STRUCTURAL AND N M R STUDIES OF POLYISOPRENOIDS AND RELATED COMPOUNDS

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			Page
CHAPTER I:	SOLVENT SHIFTS IN CYCLC THERS AND OTHER HETEROCYCLIC OMPOUNDS		1 - 48
	Introduction	...	1
	Present Work	…	3
	Experimental	…	33
	References	…	46
CHAPTER II:	LONG RANGE SHIELDING BY AN ALKYL		49 - 117
	Introduction		49
	Present Work	...	53
	Experimental	...	98
	References	…	115
CHAPTER III:	THE CONFORMATION OF PRIMARY HYDROXYL GROUPS IN TERPWNOIDS		118 - 167
	Introduction		118
	Present Work	…	120
	Experimental	…	151
	References	…	166
		…	
CHAPTER IV:	THE CONFORMATION OF ESTERS , ACIDS AND ALDEHYDES IN TERPENOIDS		168 - 211
	Introduction	…	168
	Present Work	…	171
	Experimental	…	204
	References	…	210
	SUMMARY	…	215
			216

CHAPTER I

SOLVENT SHIFTS IN CYCLIC ETHERS AND OTHER HETEROCYCLIC COMPOUNDS

INTRODUCTION

COMPUTERISED

In the last few years it has been shown that proton resonances in NMR spectra are shifted if a change in the solvent is made[1,2,3]. These shifts though occurring in the case of almost all solvents, have special significance only when one of the solvents is aromatic in nature.

The most widely studied of these solvents is benzene and the shifts observed in benzene relative to those in carbon tetrachloride or deuterio-chloroform can be used in structural, stereochemical and conformational problems[1-34]. Among the compounds whose solvent shifts are very thoroughly investigated are the ketones[4,6,8], in which cyclic ketones predominate.

In six membered cyclic ketones it has been found[6,8] that the shift of an adjacent methyl group in benzene relative to that in deuterio-chloroform has a maximum value of $\sim$ +18 to +20 cps when it is axial and has a slightly negative or zero value when it is equatorial.

An empirical rule in the case of the ketones has been proposed[6,8]. This rule states that if a plane is drawn perpendicular to the carbonyl group and passing through the carbon atom of the carbonyl group then those groups which lie on the same side of the plane as the oxygen atom, are deshielded in benzene, whereas those on the other side are shielded. The groups lying near the plane suffer very small effects.

This solvent shift is associated with the formation of 1:1 benzene-ketone complex. Several studies[1,2,3,6,8,32] regarding its mechanism have been made.

It has been recently observed[26] that these solvent induced shifts are positive in the case of lactones for both equatorial and axial methyl substituents, the axial methyl group having more positive value. Thus in the case of γ-lactones the values are 27 ± 3 cps when the methyl group is quasi-axial and 14 ± 3 [illegible] it is quasi-equatorial. Similar results have also been obtained in the case of δ-lactones[26]. In extending the ideas regarding the carbonyl group these results appeared anamolous particularly in the case of compounds with an equatorial methyl substituent, as this methyl group lies very close to the reference plane.

To ascertain whether this behaviour of lactones can be accounted for by ascribing a positive contribution from the ether oxygen atom of the lactone in case of both axially and equatorially substituted methyl groups, a few known and new rigid cyclic ethers having no interfering substituents were prepared. The spectra of these compounds have been examined in deuterio-chloroform and benzene. The results obtained go to show that the ether oxygen also influences the line position on passing from deuterio-chloroform to benzene as a solvent.

PRESENT WORK

Before discussing the solvent induced shifts in the NMR spectra of different ethers, the mode of preparation of some of the ethers is presented.

PREPARATION OF OXIDES:

Oxide VII

α-Santonin (I) has been converted to the oxide VII, by the sequence of reactions outlined in Chart 1. In the known sequence[36] the diol VI was cyclised by refluxing in benzene with p-toluene-sulphonic acid. As the yields obtained were rather low and the purity of the product was not satisfactory a better cyclisation procedure had to be devised. The use of p-toluene sulphonyl chloride in pyridine had been used for cyclisation of an analogous compound[36] (C_3 keto derivative of VI). With this reagent a clean product in good yield was obtained. Characterisation of the oxide (VII) was possible by comparison of the physical properties with those reported earlier. The characterisation was aided by an examination of I.R. spectrum (no hydroxyl absorption) which had a moderate absorption at 1036 cm^{-1} assignable to the ether linkage. The NMR spectrum (see spectral section) confirmed its structure.

The oxide XIV

Starting from β-santonin* (VIII) and following the same reaction scheme the deoxolactone XII had been prepared[35-37] (Chart 2)

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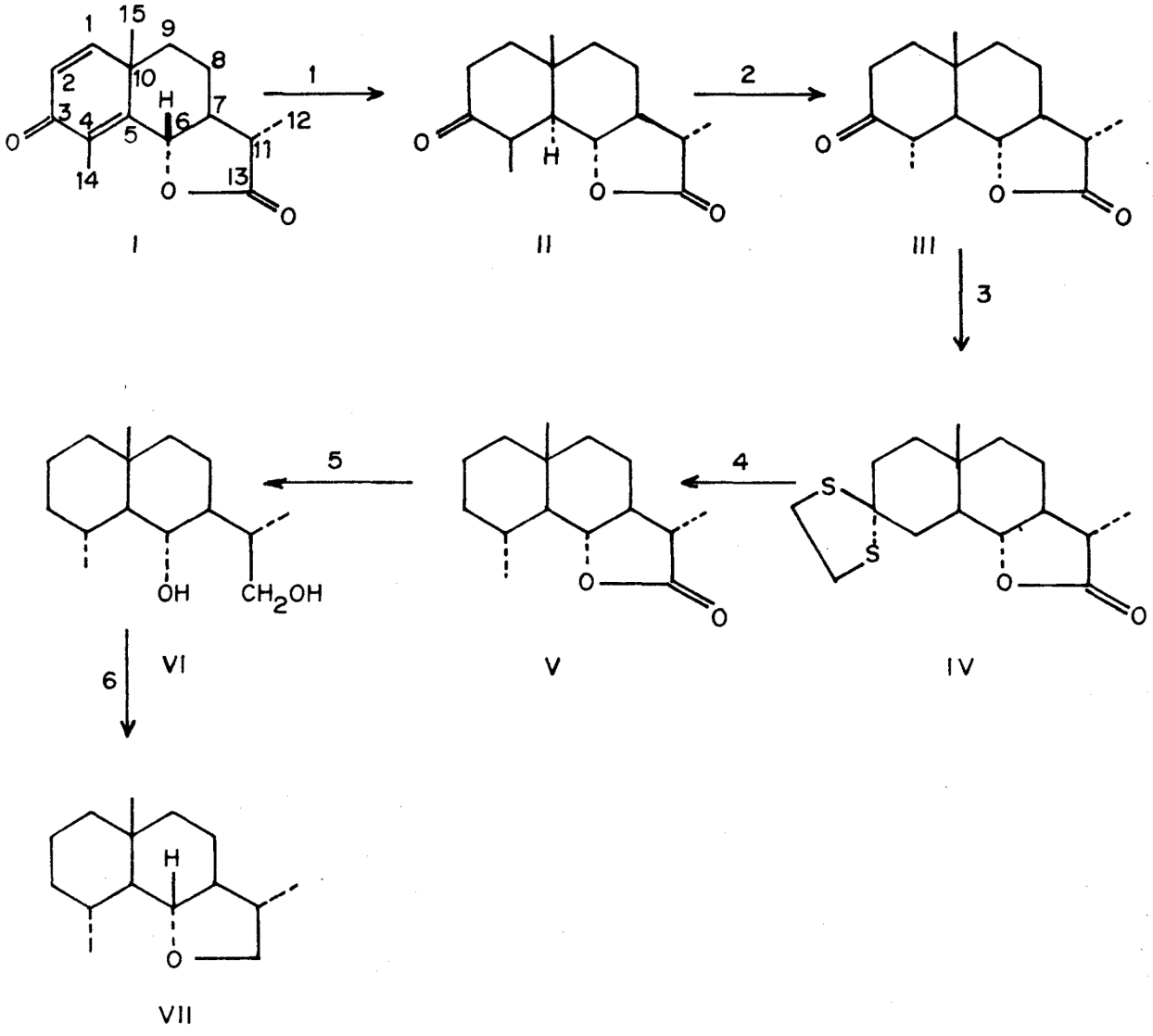
* We are thankful to Prof. W. Cocker for a generous gift of this sample.

CHART - I

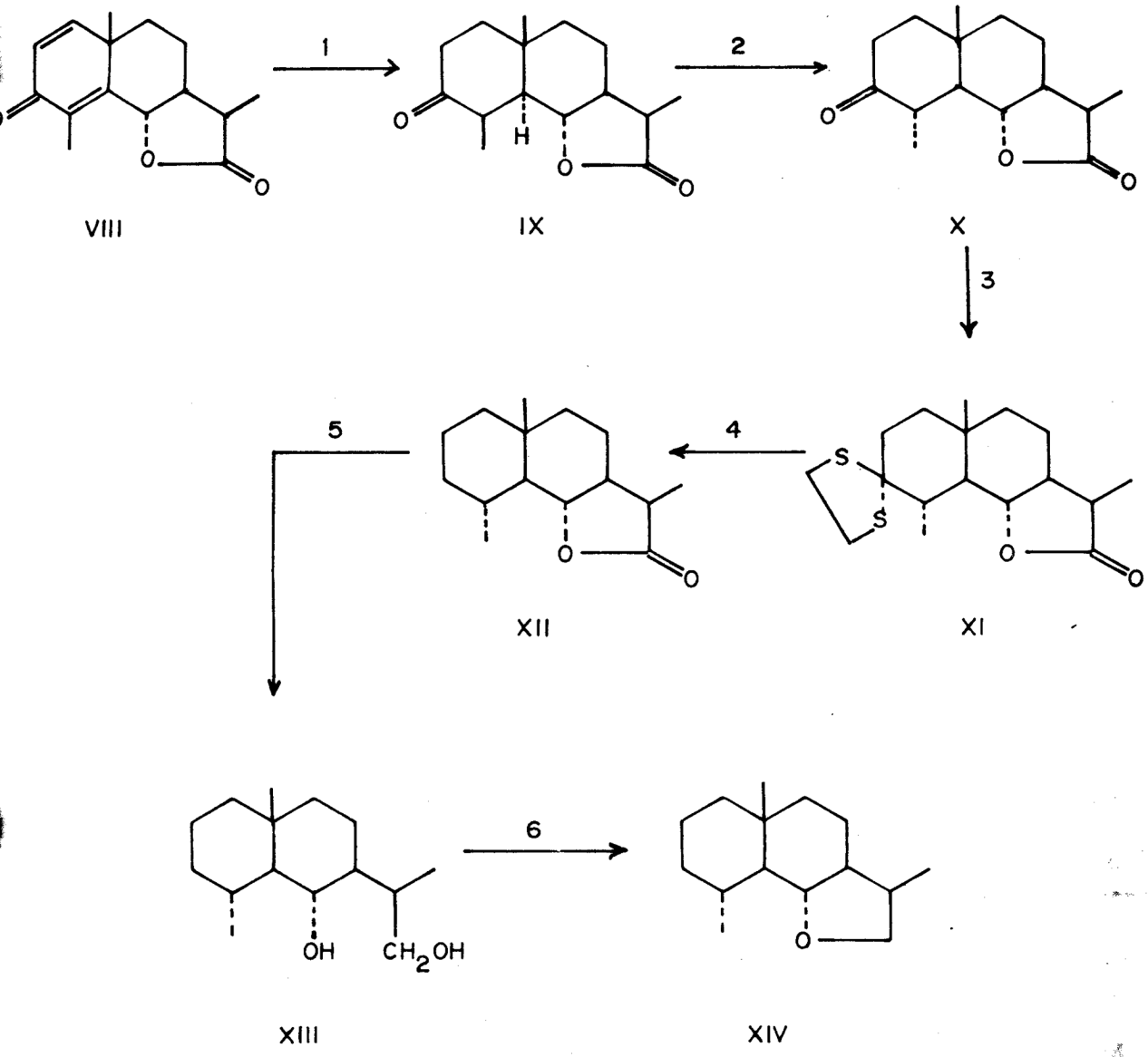
SYNTHESIS OF 5α(H),4,6,11β(H) EUDESMAN-6-13 OXIDE (VII)



1) $Pd/SrCO_3$-H_2/EtoAc
2) AcOH/p-toluene sulphonic acid
3) BF_3-Etherate-Ethanedithiol-AcOH
4) Raney Nickel-Dioxane
5) Lithium aluminium hydride
6) p-Toluene sulphonyl chloride/Pyridine.

CHART - 2

SYNTHESIS OF 5, 11 ∝ (H), 4,6 β (H) EUDESMAN-6-13-OXIDE (XIV)



VIII IX X XI XII XIII XIV

1) Pd/C - H_2/EtoAc
2) p-Toluene sulphonic acid/Acetic acid
3) BF_3-Etherate, ethanedithiol, AcOH
4) Raney nickel-Dioxan
5) Lithium aluminium hydride
6) p-Toluene sulphonyl chloride/Pyridine.

Reduction of the lactone provided the diol XIII, as a crystalline solid whose IR absorption at 3360 and absence of lactone absorption were sufficient evidence for its characterisation. Cyclisation using p-toluene sulphonyl chloride and pyridine afforded a mobile liquid (homogeneous by G.L.C. and T.L.C.) in excellent yield. The I.R. of this compound had no hydroxyl absorption and a strong absorption at 1025 cm^{-1} (oxide). Further confirmation of its structure was provided by the NMR spectrum, the analysis of which is summarised in Table 1.

Table 1

Line position	Nature	No. of protons	Assignment
249.5	q, J = 9 and 7	1	$C_6\beta$-H
199.5	q, J = 10 and 3.5	2	C_{13}-H_2
59, 65	d, J = 6	3	C_4-CH_3
61, 67	d, J = 6	3	C_{11}-CH_3
61	s	3	C_{10}-CH_3

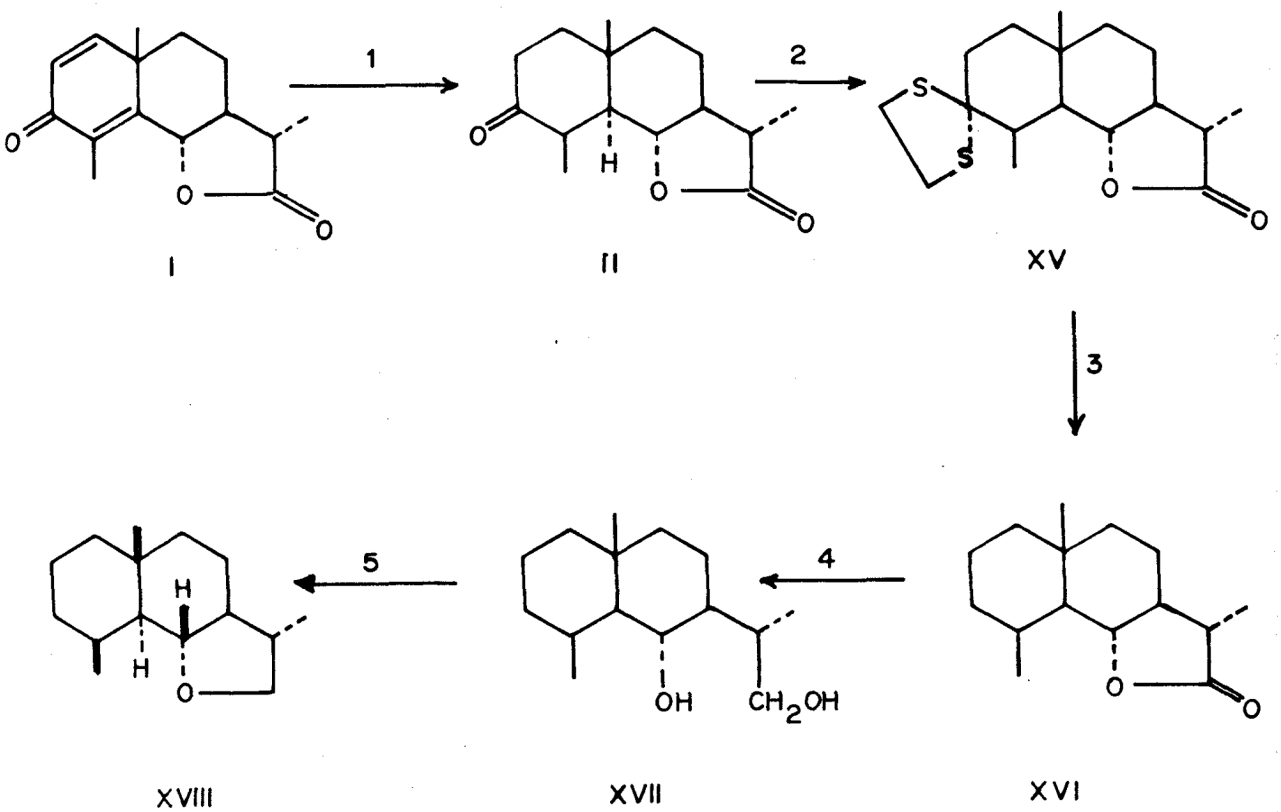
s = singlet, d = doublet, q = quartet

The oxide (XVIII)

This oxide, epimeric with VII at C-4 was prepared from ∝-santonin (vide Chart 3). The conversion of ∝-santonin (I) to the diol XVII has been reported earlier[35,38]. Cyclisation of the diol by the usual method furnished the oxide whose physical properties differed from those of the oxide prepared by lead tetra acetate cyclisation

CHART-3

SYNTHESIS OF 4,5α(H), 6, 11 β(H) – EUDESMAN-6-13 OXIDE (XVIII)



I II XV XVI XVII XVIII

1) $Pd/SrCO_3$ $-H_2$ / EtoAc
2) BF_3-Etherate, Ethanedithiol, AcOH
3) Raney nickel-Dioxane
4) Lithium aluminium hydride
5) p-Toluene sulphonyl chloride/Pyridine.

of an eudesmol derivative[39]. As the purity of the oxide prepared in the present investigation was carefully checked by both T.L.C. and G.L.C., it appears that the earlier prepared sample may not be homogeneous. The spectral proof of the structure (see later) ruled out any possibility of rearrangement during cyclisation.

The oxide XXV

By following the reaction sequence used in the earlier examples 6 epi-santonin (XIX) was converted through the known[40] deoxolactone (XXIII) into a diol (XXIV) characterised by its I.R. spectrum (absence of lactone and presence of hydroxyl absorption at 3300 cm^{-1}). The cyclised oxide obtained as a homogeneous (T.L.C., G.L.C.) mobile liquid was identified by its I.R. spectrum (1020 cm^{-1} oxide). Analysis of the NMR spectrum is presented in Table 2.

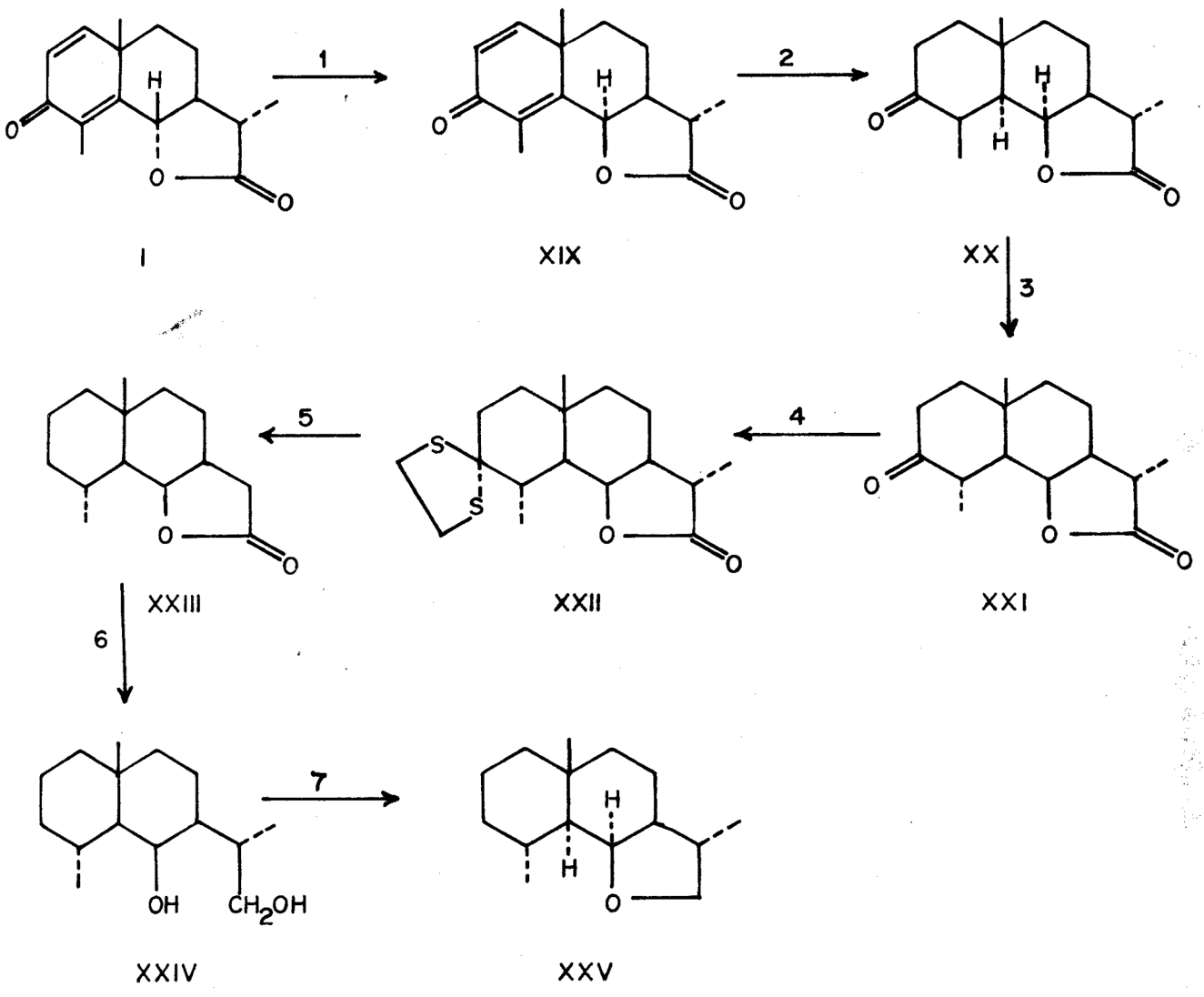
Table 2

Line position	Nature	No. of protons	Assignments
241	t, J = 3.5	1	C_6-α-H
197	q, J = 9 and 3.5	1	C_{13}-β-H
249	q, J = 9 and 7	1	C_{13}-α-H
59, 65	d, J = 6	3	C_4-CH_3
53, 60	d, J = 7	3	C_{11}-CH_3
59	s	3	C_{10}-CH_3

s = singlet, d = doublet, t = triplet, and q = quartet.

CHART - 4

SYNTHESIS OF 5,6 ∝(H), 4,11 β(H) - EUDESMAN-6-13 OXIDE (XXIV)



1) DMF-HCl
2) Pd/C-H_2-EtoAc
3) EtOH-Perchloric acid
4) BF_3-Etherate, Ethanedithiol/AcOH
5) Raney nickel/Dioxan
6) Lithium aluminium hydride
7) p-Toluene sulphonyl chloride/Pyridine.

Solvent shifts in cyclic ethers

An examination of the NMR spectrum of the oxide (VII) in deutero chloroform (Fig. 1) reveals the presence of a singlet at 51.5 cps for C_{10}-methyl. The C_{11} and C_4-methyls appear as doublets centered at 59.5 (J = 7 cps) and 62 cps (J = 6 cps) respectively. The C_6 proton appears at 240 cps as a triplet (J = 10 cps). The methylene protons attached to the ether oxygen appear at 197 cps as an AB quartet (J = 9 cps).

In benzene (Fig. 2) however the C_{10} and C_{11} methyls and the C_6 and C_{12} hydrogen are shielded, whereas the C_4-equatorial methyl is deshielded. In pyridine also there is shielding of C_{10} and C_{11}-methyls and deshielding of C_4-methyl*. The magnitude of the shift being smaller in pyridine the use of benzene was naturally preferred. Further more recovery of compound from benzene poses less difficulty.

An explanation for these solvent induced shifts would require the formation a collision complex between benzene and the ethers oxygen. In analogy to the empirical rule established for carbonyl compounds a similar result in the ether series must also have a similar explanation. For this purpose one can consider a plane perpendicular to the plane made by the ether oxygen and the two carbons holding it

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* The C_{13} and C_6 hydrogens are not clearly seen in the pyridine spectrum.

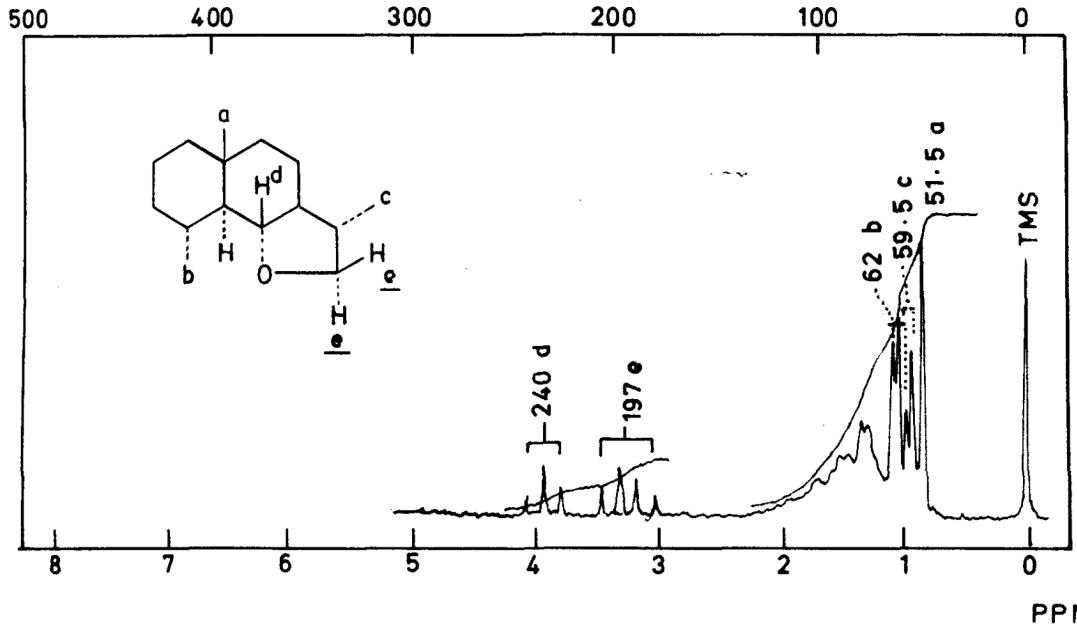


FIG. 1. NMR SPECTRUM OF 5α(H),4,6,11β(H) EUDESMAN 6-13 OXIDE ($CDCl_3$)

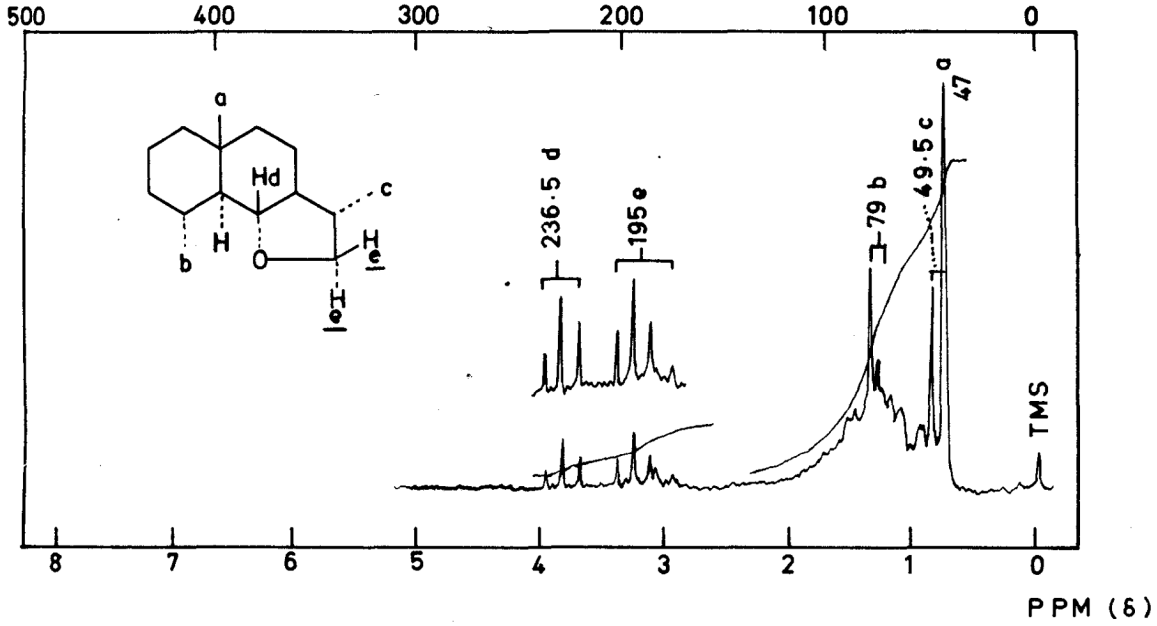


FIG. 2. NMR SPECTRUM OF 5α(H),4,6,11β(H) EUDESMAN 6-13 OXIDE (BENZENE)

(i.e. C_6 and C_{13} in oxide VII) and passing through the mid point of the carbon oxygen bonds, then protons on the same side as the oxygen atom (4 ∝ Me for example) are deshielded and protons lying behind the plane (i.e. away from the ether oxygen) are shielded (e.g. C_{11} methyl in compound VII). Protons lying near the plane suffer relatively smaller shifts (e.g. C_6-H C_{13}-H and C_{10} methyl in compound VII).

With this simple generalisation it is easy to explain the shifts observed. Thus, in compound XIV, in which the C_{11} methyl group is β oriented, the observed shifts (Figs. 3 and 4) because of solvent change are practically the same as in compound VII (Table 3).

A comparison of the solvent shifts in compound XVIII and compound VII reveals that except in the case of C_4-methyl the shifts are practically the same; for the C_4-methyl the stereochemistry has changed, the C_4 methyl group in XVIII being axially oriented. Due to its axial orientation this methyl group has come closer to the reference plane with the result that though it is deshielded this deshielding is smaller in magnitude (Figs. 5 and 6).

Change of orientation of the lactone ring at C_6 from trans to cis geometry (XXIV) causes several differences (Figs. 7 and 8) as compared to oxide VII. Firstly the C_4-methyl though in the equatorial orientation is now very close to the plane and therefore is barely influenced. The result is very small (0.8 cps) shielding. The second important change is in the relative position of C_{10}-methyl group which now falls into the deshielding side of the

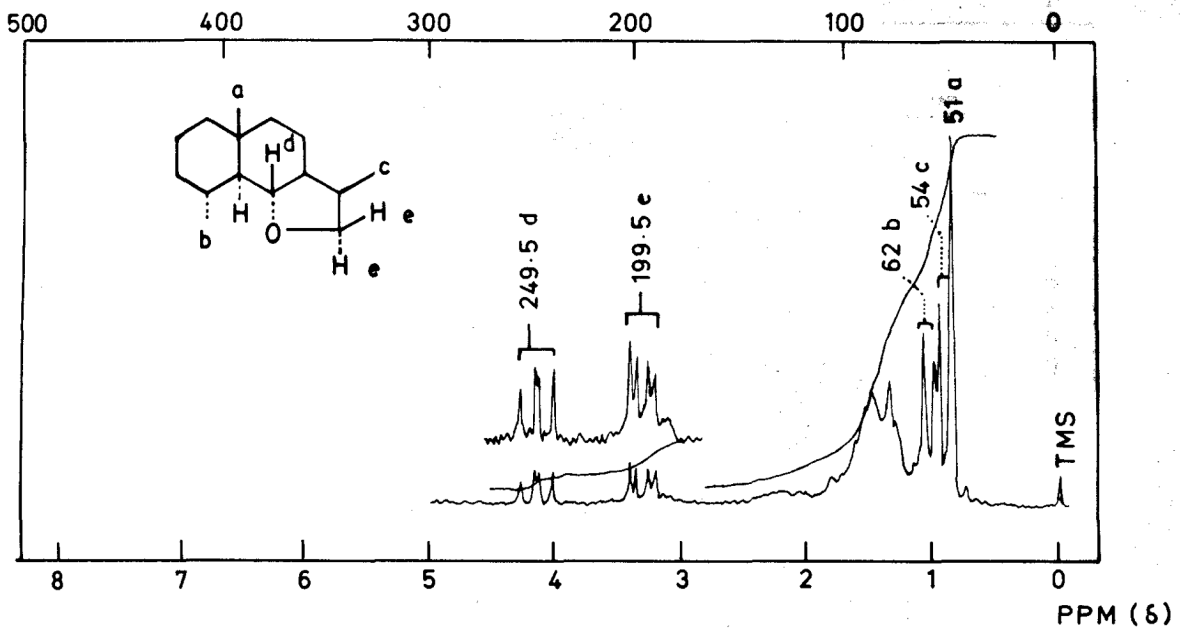


FIG. 3. NMR SPECTRUM OF 5,11α (H) 4,6 β (H) EUDESMAN 6-13 OXIDE ($CDCl_3$)

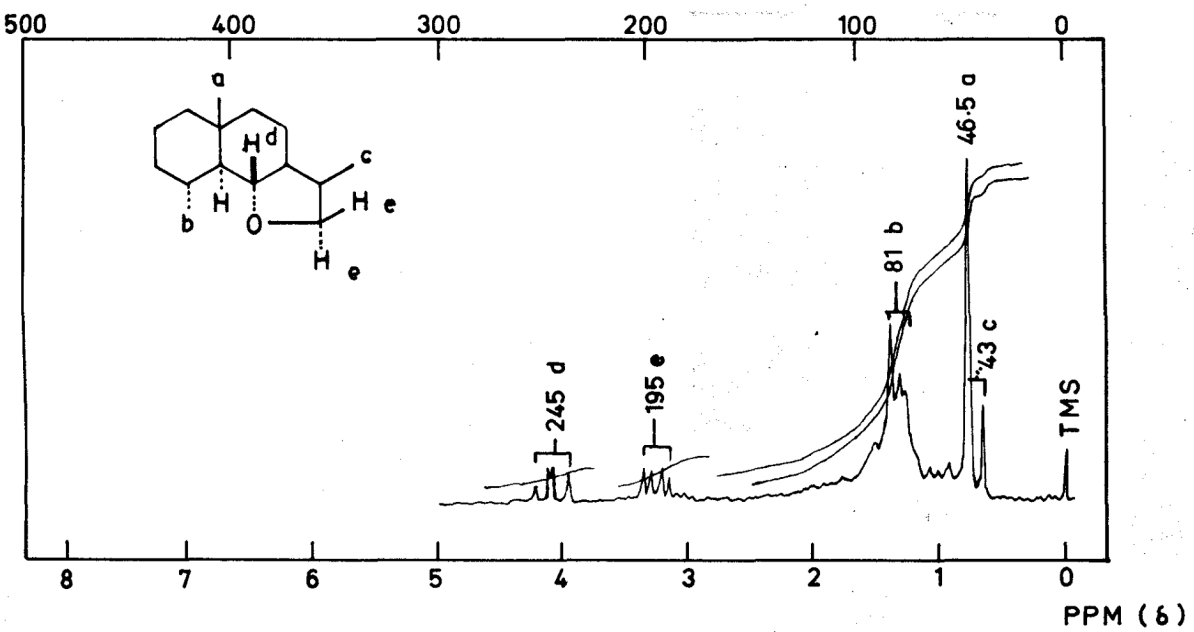


FIG. 4. NMR SPECTRUM OF 5,11 α (H) 4,6 β (H) EUDESMAN 6-13 OXIDE (C_6H_6)

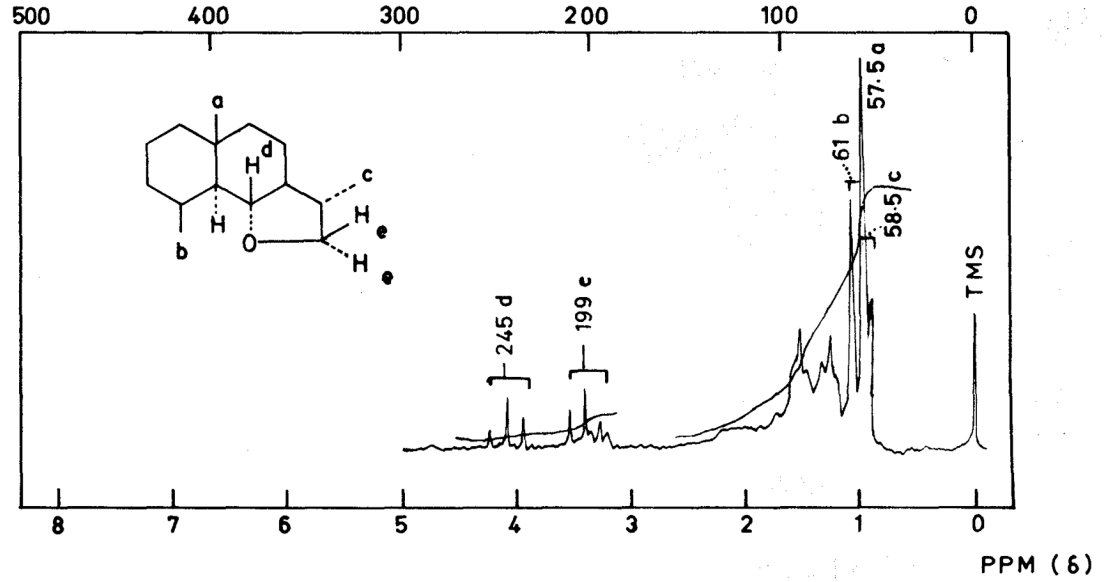


FIG. 5. NMR SPECTRUM OF 4,5 α (H) 6,11 β (H) EUDESMAN-6-13 OXIDE ($CDCl_3$)

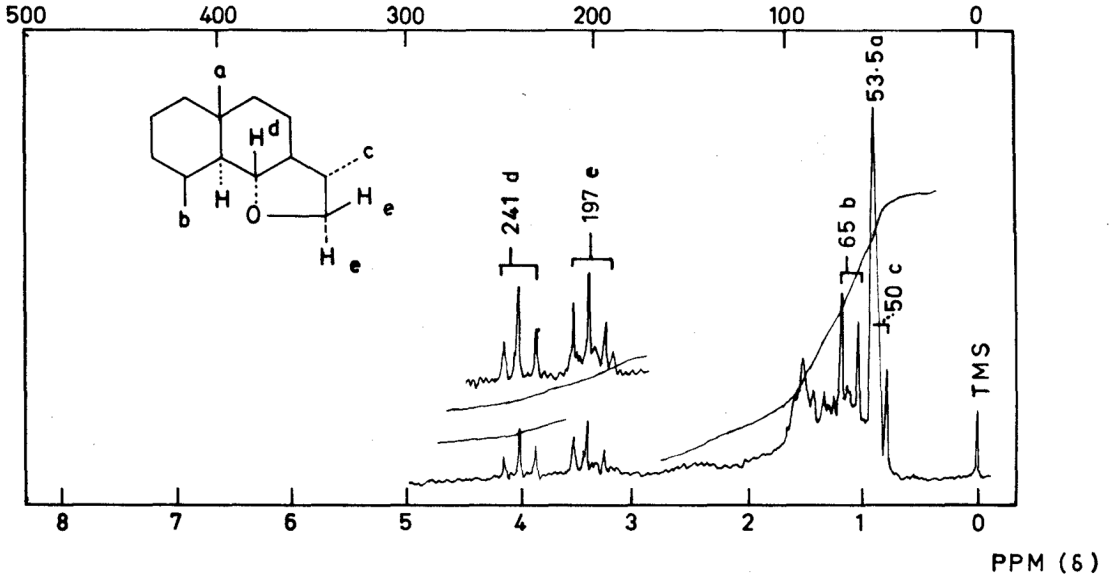


FIG. 6. NMR SPECTRUM OF 4,5 α (H) 6,11 β (H) EUDESMAN-6-13 OXIDE (BENZENE)

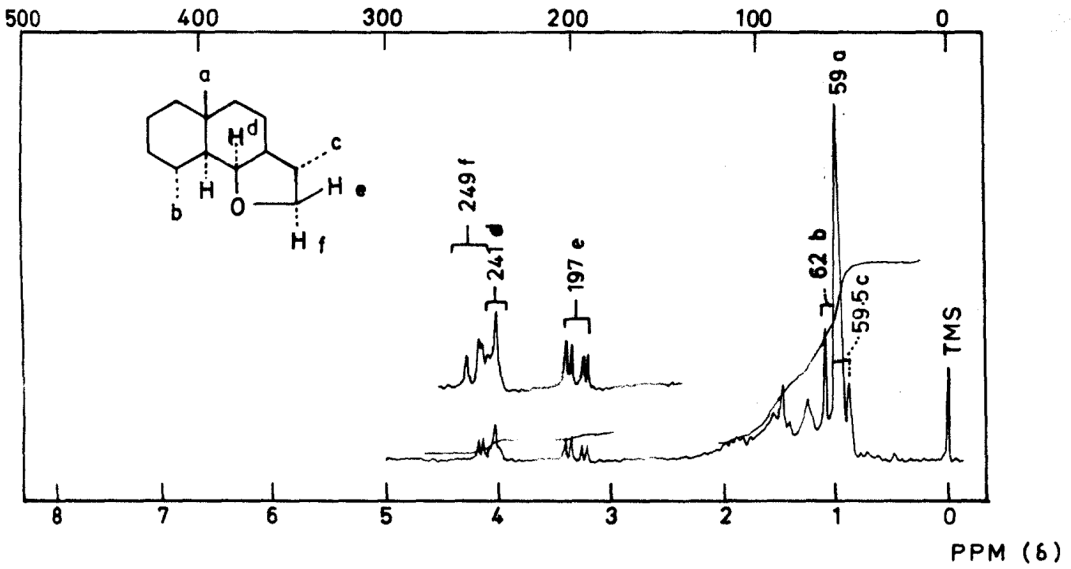


FIG. 7. NMR SPECTRUM OF 5,6 α (H) 4,11 β (H) EUDESMAN-6-13 OXIDE ($CDCl_3$)

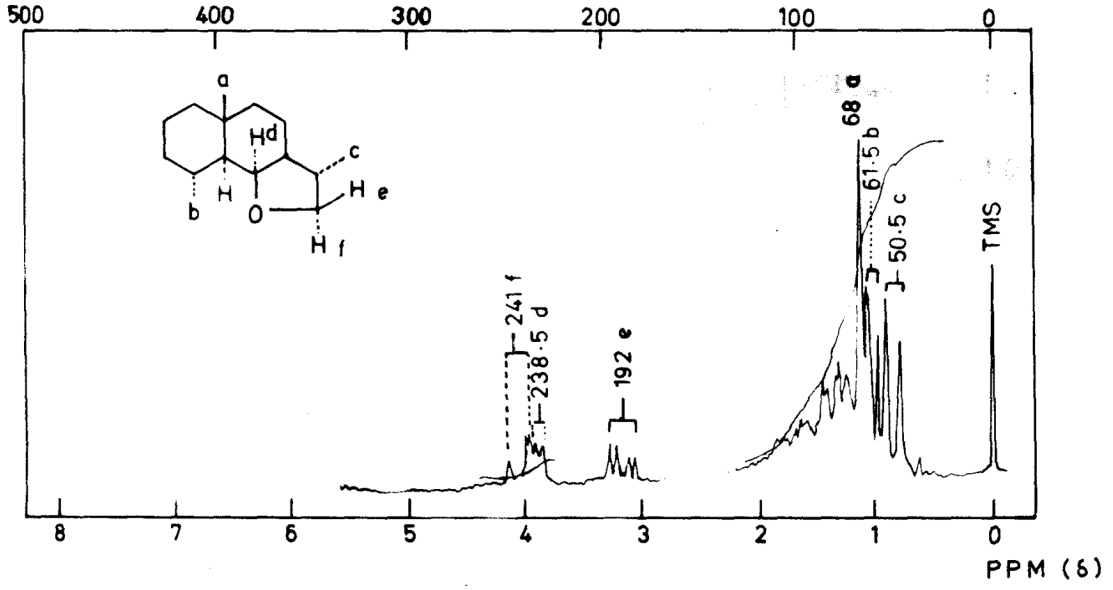
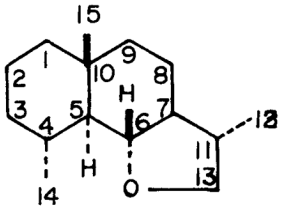
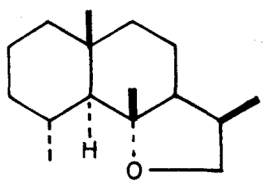
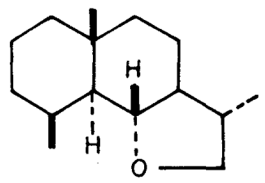
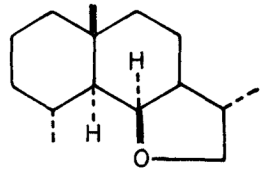


FIG 8. NMR SPECTRUM OF 5,6 α (H) 4,11 β (H) EUDESMAN-6,-13 OXIDE (BENZENE)

TABLE 3

No.	Compound	Solvent	Chemical shift of the				
			C_4-CH_3	C_6-H	C_{13}-H_2	C_{11}-CH_3	C_{10}-CH_3
VII		$CDCl_3$	59,65	240	197	56,63	51.5
		C_6H_6	76,82	236.5	195	46,53	47
		$\Delta = \delta CDCl_3 - \delta C_6H_6$	-17	+3.5	+2	+10	+4.5
		Pyridine	70,76	-	-	50,57	48
		$\Delta = \delta CDCl_3 - \delta$ Py.	-11	-	-	+6	+3.5
XIV		$CDCl_3$	59,65	249.5	199.5	51,57	51
		C_6H_6	78,84	245	195	40,46	46.5
		$\Delta = \delta CDCl_3 - \delta C_6H_6$	-19	+4.5	+4.5	+11	+4.5
XVIII		$CDCl_3$	58,64	245	199	55,62	57.5
		C_6H_6	62,68	241	197	46.5, 53.5	53.5
		$\Delta = \delta CDCl_3$ δC_6H_6	-4	+4	+2	+8.5	+4
XXV		$CDCl_3$	59,65	241	197 249	53,60	59
		C_6H_6	58.5, 64.5	238.5	192 241	47,54	68
		$\Delta = \delta CDCl_3 - \delta C_6H_6$	+0.5	+2.5	+5 +8	+6	-9

reference plane, and is deshielded by 9 cps. Furthermore in this particular case the two C_{13}-hydrogens are well separated and appear as two quartets. Both these hydrogens in benzene show the expected shielding. The results quoted so far seem to clearly establish the validity of the plane suggested above. However it was thought necessary to study carefully other compounds with different skeletons to confirm this point.

In the 16 oxosteroid*(XXVI) it could be anticipated that the C_{13} methyl should feel a large solvent induced shielding, the C_{17}-α-methyl a small shielding and the C_{17}-β-methyl should feel a small deshielding. In agreement with this the solvent induced changes seen in the NMR spectra (Table 4) reveal a shielding of one of the methyls by 10 cps and another by 3 cps while the third was deshielded by 3 cps.+

An application of this rule in the case of a tetrahydropyran derivative is seen for the 1α-a-oxa-D-homosteroid++ XXVII in which it can be expected that the C_{13}-methyl should feel a shielding on changing the solvent from deutero-chloroform to benzene as this methyl group is behind the reference plane which passes through the C_{11} carbon atom. In keeping with this the C_{13} methyl group is shielded by 5 cps. Once again the C_{10} methyl group would not feel any effect due to the ether oxygen.

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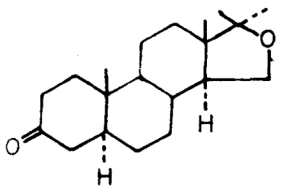
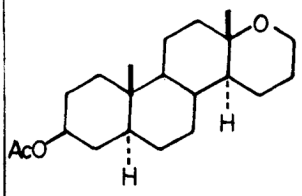
* We are grateful to Prof. Kierstead for a generous sample of this compound.

\+ The C-10 methyl group is very far from the reference plane and therefore is not likely to be shifted by the ether oxygen.

++ We are grateful to Prof. Petit for a sample of this steroid.

TABLE 4

SOLVENT INDUCED SHIFTS IN 5α-STEROIDS

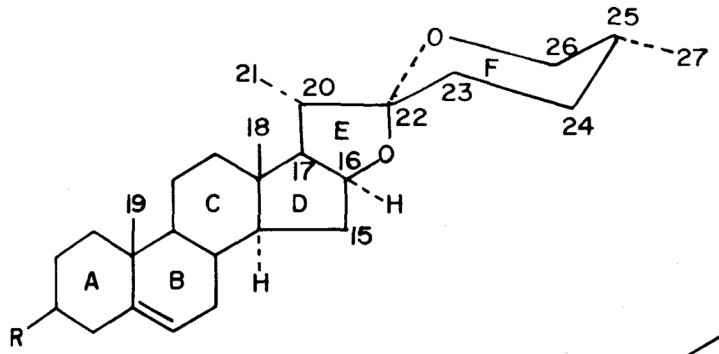
No.	Compound	Solvent	Chemical shift of the	
			C_{13}-CH_3	C_{17}^{α}-CH_3, C_{17}^{β}-CH_3
XXVI		$CDCl_3$	54	68, 69
		C_6H_6	44	71, 66
		Δ= $CDCl_3$ - C_6H_6	+10	-3, +3
XXVII		$CDCl_3$	69	-
		C_6H_6	64	-
		Δ= $CDCl_3$ - C_6H_6	+5	-

This rule can also suitably explain the solvent induced shifts observed by Bhacca and Williams (Table 5) in steroidal sapogenins[7]. Naturally in these compounds, as they contain two oxygen functions, two planes must be considered.

Thus in the case of diosgenin (XVIII, Chart 5) the plane to be considered for the oxygen atom held by C-16 and C-22 (hereafter referred as oxygen 1) will pass through carbon atom 23 causing C-16-hydrogen to be slightly deshielded and causing an appreciable deshielding of C-26 and C-27 hydrogen atoms. On the other hand there will be a shielding of C-21 hydrogen atoms. The C-18 hydrogen atoms are close to the reference plane but are on the shielding side.

