A THESIS ENTITLED

"STUDIES IN NATURAL PRODUCT CHEMISTRY"

SUBMITTED TO THE

UNIVERSITY OF GLASGOW

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE FACULTY OF SCIENCE

BY

DONALD M. GUNN, B.Sc.

Chemistry Department

September, 1967.

ProQuest Number: 11011814

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.

ProQuest 11011814

Published by ProQuest LLC (2018). Copyright of the Dissertation is held by the Author.

All rights reserved.
This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to Dr. K. H. Overton for his constant guidance and encouragement throughout this period of research, and also to Dr. J.D. Connolly and Dr. R. McCrindle for many helpful discussions.

This work was carried out during the tenure of a grant from the Department of Scientific and Industrial Research.

CONTENTS

Contents - Contd. Page

SECTION III

SECTION I

CONSTITUENTS OF ONONIS SPINOSA L. :-

ACETATES A and B

SUMMARY

This section deals with the structural elucidation of acetates A and B, isolated from acetylated Ononis spinosa L. root extract. Acetate A has been identified as the tetra-acetate of inermin 7-β-D-glucoside, and acetate B as the tetraacetate of homoinermin 7-β-D-gluco-side. The discussion of acetates A and B is prefaced by a brief review of the naturally occurring pterocarpans and a discussion of their probable biogenesis.

INTRODUCTION

It is now over 100 years since the constituents of the roots of Ononis spinosa L.were first investigated. At that time Hlasiwetz[1] isolated the glycoside ononin (A1), probably the first isoflavone to be described, and α-onocerin (A2), a triterpenoid. The constitution of ononin is the subject of several papers by Hemmelmayer[2] at the beginning of the century, and was reinvestigated by Wessely et al[3] in the 1930's and later by Baker et al[4], and established as that of diadzin methyl ether, since hydrolysis produces glucose and formononetin (A3)[2,4]. It has also been synthesised by methylating diadzin (A4)[5], and by glucosiding formononetin[6].

Since Hlasiwetz first isolated α-onocerin (A2) in 1855, many detailed investigations[7-14] have been carried out in attempting to elucidate its structure, but success was achieved only in 1955 by the classical work of Barton and Overton[15]. During this study when α-onocerin was isolated as the diacetate by column chromatography of the acetylated Ononis spinosa root extract, a more polar fraction was obtained,which forms the basis of the present

investigation. This more polar fraction was chromatographed yielding material which on careful fractional crystallisation afforded two acetates, A (A5) and B (A6) with sharp melting points and clearly defined nuclear magnetic resonance spectra. The two acetates A and B are now identified by chemical and spectroscopic evidence as respectively the tetraacetates of inermin 7-β-D-glucoside (A7) and of homoinermin 7-β-D-glucoside (A8). The parent aglycone (A10) of acetate B, so far undescribed, is here designated, homoinermin, by comparison with inermin (A9) and by analogy with pterocarpin (A11) and homopterocarpin (A12).

The pterocarpans are a group of naturally occurring heterocyclics having a 3,4-dihydro-2H-benzofurobenzopyran nucleus (A13). The isolation of fourteen such compounds from nature has been described[16-25]. The compounds have two asymmetric centres, and although it is possible to construct a Dreiding model with a trans junction, this is evidently a highly strained system, and the relatively unstrained cis junction is considered more likely. In this investigation with acetates A and B, it is concluded that the relative configuration of the centres is H, H cis.

A similar conclusion has been reached by Suginome[26] for homopterocarpin (A12), by applying the Karplus equation[27]. The absolute configuration[28] of C-4 in trifolirhizin (A7) has recently been established[29] as R, and accepting the cis relationship, the absolute configuration of this compound is 3,R:4,R. Since trifolirhizin can be hydrolysed to (-)-inermin (A9), and this in turn converted into (-)-pterocarpin (A11)[19], the absolute configurations of these three compounds are established. Of the eleven other natural members of this class, nine have high negative optical rotations, as have the acetates A and B, and their free glucosides (see experimental), and in all probability these have the same R:R configurations. In contrast, the remaining two (+)-sophojaponicin (A14)[18], and (+)-pisatin (A15)[20], should have S:S configurations.

In order to explain the splitting of the nuclear magnetic resonance signal due to the isolated proton at C-4 in the spectrum of pisatin (A15), Perrin and Perrin[30] suggested that the pyran ring can exist in two energetically similar conformations. Very recently a rigorous conformational study on these systems has been carried out by Pachler and Underwood,[31] by detailed analysis of the nuclear

magnetic resonance spectra of various members of this series. As already concluded[26,32] the two heterocyclic rings must be cis fused, and thus there are two possible conformations as depicted in Fig. I. It would be expected that the proton-proton coupling constants for these two conformers should be significantly different, and the actual conformation, if one is preferred, could be derived unambiguously from the experimentally determined coupling constants. From the theoretically calculated angle dependence of vicinal proton-proton coupling constants,[27] and the knowledge of substituent effects[33-35] on these couplings, it was possible to evaluate coupling constants for the heterocyclic ring protons for both conformers. Comparison of the experimentally determined coupling constants and the expected couplings revealed that the benzofurobenzopyran ring system of the compounds studied exist in conformation I (Fig. I), with the six membered ring in a staggered half chair conformation joined to the planar five membered ring. Pachler[31] concludes that the molecules in this series very probably exist in conformation I only, and that, if the molecules undergo conformational interconversion between I and II, [as suggested for pisatin (A15)[30]], the equilibrium will be much in favour of the former.

So far the pterocarpan group has not been exposed to biosynthetic studies, but it is likely that the initial steps are those of typical flavone biosynthesis. The biosynthesis of flavones and flavonols has been fairly rigorously investigated and it has been established that ring A is acetate-derived, and ring B originates from the shikimic acid pathway. There is excellent evidence[36] for the steps indicated for the shikimic-prephenic acid route outlined in Fig. II, and further modification can easily be envisaged which would lead to ferulic (A16), caffeic (A17), syringic (A18), gallic (A19), benzoic and other common plant acids. It must, however, be supposed that the general system based on shikimic and prephenic acids can be entered at several points; phenylalanine, for example, often serves as well as shikimic acid or glucose for the biosynthesis of compounds related to ferulic acid, despite the necessity for hydroxylation. Indeed, insertion and removal of hydroxyl groups are both very common features in this area, though a detailed understanding of these processes has yet to come.

The acids above belong to the C_6C_3 and C_6C_1 classes defined by Robinson[37], and when combined with three or four acetate units, they enter the $C_6C_3C_6$ class, and it

immediately becomes evident why so many flavonoids have phloroglucinol nuclei for ring A and catechol or pyrogallol nuclei for ring B. This observation, that the hydroxylation pattern in the two rings reflects their origin, was first appreciated by Robinson[37] but owes it present status as an important corollary of the acetate theory to Birch.[38] The validity of these views has now been amply substantiated by tracer studies.

Typical tracer work in this field can be exemplified by biosynthetic studies on three flavones, the pentahydroxyflavones, tricin (A20), and quercitin (A21) and the hexahydroxyflavone, myricetin (A22). The carbon skeleton of labelled tyrosine is directly incorporated into myricetin without degradation[39]; tricin is found to be labelled[40] when produced by wheat from supplied [β-^{14}C] ferulic acid (A16), and, Fig. III, much more detailed experiments[41,42] have shown that [1-^{14}C]- and [2-^{14}C]- acetate are used by buckwheat, Fagopyrum tartaricum, for the synthesis of the phloroglucinol ring of quercitin, (A21). Further experiments[43] indicate that uniformly labelled phenylalanine is transformed into quercitin, which by degradation to the acetophenone, (A23), and dimethoxy-benzoic acid, can be

shown to possess six labelled atoms in ring B, the three others appearing at positions, 2,3 and 4 as predicted. Also β-labelled cinnamic acid led to the acetophenone (A23), now labelled only at the β-carbon.

Geissman and Hinreiner[44] pointed out in 1952 that formononetin (A3), biochanin A (A24), and other isoflavones can be looked upon as flavones modified by migration of ring B from position 2 to 3, or by an equivalent process occurring at some earlier stage in the normal flavonoid biosynthesis. Their suggestion has been completely justified by very thorough studies on formononetin (A3), conducted by Grisebach[45,46], who, after establishing that acetate could supply ring A, and phenylalanine all the other skeletal carbon atoms, examined in three separate experiments the utilisation of [1-^{14}C]-, [2-^{14}C]- and [3-^{14}C]- phenylalanine by red clover, Trifolium pratense. The three results, Fig. IV, leave no doubt that ring B has indeed undergone a 1,2 shift, although the stage at which this happens remains obscure. Enzmatic reduction could now make entry into the isoflavanone series possible.

Further stages in pterocarpan biosynthesis are still a matter of conjecture, but an interesting conversion[47,48]

occurs in vitro, when isoflavanones, oxygenated at the 2' position in ring B, such as sophorol, (A25), and O-dimethyl sophorol (A26), are warmed with dilute acid. Both are converted to anhydrosophorol (A27), which has a dehydropterocarpan system. A similar biosynthetic pathway is perhaps conceivable, which, followed by an enzymatic reduction would lead to the formation of the pterocarpan system. This as yet untested postulate of pterocarpan biosynthesis via the isoflavone, perhaps gains some support from the fact that the isoflavone, ononin (A1), as previously mentioned, is a major constituent of Ononis spinosa L.root extract.

DISCUSSION

Column chromatography of the more polar fraction, obtained after isolation of α-onocerin (A2), of the acetylated Ononis spinosa L root extract, yielded material which, on careful fractional crystallisation, afforded two acetates A and B, with distinct physical properties.

Elementary analysis and mass spectral data suggested a molecular formula, $C_{30}H_{30}O_{14}$ for acetate A, (A28), m.p. 188-189°, $[\alpha]_D$ -104°; molecular weight by mass spectrum 614. Integration of the nuclear magnetic resonance spectrum for the thirty protons in the structure implies that compound A is a tetraacetate (12 H's at 7.9 - 8.0 τ). Alkaline hydrolysis or lithium aluminium hydride reduction readily confirms this assignment, affording a much more polar compound, (A30), $C_{22}H_{22}O_{10}$, m.p. 219-221°, $[\alpha]_D$ -166°, M.W. 446. Likewise acetate B, (A29), $C_{30}H_{32}O_{13}$, m.p. 173-174°, $[\alpha]_D$ -109°, M.W. 600, also a tetraacetate, can be hydrolysed to compound (A31), $C_{22}H_{24}O_9$, m.p. 265-266° $[\alpha]_D$ -143°, M.W. 432. Some difficulty was encountered in obtaining constant figures for elementary analysis and reproducible melting points with compounds (A30) and (A31) due to their great tendency to occlude

solvent molecules, but careful drying (see Experimental) gave reproducible results. The infra-red spectra of these compounds have strong hydroxyl absorption but no carbonyl absorption, whereas the spectra of the acetates reveal strong bands in the region of 1765 and 1225 $cm.^{-1}$, due to acetate groupings, but no hydroxyl bands, implying that in compounds (A28) and (A29), the only carbonyl groupings present must exist as acetate functions.

The first real clue to the structures of acetates A and B came from their mass spectra fragmentation patterns. The high mass regions (m/e $>$ 350) of these spectra are relatively simple, the only appreciably abundant ions being the molecular ions at m/e 614 and 600 respectively. The lower regions are virtually superimposable, commencing at m/e 331 in both cases, [m^* 178.2 (178.4) and 182.5 (182.6)], and characteristic fragmentation can be followed from here to the base peak (m/e 169) and beyond, by the presence of metastable peaks (m^*).

In 1963, Biemann[49], one of the foremost exponents of organic mass spectrometry interpretation, made the first really detailed study of the fragmentations of the acetates of pentoses and hexoses. In the mass spectra of simple sugar acetates, such as α- and β-D-glucopyranose penta-

acetates, and the α- and β-D-mannopyranose pentaacetates, three primary fragmentation schemes are observed. (Fig. V; R = $-\overset{\overset{O}{\|}}{C}-CH_3$ for β-D-glucopyranose pentaacetate). There is some doubt as to the primary process involved in scheme C and the structure of the ion formed. The allyl ion C_1' might be favoured over the cyclopropyl ion C_1'' because, in addition to better stabilisation, it also contains a double bond which would facilitate the elimination of ketene to lead, by secondary fragmentation, to the abundant ion of mass 115 in these derivatives. These schemes give rise to their own unique secondary and multiple fragmentations. Biemann also noted that fragmentation series a becomes more pronounced in the spectra of the methyl, and even more so in the phenyl glucoside tetraacetate at the expense of schemes b and c, when compared with the spectra of α- and β-D-glucopyranose pentaacetates.

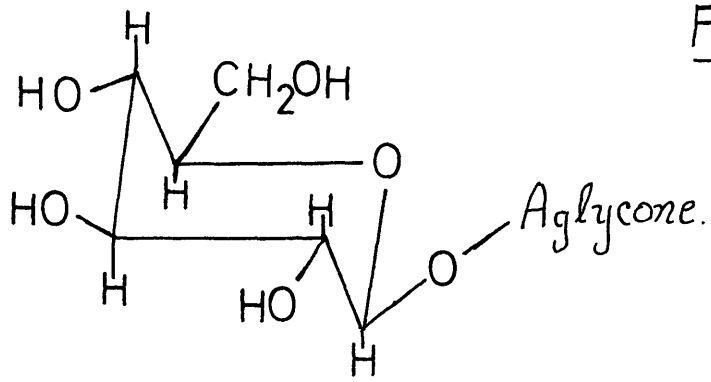
In the spectra of acetates A and B, schemes b and c are not discernible, while fragmentation scheme a virtually constitutes the spectra from mass 331 downwards. (For subsequent fragmentations, see Experimental). This overwhelming predominance of scheme a can most probably be explained if a more stable radical, such as phenoxide

radical, was being formed in the primary process. This interpretation has recently been supported by work of Pearl and Darling,[50] and it is now possible to conclude that acetates A and B contain an acetylated sugar moiety of the pyranose type, linked to an aglycone (most probably) aromatic in character.

The only identifiable product from acid hydrolysis of the free glycosides (A30) and (A31) was glucose, augmenting the mass spectra interpretation, characterised by its R_f values in various solvent systems, and by mixed melting point comparison (207-209°) and comparison of the infra-red spectrum of the derived phenylozazone with authentic glucosazone. None of the ether-soluble components from this hydrolysis could be characterised, which is not surprising when the complete structures of the aglycones were elucidated. Enzymatic hydrolysis with emulsin, β-glucosidase, under control conditions in citrate buffer hydrolysed the glucosides (A30) and (A31), revealing that a β-glucoside linkage is involved.

The above evidence leads to the part-structure shown in Fig. VI for (A30) and (A31). The distinction between acetates A and B must therefore be in the nature of their aglycones.

Fig VI



The parent aglycones must now have molecular constitutions of $C_{16}H_{12}O_5$ and $C_{16}H_{14}O_4$, and their structures are deduced by interpretation of the nuclear magnetic resonance and ultra-violet spectra of their corresponding glucoside tetraacetates (A28) and (A29). There are many similarities in the nuclear magnetic resonance spectra of acetate A (A28) and acetate B (A29), but the most striking difference is the presence of a three proton singlet at 6.20 τ in B, absent in A, at the expense of a two proton broadened singlet at 4.14 τ, not detectable in B. This variation, taken in conjunction with the difference in molecular formulae, immediately pinpoints the different nature of the aglycones. Acetate A (A28) thus contains a methylenedioxy group as opposed to the methyl ether function of acetate B (A29). Integration of the aromatic region for acetates A and B reveals the presence of five and six protons respectively, and this coupled with the

fact that the remaining two oxygen atoms in the acetates must exist as ether linkages, confirms the inference previously drawn from mass spectroscopic results for the presence of aromatic aglycones, probably of the flavanoid type, in these compounds.

At first glance, even the aromatic region of these nuclear magnetic resonance spectra appear rather complex, but if the chemical shifts of the aromatic protons are considered with relation to their environment to oxygen atoms in the flavanoid system,[51] analysis of the spectra can be attempted. The chemical shift of aromatic protons which are not adjacent to an oxygen atom will be at a value similar to that of unsubstituted benzene (i.e. between 2.6 - 2.8 τ). If, however, an aromatic proton is adjacent to an oxygen atom it will be shifted upfield (i.e. between 3.2 - 3.4 τ), while if it is adjacent to two oxygen atoms it will be shifted to still higher magnetic field values (i.e. 3.4 - 3.6 τ).

In the spectrum of acetate A (A28), with five aromatic protons, only one low field aromatic proton [H_c] (see Fig. VII) is observed at 2.62 τ as a doublet (J = 8.5 c./sec.; ortho coupling) which collapses to a singlet by irradiation at 3.32 τ. Centred at 3.32 τ

is a quartet (J = 8.5; 2.4 c./sec.; ortho and meta coupling) weight one proton [H_b], the major coupling being removed by double irradiation at 2.62 τ. Also in this region is a one proton singlet [H_e] at 3.30 τ, showing no detectible coupling. The remaining two aromatic protons of acetate A appear as a doublet [H_a] at 3.42 τ, (J = 2.4 c./sec.) and a singlet at 3.59 τ [H_d].

Use of the chemical shift values and coupling constants of these aromatic protons now leads directly to the identification of two aromatic nuclei, substituted 1,2,5- and 1,2,4,5- respectively and oxygenated as shown in Fig. VII with the methylene bridge attached to the only two adjacent oxygen atoms.

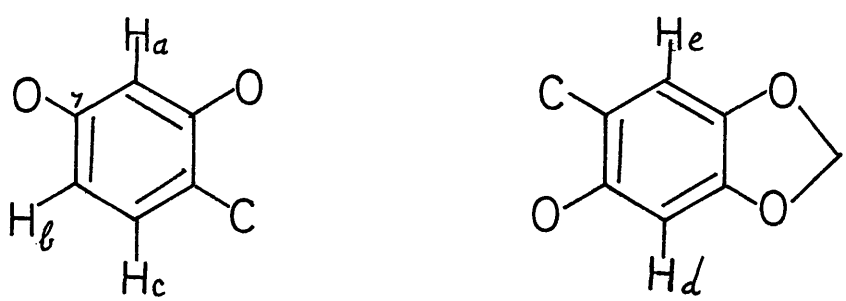


Fig VII

The oxygen atom at C-7 is most likely involved in the glycoside link since it has two adjacent aromatic protons. The two remaining oxygens are present, as the evidence suggests, as ether linkages - one in the normal flavanoid pyran ring and the other attached as usual to C-4, but not in the case as ketonic oxygen. Combination of the two aromatic nuclei, shown in Fig. VII, with the inclusion of the final carbon atom leads to two possible structures (A32) and (A33). A distinction between these structures is possible. Both the parent aglycone, inermin (A34) of nuclear structure (A32), isolated from Andira inermis, and the methylated derivative, pterocarpin, (A35), isolated from sandalwood in 1874 by Cazeneuve, (although its structure was only finally elucidated[52] in 1961 after many detailed investigations) are known. The ultra-violet spectra of acetate A (A28) and its free glucoside (A30) are virtually superimposable on the corresponding spectra of inermin and pterocarpin. The recently isolated and identified 7-glucoside of inermin, trifolirhizin,[51] from red clover (Trifolium pratense L.) has identical ultra-violet and infra-red spectra to those of the free glucoside (A30). The derived acetate[52a] of trifolirhizin has melting point

and rotation equivalent to acetate A (A28). It is now possible to conclude that acetate A is the tetraacetate of inermin 7-β-D-glucoside [i.e. (A28)].

