison of the n.m.r. spectra showed that there was
a marked interaction between the 9(11)-en-12-one system and the
"isolated" 15(16)-unsaturation. (See Table VI).

TABLE VI

N.M.R. VALUES ILLUSTRATING THE HOMOCONJUGATION EFFECTS OF THE 15-EN-12-ONE
AND   9(11),15-DIEN-12-ONE SYSTEMS.

| COMPOUND | | H-3 | H-11 | H-15 | H-16 | CH$_3$-17 | 18- | 19- | 20- |
|---|---|---|---|---|---|---|---|---|---|
|  | (3) | 4.93 | | 6.03 | 5.65 | 1.12 | 1.12 | 0.87 | 0.77 |
|  | (8) | 4.93 | | | | 1.10 | 1.13 | 0.88 | 0.97 |
|  | (201) | 4.95 | 5.70 | | | 1.18 | 1.13 | 0.87 | 1.18 |
|  | (200) | 4.95 | 5.18 | 6.47 | 5.70 | 1.23 | 1.13 | 0.87 | 1.07 |
|  | (202) | 4.48 | 5.69 | | | | | | |

Inspection of the table shows that the C-20 methyl group is shielded by the presence of a 15(16)-double bond [169] and deshielded by the neighbouring 9(11)-double bond. This is readily explained since the C-20 methyl group is in the plane of the 15(16)-$\pi$-orbital, a region of high electron density. However the perpendicular relationship that this methyl group has with the 9(11)-double bond places it in a region of low electron density where there is no shielding effect.

Noteworthy are the H-11 resonance values and the H-15 resonance values, which are obviously intimately related. The value $\delta$ 5.70 for the H-11 resonance is typical for such an isolated $\alpha$,$\beta$ -unsaturated C-ring system.

For example in the analogous tricylic pimarane derivative (202) listed in Table VI[10] this signal occurs at $\delta$ 5.69. Introduction of the 15(16)-double bond in (200) shields this proton by 0.52 p.p.m., leaving no doubt that both unsaturated systems are in fact interacting. Similarly the H-15 resonance is instructive. Comparing the ring A ketol unsubstituted in the C-ring * (3 $\alpha$ - hydroxy-stach-15-en-2-one) [2] with that having a 12-carbonyl (1) shows that the H-15 resonance undergoes a downfield shift from $\delta$ 5.58 to $\delta$ 6.02, a shift of 0.44 p.p.m., on introduction of the 12-carbonyl, good evidence of electron density transfer from the double bond to the carbonyl (homoconjugation). Introduction of the 9(11)-double bond causes a further down field shift of 0.44 p.p.m. (6.03 to 6.47 $\delta$ ) for this H-15 proton. The diagram shows

---

* Footnote: The n.m.r. data for the 3 $\alpha$ -acetoxy-stach-15-en-2-one has not been reported, hence the free ketols are compared.

two possible ways in which electronic delocalisation could take

place: from C-15 to C-12 via C-16 and ultimately to the

C-9-C-11 system; or directly from C-15 to C-9,
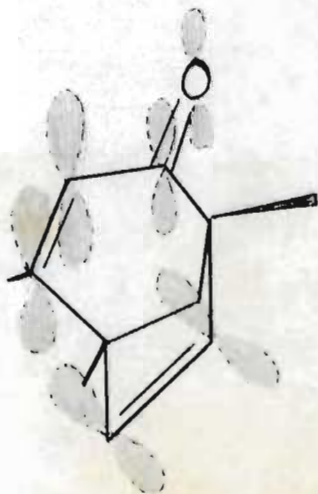


Since it appears that homoconjugation of the C-15,C-16,C-12,O-12

system does occur without the necessity of the 9(11)-double bond,

it is felt that charge transfer is probably via the indirect route

through the carbonyl carbon even in the presence of the 9(11)-ene

system.

17.2.2    This homoconjugation in $\beta$, $\gamma$ -unsaturated ketones has been

investigated by Guru data and Stothers [170] in relation to the

[13]C-carbonyl signals.  The present compounds should provide a very

interesting ^{13}C-relationship which should parallel the H-n.m.r. data.

17.3. A pilot photochemical reaction on a very small quantity of (200) showed that the material was all consumed in a short time, thus an investigation of the photochemistry of the system should be interesting and will be carried out at a later stage.
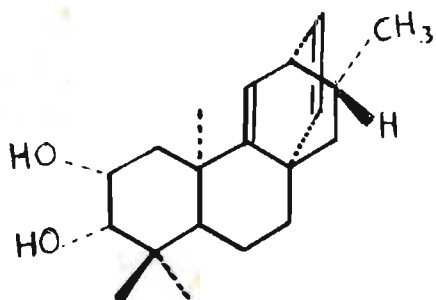
17.4 Further chemistry to be investigated involves the $9(11),15(16)$-dien-12-tosylhydrazone decomposition with $NaBH_4$. It is of value to determine if this $\alpha$, $\beta$ -unsaturated tosylhydrazone will also rearrange to a novel atisa-diene system (203) (SECTION 13.1.) or if simple elimination with concomitant double bond migration to yield the 11,15-diene (204) results.
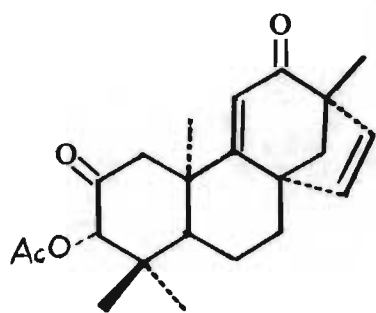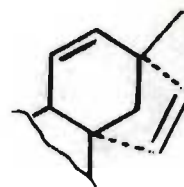
200
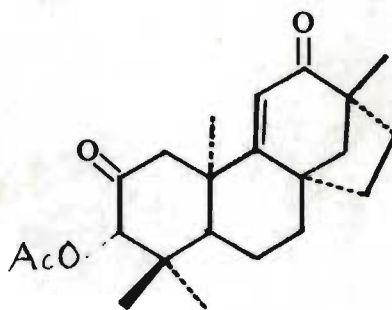
201

203

204

C H A P T E R   1 8

EPOXIDATION AND THE BAYER-VILLIGER OXIDATION

18.1     ALKALINE PEROXIDE

Alkaline hydrogen peroxide has been used both as a method of oxidizing a vicinal diketone to the seco-dicarboxylic acid [171-173] as well as to effect Bayer-Villiger oxidation [176] of ketones. [175] Both reactions occurred simultaneously and in quantitative yield when the $\alpha$-ketol (1) was treated at $0^{\circ}$ with alkaline hydrogen peroxide. The initial lactone function in the C-ring opened under the basic conditions and the tertiary hydroxyl function at C-13 was eliminated during the mild acid workup yielding as the final product the spiro compound (205), (5S,6'S,7'R,8'S)-2,7'-dimethyl-8'-(2,2-dimethyl-carboxymethyl)-spiro [4.5] deca-1,3-dieno-6',7'-diacetic acid. [190]



205
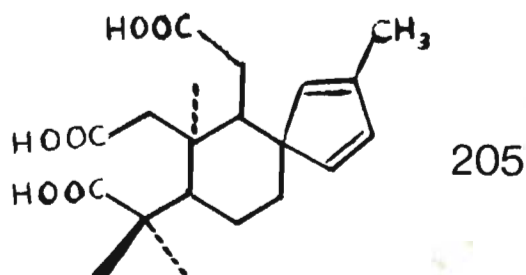
This structure was assigned on the basis of its formula and the u.v. and n.m.r. spectra as well as the mass spectral fragmentation. The formula $C_{20}H_{28}O_6$ accounted for all the carbon atoms such that no skeletal groups had been lost. The n.m.r. spectrum had a doublet signal at $\delta$ 1.8$\lambda$ (J=1.5H$_3$) for one of the methyl groups, as well as an olefinic one-proton multiplet at $\delta$

5.70 (H-1). Irradiation of either signal caused the other to be enhanced in peak height, the methyl signal especially giving a very sharp singlet. The two other olefinic protons also showed further long range coupling to this olefinic signal as shown by spin tickling experiments. However owing to the closeness of the chemical shifts of these three protons, no proper complete decoupling experiments could be carried out at 60 $MH_z$. A u.v. maximum at 254 n.m. ($\epsilon$ 1392) required the presence of a conjugated system. The mass spectrum contained the characteristic[5] fragmentation of the A-ring seco acid, with minor differences, and interestingly the 6'-acetic acid substituent was only lost at a late stage in the main fragmentation pathway. However a detailed discussion of this fragmentation is deferred until the fragments have been carefully mass measured to establish their identity.

Similar alkaline-peroxide treatment of the diosphenol (18) on the sole occasion it was tried fortuitiously gave the simple ring A seco acid (227). Periodate-permanganate oxidation of the dihydroketol (2) gave instead the 15,16-dihydro-A-seco acid (228), which was converted to the dimethyl ester (229) with diazomethane.

### 18.2.1. m-CHLOROPEROXYBENZOIC ACID

meta-Chloroperbenzoic acid is widely used as a reagent both for epoxidations of alkenes as well as for Bayer-Villiger oxidations[177]. When this reagent was used in cold chloroform on the ketol acetate (3), an extremely rapid reaction followed (t.l.c.) and a compound was obtained which analysed for $C_{22}H_{30}O_6$ (206).

The presence of one deshielded methyl group at $\delta$ 1.48 was consistent with the grouping $-O-C-CH_3$ and thus defined the direction of insertion of the oxygen atom to be between C-12 and C-13. Furthermore a pair of doublets in the region of $\delta$ 3.5 showed the presence of an epoxide, substantiated by the absence of any signals in the olefinic region.

This compound was then assigned the structure (206).

18.2.2. However prior conversion of the 12-ketone to a dioxyethane ketal prevented the Bayer-Villiger oxidation and gave only epoxide instead. In this way (77) was epoxidized to (207) via (89).



$89 \longrightarrow$  207    208
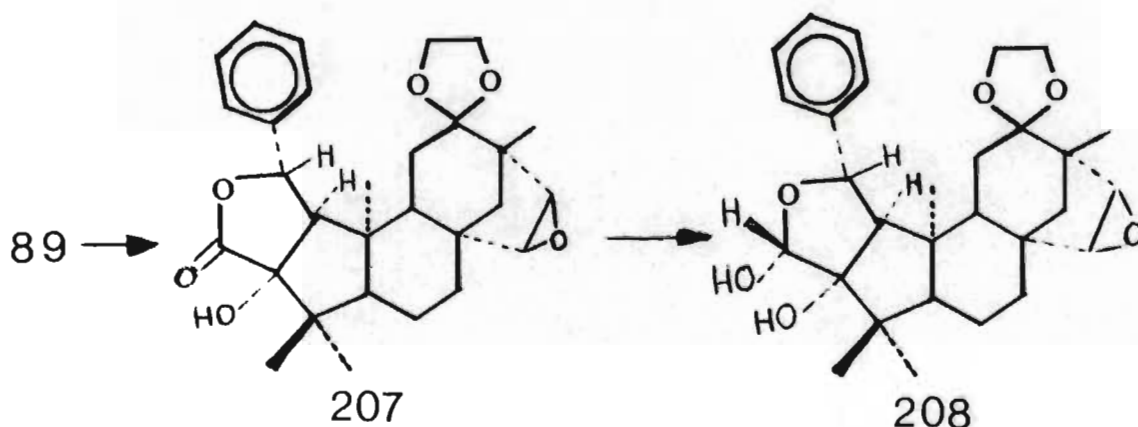
The epoxide function in (207) on reduction with LiAlH$_4$ in THF failed to open as had been noted by Hanson[135]. Instead the cyclic ring A hemiacetal (208) was obtained in good yield (see SECTION 9.1)

18.3. PERFORMIC ACID

Using performic acid generated in situ on (3) gave a fair yield of the epoxide (152). Examination of the reaction mixture by t.l.c. however indicated that even here some lactone formation had concurred.

## 18.4     THE 15,16-ADDUCTS

A pilot reaction using t.l.c. showed that the 15(16)-
dihydro compound (8) also gave a Bayer-Villiger product with
m-chloroperbenzoic acid, but the presence of the 15,16-dibromide
or similar addition compounds, completely inhibited this oxidation.
However, the presence of the epoxide function did not inhibit the
oxidation since preformed epoxide (152) on treatment with
m-chloroperbenzoic acid gave the same lactone-epoxide (206) as
before.  This was unexpected.  Arguments based on the electron-
withdrawing ability of halogen, acetate or nitrate adjacent to the
migrating centre (C-13) were discarded since the epoxide should
have then exhibited similar behaviour.  A steric factor may be
involved.  The mechanism [176] of the Bayer-Villiger oxidation
involves nucleophilic attack by the peracid on the polarised carbonyl
group, followed by alkyl group migration:
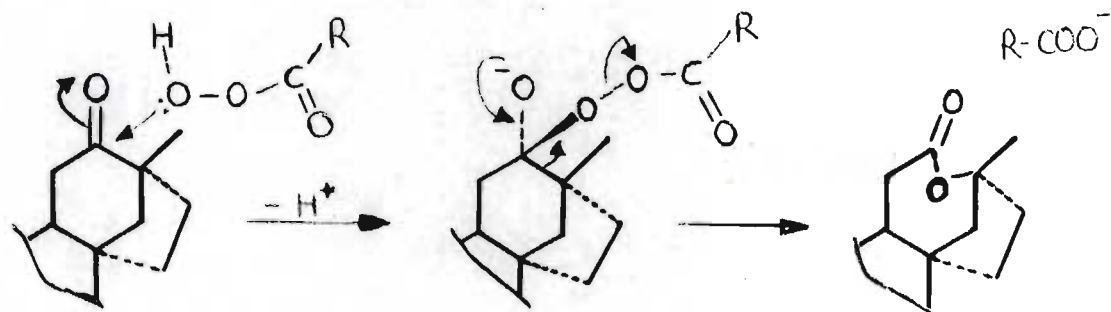


On steric grounds the 12-carbonyl would be expected to be attacked
preferentially from the $\beta$-face so that a steric hindrance factor would be
improbable.  However if $\alpha$-face attack was involved then of course the
large, electronegative 16-endo substituents would repel the incoming
nucleophilic oxygen, whilst this of course does not hold for the
exo orientated epoxide.

This meant however that $\alpha$-face attack at the carbonyl would have to occur with 100% stereospecificity, an apparently improbable conclusion.

18.5.1.  Epoxidations with m-chloroperbenzoic acid of 15-en-12-ols occurred normally as expected.  Thus (23) was converted to (209) in excellent yield.

18.5.2.  Attempted rearrangement of this compound (209) to the D-homo-C-nor-15,16-epoxide (210) by elimination of the 12 $\alpha$-alcohol with POCl$_3$ in pyridine, resulted instead in substitution with inversion at C-12 by  chloride ion to give (211).  This unexpected reluctance to rearrangement was unusual after the excellent results obtained with (23) and (21) (see SECTION 3.5) and may be due to electronic effects.  It is planned to use a similar case, such as the 15,16-dibromide derivative instead of the epoxide, to test the influence of other electronegative groups on this rearrangement.

18.6    CHROMIC ACID

18.6.1.  Jones oxidation of the ring A 1,2-$\alpha$-ketol gave a norketone (67) as previously indicated (SECTION 6.1).  This crude compound was sometimes contaminated by a less mobile spot on t.l.c. which could be removed by recrystallisation.  The mass spectrum of the impure nor-ketone contained an impurity with 16 mass units higher than (67)

and by analogy to the work on related compounds [178,179] this was

assumed (see later) to be traces of epoxide, especially since

increasing the amount of Jones reagent intensified this spot.

For most compounds however this oxidation was not used as a method

for making the epoxide as the $\alpha$-ketol or diosphenol functions

present in ring A in most compounds used in this work would not

have survived this treatment. However the benzaldehyde-lactone

(77) prepared as described before (SECTION 8.1) had been found to

be exceptionally stable to base or acid and it was used successfully

to test this method. Thus (77) was oxidized slowly in cold acetic

acid (and/or acetic anhydride) with chromium trioxide to give the

15,16-epoxide (212) exclusively. Heating on a steam bath gave a

rapid reaction without detracting from the yield and was found to

be the most convenient procedure for preparing this epoxide. The

same compound was formed using formic acid and hydrogen peroxide

in acetic anhydride as before.


18.7.    ATTEMPTED ACID-CATALYSED OPENING OF THE 15,16-EPOXIDE

Carbonium ion rearrangements following acid-catalysed ring opening

of epoxides in similar environments are well known [180]. Thus

stachenol epoxide rearranges to a kaurane diol on treatment with

BF$_3$, [12,135] and a similar result [181] was obtained on reaction of

erythroxylol A epoxide (213)



213
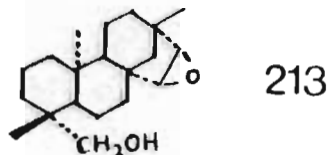
which yielded at least 13 compounds with formic acid, one of which,

surprisingly, was the stach-9(11)-en-12,19-diol.    Other epoxides

have been studied in the kaurane series. [182,183]

18.7.1. Since (212) could be prepared readily in large quantities this compound offered interesting possibilities for further work and a preliminary experiment was carried out. The epoxide was found to open with $BF_3$ in benzene to give 2 major more polar products which have not as yet been investigated.

18.7.2. The recommended procedure [184] for opening epoxides to trans-diols has been the use of a trace of perchloric acid in aqueous tetrahydrofuran at room temperature. A trial run using this procedure gave no reaction. Eventually the acid concentration was stepped up to 20% concentrated perchloric acid in tetrahydrofuran and the mixture refluxed for 14 hours with no trace of reaction. Thus it was concluded that this epoxide was stable to aqueous acid. Since (212) could be prepared in reasonable yield in formic acid with hydrogen peroxide(see above) at $60^{o}$ it could be safely concluded that the formic acid would also not effect epoxide opening in contrast to the work of Murray, Mills and Young [181] on erythroxylol A epoxide (213).

18.7.3. This exceptional stability was attributed to the presence of the 12-carbonyl group mainly on the strength of this contrasting behaviour with that reported by the other workers using 12-unsubstituted epoxides. The main reaction pathway for the reported rearrangements involves fission of the epoxide ring at the 16 position, generating a carbonium ion (classical or otherwise) which then rearranges by migration of the C-12:C-13 bond to C-12:C-16.

It may be that the electron withdrawing influence of the carbonyl group destabilises the required transition state and the reactions do not occur. However the failure of the 15-exo, 16-endo-diol to form is peculiar in the light of the ease of trans addition of halogens and pseudo halogens to the 15(16)-double bond (Chapter 14).



152



206



209



210



211



212



227



228
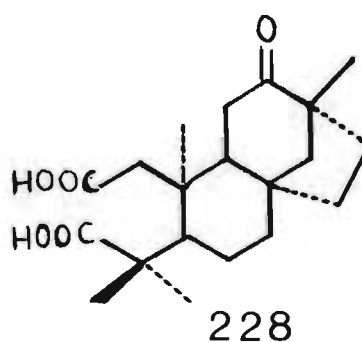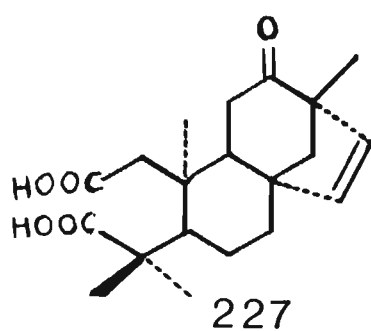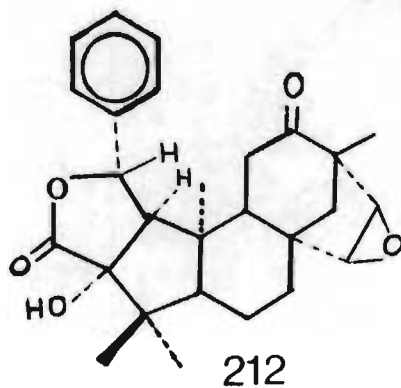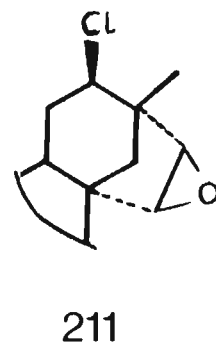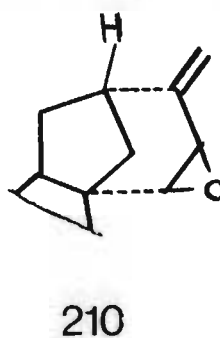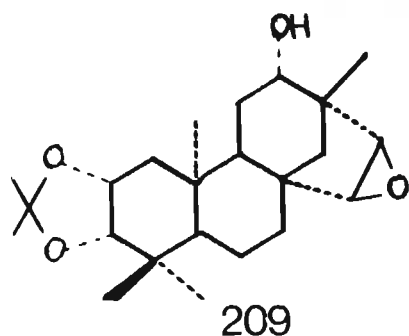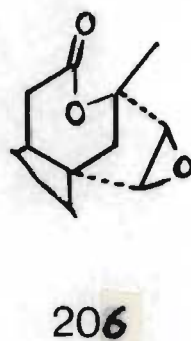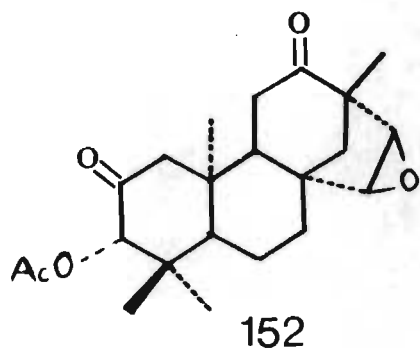
# C H A P T E R   1 9

## ISOLATION OF THE MINOR DITERPENE CONSTITUENTS OF <u>ANDROSTACHYS</u> <u>JOHNSONII</u>

<u>19.1</u>     Column chromatography of the crystalline material left after removal of the crystalline $\alpha$-ketol furnished several diterpenes. The first eluted was a hydrocarbon fraction in very small quantity and this was not further investigated. Further elution gave stachenone (215) which was characterized as its 2,4-dinitrophenylhydrazone [2] and later as the 2-benzylidene derivative, (216).

The next fraction was impure stachenol (5) which on rechromatography was separated into a very small quantity of $3\beta$-stachenol (217), identified by its n.m.r. spectrum, [12] and pure stachenol ($3\alpha$-stachenol). This is the first time that stachenol and its axial epimer have been obtained naturally. Up to the present stachenol had always been prepared by reduction of stachenone. Although not isolated from Tambooti extract, [2,135] examination of the crude extract on t.l.c. by us demonstrated the presence of stachenol in that wood as well. <u>Androstachys johnsonii</u> proved to be a rich source of stachenol.

Further elution of the main extract gave a yellow gum which resisted all attempts at crystallisation. A portion of this gum was converted into a crystalline, extremely insoluble dioxime (218) m.p. 289-290$^{\text{o}}$. Accurate mass measurement gave the formula $C_{20}H_{30}N_2O_2$ consistent with a diketone. Another portion of the yellow gum was reduced with NaBH$_4$ to give a mixture consisting mainly of a diol together with some triol originating from diosphenol present in the gum.

Chromatography gave the pure diol ( 219) $C_{20}H_{32}O_2$, whose n.m.r.
spectrum was consistent with the $3\alpha$ ,12 $\alpha$-dihydroxy-stach-15-ene
diol structure. This was further indicated by the formation of a
pink colour with the anisaldehyde - $H_2SO_4$ spray on a t.l.c. plate,
a reaction characteristic for the 12 $\alpha$ -alcohols and the derived
D-homo-C-nor dienes (e.g. 14). Co-chromatography on t.l.c. of
the crude hexane extract of <u>Androstachys johnsonii</u> indicated that
a compound with similar chromatographic behaviour to (219) was
present.

The diosphenol (18) was isolated from the acetone extract
of the first heartwood samples (NDO 133) in small quantities [185],
both as the yellow diketone and as the enolone. Later samples of
wood (NDO 140  and NDO 141) gave the diosphenol (18) as the major
component of the hexane extract with no isolatable $\alpha$ -ketol (1)
although the latter was present in minor quantity as shown by t.l.c.

19.2     The mother liquors from the recrystallisation of the $\alpha$ -
ketol ( 1) were very rich in $\alpha$ -ketol (1) and diosphenol (18) and
several derivatives were successfully prepared on a large scale
using this crude extract.  The benzaldehyde condensation product
(77) was very easily prepared by this method.  The crude (77)
on recrystallisation gave a yellow mother liquor which deposited
further (77) mixed with yellow crystalline material.  This mixture
was efficiently hand separated and t.l.c. of the yellow crystals
indicated them to be a mixture of at least five compounds! Chroma-
tography resulted in a clean separation of four of these components.
The first eluted was 2-benzylideno-stachenone (216) as shown by its

preparation from authentic stachenone. The second component

analysed for $C_{27}H_{32}O_2$ and exhibited two carbonyl bands in the i.r.

spectrum at 1667 ( $\alpha$ , $\beta$ -unsaturated ketone) and 1705 (saturated

cyclohexanone) $cm^{-1}$, with no hydroxyl absorption. The n.m.r.

spectrum clearly established its structure as the 2-benzylideno-

stach-15-en-3,12-dione (220), since it was nearly identical to

that of (216). However, wheareas in the latter (216) the olefinic

protons resonated as two doublets at $\delta$ 5.45 and 5.70 in the

diketone (220) these appeared at $\delta$ 5.63 and 6.07, a downfield

shift of 0.18 p.p.m. for H-16 and 0.37 p.p.m. for H-15 consistent

with the homoconjugative effect of a 12-ketone. This was further

substantiated when the 12-ketone function was rearranged with

sulphuric acid in acetic anhydride[52] to give the D-homo-C-nor

conjugated ketone (221) with the identical double bond pattern to

(109). Similarly, the conversion of (220) to (221) resulted in

an upfield shift of the 20-methyl group by 0.1 p.p.m. due to the

increased shielding by the double bond. It was then reasonable to

expect the dioxime (218) to be that of the unsubstituted stach-15-

en-3,12-dione, and the diol (219) then had to be 3$\alpha$ ,12$\alpha$ -

dihydroxy-stach-15-ene.

Further elution gave the third component (222), $C_{27}H_{34}O_2$,

whose i.r. spectrum clearly indicated the presence of a hydroxy

group. The ring A 2-benzylideno-3-one was again apparent from the

n.m.r. spectrum, which also showed the hydroxy group to be tertiary

since no methylene or methine protons were present as in a primary
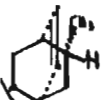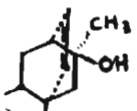
or secondary alcohol.

(222)

The occurrence of a different skeleton in this compound ∧became

obvious on observing the olefinic region. Instead of the usual

AB quartet for the stachane 15,16-double bond, there appeared a

five line pattern integrating for two hydrogens. This consisted

of a doublet at $\delta$ 5.83 (J 7.5 Hz) and a partially resolved quartet

at $\delta$ 6.11 (J6 and 8Hz). With a second stationary r.f. signal at

$\delta$ 2.30 the olefinic one-proton quartet collapsed to a very broad

doublet (J 7.5 Hz). Thus the partial structure -CH-CH=CH-CR- was

present. Use of the europium shift reagent Eu(FOD)$_3$ caused the

methyl groups to move downfield but had no significant effect on

the double bond protons indicating that the tertiary hydroxyl

group, which complexed strongly, was not oriented towards the double

bond. These europium shift experiments also confirmed the stereo-

chemistry of the benzylidene grouping. Since the styrene hydrogen

was appreciably deshielded on addition of Eu(FOD)$_3$, whilst the

aromatic proton resonance remained practically unaffected this

could only be explained by a structure which had the styrene hydrogen

on the same side as the 3-keto group which complexed with the

Eu(FOD)$_3$. Of the known diterpene skeletons including the new ones

prepared during this work, the only tetracyclic structure which

could accomodate the above groupings was of the atisane type.

However atisanes have the 17-methyl group secondary whilst in (222)

there was no indication of any splitting. Furthermore only four

tertiary positions for the hydroxyl group were possible in the

normal atisane skeleton, at the     5,9,12 and 13 positions. 5

and 9 were thought unreasonable because of the similarity of the

ring A n.m.r. pattern of (216),(220) and (222).

Position 12 could then not accomodate the part structure indicated above, in order to give the olefinic pattern shown. The only alternative was to place the tertiary hydroxyl geminal to the 17-methyl group on C-13. This would then account for the tertiary 17-methyl group in an atisane.

The orientation of the 17-methyl group towards the double bond should shield it to a great extent (see (131), section 13.2.2.) whilst the presence of the oxygen substituent at C-13 should deshield it. Taking the resonance position of the 17-methyl group in (216) at $\delta$ 1·01 as the standard and a comparison with two atisane derivatives (139) and (135) indicated a net shielding effect of 0.3 p.p.m. On the other hand the 17-methyl group resonance in the lactone (206) appears at $\delta$ 1.48 which is a deshielding of 0.47 p.p.m. The algebraic sum of +0.30 and -0.47 p.p.m. gives a net deshielding of 0.17 compared to (216). Thus (222) should have the 17-methyl group resonance at $\delta$ 1.17 whereas it is in fact at $\delta$ 1.16, a remarkable close agreement.

## TABLE VII

### N.M.R. CHEMICAL SHIFT OF THE 17-METHYL GROUP

| STRUCTURE | NUMBER | 17-METHYL RESONANCE $\delta$ |
|---|---|---|
| | 216 | 1.01 |
| | 139 | 0.72 |
| | 135 | 0.70 |
| | 206 | 1.48 |
| | 222 | 1.16 |

Furthermore, attempted elimination of the hydroxyl group with **p**-toluene sulphonic acid or oxalic acid gave a mixture of three chromatographically similar components which have not yet been further investigated.

A further compound (223) was isolated by preparative t.l.c. from a fraction containing an admixture of (222) and this more polar compound. The double bond pattern in the n.m.r. was similar to that discussed for (222) but the styrene hydrogen was absent. The i.r. indicated an intramolecular hydrogen bond with the carbonyl($\nu$ max 3536 cm$^{-1}$) and thus the structure was thought to be the primary aldol product in the formation of (222).
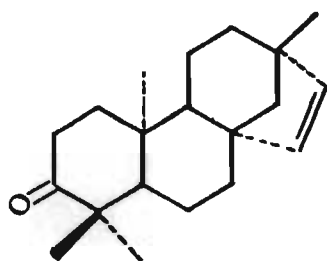
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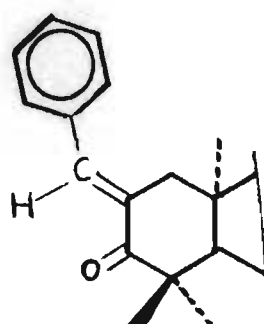
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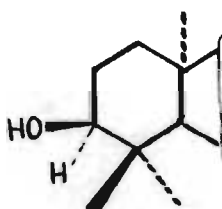
217

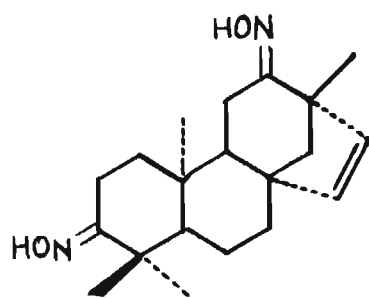218


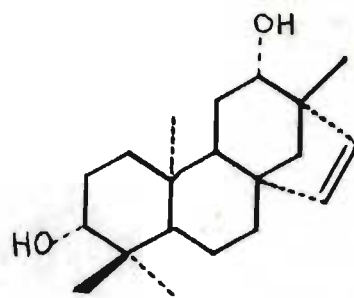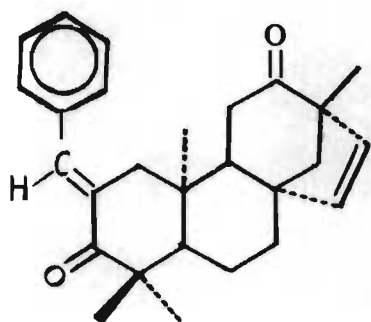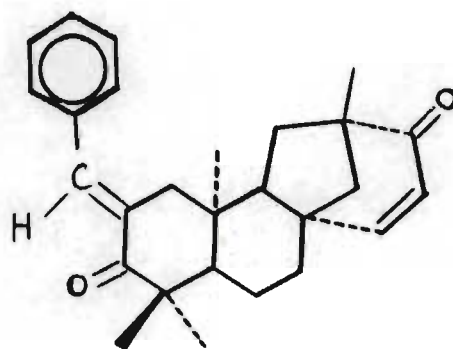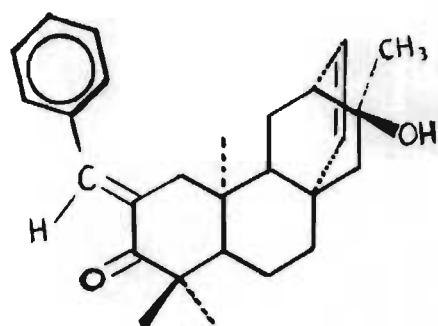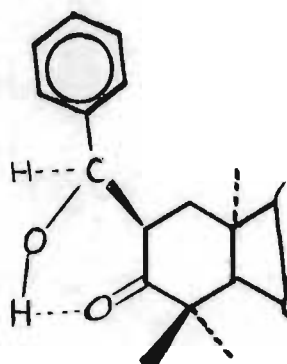
219



220



221



222



223

## BIOLOGICAL ASPECTS

The biosynthetic significance of such large quantities of tetracyclic diterpenes in the heartwood remains obscure. Although it is known that kauranes can be converted to gibberellins, the well-known growth hormones, no apparent "use" of beyeranes by the plant is known.

Mention has been made that the wood is extemely resistant to termite attack and the extract appears to retain this insect repellant qualities against cockroaches at least. It is then possible that some diterpenoid constituent is responsible for this effect. Since this is beneficial to the plant, making it less vulnerable to insect attack during its lifetime it may have resulted in a natural selection of individuals having higher concentrations of these diterpenoids with the end result noted here.

The production of these materials in these quantities in the first place cannot be explained except possibly by invoking a derangement of the normal diterpenoid metabolic pathways during the senescence of the cambial cells prior to their lignification and death.

EXPERIMENTAL

## EXPERIMENTAL

All melting points were determined on a Kofler micro hot-stage and are uncorrected.

Optical rotations were measured on a Perkin-Elmer 141 M automatic polarimeter at 589 nm using chloroform solutions at room temperature (20-24$^{\circ}$), unless otherwise specified.

Infra-red spectra were recorded from KBr discs using a Perkin-Elmer 521 and are given in RECIPROCAL CENTIMETRE (cm$^{-1}$).

Ultraviolet absorption spectra were recorded in 95% ethanol using a Beckmann DB u.v./visible grating spectrophotometer (or a Unicam SP 1800 ultraviolet spectrophotometer) and are given in nm. Mass spectra were recorded on an A.E.I. MS 9 double-focussing mass-spectrometer.

N.m.r. spectra were recorded in deuterochloroform solution unless otherwise specified. The spectra were obtained on a Varian T60, Varian HA-100 as well as a Varian XL-100 spectrometer. The spectra reproduced here are those taken with a T60 for convenience of reproduction. The values are all reported on the $\delta$ scale and are with reference to tetramethylsilane (TMS) used as the internal lock. The chemical shift values are accurate to 0.015 ppm, and the coupling constants to 0.5 Hz (for 60 MHz measurements) or 0.25 Hz (for 100 MHz measurements).

## CHROMATOGRAPHY

THIN LAYER CHROMATOGRAPHY (t.l.c.): This was performed using a 0.3 mm thickness of Merck Kieselgel G No. 7731.

PREPARATIVE LAYER (p.l.c.) : This was carried out as above except that the plates were coated with a 1 mm thickness of silica gel.

COLUMN CHROMATOGRAPHY: Merck silica gel was used. For very large columns the coarse particle size No. 7733 (0.2 - 0.5 mm) was used. Routine columns used the medium size No. 7734 (0.063-0.200 mm), whilst for careful spearations of closely eluted compounds the fine grade No. 7729 (under 0.08 mm) was used. Occasionally basic alumina was used (Hopkin and William - activity 1).

SOLVENT SYSTEMS:

The common system used was a benzene-ethyl acetate mixture (9:1). For less polar compounds a hexane-ethyl acetate mixture (19:2) was used. For more polar compounds a benzene-ethyl acetate mixture (2:1) was employed. Very polar compounds such as the triols and acids required the use of a mixture consisting of chloroform-ethyl acetate-acetic acid (50:40:1 or 5:4:1 depending on polarity).

DETECTION:

A spray reagent made up of a solution of anisaldehyde (5 ml), concentrated sulphuric acid (5 ml) and ethanol (90 ml) was used.

Heating at 120$^O$ for 1-5 minutes developed the colours.   This
spray reagent was found to be the most sensitive tried.

VACUUM-EVAPORATION:  The term "evaporation under reduced
pressure" implies the use of a rotatory vacuum evaporator.

YIELDS:  These are quoted for analytically pure material and
usually refer to the first crop of crystals obtained.

## ISOLATION OF THE HEXANE-SOLUBLE HEARTWOOD CONSTITUENTS.

Three batches of Androstachys johnsonii were obtained
from Punda-Malia in the Kruger National Park.   The first batch
NDO 133 yielded the α-ketol (1) as the major constituent
whilst the other two NDO 140 and NDO 141 yielded the diosphenol
(18).

The milled, air-dried heartwood (227g) was extracted
three times with cold hexane, the last extract being colourless
unlike the previous yellow ones.   Evaporation of the combined
extracts deposited masses of colourless rods m.p. 160$^O$.
Filtration and further evaporation gave a further crop.   The
total yield of crystalline material was 12g (5.3% of heartwood
or 38% of hexane extractives).

The hexane mother liquor on complete evaporation gave
19g of solids (8.7%).   Extraction with hot hexane did not
increase the yields.

On a large scale the total hot hexane extracts were allowed to evaporate to a yellow solid. Any oil at this stage was decanted off and labelled "Mother Liquor 1". The pale yellow friable solid (275g) was redissolved in hot hexane and allowed to crystallise once more. The supernatant was again decanted and labelled "Mother Liquor 2". The sticky yellow crystals were now dissolved in a minimum of hot ethanol (about 150ml) diluted with hexane (about 500-750ml) and boiled down to a volume of about 300ml and allowed to crystallise. This supernatant was labelled "Mother Liquor 3" (ML 3). The pale yellow material so obtained was highly crystalline and could now be used as such for making derivatives such as the acetate or benzoate. However pure material was obtained by recrystallising a fourth time from ethanol-hexane as before. In this way a yield of 58g of (1) was obtained from 275g of extract (these figures represent those collected at one actual instance and are by no means maxima or minima).

The pure $\alpha$-ketol (1), 3$\alpha$-hydroxystach-15-ene-2,12-dione was obtained as colourless spars, giving a red colour with alkaline, methanolic triphenyltetrazolium chloride solution. The compound could be readily grown into large crystals and one crystal was grown from ethanol into a large orthorhombic spar measuring 3.5 x 1.2 x 0.8cm.

The compound (1) had m.p. 163-165.5$^{\circ}$, $(\alpha)_D$ - 329.3$^{\circ}$(c 2.0). (Found C,75.73; H,8.85; $M^+$ 316.2022. $C_{20}H_{28}O_3$ requires C,75.91; H,8.92; $M^+$ 316.2038).

$\lambda_{max}$($\varepsilon$): 296 (240) and 215 (4110) end absorption.

$\nu_{max}$ : 3525 (broad), 1705(broad), and 767 cm$^{-1}$.

$\delta$ : 0.68(3H,s,20-Me); 0.72(3H,s,19-Me); 1.08(3H,s,17-Me); 1.18(3H,s,18-Me); 3.73(1H,br.s, exchanged with $D_2O$,3-OH), 3.90(1H,s,H-3β); 5.62 and 6.00(2H,ABq,$J_{15,16}$5.5 Hz, 16- and 15-H resp.).

## HYDROGENATION OF (1) TO 3α-HYDROXYSTACHANE-2,12-DIONE (2).

The ketol (1) (3g) in ethanol (50ml) was hydrogenated using a Pd/C catalyst (30%, 200mg) until no more hydrogen was consumed (2.2ml at NTP, 1.0 mole equivalent). Filtration through Whatman No.542 paper removed the catalyst; the solution was then concentrated to 20ml, a little water was added and the sample allowed to crystallise to needles, m.p. 107-108$^{O}$, $[\alpha]_D$ - 33.7$^{O}$(c 2.05).

(Found M$^+$ 318.2193; $C_{20}H_{30}O_3$ requires 318.2194).

$\lambda_{max}(\epsilon)$: 284 (71) and 210 (2150) end absorption.

$\nu_{max}$ : 3483,3400(b), 1705(b), 1115 cm$^{-1}$.

$\delta$ : 0.72, 0.95, 1.10 and 1.21(19-,20-, 18- and 17-Me resp.); 3.82(1H,b.s., EXCHANGED WITH $D_2O$, 3-OH); 3.91(1H,d,J= 1 Hz, coupling through carbonyl, 3β-H).

## 3α-ACETOXYSTACH-15-ENE-2,12-DIONE (3).

The ketol (1) (1g) was dissolved in pyridine (5ml) and added acetic anhydride (3ml). Left overnight at room temperature (r.t.), poured into crushed ice-water (100ml),

filtered and recrystallised from aqueous methanol giving large, well-shaped rhombs m.p. 169-170°, $(\alpha)_D$ -356.3° (c 2.00); (Found C, 73.43; H,8.51; $M^+$ 358.21557.   $C_{22}H_{30}O_4$ requires

C, 73.71; H,8.44; $M^+$ 358.21439)

$\lambda_{max}$ $(\varepsilon)$:   296 (233) and 210 (4010) end absorption.

$\nu_{max}$   :   3380 (overtone), 1740, 1720, 1692, 1230, 763 $cm^{-1}$.

$\delta$   :   0.75(3H,s,20-Me); 0.84(3H,s,19-Me); 1.10(6H,s,17-

and 18-Me); 2.14(3H,s,Acetoxyl); 4.90(1H,s,H-3β);

5.63 and 6.02(2H,ABq,$J_{15,16}$ 5.5H$_z$, 16-and 15-H resp.).

The crude, crystalline product obtained after pouring into water could be used for further reactions without recrystal-lisation.

### 3α-HYDROXYSTACH-15-ENE-2,12-DIONE-2,12-DIOXIME  (4)

The ketol (1) (1.0g) in ethanol (20ml) and pyridine (5ml) containing hydroxylamine sulphate (or chloride) in water (1.5g in 5ml) was refluxed overnight, removed part of the solvents under reduced pressure and diluted with water.   The crystals so obtained (0.95g) were recrystallised with difficulty from ethanol to give cubes, m.p. 275-277° with decomposition, $(\alpha)_D$ -133°,   (c 2.11).

(Found C, 68.92; H,8.78; N,7.92; $M^+$ 346.2269.   $C_{20}H_{30}N_2O_3$ requires

C, 69.33; H,8.73; N,8.09; $M^+$ 346.2256).

$\nu_{max}$:   3475, 3400(b), 1660, 1655, 1445, 1405, 1380, 905, 708$cm^{-1}$.

## 3α-HYDROXYSTACH-15-ENE (5)

The ketol (1) (1.5g), hydrazine hydrate (5ml), ethanol (20ml) and digol (45ml) were refluxed for 30 minutes, then added KOH (7.5g) in $H_2O$ (10ml) and refluxed for a further 3.5 hrs. Distilled volatiles until temperature reached 210° and then refluxed for a further 2.5 hours. Cooled, acidified and diluted with water. Extracted with hexane, concentrated, and chromatogrammed on silica gel (Merck 7734, 60g in hexane). Elution with hexane gave a hydrocarbon fraction which crystallised from ethanol to give mainly stachene (19). Gas-liquid chromatography (g.l.c.) was performed on a Pye Unicam 104, single column instrument with a flame-ionisation detector. A glass column (7ft by 4mm internal diameter) packed with SE 30 (2% on chromosorb-W-HMDS) at an oven temperature 225° was utilised for the hydrocarbon separation. The samples (100mg in 1.0ml $CHCl_3$, 0.2μl) were injected into the injection port (maintained at 280°) using a $N_2$ flowrate of 40ml/min. The sample of crude stachene was resolved into three peaks, the most mobile compound (20%), stachene (19) (67%) and the least mobile (13%); the proportions were estimated purely from peak heights since the peaks were very sharp and did not tail at all. M.p. 35-40° (lit.[188] 29.5-30°), $M^+$ 272.2510, $C_{20}H_{32}$ requires 272.2504.

Further elution with benzene-hexane-ethanol (50:50:0.25) gave (5), needles from aqueous ethanol, m.p. 159-161° (lit.[2] 164°),[189] $[\alpha]_D$ +36° (c 1.0) (lit.[2] +28°).

(Found $M^+$ 288.2461; $C_{20}H_{32}O$ requires $M^+$ 288.2453).

$\nu_{max}$: 3300(b), 3030, 1590, 1045, 750 $cm^{-1}$.

