Oxidative Reactions

of some

Tetracyclic Diterpenoids.

THESIS

presented to the University of Glasgow

for the degree of Doctor of Philosophy

by

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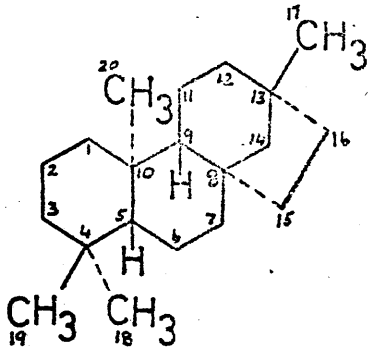
Oxidative Reactions of some Tetracyclic Diterpenoids.

SECTION A.

Naturally occurring Beyeranes.

1. Tetracyclic Diterpenoids Related to Beyerane.



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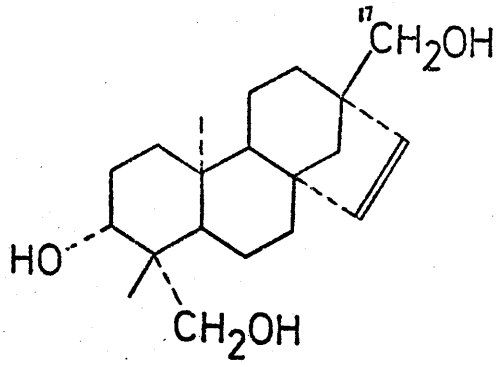

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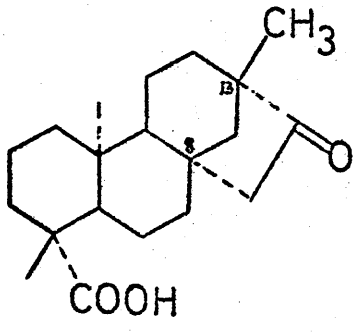

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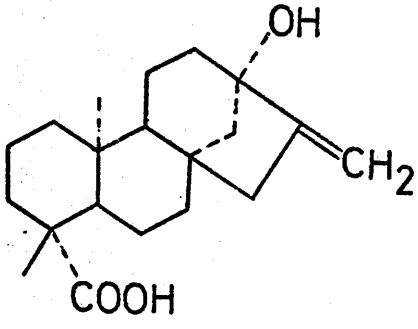

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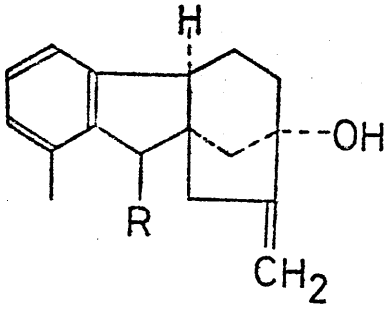
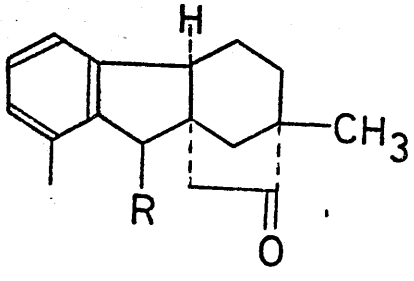


5 R=COOH

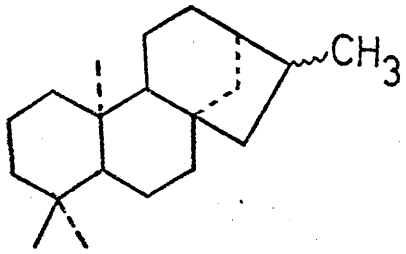


6 R=COOH

The carbon framework of the diterpenoids discussed in this review is based on the saturated hydrocarbon beyerane (1), formally derived from beyerol[1](2), the 17-cinnamate of which was the first naturally occurring diterpenoid to be identified having this skeleton. A common structural feature of those compounds of natural provenance is the Δ^{15}-double bond in ring D, which forms part of a bicyclo-[3,2,1]-octene system.

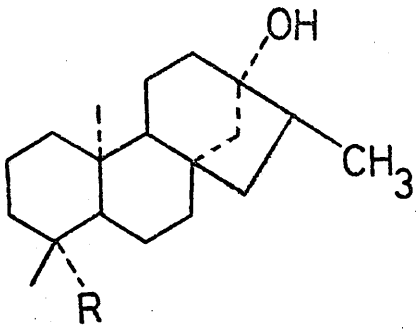
The rigorous establishment of the carbocyclic system was based on extensive investigations by Djerassi and Mosettig[2-7], who determined the relative and absolute stereochemistry of isosteviol (3) prior to the isolation of beyerol. Since the former is of prime importance in the chemistry of the beyeranes, its structural determination is worthy of further comment.

Isosteviol (3), which does not occur naturally, was obtained[2] from acid catalysed hydrolysis of stevioside, a triglucoside from Stevia rebaudiana. It was subsequently shown that this keto-acid originated from steviol (4), another hydrolysis product[2], in a manner analogous to the then known allogibberic (5)-gibberic acid (6) transformation[8]. This relationship between these respective pairs of isomers was further used in a study[3] of the optical rotatory dispersion curves of the ketones (3) and (6) and the nor-ketones derived from steviol and allogibberic acid on oxidative cleavage of the exocyclic methylene groups. The close similarity of the respective pairs of curves served to define the orientation of



7a 16β-CH_3

b 16α-CH_3

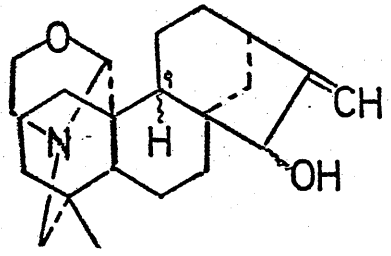


8a R=COOH

b R=CHO

c R=CH_3

d 16α-CH_3, R=COOH



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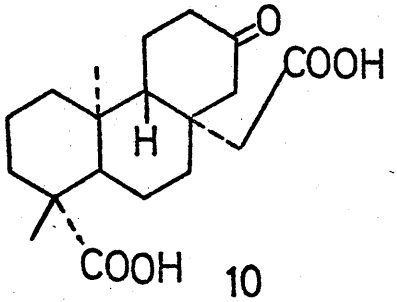

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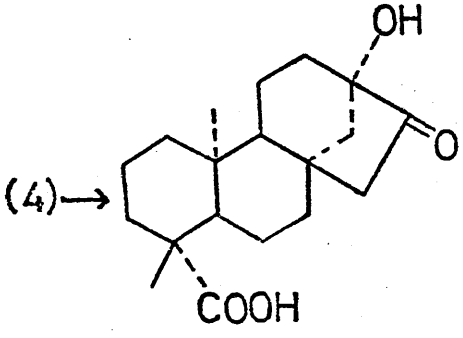

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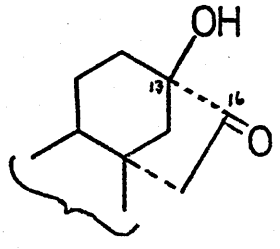

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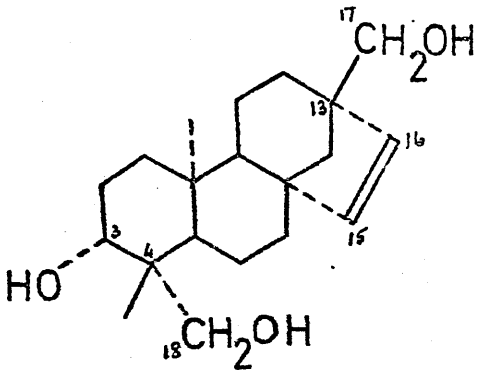
the two carbon bridge between C-8 and C-13 in isosteviol. The epimeric C-16 hydrocarbons, stevane A(7a) and stevane B(7b), were prepared[3] and their identity with the epimeric kauranes shown by comparison of their physical constants including their X-ray powder photographs.

Conversion of the hydroxy-acid (4) to stevane A(7a) was effected[3] by the following transformations. Hydrogenation of the exocyclic double bond gave α-dihydrosteviol (8a) which was converted via the alcohol to the aldehyde (8b). The derived thioacetal on desulphurisation generated the required saturated alcohol (8c). Subsequent replacement of the tertiary hydroxyl group by bromine using phosphorous pentabromide, then hydrogenolysis of the bromine over Raney nickel gave stevane A(7a). The C-16 epimer, stevane B[3](7b), was prepared by an identical route but for the initial stages. These involved catalytic reduction of stevioside which, for steric reasons, permitted hydrogen to add to the β face, and subsequent hydrolysis of the sugar residues, to give β-dihydrosteviol (8d). Since the chemistry and stereochemistry about the C/D ring junction in isosteviol had been determined, there remained in doubt the configurations about the three asymmetric centres at 5, 10 and 9.

Stevane B(7b) was shown[4] to be identical with the hydrocarbon derived from the Garrya alkaloid, garryfoline (9), which at the time of the comparison was of known configuration at all centres except C-9. Thus evidence of a trans fused A/B ring junction



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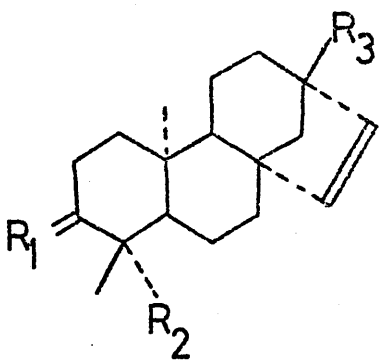
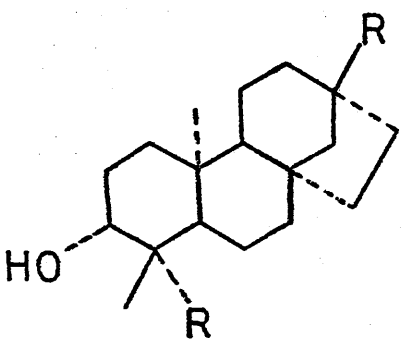


13 R_1=O, R_2=R_3=CH_3

14 R_1=H_2, R_2=R_3=CH_3

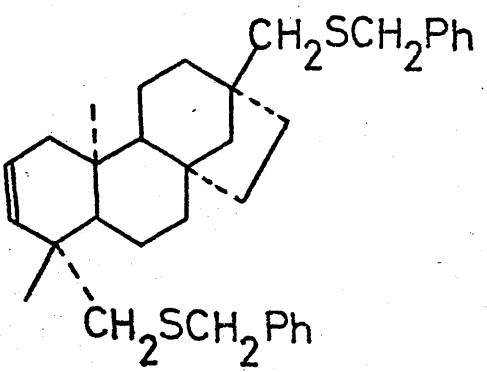
15 R_1=H_2, R_2=CH_2OH, R_3=CH_3



16 R=CH_2OH

18a R=CH_2OTs

b R=CH_2SCH_2Ph

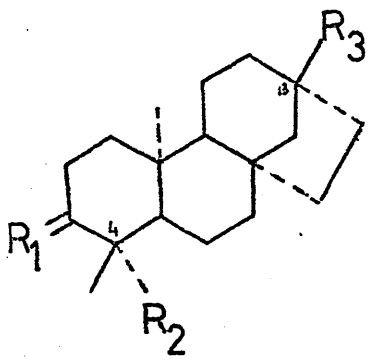


17

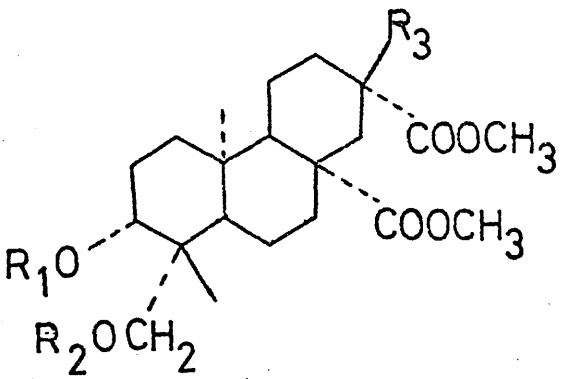
(5β-hydrogen, 10α-methyl) in both steviol and isosteviol was obtained. The rotatory dispersion curves of the keto-dicarboxylic acid (10) (vide infra) and the trans fused 5α, 3-ketosteroids show an antipodal relationship to each other. Thus the stereochemistry of isosteviol is completely defined[5,7] as trans-anti-trans with a β-orientation of the C-9 hydrogen. The ketol (11), derived from steviol on ozonolysis, gave the isomeric ketol (12) on treatment with base. The latter compound, on oxidative cleavage of the C 13 - C 16 bond with periodate, generated the hydroxy-dicarboxylic acid (10) used in the above o.r.d. comparisons.

Isostevane, derived from isosteviol, is therefore of known relative and absolute stereochemistry and has been used in structural correlations, either directly or indirectly (via beyerol), with other naturally occurring beyerane diterpenoids. In this way the carbocyclic skeletons of beyerol[1](2), stachenone[1b,9](13), (-)-hibaene[10] (14 antipode) and erythroxylol A[11,12] (monogynol[13,14]) (15) have been deduced.

Beyerol[1](2), occurring naturally as its 17-monocinnamate, has its three hydroxyl functions, two primary and one secondary, attached to carbons 3, 17 and 18. The tris-methanesulphonate of dihydrobeyerol (16) on treatment with the sodium salt of benzyl thiol underwent[1a] substitution and elimination giving the unsaturated dithioether (17). This on desulphurisation followed by hydrogenation gave isostevane. The 17,18-ditoluene-p-sulphonate (18a), on conversion[1a] to the dibenzyl thioether (18b)

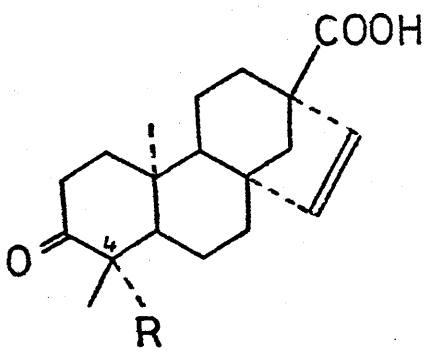


19 R_1=α-OH, β-H, R_2=R_3=CH_3



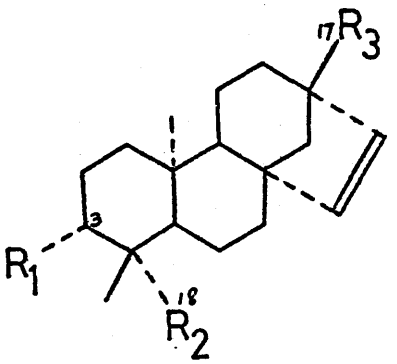
21 R_1=R_2=H , R_3=CH_2OH

22 R_1+R_2=$CHCH_3$, R_3=COOH



20 R=CHO

26 R=CH_2OAc



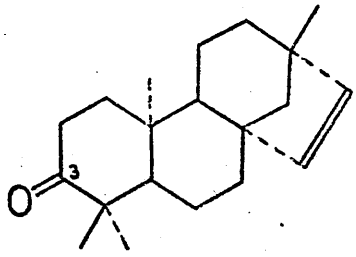
23 R_1=H, R_2=R_3=CH_2OH

24 R_1=OH, R_2=CH_2OH , R_3=CH_3

25 R_1=OH, R_2=CH_3 , R_3=CH_2OH

followed by reduction, gave compound (19), readily derived from the naturally occurring stachenone[9](13). This interconversion with isostevane served to define unambiguously the carbon skeleton, and its absolute stereochemistry, present in both beyerol and stachenone.

The 1,3-relationship[1a] of a primary and secondary hydroxyl group in beyerol was readily illustrated by the formation of an ethylidene derivative with acetaldehyde, and also by the base catalysed decarbonylation of the derived 1,3-keto-aldehyde (20), which generated a secondary methyl group. The latter information served to confirm the geminal attachment of methyl and aldehyde groups at C-4. That the second hydroxymethyl group was attached to C-13 was proved by a sequence of reactions involving oxidative rupture of the double bond between carbons 15 and 16. The triol diester[1a](21) so formed was protected as the ethylidene derivative and the remaining primary hydroxyl oxidised to the acid. The decarboxylation of this compound (22) showed that it must be a malonic acid half-ester. Evidence for an axial hydroxymethyl group at C-4 in beyerol was derived from spectroscopic studies[1]. Thus the chemical shift values for the -C$\underline{H}$O and -C$\underline{H}_2$OAc protons (at C-18) in a number of derivatives of beyerol were in accord with an axial configuration. This being so, the intramolecular hydrogen bonding observed in the infra red spectrum of beyerol requires an equatorial orientation of the hydroxyl at C-3. This assignment is supported by the



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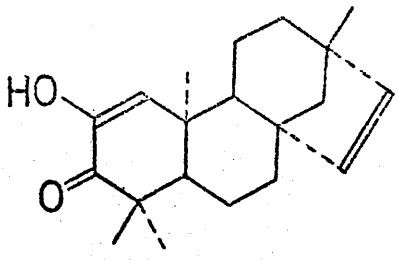

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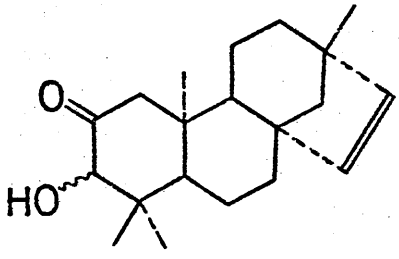

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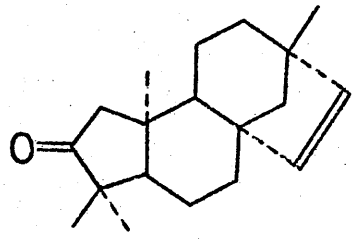

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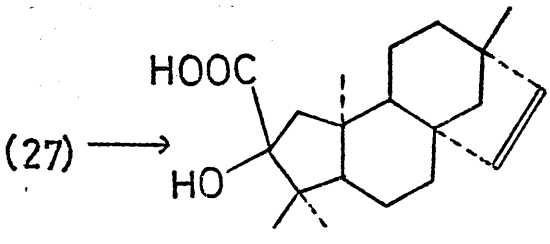

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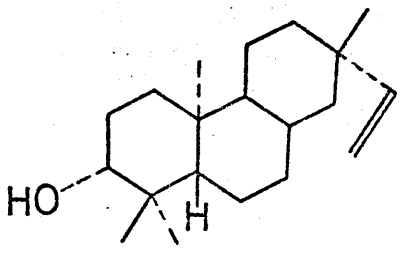

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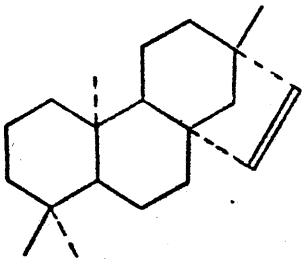
regeneration of beyerol on lithium aluminium hydride reduction of the keto-aldehydo-acid (20). The chemically derived structure of beyerol (2) is in full agreement with an X-ray analysis[15] carried out by O'Connell and Maslem.

Erythroxydiol A[11,12,16](hydroxymonogynol[13,14]) (23), beyer-15-en-3α,18-diol[16] (24), beyer-15-en-3α,17-diol[16] (25), and 3-keto-18-acetoxybeyer-15-en-17-oic acid[17] (26), all having a normal oxygenation pattern, occur naturally and have been correlated with beyerol.

Stachenone[9] (13), isolated from Spirostachys africana, on autoxidation in t-butanol containing potassium t-butoxide yielded a diosphenol (27) which also occurs naturally. The latter compound could also be formed by bismuth oxide treatment of a third constituent, the α-ketol (28). Stachenone and the product derived from its treatment with methylmagnesium iodide gave 1,7-dimethyl and 1,2,7-trimethylphenanthrene respectively after dehydrogenation thus establishing position 3 for the keto grouping. Trans fusion of the A/B junction was demonstrated by the molecular rotation differences of stachenone, the ketone (29)*

*Synthesis of the ketone (29) was effected by base catalysed benzilic acid rearrangement of the diosphenol (27). Lithium aluminium hydride reduction of the resulting hydroxy-acid (31) to the corresponding diol then oxidative scission with periodate generated the desired compound.



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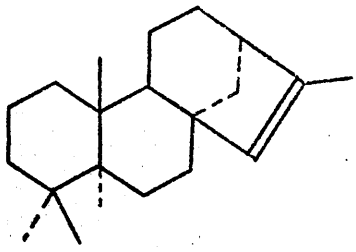

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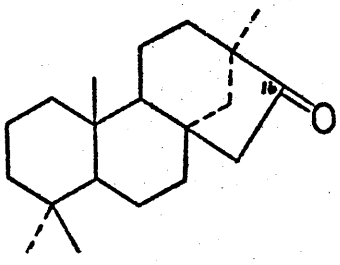

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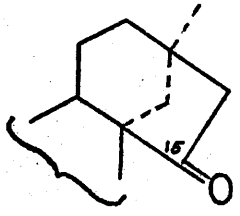

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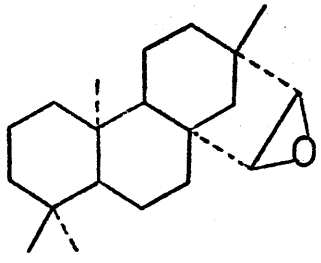
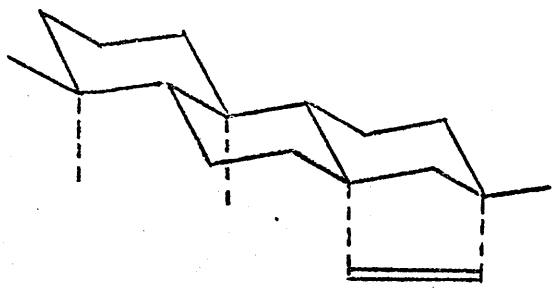


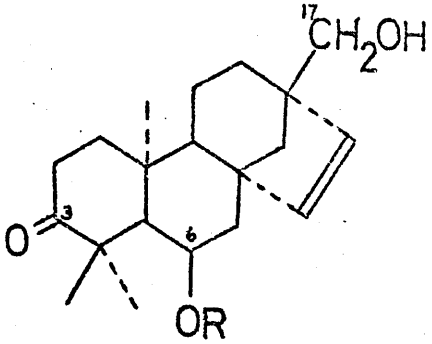
35

and various derivatives. The results suggested the presence of a 5β-hydrogen, 10α-methyl system since the rotational differences were in the same sense as those in the darutigenol[18] (30) series but in the opposite sense to those of the naturally occurring triterpenes. The rotatory dispersion curve of A-norstachenone (29) being similar in shape and magnitude but antipodally related to 3,3-dimethyl-A-nor-5α-cholestanone, confirmed this assignment.

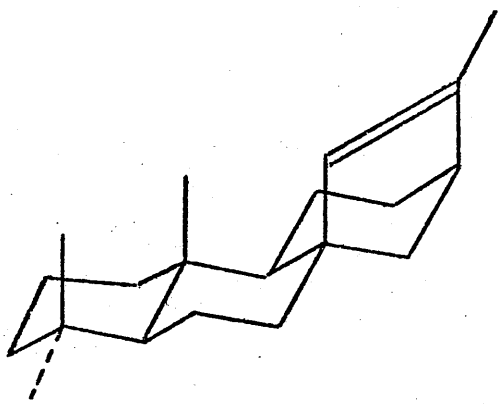
The enantiomeric beyer-15-enes [(+)-stachene[11,12](14) and (-)-hibaene[14] (14 antipode)] have been isolated from botanically unrelated sources. A sharply melting hydrocarbon, cupressene[19], has been shown[20] in fact to be a eutectic mixture of isophyllocladene (32) and (-)-hibaene. On hydroboration of the beyerene double bond and oxidation of the resulting secondary alcohols, (-)-hibaene gave two ketones that differed markedly in reactivity[10]. The more polar ketone formed (33) gave a dinitrophenylhydrazone and underwent the Baeyer-Villiger reaction whereas the less polar isomer (34) was inert to the respective reagents. Models show that the ketonic function at C-16 is sterically more accessible than that at C-15 which must account for the lack of reactivity of the less polar ketone. The rotatory dispersion curve[10] of the more reactive 16-ketone (33) was found to be antipodally related to that of isosteviol. This required a similar relationship to exist between the saturated hydrocarbons derived from (-)-hibaene and isosteviol, which was shown to be the case. The antipodal olefin, (+)-hibaene, has been identified by direct



14a



37 R=Ac
38 R=H



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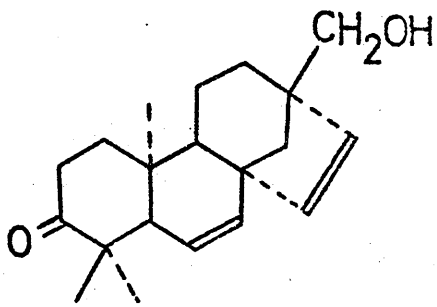

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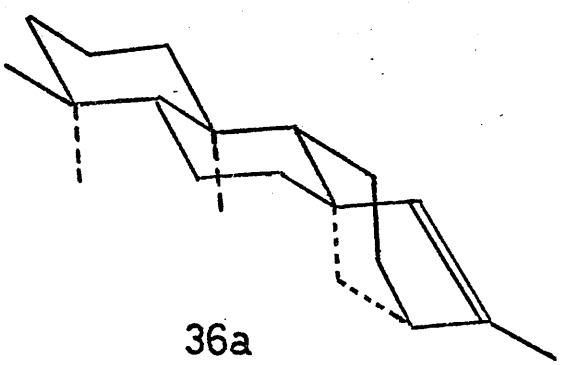

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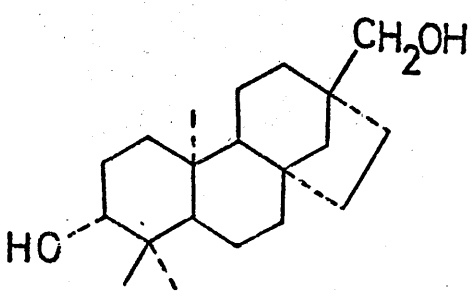


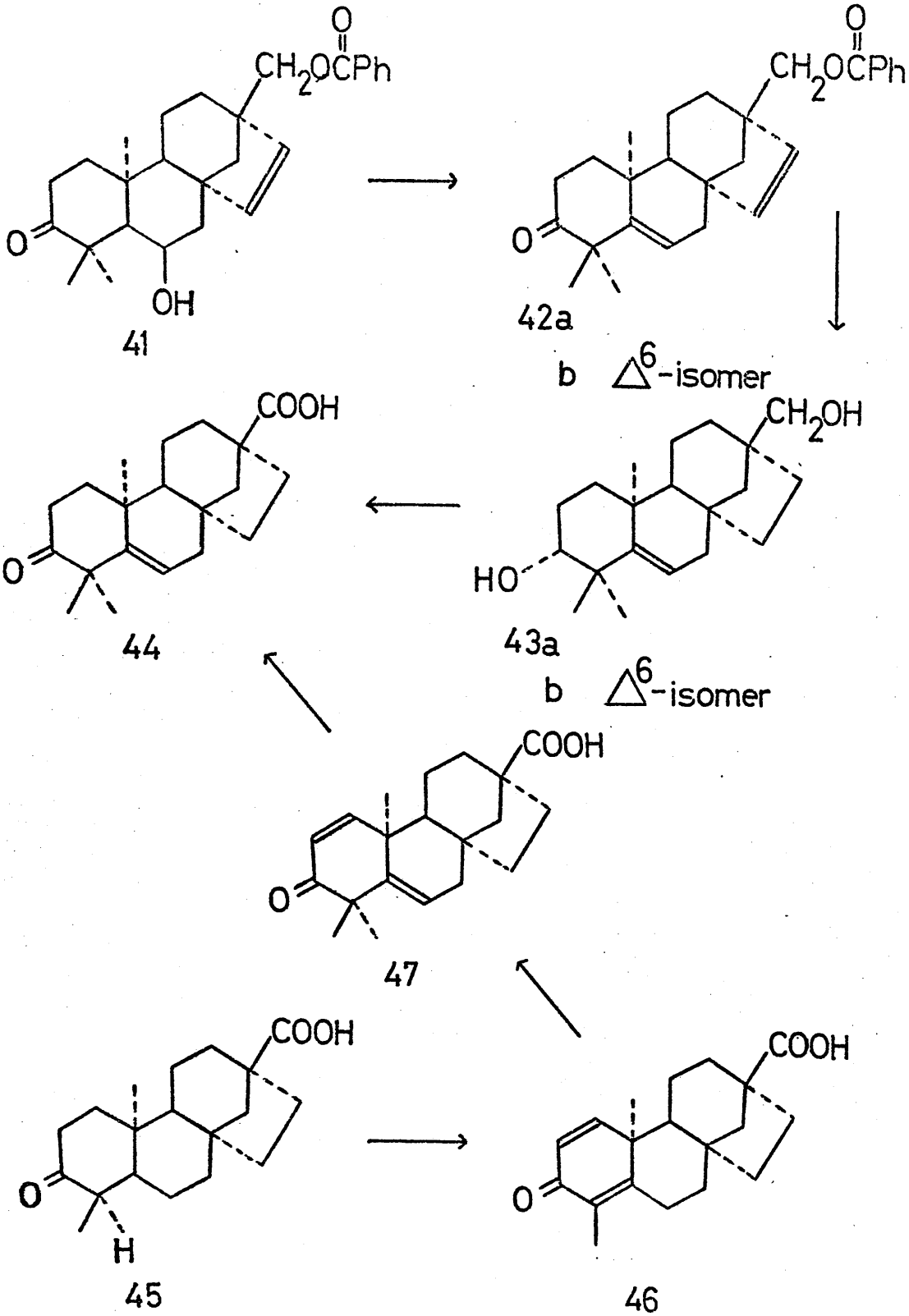
40

comparison[11,12,14] with (-)-hibaene and stachene, the latter being derived from stachenone. The β-epoxide (35) obtained on peracid oxidation of (+)-hibaene is identical to a constituent isolated[14,21,22] from Erythroxylon monogynum.

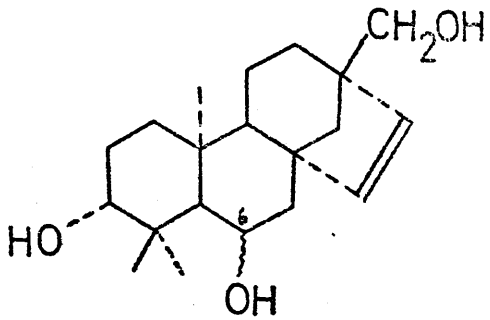
The proton magnetic resonance spectra of the naturally occurring beyerenes exhibit an AB quartet centered around τ 4·4 and having a typical proton-proton coupling constant of 5·5 c./sec. These signals, integrating for two hydrogens, are characteristic[12] of the cis-disubstituted double bond in the five-membered ring. Since no additional coupling can be observed, the allylic carbons must be fully substituted, further confirming the attachment of the ethylenic bridge to two quaternary centres. By analogy with the magnetic anisotropy of the carbonyl function, this double bond in the beyerene skeleton causes a significant shielding of the C-10 methyl group in the n.m.r. spectrum[1,23]. This effect, which can be removed by hydrogenation or epoxidation, is consistent with the 10-methyl group lying in the shielding cone of the π-electron system. This requirement is fulfilled by the trans-anti-trans configuration of the beyerene (14a) and isophyllocladene (32a) skeletons but not by the trans-anti-cis isokaurenes (36a).

A trioxygenated beyer-15-ene (37) having a 6β-acetoxy grouping has been isolated[17] from Beyeria leschenaultii. The presence of a ketone, a hydroxymethyl group, and a secondary acetoxy function was inferred from spectral evidence.

CHART I

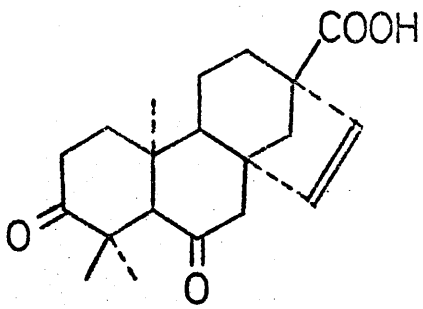

O
CH2OCPh
O
OH
41
42a
b Δ6-isomer
CH2OH
HO
43a
b Δ6-isomer
COOH
O
44
47
45
46
H

Correlation with beyerol was achieved in the following way. Removal of the acetate and treatment of the keto-diol (38) with benzoyl chloride selectively esterified the primary alcohol. Dehydration followed by removal of the benzoate with methanolic potassium hydroxide gave 3-ketobeyer-6,15-dien-17-ol (39) which on hydrogenation and lithium aluminium hydride reduction gave 3α,17-dihydroxybeyerane (40). Preparation of the latter compound from beyerol was also effected. This evidence placed the ketone at 3 and the hydroxyl at 17. That the remaining acetoxyl function in (37) was attached to C-6 was shown by the following series of interconversions[17] (see Chart I). Solvolysis of the toluene-p-sulphonate derived from (41) gave a mixture of $\Delta^{5,15}$ and $\Delta^{6,15}$-dienes (42) which proved to be inseparable. Lithium aluminium hydride reduction of the mixture and selective hydrogenation of the beyerene double bond followed by chromatography over silver nitrate-alumina gave the individual diols (43). Oxidation of the Δ^{5}-isomer (43a) gave the unsaturated keto-acid (44) which could also be prepared from (45), a known degradation product of beyerol. The cross-conjugated dienone (46), resulting from dehydrogenation of (45) with dichloro-dicyanoquinone, was alkylated with methyl iodide to give the 3-ketobeyer-1,5-dien-17-oic acid (47). Selective hydrogenation of the latter compound yielded the desired Δ^{5}-keto-acid (44). The preparation of the keto-acid (44) from both sources



48 6β-OH

49 6α-OH



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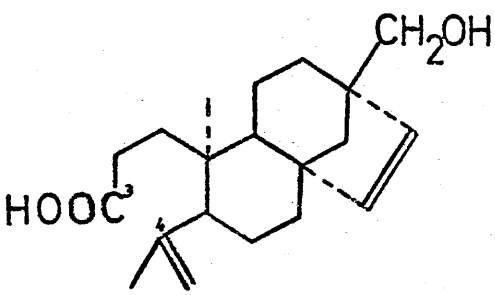

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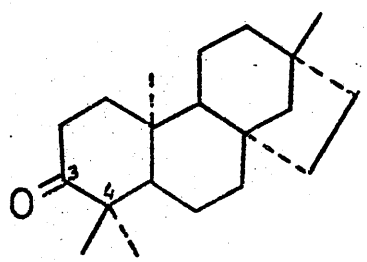

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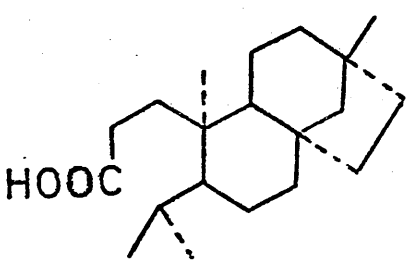

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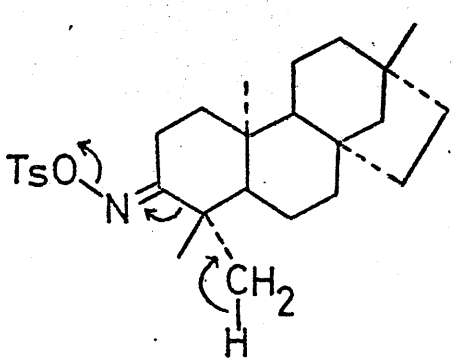

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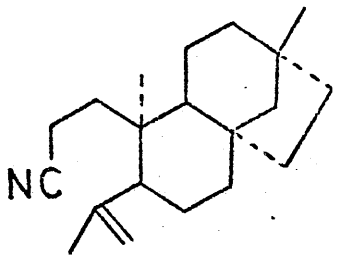
necessitates that the acetoxy group in (37) must be at C-6.