Acetate B (A29) differs only from acetate A, (A28) by a methoxy group (6.29 τ; three proton singlet) replacing the methylenedioxy function, as already mentioned. This is borne out by the presence of an additional aromatic proton in the nuclear magnetic resonance spectrum of acetate B. In this case there are two, one proton doublets (J = 8.5 c./sec.; ortho couplings) at 2,57 [H_c] and 2.87 τ [H_f] (Fig. VIII) in the low field region of aromatic resonances. Irradiation at 3.32 and

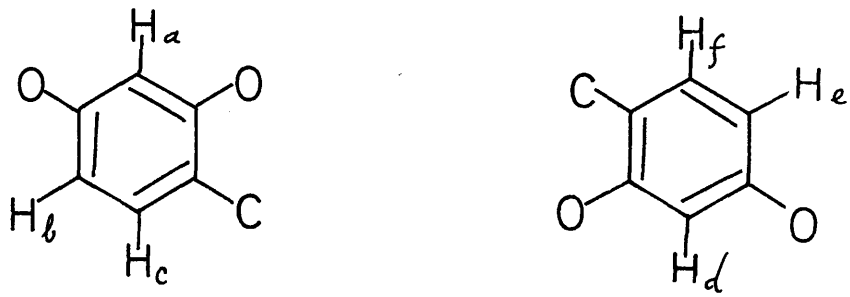


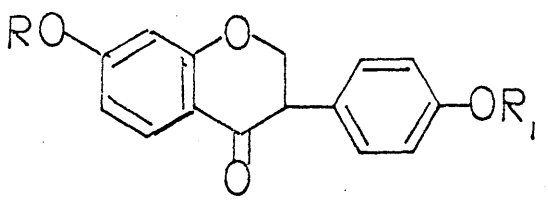
Fig VIII

3.39 τ respectively collapses these doublets to singlets. Two protons [H_b] and [H_e] exist as one proton quartets at 3.32 and 3.39 τ with characteristic ortho and meta

coupling constants (J = 8.5; 2.4 c./sec.). Finally, in the high field region, [H_a] and [H_d] appear as one proton doublets (J = 2.4 c./sec.; meta coupling) at 3.53 and 3.58 τ respectively. This data leads directly to the formulation of two aromatic nuclei with identical oxygenation and substitution patterns (see Fig. XXII). Combination of these two nuclei with the inclusion of the final carbon atom, abiding by the restrictions previously imposed for acetate A, leads to the unique structure (A36) for the parent aglycone of acetate B.

This aglycone (A36) has so far not been described, but its methylated derivative, homopterocarpin,(A37), was isolated along with pterocarpin (A34) by Cazeneuve, and by analogy it was decided to name the aglycone (A36) homoinermin. The ultra-violet spectra of the acetate B (A29) and its free glucoside (A31), differ vastly from the corresponding spectra of acetate A (A28) and its glucoside (A30), but are virtually identical to the ultra-violet spectrum of homopterocarpin (A37). Therefore acetate B is identified as the tetraacetate of homoinermin 7-β-D-glucoside [i.e. (A29)].

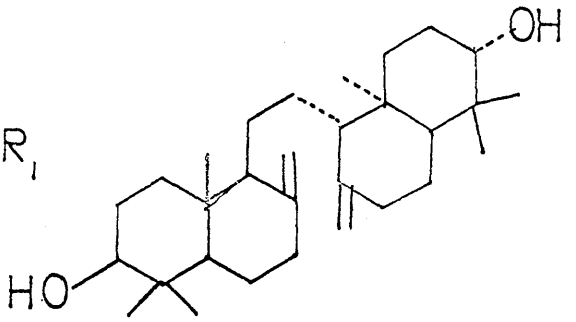
The heterocyclic ring protons and those on the sugar residue, with the exception of the acetate methyls, appear in the 4.4 - 6.8 τ region of the nuclear magnetic resonance spectra of acetates A and B. The only discernible system in this eleven proton complex is a one proton doublet (J = 6.5. c./sec.) at 4.56 τ. This proton must, by its chemical shift, be either the C-4 proton or the anomeric proton.[53,54] The coupling constant is consistent with that of the anomeric proton in a β-glucoside,[55] as opposed to an α-glucoside. However, this doublet collapses to a singlet on double irradiation at 6.56 τ, which is outwith the expected resonance[53] of the remaining glucoside ring protons. The coupling of the C-4 proton, as discussed in the introduction, implies that the relative configuration at C-3 and C-4 in acetates A and B is H, H cis, and thus the absolute configuration, as recently established,[29] is 3,R; 4,R. Assignment of the remaining protons in this complex region of the spectra was not attempted.



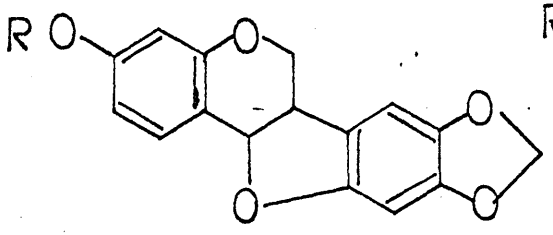
A1 R = $C_6H_{11}O_5$; R_1 = Me.

A3 R = H ; R_1 = Me.

A4 R = $C_6H_{11}O_5$; R_1 = H.



A2

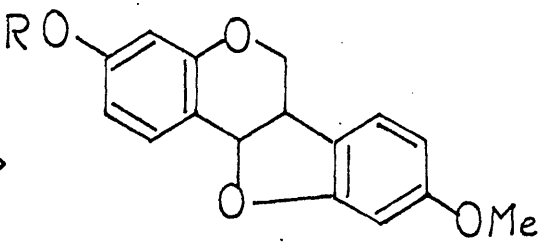


A5 R = Glucose tetraacetate.

A7 R = $C_6H_{11}O_5$

A9 R = H.

A11 R = Me.

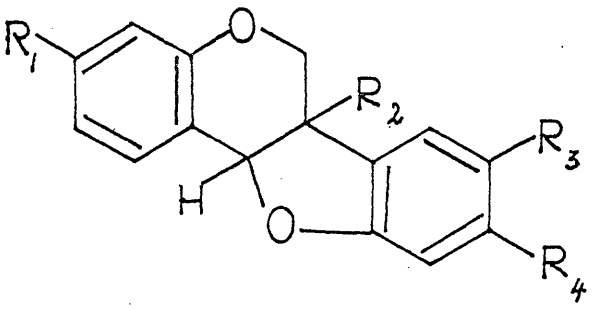


A6 R = Glucose tetraacetate.

A8 R = $C_6H_{11}O_5$

A10 R = H.

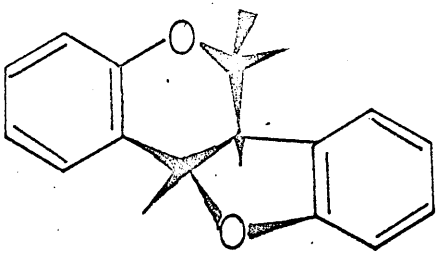
A12 R = Me.



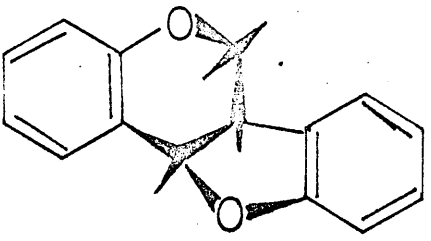
A13 $R_1 = R_2 = R_3 = R_4 = H$.

A14 $R_1 = C_6H_{11}O_5$; $R_2 = H$; $R_3 + R_4 = O\text{-}CH_2\text{-}O$.

A15 $R_1 = OMe$; $R_2 = OH$; $R_3 + R_4 = O\text{-}CH_2\text{-}O$.

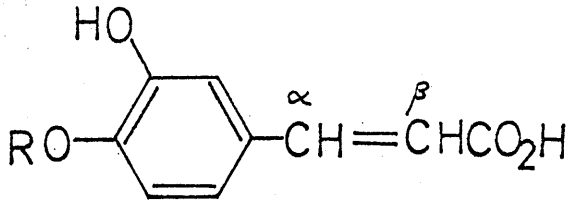


I



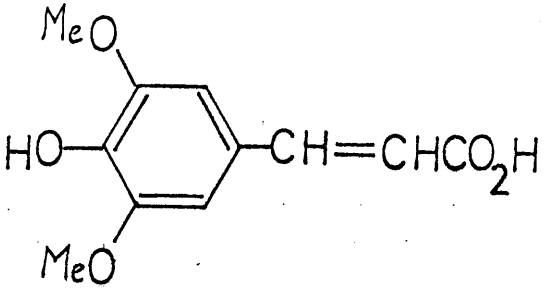
II

Fig I

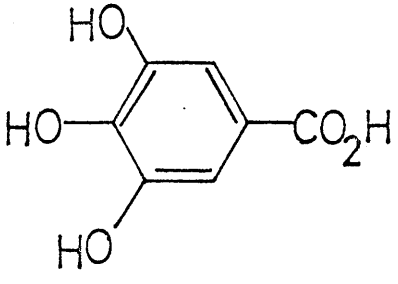


A16 R = Me

A17 R = H.



A18



A19

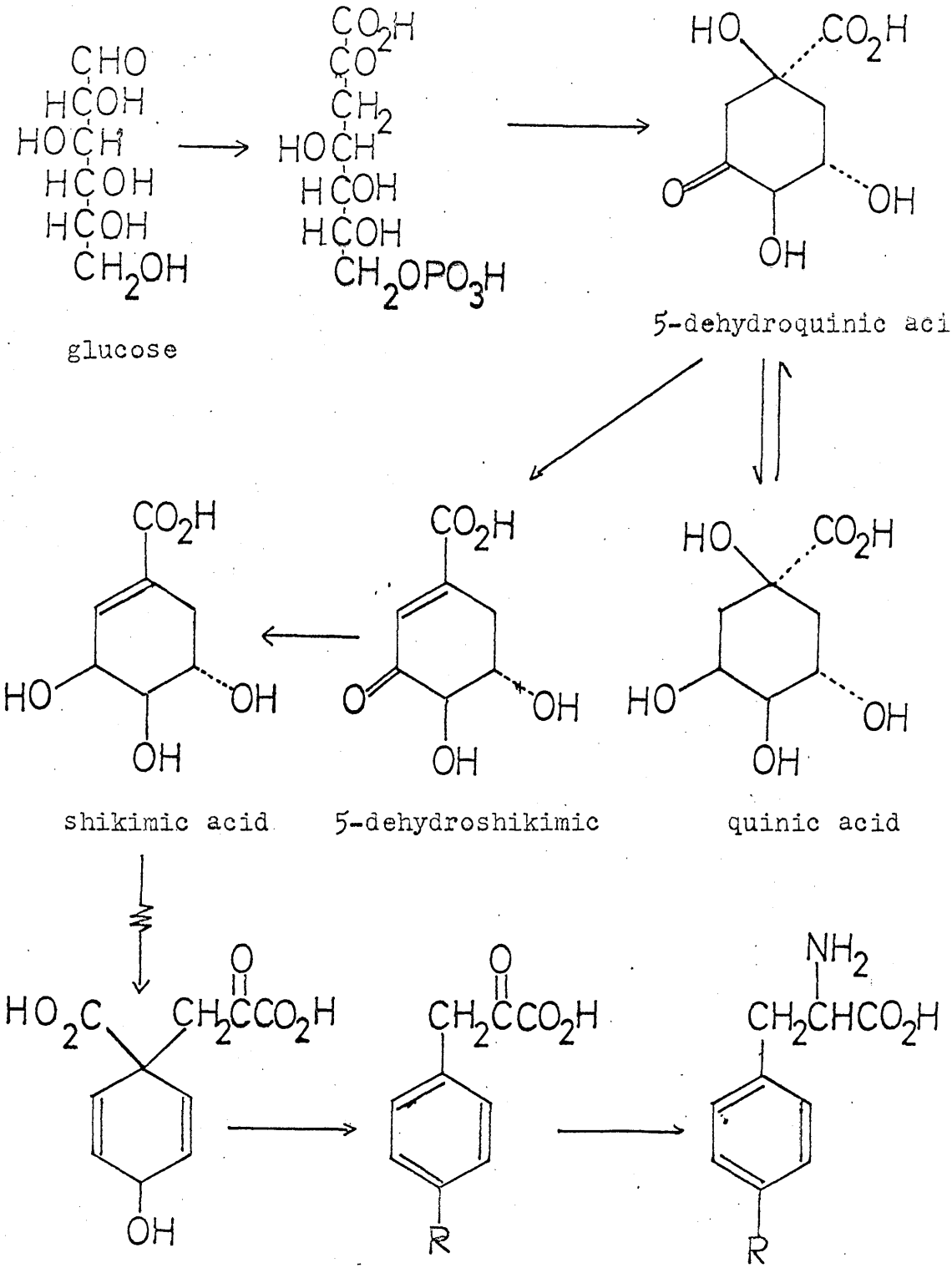
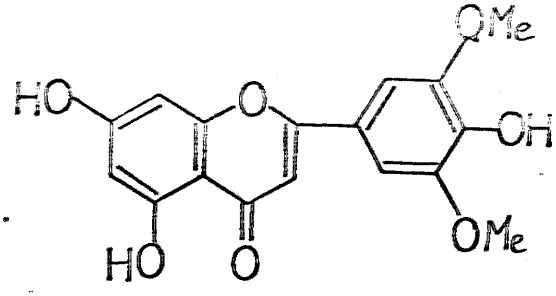
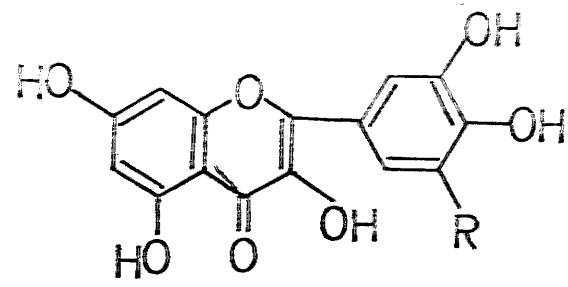

glucose
5-dehydroquinic acid
shikimic acid
5-dehydroshikimic
quinic acid
R = H, or OH.
R=H, phenylalanine
R=OH, tyrosine

Fig II

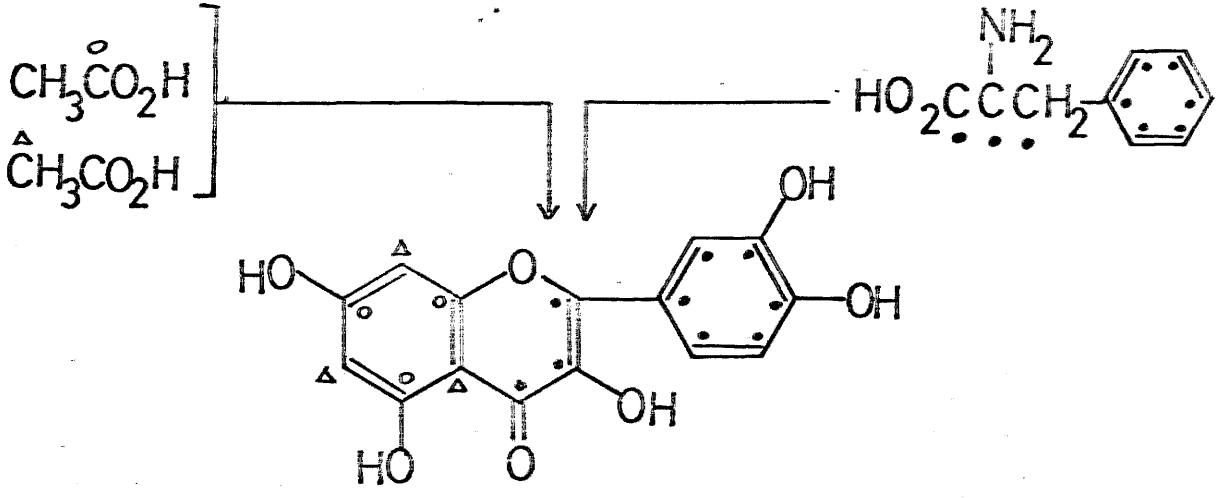


A20

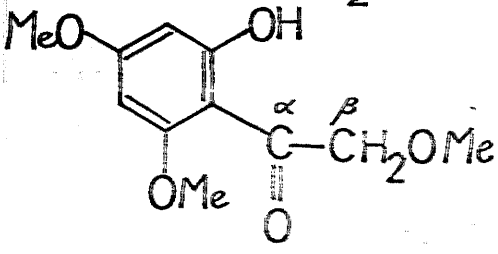


A21 R = H

A22 R = OH



A21



A23

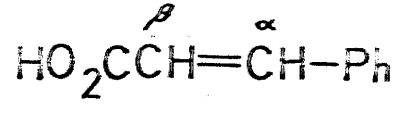
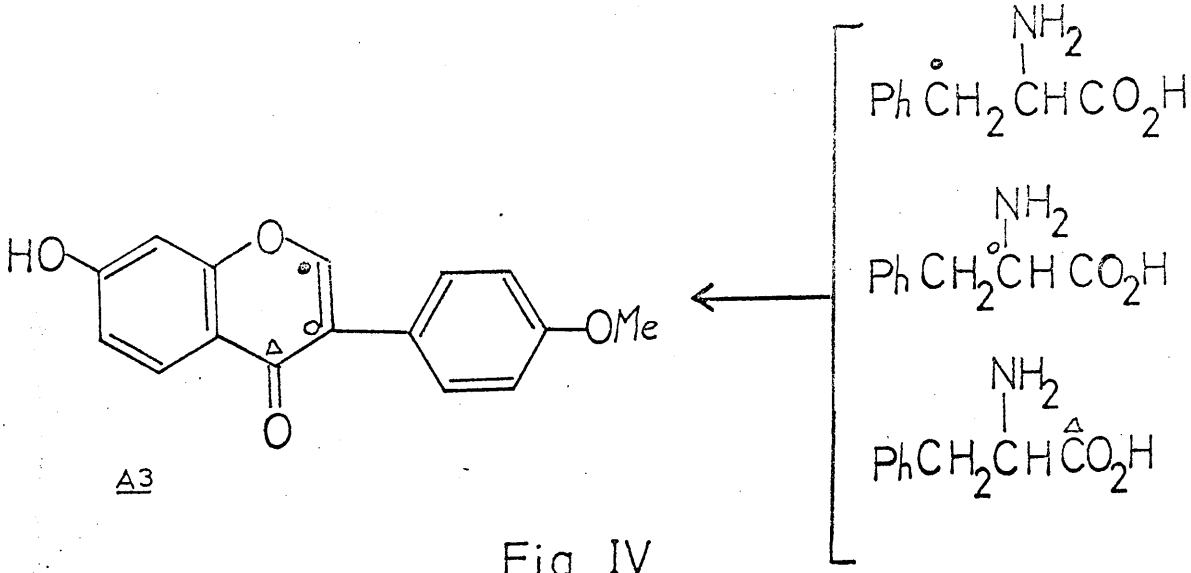
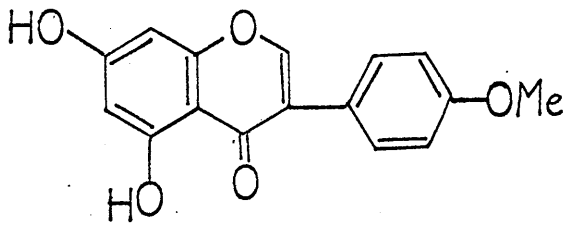