$\delta$ : 0.73(3H,s,20-Me); 0.77(3H,s,19-Me); 0.98(6H,s,17-and 18-Me)

3.18(1H,m,W½18Hz,3β-H); 5.43 and 5.67(2H,ABq,$J_{15,16}$

5.5Hz, 16- and 15-H resp.).

The derived acetate 3α-ACETOXYSTACH-15-ENE was prepared from stachenol (32mg), procedure as for (3), to yield the acetate (32mg) m.p. 121-123.5°(lit.[2] 117.5-119.5°), $(\alpha)_D$+13° (c 2.1)(lit.[2] +12°).

(Found $M^+$ 330.2560, $C_{22}H_{34}O_2$ requires 330.2558).

$\nu_{max}$: 3435(overtone), 3038, 1720, 1240, 750, 737 $cm^{-1}$.

## 3α-HYDROXYSTACH-15-ENE-2,12-DIONE-2,12-BIS-(ETHANEDITHIO KETAL) (6).

To the α-ketol (1) (1.0g) in glacial acetic acid (12ml) was added ethanedithiol (1.0ml) and boron trifluoride-etherate ($BF_3Et_2O$, 1.0ml). After 10 minutes compound crystallised out and left overnight. Added $H_2O$ (5ml), filtered and washed with ethanol. Recrystallised from ethanol-chloroform giving threads (1.0g, 68.5% yield), m.p. 293-295° (dec.); $(\alpha)_D$-28.5° (c 0.76).

(Found $M^+$ 468, M-28, 440.1332, $C_{24}H_{36}OS_4$ requires

M-28, 440.1336).

$\nu_{max}$: 3505, 3045, 3005, 755 $cm^{-1}$.

$\delta$ : 0.93, 0.98, 1.06(3x3H,3xs,3xMe); 1.29(3H,s,17Me);

3.0-3.4(8H,m,2x-$SCH_2CH_2S$-); 5.73(2H,ABq,J5Hz).

## 3α-HYDROXYSTACHANE (7)

(6) (0.800g) in THF was added to a slurry of Raney nickel (10g) in ethanol, and the mixture refluxed 7 hours. Filtered, evaporated and diluted with water to give crystals of (7) (0.280g, 56.5% yield) m.p. 151-153$^O$ (lit.[2] 158-159$^O$), $(\alpha)_D$ -4$^O$ (c 1.4) (lit.[2] -4$^O$).

$\nu_{max}$: 3300(v.b), 1450, 1045, 975 cm$^{-1}$.

Acetylation as for (3) afforded 3α-ACETOXYSTACHANE, m.p. 143-146$^O$ (lit.[2] 146-147$^O$), $(\alpha)_D$ -15$^O$ (c 0.94)(lit.[2] -12$^O$).

$\nu_{max}$: 1722, 1240 (b).

## 3α-ACETOXYSTACHANE-2,12-DIONE (8).

(i) Acetylation of the 15,16-dihydroketol (2) as for (3) gave the acetate.

(ii) Similarly hydrogenation of (3) using Pd/C as before for (2) gave (8) as colourless spars from aqueous methanol, m.p. 215-216$^O$ (sublimes above 175$^O$), $(\alpha)_D$ -112$^O$ (c 2.07). (Found C,73.41; H,9.09; M$^+$ 360.2310. C$_{22}$H$_{32}$O$_4$ requires C,73.30; H,8.95; M$^+$ 360.2300).

$\lambda_{max}(\varepsilon)$: 288(59) and 210(564) end absorption.

$\nu_{max}$: 3395(overtone), 1742, 1724, 1708, 1235, 680 and 667cm$^{-1}$.

$\delta$ : 0.86(3H,s,19-Me); 0.96(3H,s,20-Me); 1.08 and 1.11 (2x3H,2xs,17-and18-Me); 2.15(3H,s,ACETOXYL);4.93 (1H,s,3β-H).

## 3α-ACETOXY-11β-BROMOSTACHANE-2,12-DIONE (9)

Dihydroketol (2) (0.937g) in glacial acetic acid (5ml) and acetic anhydride (5ml) was treated with bromine (0.5ml) and left overnight. Poured into ice, filtered and re-crystallised from aqueous ethanol or aqueous acetone. Using the previously prepared acetate (8) gave the same product as leaflets, m.p. 238.5-239.5°(dec.).

On a different occasion (2) was brominated at reflux in a mixture of chloroform and some acetic anhydride for 5 hours. Took off solvents under vacuum and recrystallised from a mixture of ethanol-acetone to give leaflets, m.p. 247-249°(dec.), $[\alpha]_D$ -85.1° (c 2.01).

(Found C, 60.39; H, 7.27; $M^+$ 438.1412. $C_{22}H_{31}O_4Br$ requires

C,60.14; H, 7.11; $M^+$ 438.1406.

$\lambda_{max} (\varepsilon)$: 294 (86), 237.5sh (448) and 210 (2008) e.a.

$\nu_{max}$ : 1740, 1725, 1715, 1235, 1090, 905, 735 $cm^{-1}$.

$\delta$ : 0.85(3H,s,19-Me); 0.96(3H,s,20-Me); 1.13(3H,s,18-Me);

1.27(3H,s,17-Me); 2.16(3H,s,ACETOXYL); 2.43

(1H,d,$J_{9,11}$ 6.5Hz,9β-H); 2.67(2H,t,$J_{gem}$ 12Hz,1β-H and 1α-H);

4.23(1H,d,$J_{11,9}$ 6.5Hz,11α-H); 4.97(1H,s,3β-H).

## 3α-BENZOYLOXY-STACH-15-ENE-2,12-DIONE (11)

Ketol (1) (5.0g) was dissolved in pyridine (30ml), cooled in ice and added benzoyl chloride (5.0ml). Left at 0-5° for two days, poured into ice water, allowed to solidfy

and recrystallised from aqueous acetone in spars (6.6g,
99%), m.p. 224-226$^{\circ}$, $\{\alpha\}_D$ -292$^{\circ}$ (c 2.01).
(Found C,76.78; H,7.71; M$^+$ 420.2324; $C_{27}H_{32}O_4$ requires
C,77.11; H,7.67; M$^+$ 420.2300).

$\nu_{max}$ : 3055, 1735, 1717, 1705, 1602, 1585, 1283, 1120,767,710.

$\delta$ : 0.80(3H,s,20-Me); 1.02(3H,s,19-Me); 1.10(3H,s,17-Me);

1.18(3H,s,18-Me); 5.17(1H,s,3$\beta$-H); 5.63 and 6.02

(2x1H,2xd,$J_{15,16}$5.5Hz,16-and 15-H resp.); 7.50 and

8.08 (3xH and 2xH, 2xm, aromatic protons).

## 3$\alpha$-BENZOYLOXY-12$\alpha$-HYDROXY-STACH-15-ENE-2-one (12)

Ketol benzoate (11) (1.500g) was dissolved in THF (10ml),
diluted with ethanol (20ml) and cooled in ice. Added a
solution of boric acid (300mg) in ethanol (5 ml), followed
by NaBH$_4$ (33mg). Stirred at 5$^{\circ}$ for 5 hours, left o.n.,
acidified, vacuum evaporated and poured residue onto ice.
Solid (1.5g) was chromatographed in benzene on silica gel
(60g 7729 in hexane). Eluted with hexane containing pro-
gressively increasing amounts of benzene, then with pure
benzene and finally with benzene containing ethyl acetate.
Unreacted (11) was eluted first, followed by impure ketol-
3$\alpha$-benzoate-12$\beta$-ol (40mg) identified by its mmr spectrum:
$\nu_{max}$: 3470, 3065, 1680, 1708, 1600, 1578, 1273, 767, 752,
713and 707 cm$^{-1}$.

$\delta$ : 3.67 (1H, b.s,W$_{\frac{1}{2}}$7Hz,12$\alpha$-H).

Then was eluted the 12α-ol (12) (0.60g).   This was all used up for subsequent steps.

$\nu_{max}$: 3540(b), 1735, 1710, 1602, 1585, 1275, 1115, 760, 751, 710, 703, 682 cm$^{-1}$.


## 3α-BENZOYLOXY-14(13→12)ABEO-STACHA-15(16),13(17)-DIENE-2-ONE(14).

The 12α-alcohol (12) (0.952g) was dissolved in dry pyridine, cooled in ice and added mesylchloride (0.4ml, 100%excess).   Left o.n. at 5$^{O}$, poured onto ice and re-crystallised from aqueous THF giving 3α-BENZOYLOXY-12α-MESYLOXY-STACH-15-ENE-2-ONE (13) as leaflets (0.572g), m.p. 157-158$^{O}$(dec.).   T.l.c. showed this to be impure in that compound (14) had already formed to some extent, and thus was not characterised further.

Compound (13) (0.557g) was dissolved in glacial acetic acid (20ml) and refluxed with freshly fused sodium acetate (1.0g) for 2.5 hours.   Poured on to ice, and recrystallised from ethanol-acetone-water giving 0.190g leaflets, m.p. 180-185$^{O}$, $(\alpha)_D$ +128$^{O}$(c 2.04).

(Found M$^+$ 404.2351; C$_{27}$H$_{32}$O$_3$ requires M$^+$ 404.23513).

$\lambda_{max}$(ε): 300sh(53), 280.5(873), 272.7(1091), 230(31530)

$\lambda_{max}$ calculated:                                   229

$\nu_{max}$ : 3080, 3018, 1735, 1726, 1708, 1634, 1601, 1587, 1448, 1297, 1115, 873, 710 cm$^{-1}$.

δ       : 0.77(3H,s,20-Me); 1.03(1H,s,19-Me); 1.18(1H,s,18-Me);

2.27(2H,s,C-1 methylene); 2.87(1H,br m,allylic 12-H);

4.48 and 4.62(2x1H,AB q, $J_{gem}$ 2.0 Hz,17-olefinic CH);

5.16(1H,s,3β-H); 5.72 and 5.92(2x1H,AB q,$J_{15,16}$ 9.5 Hz,

15- and 16-H).   7.4 - 8.2(5H,m, aromatic).

## 2α, 3α, 12α-TRIHYDROXYSTACHANE (15)

(i)   2α, 3α, 12α-Trihydroxystach-15-ene (16) in THF-
ethanol was reduced with $H_2$ using Pd/C as for (2).   Re-
crystallised from aqueous THF-ethanol, needles m.p. 226-227°
(subl), $[\alpha]_D^{22°}$ -26.7° (c 2.01, THF).

(ii)   2α-Acetoxystachane-3,12-dione (30) was reduced
in THF-ethanol with excess $NaBH_4$ overnight at room temperature.
Added 1.0ml NaOH (30%), heated to reflux 5 minutes, cooled,
acidified, poured into ice and recrystallised  aqueous
ethanol giving needles, m.p. 226-227°(subl.) $[\alpha]_D^{22°}$ -30.8°
(c 2.05, THF).
(Found C,74.01; H,10.42; $M^+$ 322.2503.  $C_{20}H_{34}O_3$ requires
    C,74.49; H,10.63; $M^+$ 322.2508.
$\nu_{max}$:   3558, 3550-3050 (v.b.), 1450, 1390, 1045, 1020, 973cm$^{-1}$.

## 2α, 3α, 12α-TRIHYDROXYSTACH-15-ENE (16)

Ketol (1) (5.0g) was dissolved in ethanol (30ml) and
added $NaBH_4$ (1.0g).   Left cold overnight, poured into ice
and acidified with HCl.   Recrystallised from ethanol-THF-
water or by slow evaporation from ethyl acetate as large
rhombs (2.8g first crop), m.p. 223-226° (sublimes near 175°),

$(\alpha)_D$ - 38$^O$ (c 2.07 in THF).

(Found C, 74.69; H,10.056; M$^+$ 320.2341. C$_{20}$H$_{32}$O$_3$ requires

    C, 74.96; H, 10.06; M$^+$ 320.2351).

$\nu_{max}$: 3425 (v.b.), 3035, 765 cm$^{-1}$.

  $\delta$ : 1.03, 1.03, 1.05, 1.12 (4x3H,4xs,4xMe); 3.30(2H,m,

    3$\beta$- and 12$\beta$-H); 4.07(1H,m,2$\beta$-H); 5.55 and 5.83(2H,

    AB q, J 6.0 Hz, 16- and15-H resp.).


## 2$\beta$, 3$\alpha$, 12$\alpha$-TRIHYDROXYSTACH-15-ENE (17).

    2$\beta$-Acetoxystach-15-ene-3,12-dione (33) (0.75g) was

dissolved in ethanol-THF and reduced with NaBH$_4$ (1.0g) and

NaOH soln. (10%, 1.0ml) o.n.  Acidified with HCL, evaporated

to small volume and poured into ice.  Granular precipitate

recrystallised from ethanol-water giving white needles

(0.27g first crop), m.p. 218-221.5$^O$, $(\alpha)_D^{22O}$ -10.55$^O$(c 1.86).

(Found M$^+$ 320.2351;  C$_{20}$H$_{32}$O$_3$ requires M$^+$ 320.2351).

$\nu_{max}$: 3615, 3600-3100(v.b.), 3045, 1055, 755 cm$^{-1}$.


## 2-HYDROXYSTACH-1,15-DIENE-3,12-DIONE (18).

    a) $\alpha$-ketol (1) (3.0g) in glacial acetic acid (40ml) was

refluxed with Bi$_2$O$_3$ (4.5g) for 0.5 hours.  Decanted, washed

bismuth salts with hot acetic acid (10ml), combined extracts,

evaporated to dryness and dissolved residue in benzene (10ml).

Chromatogrammed on silica (7734,60g in benzene).  Eluted with

benzene and then benzene-ethylacetate (2%) when (18) was obtained.

Recrystallised from aqueous methanol giving large prisms (1.5g) which gave a brown colour with methanolic ferric chloride; m.p. 170-173$^{\circ}$, $[\alpha]_D$ - 374$^{\circ}$ (c 2.3). (Found M$^+$ 314.1880; $C_{20}H_{26}O_3$ requires 314.1887).

$\lambda_{max}(\varepsilon)$: 270 (9420), 210 (3670) end absorption.

$\lambda_{max}^{NaOH}(\varepsilon)$: 313.5(4920), 215(3599) end absorption.

$\nu_{max}$: 3410, 3055, 1700, 1667, 1648, 1570, 963, 867, 765.

$\delta$ : 1.10, 1.12, 1.13 and 1.25(4x3H, 4xs, 4xMe); 5.71 and 6.10(2H,ABq, J=5.5Hz, 16-H and 15-H); 6.12(2H,s, one H exchangeable with $D_2O$; H-1 and OH).

b) $\alpha$-ketol-3$\alpha$-nitrate (27) (1.0g) in DMSO (10ml) was treated with sodium acetate trihydrate (1.0g) in the cold o.n. Poured into ice-water (80ml), and recrystallised as above, giving (18) (0.73g, 84% yield).

c) $\alpha$-ketol (1) (1.0) in ethanol (20ml was treated with NaOH (10%, 5 drops) and left open. T.l.c. showed no starting material after two days. Acidified, poured into water and recrystallised from methanol giving a variable yield of (18) of between 30 - 60%. An attempt at using triethylamine as the basic catalyst as well as the use of an ion-exchange resin in the OH$^-$ form failed to give any reaction at room temperature.

d) Large quantities of (18) were eventually obtained from later batches of A. johnsonii (NDO 140 and NDO 141) using the same crystallisation procedure as for (1). The

first and second mother liquors in this case were dark red instead of the light yellow of the previous wood sample.

## 2α, 3α-ISOPROPYLIDENEDIOXY-12α-HYDROXYSTACHANE (21).

2α, 3α-Isopropylidenedioxy-12α-hydrosystach-15-ene was hydrogenated in ethanol-THF with Pd/C.  The product was recrystallised from acetone-THF, m.p. 212-214°, $(\alpha)_D$ -50°, (c 1.55) (Found C,76.33; H,10.81. $C_{23}H_{38}O_3$ requires C,76.20; H,10.57).

(Found  M-15= 347.2585;  $C_{22}H_{35}O_3$ requires M-15 = 347.2586).

$\nu_{max}$: 3490, 1380, 1365, 1250, 1200, 1050, 1035, 880,833cm$^{-1}$.

$\delta$   : 0.92, 0.98, 1.02, 1.11(4x3H,4xs,4xMe); 1.33 and 1.50

(2x3H,2xs,ACETONIDE Me);  3.40(1H,m,$W_{\frac{1}{2}}$=18Hz,12β-H);

3.72(1H,d,J=7Hz,3β-H);  4.32(1H, triplet of doublets,

J= 2 and 7 Hz, 2β-H).

## 2α, 3α-ISOPROPYLIDENE DIOXY-14(13→12) ABEO-STACH-13(17)-ENE(22).

(21) (1.5g) in pyridine (20ml) at 0-5° was treated with POCl (3.0ml).  Left cold overnight, at room temperature for a further 24 hours and then at 60° for 2 hours.  Poured into ice-cold brine.  Crystallised from a mixture of THF-acetone-methanol containing a trace of pyridine, giving 1.21g of product, m.p. 150-156°, $(\alpha)_D$-25°, (c 2.1).

$\nu_{max}$: 3074, 1255, 838 and 792 cm$^{-1}$.

$\delta$   : 1.00(6H,s,2xMe); 1.34 and 1.52(2x3H,s,ACETONIDE Me);

2.77(1H,b.m,allylic H); 3.75(1H,d,J 6.5Hz, 3β-H);

4.37(1H,triplet of doublets,$J_{2\beta,3\beta}$= $J_{2\beta,1\beta}$ = 2.0Hz,

$J_{2\beta,1\alpha}$= 6.5Hz, 2β-H) 4.50(2H,quartet, overlapped by

2β-H, 17-C olefines).

## 2α, 3α-ISOPROPYLIDENEDIOXY-12α-HYDROXYSTACH-15-ENE (23)

a)   2α, 3α, 12α-triol (16) (0.70g) was suspended in
dry acetone (20ml), and added HClO₄ (70%, 3 drops).   Sus-
pension immediately clarified, and t.l.c. showed that most
of starting material had disappeared.   Left o.n. then
poured into ice-sodium bicarbonate solution.   Crystallised
from aqueous acetone, giving 0.28g needles in the first
crop.

This compound (23) was made on a large scale as follows.
Mother liquor 3 from ketol crystallisations (100g) in
ethanol (300ml) was reduced at 5° with NaBH₄ (5g).   After
48 hours heated on steam 2 hours, cooled and poured into
dilute HCl-ice (2l).   Filtered off and dried (100g).
This consisted of a mixture of mono-, di- and triols.

Boiled a few hours (3-4) with hexane (600ml), decanted
and repeated.   Combined colourless hexane extracts and
evaporated. (These contained mainly mono-alcohols with some
diols.)   The residue previously extracted with hexane was
now boiled with benzene (600ml), decanted and evaporated
yellowish solution.   T.l.c. indicated that benzene removed
most of mono- and diols left as well as some triol.   Residue
was nearly pure triols.   Suspended this residue (45g) in
dry acetone (300ml), added 2,2-dimethoxypropane (10ml) and

HCLO$_4$ (70%, 6ml). Solid quickly went into solution, the latter turning dark. Slowly over 9 days pure (23) crystallised out. Supernatant decanted and solid recrystallised from acetone to give 15 - 20 g of (23). Supernatant gave more solid, but was usually poured into dilute sodium bicarbonate solution (3ℓ) and the precipitated material recrystallised.

The hexane and benzene extracts on chromatography on silica gel and eluting with hexane-ethylacetate (7:3) gave copious quantities of pure STACHENOL (5) m.p. 159-161$^{\circ}$ as above. A 3:2 solvent mixture gave small quantities of diols, which have not as yet been investigated. Hexane-ethylacetate (2:3) gave the 2α, 3α, 12α-triol (16) which crystallised from ethylacetate in large rhombs. Acetonide (23) had m.p. 194-196$^{\circ}$, $(\alpha)_D$ -48$^{\circ}$ (c 2.24).

(Found C, 76.52; H,10.07; M$^+$ 360.2670. C$_{23}$H$_{36}$O$_3$ requires

C, 76.62; H,10.06; M$^+$ 360.2664).

$\nu_{max}$: 3490, 3052, 3027, 3012, 1047, 750 cm$^{-1}$.

$\delta$ : 0.97(9H,s,3xMe); 1.12(3H,s,Me); 3.47(1H,sextet,

X part of ABX,J$_{AX}$ + J$_{BX}$ = 15Hz,12β-H); 3.41(1H,d,

J$_{2,3}$= 6.5Hz,3β-H); 4.35(1H, triplet of doublets,

J$_{2\beta,3\beta}$ = J$_{2\beta,1\beta}$ =2.0 Hz,J$_{2\beta,1\alpha}$ = 6.5Hz,2β-H); 5.61

and 5.85(2H,ABq,J=6.0 Hz,16- and 15-H).

## 2α, 3α -ISOPROPYLIDENEDIOXY-14(13→12)ABEO-STACHA-15(16), 13(17)-DIENE (24).

The triol acetonide (23) (2.0g) in dry pyridine (40ml) was treated at 0-5$^O$ with $POCl_3$ (2.0ml) and left at room temperature for 48 hrs. Warmed to 60$^O$ for 0.5 hours then poured into ice-sodium acetate solution. The crystalline solid was recrystallised from acetone-THF as beautiful laths (1.48g), m.p. 180-185$^O$, $(\alpha)_D$ +139$^O$ (c 2.5).
(Found  C, 80.74; H, 10.28.  $C_{23}H_{34}O_2$  requires

      C, 80.65; H, 10.01).

$\lambda_{max}(\epsilon)$: 238.5(17600) and 210 (5372) e.a.

$\nu_{max}$   : 3075, 30.7, 1250, 1055, 1030, 883, 875(vs), 838,

        793 cm$^{-1}$.

$\delta$     : 0.94(6H,s,2xMe); 1.00(3H,s,Me); 1.33 and 1.50

        (3H and 3H,s, acetonide Me); 2.82(1H, broad q,

        $W_{\frac{1}{2}}$14Hz, allylic H-12);  3.71(1H,d,$J_{3,2}$= 6.0

        Hz, 3β-H);  4.30(1H, triplet of doublets, $J_{2\beta,3\beta}$=

        J = 2.0 and 6.0 Hz, 2β-H); 4.46 and 4.58

        (2H,AB quartet, $J_{gem}$ = 2.0Hz, 17-olefines); 5.80

        (2H,t,J=10Hz, 15-and 16-H).

## 2α, 3α, 12α-TRIACETOXY-STACH-15-ENE (25).

The 2α, 3α, 12α-triol (16) was acetylated as for (3). Crystallised from aqueous methanol as needles, m.p. 147-149$^O$, $(\alpha)_D$ -15$^O$ (c 2.07).

(Found   C, 70.12; H,8.59, $M^+$ 446.2663.  $C_{26}H_{38}O_6$ requires

C, 69.93; H,8.58; $M^+$ 446.2668).

$\nu_{max}$ :  1737, 1723, 1240(b), 1025, 763, 757, 745 $cm^{-1}$.

$\delta$   :  0.88(3H,s,Me); 0.975(6H,s,2xMe); 1.04(3H,s,Me);

1.96(9H,s,3x ACETOXYL); 4.52(1H,d,J=4Hz,3β-H);

5.51 and 5.75(2H,AB quartet, J = 5.75Hz, 16- and

15-H resp.); 4.66 (1H, m, 12β-H); 5.22 (1H, q, J= 3.5

and 7.0 Hz, 2β-H).


## 2-ACETOXYSTACHA-1, 15-DIENE-3,12-DIONE (26)

a)   The same procedure as for (18) was followed except
that the residue instead of dissolving in benzene, was dissolved
in pyridine (2 ml) and acetic anhydride (10ml).   Worked
up as for (3) and recrystallised from aqueous ethanol or
aqueous methanol giving very large, well-shaped rhombs
(1.98g).


b)   The diosphenol (18) from the plant was acetylated
as for (3) giving huge rhombs from methanol (2x1x1cm),
m.p. 135-137°, $[\alpha]_D$ -334°(c 2.43).

(Found   C,74.39; H,7.848; $M^+$ 356.1978.  $C_{22}H_{28}O_4$ requires

C,74.13; H,7.92;  $M^+$ 356.1987).

$\lambda_{max}$ : 296 (386) and 234 (12204).

$\nu_{max}$ :  3500, 3382, 3035, 1763, 1695, 1650, 1199, 1026,

910, 763 $cm^{-1}$.

$\delta$   :  1.11(6H,s,2xMe); 1.13(3H,s,Me); 1.18(3H,s,Me);

2.18(3H,s,ACETOXYL); 5.71 and 6.07(2H,AB quartet,

J = 5.5Hz, 16- and 15-H resp.); 6.44(1H,s, olefinic

H-1).

## STACH-15-ENE-2,12-DIONE-3α-NITRATE (27).

The ketol (1) (1.0g) was dissolved in acetic acid
(3ml), and acetic anhydride (5 ml), cooled in ice and added
slowly concentrated $HNO_3$ (2-3ml), allowing the reaction to
warm up but not to get too hot.   After 5 min. poured into
ice, filtered and crystallised from aqueous methanol or
aqueous acetone to give leaflets, 0.76g pure, plus a smaller
second crop from mother liquor.   On a larger scale (never
more than 3.0g) the initial solid obtained on pouring into
water, was redissolved in the minimum of cold acetone and
again poured into ice, followed by crystallisation.   In
this way occluded acid was removed and better yields were
obtained.   M.p. 193-194$^O$ (dec. with vigorous bubbling),
$(\alpha)_D$ -407$^O$ (c 1.84);   intense blue colour with diphenylamine-
conc. $H_2SO_4$, and no colour with alkaline TTC.
(Found C, 66.46;   H,7.75;   N,3.28;   $M^+$ 361.1884. $C_{20}H_{27}O_5N$ re-
quires C, 66.46;   H,7.53;   N,3.88;   $M^+$ 361.1889).

$\lambda_{max}(\varepsilon)$:   295(215) and 210 (5370) end absorption.

$\nu_{max}$   :   1728,1715,1700,1649,1635,1300,1293,1285,1087,990,
   850 (vs), 760 cm$^{-1}$.

$\delta$   :   0.80(3H,s,20-Me); 0.88(3H,s,19-Me); 1.12(3H,s,
   17-Me); 1.25(3H,s,18-Me); 2.27(4H, broad s); 5.03
   (1H,s,3β-H); 5.67 and 6.03(2H,AB quartet, J = 5.5 Hz,
   H-16 and H-15 resp.).

## 3α- HYDROXYSTACH-15-ENE-2,12-DIONE-12-p-TOLUENESULPHONYL-HYDRAZONE (28).

The α-ketol (1) (1.05g, 0.03M) was dissolved in glacial

acetic acid (15ml), added p-tosylhydrazine (0.52g, 0.03M)
and stirred to dissolve, then set aside.   Within 10-20
minutes set to a hard crystalline mass which was diluted
with  ethanol (insoluble) to make a paste.   After 2-6 hours
filtered and washed with ethanol giving an 80-95% yield
of crystalline material which was pure (1.26 to 1.46g).
Recrystallisation from acetone resulted in hydrazone
exchange, regenerating the parent 12-ketone overnight, but
if carried out quickly gave good crystals.   The best re-
crystallising medium was dioxan or THF diluted with methanol.
The material was thus obtained in needles which did not
keep for more than a few weeks and became discoloured (see
however 29).   M.p. 210-216$^O$ (dec.).        M.W. 484.
(Found $M^+$ - $C_7H_8N_2SO_2$ =  300.2088; $C_{20}H_{28}O_2$ requires 300.2089).
$\nu_{max}$:   3415(b), 3240(b), 3050, 1925(w), 1707, 1640, 1597,

1165, 815, 767, 750, 663, 600, 547 $cm^{-1}$.

$\delta$   :   0.67(3H,s,Me); 0.69(3H,s,Me); 1.13(3H,s,Me); 1.16

(3H,s,Me); 2.40(3H,s,aromatic Me); 3.92(1H,br,3β-H);

5.47 and 7.83(4H, AA´MM´, pseudo J = 9Hz, 1,4-

disubstituted aromatic ring); 8.21(1H, broad s, NH).

## 2α-HYDROXYSTACHA-1,15-DIENE-3,12-DIONE-12-p-TOLUENESULPHONYL-HYDRAZONE (29).

a)   (28) (0.6g) in dioxan (8ml) and ethanol (5ml) was
treated with KOH (400 mg) and $H_2O$ (3ml) at room temperature.
After 1 hour t.l.c. showed some reaction to a less polar spot.

Warmed to $70^O$ for 2 minutes and left overnight when the reaction was complete.   Poured into ice, acidified clear solution with acetic acid and crystallised solid from acetone-methanol-water giving 0.55g of colourless needles, which gave a negative TTC test and a positive ferric chloride test (brown).   This material was stable indefinitely.

b)   Prepared as for (28) and recrystallised from THF-methanol, giving an excellent yield as for (28).   Ethanol could be substituted for acetic acid as a reaction medium but the rate of reaction was then very slow.   Addition of a few drops of glacial acetic acid markedly increased the rate. Heating the reaction mixture was detrimental as the selectivity at C-12 was then lost and a mixture of "hydrazones" was obtained as a yellow oil.

(29)   had m.p. 255-256$^O$ (dec.); $[\alpha]_D^{22}$ -158.9$^O$(c 1.68 in THF).

(Found  C, 67.27; H, 7.27; N, 5.85; $M-C_7H_8N_2SO_2$ = 298.1940. $C_{27}H_{34}N_2O_4S$ requires C,67.19; H,7.10; N,5.80.  $C_{20}H_{26}O_2$ has m/e 298.1933).

$v_{max}$: 3430(b),3180,3065,1665,1645,1605,1575,1160,936,763,582cm$^{-1}$.

$\delta$  : 1.00, 1.07, 1.14 and 1.16(4 x 3H, 4 x s, 4xMe); 2.40

(3H,s, aromatic Me); 5.50 and 5.85(2H, ABq, J = 6Hz,

H-16 and H-15); 6.20(1H,s,H-1); 7.28 and 7.86(4H,

AA´MM´, pseudo J = 8Hz, 1,4-disubstituted aromatic ring).

## $2\alpha$-ACETOXYSTACHANE-3,12-DIONE (30).

The diosphenol acetate (26) (1.0g) in THF (50ml) was hydrogenated using Pd/C. After no more $H_2$ absorbed (2 moles), filtered and crystallised from THF or methanol giving 0.97g of needles, which gave a positive TTC test, m.p. 156-158°, $(\alpha)_D$ -157.3° (c 2.16). (Found C, 72.98; H,8.986; $M^+$ 360.2310. $C_{22}H_{32}O_4$ requires C, 73.30; H,8.95; $M^+$ 360.2300).

$\lambda_{max}$ : 286(87).

$\nu_{max}$ : 1745, 1730, 1710, 1293 cm$^{-1}$.

$\delta$ : 0.90, 1.08, 1.08 and 1.20 (3 x s, 4 x Me); 2.12 (3H,s,Acetate); 5.58(1H,q, J = 8.3, 11.2 Hz, $2\beta$-H).

## 1:1 COMPLEX OF 15,16-DIHYDRODIOSPHENOL ACETATE (32) AND 15,16-DIHYDRO-$2\alpha$-ACETOXY-3,12-DIONE (30).

Hydrogenation of (26) in ethanol using Pd/C gave masses of needles as mixture went practically solid when 1 mole equivalent of hydrogen had been taken up. At this stage addition of acetone and filtration removed the catalyst and crystallisation gave needles of (31) (practically quantitative yield), m.p. 173-188°, giving a positive TTC and identified by its n.m.r spectrum which was the same as a superimposition of the spectra of the two separate compounds.

## 2-ACETOXYSTACH-1-ENE-3,12-DIONE (32)

a) Using the $Bi_2O_3$ oxidation as for (18) and then acetylating as for (26).

b) Hydrogenation of the diosphenol acetate (26) using a 10% Pd/C catalyst which was fortuitously rather inactive, allowed the 15,16-double bond to be hydrogenated much more rapidly than the 1-ene and after 1 mole of $H_2$ absorbed, crystallisation gave (32) in very good yield. Needles from aqueous methanol, m.p. 204-207°, $(\alpha)_D$ -87.9(c 2.0). (Found $M^+$ 358.2148; $C_{22}H_{30}O_4$ requires $M^+$ 358.2144).

$\lambda_{max}$ : 329(88) and 238(9870).

$\nu_{max}$ : 1757, 1705, 1678, 1213, 1200 and 1185, 1034cm$^{-1}$.

$\delta$ : 1.10, 1.13, 1.20 and 1.26(4x3H, 4xs, 4xMe); 2.17(3H,s,ACETOXYL); 6.53(1H,s,H-1 olefin).

## 2β-ACETOXYSTACH-15-ENE-3,12-DIONE (33).

α-ketol (1) (3.0g) was dissolved in acetic anhydride (25ml), cooled in ice and added anhydrous $AlCl_3$ (4.0g). Warmed for 10-30 min. when acetyl chloride refluxed and HCl evolved. Left cold 5 hours and poured into ice. Sticky solid which formed on the surface was skimmed off and crystallised from methanol or ethanol giving 0.810g (24%) of the isoketol acetate. Extraction of the water with ethyl acetate gave a further small crop. Compound (33)

had m.p. 228-231$^{O}$ (variable depending on rate of heating and ranges from 227-235$^{O}$), $(\alpha)_D$ -322$^{O}$ (c 2.0).

(Found  C,73.98; H,8.552; M$^{+}$ 358.21557, M-(103) = 255.1751; $C_{22}H_{30}O_4$ requires C,73.71; H,8.44; M$^{+}$ 358.21440, M-(103) = 255.1749, loss of $C_4H_2O_3$).

$\lambda_{max}(\epsilon)$: 296(225) and 210 (3440) end absorption.

$\nu_{max}$    : 3435, 3382(overtones), 3056, 1745, 1725, 1695, 1235, 763 cm$^{-1}$.

$\delta$       : 1.11, 1.17, 1.17, 1.17 (4x 3H,4xs,4xMe); 2.14 (3H,s,ACETOXYL); 5.58(1H,q,J=6.0,13.0Hz); 5.68 and 6.11 (2H,ABq, J = 5.50 Hz, H-16 and H-15 olefines).

## ENT-2$\alpha$-ACETOXY-11(12→16)ABEQ-ATIS-13-ENE-3,12-DIONE (34)

The isoketol acetate (33) (0.115g) in acetic anhydride (3ml) was treated cold with concentrated $H_2SO_4$ (5 drops). After 5 minutes poured into ice-water (50ml), filtered the crystalline material and crystallised from aqueous methanol giving 0.103 g of needles, m.p. 230-231$^{O}$,  $(\alpha)_D$ +165$^{O}$(c 2.08). (Found  M$^{+}$ 358.2145;  $C_{22}H_{30}O_4$ requires M$^{+}$ 358.2144).

$\lambda_{max}$: 326(98) and 238 (10260)

$\nu_{max}$: 3480, 3427, 3345(overtones), 3014, 1747, 1724, 1685, 1235 cm$^{-1}$.

$\delta$    : 1.00(3H,s,20-Me); 1.15, 1.15 and 1.20(3x3H,3xs,3xMe); 2.12(3H,s,ACETOXYL); 5.57(1H,q,J=6.0 and 13.0Hz, ent-2β-H); 5.92(1H,d,J = 9.5, 13-H); 6.95(1H, d of d, J = 9.5 and 2Hz, 14-H).

## 2β-ACETOXYSTACHANE-3,12-DIONE (36).

Unsaturated analogue (33) was hydrogenated in ethanol-THF with Pd/C (30%) as for (2). Needles, m.p. 221-223$^O$ (sublimes), $[\alpha]_D$ -54$^O$ (cl.13).

(Found C,73.11; H,8.848; M$^+$ 360.2307. $C_{22}H_{32}O_4$ requires

C,73.30; H,8.95; M$^+$ 360.2300).

$\lambda_{max}(\varepsilon)$: 288(62) and 210(423) e.a.

$\nu_{max}$ : 3455, 3435, 3380(overtones), 1745, 1725, 1700,
1235, 1025, 975, 870 cm$^{-1}$.

$\delta$ : 1.07, 1.13, 1.13(3x3H,3xs,3xMe); 1.35(3H,s,20-Me);
2.13(3H,s,ACETOXYL), 5.58(1H,q,J=6.0 and 13.0 Hz).

## 1β, 11β-DIBROMOSTACHANE-2,3,12-TRIONE (37).

The 15,16-dihydrodiosphenol acetate (32) in glacial acetic acid was treated with a solution of bromine in acetic acid until red and left overnight. Poured into water and crystallised yellow solid from acetone-methanol-H$_2$O (v. soluble in acetone), giving long, bright yellow needles, m.p. 184-193$^O$ (dec), $[\alpha]_D$ + 29.9$^\circ$ (c 2.02).

(Found M$^+$ + H-Br = 394.1133. $C_{20}H_{27}O_3Br$ requires m/e 394.1141.

$\lambda_{max}(\varepsilon)$: 432 (77), 235 sh (1900) and 210 e.a. (3280).

$\nu_{max}$ : 3425 and 3410 (overtones),3020, 1720, 1710, 1450
and 710 cm$^{-1}$.

$\delta$ : 1.11, 1.26, 1.33 and 1.36(4x3H,4xs,4xMe); 2.62(1H,d,
J=9.0hz, 9β-H); 4.51(1H,d,J=9.0Hz,11α-H); 5.47
(1H,s,1α-H).

## 15,16-DIHYDRO-BENZALDEHYDE-LACTONE (38)

a)  (77) in THF was hydrogenated as for (2).  Quanti-
tative yield of the rather insoluble (38).

b)  Prepared from the 15,16-dihydroketol (2) using
the method as described for (77).  Needles, sublime very
easily at atmospheric pressure at 285-290°, m.p. 302-304°,
$(\alpha)_D$ -127° (c 2.38).

(Found  C, 76.94; H,8.24; $M^+$ 422.2443.   $C_{27}H_{34}O_4$  requires
       C, 76.74; H,8.11; $M^+$ 422.2457).

$\nu_{max}$: 3410, 1747, 1707, 1455, 1195, 995, 772, 716 cm$^{-1}$.

δ    : 1.03, 1.03, 1.10, 1.17(4x3H,4xs,4xMe); 2.68(1H,d,

       J = 9Hz, 1α-H); 4.00(1H,b,exchanged with $D_2O$,OH);

       5.15(1H,d,J=9Hz,benzylic H); 7.10-7.50(5H,m,aromatic

       protons).

## 3α-METHANESULPHONYLOXY-STACH-15-ENE-2,12-DIONE (45)

The α-ketol (1) (1.0g) in dry pyridine was treated at
5° with methanesulphonyl chloride (1.0ml).  Left in
refrigerator for 48 hours, poured into ice, dissolved in
methanol or acetone (easier) and charcoaled.  Crystallised
from aqueous acetone giving large colourless leaflets in
a nearly quantitative yield.  M.p. 175-176°, $(\alpha)_D$ -311°
(c 2.05).

(Found $M^+$ 394.1840.   $C_{21}H_{30}O_5S$ requires $M^+$ 394.1814).

$\lambda_{max}(\varepsilon)$: 295.4(232) and 210(3443)e.a.

$\nu_{max}$ : 3430, 3403(overtones), 3058, 3030, 1725, 1710, 1593, 1450, 1345, 1172, 999, 960, 763 $cm^{-1}$.

$\delta$ : 0.78, 0.87, 1.10 and 1.23(4x3H, 4xs, 20,19,17 and 18-Me resp.); 3.20(3H,s,$CH_3-SO_2-$); 4.86(1H,s,3β-H); 5.65 and 6.02(2H,ABq,J=5.5Hz, 16- and 15-H resp.).

## 3α-p-TOLUENESULPHONYLOXY-STACH-15-ENE-2,12-DIONE (46).

Ketol (1) (1.0g) in dry pyridine (10ml) was treated with p-toluenesulphonyl chloride (1.0g), left overnight cold and then poured into water. Crystallised from aqueous acetone (insoluble in MeOH), giving long spars (1.1g, 76%), m.p. 202-203° (dec.), $(\alpha)_D$ - 214° (c 2.83).

(Found C, 69.06; H, 7.39; $M^+$ 470.2145. $C_{27}H_{34}O_5S$ requires C, 68.91; H, 7.28; $M^+$ 470.2127).

$\nu_{max}$: 1727, 1700,-598, 1340, 1175, 980, 862 and 686 $cm^{-1}$.

$\delta$ : 0.72. 0.78, 1.09 and 1.13(4x3H,4xs,20,19,17 and 18 Me resp.); 2.42(3H,s,aromatic Me); 4.84(1H,s,3β-H); 5.62 and 5.97(2H,AB quartet, J 6Hz, 16- and 15- protons); 7.28 and 7.82(4H, AA´MM´, pseudo J = 8Hz, 1,4 - disubstituted aromatic ring).

## 1β-ACETOXYSTACH-15-ENE-2,12-DIONE (47).

Ketol mesylate (45) or tosylate (46) (1.0g) in glacial acetic acid (20ml) was refluxed with anhydrous sodium acetate

(2.0g) for three hours.   Took off half the acetic acid
under vacuum and poured residue into ice-water (150ml).
Filtered.   N.m.r. of crude product showed presence of other
3-acetoxy epimers (see TABLE $\underline{\text{II}}$ )  and percentages were ob-
tained by extracting the total aqueous mixture with $CH_2CL_2$,
washing organic layer with $NaHCO_3$ soln., water, drying and
evaporating.   This residue was then used for the n.m.r.
estimations.   Pure (47) was obtained after two crystallisations
from aqueous methanol (0.63g from (45), as twinned needles,
m.p. 176-178$^O$,  $(\alpha)_D$ -387$^c$(c 2.11).
(Found C,73.55; H,8.35; $M^+$ 358.2124. $C_{22}H_{30}O_4$ requires

C,73.71; H,8.44; $M^+$ 358.2144).

$\lambda_{max}$  : 297 (290).

$\nu_{max}$  : 3073, 3042, 1755, 1710, 1705, 1225, 1030 and 752 cm$^{-1}$.

$\delta$  : 0.77, 0.87, 1.10, 1.10(4x3H,4xs,20,19,18 and

17.Me); 2.12(3H,s,ACETOXYL); 4.22(1H,bs,$W_{\frac{1}{2}}$ 3 Hz,

1$\alpha$-H); 5.61 and 6.03(2H,ABq,J=5.5Hz, 16- and 15-

H resp.).


## 1$\beta$-HYDROXYSTACH-15-ENE-2,12-DIONE (48).


a)   Acid Hydrolysis:   (47) (1.0g) in methanol (20ml)
was refluxed for 3 days with conc. HCl (2ml) until t.l.c.
showed complete hydrolysis.   Evaporated most of solvent
off and poured residue into ice-cold sodium acetate solution.
Crystallised from hexane-ether or hexane-ethanol as leaflets,
yield 0.49g.

b) <u>Alkaline Hydrolysis</u> (best and most rapid). (47)

(1.0g) in methanol (20ml), added NaOH (30%,0.3ml) and left

overnight (use of larger quantities of base did not decrease

the yield), then added glacial acetic acid (0.1ml), poured

into water, filtered and crystallised from aqueous methanol,

leaflets (0.8g); m.p. 191-193$^O$; $\{\alpha\}_D$ - 356$^O$ (c 2.19).

(Found C,75.91; H,8.81; M$^+$ 316.2045. C$_{20}$H$_{28}$O$_3$ requires

C,75.91; H,8.92; M$^+$ 316.2038).

$\lambda_{max}$ : 296 (212), 220sh (3350) and 210e.a.(4110).

$\nu_{max}$ : 3400(broad), 3070, 1725, 1690, 1595 and 753 cm$^{-1}$.

$\delta$ : 0.67, 0.85, 1.08, 1.08(4x3H,4xs,20,19,18 and

17-Me); 3.07(1H,d,J=12.5Hz,3$\alpha$-H); 3.33(1H,bs,W$_{\frac{1}{2}}$3Hz,

1$\alpha$-H); 4.03(1H,s,exchanged with D$_2$O,1$\beta$-OH); 5.60

and 6.06(2H,ABq,J=5.5Hz,16- and 15-H resp.).

### 3$\alpha$-TOSYLOXYSTACH-15-ENE-2,12-DIONE-12-ETHANEDITHIOKETAL (49).

This compound could be prepared by tosylating the 12-

monoketal in 95% yield but the most convenient and highest

yield method was as follows:- The ketol tosylate (46)

(3.0g) was dissolved in glacial acetic acid (50ml) and cooled.

Added ethanedithiol (1.0ml) and $BF_3.Et_2O$ (1.0ml) and left 2 - 3 hours during

which time product (49) crystallised out in very large

rhombs. These were filtered off and washed with plenty

of methanol and were analytically pure (3.4g, 97.5%). The

acetic acid filtrate gave a further small quantity on dilution

with water. Crystallised from acetone-THF, m.p. 182-185$^O$

(dec.), $\{\alpha\}_D$ -5$^O$ (c 2.96).

(Found C,64.01; H,7.13; M$^+$ 546(weak), M-28 = 518.1623.

$C_{29}H_{38}O_4S_3$ requires C,64.00; H,7.00;  M-28 = 518.1619.