Establishment of the configuration of this acetoxy group was deduced from acetylation experiments[17] on the C-6 epimeric triols (48) and (49). The isomer having the 6β-hydroxyl was prepared by direct lithium aluminium hydride reduction of the acetate (37) whereas hydrolysis of (37), oxidation to the diketo-acid (50) and lithium aluminium hydride reduction gave beyer-15-en-3α,6α,17-triol (49). The 3α,6β,17-triol (48) gave the corresponding triacetate under mild conditions while the 3α,6α,17-triol (49) yielded only the 3α,17-diacetate. This requires that in the former, the natural series, the hydroxyl at 6 must be equatorial.

A novel modification of the beyerene skeleton has recently been reported[17,24] following the isolation of the hydroxy-carboxylic acid (51). The 3,4-seco system, a feature previously unknown in the tétracyclic diterpenoids, has been shown by fission of the 3,4 bond of certain functionalised beyeranes using routes analogous to those devised for the synthesis of the 3,4-seco-triterpenes. Thus photolysis of the 3-oxo-4,4-dimethyl system of stachanone (55) in aqueous acetic acid resulted in the oxidative rupture of the C 3 - C 4 bond forming the saturated carboxylic acid (56). Alternatively, an abnormal Beckmann rearrangement has been utilised for the cleavage of ring A. The ketoxime toluene-p-sulphonate (57) undergoes a 5-centre fragmentation reaction[25] which resulted in the formation of the



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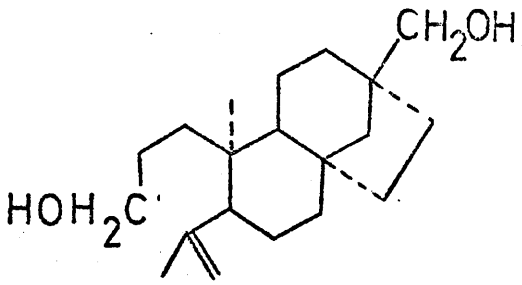

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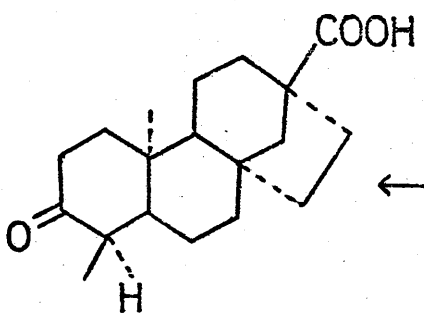

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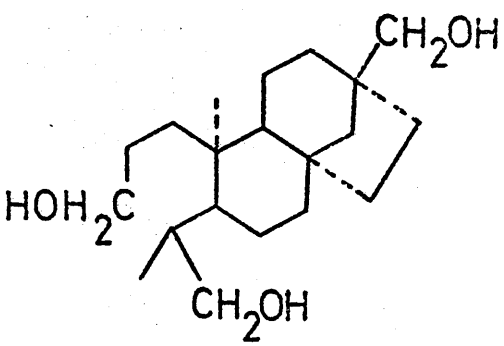

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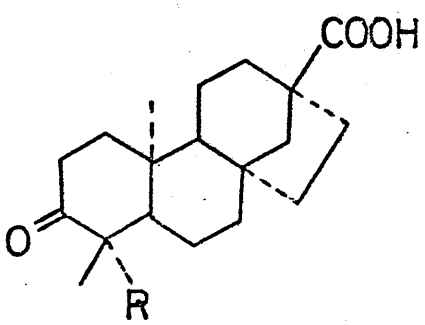
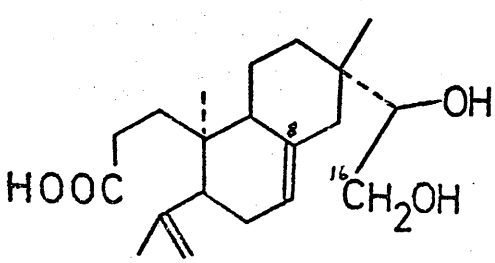


54 R=COOH or CHO

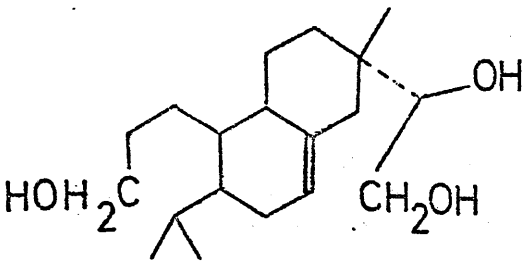


59

substituted cyano compound (58). Presumably heterolytic fission of the tosyl-nitrogen bond would give rise to electron deficient nitrogen and result in the rearrangement shown in (57) with loss of a proton to an external base. The products obtained from photolysis and abnormal Beckmann reactions have been correlated with the seco-beyerene of natural provenance.

This seco-system has been further confirmed by use of (51) in the synthesis of the nor-beyerane (45). Cyclisation to generate ring A was achieved by the following reaction sequence. The dihydroxy compound (52) was obtained from the natural product (51) by reduction of the acid and preferential saturation of the cyclopentene ring. Hydroboration of the isopropenyl group gave the triol (53) which, after oxidation and cyclisation by heating in acetic anhydride yielded the keto-acid (45). The latter compound probably arises from a nucleophilic displacement of acetate from a mixed anhydride intermediate at C-3 by an anion formed at C-4. The 1,3-dicarbonyl intermediate (54) so formed could decarbonylate to the nor-ketone (45). This ketone has been independently prepared[17] from beyerol.

Synthesis of the 3,4-seco-beyerane system has been effected from 15,16-dihydroxy-3,4-seco-pimara-4(18),7-dien-3-oic acid (59), isolated[26] from Beyeria brevifolia, by bond formation between C-8 and C-16 to generate ring D. Conversion of the dihydrotriol (60) to the related diene (61) was carried out by periodate cleavage of the vicinal glycol and treatment of the resulting



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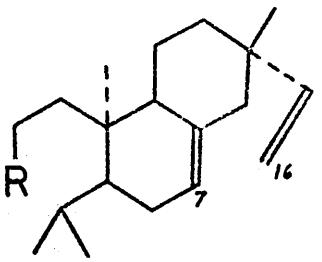
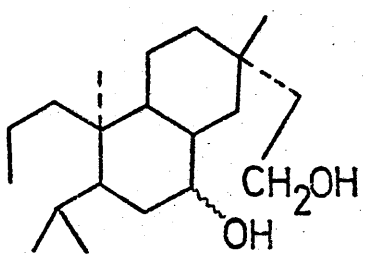


61 R=CH_2OH

62 R=CH_3



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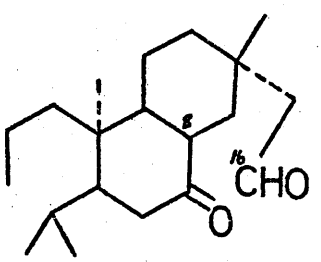

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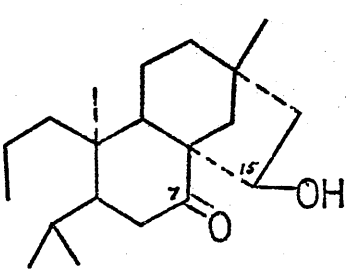


65

nor-aldehyde with Wittig's reagent. Transformation of the alcohol (61) to the corresponding hydrocarbon (62), followed by hydroboration of this diene resulted in oxygenation of carbons 7 and 16 forming secondary and primary hydroxyl functions respectively. Oxidation of this diol (63) gave the keto-aldehyde (64) which on Claisen condensation between carbons 8 and 16 generated ring D of 7-oxo-15β-hydroxy-3,4-seco-beyerane (65).

Thus to date, 19 diterpenoids of the Beyerane class have been isolated. These natural products together with their melting points, rotations and sources are listed in Table I.

TABLE I

NATURALLY OCCURRING BEYERANE DITERPENOIDS.

Name.	Formula Number.	m.p.	$[\alpha]_D^{CHCl_3}$	Source.	Reference.
beyer-15-en-3α,17,18-triol (beyerol)	2	242-243	+61 *	Beyeria leschenaultii	1
3-keto-18-acetoxybeyer-15-en-17-oic acid (as methyl ester)	26	135-136	+83	Beyeria leschenaultii	17
3-keto-6β-acetoxybeyer-15-en-17-ol	37	166-167	-104	Beyeria leschenaultii	17
beyer-15-en-3α,18-diol	24	149-150	+39 **	Helicrysum dendroideum	16
beyer-15-en-3α,17-diol	25	168-170	+36 **	Helicrysum dendroideum	16
beyer-15-en-17,18-diol (hydroxymonogynol erythroxydiol A)	23	179-180 179-181	+52 +60	H. dendroideum Erythroxylon monogynum	16 11,12 13,14
beyer-15-en-17-ol (erythroxylol B)	122	121·5-123	+67	Erythroxylon monogynum	12

*pyridine solution; **ethanol solution.

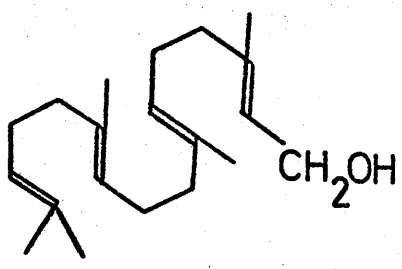
TABLE I

Name.	Formula Number.	m.p.	$[\alpha]_D^{CHCl_3}$	Source.	Reference.
beyer-15-en-18-ol (erythroxylol A, monogynol)	15	119-120	+39	Erythroxylon monogynum	11,12 13,14.
beyer-15-ene (hibaene, stachene)	14 (or antipode)	30-33 29·5-30	+33 -49·9	E. monogynum Thujopsis dolabrata Cupressus macrocarpa Podocarpus ferrugineus	11,12 14. 19,20
beyerane-15(16)-epoxide (hibaene epoxide)	35	74-75	+20·5	Erythroxylon monogynum	14,22
18-hydroxybeyerane-15(16)-epoxide (erythroxylol A epoxide)	124	115-116·5	+18·5	Erythroxylon monogynum	22
18-acetoxybeyerane-15(16)-epoxide (erythroxylol A acetate epoxide)	120	143·5-145	+14.5	Erythroxylon monogynum	22

TABLE I.

Name.	Formula Number.	m.p.	$[\alpha]_D^{CHCl_3}$	Source.	Reference.
18-norbeyer-15-en-4α-ol	119	b.p.100°/ 0·07 mm.	+25	Erythroxylon monogynum	22
18-norbeyer-15-en-4β-ol	121	114-116·5	+49	Erythroxylon monogynum	22
3-ketobeyer-15-ene (stachenone)	13	35-36·5	+22	Spirostachys africana	9
2-ketobeyer-15-en-3-ol	28	129	+30	Spirostachys africana	9
3-ketobeyer-1,15-dien-2-ol	27	132	+49	Spirostachys africana	9
17-hydroxy-3,4-secobeyer-4(18),15-dien-3-oic acid	51	-	-	Beyeria leschenaultii	17,24
beyer-15-en-18-oic acid*				Montanoa tomentosa	

*Private communication with Dr. D. Walls A. Probably co-occurs with kaur-15-en-18-oic acid



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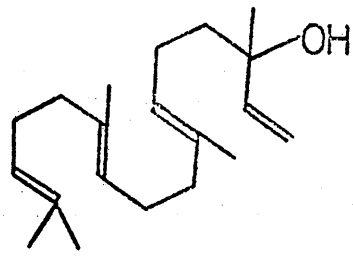

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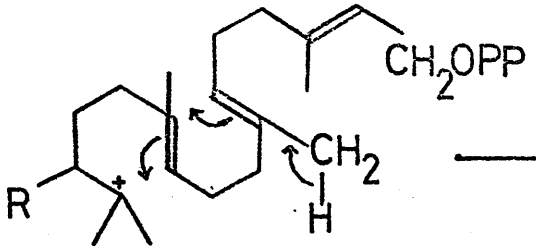
Biogenesis of the Beyeranes.

The vast number and variety of terpenoid compounds have, with the advent of Ruzicka's Biogenetic Isoprene Rule[27], been rationalised into smaller classifications of structural types. Thus the diterpenoids are considered as arising *in vivo* from geranylgeraniol (66) or geranyllinalool (67), formally written as the result of head-to-tail linking of four 1,1-dimethylallyl units.

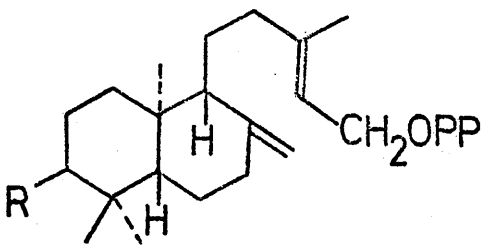
The biogenesis of the tetracyclic Beyerane diterpenoids must therefore account for the formation of the four rings from the acyclic precursor as well as accommodate the known features of the skeleton, namely, the trans A/B ring junction, the trans relationship which invariably exists between the C-9 hydrogen and the C-10 methyl, and the axial orientation of the ethylenic bridge. In addition, the biogenetic scheme should encompass other existing skeletal types which are sufficiently closely related to suggest a common biosynthetic pathway. Thus tetracarbocyclic diterpenoids having a bicyclo-[3,2,1]-octane or bicyclo-[3,2,2]-octane systems constituting rings C and D should be included in the proposed scheme.

In the currently held theory[27,28], it is convenient to visualise the cyclisation occurring by a stepwise process. Thus the formal generation of a carbonium ion at the terminal double bond of the acyclic chain (C-4 of the products) (68) could induce concerted formation of rings A and B of the bicyclic

SCHEME I



68 R=H or OH



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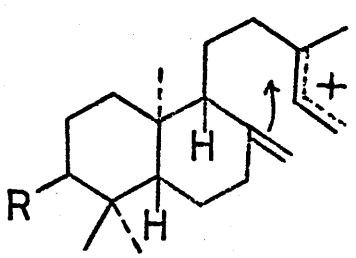

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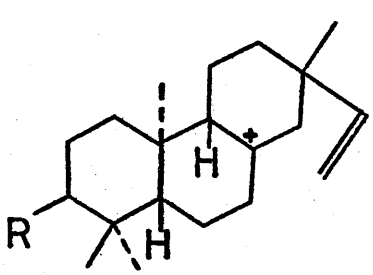

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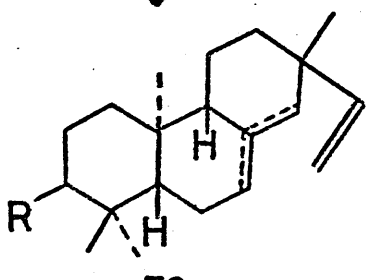

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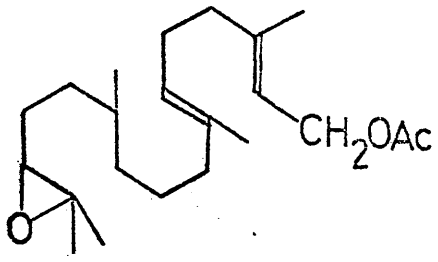
Labdane intermediate (69) (Scheme I). The carbonium ion (68) might be regarded as the product from protonation of the olefinic bond or alternatively, by analogy with the biosynthetic studies on the cyclisation of squalene[29], may be formed by the opening of a terminal epoxide to give oxygenation at position 3 in the final product (well known in the Beyeranes).

The second step in the proposed biogenesis is the generation of ring C following formation of the bicyclic intermediate (69). This may occur via the allylic carbonium ion (70) which would be formed following loss of the pyrophosphate residue. Bond formation from the sterically favoured[30] α-side of the exocyclic double bond due to attack by the formal electrophilic centre at C-13 would yield the ion (71). This species could then deprotonate to the natural $\Delta^{7,15}$ or $\Delta^{8(14),15}$-pimaradienes (72) which occur with either possible configuration at C-13.

That the cyclisation of the acyclic polyene chain probably involves the proposed mechanism is supported by the <u>in vitro</u> experiments of Johnson[31] and van Tamelen[32] who have shown that polycyclic products can be formed stereospecifically from acyclic precursors. Thus the non-enzymic cyclisations of (73)[32] using a Lewis acid catalyst gives rise to (74) in low yield (10%), and the tetraene[33] (75) gives rise to the tetracyclic product (76) in yields as high as 30%. In addition to the stereospecificity of the products, a degree of asymmetry can also be induced. Thus the Lewis acid catalysed opening of the asymmetric acetal[34] (77)



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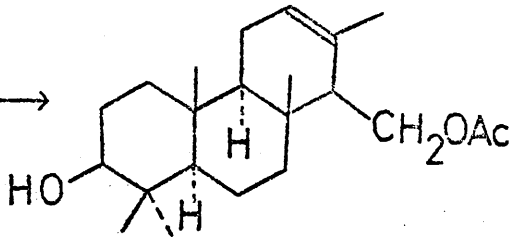

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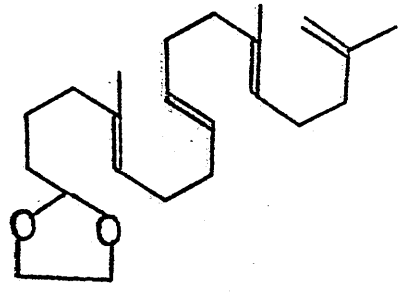

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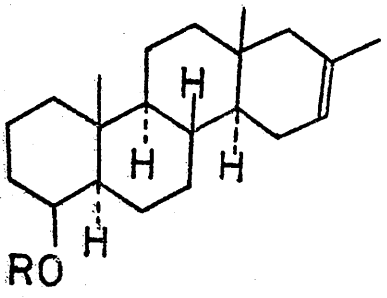

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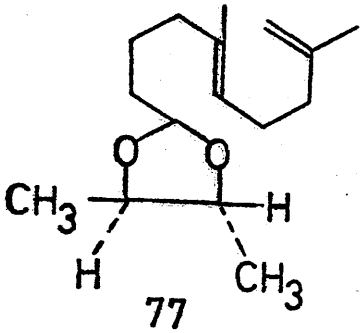

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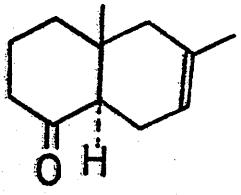

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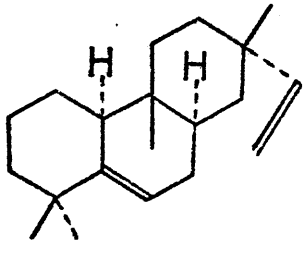

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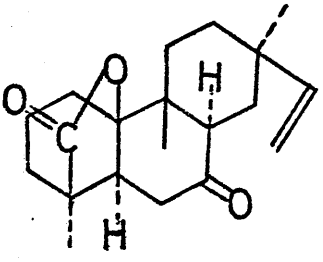


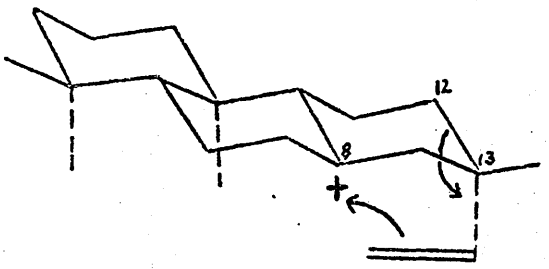
80

gives rise to optically active products of the type (78) after removal of the oxygenated side chain and oxidation of the hydroxyl group.

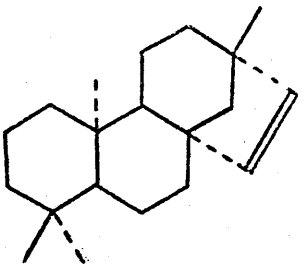
The generation of the bicyclic intermediate (69) in the biogenesis by this concerted trans addition of the double bonds immediately rationalises the stereochemical relationship between the substituents on carbons 5, 10 and 9. Thus the naturally occurring labdanes, pimaranes and the diterpenoids formally derivable from them, should conform to a trans-anti configuration, or be related by a backbone rearrangement. This implication has been fully substantiated by the stereochemical elucidation of the known polycyclic terpenoids of these types. A few compounds, such as rimuene[35] (79) and rosenonolactone[36] (80), previously formulated as having a trans-syn structure, have since been shown to conform to the expected trans-anti configuration.

A route[28] to the tetracyclic (and pentacyclic) diterpenes (Scheme II) involving the ionic species (71a), generated either from a suitably orientated pimaradiene or from the above cyclisation (Scheme I), has been proposed by Wenkert. Electrophilic attack of the formal cationic centre at C-8 on the axial vinyl group, with anchimeric assistance from the C12 - C13 bond would produce the non-classical ion (81a). Collapse of the protonated cyclopropyl ring may result in the formation of the beyerene (14), kaurene (36), atisirene (82) skeletons or alternatively deprotonation would give trachylobane (83).

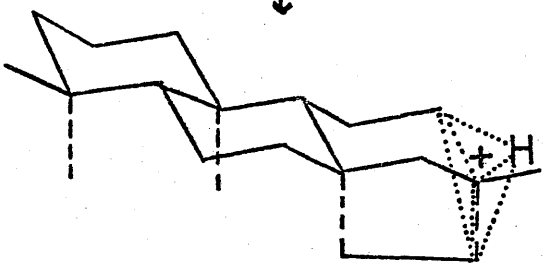
SCHEME II



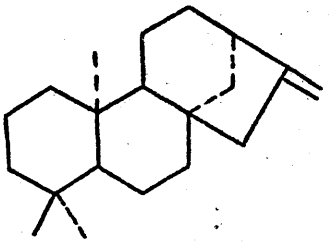
71a



14



81a



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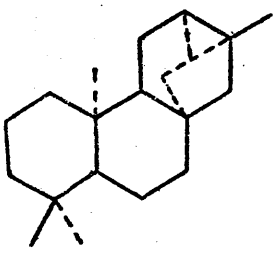

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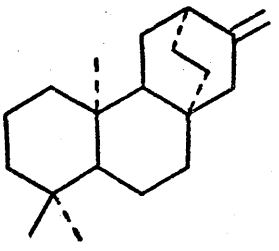
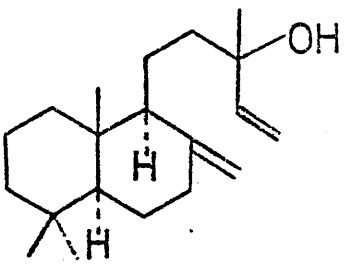


82

This pathway to the beyeranes is supported by the in vitro interconversions of the beyerene skeleton with those of the biogenetically related diterpenoids, and from identification of the naturally co-occurring metabolites from the same botanical sources. The detailed biosynthetic studies[37,38] that have been carried out on the mould metabolites from Gibberella fujikuroi, are absent in the beyerene series, probably due to practical difficulties in feeding and isolation of products associated with higher plant systems. Although the latter biosynthetic evidence, which has been reviewed elsewhere[39], does not directly concern the beyeranes, the kaurane biogenesis follows the same pathway[28] and differs only in the breakdown of Wenkert's non-classical ion (81a). Thus it is of interest to note that gibberellic acid and the intermediate kaurenolides have been shown[39] to incorporate labelled geranylgeraniol (either free or as the pyrophosphate) (66), labdadienol (84) and $\Delta^{8(14),15}$-pimaradiene (72). That the gibberellic acid obtained from these studies was labelled specifically followed from the degradation scheme shown (in accord with the proposed biogenesis).



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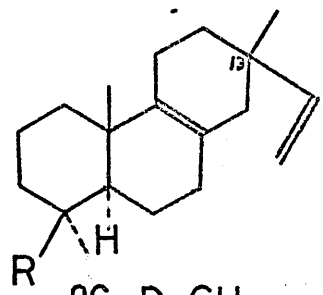
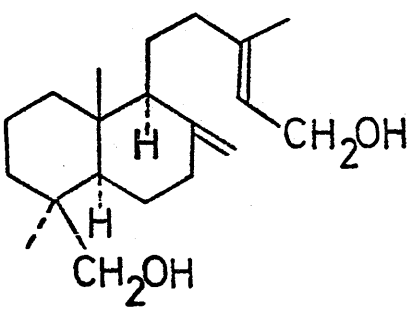


86 R=CH_3

89 R=CH_2OH



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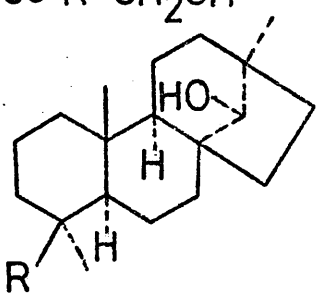
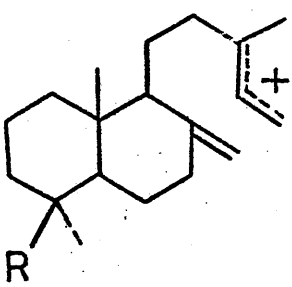


87 R=CH_3

90 R=CH_2OH



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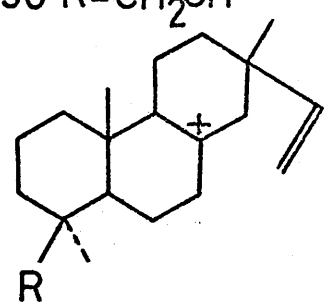

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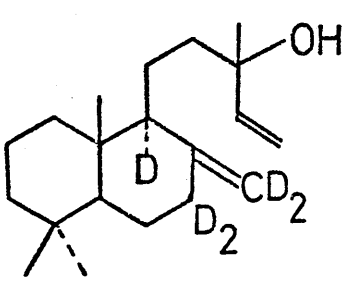

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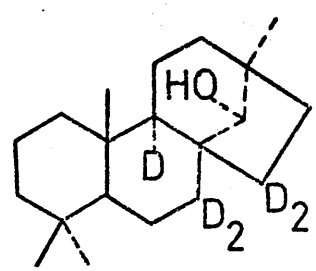
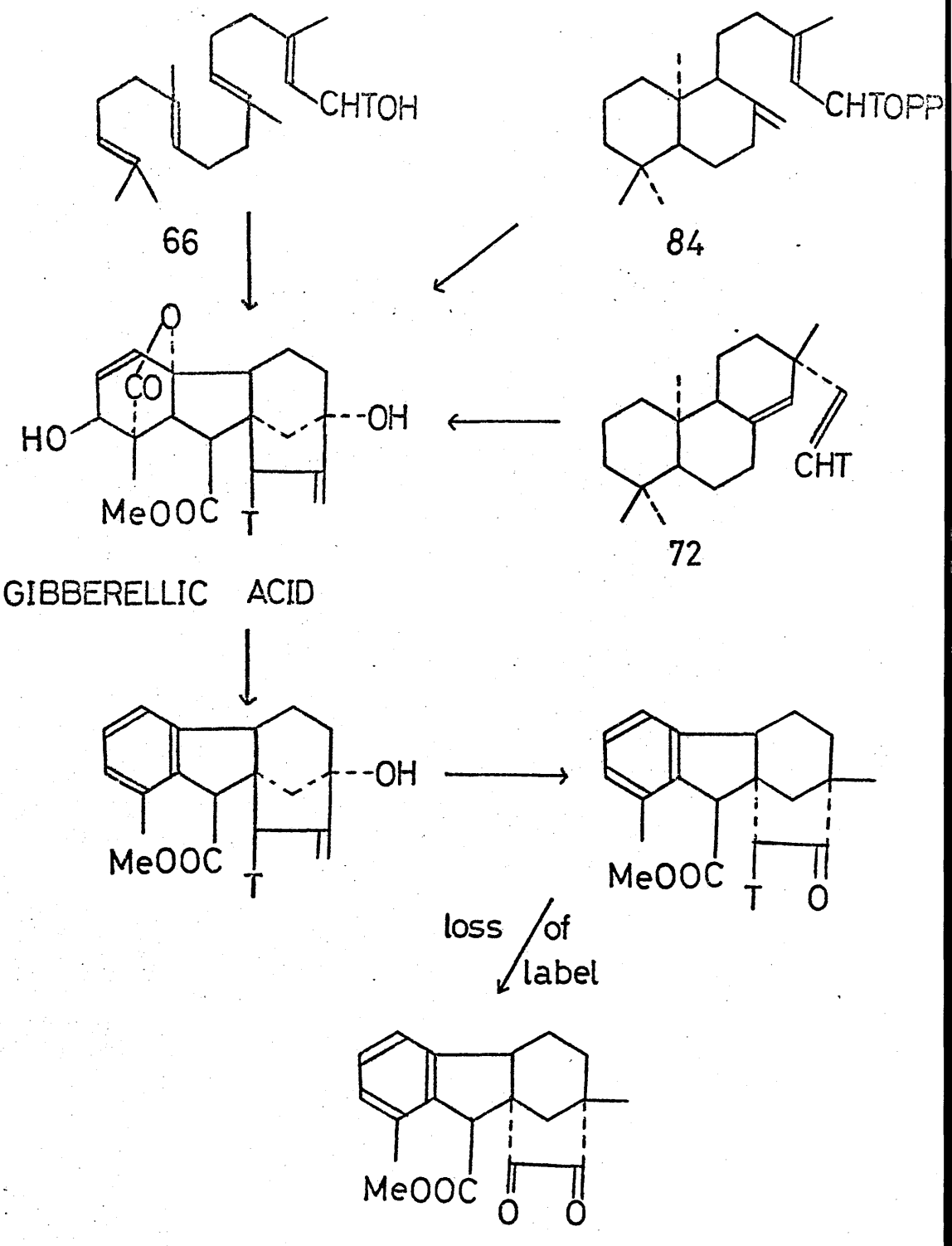
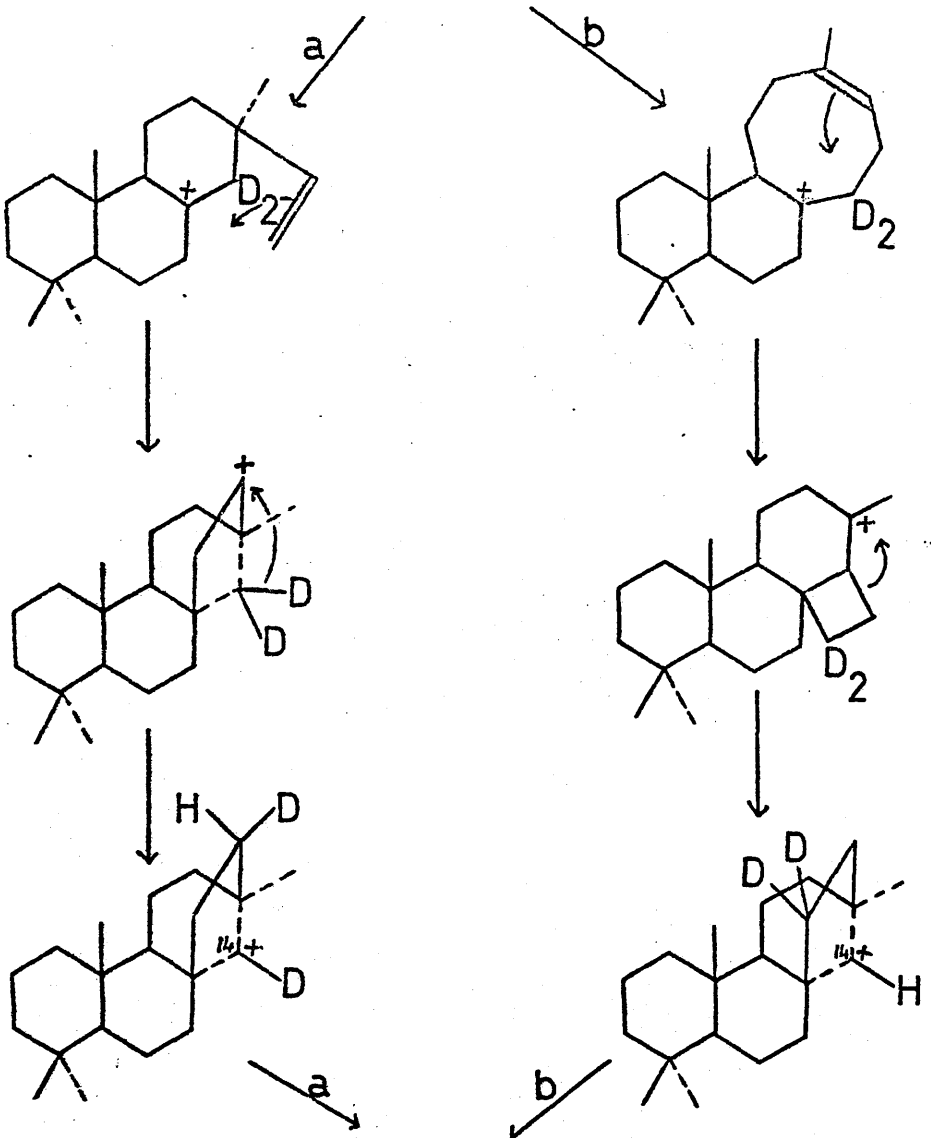


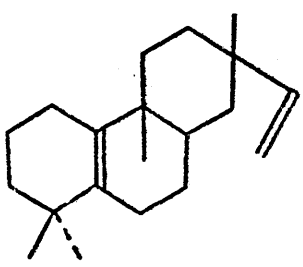
93


CHTOH
66
CHTOPP
84
O
CO
HO
OH
MeOOC
T
CHT
72
GIBBERELLIC ACID
OH
MeOOC
T
MeOOC
T
O
loss of label
MeOOC
O
O

(92)

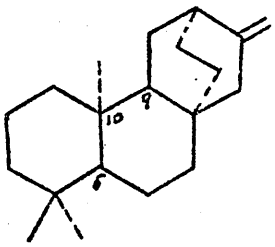


(93)

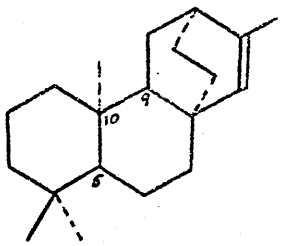


94

Indirect evidence of a similar nature can be derived from the *in vitro* acid catalysed cyclisations[30,40,41] of bicyclic labdenoids to tricyclic (pimaradienes) and tetracyclic (beyerene) products. Thus manool (85), with aqueous formic acid, gave a mixture of $\Delta^{8,15}$-pimaradienes (86) epimeric at 13 and the tetracyclic alcohol (87). Similarly agathadiol (88) gave a corresponding mixture of hydroxy-pimaradienes (89) and the dihydroxy-beyerane (90). These cyclisations presumably proceed through an allylic carbonium ion of the type (70) which, on ring formation, would result in the cationic intermediate (91). This latter ion may deprotonate to give the tricyclic products or permit further cyclisation with resulting formation of ring D as proposed in the biogenesis. However, the formation of ring D in this instance would appear[42] to follow an alternative route to that proposed in the biogenesis. Thus the cyclisation of the pentadeuteriomanool (92) gave rise to the labelled product (93) by the proposed route (b) rather than by path (a) which would give rise to a tetracyclic product having deuterium on C-14. Alternatively the cationic intermediate (91) may induce a concerted methyl-hydride rearrangement to the rosane (or enantiorosane) skeleton. This rearrangement has been observed[40,41] *in vitro* by the isolation of the rimuene isomer (94) from the products obtained on formic acid treatment of manool (85). In addition, the C-13 epimeric $\Delta^{8,15}$-pimaradienes (86) have been independently shown[41] to yield the corresponding $\Delta^{5(10),15}$-rimuene (94).