Fig III

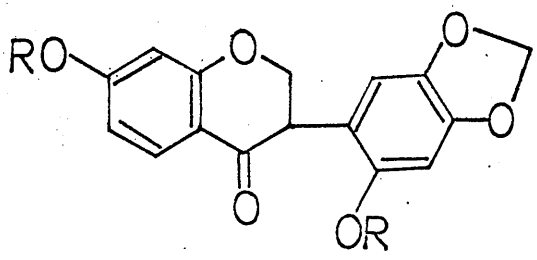


A3

Fig IV

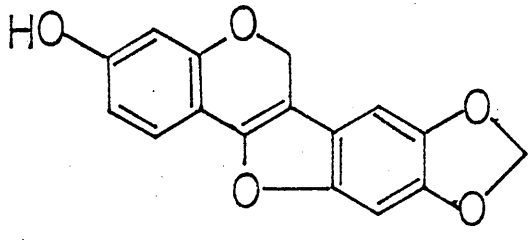


A24

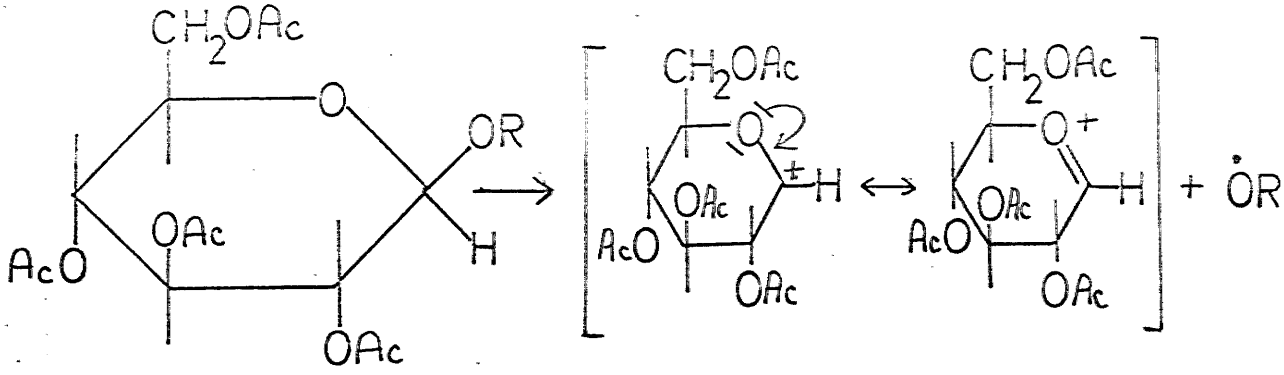


A25 R = H.

A26 R = Me.

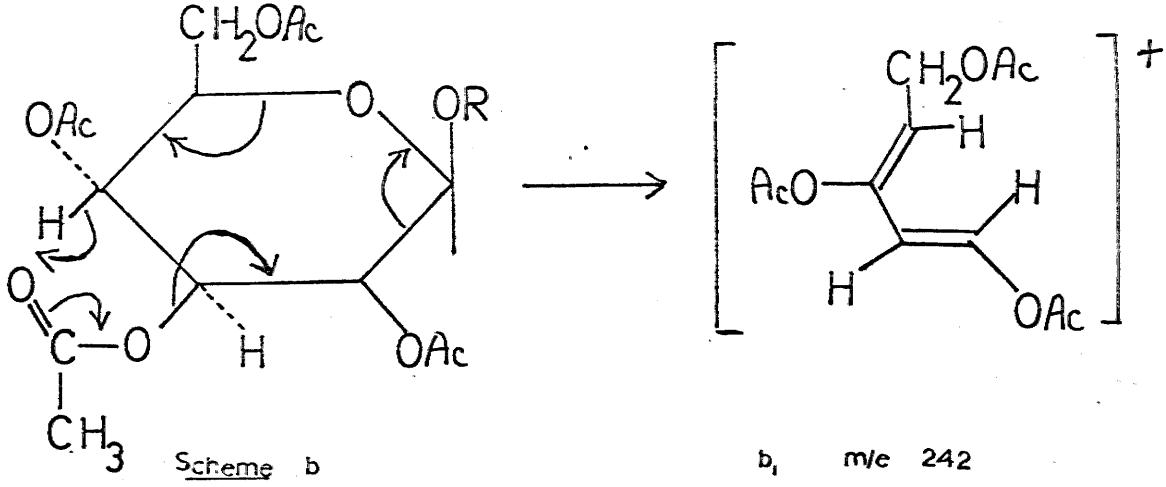


A27



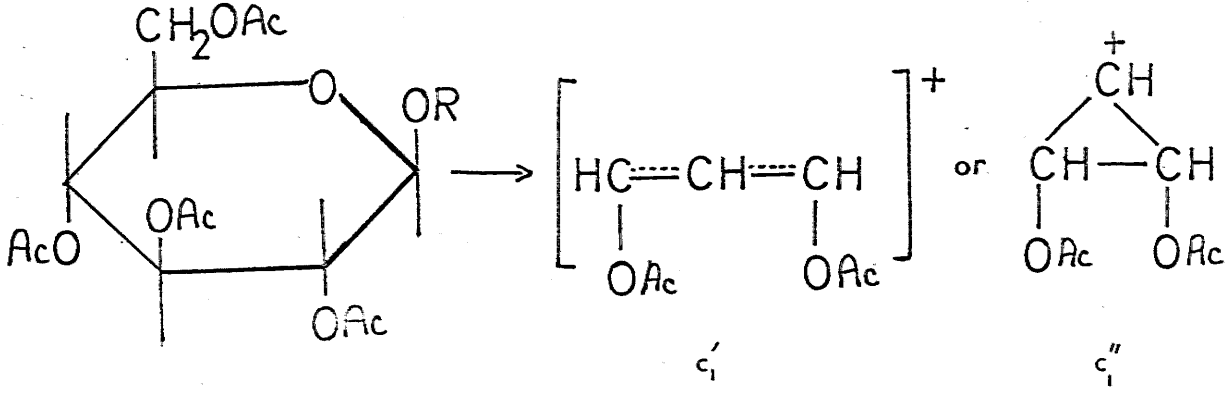
Scheme a

a, m/e 331



Scheme b

b, m/e 242

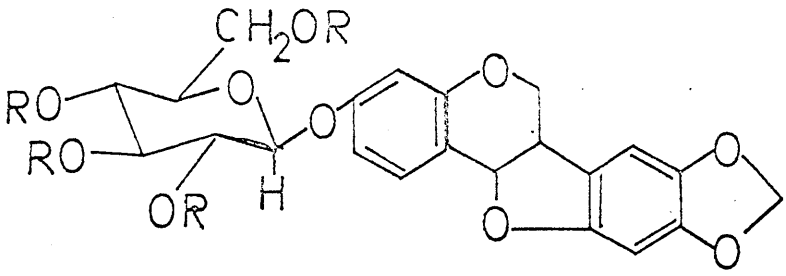


Scheme c

c′1 c″1

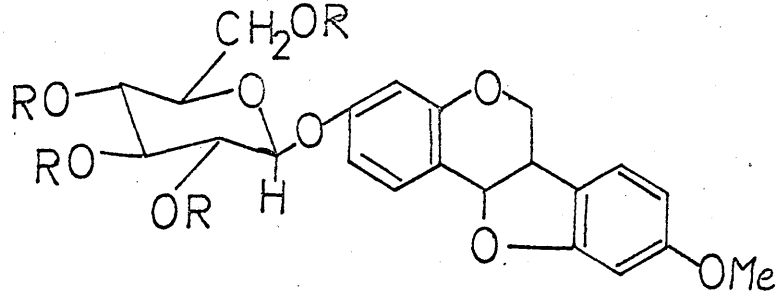
c m/e 157

Fig V



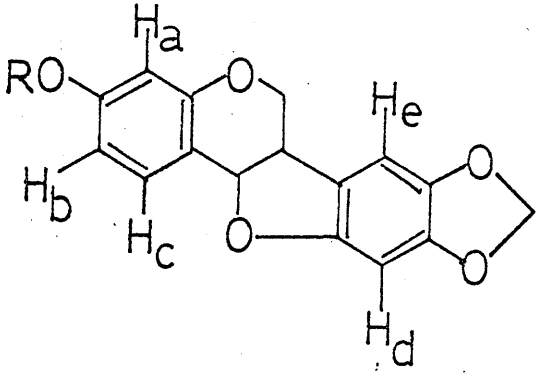
A28 R= CH_3CO

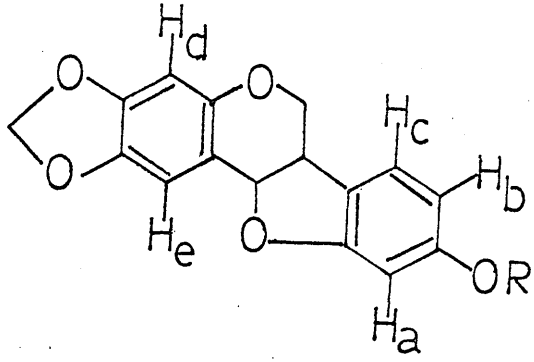
A30 R= H.



A29 R = CH_3CO

A31 R = H



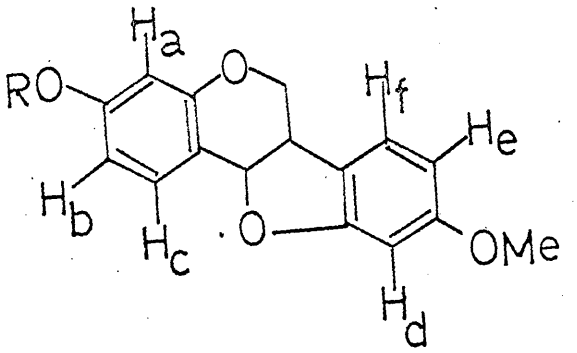


A32 R= Glucose tetraacetate.

A33 R= Glucose tetraacetate.

A34 R = H.

A35 R = Me.



A36 R=H.

A37 R=Me.

GENERAL EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations refer to chloroform solutions at room temperature, unless otherwise specified. Infra-red solution spectra were kindly recorded by Mrs. F. Lawrie on the Unicam S.P.100 double beam spectrophotometer and were recorded linearly in $cm.^{-1}$ as percentage transmission. Other infra-red spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Ultra-violet spectra were determined for EtOH solution on a Unicam S.P. 800 spectrophotometer. Microanalyses were carried out by Mr. J.M.L. Cameron, B.Sc. and his staff. Proton magnetic resonance spectra were determined on the Perkin-Elmer R.10, 60 megacycle, and the Varian H.A. 100, 100 megacycle spectrometers by Mr. J. Lennon and Mr. J. Gall respectively, tetramethylsilane being used as an internal reference in deuteriochloroform solutions unless otherwise specified. Mass spectra were obtained with an A.E.I., M.S.9 mass spectrometer by Miss J. Wilkie. Gas-liquid chromatography was performed on Pye Argon and Perkin-Elmer F.11 chromatographs. Gas-liquid mass spectral analyses were carried

out on the L.K.B. spectrometer by Miss H. Humphries. The Rotatory Dispersion Curve was kindly measured by Professor W. Klyne. Merck Kieselgel G was used for analytical and preparative thin layer chromatography. Woeln Grade I alumina deactivated to the appropriate Brockmann grade, Spence's Grade H deactivated with 5% of 10% HOAc and silica gel impregnated with 10% $AgNO_3$ were used for column chromatography, light petroleum or petrol refers to the fraction of b.pt. 60-80°.

EXPERIMENTAL

Isolation of Glycoside Acetates [A] and [B][15]

Commercial Ononis spinosa root (1 kg.), small chips, was refluxed with 95% ethanol (3 l.) for 3 hrs. The extraction was repeated with two further portions (3 l. each) of the same solvent. The combined extracts were concentrated in vacuo to 500 ml. and potassium hydroxide (10 g.) in water (50 ml.) added. Solution was refluxed for 1 hr., diluted with water (500 ml.), and left overnight at room temperature. The crude product (7-8 g.) was collected, dried at 100°, suspended in dry pyridine (50 ml.) and acetic anhydride (25 ml.) on a steam bath for 30 mins. On cooling the diacetate of α-onocerine (A2), crude, separated. After washing thoroughly with methanol, it was chromatographed on alumina. Benzene-petrol (1:1) eluted α-onocerin diacetate, which crystallised from chloroform-acetone (1.35 g.), m.p. 222-224°. Elution with benzene afforded material (1 g.) which on fractional crystallisation from chloroform-methanol yielded acetate A, needles, m.p. 187-189°, $[\alpha]_D$ -104° (C = 1.5); M.W. (by mass spectrum). 614 $[P^+]$ $\xrightarrow{m^* 178.4}$ 331 [Tetraacetyl-

glucose oxonium ion; $\nu_{max.}^{CCl_4}$ 1765 and 1222 (acetate), 1622 and 1590 (aromatics); $\lambda_{max.}^{EtOH}$ 310 mμ, (log ε = 3.89), 284.5 mμ (log ε = 3.66); 279.5 mμ (log ε = 3.59); n.m.r. signals at 7.933 (3H), 7.965 (6H), 7.979 τ (3H), (12 acetate methyl protons), 4.14 τ (2H) (broadened singlet, $-O-CH_2-O-$), in 2.5 - 3.7 τ region (5 aromatic protons); (Found: C, 58.84; H, 4.78. $C_{30}H_{30}O_{14}$ requires C, 58.62; H, 4.89%), and

acetate B, needles, m.p. 172.5-174°; $[\alpha]_D$ -109° (C = 0.91); M.W. (by mass spectrum) 600 [P^+] $\xrightarrow{m^* 182.6}$ 331 [Tetra-acetylglucose oxonium ion]; $\nu_{max.}^{CCl_4}$ 1760 and 1230 (acetate), 1620 and 1580 (aromatics); $\lambda_{max.}^{EtOH}$ 312 mμ (log ε = 3.03); 284.5 mμ (log ε 3.74), 279.0 mμ (log ε = 3.65); n.m.r. signals at 7.936 (3H), 7.963 (6H), 7.980 τ (3H) (12 acetate methyl protons) 6.20 τ (3H, singlet; -OMe) in 2.5 - 3.7 τ region. (6 aromatic protons); (Found: C, 59.70; H, 5.23. $C_{30}H_{32}O_{13}$ requires C, 60.0; H, 5.34%). The lower regions of the mass spectra of acetates A and B are virtually identical, commencing at m/e 331 fragmentations can be followed by metastable ions (m^*).

m/e 331 m^* 223.3 > 272 m^* 164.2 > 211 m^* 135.3 > 169 m^* 95.4 > (12)

m^* 86.3 → 169

m^* 105.4 → 169

m^* 70.3 → 109

Glycosides [A] and [B]

a) Alkaline hydrolysis: Glycoside tetraacetate (800 mg.) in 5% methanolic potassium hydroxide (25 ml.) was refluxed for 1 hr. Boiling water (20 ml.) was added, and, on cooling, the product was filtered, washed and dried, yielding a white solid (595 mg.), the free glycoside.

b) Lithium aluminium hydride reduction: Glycoside tetraacetate (500 mg.) and lithium aluminium hydride (700 mg.) in tetrahydrofuran (50 ml.) were refluxed for 1 hr. Work up by addition of saturated sodium sulphate solution, followed by filtration and removal of solvent afforded the free glycoside (345 mg.).

Due to the inconsistency of melting points found for flavanoid glycosides depending upon the state of dryness, both glycosides, [A] and [B], were crystallised from methanol, and dried under identical conditions, 150° at 0.1 m.m. Hg for 48 hr.

Glycoside [A] m.p. 219-225° (shrinking at ~140°) as needles from methanol; $[\alpha]_D$ -166° (pyridine, C 1.02); $\nu_{max.}^{nujol}$ 3330 (broad hydroxyl), 1620, 1585 (aromatics) cm.$^{-1}$; $\lambda_{max.}^{EtOH}$ 310.5 mμ (log ε = 3.71), 284.5 mμ (log ε = 3.58) 279 mμ (log ε = 3.51). (Found: C, 59.33; H, 5.28. $C_{22}H_{22}O_{10}$ requires C, 59.19; H, 4.97%).

Glycoside [B] m.p. 265-266° (shrinking at ~ 160°) as needles from methanol; $[\alpha]_D$ -143 (pyridine, C 0.78); $\nu_{max.}^{nujol}$ 3340 (broad hydroxyl), 1620, 1580 (aromatics) cm.$^{-1}$ $\lambda_{max.}^{EtOH}$ 311.5 mμ (log ε = 3.01), 284.5 mμ (log ε = 3.61) 279.0 mμ (log ε = 3.59). (Found: C, 61.03; H, 5.62. $C_{22}H_{24}O_9$ requires C, 61.10; H, 5.59%).