$\nu_{max}$: 1735, 1597, 1175, 994, 850(d), 755 and 680 cm$^{-1}$.

$\delta$  : 0.68, 0.77, 1.10 and 1.28(4x3H,4xs,20-,19-,18- and

17-Me resp.); 2.42(3H,s,AROMATIC Me); 3.0-3.4

(4H,m,-s-CH$_2$CH$_2$-s-); 4.63(1H,s,3$\beta$-H); 5.67(2H,ABq,

J=5.5Hz,H-15 and H-16); 7.28 and 7.80(4H,AA$^1$MM$^1$,

pseudo J = 8.0Hz, 1,4-disubstituted Ph).

## 1$\beta$-ACETOXYSTACH-15-ENE-2,12-DIONE-12-ETHANEDITHIOKETAL (50).

Ketol -3$\alpha$-tosylate-12-ethanedithioketal (49) (1.16g),
anhydrous sodium acetate (2.0g, freshly fused) and glacial
acetic acid (25ml) were refluxed for 2 hours.  Removed
most of solvent in vacuo, poured into water, filtered and
crystallised from acetone-THF, giving 0.62g of needles,
m.p. 215-219$^\circ$;  $(\alpha)_D$ -68$^\circ$ (c 0.98).

$\nu_{max}$: 3043, 1745, 1725, 1218, 1030 and 750 cm$^{-1}$.

$\delta$  : 0.74, 0.84, 1.07 and 1.88(4x3H,4xs,20,19,18 and

17-Me);  2.17(3H,s,ACETOXYL); 2.73(1H,d,J=12Hz,3$\alpha$-H);

3.0-3.3(4H,m,-S-CH$_2$-CH$_2$-S);  4.60(1H,bs,W$_{\frac{1}{2}}$3Hz,1$\alpha$-H);

5.70(2H,ABq,J=5.5Hz, 15- and 16-protons).

## 1$\beta$,2$\alpha$-DIHYDROXYSTACH-15-ENE-12-ONE-12-ETHANEDITHIOKETAL (51).

Acetate (50) (0.46g) in dioxan-ethanol (5ml+20ml) was

reduced with $NaBH_4$ (0.10g) and NaOH(10%, 0.3ml). After 1 hour at r.t. heated briefly to $70^O$, left overnight, acidified with dilute HCl and poured on to ice. Crystallised from methanol-acetone-water (0.29g first crop), m.p. 215-219$^O$(dec.); $[\alpha]_D$ -61$^O$(c 0.69).

(Found  C,66.93;  H,8.72      $C_{22}H_{34}O_2S_2$ requires

C,66.96;  H,8.68.)

$\nu_{max}$:   3435(b), 3045, 1040, 1010 and 755 cm$^{-1}$.

$\delta$   : 0.93, 0.97 and 1.02(3x3H,3xs,18,19 and 20-Me);

1.28(3H,s,17-Me); 3.22(4H,m,-s-CH$_2$CH$_2$-s-); 3.50

(1H,d,J=4.0h$_3$,1$\alpha$-H); 3.94(1H,q,J= 3 x 4 Hz,

2$\beta$-H);  5.74(2H,ABq,J=5.5Hz,15-and16-H).

This compound failed to form an acetonide using the procedure described for (23).


## 1$\beta$,2$\alpha$-DIACETOXYSTACH-15-ENE-12-ONE-12-ETHANEDITHIOKETAL (52)


Prepared as for (3).  Crystallised from hexane or aqueous methanol, m.p. 146-150$^O$; $[\alpha]_D$ -29$^O$ (c 2.15).

$\nu_{max}$:  1742, 1727, 1245, 1220, 1024 and 756 cm$^{-1}$.

$\delta$   : 0.93, 1.02, 1.02(3x3H,3xs,3xMe); 1.27(3H,s,17-Me);

2.00 and 2.15(2x3H,2xs,ACETOXY);  3.0-3.3(4H,m,-

SCH$_2$CH$_2$S-);  4.86(2H,m,overlapping 1$\alpha$- and 2$\beta$-H);

5.75(2H,ABq,J=5.5Hz, H-16 and H-15 resp.).

## 3β-ACETOXYSTACH-15-ENE-2,12-DIONE (53).

α-Ketol (1) (3.2g) in dry benzene (50ml) was degassed with $N_2$ for 30 min.    Added p-tosic acid (50mg) and pyrrolidine (3ml, dry) and refluxed overnight (15 hours) under $N_2$ (oxygen free).    Cooled and added acetic anhydride (10ml).    Left 12 hours, removed most of benzene under vacuum and poured reddish liquid into ice-sodium acetate solution (250ml, 10-15g NaOAc).    Cloudy water layer slowly crystallised into long white needles and red oil also crystallised.    Filtered, charcoaled in methanol and crystallised into long, white needles (2.0g, 55%), m.p. 183-184°, $[\alpha]_D$ -310° (c 2.2).    (Found C,73.91; H,8.58; $M^+$ 358.2148. $C_{22}H_{30}O_4$ requires C, 73.71;  H, 8.44;  $M^+$ 358.2144).

$\lambda_{max}(\varepsilon): 298\ (254)$ and $212\ (8390)$.

$\nu_{max}$: 3385 (overtone),3048,1747,1725,1700,1230 and 763 $cm^{-1}$.

δ    :    0.89, 0.94, 1.03 and 1.10 (4x3H, 4xs,4xMe); 2.13

(3H,s,ACETOXYL);    4.70 (1H,s,3 -H); 5.65 and 6.04

(2H,ABq,J=5.5Hz, H-16 and H-15 resp).

Hydrolysis of this product in methanol using dilute NaOH (1.0g (53), 14ml MeOH, 0.3 ml NaOH, 10%) gave the epiketol (54) which is described fully in reference 46, although it was first prepared at this stage.

## 3β-ACETOXYSTACHANE-2,12-DIONE (15,16-DIHYDRO 53).

Hydrogenation of (53) as for preparation of (8) gave leaflets from aqueous ethanol, m.p. 200-201°, $[\alpha]_D$ -58°

(c 2.84).

(Found C, 73.17; H,9.05; $M^+$ 360.2299.   $C_{22}H_{32}O_4$ requires

C, 73.30; H,8.95; $M^+$ 360.2300).

$\lambda_{max}$ : 292(88).

$\nu_{max}$   : 1743, 1735, 1702, 1225 and 1040 $cm^{-1}$.

$\delta$      : 0.93, 1.00, 1.07 and 1.08(4xs, 4xMe); 2.12

(3H,s, ACETATE); 4.77(1H,s,3$\alpha$-H).

## 1β-(2-HYDROXYETHOXY)-STACH-15-ENE-2,12-DIONE (65).

Freshly distilled ethanediol (20ml,b.p. 190-195$^O$)
and dried, powdered KF(2.0g,32mM) were heated to 145-155$^O$
with stirring in an oil bath and the ketol 3$\alpha$-mesylate (45)
(2.0g, 5mM) was dropped in solid in one batch.   Stirred
for two hours.   T.l.c. showed complete reaction to a
more polar spot after 1 hour.   Cooled and poured into ice.
Failed to crystallise from alcohol.   Colourless gum
dissolved in benzene and chromatographed on silica (20g, Reichreagent
7734) in hexane.   Eluted with hexane-ethyl acetate (95:5,
90;10, 80;20 and 70;30).   Traces of crystalline material
were eluted first but were not investigated.   Then the
polar compound was obtained as a colourless gum (1.5g).
(Found $M^+$ 360.2307.   $C_{22}H_{32}O_4$ requires $M^+$ 360.2300).

$\nu_{max}$: 3460, 1705 and 757 $cm^{-1}$.

$\delta$ : 0.68, 0.85, 1.10 and 1.10(4x3H,4xs,20-,19-,18- and

17-Me resp.); 2.86(1H,d,J=12.5,Hz,3$\alpha$-H); 3.00

(1H,b.s.,$W_{\frac{1}{2}}$= 3Hz,1$\alpha$-H); 3.3-3.9(4H,m,-o-CH$_2$CH$_2$OH);

5.60 and 6.04(2H,ABq,J=5.0Hz,H-16 and H-15 resp.)


## 1$\beta$-BENZYLOXYSTACH-15-ENE-2,12-DIONE (66)


Benzyl alcohol (20ml) and dry, powdered KF(2g) were

stirred at 150$^O$ ±5$^O$ and the $\alpha$-ketol tosylate (46) (2.2g)

added. Stirred for 2 hours. Cooled, filtered off salts,

washed residue with ethanol and evaporated to a small

volume. Benzyl alcohol could not be completely removed

(a high vacuum pump was not available) even by washing with

calcium chloride. Chromatogrammed on silica (20g, 7734

in hexane) and eluted with hexane. Obtained a very small

quantity of white needles (66) which were characterised

by their n.m.r. Further elution with more polar solvents

gave yellow oils containing much benzyl alcohol. The

n.m.r. data of (66) was:

$\delta$ : 0.67, 0.85, 1.08 and 1.08(4x3H,4xs,20-,19-,18-and

17-Me resp.); 2.86(1H,d,J=12.5Hz, 3$\alpha$-H); 3.06(1H,

b.s.,$W_{\frac{1}{2}}$=3Hz,1$\alpha$-H); 4.30(2H,s,PhCH$_2$-O-); 5.57 and 6.02

(2H,ABq,J=5.5Hz,H-16 and H-15 resp.); 7.30(5H,s,C$_6$H$_5$-).

## A-NOR-STACH-15-ENE-1,12-DIONE (67)

The $\alpha$-ketol (48) (2.17g) in acetone (30ml, redistilled from $KMnO_4$), and $MnSO_4$ (20mg) were mixed and cooled to $0^O$ (better $-15^O$). Added Jones reagent[70] (9.0ml, 8 N) when solution effervesced ($CO_2$ -checked with $Ba(OH)_2$ soln.). Left cold one hour, added methanol (10ml), decanted organic layer from Cr salts and poured into ice after evaporating under reduced pressure to $\frac{1}{4}$ volume. Filtered solid and dried (1.45g, 74%) which was practically pure by t.l.c. Crystallisation from aqueous methanol gave the pure compound (67) (0.58g, 29.5%, first crop). M.p. 144-146$^O$, $(\alpha)_D$ -443$^O$ (c 2.21).

(Found C, 79.52; H, 9.19; $M^+$ 286.1928. $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15; $M^+$ 286.1932).

$\lambda_{max}(\varepsilon)$: 300 (214).

$\nu_{max}$ : 3435 and 3385 (overtones), 3060, 1735, 1703 and 760 $cm^{-1}$.

$\delta$ : 0.97, 1.10, 1.12 and 1.16 (4x3H, 4xs, 4xMe); 1.77 and 2.70(2H, ABq, J=14.0Hz, 2$\alpha$- and 2$\beta$-H resp.); 5.68 and 5.98(2H, ABq, J=5.5Hz, H-16 and H-15 resp.).

## A-NOR-STACH-15-ENE-2,12-DIONE (68).

Benzilic acid (69) (0.75g) in glacial acetic acid (4 ml) and chloroform (4ml) was treated with lead tetra-acetate(suspension in acetic acid, 3g). Reaction became warm and $CO_2$ was evolved. After 18 hours added ethanediol

(1.0ml) and evaporated most of the solvents. Poured into water when the pure, crystalline compound was obtained (0.63g,97.5%). Crystallisation from aqueous methanol gave the pure ketone as needles, (0.5g first crop), m.p. 156-158°, $(\alpha)_D$ -514.5° (c 2.0). (Found $M^+$ 286.1938. $C_{19}H_{26}O_2$ requires $M^+$ 286.1933).

$\lambda_{max}(\epsilon)$ : 298 (240).

$\nu_{max}$ : 3447 and 3385(overtones), 3060,1735, 1710, 774 and 762 cm$^{-1}$.

$\delta$ : 0.80(3H,s,20-Me); 1.01, 1.03, 1.10(3x3H,3xs,3xMe); 5.73 and 6.19(2H,ABq,H-16 and H-15 resp.).

## A-NOR-2α-HYDROXYSTACH-15-ENE-12-ONE-2β-CARBOXYLIC ACID (69).

α -Ketol (1) (1.0g) or diosphenol (18) (1.0g) in ethanediol-monomethyl ether (10ml) was heated on steam for 1 hour with Ba(OH)$_2$, 8H$_2$O (2.0g, 2eq.), then left cold overnight. Poured into ice-dilute HCL and recrystallised the crystalline solid from aqueous methanol giving leaflets (0.9g), m.p. 229-230°, $(\alpha)_D$ -361° (c 2.4).

$\nu_{max}$ : 3530(sharp) 3400, 3350-2500(v.broad),1700(broad), 1068 and 760 cm$^{-1}$.

$\delta$ : 0.98, 1.02, 1.02 and 1.10(4x3H,4xs,4xMe); 5.65 and 6.05(2H,ABq,J=5.5Hz,H-16 and H-15 resp.); 7.10(2H, very broad hump, EXCHANGED WITH D$_2$O, -OH and -COOH).

## METHYL A-NOR-2α-HYDROXYSTACH-15-ENE-12-ONE-2β-CARBOXYLATE.

Prepared from (69) in methanol using excess ethereal diazomethane, leaflets from aqueous methanol, m.p. 148-149$^O$, $[\alpha]_D$ -362$^O$ (c 2.026).

(Found C, 72.68; H,8.727; M$^+$ 346.2151. C$_{21}$H$_{30}$O$_4$ requires C, 72.80; H,8.73; M$^+$ 346.2144).

$\lambda_{max}(\epsilon)$: 298(215) and 210 (4005) e.a.

$\nu_{max}$ : 3440, 3080, 3045, 1708, 1700, 1255, 763, 755 and 750 cm$^{-1}$.

$\delta$ : 0.88, 0.94, 0.94, 1.04(3xs, 4xMe); 3.22(1H,b., OH); 3.68(3H,s,COOMe); 5.56 and 5.96(2H, AB q, J = 5.5 Hz, H-16 and H-15 resp.).

## A-NOR-2α-ACETOXYSTACH-15-ENE-12-ONE-2β-CARBOXYLIC ACID.

This was prepared from (69) in pyridine-acetic anhydride. Needles from aqueous methanol m.p. 196$^O$ and 206-211$^O$(dec.); $[\alpha]_D$ -287$^O$(c 0.60).

(Found M$^+$ 374.2088 C$_{22}$H$_{30}$O$_5$ requires M$^+$ 374.2093).

$\lambda_{max}(\epsilon)$: 297.5(155) and 210(3369) e.a.

$\nu_{max}$ : 3400, 3200 (broad), 1736, 1705, 1270, 1260, 1240, 760 and 750 cm$^{-1}$.

## 12-(1,3-DIOXOLANO)-STACHA-2,15-DIENO[2,3-b]DIOXANE (70).

α-Ketol (1) (3.0g) was refluxed with a water separator

using toluene (50ml), ethanediol (10ml) and p-tosic acid catalyst (0.3g) for 2 hours until homogeneous.  Cooled, poured into NaHCO$_3$ solution, extracted with EtOAc, evaporated and crystallised from methanol containing a few drops of pyridine giving 2.34g crystals (pure), m.p. 175-177$^O$, $(\alpha)_D$ -30$^O$ (c 2.48).

(Found M$^+$ 386.2464.    C$_{24}$H$_{34}$O$_4$ requires M$^+$ 386.2457).

$\nu_{max}$ :  3057, 3045, 1705 (-O-C=C-O-) and 755 cm$^{-1}$.

$\delta$    :  0.81, 0.95, 0.98 and 1.07(4x3H,4xs,4xMe);3.93

(4H,m,12-OCH$_2$CH$_2$-O-);  4.00(4H,s,p-dioxene);  5.68

and 5.83(2H,ABq,J=5.5Hz,H-15 and H-16).

## 12-OXOSTACHA-2,15-DIENO(2,3-b)DIOXANE (71).

Procedure as for (70) but the NaHCO$_3$ was omitted from the aqueous wash and a drop of HCl (conc.) was added to the aqueous acetone from which (71) was crystallised.  From ketol (1) (3.0g) gave leaflets (3.0g, 92.5%); m.p. 195-197.5$^O$(sublimes 180-190$^O$), $(\alpha)_D$ -319$^O$, (c 2.2).

(Found M$^+$ 342.2202.  C$_{22}$H$_{30}$O$_3$ requires M$^+$ 342.2195).

$\lambda_{max}(\epsilon)$: 296(204) and 210 (5878) e.a.

$\nu_{max}$  : 3075, 3055, 1702, 1590, 766 and 757 cm$^{-1}$.

$\delta$     : 0.87, 0.97, 1.10 and 1.10(4x3H,4xs,20-,19-,18-
and 17-Me resp.); 2.20 -2.80(2H,m,11$\alpha$- and 11$\beta$-
protons, removed by deuteration);  4.00(4H,s,
dioxene protons); 5.63 and 6.08(2H,ABq,J=5.5Hz,
H-16 and H-15 resp.).

Compound (71) was also made by dissolving the $\alpha$-ketol (1) (1g) in dry benzene (25ml), adding dry ethanediol (10-15 ml) and boron trifluoride-etherate (10ml) whilst keeping

the mixture cold. Set to crystalline mass overnight. Poured into ethylacetate, washed with water and re-crystallised as above. The 12-ketal was also formed under these conditions and HCl was therefore added during the crystallisation.

## 12-OXOSTACH-2-ENO[2,3-b]DIOXANE(15,16-DIHYDRO 71).

a) Conveniently prepared by the $BF_3$ method described above, using the 15,16-dihydroketol (2) (3.0g) since the product crystallised from in the reaction. Crystals were filtered off, washed with methanol and recrystallised from aqueous acetone (3.0g).

b) Hydrogenation of (71) using a Pd/C or Pt catalyst at atmospheric pressure as for (8), m.p. 180-183.5°,

$(\alpha)_D$ -68° (c,1.98).

(Found $M^+$ 344.2345. $C_{22}H_{32}O_3$ requires $M^+$ 344.2351).

$\lambda_{max}(\epsilon)$: 284 (30.6) and 210 (1352) e.a.

$\nu_{max}$ : 1705, 1450, 1110, 1075, 912 cm$^{-1}$.

$\delta$ : 0.93, 1.06, 1.06 and 1.06(4x3H,2xs,4xMe); 3.94 (4H,s,-OCH$_2$CH$_2$O-).

## 3α-BENZOYLOXYSTACH-15-ENE-2,12-DIONE 2,12-BIS-(ETHANEDIOXY-KETAL) (73).

Ketol-3α-benzoate (11) (5.0g) in toluene (200ml) con-

taining ethanediol (15ml) and p-tosic acid (100mg), was refluxed with a water separator for 4 hours.   Washed with bicarbonate solution, evaporated to a crystalline mass and recrystallised from aqueous acetone containing a few drops of pyridine giving 4.0g needles (first crop), m.p. 234-239$^{\rm O}$, $(\alpha)_{\rm D}$ 0$^{\rm O}$ (c 2.15 in CHCl$_3$).   (Note the zero rotation!) (Found C,73.25; H,8.10.  C$_{31}$H$_{52}$O$_6$ requires C,73.20; H7.93).

$\nu_{max}$:  3055, 3033, 1727, 1720, 1715, 1450, 1270, 760 and 708 cm$^{-1}$.

$\delta$  :  0.91, 0.97, 0.97 and 1.13(4x3H,3xs,4xMe); 3.4-4.2 (8H,m,2x-OCH$_2$CH$_2$O-); 5.06(1H,s,3$\beta$-H); 5.67 and 5.84 (2H,ABq,J=5.5Hz,15-H and 16-H);  7.4-8.2(5H,m, aromatic protons).

## 3$\alpha$-HYDROXYSTACH-15-ENE-2,12-DIONE-12-ETHANEDITHIOKETAL (74).

$\alpha$-Ketol (1) (2.0g) in glacial acetic (30ml) was mixed with ethanedithiol (2.0ml) and BF$_3$.Et$_2$O (1.0ml).   After 15 min. H$_2$O (10ml) was added, left 1 hour to digest, diluted with 20ml H$_2$O, filtered and washed with cold methanol. Crystallised from aqueous acetone giving 1.7g of product m.p. 195-200$^{\rm O}$(dec.); $(\alpha)_{\rm D}$ -15$^{\rm O}$ (c 2.04). (Found C, 67.12;  H,8.08.  C$_{22}$H$_{32}$O$_2$S$_2$ requires C, 67.30;  H,8.22).

$\nu_{max}$:  3497, 3475, 3046, 1705, 1390, 856, 770 and 755 cm$^{-1}$.

The <u>derived acetate</u> (76) was obtained by simple

acetylation or by treating the ketol acelate (3) with the ethanedithiol-BF$_3$ reagent. This same reagent under the above conditions (5-15$^O$) displaced a 12-ethaneoxythioketal to give (76). Large, chunky crystals from aqueous acetone-methanol, m.p. 230-232.5$^O$, $(\alpha)_D$ -74$^O$ (c 2.16). $\nu_{max}$: 3045, 1742, 1725, 1230, and 760 cm$^{-1}$.

$\delta$ : 0.74, 0.85, 1.10 and 1.30(4x3H,4xs,20-,19-,18- and 17-Me resp.); 2.17(3H,s,ACETOXYL); 3.0-3.4(4H,m,-SCH$_2$CH$_2$S-); 4.94(1H,s,3$\beta$-H); 5.63 and 5.73(2H,ABq, J=5.5Hz,H-15 and H-16).

## 3$\alpha$-ACETOXYSTACH-15-ENE-2,12-DIONE-12-ETHANEOXYTHIOKETAL (75).

$\alpha$-ketol acetate (3) (0.5g) was dissolved in glacial acetic acid (10ml), added 2-mercaptoethanol (0.6ml) and then BF$_3$-Et$_2$O(0.4ml). After 30min, added water (2-3ml) when the mixture went solid. Crystallised from aqueous methanol-acetone as leaflets (0.48g), m.p. 212-221$^O$, $(\alpha)_D -67.3° (c\ 0.76)$ $\nu_{max}$: 3046,1743,1725,1235,763 and 755 cm$^{-1}$.

$\delta$ : 0.70, 0.83, 1.10 and 1.10(4x3H,3xs,20-,19-, 18- and 17- Me resp.); 2.15(3H,s,ACETOXYL); 2.7-3.1 (2H,m,-CH$_2$-S-); 3.4-4.5(2H,m,-CH$_2$-O-); 4.92(1H,s, 3$\beta$-H); 5.70(2H,distorted ABq,J=5.5Hz, H-15 and H-16).

This "compound" (75) was actually a mixture of the two isomers at C-12 as shown by t.l.c., hence the odd n.m.r. pattern for the double bond and the drawn-out m.p.

## THE BENZALDEHYDE-LACTONE (77)

a)  $\alpha$-ketol (1) (1.0g) in ethanol (10ml) was treated with benzaldehyde (1.0ml) and NaOH (10%,2ml).   Stirred overnight, added $H_2O$ (10ml), filtered crystals and re-crystallised from ethanol (0.6g).

b)  "Mother liquor 2" from ketol recrystallisations (100g) in ethanol (200ml) was added benzaldehyde (20ml), cooled in ice and added NaOH (30%, 30ml).   Stirred vigorously with access to air overnight when mixture set to a stiff paste, added $H_2O$ (200ml), digested 6 hours and filtered.   Washed yellow crystals with water and aqueous, ice-cold methanol (50%) and the resulting white product crystallised from acetone-methanol.   The first crop obtained was very pure (35g), later crops were combined and recrystallised to give a further 15g pure material.

Needles, sublime at  $230^O$ and m.p. $272-273^O$; $[\alpha]_D$ $-347^O$ (c 2.06).

(Found C, 77.35; H,7.66; $M^+$ 420.2297.   $C_{27}H_{32}O_4$ requires
C, 77.11, H,7.67; $M^+$ 420.2300).

$\lambda_{max}$ (log $\varepsilon$): 298(2.3600), 270(2.3033), 266(2.3997),
264(2.3846), 260(2.4286), 254(2.3077),
250sh(2.1869), 244(2.1253).

$\nu_{max}$: 3400, 1750($\gamma$-lactone), 1705,770,760 and 705 $cm^{-1}$.

$\delta$  : 1.00, 1.03, 1.08 and 1.13(4x3H,4xs,20-Me and 19-
18- and 17-Me); 2.67(1H,d,J=9.0Hz,1$\alpha$-H); 3.26(1H,s,
EXCHANGED WITH $D_2O$, 2$\alpha$-OH); 5.17(1H,d,J=9.0 Hz,

Benzylic H); 5.62 and 6.01(2H,ABq,J=5.0 Hz,H-16
and H-15 resp.), 7.70(5H,s, aromatic protons).


## BENZALDEHYDE-LACTONE-12-OLS (79 and 80).


a)  Using $NaBH_4$ :-

(77) (2.5g) in THF-ethanol was reduced in the cold with
$NaBH_4$ as described for (16).  Solid obtained (2.6g)
was chromatogrammed on silica gel (7734, 30g, hexane) and
elution with hexane-ethyl acetate  (95:5 to 90:10) gave
the 12β-axial alcohol (80) (0.7g, 38%); further elution
with (80:20) gave the 12α-equatorial alcohol (79) (1.15g,
62%) contaminated with traces of a slightly faster-moving
compound  (81).


b)  Using $LiAL(t-BuO)_3H$:-

(77) (3.0g) was dissolved in dry THF (80ml, redis-
tilled from LAH), cooled to $-10^{\circ}$ in a methanol-ice bath,
added $LiAL(t-BuO)_3H$ (5.0g) and stirred under $N_2$ for 2 hours
then at room temperature for 12 hours.  Added ethyl
acetate and water, poured into ice-dil. HCl(500ml),
and filtered off solid.  Crystallisation from methanol
gave (80) (2.1g, 70%) contaminated with a trace of compound
(81).  Recrystallisation gave the pure compound (80),
needles m.p. 219-220$^{\circ}$, $(\alpha)_D$ $-46^{\circ}$ (c 2.28).
(Found $M^+$ 422.2449.  $C_{27}H_{34}O_4$  requires $M^+$ 422.2457).
$\nu_{max}$:  3626, 3605, 3415(broad), 3215, 1755, 1215, 747 $cm^{-1}$.

$\delta$ : 0.90, 1.00, 1.07 and 1.12(4x3H,4xs,4xMe); 2.74(1H,d,

J=9.0Hz,1$\alpha$-H); 3.31(1H,m,W$_\frac{1}{2}$7Hz,12$\alpha$-H); 3.44(1H,s,

EXCHANGED WITH D$_2$O); 5.24(1H,d,J=9.0Hz,benzylic H);

5.33 and 5.72(2H,ABq,J=5.5Hz, H-16 and H-15 resp.);

7.45(5H,s, aromatic protons).

## BENZALDEHYDE-LACTONE-ent-ATISA-13(14),16(17)-DIENE (82).

12$\beta$-axial isomer (80) (1.35g) in dry pyridine (15ml)

was treated with POCl$_3$ as for (24). Chromatogrammed solid

on alumina (30g, basic, in Hexane) and eluted with hexane-

ethylacetate (84:16) giving the crystalline diene. Re-

crystallised from aqueous methanol in needles (400mg),

m.p. 180-185$^O$ (phase change at ~160$^O$).

(Found M$^+$ 404.2355. C$_{27}$H$_{32}$O$_3$ requires 404.2351).

$\nu_{max}$: 3425(b),1750,1640,1606,1197,990,777,723,715,705 & 690cm$^{-1}$.

$\delta$ : 0.83, 1.06 and 1.12(3x3H,3xs,3xMe); 2.70(1H,d,

J=9.0 Hz,1$\alpha$-H); 3.38(1H,s,EXCHANGED WITH D$_2$O,3-OH);

4.60(2H,m,C-17 methylene); 5.67(1H,d,J=9.0 Hz,

benzylic H); 6.0(2H,m,H-15 and 16); 7.41(5H,s,

aromatic protons).

The presence of the ent-ATISA-13(14),15(16)-DIENE ISOMER

(83) in trace amounts was shown by the presence of signals

in the n.m.r. spectrum as shown:

$\delta$ : 1.67(doublet, J=1.5Hz, collapses to a singlet on

irradiation at 5.67, 17-vinyl methyl); 5.67(quartet,

J=1.5Hz, collapses to a singlet on irradiation at

1.67, 14-olefinic proton).

## A-NOR-1β-HYDROXYBENZYL-2β-HYDROXYMETHYL-2α-HYDROXYSTACH-15-ENE-12-ONE-12-ETHANEDIOXYKETAL (84).

The benzaldehyde-lactone-12-ethanedioxyketal (89) (2.2g) in diglyme (60ml, purified with Na and distilled) was heated to 80-100° with LAH (1.0g) under $N_2$ for 15 hours. Worked up with ethyl acetate (10ml), ethanol (5ml) and $H_2O$ (10ml) then poured into water (800ml). Added KOH (6g) and tartaric acid (10g). Left 24 hours, filtered off solid, dried and crystallised from THF-methanol. Recrystallised from plain methanol giving 2 crops (0.64g and 0.50g) of large rhombs, m.p. 245-251°(profuse sweating); $[\alpha]_D^{22}$ -30° (c 2.03).

(Found $M^+$ 468.2874. $C_{29}H_{40}O_5$ requires $M^+$ 468.2875).

$\nu_{max}$: 3545, 3495, 3355, 3086, 3062, 3020, 1600,1117, 767 and 700cm$^{-1}$.

δ : 0.95, 1.00, 1.03 and 1.15(4x3H,4xs,4xMe);

2.87(1H,d,J=5Hz, EXCHANGED WITH $D_2O$, OH); 3.03(1H,s, EXCHANGED WITH $D_2O$, OH); 3.52(2H,d,J=5.0Hz, collapses to a 2H singlet on $D_2O$ exchange, -$CH_2$-O-H methylene); 3.4-4.1(4H,m,-$OCH_2CH_2O$-); 5.23(1H,quartet,J=2 and 5Hz, collapses to a 1H singlet on $D_2O$ exchange, benzylic-CH-OH);5.73 and 5.94(2H,ABq,J=5.5Hz,H-16 and H-15 resp.); 7.37(5H,m,aromatic protons).

## A-NOR-1β-HYDROXYBENZYL-STACH-15-ENE-2,12-DIONE-12-ETHANE-DIOXYKETAL (85).[75]

The triol (84) (1.0g) was dissolved in dioxan (20ml), added solid $H_5IO_6$ (1.0g) followed by water (1 ml). Immediate precipitation of crystalline material. After 1.5 hr. poured into brine, filtered and crystallised from aqueous methanol in large colourless crystals (0.5g first crop), m.p. 164-170° (dec.).

$v_{max}$ : 3485, 1600 and 755 cm$^{-1}$.

$\delta$ : 0.71(3H,s,20-Me); 0.97, 1.00 and 1.13(3x3H, 3xs, 3xMe); 2.24(1H,d,J=3.0hz,1α-H); 2.75(1H,d,J= 4.0 Hz, EXCHANGES WITH $D_2O$, OH); 3.5-3.9(4H,m, $-OCH_2CH_2O-$); 5.06(1H,t,J=3.0 Hz, collapses to a doublet J=3.0 Hz on shaking with $D_2O$; collapses to a sharp singlet on irradiation at 2.24, benzylic-CH-OH); 5.70 and 5.85(2H,ABq,J=5.5Hz, H-16 and H-15); 7.31(5H,s, aromatic).

## BENZALDEHYDE-LACTONE-12-ETHANOXYTHIOKETAL (87).

(77) (2.0g) in glacial acetic acid (30ml) was cooled to room temp. added β-mercapto-ethanol (2.0ml) and $BF_3Et_2O$ (2.0ml). AFter 2-3 min. went solid. Left 2 hrs., added a few ml $H_2O$ and filtered. Washed insoluble solid with methanol. Crystallised from THF in needles (1.52g, and a further 0.5g), m.p. 306-310°.

(Found $M^+$ 480.2339.  $C_{29}H_{36}O_4S$  requires $M^+$ 480.2334).

$\nu_{max}$:  3435, 3053, 1755, 781, 770 and 705 $cm^{-1}$.

$\delta$($D_6$-DMSO):  0.87, 0.95, 0.95 and 0.95(4x3H,2xs,4xMe);

This was once again a mixture of the two 12-isomers (c.f. 75).

## REDUCTION OF LACTONE (87) TO AN ETHYL ACETAL (88).

(87) (438mg) was reduced with excess LAH (500mg) in dry THF (40ml) under reflux for 15 hours.  Added ethyl acetate, ethanol, water (3x3ml) then conc. HCl until precipitated material redissolved.  Filtered off small amount of Al salts, removed most of solvent under vacuum and washed crystalline material with $H_2O$.  Recrystallised from aqueous acetone to needles (230 mg first crop), m.p. 204-210° (phase change at 200°), $\{\alpha\}_D$ -101° (c 0.98).

(Found $M^+$ 510.2789.  $C_{31}H_{42}O_4S$ requires $M^+$ 510.2804).

$\nu_{max}$: 3526, 3050, 1090, 1042, and 755 $cm^{-1}$.

$\delta$  : 1.00, 1.66, 1.66 and 1.66(4x3H,2xs,4xMe); 1.15

(3H, quartet, $X_3$ part of $ABX_3$, ETHYL $CH_3$); 2.40

(1H,d,J=8.0 Hz, 1α-H); 2.5-3.0(3H,m,$-CH_2$S- + -CH-O-);

3.3-4.2(3H,m,ETHYL $CH_2$-O (AB) and -CH-O-); 3.47(1H,s,

EXCHANGED WITH $D_2O$, 3α-OH); 4.76(1H,s, acetal proton);

4.85(1H,d,J=8.0 Hz, benzylic H); 5.55 and 5.85

(2H, ABq, J=5.50 Hz, H-16 and H-15 protons resp.);

7.4(5H,m, aromatic H).

By comparison to (75) this compound (88) appears to be one pure isomer of the two possible 12-ketals, and is assigned the O-$\beta$,S-$\alpha$-configuration by the aromatic signal shape (c.f. 89) and the shielding of one of the -O-CH$_2$-ketal protons by the $\beta$-orientated aromatic ring. Note yield is approximately 50% of the expected as required of one half of the isomeric mixture possible.

## BENZALDEHYDE-LACTONE-12-ETHANEDIOXYKETAL (89).

(77) (2.0g) was refluxed with toluene (60ml) and ethanediol (6.0ml) containing p-tosic acid (100mg) as for (73). Crystallised on cooling. Filtered, washed off with benzene and combined filtrates and washings shaken with NaHCO$_3$ soln. and water. Evaporation and recrystallisation from aqueous acetone (trace pyridine) gave needles (2.2g, 100%), m.p. 276-281$^O$, $\{\alpha\}_D$ -86$^O$ (c 2.22). (Found M$^+$ 464.2564. C$_{29}$H$_{36}$O$_5$ requires M$^+$ 464.2563).

$\nu_{max}$: 3075, 3020, 1628, 1585, 1255, 1055, 1030, 875, 840 and 793 cm$^{-1}$.

$\delta$ : 0.58 (1H,m); 0.90, 0.93, 1.06 and 1.10(4x3H,4xs,4xMe); 2.73(1H,d,J=8.5Hz,1$\alpha$-H); 3.18(1H,s,EXCHANGED WITH D$_2$O, 3-OH); 3.0-3.8(4H,m,-OCH$_2$CH$_2$O-); 5.30(1H,d, J = 8.5 Hz, benzylic H); 5.61 and 5.75(2H, ABq, 5.5 Hz, H-15 and H-16); 7.38(5H,s, aromatic protons).

## PREPARATION OF METHYL ACETAL-12-OXIME (91).

Hemiacetal (92) (1.0g) in methanol (30ml) was deketalised by warming with p-tosic acid (100mg) for 30 min. Added aqueous $NH_2OH.HCl$ (0.3g in 5ml) and pyridine (5ml); heated on steam allowing solvent to slowly evaporate. Oxime crystallised out. Filtered and recrystallised from acetone-methanol-water giving excellent crystals (0.8g), m.p. 212-213.5$^{\circ}$, $[\alpha]_D^{22}$ -268$^{\circ}$ (c 2.68).

(Found M$^+$ 433.2622. $C_{28}H_{37}NO_4$ requires M$^+$ 433.2617).

$\nu_{max}$:    3530 (b), 3310(vb), 3135, 3060, 1037 (b), 945, 763 and 700 cm$^{-1}$.

$\delta$    :    1.03(9H,s,3xMe); 1.11(3H,s,Me); 2.33(1H,d,J=7.0 Hz, 1$\alpha$-H); 3.37(3H,s,OMe); 3.40(1H,s,EXCHANGES WITH D$_2$O, 2$\alpha$-OH); 4.65(1H,s, -O-CH-O-); 4.82(1H,d, J=7.0 Hz, benzylic H); 5.48 and 5.87(2H,ABq, J=5.5Hz, H-16 and H-15 resp.); 7.30(5H,m,aromatic); 8.70(1H,s,EXCHANGES WITH D$_2$O, =NOH).

The 12-dioxyketal-analogue of (91) was obtained in trace amounts on one occasion as follows. The crude (92) was dissolved in methanol and heated with a trace of p-tosic acid as above. Removal of the solvent and chromatography of the resulting oil on silica gel (7734, 30g in hexane) using hexane-ethyl acetate (95:5) gave a small crystalline fraction of (90) identified solely by its n.m.r. spectrum.

$\delta$    :    0.90, 0.97, 1.03 and 1.05(4x3H,4xs,4xMe); 2.28(1H,d, J=7.5 Hz, 1$\alpha$-H); 3.37(4H,s,OMe + OH); 3.2-3.8(4H,m,

-OCH$_2$CH$_2$O-); 4.63(1H,s,-O-CH-O-); 4.83(1H,d,J=7.5 Hz,

benzylic H); 5.58 and 5.78(2H,AB q, J = 5.5 Hz, H-16

and H-15 resp.); 7.37(5H,m, aromatic protons).


The main fraction eluted with the same solvent system

was the 12-oxo-analogue as an oil (subsequently all converted

to the crystalline oxime (91)).

δ : 1.03(12H,s,4xMe); 2.24(1H,d, J= 7.5 Hz, 1α-H);

3.37(3H,s,OMe); 3.41(1H,s, EXCHANGED WITH D$_2$O, OH);

4.65(1H,s, -O-CH-O-); 4.82(1H,d, J = 7.5 Hz, benzylic H);

5.55 and 6.02(2H, AB q, J = 5.5 Hz, H-16 and H-15 resp.);

7.33(5H,s, aromatic protons).


REDUCTION OF THE LACTONE FUNCTION TO THE FREE HEMIACETAL (92).


The 12-dioxyketal lactone (89) (10g) was reduced in

dry THF (300ml) with excess LAH (3.0g) for 15 hr. Destroyed

excess hydride with 10% NaOH solution, poured into water

(2ℓ), added tartaric acid (10g) and left overnight. Ex-

tracted with methylene chloride and evaporated under reduced

pressure to a thick oil which could be used as such for

preparing derivatives. This oil on t.l.c. appeared as

a major faster spot and a minor more polar spot, probably

both anomers. Chromatography on silica gel (7734, 100g

in hexane) gave (92) (8g) on elution with hexane-ethyl

acetate (92-8 to 80 -20%). Obtained as silky, soft

needles or a glass; indefinite melting point (softening

gradually), $[\alpha]_D$ $-89^O$ (c 2.4).

(Found $M^+$ 466.2719. $C_{29}H_{38}O_5$ requires $M^+$ 466.2719).

$\nu_{max}$: 3510, 3420, 3030, 1145, 1115, 1035(b), 760 and

700 cm$^{-1}$.

$\delta$ : 0.90, 0.93, 1.00(12H,3xs,4xMe); 2.30(1H,d, J = 7.5 Hz,

1$\alpha$-H); 3.35(1H,s,EXCHANGED WITH $D_2O$, OH); 3.0-3.8

(4H,m, -OCH$_2$CH$_2$O-); 4.47(1H,d, J = 3.5 Hz, collapses

to a singlet on irradiation at 5.10, EXCHANGES WITH

$D_2O$, -O-C-OH); 4.81(1H,d, J= 7.5 Hz, benzylic H);

5.08(1H,d, J = 3.5 Hz, collapses to a singlet on

irradiation at 4.47 and on shaking with $D_2O$, -O-CH-O-),

5.60 and 5.77(2H, AB q, J = 5.5 Hz, H-16 and H-15

resp.); 7.43(5H, m, aromatic).


(93), the p-bromobenzoate of (92) was prepared from

(92) (0.5g) in dry pyridine (10ml) with p-bromobenzoyl

chloride (0.5g).  Left at r.t. 2 days, poured into ice-

water, filtered and extracted solid with boiling acetone

(3 x 20ml), filtering off insoluble aromatic anyhdride.

Concentration and crystallisation gave twinned needles

(0.5g), m.p. 206-208$^O$, $[\alpha]_D$ +25.6$^O$(c 2.11).

$\nu_{max}$: 3593, 3057, 3040, 1730, 1588, 1260, 1065, 755 and

700 cm$^{-1}$.

$\delta$ : 0.90, 1.03, 1.05 and 1.20(4 x 3H, 4xs, 4xMe);

2.60(1H,d, J = 7.5 Hz, 1$\alpha$-H); 2.58(1H, broad s,

EXCHANGED WITH $D_2O$, OH); 3.07(1H,m) and 3.57(3H,m)

both -OCH$_2$CH$_2$O-.  5.07(1H,d, J = 7.5 Hz, benzylic H);

5.63 and 5.81(2H, AB q, J = 5.5 Hz, H-16 and H-15

resp.); 6.44(1H,s, -O-CH-OBz); 7.2-8.1 (9H, over-

lapped AA'MM' and multiplet systems, aromatic protons).


PREPARATION OF THE ETHYL ACETAL-12-OXIME-p-BROMOBENZOATE(94).


The ethyl acetal-12-oxime (95) (0.4g) in dry pyridine

was treated with excess p-bromobenzoyl chloride (0.4g)

and left at 5$^{\circ}$ for 72 hours.   Poured into ice, filtered,

extracted solid with acetone and filtrate allowed to

evaporate to an oil which crystallised over a period of

days.   Poured off supernatant, redissolved in methanol-

acetone obtaining very good rhombs of (94), (0.4g),

monoclinic, space group P2$_1$; m.p. 140-150$^{\circ}$ (vigorous dec.).

X-ray structure was determined on this compound.

$\nu_{max}$:   3557, 3475, 1745, 1730, 1620, 1585, 1270, 1255,

1070, 1010, 900, 753 and 700 cm$^{-1}$.

$\delta$   :   1.11 and 1.36(9H and 3H; 2xs, 4xMe); 2.38(1H,d,

J = 7.5 Hz, 1$\alpha$-H); 3.44(1H,s,EXCHANGES WITH D$_2$O, OH);

3.3-4.1(2H,m,ABX , -O-CH$_2$CH$_3$);   4.77(1H,s,-O-CH-O-);

4.78(1H,d,J = 7.5 Hz, benzylic H); 5.58 and 5.95

(2H, AB q, J = 5.5 Hz, H-16 and H-15); 6.47(1H,t,

J= 7.0 Hz, endo-ortho-aromatic H);   7.01(2H,t,

J = 7.25 Hz, meta-protons); 7.30(1H, exo-ortho-

aromatic H); 7.48(5H,s, aromatic protons).

## PREPARATION OF THE ETHYL ACETAL-12-OXIME (95).

Hemiacetal (92) (1.0g) in ethanol (20ml) at $60^\circ$ for
24 hours with p-tosic acid (100mg). Then added hydroxylamine
hydrochloride (0.5g) in water (5ml), followed by pyridine
(5ml) and left at $60^\circ$ for a further 24 hours. Next
allowed solvent to evaporate to dryness. The pink,
crystalline mass recrystallised from methanol in excellent
crystals, m.p. 197-201$^\circ$ (dec.), $[\alpha]_D$ -285$^\circ$ (c 2.1).
(Found C, 74.88; H,8.30. N,2.96. $C_{29}H_{39}NO_4$ requires
C, 74.81; H,8.44; N,3.01).
$\nu_{max}$: 3510, 3275, 1042, 940, 763, 755 and 700 cm$^{-1}$.
$\delta$(CDCl$_3$): 1.04(s, 4xMe); 2.36(1H,d, J= 7.5 Hz, 1$\alpha$-H); 3.45
(1H,s, EXCHANGES WITH D$_2$O, 3$\alpha$-OH); 3.44 and 3.77
(2H, $\underline{ABX_3}$, -O$\underline{CH}_2$CH$_3$); 4.75(1H,s, -O-CH-O-);
4.80(1H,d, J = 7.5 Hz, benzylic H); 5.47 and 5.84
(2H, AB q, J = 5.5 Hz, H-16 and H-15); 7.0 -7.6
(5H,m, aromatic protons); 8.40(1H, very broad,
EXCHANGES WITH D$_2$O, N-OH).

$\delta$(C$_6$H$_6$): 1.07(6H,s, 2xMe); 1.20 and 1.28(2x3H, 2xs, 2xMe);
2.43(1H,d, J = 7.5 Hz, 1$\alpha$-H); 3.17 and 3.66(2H,
$\underline{ABX_3}$, J$_{AB}$ = 9.5 Hz, J$_{AX}$ = 7.5 Hz, J$_{BX}$ = 7.0 Hz,
A = $\beta$-H, B = $\alpha$-H, X$_3$= Me).