82



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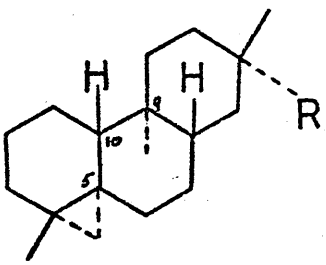
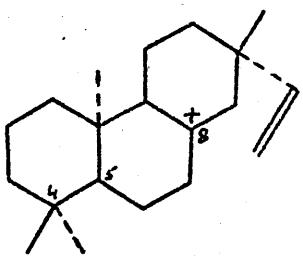


97 R= $CH{=}CH_2$

98 R= $CH(OH){\cdot}CH_2OH$



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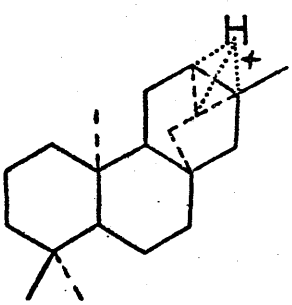
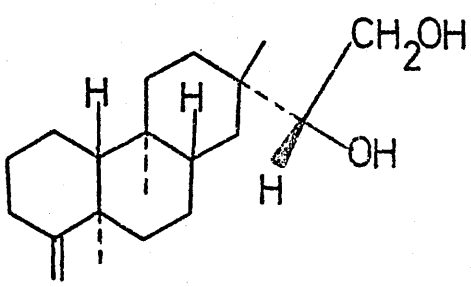
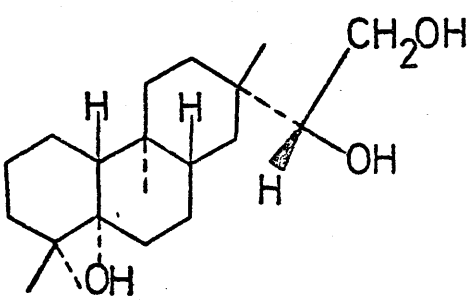


81



99

100 Δ^3-isomer



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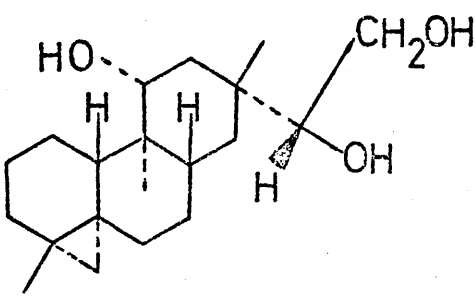
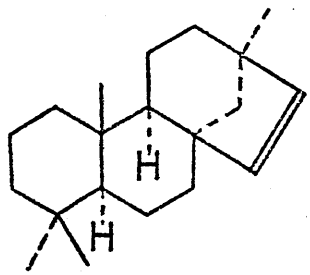


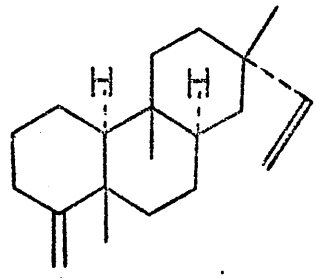
102

Evidence derived from examination of the stereochemistry of constituents from the same botanical source may be quoted in support of this biogenetic scheme. Thus Erythroxylon monogynum furnishes the hydrocarbons[43] $\Delta^{8(14),15}$-pimaradiene, (+)-hibaene, atisirene (82) [and isoatisirene (96)], and the rearranged hydrocarbon, devadarene (97). These skeletal types can be formally related through the carbonium ions (91) and (81). Devadarene, together with the related erythroxydiols X[44-46] (98), Y[44,46] (99) and Z[44] (100) and the erythroxytriols P[47] (101) and Q[46,47] (102), can in principle be derived from the ion (91) by an extensive backbone rearrangement. If, after rearrangement, the methyl migration from C-4 to C-5 is incomplete, deprotonation generates the cyclopropane ring. Confirmation of the enantiorosane skeleton in these compounds has been derived from a correlation[44] of the erythroxydiols with rosenonolactone and independently by X-ray analysis[48].

It is interesting to compare the constituents of E. monogynum with those of Thujopsis dolabrata since in both cases similar tetracyclic and tricyclic compounds have been isolated. In the former, (+)-hibaene and erythroxydiol Y have the same stereochemistry at 13 as expected but surprisingly (-)-hibaene (14 antipode) and dolabradiene[49] (103), from T. dolabrata, although having the same absolute stereochemistry (enantiomeric with that from E. monogynum), differ in their configurations at C-13.



14-antipode



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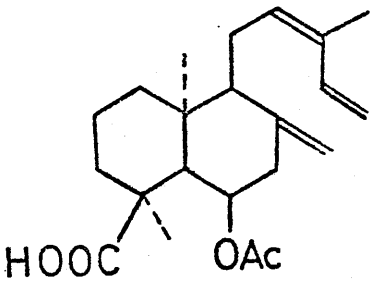
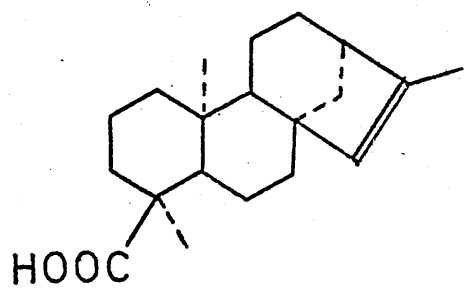


104



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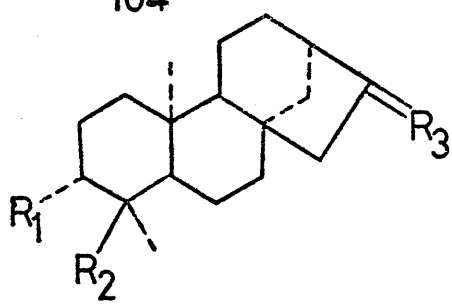
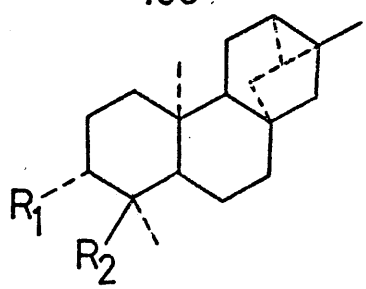




105 R_1=H, R_2=CH_3, R_3= α-CH_3,β-OH

106 R_1=OAc, R_2=COOH, R_3=CH_2

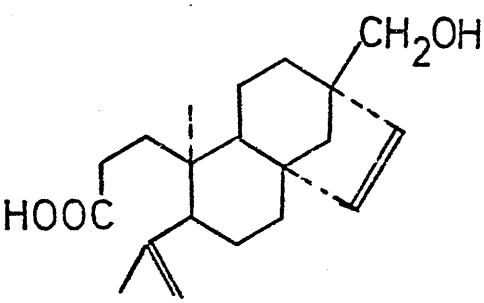
107 R_1=H, R_2=COOH, R_3=CH_2

109 R_1=H, R_2=CH_2OH

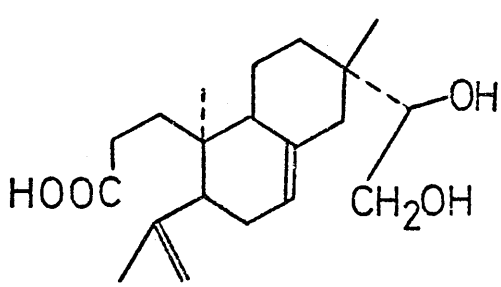
110 R_1=OH, R_2=COOH

111 R_1=OAc, R_2=COOH

112 R_1=H, R_2=COOH



51

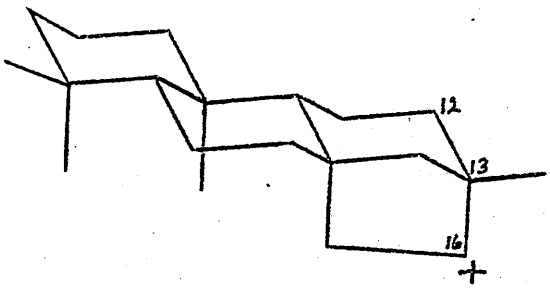


59

This has been proved by a direct comparison[14] of the tetracyclic hydrocarbons and by a correlation[50] of erythroxydiol Y with dolabradiene. This suggests that formation of the presumed pimaradiene precurson in T. dolabrata is non-stereospecific and that each pimaradiene is metabolised in the biosynthesis of only one of the two compounds (14 antipode) and (103).

Examples of bicyclic and tetracyclic diterpenoids, or tricyclic and tetracyclic diterpenoids (although not all three skeletal types) occurring together are known. This is not unexpected if such compounds follow a common biogenetic pathway. Thus labdenoid (bicyclic) (104), kaurenoid (tetracyclic) (105-108) and trachylobanoid (pentacyclic) (109-112) constituents have been isolated[51] from Trachylobium verrucosum. Again, the unusual 3,4-secobeyerene[17,24] (51), from Beyeria leschenaultii, has a close parallel in the 3,4-secopimarene (59) which has been isolated[26] from B. brevifolia. A further example of diterpenoids with the labdane and kaurane skeletons occurring naturally has been found in the Australian Euphorbiaceae[52]. These, in many cases, not only possess the same relative stereochemistry but also have the same oxygenation pattern[51]. Thus the kaurene and beyerene diterpenoids from Helichrysum dendroideum[16] have oxygen functions at 3, 17 and 18 as well as the trans fused A/B ring fusion.

The structural relationship of the hibaene (beyerene) skeleton to those of kaurene, atisirene and trachylobane has been



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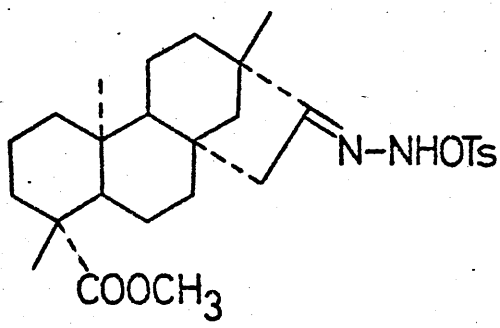

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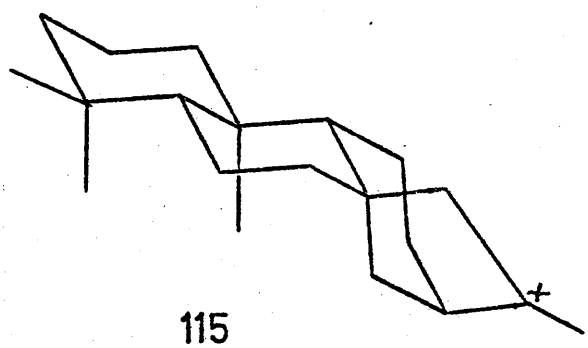

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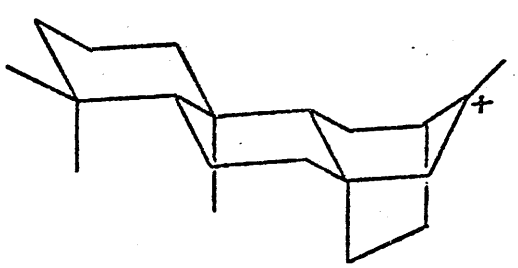

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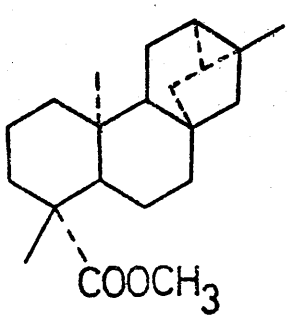
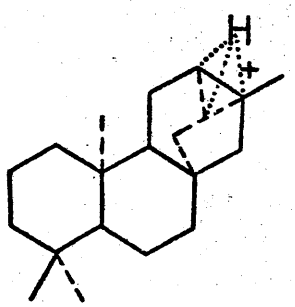


118

demonstrated chemically by their acid catalysed interconversions. Thus treatment[53,54] of (+)-hibaene with dry hydrogen chloride resulted in the formation of kaurene-isokaurene and atisirene-isoatisirene. The product mixture can be considered as resulting from rearrangement induced by a formal cationic centre at C-16. Thus the ion (114) on migration of the C 12-C 13 bond would yield the thermodynamically more stable tertiary carbonium ion (115). This latter species on deprotonation can give rise to the major products, the kaurene-isokaurene mixture. If, however, a 1,3 hydride shift (from C-12 to C-16) occurs in the proposed ion (114) followed by a migration of the C 13 - C16 bond to the centre of electron deficiency now at C-12, the tertiary carbonium ion (116) would result. This could then yield the atisirene-isoatisirene mixture. The proposed mechanism would also account for the results obtained on solvolysis of the toluene-p-sulphonates of substituted 16β-hydroxy-beyeranes[55] as well as the boron trifluoride catalysed opening of substituted beyerane-15(16)-epoxides[56,57]. The conversion of a hibane system to a trachylobane skeleton requires more energetic conditions. This would be expected since a cyclopropane ring is generated. Thus the decomposition[58] of the tosylhydrazone of isosteviol methyl ester (117) gave methyl trachyloban-18-oate (118) together with methyl kauren-18-oate and methyl isokauren-18-oate. The trachylobane-hibaene[59] and kaurene-hibaene[57] rearrangements have also been reported. Thus trachylobane,

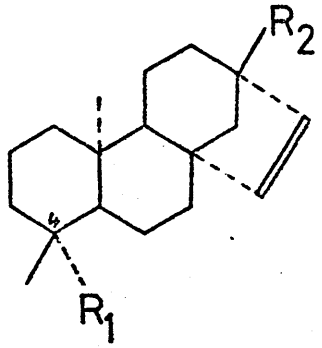


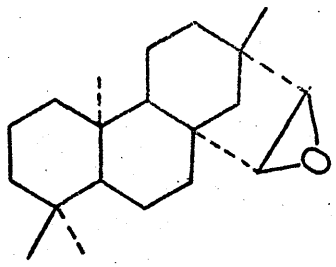
81

on treatment with acetic acid/acetic anhydride in the presence of perchloric acid, yielded the beyerane, kaurane and atisane carbocyclic skeletons. Kaurene in refluxing xylene with iodine as catalyst gave hibaene. It has been observed that the composition and nature of the products formed in these and related interconversions (atisirene-kaurene and trachylobane-atisirene)[54] vary both with substrate and with the conditions employed. This suggests that equilibrium between the different skeletal types is not readily attained and eliminates the possibility of a common ionic intermediate. Hence the non-classical ion (81), proposed in their biogenesis, cannot, at least in vitro, exist to any appreciable extent.

It would therefore appear from in vitro interconversion of the polycyclic diterpenoids and from evidence derived from co-occurring metabolites that the biogenetic pathway proposed is substantially correct, even although biosynthetic evidence is at present lacking.

2. The Constituents of *Erythroxylon monogynum* Roxb.



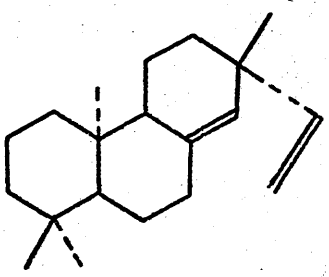


35

14 $R_1=R_2=CH_3$

15 $R_1=CH_2OH$, $R_2=CH_3$

23 $R_1=R_2=CH_2OH$



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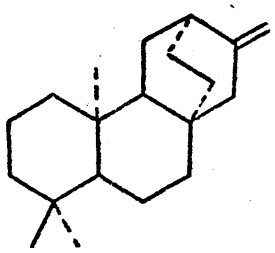
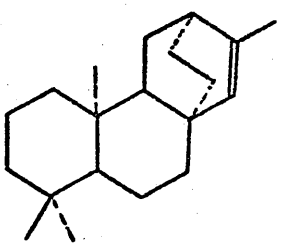


82

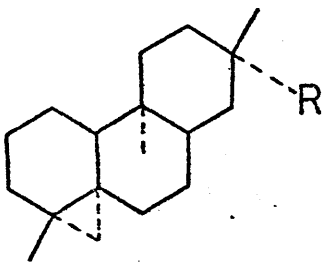


96

The constituents of Erythroxylon monogynum Roxb., a small tree native to Ceylon and certain areas of India[60], have in recent years been the subject of much investigation. Two groups of workers, one in Glasgow, the other in Poona, have shown the timber to be a rich source of diterpenoids conforming to the beyerane and enantiorosane skeletal types.

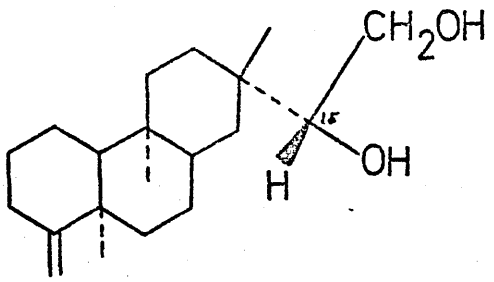
When the present study was commenced four diterpenoids of the beyerane type had been positively identified. These constituted a hydrocarbon [(+)-hibaene[11,12,14] (14)], an epoxide [(+)-hibaene epoxide[14,21,22] (35)], an alcohol [erythroxylol A[11,12] (monogynol[13,14])(15)], and a diol [erythroxydiol A[11,12] (hydroxymonogynol[14])(23)]. The hydrocarbon was identified by correlation[12,14] with both (+)-stachene and (-)-hibaene, whereas the epoxide could be readily synthesised[14,22] by treatment of (+)-hibaene (14) with either perbenzoic acid or monoperoxyphthalic acid. The structure of the diol (23) was confirmed by a direct comparison[14] of the derived dihydro-diacetate with an authentic sample[1] of 17,18-diacetoxybeyerane. Identification of erythroxylol A[12] was effected by (a) reduction of the alcohol to the corresponding hydrocarbon (14), and (b) defining the position and orientation of the hydroxymethyl group as C-4 and axial from spectral and pK^{*}_{mcs} (cf. isosteviol[7]) measurements.

In addition to (+)-hibaene, the hydrocarbon fraction was later shown[42] to contain $\Delta^{8(14),15}$-pimaradiene (72),



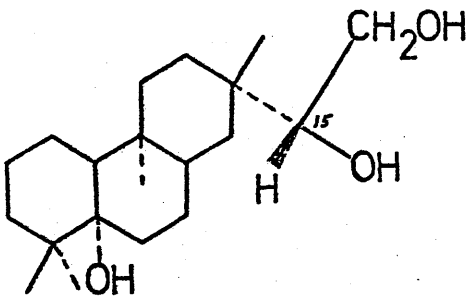
97 R= $CH=CH_2$

98 R= $C^{15}H(OH)\cdot CH_2OH$



99

100 Δ^3 - isomer



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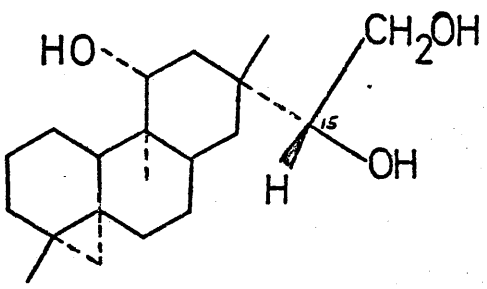

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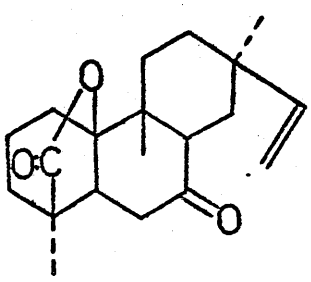

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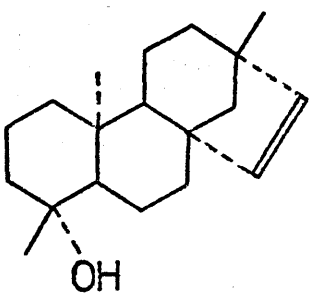
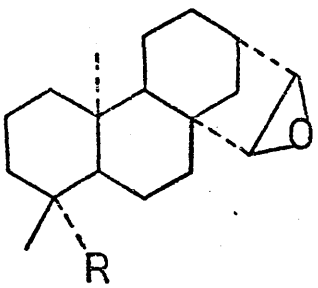


119

atisirene (82), isoatisirene (96) and the rearranged pimaradiene, devadarene (97). The occurrence of five diterpenoids related to devadarene has also been reported. These are erythroxydiol X[43-45] (98), erythroxydiol Y[43,45] (99), and erythroxydiol Z[43](100) and the erythroxytriols P[46] (101) and Q[45,46] (102), the latter occurring naturally as its 11α-acetate. The enantiorosane skeletons have been confirmed by correlation[43] with rosenonolactone (80) and the position of the cyclopropane ring in (97), (98) and (102) determined conclusively by X-ray analysis[47]. The X-ray structure analysis also served to define the stereochemistry about C-15 of the hydroxylated side chain.

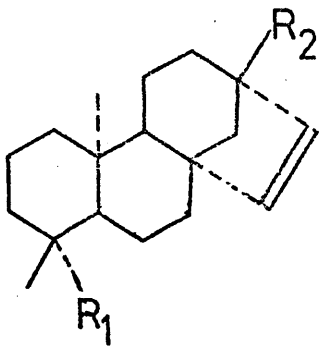
The following discussion concerns the structural elucidation of five new Beyeranes isolated, as further constituents, from the light petroleum extractive of this timber.

Chromatography of the crude extract[12] over alumina and elution with light petroleum gave a hydrocarbon fraction from which (+)-hibaene was isolated. On increasing the polarity of the eluant [ether-light petroleum (1:3) and (1:1)] a complex oily mixture[12] was obtained which contains (+)-hibaene epoxide. This mixture, after further chromatography[22], gave 4α-hydroxy-18-norhibaene[22] (119), b.p. 90°/0·02mm., $[\alpha]_D$+25°, and a less complex mixture from which, after preparative t.l.c. and crystallisation from methanol, erythroxylol A acetate epoxide[22] (120), m.p. 143·5-145°, $[\alpha]_D$+14·5°, was isolated.



120 $R=CH_2OAc$

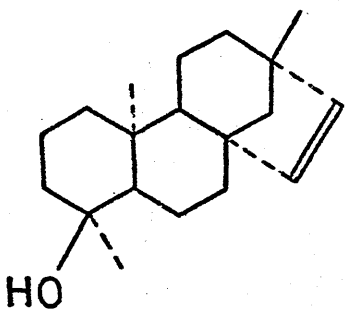
124 $R=CH_2OH$



15 $R_1=CH_2OH$, $R_2=CH_3$

122 $R_1=CH_3$, $R_2=CH_2OH$

123 $R_1=CH_2OAc$, $R_2=CH_3$

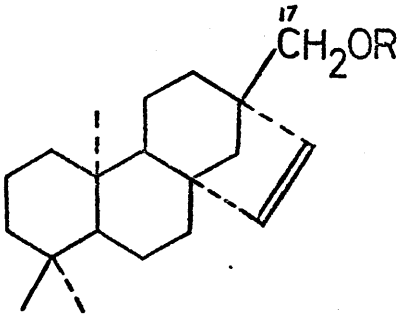


121

Subsequent elution of the crude extract[12] with ether afforded the largest single (crystalline) fraction which on crystallisation from pentane gave erythroxylol A (15). Gradient elution chromatography[12] of the mother liquors yielded initially erythroxylol A with traces of 4β-hydroxy-18-norhibaene[22] (121), then a second diterpene alcohol, erythroxylol B[12] (122), m.p. 121·5-123°, $[\alpha]_D$+67°. The nor-alcohol (121), m.p. 114-116°, $[\alpha]_D$+49°, present in only very small amounts in the extractive was isolated in the following way[22]. Repeated removal of erythroxylol A from the crude crystalline chromatographic fraction then mild acetylation of the mother liquors (such that only the primary alcohol reacted) gave the now easily separable mixture of the nor-alcohol (121) and the far less polar erythroxylol A acetate[11,12] (123). From the compounds more polar than erythroxylol B [methanol-ether (1:99)], but less polar than the erythroxydiols[43], erythroxylol A epoxide[22] (124), m.p. 115-116·5°, $[\alpha]_D$+18·5°, was obtained.

Erythroxylol B.

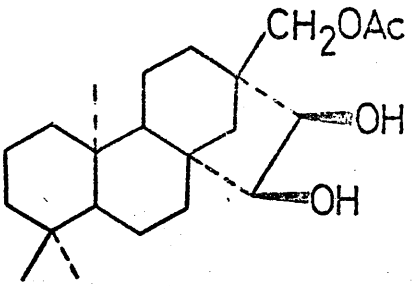
Erythroxylol B (122), has analytical and mass spectral data (parent m/e 288) in accord with the molecular formula $C_{20}H_{32}O$, isomeric with erythroxylol A. That it possessed a hibaene skeleton having one methyl oxygenated appeared likely from its n.m.r. spectrum which shows, in addition to three quaternary methyl signals [3H, s, τ 9·25, 9·18 and 9·13], an AB quartet [2H, τ 6·52 and 6·50, J 10 c./sec.] attributed to a hydroxymethyl



122 R=H

125 R=Ts

126 R=Ac



127

group[61]. A second quartet [2H, τ 4·45 and 4·20, J 5·5 c./sec.], indicative of a cis-disubstituted cyclopentene ring[62], is characteristic of the olefinic bond in the beyerene skeleton[12]. Further, since neither of these quartets evidence any additional coupling, it may be concluded that the allylic carbon atoms of the double bond are fully substituted and that the primary hydroxyl function is attached to a tertiary centre. This latter conclusion is substantiated by the mass spectrum which, lacking a peak due to the loss of water, exhibits a significant peak at m/e 257 (M-31) attributed to the loss of CH_2OH[63].

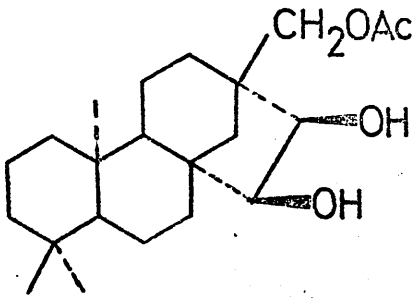
Confirmation of the (+)-hibaene skeleton was obtained[11,12] by lithium aluminium hydride reduction of the derived toluene-p-sulphonate (125) which partially regenerated the parent alcohol and also afforded a hydrocarbon, identical in all respects with an authentic sample of stachene.

That erythroxylol B is 17-hydroxyhibaene can be deduced from the following oxidative sequence[12] which related the hydroxymethyl grouping to the ethylenic bond[1]. Osmylation of erythroxylol B acetate (126) in ether resulted in the formation of only one triol monoacetate (127)[CH_2OAc, ABq, τ 6·10 and 5·81, J 11 c./sec.] which, lacking signals in the vinyl region, shows a new quartet [2H, τ 6·21 and 5·80, J 7 c./sec.] consistent with the partial structure $-\overset{|}{C}\cdot CH(OH)\cdot CH(OH)\cdot\overset{|}{C}-$. It was found

that the best method* of work up was as follows. The ether solution was concentrated by careful evaporation under reduced pressure, diluted with benzene then hydrogen sulphide passed in for 1 to 2 hours until the solution was saturated. Nitrogen was then passed through the solution to remove excess hydrogen sulphide. This appeared to accelerate the coagulation and precipitation of the osmium sulphide since the resulting clear solution could be decanted. Filtration of the solution and evaporation of the solvent gave crystalline material which yielded the desired product (71%) after chromatography to remove small amounts of a more polar product.

The infra red spectrum of (127) is interesting since it shows both free and intramolecularly hydrogen bonded hydroxyl [$\nu_{max}(CCl_4)$ 3632, 3504 and 3445 cm.$^{-1}$] and carbonyl [ν_{max} 1744 and 1719 cm.$^{-1}$] bands. That osmylation had occurred on

*This work up in benzene is superior to more usual procedures since these can give rise to colloidal osmium sulphide which is difficult to remove. It was also found that work up of the reaction mixture with aqueous sodium bisulphite resulted in the isolation of a greenish foam, presumably the osmate ester. This material (only readily soluble in chloroform and benzene) on H_2S work up in benzene gave rise to a mixture containing predominantly the triol monoacetate (127).



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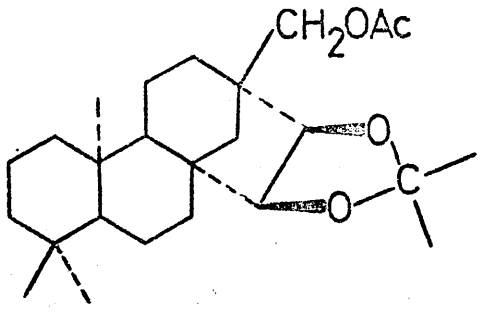

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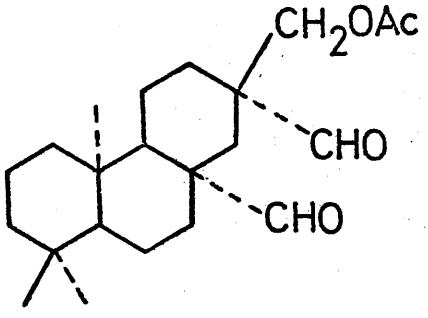

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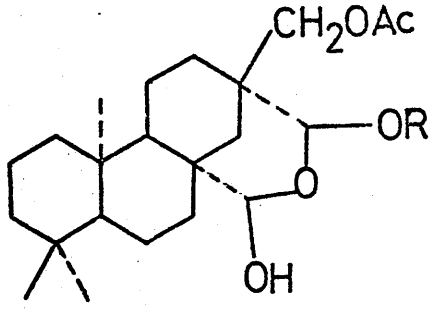
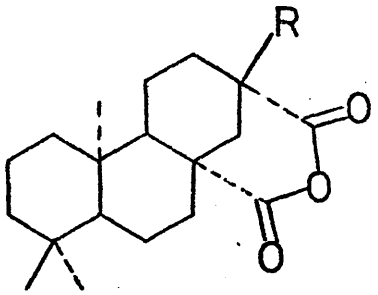


130 R=H or CH_3

the less hindered β-face is probable since the corresponding acetonide acetate (128) [$(C\underline{H}_3)_2C$=, 3H, s, τ 8·73 and 8·59; -C<u>H</u>(OR)-C<u>H</u>(OR)-, 2H, ABq, τ 5·80 and 5·42, J 6 c./sec.: ν_{max} (CCl_4) 1742 cm.$^{-1}$ (acetate)] was readily formed at room temperature by treating the diol (127) with anhydrous copper sulphate in acetone. Examination of molecular models suggests that more forcing conditions would be required to form the extremely hindered α-acetonide if, indeed, it would form at all.

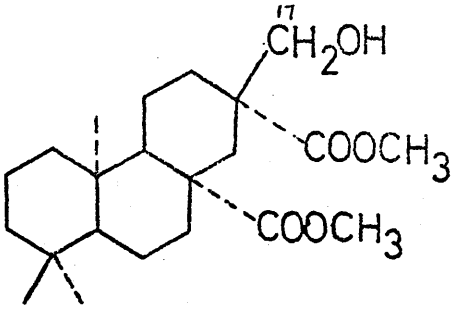
Cleavage of the diol (127) with sodium periodate generated the unstable acetoxy-dialdehyde (129) [two 1H singlets, τ 0·68 and 0·26 (CCl_4): ν_{max}(CCl_4) 1753, 1228 (acetate) and 1725 cm.$^{-1}$ (aldehyde)] which is best kept at 0° under nitrogen. The aldehyde resonance at τ 0·68 is high for an axial grouping[64] but since the original double bond was of the beyerene type, both aldehyde groups must of necessity be axial. The dialdehyde is formed in the reaction together with an unidentified more polar (t.l.c.) compound. Sublimation of the crude reaction products yielded solely the dialdehyde, while the residue contained a higher proportion of aldehyde than the initial mixture. This would suggest that this second product is a hydrate or methanol adduct of the type (130), which, on thermal treatment, can regenerate the acetoxy-dialdehyde (129).