Acidic hydrolysis of Glycosides [A] and [B]

The glycoside (200 mg.) in a solution of concentrated sulphuric acid and acetic acid (1:9) was refluxed for 2 hr. The reaction mixture was diluted with water and extracted continuously overnight with ethyl acetate. The aqueous layer was neutralised with 6N sodium hydroxide, and evaporated. The residue was digested with absolute ethanol, decolourised with active charcoal, and evaporation of solvent afforded an oil. Paper chromatography of this oil in two solvent systems, ethyl acetate-isopropanol-water (1:2:1) and butanol-acetic acid-water (6:1:2) revealed a spot at R_f 0.60 and 0.18 respectively, identical with that of glucose for the systems.[56] The oil also yielded an osazone identified as glucosazone by m.m.p. (207-209°) and i.r. spectra comparison. All attempts to isolate the aglycone were unsuccessful.

Enzymatic hydrolysis of Skimmin (a known β-glucoside), Glycoside [A] and Glycoside [β].

The glycoside (10 mg.) was added to a citrate buffer of pH 5 (1 ml.) and brought into solution. To this solution, solid emulsin (β-glucosidase, 7.5 mg.) was added, the mixture shaken and allowed to incubate at room temperature. Reaction times were, for skimmin, 1 hr., and for glycosides [A] and [B], 5 days. It was observed by paper chromatography that the glycoside was being degraded to a less polar product, probably the aglycone. The presence of the glycoside residue was detected, as above, on analytical paper chromatography in various solvent systems, and identified as glucose.

REFERENCES

1. H. Hlasiwetz, J.prakt.Chem., 1855, XLVI, 419.
2. F. von. Hemmelmayer, Monatsh.Chem., 1902, 23, 133; 1903, 24, 132; 1904, 25, 555; Ber., 1900, 33, 3538.
3. F. Wessely, F. Lechner and K. Dinjaski, Monatsh.Chem., 1931, 57, 395; 1933, 63, 201.
4. W. Baker and W.D. Ollis, Nature, 1952, 169, 706.
5. L. Farkas and J. Várady, Chem.Ber., 1959, 92, 819.
6. G. Zemplén, L. Farkas and A. Bien, Ber., 1944, 77, 452.
7. H. Thoms, Ber., 1896, 29, 2985.
8. H. Thoms, Arch. Pharm., 1897, 235, 28.
9. F. von Hemmelmayer, Monatsh. Chem., 1906, 27, 181.
10. F. von Hemmelmayer, Monatsh. Chem., 1907, 28, 1385.
11. H. Brunswik, Z.wiss Mikroskopie, 1922, 39, 316.
12. H.D. Dieterle and A Salomon, Arch. Pharm., 1934, 142.
13. H. Schulze, Z. physiol. Chem., 1936, 238, 35.
14. J. Zimmerhann, Helv.Chim.Acta., 1938, 21, 853.
15. D.H.R. Barton and K.H. Overton, J.Chem.Soc., 1955, 2639.
16. A. McGookin, A. Robertson and W.B. Whalley, J. Chem. Soc., 1940, 787.
17. W. Cocker, T. Dahl, C. Dempsey and T.B.H. McMurry, J. Chem. Soc., 1962, 4906.

18. S. Shibata and Y. Nishikawa, Chem. Pharm. Bull., Japan, 1963, 11, 167.

19. J. B-son Berdenberg and P.K. Hietala, Acta. Chem. Scand., 1961, 15, 696, 936.

20. D.R. Perrin and W. Bottomley, J.Amer.Chem.Soc., 1962, 84, 1919.

21. B.L. van Duuren, J. Org. Chem., 1961, 26, 5013.

22. Y. Fujise, T. Toda, and Shô Itô, Chem. Pharm. Bull., Japan, 1965, 13, 93.

23. D. R. Perrin, Tetrahedron Letters, 1964, 29.

24. C. v.d. M. Brink, W. Nel, G.J.R. Rall, J.C. Weitz and K.G.R. Pachler, J.S. African, Chem. Inst., 1966, 19, 24.

25. S.H. Harper, A.D. Kemp and W.G.E. Underwood, Chem. Comm., 1965, 309.

26. H. Suginome and T. Iwadare, Experientia, 1962, XVIII, 163.

27. M. Karplus, J.Chem.Phys., 1956, 30, 11.

28. R.S. Cahn, C.K. Ingold and V. Prelog, Experientia, 1956, XII, 81.

29. S. Ito, Y. Fujise and A. Mori, Chem.Comm., 1965, 595.

30. D.D. Perrin and D.R. Perrin, J.Amer.Chem.Soc., 1962, 84, 1922.

31. K.G.R. Pachler and W.G.E. Underwood, Tetrahedron, 1967, 23, 1817.

32. H. Suginome, Experientia, 1962, XVIII, 161.

33. H. Booth, Tetrahedron Letters, 1965, 411.

34. D.H. Williams and N.S. Bhacca, J. Amer. Chem. Soc., 1964, 86, 2742.

35. R.J. Abraham, L. Cavalli and K.G.R. Pachler, Mol. Phys. in press.

36. T.W. Goodwin, Recent Advances in Biochemistry, Churchill, London, 1960.

37. R. Robinson, Structural Relations of Natural Products, Clarendon Press, Oxford, 1955.

38. A.J. Birch, Fortschr.Chem.org.Naturstoffe, 1957, 14, 186; Chem. Soc. Spec. Publ., 1958, 12, 4; Proc. Chem. Soc., 1962, 1.

39. E.E. Conn and T. Swain, Chem. and Ind., 1961, 592.

40. H. Reznik and R. Urban, Naturwiss., 1957, 44, 592.

41. J.E. Watkin, E.W. Underhill and A.C. Neish, Canad. J. Biochem. Physiol., 1957, 35, 229.

42. T.A. Geissman and T. Swain, Chem. and Ind., 1957,984.

43. E.W. Underhill, J.E. Watkins and A.C. Neish, Canad. J. Biochem. Physiol., 1957, 35, 219.

44. T.A. Geissman, E. Hinreiner, Botany Reviews, 1952, 18, 77.

45. H. Grisebach, Z. Naturforsch., 1959, 14B, 802.

46. H, Grisebach and N. Doerr, Z. Naturforsch, 1960, 15B, 284.

47. H. Suginome, J. Org. Chem., 1959, 24, 1655.

48. H. Suginome, Tetrahedron Letters, 1960, 16.

49. K. Biemann, D.C. De Jongh and H.K. Schnoes, J. Amer. Chem. Soc., 1963, 85, 1763.

50. I. A. Pearl and S.F. Darling, Tetrahedron Letters, 1967, 1869.

51. J. B-son Bredenberg and J.N. Shoolery, Tetrahedron Letters, 1961, 285.

52. A. Robertson and W.B. Whalley, J.Chem.Soc., 1954, 1440.

53. R.U. Lemieux, R.K. Kullnig, H.J. Bernstein and W.G. Scheneider, J.Amer.Chem.Soc., 1958, 80, 6098.

54. L.D. Hall, Advances in Carbohydrate Chemistry, 1964, 19, 51.

55. R.U. Lemieux and J.W. Lown, Canad. J. Chem., 1963, 41, 889.

56. C.G. Nordström and T. Swain, J.Chem.Soc., 1953, 2764.

SECTION II

CONSTITUENTS OF ERYTHROXYLON MONOGYNUM ROXB. :-

ERYTHROXYTRIOLS P and Q.

SUMMARY

The structures of erythroxytriol P and erythroxytriol Q aceate, which occur in the heartwood of Erythroxylon monogynum Roxb., have been suggested on the basis of spectroscopic and chemical evidence. Ozonolysis of erythroxytriol X acetonide leads to an α-cyclopropyl ketone and unexpectedly to an α-ketol. The discussion is preceded by a review of relevant diterpene biogenesis.

REVIEW OF DITERPENE BIOGENESIS

The biogenesis of terpenes has long been of intriguing interest to chemists. The history of terpene biogenesis has until recently mainly been the history of the "Isoprene Rule", an account of which has been neatly reviewed by Ruzicka.[1] Detailed study in the early 1900's of the then isolated monoterpenes resulted in the theory that such compounds were made up of a carbon skeleton derived from two isoprene units, attached in a "head to tail" manner, but although the majority of natural terpenes can be built up, on paper, from "isoprene units", exceptions were soon noted. It was not until Ruzicka recognised, during his work in the area of higher terpenes, that even these irregular structures could arise by rational rearrangement of polyisoprenes, such as farnesol in the generation of sesquiterpenes, that a basis for the "Biogenetic Isoprene Rule" was provided. These original ideas were of invaluable assistance in the structural elucidation of many terpenoid compounds. In accounting for the structure of eremophilone, Robinson[2] enlarged the early hypothesis, and later Ruzicka[3] published his Biogenetic

Isoprene Rule, following suggestions, by Woodward and Bloch[4] and Dauben[5] and their respective co-workers, concerning the way in which squalene is biogenetically related to lanosterol and cholesterol. The substance of this Rule can be summarised by describing terpenoids as compounds which are derived by combination of isoprene (C5) units to aliphatic analogues, such as geraniol (C10), farnesol (C15), geranylgeraniol (C20), geranylfarnesol (C25) and squalene (C30), which subsequently cyclise, and, in several instances, rearrange via acceptable mechanisms to give the individual members of the mono-, sesqui-, di-, sester, tri- terpenoids respectively, outlined in Fig. I.

Mechanistically terpene biosynthesis has three distinct phases; (a) synthesis of mevalonate from thiol esters, (b) formation of polyisoprene chains via phosphate derivatives and (c) cyclisation with or without rearrangement. For some time now it has been recognised that acetic acid, in the guise of acetyl co-enzyme A, is the precursor in all natural product synthesis. Using acetate labelled ^{13}C or ^{14}C, it has been possible to show that acetic acid is the carbon source for the biosynthesis of all steroids and terpenoids investigated to date, for

example geraniol,[6] squalene,[7] rosenonolactone[8,9] and giberellic acid.[10] Such work is exemplified by the intensive studies by Cornforth and Popjak[11,12] on labelled acetate (B1) incorporation into cholesterol (B2) as shown. Although the intermediacy of a C_5 unit derived from acetate was most probable, a true understanding of the derivation of this unit was not achieved until Folkers[13] isolated mevalonic acid (B5) which can be derived from acetyl co-enzyme A (B3) by a sequence of Claisen-like condensations, Fig. II. Although the thiol esters of acetic, acetoacetic and β-hydroxy-β-methylglutaric acids are normally inter-convertible, the mevalonate synthesis is controlled by the reduction of hydroxy-methylglutaryl-CoA (B4). This reduction requires two molecules of reduced nicotinamide adenine dinucleotide phosphate (TPNH) and is virtually irreversible. There is also an alternative path to the intermediate hydroxy-methylglutaryl-CoA from Leucine (B6) but it is considered very much less important.

At this point it is appropriate to mention the differences in the initial steps in the acetate pathways to polyketides and terpenoids. Although at first glance the structures of isoprenoid substances may appear to bear

little relation to the structures of polyacetate-derived compounds, (Section A), the two types are in fact closely related, c.f. Fig. III, but the paths from acetyl-CoA to polyketides and isoprenoids diverge at this early stage. The polyacetate substances are derived from a continously linear linkage of acetate (or malonate) units, and the branched isoprenoids result from a condensation of the central carbonyl group of acetoacetyl co-enzyme A. The balance between these important biosynthetic pathways is at least partly controlled by two reactions; on the one hand, the carboxylation of acetyl-CoA, and on the other, the reduction of hydroxy-methylglutaryl-CoA.

The importance of mevalonic acid (B5) [MVA], as a precursor in the biosynthesis of polyisoprenoids, has been shown by its ability to replace acetate in the biosynthesis of cholesterol,[14] a conversion that is almost quantitative in certain biological systems. The particular intermediacy of this acid in terpenoid biosynthesis was further demonstrated by Birch and Arigoni. These workers and their colleagues achieved 2-^{14}C-MVA incorporation into the triterpenes soyaspogenol A (B7),[15] lupeol (B8), betulin (B9) and betulinic acid (B10),[16] and into diterpenes rosenono-

lactone (B11),[8,9] pleuromutilin (B12)[17] and gibberellic acid (B13).[10]

Mevalonic acid (B3, however, is a six-carbon unit, and as expected it loses one of its carbon atoms on incorporation into terpenoids and steroids, as demonstrated by Tavormina et al[14] with 2-^{14}C-MVA yielding labelled cholesterol, and 1-^{14}C-MVA affording inactive cholesterol. The C-1 carbon atom of mevalonate is lost, most likely via a decarboxylation mechanism, in the formation of the (C5) biological isprene unit. The steps involved require adenosine triphosphate (ATP), the first being the monophosphorylation of mevalonate yielding mevalonate-5-phosphate (B14). This transformation is carried out by the enzyme, mevalonic kinase, which has been partially purified from various sources, yeast extract,[18] higher plants,[19] and rabbit[20] and hog liver.[21] Further incubation[22,23] of mevalonate with this yeast or hog liver extract leads to the corresponding pyrophosphate (B15). The enzyme involved in this second phosphoration is phosphomevalonic kinase, also isolated from yeast[24] and from hog liver.[25] This enzyme catalyses the phosphorylation of phosphormevalonic acid to mevalonic acid-5-pyrophosphate with adenosine triphosphate

(ATP), liberating stoichiometric quantities of adenosine diphosphate (ADP) during the reaction. From mevalonic acid-5-pyrophosphate (B15), there originates the long-sought biological isoprene unit, identified as Δ^3-isopentenyl pyrophosphate (B16) by Bloch's group[22,24] and by Lynen's group.[26] Bloch proved the chemical constitution of this intermediate by a series of elegant experiments using 1-^{14}C-mevalonate, 2-^{14}C-mevalonate and adenosine triphosphate (P^{32}), alone and in combination. Lynen,[26] on the other hand, was able to isolate the intermediate and identify it as Δ^3-isopentenyl pyrophosphate by blocking an enzyme preparation with iodoacetamide, and he also showed that 2-^{14}C-MVA gave rise to Δ^3-isopentenyl pyrophosphate with the ^{14}C activity solely in the methylene group. This latter transformation from mevalonic acid-5-pyrophosphate to Δ^3-isopentenyl pyrophosphate requires ATP[27] and during the conversion carbon dioxide and ADP are produced at the same rate as Δ^3-isopentenyl pyrophosphate. Conversion of MVA with the hydroxyl oxygen labelled as O^{18} gives rise to inorganic phosphate containing O^{18}, confirming that the 3-hydroxyl group in MVA is activated as its phosphate ester before expulsion. The fact that no

uptake of deuterium is observed in the formation of Δ^3-isopentenyl pyrophosphate suggests that the decarboxylation at C-1, and the dehydration at C-3 must be concerted processes. The sequence of reactions from MVA to isoPP can be depicted as shown in Fig. IV.

Before considering the formation of the polymeric (C5) units, the aliphatic precursors of the terpenes, it is necessary to consider the isomerisation of isoPP to dimethylallyl pyrophosphate (B17). This process, involving proton rearrangement at an enzyme surface, and resulting in the incorporation of one atom of deuterium if the isomerisation occurs in a medium of deuterium oxide, is indeed essential for terpenoid biosynthesis, as Lynen[28] and Bloch[29] have shown. In biological systems in which only one or other of these isoprene units are present, products of the C15 carbon chain of farnesyl pyrophosphate (B19) are inhibited. It also follows that the reactions of the dimethylallyl pyrophosphate must be much more rapid than the reversal of the isomerisation, and the forward isomerisation may well be the rate determining step in the polymerisation sequence. The stereochemistry of all these reactions is, of course, under full enzymatic

control, and as already mentioned the C-2 of mevalonate furnishes specifically both the methylene group of isoPP, and the trans-methyl group of dimethylallyl pyrophosphate. Such an isomerisation process would explain the presence of two of the three or four deuterium atoms found by Bloch[30] in squalene during its synthesis in a medium containing deuterium oxide. These two would be positioned on the terminal isopropyl methyl groups, whereas the other one or two deuteriums located at the centre of the squalene chain were considered by Bloch to result from a reductive mechanism.

The polymerisation sequence is now envisaged, Fig. V, as proceeding by an ionisation of the carbon-oxygen bond of the dimethylallyl pyrophosphate to create a cationic centre with alkylation of the reactive double bond of isoPP. Subsequent loss of a proton affords geranyl pyrophosphate (B18), the immediate precursor of the mono-terpenes. The cationic species is not postulated to be a discrete intermediate as it is most probable that the ionisation of the pyrophosphate fragment is concerted both with the formation of a carbon-carbon bond and with proton loss. The geranyl pyrophosphate so formed is itself an allylic pyrophosphate

and can similarly allylate another molecule of isoPP to yield farnesyl pyrophosphate (B19) the probable precursor of the sesquiterpenoids. Continuation of this process leads to the C20 geranylgeranyl pyrophosphate (B20) from which the diterpenes can be derived, and from further addition it is possible to account for the ubiquinones and sesterterpenes, Fig. I.

These polyisoprenoid pyrophosphates can be decomposed hydrolytically to the corresponding primary alcohols (e.g. geraniol) or their allylic isomers (e.g. linalool). Alternatively they may generate allylic cations which may act as alkylating agents, either intermolecularly, as already described, or intramolecularly (i.e. by cyclisation). The carbonium ions generated in the intramolecular reactions may also be susceptible to rearrangements of the Wagner-Meerwein type, and it has been the particular contribution of Ruzicka[3] and his school to set out in detail the hypothesis that complex isoprenoids are generated by stereospecific carbonium alkylation and rearrangement reactions of the folded polyisoprene chain.

Ruzicka's proposed sequence for the cyclisation of squalene can be extended to include the cyclisation of geranylgeranyl pyrophosphate (B20), and Wenkert[35] has shown that all the known types of diterpenes could arise following an initial cyclisation of the type shown in Fig. VI. This cyclisation initiated by protonation is analogous to the cyclisation of squalene, originally thought to be initiated by oxygenation (i.e. $^{+}$ OH), but now, in certain media at least, considered to be cyclised by acid opening of 2,3-oxidosqualene (see Review of Epoxide Isomerisation). The intermediate precursor is manoyl pyrophosphate (B21), which by subsequent additions, eliminations and rearrangements proceeding in a stereospecific trans diaxial manner affords the individual diterpenes. As expected, the stereochemistry of most diterpenes accords with this mode of formation from geranylgeranyl pyrophosphate (B20) in the chair-chair conformation (B22) giving rise to the intermediate bicyclic pyrophosphate (B21), with a trans-anti backbone. However there was at that time a small group assigned with a trans-syn backbone, which could owe their origin to cyclisation of (B20) in a chair-boat conformation, affording an intermediate bicyclic trans-syn pyrophosphate.