## A-NOR-1$\beta$-FORMYLOXYBENZYL-STACH-15-ENE-2,12-DIONE-12-ETHANEDIOXYKETAL (96).

Hemiacetal (92) (1.0g) in acetic acid (10ml) and

chloroform (5 ml) was treated with excess lead tetra-
acetate in acetic acid (3g suspension).    After 15 hours
added ethanediol (5 ml), removed chloroform under vacuum,
diluted with water and crystallised from methanol giving
colourless crystals (0.62g), m.p. 136-139$^O$.

(Found M$^+$   464.2555.        $C_{29}H_{36}O_5$   requires

   M$^+$    464.2563.

$\nu_{max}$: 1738, 1720, 1601, 1583, 1150(b) and 763 cm$^{-1}$.

$\delta$    : 0.73, 0.93, 1.03 and 1.10(4xs, 4xMe); 2.53(1H,d,

   J= 5.5 Hz, 1$\alpha$-H); 3.4-4.0(4H,m, $-O-CH_2CH_2-O-$);

   5.73(2H,s,H-15 and H-16); 6.22(1H, doublet with

   shoulders, J = 5.5 Hz, coupling through carbonyl to

   formyl proton); 7.35(5H,m, aromatic protons); 7.95

   (1H, singlet with shoulder, H-COO-).


## PREPARATION OF THE TOLLENS REACTION PENTOL (97)


The $\alpha$-ketol (1) (3.0g) in ethanol (30ml) and formalin
(6ml) was treated with NaOH solution (10%, 8ml), heated on
steam until volume was halved, added water (5ml) and cooled.
Crystalline material was recrystallised from a large volume
of ethanol giving fine needles (1.0g), m.p. 266-267$^O$ (dec.).
(Found M$^+$ at 380; M-CH$_2$OH = M-31 = 349.2388.  $C_{22}H_{36}O_5-$
$CH_2OH(C_{21}H_{33}O_4)$ requires M-31 = 349.2379).

$\nu_{max}$: 3658, 3600-3100(v.b.), 1045, 762 cm$^{-1}$.

$\delta(D_6$-DMSO): 0.92, 0.92, 0.99 and 1.05(3xs,4xMe); 3.03(2H,b s),

   3.33(2H,b s); 3.70(2H, b s ); 4.20(5H,b,5xOH?);

   5.48 and 5.82(2H,AB q, J = 5.5 Hz, H-16 and

   H-15).

## PREPARATION OF DIACETONIDE OF PENTOL (98).

(97) (0.14g) was suspended in dry acetone (10ml), added perchloric acid (70%, 1 drop) when material all dissolved and then needles slowly formed. Poured into dilute sodium bicarbonate soln. and recrystallised from aqueous acetone giving needles (0.11g), m.p. 244.5-245.5$^{\circ}$; $(\alpha)_D$ -226$^{\circ}$ (c 2.15).

(Found M$^+$ 460.3194. $C_{28}H_{44}O_5$ requires M$^+$ 460.3189).

$\nu_{max}$: 3550, 1385, 1370, 893, and 752 cm$^{-1}$.

$\delta$ : 0.93, 1.00, 1.03 and 1.09(4xs, 4xMe); 1.40(s, 4xMe,diacetonide); 1.91(1H,d,J=10.8 Hz, 9$\alpha$-H); 2.18 (1H,d, J = 14.0 Hz, 1a-$\beta$-hydroxymethylene proton?, -CH$_2$-O-, hindered rotation); 2.92(1H,d, J = 10.8 Hz, 12$\beta$-H); 3.47(2H,q, J= 9.0 and 11.7 Hz, 11a-oxymethylene); 3.80(1H,t, J=11.0 Hz, 1$\alpha$-H); 4.10 (1H,d, J = 8.5 Hz, 1$\beta$-H); 4.30(1H,q, J= 4.5 and 10.8 Hz, 2$\beta$-H); 5.67 and 5.88 (2H,AB q, J = 5.5 Hz, H-16 and H-15).

## THE FORMALDEHYDE-LACTONE (99).

a) The $\alpha$-ketol (1.0g) in methanol (20ml) was treated with saturated sodium bicarbonate (4ml) and formalin (2ml). Left open to the air for 5 - 6 days when silky needles separated.

b) The diosphenol (18) in methanol as above gave a solid mass of the derivative after 30 min. at room temperature.

The product (99) recrystallised from aqueous methanol as white, silky needles, m.p. 219-222°, $[\alpha]_D$ -398° (c 1.45). (Found $M^+$ 344.1978. $C_{21}H_{28}O_4$ requires $M^+$ 344.1987).

$\nu_{max}$: 3300, 1770, 1690.

$\delta$ : 1.05(12H,s,3xMe); 1.08(3H,s,17-Me); 2.77(1H, obscured

q, $J_{AX} + J_{BX}$ = 20.0 Hz, 1α-H); 3.39(1H,s, EXCHANGES

WITH $D_2O$, 2α-OH);

AT 60 MHz: 4.03 and 4.31(2H, ABX, 2x triplet, $J_{AX} = J_{BX}$=

7.0 Hz, $J_{AB}$ = 10.0 Hz, -O-CH$_2$-R protons).

AT 100 MHz: 4.01 and 4.26(2H, ABX, 2x triplet, $J_{AX} = J_{BX}$=

$J_{AB}$ = 10.0 Hz); 5.67 and 6.06(2H,AB q, J = 5.5

Hz, H-16 and H-15 resp.).


## 3α-HYDROXYSTACH-15-ENE-2,12-DIONE-2,12-DIOXIME DIACETATE (101).


The extremely insoluble dioxime (4) (0.71g, absolutely free of pyridine) was suspended in acetic anhydride (10ml), heated briefly (0.5 min) when the compound all dissolved, allowed to cool overnight, poured into water and crystallised from aqueous methanol giving needles (0.82g), m.p. 106-110°, 160-164° (dec.), $[\alpha]_D$ +7° (c 2.2).

$\nu_{max}$: 3555, 3494, 3290 (b), 3060, 1746, 1644, 1625, 1605,

1213(b) and 763 cm$^{-1}$.

$\delta$ : 0.70, 0.78, 1.18 and 1.31(4xs,4xMe)- 2.23(6H,s,2x

ACETATE); 3.96(1H,s,3β-H); 5.65 and 5.92(2H, AB q,

J = 5.5 Hz, H-16 and H-15).

## $3\alpha$-BENZOYLOXYSTACH-15-ENE-2,12-DIONE-12-OXIME (102).

Ketol benzoate (11) (1.0g) was dissolved in pyridine (5 ml) and ethanol (10ml). Added hydroxylamine sulphate (0.195g, 1 eq.) in water (5 ml). Heated on steam briefly, diluted with water (10ml), and allowed to crystallise. Recrystallised from aqueous acetone giving 0.75g product. Filtrate from reaction gave a further small amount on dilution. M.p. 278-280$^O$ (dec.), $(\alpha)_D$ -147$^O$ (c 2.0).

(Found M$^+$ 435.2399. $C_{27}H_{33}O_4N$ requires M$^+$ 435.2409).

$\lambda_{max}(\varepsilon)$: 281.5(41), 275(787), 270(712), 230(12450) and 210 (9740) e.a.

$\nu_{max}$ : 3415, 3250(b), 3135(b), 3060, 1735, 1715, 760 and 710 cm$^{-1}$.

The derived oxime acetate (103) was prepared as for (101). Crystallised from acetone-methanol, m.p. 219-221$^O$ (dec.). MW 477.

(Found M-42 435.2399; $C_{27}H_{33}NO_4$ requires 435.2409).

$\nu_{max}$: 3062, 1765, 1735, 1715, 1634, 1600, 1583, 915, 773 and 715 cm$^{-1}$.

## $3\alpha$-BENZOYLOXY-12,13-SECOSTACHA-13,15-DIENE-2-ONE-12-NITRILE(104).

(102) or (103) (1.6g) in acetic anhydride (10ml), refluxed 72 hours. Took off all solvent under vacuum, dissolved residue in benzene and filtered through silica gel (10g, 7734). Crystallised the first three fractions from

methanol (1.0g yield); m.p. 186-189.5$^{O}$, $\{\alpha\}_D$ -60$^{O}$ (c 1.3).
(Found M$^+$ 417.2303. $C_{27}H_{31}NO_3$ requires M$^+$ 417.23038).

$\nu_{max}$: 3060, 2236, 1725-1710(b), 1620, 1600, 1585, 800
and 707 cm$^{-1}$.

$\delta$ : 0.93, 1.06 and 1.23(3xs, 3xMe); 1.95(3H,d,J= 1.5
Hz, collapses to a singlet on irradiation at 5.83,
17-Me); 2.58(2H,s,C-1 methylene); 5.26(1H,s,3β-H);
5.83(1H,m,14-H); 6.30(2H,m,H-15 and H-16); 7.55 and
8.11 (3H and 2H multiplets resp., aromatic protons).

The presence of 25% of the exocyclic diene was evident from
a signal at 4.90 (m, olefinic methylene) and very slight
doubling of the methyls and the 3β-H.

## 3ξ-METHOXY-12-OXO-2,3-SECOSTACH-15-EN-2,3ξ-LACTONE(106).

α-Ketol (1) (1.0g) in methanol (15ml) and water (5ml)
treated with periodic acid (1.0g), and a trace p-tosic acid.
After 24 hrs. filtered off needles and recrystallised from
aqueous methanol (0.45g). M.p. 207-210$^{O}$, $\{\alpha\}_D$ -272$^{o}$ (c 0.79).
(Found M$^+$ 346.2138. $C_{21}H_{30}O_4$ requires M$^+$ 346.2144).

$\nu_{max}$: 3066, 1720, 1706, 1594, 985 and 765 cm$^{-1}$.

$\delta$ : 0.93, 1.01, 1.06 and 1.10(4 x s, 4 x Me); 3.52(3H,s,
OMe); 4.60(1H,s, -O-CH-O-); 5.68 and 6.10(2H, AB q,
J = 5.5 Hz, H-16 and H-15 resp.).

## ENT-3β-NITRATO-11(12→16)ABEO-ATIS-13-ENE-12-ONE (107).

(27) treated as for (109) with sulphuric acid.
Crystallised from aqueous methanol in needles, yield 0.4g
from 1.0g of (27).   M.p. 201-208$^O$ (vigorous bubbling),
$[\alpha]_D$ -266$^O$ (c 2.04).
(Found $M^+$ at 361.   M-46 = 315.1953.  $C_{20}H_{27}O_3$ requires
m/e 315.1960).
$\nu_{max}$:  1730, 1680, 1630, 1292 and 857 cm$^{-1}$.
$\delta$   :  0.65(s,20-Me); 0.88(s,19-Me); 1.22 and 1.27(2xs,17-
and 18-Me); 5.03(1H,s, ent-3α-H); 5.88(1H,d, $J_{AB}$= 10.0
Hz, 13-H); 6.88(1H,q,$J_{BA}$ = 10.0 Hz, J = 2.0 Hz,14-H).


## ENT-3β-HYDROXY-11(12→16)ABEOATISAN-12-ONE (108).

(107) in ethanol was hydrogenated under pressure
(50 atmospheres) using Pd/C.   Large rods from ethanol,
m.p. 197-201$^O$.
(Found $M^+$ 318.2193.   $C_{20}H_{30}O_3$ requires 318.2195).
$\nu_{max}$:  3456, 3385, 1700, 1235 cm$^{-1}$.
$\delta$   :  0.77(s,20-Me); 0.98(s,19-Me); 1.15 and 1.20(2xs,
18- and 17-Me); 3.25(1H, v.b., EXCHANGES WITH $D_2O$,
-OH);   3.90(1H,s, ent-3α-H).


## ENT-3β-ACETOXY-11(12→16)ABEOATISAN-13-ENE-12-ONE (109).

(i)   α-Ketol or α-ketol acetate (1 or 3) (1.0g) in
acetic anyhdride (10ml) was cooled in ice and added conc.

sulphuric acid dropwise (2-3ml). After five minutes

poured onto ice and crystallised from aqueous methanol,

(0.87g).

(ii) As in (i) but used $HClO_4$ (70%, 20 drops).

(iii) As in (i) but used $BF_3$-etherate (1.0ml) and

warmed to $60°$ for 2 minutes before quenching.


Very long needles m.p. 226-228.5$°$ (phase change at

190$°$), $[\alpha]_D$ + 128$°$ (c 2.04).

(Found C, 73.75; H,8.28; $M^+$ 358.2148. $C_{22}H_{30}O_4$ requires

C, 73.71; H,8.44; $M^+$ 358.2144).

$\lambda_{max}(\varepsilon)$: 324(92), 305(82) and 236(7750).

$\nu_{max}$: 1742, 1716, 1665, 1235 and 820 cm$^{-1}$.

$\delta$ : 0.63(s,20-Me); 0.87(s,19-Me); 1.13(s,18-Me);

1.22(s,17-Me); 2.17(3H,s,ACETOXY); 4.93(1H,s,

ent-3α-H); 5.87(1H,d,$J_{AB}$ = 10.0 Hz, 13-H); 6.88

(1H,q,$J_{BA}$ = 10.0 Hz, J = 2.0 Hz, 14-H).


ENT-3β-ACETOXY-11(12→16)ABEOATISAN-12-ONE (111).


(109) was hydrogenated in ethanol using Pd/C as for

(2). Crystallised in large plates from ethanol, m.p.

213-214$°$(sublimes), $[\alpha]_D$ -41$°$(c 2.07).

(Found C, 73.37; H,9.10; $M^+$ 360.2320. $C_{22}H_{32}O_4$ requires

C, 73.30; H,8.95; $M^+$ 360.2300).

$\lambda_{max}(\varepsilon)$ :   287(62) and 210(414) e.a.

$\nu_{max}$   :   1750, 1725, 1705, and 1240 $cm^{-1}$.

$\delta$   :   0.96, 1.02, 1.12 and 1.14(4xs, 19-, 20-, 18-
      and 17-Me resp.);   2.16(3H,s, ACETATE);   4.95
      (1H,s, 3β-H).

## 3α-p-BROMOBENZOYLOXYSTACH-15-ENE-2,12-DIONE.

α-Ketol (1) (1.0g) in dry pyridine treated with
p-bromobenzoyl chloride (1.0g).   After 24 hr. quenched
with water.   Very insoluble material in methanol or
ethanol, therefore washed thoroughly with alcohol.   Cake
crystallised in large hexagonal prisms from THF-methanol,
m.p. 252-255°(subl. ~120°), $\{\alpha\}_D$ -216° (c 2.45).

$\nu_{max}$:   1735, 1725, 1708, 1586, 1395, 1300, 850, 765 and
      757 $cm^{-1}$.

## ENT-3β-p-BROMOBENZOYLOXY-11(12→16)ABEOATIS-13-ENE-12-ONE(112).

The α-ketol p-bromobenzoate from above was dissolved
with difficulty in hot glacial acetic acid, added acetic
anhydride, cooled and treated with conc. sulphuric acid as
for (109).   Crystallised the very insoluble material from
THF in triclinic crystals (space group PI), m.p. 297-299°,
$\{\alpha\}_D$ +143° (c 1.52).

(Found $M^+$ 498.1411.   $C_{27}H_{31}O_4$ Br requires $M^+$ 498.1406).

$\nu_{max}$:  1715, 1675, 1590 and 750 $cm^{-1}$.

## ENT-14R-2-OXO-3β-ACETOXY-14-CARBOXY-12,13-SECO-11(12→16) ABEOATISANO-12,14-LACTONE (117).

To α-ketol (1) (1.0g) in acetic anhydride (15ml) was added a few drops conc. sulphuric acid, one drop of pyridine, diluted with acetone (redistilled from $KMnO_4$, 20ml), cooled in ice and added $KMnO_4$ in aqueous acetone (0.3g) with stirring.   After 3 minutes poured into ice, added potassium bisulphite and left overnight.   Crystals (0.03g) deposited, these were filtered off and were pure.   The compound gave a red colour with TTC and effervesced with bicarbonate solution.   M.p. 250-251$^O$ (dec.).

(Found $M^+$ 406.2011.  $C_{22}H_{30}O_7$ requires $M^+$ 406.1991).

$\nu_{max}$: 3650, 3460, 3230(all broad), 2730, 1750, 1735, 1715, 1705, 1235 and 910 $cm^{-1}$.

δ(PYRIDINE): 0.82(20-Me); 0.90(19-Me); 1.09(18-Me);
                1.39(17-Me); 2.18(ACETOXY).

## PRODUCT FROM REACTION OF THE 15,16-DIHYDROKETOL WITH ACETIC ANHYDRIDE-SULPHURIC ACID (118).

Dihydroketol (2) (0.5g) was dissolved in acetic anhydride (10ml), added conc. sulphuric acid slowly (3 ml), left 5 minutes, crystals formed in the solution; poured

into ice and filtered.    Very insoluble in the usual

solvents.    Recrystallised from THF, (0.3g) leaflets

giving a positive TTC test.    M.p. 253-254$^O$ (dec.),

$(\alpha)_D$ -75$^O$ (c 1.02).

(Found fragment ion 440.1865.    $C_{25}H_{28}O_7$ requires

440.1835).

$\nu_{max}$: 1755, 1742, 1725, 1237(b), 810(v.s.) and 765cm$^{-1}$.

δ(CDCl$_3$+D$_6$-DMSO): 0.88, 1.12, 1.12 and 1.56(3xs,4xMe);

2.10 and 2.16(2xs, 2xCH$_3$CO-);

2.60(9H,s, 3xCH$_3$CO-); 4.25(1H,d,J=3.0

Hz); 4.92(1H,s,3β-H).

## 12-ACETOXYSTACHA-2-11-15-TRIENO-(2,3-b)-DIOXANE (120).

(i)    PREPARATION OF SODIUM BIS-TRIMETHYSILYLAMIDE (119).

Hexamethyldisilazane (20ml,16g) was refluxed under dry

nitrogen, in dry benzene (35ml) with sodamide (3.90g)

until all the solid had dissoved and no more ammonia

was evolved.    This solution contained approximately

0.45g of the bis-trimethylsilylamide anion per ml.

(ii)   (71) (0.79g) in dry THF (15ml) was treated with

the base (119) (4.0ml) and left 3 hours at room tem-

perature under dry nitrogen.    Cooled in liquid nitrogen

added a solution of acetic anhydride (10ml) in THF

(10ml), and stirred as the sample was allowed to warm

up.    After a further 12 hours poured into cold sodium

carbonate solution, extracted with methylene chloride,

washed with water, dried and evaporated.   Crystallised

from aqueous methanol(very soluble in methanol) giving

0.4g pure material, m.p. 116-119$^\circ$.

(Found $M^+$ 384.2300.   $C_{24}H_{32}O_4$ requires

$M^+$ 384.2297).

$\nu_{max}$: 3052,3040,1740,1703,1654,1210,919 and 770 cm$^{-1}$.

$\delta$      : 0.78, 0.94, 1.03 and 1.09(4xs,20-,19-,18- and

17-Me resp.); 2.12(3H,s,ACETOXY); 3.98(4H,s,

-OCH$_2$CH$_2$O-); 4.95(1H,d,J=2.5 Hz, collapses to

a singlet on irradiation at 2.17, 11-H);

5.65 and 6.17(2H,ABq,J=5.5 Hz, H-16 and H-15

resp.).

2$\alpha$, 3$\alpha$-DIHYDROXYSTACH-15-ENE-12-ONE (121).

The diosphenol-12-dioxyethaneketal (156) (2.0g) in

dioxan-ethanol (10-20ml resp.) was reduced with NaBH$_4$

(0.2g) at 5$^\circ$ o.n.   Poured into ice, acidified with dilute

HCl, filtered and crystallised from aqueous methanol (1.5g).

On standing in water after acidification the material often

crystallised in long silky needles.   M.p. 156-161$^\circ$, $(\alpha)_D$

-354.6$^\circ$ (c 2.08).

(Found $M^+$ 318.2187.   $C_{20}H_{30}O_3$ requires

$M^+$ 318.2195.

$\nu_{max}$: 3575, 3400(b), 1700 and 762 cm$^{-1}$.

## 2α,3α-DIACETOXYSTACH-15-ENE-12-ONE (232).

Prepared by acetylating (121) in pyridine as for (3). Needles from aqueous acetone, m.p. 159-160.5$^O$, 168-173$^O$; $\{α\}_D$ -286$^O$ (c 2.15).

$ν_{max}$: 3462 and 3395 (overtones), 1738, 1705, 1240 (b), and 752 cm$^{-1}$.

δ : 0.92, 1.04, 1.08 and 1.08 (3xs,4xMe); 2.03(6H,s, 2x ACETOXY); 4.58(1H,d, J = 3.5 Hz, 3β-H); 5.33 (1H,q, J = 3.5 and 7.0 Hz, 2β-H); 5.63 and 6.08 (2H,AB q, J = 5.5 Hz, H-16 and H-15 resp.).

## 11β-METHYL-12-OXO-STACHA-2,15-DIENO-[2,3-b]-DIOXANE (122).

(71) (0.75g) in dry THF (15ml) was treated with the base (119) (4ml) as for (120). After three hours at room temperature added MeI (6ml) and left 30 min. at r.t. Refluxed 45 min., left cold 12 hours, poured into ice water, acidified with HCl, extracted with methylene chloride, dried and evaporated. Crystallised from methanol (not too soluble) as leaflets, (0.6g), m.p. 144-146$^O$. (Found M$^+$ 356.2355. C$_{23}$H$_{32}$O$_3$ requires M$^+$ 356.2351.

$ν_{max}$: 3063, 1700, 1215 and 774 cm$^{-1}$.

δ : 0.87, 0.94, 1.07 and 1.14(4xs,4xMe); 1.30(3H,d, J=8.0 Hz, 11β-Me); 2.1-2.65(2H,m,11α- and 1α-H overlapped); 3.98(4H,s, -OCH$_2$CH$_2$-O-); 5.45 and 6.12(2H,AB q, J = 5.5 Hz, H-16 and H-15 resp.).

## 2-METHOXY-11β-METHYL-STACH-1,15-DIENE-3,12-DIONE (123).

The diosphenol (18) (2.03g) in dry THF (30ml) was treated with the base (119) (20ml) as for (122). Na salt gelled out. After 3 hr. added MeI (12ml) and refluxed 45 min. Worked up as for (122). Very soluble in methanol from which large crystals were obtained (1.0g) contaminated with traces of iodine. Recrystallisation from aqueous methanol gave 0.78g pure (123), m.p. 155-157° (sublime ~140°).

(Found $M^+$ 342.2188. $C_{22}H_{30}O_3$ requires

$M^+$ 342.2195).

$\nu_{max}$: 1685(b), 1625, 1100, 782 and 738cm$^{-1}$.

$\delta$ : 1.07, 1.11, 1.20, 1.20(3xs,4xMe); 1.43(3H,d, J = 7.0

Hz, 11β-Me); 2.60(1H,m,11α-H); 3.57(3H,s,OMe);

5.52 and 6.12(2H,AB q, J = 5.5 Hz, H-16 and H-15

resp.); 5.97(1H,s, C-1 olefinic proton).

## ENT-3β-ACETOXY-12-CHLOROATISA-13,15-DIENE-2-ONE (126).

Ketol acetate (3) (0.6g) in a mixture of very dry benzene (65ml) and toluene (15ml) was cooled in ice and added $PCl_5$ (0.5g) and stirred 2 hr. at 0°. Poured into cold sodium bicarbonate, left overnight, washed with water, dried and evaporated. Crystallised in leaflets from methanol. T.l.c. indicated one major compound with traces of material with very similar mobility; chromatography

did not remove impurities. The n.m.r. and mass spectra also indicated impurities. M.p. 190-199$^O$, some crystals remained and melted at 209$^O$.

(Found M$^+$ 376.1803. $C_{22}H_{29}O_3Cl$ requires M$^+$ 376.1805; also impurities M$^+$ 410.1406. $C_{22}H_{28}O_3Cl_2$ requires M$^+$ 410.1415).

$\nu_{max}$: 1745, 1720, 1235, 713 and 668 cm$^{-1}$.

$\delta$ : 0.63, 0.85 and 1.13(3xs, 20-, 19- and 18-Me resp.);

1.85(3H, d, J = 2.0 Hz, collapses to singlet on

irradiation at 5.70, vinyl 17-Me); 2.16(3H, s,

acetoxyl); 4.92(1H, s, <u>ent</u>-3α-H); 5.70(1H, m, $W_{\frac{1}{2}}$

4 Hz, collapses to a singlet on irradiation at

0.85, 15-H); 5.95 and 6.33(2H, AB q, J=8.0 Hz,

H-14 and H-13 resp.).

The $C_{22}H_{28}O_3Cl_2$ impurity had: 4.78(m); 5.37(b, m); 6.01(1H, d, J = 7.0 Hz, "H-14").

On one occasion[191] the reaction mixture was left overnight with sodium carbonate and oxidation of the ring A-ketol function occurred giving the corresponding diosphenol which was purified to a large extent by chromatography. This had

$\nu_{max}$: 344, 3420, 1665, 1650, 1395, 1380, 1220, 905 and
863 cm$^{-1}$.

$\delta$ : 0.93, 1.08 and 1.22 (3 x s, 3 x Me); 1.80(3H, d,

J = 2 Hz, collapses to sharp singlet on irradiation

at 5.66, vinyl 17-Me); 5.66(1H, m, collapses to a

singlet on irradiation at 1.80, 15-H); 5.86(1H, s,

vinyl l-H);   5.97 and 6.34(2H, AB q, J = 8.0 Hz,

H-14 and H-13 resp.).

The same impurity peaks were also present.

## ENT-(16S)-2β,3β-DIHYDROXY-ATIS-13-ENE (131).

(28) or (29)(1.86g) in dioxan (20 ml) and ethanol

(20ml),added NaBH$_4$ (1.2g) at 5-10$^\circ$ and stirred o.n. or

refluxed 1 hour.    Poured into ice, acidified with HCl and

crystallised the solid from aqueous methanol, needles

(0.56g).    Using unrecrystallised (28), obtained 14g

(131) from 20g (1), i.e. 73% conversion.    M.p. 190-192$^\circ$

(phase change at   165$^\circ$),$(\alpha)_D$ -10.3$^\circ$ (c 1.34 in THF).

(Found C, 78.68; H, 10.48; M$^+$ 304.2401.   C$_{20}$H$_{32}$O$_2$ requires

C, 78.90, H, 10.59; M$^+$ 304.2402.

Base peak m/e 262.1934.   C$_{17}$H$_{26}$O$_2$ (M-propene) requires

m/e 262.1933.)

$\nu_{max}$: 3552, 3490, 3425(b), 725, 715 and 700 cm$^{-1}$.

δ   : 0.72(3H,d, J = 6.5 Hz, 17-Me); 0.86, 1.00 and 1.00

(9H,2xs, 20, 19 and 18-Me); 2.25(1H,b.m., allylic

H-12); 3.16(1H,b,W$_{\frac{1}{2}}$ 9 Hz, ent-3α-H); 4.04(1H,q,

J = 3.5 and 7.0 Hz, ent- 2α-H);   5.87(1H, apparent s,

H-14); 5.94(1H, apparent doublet, J = 3.0 Hz,

collapses to a singlet on irradiation at 2.25, H-13).

THE ACETONIDE was prepared from 0.5g of the diol (131) as

for (23).    Crystals came out immediately on addition of
the acid catalyst.    Very insoluble in most solvents,
recrystallised from THF as needles, m.p. 182-184$^O$,
$[\alpha]_D$ -29$^O$ (c 2.02).

(Found C, 79.91; H, 10.72; M$^+$ 344 (v. weak), M-15
m/e 329.2489.  C$_{23}$H$_{36}$O$_2$ requires C, 80.18; H, 10.53;
M-15 at 329.2480).

$\nu_{max}$: 1381, 1365, 1254, 883, 878, 838, 731 and 707 cm$^{-1}$.

$\delta$    : 0.70(3H,d, J =7.0 Hz, 17-Me); 0.74, 0.89 and 0.97

(3xs,3xMe); 1.29 and 1.44(2xs,ACETONIDE-Me); 3.67

(1H,d, J = 6.25 Hz, ent-3α-H); 4.21(1H,triplet of

doublets, J = 2.0 and 6.0 Hz, ent-2α-H); 5.82(1H,

s,H-14); 5.84(1H,d, J = Hz, H-13).


THE 2,3-O-BENZYLIDENE derivative was prepared from the
diol (131) (0.5g), benzaldehyde (1.0ml), and p-tosic acid
(20mg) in refluxing toluene (50ml) with azeotropic removal
of water for 1 hour.    Washed toluene with bicarbonate,
evaporated and crystallised the rather insoluble material
from acetone, 0.35g needles, m.p. 165-169$^O$.

(Found C,82.34; H,9.23.    C$_{27}$H$_{36}$O$_2$ requires

C,82.61; H,9.24).


For the 2,3-diacetoxy compound, see (231).

## ENT-(16S)-1α-p-BROMOBENZOYLOXY-ATIS-13-ENE-2-ONE (135) [44].

The partially purified 1-hydroxy-2-one (142) (0.97g) in dry pyridine (10ml) was reacted with p-bromobenzoyl chloride (0.5ml, molten). Left 48hr. room temperature, poured into water, extracted solid with hot methanol (x3) leaving a residue of p-bromobenzoic anhydride[192]. Extracted, stripped of solvent, dissolved in hexane and chromatogrammed on silica gel (7734, 20g in hexane). Elution with hexane gave (135) pure as needles (0.44g) from hexane or ethanol. The single crystals for the X-ray analysis were grown from a mixture of ethanol, hexane and acetone and were triclinic, space group PI. M.p. 166-170°, $(\alpha)_D$ -52.0° (cl.2).

(Found $M^+$ 484.1620. $C_{27}H_{33}O_3Br$ requires $M^+$ 484.1613).

$\nu_{max}$: 1717, 1589, 1270, 1010, 850, 757, 728, 705 and 681 cm$^{-1}$.

$\delta$ : 0.67(3H,s,20-Me); 0.70(3H,d, J = 6.0 Hz, 17-Me); 0.89 and 1.12(2xs,19- and 18-Me); 2.26(1H,m, allylic 12-H); 2.70(1H,d, J = 12.5 Hz, ent-3β-H); 4.60(1H,bs,$W_{\frac{1}{2}}$ 3 Hz, ent-1β-H); 5.93(1H,s, 14-H); 6.00(1H,d, J = 3 Hz, 13-H); 7.5-8.0(AA'MM' "quartet", 1,4- disubstituted aromatic ring).

From the column was also obtained two compounds in very small yield. These were both p-bromobenzoates and the n.m.r. readily identified one as the ent-(16S)-2α-p-bromobenzoyloxy-atis-13-en-3-one and the more polar ent-

(16S)-3β-p-bromobenzoyloxyatis-13-en-2-one, both derived from the 3-acetates formed on acetolysis and then base-catalysed ketol isomerisation.

## 2α,3α-DIHYDROXY-STACHANE (136).

(i)   PREPARATION OF 15,16-DIHYDROKETOL-12-p-TOSYLHYDRAZONE. This was prepared as for (28) from (2) (1.05g) in glacial acetic acid with p-tosylhydrazine (0.65g). Obtained 0.6g pure hydrazone.

(ii)   TOSYLHYDRAZONE ELIMINATION - Procedure as for (131). Beautiful needles from aqueous methanol, m.p. 204-206° (lit.[2] 200-205°).

(Found $M^+$ 306.2563, $C_{20}H_{34}O_2$ requires $M^+$ 306.2559).

$\nu_{max}$: 3565, 3548, 3480, 3408, 1370, 1355, 1050, 974 cm$^{-1}$.

δ   : 0.92, 0.98, 0.98 and 1.20(3xs, 4xMe); 3.17(1H,m,3β-H); 4.07(1H,m,2β-H).

## 2α, 3α-DIACETOXYSTACHANE, SEE (233).

## ENT-(16S)-3β-HYDROXYATIS-13-EN-2-ONE (139).

The atisane diol (131) (4.7g) in dry benzene (150ml) was stirred under reflux on steam with the silver carbonate

on celite reagent[126] (10-12g) for 5-15 minutes.   T.l.c.
indicated that the reaction was extremely fast, usually
over in under 10 minutes.   Filtered off celite, washed
residue with benzene, combined filtrates and evaporated.
Addition of methanol to the resulting thick oil gave a
mass of crystals which were recrystallised from aqueous
methanol to give 2.8g of pure ketol (139), m.p. 167-171$^{\circ}$;
$\{\alpha\}_D$ + 1.04$^{\circ}$ (c 2.00).

$\nu_{max}$:   3522, 3030, 1712, 732, 708 and

625 cm$^{-1}$.

$\delta$    : 0.53 and 0.66(2xs, 20- and 19-Me resp.); 0.72(3H,

d, J = 6.0 Hz, 17-Me); 1.17(3H,s, 18-Me); 2.30

(1H,m, allylic 12-H); 3.37 and 3.87(2H,AB q,

J = 5 Hz, 3-OH and 3-H resp.); 5.90(1H, "singlet"

14-H); 5.93(1H, "doublet", J = 6.0 Hz, 13-H).


The 13- and 14-H in fact constitute an AB system with very
weak outer lines, the 13-H then undergoes further coupling
to the 12-allylic hydrogen.


The mother liquor from the crystallisation of the
ketol was a mixture of the ketol and the diosphenol.   This
was converted into the benzaldehyde-lactone-atisane derivative
(compare 77) in excellent yield, by reaction with benzalde-
hyde and alkali in ethanol.   This compound could not be
prepared from the tosylhydrazone of (77) (which was easily
made) since the NaBH$_4$ reaction was unexpectedly very complex
and has not yet been investigated fully.

## ENT-(16S)-3β-TOSYLOXY-ATIS-13-EN-2-ONE (140).

This was prepared from the (139) ketol as for (46).    Crystallised well from aqueous acetone (yield 3.6g from 2.8g (139)).    M.p. 202-203$^O$ (dec.) $[\alpha]_D$ (Found $M^+$ 456.2343 and M-PROPENE at m/e 414.1866. $C_{27}H_{36}SO_4$ requires $M^+$ 456.2334 and M-42 at m/e 414.1865). $\nu_{max}$: 3095, 3047, 3025, 1735, 1597, 1353, 1175, 980, 857, 675 and 550 cm$^{-1}$.

## ENT-(16S)-1α-ACETOXY-ATIS-13-EN-2-ONE (141).

The tosylate (140) was acetolysed for 3 hours (1 hr was found to be insufficient) as for (47).    1.1g of tosylate gave 0.6g acetate (73%) which was not crystallised but gave a satisfactory n.m.r.

$\delta$ : 0.62(s,20-Me); 0.75(d,J=6.0 Hz, 17-Me); 0.86 and 1.13(2xs,19- and 18-Me resp.); 2.13(3H,s,ACETATE); 2.30(1H,m,allylic 12-H); 2.68(1H,d,J$_{gem}$12.0 Hz, ent-3β-H); 4.37(1H,d, J = 1.5 Hz, ent-1β-H); 5.93 (1H,s,14-H); 6.00(1H,d, J = 2.5 Hz, 13-H).

## ENT-(16S)-1α-HYDROXY-ATIS-13-EN-2-ONE (142).

The above acetate (141) (0.6g) was dissolved in methanol (20ml) in which it was very soluble, and added

NaOH (10%, 0.5ml). The ketol rapidly crystallised out as a mass of needles. Poured into water. Recrystallised from THF-methanol as needles (46% from (140)), m.p. 204-207° (phase change ~170°).

(Found C, 79.51; H,9.91; $M^+$ 302.2253 and M-42 260.1773. $C_{20}H_{30}O_2$ requires C,79.42; H,10.00; $M^+$ 302.2246 and M-42 260.1776).

$\nu_{max}$: 3430(b), 3040, 3027, 1710, 724 and 702 $cm^{-1}$.


The mother liquors contained more of (142) as well as other ketols, possibly the ent-3β-hydroxy-2-one and the ent-2α-hydroxy-3-one as borne out by the p-bromobenzoylation described above.



## 2α,3β,12α-TRIHYDROXYSTACH-15-ENE (143)


The crude 3β-acetoxy-2,12-dione (53) (0.6g) in ethanol was reduced with NaBH$_4$ as for (16). After 12 hr. added KOH (1g) and heated on steam 1 hr. Poured into ice-cold dilute HCl. Crystallised from aqueous methanol (0.31g), m.p. 193-200°, $(\alpha)_D$ -50.4°(c 2.1 in THF).
(Found $M^+$ 320.2347. $C_{20}H_{32}O_3$ requires $M^+$ 320.2351).
$\nu_{max}$: 3600 - 3050 (v.b.), 763 $cm^{-1}$.



## 3α,16α-DIACETOXY-15β-ACETOXYMERCURY-STACHANE-2,12-DIONE(144).


To a solution of the ketol acetate (3) (1.0g) in glacial acetic acid (25ml) was added mercuric acetate (2.0g, 2.0moles)

when most but not all dissolved. Cooled to $5^O$ and added boron trifluoride-etherate (1.0ml) which caused the immediate solution of all the remaining solid and a yellowing of the solution. After 2 hr. poured into ice-water (200ml) when no solid precipitated. Addition of solid KOH to a pH 6 caused a precipitate to appear. Crystallised from aqueous methanol in large needles, 0.97 g.

The same product was formed using perchloric acid (70%) instead of $BF_3$, but the material was not so pure. M.p. 214-222$^O$. (The analysis gave a low carbon possibly due to the presence of some of the hydroxy mercury derivative formed during the alkaline work up. Gave a residue on analysis.

(Found C,45.13; H,5.3; M- Hg(OAc)$_2$ m/e 358.2130. $C_{26}H_{36}O_8Hg$ requires C,46.12; H,5.36; M-Hg(OAc)$_2$ m/e 358.2144).

$\nu_{max}$: 3475(b,impurity); 1745,1614,1595,1240,1225 and 684cm$^{-1}$.

$\delta$ : 0.87, 0.92, 1.10 and 1.12(3xs, 4xMe); 2.03(6H,s, HgOAc and 16-OAc); 2.16(3H,s,3$\alpha$-ACETOXY); 2.86(1H,q, J = 2.5 and 5.5 Hz, 15$\alpha$-H); 4.90(1H,s,3$\beta$-H); 5.16 (1H,d, J = 5.5 Hz, 16$\beta$-H).

## 3$\alpha$,16$\alpha$-DIACETOXY-15$\beta$-BROMOSTACHANE-2,12-DIONE (145).

The same procedure as for (144) was followed using 3.0g of (3). 30 minutes after adding $BF_3$, added freshly fused sodium acetate (10g) and then bromine until the solution remained red (3ml). Left o.n. at r.t., poured

into water and crystallised from acetone-THF.    Well
shaped rhombs (1.8g), m.p. 262-264.5$^O$, $(\alpha)_D$ -117$^O$ (c 2.77).
Positive Beilstein test.

(Found M-42 = 454.1363 (loss of ketene). $C_{24}H_{33}O_6Br$ re-
quires M-42 = 454.1355).

$\nu_{max}$: 3624, 3525, 1740, 1720 and 1233 cm$^{-1}$.

$\delta$    : 0.88, 0.98, 1.10 and 1.12 (3xs,4xMe); 2.05 and 2.13

   (2xs, 2xCH$_3$, 16$\alpha$- and 3$\alpha$-ACETATES resp.); 4.46(1H,

   q, J = 2.0 and 4.0 Hz, collapses to a doublet with

   J = 4.0 Hz on irradiation at 1.30 and to a doublet

   with J = 2.0 Hz on irradiation at 5.63, 15$\alpha$-H);

   4.93(1H,s,3$\beta$-H); 5.59 (1H,d, J = 4.0 Hz, collapses

   to a singlet on irradiation at 4.16, 16$\beta$-H).


## 3$\alpha$,16$\alpha$-DIACETOXY-15$\beta$-IODO-STACHANE-2,12-DIONE (146).


The ketol acetate (3) (1.0g) was stirred with a sus-
pension of silver acetate (1.4g) in glacial acetic acid
(75ml) and added iodine (2.0g).    After 1 hour added
NaCl (1.0g), filtered, washed residue with benzene and
evaporated filtrates.    Crystallised from acetone-methanol
(insoluble in the latter) as excellent rhombs, (0.55g),
m.p. 240-249$^O$ (dec.), $(\alpha)_D$ -132$^{\circ}$ (c 2.94).

(Found C,52.36; H,6.38; M-42 = 502.1217.  $C_{24}H_{33}O_6I$ requires

   C,52.95; H,6.11; M-42 = 502.1218).

$\nu_{max}$: 3625, 3525, 1740, 1718, and 1234 cm$^{-1}$.

$\delta$    : 0.91, 0.96, 1.11 and 1.14 (4xs,4xMe); 1.45(1H,q,

J=2.5 and 12.5 Hz, 14β-H?); 2.04 and 2.16(2xs,

2xMe, 16α- and 3α-ACETOXYL resp.); 4.49 (1H,q,

J=2.5 and 5.0 Hz; collapses to a doublet with

J=2.5 Hz on irradiation at 5.74 and collapses to

a doublet with J=5.0 Hz on irradiation at 1.45,

15α-H);   4.93(1H,s,3β-H); 5.73(1H,d,J=5.0 Hz,

collapses to a singlet on irradiation at 4.50,

16β-H).


## 3α-ACETOXY-15β-IODO-16α-NITRATOSTACHANE-2,12-DIONE (147).


To a solution of the ketol acetate (3) (1.0g) in

acetonitrile (20ml) was added silver nitrate (0.5g) and

allowed to dissolve.   Iodine (0.8g) was then added with

vigorous stirring and t.l.c. indicated the reaction to be

over in 2-3 minutes.   Filtered off silver iodide, washed

it with acetone and combined filtrates evaporated to 10ml

and poured into water containing sodium thiosulphate.

Filtered off crystalline precipitate and recrystallised

from aqueous acetone (insoluble MeOH), m.p. 207-210°

(vigorous decomposition), $[\alpha]_D$ -14° (c 0.7).   Yield 1.18g

(77%).

(Found $M^+$ 547 very weak, M-42 at 505.0959.   $C_{20}H_{30}O_7NI$

requires $M^+$ at 547 and M-42 at 505.0963).

$\nu_{max}$: 1738, 1720, 1642, 1284, 1275, 1230 and 840 cm$^{-1}$.

δ   : 0.90, 0.95, 1.13 and 1.20 (4xs, 19-, 20-, 18- and

17-Me resp.); 2.17(3H,s, ACETATE); 4.61(1H,q,J= 2.0
and 4.5 Hz, collapses to a doublet J = 2.8 Hz on
irradiation at 5.80 and to a doublet J = 4.5 Hz on
irradiation at 1.43, 15α-H);  4.92(1H,s, 3β-H);
5.80(1H,d,J = 4.5 Hz, collapses to a singlet on
irradiation at 4.62, 16β-H).

## BENZALDEHYDE-LACTONE-12-ONE-15β-IODO-16α-NITRATE (148)

Prepared from (77) (0.5g), silver nitrate (0.205g),
iodine (0.31g) and acetonitrile (10ml) as for (147).
Crystallised from methanol or acetone-methanol as feathery
needles, m.p. 194-196$^O$ (dec.).
(Found C,53.54; H,5.56; N,2.15.  $C_{27}H_{32}NO_7I$ requires
    C,53.21; H,5.29; N,2.30).

## 3α-ACETOXY-STACHANE-2,12-DIONE-15β,16α-DIBROMIDE (149).

The ketol acetate (3) (1.006g) was refluxed in dry
chloroform (25ml) with dibenzoyl peroxide (20mg) adding
N-bromosuccinimide in batches (2 x 0.540g, total 2 moles)
as the initially reddish solution went colourless.
Cooled, washed with sodium sulphite solution, water and
dried.  Evaporation gave a thick oil which crystallised
on addition of methanol in which the crystals were insoluble.

Recrystallised from aqueous acetone giving 0.75g pure material. The mother liquors contained more (149) mixed with the 11, 15, 16-tribromide and boiling this mixture in acetone containing sodium acetate (1.0g) gave a further crop of (149) as the 11-bromine was removed. M.p. 236-240$^O$ (dec.) (phase change at ~220$^O$); $(\alpha)_D$ -81$^O$ (c 2.25).

(Found C,50.41; H,5.72; M$^+$ at 516 (very weak), M-42 474.0390. $C_{22}H_{30}O_4Br_2$ requires C,50.98; H,5.79; M-42 474.0406). The mass spectrometer detected traces of the tribromide.

$\nu_{max}$: 1743, 1720, 1245, 765 and 665cm$^{-1}$.

$\delta$ : 0.90 , 0.98, 1.12 and 1.16(3xs,19-,20-,18- and 17-
   Me resp.); 2.16(3H,s,ACETATE); 4.38(1H,d, J = 5.60
   Hz, collapses to a singlet on irradiation at 4.65,
   16β-H); 4.69(1H,q, J = 2.0 and 5.6 Hz, collapses
   to a doublet J = 2.0 Hz on irradiation at 4.34 and
   to a doublet J = 5.6 Hz on irradiation at 1.43,
   15α-H); 4.91(1H,s,3β-H).