Jones oxidation of the dialdehyde or alternatively the acetoxy-diol (127) afforded a product whose infra red spectrum



131 R=$\overset{17}{C}H_2OAc$

136 R=H



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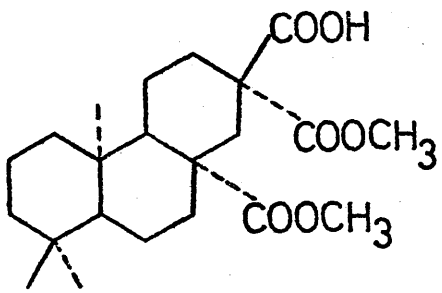

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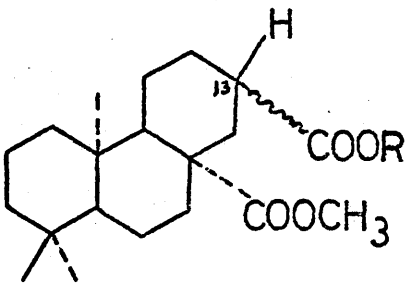
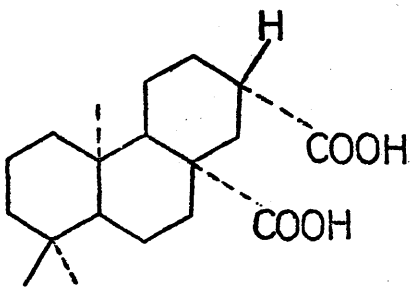


134 R=CH_3

134a R=H



135

[$\nu_{max}(CCl_4)$ 1803, 1766 (anhydride), and 1758 cm.$^{-1}$ (acetate)] showed it to be the substituted glutaric anhydride (131) rather than the corresponding dicarboxylic acid. That the cyclic anhydride was obtained, furnished additional proof for an unsaturated five-membered ring in erythroxylol B.

Base catalysed hydrolysis of the acetoxy-anhydride gave the corresponding hydroxy-dicarboxylic acid as a foam. Treatment with diazomethane and preparative t.l.c. gave the crystalline dimethyl ester (132) [$(CH_3OCO)_2$, 3H, s, τ6·46 and 6·35] which exhibits intramolecular hydrogen bonding to one of the methoxycarbonyl groups [$\nu_{max}(CCl_4)$ 3640 and 3540 (hydroxyl), and 1728 and 1706 cm.$^{-1}$ (ester)]. Additional evidence that hydrolysis of the acetoxy grouping had also occurred was obtained from the n.m.r. spectrum, where it was noted that the signals from the C-17 methylene protons had altered from a quartet [2H, τ5·99 and 5·61, J 10 c./sec.] in the acetate (131) to a singlet [2H, τ6·62] at higher field in the alcohol (132). Oxidation of (132) with Jones reagent generated the carboxylic acid (133), which shows a broad asymmetric carbonyl band in the i.r. spectrum [ν_{max} 1725 cm.$^{-1}$; $\Delta_{\nu\frac{1}{2}}$ 60 cm.$^{-1}$]. Decarboxylation of this substituted malonic acid half-ester (133) readily occurred on pyrolysis at or above its melting point, giving only one of the possible C-13 epimeric nor-diesters (134) [ν_{max} 1722 cm.$^{-1}$; $\Delta_{\nu\frac{1}{2}}$ 35 cm.$^{-1}$] which shows two methoxycarbonyl signals in the n.m.r. [3H, s, τ6·47 and 6·38].

It was found that the decarboxylation could be conveniently carried out in a partially evacuated sublimation tube. After approximately five minutes, bubbles, presumably carbon dioxide evolution, could no longer be observed in the melt. Re-evacuation of the tube permitted sublimation to occur so that the product could be readily isolated.

In an attempt to determine the stereochemistry at C-13 for the nor-diester (134), it was assumed that ring cleavage, under mild conditions, of the derived anhydride (136) would lead to the diaxial acid (135). Esterification would then give an ester identical to, or epimeric with, that obtained in the decarboxylation step. It was found, however, that saponification of (134) in either aqueous methanol or aqueous dioxan resulted in the formation of more than one product (two elongated overlapping spots on t.l.c.). Since further base treatment produced no change in product composition (t.l.c.) it was assumed that hydrolysis was complete. The i.r. spectrum of this mixture shows a broad hydrogen bonded absorption between 3480 and 2500 $cm.^{-1}$ characteristic of a carboxylic acid function. However, the n.m.r. spectrum shows two singlet signals at τ 6·48 and 6·33 (CCl_4), which together integrate for three hydrogens. This would imply that a very hindered ester grouping is still present[10] in each product. It would therefore seem plausible that base has induced hydrolysis at the less hindered C-13 methoxycarbonyl group together with epimerisation at that

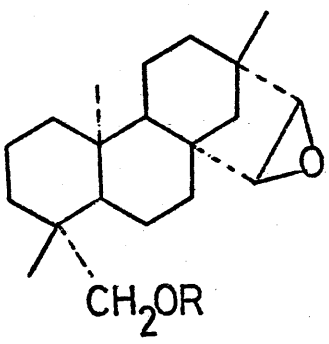
centre. Hence the two signals in the n.m.r. can be attributed to the same axial ester grouping which is situated in two magnetic environments, one with the carboxylic acid (at 13) equatorial, the other with the acid axial.

The identity of erythroxylol B having been satisfactorily confirmed, further attempts to identify the components of the hydrolysis mixture were abandoned.

Two Diterpene Epoxides.

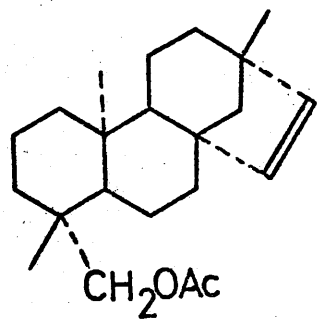
During the isolation of erythroxylol B it was noted that four minor constituents, later shown to be two epoxides and two tertiary alcohols, gave a characteristic colour reaction on t.l.c. After spraying the t.l.c. plates with a solution of ceric ammonium sulphate in dilute sulphuric acid followed by heating in an oven, these four compounds each stained a vivid transient blue.

From the spectral features of compounds (124), $C_{20}H_{32}O_2$, and (120), $C_{22}H_{34}O_3$, it was evident that both were naturally occurring epoxides since both show absorption at 850 $cm.^{-1}$ (CCl_4) in the i.r. In addition, their n.m.r. spectra (CCl_4) show AB quartets at τ 7·17 and 6·80, and τ 7·14 and 6·76 respectively (J 3 c./sec.) similar to those found[14,22] for (+)-hibaene epoxide. Epoxide (124), showing C-methyl resonances at τ9·09, 9·09 and 9·03, and epoxide (120), showing methyl signals at τ 9·05, 9·04 and 9·02, differ in that the former is an alcohol [ν_{max} 3625 and 1020 $cm.^{-1}$: CH_2OH, ABq,



120 R=Ac

124 R=H

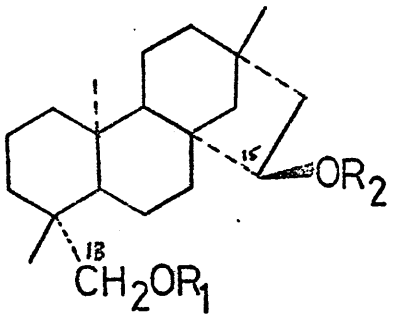


123

τ 6·63 and 6·39, J 11 c./sec.] and the latter an acetate [ν_{max} 1743 and 1243 cm.$^{-1}$: CH_2OAc, ABq, τ 6·17 and 5·80, J 11 c./sec.; $OCOCH_3$, τ 8·04]. An additional feature of both n.m.r. spectra is the high-field signals which constitute the upper half of an AB quartet. These at τ 9·58 (J 11 c./sec.) in (124) and τ 9·57 (J 11 c./sec.) in (120) can be attributed[65] to the 14α-proton of the beyerane skeleton which is shifted upfield due to the shielding effect of the epoxide ring.

Interrelation of these two compounds was easily effected since lithium aluminium hydride reduction of the acetate (120) generated the alcohol (124) almost quantitatively. The structure and stereochemistry of the epoxides follow from the synthesis of (120). Erythroxylol A acetate (123), when kept with m-chloroperbenzoic acid, is transformed into the corresponding epoxide in high yield. This proved to be identical to the epoxide of natural provenance by comparison of spectra, mixture melting point and optical rotation. The formation of the β-epoxide is predicted[1] since oxidation should take place on the less hindered side of the double bond.

The epoxide (124) is completely stable to lithium aluminium hydride in refluxing tetrahydrofuran. Ring opening can be effected only by adding lithium aluminium hydride to a solution of the epoxide in ether, allowing the ether to distill off, then fusion of the resulting mixture overnight. In this way, one diol, m.p. 212-213°, is formed. This diol (137), derived

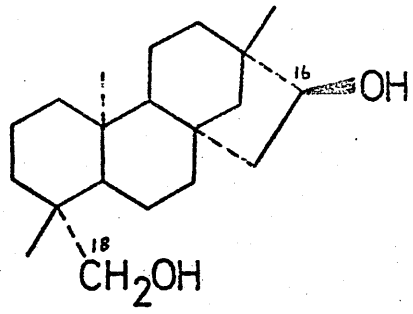


137 $R_1=R_2=H$

141 $R_1=R_2=Ac$

142 $R_1=Ac$, $R_2=H$

143 $R_1=H$, $R_2=Ac$



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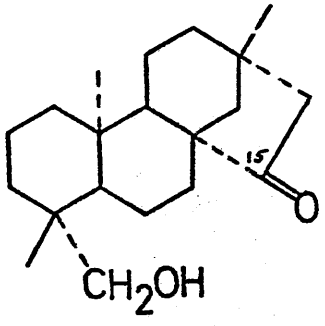

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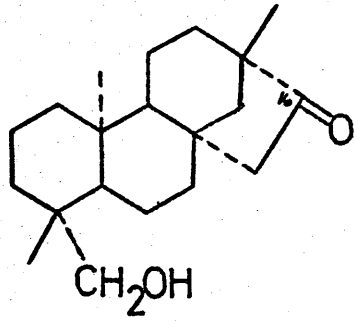
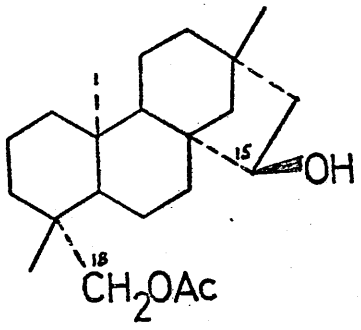


140

from erythroxylol A epoxide, proved to be identical to one of the products (15β,18-dihydroxyhibane) obtained on hydroboration of erythroxylol A; the other hydroboration product was formulated as the 16β,18-diol (138). Since only the 15β,18-diol was obtained from (124), this is consistent with trans opening of the epoxide ring with hydride attack at the sterically more accessible 16-position of the hindered α-face.

Allocation of structures (137) and (138) for the two diols from hydroboration followed from the optical rotatory dispersion curves of the derived 15-ketone (139) and 16-ketone (140) which were found to be similar both in shape and magnitude, but opposite in sign, to the values quoted[10] for the 15- and 16-keto-(-)-hibanes of known structure and configuration. Acetylation of the 15β,18-diol (137) with acetic anhydride and pyridine afforded a mixture which, after repeated preparative t.l.c., gave four major products, including recovered starting material. Of the acetylated material, the least polar product (t.l.c.) was the 15β,18-diacetate (141) (23%, based on diol consumed) whose structure follows from analytical ($C_{24}H_{38}O_4$) and spectral [ν_{max} 1725 cm.$^{-1}$] data. Thus the n.m.r. spectrum shows a singlet at τ7·97 (6H), an AB quartet at τ6·15 and 5·80 (J 11 c./sec.) and two broad, unresolved, low-field signals at τ4·79 and 4·67 (1H) consistent with the presence of primary and secondary acetoxy groups. The two isomeric monoacetates, both analysing for $C_{22}H_{36}O_3$, can be distinguished from their spectral features. The less polar 15β-hydroxy-18-acetate (142) (40%)



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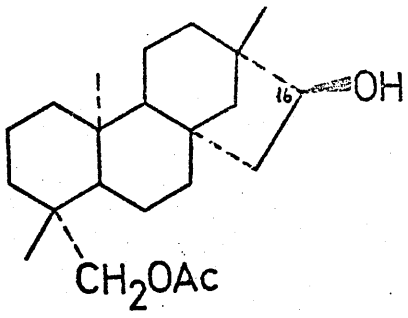

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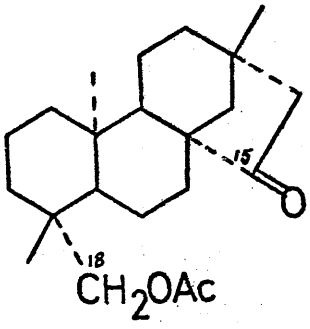
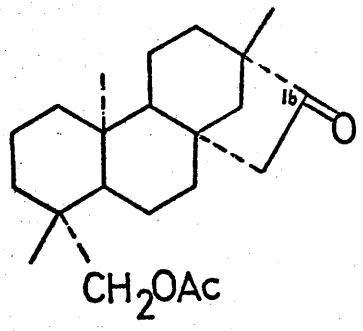


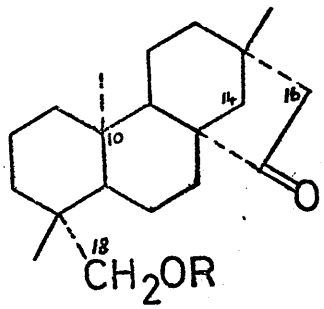
144



146

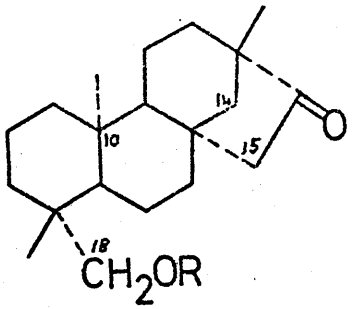
[ν_{max} 1730 cm.$^{-1}$] shows in the n.m.r. a three proton singlet at τ 7·97 [$\underline{CH}_3OCO$] and an unresolved multiplet at τ 5·75 [$\underline{CH}(OH)$] superimposed on the signals attributed to the C-18 methylene-acetoxy group [$\underline{CH}_2OAc$, ABq, τ6·19 and 5·77, J 11 c./sec.]. The more polar, isomeric primary alcohol (143) (10%) also shows the features of an acetoxy function in the i.r. [ν_{max} 1725 cm.$^{-1}$] and n.m.r. [3H, s, τ7·99] spectra. Here, however, the 15α-proton gives rise to two unresolved signals at much lower field [τ 4·78 and 4·65] whereas the C-18 methylene protons appear at τ 6·59 and 6·29 (ABq, J 10·5 c./sec.) consistent with the assignment of a primary alcohol group.

Jones oxidation of the 15β-alcohol (142) gave the corresponding 15-ketone (144) [ν_{max} 1728 cm.$^{-1}$] which shows the C-18 methylene protons at τ 6·10 and 5·68 (ABq, J 11 c./sec.) in the n.m.r. Similar treatment of the 16β-alcohol (145) yielded the more polar 16-ketone (146) whose spectral features [ν_{max} 1732 cm.$^{-1}$: $\underline{CH}_2OAc$, ABq, τ6·12 and 5·76, J 11 c./sec.] are similar to those of the 15-isomer (144), and illustrate the close structural relationship between the two ketones. Comparison of the i.r. carbonyl frequencies and chromatoplate mobilities of (144) and (146) with those quoted[10] for the corresponding ketones derived from (-)-hibaene lend support to the structures postulated. Regeneration of the free hydroxyls from (144) and (146) was effected, in each case, by hydrolysis in refluxing aqueous methanol. These isomeric ketols thus formed again show similar spectral features. Thus the



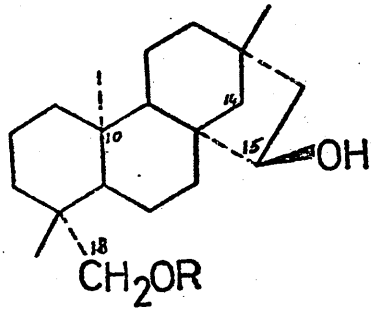
139 R=H

144 R=Ac



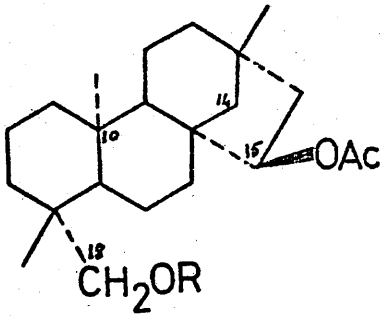
140 R=H

146 R=Ac



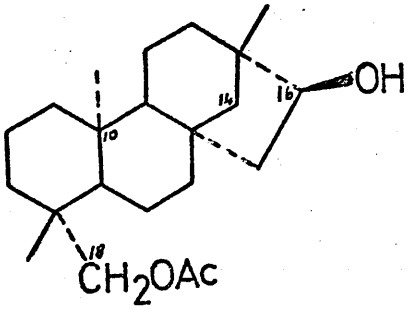
137 R=H

142 R=Ac



141 R=Ac

143 R=H



145

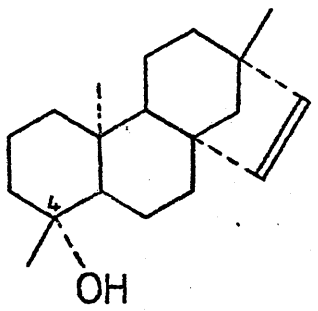
15-keto-alcohol (139) shows in the i.r. both hydroxyl and carbonyl frequencies at 3624 and 1723 cm.$^{-1}$ respectively, as does the 16-keto-isomer (140) [ν_{max} 3622 and 1730 cm.$^{-1}$]. The rotatory dispersion curves obtained for the ketols (139) and (140) prove beyond doubt the identity of these isomeric compounds and hence prove the structures of the diols from which they were derived.

A significant feature of these ring D functionalised compounds, is the marked deshielding of the 15α-proton observed in the n.m.r. spectra. Thus the signals attributed to the 15α-proton in the 16-keto-18-acetate (146) and the 16-keto-18-alcohol (140) appear, in each case, as half of a geminally coupled quartet at τ 7·34 and 7·32 (J 19 c./sec.) respectively. These signals have, in addition, a smaller although significant coupling of approximately 1·5 c./sec. The up-field half of these quartets (due to the 15β-proton) is obscured by the methylene envelope. By comparison, the C-16 protons of the corresponding 15-ketones (144) and (139), which should also appear as an AB quartet, are observable only as unresolved multiplets at τ 7·99. As has been noted previously, the n.m.r. spectrum of the 15β,18-diacetate (141) and the 18-hydroxy-15β-acetate (143) both show the 15α-proton as two unresolved signals at τ 4·79 and 4·67, and τ 4·78 and 4·65 respectively. These signals are lower than might be anticipated [cf. the C-18 methylene protons in (141) centered

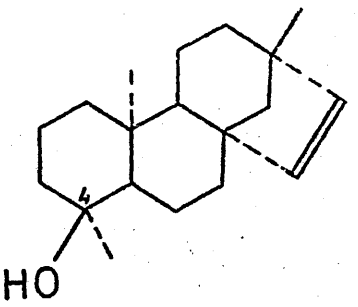
at τ5·97]. Again the 15α-protons of the 15β,18-diol (137) and the 15β-hydroxy-18-acetate (142) appear, in each case, as an unresolved signal at τ5·75. This is also lower than expected since the 16β-hydroxy-18-acetate (145) has the unresolved 16α-proton signal at τ6·26. These spectra show that the signals due to the 15α- and 16α-protons are broadened by the same small coupling observed in the 16-ketones (146) and (140). In all the above cases, the significant deshielding of the 15α-proton is attributed to the severe steric interaction that this hydrogen undergoes with the C-10 methyl group which is apparent on examination of molecular models. The small additional coupling observed is consistent with a long range effect from the 14β-proton through a co-planar W configuration[66]. This deshielding effect would appear to be characteristic of this particular type of system and provides additional proof of the β-orientation of the epoxide ring in (120) and (124). Thus one half of the signals (15α-H) attributed to protons on the cis-disubstituted epoxide ring are markedly deshielded.

Two Nor-diterpene Alcohols.

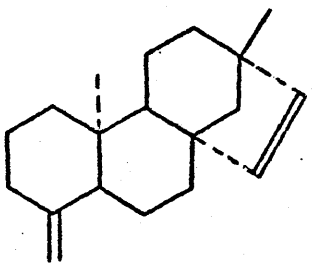
The close structural relationship between the two isomeric, $C_{19}H_{30}O$, nor-diterpene alcohols (121) and (119) [υ_{max} 3612 and 918, and 3613 and 935 cm.$^{-1}$ respectively], isolated from the E. monogynum trunkwood, was evident from their mass spectral fragmentation patterns. These were identical apart from minor differences in intensity of only a few peaks; in each case, one



119



121



150

151 Δ^3-isomer

152 Δ^4-isomer

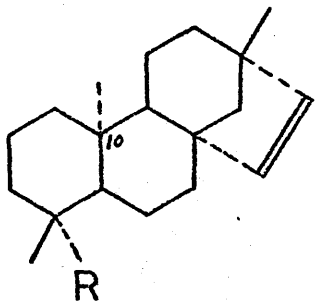
of the most intense peaks, at m/e 256, was indicative of a facile loss of water. Both compounds, being inert to acetylation and also lacking signals in their n.m.r. spectra attributable to carbinyl protons, must contain tertiary hydroxyl functions.

The n.m.r. spectrum of (121) shows an AB quartet [2H, τ 4·56 and 4·34, J 5·5 c./sec.] typical of the cis-disubstituted double bond of the hibaene skeleton in addition to three quaternary C-methyl resonances [3H, s, τ9·30, 9·01 and 8·68]. Similarly the isomeric alcohol (119) exhibits the same spectral features [2H, ABq, τ4·63 and 4·35, J 5·5 c./sec.; 3H, s, τ9·15, 9·04 and 8·91]. Since one methyl signal is down-field, in each case, it appeared likely that the compounds were the epimeric C-4 alcohols based on an 18-norhibaene skeleton.

Structural assignment of the isomeric alcohols was provided by the following dehydration experiments. Treatment of the alcohols with phosphoryl chloride and pyridine gave the same three isomeric $C_{19}H_{28}$ dienes (150), (151) and (152), but in different proportions. The diene (150), which could be separated from the two other isomers by preparative t.l.c. on silver nitrate-impregnated silica, was formulated as the $\Delta^{4(19),15}$-norhibaene. This is in accord with both i.r. [ν_{max} 3080 and 890 cm.$^{-1}$ (exomethylene)] and n.m.r. data. The latter spectrum shows two broad singlets at τ5·95 and 5·36 (1H each) together with only two tertiary methyl signals at τ9·44 and 9·00. The diene (152), exhibiting only the cis-disubstituted olefin signals [2H, ABq,

τ4·53 and 4·16, J 5·5 c./sec.] in the vinyl region of its n.m.r. spectrum and a vinylic methyl [τ8·41] was assigned the $\Delta^{4,15}$-18-norhibaene structure. The remaining diene (151) was separable from the tetrasubstituted isomer (152) only on g.l.c. Absorption around τ4·50, superimposed on the signals due to the hibaene double bond, is consistent with the presence of a trisubstituted double bond in this compound.

There is ample evidence[67,68] from dehydration studies on steroidal tertiary alcohols that, under similar experimental conditions, elimination with these reagents requires a co-planar transition state. By analogy, the isomer having the axially oriented hydroxyl group would, by a trans diaxial elimination of water, be expected to generate all three alkenes but with the most highly substituted isomer in predominance[68]. The epimeric alcohol, having an equatorial hydroxyl group with only the C-19 methyl hydrogens capable of an antiperiplanar configuration, should therefore yield mainly the compound having the exocyclic double bond. The alcohols were assigned configurations (119) and (121), since the $\Delta^{4(19),15}$, $\Delta^{3,15}$, and $\Delta^{4,15}$-dienes were formed in the ratios 1 : 1 : 12 and 2 : 1 : 1 respectively (as estimated from g.l.c.). The product ratios found probably reflect the relative amounts of the respective dienes actually formed in the reaction since the exocyclic diene (150) could be recovered completely unchanged after being resubmitted to the dehydration condition.

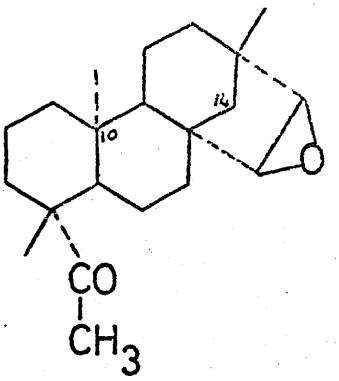


119 R=OH

153 R=$COCH_3$

154 R=CHO

155 R=$\overset{19}{C}H(OH)\cdot CH_3$



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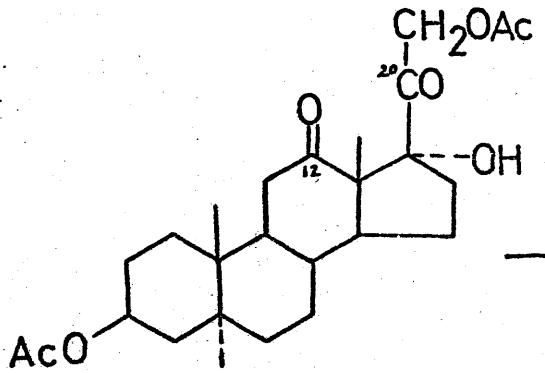
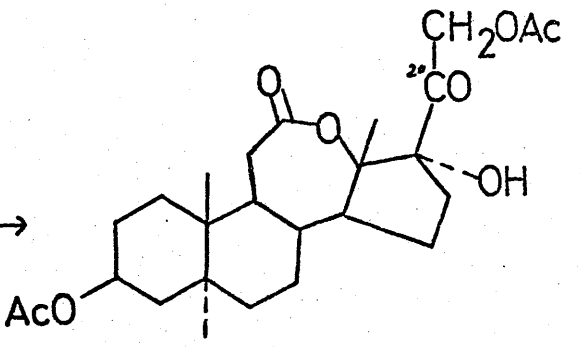


157



158

It was hoped that additional proof of structure could be obtained by a synthesis[22] of the axial alcohol (119) from erythroxylol A via a Baeyer-Villiger oxidation of the derived methyl ketone[22] (153). The aldehyde[12] (154) with methylmagnesium iodide was converted into a mixture which, after preparative t.l.c., yielded the methyl carbinol[22] (155) as major product. This on crystallisation from methanol gave a colourless solid, melting over 17°, consistent with its being a mixture of two compounds epimeric at C-18. This carbinol mixture [υ_{max} 3620 cm.$^{-1}$] shows in the n.m.r., a one proton quartet at τ5·71 (J 6 c./sec.) and a three proton doublet at τ8·98 (J 6 c./sec.) confirming the presence of the grouping $-\overset{|}{\underset{|}{C}}-CH(OH)-CH_3$.

Oxidation of the alcohol (155), which destroys the centre of asymmetry, resulted in the formation of one sharp-melting methyl ketone[22] (153). The latter compound exhibits, in addition to three quaternary methyl resonances at τ9·47, 9·01 and 8·94, a singlet at τ7·94 (3H) due to a methyl group adjacent to, and hence deshielded by, a ketonic function. The high-field resonance at τ9·47 is attributed to the C-10 methyl group which is diamagnetically shielded by both the carbonyl and olefinic centres. Surprisingly, the carbonyl group gives rise to two absorption bands in the i.r. [υ_{max} 1703 and 1696 cm.$^{-1}$] which may possibly be due to rapidly interconverting rotamers (ring A chair) or conformational isomers (ring A distorted boat and

chair) since the signals in the n.m.r. show no peak-broadening (for low temperature studies see p. 79).

Baeyer-Villiger oxidation of the methyl ketone (153) with m-chloroperbenzoic acid resulted in its quantitative conversion, after only ten minutes at room temperature, to the epoxy-ketone (156) [υ_{max} 850 cm.$^{-1}$], also formed in minor amounts during the oxidation of the methyl carbinol (155) with chromium trioxide[69,70] in aqueous acetic acid. In accord with the reduction in shielding of the 10-methyl group on epoxidation of the double bond, the three quaternary methyl signals now appear at τ 9·27, 9·00 and 8·90. In addition, signals at τ 7·12 and 6·70 (2H, ABq, J 3 c./sec.) are consistent with the presence of the β-epoxide ring, as are the high-field signals at τ 9·56 (J 11 c./sec.) due to the 14α-proton. Again the i.r. spectrum shows two bands at 1705 and 1698 cm.$^{-1}$, similar in nature to those observed for the methyl ketone (153). In an endeavour to induce the Baeyer-Villiger reaction, catalysis with sulphuric acid[71] was attempted. This has been found to be successful[72] for the oxidation of the 12-ketosteroids which are normally resistant to peracid. Even under these forcing conditions for conversion of (157) to (158) no reaction occurred at C-20 presumably due to a screening effect of the adjacent acetoxy function. Under these reaction conditions, the keto-epoxide (156) was converted into a complex mixture of polar compounds which probably emanate from the acid opening and

rearrangement of the epoxide ring. Since all of these products appeared in almost equal amounts (solely by t.l.c.), no separation or identification was attempted.

Although the partial synthesis of the nor-diterpene alcohol, via the methyl ketone (153), has not proved possible under Baeyer-Villiger conditions, the presence of the nor-alcohols (121) (4%) and (119) (trace) has been shown[22] in the complex product mixture resulting from treatment of erythroxylol A (15) with chromic acid in an acetic acid medium. The formation of these unexpected products which must arise from oxidative scission of the C 4 - C 18 bond will be discussed in greater detail in Section B.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Specific rotations refer to chloroform solutions at room temperature. I.r. solution spectra were invariably recorded in carbon tetrachloride (0·1 mm. cell) in the section dealing with the nor-diterpene alcohols. In the sections dealing with erythroxylol B and the epoxides, chloroform solutions were used unless otherwise stated. These spectra were recorded on Perkin-Elmer 257 and Unicam SP 100 Mark II spectrophotometers. In the section dealing with the nor-diterpene alcohols the n.m.r. spectra were invariably recorded in carbon tetrachloride solution. In the other sections, the n.m.r. spectra were recorded in deuteriochloroform unless otherwise stated. These spectra were recorded on Perkin-Elmer R-10 and Varian Associates HA-100 spectrometers using approx. 0·3m solutions and tetramethyl silane as internal standard. Mass spectra were recorded with AEI-GEC MS 12 mass spectrometer. Analytical g.l.c. separations were performed with Perkin-Elmer F 11 and Pye-Argon chromatographs using 2·5% SE 30 and 3% OV 22 columns respectively. Data were recorded with a LKB 9000 gas chromatograph-mass spectrometer by use of a 1% SE 30 column at 175°.

Woelm Grade I alumina (neutral) deactivated to the appropriate grade according to Brockmann, and Merck Grade H alumina was used for chromatography. Kieselgel G (Merck) was used for both analytical (0·25 mm.) and preparative (0·5 mm.) t.l.c.

T.l.c. plates were sprayed with a solution of ceric ammonium sulphate (5 g.) in concentrated sulphuric acid (50 ml.) diluted to 500 ml., and then warmed at 195° for approx. 3 min. Light petroleum refers to the fraction b.p. 40-60°. Solutions were dried over anhydrous magnesium sulphate.

Extraction Procedure.

Powdered trunkwood of Erythroxylon monogynum Roxb. (463 g.) was extracted in a Soxhlet apparatus with light petroleum. Evaporation of the solvent from the extractive left a near colourless, viscous oil (37·3 g.). A fraction (26·4 g.) of this was chromatographed over alumina (Merck, 375 g.) in light petroleum to give a non-polar fraction (790 mg.) from which (+)-hibaene (14) has been isolated. Increasing the polarity of the eluant [ether-light petroleum (1:3) and (1:1)] gave an oily complex mixture (2·55 g.) which yielded (+)-hibaene epoxide (35). Elution with ether afforded a series of crystalline fractions (12·95 g.) from which erythroxylol A (15) could be obtained after crystallisation from pentane. A series of more polar fractions (9·33 g.), containing the erythroxydiols and erythroxytriols, were obtained on elution with methanol-ether mixtures (up to 25% methanol).

A fraction (153 mg.), containing the material more polar than (+)-hibaene epoxide but less polar than erythroxylol A was adsorbed on alumina (Merck, 6 g.) in benzene. Elution with ether-benzene (1:9) gave 4α-hydroxy-18-norhibaene (119) (10 mg.),

b.p. 100-102° / 0·03 mm., $[\alpha]_D$+25° (c 0·31) [Found: M, 274 (mass spectrometry). $C_{19}H_{30}O$ requires M, 274]. The mass spectrum shows peaks at m/e 274, 256, 241, 189, 161, 135, 106, 105, 93, 91 and 81. Further elution with ether-benzene (1:9) followed by preparative t.l.c. [ethyl acetate-light petroleum (1:9)] gave erythroxylol A acetate epoxide (120) (34 mg.), m.p. 143·5-145° (plates from methanol), $[\alpha]_D$+14·5° (c 1·29) (Found: C, 76·15; H, 9·75. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%).

The mother liquors (9·39 g.) from the crystallisation of erythroxylol A were chromatographed over alumina (Merck, 350 g.) using gradient elution [ether-light petroleum (5 l., 3:1) dropping into ether-light petroleum (2 l., 1:9)] gave successively almost pure erythroxylol A (3·47 g.), a mixture (approx. 1:1) of erythroxylols A and B (3·43 g.) and a solid fraction (1·66 g.) which, after crystallisation as needles from n-heptane, gave erythroxylol B (122), m.p. 121·5-123°, $[\alpha]_D$+67° (c 1·17) (Found: C, 83·45; H, 11·25. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%).