The latter group initially included eperuic acid (B23), rimuene (B24), rosenonolactone (B11), gibberellic acid (B13) and cafestol (B25), but now eperuic acid[31] has been shown to have the normal trans-anti backbone, although it clearly arises from the antipode of the intermediate bicyclic pyrophosphate (B21). Rimuene also has been shown to posess the same trans-anti stereochemistry. Scott and his coworkers[32] by x-ray and circular dichroism studies have shown that the previously assigned configuration at C-9 in cafestol was in error, and have pointed out, as is illustrated below, that rosenonolactone and gibberellic acid do in fact conform to a trans-anti precursor, subsequent skeletal rearrangements resulting in the trans-syn backbone.

Isotopic studies[17,33,34] with the fungal diterpenoids have proved most interesting. The biogenesis of rosenonolactone a co-metabolite of trichothecin is outlined in Fig. VII. The labdane precursor is converted to the allylic cation which cyclises in the manner shown, with a 1,2 shift of the methyl group. Oxygenation reactions then yield rosenonolactone. This sequence fully explains the stereochemistry of the product, with the unusual trans-syn-trans arrangement, and also the isotopic data, especially

the labelling of the α-methyl group in ring A, and not the β-carboxyl group by 2-^{14}C-MVA. The biogenesis of a more complex series of metabolites, from Gibberella sp., including the important hormone gibberellic acid is outlined in Fig. VIII. The compounds in this series are enantiomeric with the 'normal" diterpenes, and the precursor must be the mirror image of (B21) [i.e. (B26)]. The formation of ring D is known to involve Wagner-Meerwein rearrangement as shown and not the alternative, 1,2-methyl shift. These two different routes would be expected to lead to different labelling in the vinylidene grouping, when 1-^{14}C-acetate is used as precursor. Also in this enantiomeric series, it is the β-carbon of the gemdimethyl group which is labelled by 2-^{14}C-MVA incorporation, and the α-carbon which ultimately undergoes oxidations. Contraction of ring B in forming gibberellic acid clearly follows the oxidative attack, which is partly illustrated in kaurenolide (Fig. VIII).

In the biosynthetic studies of Birch and Arigoni, the Biogentic Isoprene Rule is supported in every way, as is the theory that diterpenoids conform to a trans-anti precursor rule by having the labdane pyrophosphate (B21) or its antipode (B26) as a biogenetic intermediate.

The differences are introduced by subsequent rearrangements (and transformations) of the basic labdane skeleton,

In a theory to rationalise the biogenetic formation of the major constituents of Erythroxylon Monogynum Roxb., it must be assumed that in this case geranylgeranyl pyrophosphate cyclises in the chair-chair conformation giving rise to the antipodal labdane pyrophosphate intermediate (B26) which is the likely precursor of the hydrocarbon, stachene (B27) and the tetracyclic alcohols A (B28) and B (B29) [cf. biogenesis of hibaene ≡ (-) stachene in Fig. IX]. The erythroxydiols and triols most probably arise from the same precursor (B26) (see Fig. X). Closure of ring C, with presumably concerted skeletal rearrangement and with the formation of a cyclopropane ring, as shown, gives rise to (B30) which on hydroxylation of the side chain would afford erythroxydiol X (B31). Further secondary transformations would result in the formation of the triol monoacetate Q (B32). Similar primary rearrangement of (B26) would be predicted to lead to the remaining naturally occurring erythroxydiols Y (B33) and Z (B34).

Finally it is of interest to note that there is a small group of diterpenes which do not have the labdane pyrophosphate type precursor. In these cases, geranyl-geranyl pyrophosphate assumes the conformation (B36), and on cyclisation affords the monocyclic diterpene, cembrene (B37) and its relatives,[36] the bicyclic diterpenoids related to verticillol[37] (B38) and the tricyclic diterpenes of the taxane series, typified by taxinin[38,39] (B39).

ERYTHROXYTRIOLS P AND Q[40,41]

The light-petroleum-soluble extractive of the trunkwood of E. monogynum affords[42,43] the hydrocarbon, stachene (B27), and the tetracyclic alcohols A (B28) and B (B29) by gradient elution chromatography and fractional crystallisation. Further elution yields a mixture of diols and triols [followed by the tetracyclic diol[43] (B40)] which can be conveniently separated by gradient elution of the derived acetonides from silver nitrate-impregnated silica gel., the diol acetonide mixture is resolved[44,45,46] into its components, diol X acetonide (B41), diol Y acetonide (B42) and diol Z acetonide (B43). The most polar fractions from this chromatogram contain the acetonides, triol P acetonide (B44) $C_{23}H_{40}O_3$, m.p. 142-143°, $[\alpha]_D$ + 31° and triol Q acetonide acetate (B45) $C_{25}H_{40}O_4$, m.p. 111-113°, $[\alpha]_D$ - 17°. The discussion which follows concerns the elucidation of the structure and stereochemistry of erythroxytriols P and Q.

Treatment of triol Q acetonide acetate (B45) with lithium aluminium hydride afforded triol Q acetonide (B46), $C_{23}H_{38}O_3$, m.p. 103-105°; 115-116°, $[\alpha]_D$ + 5°.

The free triol Q (B47), $C_{20}H_{34}O_3$, m.p. 181-183°, $[\alpha]_D$ - 10° (EtOH) could also be regenerated from triol Q acetonide acetate, and is probably identical to hydroxydevadarool,[47] m.p. 181.5-182°, $[\alpha]_D$ - 3.75°(etOH), also isolated from E. monogynum.

In the nuclear magnetic resonance spectrum of triol Q acetonide (B46), two regions are virtually identical with those attributable to the acetonide and cyclopropane functions in the nuclear magnetic resonance spectrum of erythroxydiol X acetonide (B41),[45] suggesting that these functions and their immediate environment are common to the two compounds.

Oxidation of triol Q acetonide (B46) with the Sarett reagent afforded the corresponding ketone (B48), $C_{23}H_{36}O_3$, m.p. 92-93°, $[\alpha]_D$ + 124°, $\nu_{max.}^{CCl_4}$ 1704 cm.$^{-1}$, λ_{max} 296 mμ (ε 55) whose nuclear magnetic resonance spectrum clearly indicated retention of the acetonide (3H multiplet τ 5.96 - 6.40) and cyclopropane ring (1H doublets at τ 9.43 and 9.92). The mass spectrum had a strong peak (50%) at m/e 101 corresponding to $C_5H_9O_2^+$, characteristic of acetonide function[48] and this was absent in the mass spectrum of the derived diol (B49), m.p. 167-169° $\nu_{max.}^{CCl_4}$ 1704, 3580 and 3631 cm.$^{-1}$.

Huang-Minlon reduction of the acetonide ketone (B48) afforded diol X acetonide (B41) as the sole product. Triol Q is therefore a monohydroxylated diol X in which the additional hydroxyl function is secondary.

The environment of the secondary hydroxyl group in (B46) can be deduced from the nuclear magnetic resonance spectra of triol Q acetonide acetate (B45), the epimeric acetate (B50), and the keto-acetonide (B48) and from deuteration experiments with the last compound.

Triol Q acetonide acetate (B45) exhibits in the nuclear magnetic resonance spectrum a one-proton quartet centred at τ 5.07 ($>$CH-OAc) arising from an axial proton (J = 10, 6 c./sec.) so that the acetate residue must be equatorial. Borohydride reduction of the ketone (B48) afforded exclusively the epimeric alcohol (B51), $C_{23}H_{38}O_3$, m.p. 113-115°, $[\alpha]_D$ + 36°, $\nu_{max.}^{CCl_4}$ 3632 cm.$^{-1}$. The derived acetate (B50), $C_{25}H_{40}O_4$, m.p. 119-121°, $[\alpha]_D$ + 34°, had in its nuclear magnetic resonance a one-proton triplet, centred at τ 5.12 ($W_{\frac{1}{2}}$ 9 c./sec.[47]) arising from an equatorial proton, so that the acetate in this case must be axial. In accordance with these assignments the peak at m/e 344 (P - 18) in the mass spectrum of the axial alcohol (B 51) was much more

abundant (1800 x P) than in that of the equatorial alcohol (B46) (12 x P). Further support comes from the respective dehydration products of the two alcohols discussed below. The nuclear magnetic resonance spectra of both acetates strongly suggests that the nuclear hydroxyl of triol Q has only two hydrogens on adjacent carbon and this is supported by base-catalysed deuterium exchange of the ketone (B48) [16% d_0, 61% d_1, 12% d_2, 0% d_3 after 96 hrs. at 60° in NaOD/D_2O-dioxan]. Moreover the nuclear magnetic resonance spectrum of this ketone shows that both hydrogens are attached to the same α-carbon atom, since two one-proton doublets at τ 7.08 and 8.23 (both disappear on deuterium exchange) are mutually coupled (nuclear magnetic resonance) and must, from their coupling constant (J = 13 c./sec.) and the fact that they show virtually no other coupling, be geminal and isolated. Monitoring of the exchange reaction by nuclear magnetic resonance shows that the hydrogen resonating at τ 7.08 is exchanged first. This could mean, in agreement with previous observations,[49,50] that the axial hydrogen is exchanged first, although it cannot safely be assumed that of two protons situated on the same carbon atom adjacent to carbonyl the one resonating at lower field is necessarily axial.[51]

These observations lead to the functional sequence -C-CHOH-CH_2-C- and this can be fitted into the structure of diol X acetonide (B41) only if the secondary hydroxyl is placed at either position 11 or 12. A number of observations would support such a hindered location. Thus reduction of the ketone (B48) exclusively to the axial alcohol is reminiscent of the classical precedent of 11-oxo-steroids.[52,53] The lack of reactivity of the ketone B48) at both the carbonyl carbon and the adjacent methylene carbon is apparent by its failure to react under conditions that would lead to ketal formation, diosphenolation, α-bromination, or α-acetoxylation and condensation with benzaldehyde (see Experimental section).

Of the two available positions, the secondary hydroxyl must be attached to C-11 rather than C-12 for the following reasons. Dehydration of the epimeric alcohols (B51) and (B46) with thionyl chloride in cold pyridine led in each case to one major product. Thus the axial alcohol (B51) afforded the olefin (B52) $C_{23}H_{36}O_2$ (in 75% yield by g.l.c.) which was separated from the two minor dehydration products by preparative t.l.c. on silver nitrate-silica gel. As expected, this compound showed in its nuclear magnetic resonance spectrum in

addition to multiplets characteristic of the acetonide and cyclopropane functions, an AB quartet arising from the vinyl protons at τ 4.03 and 4.69 (J = 9.6 c./sec.) with subsidiary coupling (1 c./sec.) of the proton at τ 4.69 (homoallylic coupling of H-11 with H-8, H-10 or H-20). One of the two minor dehydration products [obtained about 90% pure (g.l.c.) from the preparative chromatoplate] revealed in its nuclear magnetic resonance spectrum one secondary and two tertiary methyl groups and no vinyl protons, and might therefore be formulated as (B53). Hydrogenation of the olefin (B52) with palladised carbon (10%) in ethanol led to diol X acetonide (B41).

Dehydration of the equatorial alcohol (B46) under the same conditions gave as major product (90% by g.l.c.) the olefin (B54), $C_{23}H_{36}O_2$. Its structure is assigned on the basis of its nuclear magnetic resonance spectrum (only two tertiary methyl groups, but in addition, a two-proton doublet at τ 5.16 and 5.20, characteristic of a vinylidene group), the geometry of its precursor (B46) which would be expected to lead to such a structure, and the formation and nature of the derived nor-ketone (B55). Osmylation of the olefin (B54) and cleavage with periodate

of the resulting mixture of diols, afforded the nor-ketone (B55), $C_{22}H_{34}O_3$, m.p. 142-143°, $[\alpha]_D$ + 67° $\nu_{max.}^{CCl_4}$ 1696 (cycloheptanone) cm.$^{-1}$. In the nuclear magnetic resonance spectrum the low-field doublet present in its precursor (B54) was replaced by a diffuse two-proton multiplet (τ 6.8 - 7.4; 2 >CH-CO-). Under basic catalysis the nor-ketone (B55) smoothly exchanges two protons for deuterium (11% d_0, 18% d_1, 71% d_2, 0% d_3 after 72 hrs. at 70° in NaOD/D_2O-dioxan). Exposure of the nor-ketone to a solution of hydrogen chloride in chloroform at 20° and replacement of the acetonide function, led to a mixture of two unsaturated ketones (9:1 by g.l.c.), with infra-red bands at 1700 and 1670 cm.$^{-1}$, presumably to be formulated as (B56) and (B57) with the unconjugated ketone preponderating ($\lambda_{max.}$ 254 mμ, ε ~1000), as previously noted[54,55] in a cycloheptenone system.

The highly stereoselective dehydration paths followed by the two alcohols which substantiate the configurations assigned to them, entirely accord with established precedent[56] and do not require further comment.

In this department, workers in this field have favoured,[45] on the basis of previous work, the 4,5- (B41) over the alternative 9,10-cyclopropane structure (B58)

for erythroxydiol X. The definitive distinction between these alternatives, which was previously lacking is now supplied by the reaction of erythroxytriol Q, when taken in conjunction with its conversion by two routes into erythroxydiol X.

A recent X-ray structure determination[61] confirms in every detail formulation of the triol as in (B47) and hence of diol X as (B31). It also provides definitive support for the configuration at C-10, formerly inferred on biogenetic grounds, and at C-15, previously undefined.

Triol P acetonide (B44) has in its nuclear magnetic resonance spectrum signals typical of the acetonide function present in triol Q acetonide (B45). It lacks cyclopropyl proton signals but instead has a fourth tertiary methyl group. In place of an olefinic double-bond (absence of signals in the spectrum below τ 6; transparent unthe ultra-violet above 200 mμ; tetranitromethane negative), it contains a tertiary hydroxyl group [$\nu_{max.}^{CCl_4}$ 3625 cm.$^{-1}$; no $\rangle$C<u>H</u>-OH signal in the nuclear magnetic resonance spectrum; appreciable peak in the mass spectrum at m/e 346 (P-18)]. These properties suggest the alternative structures (B59), (B60) or (B61). A low-field nuclear magnetic resonance methyl signal to be

expected if the structure were (B61) is absent (3H singlets at τ 8.98, 9.06, 9.10 and 9.13).

Strong support for the suggested structure (B59) comes from the dehydration of triol P acetonide (B44) with thionyl chloride in cold pyridine. The major product (B62) (88% by g.l.c.), $C_{23}H_{38}O_2$, m.p. 85-86°, $[\alpha]_D$ - 29°, is accompanied (12%) by the previously obtained[46] isomer (B63). Isomerisation of the olefin (B62) with a solution of hydrogen chloride in chloroform at 20° afforded a mixture of (B62) (53%), (B63) (34%), and two minor products that were not further investigated.

Of the two possible structures for the major olefin, (B62) is preferred to (B64) because of two properties that resemble rimuene (B24).[57] Thus in the nuclear magnetic resonance spectrum there is a signal from a tertiary methyl group at high-field (τ 9.35) ascribed here, as in rimuene (τ 9.38) to the shielding effect of the Δ^5-olefinic double bond on the C-9 methyl group. Furthermore two major fragments in the mass spectrum of (B62) at m/e 136 and 121 arise, as in rimuene, from retro-Diels-Alder fission of ring B.

Finally it is of interest to comment upon the results obtained when diol X acetonide (B41) was ozonised in

methylene chloride-pyridine (2:1) at -70°. This reaction was undertaken during the early stages of this work in the hope of obtaining the two α-cyclopropyl ketones at positions 3 and 6 for comparison with the ketone (B48). Moreover the novel conversion of the ester (B65) into the corresponding α-cyclopropyl ketone (B66) reported by Ourisson[58] and apparently relatively specific to the trachylobane system, appeared to be of sufficient intrinsic interest to merit further investigation with the readily accessible diol X acetonide (B41). When this was ozonised under the conditions of Ourisson, and the products separated by preparative thin-layer chromatography, the cyclopropyl ketone (B67), $C_{23}H_{36}O_3$, m.p. 125-126°, was obtained in 33% yield, allowing for recovered starting material. This new ketone (B67) had $\nu_{max.}^{CCl_4}$ 1683 cm.$^{-1}$ (α-cyclopropyl ketone). However there was no evidence for the formation of a second cyclopropyl ketone.

The nuclear magnetic resonance solvent shifts,[59] ($CDCl_3$ to benzene) were particularly informative in distinguishing between the 3- and 6-positions for the carbonyl group. Thus the cyclopropyl proton at τ 9.25 experienced a large positive shift (+ 0.50 τ) and the

shifts of the methyl groups, C-20 (+ 0.20 τ), C-19 (-0.24 τ) and C-17 (+0.05 τ) were all in accordance with prediction[59] for a C-3 but not for a C-6 ketone.

The following further properties of ketone (B67) accorded with the assigned structure. Huang-Minlon reduction smoothly afforded diol X acetonide (B41). Two hydrogens were exchanged for deuterium under basic catalysis (2% d_0, 6% d_1, 91% d_2, 1% d_3 after 72 hr. with NaOD in D_2O-dioxan at 60°). With isopropenyl acetate and toluene-p-sulphonic acid, the ketone (B67) formed an enol acetate (B68) $C_{25}H_{38}O_4$ m.p. 110-111°, $\nu_{max.}^{CCl_4}$ 1759 and 1215 cm.$^{-1}$ (enol acetate), one proton quartet in the nuclear magnetic resonance spectrum at τ 5.12 (J = 7, 2 c./sec. with 2H-1 protons at τ 8.13 and 8.30). Reaction of the ketone (B67) with oxygen and potassium t-butoxide in t-butyl alcohol, afforded diosphenol (B69) $C_{23}H_{34}O_4$, m.p. 168-170°, $\lambda_{max.}$ 268 (ε 3500), 240 (ε 3650) (EtOH) and 314 mμ (ε 3130) (0.1 N-NaOH/EtOH), $\nu_{max.}^{CCl_4}$ 1653 (C=C), 1673 (CO) and 3448 (bonded hydroxyl) cm.$^{-1}$; one proton in the nuclear magnetic resonance spectrum at τ 4.36 (doublet J = 3.2 c./sec.; H-1) coupling with one proton at τ 7.55 (H-10). The solvent shifts[59,60] ($CDCl_3$ to benzene; see Experimental section) are in

accord with the suggested structure.