(149) (0.2g) when stirred at room temperature in ethanol (10ml) and acetic acid (3ml) with zinc dust (3g) for four hours, filtered, evaporated, diluted with water and crystallised gave a quantitative recovery of the parent olefin (3).

## 3α-ACETOXY-STACHANE-2,12-DIONE-15β,16α-DICHLORIDE (150).

A solution of the ketol acetate (3) (1.0g) in dry pyridine (8ml) was cooled in ice and added sulphuryl chloride (1.0ml) very slowly (exothermic). Left cold overnight, poured into water. Material slightly soluble in methanol and very soluble in acetone (compare 149). Crystallised once from aqueous acetone-methanol and once from aqueous methanol giving leaflets (0.5g), m.p. 231-240$^{\text{O}}$, $(\alpha)_D$ -109$^{\circ}$ (c 2.09).

(Found M$^+$ 428.1517. $C_{22}H_{30}O_4Cl_2$ requires M$^+$ 428.1521).

$\nu_{max}$: 1744, 1720, 1240, 855 and 676 cm$^{-1}$.

$\delta$ : 0.90, 0.98, 1.12 and 1.16 (4xs, 19-, 20-, 18- and 17-Me resp.); 1.17(3H,s,ACETATE); 4.17(1H,d, J=5.60 Hz, 16β-H); 4.57(1H,q, J = 2.0 and 5.60 Hz, 15α-H); 4.93(1H,s,3β-H).

## 3α-ACETOXY-15β,16β-EPOXYSTACHANE-2,12-DIONE (152).

Ketol acetate (3) (1.0g) was dissolved in acetic anhydride (10ml) and formic acid (90%, 10ml), allowed to warm up as water was consumed, cooled, added hydrogen peroxide (30%, 2ml) and heated on steam intermittently for 15-20 minutes at 70-80$^{\text{O}}$. Cooled, poured into ice, added KOH (5g, solid) and filtered. Crystallised from aqueous acetone, 0.65g leaflets, m.p. 244-251$^{\text{O}}$, $(\alpha)_D$ -134$^{\text{O}}$ (c 2.25).

(Found C,69.22; H,8.01. $C_{22}H_{30}O_5$ requires C,70.56; H,8.07 indicating the presence of some Bayer-Villiger product which however was not detectable on t.l.c. or by n.m.r.

$\nu_{max}$: 1750, 1740, 1715, 1240 and 835 cm$^{-1}$.

$\delta$ : 0.90, 0.97, 1.13 and 1.16(4xs, 19-, 20-, 18- and 17-Me resp.); 2.17(3H,s, ACETATE); 3.23 and 3.57 (2H, AB q, J = 2.5 Hz, 15$\alpha$- and 16$\alpha$-H); 4.93 (1H,s, 3$\beta$-H).


## 3$\alpha$-FORMYLOXY-15$\beta$,16$\beta$-EPOXYSTACHANE-2,12-DIONE.

Ketol (1) (1.0g) was heated on steam with formic acid (10ml, 90%) for 15 min., cooled, added hydrogen peroxide (1.0ml, 30%), heated for 15 min. at 60-70$^{\circ}$ and poured into ice. Added KOH (1g), filtered and crystallised from aqueous acetone-methanol (insoluble in methanol). 0.22g leaflets, m.p. 238-242$^{\circ}$, $(\alpha)_D$ -189$^{\circ}$ (c 2.14).

$\nu_{max}$: 1733, 1715, 1700, 1170, 837cm$^{-1}$.

$\delta$ : 0.93, 1.02, 1.17 and 1.17(3xs, 4xMe); 3.25 and 3.58 (2H, AB q, J=2.5 Hz, 15$\alpha$- and 16$\alpha$-H); 5.04(1H,s, 3$\beta$-H); 8.18(1H,d, J = 1 Hz, H-CO-O-CH coupling, formyl proton).


In the case of both epoxides, when the reaction mixture was poured into water little, if any, solid precipitated until the pH was raised by the addition of alkali.

## 2-PYRROLIDINO-STACHA-1,15-DIENE-3,12-DIONE (153).

(i)   Ketol (1) (1.0g) was refluxed for 20 hr. with pyrrolidine (2ml) and tosic acid (100mg) in benzene (60ml).   Cooled, washed with water, evaporated and crystallised yellow oil from methanol, long needles or spars (0.95g), m.p. 190-193° (dec.),   $[\alpha]_D$ -319°(c 2.4).

(ii) From Mother Liquors.

Mother liquor 1 or 2 from ketol recrystallisation (90g), in methanol (300ml) was refluxed with pyrrolidine (20ml) and p-tosic acid (0.3g) overnight.   Removed $2/3$ of the solvent by distillation and cooled at 5° when the solution set to a thick, crystalline mass.   Filtered, washed the crystals with cold methanol and dried.   Essentially pure (153) in a yield of 40g.   The filtrate and washings deposited more crystals.   The filtrate was used to isolate the ketones and alcohols such as (5), (215), (216), (220) and (222).

(Found C,78.58; H,9.07; N,3.64; $M^+_{BASE\ PEAK}$ 367.2507. $C_{24}H_{33}O_2N$ requires C,78.43; H,9.05; N,3.81; $M^+$ 367.2511).

$\nu_{max}$: 1705, 1670, 1600 and 765cm$^{-1}$.

$\delta$   : 0.92, 1.11, 1.11 and 1.17(3xs,4xMe); 5.34(1H,s,1-H); 5.70 and 6.10(2H, AB q, J=5.5 Hz, H-16 and H-15 resp.).

## 2-PYRROLIDINO-STACH-1-ENE-3,12-DIONE.

This was the sole compound isolated on pressure hydrogenation of (153) (50 atmospheres) using a Pd/C catalyst (30%) in ethanol-THF. Needles from the same solvent, m.p. $170-173^O$(dec.), $[\alpha]_D$ $-115^O$ (c 2.3). (Found $M^+$ 369.2675. $C_{24}H_{35}O_2N$ requires $M^+$ 369.2668).

$\delta$ : 1.11, 1.11, 1.11 and 1.17(2xs,4xMe); 5.40(1H,s, 1-H).

## 2-HYDROXY-STACH-1,15-DIENE-3,12-DIONE-12-ETHANEDIOXY KETAL (156)

The diosphenol (18) (1.0g) was dissolved in a mixture of dry toluene (100ml) and dry ethanediol (2ml) containing p-tosic acid (50mg) and refluxed with a water separator for 3 hours (no longer and no less otherwise messy). Cooled, diluted with 100ml ethyl acetate, washed thoroughly with aqueous bicarbonate, dried and evaporated to an oil which usually crystallised spontaneously or on addition of alcohol. Crystallised from methanol in which it was not too soluble, 0.85g spars, m.p. $183-186^O$.

$\delta$ : 0.98, 0.98, 1.09 and 1.20(3xs,4xMe); 3.58(4H,m,$-OCH_2CH_2O-$), 5.74(2H,s,15-and 16-H); 6.07(1H,b.s., exchanged with $D_2O$, -OH); 6.17(1H,s,1-H).

ENT-11(12→16)ABEOATIS-13-ENE-2,3,12-TRIONE (157).

The pyrrolidine enamine (153) (4.0g) was dissolved
in acetic acid-acetic anhydride (15ml and 15ml), cooled
in ice and added conc. sulphuric acid (about 3 ml).   After
5 min. poured into ice.   Adjusting the pH to 6-6.5 with
KOH caused hydrolysis of the enamine and a pale yellow
solid separated.   Crystallised from aqueous methanol
as yellow needles (3.0g).   M.p. 205 -209$^{\circ}$.

$\delta$ :   0.80(3H,s,20-Me); 1.19, 1.24 and 1.24(2xs,3xMe);

5.95(1H,d,J=9.5Hz, 13-H); 7.02(1H,q,J=2 and 9.5 Hz,

14-H).

A trace of alkali immediately converted the diketone into
the enolised, colourless form.

3$\alpha$-ACETOXY-STACHA-9(11),15-DIENE-2,12-DIONE (200).

The ketol acetate (3) (3.0g) was refluxed in t-butanol
(150ml) containing pyridine (2 drops) and selenium dioxide
(3.0g) for 24 hours.   Filtered through celite and charcoaled
but this failed to remove the selenium.   Evaporated under
vacuum, dissolved the red crystalline residue in benzene
and chromatogrammed on silica gel (7734, 10g) in hexane.
Elution with benzene gave (200) still slightly contaminated
with selenium.   Crystallised from methanol as large 8-
sided tabloids, (2.0g), practically pure but Se detected

from its smell.    Sublimation[193] at 150$^O$, 1mm Hg pressure
gave a crystalline, very pure sample, m.p. 149-151$^O$
(sublimes),  $(\alpha)_D$ -352.6$^O$ (c 2.91).
(Found M$^+_{BASE\ PEAK}$  356.2003.   $C_{22}H_{28}O_4$ requires M$^+$ 356.1987).
$\lambda_{max}(\varepsilon)$ : 344(70), 272(2405), 238(6370).
$\nu_{max}$   : 1745, 1725, 1675, 1598, 1578, 1230, 870 and 775 cm$^{-1}$.
$\delta$(60 MHz): 0.87, 1.07, 1.14 and 1.22(4xs,19-, 20-, 18- and

17-Me resp.); 2.15(3H,s,ACETATE); 2.62(2H,

triplet, $J_{gem}$ = 12.5 Hz, 1$\alpha$- and 1$\beta$-H); 4.94

(1H,s,3$\beta$-H); 5.19(1H,s,11-H); 5.70 and 6.46

(2H,AB q, J = 5.0 Hz, H-16 and H-15 resp.).


(100 MHz):The 20-Me is broadened and has a shoulder

J 0.75 Hz.    The 2.62 triplet is now an AB

quartet, J = 12.5 Hz, with the upfield proton

(1$\beta$-H) very much broader than the lower field

partner (1$\alpha$-H), indicating W coupling with the

20-Me.    At 2.07 and 2.31(2H,AB quartet, $J_{gem}$=

10.0 Hz, 14$\alpha$- and 14$\beta$-H resp.).    This assign-

ment is based on the fact that the 2.31 signal

is broadened as is the H-16 resonance and these

two protons are the only two possible which can

show pseudo-W coupling.


3$\alpha$-ACETOXY-STACH-9(11)-ENE-2,12-DIONE (201).


This was prepared from (13) following the procedure a
above.    M.p. 169-178$^O$, $(\alpha)_D$ -154$^O$ (c 2.39).

(Found M$^+$ 358.2156. C$_{22}$H$_{30}$O$_4$ requires M$^+$ 358.2144).

$\lambda_{max}$ ($\varepsilon$) : 310(80), 239(13970) and 210(3200) e.a.

$\nu_{max}$ : 1745, 1728, 1672, 1595, 1237 and 878 cm$^{-1}$.

$\delta$ : 0.87, 1.13, 1.18 and 1.18(3xs, 19-, 18-, 20-
and 17-Me resp.); 2.16(3H,s,ACETATE); 2.42, 2.63,
2.67 and 2.87(2H, AB q, J = 12.5 Hz, 1$\beta$- and
1$\alpha$-H); 4.94(1H,s,3$\beta$-H); 5.69(1H,s,11-H).

The 1$\beta$-H shows W coupling with the 20-Me.


## (5S,6S,7R,8S)-2,7-DIMETHYL-8-(2,2-DIMETHYLCARBOXYMETHYL)-SPIRO(4.5)DECA-1,3-DIENO-6,7-DIACETIC ACID (205).


A solution of KOH (5.0g) in ethanol (20ml) was cooled
and added to a cold solution of the ketol (1) (3g) in
ethanol (100ml). Added hydrogen peroxide (30ml, 30%) and
left overnight in the refrigerator. Took off most of the
ethanol under reduced pressure, diluted with water (100ml)
and acidified with HCl. The dry solid (3.5g), pure by
n.m.r. was crystallised from aqueous methanol in needles,
m.p. 251-252$^{\circ}$ (dec.), $(\alpha)_D$ -50.5$^{\circ}$ (c 2.0 in ethanol).
(Found M$^+$ 364.18817. C$_{20}$H$_{28}$O$_6$ requires M$^+$ 364.18857).

$\lambda_{max}$ ($\varepsilon$) : 254(1392) and 210(1374) e.a.

$\nu_{max}$ : 3500-2400(v.b.); 1700(b.), 799 and 792 cm$^{-1}$.

$\delta$(D$_6$-DMSO + CDCl$_3$): 0.96, 1.23 and 1.23(2xs, 20-, 19- and
18-Me resp.); 1.82(3H,singlet with
shoulder, collapses to a sharp singlet on
irradiation at 5.70, vinyl 2-Me); 5.70
(1H,m,W$_{\frac{1}{2}}$=5 Hz, collapses to a narrow

multiplet $W_{\frac{1}{2}} = 3\frac{1}{2}$ Hz on irradiation at 1.82,

olefinic 1-H); 6.16(1H,doublet of doublets,

J=5.5 and 1.5 Hz, olefinic H); 6.43(H, doublet

of doublets, J=5.5 and 2.0 Hz, olefinic H);

5.0-7.7(3H, very broad, EXCHANGED WITH $D_2O$,

3x-COOH).

## 2-OXO-3α-ACETOXY-15β,16β-EPOXY-12,13-SECOSTACHANO-12,13-LACTONE (206).

A solution of the ketol acetate (3) (1.0g) in dry

chloroform (50ml) was treated with m-chloroperoxybenzoic

acid (1.0g) and left at 5° overnight.   T.l.c. showed

the reaction to be over in 2 minutes.   Washed with bi-

carbonate, water, dried and evaporated to a crystalline

residue.   Recrystallised from lots of acetone or THF as

plates (1.0g), m.p. 305-308°, $[\alpha]_D$ -52° (c 3.6).

(Found C, 67.97; H,7.91; $M^+$ 390.2036.  $C_{22}H_{30}O_6$ requires

C, 67.67; H,7.74; $M^+$ 390.2042).

$\nu_{max}$: 3065, 1742, 1723, 1235, 835 and 642 $cm^{-1}$.

δ   : 0.88, 0.93, 1.15 and 1.48(4xs,19-, 20-, 18- and

17-Me); 2.18(3H,s,ACETATE); 3.50 and 3.63(2H, AB q,

J = 2.2 Hz, 15α- and 16α-H); 4.96(1H,s,3β-H).

## BENZALDEHYDE-LACTONE-15β,16β-EPOXIDE-12-ETHANEDIOXYKETAL(207).

The 12-ketal of the lactone (89) (2g) was dissolved in

dry chloroform (40 ml) and treated with m-chloroperoxybenzoic

acid (2g).    Worked up as for (206) and crystallised from acetone-methanol (insol. MeOH) giving 2g crystals, m.p. 285-289$^O$.

(Found C,73.14; H,7.64.   $C_{29}H_{36}O_5$ requires C,72.48, H,7.55).

$\nu_{max}$:   3430, 1753, 785 and 610 cm$^{-1}$.

$\delta$   :   0.93, 1.07, 1.11 and 1.14(4xs, 4xMe); 2.77(1H,d,
         J=8.5 Hz, 1$\alpha$-H); 3.16 and 3.38(2H, AB q, J=3.5
         Hz, 15$\alpha$- and 16$\alpha$-H); 3.40(1H,s,EXCHANGED WITH $D_2O$,
         2$\alpha$-OH); 2.97-3.70(4H,m,12-ketal protons); 5.15
         (1H,d, J = 8.5 Hz, benzylic H); 7.36(5H,s,aromatic).


HYDRIDE REDUCTION OF (207) TO THE HEMIACETAL-EPOXIDE(208).

      (207) was reduced in dry THF with excess LAH as for
(92).    Worked up with ethanol and water, no acid. Ex-
tracted with ethyl acetate, washed with alkali and evaporated.
Crystalline residue crystallised from acetone as needles in
a very good yield, m.p. 220-223$^O$.

$\nu_{max}$:   3525, 3375(b), 843, 760 and 697 cm$^{-1}$.

$\delta$   : 0.93, 1.02, 1.08 and 1.15(4xs, 4xMe); 2.35(1H,d, J=
         7.5 Hz, 1$\alpha$-H); 2.97, 3.12, 3.16 and 3.29(2H, AB q,
         J = 8.0 Hz, 15$\alpha$- and 16$\alpha$-H); 3.48(1H,s, EXCHANGES
         WITH $D_2O$, 2$\alpha$-OH); 3.3-3.8(4H,m,12-ketal); 4.67(1H,d,
         J = 3.0 Hz, EXCHANGES WITH $D_2O$, 3$\alpha$-OH); 4.74(1H,d,
         J = 7.5 Hz, benzylic H); 5.09(1H,d, J = 3.0 Hz,
         sharpens to a singlet on exchange of OH with $D_2O$,
         -O-CH-O-H); 7.2-7.7(5H,m,aromatic).

## 2α,3α-O-ISOPROPYLIDENO-12α-HYDROXYSTACHANE-15β,16β-EPOXIDE (209)

Triol acetonide (23) (2.2g) was dissolved in chloroform and added m-chloroperoxybenzoic acid (1.9g).  Left at room temperature for 24 hours.  Diluted with more chloroform, washed with bicarbonate, dried and evaporated. Crystallised from methanol (2.2g), m.p. 227-231$^{\circ}$,$(\alpha)_D$ -36$^{\circ}$, (c 2.95).    M.W. 376.

(Found M-15 = 361.2389.  $C_{23}H_{36}O_4$ requires M-15=361.2379).

$\nu_{max}$:    3467, 3054, 3038 and 845 cm$^{-1}$.

δ    : 0.48(1H,d, $J_{gem}$=11.5 Hz, 14α-H[194]), 0.97, 1.00, 1.15 and 1.15(3xs, 4xMe); 1.33 and 1.50(2xMe, acetonide); 3.27 and 3.40(2H, AB q, J = 3.5 Hz, 15α- and 16α-H); 3.50(1H,m, overlapped, 12β-H); 3.73(1H,d, J=6.5 Hz, 2β-H); 4.32(1H, t of d, J = 1.5 and 6.5 Hz; 2β-H).

## 12β-CHLORO-2α,3α-O-ISOPROPYLIDENO-STACHANE-15β,16β-EPOXIDE (211).

The alcohol (209) (0.65g) in pyridine was treated with phosphorus oxychloride as for (24).  Crystallised from aqueous acetone-methanol as excellent needles, (0.26g), m.p. 169-172$^{\circ}$,$(\alpha)_D$ -43$^{\circ}$ (c 1.82).

(Found M-15 = 379.2032 ($C_{22}H_{32}ClO_3$).  $C_{23}H_{35}O_3Cl$-15 requires  379.2038).

$\nu_{max}$: 1381, 1250, 1041, 842, 837, and 830 cm$^{-1}$.

$\delta$ : 0.97, 1.01, 1.10 and 1.14(4xs,4xMe); 1.33 and 1.48

:(2xs,2xMe, acetonide); 3.04 and 3.36(2H, AB q,

J = 3.0 Hz, 15$\alpha$- and 16$\alpha$-H); 3.74(1H,d, J = 6.5 Hz,

3$\beta$-H); 4.32(2H; 1H, t of d, J = 1.5 and 6.5 Hz,

2$\alpha$-H; 1H, overlapped m, W$\frac{1}{2}$ less then 10 Hz, 12$\alpha$-H).


## 15$\beta$,16$\beta$-EPOXIDE OF BENZALDEHYDE-LACTONE (77)-(212).


The lactone (77) was dissolved in acetic acid (4.2g
in 50 ml), added chromium trioxide (0.88g) and warmed on
steam for 20 min.   Left cold overnight, poured into water,
filtered off pale green solid and crystallised it from
aqueous methanol as needles, 2.2g, m.p. 250-255$^{\text{O}}$.

$\nu_{max}$: 3635,3436 and 3373(b),1758,1712,1626,840 and 710cm$^{-1}$.

$\delta$   : 1.09, 1.09, 1.09, 1.16(2xs, 4xMe); 2.67(1H,d, J=8.5

Hz, 1$\alpha$-H); 3.15 and 3.58(2H,ABq, J=2.5 Hz, 15$\alpha$- and

16$\alpha$-H);  3.63(1H, b.s., EXCHANGES WITH D$_2$O, 2$\alpha$-OH);

5.11(1H,d, J=8.5 Hz, benzylic H); 7.36(5H, m, aromatic).


## CHROMATOGRAPHIC SEPARATION OF SOME CONSTITUENTS OF THE HEXANE EXTRACT.


Prepared a column with silica gel (7734, 500g) in hexane
and dissolved 20g of the Mother Liquor I in hexane-benzene
(200 + 30ml).   Eluted with hexane then with increasing
concentrations of benzene in hexane, then pure benzene and

finally benzene-ethyl acetate mixtures.

STACHENONE (215) was eluted first after a very small hydrocarbon fraction. This ketone was not obtained pure but characterised as its 2,4-dinitrophenylhydrazone,[191] m.p. 205-207° (lit.[2] 194-196°).

The 60% benzene in hexane mixture eluted a mixture of 3α- and 3β-stachenol. This was rechromatogrammed on silica gel and elution with hexane gave pure STACH-15-EN-3β-OL (217), m.p. 85° (lit.[12] 88-90°). (Found $M^+$ 288.2462. $C_{20}H_{32}O$ requires $M^+$ 288.2453. $\nu_{max}$ : 3380(b.), 760cm$^{-1}$.

δ : 0.76, 0.84, 0.94 and 0.98(4xs, 20-, 19-, 18- and 17- Me resp.[12]); 3.38(1H,m,$W_{\frac{1}{2}}$7 Hz, 3α-H); 5.43 and 5.68 (2H, AB q, J=5.5 Hz, H-16 and H-15 resp.).

Further elution of the small column gave STACH-15-EN-3α-OL (5). Continued elution of the main column with benzene gave a yellow gum which had i.r. bands at 1700 cm$^{-1}$ (very strong) as well as the stachene olefin band at 750 cm$^{-1}$.

Part of this gum (0.422g) was dissolved in ethanol (6ml), added hydroxylamine sulphate in water (0.45g in 4 ml) followed by pyridine (5ml) and heated 10 min. Crystals separated. Left 1.5 hr., poured into sodium acetate solution and filtered. Extracted solid thoroughly with acetone. Insoluble residue was a pure dioxime, STACH-15-ENE-3,12-DIONE-3,12-DIOXIME (218), m.p.289-290° (dec.).

(Found $M^+$ 330.2316. $C_{20}H_{30}N_2O_2$ requires $M^+$ 330.2307).

$\nu_{max}$: 3325(b), 3054, 1666, 1388, 943 and 930, 814 and 757cm$^{-1}$.


The second part of the yellow gum was reduced in ethanol with NaBH$_4$, procedure as for (16). The crude material was chromatogrammed on silica gel(30g, 7734 in hexane) using benzene as a solvent. Elution with hexane-ethyl acetate (70;30) gave the pure diol, 3α,12α-DIHYDROXY STACH-15-ENE (219) crystalline from aqueous methanol (0.27g), m.p. 187-189°.

(Found $M^+$ 304.2407. $C_{20}H_{32}O_2$ requires $M^+$ 304.2402).

$\nu_{max}$: 3350(b), 3050, 1040, 1030, and 752cm$^{-1}$.

δ : 0.76, 0.79, 0.98 and 1.09 (4xs, 4xMe); 3.18(1H, m, 3β-H); 3.42(1H,m,12β-H); 5.54 and 5.79(2H, AB q, J = 5.6 Hz, H-16 and H-15 resp.).


## CHROMATOGRAPHY OF THE MOTHER LIQUORS FROM THE PREPARATION OF (77) FROM THE HEXANE EXTRACT.

(See 77)

Chromatogrammed 3g of the yellow crystals dissolved in benzene (25ml) on a silica gel column (7734, 30g in hexane). Eluted with hexane-ethyl acetate mixtures. (On a large scale used 25g of crystals, finely ground and mixed with silica gel (7733, 20g), slurried in hexane and placed on a prepared silica gel column (7729, 250g in hexane)).

2% ethyl acetate in hexane eluted the 2-BENZYLIDENO-STACH-15-ENE-3-ONE (216) (0.34g). This material was identical to that prepared from stachenone according to the procedure used for steroids in reference 78. Pale yellow laths from MeOH. M.p. 114-116°, $(\alpha)_D$ +125.7° (c 2.20). (Found M$^+$ 374.2602. $C_{27}H_{34}O$ requires M$^+$ 374.2609).

$\nu_{max}$: 3020, 1673, 1590, 760, 745 and 694cm$^{-1}$.

$\delta$ : 0.67(3H,s,20-Me); 1.01(3H,s,17-Me); 1.13 and 1.17(2x3H,2xs, 18- and 19-Me); 2.22(1H, d of d, $J_{gem}$=16.0 Hz, $J_{Allylic}$= 2 Hz, plus broadening due to W coupling to 20-Me by 2 Hz, 1β-H); 3.03(1H, d of d, $J_{gem}$=16.0 Hz, $J_{Allylic}$=2 Hz, 1α-H); 5.45 and 5.70(2H, AB q, J= 5.5 Hz, H-16 and H-15); 7.33 (5H,s,aromatic); 7.47(1H,quartet, $J_{Allylic}$= 2 and 2 Hz, styryl proton).

Elution with 4% solvent mixture gave 2-BENZYLIDENO-STACH-15-ENE-3,12-DIONE (220), 0.87g from methanol as long, pale yellow needles,m.p.168-171.5°, $(\alpha)_D$ -160.8° (c 2.29). (Found M$^+$ 388.2411. $C_{27}H_{32}O_2$ requires M$^+$ 388.2402).

$\nu_{max}$: 3066, 3050, 1705, 1667, 1593, 765, 750 and 700cm$^{-1}$.

$\delta$ : 0.73 and 1.10(2x3H, 2xs, 20- and 17-Me resp.); 1.18(6H,s,19- and 18-Me); 2.86(1H, d of d, $J_{gem}$= 16.0 Hz, $J_{Allylic}$ 2.0 Hz, 1α-H); 5.63 and 6.07 (2H, AB q, J = 5.5 Hz, H-16 and H-15 resp.); 7.33 (5H,s, aromatic); 7.50(1H, q, 2x $J_{Allylic}$ 2.0 and 3.0 Hz, styryl proton).

Elution with 8-10% solvent mixture gave the new
diterpene ENT-16α-HYDROXY-2-BENZYLIDENO-ATIS-13-ENE-3-
ONE, (222) as pale yellow hexagonal plates from MeOH, m.p.
193-198° (dec. bubbling), $(\alpha)_D$ + 104° (c 2.02).
(Found C, 82.90; H, 8.98. $C_{27}H_{34}O_2$ requires

C, 83.03; H, 8.77. $M^+$ 390.2562. Calculated for
$C_{27}H_{34}O_2$ $M^+$ 390.2559).

$\nu_{max}$: 3490, 3040, 1665, 1590, 916, 780, 755, 730 and 698cm$^{-1}$.

$\delta$ : 0.53(3H,s,20-Me); 1.16(9H,s,17-,18-, and 19-Me);
1.87(1H,s, EXCHANGES WITH $D_2O$, OH); 2.23(1H,broad
d of d, $J_{gem}$=16.0 Hz, $J_{Allylic}$=3.0 Hz, 1β-H); 2.83
(1H, d of d, $J_{gem}$=16.0 Hz, $J_{Allylic}$=2.0 Hz, 1α-H);
5.83(1H,d,J=7.5 Hz, 14-H); 6.10(1H,t, $J_{13,12}$= 6.0
Hz, collapses to a doublet $J_{13,14}$= 7.5 Hz on
irradiation at 2.30, 13-H); 7.30(5H,s, aromatic);
7.50(1H,q,$J_{Allylic}$= 2.0 and 3.0 Hz, styryl proton).

## ENT-2-BENZYLIDENO-11(12→16)ABEO-ATIS-13-ENE-3,12-DIONE(221).

Treatment of the benzylidenodiketone (220) (0.71g)
with acetic anhydride (20ml) and sulphuric acid (1ml) as
for compound (109) gave 0.52g pale yellow rods from acetone-
methanol, m.p. 208-212°, $(\alpha)_D$ +103.5° (c 2.11).
(Found $M^+$ 388.2402. $C_{27}H_{32}O_2$ requires $M^+$ 388.2402).
$\nu_{max}$: 1670, 1592, 1573 and 700cm$^{-1}$.
$\delta_{max}$: 0.61(3H,s,20-Me); 1.19(6H,s, 18-and 19-Me); 1.56(3H,
s, 17-Me); 2.32(1H,broad d of d, $J_{gem}$ = 18.0 Hz,
$J_{Allylic}$ = 3.0 Hz, 1β-H); 2.76(1H, d of d, $J_{gem}$=18.0

Hz, $J_{Allylic}$= 2.0 Hz, collapses to a doublet $J_{gem}$=

18.0 Hz on irradiation at 7.88, 1α-H); 5.83(1H,d,

J = 10.0 Hz, 13-H); 6.93(1H, d of d, J = 2.0 and 10.0

Hz, collapses to a doublet, J = 10.0 Hz, on irradiation

at 1.53, 14-H); 7.33(5H,s, aromatic); 7.50(1H,q,

$J_{Allylic}$ = 2.0 and 3.0 Hz, styryl proton).


Further elution of the column gave a fraction after

pure (222) which contained (222)  mixed with a more polar

compound (223).   From the large scale (25g) column a

0.12g sample of this polar compound (223) was obtained

by p.l.c. using 3 x 20 x 20cm plates.   The sample was

applied in methylene chloride and eluted with benzene-ethyl

acetate (90:10).   Extracted silica gel with methylene

chloride, evaporated and crystallised from hexane.   M.p.

185-189.5°.

(Found $M^+$ at 420.   M-28 = 392.2720.   Calculated for

$C_{27}H_{36}O_2$ m/e 392.2715).

$\nu_{max}$: 3536, 1755, 1676, 1623, 1492, 755, 730 and 695cm$^{-1}$.

$\delta$   : 0.76, 1.02, 1.13 and 1.13(3xs, 4xMe, 20-, 17-,

19- and 18-Me resp.); 1.60(1H, EXCHANGED WITH $D_2O$,OH;

2.40(1H,b,collapses on irradiation at 6.33, ent-

2β-H); 5.82(1h,d,J= 8.0 Hz, 13-H); 6.13(1H, t,

J = 7.0 Hz, 14-H, perturbed on irradiation at 2.30);

6.33(1H, b.s., collapses to a sharp singlet on

irradiation at 2.30, benzyl-H); 7.23(5H,b.s., aromatic).

ENT-3β-TOSYLOXY-11(12→16)ABEO-ATIS-13-ENE-2,12-DIONE (224)

This was prepared from (46) (1.0g) in acetic anhydride

(15ml) as for (109).   Crystallised from acetone-THF,

(0.86g), m.p. 186-187$^O$, $\{\alpha\}_D$ + 157$^O$ (c 2.08).

(Found C, 68.33; H, 7.40.   $C_{27}H_{34}O_5S$ requires

        C, 68.91; H, 7.28).

$\nu_{max}$: 1733, 1685, 1597, 1170 and 675 cm$^{-1}$.

δ    : 0.57 and 0.80 (2x3H, 2xs, 20- and 19-Me resp.);

        1.13 and 1.20(2x3H, 2xs, 18- and 17-Me resp.);

        2.43(3H,s, aromatic Me); 4.83(1H,s, ent-3α-H);

        5.85(1H,d,J = 10.0 Hz, 13-H); 6.85(1H, d of d,

        J = 2.0 and 10.0 Hz, 14-H);   7.23, 7.36, 7.75 and

        7.90(AA'MM' system, 1,4-disubstituted aromatic ring).

ENT-11(12→16)ABEO-ATIS-13-ENE-2,12-DIONE-2β-ACETATE-

BENZALDEHYDE-LACTONE (225).

The lactone (77) was treated as for 109.   Yield 0.25g

from 0.3g of (77).   Crystallised from aqueous methanol in

long needles, m.p. 252-253$^O$ (phase change 120-130$^O$),

$\{\alpha\}_D$ +27.0$^O$ (c 2.71).

(Found M$^+$ at 462.   M-86 (loss of $CH_2$=C=O+$CO_2$) = 376.2401.

$C_{26}H_{32}O_2$ requires m/e 376.2402).

$\nu_{max}$: 1755, 1742, 1685, 1235, 1200, 780, 768, 713 and

        700cm$^{-1}$.

$\delta$ : 0.73, 1.00, 1.18 and 1.20(4xs,20-,19-,18-, and 17-

Me resp.); 2.15(3H,s, ACETATE); 3.12 (1H,d,J = 8.5

Hz, ent-1β-H); 5.17(1H,d, J = 8.5 Hz, benzylic H);

5.76(1H,d, J = 9.5 Hz, 13-H); 6.80(1H, d of d,

J = 2.0 and 9.5 Hz, 14-H); 7.40(5H,m, aromatic).

## BENZALDEHYDE-LACTONE-2α-ACETATE (226).

The lactone (77) (5.0g) in acetic anhydride (50ml)
was heated to 100° with p-tosic acid (0.5g) for 10-20
minutes.   Left cold overnight, poured into ice, and
crystallised from acetone-methanol (5.5g yield), m.p.
270-274°.   $(\alpha)_D$ -291.6° (c 2.16).
(Found $M^+$ 462.2400. $C_{29}H_{34}O_5$ requires $M^+$ 462.2406).
$\nu_{max}$: 3057, 3006, 1755, 1744, 1706, 1135, 782, 774, 757,

735, 716 and 700 $cm^{-1}$.

$\delta$ : 0.84, 1.00, 1.17 and 1.17(3xs, 4xMe, 20-, 19-,

18- and 17-Me respectively); 2.12(3H,s, ACETATE);

3.07(1H,d, J = 8.5 Hz, 1α-H); 5.12(1H,d, J = 8.5

Hz, benzylic H); 5.59 and 5.97(2H, AB q, J = 5.5

Hz, H-16 and H-15 resp.); 7.43(5H,m, aromatic).

## 12-OXO-2,3-SECOSTACH-15-EN-2,3-DIOIC ACID (227).

The diosphenol (18) (2.0g) in ethanol (50ml) was
treated with KOH (3g) in ethanol, cooled and added $H_2O_2$

(30%, 10ml).   Left at 5° for 48 hr.   Took off solvent,
poured residue into ice-dilute HCl.   Crystallised solid
from aqueous methanol as soft, silky needles, (0.95g),
m.p. 173-176°.

(Found $M^+$ 348.1945.  $C_{20}H_{28}O_5$ requires $M^+$ 348.1937.

$\nu_{max}$:   3700-2400 (v.b.); 1720 and 1690(b), and 765 cm$^{-1}$.

$\delta$ (D$_6$-DMSO-CDCl$_3$): 0.87, 1.10, 1.18 and 1.27(4x3H, 4xs,

4xMe); 5.59 and 6.05(2H, AB q, J=5.5

Hz, H-16 and H-15 resp.); 10.73(2H,b.s.,

EXCHANGED WITH D$_2$O, 2x COOH).


## 12-OXO-2,3-SECOSTACHANE-2,3-DIOIC ACID (228).


Used essentially the procedure in reference 2.
15,16-Dihydroketol (2) (0.9g) was dissolved in t-BuOH(100ml)
added potassium carbonate (1.8g), sodium periodate (7.5g)
in water (150ml) and potassium permanganate (0.2g).
Stirred magnetically for 36 hours, removed half of the
alcohol under reduced pressure, decolourised with SO$_2$,
made distinctly acid with H$_2$SO$_4$ and removed the remainder
of the alcohol under vacuum.   Seco acid crystallised out
at this point and was filtered off.   Extraction with ether
and further work up gave a little more material.   The
filtered crystals were crystallised from aqueous methanol
as square plates (0.4g), m.p. 250° sharp, $(\alpha)_D$ -90°
(c 1.43).

(Found C, 68.13; H,8.49; M-18 = 332.19723.  $C_{20}H_{30}O_5$ re-
quires C, 68.55; H,8.63; M-18 = 332.19875).

$\lambda_{max} (\varepsilon)$:  283.5(47) and 210 (263) e.a.

$\nu_{max}$:  3250(b), 1740, 1718 and 1690 (b), 837(b) and

795 $cm^{-1}$.

## DIMETHYL 12-OXO-2,3-SECOSTACHANE-2,3-DIOATE (229).

The dihydroseco acid (228) was dissolved in methanol
and treated with excess ethereal diazomethane.   Evaporated
solvents, charcoaled yellow gum and crystallised from
aqueous methanol as needles, m.p. 154-156$^{O}$.

$\nu_{max}$:  1739, 1727, 1700, 1140 (b) $cm^{-1}$.

## PREPARATION OF THE 11β-BROMO-15,16-DIHYDRO-BENZALDEHYDE-LACTONE (230).

(i)  The dihydrolactone (38) in chloroform was treated
with $Br_2$.

(ii) (38) in acetic acid-THF containing some acetic an-
hydride was treated with $Br_2$.

Both methods:  left 3 hr., diluted with chloroform,
washed well with bicarbonate, water, dried and evaporated
to an oil.   Dilution with benzene or methylene chloride
and adding much hexane caused the formation of MONOCLINIC
crystals, m.p. 254-269$^{O}$ (phase change to orthorhombic)
with decomposition.   Careful solution of this material
in COLD methanol and slow evaporation gave ORTHORHOMBIC

crystals, m.p. 267-269° (dec). Recrystallisation gave
m.p. 270-272°. Heating for even 30 seconds with methanol
gave back (38). However the other solvents (benzene,
hexane, chloroform) could be used hot without effecting this
change. Both sets of crystals were of excellent shape
but the monoclinic form slowly (3 days) reverted to the
orthorhombic form with loss in crystallinity.
(Found $M^+$ 502.1538. $C_{27}H_{33}O_4Br$ requires $M^+$ 502.1543).
The X-ray structure was determined[31] on this compound.
$\nu_{max}$: 3355(b), 1750, 1725, 1218, 714, 700 and 680 cm$^{-1}$.
$\delta$ : 1.09, 1.09, 1.14 and 1.35(3xs,4xMe); 1.94(1H,d,
    J = 12.5 Hz, 9β-H); 3.28(1H,b.s., EXCHANGED WITH
    $D_2O$, 2α-OH); 3.50(1H,d,J=7.5 Hz, 1α-H); 4.67(1H,d,
    J = 12.5 Hz, 11α-H); 5.12(1H,d,J= 7.5 Hz, benzylic
    proton); 7.27(5H,b.s., aromatic).

## ENT-(16S)-2β,3β-DIACETOXY-ATIS-13-ENE (231).

The diol (131) (0.606g) was acetylated in pyridine as
for (3). Crystallised from aqueous methanol as needles
(0.770g), m.p. 173-174.5° $(\alpha)_D$ -35° (c 0.85).
(Found C,74.04; H,9.32; $M^+$ 388.2626. $C_{24}H_{36}O_4$ requires
    C,74.19; H,9.34; $M^+$ 388.2613).
$\nu_{max}$: 1740, 1240, 727, 713 and 700 cm$^{-1}$.
$\delta$ : 0.72(3H,d, J = 7.0 Hz, 17-Me); 0.84, 0.89 and 1.00
    (3x3H, 3xs, 18-, 19- and 20-Me); 2.00(6H,s,2x
    ACETATE); 2.23(1H, m, 12-H); 4.58(1H,d, J = 3.5

Hz, <u>ent</u>-3α-H); 5.27(1H,q, J = 3.5 and 7.0 Hz, <u>ent</u>-2α-H); 5.80 and 5.90 (1H, doublet, J = 6.0 Hz, 14-H); 5.95 and 6.10 - centres of two doublets (1H, d of d, J = 3.5 Hz  and 6.0 Hz, 13-H).


## 2α,3α-DIACETOXY-STACHANE (233).


This was prepared[191] by acetylating the 2,3-diol (136). Crystallised from aqueous methanol as needles, m.p. 144-146.5°, $(\alpha)_D$ -32.0° (c 2.5).

$\nu_{max}$: 3465, 1740, 1393 and 1385, 1240 and 938 cm$^{-1}$.

δ   : 0.90, 0.95, 1.05 and 1.20 (4xs, 4xMe); 2.03(6H,s,

   2xACETATE); 4.65(1H,d,J = 3.5 Hz, 3β-H); 5.37

   (1H,q, J = 3.5 and 7.0 Hz, 2β-H).


## ENT-1α-ACETOXY-11(12→16)ABEOATIS-13-ENE-2,12-DIONE (235).


This was prepared by acetolysis of (224) using the procedure for (47).   Crystallised in long needles from aqueous methanol, m.p. 220-222°, $(\alpha)_D$ +81.25° (2.69).

(Found C,73.44; H, 8.51.   $C_{22}H_{30}O_4$ requires

   C,73.71; H, 8.44).

$\nu_{max}$: 1752, 1712, 1675, 1230 and 820 cm$^{-1}$.

δ   : 0.74, 0.88, 1.12 and 1.20(4xs, 20-, 19-, 18- and

   17-Me resp.);   2.17(3H,s, ACETATE); 2.67(1H,d,

$J_{gem}$ = 12.5 Hz, <u>ent</u>-3β-H); 4.30(1H, singlet with shoulder J = 1.8 Hz, <u>ent</u>-1β-H); 5.87(1H,d, J = 9.5 Hz, 13-H); 6.90(1H, d of d, J = 2.0 and 9.5 Hz, 14-H).

# THE NUCLEAR MAGNETIC RESONANCE SPECTRA

(in order of compound numbers)

+ D₂O

CHART S-60T
MADE IN U.S.A.

200

300.