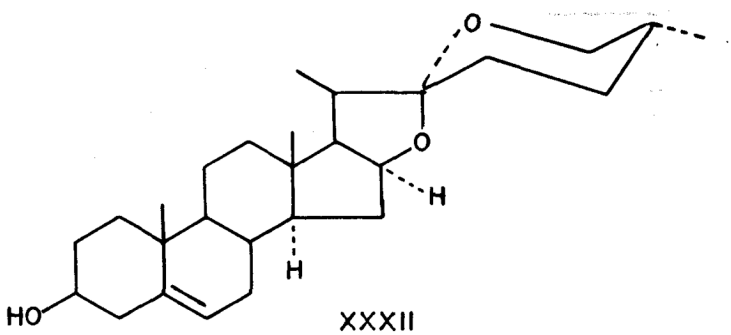
The second plane to be considered is that due to the oxygen held by C-22 and C-26 (hence forth called as oxygen 2). This will pass through C-17 and cause deshielding of C-16, C-21 and C-18 hydrogen atoms. The C-27 hydrogens would be shielded whereas of the C-26 hydrogens the axial hydrogen will be shielded while the equatorial one would be almost in the plane. The overall results therefore would be obviously deshielding of C-16 and C-26 hydrogen atoms. In the case of C-27 hydrogen atoms one plane (due to oxygen 2) causes shielding while the other (due to oxygen $\frac{1}{2}$) results in deshielding. The net result is governed by the plane of oxygen 2 as this oxygen is closer to these hydrogens.

In the case of the C-21 hydrogen oxygen 2 causes deshielding whereas oxygen 1 results in shielding as oxygen 2 is closer in space ($\sim 2.5^{\circ}A$), oxygen 1 is about $3.8^{\circ}A$ from this carbon) the result is deshielding.

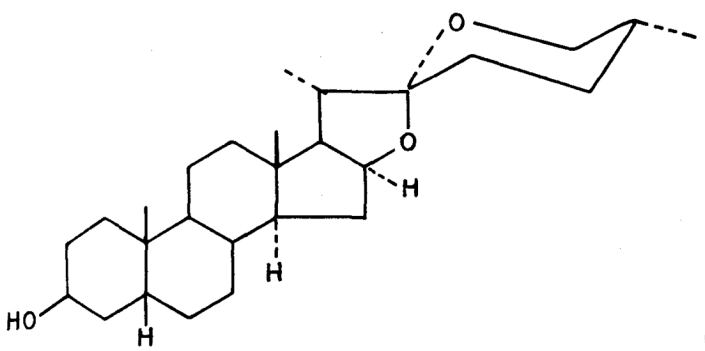


XXVIII , R = OH

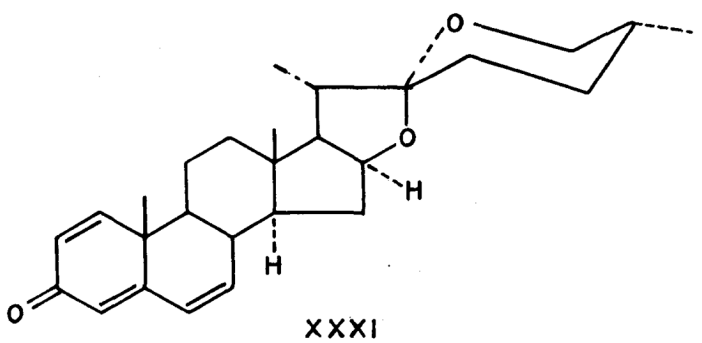
XXIX , R = OAc



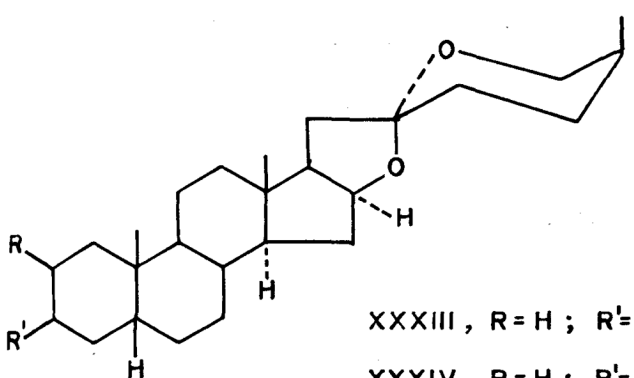
XXXII



XXX



XXXI



XXXIII , R = H ; R' = OH

XXXIV , R = H ; R' = OAc

XXXV , R = R' = OAc

CHART - 5

TABLE 5

SOLVENT SHIFTS (Δ = $CDCl_3$ - C_6H_6 cps) OF PROTON RESONANCES IN THE NMR SPECTRA OF STEROIDAL SAPOGENINS.[7]

Compound	RESONANCE					
	16α-H	26-H	27-H	21-H	19-H	18-H
XXVIII	-11.4	~ -7.2	+7.2	-13.8	+6.6	-2.4
XXIX	-	~ -8.4	+6.6	-13.8	+8.4	-1.8
XXX	-13.8	~ -8.4	+7.2	-15.0	+2.4	-3.6
XXXI	-12.6	~ -9.0	+7.2	-10.8	+28.2	+3.6
XXXII	-10.2	~ -9.0	+4.8	0.00	+4.8	-1.2
XXXIII	-13.2	-3.6/-10.8	-1.2	-12.0	+3.0	-2.4
XXXIV	-13.8	-4.8/-11.4	-1.2	-13.2	+5.4	+3.0
XXXV	-15.6	-4.8/-12.6	-1.2	+9.6	+9.6	0.6

Based on these arguments one would expect shielding of C-18 hydrogens due to preponderance of oxygen 1 effect. The observed result is almost a negligible shift. This reflects the fact that from the plane of oxygen 1 the C-18 hydrogens will have veryminor shielding (as it is very close to the plane). On the other hand the plane of the oxygen 2 clearly deshields and though far from C-18 hydrogens will therefore probably explain the overall deshielding.

The shifts of diosgenin acetate (XXIX) will be expected to be similar to those observed for disogenin as the C-3 acetate is far removed from the centres under consideration. The observed values therefore very nicely agree with the expectation.

In smilagenin (XXX) the only difference as compared with diosgenin is that B ring is saturated and now A/B ring junction is cis. As these changes are far removed from centres under study it can be anticipated that solvent shifts would be similar to diosgenin. The observed values support this reasoning.

In $\Delta^{1,4,6}$ spirostan-trien-3-one (XXXI) similar arguments can explain the observations.

In neodiosgenin (XXXII) the only change as compared with diosgenin is in the location of C-20 methyl which is now β-oriented. Examination of models would indicate that in order to avoid the heavy interactions between C_{13} methyl and C_{20} methyl there will be a slight twisting of the C_{20} methyl towards the C_{12} equatorial hydrogen (away from C_{13} methyl).

A very large twist is also not possible as then the C_{23} equatorial hydrogen would become too close to the C_{13} methyl. This slight twisting does not effect the relative positions of C-16, C-26, C-27 or C-18 hydrogens about the planes of oxygen 1 and oxygen 2*. Therefore the solvent induced shifts of these hydrogens should be essentially the same as in diosgenin. The observed values adequately support this argument.

The only change in neo-diosgenin would be that due to the C_{21} hydrogens. These should be shielded by the plane of oxygen 1 and deshielded by plane of oxygen 2. As the C_{21} carbon lies almost equi-distant ($\sim 3.4^{o}$A) from oxygen 1 and oxygen 2 these effects would then be cancelled out. The expected result therefore would be an almost negligible shift. The observed shift is 0.00 cps, supporting the above rationalisation.

In sarsapogenin (XXXIII) C_{26}^{25} methyl group is axially oriented. As no other change in the nature of C, D, E or F rings has been made in comparison with diosgenin, solvent shifts for C-16, C-18 and C-21 hydrogen would correspond to those of diosgenin.

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* For brevity the words, the plane of oxygen 1 and oxygen 2 are used. These planes imply the planes to be considered for solvent induced shifts due to an oxide function which must be perpendicular to the plane of the oxygen carbon bonds and passing through the mid points of these bonds.

In the case of C-27 hydrogens the position is now reversed. The oxygen 1 plane causes a shielding while that of oxygen 2 causes a small deshielding (very close to the plane). As effect of oxygen 2 would have a greater contribution (because of its closeness) the overall effect is expected to be small (either shielding or deshielding). The observed value is in agreement with expectation. In the spectra of this compound the C-26 hydrogens appear as separate signals. As mentioned earlier the equatorial C-26 proton is having negligible effect due to oxygen 2 plane and is deshielded by the plane of oxygen 1, the overall result therefore should be appreciable deshielding. On the other hand though axial C-26 proton is deshielded by oxygen 1 plane it is shielded by oxygen 2 plane overall therefore this proton should have a small shift as compared with the equatorial proton. Hence that proton which has a small shift in this particular case must represent the axial proton.

The two other examples (XXXIV and XXXV) with C-27 axial methyl would naturally be expected to have similar solvent shifts to the protons considered for sarsapogenin (XXXII) as the changes are only in ring A. The observed values confirm this expectation. Bhacca and Williams[7] also observed shifts for the C-19 hydrogens in all these compounds. These shifts are difficult to explain as these hydrogens are far removed from the acetal oxygen atoms which are the

cites at which complexing has been considered in these cases*.

We can now look at the solvent induced shifts in the case of simple organic compounds. These solvent induced shifts (Table 6) can be used to fix the conformation of simple ethers, When the solvent induced shifts of tetrahydrofuran are examined, it is observed, as expected, that ∝ protons feel a shielding of 9 cps whereas β protons which are further from the plane feel a larger shielding (21 cps).

In diethyl-ether the solvent induced shifts demonstrate that the β protons are closer to the plane than the ∝ protons. A gauche-guache conformation (a) which would have similar orientation of ∝ and β protons

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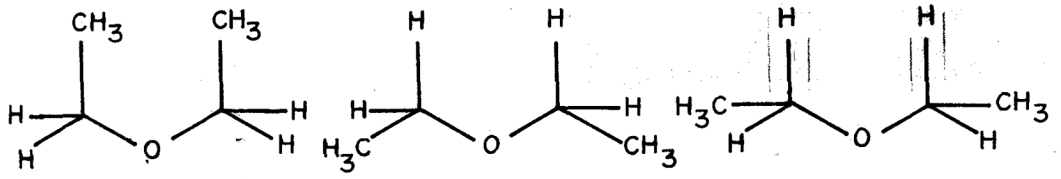
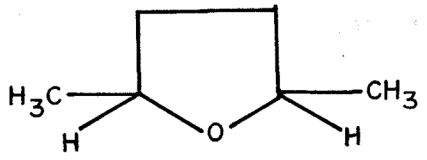
* It is possible that some amount of complexing can take place at C-3 oxygen atom. (see later)

as tetrahydrofuran, can therefore be ruled out. Stability consideration would also suggest large non-bonded interaction which would destabilise this conformation. In the zig-zag conformation (b) the two β carbon atoms and the oxygen atoms are in one plane the ∝ proton should be shielded whereas the β protons should be deshielded (by small amount). The results (Table 6), however, can be satisfactorily explained by the conformation (c) in which the β methyl group are cis related about the plane made by the ∝-carbons and the oxygen atom. This conformation is in a way similar to that of cis-∝-∝' dimethyl tetrahydrofuran (XLIII).



(a) (b) (c)



(XLIII)

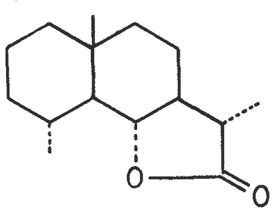
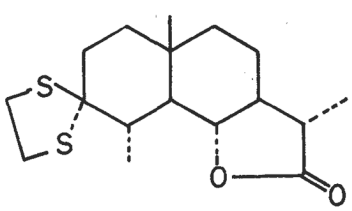
TABLE 6

SOLVENT SHIFTS IN SIMPLE COMPOUNDS

No.	Compound	Chemical Shift in $CDCl_3$		In benzene		Shift in benzene	
		α-H	β-H	α-H	β-H	α-H	β-H
VI	Diethyl ether	208	71	200	66	+8	+5
VII	Tetrahydrofuran	224	110	215	89	+9	+21
XXVIII	Triethyl amine	155	63	147	60	+8	+3
XXIX	Pyrrolidine	175	103	162	87	+13	+16
L	thyl mercaptan	154	79	130	59	+24	+20
LI	thyl alcohol	223.5	74.5	210.5	64	+13	+10.5
LII	Tetrahydrothiophene	170	116	155	93	+15	+23

TABLE 7

DESHIELDING BY A SULPHUR ATOM

No.	Compound	Chemical shift C_4-CH_3	C_4-CH_3	Shift in benzen C_4-CH_4
		59,66	65,72	-6
		76,83	93,100	-17

If complexing is possible with ether oxygen it can be expected that this complexing must involve the oxygen lone pair. If such is indeed the case then any atom (like nitrogen or sulphur having such a lone pair should complex with a benzene molecule. This should result in solvent induced shifts in these compounds also. Here too the same generalisations for the solvent shifts should be valid.

In agreement with this expectation the β protons of tetrahydro thiophene (XLII, Figs. 9 and 10) are more shielded (23 cps) as compared to ∝ protons (15 cps), when benzene spectra are examined in comparison with $CDCl_3$ spectra. This behaviour parallels that of tetrahydrofuran where also shift of β protons (+21 cps) is larger than the shift of ∝ protons (+9 cps). It is significant to note that the sulphur atom gives rise to larger solvent induced shifts than an oxygen atom.

It is significant that even in pyrrolidine the same position as in tetrahydro-thiophene and tetrahydrofuran holds, the ∝ proton feeling slightly smaller shifts (+13 cps) than β protons (+16 cps).

The more interesting example is that of trimethylamine (Figs. 11 and 12) wherein 3 planes can be considered of these two planes will cause shielding of both ∝ and β protons whereas in a third there will be a deshielding of both. The overall result therefore should be a shielding similar in nature to that observed for diethyl ether. The values observed are in accord with this expectation.

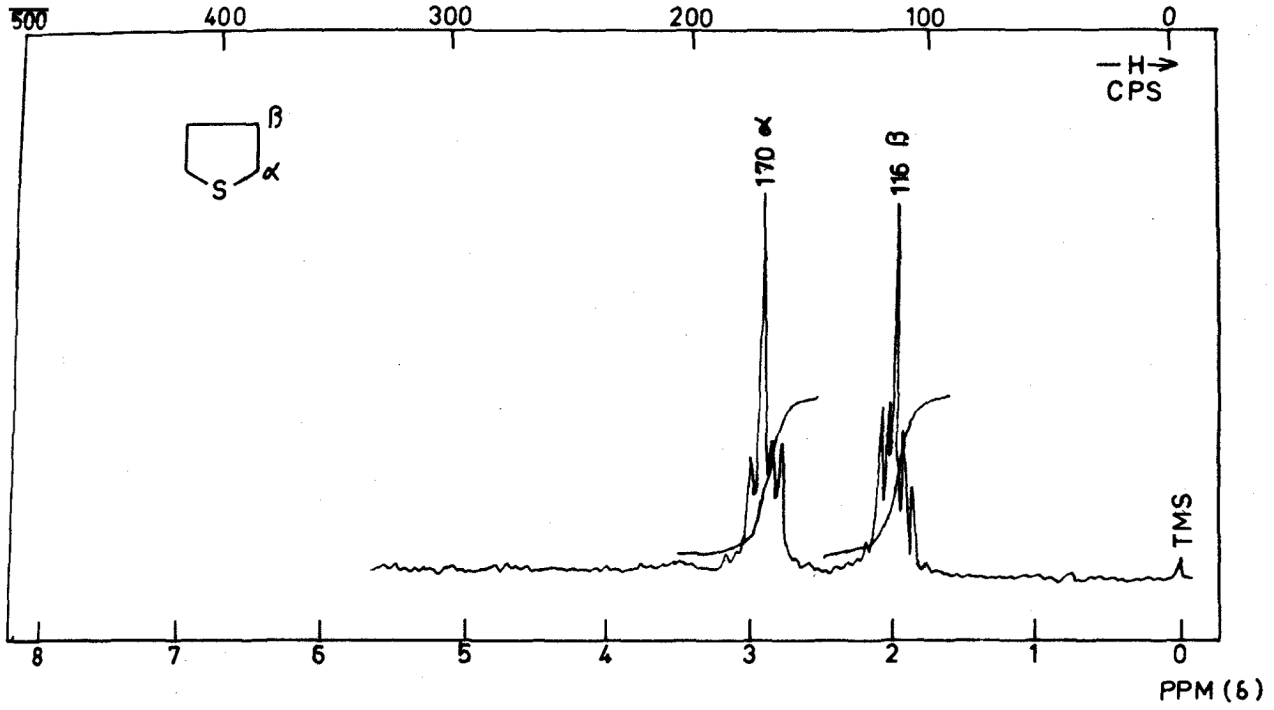


FIG. 9. NMR SPECTRUM OF TETRAHYDROTHIOPHENE ($CDCl_3$)

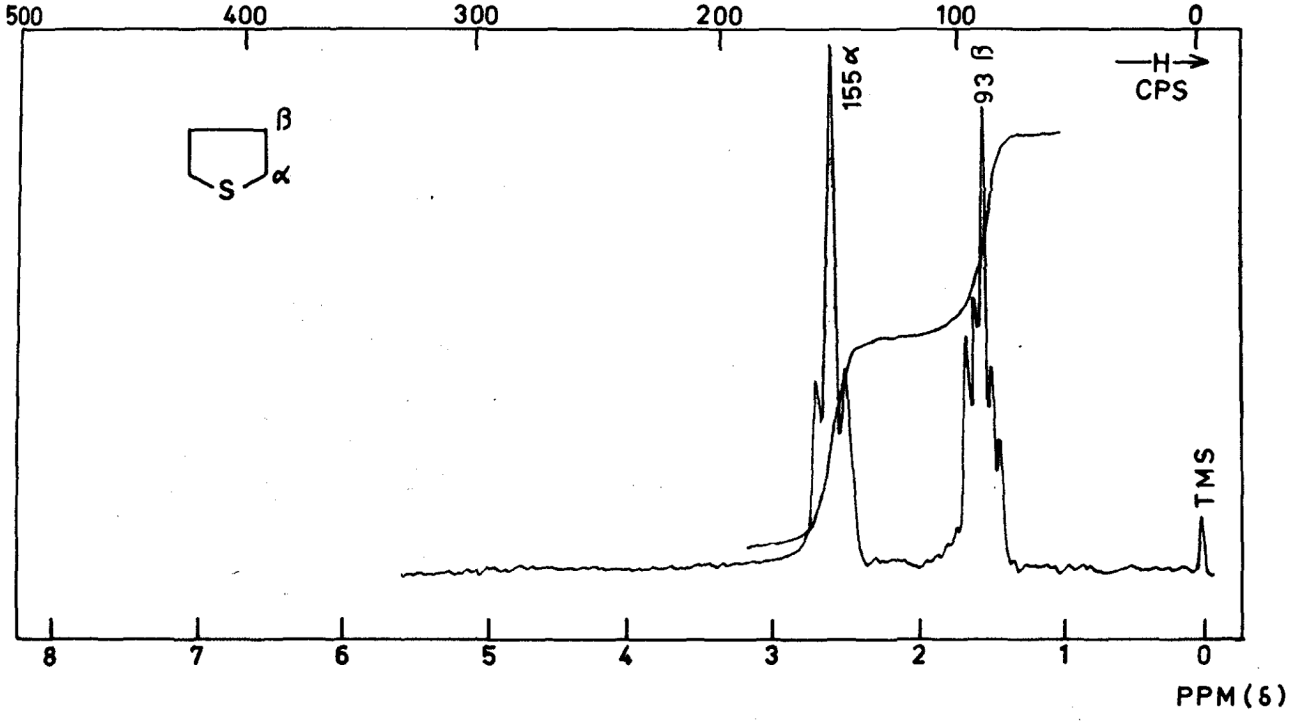


FIG. 10. NMR SPECTRUM OF TETRAHYDROTHIOPHENE (BENZENE)

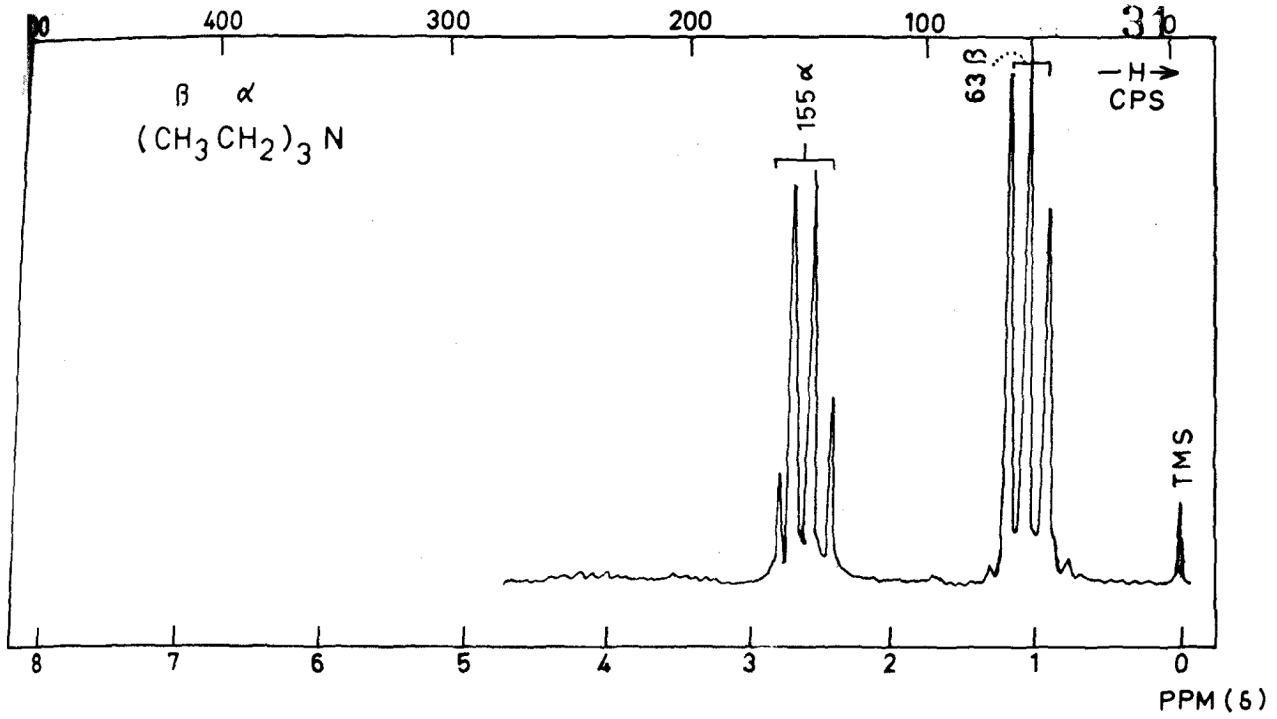
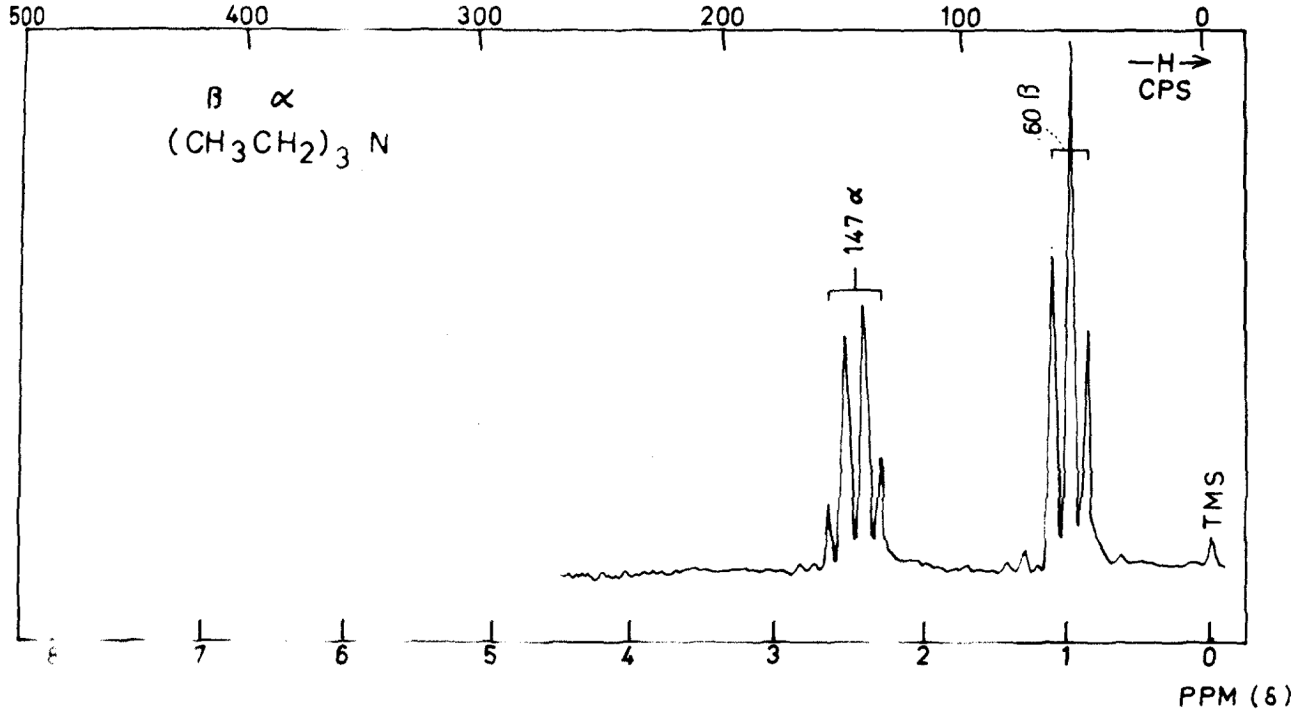


FIG. 11. NMR SPECTRUM OF TRIETHYL AMINE ($CDCl_3$)



F . 1. NMR SPECTRUM OF TRIETHYL AMINE (BENZENE)

It has so far been assumed that such shielding only occurs in compound in which a hetero atom is bound to two carbon atoms but as the mechanism of this shielding requires complexing with a lone pair of electrons, it ~~it~~ can be expected that alcohols, thiols and amines should feel solvent induced chemical shifts. In agreement with this the protons of ethyl alcohol exhibit a solvent induced shielding.

This shielding is larger for α protons (13 cps) than for β protons (10.5 cps). This can be rationalised in the following manner. There are several different orientations of the oxygen hydrogen single bond in relation to the ethyl group. In half of these both α and β protons are shielded (β more than α) while in the other half the α proton is shielded while the β proton is deshielded. The net result therefore is a larger shielding of α protons as compared with β protons.

In a similar manner the larger shielding of the α protons of ethane thiol as compared to the β proton can also be explained once again the magnitude of the shielding caused by sulphur atom is much larger than that caused by an oxygen.

A solvent induced deshielding by a sulphur atom is seen in the case of the ethylene thioketal (IV, Table 7). Models show that in this compound the C_4--α CH_3 is held in front of the reference plane made on the nearer of the two sulphur atoms the overall shift being -17 cps. The net shift however caused by thioketal is only 11 cps, 6 cps being the solvent induced deshielding caused by the lactone (V).

EXPERIMENTAL

Melting points are uncorrected and have been taken in a Gallenkamp melting point apparatus. Optical rotations were determined on a Perkin-Elmer spectropolarimeter or a Carl Zeiss polarimeter in chloroform solution. When the temperature is not specifically mentioned, it refers to rotation at 30°. Ultraviolet spectra were taken in ethanol on Perkin-Elmer Model 350 spectrophotometer. Infrared spectra were recorded as nujol mulls unless otherwise stated, on a Perkin-Elmer model 221 spectrophotometer or Perkin-Elmer Infracord. The maxima are reported in cm^{-1}. Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer as 10% solution in deuterio-chloroform unless otherwise stated using tetramethyl silane as the internal standard. The chemical shifts are reported in cps from tetramethyl silane.

Chromatograms have been run on Brockman[41] Grade II alumina (neutral) unless otherwise stated. Thin layer chromatography was carried out on silica gel mixed with plaster of paris (15%) as binder. The plates were sprayed with conc. H_2SO_4.

Pet. ether refers to the fraction boiling between 60-80°C.

Analytical G.L.Cs were carried out on an "Aerograph" (Model A-350-B) using 6x0.25" columns packed with 20% diethylene glycol polysuccinate on chromosorb W (60-80 mesh) - column P, employing hydrogen as carrier gas.

3-Oxo 4,5∝(H) 6,11 β(H) eudesman-6-13 olide (II)* [43,44]

Santonin (I, 20 g) in ethyl acetate (600 ml) was hydrogenated over 2% palladium strontium carbonate catalyst at room temperature and pressure, for two hours. Absorption of hydrogen ceased after uptake of two moles. The catalyst was filtered off and washed with little boiling ethyl acetate. Removal of the solvent followed by three crystallisations from ethanol gave the tetrahydro compound II (12 g).

M.P.	146°	Lit.[43]	146-147°
$[\alpha]_D^{28}$	+60°	Lit.[43]	+64°

I.R. 1775 cm^{-1} (γ-lactone), 1712 cm^{-1} (cyclohexanone)

2% Palladium strontium carbonate catalyst was specially used as it gives pure tetrahydrosantonin (II) in good yield.

It was prepared as follows.

Palladium chloride (1 g) was dissolved in con.HCl (2 ml) and diluted (to 200 ml) with distilled water; freshly precipitated strontium carbonate (precipitated by mixing equivalent quantities of strontium chloride and potassium carbonate solution) was added in small quantities with stirring till CO_2 evolution stopped. Excess of $SrCO_3$ (30 g) was added and the mixture was stirred for ten hours. The solid was filtered, washed thoroughly with water, methanol and ether. The catalyst was finally dried at 60° for five hours.

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* The nomenclature used for various santonin derivatives here and in next chapter is that of Cocker and McMurry[42].

3-Oxo 5∝(H) 4,6,11β(H) eudesman 6-13 olide (III)[43,44]

A mixture of the ketolactone II(6 g), p-toluene sulphonic acid (4.6 g) and acetic acid (150 ml) was set aside overnight at room temperature. The mixture was then diluted with water and extracted with ether (5x30 ml). The combined ether extracts were washed free of acetic acid by $NaHCO_3$ solution. Removal of the solvent after drying over anhydrous sodium sulphate gave a solid which was crystallised from ethanol to yield the expected 4∝-methyl lactone III (4.25 g).

M.P. 155-156° Lit. 157°

$[\alpha]_D$ +25 Lit. +28°

I.R. 1776 cm^{-1} (γ-lactone), 1702 cm^{-1} (cyclohexanone)

Thioketal of 3-oxo-5∝(H), 4,6,11β(H)-eudesman-6-13-olide (IV)[35]

To the keto lactone III (2 g) dissolved in acetic acid (16 ml), ethanedithiol (2 ml) and BF_3 etherate (4 ml) were added and mixture was allowed to stand overnight at room temperature. It was then poured in ice cold water and extracted with ether (4x25 ml). The combined ether extracts were washed with 5% bicarbonate solution and water and dried over anhydrous sodium sulphate. Removal of the solvent and crystallisation from ethanol furnished the thioketal (2 g).

M.P. 194° Lit.[35] 195-196°

$[\alpha]_D$ +40.8° Lit.[35] +44.7°

I.R. 1780 cm^{-1} (lactone)

Hydrogenolysis of the thioketal: 5∝(H),4,6,11β(H) eudesman-6-13 olide (V)[35]

Above thioketal (1 g) in dry dioxane (100 ml) was refluxed with Raney nickel (8 g) for eight hours.

Raney-nickel was filtered off and d oxan was removed in vacuo. The crude product crystallised from ethanol to yield the deoxo lactone (V) (0.720 g).

M.P. 154° Lit.[35] 154°

$[\alpha]_D$ +30° Lit.[35] +26.4 ± 1

I.R. 1774 cm^{-1} (lactone)

5∝(H) 4,6,11 β(H) eudesman 6,13-diol (VI)[35]

Deoxo lactone V (472 mg) in ether-benzene mixture (42 ml, 6:1) was added dropwise to ension of lithium aluminium hydride (152 mg) in ether benzene mixture (21 ml, 6:1). The mixture was refluxed with stirring for six hours. After cooling, excess of LAH was destroyed by adding ice pieces. The organic layer was separated and the milky aqueous layer was extracted with ether (3x20 ml). Combined ether extracts were washed with water, dried over sodium sulphate and brought to dryness. Crystallisation of the residue from ethanol yielded the diol (425 mg).

M.P. 154° Lit.[35] 154-155°

$[\alpha]_D$ -27° Lit.[35] -28.3 ± 1

I.R. 3260 cm^{-1} (OH)

5∝(H) 4,6,11 β(H) eudesman 6-13 oxide (VII)[38]

Diol VI (300 mg) was allowed to stand in pyridine (5 ml) with p-toluene sulphonyl chloride (460 mg) for 24 hours. The mixture was then poured in water and extracted with ether (4x25 ml). Combined ether extracts were washed with 2N HCl, water and shaken well with 10% aqueous alkali for five minutes. Removal of the solvent after drying over

sodium sulphate left an oil which was chromatographed on silica gel. Elution with pet. ether yielded an oxide (206 mg, single spot in T.L.C.) which was distilled under vacuo.

B.P. 140°C(bath temp.)/3 mm. Lit.[35] 132-133°/8 mm.
$[\alpha]_D$ -29° Lit.[35] -30.64°
GLC - single peak
I.R. 1035 cm^{-1} (oxide)

Analysis:

Found: C, 81.12; H, 11.87%
$C_{16}H_{26}O$ requires: C, 81.02; H, 11.79%.

3-Oxo-4,5,11α(H) 6β(H) eudesman-6-13 olide (IX)[36,45]

β-Santonin* (5 g) in ethyl acetate (300 ml) was stirred in an atmosphere of hydrogen with 10% Pd/C catalyst (1.5 g). Absorption of hydrogen (2 moles) ceased after two hours. The catalyst was filtered and the filtrate concentrated to a small volume. The tetrahydro compound (IX, 3.1 g) crystallised out on cooling.

M.P. 207-208° Lit.[45] 206-208°
$[\alpha]_D$ +116° Lit.[45] +118°
I.R. 1780 cm^{-1} (γ-lactone), 1710 cm^{-1} (cyclohexanone)

3-Oxo-5,11 α(H) 4,6 β(H)-eudesman-6-13-olide (X)[45]

The mixture of C_4β-Me keto lactone (IX, 3 g), acetic acid (60 ml) and p-toluene sulphonic acid (2.7 g) was allowed to stand for hours at room temperature. This was poured

* We are thankful to Prof. W. Cocker for a generous sample of β-santonin.

in water and worked up as usual. Crystallisation from ethanol gave the epimerised product (2.1 g).

M.P.	124°	Lit.[45]	125-126°
$[\alpha]_D$	+77.5°	Lit.[45]	+81.9°

I.R. 1780 cm^{-1} (lactone) and 1715 cm^{-1} (cyclohexane)

Ethylene thioketal of 3-oxo-5,11 α(H),4,6β(H)-eudesman-6-13 olide (XI)[35]

A mixture of C_4α Me tetrahydro-lactone (X, 2 g), acetic acid (16 ml), ethanedithiol (2 ml) and BF_3 etherate (4 ml) was allowed to stand for 24 hours. Thioketal obtained (2.4 g) was crystallised from ethanol.

M.P.	155°	Lit.[35]	155°
$[\alpha]_D$	+70°	Lit.[35]	+76

IR 1775 cm^{-1} (γ-lactone)

Hydrogenolysis of thioketal (XI) -5,11 α(H),4,6 β(H) eudesman-6-13 olide (XII)[37]

The thioketal (1.8 g) was desulphurised in the usual way. The 3-deoxo compound, obtained, was crystallised from pet. ether in needles.

M.P.	75-76°	Lit.[37]	75-76°
$[\alpha]_D$	+81.94		

I.R. 1780 cm^{-1}

5,11 α(H) 4,6 β(H) eudesman 6,13 diol (XIII)

Lithium aluminium hydride reduction of the deoxo lactone XII, in the usual way afforded a diol in 85% yield from pet. ether-ethyl acetate.

M.P. 147-148°

$[\alpha]_D$ -5.8

I.R. 3350 cm^{-1} (OH)

Analysis:

Found: C, 74.67; H, 11.99%

$C_{15}H_{28}O_2$ requires: C, 74.95; H, 11.74%

5,11 α(H) 4,6 β(H) eudesman 6-13 oxide (XIV)

The above diol (300 mg) was cyclised by keeping in pyridine (5 ml) and p-toluene sulphonyl chloride (480 mg) for 24 hours. Usual work up afforded a mobile liquid (single spot in TLC 260 mg). This was distilled under vacuo and characterised as the expected oxide.

B.P. 165° (bath temp.)/2.5 mm.

$[\alpha]_D$ +49.58°

I.R. 1025 cm^{-1} (oxide)

Analysis:

Found: C, 81.04; H, 12.01%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%.

Ethylene thioketal of 3-oxo-4,5 α(H), 6,11 β(H) eudesman 6-13 oxide (XV)[35]

A mixture of lactone (II, 2 g), acetic acid (20 ml), ethane dithiol (2 ml) and BF_3 etherate (4 ml) was allowed to stand overnight at room temperature. Usual work up followed by crystallisation from ethanol afforded the thioketal (XV, 2 g).

M.P.	166°	Lit.[35]	166-167°
$[\alpha]_D$	+35°	Lit.[35]	+37.9°.

Hydrogenolysis of the dithioketal (XV) 4,5 ∝(H),6,11β(H) eudesman-6-13 olide (XVI)[35]

The thioketal (1.63 g) was desulphurised as usual by refluxing with Raney-nickel in dioxan. Work up left a residue which crystallised from ethanol to give the deoxo compound (XVI).

M.P.	148-149°	Lit.[35]	137-138° (unsharp)
$[\alpha]_D$	+84°	Lit.[35]	+92°
I.R.	1770 cm^{-1} (lactone)		

4,5 ∝(H) 6,11 β(H)-eudesman-6,13 diol (XVII)[35]

The above deoxo compound (472 mg) in ether (42 cc) was reduced with LAH (152 mg) in the manner described before. The diol obtained (450 mg) crystallised from alcohol in beautiful needles.

M.P.	108-109°	Lit.[35]	107-108°
$[\alpha]_D$	-27.3°	Lit.[35]	-28.2°
I.R.	3250, 1025 cm^{-1} (OH)		

4,5 ∝(H) 6,11 β(H)-eudesman-6-13-oxide (XVIII)[38]

The diol (300 mg) was allowed to stand in pyridine (5 ml) with p-toluene sulphonyl chloride (450 mg) for 24 hours. It was poured into water and extracted with ether (4x25 ml). Total ether extracts were washed with 2N HCl, water and then shaken well with 10% alkali. Removal of the solvent after drying over sodium sulphate yielded a thick oil (276 mg) which showed very close two spots on T.L.C. Careful chromatography on alumina grade I gave in later pet. ether fractions a single spot (TLC) mobile liquid (223 mg) which was distilled under vacuo and identified as the expected oxide.

B.P. 140-160° Bath temp./2.5 mm.

Lit.[39] 110-120°/3 mm.

$[\alpha]_D$ -3.640° Lit.[39] -25.96°

I.R. 1020 cm^{-1} (oxide)

G.L.C. single peak

Analysis:

Found: C, 80.82; H, 11.86%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79

First pet ether fraction yielded 30 mg of an oil which was not investigated.

6α(H)-Santonin (XIX)[46,47]

Santonin (25 g) was heated on steam-bath with dimethyl formamide (250 ml) containing 5% HCl [prepared by passing dry HCl (12.5 g.) in dry dimethyl formamide (250 ml)] for five hours.

The reaction mixture was cooled to room temperature, diluted (to 1250 ml) with water and extracted with ether. The ether extract was washed with dil. KOH solution and then with water. Removal of the solvent after drying on sodium sulphate yielded a coloured gum. It was chromatographed on neutral alumina (500 g.) and eluted with benzene to furnish 6α(H) santonin which was crystallised from pet. ether-ethyl acetate.

M.P. 103° Lit.[46] 103-104°

$[\alpha]_D$ -330° Lit.[46] -332°

I.R. 1770 cm^{-1} (lactone), 1660 cm^{-1} (α,β-unsaturated ketone)

1630 and 1602 cm^{-1} (conjugated C-C double bond)

3-Oxo-4,5,6∝(H) 11β(H)-eudesman 6-13 olide (XX)[40]

6∝(H)-Santonin (XIX, 5 g) in ethyl acetate (150 ml) was hydrogenated over 10% Pd/C catalyst (1 g). Absorption of hydrogen ceased after 4 hours. The catalyst was filtered off and the filtrate was washed thoroughly with 5% sodium bicarbonate solution and water and dried over sodium sulphate. The residue obtained after removal of solvent was crystallised from pet. ether-ethyl acetate to provide the product (1.250 g).

M.P.	196-197°	Lit.[40]	196-197°
$[\alpha]_D$	-132°	Lit.[40]	-136°
I.R.	1770 cm^{-1} (γ-lactone) and 1710 cm^{-1} (cyclohexanone)		

3-Oxo-5,6,6∝(H) 4,11 β(H)-eudesman-6-13 olide (XXI)[40]

Tetrahydro 6-∝ santonin (XX, 1.25 g) in alcohol (50 ml) containing perchloric acid (4 drops) was refluxed for 14 hours. Reaction mixture was then cooled, poured in water and extracted with ether (4x25 ml). Combined ether extracts were washed with bicarbonate solution and water and finally dried over anhydrous sodium sulphate. The residue obtained on removal of solvent crystallised from pet. ether-ethyl acetate to yield the epimerised product.

M.P.	166°	Lit.[40]	166°
$[\alpha]_D$	-118°	Lit.[40]	-113°
I.R.	1775 cm^{-1} (γ-lactone) and 1703 (cyclohexanone)		

Ethylene thioketal of 3-oxo-5,6 ∝(H) 4,11 β(H)-eudesman-6-13-olide (XXII)[40]

A mixture of C_4-∝Me tetrahydro compound (XXI, 1 g) acetic acid (5 ml), ethanedithiol (1 ml) and BF_3 etherate (2 ml) was allowed to stand overnight. Usual work up and subsequent crystallisation gave the thioketal (1.148 g).

M.p. 213° Lit.[40] 214-215°

$[\alpha]_D$ -80° Lit.[40] -84.7°

I.R. 1785 cm^{-1} (lactone)

Hydrogenolysis of thioketal (XXII); 5,6∝(H) 4,11 β(H)-eudesman-6-13 olide (XXIII)[40]

The above thioketal (1 g) was desulphurised by refluxing with Raney-nickel (3 g) in dioxan (60 ml). Usual work up afforded a gum (TLC, single spot) which was crystallised from aq. methanol to furnish the deoxo compound (600 mg).

M.P. 100° Lit.[40] 99-100°

$[\alpha]_D$ -140°

I.R. 1786 cm^{-1} (γ-lactone)

5,6 ∝(H) 4,11 β(H)-eudesman-6,13-diol (XXIV)

The deoxo compound (500 mg) was reduced with lithium aluminium hydride in the usual manner to afford a diol (400 mg) in needles from methanol.

M.P. 92-93°

$[\alpha]_D$ -2.2

I.R. 3300 cm^{-1}

Analysis:

Found: C, 75.16; H, 11.81%

$C_{15}H_{26}O_2$ requires: C, 74.95; H, 11.74%.

5,6 α(H) 4,11 β(H) eudesman 6-13 oxide (XXV)

The diol (250 mg) was allowed to stand in pyridine (5 ml) with p-toluene sulphonyl chloride (375 mg) for 24 hours at room temperature. Usual work up gave a colourless mobile oil (220 mg, single spot on TLC). This was distilled under vacuum.

B.P. 105-115° (Bath temp)/2.5-3 mm.

$[\alpha]_D$ -32.5

G.L.C. single peak

I.R. 1020 cm^{-1} (oxide)

Analysis:

Found: C, 81.00; H, 11.90%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%.

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CHAPTER II

LONG RANGE SHIELDING BY AN ALKYL GROUP

INTRODUCTION

It has been known since long[1,2] that axial protons in cyclohexane ring resonate at higher field than the equatorial protons. It was generally believed[1,2] that this shielding or deshielding is due to the C_2-C_3 bond which shields the axial proton and deshields the equatorial proton (Fig. 1).

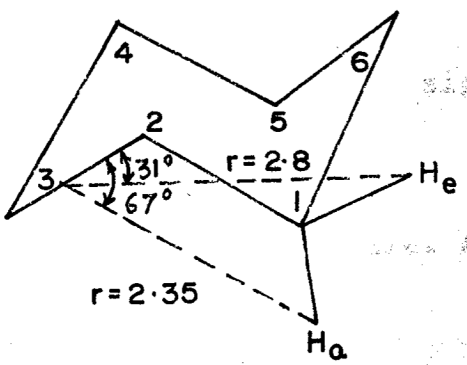


Fig. 1

Long range shielding in cyclohexane

Bhacca and Williams[3] have summarised the shielding and deshielding of ring protons of cyclohexane by replacement of one axial or equatorial hydrogen by different functional groups such as hydroxyl, acetoxyl, thiol etc. Since then several studies of this type have been made.

Studies involving shielding and deshielding by alkyl substituents is comparatively more recent.

In a detailed study of the anisotropy of the C-C single bond, Zürcher[2] supplied a possible explanation for such shielding and deshielding.

However, by a very careful analysis of the effects of alkyl substituents on ring protons in different cyclohexanols Eliel et al[4] demonstrated that shielding is not the contribution of the anisotropy of C-C single bond alone; the major contribution to such shielding is due to the syn-axial hydrogens which implies a contribution by the anisotropy of the C-H bond. This suggestion is in direct contrast to an opinion[1] that the C-H anisotropy would not have any significant contribution.

The results obtained by Eliel et al and corroborated by other workers[5,6] are briefly summarized below.

An equatorial methyl group causes a shielding of the equatorial hydrogens on the adjacent carbon by +17 cps (+ = shielding); and on C_3-equatorial hydrogen it has a negligible effect. (~ 1 cps). This methyl group causes a shielding of axial hydrogen at C_2 by 28 cps, whereas there is a small deshielding effect (~ 2 cps) on C_3 axial hydrogen. Fig. 2 summarises these results.

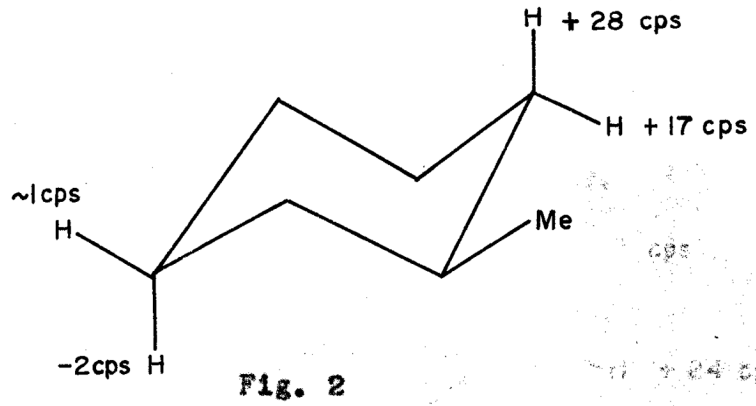


Fig. 2

Effect of equatorial methyl on protons of a cyclohexane ring.

A very significant finding was the observation that the shielding is not uniform for different alkyl groups. Thus an equatorial alkyl substituent has different shielding effects on the adjacent axial proton, the shielding being 28, 21, 11 and 2 cps when the alkyl group is a methyl, ethyl, isopropyl and t-butyl respectively.

Similar values have been observed in cyclohexyl-amines[7] and phthalimido cyclohexanes[7].

The different effects observed for alkyl substituents is even more dramatic when one considers the effect of the equatorial methyl on the vicinal equatorial proton. Two series in which this has been well established are the 2 alkyl cyclohexyl amines[7] and the neo-menthols[8] which suggests that the magnitude of shielding is in the order: methyl + 24 cps >> ethyl, n-propyl, n-butyl (+12 cps) > isopropyl, cyclohexyl (0.0) > t-butyl (-12 cps). In this series therefore t-butyl causes an appreciable deshielding.

An axial methyl group causes a large shielding (+24 cps) of the adjacent equatorial proton whereas it deshields both the C_2-axial hydrogen (-12 cps) and the C_3-axial

hydrogen (-11 cps). In quinalizidines[6] this deshielding of the C_3-axial proton has been found to be 16 cps. The axial methyl also deshields (6 cps) the C_3-equatorial proton. Fig. 3 summarises these results.

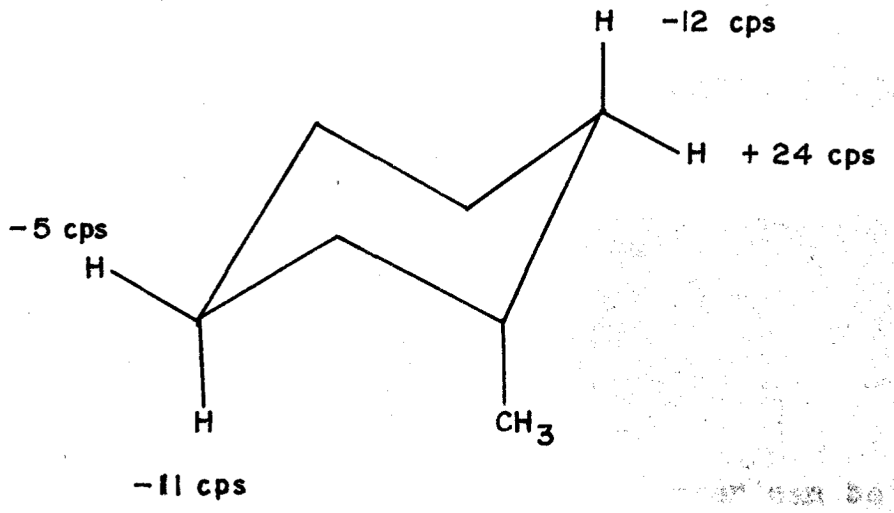


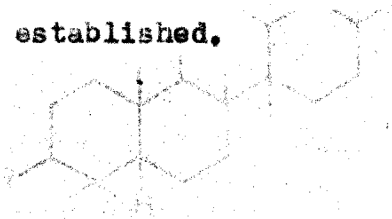
Fig. 3

Effect of axial methyl on remaining cyclohexyl protons

Such effects have been used by Booth[6] to explain several very interesting results in disubstituted cyclohexanes and some cis-decalin derivatives.