A second major product (25%) from the ozonolysis of diol X acetonide (B41) is formulated as the α-ketol (B70), $C_{20}H_{32}O_2$, m.p. 82-84°, $\nu_{max.}^{CCl_4}$ 1705 (CO) and 3484 (bonded hydroxyl) $cm.^{-1}$; nuclear magnetic resonance signals at τ 8.78 (3H, CH_3-CO) and 5.57 (2H singlet, $HOCH_2$-CO), since on acetylation it afforded the known keto-acetate (B71), m.p. 93-95°; 103-104°. The rather unexpected formation of an α-ketol CO-CH_2OH from the acetonide of the related α-glycol CHOH-CH_2OH under conditions of ozonolysis is of mechanistic interest and may have practical utility in the steroid field.

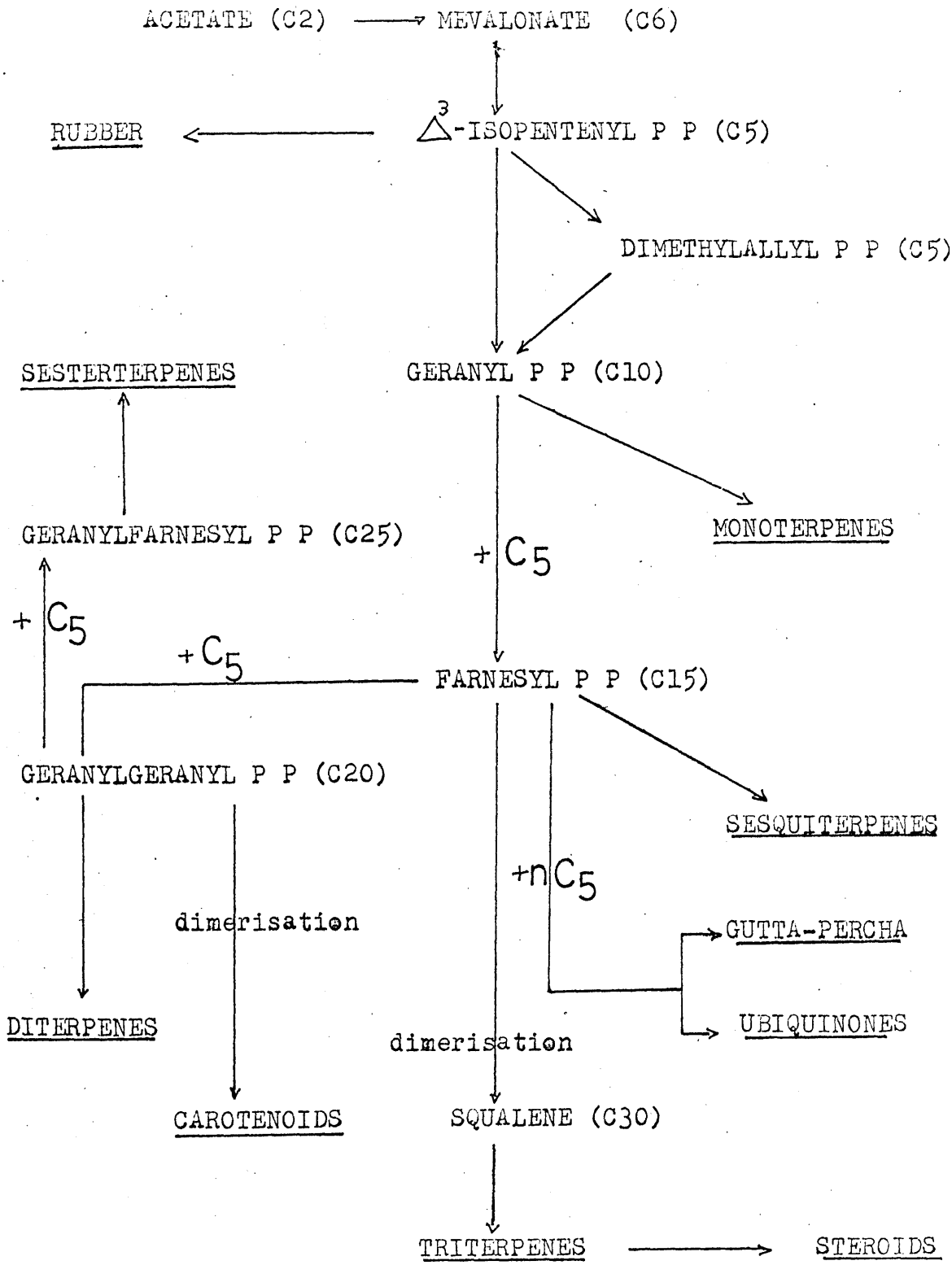
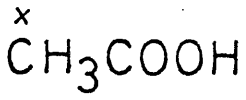
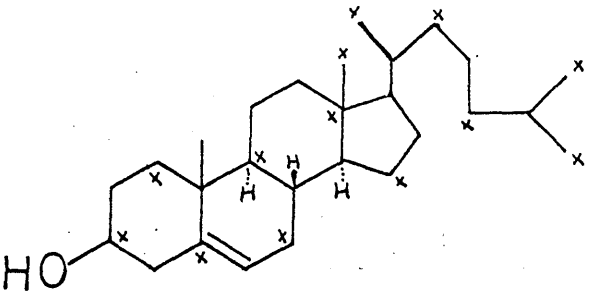

ACETATE (C2)
MEVALONATE (C6)
Δ^3-ISOPENTENYL P P (C5)
RUBBER
DIMETHYLALLYL P P (C5)
SESTERTERPENES
GERANYL P P (C10)
MONOTERPENES
GERANYLFARNESYL P P (C25)
+ C_5
+ C_5
+ C_5
FARNESYL P P (C15)
GERANYLGERANYL P P (C20)
SESQUITERPENES
+n C_5
dimerisation
GUTTA-PERCHA
UBIQUINONES
DITERPENES
dimerisation
CAROTENOIDS
SQUALENE (C30)
TRITERPENES
STEROIDS

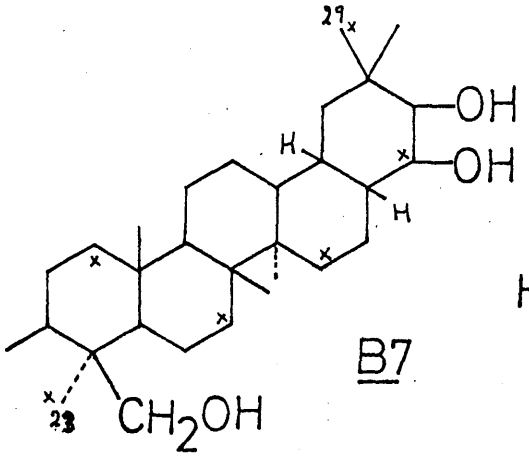
Fig I



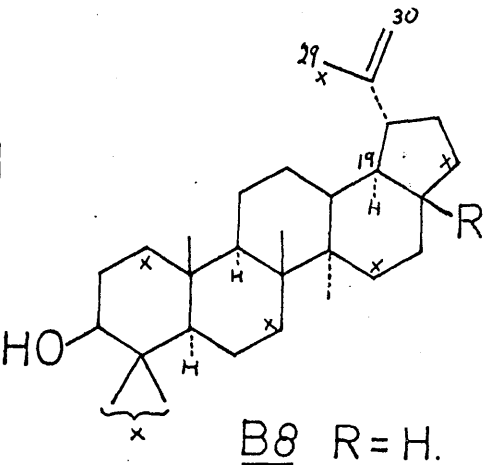
B1



B2



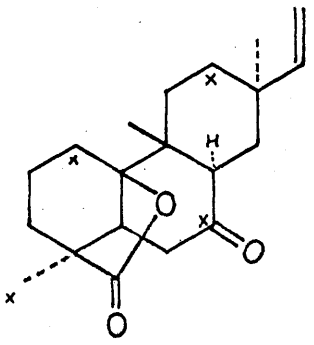
B7



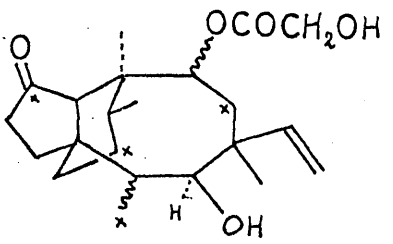
B8 R = H.

B9 R = CH_2OH

B10 R = COOH



B11



B12

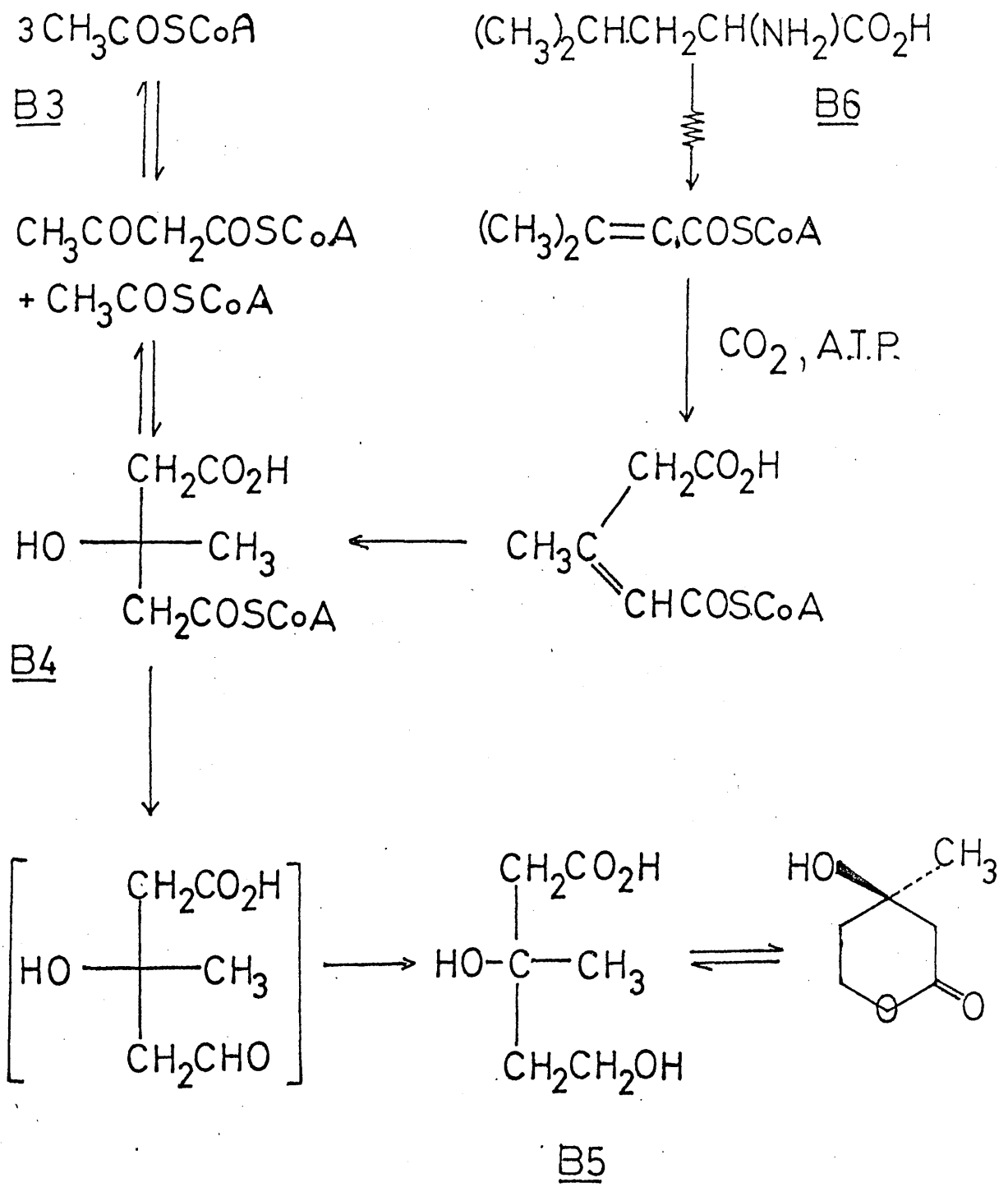

3 CH3COSCoA
B3
CH3COCH2COSCoA
+ CH3COSCoA
(CH3)2CH.CH2CH(NH2)CO2H
B6
(CH3)2C=C.COSCoA
CO2, A.T.P.
CH2CO2H
HO
CH3
CH2COSCoA
B4
CH2CO2H
CH3C
CHCOSCoA
CH2CO2H
HO
CH3
CH2CHO
CH2CO2H
HO-C-CH3
CH2CH2OH
B5
HO
CH3
O
O

Fig II

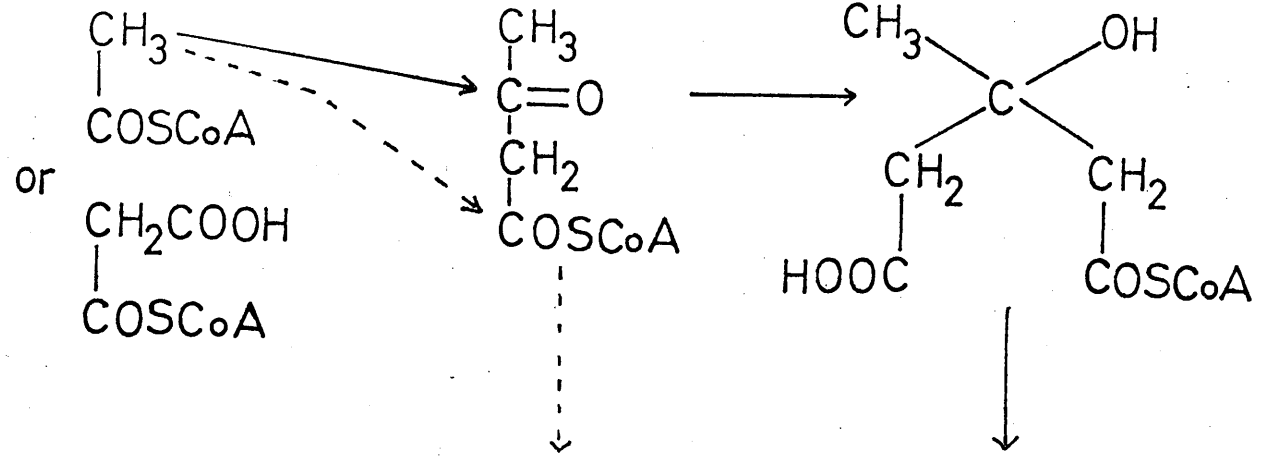
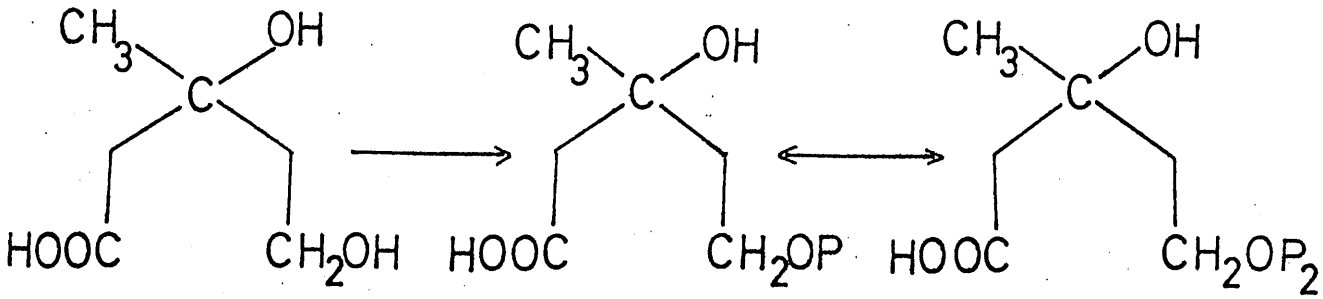
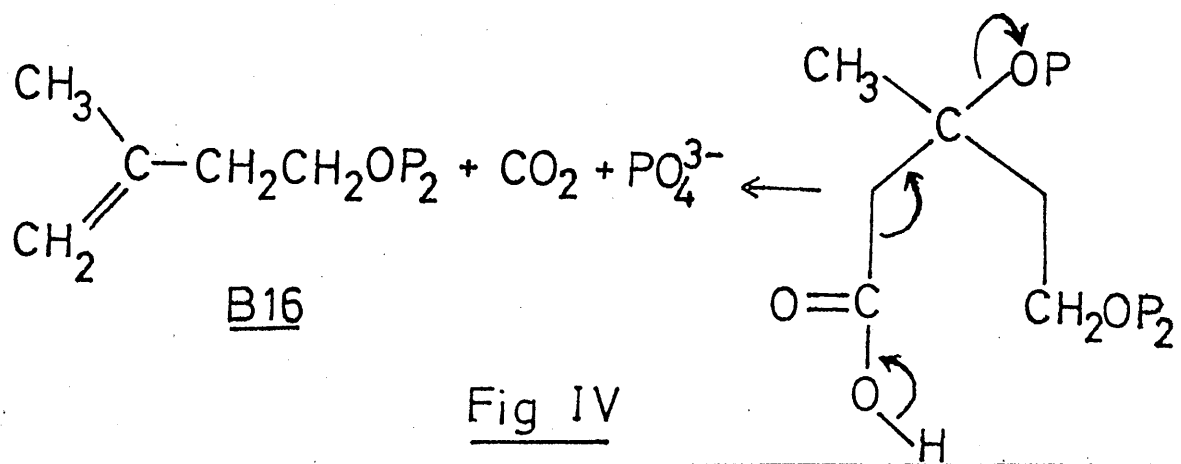