CHART S-60T
MADE IN U.S.A.
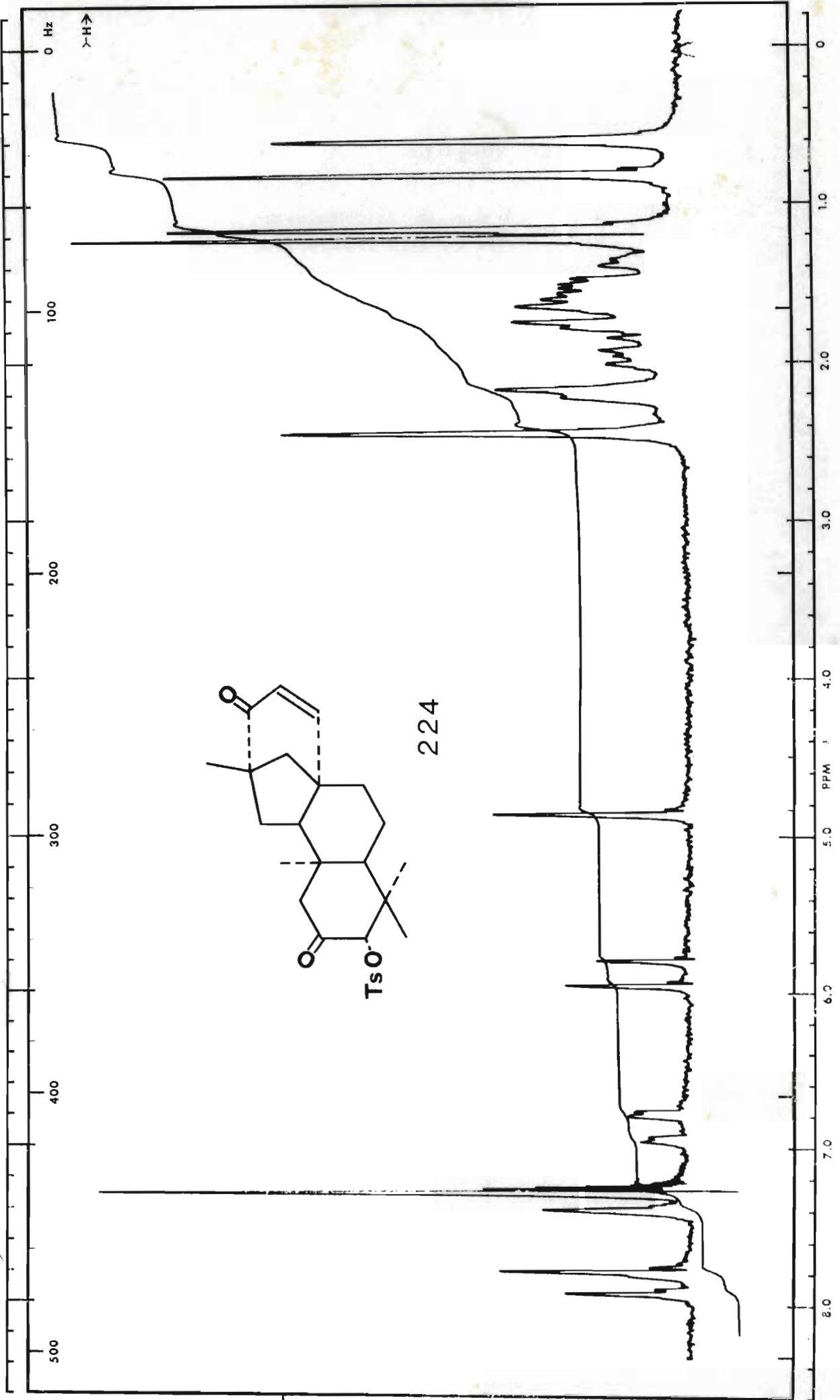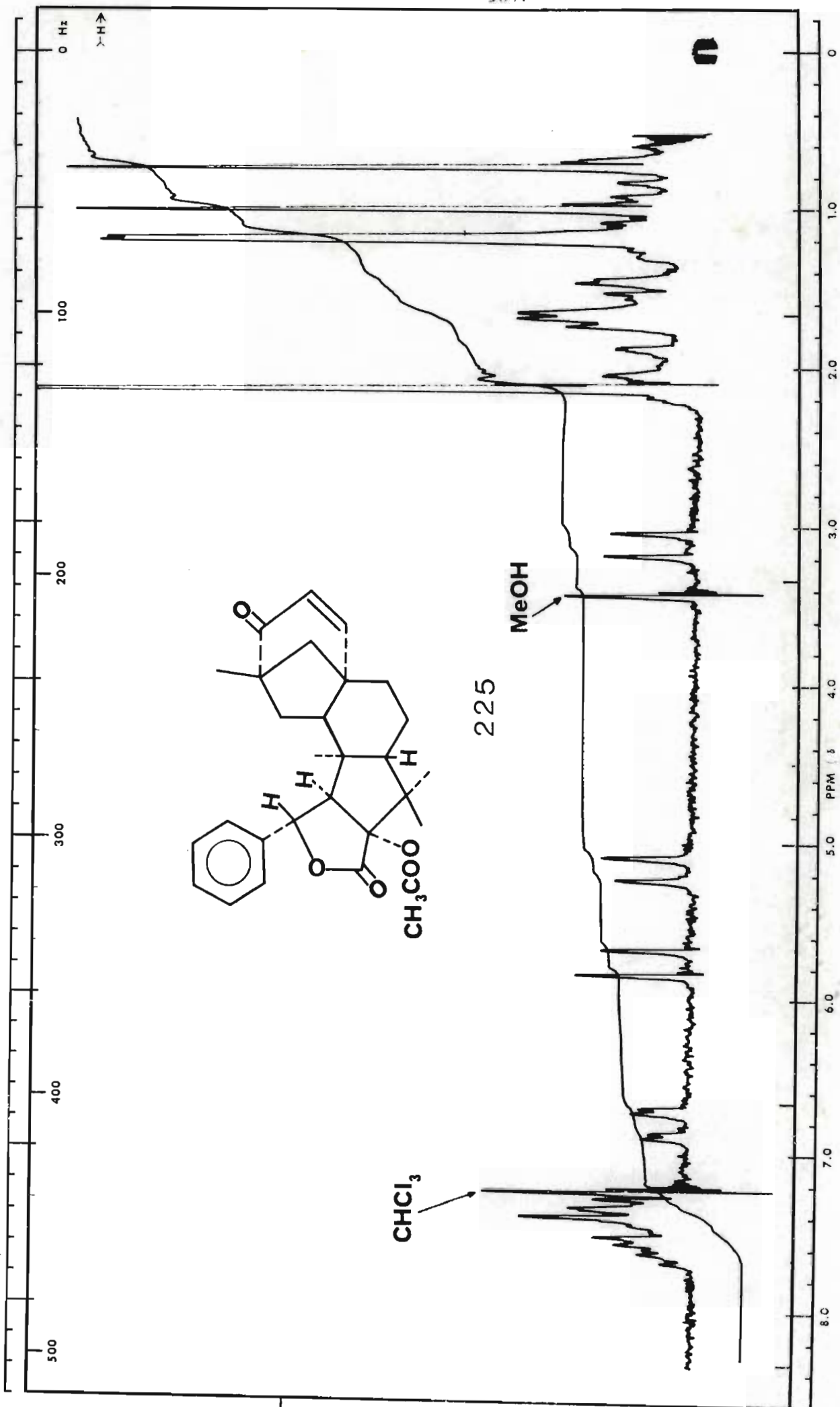
3

5

302.



CHART S-60T
MADE IN U.S.A.

305.

14

CHART S-60T
MADE IN U.S.A.

23

24

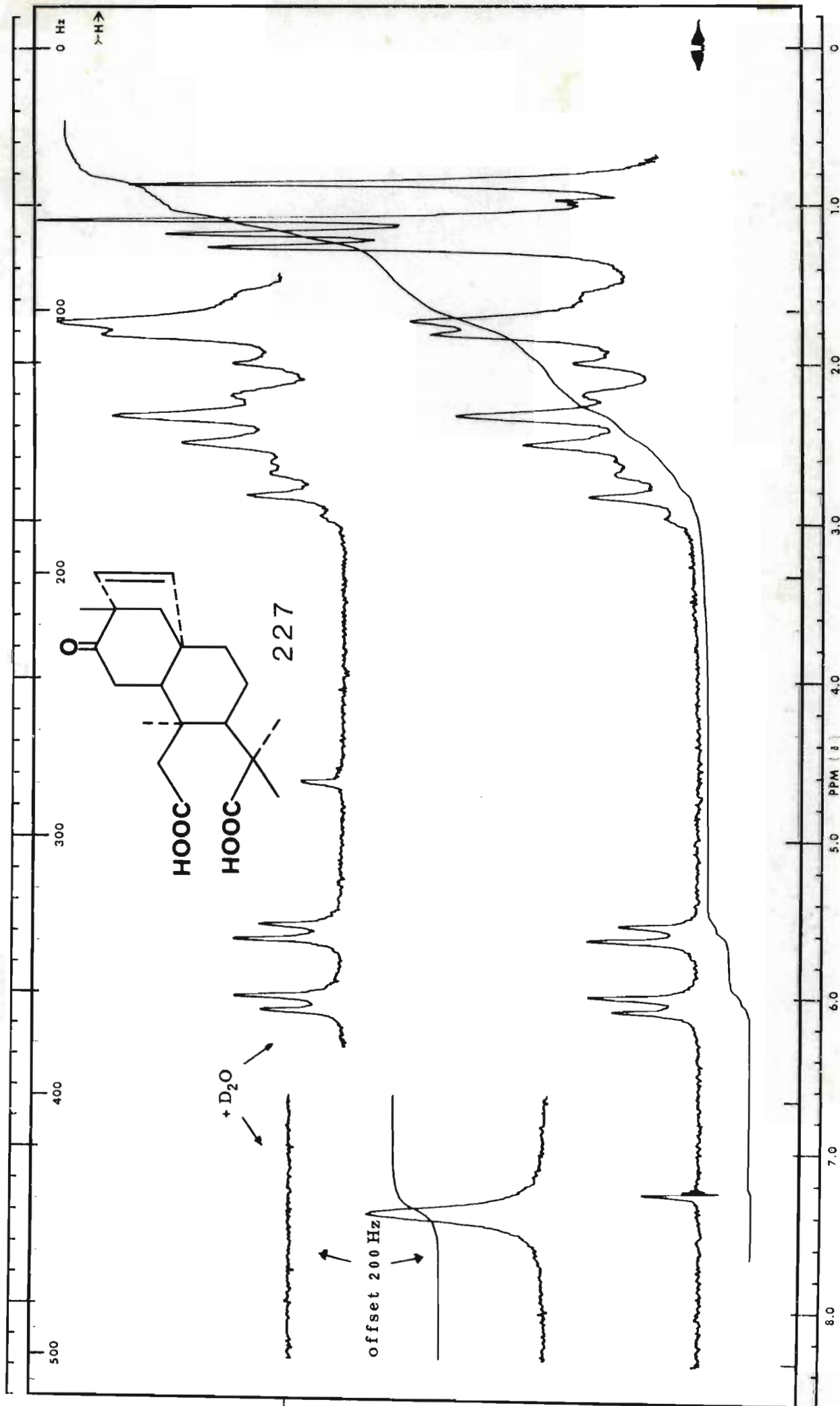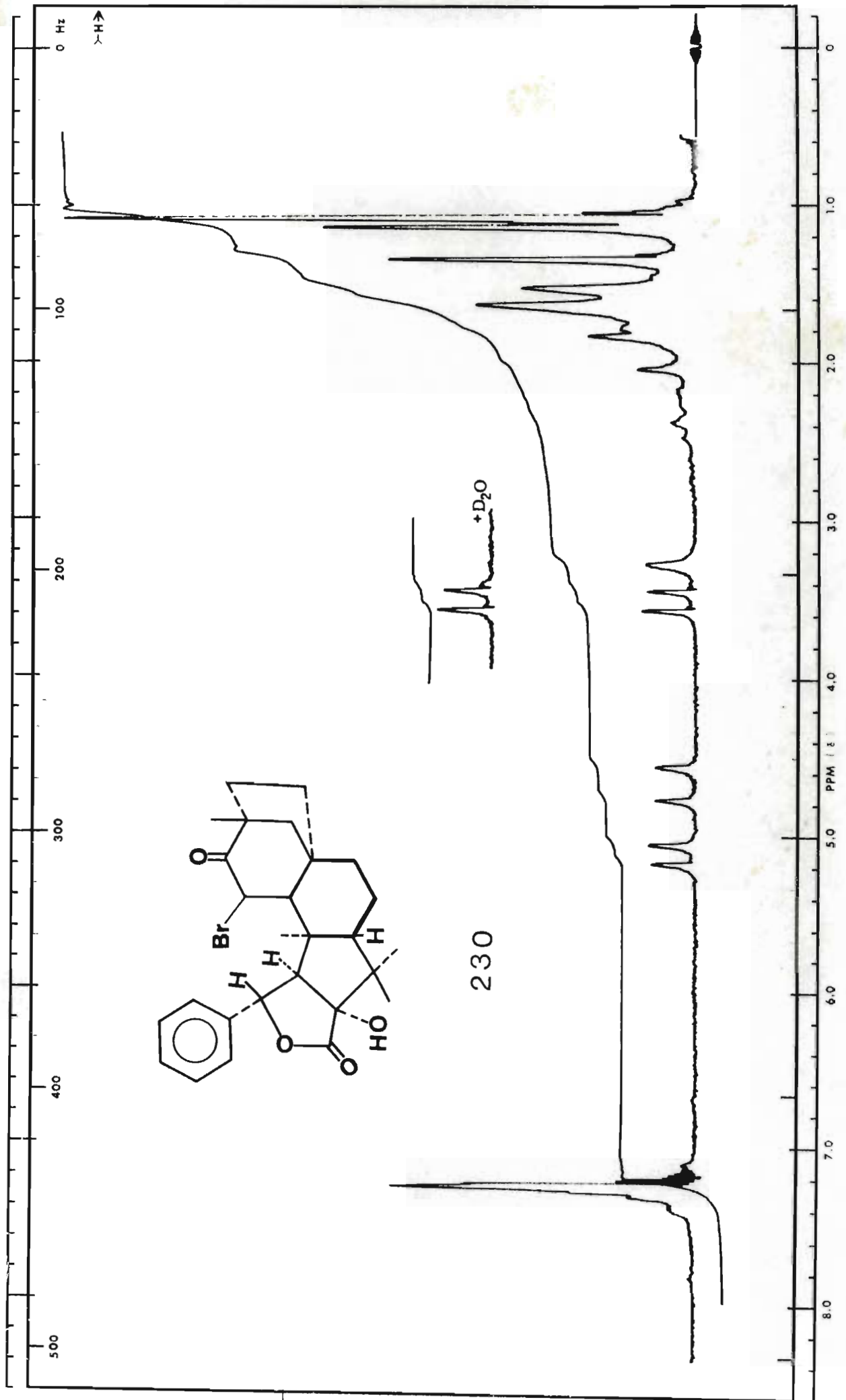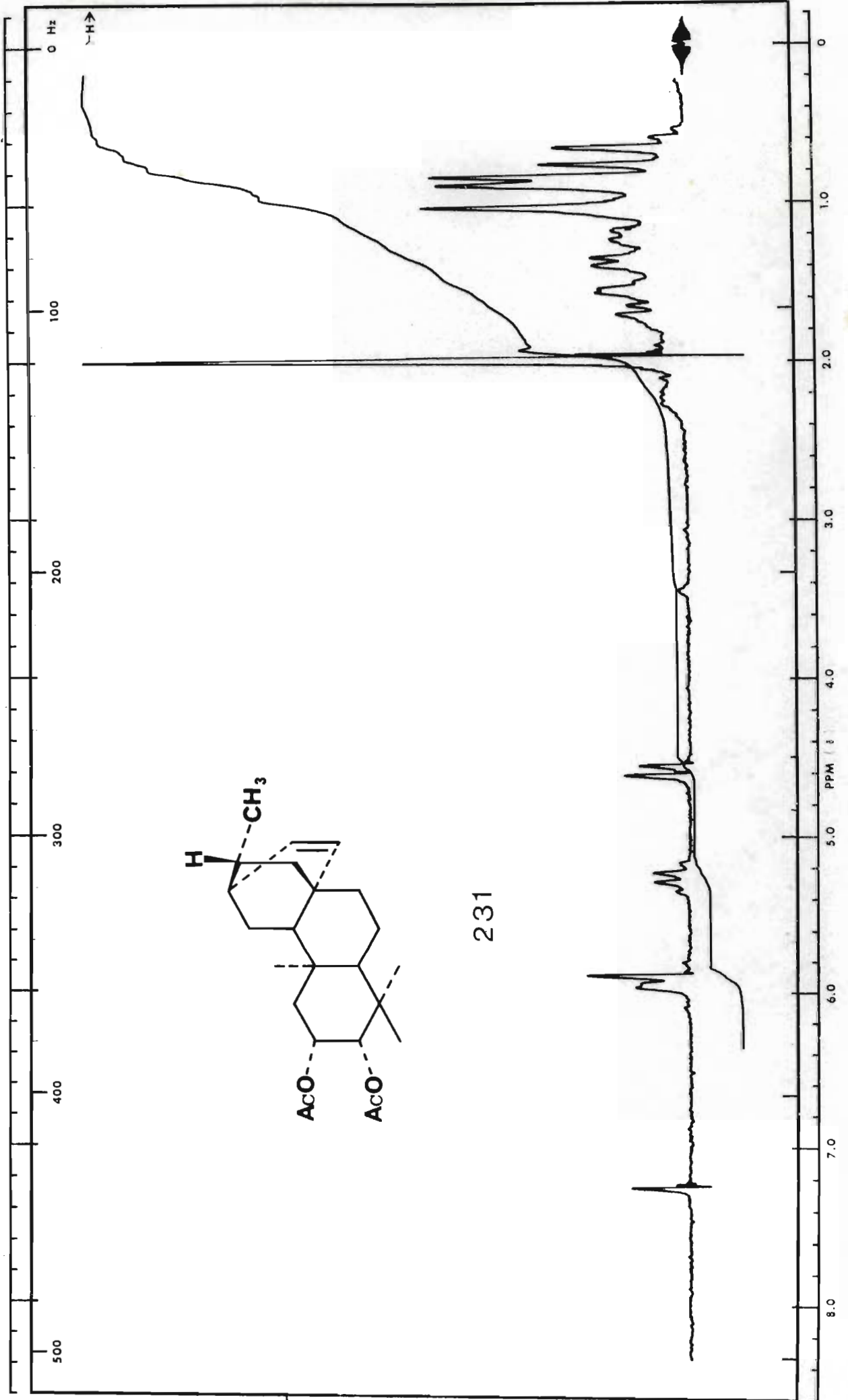CHART S-60T
MADE IN U.S.A.

26

CHART S-60T
MADE IN U.S.A.

27

sweep width 100 Hz

offset 275 Hz

30

500    400    300    200    100    0 Hz

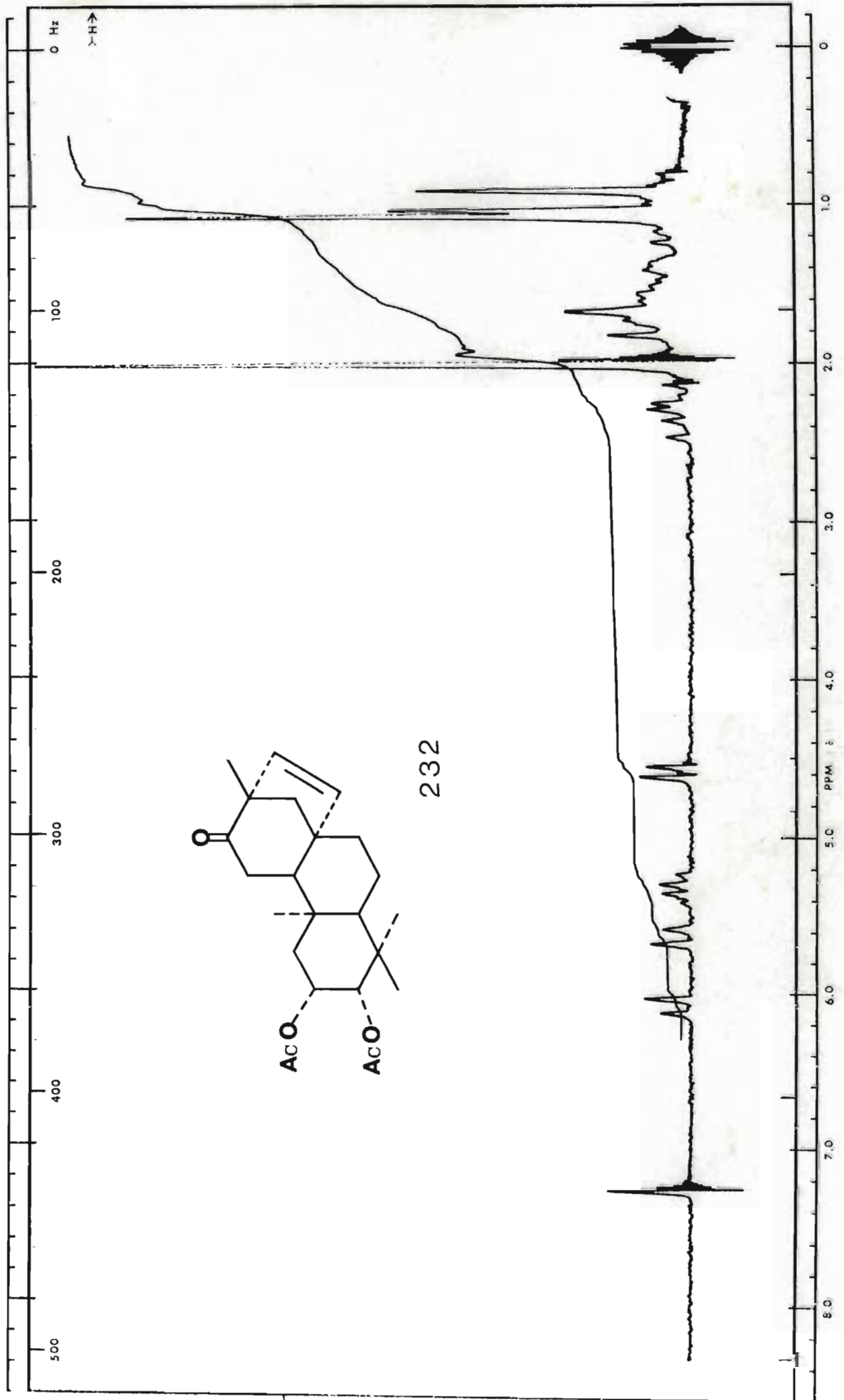8.0    7.0    6.0    5.0    PPM (δ)    4.0    3.0    2.0    1.0    0

CHART S-60T
MADE IN U.S.A.

32

313.

CHART S-60T
MADE IN U.S.A.

36

37

CHART S-60T
MADE IN U.S.A.

46

CHART S-60T
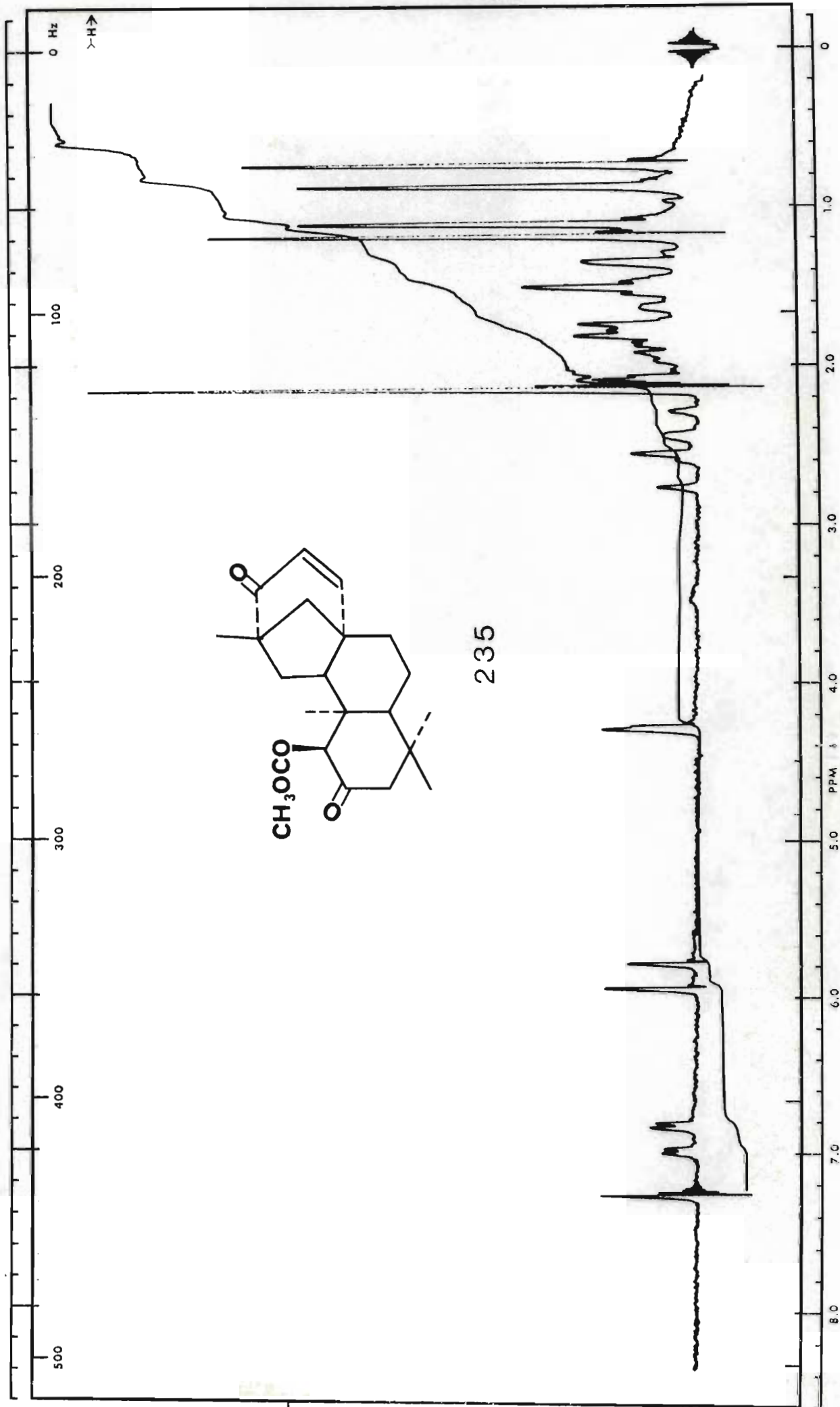MADE IN U.S.A.

47
(CRUDE)

CHART S-60T
MADE IN U.S.A.

+ D₂O

48

51

319.

CHART S-60T
MADE IN U.S.A.

53

$H_2-53$

65

HO—CH₂CH₂—O

+D₂O

66

323.



67

67

2-H₂

11β-H

CHART S-60T
MADE IN U.S.A.
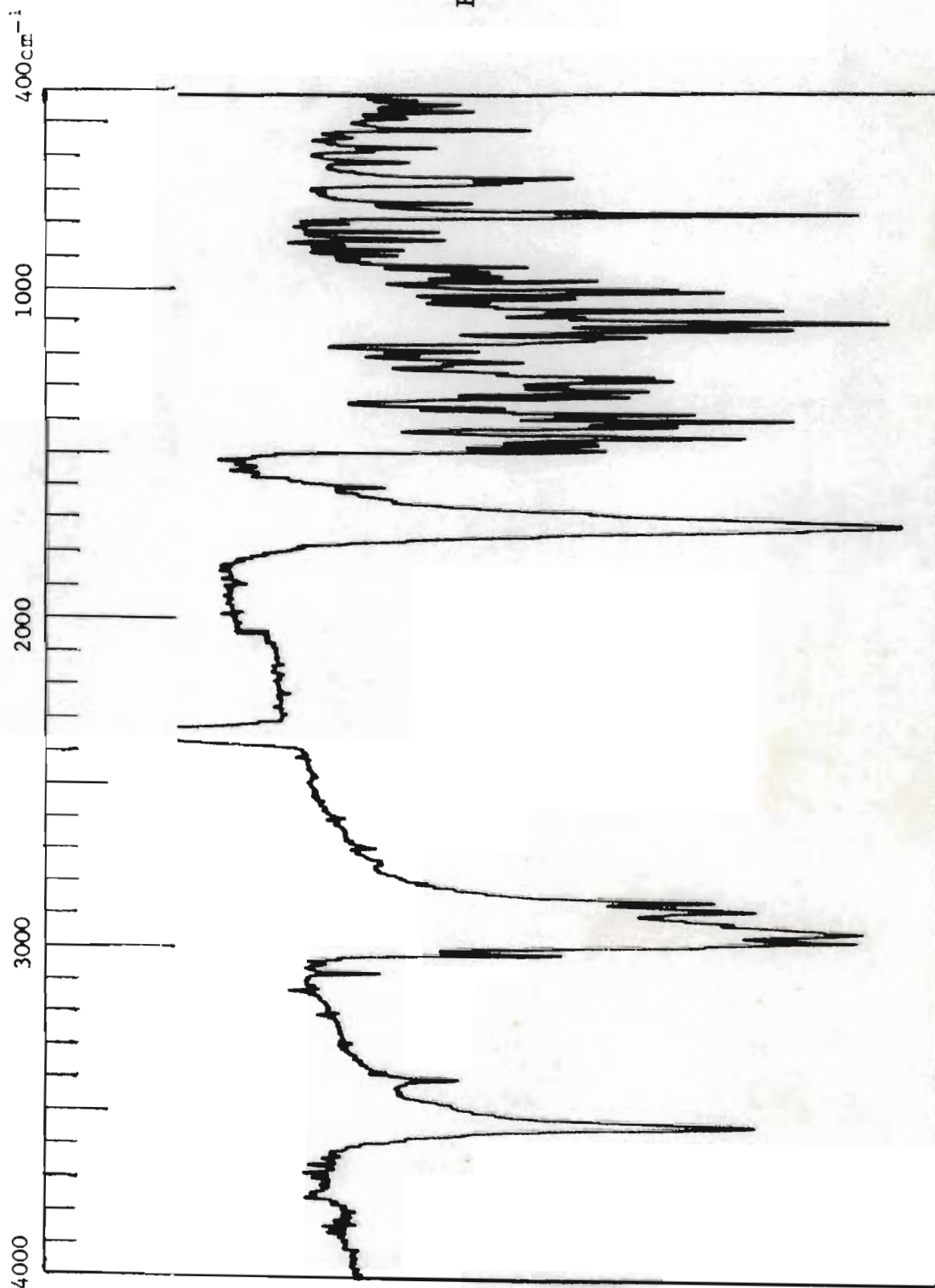
67

-2-

68

68

17–Me

11–H₂

– 5 –

CHART S-60T
MADE IN U.S.A.

CHART S-60T
MADE IN U.S.A.

69

+ D₂O

70

CHART S-60T
MADE IN U.S.A.

71

73

75

76

CHART S-60T
Made in U.S.A.

82

341.

CHART S-60T
MADE IN U.S.A.

CHART S-60T
MADE IN U.S.A.

90

CHCl₃

CHART S-60T
MADE IN U.S.A.

500    400    300    200    Ph    HON 100    0 Hz

>—H→

+ D₂O

offset 50 Hz

offset –90 Hz    +D₂O

91

CHCl₃

Me₂CO

8.0    7.0    6.0    5.0    PPM    4.0    3.0    2.0    1.0    0

CHART S-60T
MADE IN U.S.A.

345.

CHART S-60T
MADE IN U.S.A.

CHART 5-60T
MADE IN U.S.A.
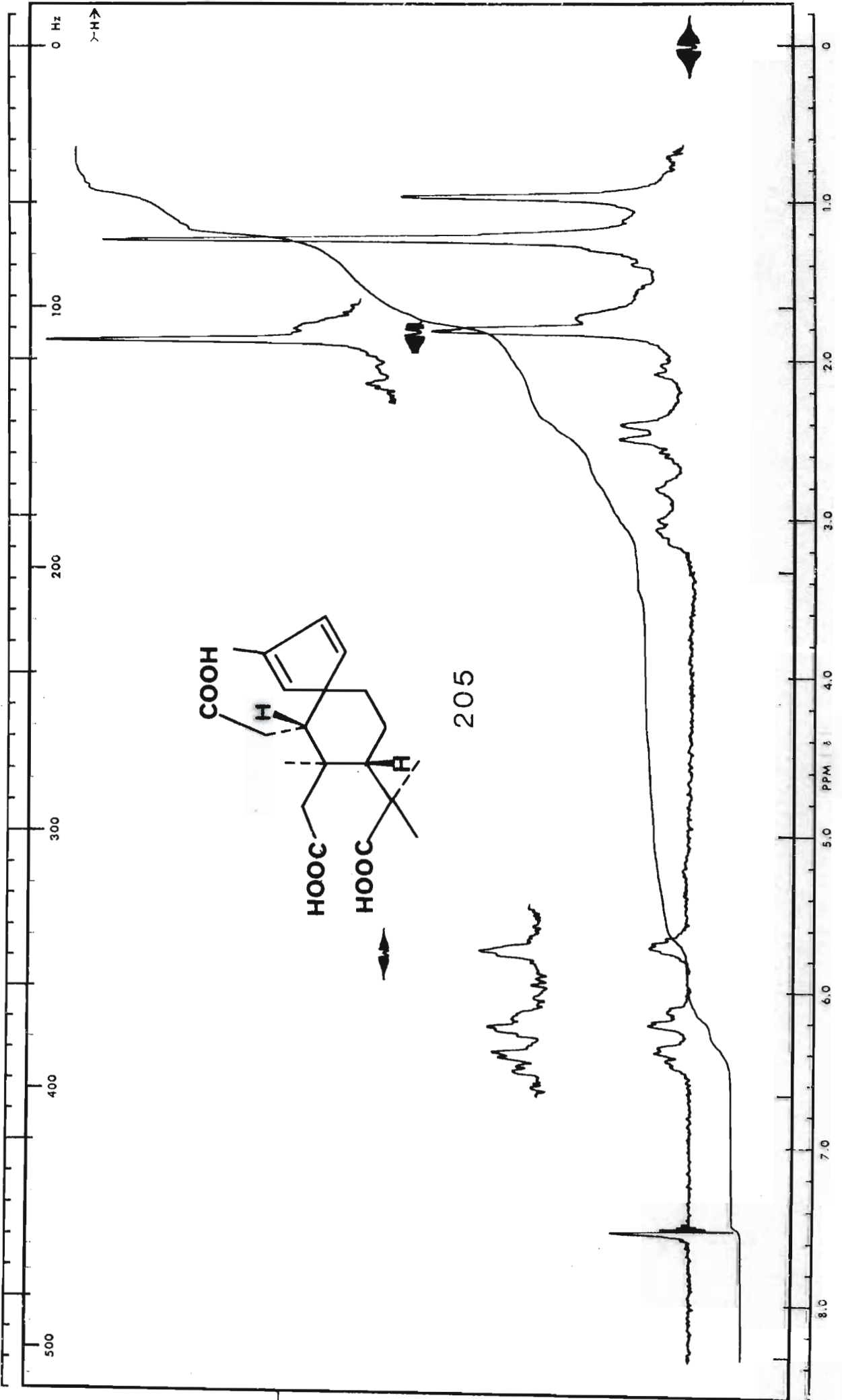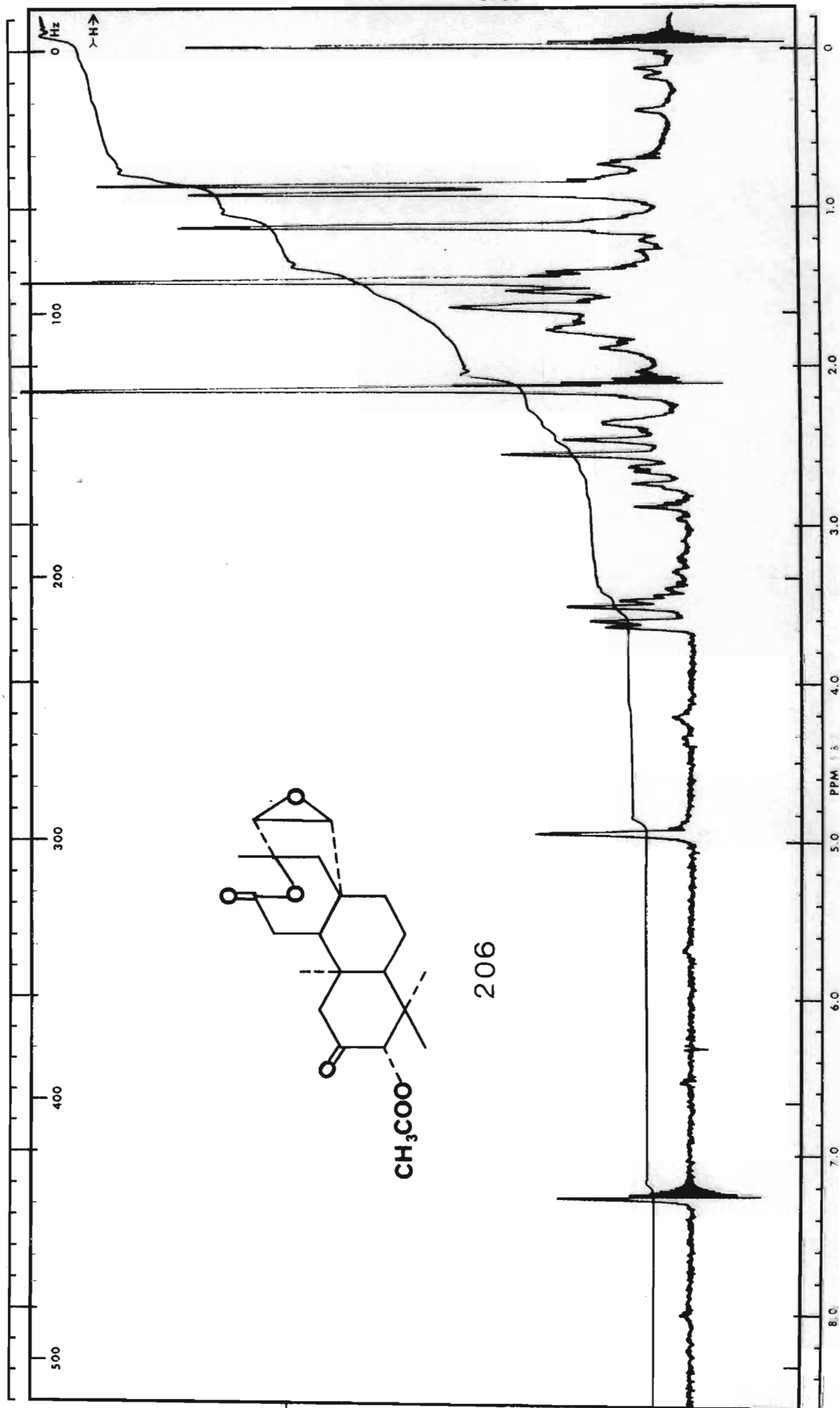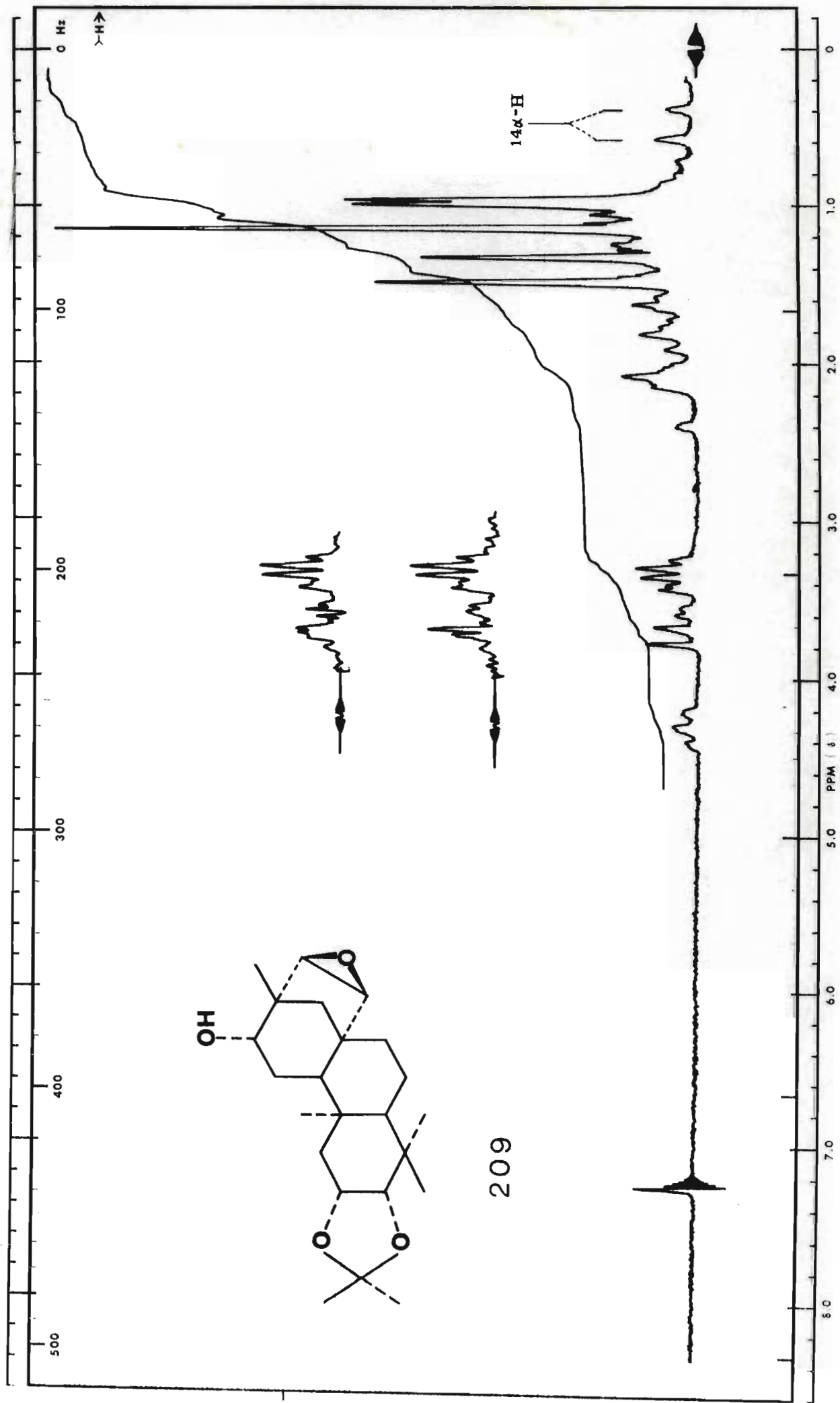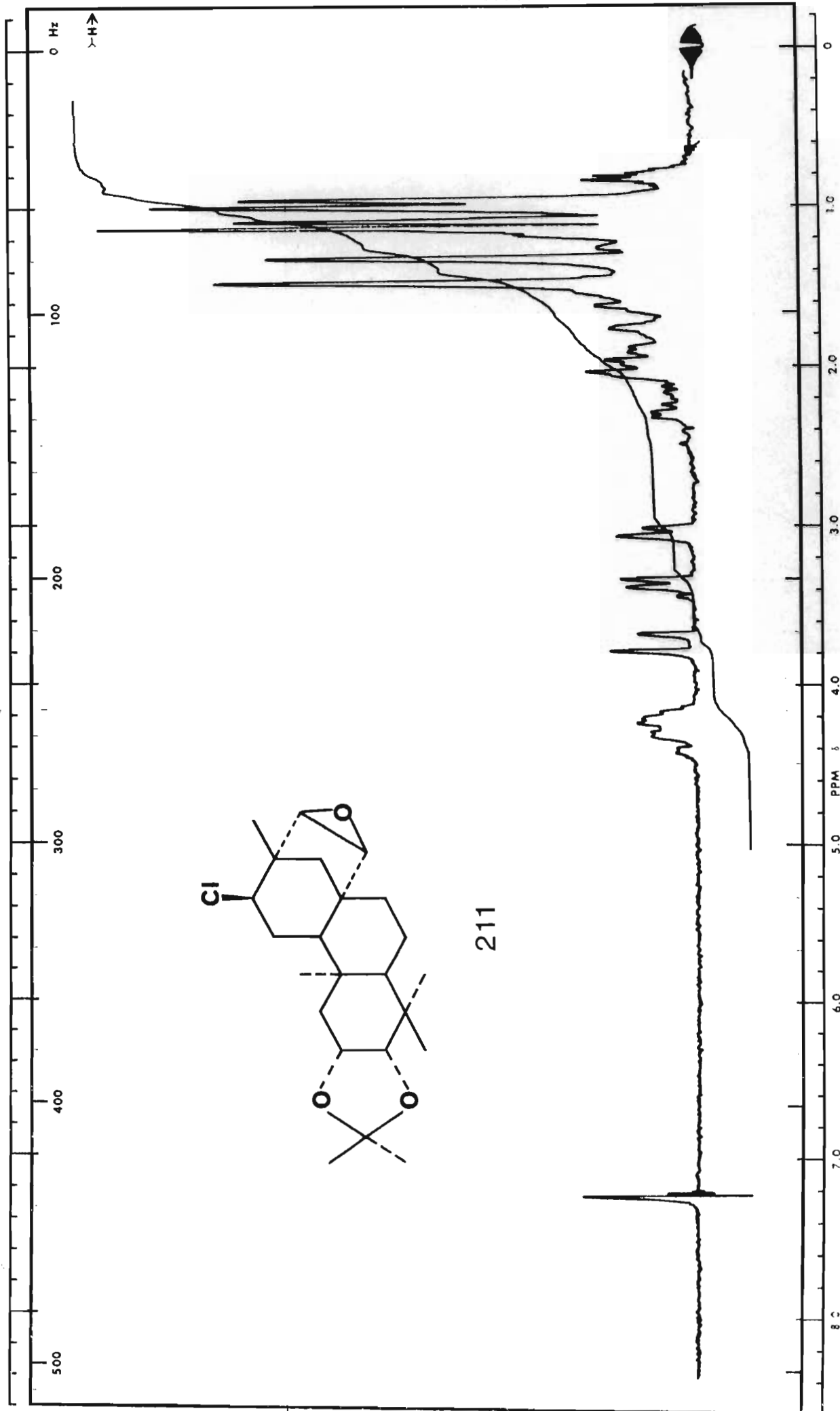
94

H₂O

MeOH

+ D₂O

Me₂CO

96

CHART S-60T
MADE IN U.S.A.

98

+D₂O

99

351.

CHART S-60T
MADE IN U.S.A.

104

CHART S-60T
MADE IN U.S.A.

106

CH₃O

CHART S-60T
MADE IN U.S.A.

109

111

CHART S-60T
MADE IN U.S.A.

OCOCH₃

120

122

CHART S-60T
MADE IN U.S.A.

123

126

CHART S-60T
MADE IN U.S.A.

SEE 126

MeOH

CHART S-60T
MADE IN U.S.A.

131

CHART 5-60T
MADE IN U.S.A.

141

363.

CHART S-60T
MADE IN U.S.A.

145

CHART S-60T
MADE IN U.S.A.

147

CH₃OCO

CHART S-60T
MADE IN U.S.A.

150

153

MeOH

CHART S-60T
MADE IN U.S.A.

156

+ D₂O

CHART S-60T
MADE IN U.S.A.

157

200

CHART S-60T
MADE IN U.S.A.

CHART S-60T
MADE IN U.S.A.

201

205

373.



CHART S-60T
MADE IN U.S.A.

206

CH₃COO

374.

CHART S-60T
MADE IN U.S.A.

14α-H

209

211

376.