In order to ensure that their systems did not have conformational mobility Eliel et al[4] had chosen examples wherein one of the substituents was large enough (isopropyl or t-butyl) to prevent ring flip; as this substituent preferred to exist in the equatorial geometry, the orientation of other substituents was also fixed.

To have some examples in rigid skeletons wherein these effects would be more useful in assigning the geometry to a methyl group in an unknown structure, the present investigations chose examples from steroid and santonin field in which the configurations have been rigorously established.



Present Work

The work described in this chapter can be considered in two sections. In the first of these, preparation of suitable compounds having a rigid skeleton is described. In the second the spectral shifts observed through long range shielding by alkyl groups is discussed.

Preparation of suitable compounds

Cholestanol, its acetate and methyl ether were prepared by known procedures[37] starting from cholesterol.

Lupeol was obtained in a pure state through chromatography of a mixture rich in lupeol*. The lupeol thus isolated was characterised by its physical constants and spectral data. Its hydrogenation over Adam's

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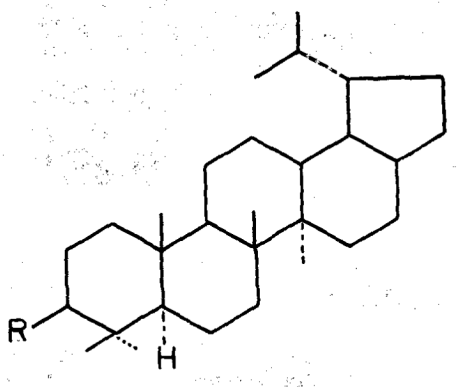
* We are indebted to Mr. C. Quasim of this laboratory for this sample.

catalyst as described by Heilbron et al[9] afforded lupanol (XIV, R = OH).



XIV

Lupanol acetate (XIV, R = OAc) was prepared by the usual method while the methyl ether (XIV, R = OMe) was prepared by a method modified by Narayanan and Iyer[10].

The santonin alcohol represented by (V, R = OH) has been prepared earlier[11] by hydrogenation of ∝-santonin using platinum oxide and acetic acid*. However in this method the formation of another compound is also reported[11]. The purification of the desired alcohol being achieved through its acetate. In our hands this method gave, as reported, the alcohol (IV) in about 10% yield as an ether insoluble residue. Its NMR clearly demonstrated this structure, as the C_6 proton appears as a quartet.

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* This major alcohol (M.P. 110-111°) obtained in this reduction was characterised by Cocker and McMurry[11] as 3∝-hydroxy 4,5 ∝(H) 6,11 β(H)-eudesman 6-13-olide, but recently[12] it has been established beyond doubt by NMR studies of the acetate and alcohol that the C_3-proton is axial. Rotational changes[11] from alcohol to acetate and steric considerations[11] also support this finding.

centered at 264 cps (J = 10 and 4 cps). The C_6 axial hydrogen has a vicinal C_7-axial proton which would account for the 10 cps coupling while the small (4 cps) coupling should be due to coupling with the C_5 equatorial proton. The C_3 proton appeared as a narrow signal (WH = 7 cps) at 225 cps. Its position and nature indicates that this proton is equatorial.

Crystallisation of the ether soluble portion gave the desired alcohol (V, R = OH) in comparatively low yield (55%). Besides, the melting point (low by 3.4°) suggested that this sample was not very pure.

An alternate method, involving hydrogenation of santonin to tetrahydrosantonin (II) using 2% $Pd/SrCO_3$, and reduction of the tetrahydrosantonin on platinum oxide in acetic acid, exclusively furnished the required alcohol V (R = OH) of high purity. This gave the reported physical constants. When the hydrogenation of tetrahydrosantonin (II) was carried out, with the same solvent and catalyst, under pressure (60 psi) the corresponding acetate (V, R = OAc) could directly be obtained in 79% yield.

Reduction of tetrahydrosantonin to corresponding alcohol (V, R = OH) could also be achieved by sodium borohydride[13] (Chart 1).

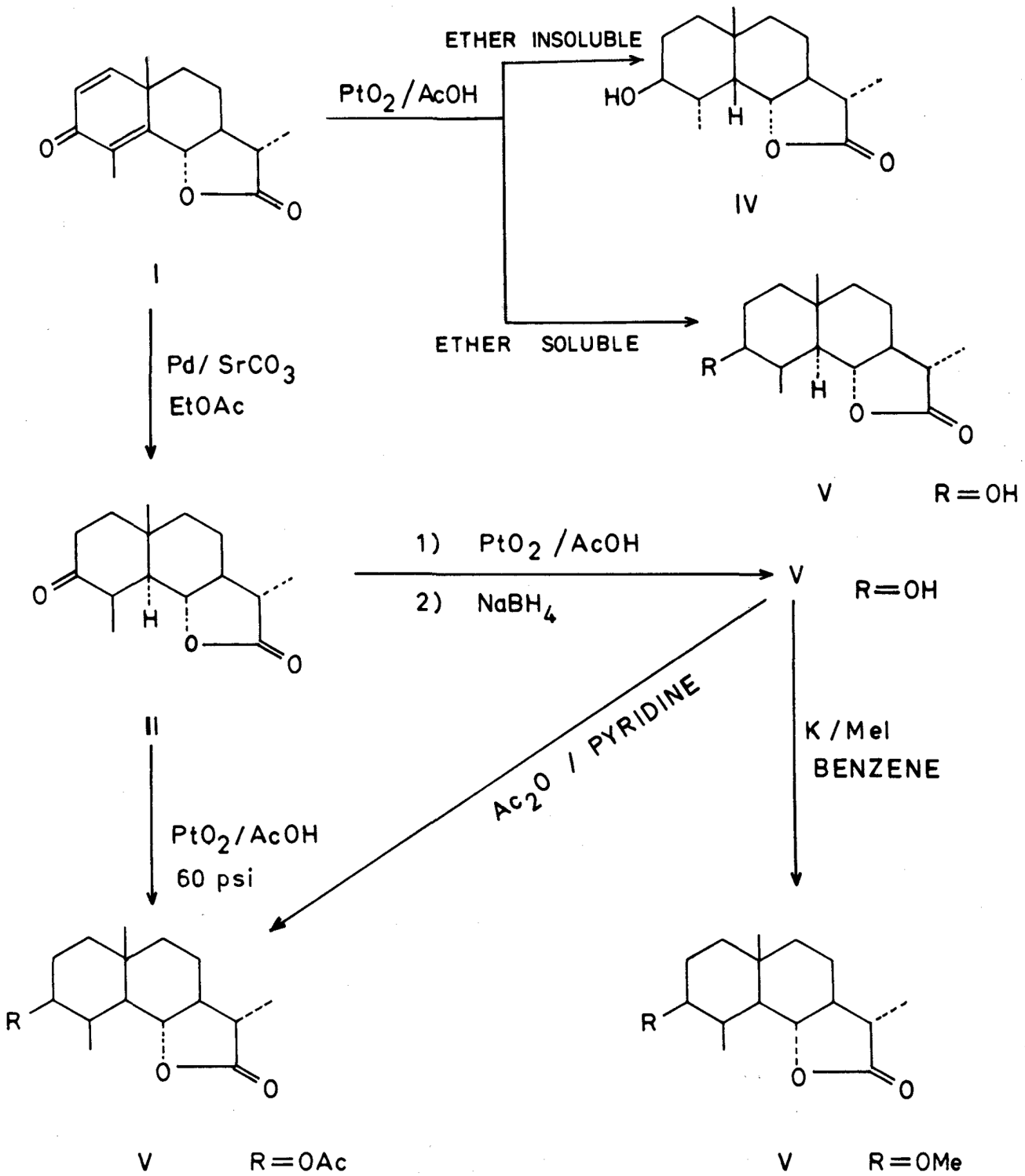

ETHER INSOLUBLE
PtO2 / AcOH
HO
H
O
O
IV
I
Pd/ SrCO3
EtOAc
ETHER SOLUBLE
R
H
O
O
V R=OH
1) PtO2 /AcOH
2) NaBH4
V R=OH
H
O
O
II
K / Mel
BENZENE
Ac2O / PYRIDINE
PtO2/AcOH
60 psi
R
O
O
V R=OAc
R
O
O
V R=OMe

CHART – 1.

The methyl ether of this alcohol was prepared by treatment with potassium and methyl iodide as reported earlier[10]. It may be pointed out that alkali formed in destroying excess of potassium with metahnol opens the lactone ring, to the hydroxy acid, to some extent. It is therefore necessary to acidify and warm the mixture after destroying potassium. The yield of methyl ether is low. This methyl ether was characterised by its infrared spectrum wnich had no hydroxyl absorption but displayed characteristic absorption for an aliphatic ether (1108 cm^{-1}) and a γ-lactone (1770 cm^{-1}). The NMR spectrum (Fig. 4) showed the C_3-proton as a broad signal at 195 cps (axial proton). The NMR spectrum also revealed the methoxy methyl at 200 cps as a sharp singlet. The C_6 proton a peared as a triplet (J = 10 cps). These couplings represent axial-axial couplings with C_5 and C_7 hydrogens. This not only shows the intact lactone but also established that no change has taken place in the stereochemistry of the lactone. The C_{10} methyl appeared at 63.5 cps while C_4 and C_{11} secondary methyls appeared as doublets centered at 73 and 53.5 cps respectively (J = 7 cps each). This and the elemental analysis clearly established that this is the desired methyl ether (V, R = OMe).

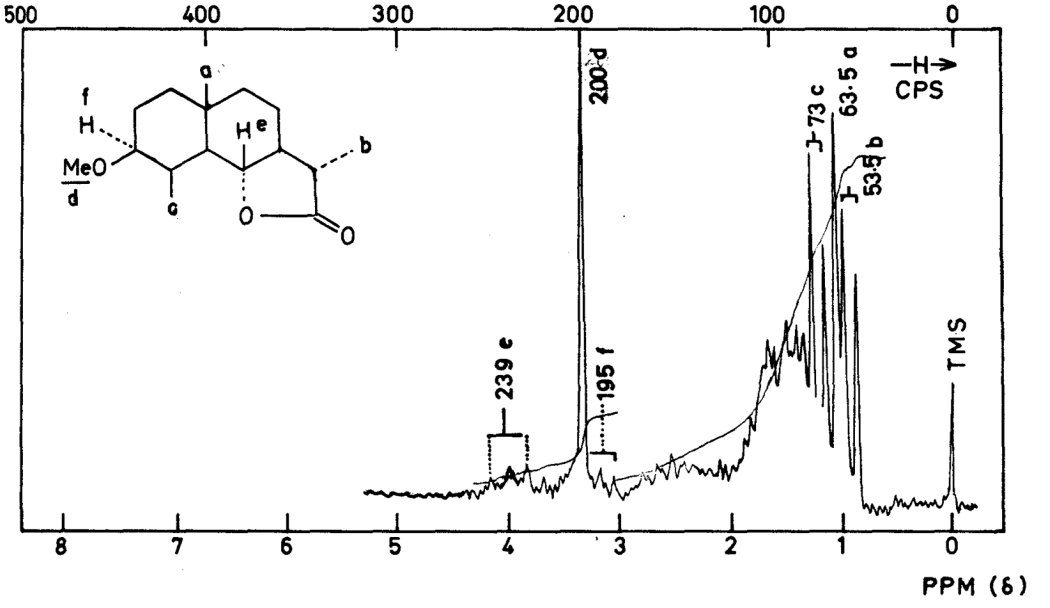


FIG 4. NMR SPECTRUM OF 3β-METHOXY-4,5α(H), 6-11β(H)-EUDESMAN-6*13-OLIDE

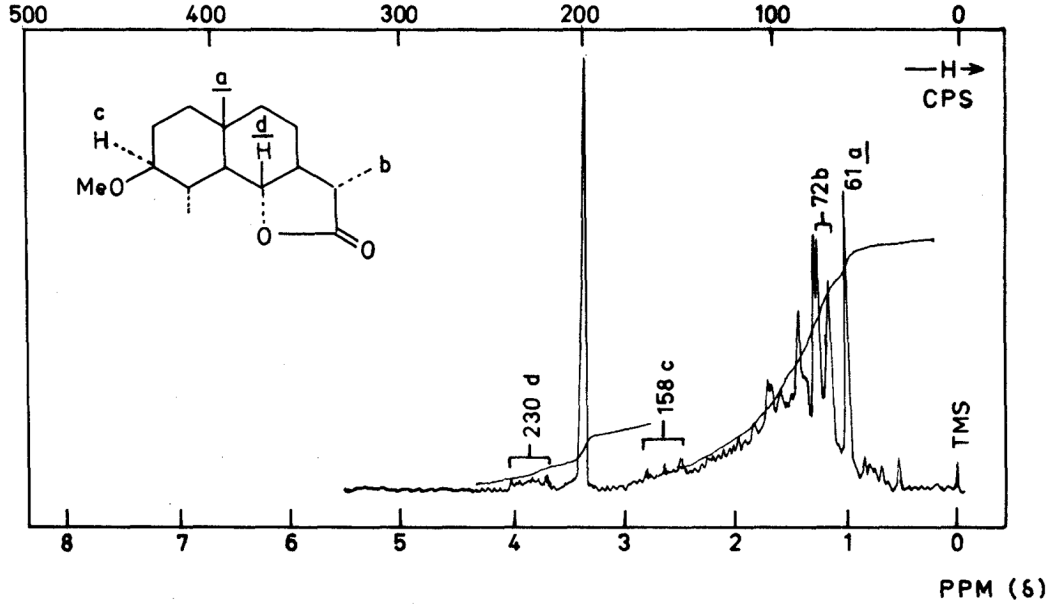


FIG. 5 NMR SPECTRUM OF 3 β-METHOXY-5α(H), 4, 6, 11 β(H)-EUDESMAN-6-13-OLIDE

In order to obtain the hydroxy lactone with a 4α methyl group (VI, R = OH), tetrahydro santonin (II) was converted to tetrahydro santonin (III) by acid catalysed epimerisation[14] at C_4. Reduction[11] of this ketone (III) with sodium borohydride gave the 3β-alcohol (VI, R = OH) as the major product (81%). Inverted dry column chromatography[15] of mother liquors afforded the C_3 epimer (VII, R = OH) in low yield (15%). Catalytic reduction of the above ketone however furnished the C_3-α epimer in 42% yield. (Chart 2)

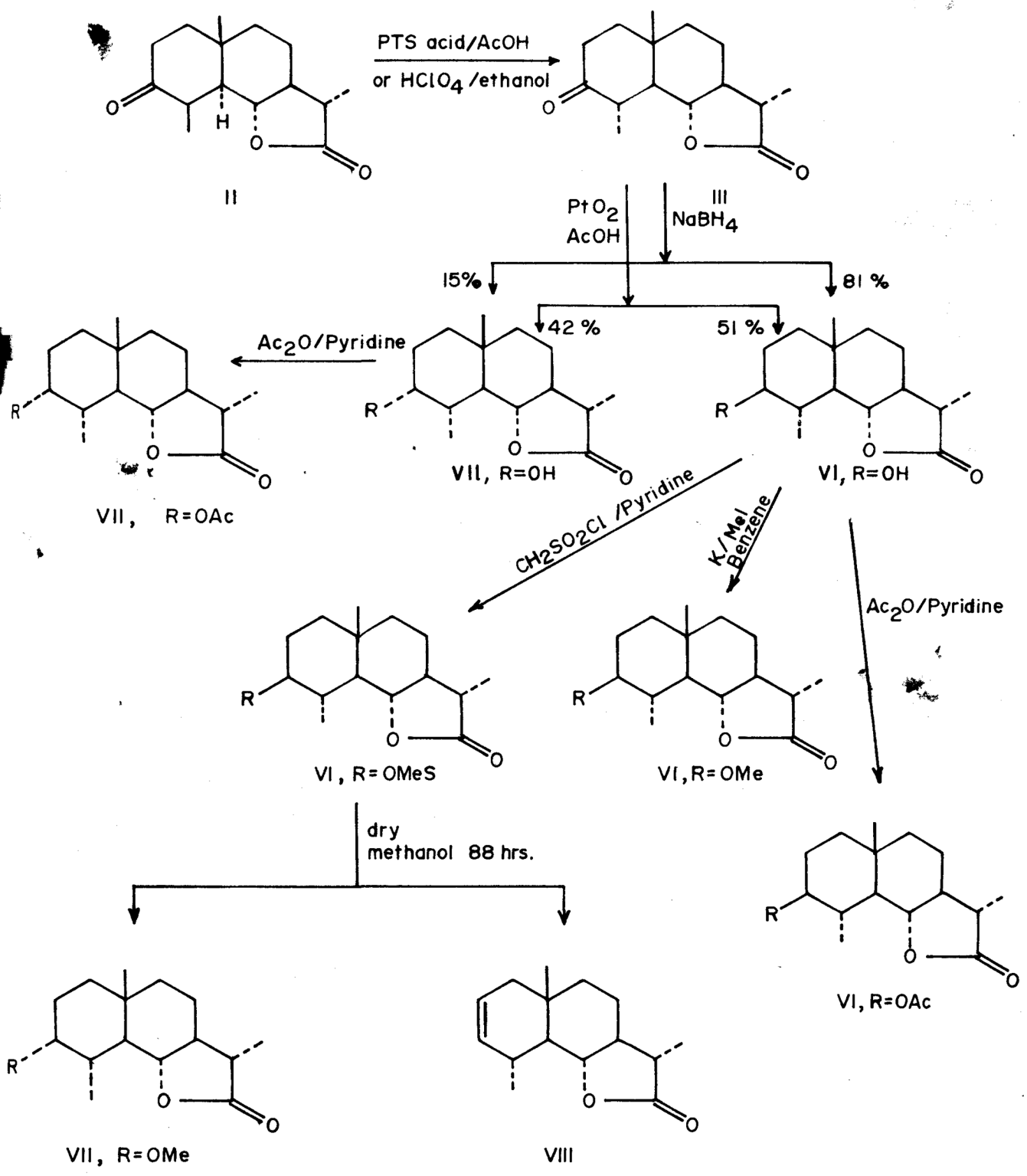
Acetylation of VI (R = OH) was comparatively easy whereas that of VII (R = OH), because of its axial geomtry required more drastic conditions.

The methyl ether (VI, R = OMe) was prepared from the corresponding alcohol by the usual method. Its yield was poor; though appreciable starting material was recovered. This compound was characterised by its I.R. spectrum which displayed ether absorption at 1095 cm^{-1} and absence of any hydroxyl band. The band at 1770 cm^{-1} could be assigned to the intact γ lactone. The NMR data (Fig. 5) given in Table 1 also confirms its structure.

In the case of VII (R = OMe) solvolysis of the mesylate[16] (VI, R = OMeS) provided a convenient route for the preparation of this compound.

This solvolysis afforded a mixture of two products besides the unreacted mesylate. Separation by column chromatography over silica gel provided in earlier benzene

CHART - 2


PTS acid/AcOH
or $HClO_4$ /ethanol
II
III
PtO_2
AcOH
$NaBH_4$
15%
81 %
42 %
51 %
Ac_2O/Pyridine
VII, R=OAc
VII, R=OH
VI, R=OH
CH_2SO_2Cl /Pyridine
K/MeI
Benzene
Ac_2O/Pyridine
VI, R=OMeS
VI, R=OMe
VI, R=OAc
dry
methanol 88 hrs.
VII, R=OMe
VIII

fractions a crystalline solid m.p. 146-47°, $[\alpha]_D$ + 21° whose I.R. spectrum indicated an intact lactone (1775 cm^{-1}) and olefinic absorption (1660 cm^{-1}) which must be cis disubstituted (690 cm^{-1}). The NMR spectrum (Fig. 6) provided incisively that this olefin is the Δ^2 olefin (VIII) as it showed a very characteristic AB quartet centered at 330 cps (J = 11 cps, δ AB 11.5 cps). Apart from this quartet one quaternary methyl (singlet at 57 cps), one doublet (6H, centered at 72 cps, J = 7 cps) and a proton on carbon carrying oxygen (triplet at 228.5 cps J = 10 cps) could be detected.

The later benzene fractions gave the methyl ether (VII, R = OMe). Its IR spectrum displayed bands at 1770 cm^{-1} (γ lactone) and 1097 (OCH_3). The detailed analysis of the NMR spectrum (Fig. 7) shown in Table 1 established its structure.

Table 1

Analysis of the NMR spectra of the methyl ether VI (R = OMe) and VII (R = OMe)

Line position In VI	Line position In VII	Nature	No.of protons	Assignment
205	200	Singlet	3H	Methoxyl methyl
230	229	Triplet (J=10 cps)	1H	C_6-H
158	190	Broad in VI Narrow in VII	1H	C_3 H
61	59	Singlet	3H	C_{10}-CH_3
72, 74	69, 71	Doublets (J=7 cps)	3H each	C_{11}- and C_4-CH_3

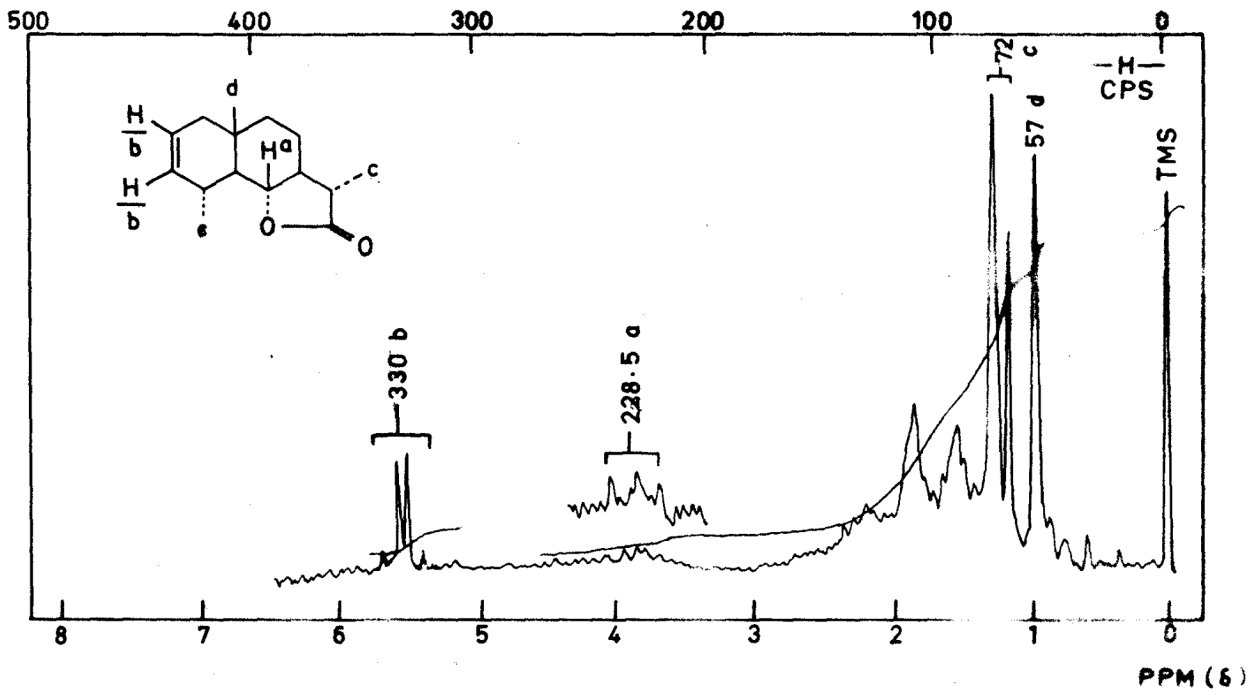


FIG. 8 NMR SPECTRUM OF 5α(H) 4.6.11β(H)-EUDESMAN-2-on-6-13 OLIDE (VIII)

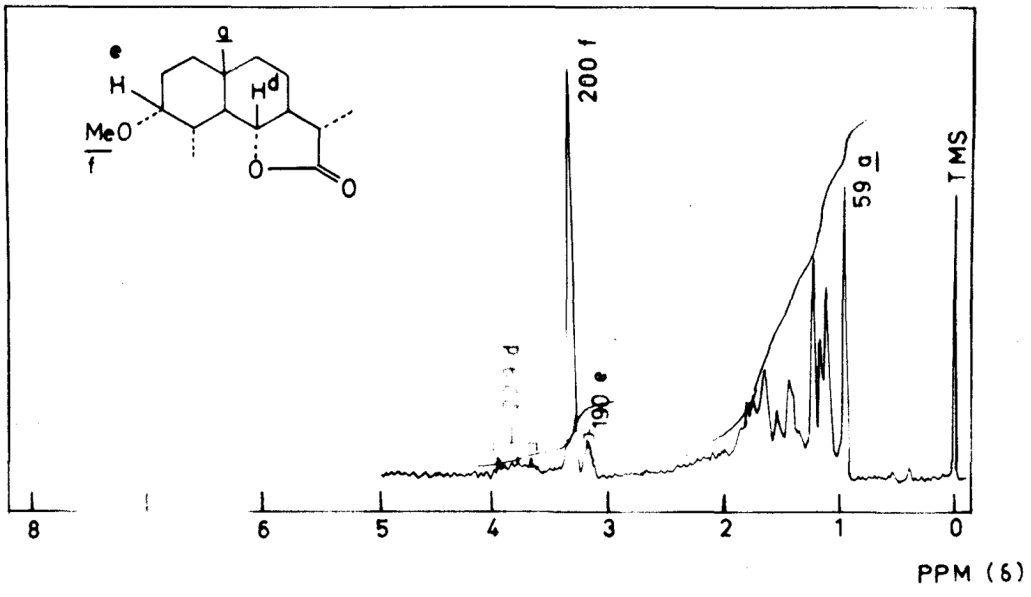


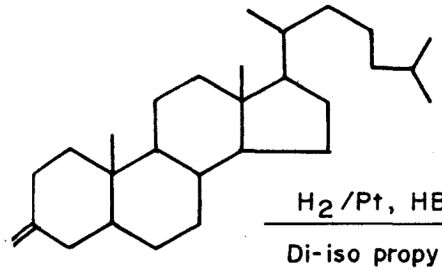
FIG. 7 NMR SPECTRUM OF 3α-METHOXY 5α(H), 4, 6, 11β(H)-EUDESMAN-6-13 OLIDE

The best known method[17] for preparing epicholestanol is the hydrogenation of cholestan-3-one in acid medium. Though yields up to 70% have been reported by this method, in the present investigation the yield of epicholestanol was rather poor (~ 17%). The only change that was made being the replacement of dibutyl ether by di-isopropyl ether as a solvent.

In view of this an alternate method starting from cholestanyl tosylate was preferred. In this reaction cholestanyl tosylate (IX, R = OTs) was subjected to formolysis with dimethyl formamide. It has been reported[18] that the ratio of epi-chole-stanyl formate (X, R = OCHO) to the Δ^2 olefin (XI) is 3:1. We were however able to get the formate in ~60% yield. Hydrolysis of the formate (characterised by its physical constants and spectral data) afforded epi cholestanol (X, R = OH) in quantitative yield.

In view of the known difficulty to acetylate epicholestanol[19], epicholestanyl acetate (X, R = OAc) was directly prepared by the action of a mixture of BF_3 etherate and acetic anhydride on cholestanyl methyl ether[13] (IX, R = OMe) at 0^o for fifteen hours. From the resulting mixture of products (Chart 3) the required acetate (X, R = OAc) was isolated in (27%) by Inverted dry column chromatography[15], along with the epimeric acetate (IX) and Δ^2 olefin (XI).

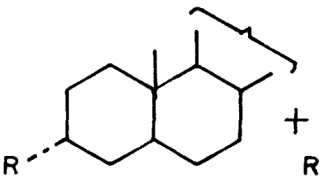
CHART- 3



CHOLESTAN- 3 ONE

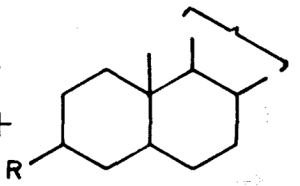
H_2 /Pt, HBr

Di-iso propyl ether



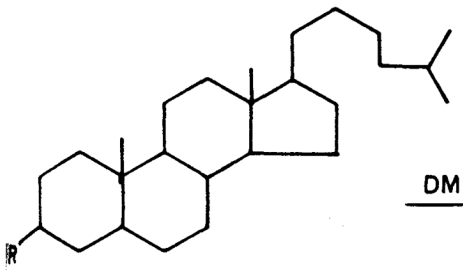
17 %

X , R=OH



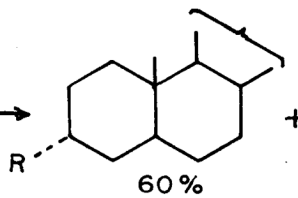
80 %

IX , R=OH



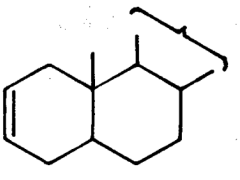
IX, R=OTs

DMF, 78°, 24 hrs.



60 %

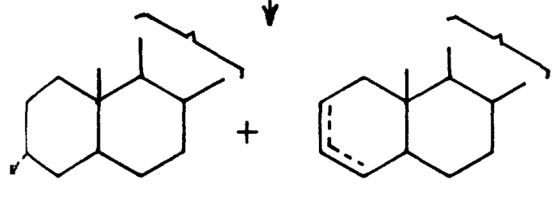
X,R=OCHO



XI

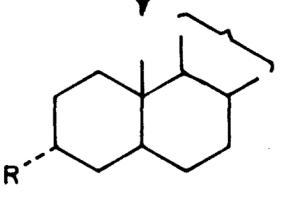
Methanol

90 hrs.

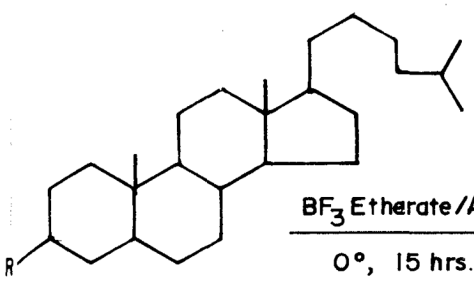


X, R= OMe

OH^-



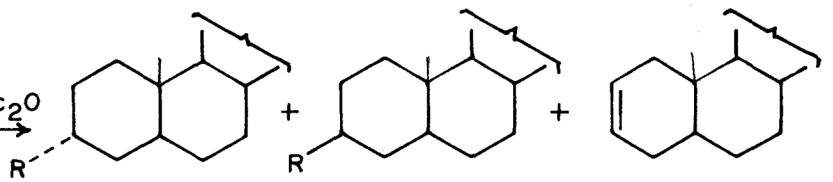
X, R=OH



IX, R= OMe

BF_3 Etherate/Ac_2O

0°, 15 hrs.



X, R=OAc

IX, R=OAc

XI

When cholestanyl tosylate (IX, R = OTs) was subjected to methanolysis under the conditions reported by Nace[16] the major product (73% (Chart 3) is the desired methyl ether (X, R=OMe) characterised by its physical constants.

In applying the above reactions to get 3α epimers in 4β methyl santonin derivatives, the mesylate (V, R = OMeS) was refluxed with methanol to get the methyl ether formed through inversion at C_3. However in practice it was observed that the product of the above reaction contained apart from a large amount of unchanged mesylate two other compounds (TLC). Separation of this mixture by chromatography over silica gel gave all three compounds in pure form.

The fastest moving of these (XIII) had infrared vibration corresponding to γ lactone (1775 cm^{-1}) and a tri-substituted olefin (1660, 790, 860 cm^{-1}). The NMR spectrum (Fig. 8) of this had signals ascribable to a quaternary methyl (singlet 55.5 cps) a secondary methyl (doublet at 72 cps; J = 7 cps), a vinylic methyl (broad singlet at 110 cps), a proton on a carbon carrying oxygen (multiplet at 238 cps) and an olefinic proton (multiplet at 325 cps). The presence of slight traces of Δ^2 olefin in this compound could be established by the minor signals at 62.5 and 335 cps*.

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* An authentic specimen of Δ^2 olefin has important signals[20] at this position.

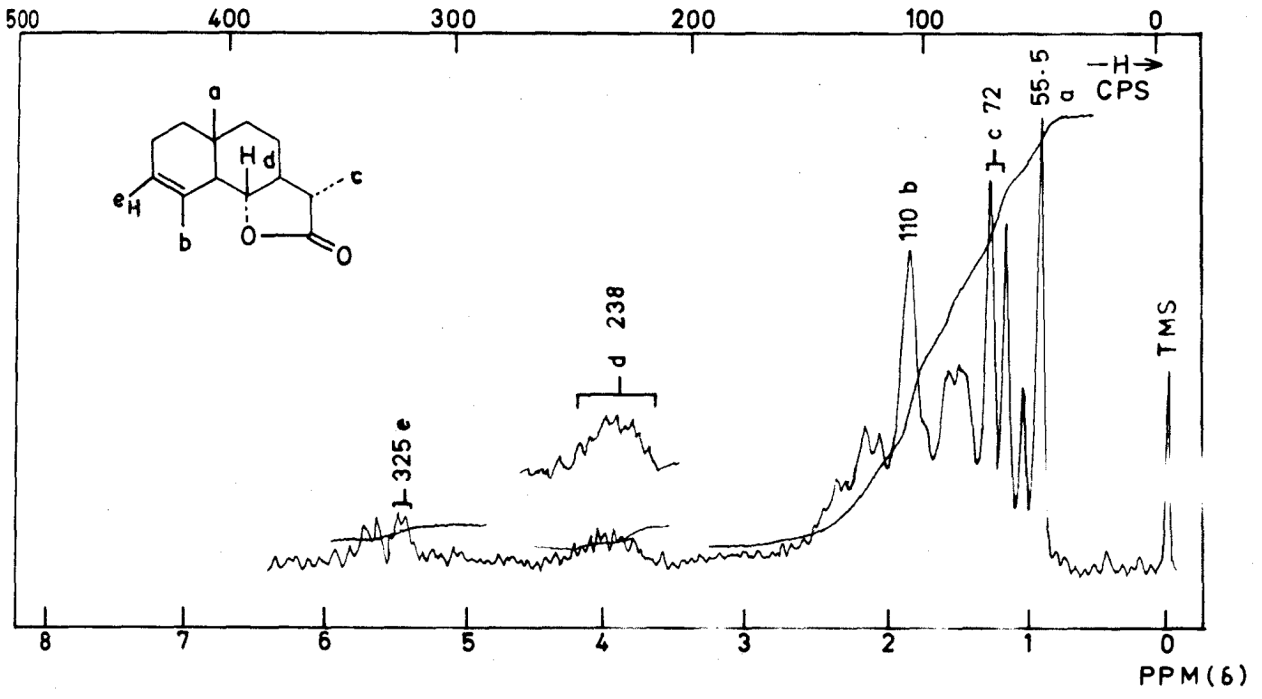


FIG. 8. NMR SPECTRUM OF 5α (H) 6.11β (H) - EUDESM 3-en-6-13-OLIDE (XIII)

The latter fractions after crystallisation showed IR vibration for γ lactone (1780 cm^{-1}) and an exomethylene group (1660, 890 cm^{-1}).

The NMR spectrum (Table 2, Fig. 9) analysed well for a $\Delta^{4\,(14)}$ olefin (XII, Chart 4).

Table 2

NMR data of $\Delta^{4(14)}$ olefin (XII)

Line position cps	Nature of the signal	No. of protons	Assignment
51.5 cps	Singlet	3	C_{10}-CH_3
72.5 cps	Doublet (J = 7)	3	C_{11}-CH_3
238 cps	Triplet (J = 10 cps)	1	C_6-H
286] 296]	Broad signals	1] 1]	Exomethylene protons

Methanolysis of tosylate (V, R = OTs) or formolysis of mesylate (V, R = OMeS) afforded mixtures, NMR analysis of which suggested once again the same mixture of olefins without any formation of the desired methyl ether or formate respectively.

It is conceivable that in order to have suitable trans-anti geometry these compounds may pass into a conformation in which the A ring is a boat. Formation of a boat (A, Chart 5) in the transition state would be aided by the energy release arising from a relief of

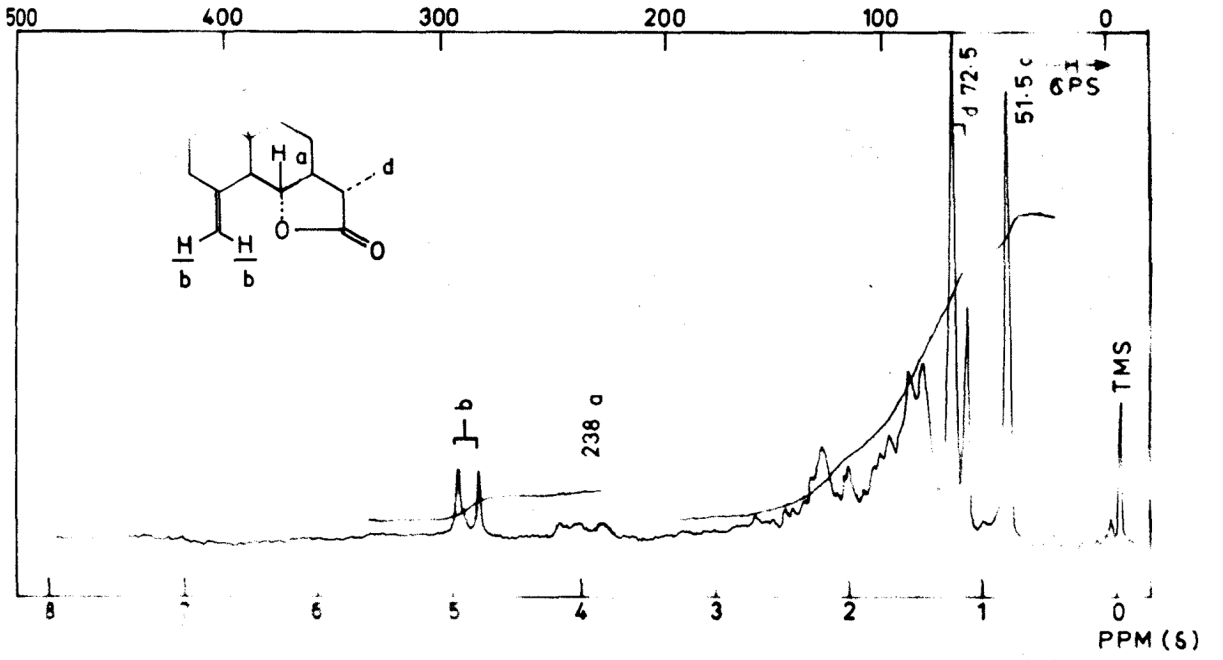


FIG. 9. NMR SPECTRUM OF 5α(H) 6 11β(H) EUDESM - 4(14)-en-6-13 OLIDE (XII)

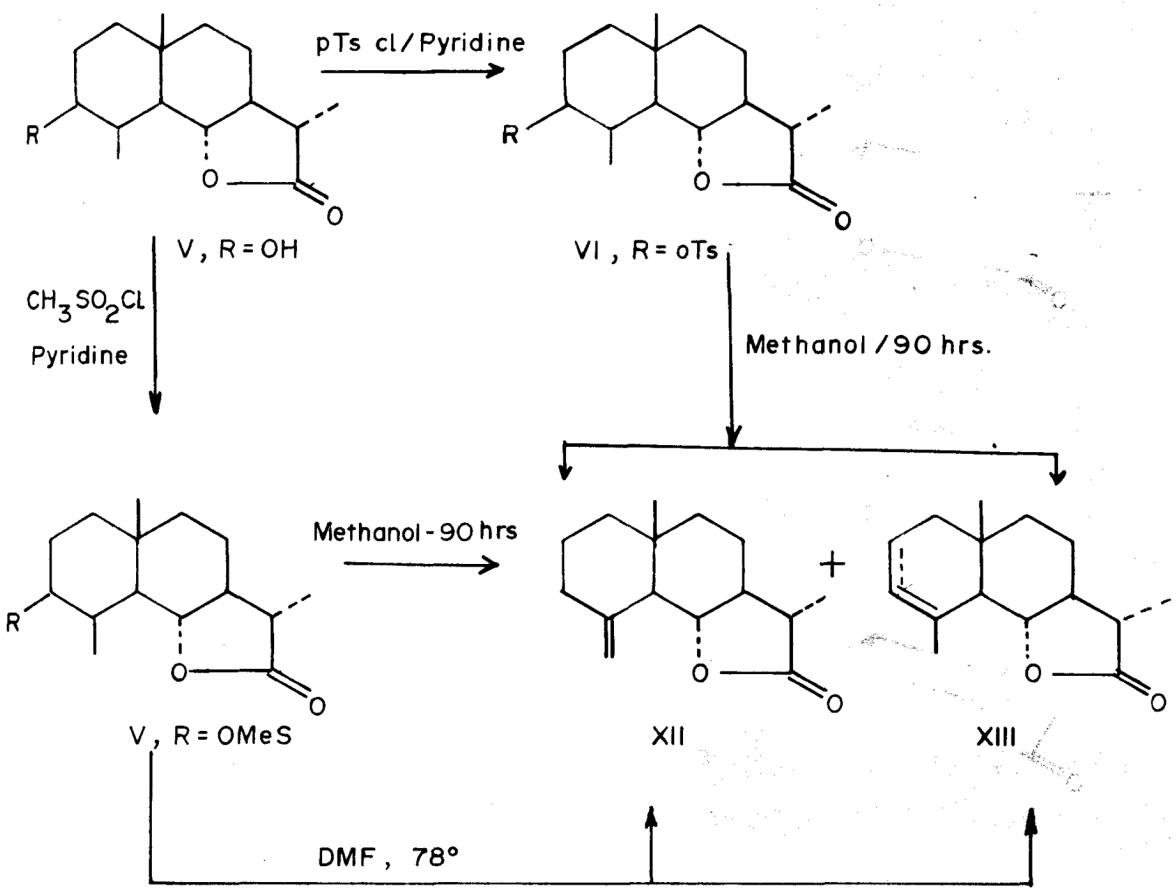
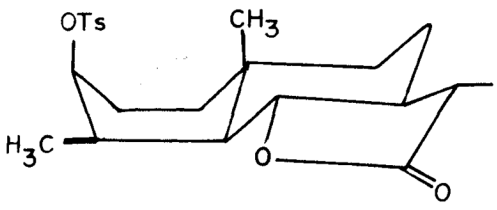
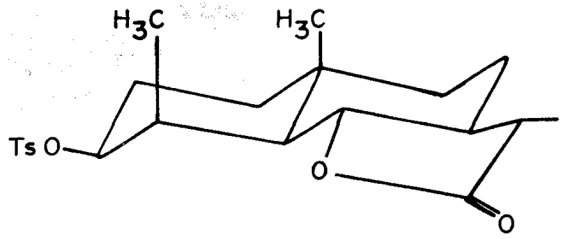

pTs cl/Pyridine
R
O
O
V, R = OH
VI, R = oTs
CH_3SO_2Cl
Pyridine
Methanol / 90 hrs.
Methanol - 90 hrs
+
V, R = OMeS
XII
XIII
DMF, 78°

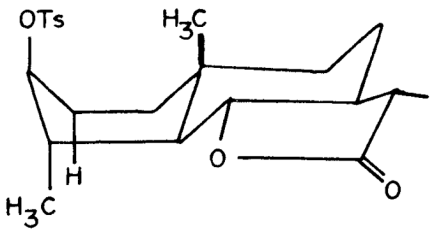
CHART – 4



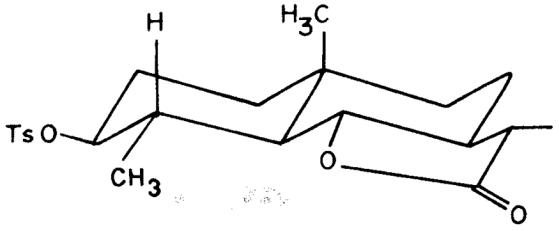
A



B



D



C

CHART - 5

1:3 diaxial methyl-methyl interactions (B). If such a boat transition state (A) can be invoked then those molecules which acquire sufficient energy to reach the transition state can easily undergo trans elimination to afford the Δ^3 or the isomeric $\Delta^{4(14)}$ olefin. This transition state would explain the almost total absence of Δ^2 olefin in this reaction. It may be relevant to point out that the corresponding 4α methyl derivative (C) gave only the Δ^2 olefin as the elimination product. A boat intermediate (D) in this later case would not have any steric relief as there is no relief of diaxial interaction as in the present case and instead the C_4-methyl now has 1:3 interaction with 2α hydrogen in the boat conformation (Chart 5). This therefore will undergo more solvolysis and less elimination.

Epilupanol acetate (XV, R = OAc) was obtained by hydrogenation of epilupeol acetate*. Prolonged hydrolysis of the acetate furnished epilupanol (XV, R = OH) in good yields. Attempted methylation of the small sample available did not afford the desired methyl ether and starting alcohol was recovered even under drastic conditions.

Attempts at preparing 3α methyl ether of lupanol by methanolysis[21,22] of the 3β tosylate were unsuccessful

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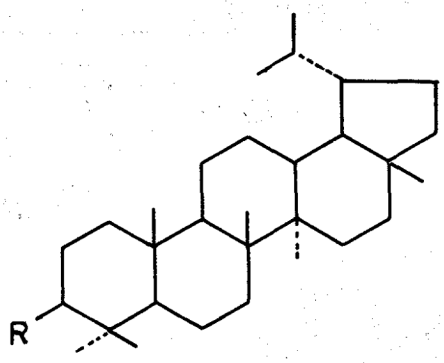
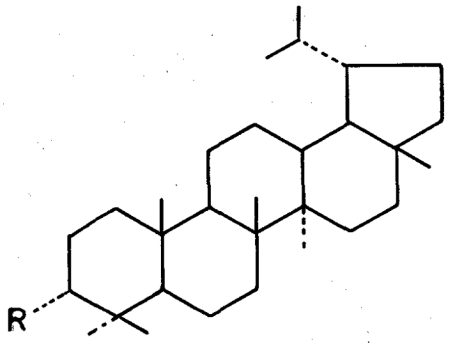
* We are grateful to Prof. T. R. Govindachari of Ciba Research Centre, Bombay for the sample of this compound.

(NMR of crude product obtained did not show any peak for OCH_3).



R = OTs
XIV



R = OMe
XV

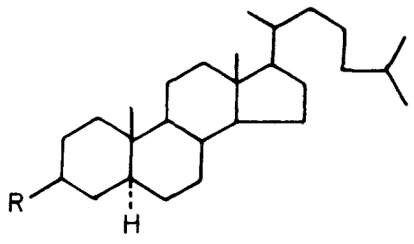
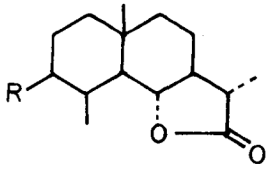
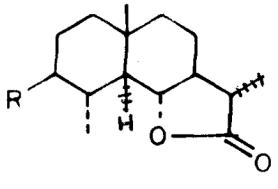
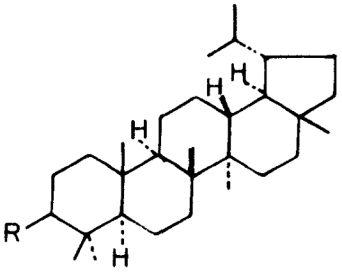
It may be mentioned in summing up that of the series of compounds whose preparation was undertaken no derivatives corresponding to 3-∝R 4,6 ∝(H) 6,11 β(H) eudesman 6-13 olide (R = OH, OAc or OMe) could be obtained. Epilupanol methyl ether also could not be obtained.

SPECTRAL SHIFTS

The NMR spectrum of cholestanol (IX, R = OH) shows the C_3 hydrogen signal as a broad multiplet centred at 215.5 cps, whereas in lupanol (XIV, R = OH). This proton signal appears as quartet centred at 191 cps (Table 3). Overall, there is therefore, a shielding of 24.5 cps by introduction of the gem-dimethyl group at C_4. It is obvious that other differences in the structure of lupanol and cholestanol would not have any effect on the signal of the C_3 hydrogen because these changes are very far removed from the centre, at present, under consideration.

TABLE 3

SHIFT OF C_3-AXIAL PROTON BY ADJACENT METHYL GROUP

No.	Compound		Chemical shift in Alcohol	Acetate	Methyl ether
IX			215.5	281	187
V			225	287	195
	Shift caused by C_4 axial methyl		-9.5	-6	-8
VI			186	261	158.5
	Shift caused by C_4-equatorial methyl		+29.5	+20	+28.5
XIV		Observed values	191	264	158.5
		Calculated values	195.5	267	166.5
		Difference	+4.5	+3	+8

To determine the contributions of each of these methyls the spectrum of santonin derivative (V , R = OH) having C_3-equatorial hydroxyl and C_4-β methyl (axial) was examined. In the spectrum of this compound the C_3 hydrogen resonates at 225 cps (broad multiplet). Thus the introduction of β-methyl at C_4 causes deshielding of 9.5 cps on C_3-axial hydrogen. The C_4-epimer of this compound (VI , R = OH) displayed (Fig. 10) its C_3 hydrogen as a broad multiplet centered at 186 cps, thus causing a shielding of the C_3-axial hydrogen by 29.5 cps+ as compared to cholestanol. These values are in good agreement with the reported values (axial methyl deshields the axial proton on adjacent carbon atom by ~12 cps and equatorial methyl shields it by ~ 28 cps) of such effects in cyclohexane derivatives. This agreement suggests that a comparison of cholestanol and santonin derivatives is justified.

If one assumes that these values are additive then the C_3-proton signal in lupanol (XIV, R = OH) would be expected to be shielded by 20 cps as compared to cholestanol (i.e. ~~is~~ at 196 cps). Using earlier values[4] this shielding would be expected to be 16 cps (i.e. the resonance should be

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+ It would be obvious that more accurate comparison can be made if 4α methyl and 4β methyl cholestanol are examined but the more readily available santonin derivatives were used because in these ring A has essentially the same features as cholestanol. Ring B substituents are too far from the C_3-hydrogen to have any significant effect.