Fig III Acetogenins Isoprenoids



B5 B14 B15



B16

Fig IV

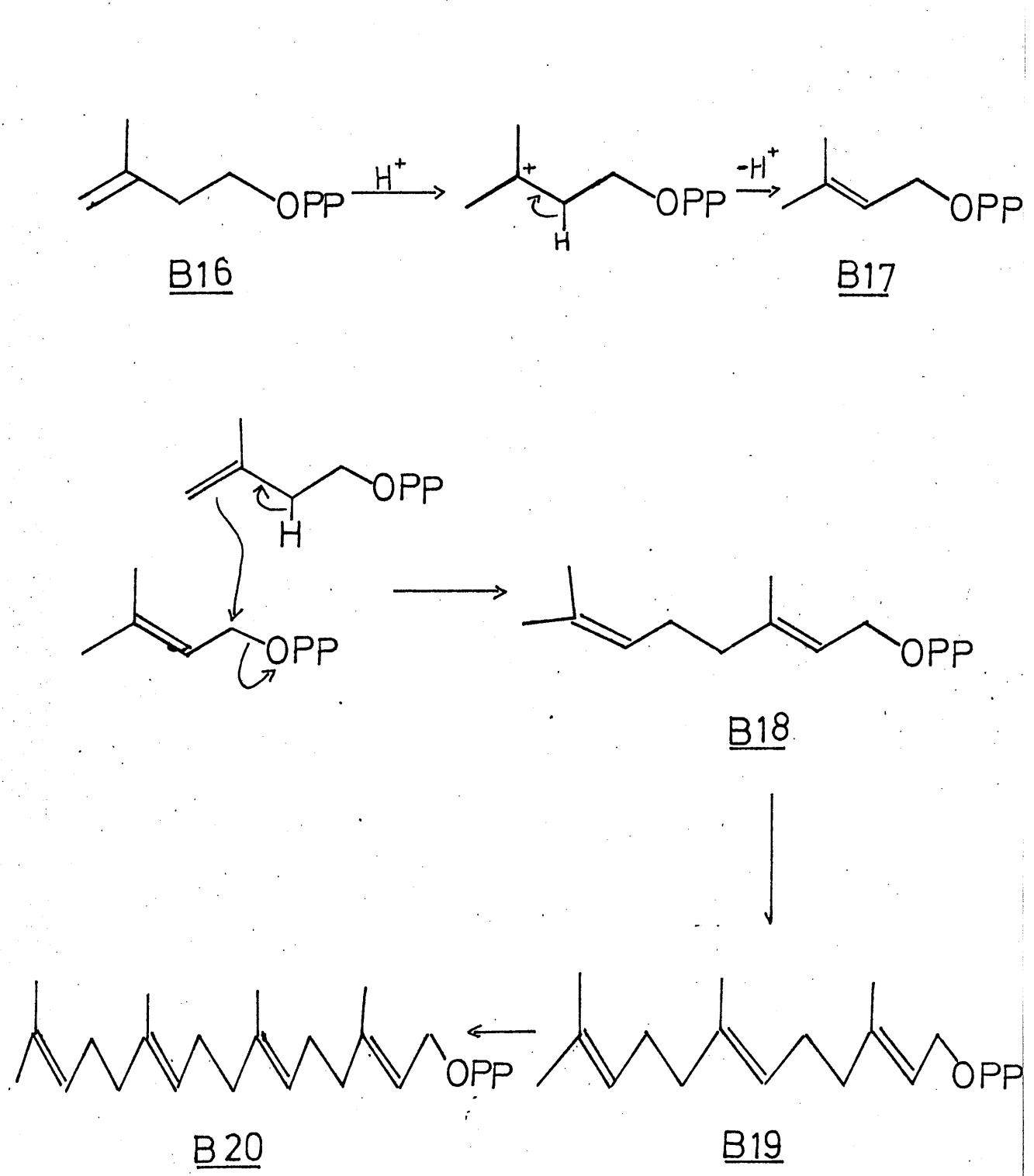
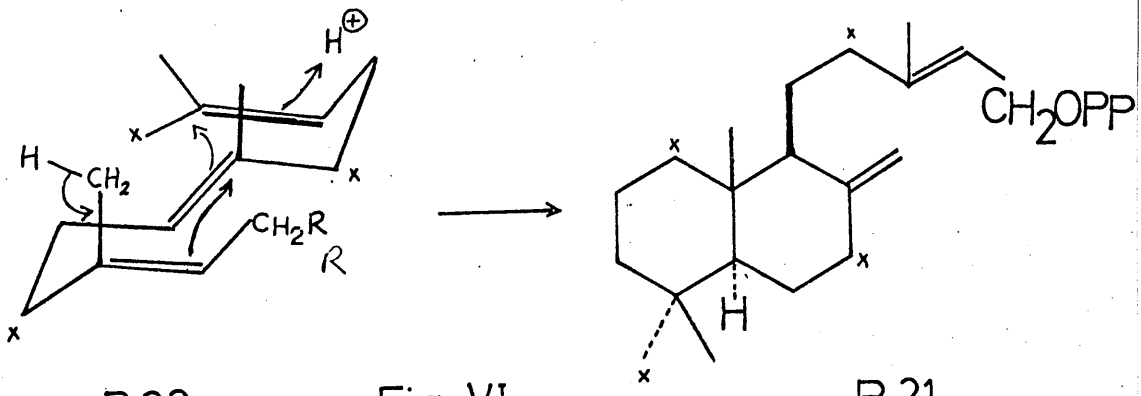
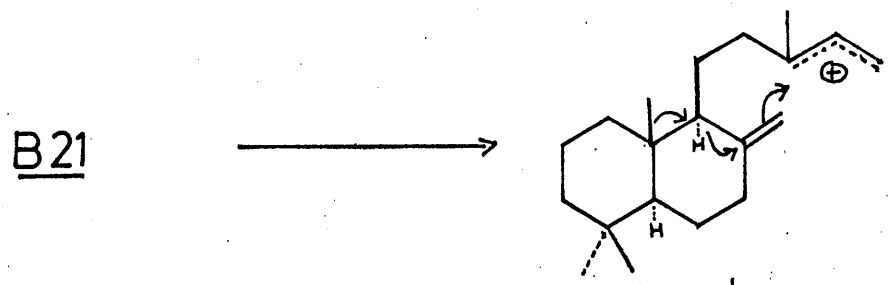
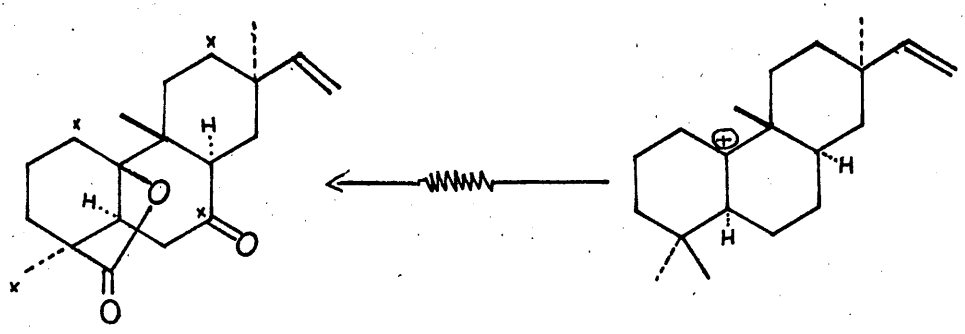


Fig V



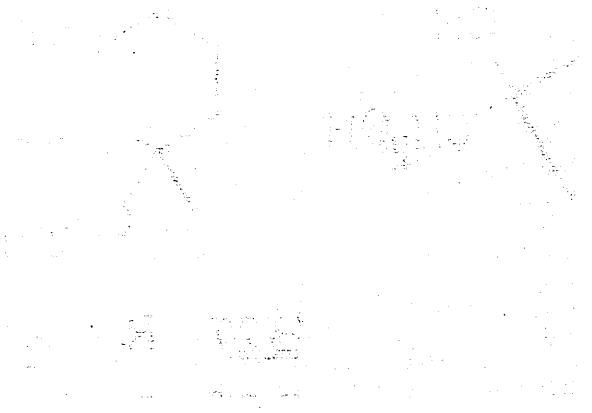
B22 Fig VI B21

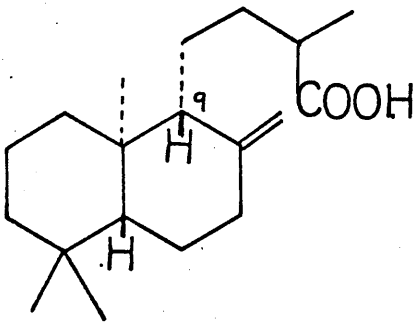




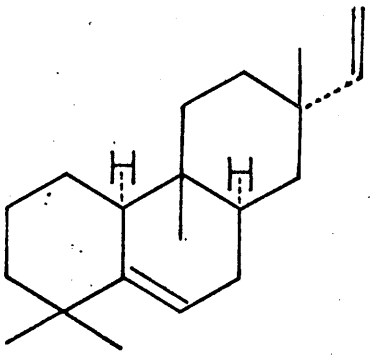
B11

Fig VII

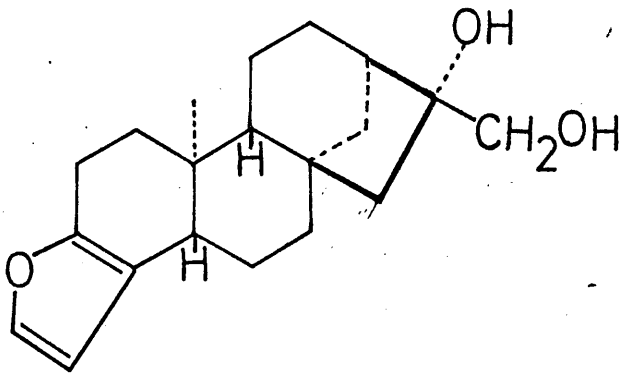




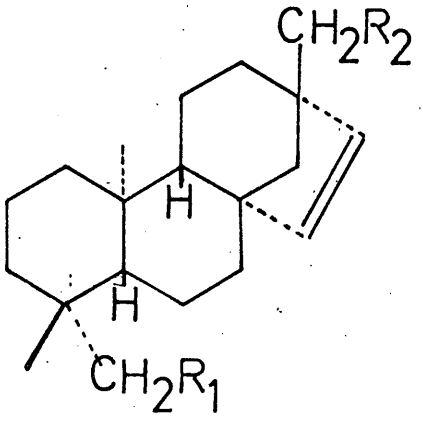
B 23



B 24



B 25



B 27 $R_1 = R_2 = H$.

B 28 $R_1 = OH$; $R_2 = H$.

B 29 $R_1 = H$; $R_2 = OH$.

B 40 $R_1 = R_2 = OH$

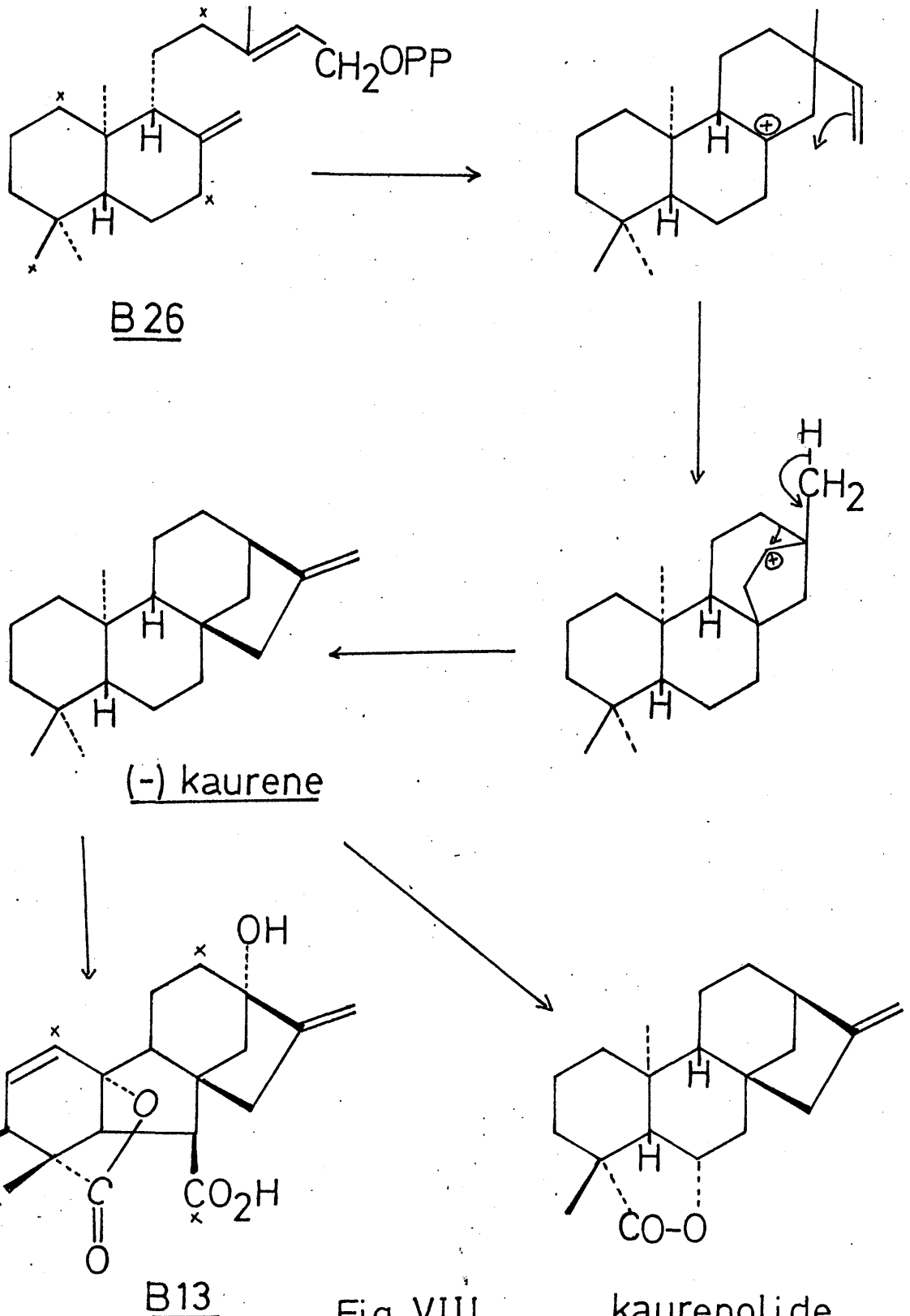

CH2OPP
H
H
B 26
H
CH2
H
H
H
(-) kaurene
OH
HO
O
C
O
CO2H
B13
H
H
CO-O
kaurenolide