A fraction (62 g.) containing mainly erythroxylols A and B was chromatographed on alumina (Merck, 2 kg.) in light petroleum-ether (3:1). Elution with ether yielded initially a mixture of erythroxylol A and a new compound having the same mobility on t.l.c. as erythroxylol B. Repeated crystallisation of erythroxylol A from the mixture, sufficiently enriched the

mother liquors in the new compound to effect its isolation. Separation of the latter by preparative t.l.c. [ethyl acetate-light petroleum (1:1)] on silver nitrate-impregnated silica, after acetylation with acetic anhydride and pyridine to remove the remaining erythroxylol A, gave 4β-hydroxy-18-norhibaene (121) (121 mg.), m.p. 114-116·5° (rods from light petroleum), $[\alpha]_D$+49° (c 1·41) (Found: C, 83·1; H, 11·05. $C_{19}H_{30}O$ requires C, 83·15; H, 11·0%). Continued elution with ether afforded erythroxylol A, followed by a mixture of erythroxylols A and B. Further elution with methanol-ether (1:99) gave a compound intermediate in polarity between erythroxylol B and the erythroxydiols. Purification by preparative t.l.c. [ethyl acetate-light petroleum (1:3)] afforded erythroxylol A epoxide (124) (415 mg.), m.p. 115-116·5° (rods from methanol), $[\alpha]_D$+18·5° (c 1·49) (Found: C, 78·65; H, 10·45. $C_{20}H_{32}O$ requires C, 78·9; H, 10·6%).

Osmylation of Erythroxylol B Acetate (126).

(i) Osmium tetroxide (200 mg.) in ether (5 ml.) was added to erythroxylol B acetate (176 mg.) in ether (5 ml.) and the mixture set aside at room temperature for 30 hr. After stirring with saturated sodium metabisulphite solution (10 ml.) for 4·5 hr., filtration and evaporation, a greenish foam (239 mg.) was obtained. This on dissolution in benzene (20 ml.), treatment with hydrogen sulphide, filtration through celite and evaporation gave a crystalline product (196 mg.) which after

chromatography over alumina (Woelm, grade 3, 12 g.) in ether-light petroleum (3:7) and elution with that solvent gave the triol-monoacetate (127) (129 mg., 66%), m.p. 151-153·5° (rods from methanol) (Found: C, 72·65; H, 9·7. $C_{22}H_{36}O_4$ requires C, 72·5; H, 9·95%).

(ii) Erythroxylol B acetate (1·73 g.) was treated with osmium tetroxide (1·5 g.) in ether (50 ml.) at room temperature for 60 hr. The bulk of the solvent was removed under reduced pressure, benzene (75 ml.) added and the solution saturated with hydrogen sulphide. Nitrogen was passed through the mixture for 1 hr. to remove excess hydrogen sulphide. This appeared to accelerate the coagulation and precipitation of the osmium sulphide leaving a clear liquid phase. The mixture was filtered through celite and the osmium residue and celite washed with ethyl acetate (50 ml.). Evaporation of the combined filtrates gave a solid product (1·93 g.), m.p. 143-153°, which, on chromatography over alumina (Woelm, grade 3, 100 g.) and elution as above, gave the triol-monoacetate (127) (1·36 g., 71%), m.p. 152-153·5° (after crystallisation).

Acetonide Formation.

The triol-monoacetate (127) (50 mg.) in AnalaR acetone (5 ml.) was stirred with anhydrous copper sulphate (50 mg.) for 14 hr. Filtration and evaporation of the solvent gave, after crystallisation from methanol, the triol-monoacetate acetonide (128) (46 mg.), m.p. 115-117·5° (Found: C, 74·1; H, 9·8. $C_{25}H_{40}O_4$

requires C, 74·2; H, 10·0%).

Oxidative Cleavages.

(i) The triol-monoacetate (127) (143 mg.) in methanol (45 ml.) was stirred with a solution of sodium periodate (112 mg.) in water (10 ml.) under nitrogen for 90 min. After dilution with water, the mixture was extracted thoroughly with ether. The combined extracts were dried and evaporated. The crude reaction mixture shows two major products as evidenced by t.l.c. [ethyl acetate-light petroleum (1:3)]. This on sublimation gave the less polar, unstable acetoxy-dialdehyde (129) (69 mg.), m.p. 125-126·5° (rods from light petroleum) (Found: C,72·6; H, 9·05. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%).

(ii) To the triol-monoacetate (127) (820 mg.) in AnalaR acetone (70 ml.) was added Jones reagent, dropwise until the solution was faintly yellow and then kept at room temperature for 1 hr. The bulk of the solvent was removed under reduced pressure and the mixture diluted with water and extracted with ethyl acetate. The extract was dried and evaporated to give crude product (820 mg.) containing traces of very polar material. A fraction (50 mg.) of this was treated with acetic anhydride (0·5 ml.) at reflux for 10 min. The acetic anhydride was removed under reduced pressure to give the acetoxy-anhydride (131) (45 mg.), m.p. 208-210°, after sublimation at 165° / 0·5 mm., as sole product (Found: C, 70·4; H, 8·5. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·6%).

Oxidation of the Acetoxy-Dialdehyde (129).

(i) The crude dialdehyde (129) (5 mg.), containing the more polar, unidentified compound (1:1), in AnalaR acetone (1 ml.) was treated with Jones reagent (3 drops) at 0°. T.l.c. [ethyl acetate-light petroleum (1:2)] of the crude reaction mixture showed that three major products were present. After further addition of Jones reagent (0·5 ml.) t.l.c. analysis showed that one compound, having the same mobility as the acetoxy-anhydride (131) was present. A portion of the mixture containing the three oxidation products was treated with diazomethane. T.l.c. showed that two compounds, those of lowest mobility, were now absent but that two new spots of greater mobility had appeared. Thus it was concluded that (a) complete oxidation of the crude aldehyde mixture resulted in the formation of only one product, and (b) two intermediate oxidation products, detected by t.l.c., were acidic in nature.

(ii) Pure acetoxy-dialdehyde (129) (50 mg.) in AnalaR acetone (10 ml.) was treated with Jones reagent for 10 min. at room temperature. The reaction mixture was diluted with water, extracted with ethyl acetate, dried and evaporated. Preparative t.l.c. [ethyl acetate-light petroleum (1:2)] of the products gave the acetoxy-anhydride (131) (30 mg.), m.p. 208-210° (after sublimation).

Hydrolysis and Methylation of the Acetoxy-Anhydride (131).

The acetoxy-anhydride (820 mg.) was heated with aqueous

sodium hydroxide (3N, 8 ml.) in refluxing methanol (50 ml.) for 2·5 hr. The cooled solution was acidified and extracted with ethyl acetate. Evaporation of the solvent gave crude hydroxy-diacid as a foam, which was esterified directly with diazomethane. Preparative t.l.c. [ethyl acetate-light petroleum (7:3)] of the products afforded the hydroxy-dicarboxylic diester (132) (620 mg.), m.p. 156-158·5° (needles from ethyl acetate-light petroleum) (Found: C, 69·65; H, 9·35. $C_{22}H_{36}O_5$ requires C, 69·45; H, 9·55%).

Oxidation and Decarboxylation of the Hydroxy-Dimethyl Ester (132).

The hydroxy-dimethyl ester (305 mg.) in AnalaR acetone (30 ml.) was treated with Jones reagent (1·5 ml.) at room temperature for 5 min. Work up gave the carboxylic acid (133) (290 mg.), m.p. 156-157·5° (decomp.) (prisms from light petroleum b.p. 60-80°) (Found: C, 67·0; H, 8·7. $C_{22}H_{34}O_6$ requires C, 67·0; H, 8·7%). This acid (133) (200 mg.) was heated at 160° in a partially evacuated sublimation tube for 10 min. On reducing the pressure in the system to 0·1 mm. sublimation of the nor-diester (134) (126 mg.) occurred. This crystallised from methanol as plates, m.p. 86-88·5° (Found: C, 72·1; H, 9·9. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%).

Attempted Hydrolysis of the Nor-Diester (134).

(i) The nor-diester (170 mg.) was heated with aqueous sodium hydroxide (3N, 2 ml.) in refluxing methanol (20 ml.) for 9 hr. The cooled solution was acidified and extracted with

ethyl acetate. Evaporation of the solvent gave a solid product (153 mg.) which on crystallisation from light petroleum gave cubes, m.p. 155-178°, probably the C-13 epimeric dicarboxylic monomethyl esters (134a). Further treatment with base produced no change in product composition as estimated from analytical t.l.c. [ethyl acetate] which shows two elongated, overlapping spots.

(ii) The nor-diester (134) (150 mg.) was heated with aqueous sodium hydroxide (3N, 3 ml.) in refluxing dioxan (3 ml.) for 5 days. The reaction mixture, after dilution and acidification, was placed in a constant ethyl acetate extractor for 24 hr. Evaporation of the extract gave a product (113 mg.) having the same composition as (i) above (estimated solely from t.l.c.).

Oxidation of Erythroxylol A Acetate (123).

Erythroxylol A acetate (613 mg.) in chloroform (15 ml.) was treated with m-chloroperbenzoic acid (630 mg.) in chloroform (15 ml.) at room temperature overnight. Filtration of the mixture through alumina (Woelm, basic, grade 1, 10 g.) and elution with chloroform (130 ml.) gave erythroxylol A acetate epoxide (120) (647 mg.), m.p. 143·5-145° (plates from methanol), $[\alpha]_D$+12·5° (c 1·18). This synthetic epoxide had m.p. (mixed m.p. undepressed), n.m.r. and i.r. spectra identical with those of the naturally occurring compound.

Reduction of Epoxides (120) and (124).

(i) A solution of erythroxylol A acetate epoxide (120) (300 mg.), from the above preparation, was heated in dry ether (20 ml.) under reflux with an excess of lithium aluminium hydride for 1 hr. Work up and crystallisation from methanol gave erythroxylol A epoxide (124) (255 mg., 97%), m.p. 115-116·5°, $[\alpha]_D$+18·5° (c 1·19). Again this material had physical properties [m.p., n.m.r. and i.r. spectra] identical with those found for the naturally occurring compound.

(ii) A solution of erythroxylol A epoxide (124) (100 mg.) was heated in dry tetrahydrofuran (12 ml.) under reflux for 24 hr. Work up and analytical t.l.c. [ethyl acetate-light petroleum (1:2)] of the product (96 mg.) showed that virtually no reaction had occurred.

(iii) A solution of erythroxylol A epoxide (124) (966 mg.) in dry ether (50 ml.) was treated with an excess of lithium aluminium hydride. The temperature of the mixture was raised (using a heating mantle) until the ether just boiled. The ether was then allowed to distill off slowly through a reflux condenser (having a slow water circulation) and without altering the temperature control on the heating mantle, the fused solid was maintained at an elevated temperature (?) overnight. To the cooled solid was added dry ether (50 ml.), followed by saturated sodium sulphate solution (dropwise, 10 ml.). The reaction mixture was filtered, dried and evaporated to give the

15β,18-dihydroxyhibane (137) (903 mg., 95%), m.p. 212-213° (after crystallisation from ethyl acetate as rods) (Found: C, 78·65; H, 11·05. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). Only by these conditions could the opening of the epoxide ring be reproduced (three times). In addition, it was found that an optimum yield could be obtained only when a fresh batch of lithium aluminium hydride was used.

Hydroboration of Erythroxylol A (15).

Erythroxylol A (1 g.) was treated with an excess of lithium aluminium hydride and boron trifluoride in ether (50 ml.) and the reaction worked up with hydrogen peroxide (30%, 10 ml.) Crystallisation of the crude product mixture (two major products by t.l.c.) from chloroform gave a solid which on recrystallisation from ethyl acetate afforded the more polar, less abundant 15β,18-diol (137) (224 mg., 21%), m.p. 212-213°. Separation of the mother liquors by preparative t.l.c. [methanol-chloroform (1:99)] afforded the less polar, more abundant compound, the 16β,18-dihydroxyhibane (138) (410 mg., 39%), m.p. 200-201° (from ethyl acetate) (Found: C, 78·4; H, 11·05%).

Acetylation of the 15β,18-Diol (137).

The 15β,18-diol (791 mg.) was kept with acetic anhydride (263 mg.) in dry pyridine (13 ml.) overnight. Work up followed by preparative t.l.c. [ethyl acetate-light petroleum (1:1)] of the products afforded unreacted diol (137) (146 mg.) (most polar on t.l.c.), 15β,18-diacetate (141) (186 mg., 23% based on diol

consumed) (least polar), m.p. 136-139° (plates from light petroleum) (Found: C, 74·0; H, 9·7. $C_{24}H_{38}O_4$ requires C, 73·8; H, 9·8%), and a mixture of two other compounds. This mixture after repeated preparative t.l.c. afforded the less polar 15β-hydroxy-18-acetate (142) (293 mg., 40%), m.p. 158-159° (from light petroleum) (Found: C, 76·0; H, 10·7. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%), and the more polar isomeric 18-hydroxy-15β-acetate (143) (74 mg., 10%), m.p. 163-164·5° (from light petroleum) (Found: C, 75·9; H, 10·45%).

Oxidation of the 15β-Hydroxy- and 16β-Hydroxy-18-acetate (142) and (145).

(i) The 15β-hydroxy-18-acetate (142) (146 mg.) in AnalaR acetone (3 ml.) was treated with Jones reagent at room temperature for 5 min. Work up and purification by preparative t.l.c. [ethyl acetate-light petroleum (1:4)] gave the 15-keto-18-acetate (144) (124 mg.) which crystallised from ether as rods, m.p. 182-183° (Found: C, 76·3; H, 9·95. $C_{22}H_{34}O_3$ requires C, 76·25; H, 9·9%).

(ii) The 16β-hydroxy-18-acetate (145) (50 mg.) in AnalaR acetone (2 ml.) was treated with Jones reagent at room temperature for 5 min. Work up and purification as above gave the 16-keto-18-acetate (146) (46 mg.), m.p. 155·5-156·5° (rods from light petroleum) (Found: C, 76·45; H, 10·05%).

From analytical t.l.c. [ethyl acetate-light petroleum (1:4)] the 16-ketone (146) is more mobile than the isomeric 15-ketone (144).

Hydrolysis of the 15-Keto- and 16-Keto-18-acetates (144) and (146).

(i) The 15-keto-18-acetate (144) (105 mg.) was heated with aqueous sodium hydroxide (3N, 0·5 ml.) in refluxing methanol (5 ml.) for 2 hr. The cooled solution was acidified and extracted with ethyl acetate after dilution with water. Evaporation of the solvent and preparative t.l.c. [ethyl acetate-light petroleum (1:3)] of the crude product gave 15-keto-18-hydroxyhibane (139) (83 mg.), m.p. 140-143° (needles from ether-light petroleum) (Found: C, 79·0; H, 10·6. $C_{20}H_{32}O$ requires C, 78·9; H, 10·6%). The o.r.d. curve in methanol at 25° (c 0·072) shows: $[\Phi]_{400}$+670°, $[\Phi]_{325}$+5600°, $[\Phi]_{281}$-5180°, and $[\Phi]_{222}$ 0°.

(ii) The 16-keto-18-acetate (146) (30 mg.) was treated with aqueous sodium hydroxide (3N, 0·5 ml.) in refluxing methanol (2 ml.) for 2 hr. Work up and isolation as above gave the 16-keto-18-hydroxyhibane (140) (23 mg.), m.p. 127-129° (after sublimation at 120-125° / 0·03 mm.) (Found: C, 78·85; H, 10·75%). The o.r.d. curve in methanol at 25° (c 0·074) shows: $[\Phi]_{400}$-445°, $[\Phi]_{316}$-4450°, $[\Phi]_{279}$+4700°, $[\Phi]_{243}$+2870°, and $[\Phi]_{213}$+4680°.

The Dienes (150), (151) and (152).

(i) 4β-Hydroxy-18-norhibaene (121) (100 mg.) in dry pyridine (10 ml.) under reflux was treated with redistilled phosphoryl chloride (2·5 ml.) for 3·5 hr. The mixture was poured into ice, extracted with ether, and the extracts washed with water and dried. Evaporation of the solvent left a yellow oil (76 mg.) which contained

at least three compounds as shown by analytical t.l.c. [ethyl acetate-light petroleum (1:4)] on silver nitrate-impregnated silica. Separation of a portion (50 mg.) of this oil by preparative t.l.c. gave a mixture (22 mg.) of the dienes (151) and (152) as the less polar fraction, and the $\Delta^{4(19),15}$-diene (150) (23 mg.), b.p. 70-72° / 0·03 mm., (Found: C, 88·85; H, 11·0. $C_{19}H_{28}$ requires C, 89·0; H, 11·0%). The dienes (152), (150) and (151) were separable by analytical g.l.c.: (i) 2·5% SE 30, 190°, nitrogen carrier at 16 lb./in.^{2}, 30, 32 and 34 min., and (ii) 3% OV 22, 150°, 35 ml. argon/min., 21,23 and 24 min. respectively. Each diene showed a parent ion at m/e 256 on the gas chromatograph-mass spectrometer but the respective fragmentation patterns showed slight differences.

(ii) 4α-Hydroxy-18-norhibaene (119) (7 mg.) in dry pyridine (2 ml.) under reflux was treated with redistilled phosphoryl chloride (0·2 ml.) for 4·5 hr. The yellow oil (5 mg.) produced consisted mainly (t.l.c. and g.l.c.) of the $\Delta^{4,15}$-diene (152) with smaller amounts of the dienes (150) and (151).

(iii) The $\Delta^{4(19),15}$-diene (150) (4 mg.) was treated with phosphoryl chloride (2 drops) in refluxing pyridine (1 ml.) as above for 90 min. Work up and isolation as above gave recovered starting material as evidenced by g.l.c., t.l.c. and i.r.

The Methyl Ketone (153).

The aldehyde (154) (180 mg.) in dry ether (5 ml.) was added to methylmagnesium iodide [prepared from magnesium (20 mg.) and methyl iodide (0·5 ml.)] in ether (7 ml.) and the mixture kept

under reflux for 30 min. The reaction mixture was worked up with dilute sulphuric acid and extracted with ether, the extracts washed with water, dried and evaporated. Purification by preparative t.l.c. [ethyl acetate-light petroleum (1:19)] gave the methyl carbinol (155) (180 mg., 95%), m.p. 40-57° (rods from methanol). The carbinol (155) (140 mg.) in acetic acid (8 ml.) was treated with a solution of chromium trioxide in 95% acetic acid (0·3N, 15 ml.) at room temperature for 30 min. After dilution with water, the mixture was extracted with ether and the extracts washed successively with water, aqueous sodium bicarbonate, water, and dried and evaporated. The residual solid gave after preparative t.l.c. [ethyl acetate-light petroleum (1:19)], the methyl ketone (153) (120 mg., 86%), m.p. 67-69° (after sublimation at 60-65° / 0·05 mm.) (Found: C, 83·85; H, 10·5. $C_{21}H_{32}O$ requires C, 83·95; H, 10·75%), and the methyl ketone epoxide (156) (15 mg., 10%), which crystallised from light petroleum as plates, m.p. 150-152° (Found: C, 79·95; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

Attempted Baeyer-Villiger Oxidation.

(i) To the methyl ketone (153) (100 mg.) in chloroform (4 ml.) was added m-chloroperbenzoic acid (90 mg.) in chloroform (4 ml.) at room temperature for 1 hr. The reaction was conveniently followed by t.l.c. [ethyl acetate-light petroleum (1:9)]. After 10 min. the methyl ketone had been converted to a new

compound which did not undergo further change. The reaction mixture was filtered through a short column of alumina (Woelm, basic, grade 2, 10 g.) and eluted with chloroform to give the methyl ketone epoxide (156) (102 mg., 97%), m.p. 150-152° (from light petroleum). Longer exposure (up to 40 hr.) of the methyl ketone epoxide to peracid produced no change in product composition (t.l.c.).

(ii) To the methyl ketone epoxide (156) (9 mg.) and m-chloroperbenzoic acid (13 mg.) in chloroform (2 ml.) at 0° was added 10% sulphuric acid in acetic acid (4 drops). The temperature of the mixture was allowed to rise to room temperature and set aside for 48 hr. The reaction mixture was neutralised with aqueous sodium bicarbonate, extracted with chloroform, dried and evaporated. The residual oil was shown by t.l.c. [ethyl acetate-light petroleum (1:3)] to consist of a complex mixture of polar compounds.

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S E C T I O N B.

Oxidative Reactions of Alcohols.

1. The Chromic Acid Oxidation of Alcohols.

Chromium in its highest valence state of (VI) has been used in the oxidation of both organic and inorganic substrates[1-3] whereby it is eventually reduced to a valence state of (III). The major application of Cr(VI) in synthetic organic chemistry has been in the conversion of alcohols to aldehydes, ketones and carboxylic acids. Consequently the use of this oxidant has received extensive investigation. In these studies, secondary alcohols have been used in preference to primary alcohols since the latter have the added complication that the aldehyde first formed is often further oxidised to the corresponding acid.

Rate studies were first carried out by Westheimer and Novick[4] on the chromic acid oxidation of isopropanol. These workers demonstrated that the rate of reaction was dependent on the concentrations of both the alcohol and ionised chromic acid. Their results, formulated in equation (1), have been

$$\text{rate} = k_a\left[HCrO_4^-\right]\left[R_2CHOH\right]\left[H^+\right] + k_b\left[HCrO_4^-\right]\left[R_2CHOH\right]\left[H^+\right]^2 \quad \ldots\ (1)$$

found to apply for all other alcohols studied[5]. The observation of a kinetic isotope effect[6] in the oxidation of deuterium labelled alcohols illustrated that the cleavage of the carbinol carbon-hydrogen bond was involved in the rate determining step. The above observations must therefore be incorporated into a scheme whereby an alcohol is converted, by a two electron process, into the corresponding carbonyl function. This is

complicated by the fact that three electrons are involved in the Cr(VI) - Cr(III) reduction which implies that Cr(V) or Cr(IV) intermediates (vide infra) are generated in situ[1-3]. Thus the alcohol may be involved either in a net two-electron oxidation by Cr(VI) with concurrent formation of Cr(IV) or in two one-electron processes with formation of two Cr(V) intermediates.

A distinction between these two possible processes can be made[7] since the oxidation of isopropanol when carried out in the presence of manganous ions, produces manganese dioxide and acetone in the ratio of 1:2. Since manganous ions do not reduce Cr(VI) under the reaction conditions, the formation of manganese dioxide must result from the reduction of an unstable chromium species of intermediate valence state (IV or V)[7,8]. If there is direct oxidation of the alcohol, one mole of Cr(IV) will be generated for each mole of ketone formed. The Cr(IV) species on further reduction to its stable state of Cr(III) may therefore only produce one-half mole of Mn(IV) from Mn(II). This is in agreement with the experimental observation. If, however, the alcohol is oxidised by two one-electron steps, two moles of Cr(V) will be formed for each mole of ketone. It follows therefore that two moles of Cr(V) will permit the formation of two moles of manganese dioxide and hence give rise to a manganese dioxide-ketone ratio of 2:1. The reaction sequence must therefore involve a direct

two-electron process as shown in equations (2). In addition,

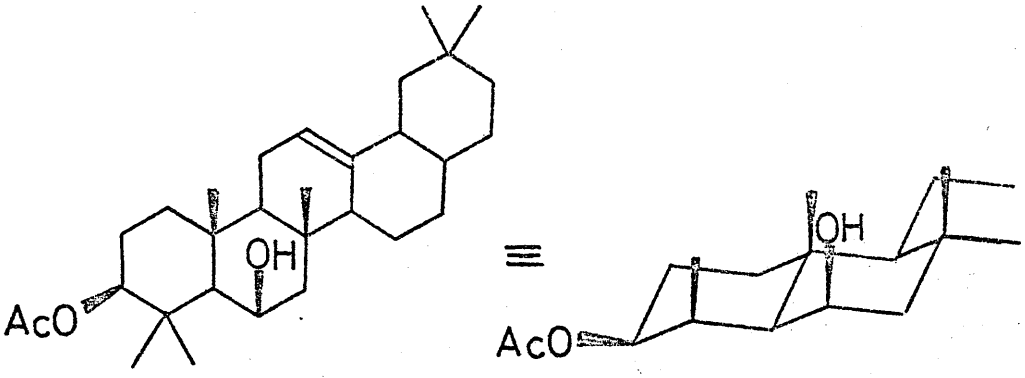
$$2R_2CHOH + 2Cr^{VI} \longrightarrow 2R_2C{=}O + 2Cr^{IV}$$
$$2Cr^{IV} + Mn^{II} \longrightarrow MnO_2 + 2Cr^{III} \quad \ldots\ (2)$$

it was found that at high concentrations of alcohol*, the reaction rate in the presence of manganous ions[7] was half that found in their absence. Again since manganous ions do not reduce Cr(VI), Mn(II) must be removing some intermediate species (normally present) which can effect reduction of the chromate as rapidly as the reacting alcohol. This intermediate has already been shown to be Cr(IV) and thus the most probable reaction scheme is shown by equations (3). From these equations,

$$R_2CHOH + Cr^{VI} \longrightarrow R_2C{=}O + Cr^{IV}$$
$$Cr^{IV} + Cr^{VI} \longrightarrow 2Cr^{V} \quad \ldots\ (3)$$
$$2Cr^{V} + 2R_2CHOH \longrightarrow 2R_2C{=}O + 2Cr^{III}$$

it would seem that Cr(V) is an important intermediate in the normal reaction since the total oxidation is effected by Cr(VI) only to the extent of one-third and by Cr(V) to the extent of two-thirds. This hypothesis is substantiated by the direct

*This effectively reduces this term in the rate equation to a constant and hence the rate becomes dependent only on the concentration of chromate ion.



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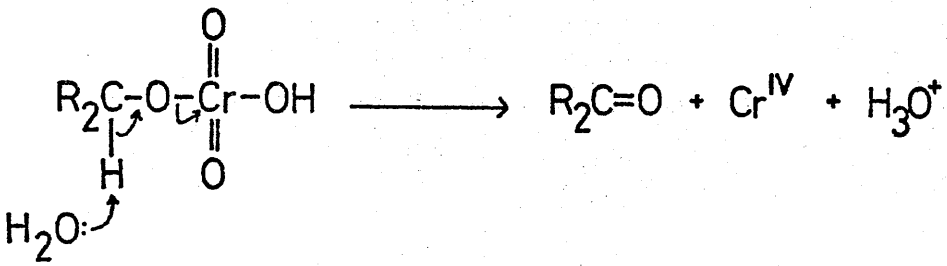
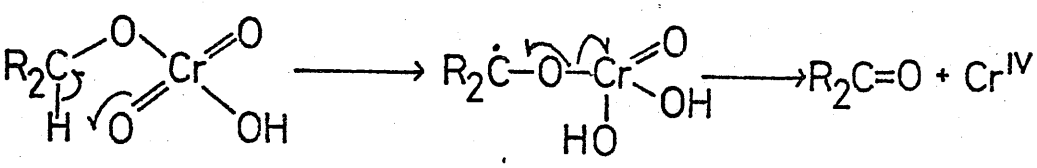
Mechanisms.

A)



B)

C)



observation[9,10] of Cr(V), by u.v. and e.s.r. spectroscopy, during the oxidation of isopropanol in aqueous acetic acid.

With the observation that organo-chromate esters could be prepared and decomposed to the corresponding carbonyl compounds in pyridine[11], it was suggested that these chromate esters could be intermediates in the oxidation reactions. support for this was derived from the oxidation of the sterically hindered alcohol[12] (159) where conditions were found such that the kinetic isotope effect was reduced to unity. In this case the rate determining step must involve some prior stage, namely the formation of the chromate ester. Evidence has since appeared demonstrating that chromate esters are formed in the reaction mixtures[13] and kinetic measurements of this pre-oxidation step have been made[14].

Although chromate esters are now accepted as intermediates in the reaction, the path by which they give rise to the oxidation products is still open to question. It is possible to formulate three mechanisms[3,10], viz. A, B and C, which will account for the known data, although at present it is not possible to differentiate between them experimentally. Mechanism A differs from B and C in that a proton is lost to an external base or solvent molecule whereas B and C each involve a unimolecular cyclic process. Mechanism B differs from C as the former proceeds by a concerted two-electron cyclic

process whereas the latter goes via a radical-chromium(V) intermediate. Mechanism C would not be easily distinguishable from B since the homolytic fission of the chromium-oxygen bond yielding the ketonic product would presumably be a very fast step in the reaction sequence[3,10].

Conformational effects in these oxidative reactions have been studied by a number of investigators[15-19] who have shown that in cyclohexyl systems, having fixed chair conformations, axial hydroxyl groups react faster than the corresponding equatorial isomers. These results were first interpreted[15,17,19] in terms of the conformational effect (hydroxyl group) on the equilibrium constants involved in chromate-ester formation and on the rate of decomposition of this intermediate. Thus the equilibrium constant for ester formation in the sterically more accessible (equatorial) alcohol should be greater than that for the more hindered axial isomer. Conversely, the rate of decomposition of the axial ester (more accessible hydrogen) should be greater than that of the equatorial ester. Since the axial hydroxyl group oxidises at a greater rate, the decomposition of the ester must be the over-riding factor and hence would favour mechanism A. These observations, however, can be accommodated if it is assumed that the activated complex is one in which the carbon undergoing oxidation is becoming trigonal. Thus the faster rate of reaction of an axial alcohol may be accounted[3,17] for by the

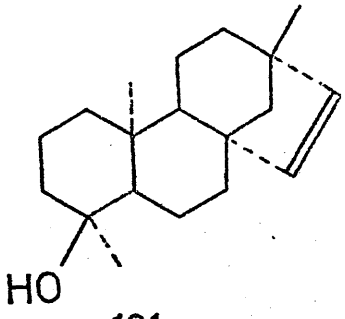
relief of non-bonded repulsive interactions in going from a tetrahedral to a trigonal state. These steric interactions in a number of secondary alcohols have been estimated[20] and correlations with the activation energy for oxidation of these compounds have been made[20]. Thus the conformational effects may also be explained by mechanisms B and C if steric acceleration plays a major role.

The decomposition of the complex ester which was thought to show general base catalysis by pyridine, and hence lend support to mechanism A, has now been shown to be incorrect[21]. Thus at the present time, mechanism B (or possibly C) appears to be favoured[3,10] although definite evidence which would exclude A is lacking.

Chromium (V), which is presumably the important chromium species of intermediate valence capable of alcohol oxidation[3], must also be considered. However this pentavalent species is unstable in aqueous solution so that relevant data has of necessity been obtained indirectly. The kinetic analysis of Westheimer and Watanabe[7] indicated that this oxidative process must also involve two electrons. In addition, kinetic data on the rate and equilibria processes occurring in the Cr(V) oxidation has been obtained using competitive techniques. These have involved chromic acid oxidation of mixtures of labelled and unlabelled isopropanol in water[6c] and aqueous acetic acid[10]. By measuring the rate of reaction in the

presence of manganous ions it is possible to determine the rate for the Cr(VI) reaction and hence the rate found in the absence of manganous ions can be used to calculate[6c] the rate constants for the Cr(V) oxidation. In this way, it has been shown that the Cr(V) oxidation shows a kinetic isotope effect[6c,10]. It was also found that the rate constants for the Cr(V) oxidation vary with the concentration of both labelled and unlabelled isopropanol and also with the concentration of acid, in a similar manner to those observed for the Cr(VI) oxidation[10]. Thus it would appear that this process proceeds by a mechanism similar to that postulated for the Cr(VI) reaction. Since Wiberg can only account for his results[10] [of the Cr(VI) oxidation of isopropanol in aqueous acetic acid] by proposing that both mono- and diesters of Cr(VI) give rise to products, it might appear that mono- and diesters of Cr(V) could also be involved in the oxidation process. Again decomposition of these esters would proceed by carbinol carbon-hydrogen bond rupture in the rate determining step.

2. The Oxidative Cleavage of some Primary Alcohols.



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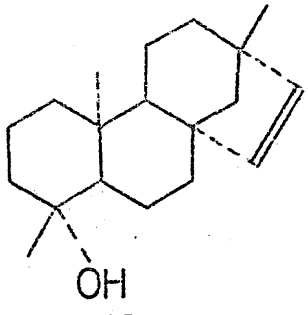

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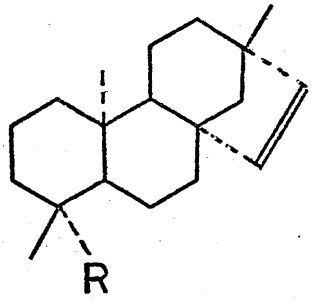
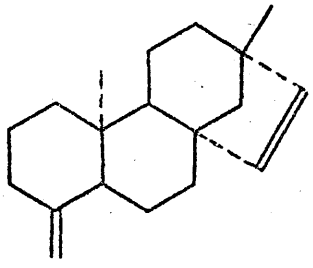


15 R=CH_2OH

123 R=CH_2OAc

154 R=CHO



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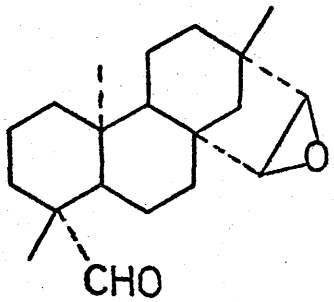
151 Δ^3-isomer

152 Δ^4-isomer



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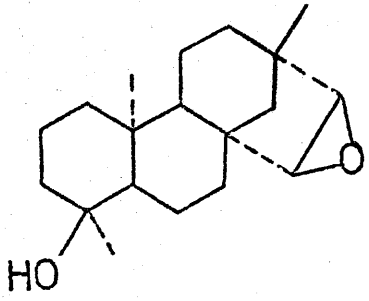

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The isolation[22] of two nor-diterpene alcohols (121) and (119) [Section A] from the light petroleum extractive of Erythroxylon monogynum Roxb. prompted an attempted synthesis[22] of the latter from erythroxylol A[23] (monogynol[24]) (15). The first step in the proposed scheme involved the oxidation of the primary alcohol (15) with chromium trioxide in aqueous acetic acid. This resulted in the isolation of a complex mixture of products which could be partially resolved by column chromatography[22]. Elution of the mixture with light petroleum yielded initially a hydrocarbon fraction followed by the major product, the aldehyde[23] (154). This hydrocarbon mixture was shown to consist predominantly of the three dienes (150), (151) and (152), previously isolated[22] from the dehydration of the epimeric nor-alcohols (121) and (119), together with a fourth unidentified compound as shown by analytical g.l.c. Subsequent elution with ethyl acetate gave an oil which was acetylated to facilitate its separation. This acetylated material, after preparative t.l.c., yielded several compounds which included erythroxylol A acetate (123) and erythroxylol A acetate epoxide (120), both of known constitution. The aldehyde epoxide[22] (160), also obtained after thin layer chromatography, was readily identified from its spectral features [CHO, τ 0·28 : υ_{max} 2725, 2707 and 1720 (aldehyde) and 850 cm.$^{-1}$ (epoxide)] and by its synthesis[22] from the aldehyde (154). In addition, three further

nor-diterpenoids were detected. These comprised 4α-hydroxy-18-norhibaene[22] (119) (present in trace amounts as shown by its characteristic staining reaction on t.l.c.), the isomeric 4β-hydroxy-18-norhibaene[22] (121) (isolated after further preparative t.l.c. on silver nitrate-impregnated silica), and 4β-hydroxy-18-norhibaene epoxide[22] (161). The latter compound was also identified from its spectral features [ν_{max} 3600, 3470 (hydroxyl) and 852 cm.$^{-1}$ (epoxide)] and by its synthesis[22] from the corresponding alcohol (121). Both the aldehyde epoxide (160) and the nor-alcohol epoxide (161) show signals characteristic of the β epoxide in their n.m.r. spectra [2H, ABq, τ 7·14 and 6·78, and τ 6·97 and 6·60 respectively, J 3 c./sec.] [Section A].