212

216

217

220

221
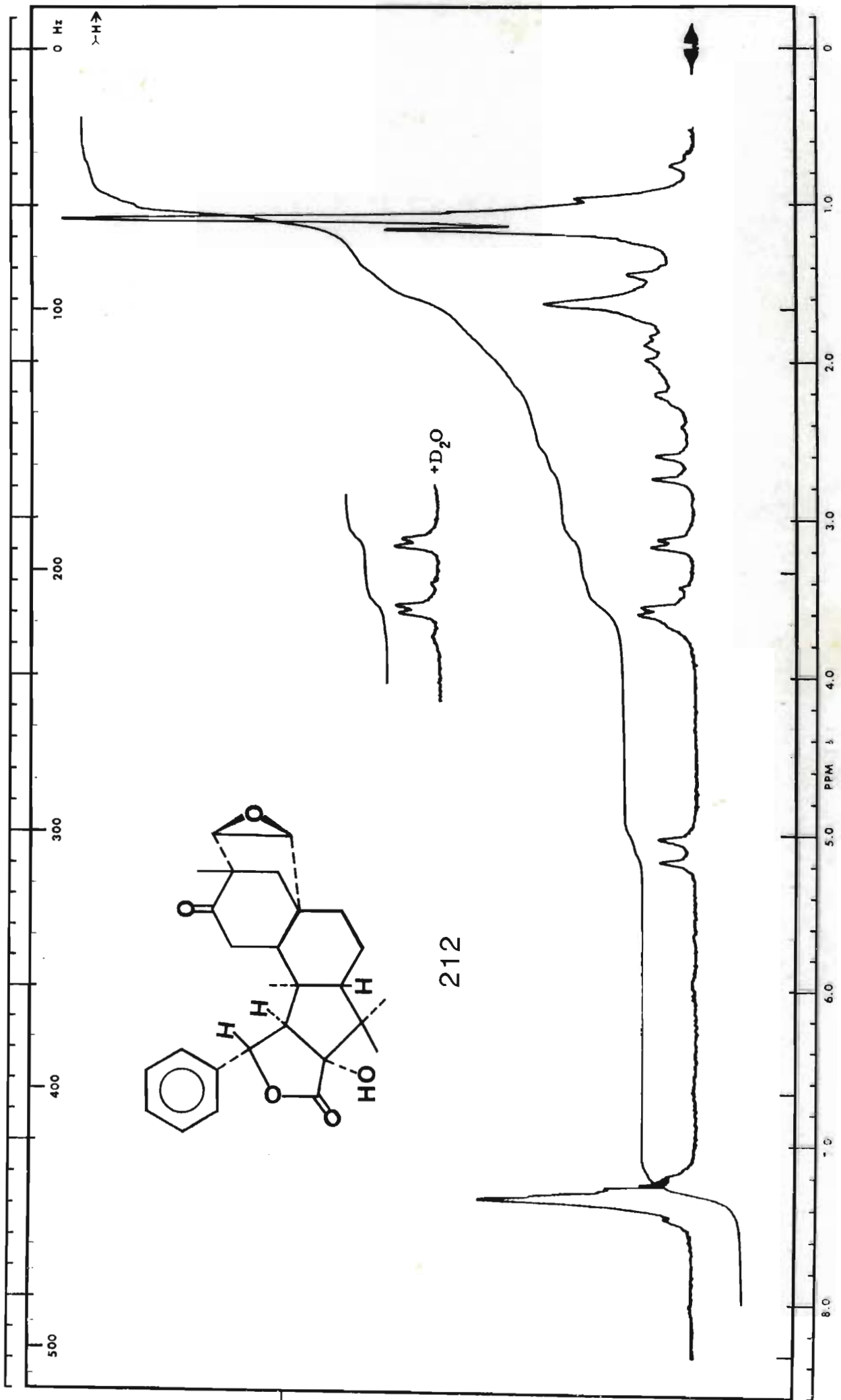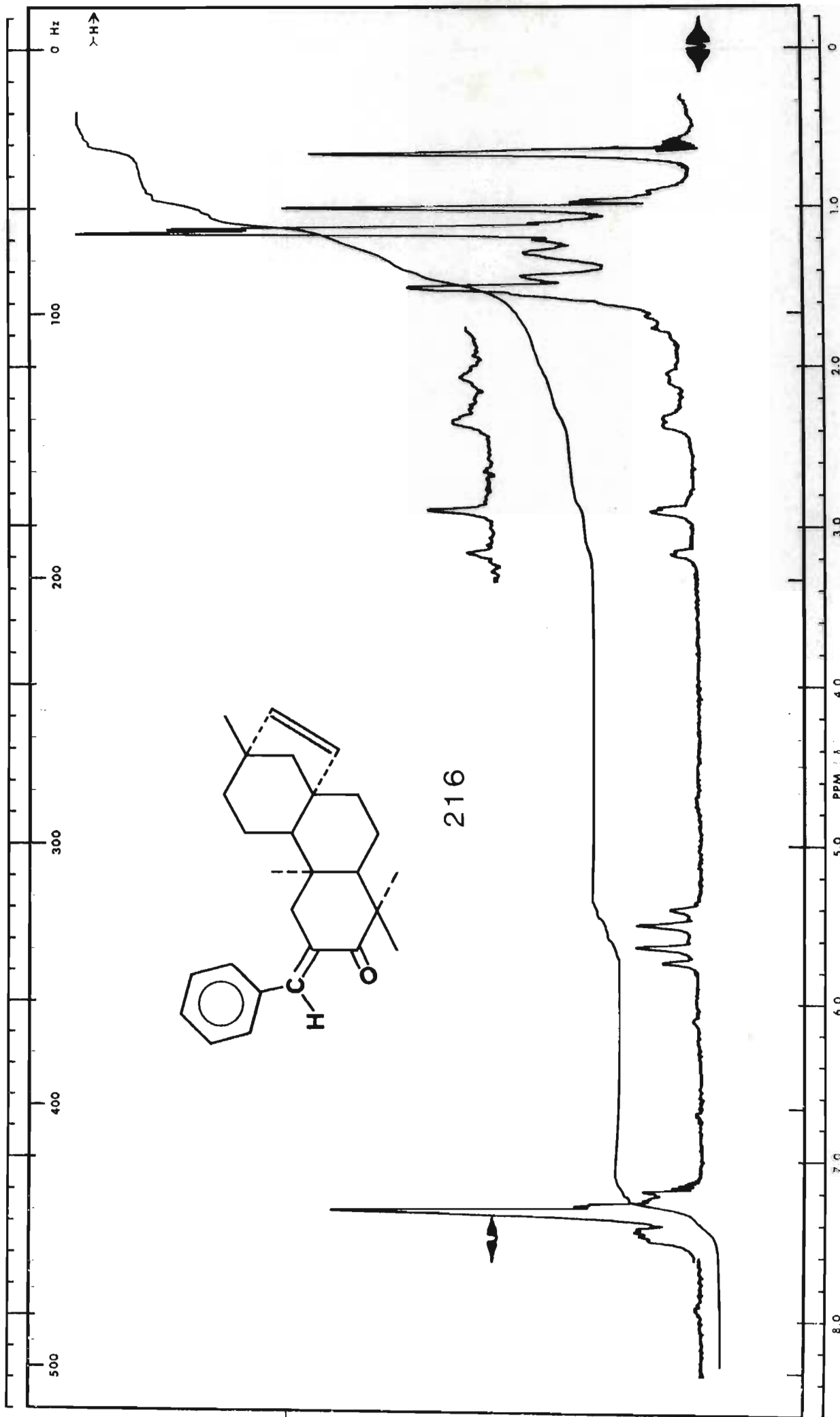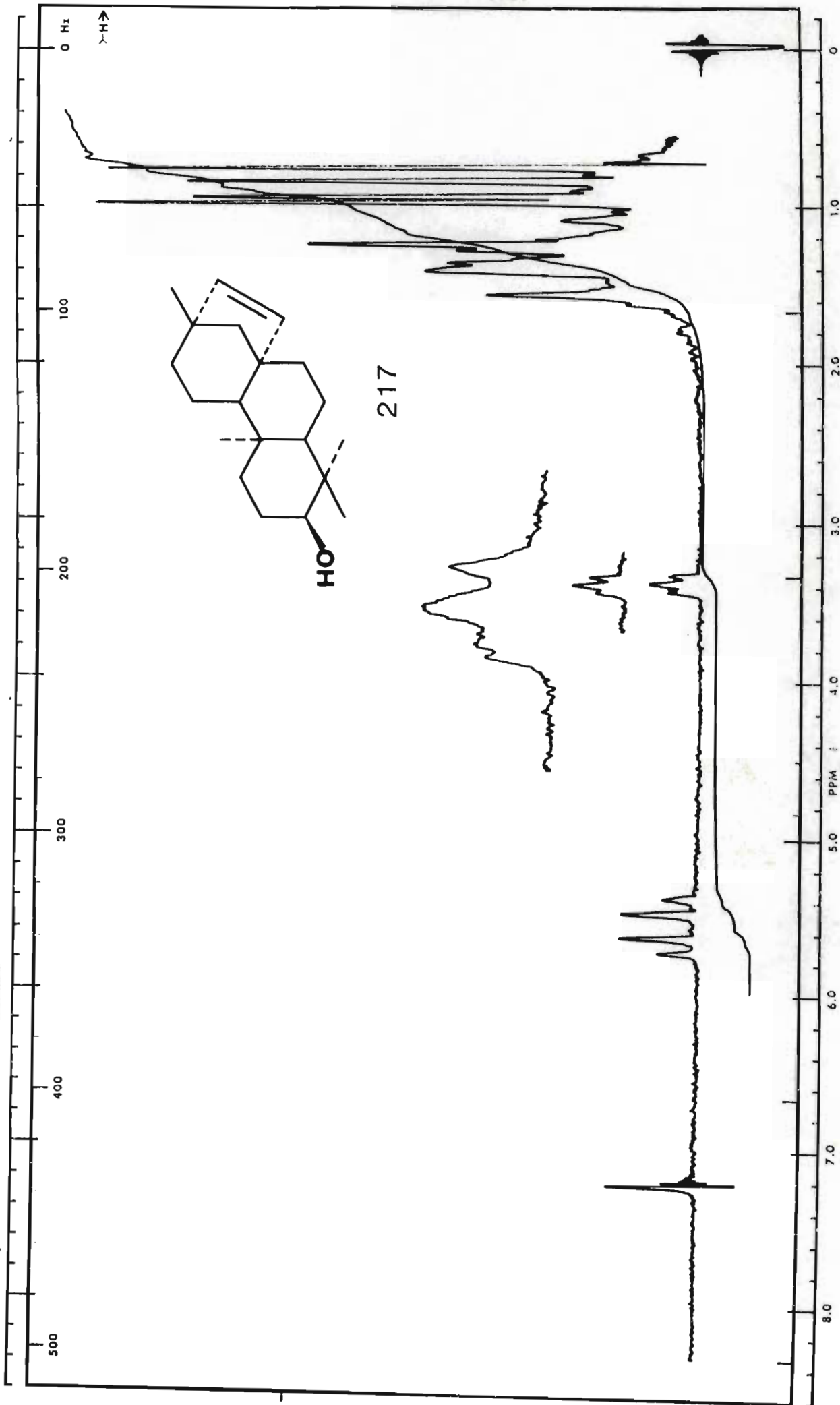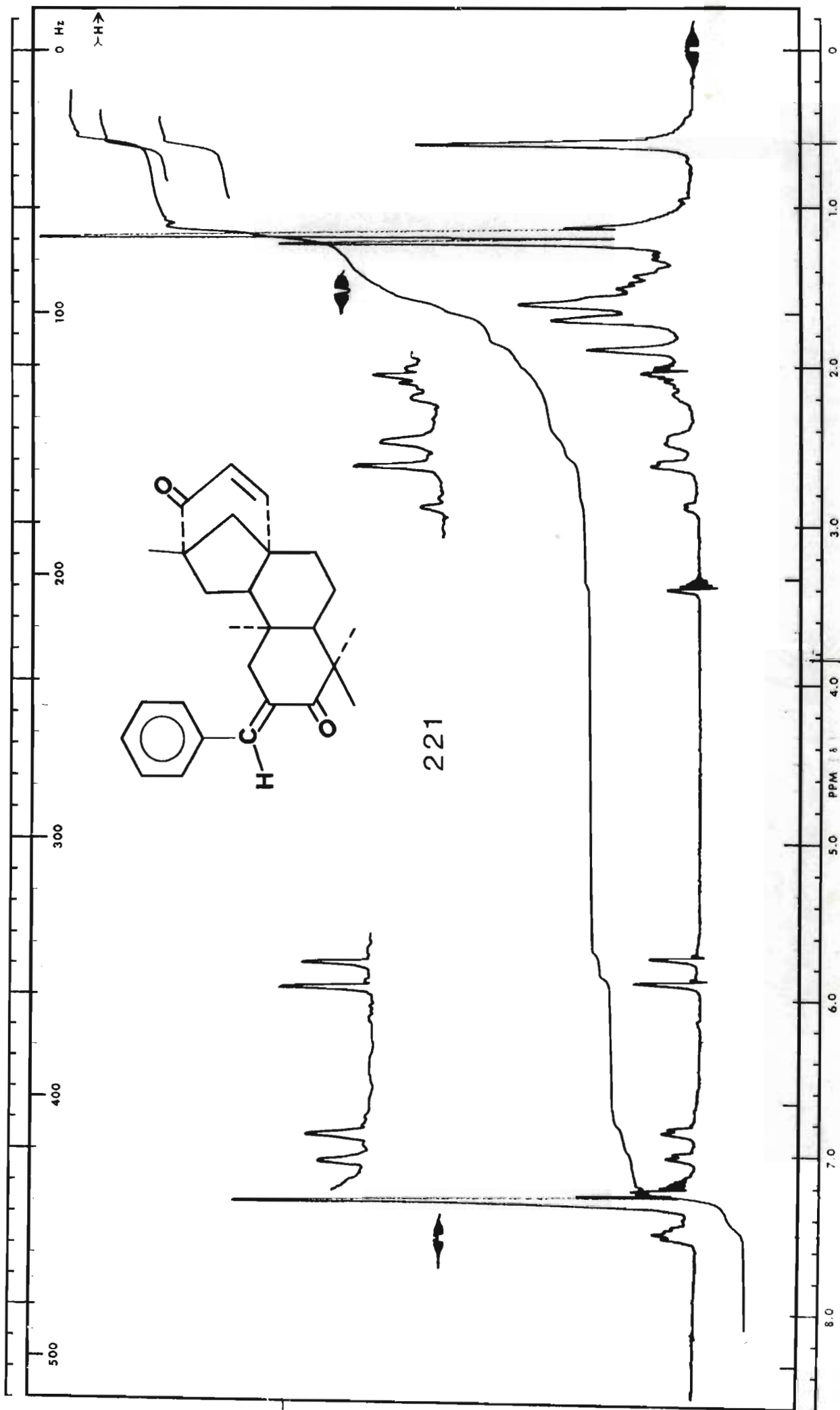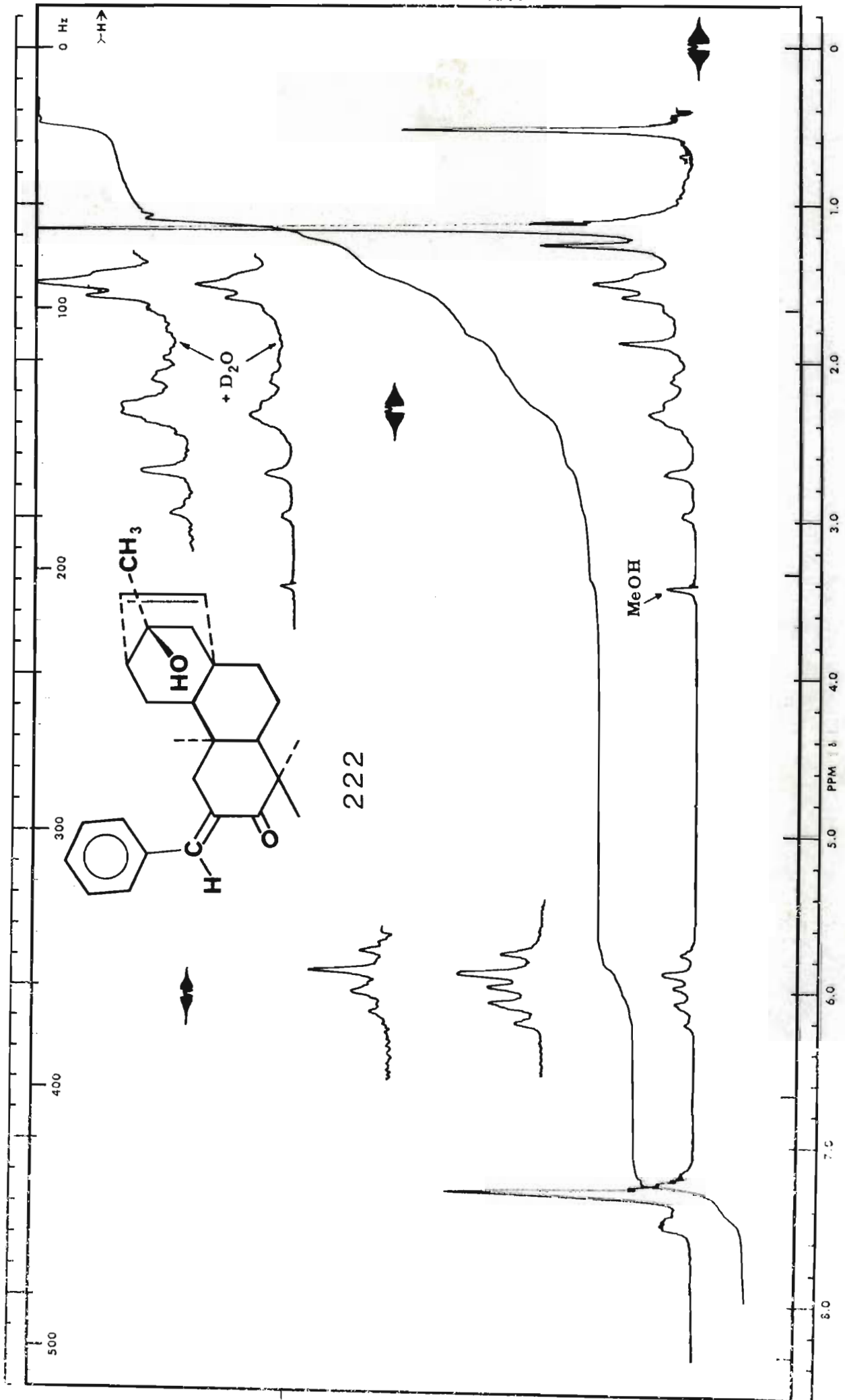
CHART S-6CT
MADE IN U.S.A.

CHART S-60T
MADE IN U.S.A.

224

225

CHART S-60T
MADE IN U.S.A.

226

386.



CHART S-60T
MADE IN U.S.A.

227

+ D₂O

offset 200 Hz

CHART S-60T
MADE IN U.S.A.

230

+D₂O

388.

CHART S-60T
MADE IN U.S.A.

231

CHART S-60T
MADE IN U.S.A.



232

235

## THE INFRARED SPECTRA

(in order of compound numbers)

1

8

393.

33

36

84

396.



92

96

97

400.



126

142

402.



147

200

400 cm$^{-1}$

404.



205

221

406.