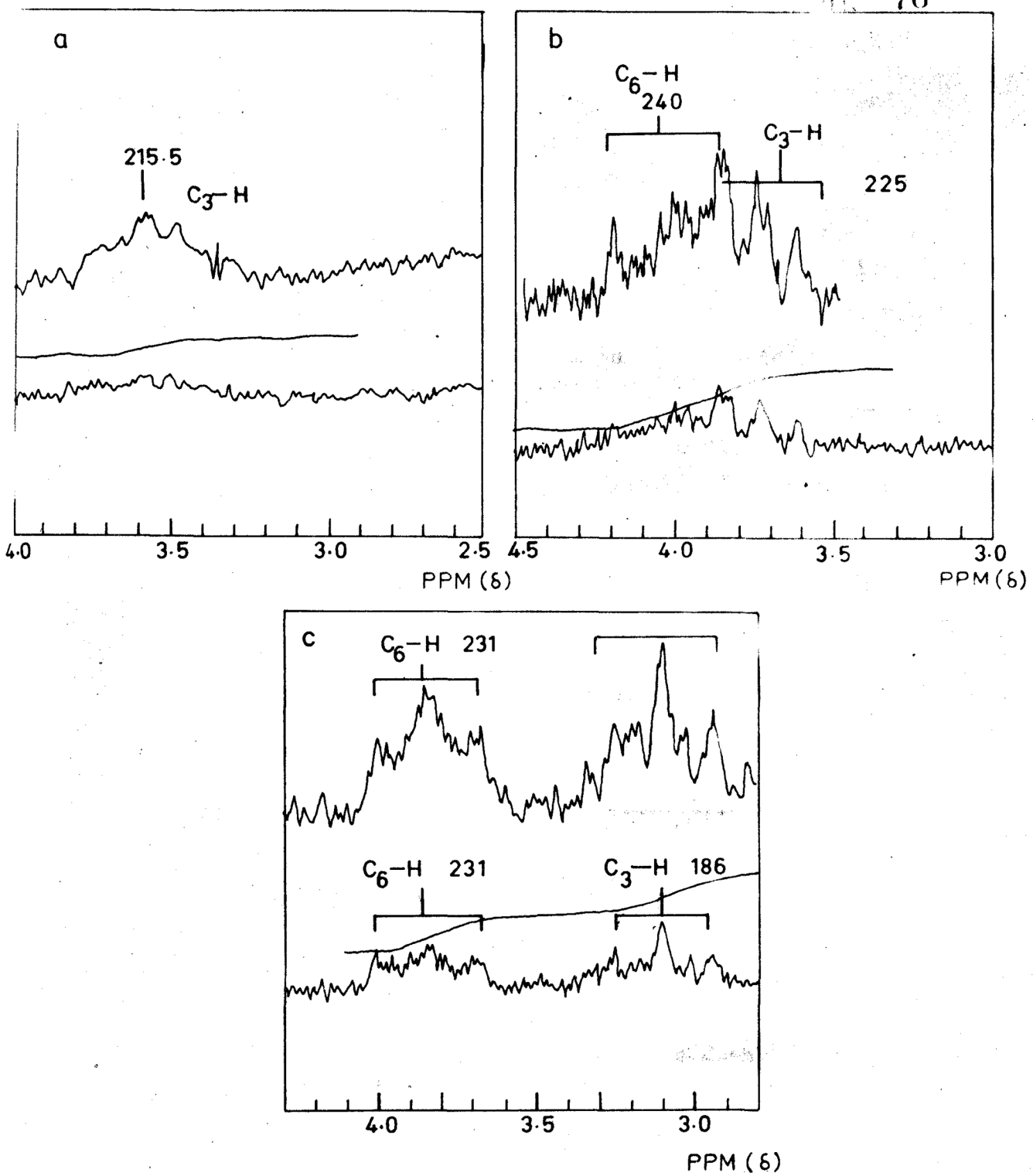


FIG. 10. NATURE OF C_3–H IN EQUATORIAL ALCOHOLS

R=OH

(a) in IX (b) in V (c) in VI

at 199 cps). The slight deviation between expected and observed values may indicate that additivity is not necessarily first order.

Similar comparisons of the acetates (Fig. 11) and methyl ethers of these derivatives (Table 3) would require the C_3-H in corresponding lupanol derivatives to resonate at 267 and 166.5 cps respectively; the observed resonances are at 264 and 168.5 cps respectively.

An examination of the differences between calculated and the observed values for lupanol derivatives brings out the fact that in all cases the observed values are at slightly higher field than the calculated ones. Another interesting observation is that shifts in the acetates are of lesser magnitude than the alcohols and methyl ethers.

With a view to observe similar effects on equatorial protons, derivatives epimeric at C_3 were examined (Table 4).

Epicholestanol (X, R = OH) has the resonance of its C_3-hydrogen at 243 cps as a narrow signal indicating its equatorial nature. The corresponding 4α-methyl santonin derivative (VII, R = OH) had its C_3-H resonance (Fig. 12) as a narrow signal at 228.5 cps. This corresponds to a shielding of the vicinal equatorial proton by an equatorial methyl by 14.5 cps. The previously reported value for such a shielding is 17 cps. The corresponding 4β methyl santonin derivative could not be prepared though several attempts (see experimental section) in this direction had been made.

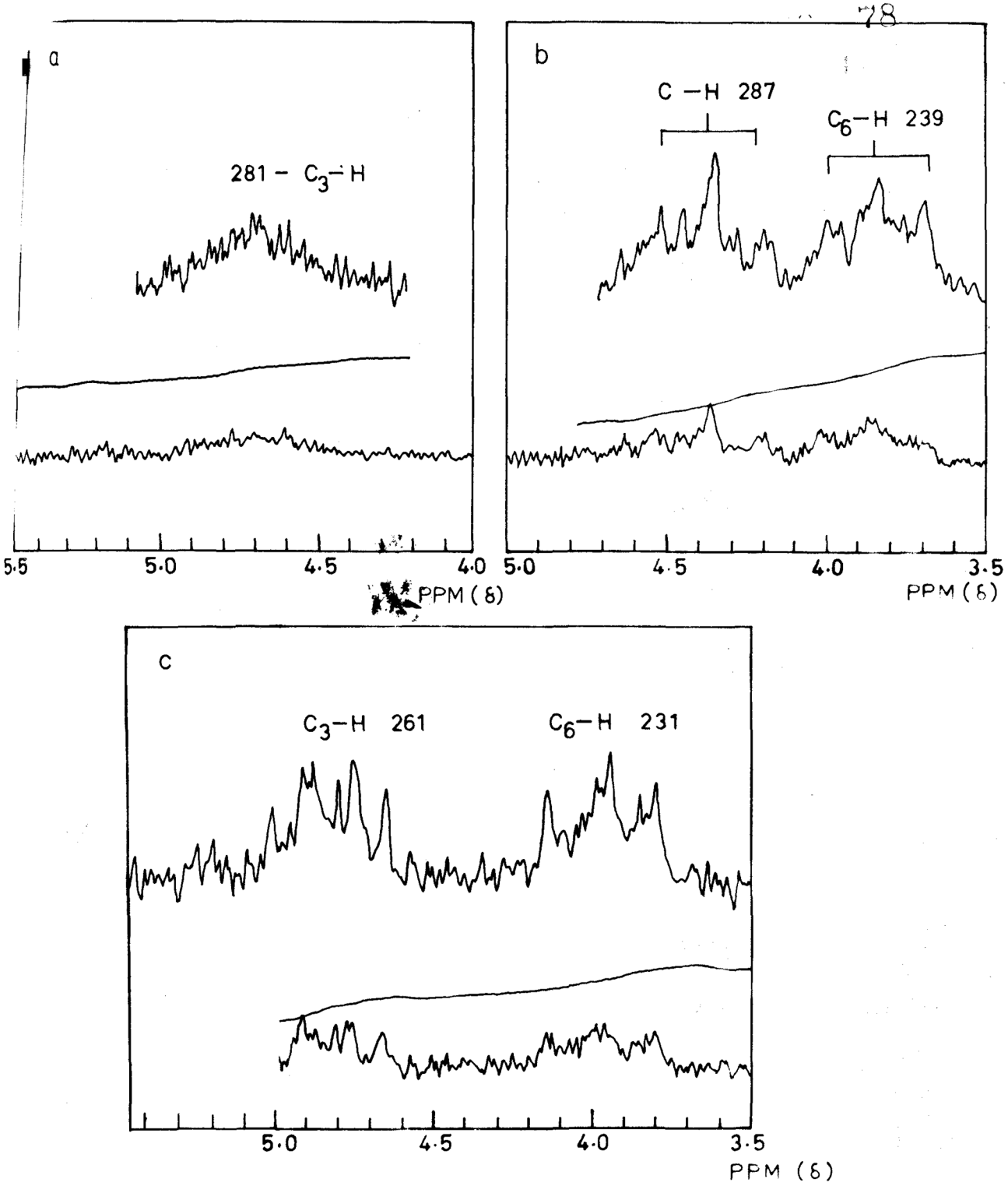


FIG. 11. NATURE OF C_3–H IN EQUATORIAL ACETATES R=OAc

(a) in IX (b) in V (c) in VI

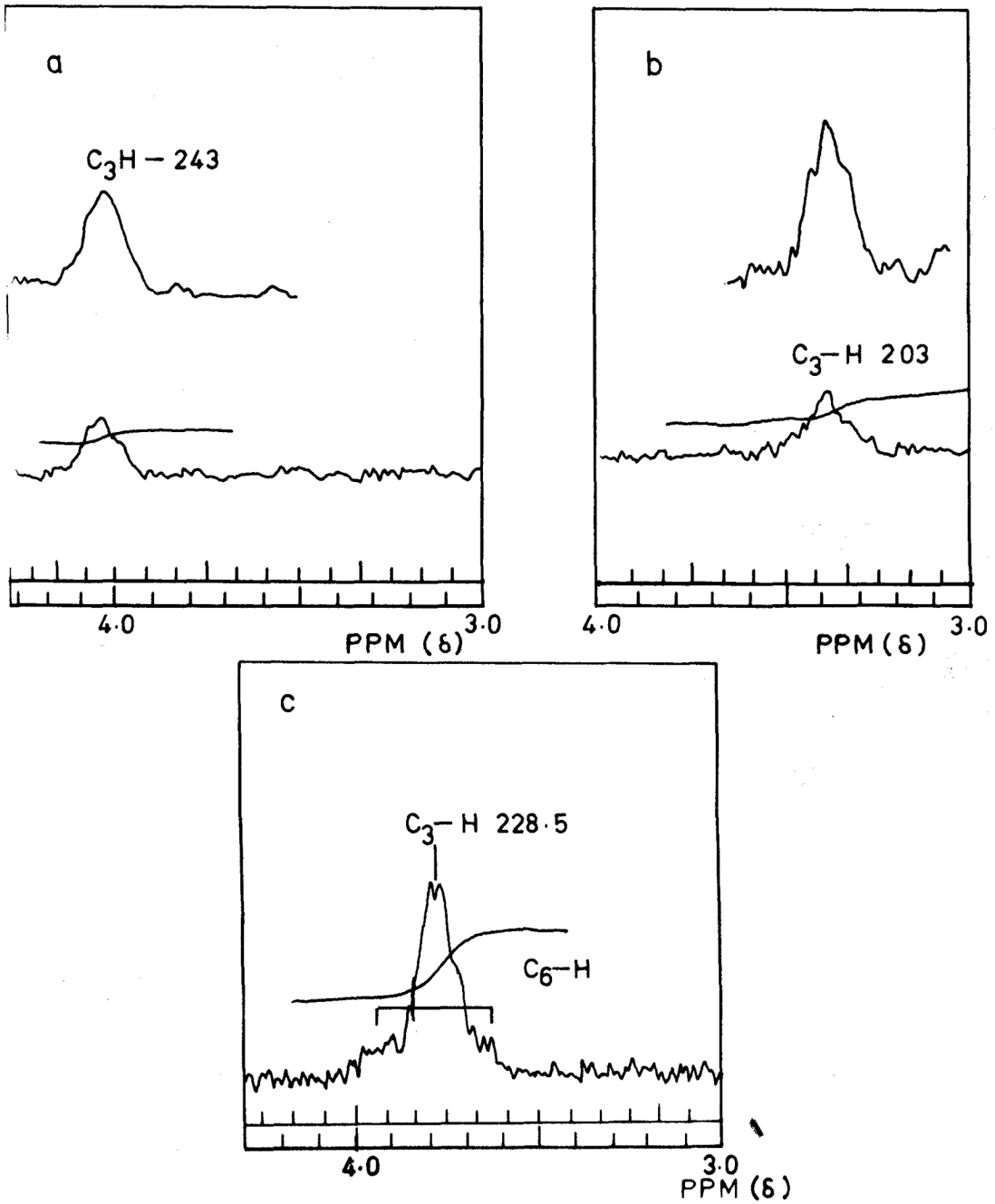


FIG. 12. NATURE OF C_3–H IN AXIAL ALCOHOLS R=OH

(a) in X (b) in XV (c) in VII

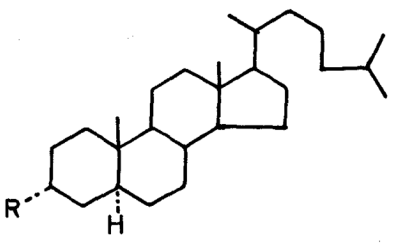
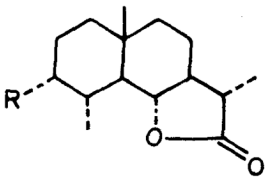
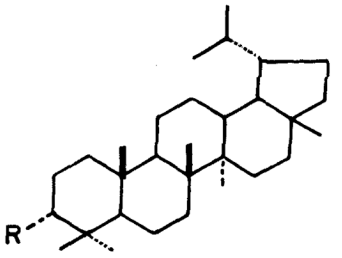
If one uses the literature value of +24 for such a shielding (equatorial hydrogen by adjacent axial methyl) the calculated value for C_3-proton of epilupanol (XV, R = OH) would be 205 cps. The observed signal for C_3-H at 203 cps in epilupanol is therefore in good agreement. The analogous shift value for the acetate is also presented in Table 4.

Using these ideas the calculated value for C_3-H of epilupanol methyl ether (XV, R = OMe) would be 166 cps. Though several attempts to prepare this compound were made, these were not successful. It can however be anticipated that in epilupanol methyl ether the C_3-hydrogen should resonate at ~166 cps.

If one looks at the C_6-hydrogen in different santonin derivatives, then it would be anticipated that though this hydrogen is in a different ring as compared with the C_4-methyl, its spatial relationship with C_4 is exactly identical with the spatial relationship of the C_2 axial hydrogen with the C_4-methyl, if the methyl at C_4 is β oriented. It can therefore be expected that this C-6 hydrogen would feel a similar long range effect of the 4β-methyl as the C_2-axial hydrogen. Eliel et al[4] have shown that an axial methyl deshields the axial hydrogen, which is in a cis 1:3 relation with it, by 11 cps. It can, therefore, be argued that the C_6-hydrogen of santonin derivatives having a 4β-methyl group would be deshielded by ~ 11 cps in comparison with santonin compounds having no methyl at this position.

TABLE 4

SHIFT OF C_3 EQUATORIAL PROTON BY ADJACENT METHYL GROUP

No.	Compound		Chemical shift in Alcohol	Acetate	Methyl ether
X			243	303	207
VII			228.5	298	190
	Shift caused by C-4 equatorial methyl		+14.5	+5	+17
	Literature shift by axial methyl on adjacent equatorial proton		24	24	24
XV		Observed values	203	278	
		Calculated values	204.5	274	166.0
		Diff.	+1.5	-4	

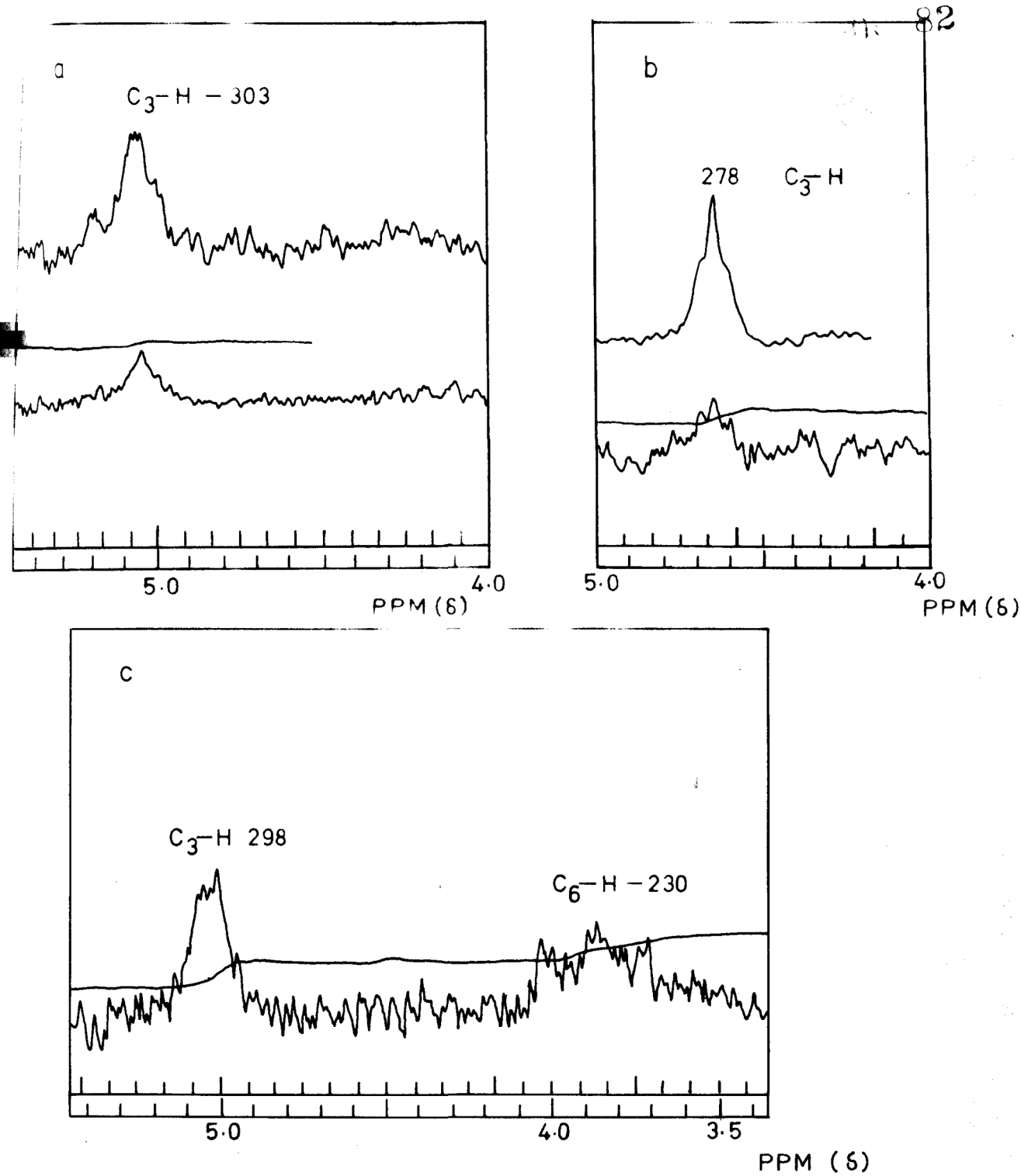


FIG. 13. NATURE OF C_3–H IN AXIAL ACETATES R =OAc

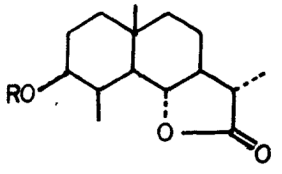
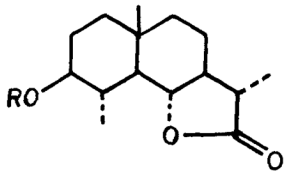
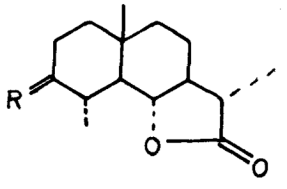
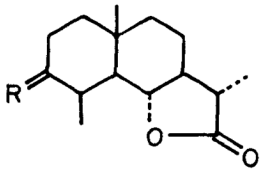
(a) in X (b) in XV (c) in VII

The position regarding the C_4-equatorial methyl and this hydrogen is not the same in comparison with the C_2-axial hydrogen and C_4-equatorial methyl group. This distance in the former is only 3.2° Å whereas in the later it is ~ 4°A. As the relative geometries are however the same the difference between the effects on these two hydrogens should be essentially one of magnitude. Eliel et al have shown[4] that in such a situation there is a deshielding of 2 cps. It can therefore be expected the C_6-hydrogen should also feel deshielding due to equatorial C_4-methyl which may perhaps be slightly larger (~ 3 cps).

From this rationalisation it can be expected that in those santonin derivatives (V,XVII) having an axial C_4-methyl, the C_6-hydrogen should be at ~8 cps lower field than the corresponding santonin derivatives having a C_4-equatorial methyl. Table 5 demonstrates the validity of this argument and elegantly shows how an understanding of these effects could help in establishing stereochemical assignments for unknown compounds.

TABLE 5

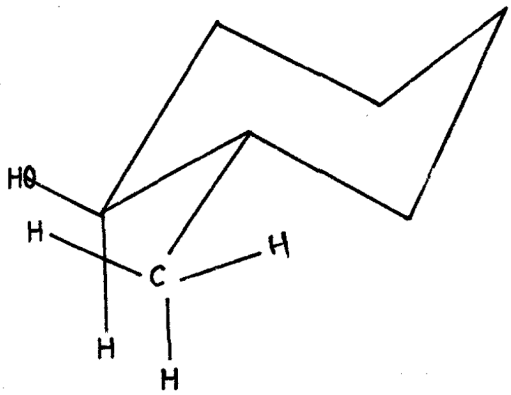
SHIFT OF C_6-AXIAL PROTON

	Compound	Chemical shift in			
		Alcohol	Acetate	Methyl ether	Mesylate
[redacted]		240	239	239	238
VI		231	231	230	231
	Difference	9	8	9	7
XVI		R = O: 232	R = H_2: 230		
XVII		238	237		
	Difference	6	7		

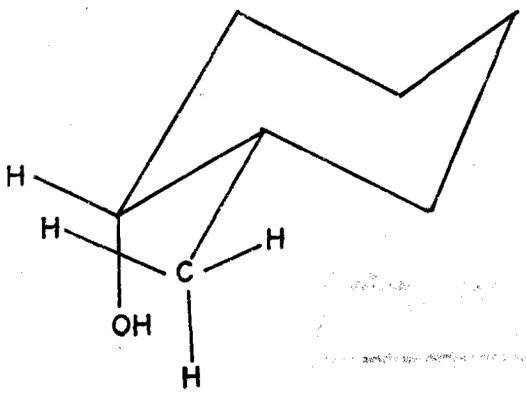
Reasons for different shifts:

Eliel et al[4] had suggested on the basis of very large differences in shielding of proton by adjacent methyl, ethyl, isopropyl and t-butyl that the carbon-carbon bond anisotropy is not the only factors and that a very important role in shielding, is played by syn-axial hydrogens. They even considered that each syn-axial hydrogen causes a shielding of ~ 20 cps. However they were unable to explain how an equatorial methyl has different shielding effects on adjacent equatorial and axial hydrogens.

If one carefully examines this particular example one can see the presence of one syn-axial hydrogen in both the cases (XVIII and XIX) in the preferred conformation wherein



(XVIII)



(XIX)

the methyl group is staggered in relation to the carbon carrying it. In both XVIII and XIX the two other hydrogens of the methyl group are placed at a dihedral angle of 120° with the concerned axial and equatorial protons respectively. The new carbon-carbon bond is placed at an angle of 60° with respect to the axial and equatorial hydrogens of the adjacent carbon. It is therefore very difficult to rationalise how the shieldings by this methyl on adjacent axial and equatorial hydrogens are 28 and 17 cps respectively even if one considers the anisotropy of both carbon-carbon and carbon-hydrogen single bonds. In agreement with this qualitative reasoning very recently Apsimon et al[23*] calculated the shifts caused in these two compounds and obtained values of +19.5 and 19.8 respectively, using a modified McConnel equation[25] and anisotropies based on the values of suitable alkyl cyclohexanols measured by Eliel et al[4] and Musher[5].

Using different anisotropy values, obtained from the chemical shifts of axial and equatorial protons of cyclohexane and equation derivatived by Zürcher[2] and Buckingham, Proechard and Whiffen[24], they obtained a second set of shift values which are 13.4 and 13.7 respectively.

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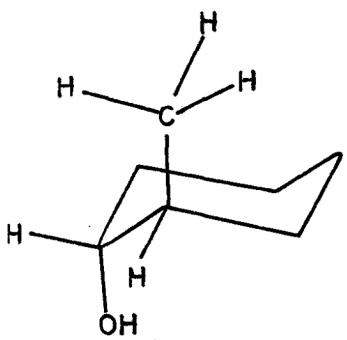
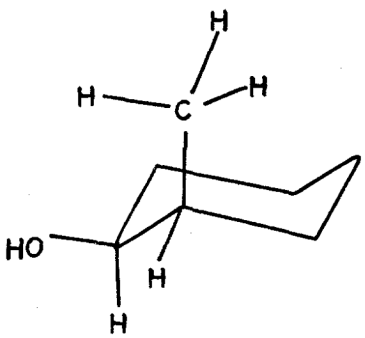
* This work of Ap-Simon et al appeared after most of our results had been completed and attempts to explain in a mathematical manner, the shifts observed through long range effects of methyl group and does not affect the qualitative arguments that are presented by us.

It is thus clear that no suitable explanation for the different shifts caused by an equatorial methyl on adjacent axial (XVIII) and equatorial (XIX) protons can be, as yet advanced.

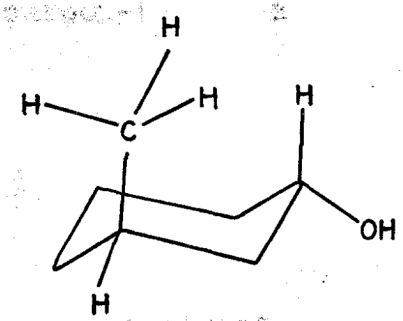
If we consider the shielding caused by an axial methyl group on the adjacent protons, then examination of models show that the equatorial proton (XX) has a syn-axial relationship with one of the hydrogens of the methyl group in the preferred conformation of this molecules (methyl group staggered with respect to the carbon holding it). Furthermore the other two hydrogens of this methyl make dihedral angles of 120° with this hydrogen and the new carbon-carbon bond.is at an angle of 60° with the equatorial hydrogen under consideration.



XX



XXI



XXII

All these factors necessitate a shielding similar to that observed in the earlier two cases wherein the geometry was exactly identical. The reported value for this shielding in cycloalkanols[4] is +24 cps.

The shift values calculated by ApSimon et al[23] are +21.4 and +14.4 cps depending upon which anisotropy value is used. In keeping with our qualitative resononing these values are quite close to those obtained, for shielding by equatorial methyl on adjacent axial (+19.5 and +13.4 cps) and equatorial protons (+19.8 and +13.7 cps).

The effect of an axial methyl on the adjacent axial proton is a deshielding of 12 cps. In the preferred conformation of this molecule (XXI) the three hydrogens of the methyl all make a dihedral angle of 120° with the concerned axial hydrogen and the carbon-carbon bond is at an angle of 180° with this carbon-hydrogen bond. This situation is therefore vastly different from the considered earlier but is in a way similar to the situation in XXII where one considers the effect of axial methyl on the axial hydrogen placed in a cis 1-3 relation with it. This similarity is reflected in an almost identical deshielding (11 cps).

The values calculated by Apsimon et al[23] are -4.4 and +1.3 cps for the effect of axial methyl on adjacent axial proton using different anisotropy values whereas the corresponding values for XXII are -0.3 and -5.4 cps. These calculated values therefore suggest

larger differences in these situation than are actually observed.

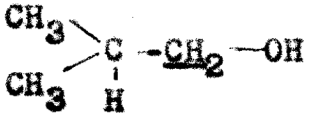
Conformations of aliphatic alcohols

From the above consideration (in highly simplified form) these arguments can be extended to come to an understanding of the conformation of simple aliphatic alcohols.

The NMR spectrum of ethanol had its $-CH_2-$ protons as a quartet centered at 223.5 cps. If the spectrum of n-propanol is examined these protons ($-\underline{CH_2}OH$) now resonate at 215 cps.

Table VI

Chemical shift of hydroxy methyl protons in simple alcohols

Compound	Chemical shift
$CH_3\ \underline{CH_2}\ OH$	223.5 (q)
$CH_3\ CH_2\ \underline{CH_2}OH$	215 (t)
	240 (m)
	205 (d)
$CH_3-CH_2-CH_2-\underline{CH_2}-OH$	216 (t)

d-doublet, t-triplet, q-quartet, m-multiplet.

If one considers the different conformations of isopropanol it can be seen that in the anti conformation (A, Chart 6) there are two hydrogens in a syn-axial relationship with these hydroxy methyl protons, hence shielding of these protons is anticipated in this conformation. On the other hand if one looks at the gauche conformation (B) or (C) one finds that there is now only one hydrogen which is feeling a syn-axial effect in each of these conformers whereas the other hydrogen has the three hydrogens of the new methyl group at 120° with regard to it. Such a relationship can be regarded (D, Chart 6) as corresponding to an effect of axial methyl on the adjacent axial hydrogen (H_1) and should therefore result in deshielding of that proton by 12 cps. The syn-axial relationship in this gauche conformation can also be regarded as similar to a shielding by axial methyl on adjacent equatorial hydrogen* and should correspond to shielding of 24 cps of H_2 (D). This gauche conformation should therefore feel a net shielding of ~12 cps (24-12).

In the anti-conformation each of the hydrogens of the hydroxy-methyl group has one hydrogen syn-axially placed to the hydrogen of the methyl and this hydrogen makes an angle of 120° with remaining two methyl hydrogens. Overall therefore both these hydrogens should behave as though they are equatorial hydrogens feeling the effect of

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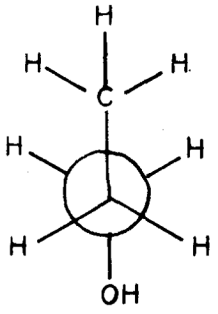
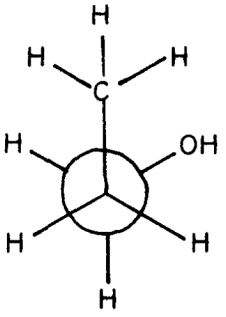
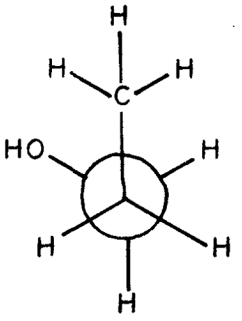
* It can also be regarded (E, Chart 6) as an equatorial methyl on the adjacent axial proton (H_2). This should cause a shielding of 28 cps giving a net shielding of 16 cps (28-12).



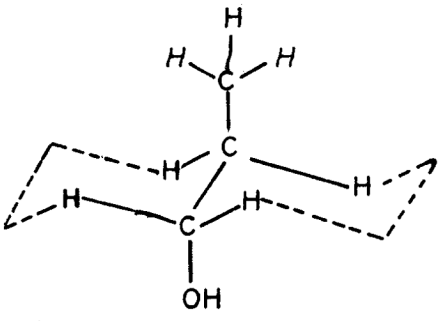
A



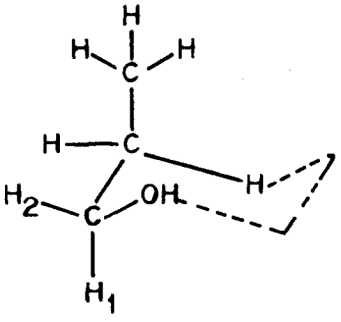
B



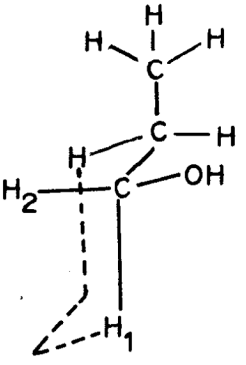
C



F



D



E

Dotted lines in these figures do not imply bonds, but merely show the similarity to a cyclohexane chair.

CHART- 6

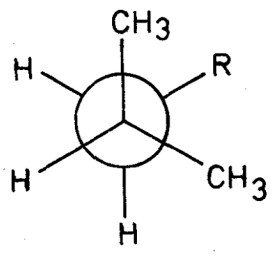
axial methyl (F) and this effect should be around 24 cps. As the observed value is much closer to the gauche conformation, it seems from the present evidence that the methyl group has a gauche conformation with regard to the hydroxyl function.

Though this may appear to be in conflict with stability requirements, it is infact not so. It has been demonstrated by several methods that in the case of n-propyl chloride and even n-propyl bromide[26] the gauche form is lower in internal energy than the anti-form by values ranging between 0.1 to 0.6 Kcal/mol. In the case of n-propyl chloride this value has been arrived at by consideration of infrared[26], electron diffraction[27] and microwave[28] studies.

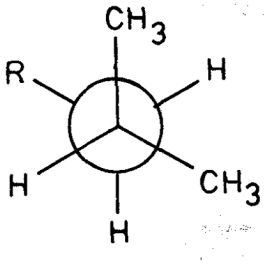
Different reasons have been proposed to explain these factors and the accepted explanation suggests that a methyl group and the chlorine atom in the gauche conformation fall either in or very close to the attractive part of the Van-der-Waal's curve[29]. It may incidentally be pointed out that in the case of n-propyl bromide such a reasoning would anticipate strong predominance of anti-form contrary to experiment. Whatever the explanation it is clear that in these molecules the anti-isomer may be less stable than the gauche. If the same reasoning that holds good for the halo compounds applies to alcohols as well the explanation of the NMR results given above would satisfy

the stability requirements also*.

A sort of confirmation for these ideas can be made by examining the spectrum of isobutyl alcohol which displays the resonance of hydroxymethyl protons at 205 cps. This indicates a shielding of 10 cps in comparison with n-propyl alcohol. As this shielding is almost the same as observed on passing from ethyl alcohol to n-propyl alcohol, it would seem that the new methyl group must have an almost identical relation with regard to methylene protons of the hydroxymethyl group. This location is only possible if the methyl group in n-propyl alcohol is gauche placed in respect to the hydroxyl group and if the new methyl group of isobutyl alcohol is also gauche placed with respect to the hydroxyl group. This reasoning requires isobutyl alcohol to have conformation (G, R = OH) in preference to an alternate conformation (E, R = OH). If isobutyl alcohol had conformation (H, R = OH) it is very difficult to visualise how both methyl groups would cause an identical shift.



(G)



(H)

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* It can be mentioned that in n-propyl mercaptan despite the high polarisability of sulphur the antiform is more stable than the gauche form by 0.4 Kcal/mol[30]. However this may be due to the larger size of the sulphur atom.

In isobutyl alcohol however the stability position is more difficult to explain as isobutyl chloride has been shown[31] to exist to the extent of 80% in gauche-anti conformation (H, R = Cl) rather than in the gauche-gauche conformation. (G, R = Cl). In view of the earlier observation of n-propyl chloride this finding is difficult to rationalise though Pauli, Momany and Bonham[31] have suggested that for a favourable interaction between the gauche methyl and the chlorine the dihedral angle should be larger than the normal 60° angle. As this cannot occur in conformation (G, R = Cl) the molecule prefers to exist in the conformation (H, R = Cl). A sort of confirmation for this comes from the observation that the Cl-methyl angle in isobutyl chloride is 60°.

If n-propyl alcohol has a gauche conformation then in n-butyl alcohol similarly the ethyl group and the hydroxyl function must also be gauche with respect to one another. Substitution of methyl in n-propyl alcohol can occur at either of the three hydrogens of the methyl group. Its occurence at the hydrogen eclipsing the hydroxyl (I, Chart 7) can be ruled out because of the extreme closeness of the new methyl to the hydroxyl group (the distance between oxygen and methyl hydrogen is 1.2°A). In the second gauche location (J, Chart 7), the methyl group should remove one of the possible factors for deshielding of hydroxy-methyl protons in isopropyl alcohol and the NMR spectrum should have the hydroxy methyl protons at the same location as in ethyl alcohol. As this is not the case this

possibility can also be ruled out. It seems fairly reasonable to presume that the new methyl group is antiplaced with respect to C_1-C_2 bond. In this conformation (K, Chart 7) the hydroxymethyl protons in n-butyl alcohol would have the same chemical shift as in isopropyl alcohol.

The NMR spectrum therefore establishes the conformation (K) for n-butyl alcohol and this conformation would agree with that expected from stability considerations, provided n-propyl alcohol exists in the gauche conformation.

In this connection it is of interest to note that 1-bromobutane on the basis of electron diffraction[32] data exists in the all anti (zigzag) conformation (L, Chart 7), in contrast, in n-butyl chloride the conformation (K) in which chlorine is gauche to ethyl abounds[33] and it appears that whereas the antiform is preferred about the C_3-C_2 bond by about 0.4 Kcal/mol, the gauche form predominates about the C_1-C_2 bond by $\sim$0.3 Kcal/mol. A very significant finding that the gauche-gauche* form (I) in which methyl and chlorine approach most closely, contributes as much as 24% and suggests some special stability, possibly London attraction between methyl and chlorine.

In isopropyl alcohol in the preferred, staggered conformation the carbinyl proton has an anti-relationship with one of the hydrogens of the new methyl group (as

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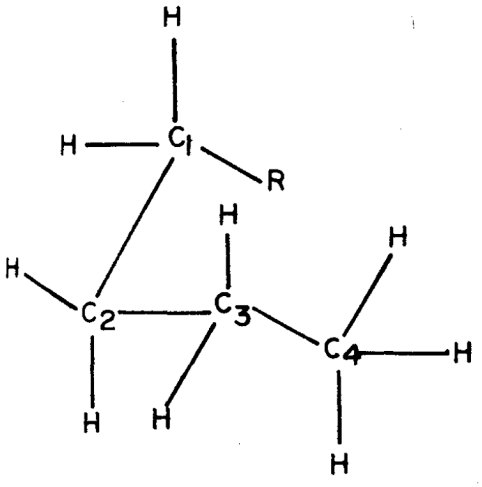
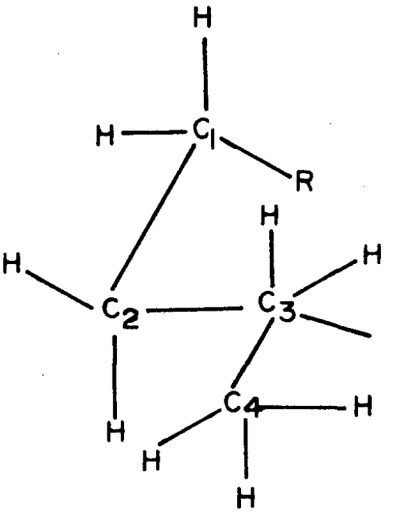
* Our NMR findings cannot rule out this conformation.

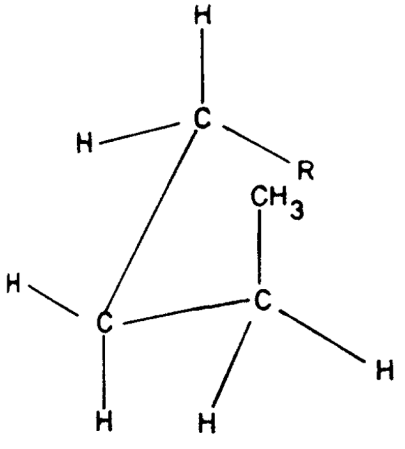
CHART - 7


H
H
C1
R
H
C2
C3
H
H
C4
H
H
H
H

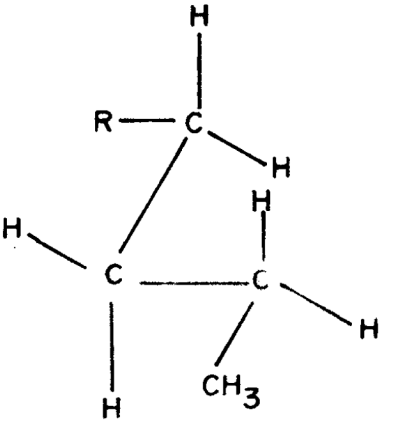
(I)


H
H
C1
R
H
C2
C3
H
H
C4
H
H
H
H

(K)


H
H
C
R
CH3
H
C
C
H
H
H

(J)


H
R
C
H
H
H
C
C
H
CH3
H

(L)

compared to ethyl alcohol). Such locations are known to cause deshielding of a proton. The other two hydrogens of this methyl group are placed at 60° with the carbinyl hydrogen and should not therefore exert any marked influence. On the whole therefore carbinyl proton of isopropyl alcohol should be deshielded in comparison with the corresponding protons of ethyl alcohol. The observed finding (a deshielding of 16.6 cps*) suggests the importance of conformational factors.

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* This explanation provides a reason for the lower frequency of methine proton apart from the usual explanation based on the increased inductive effect.

EXPERIMENTAL

For general procedures see Chapter 1.

Preparation of compounds XVI and XVII (R = H_2) is described in Chapter 1.

Cholestan-3β-ol (IX, R = OH)

Hydrogenation of cholesterol in ethyl acetate using platinum oxide as catalyst and few drops perchloric acid furnished cholestanol in high yield.

M.P. 140°

Cholestan-3β-acetate (IX, R = OAc)

Acetylation of cholestan-3β-ol using pyridine/acetic anhydride gave the acetate in quantitative yield.

M.P. 110°

Cholestan-3β-ol methyl ether (IX, R = OMe)

Cholestan-3β-ol was methylated as reported by Narayanan and Iyer[19]. The product crystallised from methanol.

M.P.	81.5-82.5°	Lit.	83°
$[\alpha]_D$	+21.6	Lit.	+20°

Lupan-3β-ol (XIV, R = OH)

Lupeol* was hydrogenated in ethyl acetate over Pt's catalyst at atmospheric pressure. Lupanol was obtained in quantitative yield.

M.P. 199-201° Lit. 201-202°

Lupan-3β-ol-acetate (XIV, R = OAc)

Acetylation of lupanol under normal conditions furnished the acetate from acetone-methanol.

M.P. 246° Lit.[9] 246-246°

$[\alpha]_D$ -2° Lit.[9] -1.8°

Lupan-3β-ol-methyl ether[10] (XIV, R = OMe)

This was prepared by the same method as cholestan-3β-ol methyl ether except that instead of refluxing with potassium for one hour, it was refluxed for three hours. The yield of methyl ether was 82%.

M.P. 227-228° Lit.[10] 227-228°

$[\alpha]_D$ +4° Lit.[10] +2.33°

3β-Hydroxy-4,5α(H) 6,11β(H)-eudesman-6-13-olide[11] (V, R = OH)

3-Oxo-4,5α(H), 6,11 β(H)-eudesman-6-13-olide (II, 2 g) in acetic acid (60 ml) was stirred in an atmosphere

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* Lupeol purified by chromatography (From the mixture rich in lupeol kindly supplied by C. Quasim of this laboratory) had M.P. 215° and $[\alpha]_D$ +26°.

of hydrogen in presence of pre-reduced Adam's catalyst. Absorption of hydrogen ceased after uptake of two moles (six hours). The catalyst was filtered off and most of the acetic acid was removed under vacuo. The concentrate was diluted with water and the precipitate was taken up in ether.

The substance obtained gave on crystallisation from ether-pet. ether exclusively the pure β alcohol (1.78 g).

M.P.	110-111°	Lit.[11]	108-110°
$[\alpha]_D^{28}$	+38°	Lit.[11]	36°

I.R. 3350 cm^{-1} (OH) 1780 cm^{-1} (γ-lactone)

3β-Acetoxy-4,5 α(H) 6,11 β(H) eudesman 6-13 olide (V, R = OAc)[11]

Hydrogenation of the keto-lactone (II, 800 mg) under pressure (60 psi) using the same catalyst and solvent furnished the acetate (V, R = OAc 460 mg) directly.

M.P.	200°	Lit.[11]	199-200°
$[\alpha]_D^{28}$	+17°	Lit.[11]	+15.4°

IR 1775 cm^{-1} (γ-lactone) 1725, 1251 cm^{-1} (acetate)

NMR: 1 H broad signal at 287 cps ($C_3\alpha$-H)

3 H sharp singlet at 123 cps (O-Ac)

The product did not depress the melting point of the acetate prepared from the alcohol by the usual pyridine/acetic anhydride method.

3β-Methoxy 4,6 α(H) 6,11 β(H) eudesman 6-13 olide (V, R = OMe)

The alcohol (V, R = OH 500 mg) in dry benzene (30 ml) was refluxed with potassium metal (500 mg) for three hours in an atmosphere of nitrogen with frequent vigorous shaking to disperse the molten potassium. Methyl iodide (10 ml) was added to the cooled reaction mixture and refluxing continued further for five hours. Excess of potassium was destroyed and the alkaline reaction mixture was acidified and warmed. It was then extracted with ether. Ether layer was washed with water and dried. Removal of solvent gave a residue (480 mg) which showed two spots on TLC, the lower one corresponding to the starting alcohol. The residue was therefore chromatographed on silica gel (15 g). 5% Ether in benzene eluted a homogenous (TLC) material (138 mg) which was crystallised from pet. ether and was characterised as the expected 3β methyl ether.

M.P. 164-166°

$[\alpha]_D^{28}$ +17.2°

IR 1770 cm^{-1} (γ-lactone) 1190, 1108 cm^{-1} (ether)

NMR: 3 H sharp singlet at 200 cps (3β-OC<u>H</u>$_3$)

1 H broad signal at 195 cps (3α-<u>H</u>)

Analysis:

Found: C, 72.40; H, 10.07%

$C_{16}H_{26}O_3$ requires: C, 72.14; H, 9.84%.

Elution of the column with ether gave the starting alcohol (340 mg)

M.P. and mixture m.p. 110°.

3β-Hydroxy-5α(H) 4,6,11 β(H)-eudesman 6-13 olide[11] (VI, R = OH)

3-Oxo-5α(H) 4,6,11 β(H)-eudesman 6-13 olide (III, 1 g) in methanol (20 ml) was added slowly with stirring to sodium borohydride (200 mg) in water (2 ml). After allowing to stand overnight at room temperature the reaction mixture was acidified with dil. HCl and was diluted with water. Precipitated material was taken up in ethyl acetate. Ethyl acetate extract was washed with water and dried over anhydrous sodium sulphate. The residue obtained on removal of solvent crystallised from ether-pet. ether and furnished the required alcohol (600 mg, single spot in TLC).

M.P.	171-172°	Lit.[11]	171-172°
$[\alpha]_D^{28}$	46°	Lit.[11]	+50.7°

I.R. 3500 cm^{-1} (OH), 1780 cm^{-1} (γ-lactone)

Mother liquors (320 mg) which showed no carbonyl absorption in U.V. had two close spots in TLC. Inverted dry column chromatography[15] of this material afforded both the compounds in pure form. The slow moving (150 mg) was the 3β alcohol while the faster moving (150 mg) was identified as the C_3α epimer. Thus on the whole the yield of 3β epimer is 81% while that of α is 16%.

3β-Acetoxy-5∝(H) 4,6,11 β(H) eudesman 6:13-olide[11] (VI, R = OAc)

The hydroxy-lactone (VI, R = OH 250 mg) was allowed to stand for twentyfour hours in pyridine (5 ml) and acetic anhydride (5 ml) under anhydrous conditions. It ~~is~~ was then poured into crushed ice and allowed to stand for two-three hours to decompose acetic anhydride. Usual work up followed by crystallisation from ether-pet. ether afforded the acetate (240 mg).

M.P. 141° Lit.[11] 143°

$[\alpha]_D^{28}$ +68° Lit.[11] +63.1°

I.R. 1780 cm^{-1} (γ-lactone) 1750, 1260 cm^{-1} (acetate)

3β-Methoxy-5∝(H) 4,6,11β(H)-eudesman-6:13-olide (VI, R = OMe)

To the hydroxy-lactone (VI, R = OH, 250 mg, dried well by boiling with dry benzene and keeping in vacuo for three hours) in dry benzene (30 ml), potassium metal (250 mg) was added and the mixture was refluxed in an atmosphere of nitrogen for three hours with vigorous shaking at intervals to disperse the molten potassium metal into small globules. Methyl iodide (5 ml) was added and refluxing continued further for five hours when potassium iodide gradually separated out.

Reaction mixture was cooled and excess of potassium was destroyed by methanol. Work up as in the earlier case afforded a material which showed two spots in TLC, the lower one corresponding to the starting alcohol.

The residue was therefore chromatographed over silica gel column. Elution with 5% ether in benzene gave a white material (90 mg) which crystallised from pet. ether and was identified as 3β methoxy-5∝(H)-4,6,11 β(H) eudesman-6-13 olide (VI, R = OMe).

M.P. 109-110°

$[\alpha]_D^{28}$ +58.12°

I.R. 1776 cm^{-1} (γ-lactone), 1195, 1095 cm^{-1} (ether)

NMR: 3H singlet at 205 cps ($O\underline{CH_3}$)

1H broad signal at 158 cps ($C_3\alpha$-$\underline{H}$)

Analysis:

Found: C, 72.04; H, 10.07%

$C_{16}H_{26}O_3$ requires: C, 72.14; H, 9.84%.

Elution with 10% ether in benzene afforded the starting alcohol.

M.P. and mixture m.p. 170°.

3∝-Hydroxy-5∝(H) 4,6,11 β(H)-eudesman 6-13 olide (VII, R = OH)

The keto lactone (III, 2 g) in glacial acetic acid (60 ml) was hydrogenated in presence of platinum oxide catalyst (400 mg). Absorption of hydrogen ceased in six hours, after 2 moles of hydrogen were absorbed. The catalyst was filtered off and most of the solvent was removed under reduced pressure. The concentrate was diluted with water and the precipitate was taken up in ether/washed free of acetic acid and dried over sodium sulphate. Removal of solvent yielded a colourless residue which showed two very close spots in TLC neither of which corresponds to starting ketone. (I.R. showed absence of ketone)

Inverted dry column chromatography[15] employing ethyl acetate:benzene (3:7) solvent system furnished both the compounds in pure form.

The faster moving (660 mg) was characterised as 3∝ hydroxy 5∝(H) 4,6,11 β(H) eudesman 6-13 olide (VII, R = OH).