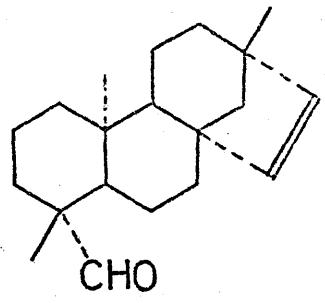
The nor-products isolated from this reaction must emanate from the direct oxidation of the primary alcohol since the derived aldehyde on further treatment with the oxidising medium yielded none of the cleavage products. Although some of the aldehyde was recovered unchanged, further more polar products were formed as shown solely by t.l.c.

To make the reaction of synthetic value, it was hoped that conditions might be found to increase the degree of fragmentation. It was found however that changing the molar ratio of chromium trioxide with respect to erythroxylol A had little effect on the proportion of nor-compounds formed (Table I). As an alternative, it was thought that an increase in the non-bonded replusive

155 R=CH_3

162 R=CH_2CH_3

163 R= Ph



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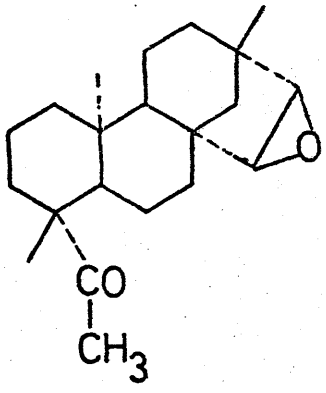

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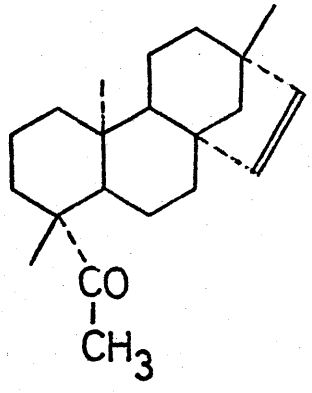
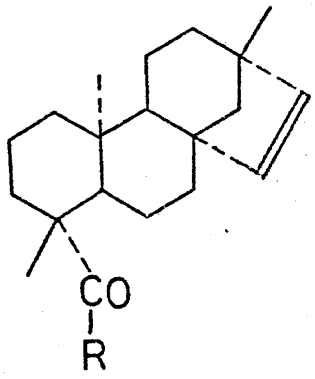


153

interactions across ring A might favour the cleavage process. Thus the methyl[22], ethyl and phenyl carbinols (155), (162) and (163), showing absorption bands at 3620, 3623 and 3628 cm.$^{-1}$ (i.r.) respectively, were prepared from the aldehyde (154) by treatment with the corresponding Grignard reagents. Support for the structures assigned was derived from the n.m.r. spectra: the methyl carbinol (155) shows a one proton quartet at τ 5·71 (J 6 c./sec.) and three proton doublet at τ 8·97 (J 6 c./sec.); the ethyl carbinol (162) shows two broad unresolved signals at τ 6·18 and 6·05 (1H) which must form the X portion of an ABX system; and the phenyl carbinol (163) shows a one proton singlet at τ 4·79 (deshielded due to the aromatic ring) and a broad singlet (5H) at τ 2·80 from the aromatic protons. These carbinols are obtained as epimeric mixtures formed by the non-stereospecific attack of the Grignard reagent on the aldehyde function and is therefore consistent with the wide melting range observed for these compounds.

These carbinols on oxidation with chromium trioxide in aqueous acetic acid gave the corresponding ketones as the major products together with the ketone epoxides. The methyl ketone[22] (153) and the methyl ketone epoxide[22] (156) were identical to the compounds previously obtained [Section A]. In each case, the expected cleavage products were detected in minor amounts (Table II). Thus it was noted that the yields of normal oxidation products had increased (approx. 70%) [as expected since

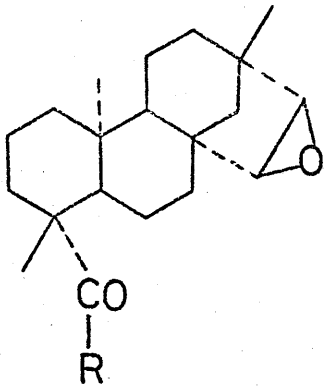


154 R=H

153 R=CH_3

164 R=CH_2CH_3

166 R=Ph



156 R=CH_3

165 R=CH_2CH_3

167 R=Ph

the ketones formed are more stable than the aldehyde (154) (approx. 40%)], but surprisingly the proportion of cleavage products had decreased slightly relative to that found from erythroxylol A.

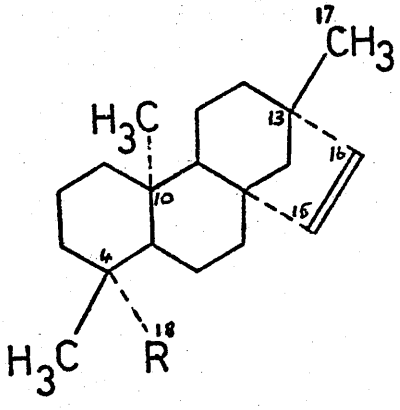
The spectral features of the above carbinols, ketones and ketone epoxides are worthy of further comment. The i.r. solution spectra of the methyl ketone (153), ethyl ketone (164) and their corresponding epoxides (156) and (165), in carbon tetrachloride, each show a split carbonyl frequency (Table III) whereas the phenyl ketone (166) and the phenyl ketone epoxide (167) show only one maxima. In chloroform solution, however, the split carbonyl frequencies collapse to one broad absorbance at slightly lower wave-number. Although these spectra now show only one maxima, several shoulders can still be observed similar to those seen in the carbon tetrachloride solution

TABLE III.

Infra Red Carbonyl Solution Spectra ($cm.^{-1}$)

	$\upsilon_{max}(CCl_4)$	$\upsilon_{max}(CHCl_3)$
Methyl ketone (153)	1703, 1696	1692*
Methyl ketone epoxide (156)	1705, 1698	1691*
Ethyl ketone (164)	1704, 1694	1689*
Ethyl ketone epoxide (165)	1705, 1695	
Phenyl ketone (166)	1683*	
Phenyl ketone epoxide (167)	1685*	

*Absorption band showing several shoulders.


17
CH3
H3C
13
16
10
15
4
18
H3C
R

spectrum of the phenyl ketones. This might suggest that the absorption bands are composite in nature due to discrete conformational (ring A boat or chair) or rotational (ring A chair) isomers permitted by the severe steric interactions present in this part of the molecule.

The n.m.r. spectra of the various carbinols, ketones and keto-epoxides allow assignment of signals to the quaternary C-methyl groups (Table IV). Thus it can be seen that the signal from the C-17 methyl does not alter appreciably and remains at τ 9·01 ± 0·02 throughout. The methyl signal at highest field in the carbinol system is attributed to that at C-10, shielded by the Δ^{15}-double bond[25]. This is confirmed

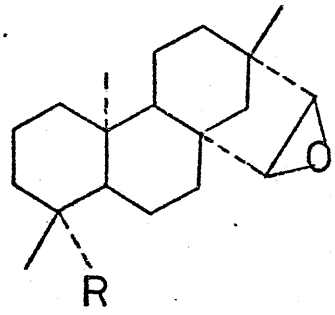
TABLE IV.

C-Methyl Resonances in the n.m.r. Spectra (CCl_4)

	C-10·CH_3	C-4·CH_3	C-13·CH_3
Methyl carbinol (155)	9·18	9·14	9·03
Methyl ketone (153)	9·47	8·94	9·01
Methyl ketone epoxide (156)	9·27	8·90	9·00
Ethyl carbinol (162)	9·18	9·12	9·01
Ethyl ketone (164)	9·51	8·97	9·02
Ethyl ketone epoxide (165)	9·31	8·93	9·02
Phenyl carbinol (163)	9·17	9·02	9·02
Phenyl ketone (166)	9·35	8·59	9·01
Phenyl ketone epoxide (167)	9·17	8·57	9·01

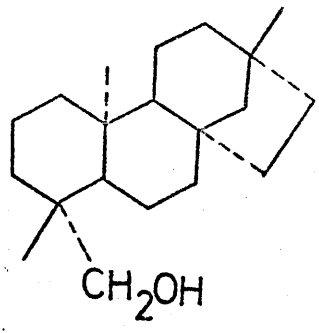
by the further shielding observed on oxidation of the carbinol to the ketone function. Epoxidation of the double bond produces a downfield shift of this signal as anticipated. The magnetic anisotropy of the carbonyl group, which causes the shielding of the C-10 methyl, deshields the C-4 methyl as can be seen from Table IV. In addition, the phenyl group deshields the C-4 methyl even in the carbinol system and on oxidation further deshielding results in the very lowfield signal at $\tau 8{\cdot}59$. The signals due to the C-4 methyl groups in the ketonic systems are unaffected by epoxidation of the double bond, since the distance between the functionalities is too large. Since the C-10 methyl signals in each case appear at such high field, this would seem to suggest that ring A is in fact in a chair conformation. Thus if, as suggested by the i.r. spectra, several conformations are present, these must be rotameric in nature (ring A chair) rather than ring A isomers (distorted boat and chair).

In an attempt to 'freeze out' the conformational isomers, the n.m.r. spectrum of the methyl ketone (153) was obtained at temperatures down to -91°. Although it can be seen from Table V that the methyl signals did not resolve, it was noted that the spectrum was in fact temperature dependent[26]. The signals assigned to the C-4 and C-13 methyl groups were unaffected by the decrease in temperature whereas the C-10 methyl signal moved upfield by 4 c./sec. and the signal from the acetyl group moved to lower field (6 c./sec.). The two temperature dependent signals



124 R=CH_2OH

160 R=CHO



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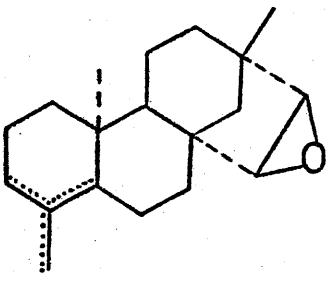

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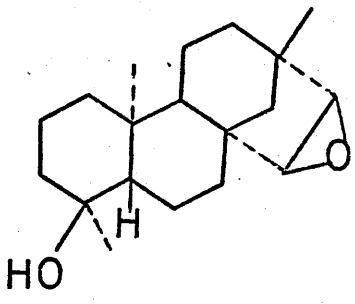

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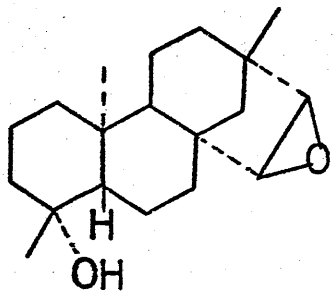

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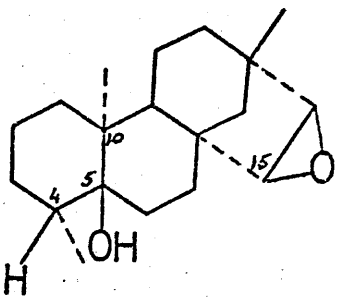


171

TABLE V.

Methyl Signals for Methyl Ketone (153) in Dichloromethane

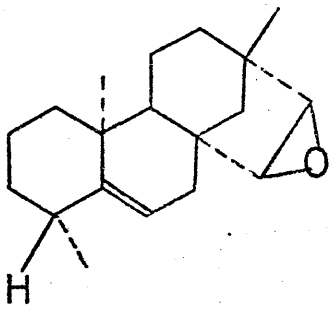
Temperature	$CH_3 \cdot CO$	$C\text{-}10 \cdot CH_3$	$C\text{-}4 \cdot CH_3$	$C\text{-}13 \cdot CH_3$
$+34^\circ$	7·91	9·45	8·93	9·02
-70°	7·86	9·49	8·92	9·02
-91°	7·85	9·49	8·91	9·02

are those which would be expected to move if, in fact, rapid rotation about the C 4 - C 18 bond is being influenced by the change in temperature[26]. Thus the magnetic field seen (as a time average) by the methyl groups at -91° is different from that observed at $+34^\circ$. This evidence, although not substantial, supports the suggestion that rotameric isomers are present.

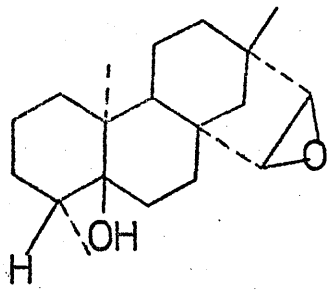
To determine whether this cleavage reaction is general for primary alcohols in the beyerane system, the oxidations of erythroxylol A epoxide (124) and dihydroerythroxylol A[23] (168) were carried out (Table II). Treatment of the epoxy-primary alcohol (124) with the oxidising medium and chromatography of the resulting oily mixture gave the corresponding aldehyde (160) as major product. A less polar fraction [ν_{max} 1642, 885 (double bond) and 848 $cm.^{-1}$ (epoxide)], having analytical and mass spectral (M 272) data in accord with the molecular formula $C_{19}H_{28}O$, was isolated which presumably contains a mixture of the isomeric olefin epoxides (169). Further separation of the residual mixture by t.l.c. resulted in the isolation of three isomeric nor-alcohol epoxides. The most polar (t.l.c.) of these

was identified as 4β-hydroxy-18-norhibaene epoxide (161) which had been isolated[22] from the products resulting from the oxidation of erythroxylol A. The nor-alcohol of intermediate mobility (parent m/e 290) was shown to be the 4α-hydroxy-18-norhibaene epoxide (170) by its synthesis from the naturally occurring alcohol (119). The nor-alcohol of greatest mobility (parent m/e 290) was tentatively formulated as (171). This alcohol shows in its n.m.r. spectrum two tertiary methyl resonances at τ 9·09 and 9·01 and a new secondary methyl signal at τ 8·99 (J 5 c./sec.).

Since a carbonium ion mechanism is proposed for the cleavage reaction (vide infra), this could account for the formation of the nor-alcohol epoxide (171). The spectral features of the latter compound would suggest that a hydride shift (from C-5 to the β-face of C-4) has occurred giving rise to a secondary methyl group. Attack of a nucleophile at C-5, the new centre of electron deficiency, would lead to this observed nor-alcohol. If this nucleophile approaches from the α-face, it must overcome the steric interaction from two 1,3-diaxial methyl groups (at C-4 and C-10), so that a β-orientation of the hydroxyl group at C-5 would seem more probable. That the trans rearrangement of the hibane skeleton has proceeded only as far as C-5 is likely since the quartet in the n.m.r. due to the epoxide protons [τ 7·14 and 6·77, J 3 c./sec.] appear in the normal position[22]. This would imply that the 15α-proton (at lower field) is interacting with the C-10



169a



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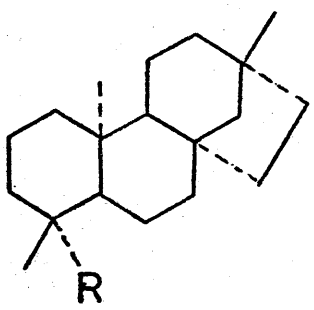
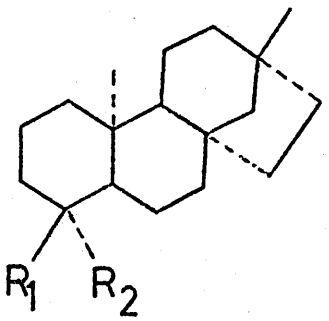


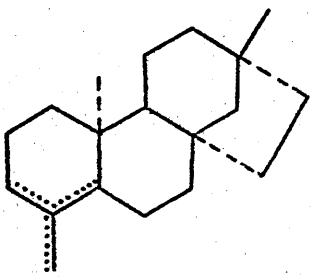
172 R=$COOCH_3$

173 R=CHO



174 R_1=CH_3 , R_2=OH

175 R_1=OH , R_2=CH_3



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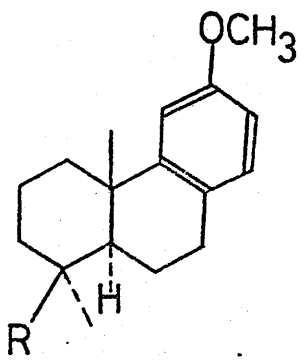


177 R=CH_2OH

178 R=CHO

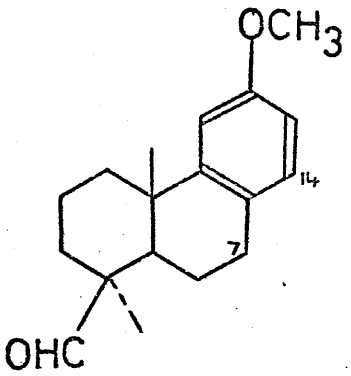
methyl group, as has been noted previously [Section A].

If this rearranged nor-diterpenoid has an axially orientated β-hydroxyl group, dehydration should, by a trans diaxial elimination[27], result in the predominant formation of the Δ^5-olefin (169a) which would be non-identical to any of the olefin epoxides formed in the oxidation. Treatment of the alcohol with freshly distilled phosphoryl chloride in pyridine, however, resulted only in the isolation of a mixture of polar material. Thus the identity of (171) has not been unambiguously established.

In continuation of this oxidative sequence, it was found that dihydroerythroxylol A[23] surprisingly gave isostevic acid, isolated as its methyl ester[28] (172), as major product. The expected aldehyde (173), isolated in much smaller amounts, was found to be extremely unstable[28] under atmospheric conditions. Thus on standing, the aldehyde gives rise to the corresponding acid[28] together with several other unidentified compounds. The yield of aldehyde may be increased by carrying out the oxidation under an atmosphere of nitrogen, but this also affects the proportion of cleavage products formed (Table II). Separation of the crude oxidation mixture resulted in the isolation of 4α-hydroxy-18-norhibane (174) [ν_{max} 3615 cm.$^{-1}$] and 4β-hydroxy-18-norhibane (175) [ν_{max} 3610 cm.$^{-1}$] both of which show three quaternary C-methyl resonances in the n.m.r. spectrum [τ 9·05, 8·98 and 8·88, and τ 9·13, 9·05 and 8·97 respectively].

Confirmation of the assigned structures was derived from hydrogenation of both naturally occurring nor-alcohols which gave products identical to those isolated from the oxidising medium. It is of interest to note that the hydrocarbon fractions from both oxidations (under nitrogen and under atmospheric conditions) differ in as much as the former (under nitrogen) shows only one peak on g.l.c. and the latter shows an additional peak of almost equal intensity. Both fractions have spectral features in accord with the olefin mixture (176) showing absorption bands at 1647 and 889 $cm.^{-1}$ (i.r.) and having a parent ion at m/e 258 ($C_{19}H_{30}$) in the mass spectrum. However the mass spectrum of the mixed hydrocarbons from the oxidation in air shows a significant peak at m/e 260 which is absent in the mass spectrum of the other fraction.

The oxidation of O-methylpodocarpinol (177) has also been carried out. Here again the major product was the aldehyde[42] (178) as was found to be the case in all but one of the oxidations studied. The assigned structure is supported by both n.m.r. [$C\underline{H}O$, $\tau 0{\cdot}22$] and i.r. [ν_{max} 2732, 2717 and 1726 $cm.^{-1}$] spectra. The amount of normal oxidation to the aldehyde seems to vary greatly (Table II) and may well be due to the insolubility of the alcohol (177) in the oxidising medium. Since the podocarpic system contains an aromatic ring, there is the possibility that benzylic oxidation will also occur (cf. totara-8,11,13-triene[29]). That this additional reaction



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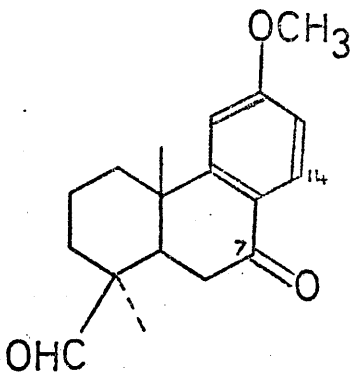

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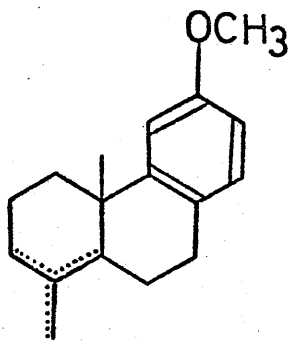

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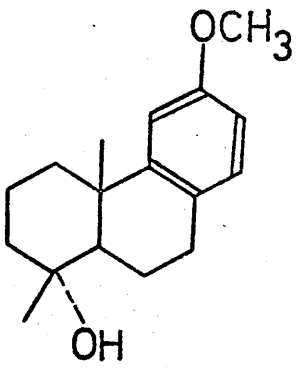


181

took place was confirmed by the isolation of the keto-aldehyde (179) showing absorption bands at 2725, 1725 (aldehyde) and 1683 $cm.^{-1}$ (ketone) in the i.r. Proof that the keto function is situated at C-7 was obtained from a comparison of the u.v. spectra (ethanol) of the aldehyde (178) [λ_{max} 201 mμ., ε 23,400; λ_{max} 225 mμ., ε 5,900; λ_{max} 280 mμ., ε 1,670] and the keto-aldehyde (179) [λ_{max} 202 mμ., ε 19,200; λ_{max} 228 mμ., ε 13,500; λ_{max} 281 mμ., ε 17,000]. This is confirmed by the n.m.r. spectrum of the benzylic ketone where it is observed that the C-14 proton on the aromatic ring has moved down-field to τ2·03 (J 8 c./sec.) from τ3·16 (J 8 c./sec.) in the aldehyde (178) due to the deshielding effect of the C-7 ketone. Also isolated from the reaction mixture was a non-polar fraction [υ_{max} 1648 and 896 $cm.^{-1}$] which, after sublimation, showed a parent ion at m/e 242 in the mass spectrum corresponding to a molecular formula of $C_{17}H_{22}O$. This fraction shows two peaks on g.l.c. and is, presumably, the mixture of nor-olefins[30] (180). One tertiary alcohol [υ_{max} 3615 and 3480 $cm.^{-1}$] showing a parent ion at m/e 260 was formulated as the 4α-noralcohol[30] (181). The n.m.r. spectrum of this compound shows only two quaternary C-methyl resonances at τ8·88 and 8·84 and a signal at τ6·29 attributed to the 12-methoxyl group. No evidence of the epimeric nor-alcohol could be found.

TABLE I.

Effect of Molar Ratio of CrO_3 with respect to Erythroxylol A.

Erythroxylol A (1×10^{-3}m) Alcohol : CrO_3	Nor-olefins ($\times 10^{-5}$m)	Nor-alcohols ($\times 10^{-5}$m)	Total Isolated Cleavage Product ($\times 10^{-5}$m)
2 : 1	1·6	5·7	7·3
1 : 1	2·0	6·3	8·3
1 : 2	1·1	7·0	8·1

TABLE II.

Products Isolated from the Oxidations,
using Substrate / CrO_3 ratios 1 : 1·1

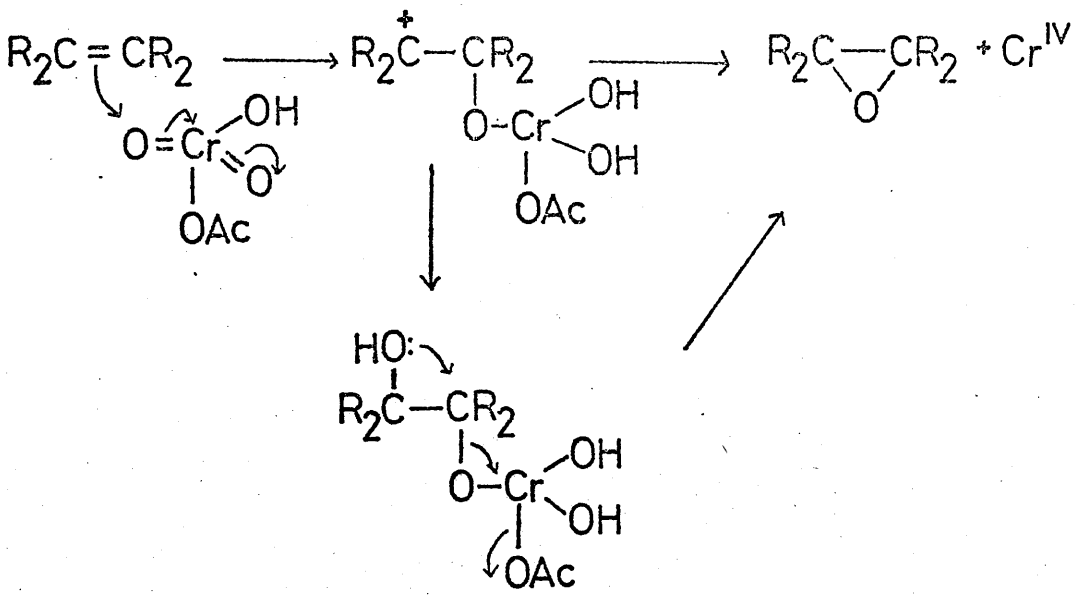
Substrate (1×10^{-3}m)	Normal Oxidation		Non-olefins ($\times 10^{-5}$m)	Non-alcohols ($\times 10^{-5}$m)	Total Cleavage Products ($\times 10^{-5}$m)
	Carbonyl ($\times 10^{-5}$m)	Carbonyl Epoxide ($\times 10^{-5}$m)			
Erythroxylol A (15)	35·6	4·6	2·3	6·4	8·7
Methyl Carbinol (155)	71·0	5·7	2·7	4·0	6·7
Ethyl Carbinol (162)	77·4 65·7	9·9 5·4	2·1 1·5	4·0 2·6	6·1 4·1[r]
Phenyl Carbinol (163)	71·4 72·2	7·1 7·1	1·7 3·8	1·6 2·2	3·3 6·0[r]
Erythroxylol A Epoxide (124)		45·3 33·6	4·7 4·4	8·5 15·3	13·3 19·7[r]
Dihydro-erythroxylol A (168)	13·6 33·2	(Acid) 27·8 19·8	9·7 5·1	27·7 17·7	37·4 22·8*
O-methyl-podocarpinol (177)	80·5+ 53·1+	7-Ketone 2·8** 8·4**	0·6 0·5	1·1 0·7	1·7 1·2[r]

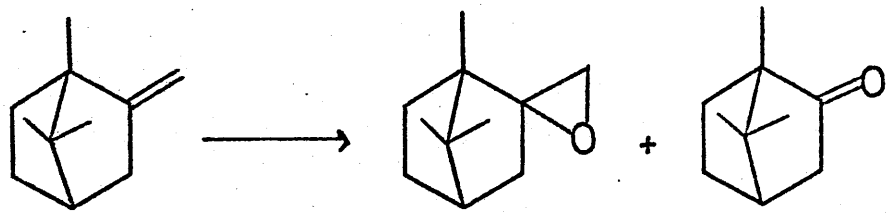
r repeat oxidation. ** benzylic oxidation.

\+ variation probably due to insolubility of substrate in aqueous acetic acid.

* these results are not comparable since oxidation carried out in an atmosphere of nitrogen.

Scheme I





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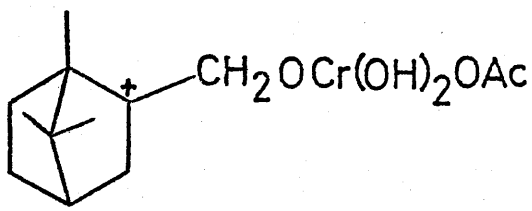

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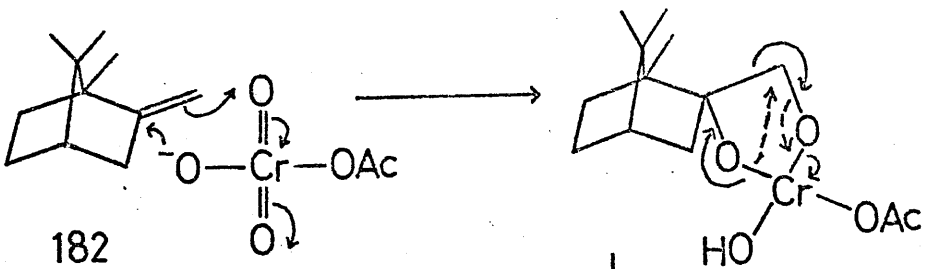
Discussion.

In this chromium trioxide/aqueous acetic acid medium, the functionalised hibaenes may clearly undergo three distinct oxidative processes (Table II). These comprise the normal oxidation of the primary and secondary alcohols, the epoxidation of the Δ^{15}-double bond (if present) and the cleavage of the C-4 hydroxymethyl group. The aldehydes formed presumably arise by a mechanism similar to that proposed[31] for the oxidation of secondary alcohols. Thus ester formation between the primary (or secondary) alcohol and the mixed anhydride, aceto-chromic acid[14], will probably be followed by an E_1 type elimination yielding the aldehyde (or ketone) and a reduced chromium species (vide supra).

The epoxidation of the reactive Δ^{15}-double bond in the hibaene skeleton is not unexpected since the epoxidation of olefins by chromic acid or its equivalent (aceto-chromic acid) has been well documented[31,32]. Epoxides have therefore been invoked as intermediates to account for some of the products obtained from chromic acid oxidations[31,33]. A mechanism proposed by Hickenbottom[34] involves nucleophilic attack by the double bond on a chromate oxygen to generate a carbonium ion-chromate ester (Scheme I) which can give rise to the epoxide by two possible routes as shown. Zeiss and Zwanzig[35] have shown, however, that 1-methylfenchene (182) yielded the corresponding epoxide (183) together with the nor-ketone (184). None of the products isolated had a rearranged skeleton as might be

Scheme II



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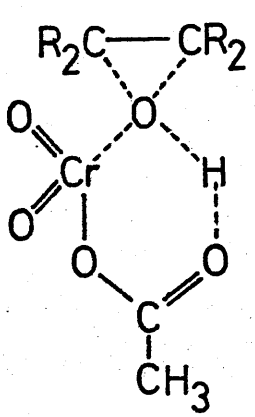
183 184



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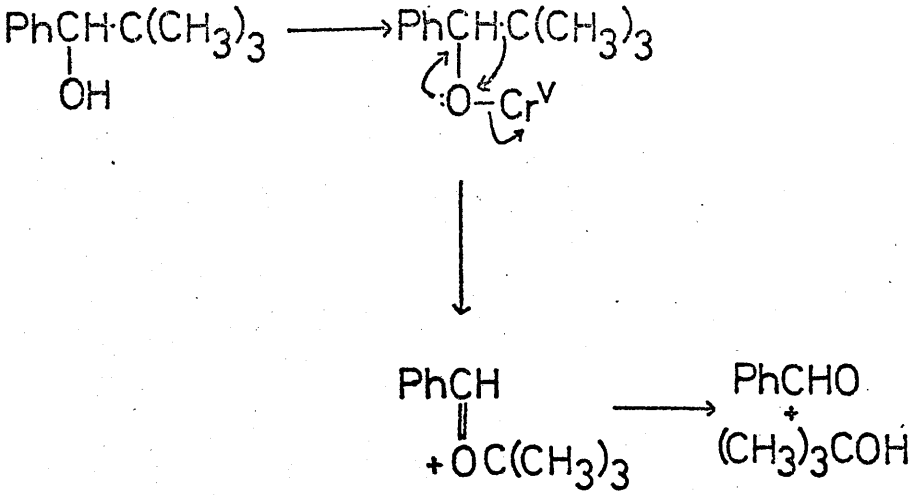
anticipated if a cationic intermediate of the type (185) were involved. From these observations an intermediate cyclic ester involving Cr(IV) was proposed[35] which could give rise to either of the observed products (Scheme II). Kinetic evidence has since been presented by Rocek[36] for the formation of a symmetrical cyclic intermediate of the type (186), analogous to an intermediate proposed in the epoxidation of olefins by peracid. Thus at present, the precise mechanism of epoxidation by Cr(VI), and whether Cr(V) or Cr(IV) participate in the reaction, is unknown.

The oxidative cleavage reaction, although novel for a primary alcohol, is not unknown for systems with complete substitution on the carbon atom adjacent to that bearing a hydroxyl group. Mosher and Whitmore[37] have isolated t-butyl alcohol and t-amyl alcohol from the oxidation of methyl t-butyl carbinol and methyl and isopropyl t-amyl carbinols respectively. A detailed study of the analogous cleavage of phenyl t-butyl carbinol to t-butanol and benzaldehyde (67%) and the simultaneous oxidation to phenyl t-butyl ketone (33%) suggested[8] that bond rupture is induced by an unstable pentavalent chromium ester. This is supported by the fact that lower yields of cleavage products are obtained when the reaction is carried out in the presence of Mn(II) and Ce(III) ions[8] and also by the direct observation of Cr(V) in aqueous acetic acid[9,10].

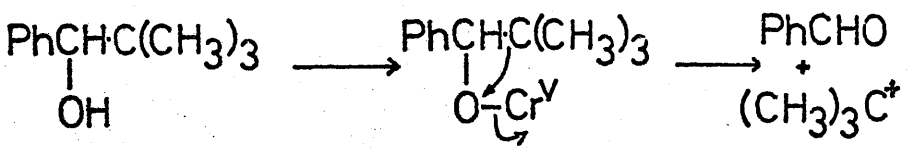
From the data available, two possible mechanisms D and E

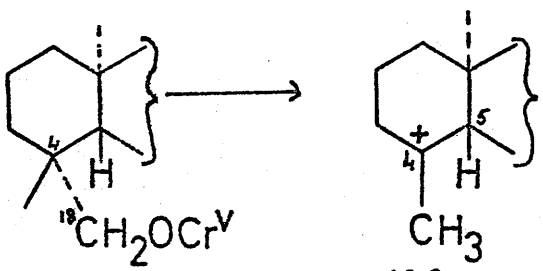
Mechanisms.