223

227

408.
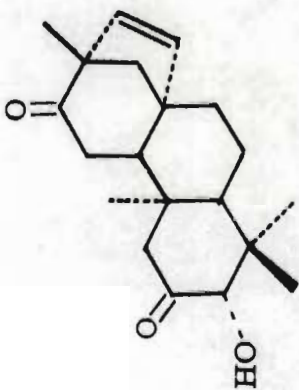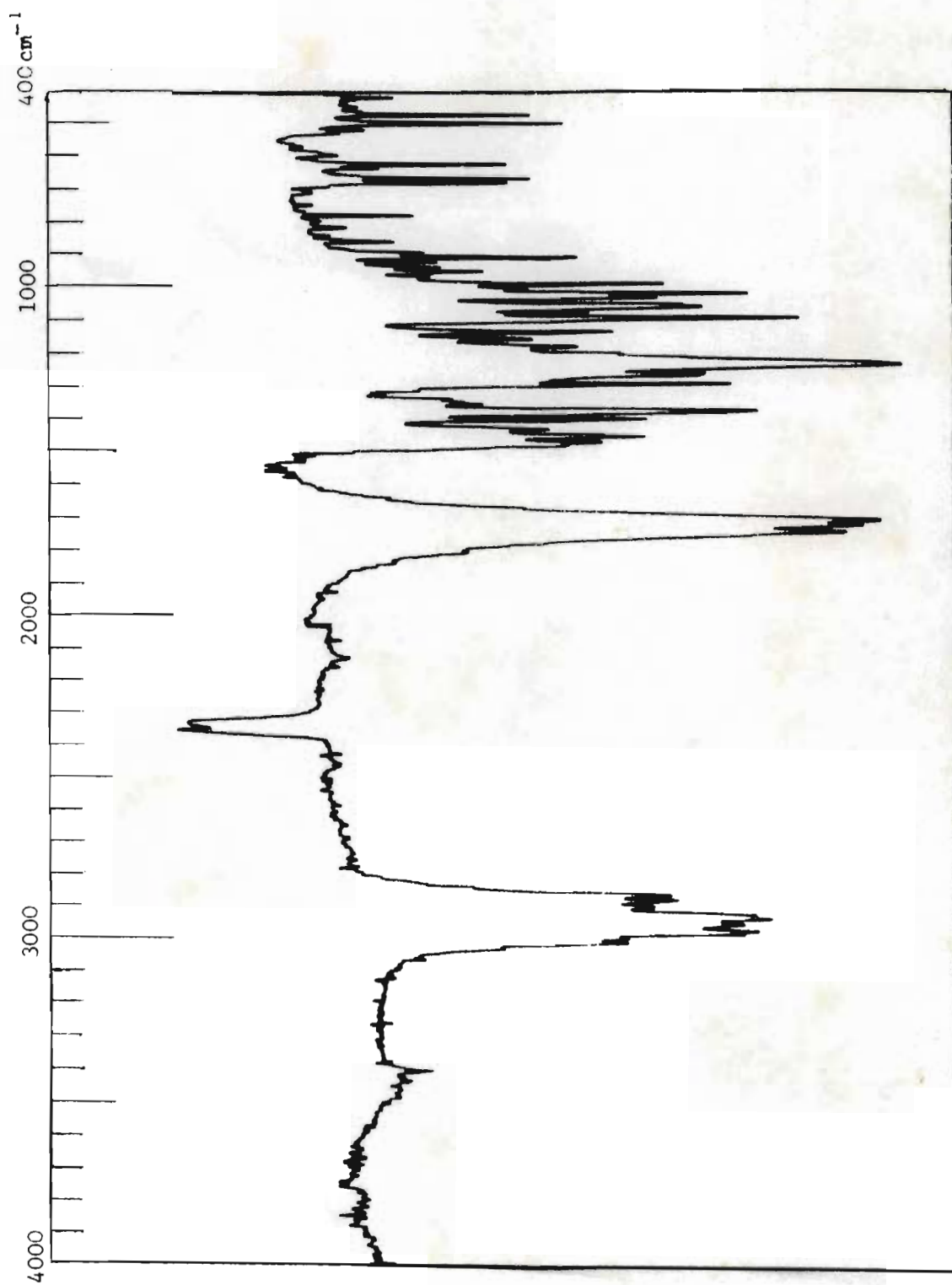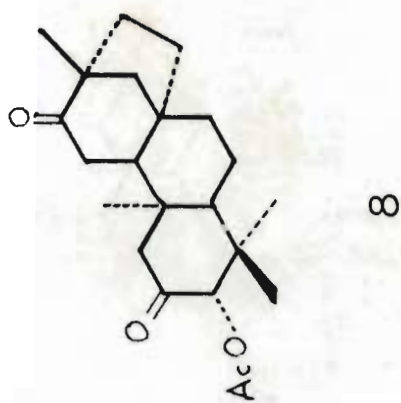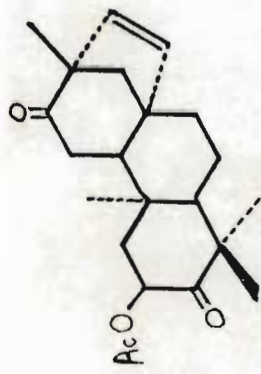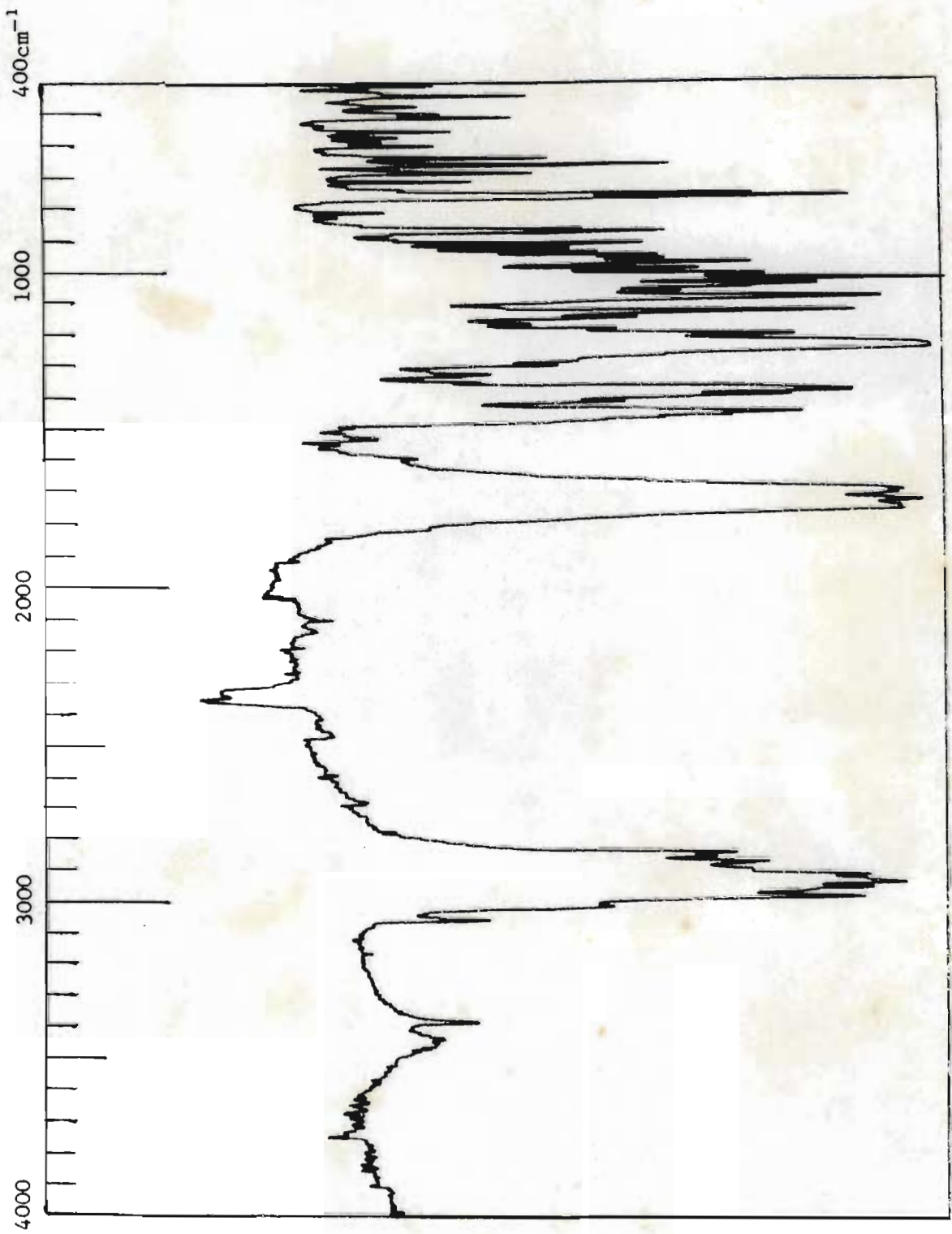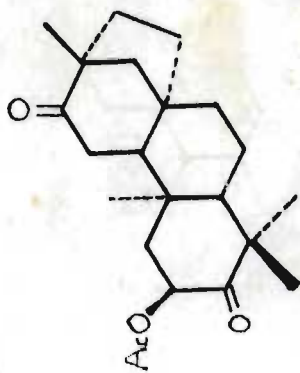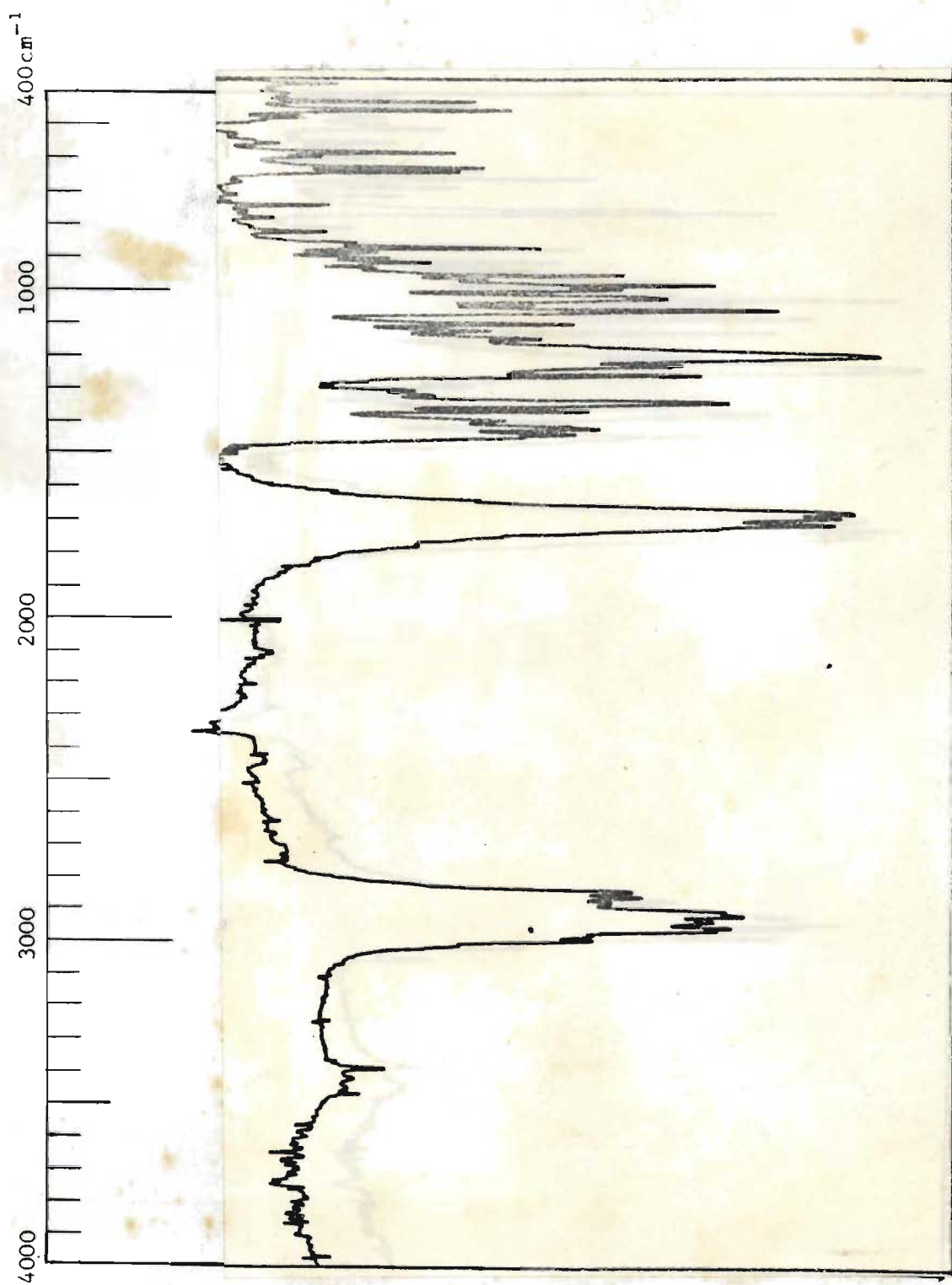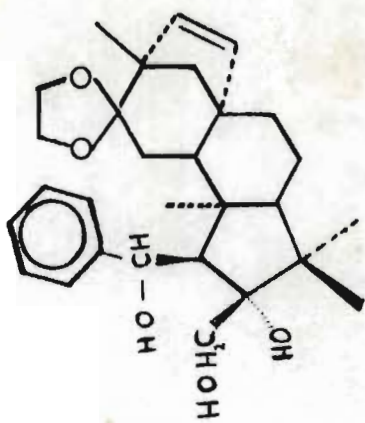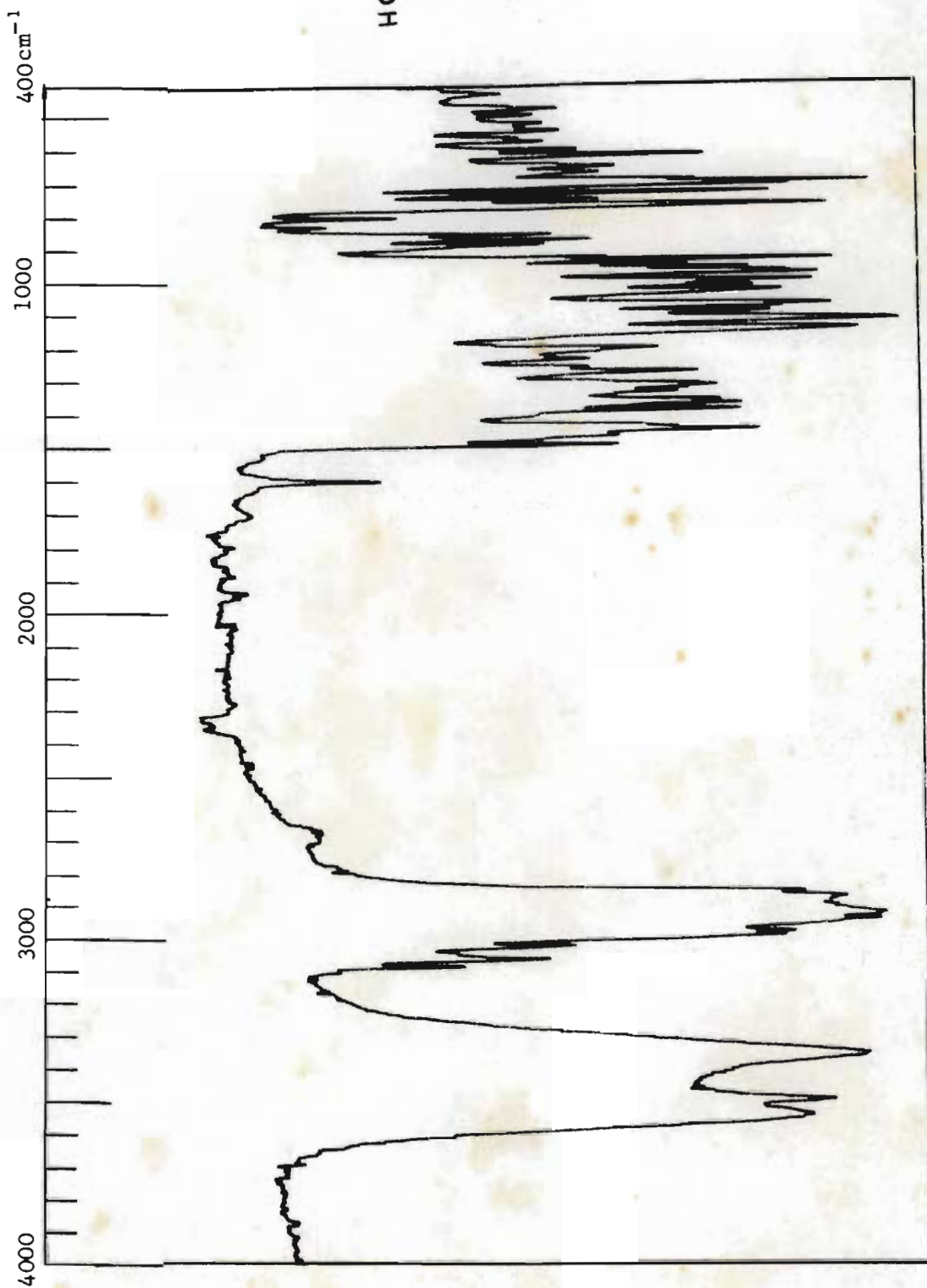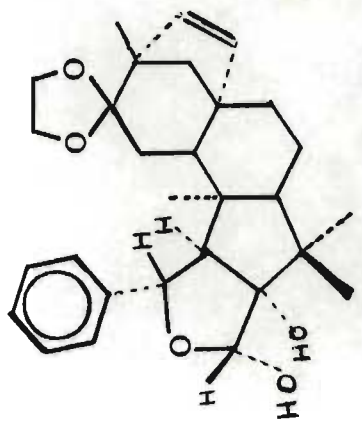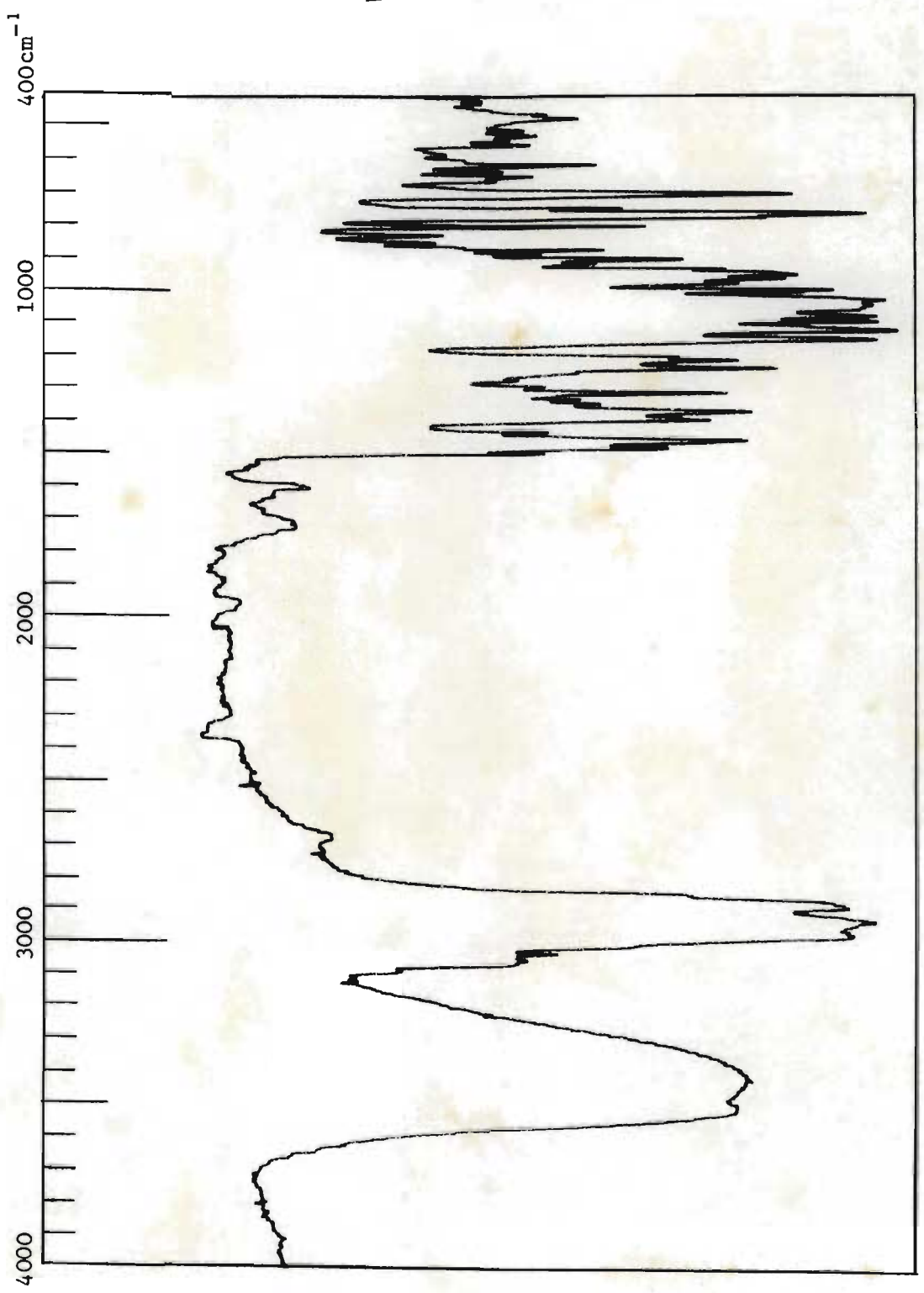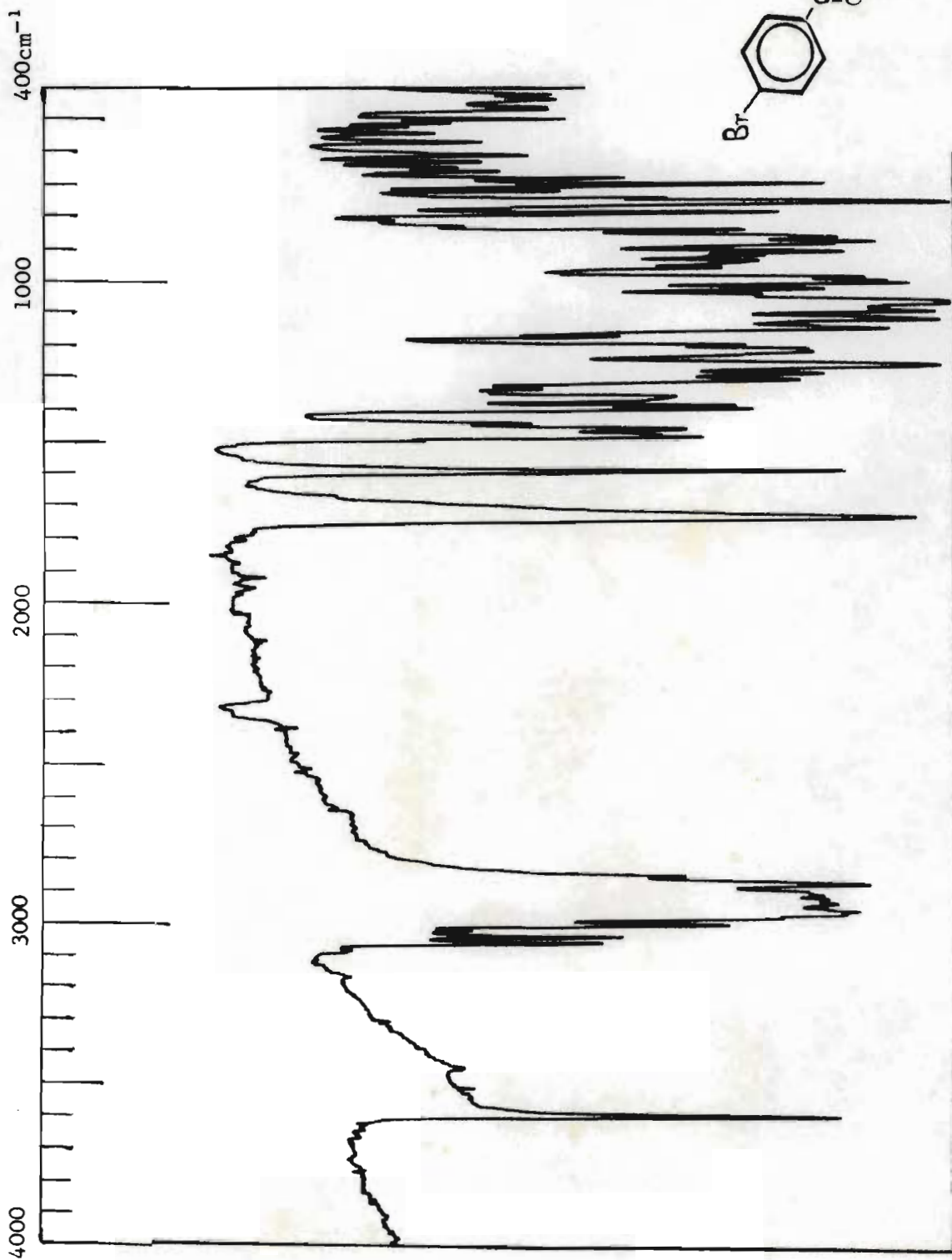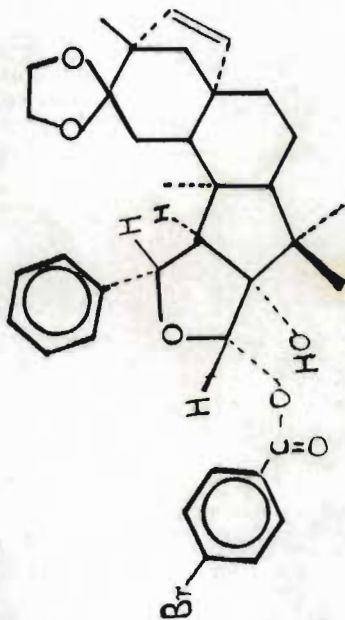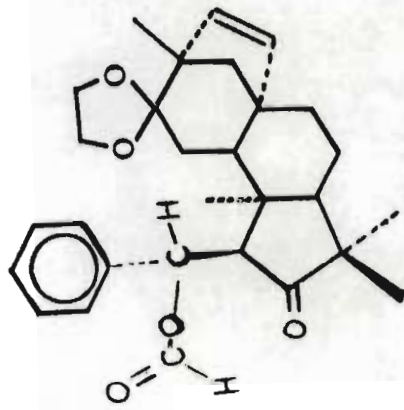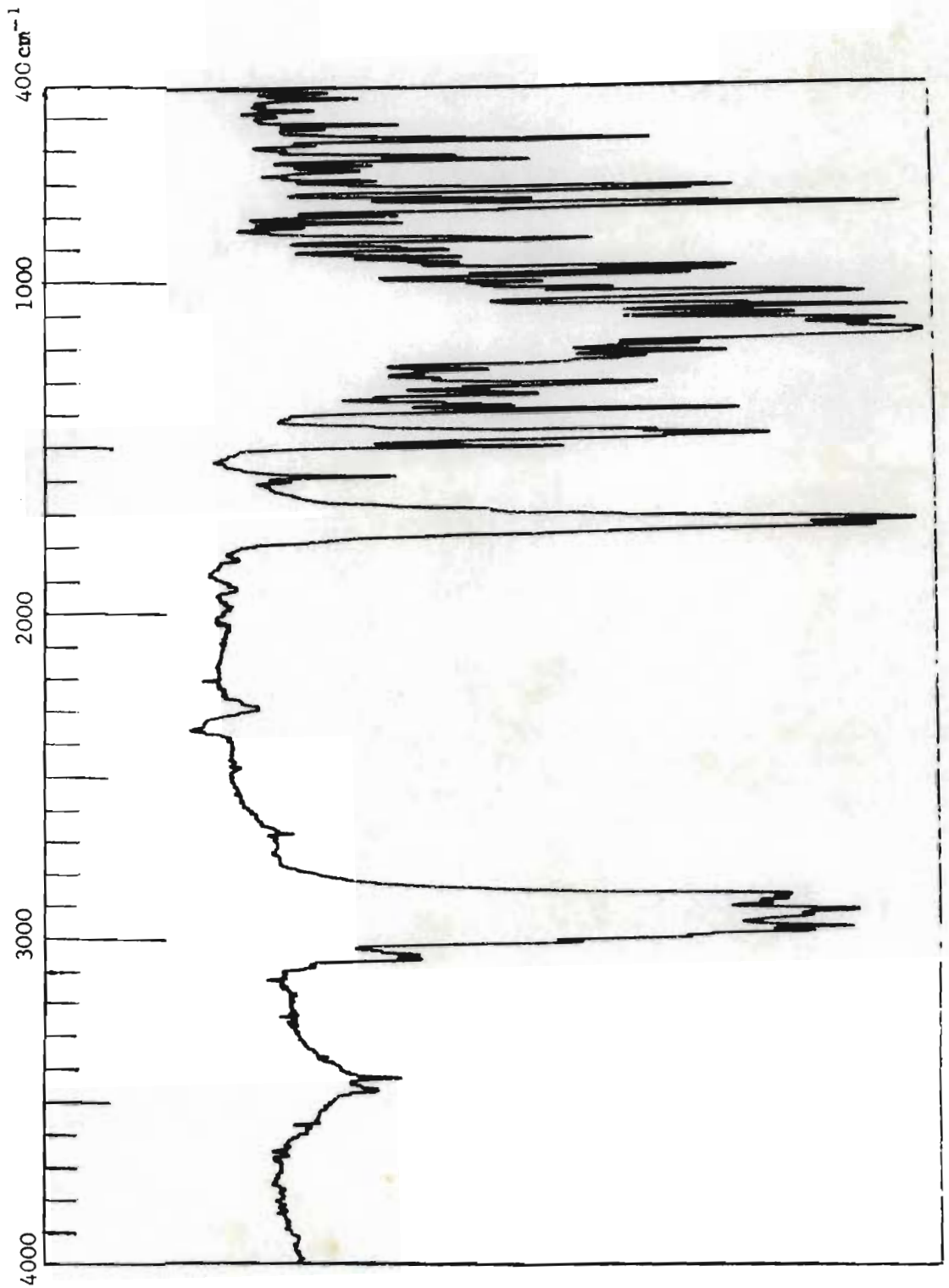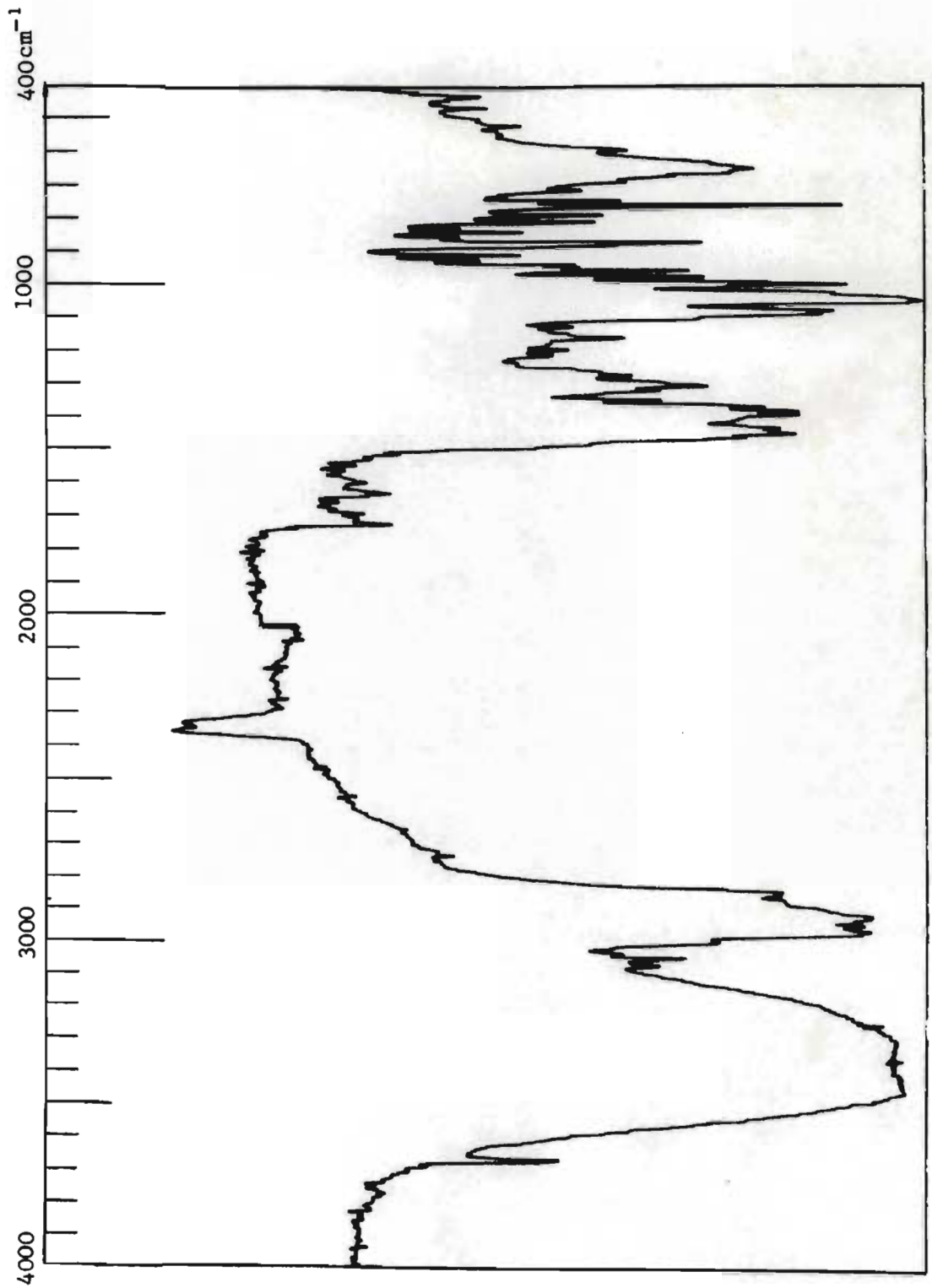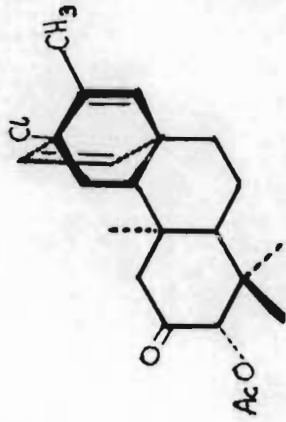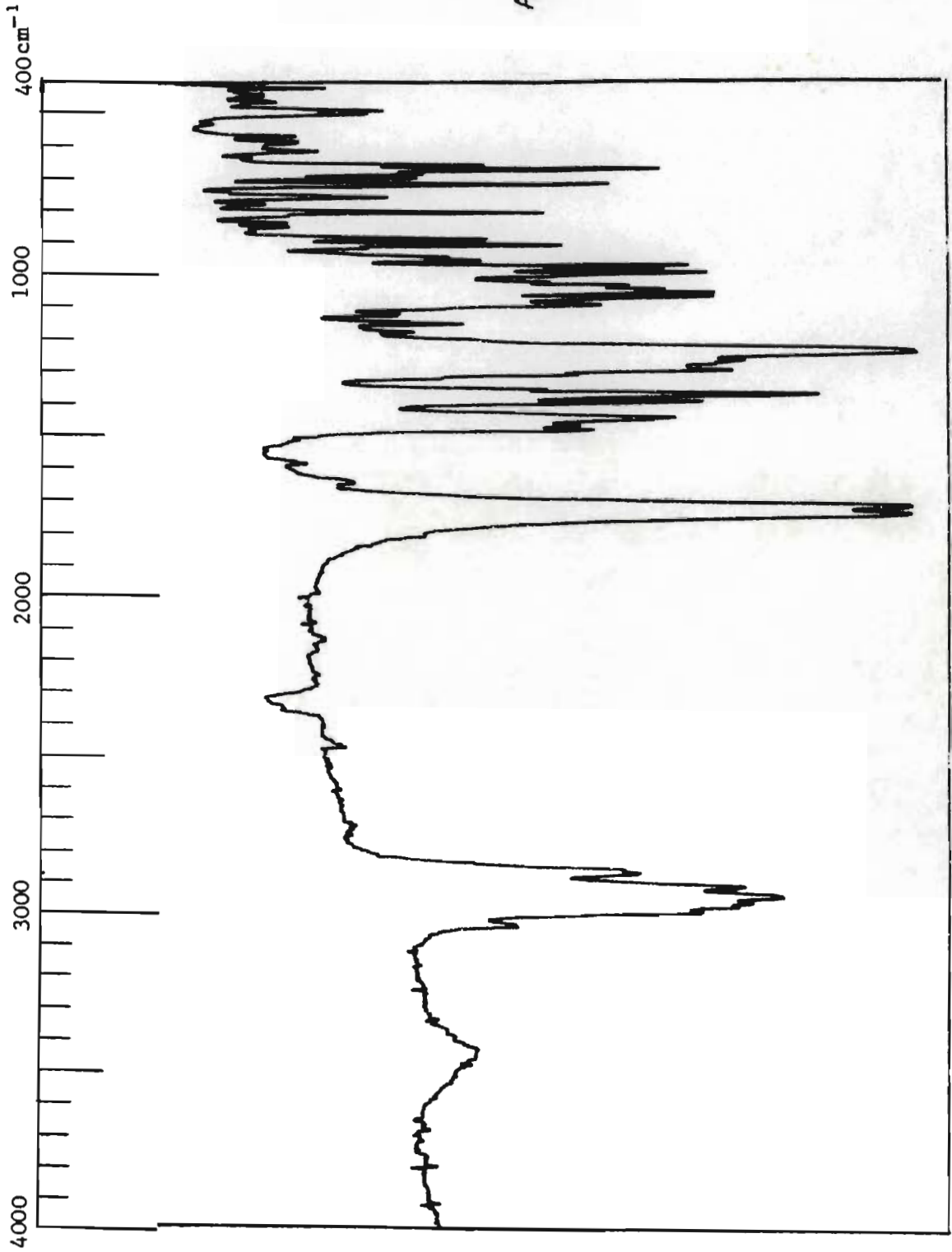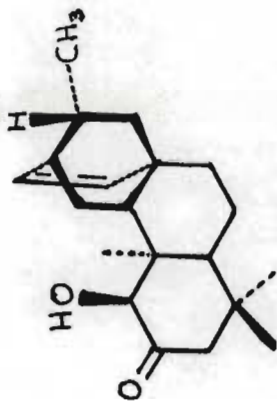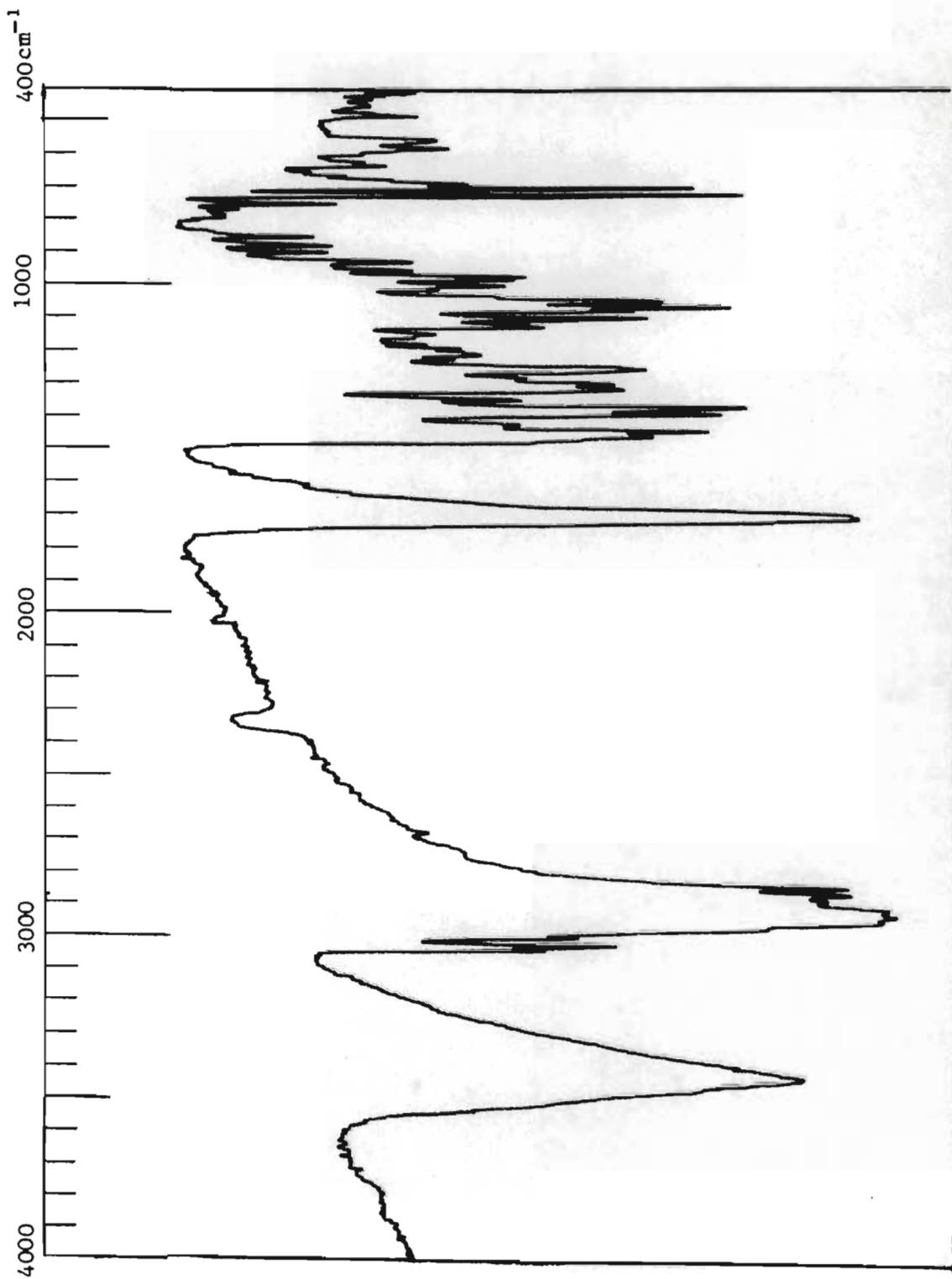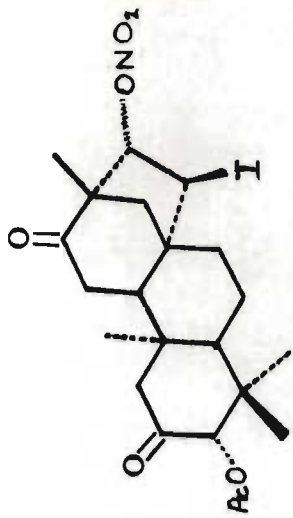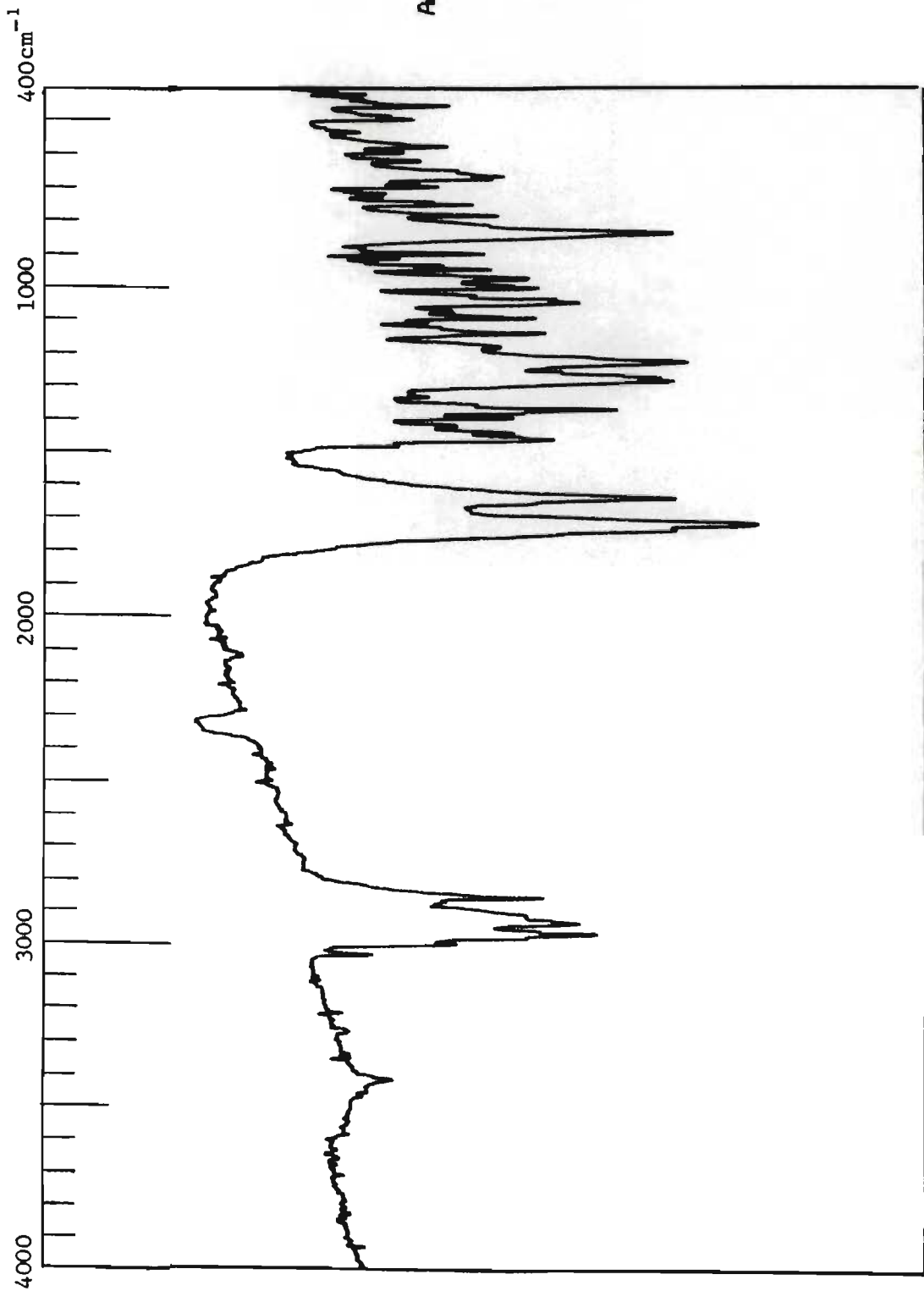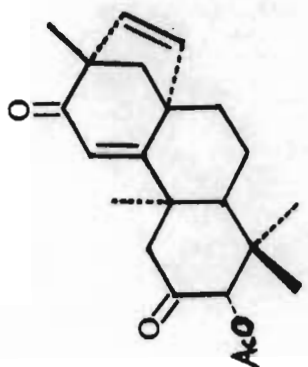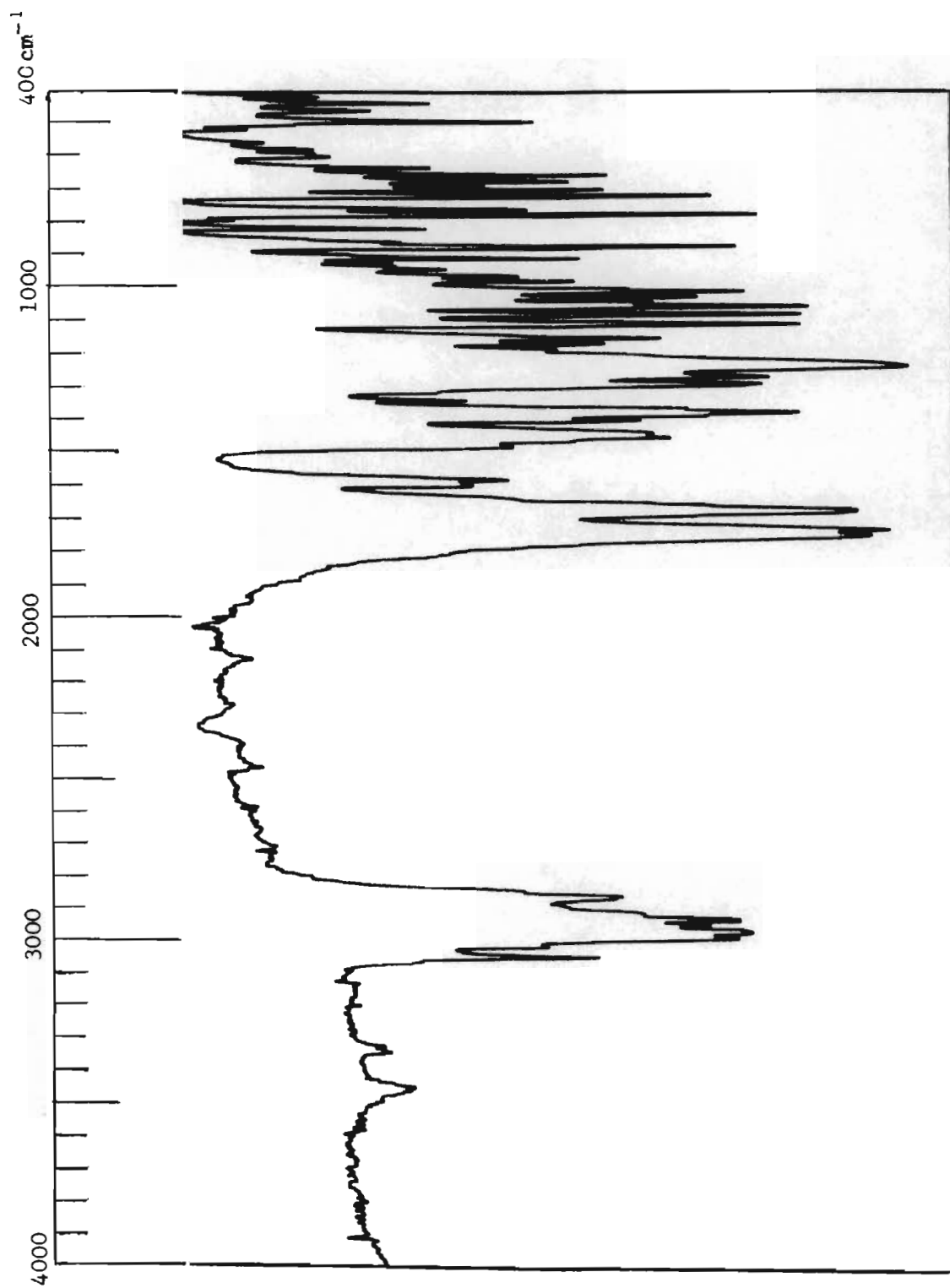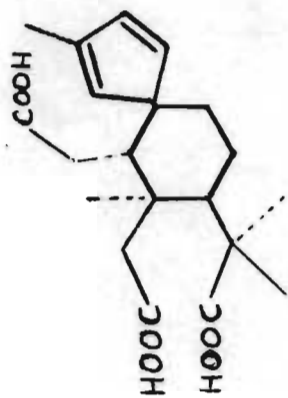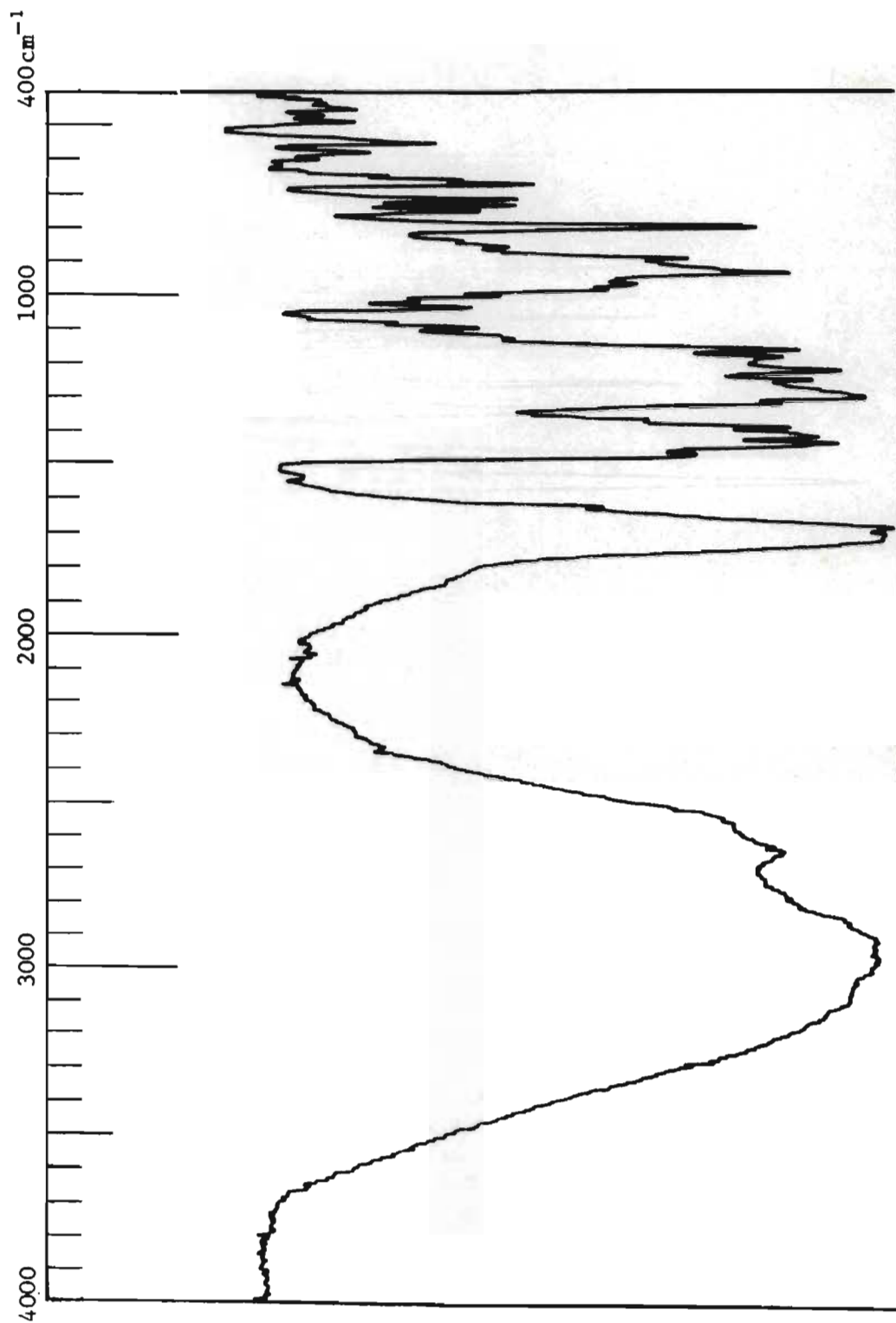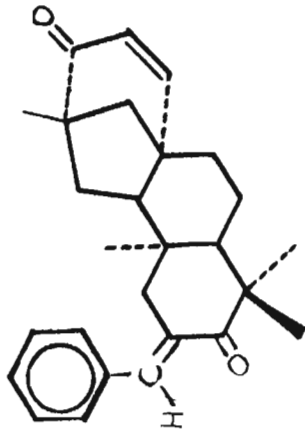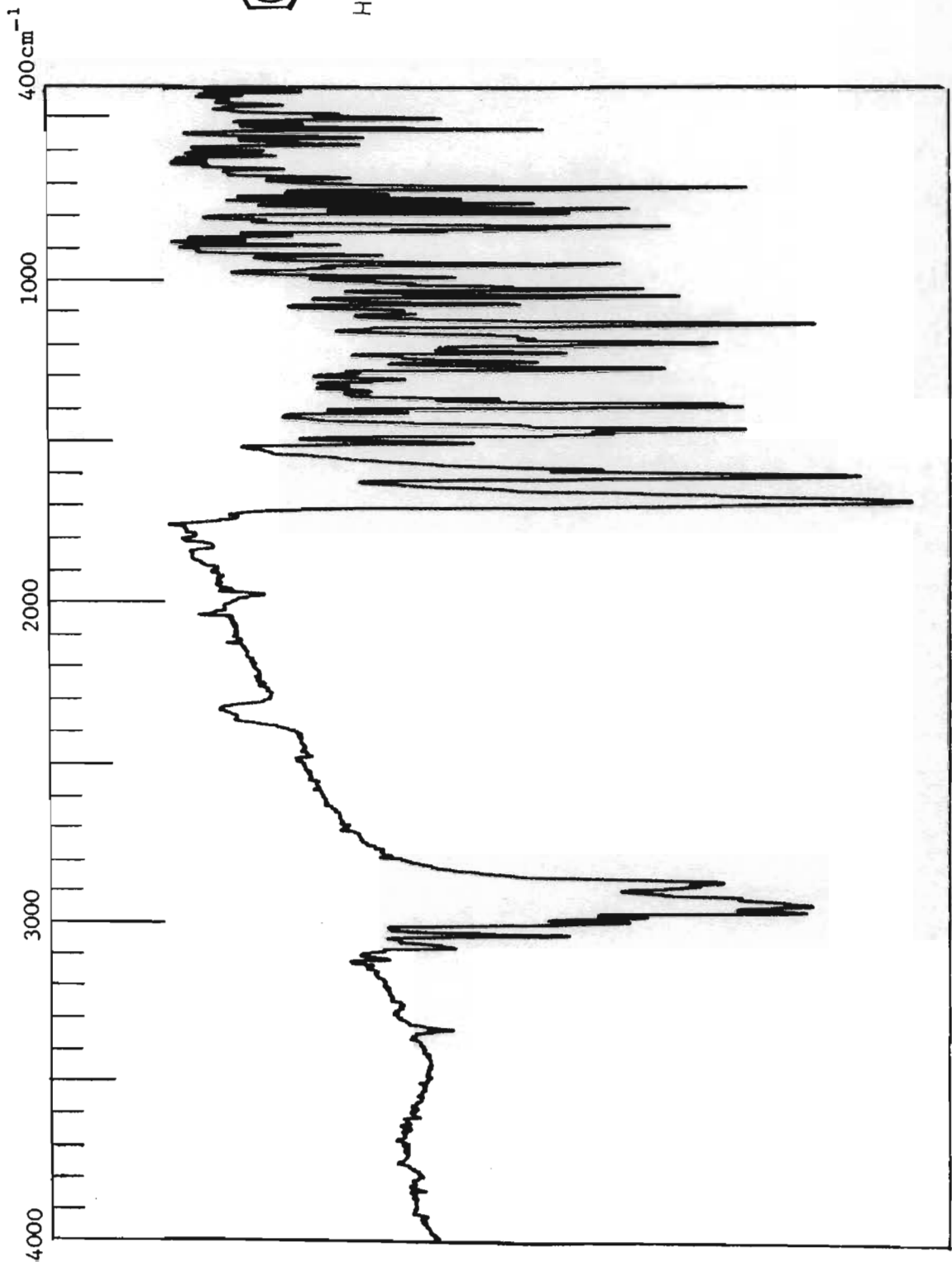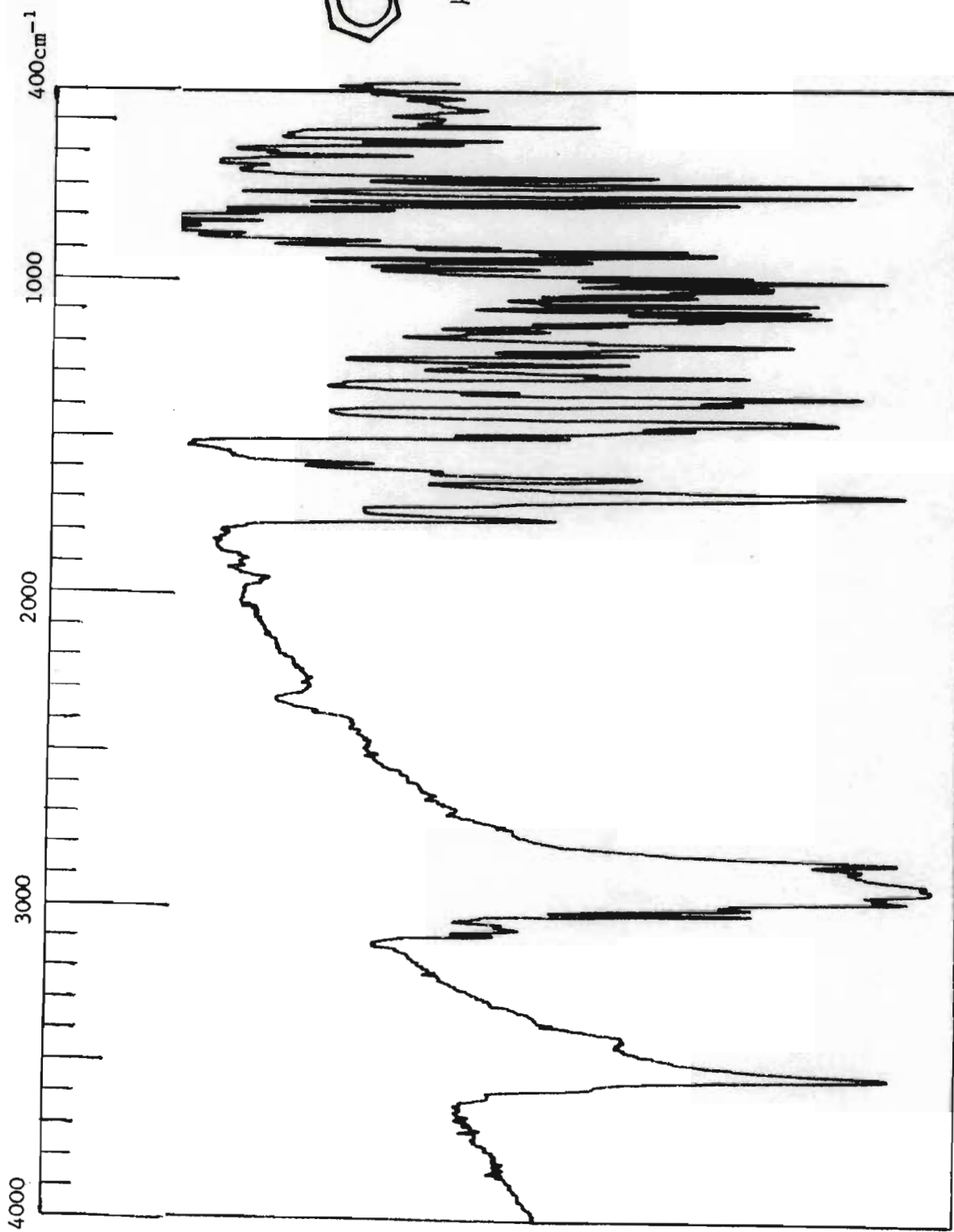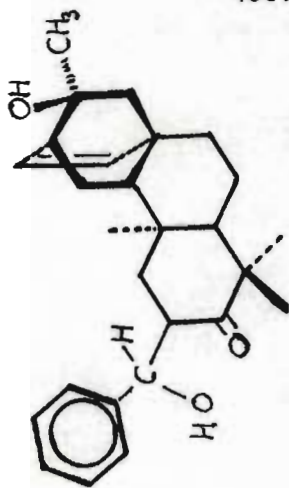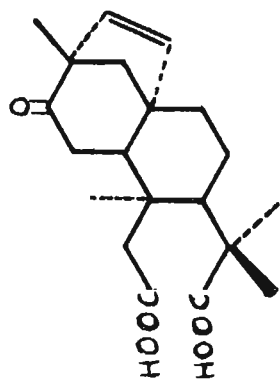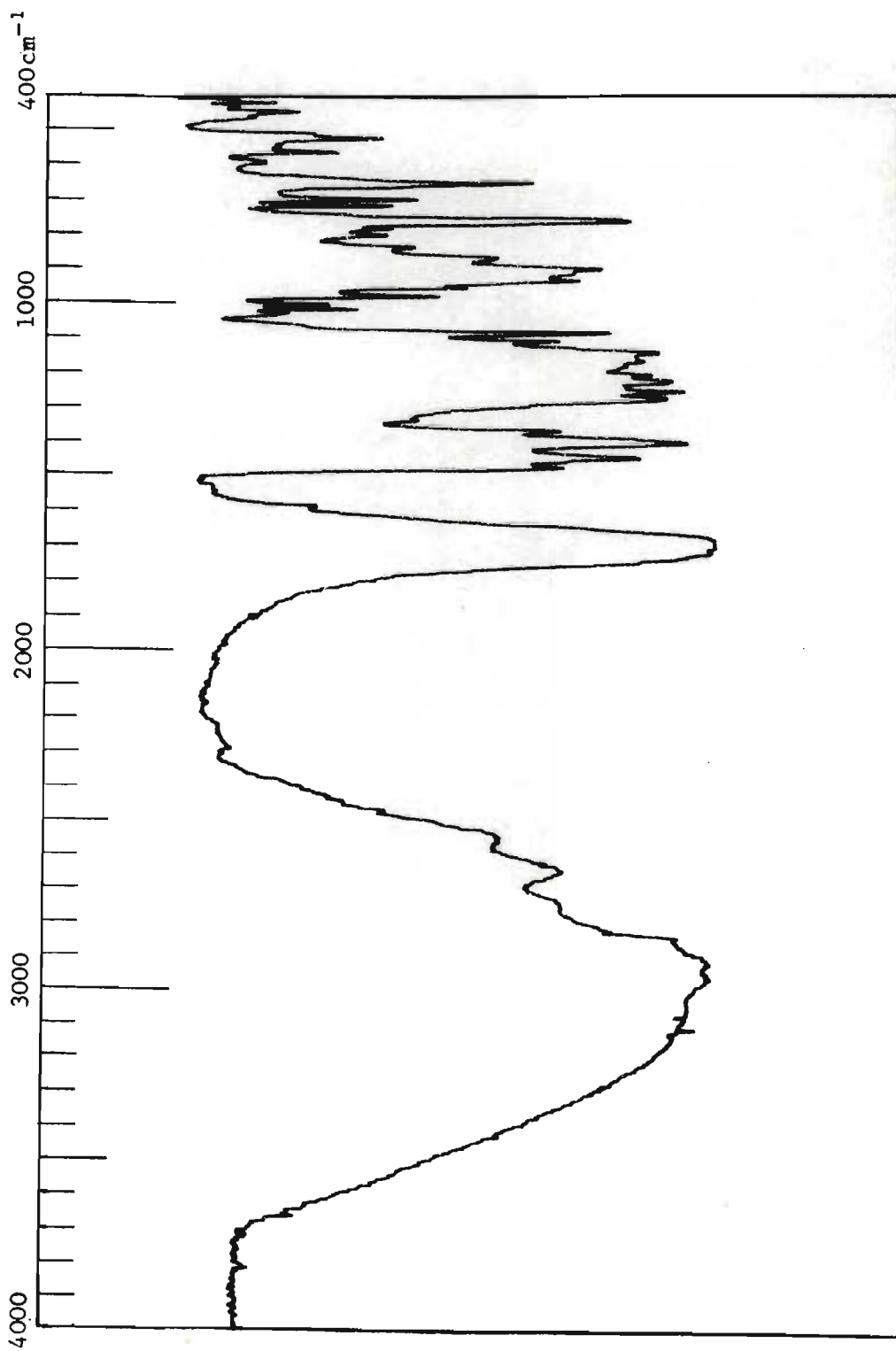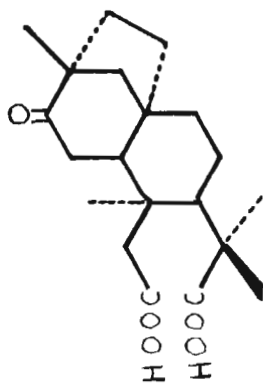


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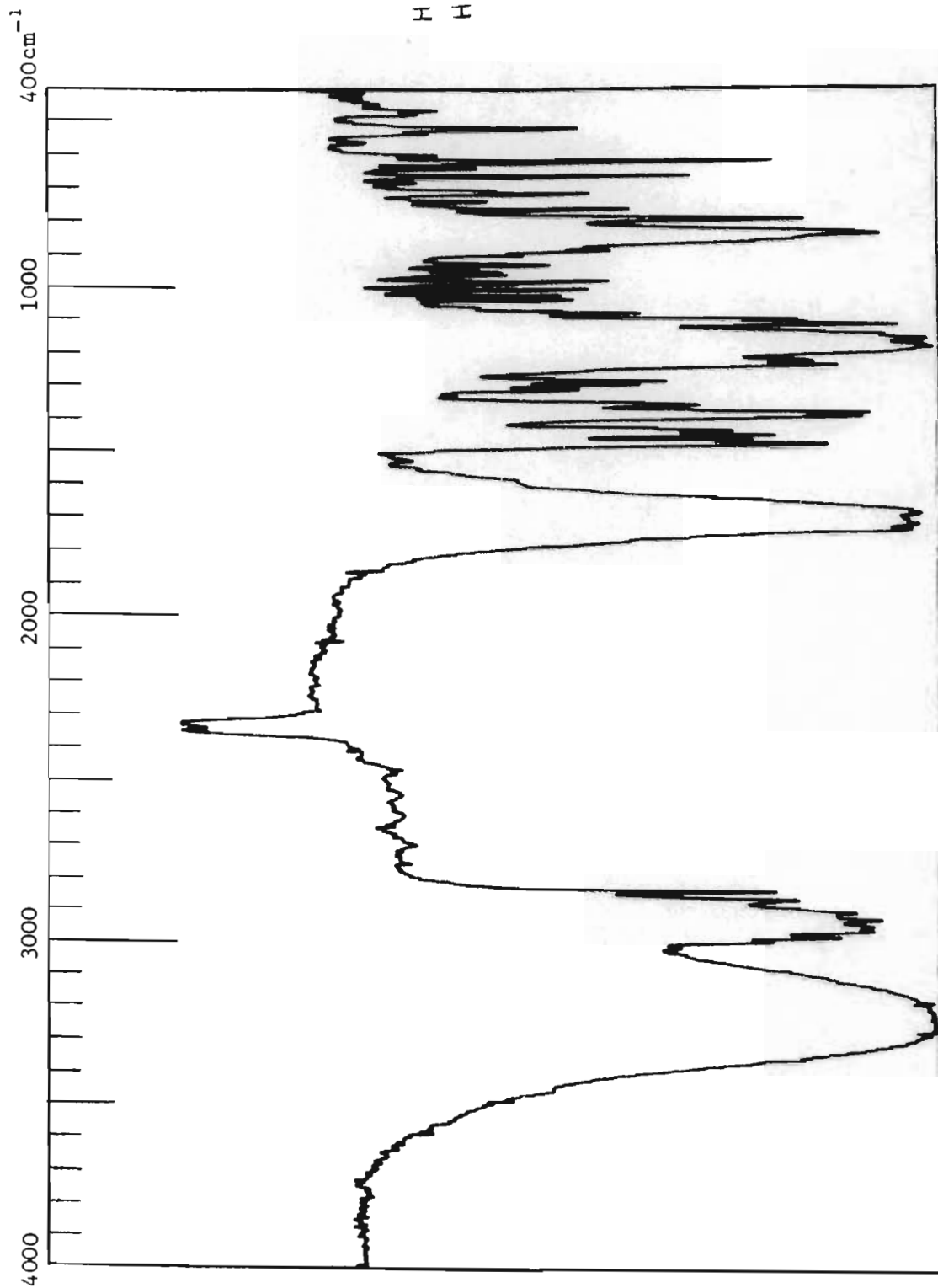
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