M.P.	143°	Lit.[11]	143°
$[\alpha]_D^{28}$	+13.6	Lit.[11]	16.6

I.R. 3600 cm^{-1} (OH), 1770 (γ-lactone)

NMR: 1 H narrow signal at 228 cps ($C_3\beta$-H)

1 H broad signal at 230 cps (C_6-H)

The slow moving/(820 mg) was the $C_3\beta$ epimer compound M.P. and mixed m.p. 171°.

Besides these, an unresolved mixture (400 mg) of these two epimers was also obtained. Assuming (from the intensity on TLC) that this mixture contains equal percentage of both epimers the yield of ∝ epimer is ~ 42% while that of β is ~ 51%.

3∝-Acetoxy 5∝(H) 4,6,11 β(H) eudesman 6:13 olide[11] (VII, R = OAc)

The above alcohol (250 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was warmed on steam bath for two hours and kept aside at room temperature for twentyfour hours. Usual work up gave a material which crystallised from ether-pet. ether mixture to afford the acetate (225 mg) as rhombs.

M.P.	153°	Lit.[11]	153-154°
$[\alpha]_D^{28}$	-30	Lit.[11]	-28.3

I.R. 1770 cm^{-1} (γ-lactone) 1750, 1260 cm^{-1} (acetate)

NMR: 1 H narrow signal at 298 cps ($C_3\beta$-H)

3 H sharp singlet at 124 cps ($OCO\underline{CH_3}$)

1 H broad signal at 230 cps (C_6-H)

3β-Hydroxy 5α(H) 4,6,11 β(H) eudesman 6-13 olide 3-mesylate
(VI, R =OMeS)

The alcohol (VI, R = OH, 1 g) in pyridine (10 ml) was cooled to 0° and to it was added precooled methane sulphonyl chloride (1 ml). Reaction mixture was kept at 15° for sixtyfour hours. It was then poured in cold water and extracted with ethyl acetate. Ethyl acetate extract was washed free of pyridine, methane sulphonic acid and dried over sodium sulphate. Residue obtained on solvent removal, crystallised from ethanol to furnish the mesylate (960 mg; TLC single spot).

M.P. 186°

$[\alpha]_D^{28}$ +61.3°

I.R. 1770 cm^{-1} (γ-lactone) 1193, 885 cm^{-1}

NMR: 1 H broad signal at 257 cps ($C_3\alpha$-H)

1 H triplet at 231 cps (C_6-H)
(J = 10 cps)

3 H singlet at 180.5 cps ($\underline{CH_3}\ SO_2^-$)

6 H doublets centered at 71 cps (J = 7 cps)
(C_4 and C_{11} $-CH_3$)

3 H singlet at 60 cps (C_{10}-CH_3)

Analysis:

Found: C, 57.97; H, 7.69%

$C_{16}H_{26}O_5S$ requires: C, 58.17; H, 7.93%.

Solvolysis of 3β-hydroxy-5α(H) 4,6,11 3(H) eudesman 6-13 olide-3 mesylate

The mesylate (VI, R = OMeS; 660 mg) was refluxed with super-dry methanol (40 ml) for ninety hours. Reaction mixture was then poured into water (200 ml) and the precipitated material was taken up in ether. Ether extract was washed with bicarbonate solution, water and dried over sodium sulphate. Removal of solvent left a colourless gummy residue (495 mg) which showed three spots on TLC the lower to one corresponding to the starting mesylate. It was therefore chromatographed on a silica gel column. First three benzene fractions gave a material (90 mg) which was crystallised from pet. ether and was characterised as Δ^2 olefin VIII (Chart 2).

M.P. 146-147°

$[\alpha]_D$ +21°

Later benzene fractions gave a pure 3α methoxy derivative (VII, R = OMe 317 mg).

M.P. 111-112°

$[\alpha]_D^{28}$ -29.6°

I.R. 1770 cm^{-1} (γ-lactone) 1195, 1108 cm^{-1} (ether)

NMR: 3 H singlet at 200 cps (OCH_3)

1 H narrow signal at 190 cps ($C_3\beta$-H)

Analysis:

Found: C, 72.31; H, 9.85%

$C_{16}H_{26}O_3$ requires: C, 72.14; H, 9.84%

Fraction D (67 mg) was unreacted starting mesylate.

Cholestan-3β-ol tosylate (IX, R = OTs)

To a cooled solution of cholestan-3β-ol (2.5 g) in dry pyridine (15 ml) was added a cold solution of p-toluene sulphonyl chloride (5.5 g) in pyridine (20 ml). The resultant mixture was allowed to stand at room temperature for twenty-four hours, after which it was poured in crushed ice. The solid was taken up in ether, washed with water, 2N HCl and again with water. The ethereal solution was dried (Na_2SO_4), filtered and evaporated to dryness. The residue crystallised from ethanol to furnish the tosylate (2.4 g).

M.P. 132-133° Lit. 135°

$[\alpha]_D$ -39.8 Lit. -39.5°

I.R. 1593, 1190, 1175 and 1095 cm^{-1}.

Formolysis of cholestan-3β-ol tosylate[18]

The above tosylate (1 g) in dimethyl formamide (40 ml) was heated at 78° for twentyfour hours. The reaction mixture was then diluted with excess of water and the precipitate was taken up in ether. Ether extract was washed with water, dried (Na_2SO_4) and ether was evaporated. Semi-solid obtained was chromatographed over silica gel. Pet. ether eluted Δ^2 olefin (XI, 121 mg) identified by M.P. and I.R. Pet. ether-benzene (1:1) eluted a substance (536 mg) which was identified as 3α-formate (X, R = OCHO).

M.P. 111-113° Lit.[18] 114°

I.R. 1720 cm^{-1} (-O-C$\overset{O}{\underset{H}{<}}$)

Ether elution afforded the starting tosylate (103 mg).

Cholestan-3∝-ol (X, R = OH)

The above formate (206 mg) was kept in 5% methanolic potassium hydroxide (20 ml) for twentyfour hours. Cholestan-3∝-ol obtained (180 mg) was crystallised from methanol.

M.P.	182°	Lit.	182°
$[\alpha]_D$	+24°	Lit.	+26°

Cholestan-3∝-ol acetate (X, R = OAc)

Reaction of BF_3-etherate/acetic anhydride on cholestan-3β-ol methyl ether[10].

Cholestan-3β-ol methyl ether (1 g) in acetic anhydride (40 ml) and dry ether (2-3 ml to dissolve the compound) was cooled to 0°. Freshly distilled BF_3-etherate (7 ml, cooled to 0°) was added and the mixture kept at 0° for fifteen hours. It was then poured into crushed ice and extracted with ether after few hours. Ether extract was washed with bicarbonate and water and dried (Na_2SO_4). The residual pale yellow oil (980 mg) was resolved into three pure compounds by Inverted dry column chromatography.[15] The fastest moving one (200 mg) was identified as Δ^2 cholestene XI. Next to that was cholestan-3∝-ol acetate (210 mg).

M.P.	94°	Lit.	95°
I.R.	1725, 1250 cm^{-1}		

The most polar compound (450 mg) was cholestan-3β-ol acetate. An unresolved mixture (105 mg) of ∝- and β- acetates was also obtained.

3β-Hydroxy 4,5 ∝(H) 6,11 β(H) eudesman 6-13-olide -3 mesylate (V, R = OMeS)

To the cooled solution of hydroxy lactone (V, R = OH, 1.7 g) in pyridine (15 ml) pre-cooled methane sulphonyl chloride (2 ml) was added and the mixture was allowed to stand at 15° for sixtyfive hours. It was then poured in water and worked up. Crystallisation from ethanol gave the mesylate (1.8 g).

M.P. 151°

$[\alpha]_D$ +12°

I.R. 1770 cm^{-1} (γ-lactone)

NMR: 1 H broad signal centered at 283 cps (C_3-H)

1 H triplet centered at 238 cps (C_6-H) J = 10 cps

3 H sharp singlet at 180 cps ($\underline{CH_3}$ SO_2)

3 H doublet centered at 64, J = 7 (C_{11}-CH_3)

3 H doublet centered at 72.8, J = 7 (C_4-CH_3)

3 H singlet at 64.8 (C_{10}-CH_3)

Analysis:

Found: C, 58.03; H, 7.67%

$C_{16}H_{26}O_5S$ requires: C, 58.17; H, 7.93%.

Solvolysis of 3β-hydroxy 4,5∝(H) 6,11 β(H) eudesman 6-13 olide-3 mesylate (V, R = OMeS)

Mesylate (800 mg) was refluxed with methanol (50 ml) for ninety hours. Usual work up gave a colourless gum (620 mg) which showed three spots on TLC (benzene), one (R_f 0.02) corresponding to starting mesylate. Other two had R_{fs} 0.25 and 0.35. It was chromatographed on silica gel. Chromatogram shows the results.

Chromatogram

Fr. No.	Solvent	Remarks
a	Pet. ether (4x25 ml)	negligible material
b	Pet. ether:benzene (3:1) (4x25 ml)	negligible material
c	Pet. ether:benzene (1:1)	single spot (R_f 0.36)
d	Pet. ether:benzene (1:1)	single spot (R_f 0.36)
e	Pet. ether:benzene (1:1)	two spots (R_f 0.36, 0.26)
f	Pet. ether: benzene (1:1)	single spot (R_f 0.26)
g	Pet. ether:benzene (1:1) 3x25 ml)	single spot (R_f 0.25)
h	Ether (4x25 ml)	starting mesylate

Fractions c and d, together (174 mg) crystallised from pet. ether and gave the following constants.

M.P. 116-122°

$[\alpha]_D$ + 114.6°

NMR and I.R. analysis indicate that it is a Δ^3 olefin (XIII)[13] with little Δ^2 olefin.

Fractions f and g were combined (60 mg), crystallised from pet. ether and was identified as 5α(H) 6,11(H) $\Delta^{4(14)}$ eudesmen-6-13 olide (XII).

M.P.	135-137°	Lit.[34]	140°
$[\alpha]_D$	+151.6°	Lit.[34]	140°

NMR analysis Table 2 and I.R. bands at 1660 and 890 cm^{-1} also suggest the above structure.

<u>Formolysis of the mesylate</u> (V = OMes)

The mesylate (250 mg) in dimethyl formamide (once distilled, 10 ml) was heated at 78°. Reaction was monitored by TLC and mesylate was found to be completely reacted in twenty four hours. Reaction mixture was cooled and poured in cold water. Material separated on cooling was collected and crystallised from methanol to give plates (163 mg).

M.P. 106-107°

I.R. 1760 cm^{-1} (lactone), 1640, 980, 880 cm^{-1} (olefin)

NMR revealed no formate proton, rather it showed that it is a mixture of the same olefins XII and XIII.

3β-Hydroxy 5∝(H) 4,6,11β(H) eudesman 6-13 olide 3-tosylate (VI, R = OTs)

To the cooled solution of the hydroxylactone (VI, R = OH, 500 mg) in pyridine (15 ml) was added p-toluene sulphonyl chloride (2 g) in pyridine (20 ml) and the mixture was allowed to stand at room temperature for twentyfour hours. It was then poured in water and extracted with ether. Total ether extracts were washed with 2N HCl, bicarbonate solution and finally with distilled water. Residue obtained on evaporation of the solvents and crystallised from alcohol to furnish the tosylate (VI, R = OTs, 650 mg).

M.P. 166-168° Lit.[13] 168-169°

$[\alpha]_D^{28}$ +24° Lit.[13] +20°

I.R. 1776 cm^{-1} (lactone) 1608, 996, 946, 849 (aromatic)

Methanolysis of 3β-hydroxy 5∝(H) 4,6,11β(H) eudesman 6-13 olide, 3 tosylate

Tosylate (500 mg) was refluxed with dry methanol (50 ml) for 102 hours.

Reaction mixture was then concentrated at reduced pressure and diluted with water. Precipitated material was extracted with ether. Ether extracts were washed with sodium bicarbonate solution and distilled water. Removal of solvent afforded the residue which showed three spots in TLC, one corresponding to the starting tosylate.

NMR of the total material revealed no peak around 200 cps (no methyl ether formation) and showed a mixture of the same two olefins (XII and XIII) as in the case of mesylate.

Epi-lupanol acetate (XV, R = OAc)

Epilupeol acetate* (250 mg) was hydrogenated in ethyl acetate (20 ml) in the presence of pre-reduced Adam's catalyst (25 mg) as described by Heilbron et al[9].

After usual work up the product was crystallised from ethanol when epilupanol acetate (220 mg) was obtained.

M.P.	164°	Lit.[35]	164°
$[\alpha]_D$	-44°	Lit.[35]	-46.32

I.R. 1750, 1260 cm^{-1} (acetate) no band at 890 cm^{-1}

Epilupanol (XV, R = OH)

Epilupanol acetate (150 mg) was kept at room temperature for fortyeight hours with methanol (20 ml) containing potassium hydroxide (1 g).

The solution was diluted with water and extracted with ether. Processing of ether extract afforded epilupanol in quantitative yield. It ~~is~~ was crystallised from acetonitrile.

M.P.	161°	Lit.[36]	160.6-163°
$[\alpha]_D$	-2°	Lit.[36]	-4.3°

I.R. 3450 cm^{-1} (OH)

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* We are indebted to Prof. T. R. Govindachari for this sample.

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CHAPTER III

THE CONFORMATION OF PRIMARY HYDROXYL GROUPS IN TERPENOIDS

INTRODUCTION

The NMR spectra of several alcohols have been studied. Among the features that have been noted in the spectra of these compounds are (1) the downfield shift by about 0.5 to 1.5 p.p.m. of the proton or protons on the carbon atom holding the hydroxyl group on esterification of the hydroxyl[1] and (2) an upfield shift by about 0.6 p.p.m. of proton(s) when the methyl ethers were studied[2]. This has actually been a very good method to identify the proton or protons on the carbon atom holding a hydroxyl group.

One of the methyls of a gem-dimethyl group or an angular methyl group in terpenoids is often oxidised to a primary hydroxyl group. In a recent study Gaudemer, Polonsky and Wenkert[3] tried to establish the configuration of this CH_2OH group in different diterpene and triterpene derivatives by making use of NMR spectroscopy. In their study they were able to show that the axial hydroxy methyl group appears at lower field (between 245 to 258 cps) as compared to its equatorial epimer (between 220 to 230 cps). They also noted that in most cases where this hydroxymethyl group is attached to a quaternary carbon, these two protons are generally non-equivalent and give rise to an AB quartet. They however indicated that there were exceptions to this generalisation, though they pointed out

that a singlet may infact represent an AB quartet in which the middle lines have coaleased and the end lines are not visible. This appearance is due to the fact that each of the middle lines in such a case would be twentythree times more intense than the end line. Their results indicate that NMR was a good tool in determining the conformation of the primary hydroxyl function. Similar results with fewer examples had also been observed earlier by Wenkert and Beak[4] and Shamma, Glick and Mumma[5].

In a study by NMR to fix the geometry of the hydroxyl group Kawazoe et al[6] demonstrated that the presence of an 11-β hydroxyl resulted in deshielding of the signals for the C-18 and C-19 protons as compared to the deoxo compounds. As they observed that the presence of 11-α hydroxyl has no such effect, they were able to conclude that this deshielding is due to the eclipsing relationship of the 11-β hydroxyl with C-10 and C-13 methyls. Shoolery and Rodgers[1a] have also observed similar effects in 11β hydroxy steroids.

If one analyses these results important conclusions appeared possible. Firstly the hydroxymethyl group attached to a quaternary carbon atom appears as an AB quartet because free rotation is not possible between it and the carbon to which it is bound. Once it is realised that free rotation is not possible it naturally follows that in suitable environment this group must have a fixed

conformation and if suitably selected compounds were prepared and their NMR spectra were studied it would be possible to determine the preferred conformation of this hydroxymethyl group.

For this purpose it was decided to make use of solvent induced chemical shifts. Making use of this method Narayanan and Venkatasubramanian[7] had been able to come to some very useful generalisations regarding the stereochemistry of diterpene esters. The usefulness of this method has now been demonstrated in the secondary alcohols having a rigid conformation. The method has then been applied to fix the conformation of a quaternary hydroxymethyl even in the absence of the parent deoxo compound.

Present Work

Prior to studying the conformation of primary alcohols it was necessary to have a suitable method for this purpose. The use of this method has been first demonstrated with secondary alcohols having a rigid geometry.

Studies on secondary alcohols

From the work of Narayanan and Venkatasubramanian[7] it was anticipated that the 11α- and 11β-hydroxysteroids would show different behaviour when their spectra are examined in $CDCl_3$ and pyridine, the shifts being enhanced in the spectra studied in pyridine solution if eclipsing geometry was already present.

In agreement with this it was found that when the spectra of 11α-hydroxyprogesterone* (I) were examined in $CDCl_3$ and pyridine solution there was no appreciable change in the location of C-18 and C-19 proton signals (See Table 1). In the case of the β-epimer* (II), however, there is an eclipsing of these methyls by the hydroxyl which caused the signals of these protons to be deshielded by 12.6 and 7.5 cps respectively in $CDCl_3$ solution as compared to those in the 11α-epimer. The $CDCl_3$ spectra of both epimers therefore makes it clear which is the α- and β-isomer. When the spectrum of the β-isomer (II) was examined in pyridine solution the downfield shift of the C-18 and C-19 protons were enhanced with the result that the comparison of the spectrum of this compound (β-isomer) in the two solvents $CDCl_3$ and pyridine showed a paramagnetic shift of these protons by 13 and 8 cps respectively.

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* We are indebted to Dr. L. M. Kogan for the samples of 11α- and 11β-hydroxyprogesterone.

TABLE 1

SOLVENT INDUCED CHEMICAL SHIFTS OF METHYL GROUPS IN SECONDARY ALCOHOLS

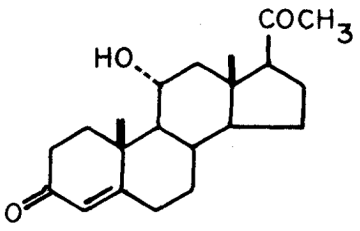
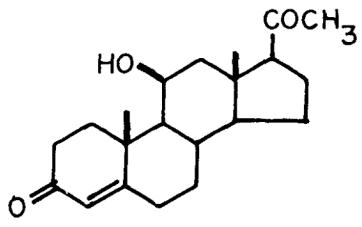
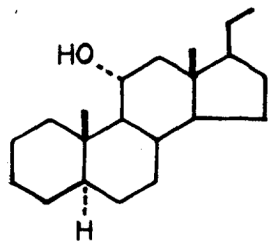
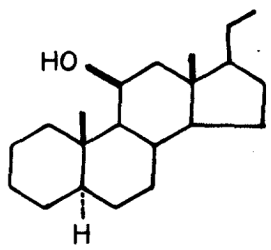
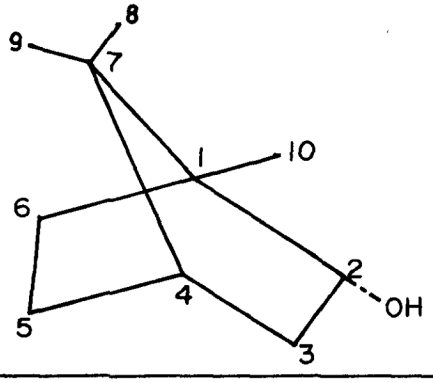
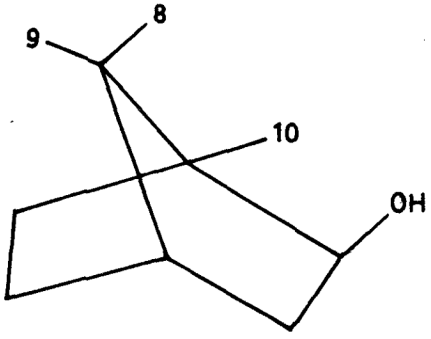
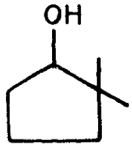
No.	Compound	Chemical shift at 60Mc				Shift in pyridine	
		In $CDCl_3$		In pyridine			
		18-H	19-H	18-H	19-H	18-H	19-H
I		42.5	79.5	43.5	79.5	-1	0
II		55	87	68	95	-13	-8
III		35	57	36	61.	-1	-4
IV		47	62	63	78	-16	-16

TABLE I (continued)

No.	Compound	Chemical shift at 60Mc				Shift in pyridine	
		In $CDCl_3$		In pyridine			
		8-H	9-H	8-H	9-H	8-H	9-H
V		52	52	52	52	0	0
VI		61	51	77	51	-16	0
VII		2 Me	-	2 Me	-	2 Me	
		57	-	58.5	-	-1.5	
		59	-	65	-	-6	

This solvent shift method therefore can be used to determine the configuration of 11-hydroxyl group without having to examine the spectra of both epimers.

That this is indeed a general phenomenon, can be seen by examining the spectra of two other epimeric alcohols in the steroid series.

The compounds chosen for this purpose were the epimeric 11-hydroxy-5-∝-pregnanes. These compounds were prepared by the reduction of 11-keto-5-∝-pregnane*.

Reduction of the ketone with sodium and alcohol is known[8] to furnish the equatorial hydroxyl derivative. In agreement with this the product obtained (III) from the 11-keto-5-∝-pregnane by above reduction showed in its NMR spectrum (Fig. 1) a broad signal (1H) centred at 237 cps assignable to C-11 axial proton and two singlets at 36 cps (3H) and 57 cps (3H) due to C-18 and C-19 protons respectively.

Lithium aluminium hydride reduction of the 11-ketone gave a product which was expected to be an 11-β alcohol. The NMR spectrum (Fig. 2) of this compound showed the C-11 proton as a narrow signal at 266 cps, i.e. at lower field than the 11β-proton in sodium alcohol reduction product. This clearly established the equatorial disposition of the proton and hence the hydroxyl to be axial. Moreover this agreed with the expectation that the hydride attack would be from the less hindered

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* We are grateful to Mr. M. R. Sarma of this Laboratory for a generous sample of this compound.

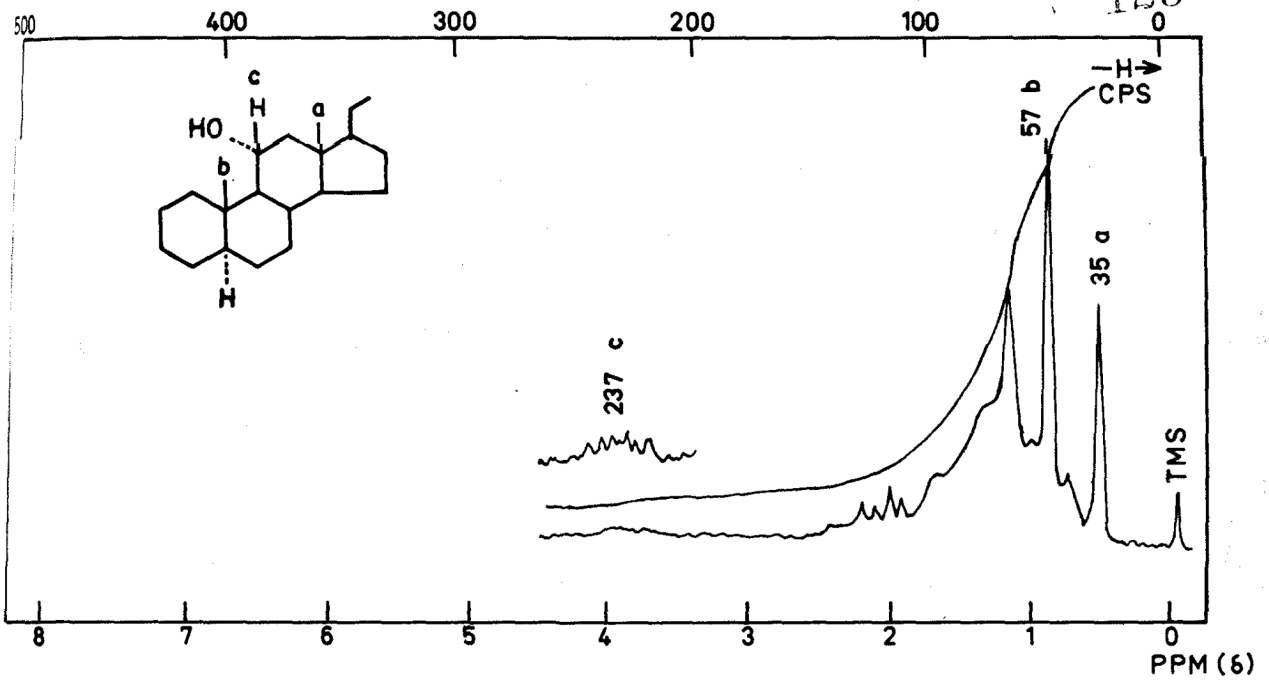


FIG. 1. NMR SPECTRUM OF 11α-HYDROXY—5α-PREGNANE ($CDCl_3$)

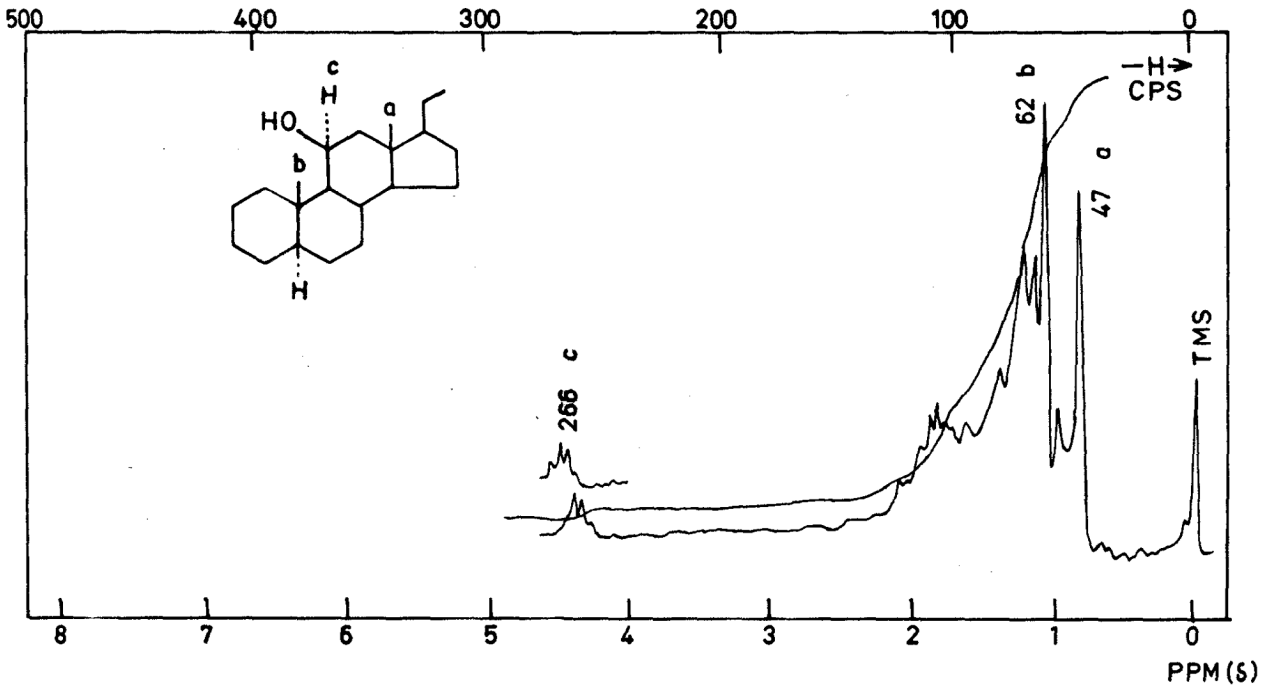


FIG. 2. NMR SPECTRUM OF 11β-HYDROXY—5α-PREGNANE ($CDCl_3$)

α side. The almost complete absence of the 11α-epimer in this reduction would be due to the fact that the 11-ketone is a hindered ketone, in which steric approach control supresses[9] the other factor (Product development control) controlling hydride reduction[10]. As was expected the 11β-epimer (IV) (Fig. 2) had its C-18 and C-19 proton signals deshielded (12 and 5 cps respectively) as compared to that of the 11α-epimer (III) when the spectra were taken in $CDCl_3$ solution.

The solvent induced shifts for these two epimeric alcohols (Fig. 3 and 4) show the same kind of behaviour as for the progesterone derivatives (See Table 1) with very large paramagnetic shifts (16 and 16 cps for C-18 and C-19 protons respectively)., - for the 11β compound and small shifts for the 11α-epimer in pyridine spectra.

Such behaviour for epimeric alcohols with eclipsing geometry is also observed for the compounds of the bicyclo [2,2,1] heptane series. Thus it is reported[11] that in $CDCl_3$ solution isoborneol (VI) reveals a paramagnetic shift of 9 cps, as compared to borneol (V) for one of its methyl groups, which is obviously the one-C-8- that is in a quasi eclipsing relation with the exohydroxyl. The spectrum of isoborneol (VI) in pyridine displays a paramagnetic shift of 16 cps for C-8 methyl group as compared to the $CDCl_3$ spectrum, while, as expected, that of borneol (V) shows no such shift.

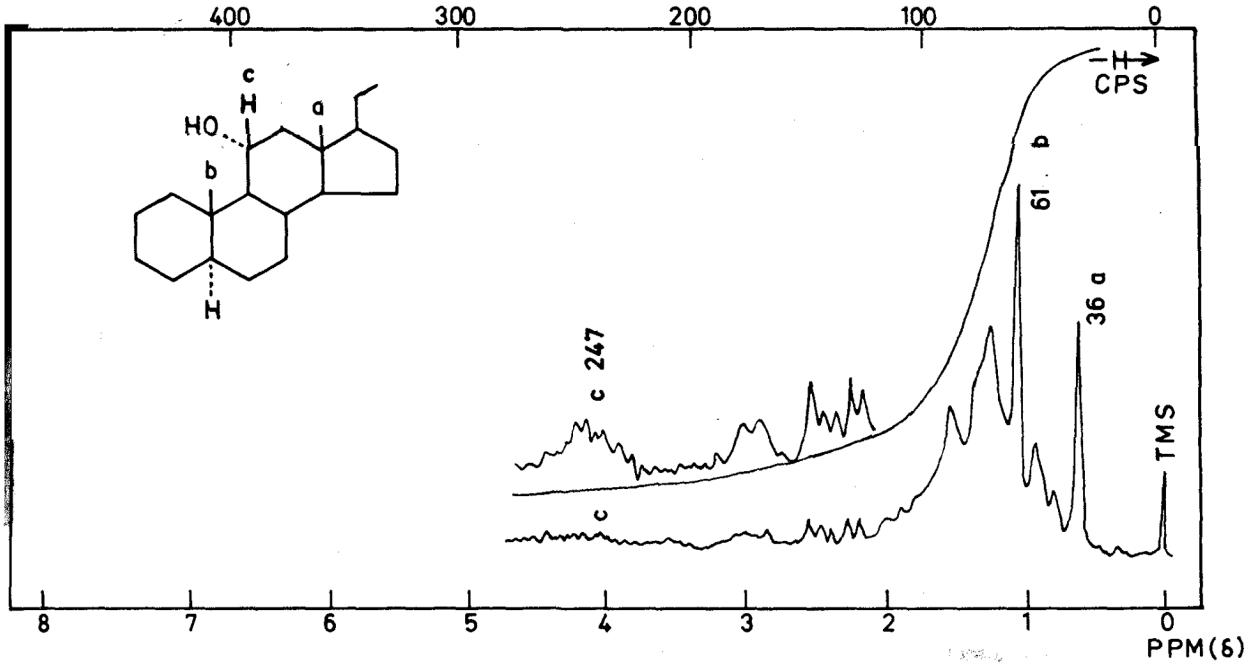


FIG. 3. NMR SPECTRUM OF 11α-HYDROXY-5α-PREGNANE (PYRIDINE)

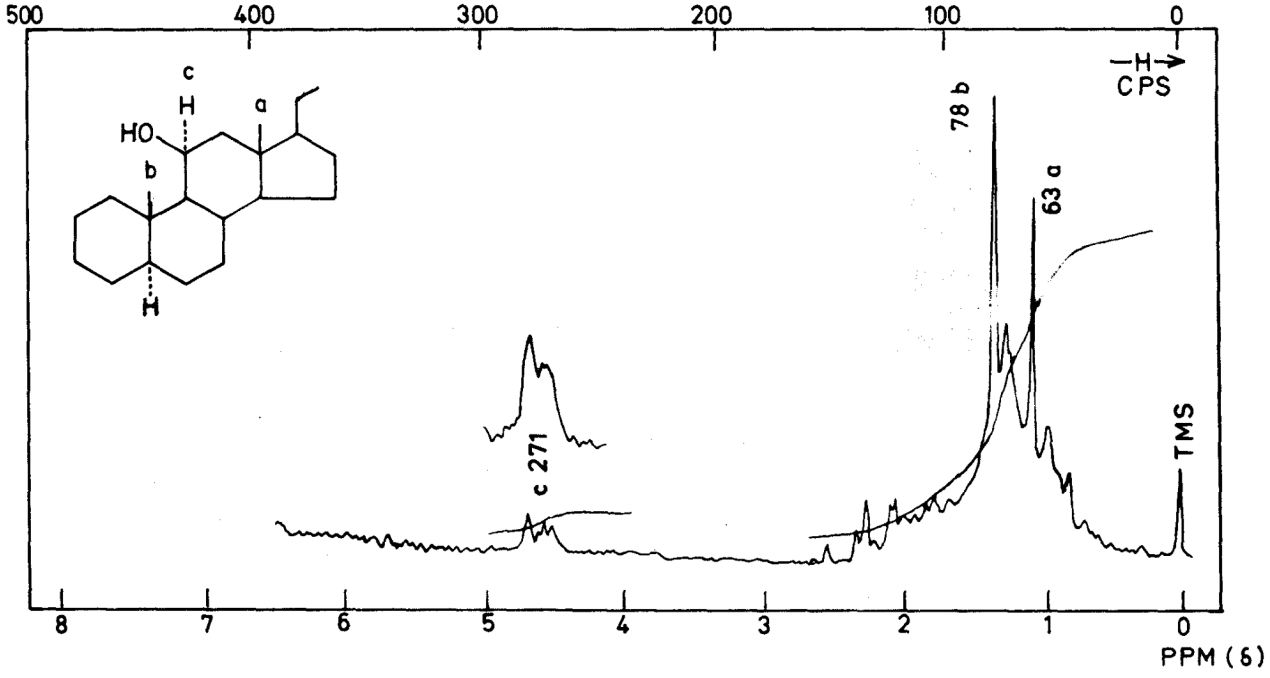
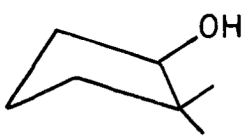


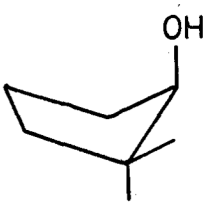
FIG. 4. NMR SPECTRUM OF 11β-HYDROXY-5α-PREGNANE (PYRIDINE)

In order to see one example in cyclopentanol series, 2,2-dimethyl-cyclopentanone* was reduced to the corresponding alcohol[12] (VII) with lithium aluminium hydride. In the spectrum of this alcohol in $CDCl_3$ solution the methyl signals were located at 57 and 59 cps. However, when the spectrum was examined in pyridine the methyl singlets appeared at 58.5 and 65 cps. In earlier examples it has been established that the methyl group eclipsed by hydroxyl shows a paramagnetic shift of about 16 cps in the pyridine spectrum.

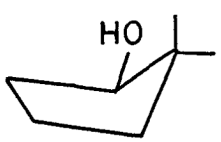
It is fairly obvious that in the present case the smaller magnitude of this shift (6 cps) arises from the flexibility of the cyclopentane ring which permits the carbon oxygen bond to have positions (A& B) slightly varying from the conformation (C) in which this bond eclipses the methyl group;



C



A



B

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* We are grateful to Dr. Sukh Dev for the sample of this compound.

Thus it can be summed up that those alcohols in which the methyl signals occur at the same position in both $CDCl_3$ and pyridine spectra must correspond to the epimer in which there is no eclipsing of methyl with hydroxyl group, when such eclipsing is present the downfield shift of the corresponding methyl is enhanced in pyridine spectra (Table 1).

Conformation of primary alcohols

(a) Axial alcohols

The results so far described relate to those compounds in which there is no possibility of any free rotation around carbon-carbon single bond as rigid ring systems have been considered. In the case of compounds having a primary hydroxyl group free rotation can be expected and different conformers may arise due to this rotation.

The compounds reported in Table 2 were prepared by known methods (see experimental). A comparison of NMR spectra of O-methyl-podocarpane (VIII), O-methyl podocarpinol (IX) and dehydroabietinol (X) (Fig. 5, 6 and 7 respectively), in $CDCl_3$, demonstrated that only o-methyl podocarpinol (IX) showed a downfield shift for one of its methyl groups. This shifted methyl is of course the C_4-equatorial methyl as the C-10 methyl in these three compounds appears almost at a fixed position, being the downfield signal in the spectrum of O-methyl podocarpane*.

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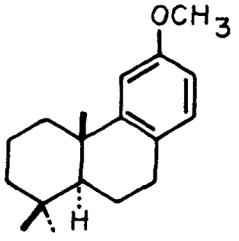
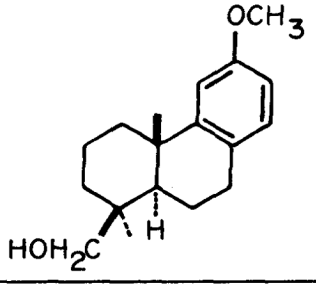
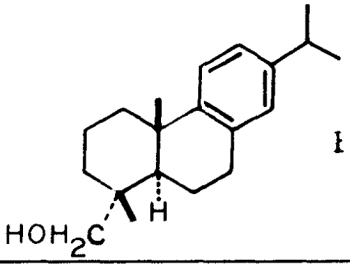
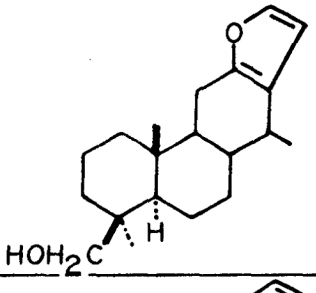
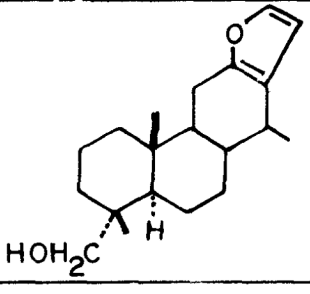
* It is well known13 that the aromatic C ring causes a downfield shift of the C-10 methyl (steroid numbering).

TABLE 2

SOLVENT INDUCED CHEMICAL SHIFTS IN PRIMARY ALCOHOLS

No.	Compound	Chemical Shift in C_4-CH_3			Chemical Shift of C_{10}-CH_3		
		In $CDCl_3$	In Pyridine	Shift in Pyr.	In $CDCl_3$	In Pyridine	Shift in Pyr
VIII		55	53	+2	70.5	70	+0.5
IX	 A	63	74	-11	71	74	-3
X	 E	53	55	-2	73	73	0
XI	 A	60	73	-13	52	50	+2
XII	 E	49	52	-3	56	52	+3

A denotes axial, and E lenotes equatorial

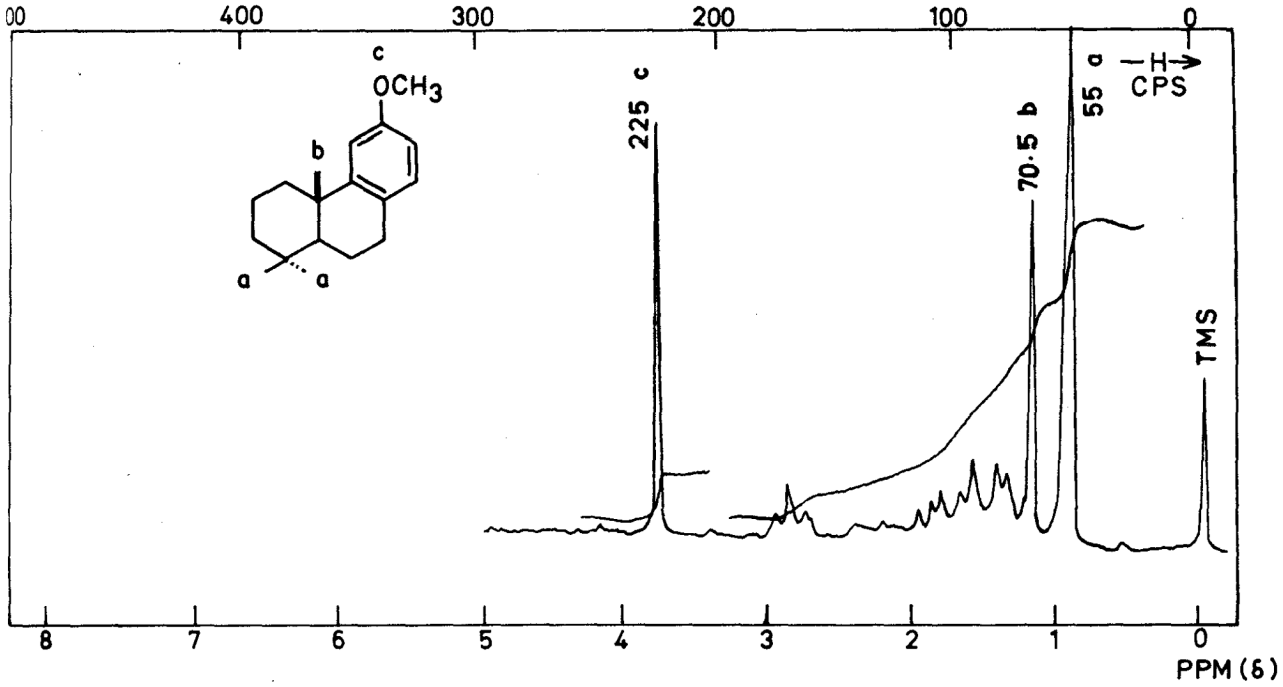


FIG. 5. NMR SPECTRUM OF O-METHYL—PODOCARPANE ($CDCl_3$)

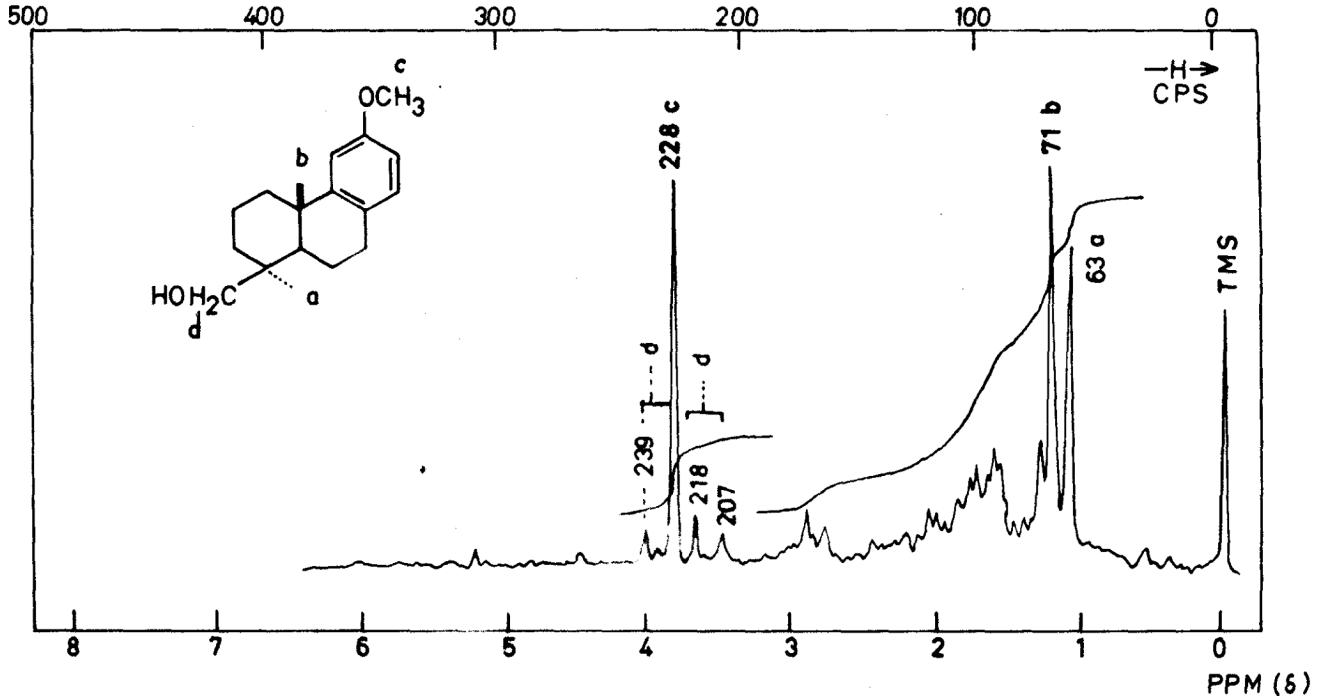


FIG. 6. NMR SPECTRUM OF OMe - PODOCARPINOL ($CDCl_3$)

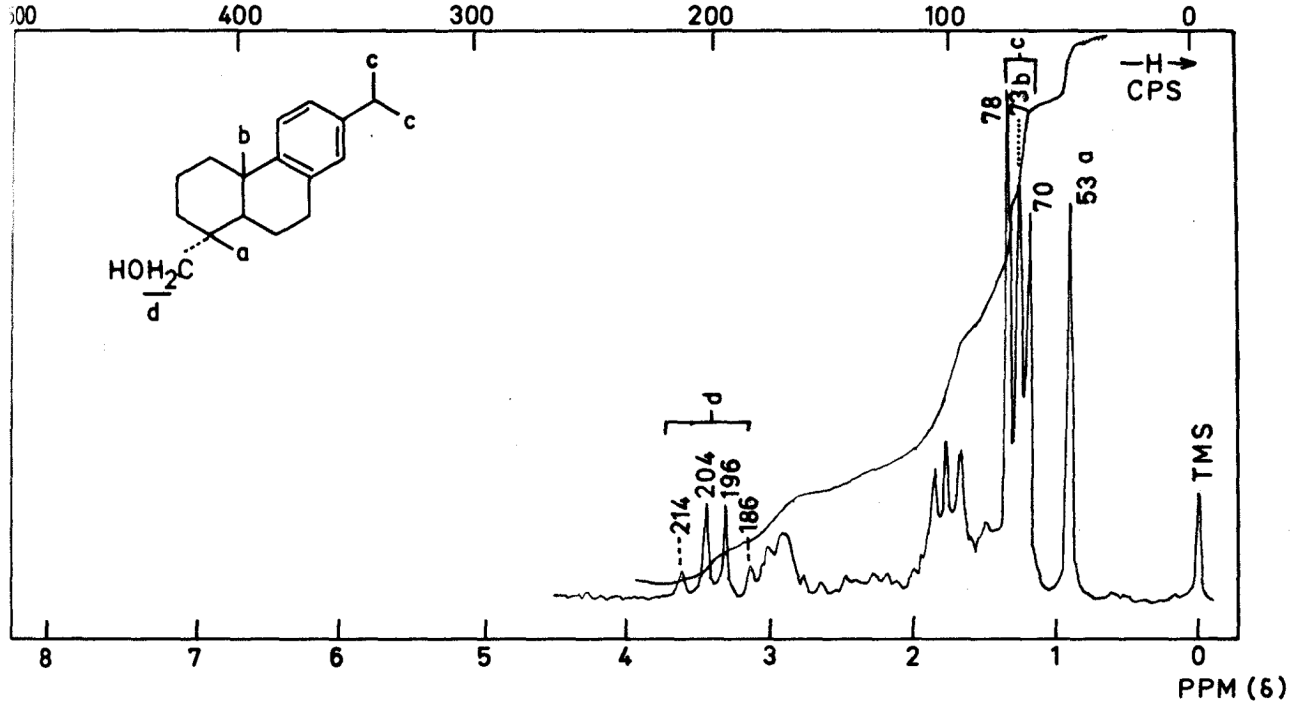


FIG. 7. NMR SPECTRUM OF DEHYDROABIETINOL ($CDCl_3$)

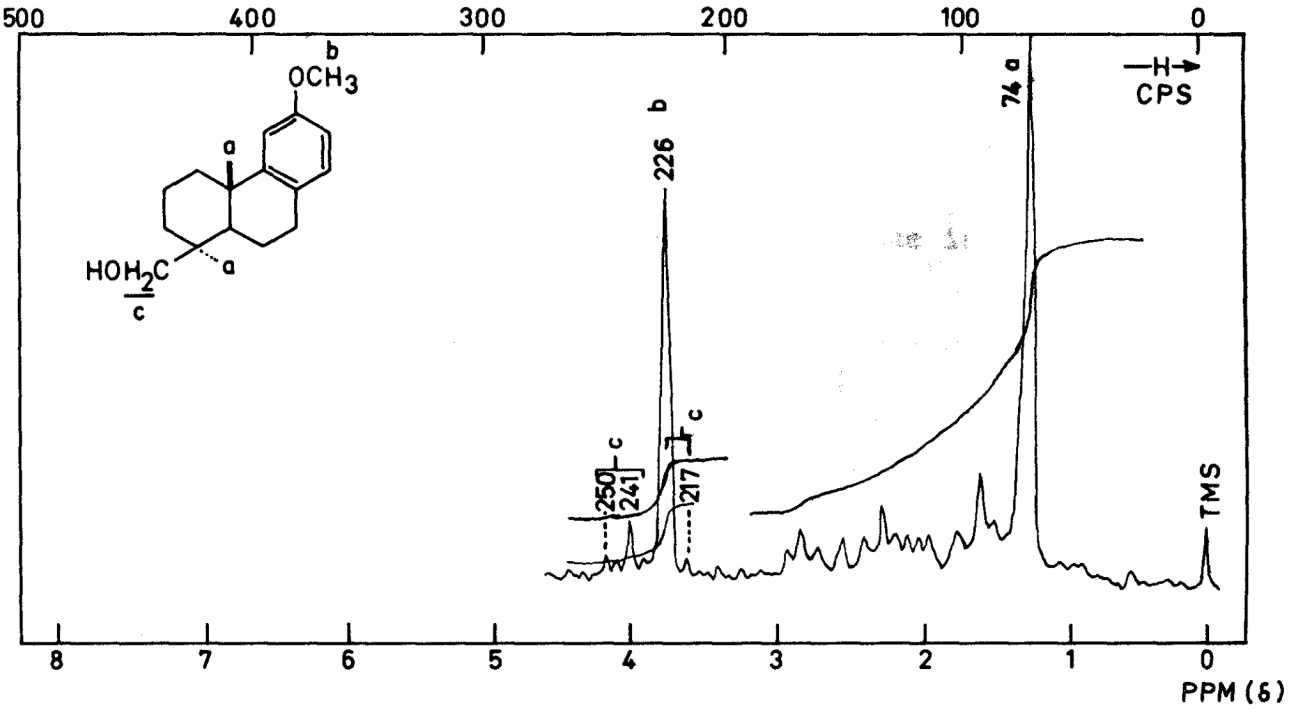
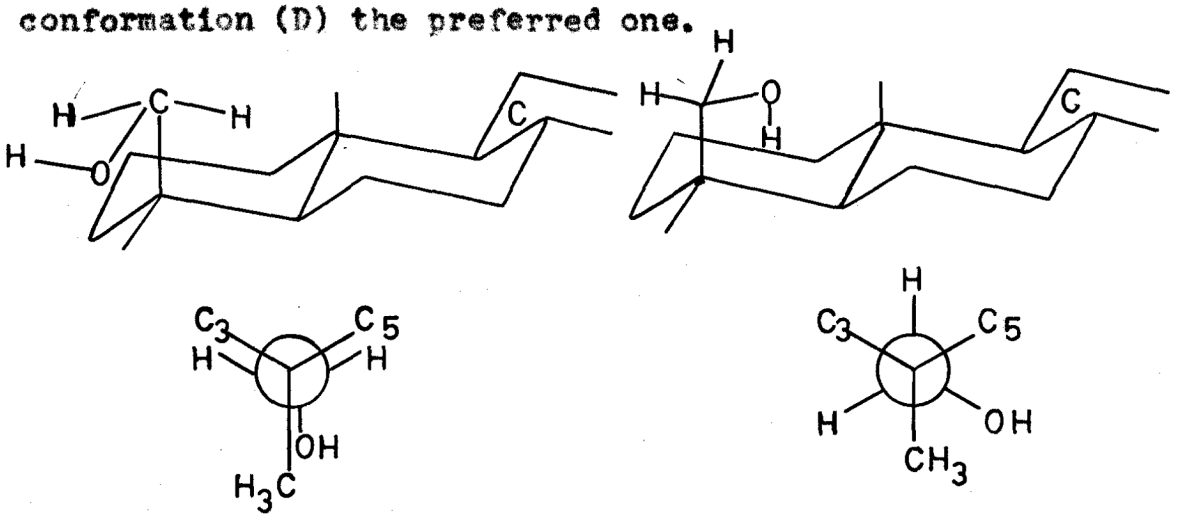


FIG. 8. NMR SPECTRUM OF OMe – PODOCARPINOL (PYRIDINE)

The shift caused by the axial hydroxymethyl is approximately 9 cps. This can be rationalised as being due to the fact that in the axial compound (IX) there would be interactions between the hydroxymethyl at C-4 and C-10 angular methyl which would force the hydroxymethyl to assume a conformation (D) in which the hydroxyl group is farthest away from the C-10 angular methyl. In such a conformation the carbon-oxygen single bond eclipses the carbon-carbon bond of the C-4 equatorial methyl.