D)



E)





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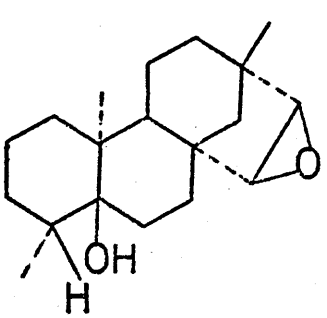


171

could be formulated. It was known, however, that phenyl t-butyl carbinol labelled with O^{18} did not give rise to labelled t-butanol[8]. This, taken in conjunction with the knowledge that the di-t-butyl acetal of benzaldehyde on hydrolysis in H_2O^{18} gave no labelled alcohol[38], served to eliminate mechanism D. Evidence in support of mechanism E, which involves a free carbonium ion, was derived from the oxidation of phenyl apocamphyl carbinol and phenyl adamantyl carbinol[39]. In the former no cleavage was observed which is in accord with the reluctance of the apocamphyl system to sustain a positive charge at the bridgehead. In addition, carbinols having less highly substituted α-carbons give rise to lower yields[40] of cleavage products as would be expected by the lower stability of secondary carbonium ions.

In the present study, the origin of the nor-diterpenoids isolated can best be explained as arising from the cleavage of the 18-hydroxymethyl group by a process analogous to mechanism E. Thus esterification of the alcohol, presumably with Cr(V), can be followed by heterolytic rupture of the C 4 - C 18 bond. The carbonium ion so formed (at C-4) could then give rise to the three nor-alkenes by deprotonation at any of the adjacent carbon atoms. Alternatively, nucleophilic attack at the centre of electron deficiency (predominantly from the less hindered side) would yield both of the epimeric nor-alcohols. The proposed mechanism involving a carbonium ion intermediate is also supported by the isolation of the rearranged nor-alcohol epoxide (171). Here it would appear

that a hydride shift has occurred from C-5 to C-4 followed by saturation of the electron deficient centre at C-5 (probably from the β-face).

From the results obtained in this series of experiments, the cleavage reaction would appear to show a dependence on steric factors in rather a surprising fashion (Table II). Replacement of one of the hydrogen atoms of the axial C-4 hydroxymethyl group in erythroxylol A by a methyl, ethyl or phenyl substituent should increase the steric compression across the α-face of the chair ring A, due to the 1,3-diaxial interaction with the C-10 methyl. If the cleavage reaction proceeds by the carbonium ion mechanism, rupture of the C 4 - C 18 bond should markedly reduce these non-bonded repulsive interactions and hence the bulkier the C-18 substituent the easier the cleavage reaction might become. Experimentally no increase in the amount of cleavage (c. 6%) of these bulky carbinols is observed relative to that found (c. 8%) for the unsubstituted primary alcohol; if anything, substitution results in a slight decrease in the degree of cleavage. Although there is an apparent increase in the products of normal oxidation from the secondary carbinol systems, it should be noted that the aldehydes, derived from the primary alcohols, are unstable both on standing under atmospheric conditions and in the oxidising medium. Thus an accurate figure for the conversion of the primary alcohols to the

corresponding aldehydes can not be given. Again, since the compounds listed in Table II were obtained after multiple isolation steps, the yields shown, although reproducible to some extent, cannot be regarded as completely accurate.

From steric considerations, the bulky substituent at C-4 (presumed to be axial with ring A in a twist chair, from examination of molecular models) should adopt a conformation whereby the preferred rotamer has the alkyl and hydroxyl groups on C-18 directed away from, and the C-18 hydrogen nearest to, the C-10 methyl group. If in normal oxidation, a mechanism involving proton abstraction [from a Cr(V) ester] by an external base gives rise to the ketonic products, the hindered environment of the C-18 proton should make this process more difficult and hence cleavage might be preferred. Again, this is not observed. However, the relief of non-bonded repulsive interactions which will occur on cleavage, will also be partially effected on conversion of the tetrahedral carbon at 18 to a trigonal state during normal oxidation. Since the oxidation of the secondary alcohols to the ketonic compounds (forming approximately 70% of the products) is still a favourable process, this could be accounted for by steric acceleration if a cyclic oxidative process were in operation (mechanism B, p.70). Thus the normal oxidative reaction and the oxidative cleavage reaction might both be favoured by an increase in steric compression across ring A and would account for the observed absence of an

increase in the proportion of cleavage products.

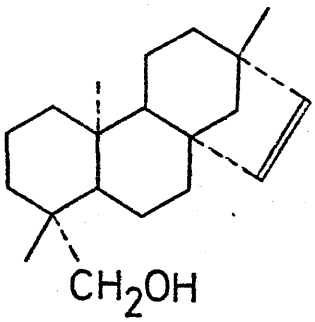
An alternative explanation for the results obtained might arise if the secondary carbinols exist to some extent with a boat ring A, although evidence of this is not available. It is probable, from n.m.r. evidence, that the derived ketones exist as rotameric mixtures with ring A in a chair conformation. This does not necessitate that the carbinol precursors exist in this form. If the boat ring A does exist, the severe steric interactions between the otherwise axial substituents at C-4 and C-10 are greatly relieved. Thus one deriving force for fragmentation would be lost while the normal oxidative process would still be favoured.

On examination of the products derived from the oxidation of erythroxylol A epoxide (124) and dihydroerythroxylol A (168), it was noted that the yields of normal oxidation products (c. 40%) (Table II) were of the same order of magnitude as that obtained from erythroxylol A (15). This is not unexpected since the environment in the region of the primary hydroxyl group is apparently identical in all three cases. However, it can be seen that much larger proportions of cleavage products were obtained from the epoxide (124) (c. 15%) and dihydro compound (168) (c. 37%). In these three primary alcohols only the functionality in ring D has changed, yet there is a marked effect on the degree of cleavage. It can be seen from molecular models that on proceeding from erythroxylol A to the corresponding

epoxide and then to the dihydro compound that the C-15 (or 15α) proton interacts more and more severely with the angular C-10 methyl group. The result of this interaction has already been observed in the n.m.r. spectra of the functionalised ring D compounds [Section A]. It would therefore seem that as the 15-proton approaches the C-10 methyl group, there is an increase in the compression between the methyl attached to C-10 and the 4α-hydroxymethyl group. This increase in internal energy must therefore account for the dramatic rise in the proportion of cleavage products. A similar long range buttressing effect has been observed[41] in the differing o.r.d. curves of a series of 3-ketones which differ in the hybridisation of C-15.

Substitution at C-4 would therefore seem to have little effect on the cleavage process, whereas modifications in ring D are found to have a surprisingly large effect. The following hypothesis is suggested. For the primary alcohols, the long range buttressing causes an increase in internal energy of ring A such that the cleavage process is favoured but which is not sufficient to cause conformational inversion of ring A. For the secondary alcohols, it is possible that ring A is conformationally distorted from the chair form. It would therefore be interesting to examine the oxidation of secondary carbinols having a tetrahedral geometry at C-15.

If ring D, and in particular the configuration about C-15, is influencing the scission of the C 4 - C 18 bond, the removal



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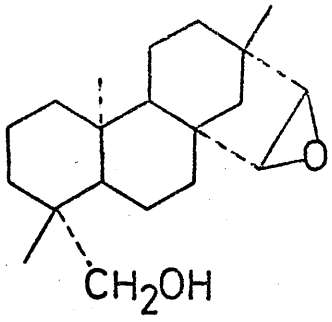

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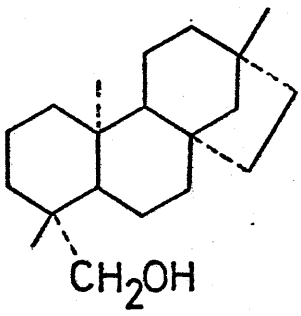
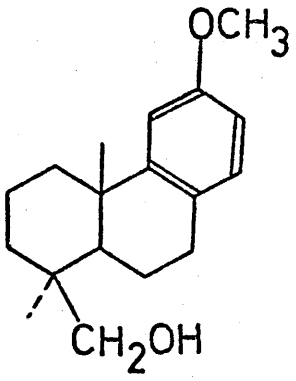


168



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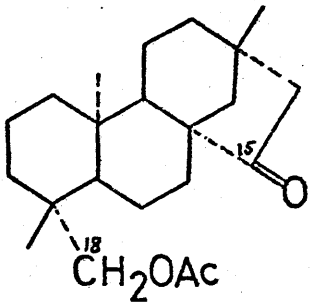
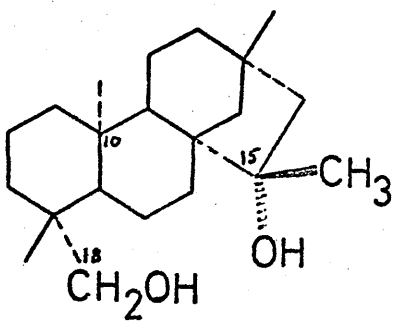


144



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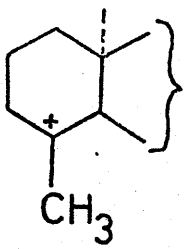
of the 1,3-diaxial interaction across ring B should markedly decrease the yields of nor-products. This has indeed been found, since the oxidation of O-methylpodocarpinol (177) gives total cleavage products amounting to approximately 1·5%. Although this reaction is complicated by varying amounts of benzylic oxidation, the amount of cleavage products is much less than found for erythroxylol A.

The carbocyclic skeletons used in these oxidations have all possessed a trans A/B ring junction with methyl and hydroxymethyl groups in a 1,3-diaxial relationship. If, however, the primary alcohol group has an equatorial orientation, its interaction with the C-10 methyl is absent and should therefore have the same effect as the removal of ring D. Thus one might predict that compounds having an equatorial $-CH_2OH$ would give rise to only very small amounts of cleavage products.

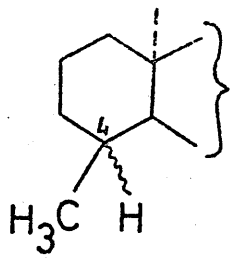
To further confirm the influence of ring D on the cleavage reaction, it was hoped that 15β-methyl-15α,18-dihydroxyhibane (187) could be prepared and oxidised. In this system the bulkier α-substituent at C-15 should serve to increase the interaction with the 10-methyl and hence increase the proportion of cleavage products. This diol has the added advantage that the 15-hydroxyl, being tertiary, should not oxidise appreciably. Up to the present time, however, the synthesis of the diol (187) from 15-keto-18-acetoxyhibane (144) has been unsuccessful. Treatment of the ketone (144) with methylmagnesium iodide

resulted only in the removal of the acetate function without significant attack on the ketone grouping. The use of methyl lithium in the synthesis has also been unsuccessful. This probably reflects both the hindered nature of the 15-ketone and also the reluctance of a 15-hydroxyl to adopt an α-orientation.

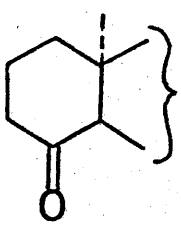
The least polar fractions derived from the oxidations of the three primary alcohols (15), (124) and (168) respectively, consisting mainly of the mixture of isomeric nor-olefins, have created an unexpected problem. The mass spectrum of each fraction shows, in addition to the parent ion expected for such olefins, a peak two mass units higher. The origin of this peak is still unresolved. It should be remembered that the hydrocarbon fraction from the oxidation of dihydroerythroxylol A under nitrogen does not show this ion in the mass spectrum whereas the corresponding fraction from the oxidation in air does. Again, the g.l.c. analysis of the hydrocarbon mixture from the former reaction shows only one peak whereas that from the latter reaction shows an additional peak of slightly shorter retention time on the column used (2·5% SE 30). The i.r. spectrum of both fractions show the expected absorption bands at 1647 and 889 $cm.^{-1}$ but the n.m.r. spectrum of the fraction from the oxidation in air shows little absorption in the vinyl region, although it can be interpreted as showing a new secondary methyl group.



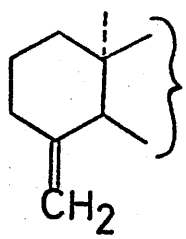
188



189



190



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The following possibilities exist.

(a) The anomalous compounds could arise as a result of a modified Cannizzaro reaction. This would necessitate an intermolecular hydride shift from an aldehyde to the proposed intermediate carbomium ion (188) and result in the formation of the nor-compound (189) and the acid corresponding to the aldehyde. However, the M+2 peak has been observed in the olefin mixture derived from the ethyl carbinol. Here an aldehyde cannot be formed and hence this possibility is eliminated.

(b) The compound could arise from decarbonylation of an aldehyde. Again, for the above reason this is not possible.

(c) The M+2 peak might be due to small amounts of a bis-norketone (190) derived from the $\Delta^{4(19)}$-olefin (191) by oxidative fission of the double bond. High resolution mass measurements were made on the M and M+2 peaks observed in the mass spectrum of the hydrocarbons derived from erythroxylol A. This gave the masses as 256·2158 ($C_{19}H_{28}$ requires 256·2190) and 258·2341 ($C_{19}H_{30}$ requires 258·2347; $C_{18}H_{26}O$ requires 258·1984) respectively. Thus the M+2 peak corresponds to $C_{19}H_{30}$ (189) which is in agreement with the n.m.r. observation that the compound has a secondary methyl group at C-4.

If this problem is to be satisfactorily resolved, labelling studies must be carried out to determine the source of the C-4 proton and hence determine how a reduction product can be formed in an oxidising medium.

EXPERIMENTAL

For general experimental see Section A. I.r. spectra refer to carbon tetrachloride solutions unless otherwise stated. N.m.r. spectra were obtained in carbon tetrachloride unless otherwise stated. High resolution mass measurements were obtained on an AEI-GEC MS 9 mass spectrometer. Aqueous acetic acid refers to glacial acetic acid-water (19:1). The oxidations were carried out using a stock solution of chromium trioxide (7·6 g.) in aqueous acetic acid (250 ml.) and using a substrate-CrO_3 ratio of 1 : 1·1 unless otherwise stated.

Oxidation of Erythroxylol A (15).

To a solution of erythroxylol A (1·7 g.) in aqueous acetic acid (20 ml.) was added a solution of chromium trioxide in aqueous acetic acid (16 ml.) and the mixture set aside at room temperature for 2 hr. It was then diluted with water and extracted with ether, and the extracts washed successively with aqueous sodium bicarbonate and water, dried and evaporated. The residual oil (1·4 g.) was chromatographed over alumina (Woelm, neutral, grade 3, 140 g.) in light petroleum. Elution with that solvent afforded initially a hydrocarbon fraction (35 mg.) containing a mixture of the three dienes (150), (151) and (152) which were identical (i.r., t.l.c., g.l.c.) to the dienes previously isolated [Section A], together with traces of a fourth unidentified compound. These were all separable on analytical g.l.c. (3% OV 22, 150°, 35 ml. argon/min., 23, 24, 21 and 17 min. respectively). The mass spectrum of this mixture, after sublimation at 70-75° / 0·03 mm., shows a parent ion (M)

at m/e 256 ($C_{19}H_{28}$) and an M+2 peak at m/e 258. Continued elution with light petroleum gave the aldehyde (154) (600 mg.), m.p. 63-65° (after sublimation at 100° / 0·04 mm.). Subsequent elution with ethyl acetate yielded an oil (440 mg.) which, after acetylation with acetic anhydride and pyridine, was further separated by preparative t.l.c. [ethyl acetate-light petroleum (1:4)]. In order of decreasing mobility the following fractions were obtained: (i) a fraction containing erythroxylol A acetate (70 mg.), m.p. 72-73·5° (from methanol); (ii) a mixture containing traces of 4α-hydroxy-18-norhibaene (119), identified solely by its characteristic staining reaction on t.l.c. [Section A], and the aldehyde epoxide (160) (81 mg.), m.p. 105-107° (after repeated crystallisation from methanol) (Found: C, 79·7; H, 10·05. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%); (iii) a fraction containing erythroxylol A acetate epoxide (120) (30 mg.), m.p. 143-145° (from methanol); (iv) a mixture which, after further preparative t.l.c. [ethyl acetate-light petroleum (1:1)] on silver nitrate-impregnated silica, yielded 4β-hydroxy-18-norhibaene (121) (76 mg.), m.p. 114-116° (from light petroleum); and (v) a fraction containing only 4β-hydroxy-18-norhibaene epoxide (161) (30 mg.), m.p. 136-138° (rods from light petroleum b.p. 60-80°) (Found: C, 78·75; H, 10·55. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%).

The results calculated for 1 x 10^{-3} moles erythroxylol A consumed are shown in Table II .

Oxidation of 18-Aldehydo-hibaene (154) and 4β-Hydroxy-18-norhibaene (121

(i) The aldehyde (154) (40 mg.) in chloroform (4 ml.) was treated with m-chloroperbenzoic acid (45 mg.) in chloroform (3 ml.) at room temperature for 30 min. Filtration of the mixture through a short column of alumina (Woelm, basic, grade 2, 5 g.) and elution with chloroform (50 ml.) gave the aldehyde epoxide (160) (83 mg.), m.p. 104-107° (from methanol), having identical i.r., n.m.r., m.p. and t.l.c. mobility to the epoxide obtained from the oxidation of erythroxylol A.

(ii) The alcohol (121) (20 mg.) in chloroform (2 ml.) was treated with m-chloroperbenzoic acid (25 mg.) in chloroform (2 ml.) at room temperature for 20 min. Work up as above yielded 4β-hydroxy-18-norhibaene epoxide (161) (15 mg.), m.p. 135-138° (from light petroleum b.p. 60-80°) identical (i.r., n.m.r., m.p. and t.l.c. mobility) to the alcohol epoxide obtained from the oxidation of erythroxylol A.

Treatment of Aldehyde (154) with CrO_3 in aqueous Acetic Acid.

The aldehyde (154) (20 mg.) obtained after sublimation to remove decomposition products was dissolved in aqueous acetic acid (1 ml.) and treated with the stock solution of CrO_3 (2 ml.) at room temperature for 1 hr. Work up as in the oxidation of erythroxylol A yielded an oil (15 mg.) which was shown to consist [solely by t.l.c., ethyl acetate-light petroleum (1:19)] predominantly of recovered aldehyde although several other products of low mobility were also present. None of the cleavage products could be identified as being present.

Effect of CrO_3 Concentration on the amount of Cleavage Products formed.

To three separate solutions of erythroxylol A (290 mg. each) in aqueous acetic acid (8, 6 and 2 ml. respectively) was added the stock solution of CrO_3 (2, 4 and 8 ml. respectively). After standing at room temperature for 1 hr., the separate reaction mixtures were worked up to give oils (274, 270 and 232 mg. respectively). Subsequent chromatography over alumina (Woelm, neutral, grade 3, 30 g.) of the separate reaction mixtures and further purification by t.l.c. yielded: erythroxylol A acetate (159) (15, 6 and trace mg. respectively), erythroxylol A acetate epoxide (120) (2·5, trace and 0 mg. respectively), the nor-olefin mixture (150-152) (4, 5 and 3 mg. respectively), and 4β-hydroxy-18-norhibaene (121) (15, 17 and 20 mg. respectively).

The results calculated for 1 x 10^{-3} moles erythroxylol A consumed are given in Table I.

Conversion of the Aldehyde (154) to the Secondary Carbinols.

(i) The aldehyde (154) (180 mg.) in dry ether (5 ml.) was added to methylmagnesium iodide [prepared from magnesium (20 mg.) and methyl iodide (0·5 ml.)] in ether (7 ml.) and the mixture kept at reflux for 30 min. The mixture was worked up with dilute sulphuric acid and extracted with ether. The extracts were washed with water, dried and evaporated to give an oil which, after preparative t.l.c. [ethyl acetate-light petroleum (1:19)], gave the methyl carbinol (155) (180 mg.), m.p. 40-57° (rods from methanol).

(ii) The aldehyde (154) (370 mg.) in dry ether (20 ml.) was

added to ethylmagnesium bromide [prepared from magnesium (90 mg.) and ethyl bromide (1·5 ml.)] in ether (20 ml.) and the mixture kept at reflux for 30 min. Work up as above and preparative t.l.c. [ethyl acetate-light petroleum (1:6)] afforded the ethyl carbinol (162) (385 mg.), m.p. 55-85° (prisms from methanol).

(iii) The aldehyde (154) (265 mg.) in dry ether (15 ml.) was added to phenylmagnesium bromide [prepared from magnesium (50 mg.) and bromobenzene (1 ml.)] in ether (15 ml.) and the mixture kept at reflux for 30 min. Work up as above and preparative t.l.c. [ethyl acetate-light petroleum (1:9)] yielded the phenyl carbinol (163) (223 mg.), m.p. 140-172° (prisms from methanol).

Oxidation of the Methyl Carbinol (155).

The methyl carbinol (155) (172 mg.) in aqueous acetic acid (7 ml.) was treated with the stock solution of CrO_3 (1·8 ml.) at room temperature for 1 hr. Methanol (5 ml.) was then added to the reaction mixture and after 5 min. the bulk of the solvent was removed under reduced pressure. The residue was neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated to give a solid (167 mg.). Preparative t.l.c. [ethyl acetate-light petroleum (1:5)] of the product mixture gave in order of decreasing mobility: (i) a hydrocarbon fraction (3·8 mg.) containing a mixture of the isomeric dienes (150-152) identical (i.r., g.l.c. and t.l.c. on silver nitrate-impregnated silica) to those

previously isolated; (ii) the major product, the methyl ketone (153) (117 mg., 71%), m.p. 67-69° (after sublimation at 60-65°/ 0·05 mm.) identical to that previously isolated [Section A]; (iii) a mixture (7 mg.) containing recovered methyl carbinol (155) with traces of 4α-hydroxy-18-norhibaene (119), the latter being identified solely by t.l.c.; (iv) the methyl ketone epoxide (156) (10 mg.), m.p. 150-152° (from light petroleum), identical to that previously isolated [Section A]; and (v) 4β-hydroxy-18-norhibaene (121) (6 mg.).

The results calculated for 1 x 10^{-3} moles methyl carbinol consumed are shown in Table II.

Oxidation of the Ethyl Carbinol (162).

(i) The ethyl carbinol (162) (186 mg.) in aqueous acetic acid (7 ml.) was treated with the stock solution of chromium trioxide (1·8 ml.) at room temperature for 1 hr. Work up as for the methyl carbinol gave an oil (174 mg.). Preparative t.l.c. [ethyl acetate-light petroleum (1:5)] of the product mixture yielded in order of decreasing mobility: (i) a hydrocarbon fraction (2 mg.) containing a mixture of the isomeric dienes (150-152) identical (i.r., t.l.c., g.l.c.) to those isolated from the erythroxylol A oxidation. The mixed hydrocarbons, after sublimation at 70-73°/0·03 mm., show in the mass spectrum a parent ion (M) at m/e 256 ($C_{19}H_{28}$) as well as an M+2 peak at m/e 258; (ii) the major product, the ethyl ketone (164) (105 mg., 65·7%), m.p. 38-41° (after sublimation at 70-75°/0·03 mm.)

(Found: C, 84·3; H, 10·9. $C_{22}H_{34}O$ requires C, 84·0; H, 10·9%); (iii) recovered ethyl carbinol (162) (22 mg.); (iv) a mixture which, after further preparative t.l.c. [ethyl acetate-light petroleum (1:5)] yielded a further quantity of the ethyl carbinol (3 mg.) and the ethyl ketone epoxide (165) (9 mg.), m.p. 133-136° (after sublimation at 140°/0·05 mm.) (M, 330. $C_{22}H_{34}O_2$ requires M, 330: from mass spectrometry); and (v) 4β-hydroxy-18-norhibaene (121) (4 mg.).

(ii) Repeat. The ethyl carbinol (108 mg.) in aqueous acetic acid (2·4 ml.) was treated with the stock solution of CrO_3 (1·1 ml.) as above. Work up and separation as above gave: (i) the hydrocarbon mixture (1·5 mg.); (ii) the ethyl ketone (67 mg., 77%); (iii) recovered ethyl carbinol (21 mg.); (iv) the ethyl ketone epoxide (9 mg.); (v) 4β-hydroxy-18-norhibaene (3 mg.).

The results calculated for 1 x 10^{-3} moles of ethyl carbinol consumed are shown in Table II.

Oxidation of the Phenyl Carbinol (163).

(i) The phenyl carbinol (163) (179 mg.) in aqueous acetic acid (7 ml.) was treated with the stock solution of CrO_3 (1·6 ml.) at room temperature for 1·5 hr. Work up as for the methyl carbinol yielded a solid product mixture (179 mg.) which was separated by preparative t.l.c. [ethyl acetate-light petroleum (1:19)]. This afforded the following fractions in order of decreasing mobility: (i) a mixture of hydrocarbons (4 mg.) identical with those previously isolated; (ii) the phenyl ketone (166) (107 mg., 72%), m.p. 155-156·5°

(plates from ether) (Found: C, 86·25; H, 9·45. $C_{26}H_{34}O$ requires C, 86·15; H, 9·45%); (iii) recovered phenyl carbinol (163) (30 mg.); (iv) the phenyl ketone epoxide (167) (11 mg.), m.p. 206-208° (prisms from ether) (M, 378. $C_{26}H_{34}O_2$ requires M, 378: from mass spectrometry); and (v) a mixture from which 4β-hydroxy-18-norhibaene (121) (2·5 mg.) was isolated after further preparative t.l.c. [ethyl acetate-light petroleum (1:5)].

(ii) Repeat. The phenyl carbinol (184 mg.) in aqueous acetic acid (6 ml.) was treated with the stock solution of CrO_3 (1·7 ml.) as above. Work up and separation as above gave: (i) the hydrocarbon mixture (2 mg.); (ii) the phenyl ketone (116 mg.); (iii) recovered phenyl carbinol (21 mg.); (iv) the phenyl ketone epoxide (12 mg.); and (v) the nor-alcohol (121) (2 mg.).

The results calculated for 1 x 10^{-3} moles phenyl carbinol consumed are shown in Table II.

Oxidation of Erythroxylol A Epoxide (124).

(i) Erythroxylol A epoxide (124) (1·46 g.) in aqueous acetic acid (23 ml.) was treated with the stock solution of CrO_3 (15·4 ml.) at room temperature for 1 hr. Methanol (10 ml.) was then added to the reaction mixture. After 5 minutes the bulk of the solvent was removed under reduced pressure and the residue neutralised with aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the extracts washed with water, dried and evaporated to give an oil (1·36 g.). The crude product was chromatographed over alumina (Merck, grade H, 60 g.) in light petroleum.

Elution with that solvent yielded initially a mixture (56 mg.) containing three major components, presumably the isomeric epoxy-olefins (169), together with a fourth unidentified compound (present in very minor amounts) which could be separated by analytical g.l.c. (2·5% SE 30, 220°, 16 lb./in.^{2} nitrogen, 24, 26, 27 and 15 min. respectively). This mixture (Found: C, 83·67; H, 10·6. $C_{19}H_{28}O$ requires C, 83·75; H, 10·35%), after sublimation at 85-90°/0·04 mm., shows in the mass spectrum a 'parent' ion (M) at m/e 272 ($C_{19}H_{28}O$) as well as an M+2 peak at m/e 274. Subsequent elution of the reaction mixture with ether-light petroleum (1:4) gave the aldehyde epoxide (160) (468 mg., 34%), m.p. 104-107° (from light petroleum), identical (i.r., t.l.c., m.p.) with that isolated previously. Elution with ether-light petroleum (1:1) gave a series of fractions containing mixtures which could be further separated by preparative t.l.c. [ethyl acetate-light petroleum (2:3)]. These mixtures yielded the following in order of decreasing mobility: (i) a rearranged nor-alcohol epoxide, tentatively formulated as (171) (10 mg.), m.p. 156·5-158° (prisms from ether-light petroleum) (M, 290. $C_{19}H_{30}O_2$ requires M, 290: from mass spectrometry); (ii) 4α-hydroxy-18-norhibaene epoxide (170) (25 mg.), m.p. 112-114° (after sublimation at 115-120°/0·04 mm.) (Found: C, 78·3; H, 10·35. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%). This compound had identical i.r. and t.l.c. mobility as the product obtained from the treatment of 4α-hydroxy-18-norhibaene with m-chloroperbenzoic

acid; (iii) 4β-hydroxy-18-norhibaene epoxide (161) (158 mg.), m.p. 136-138° (from light petroleum), identical (i.r., n.m.r., m.p., t.l.c.) to that obtained from the oxidation of erythroxylol A; and (iv) recovered erythroxylol A epoxide (29 mg.).

(ii) Repeat. Erythroxylol A epoxide (1·53 g.) in aqueous acetic acid (25 ml.) was treated with the stock solution of CrO_3 (16·5 ml.) as above. Work up gave an oil (1·32 g.) which after separation as above, gave the following fractions: (i) the mixture of nor-olefin epoxides (169) (64 mg.); (ii) the aldehyde epoxide (160) (675 mg., 45%); (iii) the rearranged nor-alcohol epoxide (171) (16 mg.); (iv) the 4α-hydroxy-18-norhibaene epoxide (170) (15 mg.); (v) the 4β-hydroxy-18-norhibaene epoxide (161) (91 mg.); and (vi) recovered erythroxylol A epoxide (35 mg.).

The results calculated for 1×10^{-3} moles erythroxylol A epoxide consumed are shown in Table II.

Oxidation of 4α-Hydroxy-18-norhibaene (119).

The alcohol (119) (7 mg.) in chloroform (1 ml.) was treated with m-chloroperbenzoic acid (12 mg.) in chloroform (1 ml.) at room temperature for 20 min. Work up as before yielded 4α-hydroxy-18-norhibaene epoxide (170) (7 mg.), m.p. 111-114° (after sublimation at 115-120°/0·05 mm.).

Attempted Dehydration of the Rearranged Nor-alcohol (171).

The nor-alcohol (171) (5 mg.) in pyridine (1·5 ml.) under reflux was treated with redistilled phosphoryl chloride (0·3 ml.)

for 3 hr. The mixture was poured on to ice, extracted with ether, and the extracts washed with water and dried. Evaporation of the solvent gave an oil which was shown by analytical t.l.c. [ethyl acetate-light petroleum (1:4)] to consist of several compounds, each more polar than the starting alcohol.

Oxidation of Dihydroerythroxylol A (168).

(i) Dihydroerythroxylol A (168) (243 mg.) in aqueous acetic acid (7 ml.) was treated with the stock solution of CrO_3 (2·8 ml.) at room temperature for 1 hr. Methanol was then added and after 5 min. the bulk of the solvent removed under reduced pressure. The residue was neutralised with aqueous sodium bicarbonate solution, extracted with ethyl acetate and the extracts washed with water, dried and evaporated. The oil (236 mg.) so obtained was separated by preparative t.l.c. [ethyl acetate-light petroleum (1:9)] which resulted in the isolation of the following in order of decreasing mobility: (i) a mixture of nor-hydrocarbons (21 mg.), presumably containing the mixture of nor-olefins (176) but which only shows two major peaks (c. 1:1) on analytical g.l.c. (2·5% SE 30, 200°, 16 lb./in.^{2} nitrogen, 10 and 11 min. respectively). This mixture (after sublimation at 70-75°/0·02 mm.) shows the expected ion at m/e 258 ($C_{19}H_{30}$) and a more intense peak at m/e 260 (M+2); (ii) the aldehyde (173) (33 mg.), m.p. 69-71·5° (after sublimation at 55-60°/0·02 mm.) (lit.[28] m.p. 68-70°). The more polar material was treated with diazomethane and subjected to further preparative t.l.c. [ethyl acetate-light petroleum (1:9)].

This yielded (i) the methyl ester of isostevic acid (172) (74 mg.), m.p. 140-143° (from methanol) (lit.[28] m.p. 143-144°); (ii) 4α-hydroxy-18-norhibaene (174) (12 mg.), m.p. 79·5-83° (after sublimation at 80-85°/0·02 mm.) (Found: C, 82·5; H, 11·6. $C_{19}H_{32}O$ requires C, 82·55; H, 11·65%) which was identical (i.r., t.l.c.) with the product obtained from hydrogenation of 4α-hydroxy-18-norhibaene (119); and (iii) 4β-hydroxy-18-norhibane (175) (52 mg.), m.p. 121-123·5° (needles from light petroleum, b.p. 60-80°) (Found: C, 82·4; H, 11·6%), which was identical (i.r., m.p., n.m.r., t.l.c.) to the product obtained from hydrogenation of 4β-hydroxy-18-norhibaene (121).

(ii) Dihydroerythroxylol A (168) (261 mg.) in aqueous acetic acid (7 ml.) was allowed to stand under a current of nitrogen for 30 min. The stock solution of CrO_3 (3 ml.) was then added dropwise over a period of 30 min. and the reaction allowed to stand at room temperature for a further 30 min. (the reaction being carried out under nitrogen). Work up as above yielded an oil (231 mg.) which after the isolation steps listed above yielded: (i) a hydrocarbon fraction (12 mg.) which showed only one peak on analytical g.l.c. (2·5% SE 30, 200°, 16 lb./in.^{2} nitrogen, 11 min.). This presumably contains the isomeric olefinic hydrocarbons (176) since the i.r. spectrum shows absorption bands at 1647 and 889 cm.$^{-1}$ and the mass spectrum of the presumed mixture shows a peak at m/e 258 ($C_{19}H_{30}$) but the M+2 peak is absent; (ii) the saturated aldehyde (173) (86 mg.); (iii) isostevic acid methyl ester (172)

(56·5 mg.); (iv) 4α-hydroxy-18-norhibane (174) (6 mg.); and (v) 4β-hydroxy-18-norhibane (175) (38 mg.).

The results calculated for 1 x 10^{-3} moles dihydroerythroxylol A consumed are shown in Table II.

Hydrogenation of the Epimeric Nor-alcohols (119) and (121).

(i) 4α-hydroxy-18-norhibaene (119) (4 mg.) in ethyl acetate (3 ml.) was hydrogenated over 10% palladium-charcoal (4 mg.) for 15 min. The catalyst was removed by filtration, washed with ethyl acetate and the solvent evaporated to give 4α-hydroxy-18-norhibane (174) (4 mg.).