In fact a second conformation (E) in which such an eclipsing is not present can also be envisaged. However, though this has a staggered conformation of the hydroxymethyl group in relation to the C-4 carbon atom it has unfavourable non-bonded interactions in which the hydrogen-hydrogen distance (hydrogen of C-4 hydroxymethyl and C-10 methyl hydrogens) is approximately 1.4 ^{0}A whereas in conformation (D) this distance is 1.45^{0}A. This hydrogen-hydrogen interaction therefore makes conformation (D) the preferred one.



D E

A confirmation for this stems from an examination of the spectra of these compounds in pyridine when C-4 equatorial methyl signal of O-methyl-podocarpinol (IX), (Fig.8) shows a considerable (i.e. 11 cps) downfield shift, while C-10 methyl position is almost unchanged, also O-methyl-podocarpinol (IX) is the only compound in which the methyl signals are at different location in $CDCl_3$ and pyridine. All these three factors together indicate that the C-4 hydroxymethyl group when it is axial has the fixed conformation as depicted in (D).

The general nature of this orientation of the hydroxymethyl group is demonstrated by considering other examples from the diterpene field.
Thus vouacopenol (XI) displays it's C-4 methyl at 60 cps in $CDCl_3$ and there is an appreciable paramagnetic shift (13 cps) of this methyl group in pyridine while the C-10 methyl is unaltered.

In its C-4 equatorial epimer i.e. vinhaticol (XII) not only is the C-4 methyl signal at a comparatively higher field (49 cps) in $CDCl_3$ spectrum but also in pyridine the signal is unshifted.

In compounds with antipodal skeleton also this relation holds good. Thus in monogynol (XIV) it is clear firstly from the downfield position of C-4 methyl as compared to the deoxo compound[14] * (XIII) that

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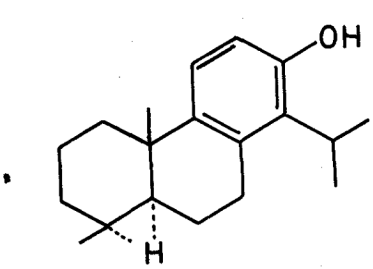
* Values for this compound are those reported in literature[14].

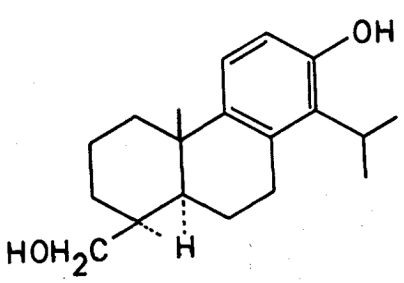
the C-4 hydroxymethyl is axial. The fact that the carbon-oxygen bond is eclipsing the carbon-carbon bond between C_4 and the equatorial methyl is evident from the pyridine spectrum of this compound (XIV) which reveals a downfield shift of 16 cps for the C-4 equatorial methyl group. Similar results were also obtained in the case of dihydromonogynol (XVI) and its deoxo compound*[14] (XV) (Table 3). These results therefore confirm the earlier findings.

Lastly two examples cited in literature may be mentioned. Lamertianic alcohol*[15] (XVII) showed the C-4 methyl at 55 cps whereas the similarly substituted polyalthyl alcohol*[16] (XVIII) displayed its C-4 methyl at 44 cps. This difference in location of methyl signals required the lamertianic alcohol to have the hydroxymethyl axial while polyalthyl alcohol must have the hydroxymethyl group equatorial. This agrees with the known geometry of these compounds.

Totarol[4] in its NMR spectrum in $CDCl_3$ showed signals at 67.2, 56.5 and 55.2 cps for its C_{10} angular



Totarol



Hydroxytotarol

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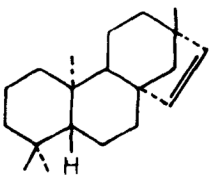
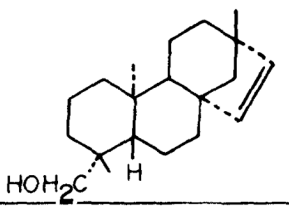
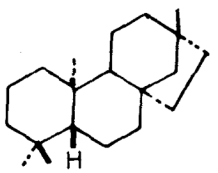
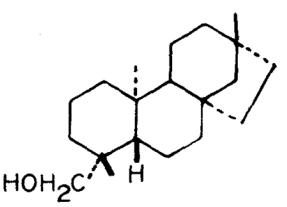
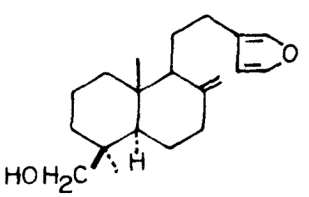
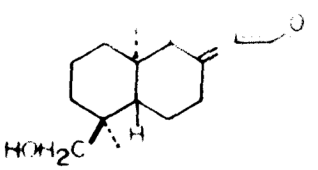
* Values for these compounds are that reported in literature.

TABLE 3

SOLVENT INDUCED CHEMICAL SHIFTS IN PRIMARY ALCOHOLS WITH ANTIPODAL SKELETON

No.	Compound	Chemical shift of the C_4-CH_3			Chemical shift of the C_{10}-CH_3		
		In $CDCl_3$	In Pyridine	shift in Pyr.	In $CDCl_3$	In Pyridine	Shift in Pyr.
XIII		49 51	-	-	-	-	-
XIV	 A	57	72	-15	43.5	47	3.5
XV		50	-	-	-	-	-
XVI	 A	58	71	-13	54	57	-3
XVII	 A	55	-	-	-	-	-
XVIII	 E	44	-	-	-	-	-

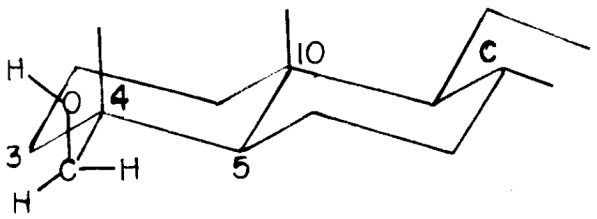
A denotes axial, and E denotes equatorial.

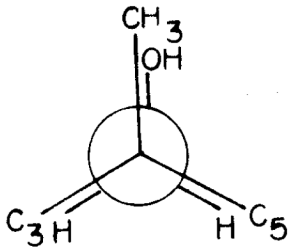
methyl and C-4 gem dimethyl respectively, but when the spectrum of hydroxy totarol was examined in the same solvent the signals at 56.5 and 55.2 cps were replaced by th nal at 62.5 cps, while the signal at 67.2 cps was unaffected. The downfield shift of C-4 methyl by ~6 cps once again confirms the axial disposition of the hydroxymethyl group in hydroxytotarol.

Equatorial alcohols

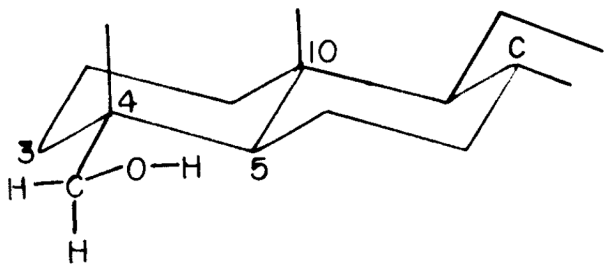
So far we have considered only the conformation of the axial hydroxymethyl substitutent. Using the same arguments as mentioned earlier it is clear that in the case of the equatorial hydroxymethyl group the conformation (F), in which the carbon oxygen bond eclipses the bond between C-4 and the axial methyl, has got no stabilisation through any factor. As such this conformation which would have severe eclipsing interactions would not be a favoured conformation. Once this is realised there is a convenient explanation for the fact that the equatorial hydroxymethyl substituent has no deshielding effect on the geminal axial methyl (compounds X and XII in Table 2).

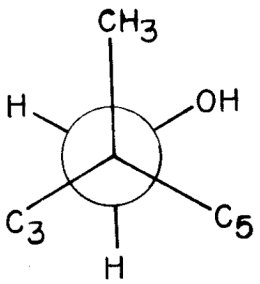
Two other conformations (G) and (H) can therefore be considered. In the conformation (G) the hydroxyl group is skew to the methyl whereas in conformation (H) this interaction is absent as the hydroxyl is now anti to this methyl. It can therefore be expected


H
O
4
10
C
3
C—H
5
H

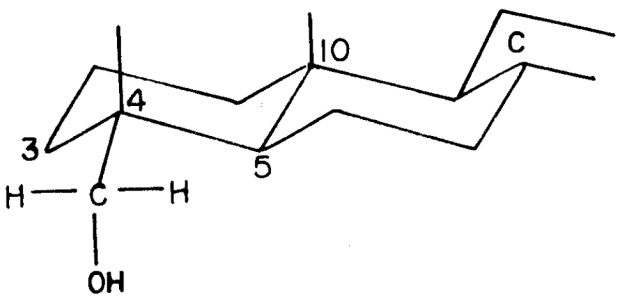

CH3
OH
C3H
H
C5

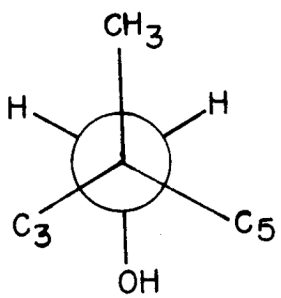
F


10
C
4
3
H—C—O—H
5
H


CH3
H
OH
C3
C5
H

G


10
C
4
3
5
H—C—H
OH


CH3
H
H
C3
C5
OH

H

that conformation (H) would be the preferred conformation being at slightly lower energy level than (G) and at appreciably lower level than (F).

So far we have only considered that (H) is the best possible conformation but have furnished no proof in this direction.

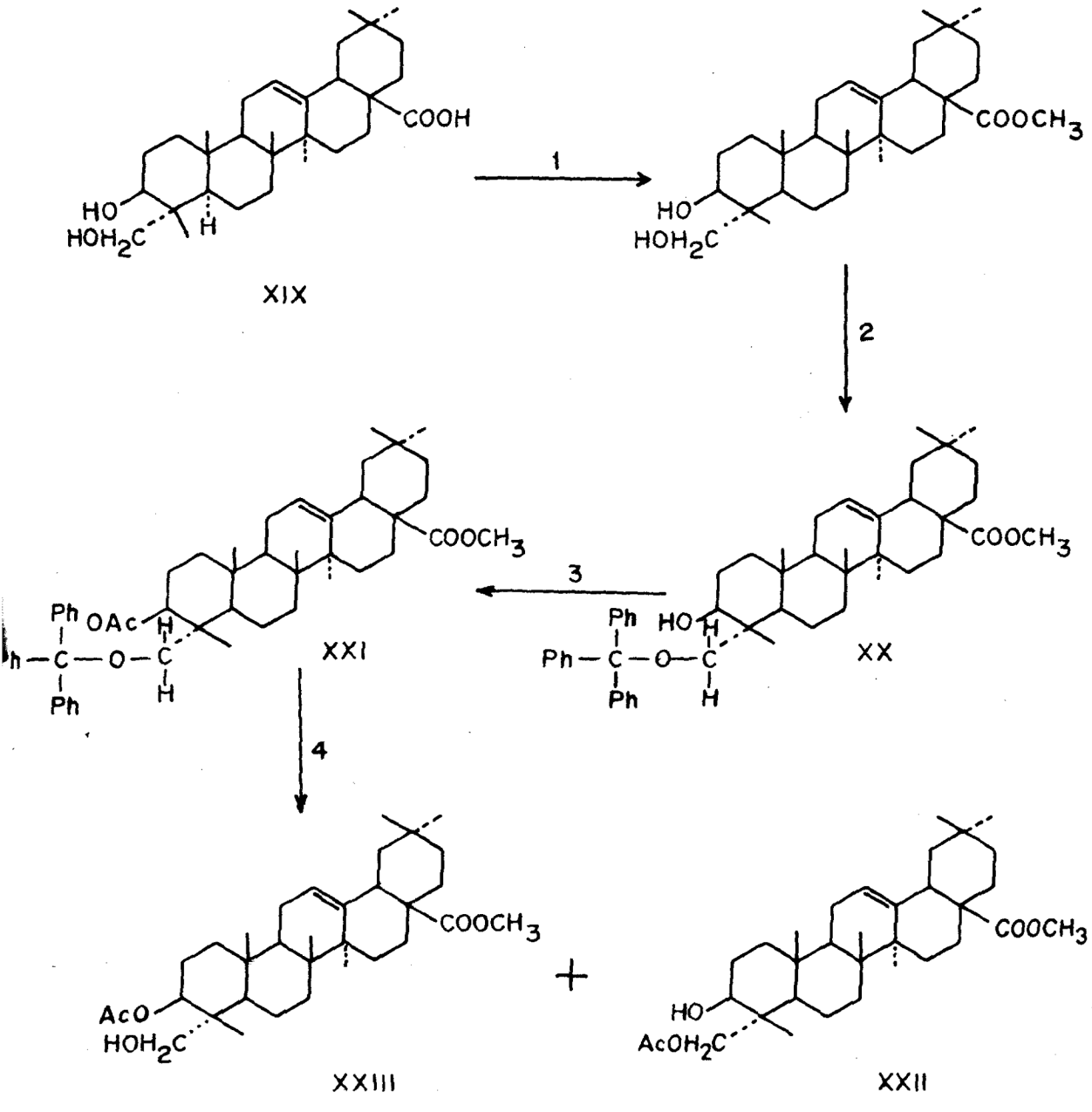
A closer examination reveals that the hydroxyl group in this conformation lies equi-distant between the axial protons at C-3 and C-5. Furthermore the distance between the hydroxyl group and the C-3 proton is equal to the distance ($\sim 2.5^{0A}$) between the hydroxyl group and the C-3 axial proton in 5α-hydroxy steroids.

If, therefore, this is the actual conformation of the C-4 hydroxymethyl group then the shift of the C-3 axial proton by a 5α-hydroxyl group or a 4α-hydroxymethyl group should be nearly the same.

In order to detect the C-3 proton it would be necessary to have a substituent on this carbon atom; and as C-4 equatorial hydroxy methyl in conformation (H) would show an effect on C-3 axial hydrogen, this C-3 substituent should necessarily be equatorial. Hence, compounds with a C-4 equatorial hydroxymethyl and an equatorial substituent at C-3 had to be obtained. For this purpose hederagenin[17] (XIX) isolated from soapnuts was converted through its methyl ester into the C-23 trityl ether (XX) according to the standard methods[18,19] (See Chart 1). The product, $C_{50}H_{64}O_4$, displayed in its I. R. spectrum hydroxyl absorption at 3400 cm^{-1} and aromatic absorption at 710 and 768 cm^{-1} and analysed well for the above formula. The NMR spectrum indicated that the primary hydroxyl group was indeed the one that has been tritylated as the signal due to these protons *[CH_2-O] was shifted upfield*, as expected, from 213 cps to 181 cps, in comparison to the starting ester.

By usual acetylation method the above trityl ether was converted to the 3-acetate (XXI) (I.R. absence of hydroxyl band and appearance of bands at 1740 cm^{-1} and 1240 cm^{-1} due to acetate). Its NMR (Fig. 9) shows a 3H singlet at 112 cps (due to $OCO\underline{CH_3}$) and a lowfield (306 cps) quartet (J = 10 and 5 cps) assignable to the C-3 proton.

CHART-1



1) CH_2N_2 2) PYRIDINE / TRITYL CHLORIDE

3) ACETIC ANHYDRIDE, PYRIDINE 4) PtO_2/H_2

SYNTHESIS OF HEDERAGENIN Me-ESTER 3-ACETATE

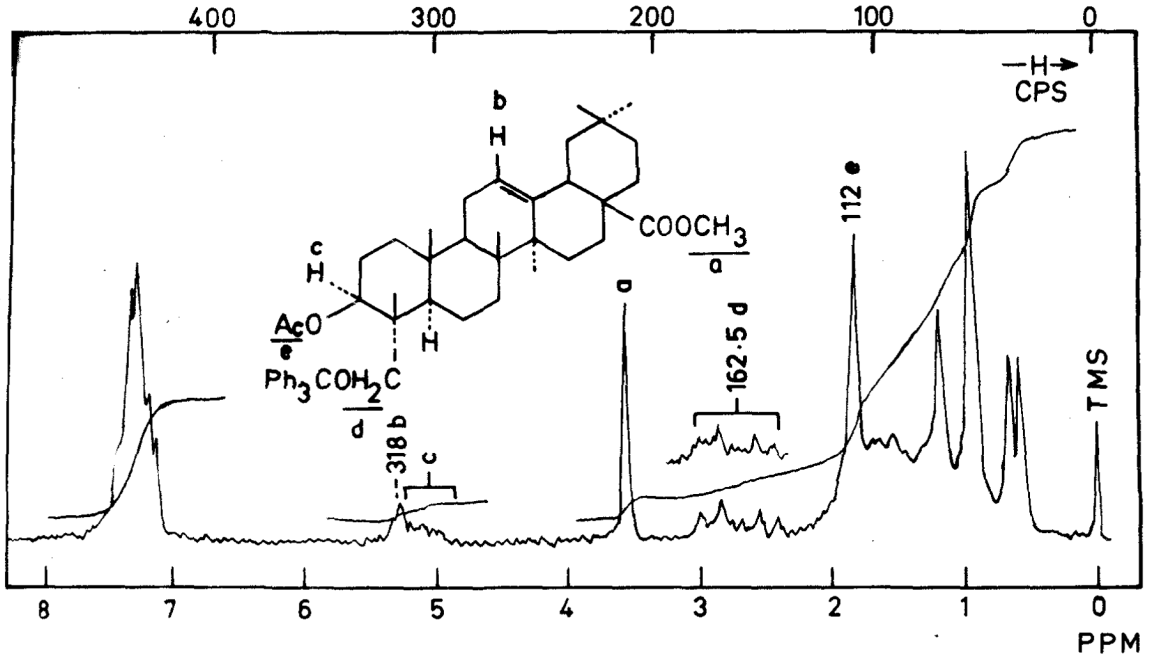


FIG. 9. NMR SPECTRUM OF HEDERAGENIN – Me – ESTER 23-O-TRITYL-3-ACETATE (CCl_4)

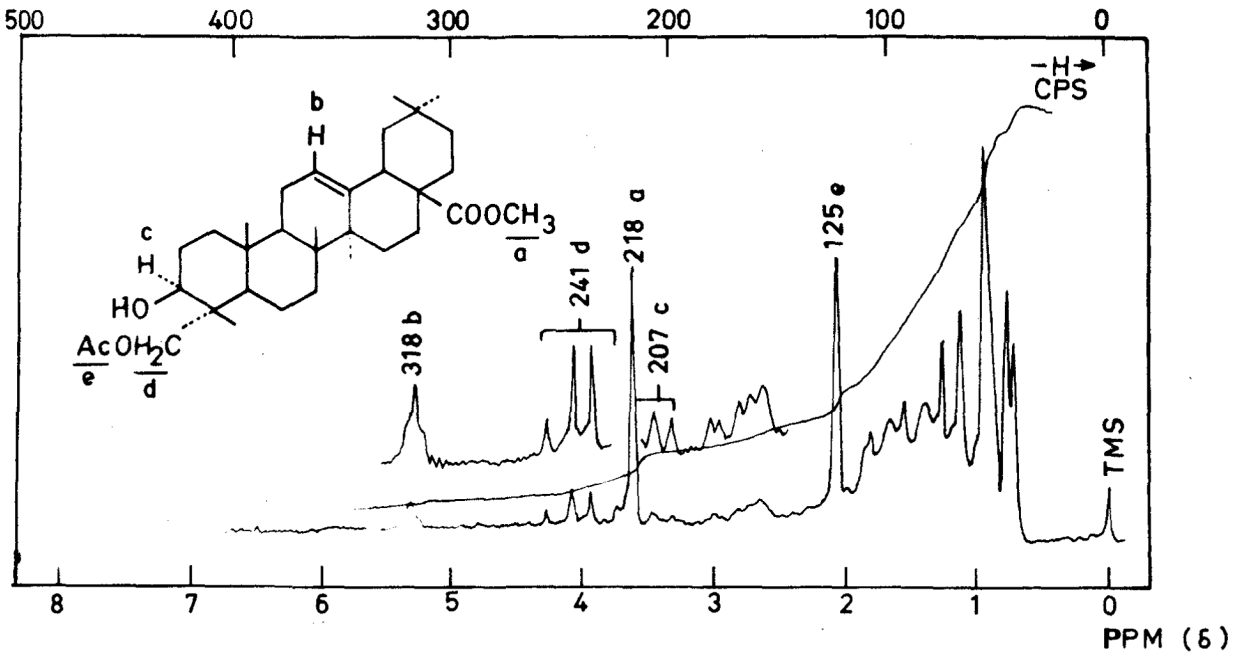


FIG. 10. NMR SPECTRUM OF HEDERAGENIN – Me – ESTER -23-ACETATE ($CDCl_3$)

Detritylation using the normal hydrogenolysis method[20] (using 10% Pd/C and methanol at atmospheric pressure) merely yielded the unreacted trityl ether acetate (XXI). It was only when the detritylation was carried out in acetic acid in presence of platinum oxide[21] catalyst with prolonged stirring in hydrogen atmosphere that appreciable detritylation had taken place. The detritylated product indicated besides the unreacted material and triphenyl methane, the presence of two compounds (T.L.C.).

This mixture was initially separated by chromatography over silica gel. The fastest moving compound as expected, was identified as triphenyl methane. The next fraction gave the unreacted trityl ether acetate (XXI), while the remaining fractions were found to be mixtures of the other two components in different proportions.

Inverted dry column chromatography[22] of these fractions using benzene-ethyl acetate (9:1) yielded both of these components in pure form, as gums.

The more polar compound was identified as hederagenin methyl ester-23-acetate (XXII) from its I.R. (Fig.11) absorption at 3400 cm^{-1} (OH), 1725, 1240 cm^{-1} (OAc) and NMR signals (Fig. 10). The latter exhibited a singlet (3H) at 125 cps (OAc), two protons 'B' quartet at 241 cps (J = 11 cps) [In hederagenin methyl ester this quartet is considerably upfield i.e. 212 cps (J = 11 cps)] and a one

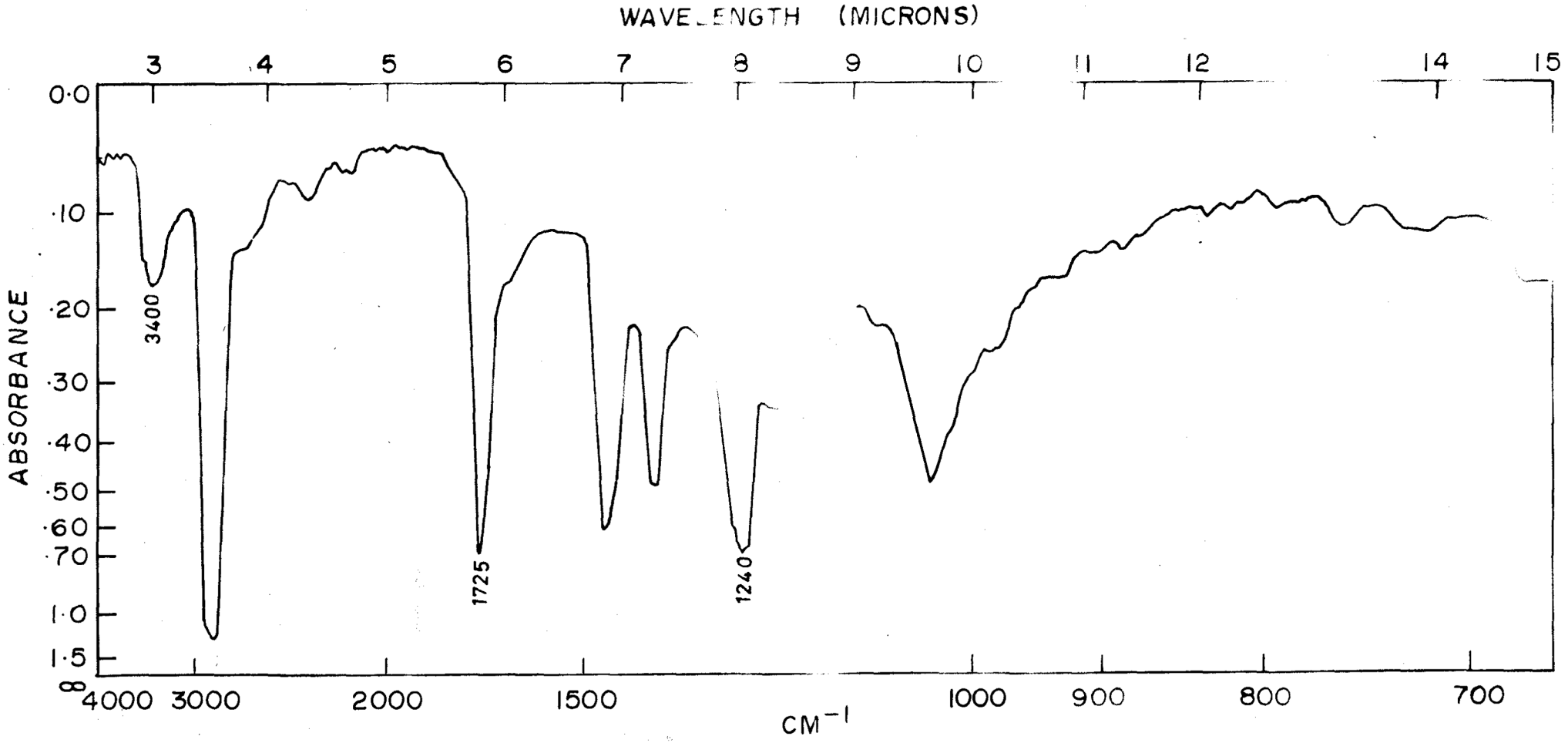


FIG. 11. IR SPECTRUM OF HEDERAGENIN – Me – ESTER – 23 – ACETATATE (XXII)

proton quartet at 207 cps (J = 9 and 7 cps) almost similar to the signal in hederagenin methyl ester. This compound must therefore be represented by (XXII) and should have been formed through acyl migration.[23,24,25]

The faster moving compound was the expected hederagenin methyl ester 3 acetate*.

Though several attempts were made to obtain this in crystalline form, the material was obtained as a colourless gum only. It however analysed well for $C_{33}H_{52}O_5$, and its I.R. spectrum indicated the presence of hydroxyl and acetate functions (3400, 1730, 1242 cm^{-1}). (Fig. 12) In the NMR spectrum the C-3 proton appeared at low field (i.e. 296 cps) as a characteristic quartet (J = 11, 5.5). The signal assignable to the methylene group carrying the hydroxyl appeared as an AB quartet at 189 cps (J = 12 cps).

When the NMR spectrum of this compound (XXIII, Fig. 14) was compared with that of β-amyrin acetate** (XXIV, Fig. 13), it clearly showed a downfield shift of the signal of the C-3 proton by 25 cps (See Table 4) revealing thereby the eclipsing of C-O bond of C-4 equatorial hydroxy methyl with C-3 axial proton.

---

* It is necessary to prepare the C3-acetate as in the spectrum of hederagenin methyl ester there is an overlapping of the signals due to C3-H and the hydroxymethyl group which makes assignments of exact positions difficult.

** Actually comparison should be made with oleanolic acid methyl ester, 3-acetate, but as the ester group in (XXIII) is very far away it obviously has no effect on the observed shifts for C-3H or C-4 and C-10 substituents and hence β-amyrin acetate would serve the purpose equally well.

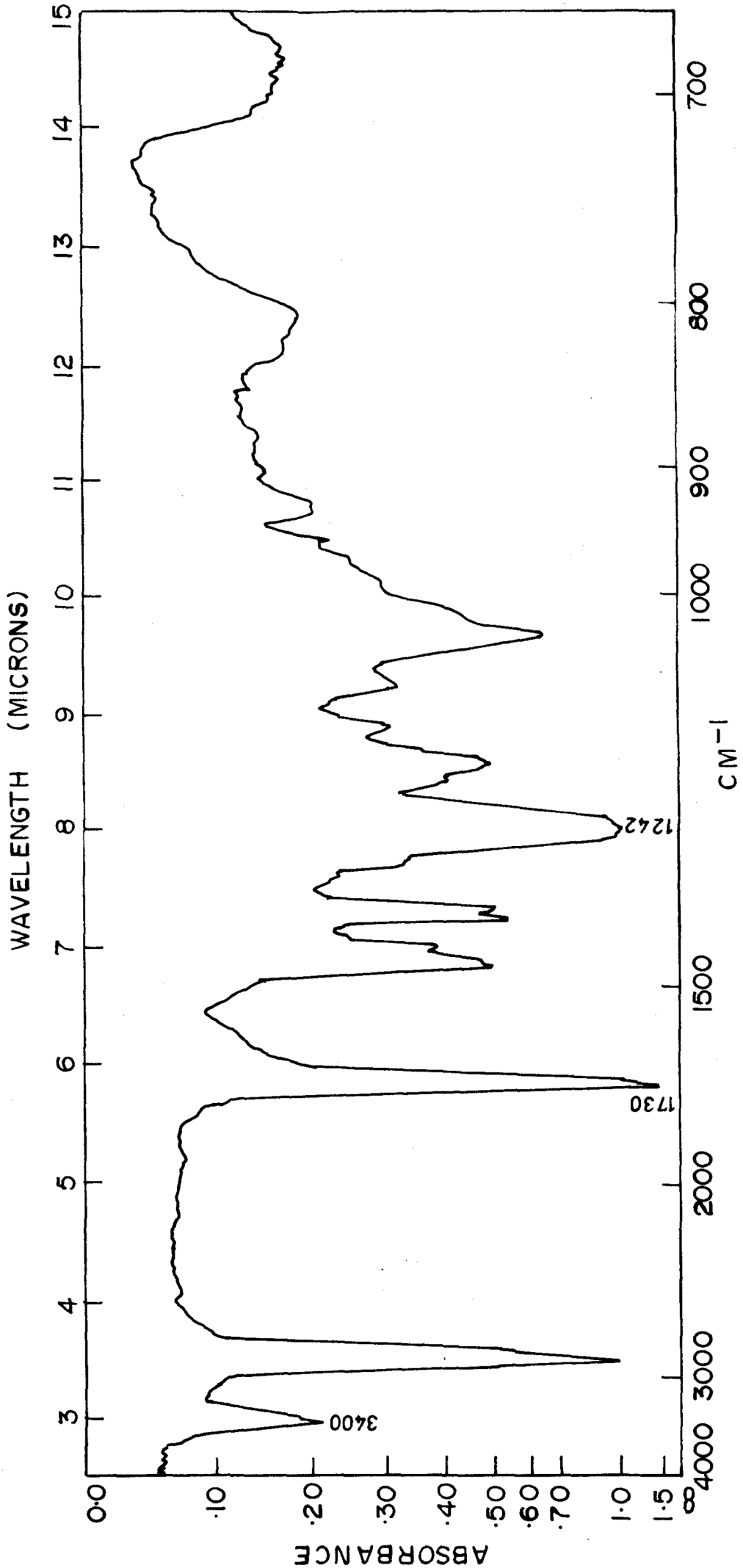


FIG. 12. IR SPECTRUM OF HEDERAGENIN - Me-ESTER 3 ACETATE (XXIII)

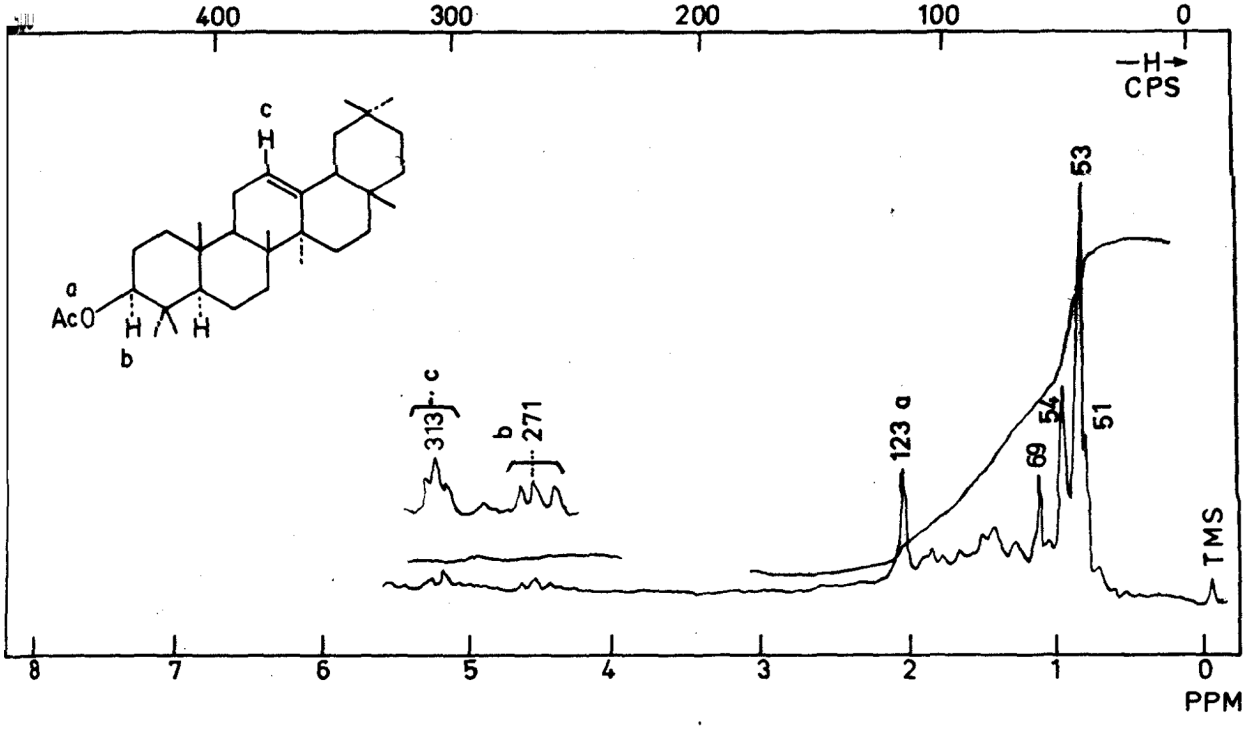


FIG. 13. NMR SPECTRUM OF β AMYRIN ACETATE ($CDCl_3$)

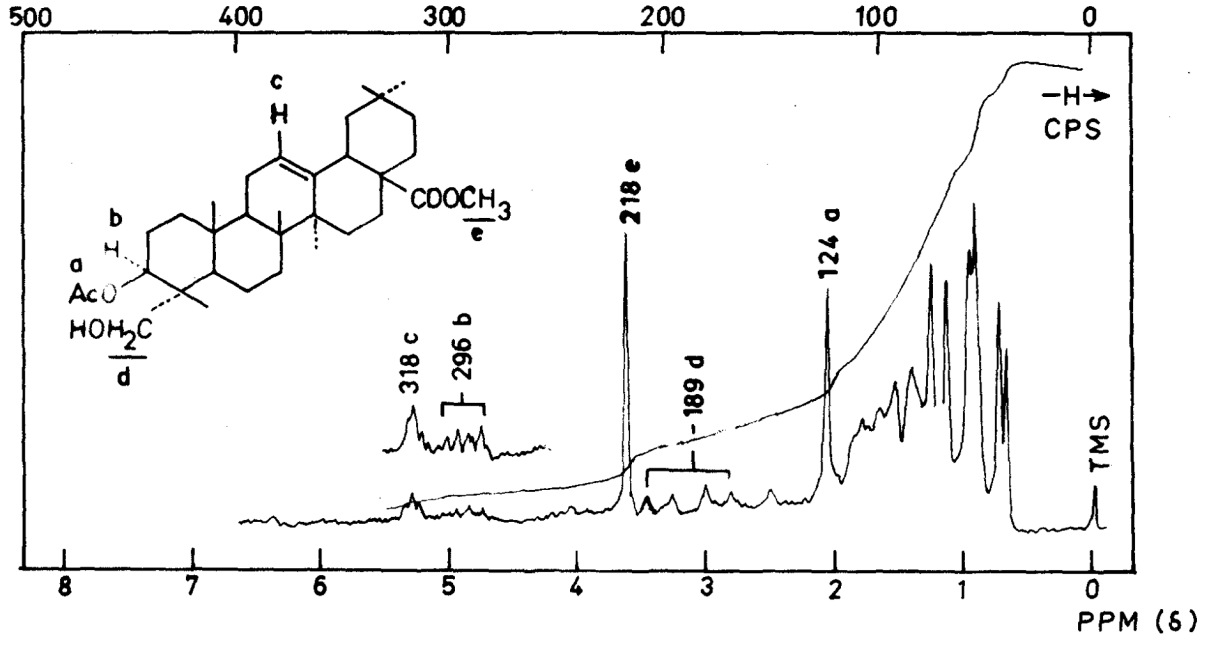
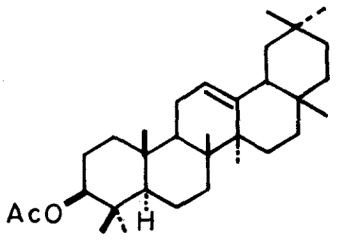
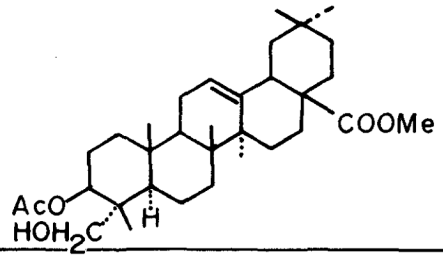
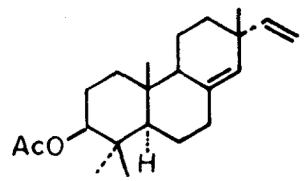
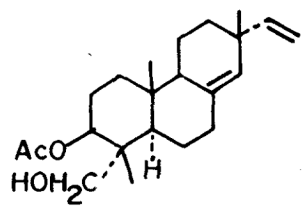
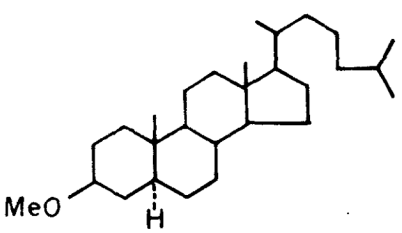
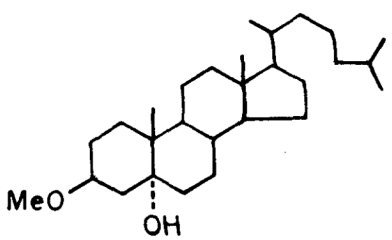


FIG. 14. NMR SPECTRUM OF HEDERAGENIN—Me-ESTER 3 ACETATE ($CDCl_3$)

TABLE 4

CHEMICAL SHIFTS OF C_3-H CAUSED BY EQUATORIAL HYDROXYMETHYL GROUP

No.	Compound	Chemical shift of C_3-H in $CDCl_3$	
XXIV		271 cps	
XXIII		296 cps	Shift of C_3-H -25 cps
XXV		268 cps	
XXVI		301 cps	Shift of C_3-H -33 cps
XXVII		187 cps	
XXVIII		217 cps	Shift of C_3-H -30 cps

A second pair of such compounds was that of the sandaracopimaradiene derivatives+ (XXV and XXVI) in which the C-4 equatorial hydroxymethyl group caused a downfield shift of the C-3 proton by 33 cps.

These two examples serve to indicate that the C-4 equatorial hydroxymethyl group does exist in the conformation (H). It had earlier been pointed out that in this conformation the distance between the oxygen of CH_2OH group and the C-3 axial hydrogen is equal to that between the oxygen of a 5α-hydroxyl and the C-3 axial hydrogen in 5α-hydroxy steroids. It was therefore felt that an elegant proof for this expectation would be provided if the spectra of such type of compound is also examined.

The most obvious compounds which would be suitable for this purpose would therefore be cholestane-3β-ol methyl ether (XXVII) and its 5α-hydroxy* derivative (XXVIII). An examination of the spectra of these two compounds in $CDCl_3$ clearly revealed a downfield shift of 30 cps for the C-3 proton in the 5α-hydroxy compound (XXVIII, Table 4). As this downfield shift is nearly the same as that observed for the C-3 proton due to C-4 equatorial hydroxymethyl, this established the previous suggested conformation (H) for these equatorial hydroxymethyl groups.

+ I am grateful to Prof. J. W. W. Morgan for the samples of these compounds.

* We are thankful to Mr. V. R. Sarma of this Laboratory for the sample of this compound.

It may be added that these conformations of the hydroxymethyl group may be vitiated by interfering substituents in the A/B rings.

EXPERIMENTAL

For general procedure see Chapter 1.

11α-Hydroxy progesterone (I)*

M.P. 168°

$[\alpha]_D^{28}$ +176°

11β-Hydroxy progesterone*(II)

M.P. 188°

$[\alpha]_D^{28}$ +222°

11α-Hydroxy-5α-pregnane (III)

To 11-keto-5α-pregnane+ (183 mg, m.p. 104°) in dry alcohol (15 ml) was added sodium (1.25 g) in small quantities. After all the sodium had reacted the reaction mixture was refluxed for two and half hours. It was then cooled, diluted with water and extracted with ether (4x25 ml). The combined extracts were washed with distilled water and dried over anhydrous sodium sulphate. Removal of ether gave a solid which crystallised from acetonitrile to yield the product (150 mg).

M.P. 148-149°

$[\alpha]_D^{28}$ -75.5°

I.R. 3300, 1025 cm^{-1} (OH)

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* These samples were kindly supplied by Dr. L. M. Kogan

\+ This sample was supplied by Mr. M. R. Sarma of our laboratory.

NMR ($CDCl_3$), Broad signal (1H) centered at 237 cps (11-axial H), 3H-singlet at 35 cps (-18 CH_3) 3H singlet at 57 cps (19-CH_3)

Analysis

Found: C, 82.98; H, 12.04%

$C_{21}H_{36}O$ requires: C, 82.83; H, 11.92%.

11β-Hydroxy-5α-pregnane (IV)

11-Keto-5α-pregnane (150 mg) in dry ether (10 ml) was added slowly to a suspension of lithium aluminium hydride (75 mg) in dry ether (10 ml). The mixture was refluxed for six hours. The excess LAH was destroyed by cold 2N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether (3x25 ml). Total ether extracts were combined, washed with distilled water and dried over anhydrous sodium sulphate. Removal of the solvent and crystallisation of the product from methanol afforded the β-alcohol (120 mg).

M.P. 124°

$[\alpha]_D^{28}$ +38°

I.R. 3500 cm^{-1} (hydroxyl)

NMR ($CDCl_3$) a narrow 1 proton signal at 266 cps (C-11 equatorial H), 3H singlets at 47 and 62 cps (18 and 19 methyls respectively).

Analysis: Found: C, 83.04; H, 12.1%

$C_{21}H_{36}O$ requires: C, 82.83; H, 11.92%.

2,2-Dimethyl cyclopentanol (VII)[12]

2,2-Dimethyl cyclopentanone* (150 mg) in dry ether (5 ml) was added dropwise to a suspension of LAH (75 mg) in dry ether (5 ml). The reaction mixture was refluxed with stirring for 5 hours. It was then cooled and excess of LAH was destroyed by cold water. The organic layer was separated and the salts were washed well with ether. The total ether extracts were combined, washed well with water and dried over anhydrous sodium sulphate. Removal of solvent gave a mobile oil (150 mg) which was distilled through a short column.

B.P. 140-142° at 710 mm. Lit. 151-152° at 744 mm.

n_D^{20} 1.4537 Lit. 1.4532.

NMR ($CDCl_3$) 57, 59 cps (Methyl signals)

180 cps (OH signal, exchanged with D_2O)

Methyl-O-methyl podocarpate[26]

Podocarpic acid (5 g), freshly distilled dimethyl sulphate (7 g) and sodium hydroxide (2.5 g) in 50% aqueous alcohol (25 ml) were refluxed on steam bath for 30 minutes. On cooling methyl-o-methyl podocarpate separated out. It was filtered and the precipitate was crystallised from petroleum ether to afford the ester (4.4 g) in beautiful needles.

M.P. 128° Lit. 128°

I.R. 1730 cm^{-1} (ester) 1510, 1620, 740, 785 cm^{-1} (aromatic)

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* This sample was kindly supplied by Dr. Sukh Dev.

O-Methyl podocarpinol (IX)[27]

Methyl-O-methyl podocarpate (4 g) in dry ether (100 ml) was added slowly to a suspension of LAH (1 g) in dry ether (50 ml) with stirring. After the reaction mixture was refluxed with stirring for six hours, the excess of LAH was destroyed by cold dil.HCl. Usual work up followed by crystallisation from methanol yielded the expected alcohol (3.5 g).

M.P. 89° Lit. 90°

I.R. 3448 cm^{-1} (OH)

O-Methyl podocarpane (VIII)[29]

O-Methyl podocarpinal* (435 mg) was refluxed with ethylene glycol (27 ml), hydrazine hydrate (0.9 ml) and potassium hydroxide (2.667 g). After two hours the reaction mixture was heated to 190° and the distillate collected. Additional hydrazine hydrate (0.5 ml) was added to the residue and the resulting mixture was refluxed for two hours. Some more material was distilled off at 196° and the distillate was again collected. The reaction mixture left over was refluxed for further six hours. It was then cooled and poured in water (200 ml). This was saturated with common salt and extracted with ether (6x25 ml). Total ether extracts were washed with brine and dried over anhydrous sodium sulphate. Removal of solvent gave a coloured residue (150 mg) which resisted crystallisation.

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* Preparation described in Chapter IV.

To account for the rest of the material the two distillates collected were examined, and surprisingly it was observed that beautiful clusters of needles appeared in the distillates. As the crystals did not dissolve on addition of plenty of water, they were separated (275 mg).

M.P. 30° Reported for O-methyl podocarpane 31°

I.R. No bands at 2700 cm^{-1} and 1710 cm^{-1}, rest of the spectrum similar to that of o-methyl podocarpinal.

NMR ($CDCl_3$)

Singlet (3H) at 225 cps	C-12 o-methyl
Singlet (3H) at 71 cps	C-10 methyl
Singlet (6H) at 55 cps	C-4 gem dimethyl

Analysis

Found: C, 83.6; H, 10.24%

$C_{18}H_{26}O$ requires: C, 83.66; H, 10.14%.

Methyl dehydroabietate[30]

Dehydroabietic acid (49 mg) in ether was treated with an excess ethereal solution of diazomethane and kept aside overnight. Excess of diazomethane was removed on steam bath. The residue was taken up in ether, washed with 5% sodium bicarbonate, water and then dried on sodium sulphate. Removal of solvent and subsequent crystallisation from aqueous methanol furnished the ester (3.5 g).

M.P. 61-61.5° Lit. 61-62.5°.

Dehydroabietinol (Y)[30]

Methyl dehydroabietate (2.6 g) in dry ether (50 ml) was reduced using LAH (1 g) under the usual conditions to provide dehydroabietinol as a viscous oil (2.35 g), which was distilled under vacuum.

B.P. 175-185° (bath temp.)/0.2 mm.
Lit. 175-180° (bath temp.)/0.2 mm.

$[\alpha]_D^{28}$ +62°

I.R. 3360 cm^{-1} (OH)

Methyl vinhaticoate[31]

Vinhaticoic acid* was esterified with ethereal diazomethane solution by the usual procedure. Residue obtained was crystallised from methanol.

M.P. 108°	Lit. 108°
$[\alpha]_D$ +64°	Lit. +66°

Vinhaticol (XII)[28]

Methyl vinhaticoate (100 mg) was reduced with lithium aluminium hydride according to usual procedure, work up and crystallisation from little methanol gave needles of vinhaticol (85 mg).

M.P. 132-133°	Lit. 133°
$[\alpha]_D$ +86°	Lit. +92°

---

* These samples were kindly supplied by Dr. F. E. King.

Methyl vouacopenate[28]

Vouacopenic acid* was esterified with diazomethane by the known method. The ester was purified by chromatography over neutral alumina. Crystallisation from methanol gave the ester as good needles.

M.P. 103°.	Lit. 103-104°
$[\alpha]_D$ +99°	Lit. 101°

Vouacopenol (XI)[28]

Methyl vouacopenate (100 mg) was reduced with etheral suspension of lithium aluminium hydride in usual fashion. Work up and crystallisation from methanol afforded vouacopenol (75 mg).

M.P. 130°	Lit. 131-132°
$[\alpha]_D$ +68°	Lit. +71

Monogynol* (XIV)

Recrystallised from acetonitrile thrice provided prisms melting at 118°. Lit. 118°.

Dihydromonogynol (XVI)[14]

Monogynol (1 g) in glacial acetic acid (30 ml) was stirred in an atmosphere of hydrogen in the presence of 10% palladised charcoal catalyst (950 mg). Absorption ceased after four hours. The catalyst was filtered and

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* These samples were kindly supplied by Dr. F. E. King.

+ We are grateful to Dr. Sukh Dev for a sample of the compound.

filterate was diluted with water. Precipitated material was extracted with ether (4x25 ml). Total ether extract was washed free of acetic acid and dried over sodium sulphate. Removal of solvent afforded a colourless gum which showed two spots in T.L.C. As its I.R. displayed bands at 1725 cm^{-1} and 1245 cm^{-1}, it could be assumed that some acetylation had taken place.

For avoiding separation, the gum was refluxed for two hours with 5% methanolic potassium hydroxide. The solution was concentrated in vacuo, and diluted with water. The precipitated material was extracted with ether (4x25 ml). Total ether extracts were washed with distilled water and dried over sodium sulphate. Removal of solvent and two crystallisations from acetonitrile afforded dihydromonogynol (800 mg).

M.P. 128° Reported 128-129°
(No colour with TNM)

Isolation of hederagenin (XIX) from soapnut

Hederagenin was isolated by the following method described by Jacobs[17] with slight modification.

Shells of soapnuts were separated from seeds and were ground to powder. This powder (500 g) was extracted twice by immersing the shells in 95% alcohol (2 litres) for twentyfour hours. Combined extracts were concentrated (to 1.5 litres) under reduced pressure. This concentrate was refluxed for three hours with 10% aqueous hydrochloric acid (1.5 litres) and allowed to stand for twentyfour hours.

The crude substance that separated was filtered and washed thoroughly with 50% alcohol. Dried material was then digested at room temperature with small amount of acetone which helped in removing the coloured material to some extent. To get rid of colouring matter the material was dissolved in 60% alcohol by the addition of requisite amount of sodium hydroxide and reprecipitated with acetic acid while hot. As the material collected on buchner was still coloured, it was treated with animal charcoal and crystallised twice from alcohol.

To remove the last traces of colour, the material was adsorbed on silica gel (50 g) and this silica gel was loaded on a silica gel column (750 g). Elution with benzene yielded some coloured gum which was not investigated. Ether eluates gave the white material (m.p. 320-322°). One crystallisation from alcohol afforded the pure hederagenin.

M.P. 326-327° Lit. 327-329°

Yield 15 g.

Hederagenin-Methyl ester

Hederagenin (5 g) was refluxed for two hours with a solution of potassium hydroxide (950 mg) in methanol (40 ml) and freshly distilled dimethyl sulphate (2 ml). The solid which separated on cooling was filtered. As it did not properly crystallise from methanol, it was chromatographed on silica gel. Elution with 25% ether in benzene gave a colourless material which showed a single spot in T.L.C. One crystallisation from methanol gave the ester in pure form (4.2 g).

M.P. 236° Lit. 230-40°

Hederagenin methyl ester 23 trilyl ether (XX)[18,19]

Hederagenin methyl ester (3.9 g , 0.008 mole) in dry pyridine (40 ml) was warmed on steam bath with triphenyl methyl chloride (3.340 g , 0.012 mole) for three hours. After standing for 24 hours at room temperature the reaction mixture was poured in crushed ice and extracted with ethyl acetate (4x30 ml). Combined ethyl acetate extracts were washed free of pyridine and dried over anhydrous sodium sulphate. Removal of solvent left a white solid (~ 7 g) which showed two spots on TLC, one of them corresponding to authentic triphenyl carbinol. The mixture was therefore chromatographed on silica gel column. Chromatogram 1 summarises the results obtained.

Chromatogram 1

Silica gel (150 g), column dia. 2.5 cm.

Fra.No.	Solvent	Sub.	Weight
1.	Pet. ether (5x100 ml)	Nil	
2.	Pet. ether-Benzene (5x100 ml) 1 : 1	White solid	1.1 g
3.	Benzene (8x100 ml)	White solid	5.7 g

Fraction 2 after crystallisation from pet. ether gave triphenyl carbinol (m.p. and mixed m.p. 164°).

Fraction 3 (single spot on TLC) on crystallisation from aqueous alcohol afforded the desired trityl ether (5.029 mg).

M.P. 145-146°

$[\alpha]_D^{28}$ +24.5

I.R. 3400 cm^{-1} (OH) 1730 cm^{-1} (ester)
710, 748, 768, 777 cm^{-1} (aromatic)

Analysis: Found: C, 82.60; H, 8.92%

$C_{50}H_{64}O_4$ requires: C, 82.37; H, 8.85%.

NMR (CCl_4) 15 proton narrow multiplet centered at 435 cps (aromatic protons, 1 proton singlet at 316 cps (vinylic $-C_{12}H$) 3H singlet at 214 cps (COOMe).

Hederagenin methyl ester, 23 trityl ether, 3 acetate (XVI)

The above compound (4 g) in pyridine (20 ml) and acetic anhydride (20 ml) was warmed on steambath for two hours. It was then kept overnight at room temperature. The solution was then poured on crushed ice and allowed to stand for 2-3 hours to decompose the acetic anhydride. Usual work up followed by crystallisation from alcohol furnished the acetate (3.85 g).

M.P. 228-229° (with preliminary sintering at 225°)

$[\alpha]_D^{28}$ +67°

I.R. (no OH band) 1730, 1242 cm^{-1} (OAc)
700 and 768 cm^{-1} (aromatic)

NMR (CCl_4) 15 proton narrow multiplet at 436 cps (Trityl), 1 proton singlet at 318 cps (vinylic C_{12}-H), 3H singlet each at 214 and 119 cps for COOMe and $OCOCH_3$ respectively.

Analysis

Found: C, 81.51; H, 8.67%

$C_{52}H_{66}O_5$ requires: C, 81.6; H, 8.67%.

Hydrogenolysis of Hederagenin-methyl ester 23-O-triphenyl methyl 3 acetate

To the trityl ether acetate (725 mg) dissolved in acetic acid (20 ml) containing ethyl acetate (2 ml) was added 2 drops of conc. HCl. The mixture was stirred in an atmosphere of hydrogen for 15 hrs. in the presence of Adam's catalyst (72.5 mg). The catalyst was filtered and the filtrate was diluted with water. The precipitated material was extracted with ether (4x25 ml). Combined ether extracts were washed with sodium bicarbonate solution and distilled water. Removal of the solvent after drying, yielded a residue which showed four spots on TLC (R_F 0.92, 0.83, 0.33, 0.21). Material was therefore chromatographed on silica gel. Chromatogram 2 shows the results obtained.

Chromatogram 2

Silica gel (25 g), column dia. 1.5 cm. (T.L.C. solvent system: Benzene + EtoAC 9 : 1)

Fra. No.	Solvent	Wt. of the material mg	Remark
1.	Pet. ether (3x25 ml)	35	Single spot in TLC R_F 0.92 identified as triphenyl methane M.P. and mixed M.P. 91°
2.	Pet. ether : Benzene (5x25 ml) 1 : 1	375	Single spot material R_F 0.83 identified as starting trityl ether acetate M.P. and mixed M.P. 226°
3.	Benzene (4x25 ml)	nil	nil
4.	Benzene : 5% Ether (5x25 ml)	275	Mixture of two component R_F 0.33 and 0.21

Fraction 4 was resolved into two components by "Inverted dry column chromatography"[22] on silica gel (250-300 mesh) using benzene-ethyl acetate (9:1) giving the faster moving compound (R_F 0.33, 95 mg) and slower moving compound (R_F 0.21, 150 mg) as colourless gums which resisted crystallisation.

Compound R_F 0.33 was identified as Hederagenin methyl ester 3 acetate (XXIII).

$[\alpha]_D^{28}$ +43.25°

I.R. 3400 cm^{-1} (OH), 1730, 1242 (COOMe, OAc)

NMR ($CDCl_3$) 1 proton signal at 318 cps (C-12 H)

1 proton quartet centered at 296 cps (J = 10 and 6 cps) (C_3-H)

3 H singlet at 218 cps (COOMe)

3 H singlet at 124 cps (OAc)

2 H quartet at 189 cps (J = 11) (23-CH_2-OH)

Analysis:

Found: C, 74.89; H, 9.77%

$C_{33}H_{52}O_5$ requires: C, 74.96; H, 9.91%.

Compound R_F 0.21 was identified as Hederagenin methyl ester 23 acetate (XXII).

$[\alpha]_D^{28}$ +52°

I.R. 3400 cm^{-1} (OH), 1725, 1240 cm^{-1} (COOMe, OAc)

NMR ($CDCl_3$) C-3H proton quartet at 207 cps (J = 9 and 7)

23 CH_2 OAc quartet at 241 cps (J = 11)

OAc singlet at 125 cps

Analysis:

Found: C, 75.06; H, 9.79%

$C_{33}H_{52}O_5$ requires: C, 74.96; H, 9.91%.

Cholestan-3β-ol methyl ether (XVII)

Preparation of this compound is described in Chapter 2. II

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CHAPTER IV

THE CONFORMATION OF ESTERS, ACIDS AND ALDEHYDES IN TERPENOIDS

INTRODUCTION

In a cyclohexane or a fused cyclohexane the normal method for determining the stereochemistry of a carboxylic acid is by determining whether the acid is axial or equatorial. This method can also be used in the case of primary alcohols and aldehydes which can be easily oxidised to the acid, hence the determination of the stereochemistry of the carboxylic function can help in these cases also.

The methods available for proving whether a carboxylic acid is axial or equatorial are based on the principles mentioned below:

1) Determination of the rate of hydrolysis of the esters[1] and comparison with suitable model compounds. Generally axial esters are more difficult to hydrolyse as compared to their equatorial epimers. It can readily be understood that if the stereochemistry is not already known, choice of model compounds causes difficulty.

2) Determination of pKa of acids[2] can also be used for this purpose. With the help of several correction factors discussed recently[3,4] the scope of this method has been enlarged.

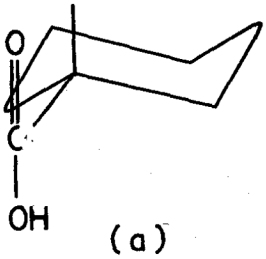
3) The C-O stretching frequency[5] of a methyl ester has been used to determine the configuration of the ester. The difficulty in this method is that interfering

acetates and other esters should be absent. Also the method is limited to those compounds in which the carbomethoxy function forms part of a gem dimethyl group.

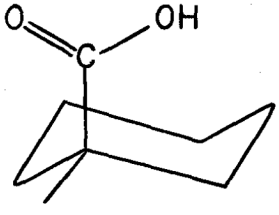
4) In a recent method Narayanan and Venkatasubramanian[6] have been able to determine the stereochemistry of terpene acids by an examination of their P.M.R. spectra. In the axial acids, the C_4 carboxyl group deshielded the C_{10} methyl by 16.8 cps when the spectrum of the ester in pyridine was compared with that of the acid in pyridine. In equatorial acids, which have no methyl group in a 1:3 cis diaxial relation, deshielding is only 4 cps.

It is only recently that interest has been focussed on the conformation of the acid function.

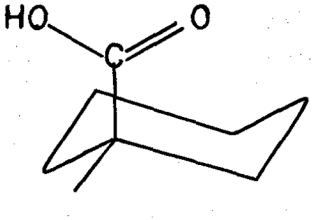
Simultaneously two groups of workers[3,4] by measurements of the pKa values came to the conclusion that in equatorial acids the favoured conformation(a) is the one which has the carboxyl group in an eclipsing orientation with the substituent at the carbon atom carrying the carboxyl function. These workers could also conclude that in axial acids either of the two conformations (b) or (c) is the preferred conformation.



(a)



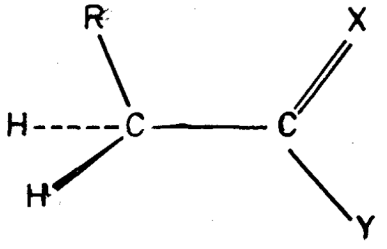
(b)



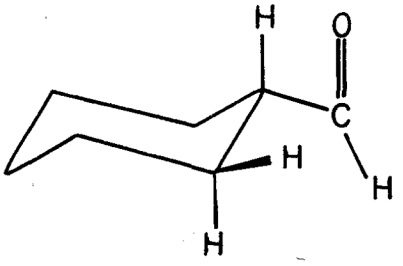
(c)

Narayanan and Venkatasubramanian[6] from comparative NMR study of axial and equatorial esters suggested that the axial esters have either conformation (b) or (c).

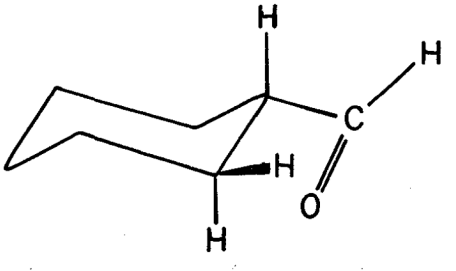
Several investigations[7] have demonstrated that the preferred conformation of a tetrahedral carbon bonded to a trigonal carbon is the one where a single bond (C-R) eclipses the (C=X) double bond.



In the case of the aldehydes attached to a secondary carbon atom two alternate conformations are possible, one (d) in which the carbonyl eclipses the hydrogen and the second (e) where the carbonyl eclipses the substituent (ring residue).



(d)



(e)

these
The choice between/two can be made by considering the spin-spin coupling constants, between an aldehyde proton and a proton on an ∝ carbon atom, as a function of temperature and solvent.[8] In the case of cyclohexyl aldehyde the second conformation (e) is more stable than the first (d). Interestingly enough this position is reversed in cyclopentyl and cyclobutyl aldehydes.

In the case of acyclic aldehydes the different substituents effect the stability of the two conformations in different ways[8].

The present work was therefore undertaken with a view to determine the exact conformations of acids, esters and aldehydes in diterpenes making use of solvent induced chemical shifts.

Present Work

In a few cases, it has been observed recently that the carbonyl group (-C=O) of carboxylic acid or its ester shields[9,10,11,6] a methyl group that has a 1,3-cis diaxial relation with it. Thus Narayanan and Venkatasubramanian[6] from a comparative NMR study of axial and equatorial esters showed that the C_{10}-methyl signal is shielded in the spectrum of C-4 axial esters as compared to those of the C_4-equatorial epimer.

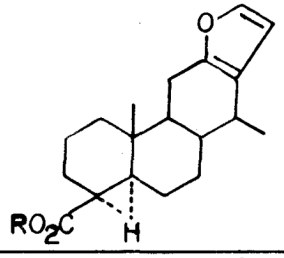
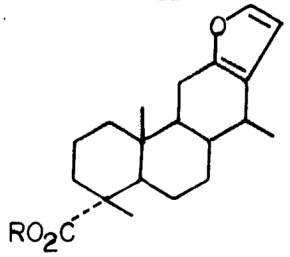
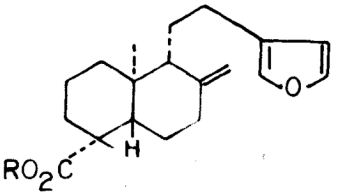
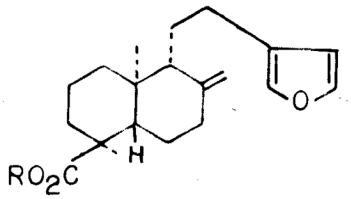
The NMR shifts of two pairs of similarly substituted C_4-epimers in $CDCl_3$ are shown in Table 1.

If one realises that this shielding is to a large extent due to the carbonyl, then only two conformations have got to be considered in the case of axial esters; as only in these two conformations carbonyl cone would be so oriented that the C_{10} methyl is placed in shielding zone of the carbonyl. For such a shielding the ester group should be held in such a conformation that the plane passing through the C_4-axial carbon and oxygen atoms attached to it has to be nearly parallel to the plane passing through C_2, C_{10} carbon atoms and the axial substituents on them. An examination of model reveals that a slight inclination towards C_2-C_{10} plane is better able to explain the observed shielding. Once this is realised, it would follow that two orientations which satisfy this requirement are possible. In one of these (f , Chart 1, R=CH_3) the carbonyl oxygen is turned towards C_6 and in other (g, Chart 1, R=CH_3) it is held away from C_6 (by rotating through 180°).

To distinguish between these possible orientation it was thought that solvent induced chemical shifts would be useful. It has been adequately demonstrated that in these solvent induced shifts in the case of carbonyl compound a simple rule[12,13] can explain the observations in passing from non-aromatic to aromatic solvents. This rule states that if a plane is drawn passing through the carbonyl carbon and perpendicular to the

TABLE - 1

CHEMICAL SHIFTS OF C_{10} AND C_4 METHYL GROUPS IN AXIAL AND EQUATORIAL ESTERS

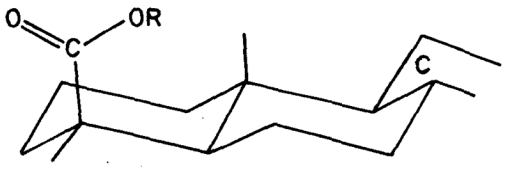
No.	COMPOUND	$CDCl_3$	
		$C_{10}-CH_3$	C_4-CH_3
III	 A	43	73
XVI	 E	57	73·5
IV	 A	30·5	70
XVII	 E	44	69·5

R = Me

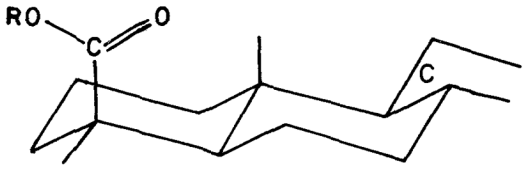
These values are taken from literature[6]. 'A' denotes axial and 'E' denotes equatorial.

CHART – 1.

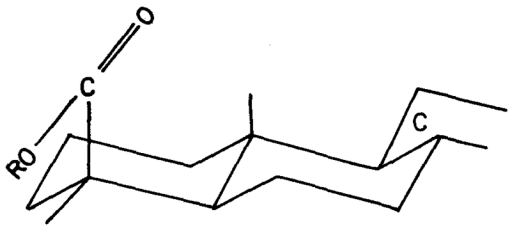
CONFORMATIONS OF AXIAL ESTERS AND ACIDS



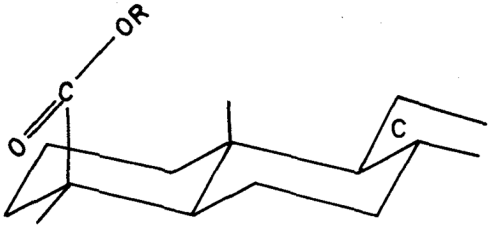
(g)



(f)



(h)



(i)

ESTERS, R = CH_3
ACIDS, R = H

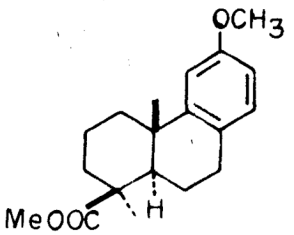
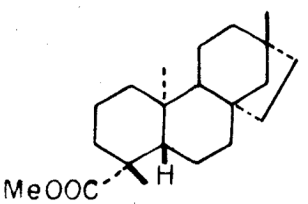
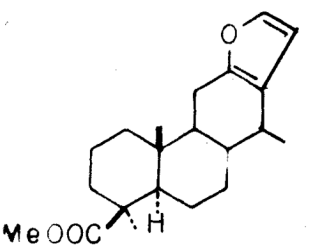
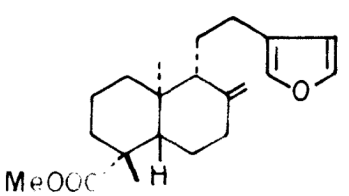
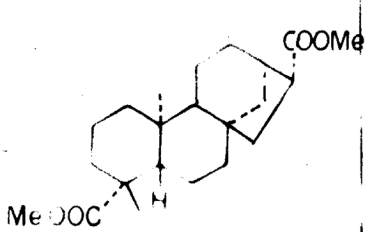
carbon-oxygen bond then those groups which are on the same side of the plane as the carbonyl oxygen will suffer a paramagnetic shift whereas those on the opposite side will suffer a diamagnetic shift when passing from non-aromatic to aromatic solvents. The groups which are nearer to the reference plane suffer relatively small effects.

It can therefore be anticipated that if the axial esters exist in the conformation (f), then C_{10}-CH_3 is in front of the reference plane of the carbonyl while methoxy methyl and the C_4-equatorial methyl group are behind it. Therefore if the spectra of the methyl esters of the acids are taken in chloroform and benzene the C_{10}-CH_3 should be deshielded in benzene and the C_4-CH_3 and methoxy methyl should be shielded.

The solvent induced chemical shifts of five representative axial esters is presented in Table 2. The shifts observed (Fig. 1 and 2) for the C_4 and C_{10} methyls on passing from $CDCl_3$ to benzene solution show that in all the cases the C_4 methyl group is shielded, the shielding varying between 5-10 cps. For the C_{10} methyl there is deshielding in four of the five esters. The only exception being methyl vouacopenate (III) where the observed shift shows a shielding of the C_{10} methyl in benzene solution. This anamoly can be explained as follows:

TABLE - 2

SHIFTS OF C-4-CH_3 AND C-10-CH_3 IN AXIAL ESTERS

No.	COMPOUND	CHEMICAL SHIFTS (CPS)				SHIFT IN BENZENE	
		$CDCl_3$		BENZENE			
		C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me
I		62·5	77	66·5	68·5	−4	+8·5
II		45	70	50	60	−5	+10
III		43	73	39·5	68	+3·5	+5
IV		30·5	70	38	64·5	−7·5	+5·5
V		45	70	49	66		+4

The values for I, III, IV & V have been taken from literature[6]

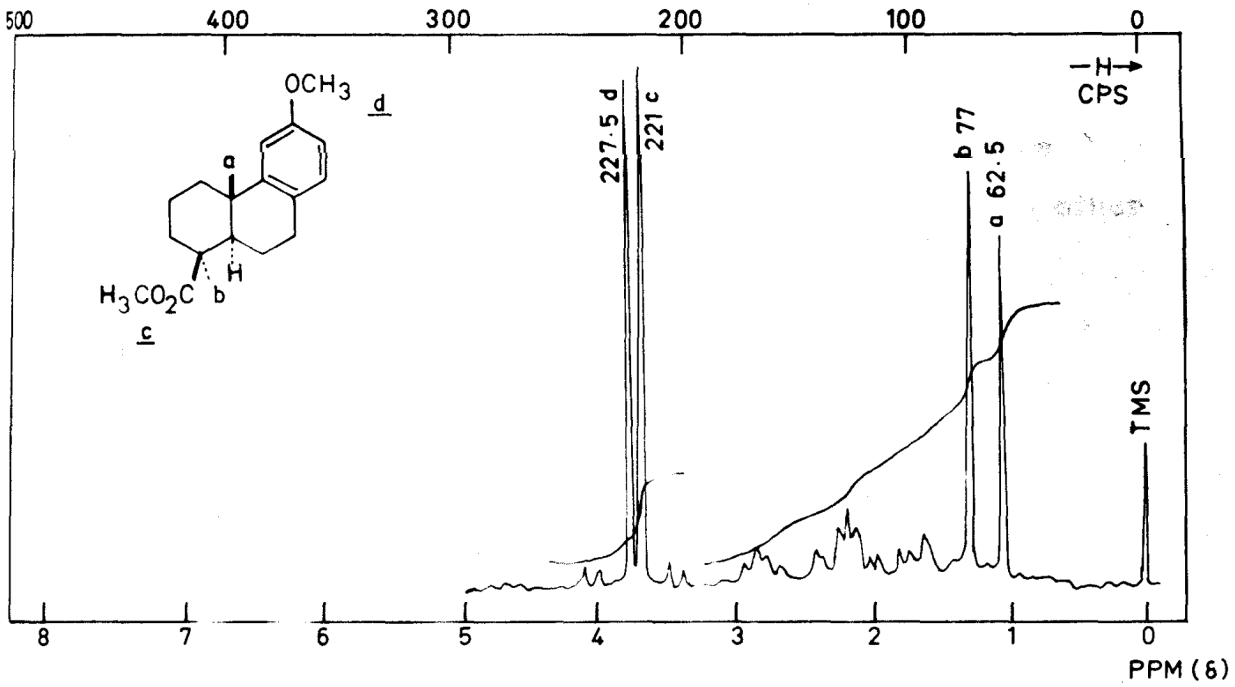


FIG. 1. NMR SPECTRUM OF OMe-METHYLPODOCARPATE IN $CDCl_3$

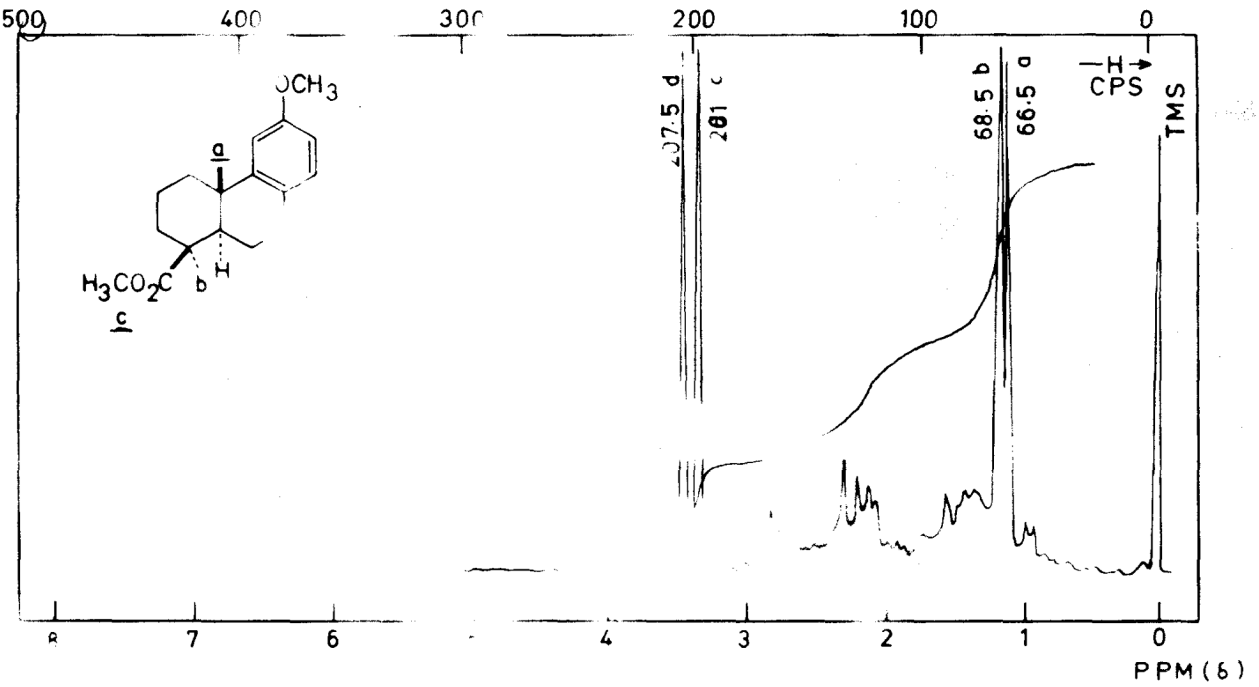


FIG . NMR SPECTRUM OF OMe-METHYLPODOCARPATE IN BENZENE

As the C_{10}-methyl in $CDCl_3$ spectrum resonates at 43 cps it should resonate at ~ 48 cps in benzene solution if one assumes a mean value of 5 cps (see other examples) for this solvent induced deshielding. The observed resonance at 39.5 cps suggested that the C_{10} methyl in this case is shielded in benzene solution.

As the stereochemistry of this compound has been rigorously established the explanation of this observed shielding must therefore arise from the fact that the aromatic solvent molecule forms a collision complex with the partly positively charged oxygen atom of the furan ring and thus the aromatic solvent molecule is so oriented as to highly shield the C_{10} CH_3 (see Chapter I). Assuming that this shielding is ~ 10 cps* then the signal which appears at 39.5 cps in benzene would have been observed at ~ 48.5 if furanoid oxygen were absent. This calculated value would now agree with the values observed in the case of other axial esters.

This kind of correction does not have to be applied in the case of other axial esters. In the case of methyl daniellate (IV) the furanoid oxygen, in the preferred conformation, is held very far from the C_{10} methyl and therefore has no effect on it.

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* Examination of model shows that the C_{10}-methyl is at the same relative position to the plane as the α proton in tetrahydrofuran. This plane has as its locus the furanoid oxygen.

The methoxy methyl in these axial esters as well as equatorial esters (see later) showed an upfield shift of ~ 18-20 cps in benzene compared to that in $CDCl_3$ (see Table 3) This shift is rather larger than that which can be accounted for by carbonyl. To see whether this shift is wholly due to carbonyl or there is some contribution due to the ether oxygen, the corresponding C_4- methoxy methyl derivatives (XXI) and (XXII) were prepared.

O-Methyl padocarpinol and dehydroabietinol were methylated with potassium and methyl iodide as described by Narayanan and Iyer[14]. The methyl ethers obtained analysed well and showed correct spectral data.

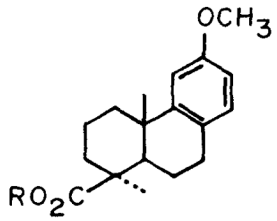
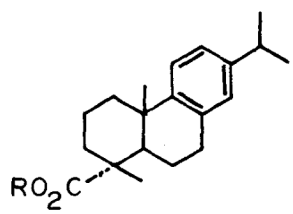
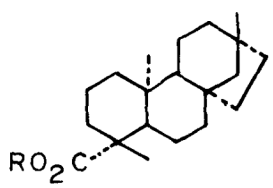
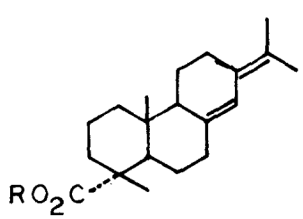
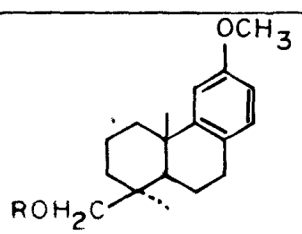
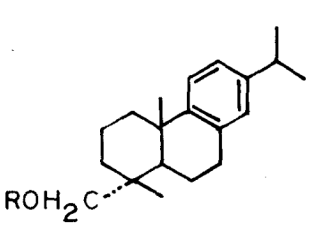
When the spectra of these methyl ethers (XXI, XXII) were recorded the C_4-methoxy methyl showed an upfield shift (~10 cps) for both the compounds in benzene as compared to $CDCl_3$.

Substraction of this shift of 10 cps from the total shift of 17-18 cps for methoxy methyl in esters leaves a net shift of ~ 7-8 cps for methoxy methyl by carbonyl. The solvent shifts for the other groups in these methyl ethers are negligible with the exception of the methylene holding the methoxyl, which also shows a shielding of 10 cps in benzene.

Had the axial carboxylic acid ester been in conformation (g) then both the C_{10} and C_4-CH_3 groups would have been shielded as both of them are now placed behind

TABLE 3

CHEMICAL SHIFT OF C_4 METHOXY METHYL

No.	Compound	Shift of C_4-OCH_3 in		Shift in benzene
		$CDCl_3$	Benzene	
I		221	201	20
XIII		221	204	17
II		219	202	17
XIV		220	204	16
XXI		198	188	10
XXII		199	189	10

R = Me

the reference plane. These arguments establish that in axial esters (f) is the preferred conformation of the carbomethoxy group.

Stability considerations

If one examines Drieding models it becomes clear that there are four possible conformations f, g, h, i (Chart I, R=CH_3) for the axial ester group. Normally the conformations similar to (h) and (i) are the preferred conformations, thus it has been demonstrated that propanaldehyde exists in a conformation similar to (h) and similar arguments[7] have been made for the formation of several compounds in which an SP^2 hybridised carbon is attached to an SP^3 hybridised carbon. However in the present case the position is complicated by the presence of a C_{10} methyl substituent. In the case of conformer (h) the distance between the carbonyl oxygen and C_{19} hydrogens is only 1.31^{o}A. In (i) the methoxyl oxygen is even closer 1.27^{o}A and there will be a heavy barrier in this conformer to free rotation of methoxy methyl around the carbon-oxygen single bond. These two conformers can therefore be anticipated to be infact less stable.

The choice then lies between (f) and (g) which represent the staggered conformers. The factor that governs the stability of these two orientation would be the interaction with the axial C_6-hydrogen: the methoxy oxygen in conformation (g) will have a larger interaction with C_6-β axial hydrogen which would force

the methoxy methyl away from C_6 thus assuming the conformation (f).

Stability considerations also therefore support the idea that these axial esters exist mainly in the conformation (f).

If one extends these ideas to the acids it becomes very obvious that from stability consideration preference for the conformation (f) would remain essentially the same, as we have considered only those interactions which involve the methoxy oxygen and not the methoxy methyl.

In keeping with this expectation the two axial acids shown in Table 4 also show the same solvent induced shifts as in the case of the esters. The C_4 methyl being behind the reference plane is shielded (7 and 10 cps) while the C_{10} methyl being in front of the reference plane is deshielded (3 and 7 cps) (Fig. 3 and 4). It may be pointed out that the solvent shifts observed in the case of acids could equally well be accounted for on the basis of a conformation like (h)* as NMR evidence is not sufficient to rule out this conformation. However the conformation (h) can be ruled out on the grounds that if esters and aldehydes (see later) have conformation similar to (f) and (g) respectively there is no reason why acids should exist in

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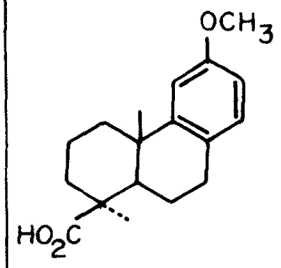
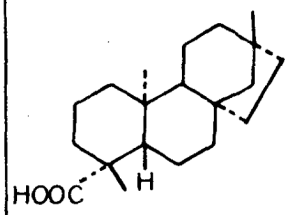
* In conformation (i) the solvent induced shifts would require C_4 methyl to be deshielded and C_{10} to be shielded and so can be ruled out.

TABLE 4

SHIFTS OF C_4-CH_3 AND C_{10}-CH_3 IN AXIAL ACIDS

No.	Compound	Chemical shift in cps				Shift in benzene in cps	
		Chloroform		Benzene			
		C_{10}-Me a	C_4-Me b	C_{10}-Me c	C_4-Me d	C_{10}-Me e	C_4-Me f
VII		67	80	70	70	-3	+10
VIII		51	74	58	67	-7	+7

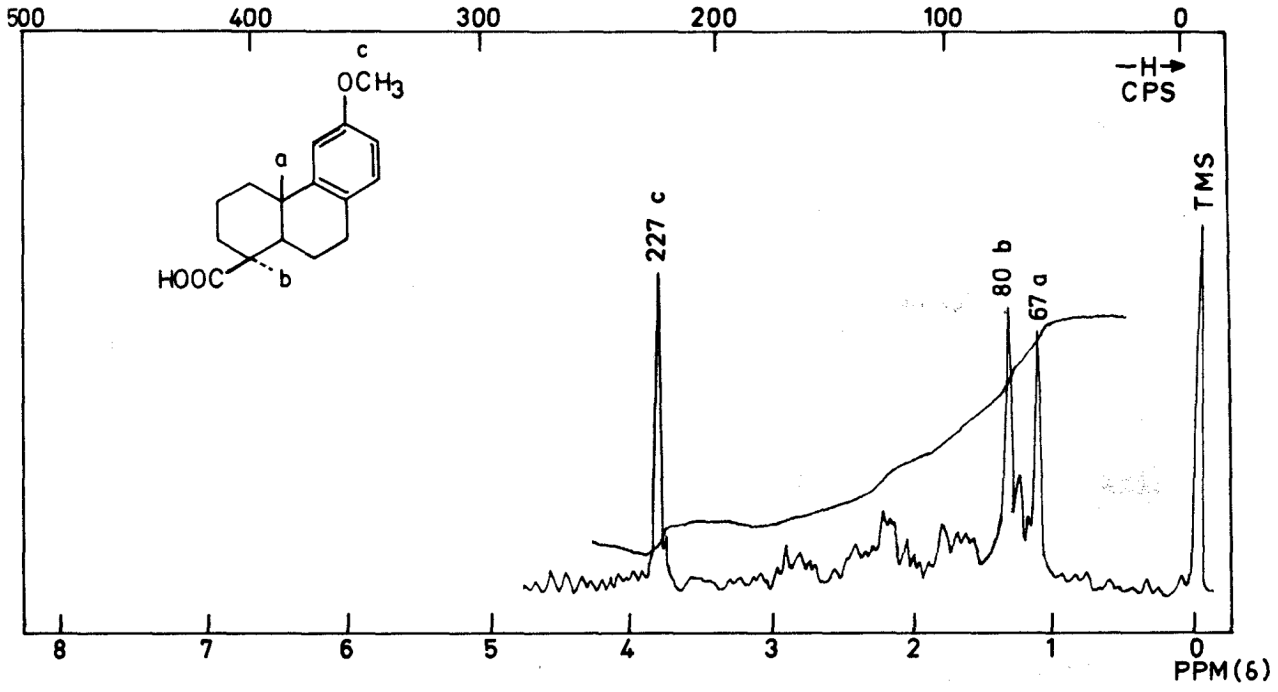


FIG. 3. NMR SPECTRUM OF O-Me PODOCARIC ACID ($CDCl_3$)

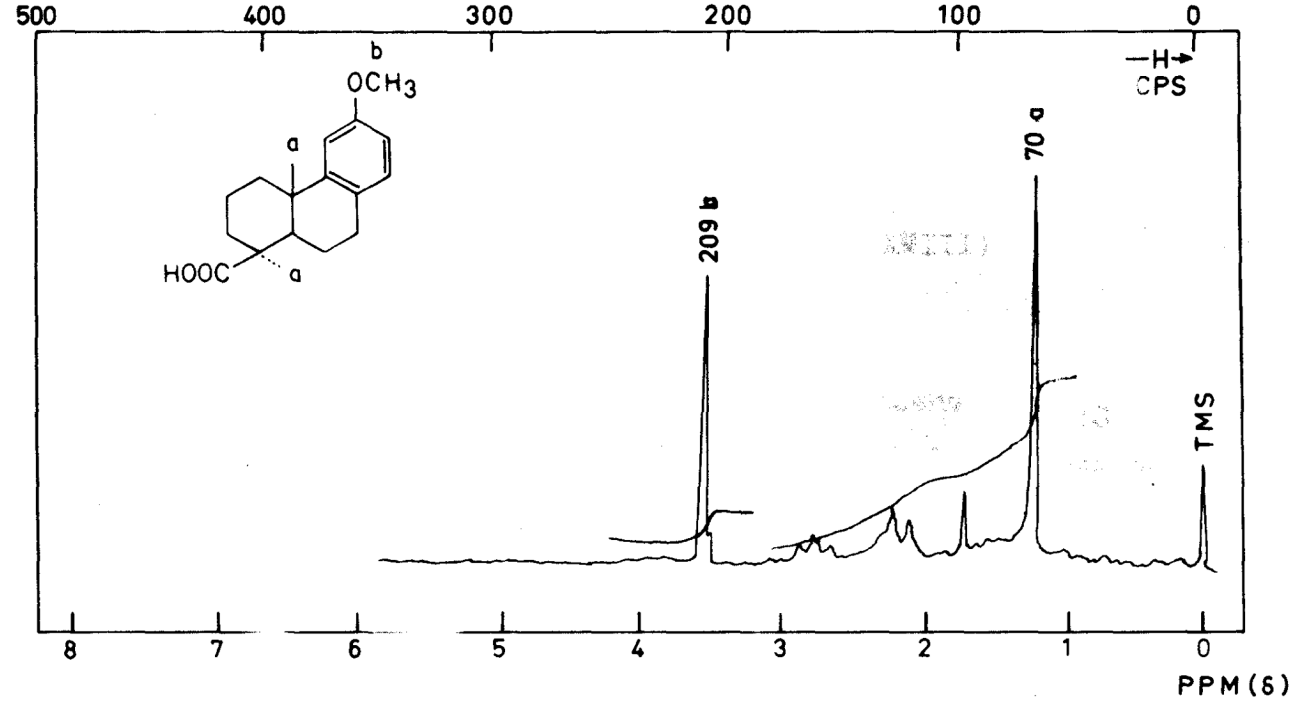
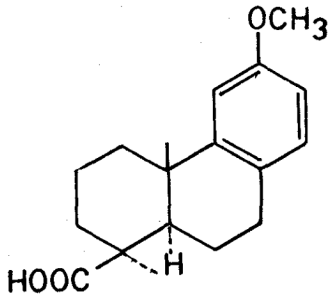


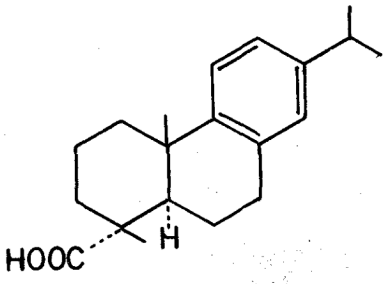
FIG. 4 NMR SPECTRUM OF OMe PODOCARPIC ACID (BENZENE)

conformation (h). Moreover Sicher, Trichy and Sipops[3], and Bekkum, Verkade and Wepster[4] had shown on the basis of pKa measurements that acids exist either in conformation (f) or (g) and lastly a comparison of two similarly substituted but not identical epimeric acids (VII) and (XVIII) reveals a shielding of the C_{10} methyl group in $CDCl_3$ solution by 6 cps in axial esters, which also necessitates the axial acid to have a conformation (f) in preference to (h).



C_{10}-Me, 67 cps

(VII)



C_{10}-Me, 73 cps

(XVIII)

When one considers the aldehydes the spectral results (Fig. 5 and 6) indicate that in benzene the C_{10} and C_4 methyls are both shielded (see Table 5) as compared to those in $CDCl_3$ solution. The shielding being larger in case of the C_4 methyl group, the aldehyde proton also in the two aldehydes are shielded in C_6H_6 as compared to $CDCl_3$ solution. These results need both the C_{10} methyl as well as C_4 methyl to be behind the reference plane of the carbonyl.

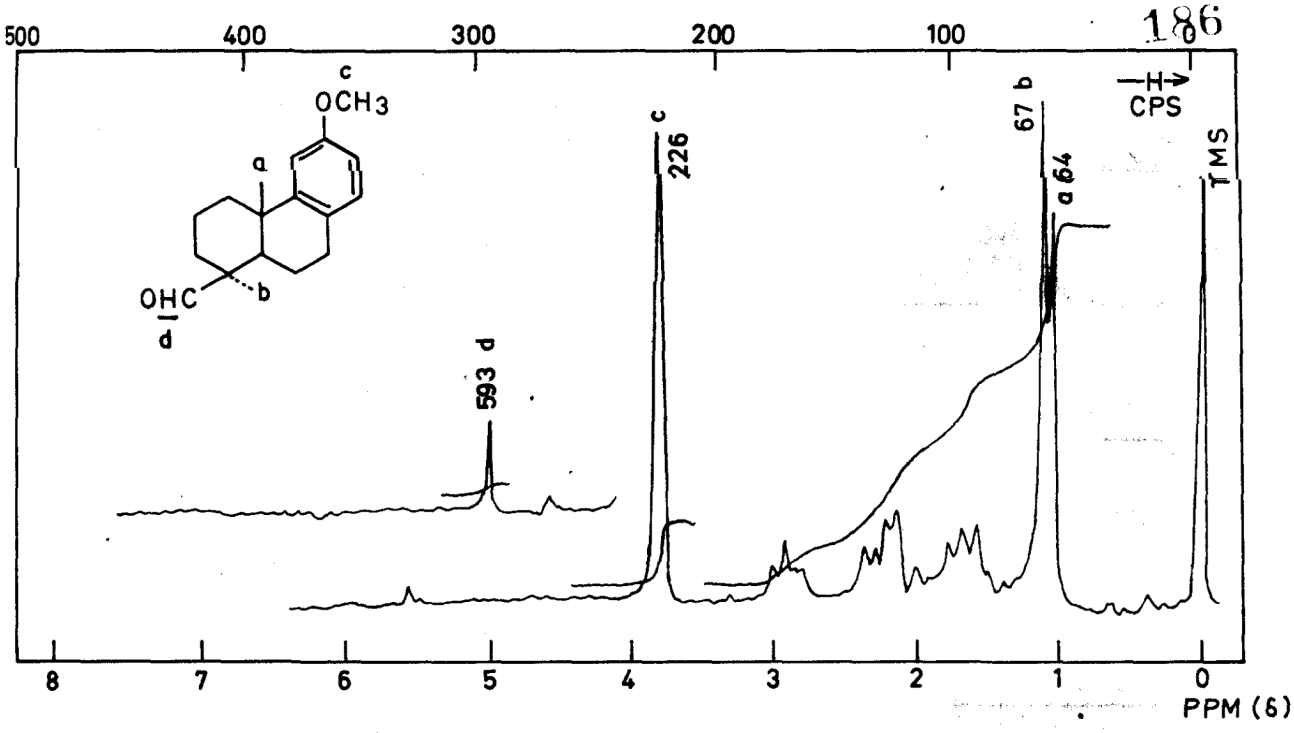


FIG. 5. NMR SPECTRUM OF O-METHYL PODOCARPINAL ($CDCl_3$)

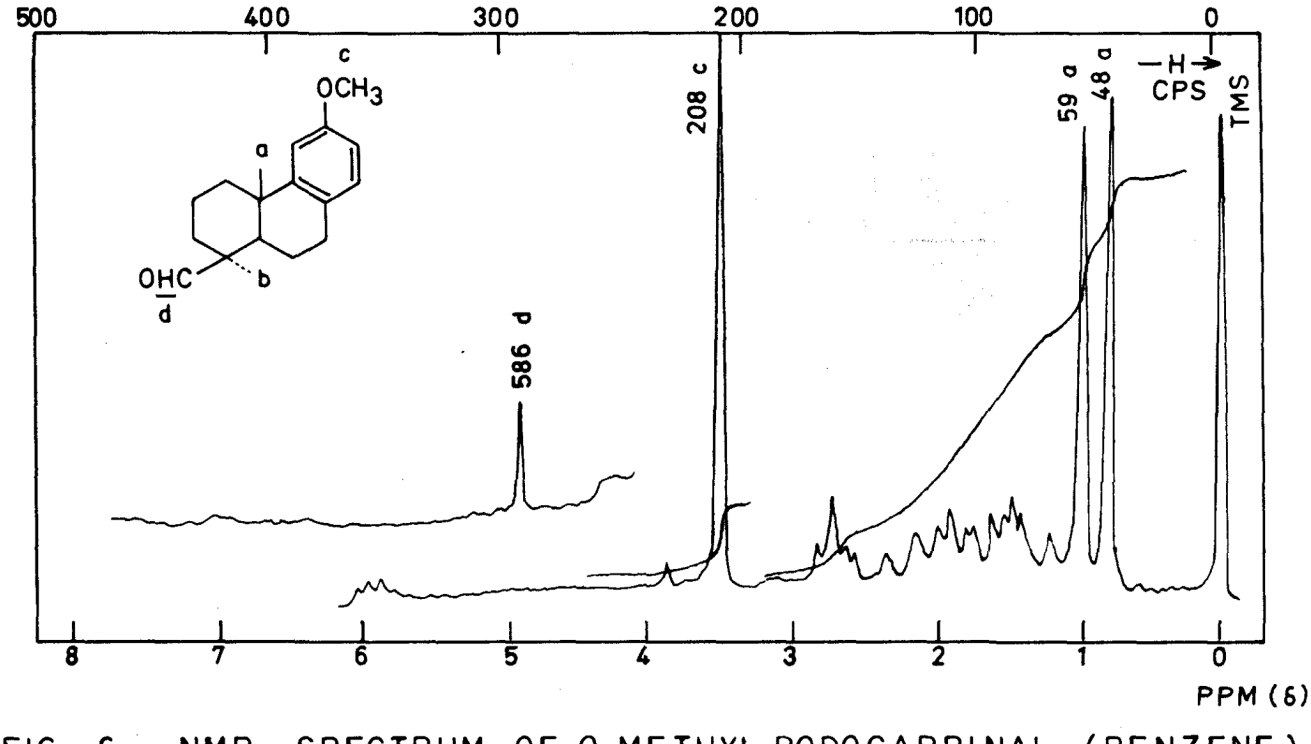
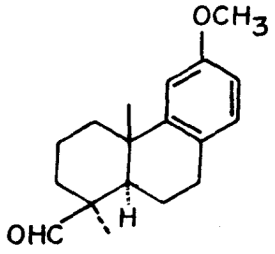
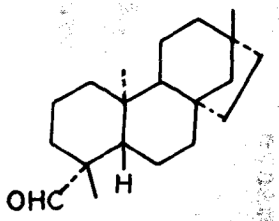


FIG. 6. NMR SPECTRUM OF O-METHYL PODOCARPINAL (BENZENE)

SHIFT OF C_4-CH_3 AND C_{10}-CH_3 IN AXIAL ALDEHYDES.