(ii) 4β-hydroxy-18-norhibaene (121) (25 mg.) in ethyl acetate (5 ml.) was hydrogenated over 10% palladium-charcoal (20 mg.) for 15 min. Work up as before gave 4β-hydroxy-18-norhibane (175) (26 mg.), m.p. 120-122° (from light petroleum).

Oxidation of O-Methylpodocarpinol (177).

(i) O-Methylpodocarpinol (177) (673 mg.) in aqueous acetic acid (20 ml.) was treated with the stock solution of CrO_3 (8·5 ml.) at room temperature for 2 hr. The reaction mixture was kept for a greater length of time at room temperature since the system was heterogeneous. Methanol (5 ml.) was then added and after 5 min. the bulk of the solvent removed under reduced pressure. The residue worked up as before with aqueous sodium bicarbonate, washed with water, dried and evaporated to give an oil (587 mg.). This was chromatographed over alumina (Merck, grade H, 90 g.) in light petroleum. Elution with that solvent gave a non-polar

fraction (3 mg.) which probably contains the mixed nor-compounds (180). This fraction, after sublimation at 90-95°/0·03 mm. (lit.[30] b.p. 100-102°/0·2 mm.), shows two peaks (c. 4:1) on analytical g.l.c. (2·5% SE 30, 230°, 16 lb./in.^{2} nitrogen, 13 and 14 min. respectively) and a peak in the mass spectrum at m/e 242 ($C_{17}H_{22}O$), the peak at M+2 being absent. Elution with ether-light petroleum (1:4) gave the aldehyde (178) (456 mg.), m.p. 133-135° (rods from light petroleum) (lit.[42] m.p. 133-135°). Subsequent elution with ethyl acetate gave a complex mixture which was acetylated with acetic anhydride and pyridine to facilitate its separation. Preparative t.l.c. (chloroform) of the acetylated material gave the following in order of decreasing mobility: (i) O-methylpodocarpinol acetate (119 mg.), m.p. 75-76° (plates from methanol); (ii) the aldehydo-ketone (179) (17 mg.), m.p. 97-99° (after sublimation at 105-110°/0·02 mm.) (M, 286. $C_{18}H_{22}O_3$ requires M, 286); and (iii) 4α-hydroxy-12-methoxy-15-norpodocarpane (181) (6 mg.), b.p. 85-88°/0·03 mm. (lit.[30] m.p. 107-109°) showing a parent ion in the mass spectrum at m/e 260 ($C_{17}H_{24}O_2$).

(ii) Repeat. O-Methylpodocarpinol (177) (539 mg.) in aqueous acetic acid (20 ml.) was treated with the stock solution of CrO_3 (7 ml.) at room temperature for 2 hr. Work up and separation as above gave: (i) the nor-compounds (180) (2 mg.); (ii) the aldehyde (178) (241 mg.); (iii) the aldehydo-ketone (179) (50 mg.); (iv) O-methylpodocarpinol acetate (96 mg.); and (v) 4α-hydroxy-

12-methoxy-15-norpodocarpane (131) (3 mg.).

The results calculated for 1 x 10^{-3} moles O-methylpodocarpinol consumed are shown in Table II.

Attempted Synthesis of 15β-Methyl-15α,18-dihydroxyhibane (187).

(i) 15-Keto-18-acetoxyhibane (144) (15 mg.) in ether (3 ml.) was added to methylmagnesium iodide [prepared from magnesium (8 mg.) and methyl iodide (50 mg.)] in ether (10 ml.) and the mixture kept at reflux for 1 hr. Work up as before and preparative t.l.c. [ethyl acetate-light petroleum (1:4)] gave 15-keto-18-hydroxyhibane (139) (10 mg.), m.p. 141-143·5° (from ether-light petroleum), identical with that previously isolated [Section A].

(ii) 15-Keto-18-acetoxyhibane (144) (15 mg.) in dry ether (1 ml.) was added to methyl lithium [prepared from lithium (20 mg.) and methyl iodide (250 mg.)] in ether (5 ml.) and the mixture kept at reflux for 4 hr. The reaction mixture was worked up with a saturated solution of ammonium chloride, extracted with ether, and the extracts washed with water, dried and evaporated. The solid residue (10 mg.) was shown by analytical t.l.c. [ethyl acetate-light petroleum (1:3)] to consist entirely of recovered keto-acetate (144).

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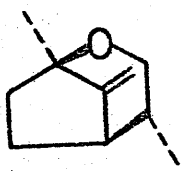
S E C T I O N C.

Insect Phagostimulants.

Steam Volatile Constituents

of

Solanum campylacanthum.



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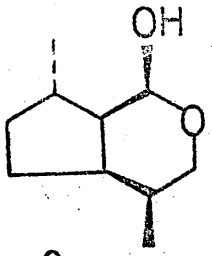

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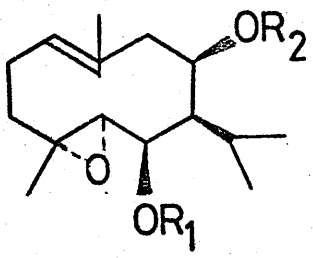

3 R_1=H , R_2=Ac

4 R_1= R_2=Ac

It has been recognised that certain species of insect will attack one plant or family of plants in preference to others[1]. One outstanding example of this is the Colorado beetle and the disastrous effect it has on the potato plant, Solanum tuberosum, but research work with such an insect is handicapped by the severe restrictions placed on its use. The coccinellid genus, Epilachna, which are known[2] to feed either on the Solanaceae or Cucurbitaceae, have also been shown, by hostplant records, to feed predominantly on plants of a single family.

It would appear likely that chemical factors are important in hostplant selection, some of the constituents acting as attractants or feeding stimulants (phagostimulants) for the insects. Such investigations have revealed attractants such as matatabiether[3] (1) and neomatatabiol[4] (2) as well as phago-repellents[5] such as the mono- and diacetates of shiromodiol[6] (3) and (4). Stride[2], studying the behaviour of the beetle Epilachna fulvosignata on the solanaceous plant Solanun campylacanthum, has concluded that the leaves of this plant must contain a phagostimulant since the larvae feed on this species preferentially.

By steam distillation of fresh leaves of S. campylacanthum, Stride isolated a volatile, pleasant smelling, yellow oil, which, when impregnated on agar jelly, stimulated the Epilachna to feed. This oil, containing his 'steam volatile factor'[2], is the subject of the following discussion. Initial qualitative g.l.c. studies

on the crude oil at Makerere University, Kampala, led to the conclusion[7] that the mixture contained up to 95% of a single compound. Later evidence[8], including t.l.c. and g.l.c. studies, did not concur with these results and suggested that the mixture contained several compounds which were probably very closely related chemically.

The crude oil can be partially resolved by t.l.c. into three fractions A, B and C (Fig. 1). It was found[7] that

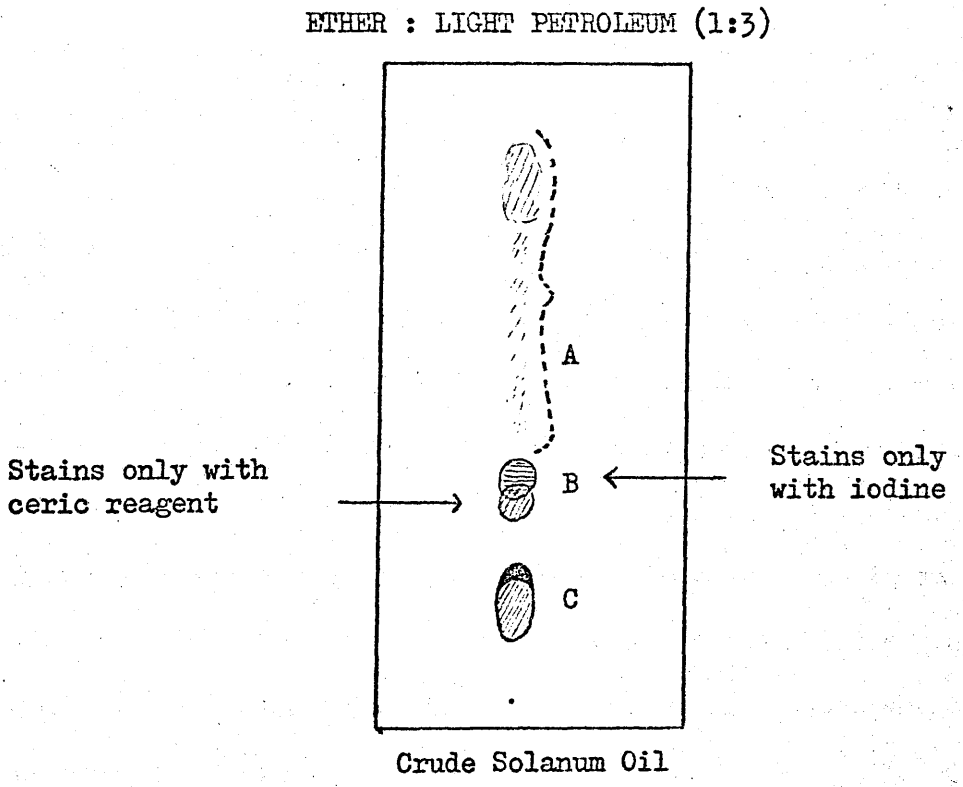

Fig. 1.

fraction B showed variable activity whereas fraction C always showed phagostimulant properties. Stride in some preliminary work came to the conclusion[7] that C was the major compound, B was probably one compound while A, which stains with difficulty, was a mixture of at least two compounds. It was therefore decided that research should be directed mainly towards the fractions B and C.

Our studies have been hampered by the pronounced volatility of the compounds involved, which even made staining on t.l.c. difficult. The t.l.c. plates had to be developed with iodine vapour, then before the spots faded, the plates sprayed with a solution of ceric ammonium sulphate (1%) in 4N sulphuric acid followed by rapid heating to 130° in an oven then kept at that temperature for four to five minutes. Iodine alone gives only a transient picture whereas ceric ammonium sulphate alone is unsatisfactory since the compounds evaporate before oxidation occurs. By use of this staining technique, it could be seen that fraction B consisted of two overlapping spots, the more mobile of which stains only with iodine whereas the less mobile stains only after treatment with the ceric reagent. In addition, fraction C was shown to stain more heavily at the head of the spot suggesting that at least two compounds were also present in this fraction.

Numerous attempts at fractionation of the crude oil were made before a suitable procedure for rough separation and recovery

was found. A convenient separation could be made as follows. The crude oil (approx. 150 mg.) was divided into two portions and subjected to preparative t.l.c. [ether-light petroleum (1:4)] on two chromatoplates. In this way overloading was reduced and a better separation of fractions A, B and C (Fig. 1) resulted. The complete extraction of the silica and then efficient removal of the solvent presented a problem. The material could be extracted by allowing ether (7 to 10 portions of 5 ml. each) to percolate through the silica until the characteristic odour of the material was no longer detectable on the silica. The solution so obtained (c. 50 ml.) was carefully concentrated to around 5 ml. Complete evaporation of the solvent by mild heating resulted in the loss of material by co-distillation and hence recovery of only a few milligrams from all three fractions.

Although the amount of recovered material was insufficient for n.m.r. spectrometry[8], the i.r. (CCl_4) suggested that hydroxylic compounds were present in fractions B and C, and the u.v. spectra, showing only end absorption, suggested that non-conjugated double bonds were probably present in both these fractions.

The difficulty of recovering the material from silica was overcome by the use of a micro Soxhlet apparatus (B 10 and B 7) such that the volume of extracting solvent could be kept to a minimum (approx. 2 ml.). Concentration of the material could

therefore be effected by very mild warming in a water bath. It was also found that the most convenient method of storing the material was adsorbed on to silica from which it could be recovered when required. If stored as an oil, the material tends to 'evaporate' and condense round the stoppers of the containers.

The crude oil was examined by analytical g.l.c. on a non-polar column whereby the components should be resolved by boiling point. From the trace obtained (1% SE 30, 10 min. at 50° then programmed at 3°/min. to 250°, 15 lb./in.^{2} nitrogen) it was seen that approximately 70% of the material had been eluted from the column after only 5 minutes, the remaining material bleeding from the column over a period of 50 minutes. The resolution of the oil into its components by use of this column was very poor. Analysis of the crude oil using a non-polar 1·5% QF 1 column gave no resolution since the trace obtained consisted only of one very broad asymmetric band. Examination of the crude oil by analytical g.l.c. on a polar column should result in resolution of the oil by polarity as well as boiling point. In this case (8% Carbowax, 20 min. at 65° then programmed at 4°/min. to 160°, 15 lb./in.^{2} nitrogen) the material was eluted from the column over a period of 1 hour and resulted in a much higher degree of separation than was found on the non-polar phases. A typical trace of the crude oil (using 8% Carbowax) is shown in Fig. 2.

From these g.l.c. analyses, it is possible to draw the following conclusions: (i) Since the retention time of the bulk

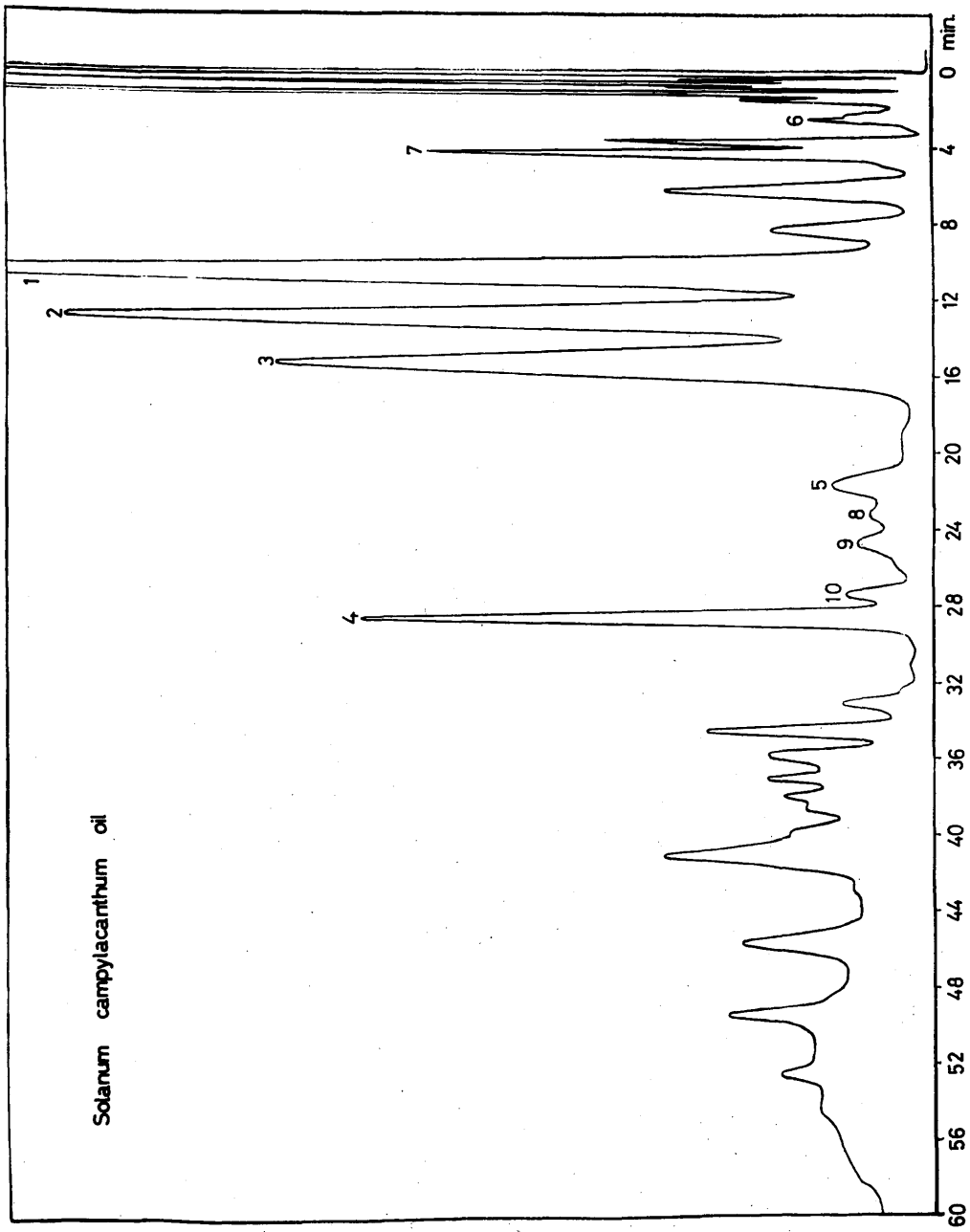

Fig. 2. Separation on 8% Carbowax.

of the material is greater on the polar phase, this suggests that the material contains polar groupings; (ii) From the examination of several samples of crude oil on the polar phase, it could be seen that these varied in composition. Whether this reflects the different seasons at which the leaves were gathered, or is a function of loss of material during the steam distillation, is not known. However, in each sample of oil, four major bands can be observed, viz. 1, 2, 3 and 4, although peak 2 is frequently the major peak (cf. Fig. 2). It was also observed that after standing for 24 hours at 0°, some of the peaks with retention times less than that of peak 1 had decreased in magnitude, suggesting that these constituents of the crude oil are extremely volatile.

Preparative g.l.c. separation of the crude oil (c. 100 mg.) was attempted using a non-polar column (5% CE 301, 15 ft., programmed at 6°/min. from 50° to 250°) in the hope that the low boiling material might be obtained separately from the higher boiling fraction. Three fractions were obtained which were examined by analytical g.l.c. (8% Carbowax) and t.l.c. This showed that no advantageous separation had been obtained since all three fractions were still complex and contained material attributed to fraction C.

After the above preliminary studies, the oil was eventually resolved in the following way. The crude oil (c. 150 mg.), sent from Uganda in sealed phials, was split into two parts. One fraction (approx. 10 mg.) was kept for g.l.c. puposes in a

sealed flask at 0° while the remainder was placed on two preparative t.l.c. plates and eluted with ether-light petroleum (3:7). The plates were divided into three regions containing A, B and C (Fig. 1) and the material stored on the silica until required. Separate elution of small portions of silica containing B and C with the micro Soxhlet apparatus gave small solution samples of these two fractions. G.l.c. analysis of fraction B showed two major peaks as anticipated from t.l.c. Mixed g.l.c. of B with the crude oil identified the constituents of B as peaks 4 and 5 (Fig. 2) having retention indices[9] (r.i.) 1405 and 1500 respectively. G.l.c. analysis of fraction C showed three major peaks which on mixed g.l.c. with the crude oil identified these as peaks 1, 2, and 3 (Fig. 2) having retention indices of 1312, 1343 and 1360 respectively (on the 8% Carbowax column).

The i.r. evidence suggesting the presence of hydroxylic compounds in C supported earlier esterification experiments[8] on band C with bromobenzene-p-sulphonyl chloride and toluene-p-sulphonyl chloride. These experiments provided evidence[8] that C contained more than one compound but, as the former reagent gave rise to two overlapping spots on t.l.c. and the latter reagent gave rise to an unstable ester or esters, no separation was attempted. In an effort to obtain stable esters which could be less volatile and more readily separated, C was treated with 3,5-dinitrobenzenesulphonyl chloride. 3,5-Dinitrobenzenesulphonyl chloride (11 mg.) in pyridine (1 ml.) was added to fraction C

adsorbed on silica. The reaction mixture was allowed to stand at room temperature for two days, then added to crushed ice, extracted with ether, dried and evaporated. Analytical t.l.c. [ether-light petroleum (1:3)] showed that one or more mobile compounds had been formed although some unreacted starting material was still present. Preparative t.l.c. [ether-light petroleum (1:6)] of this mixture gave a fraction presumably containing the ester or esters. Analytical t.l.c. of this fraction, after extraction with ether, showed two overlapping spots were present, together with at least four more polar compounds, suggesting that decomposition was again occurring.

Examination of fraction B by t.l.c. [ether-light petroleum (3:2)] on silver nitrate-impregnated silica showed that no additional separation could be effected in this manner. However, a similar examination of fraction C showed two well resolved spots after staining in the manner previously described. Elution of the remainder of C from silica and preparative t.l.c. [ether-light petroleum (7:3)] on silver nitrate-impregnated silica resulted in the isolation of two fractions. The less polar of these was shown by g.l.c. to contain the two compounds having r.i. 1312 and 1360 (peaks 1 and 3, Fig. 2) whereas the more polar contained only one compound having an index of 1343 (peak 2, Fig.2).

These two fractions constituting C (Fig. 1) were submitted for analysis by combined gas chromatography-mass spectrometry (70 eV., 5% Carbowax, isothermal 85°). This showed that compound 1 (Fig. 2,

r.i. 1312) had, in the mass spectrum, a base peak at m/e 56, and significant peaks at m/e 84, 69, 55, 43, 42 and 41, whose intensities were similar to those quoted[10] for n-hexanol. Thus this alcohol does not show a significant parent ion (M, 102) but only a peak corresponding to the loss of water (M-18, m/e 84). In the mass spectrum, compound 3 (Fig. 2, r.i. 1360) shows a base peak at m/e 57, a small parent ion (M, 100), and significant peaks at 82 (M-18), 67, 44, 43, 41 and 39, whose intensities are similar to those shown[11] for cis-hex-2-en-1-ol. Compound 2 (Fig. 2, r.i. 1343) shows a base peak at m/e 41 in the mass spectrum, a small parent ion (M, 100), and significant peaks at 82 (M-18), 69, 67, 55, 42 and 39, whose intensities resemble those shown[11] for cis-hex-3-en-1-ol.

It is therefore likely that compounds 1, 2 and 3 are n-hexanol, cis-hex-3-en-1-ol and cis-hex-2-en-1-ol respectively and would not be unexpected since C-6 alcohols seem to occur naturally in a wide variety of plant systems[12]. Additional support for the assignments made to compounds 1 and 2 came from mixed g.l.c. analysis on two columns (8% Carbowax, 70°, 16 lb./in.^{2} nitrogen, and 20% Cyano P, 65°, 13 lb./in.^{2} nitrogen) with authentic samples of n-hexanol and cis-hex-3-en-1-ol. Support for the assignment of structure to compound 3 was derived from mixed g.l.c. analysis (8% Carbowax, 70°, 16 lb./in.^{2} nitrogen) with the product derived from sodium borohydride reduction of authentic hex-2-en-1-al. The identity of these three C-6 alcohols confirms the earlier information obtained from n.m.r.[8], i.r. and u.v. spectra of the mixture of these compounds

which suggested both double bond and hydroxylic functions were present.

A sample of B, containing two compounds, was also submitted for g.c.-m.s. analysis. This showed that compound 4 (Fig. 2, r.i. 1500) had in the mass spectrum a base peak at m/e 71, a small parent ion at 154 ($C_{10}H_{18}O$), and other peaks at m/e 136 (M-18), 121 (M-18-15), 93, 80, 69, 55, 43 and 41, whose intensities resemble those shown[13] for the 70 eV. spectrum of linalool. The second constituent of fraction B (peak 5, Fig. 2, r.i. 1405) shows a base peak at m/e 57 in the mass spectrum, and much less intense peaks at m/e 99, 85, 72, 55, 43 and 41. This compound has not been unambiguously identified. However, the highest mass at m/e 99 probably is not the parent ion but corresponds to an M-15 peak since it is an odd-number mass. If the mass is 114, this corresponds to a molecular formula of $C_7H_{14}O$, having one double bond equivalent. The pattern of peaks in this mass spectrum corresponds closely to that quoted[14] for heptan-3-one although the relative peak heights vary slightly, but this may only be due to differences in inlet temperatures in the mass spectrometers. Mixed g.l.c. analysis (8% Carbowax, 80°, 16 lb./in.^{2} nitrogen) with an authentic sample of heptan-2-one shows that compound 5 has a retention time only fractionally longer than that of heptan-2-one, only one asymmetric peak being observed. Thus it is concluded that compound 5 is a C-7 ketone, probably heptan-3-one.

Preparative t.l.c. [elution thrice in ether-light petroleum

(1:4)] of the bulk of fraction B resulted in the partial separation of the two compounds. The head of the less polar band was shown to contain only one compound by g.l.c. (r.i. 1500) whereas the more polar band showed both components (8% Carbowax). Elution of the material from the head of the more mobile band using the micro Soxhlet apparatus and evaporation of the solvent yielded a small amount of a yellow oil whose i.r. [ν_{max} (CCl_4) 3608 $cm.^{-1}$] and n.m.r. [(CCl_4) $C\underline{H}_3$, s, τ 8·86, 8·52 and 8·42; $(CH_3)_2\dot{C}{=}C\underline{H}$, multiplet, τ 5·06] spectra were obtained. The latter spectrum also exhibits an ABX system of the type $\dot{C}H{=}CH_2$ at τ_X 4·24 (J_{AX} 18 c./sec., J_{BX} 11 c./sec.), τ_A 4·92 (J_{AX} 18 c./sec., J_{AB} 1·5 c./sec.) and τ_B 5·12 (J_{BX} 11 c./sec., J_{AB} 1·5 c./sec.). These spectra are identical to those obtained from an authentic sample of linalool. That this compound is the monoterpene alcohol is further supported by mixed g.l.c. analysis on two columns (8% Carbowax, 95°, 16 lb./in.^{2}; 20% Cyano P, programmed at 5°/min. from 65° to 125°, 16 lb./in.^{2} nitrogen) with an authentic sample of linalool.

The composition of the crude oil, as estimated by g.l.c., varies as follows: n-hexanol, 14-22%; cis-hex-3-en-1-ol, 22-16%; cis-hex-2-en-1-ol, 14-13%; linalool, 2·5-6·0%; heptan-3-one (?), 0·6-2·5%. Fraction A (Fig. 1) appears to contain the major part of the remaining material. This can be subdivided into the components which have a smaller retention time than compound 1 (c. 22%) and those with a greater retention time than compound 3

(c. 17%). Fraction A is therefore much more complex (Fig. 3) than either of the fractions B or C and will require further separation before any useful results can be obtained for identification of the components.

Fraction A has, however, been subjected to analysis by g.l.c. (8% Carbowax, 16 min. at 65° then programmed at 4°/min. to 160°, 16 lb./in.^{2} nitrogen) and combined g.c.-m.s. (5% Carbowax, 10 min. at 65° then programmed at 4°/min. to 150°). Many of the mass spectra obtained in this fashion are complex because of overlap of the chromatographic peaks. From these examinations the following conclusions can be drawn: (i) Compound 6 (Fig. 2 and 3, r.i. 1163) probably has a mass of 100 corresponding to a molecular formula of $C_6H_{12}O$. It shows no molecular ion but exhibits an M-15 peak at m/e 85 and further major peaks at 71, 57, 45, 43, 41, 31 abd 29. It shows no evidence of loss of water (M-18, m/e 82) and is therefore assumed to contain a carbonyl function. It is probable that it is not n-hexanal since the base peak in this mass spectrum[15] is 44. This has been confirmed by mixed g.l.c. analysis with the products derived from partial oxidation of n-hexanol with Jones reagent. The peak (r.i. 1140), assumed to be n-hexanal, has a shorter retention time than the C-6 compound in fraction A; (ii) Compound 7 (Fig. 2 and 3, r.i. 1200) has a mass of 98 corresponding to a molecular formula of $C_6H_{10}O$, necessitating two double bond equivalents. It shows a molecular ion at m/e 98, an M-15 ion at 83 but no ion corresponding

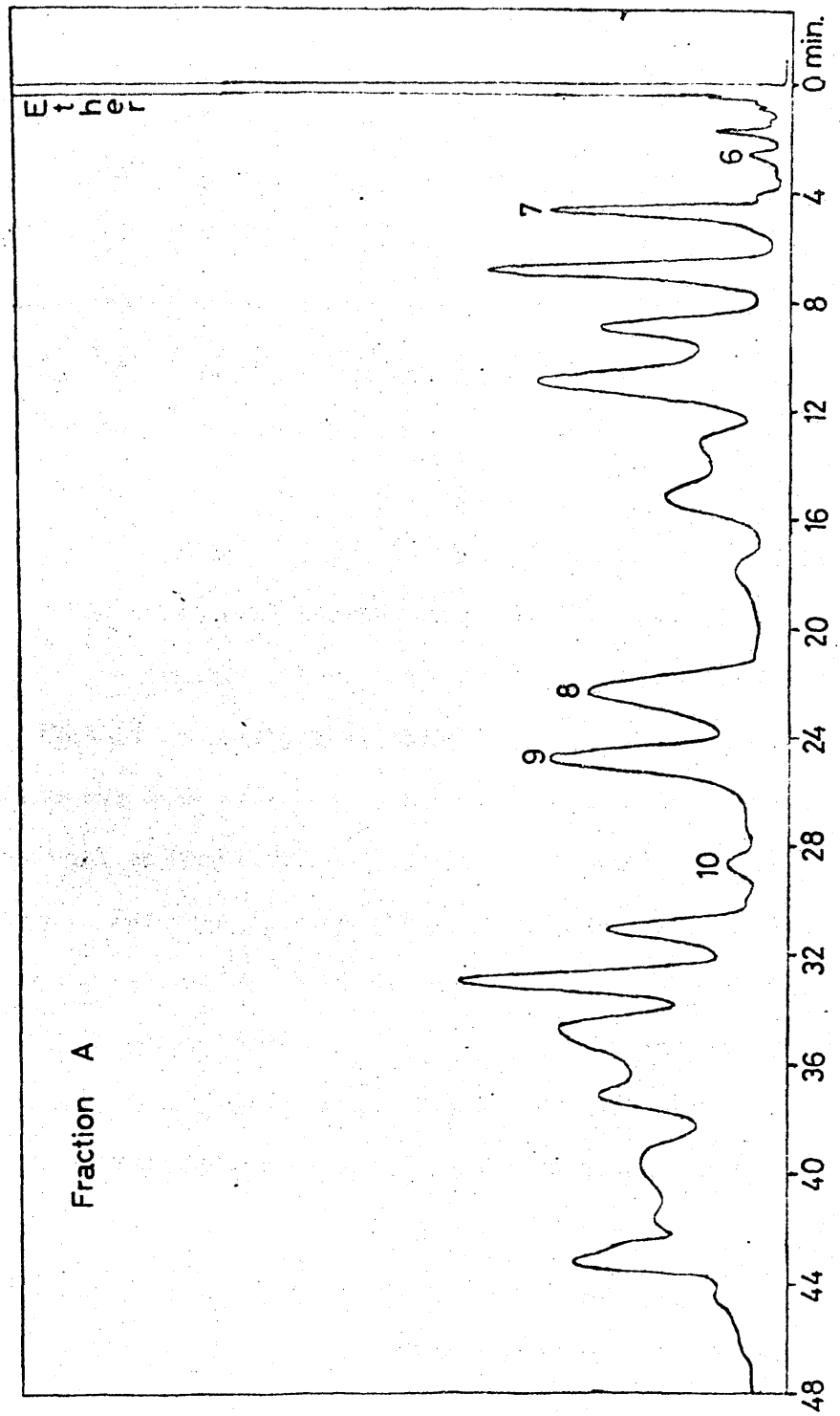

Fig. 3. Separation on 8% Carbowax.

to the loss of water, and significant peaks at 69, 57, 55, 43, 42, 41, 39 and 29. The mass spectrum is unlike cyclohexanone (base peak 55[14]) and is probably an unsaturated C-6 carbonyl compound. Mixed g.l.c. analysis with an authentic sample of hex-2-en-1-al (8% Carbowax, 40°) shows the two peaks (r.i. 1200) to coincide. Thus compound 7 may be the unsaturated aldehyde hex-2-en-1-al; (iii) Compounds 8 and 9 (Fig. 2 and 3) are presumably isomers since they give rise to almost identical mass spectra having the base peak at m/e 138 and having other significant peaks at 123, 109, 96, 82, 55, 43 and 41. If the masses of these compounds are 138, this could correspond to a molecular formula of $C_{10}H_{18}$. The retention time, however, is too long for a C-10 hydrocarbon so that it is likely that this ion corresponds to a fragment ion after the loss of water or an ester grouping. Thus these compounds may well be monoterpene alcohols ($C_{10}H_{20}O$) or esters derived from them. The mass spectra obtained from compounds with retention times greater than linalool show poor resolution and hence make interpretation impossible. However, from the spectra obtained it would seem that several of the compounds with retention indices greater than 1500 are pairs of isomers since the parts of the spectra which are discernible are almost identical. The constituents of fraction A will therefore require to be further fractionated and resubmitted to g.c.-m.s. before any useful data can be obtained for their identification.

It is of interest to note that Watanabe has shown[16] that both

hex-2-en-1-al and hex-3-en-1-ol, which occur naturally in Mulberry leaves, act as attractants for Silkworm larvae. n-Hexanol also possesses some attractivity. Thus it may be that the C-6 alcohols and hex-2-en-1-al (?) shown to be present in the steam distillate of Solanum campylacanthum, are in fact part of Stride's 'steam volatile factor' and therefore constitute some of the attractants present in these leaves although this will have to be verified experimentally.

The following Table summarises the information available at present.

Compound	Structure	Retention Index *	Molecular Formula	Mass Spectra
1	n-hexanol	1312	$C_6H_{14}O$	84,69,56,55,43, 42, 41.
2	cis-hex-3-en-1-ol	1343	$C_6H_{12}O$	100,82,69,67,55, 42,41,39.
3	cis-hex-2-en-1-ol	1360	$C_6H_{12}O$	100,82,67,57,44, 43,41,39.
4	linalool	1500	$C_{10}H_{18}O$	154,136,121,93, 80,71,55,43,41.
5	heptan-3-one (?)	1400	$C_7H_{14}O$	99,85,72,57,55, 43,41.
6	unknown	1163	$C_6H_{12}O$	85,71,57,45,43, 41,31,29.
7	hex-2-en-1-al (?)	1200	$C_6H_{10}O$	98,83,69,57,55, 43,42,41,39,29.
8	unknown	1440	$C_{10}H_{20}O$(?)	138,123,109,96, 82,55,43,41.
9	unknown	1455	$C_{10}H_{20}O$(?)	138,123,109,96, 82,55,43,41.
10	unknown	1490	$C_{10}H_{16}O$(?)	152,137,123,109, 81,67,55,43,41, 39,29.

*The retention indices were obtained from g.l.c. data using standard n-C 11, 12, 13, 14 and 15 alkanes.

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