No.	Compound	Chemical shift (cps) in $CDCl_3$			Chemical shift (cps) in Benzene			Shift in benzene		
		C_{10}-Me	C_4-Me	CHO	C_{10}-Me	C_4-Me	CHO	C_{10}-Me	C_4-Me	CHO
IX		64	67	593	59	48	586	+5	+19	+7
X		47	59	584	41	46	576	+6	+13	+8

This is inconsistent with the conformation (j, Chart 2) and is consistent with the conformation (k, Chart 2) in which C=O is turned away from C_6-H. This is because in the aldehyde the interacting groups are now the aldehyde hydrogen and the C_6-hydrogen.

Examination of models shows that in the conformation (k) the interacting groups are now at a distance of $\sim$ 1.85°A whereas the interacting groups in conformation (j) are still at the same distance $\sim$1.77°A*. In the case of the aldehydes the conformation (l, Chart 2) would still have the same destabilising factors as for the acids and esters i.e. the interaction between the carbonyl oxygen and C_{10} methyl but for the conformation (m, Chart 2) the position would now have changed as the interacting groups are now the aldehyde hydrogen and the C_{10} methyl, as inspection of Drieding models indicated the distance is now 1.5°A, this conformation can therefore also be ruled out.

It has been pointed out earlier that in secondary aldehydes in cyclohexane series the preferred conformation is like (l)while in cyclopentane and cyclobutane series the preferred conformation is like (m).

In the case of the aldehydes now investigated it is obvious that these two conformations are not the preferred ones as conformation (l) would require the C_4-methyl

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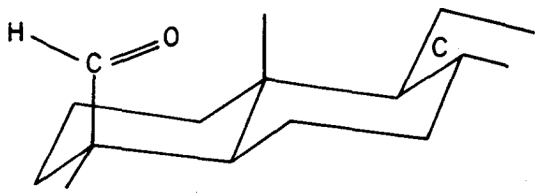
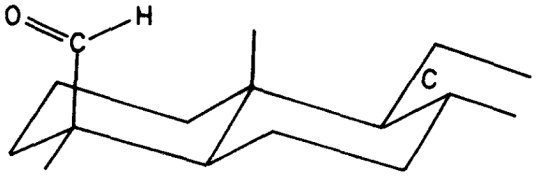
* These distances are measured considering a slight inclination of the carbonyl towards C_{10}-C_2 plane.

CHART – 2

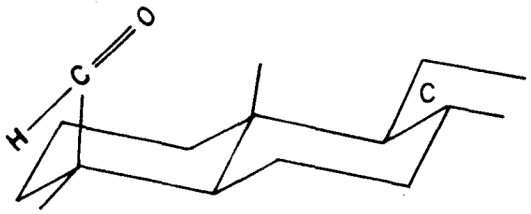
CONFORMETIONS OF AXIAL ALDEHYDES



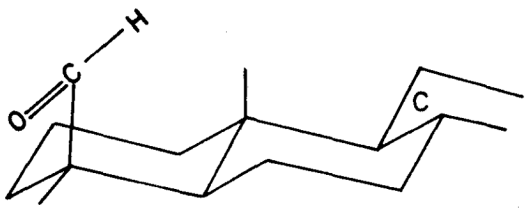
(j)



(k)



(l)



(m)

to be shielded while the C-10 methyl group would be deshielded on passing from $CDCl_3$ to benzene as solvents. Whereas under the same conditions conformation (m) would have the C_4 methyls deshielded and the C_{10} methyl group shielded. No other conformation except (k) would therefore be able to explain the observed results.

The solvent induced shifts in the NMR signals therefore requires that these aldehydes must have (k) as the preferred conformation.

From what has been said earlier it is clear that if the position of ester function is changed but its axial geometry is maintained then similar solvent induced shifts of similarly situated methyls would naturally occur and this is in fact what has been observed in the case of the C_8 axial ester (XI), a monogynol derivative. The C_{10} methyl group is now heavily shielded (~ 15 cps) as compared to the axial ethers II, III and V* in $CDCl_3$. This is because there are now two carbonyl functions placed in a cis 1:3 diaxial relation with this methyl. From this shielding it becomes clear that the C_8 ester should have a fixed geometry in which the ester group has to be parallel to the plane passing through the C_{10}-C_{11} carbon atoms and the axial groups on them. Of the two possible orientations (n and o, Chart 3) satisfying this requirement only that in which the carbonyl is oriented towards C_6 (n) would result in large solvent induced deshielding (~ 16 cps, see Table 6) of the

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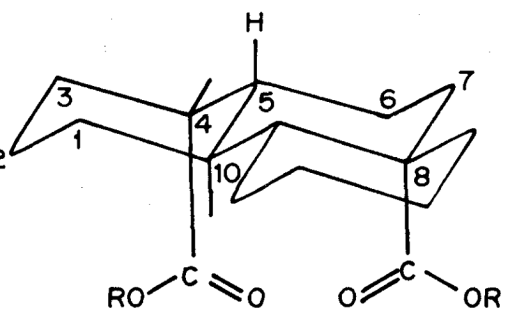
* Comparison with I is not possible as this has an aromatic C ring which is known to deshield the C_{10} methyl whereas in IV comparison is not possible because of the C_8 exo double bond which would shield the C_{10} methyl.

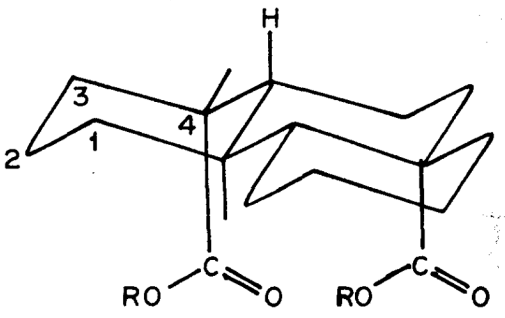
CHART - 3

CONFORMATIONS OF C_8 - AXIAL ESTERS



R = CH_3

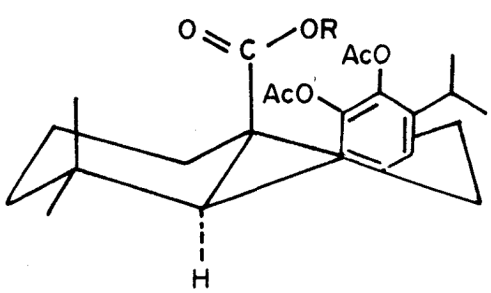
(n)



R = CH_3

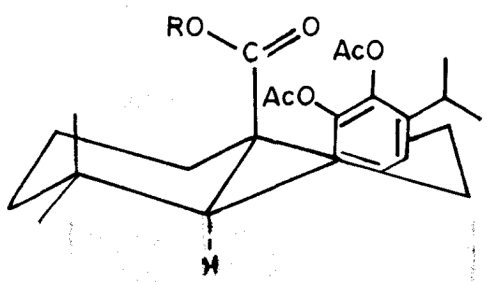
(o)

CONFORMATIONS OF C_{10}- AXIAL ESTERS



R = CH_3

(p)

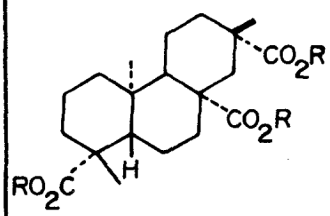
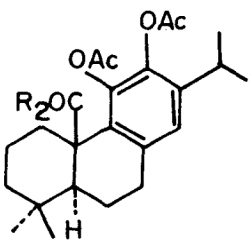


R = CH_3

(q)

TABLE 6

CHEMICAL SHIFTS IN C_{10} AND C_8 AXIAL ESTERS

No.	Compound	Chemical shift (cps) in $CDCl_3$		Benzene		Shift in benzene	
		C_{10}-Me	C_4-Me C_{13}-Me	C_{10}-Me	C_4-Me C_{13}-Me	C_{10}-Me	C_4-Me C_{13}-Me
XI		31	65.5 69	47	64 67	-16	- -
		4β-Me	4∝-Me	4β-Me	4∝-Me	4β-Me	4∝-Me
XII		45	58	47	53.5	-2	+4.5

R = Me

Values for these compounds have been taken from literature[6].

C_{10} methyl. It is worth noting that here the solvent induced deshielding is much larger than in the case of the axial esters mentioned earlier, due to the presence of two cis 1-3 diaxially located carbomethoxy functions, both of which have the carbonyls so oriented i.e. pointing towards C_6- that they will cause deshielding by solvent induced shifts.

If one considers the two possible conformations on the basis of stability then it is clear that conformation (n) which will have interactions of the carbonyl oxygen with the C_6 hydrogen, will be more stable.

It can readily be appreciated that if a carboxylic acid ester is located at C_{10} as in the salvin ester (XII) it would cause shielding of C_4-β methyl, which is in 1:3 diaxial relation with it, as compared to C_4-∝ methyl. (13 cps, compare 4β methyl with 4∝-methyl in $CDCl_3$, Table 6). This shielding of C_4-β methyl requires the C_{10} carbomethoxy function nearly parallel to the plane passing through C_4 and C_6 and the axial atoms on them. In this case, solvent induced shift (XII, Table 6) show that C_4-β methyl is deshielded by 2 cps while C_4-∝ methyl is shielded by 4.5 cps

---

* Other orientations of the C_8 ester similar to (h and i) are ruled out because of the presence of an axial substituent at C_{13} which being in cis-1-3 diaxial relation decreases the stability of this conformer. Only one orientation of C_4-carbomethoxy group is considered because the conformation of such a carbomethoxy group has been established earlier.

these results (Fig. 7 and 8) reveal that in this ester the carbonyl is pointing towards C_2. Stability considerations also show that the conformation in which carbonyl is pointing towards C_2 would be the preferred conformation. A further confirmation in this particular case arises due to the aromatic nature of ring C. This aromatic ring would cause in the conformation (p, Chart 3) a shielding of methoxy methyl of the C_{10} ester and in fact the signal appears at 210 cps whereas in the podocarpic and dehydroabietic acid methyl esters it appeared in CCl_3 solution, at $\sim$ 220 cps. Moreover the conformation like (q) would require both the C_4-β and C_4-α methyls to be shielded.

It can be seen from the above arguments that the axial esters have that conformation in which the ester function is staggered in relation to the carbon holding it* and the carbonyl occupies the more hindered position.

It seems significant to point out that in the salvin ester conformation (p) is preferred over (q) because C_8 carries no hydrogen. If a derivative having a C_{10} ester and C_8 axial hydrogen is prepared, obviously both the conformations would be identical and as a consequence solvent induced shifts due to both conformations should be observed.

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* This is only true if there is a substituent in a cis 1:3 diaxial relation with regard to the carbomethoxy function, as in the case of all the examples studied in this investigation.

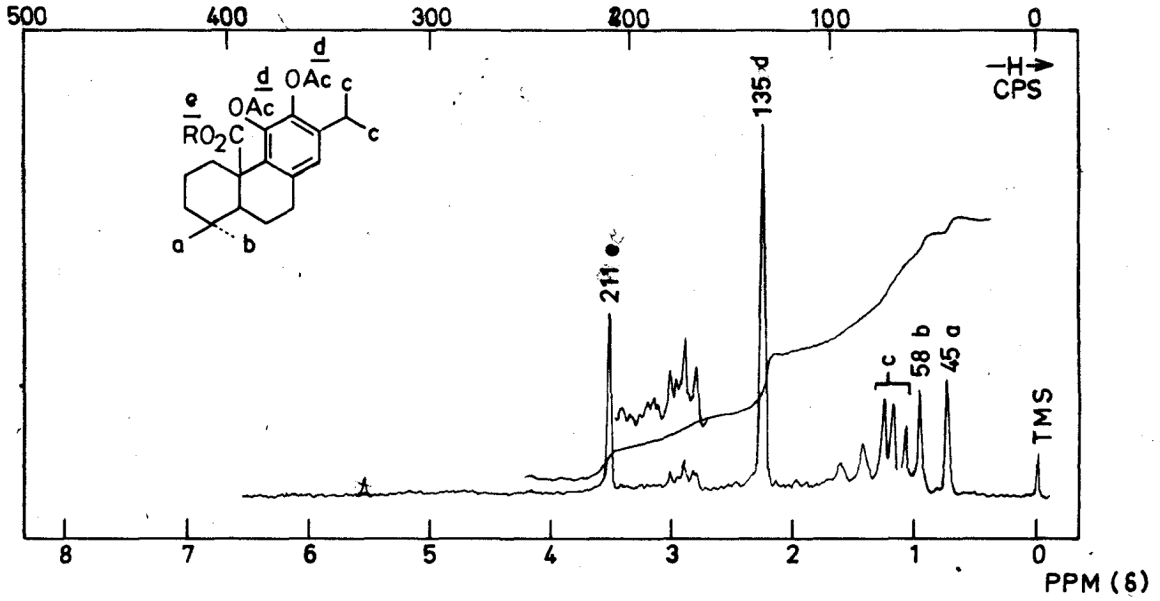


FIG. 7. NMR SPECTRUM OF SALVIN Me ESTER DIACETATE ($CDCl_3$)

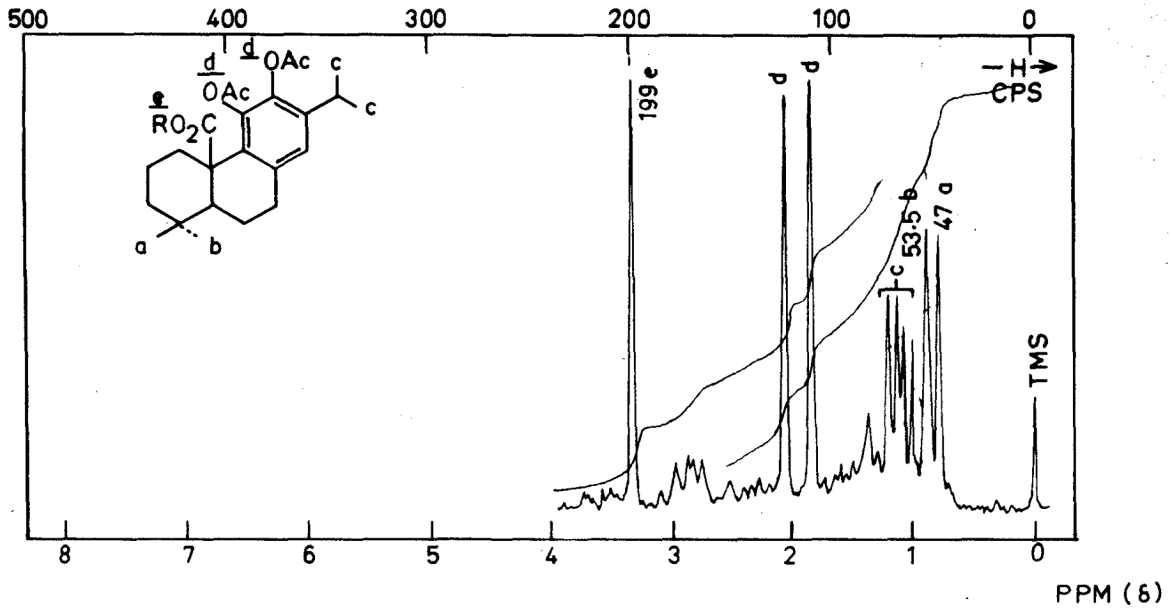


FIG. 8. NMR SPECTRUM OF SALVIN Me-ESTER DIACETATE (BENZENE)

Equatorial derivatives

So far we have dealt only with axial derivatives. We can now turn to an examination of the equatorial derivatives.

In the esters it is noticeable (Fig. 9 and 10) that the C_{10} methyl group is in all cases shielded in benzene as compared to $CDCl_3$; the shielding being usually about 4 cps (see Table 7). The only exception to this is methyl vinhaticoate (XVI) in which the shielding is 17 cps. On the other hand in all these esters the C_4 methyl group is deshielded (~ 3 cps). It has been already mentioned earlier that the furonoid oxygen of methyl vouacopenate (III) gives a benzene induced shielding of 9-10 cps. It can therefore be expected that this shielding will be of same magnitude in methyl vinhaticoate (XVI) as these compounds differ only in the stereochemistry at C_4; the former being a C_4 axial ester while the latter is a C_4 equatorial ester. This correction when applied, would require the C_{10} methyl to resonate at 49 cps in benzene solution if the furanoid oxygen were absent. This corrected value now makes the observed shielding (8 cps) for C_{10}, similar to that of the other equatorial esters.

If one looks at the equatorial acids and aldehyde the solvent induced shifts reveal (Fig. 11 to 14), as in the case of esters, a shielding of the C_{10} methyl (~ 7 cps) and practically no effect on the C_4 methyl (see Table 8).

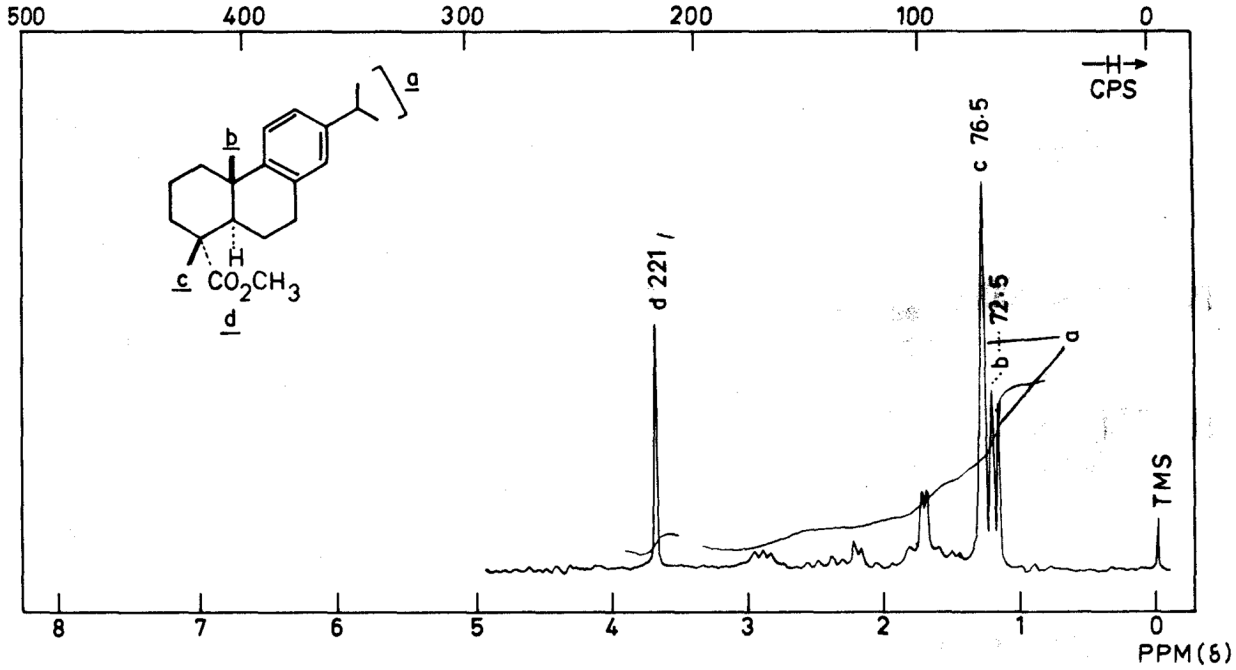


FIG. 9. NMR SPECTRUM OF METHYL DEHYDROABIETATE IN $CDCl_3$

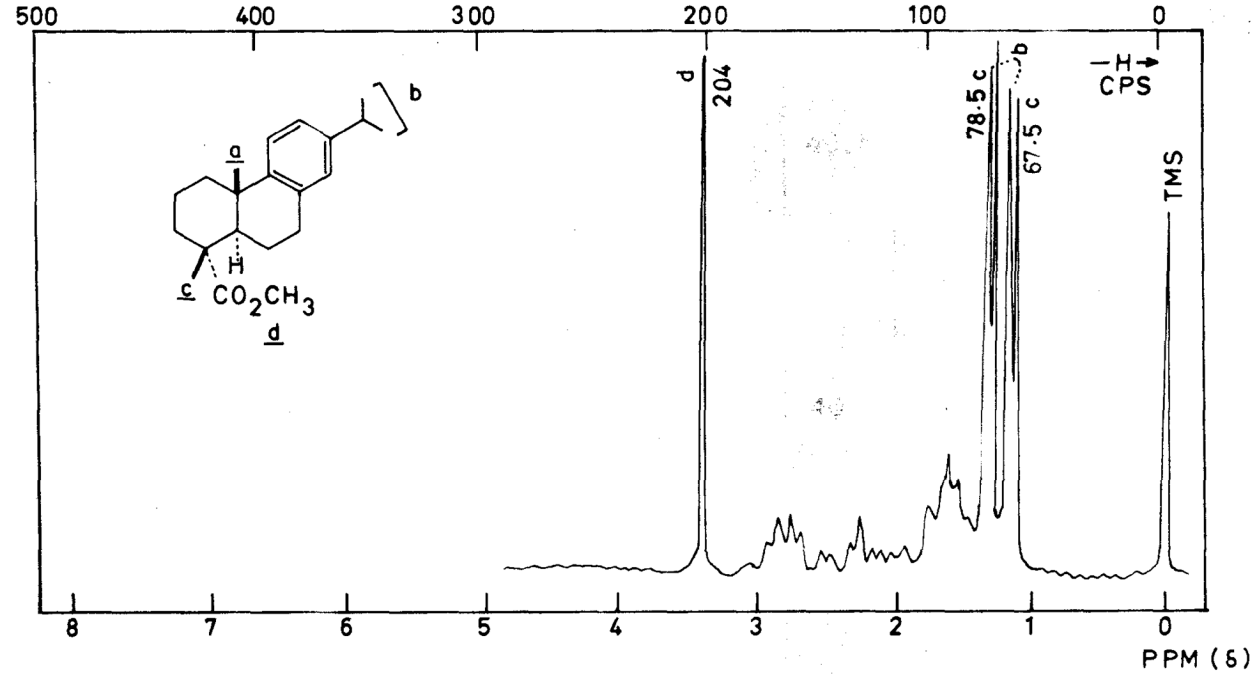
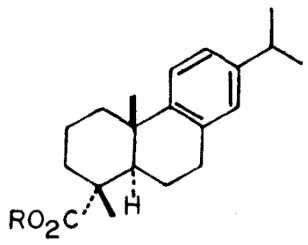
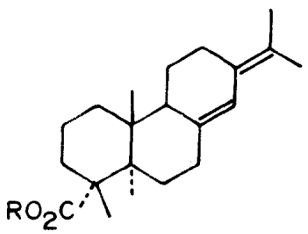
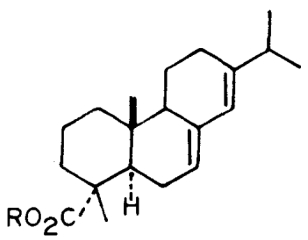
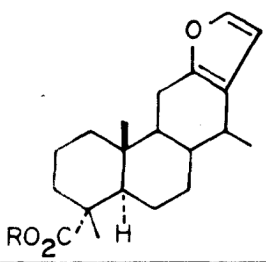
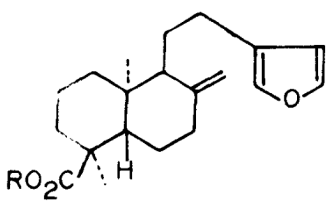


FIG. 10. NMR SPECTRUM OF METHYL DEHYROABIEATATE IN BENZENE

TABLE 7

SHIFTS OF C_4-CH_3 AND C_{10}-CH_3 IN EQUATORIAL ESTERS

No.	Compound	Chemical shift in				Shift in benzene	
		$CDCl_3$		Benzene			
		C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me
XIII		72.5	76.5	67.5	78.5	+5	-2
XIV		48	73	44	75	+4	-2
XV		50	75	49.5	80.5	+0.5	-5.5
XVI		57	73.5	40	75.5	+17	-2
XVII		44	69.5	41	73.5	+3	-4

R = Me

The values for XIII, XV, XVI, XVII are taken from literature.[6]

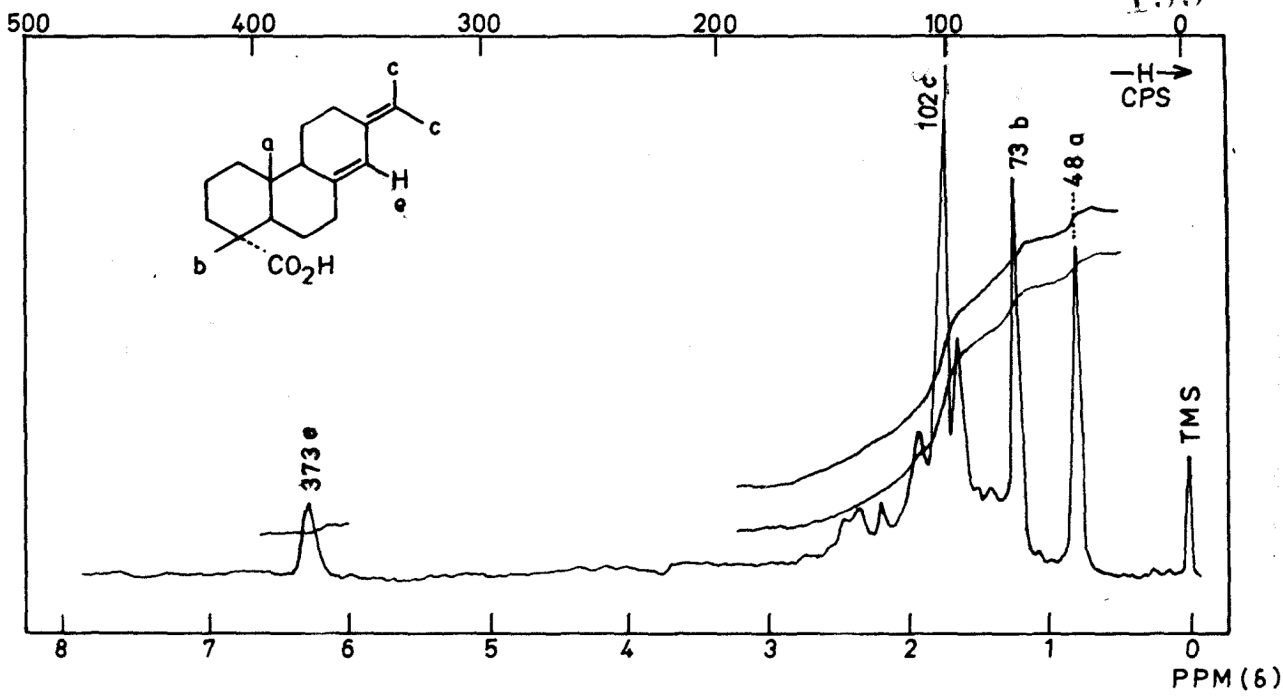


FIG. 11. NMR SPECTRUM OF NEOABIETIC ACID ($CDCl_3$)

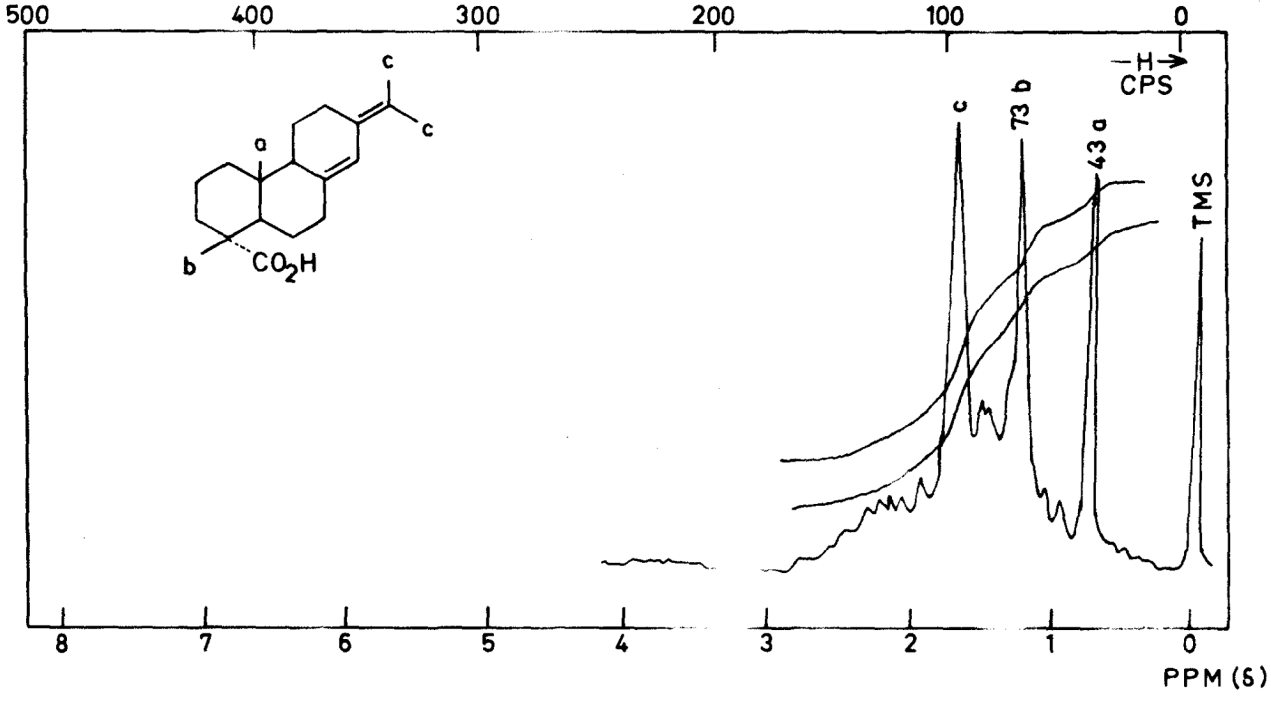


FIG 12. NMR SPECTRUM OF NEOABIETIC ACID (BENZENE)

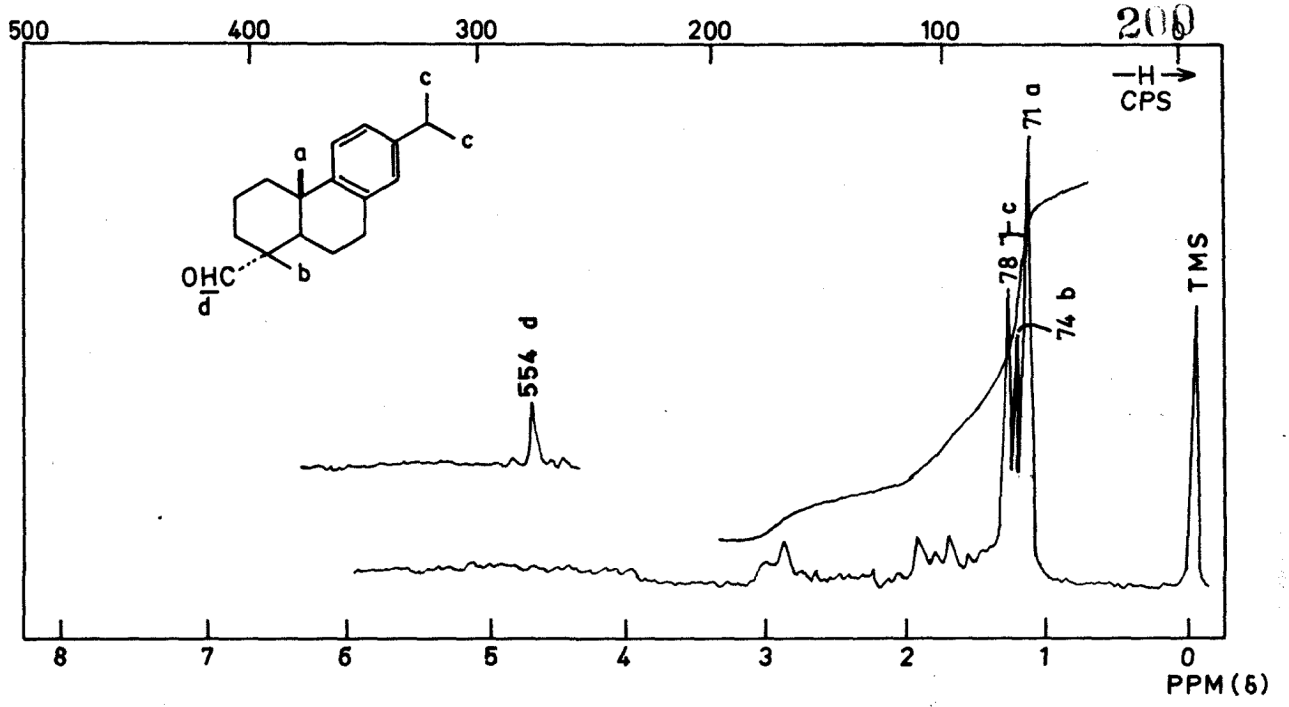


FIG. 13. NMR SPECTRUM OF DEHYDROABIETINAL ($CDCl_3$)

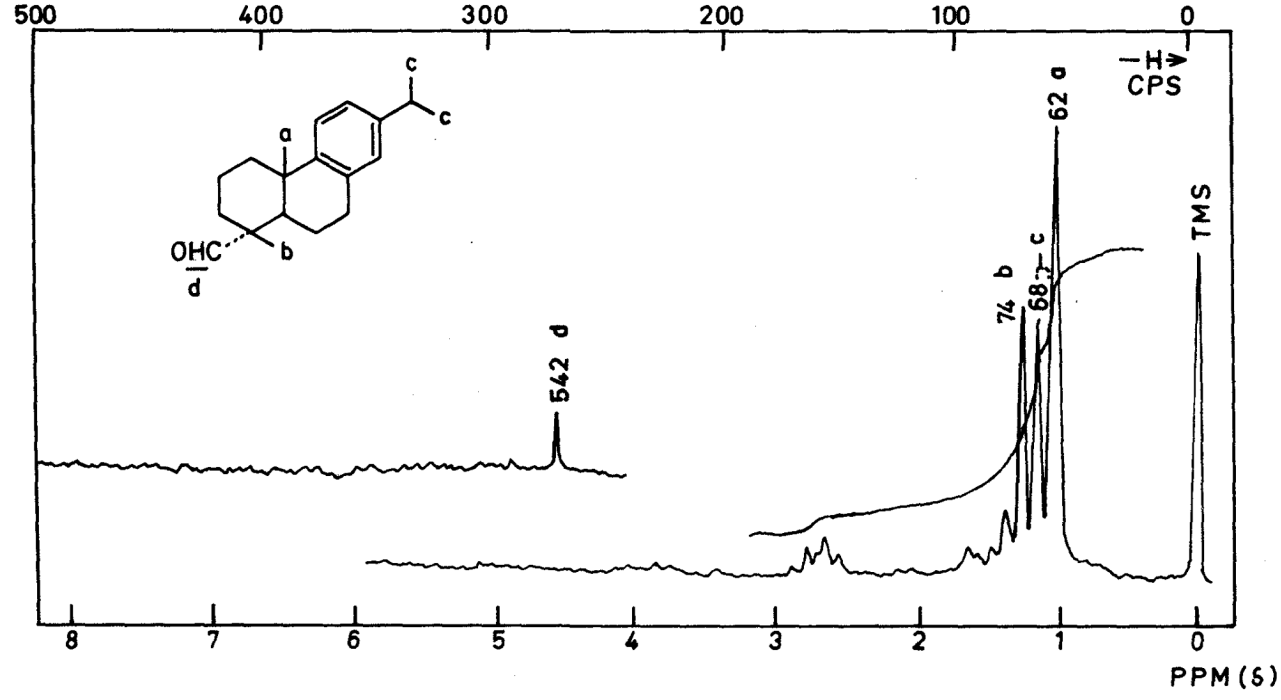
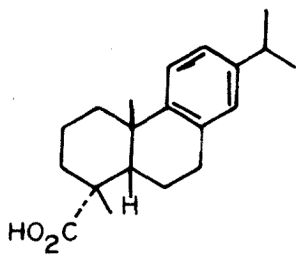
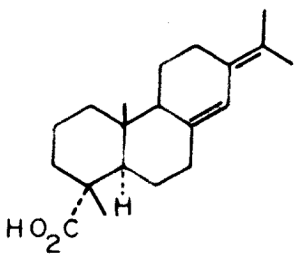
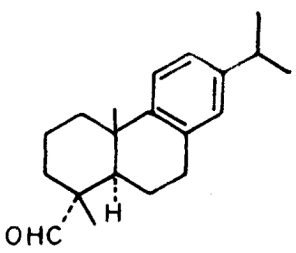


FIG. 14. NMR SPECTRUM OF DEHYDROABIETINAL

TABLE 8

SHIFT OF C_4-CH_3 AND C_{10}-CH_3 IN EQUATORIAL ACIDS AND ALDEHYDES.

No.	Compound	Chemical shift in $CDCl_3$		Chemical shift in Benzene		Shift in Benzene	
		C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me	C_{10}-Me	C_4-Me
XVIII		73	78	65	77	+8	+1
XIX		48	73	43	73	+5	0
XX		71	74	62	74	+9	0
		CHO $CDCl_3$		CHO Benzene		Shift in Benzene	
		554		[illegible]		+12	

These results can only be explained by the conformation (r, Chart 4) in which the carbonyl eclipses the C_4 axial methyl. Alternate conformation (s, Chart 4) would require both C_{10} and C_4 methyls to be shielded.

In the two staggered conformations (t, Chart 4) and (u, Chart 4) both C_4 and C_{10} methyls have to be shielded.

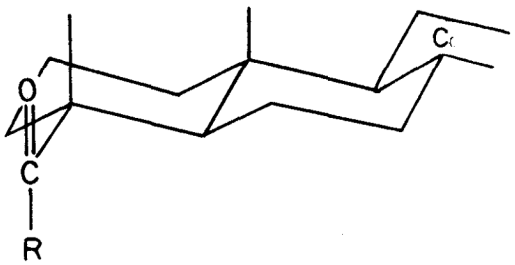
It is obvious therefore that in the equatorial este derivatives the preferred conformation is (r) in which the C_4 methyl group is so situated (near to the carbonyl reference plane) that it can be either slightly shielded or barely influenced whereas the C_{10} methyl can only be shielded

This conformation is the one that has been shown to be most stable in case of propionaldehyde[7] and other substituted aliphatic aldehydes. In this case there is no destabilisation of this conformation as occurs in the case of axial epimers where interaction between C_{10} methyl and carbonyl forces the ester to assume the staggered conformatio

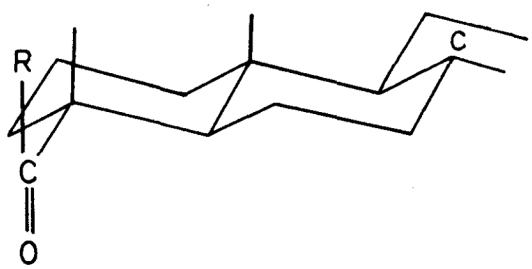
It is obvious that in the case of equatorial acids this conformation is still the preferred one but what is more important is that even for the aldehydes the conformation is the same as the substituent methoxyl hydroxyl or hydrogen has no influence on the stability of the conformation.

CHART — 4 .

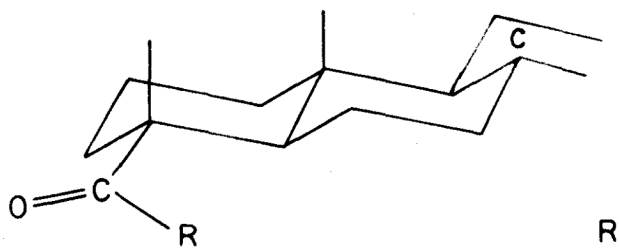
CONFORMATIONS OF EQUATORIAL ESTER, ACIDS AND ALDEHYDES



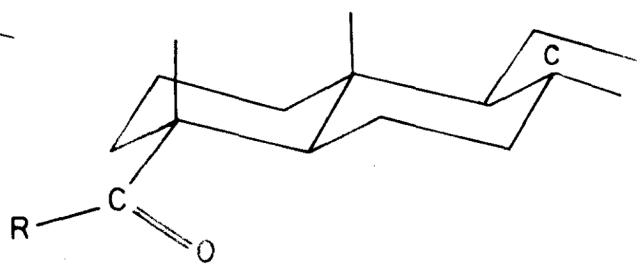
(r)



(s)



(t)



(u)

ESTERS, $R = OCH_3$

ACIDS, $R = OH$

ALDEHYDES, $R = H$

EXPERIMENTAL

For general procedure see Chapter I.

Methyl-o-Methyl podocarpate (I)[15]

Preparation described in Chapter III.

O-Methyl-podocarpic acid (VII)[15]

Methyl-o-methyl podocarpate (400 mg) was refluxed with 20% alcoholic KOH (100 ml) for 16 hours. The reaction mixture was cooled and diluted (to 250 ml) with water. The aqueous layer was extracted with ether to remove unhydrolysed ester. Acidification of aqueous layer with 4N cold HCl gave a precipitate which was taken up in ether. Ethereal layer was washed with water and dried over sodium sulphate. Removal of the solvent and subsequent crystallisation from pet. ether afforded o-methyl podocarpic acid (200 mg).

M.P. 157-158° Lit.[15] 158°

O-Methyl podocarpinal[16] (IX)

O-Methyl podocarpinol (1.4 g, preparation described in Chapter III) in pyridine (16 ml) was added slowly to a pyridine-chromium trioxide complex (prepared by adding 1.6 g CrO_4 to 16 ml of pyridine). The mixture was allowed to stand at room temperature for one and half hour. The black residue

was filtered off and washed well with ether. The filtrate was diluted with water and extracted with ether. Total ether extracts were washed free of pyridine, dried over sodium sulphate. Solvent removal afforded a residue which crystallised from aqueous methanol to furnish o-Methyl podocarpinal (850 mg) in white needles.

M.P. 132-133°. Lit.[16] 134°

I.R. 2690 cm^{-1}, 1710 cm^{-1} (CHO)

Dehydroabietic acid (XVIII)[17,18]

M.P. 171°

$[\alpha]_D$ +58°

Methyl dehydroabietate (XIII)

Preparation described in Chapter III.

Dehydroabietinal[20] (XX)

Dehydroabietinol (600 mg)(preparation described in Chapter III) in pyridine (7 ml) was added slowly to a complex formed from chromium trioxide (700 mg) and pyridine (8 ml). The reaction mixture was kept for one and half hours at room temperature. Usual work-up and crystallisation of the product from aqueous methanol yielded o-methyl podocarpinal (360 mg).

M.P. 88-89° Lit.[20] 90°

I.R. 2690, 1710 cm^{-1} (CHO)

Isostevic acid (VIII)[21]

Oxidation of dihydromonogynol by Killiani's reagent.

Killianis reagent was prepared by dissolving sodium dichromate (1.2 g) in water (2.7 ml) sulphuric acid (1.6 g) and acetic acid (2.7 ml).

To dihydromonogynol (200 mg) in acetic acid (30 ml) was added the above reagent (1.442 g) dropwise. After allowing to stand at room temperature for 24 hrs., the mixture was poured in water (60-80 ml) when a white precipitate appeared. The precipitate was collected and washed thoroughly with water. The pure acid (160 mg) was obtained after two crystallisations of the residue from acetonitrile.

M.P.	183-184°	Lit.[21]	183-184°
$[\alpha]_D$	-62°	Lit.[21]	-62°

I.R. 2660 cm^{-1} (broad), 1690 cm^{-1}

Isostevic acid methyl ester (II)[21]

Isostevic acid (100 mg) was esterified with excess of an ethereal solution of diazomethane by usual procedure. The crude ester obtained was crystallised from acetonitrile to yield pure ester (80 mg).

M.P.	140°	Lit.[21]	141-42°
$[\alpha]_D^{28}$	-40°	Lit.[21]	-41.53°

Dihydromonogynøl (X)[21]

Dihydromonogynol (200 mg) dissolved in pyridine (2 ml) was added slowly to pyridine-chromium trioxide complex (215 mg. of CrO_3 and 2 ml of pyridine).

Mixture was left aside for 24 hours at room temperature. Usual work up gave a colourless gum (single spot in T.L.C.) which resisted crystallisation.

I.R. 2670 cm^{-1} and 1730 cm^{-1} (CHO)

NMR 1 H singlet at 584 cps (C<u>H</u>O)

<u>O-Methyl podocarpinol methyl ether</u> (XXI; Chart 3)

O-Methyl podocarpinol (600 mg) was refluxed in dry benzene (30 ml) with potassium metal (400 mg) for two hours with vigorous shaking at intervals to disperse the molten metal. Methyl iodide (5 ml) was added to the cooled reaction mixture and it was refluxed for further three hours.

Excess of potassium was destroyed by cold methanol and the solvents were removed in vacuo. The residue was extracted with ether and washed with water. Removal of ether after drying over sodium sulphate left a syrupy liquid which showed two spots on T.L.C., the lower one corresponding to starting material O-methyl podocarpinol. Chromatography over silica gel in pet ether gave a thick liquid (380 mg) which was distilled under vacuo and characterised as the o-methyl podocarpinol-methyl ether.

B.P. 185-190° at/1.5 mm (bath temperature).

I.R. 1115, 1610, and 1575 cm^{-1}

NMR ($CDCl_3$)
3H singlet at 226 cps ($OC\underline{H}_3$ on aromatic ring C)
3H singlet at 199.5 cps (C_4- $CH_2O\underline{C}H_3$)
3H singlet at 72 cps (C_{10}-CH_3)
3H singlet at 62 cps (C_4 -CH_3)
2H AB quartet at 203.5 B - A = 17 cps JAB = 9 cps.

Analysis:

Found: C, 78.96; H, 9.70%

$C_{19}H_{28}O_2$ requires: C, 79.12; H, 9.79%.

Elution with alcohol gave starting alcohol (60 mg).

Dehydroabietinol-methyl ether (XXII)

Dehydroabietinol (325 mg) was dissolved in dry benzene (25 ml) and treated with potassium metal (250 mg). The mixture was refluxed for two hours with frequent shaking at intervals. Methyl iodide (5 ml) was added and the mixture was refluxed for further three hours.

Work up as above afforded a thick liquid (300 mg) which showed a single spot in T.L.C.

This was distilled under vacuum and characterised as dehydroabietinol-methyl ether.

B.P. 180-190°/1.5 mm. (bath temperature)

I.R. 1115, 1610 cm^{-1}

NMR ($CDCl_3$)

3H singlet at 198 cps (C_4- CH_2O-$\underline{CH_3}$)
6H doublet centred at 73.5 cps (C_{13}-isopropyl)
J = 7 cps

3H singlet at 53 cps (C_4-CH_3)

2H AB quartet centred at 176 cps (C_4-$\underline{CH_2}$-O)
δ_B-δ_A = 16 cps JAB = 8 cps.

Analysis:

Found: C, 84.14; H, 10.79%

$C_{21}H_{32}O$ requires: C, 83.94; H, 10.70%.

Neoabietic acid (XIX)*[22]

M.P.	167-170°	Lit.[22]	167-169°
$[\alpha]_D^{28}$	+150°	Lit.[22]	+159°

Neoabietic acid methyl ester (XIV)[23]

Neoabietic acid was esterified by ethereal diazomethane solution. The methyl ester was crystallised from little quantity of methanol by keeping at -10 to -15° for eight days.

M.P.	60°	Lit.[23]	61.5-62°

* We are indebted to Dr. K. N. Iyer for a generous sample of this acid.

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SUMMARY

SUMMARY

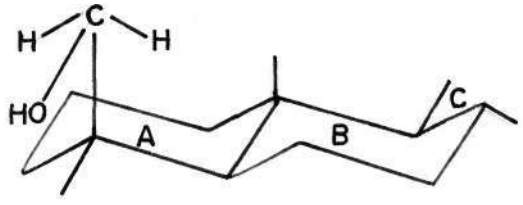
Solvent induced shifts in NMR spectra have been well studied in the case of ketones. The present study reports the shifts observed in cyclic ethers. A general rule to explain these shifts is enunciated. This rule provides a rationalization not only for the examples described here, but also for such shifts observed earlier[1] in the case of sapogenins.

This chapter also reveals that these shifts are not only applicable to cyclic ethers but to all compounds containing a lone pair of electrons.

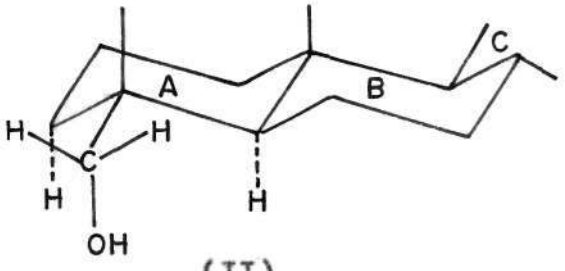
Chapter II describes long range shielding by an alkyl group in compounds having a rigid skeletons. The nature and magnitude of the shifts observed in these compounds is similar to that observed earlier in substituted cyclohexanols[2]. The present study could help in assigning the stereochemistry of a methyl group if the protons on the adjacent carbon atoms could be observed, Qualitative explanations of these shifts have been presented and these ideas have been extended to establish the conformations of simple aliphatic alcohols.

Chapter III embodies results which establish the conformations of hydroxymethyl groups in terpenoids. To accomplish this purpose a simple method of establishing

the stereochemistry of a suitably located secondary hydroxyl is presented. By using this Method, the conformation of axial and equatorial hydroxy methyl groups is shown to be represented by I and II respectively. Stability considerations also establish that these should be the preferred conformations.



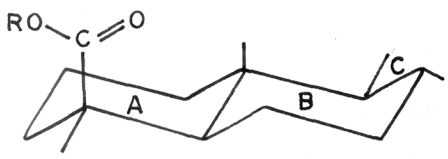
(I)



(II)

Several recent studies have been directed towards the determination of esters[5] and aldehydes.[6] For the axial acids and esters these studies have suggested alternate conformations III and IV. the study presented in Chapter IV, using solvent induced chemical shifts has clearly demonstrated that axial esters and acids in terpenoids exist in conformation III whereas the corresponding aldehydes exist in conformation IV.

These studies also unequivocally lead to conformation V for the equatorial esters, acids and aldehydes. Here too stability considerations suggest that these would be preferred conformations.



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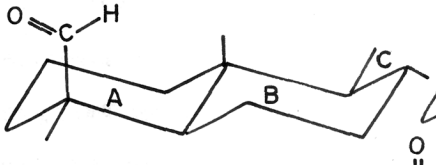

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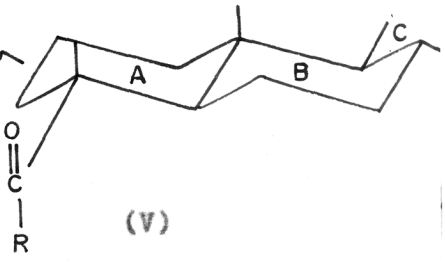

(V)

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Poona.
April, 1968.