Fig VIII

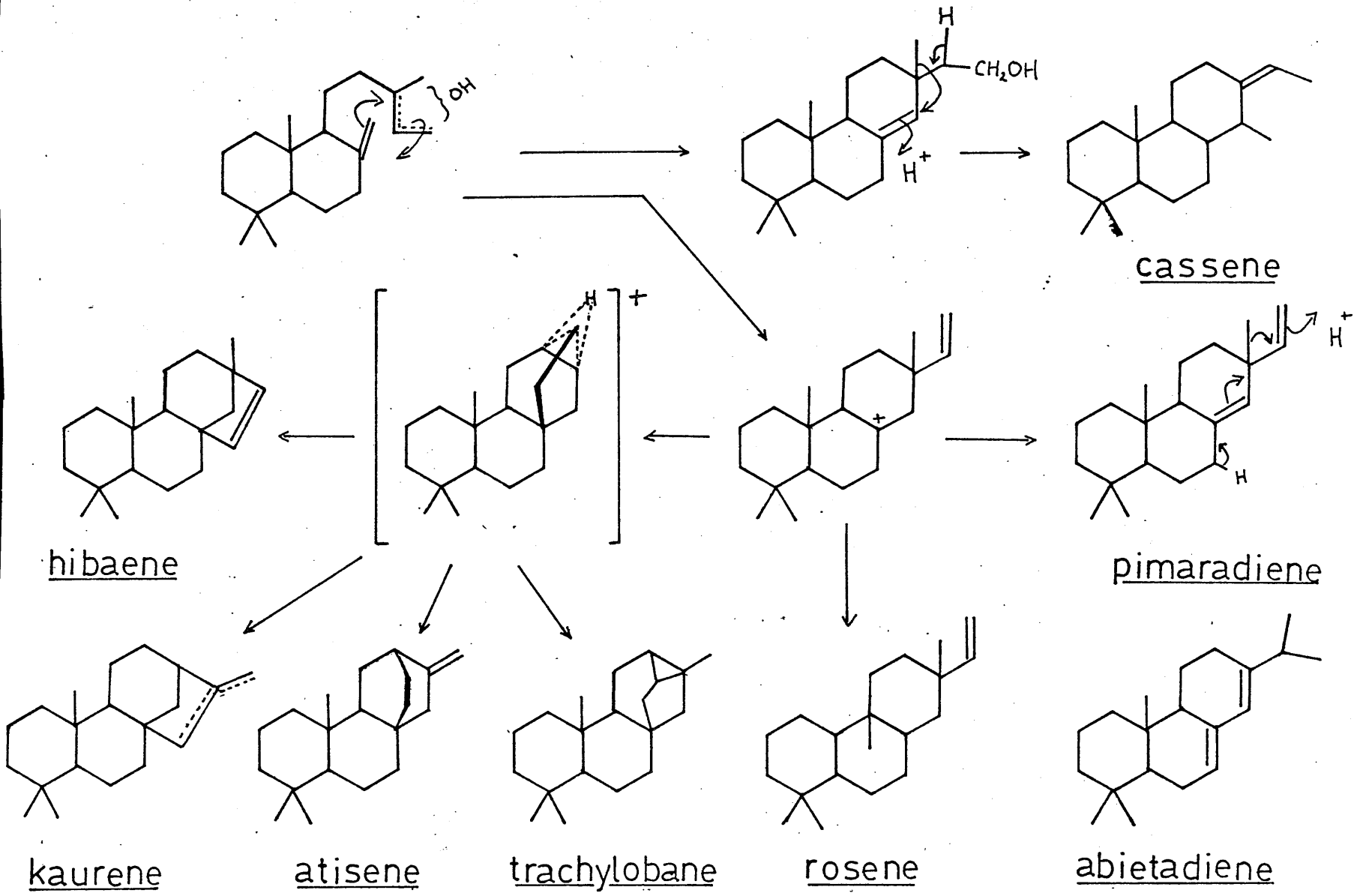
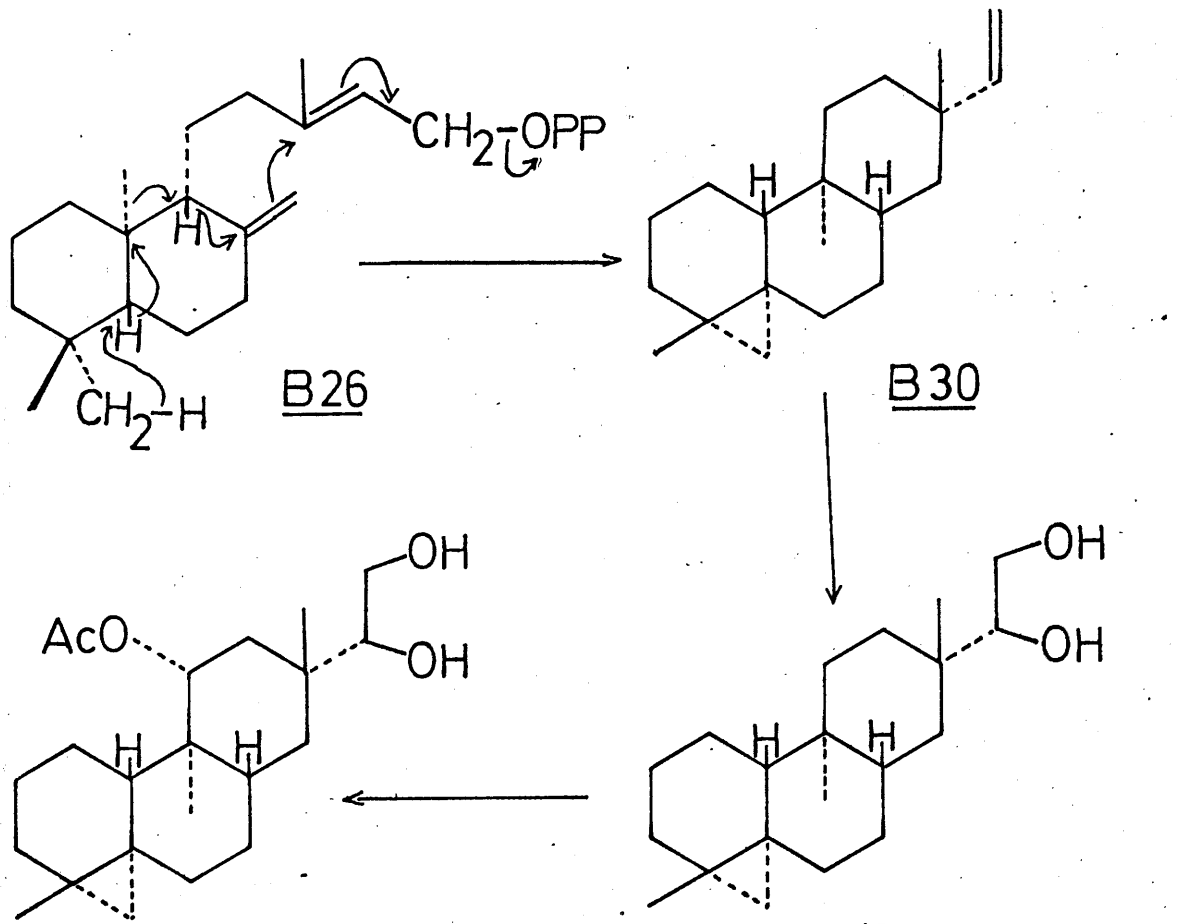
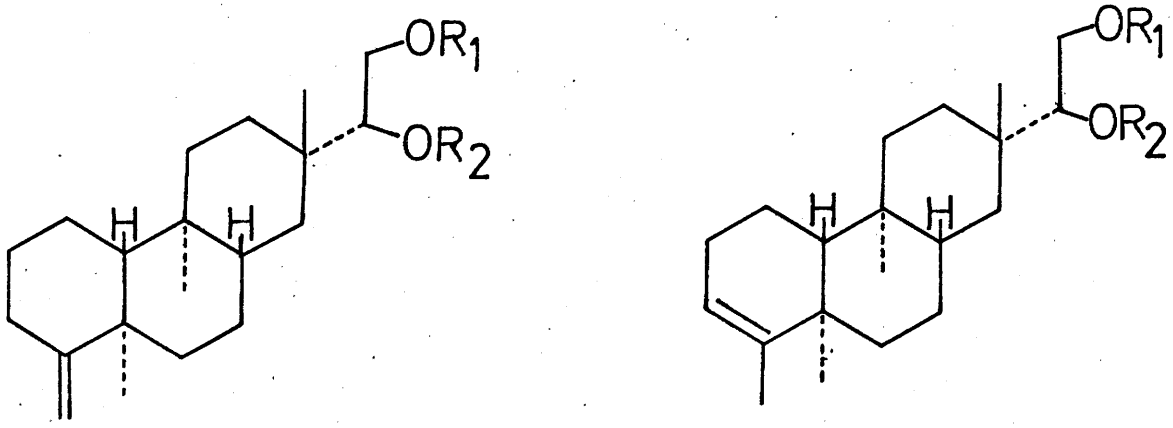

OH
H
CH2OH
H+
cassene
hibaene
pimaradiene
kaurene
atisene
trachylobane
rosene
abietadiene

Fig IX



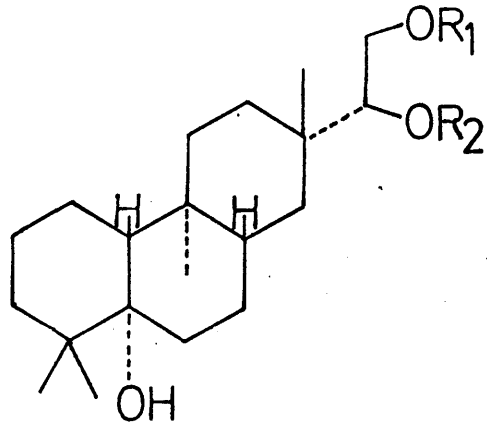
B26 B30 B31 B32

Fig X



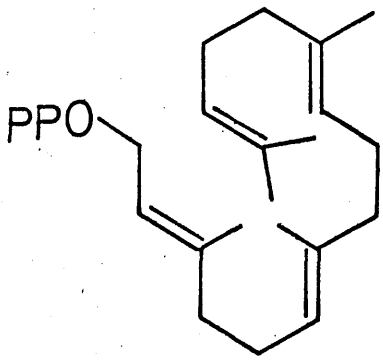
B33 $R_1 = R_2 = H$. B34

B42 $R_1 + R_2 = Me_2C=$. B43

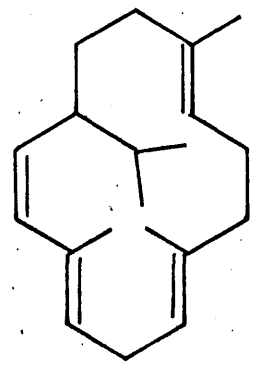


B 35 $R_1 = R_2 = H$.

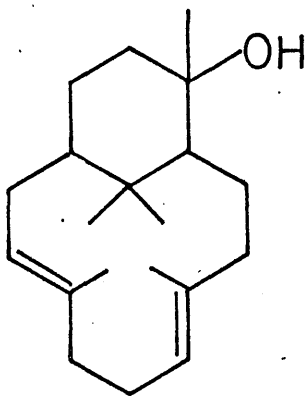
B 44 $R_1 + R_2 = Me_2C =$



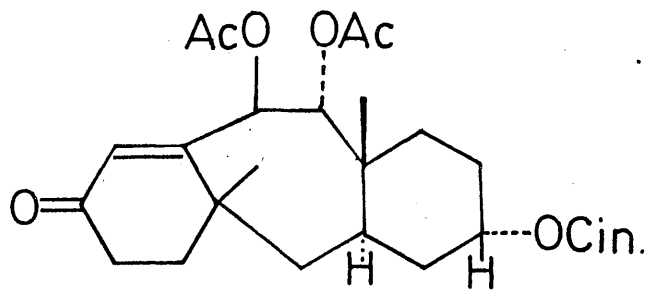
B 36



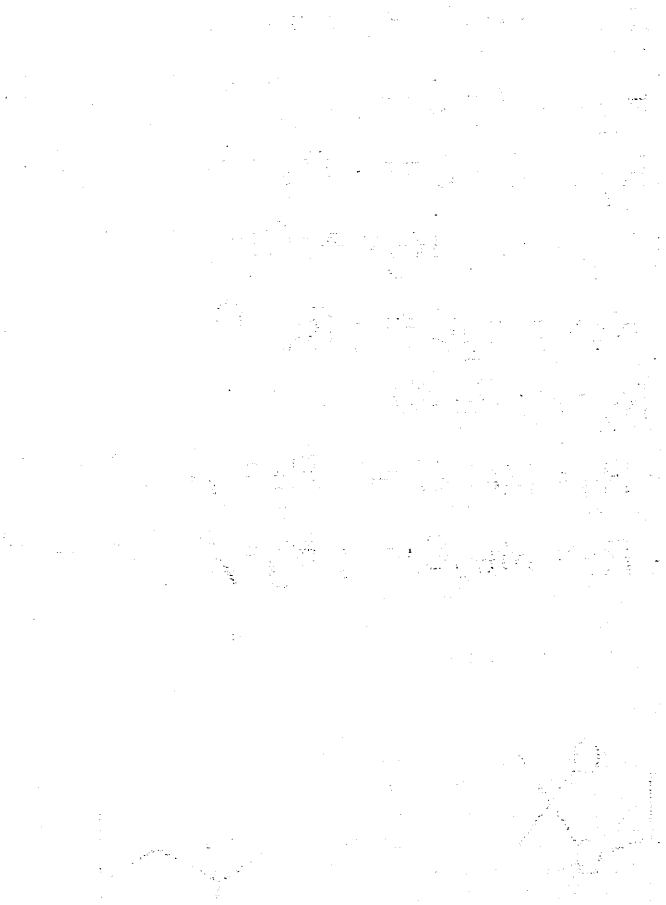
B 37

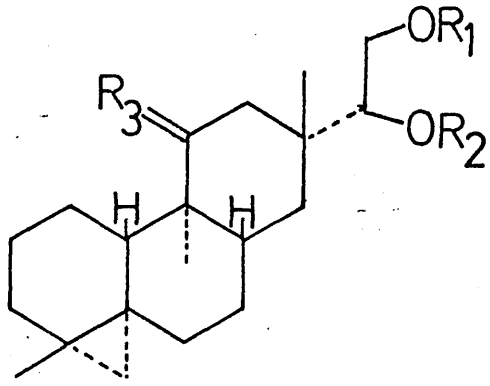


B 38



B 39





B41 $R_1 + R_2 = Me_2C=$; $R_3 = H_2$.

B45 $R_1 + R_2 = Me_2C=$; $R_3 = \alpha$-OAc, β-H.

B46 $R_1 + R_2 = Me_2C=$; $R_3 = \alpha$-OH, β-H.

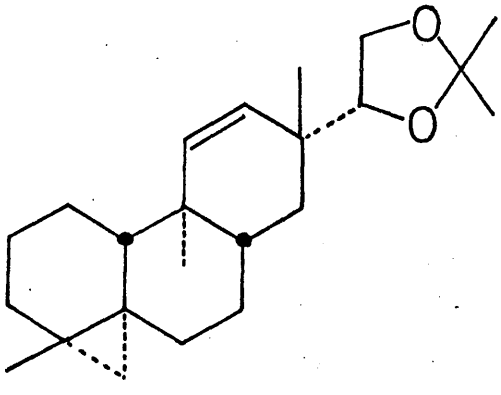
B47 $R_1 = R_2 = H$; $R_3 = \alpha$-OH, β-H.

B48 $R_1 + R_2 = Me_2C=$; $R_3 = O$.

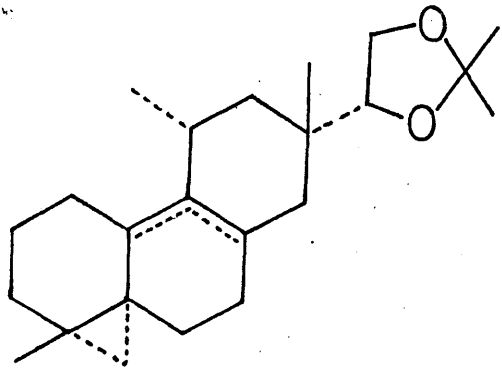
B49 $R_1 = R_2 = H$; $R_3 = O$.

B50 $R_1 + R_2 = Me_2C=$; $R_3 = \beta$-OAc, α-H.

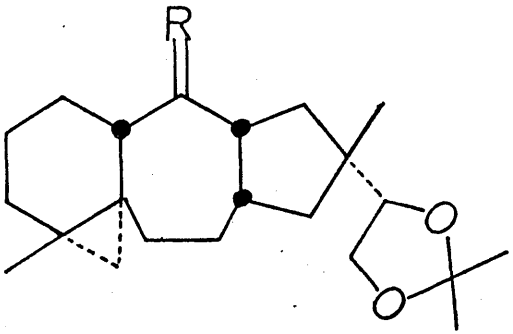
B51 $R_1 + R_2 = Me_2C=$; $R_3 = \beta$-OH, α-H.



B52

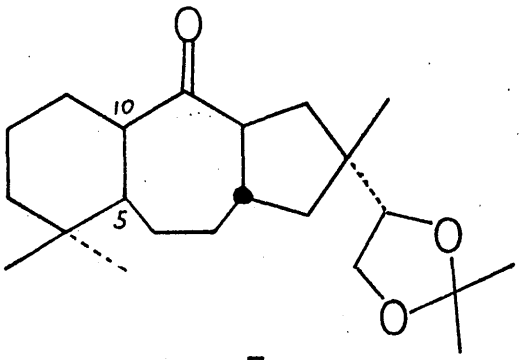


B53



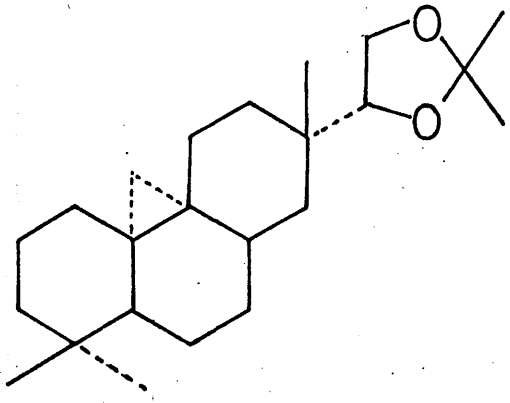
B54 R = CH_2

B55 R = O

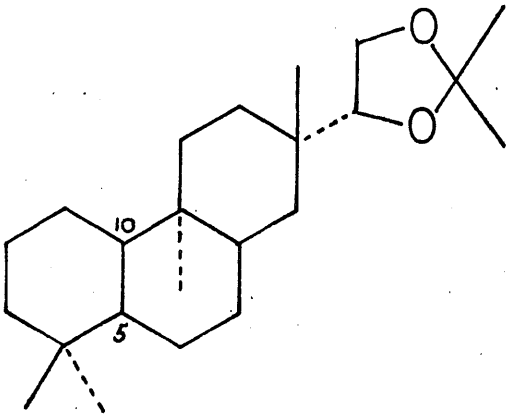


B56 Δ^5

B57 $\Delta^{5(10)}$



B58



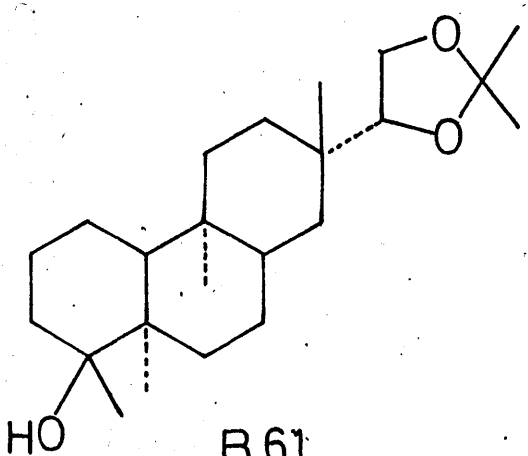
B59 5-OH

B60 10-OH

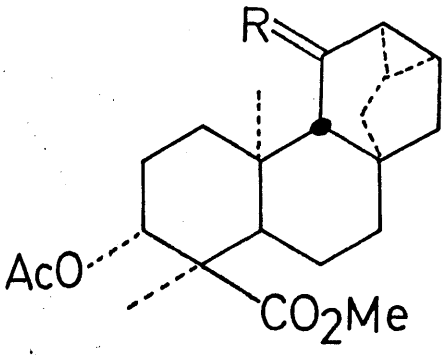
B62 Δ^5

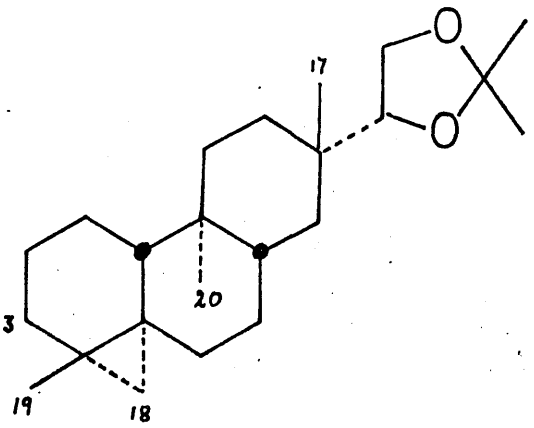
B63 $\Delta^{5(10)}$

B64 $\Delta^{1(10)}$



B61





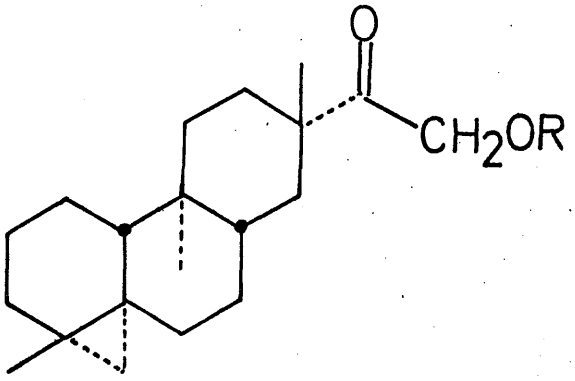
B 65 R = H_2

B 66 R = O

B 67 3 ketone.

B 68 Δ^2-3-OAc.

B 69 Δ^1-2-OH, 3-ketone.



B 70 R = H

B 71 R = Ac

EXPERIMENTAL

Isolation of Triol P and Triol Q Acetate as their Acetonides.

The light-petroleum-soluble extractive (204 g.) of the trunkwood of E. monogynum (2 kg.) was initially chromatographed in light petroleum over silica gel (3 kg.) to spearate stachene and the tetracyclic alcohols A and B from the tricyclic diols and triols. In this way, elution with ether and methanol-ether mixtures (up to 25% methanol) afforded the mixture of diols and triols (65 g.). This mixture in AnalaR acetone (1 l.) was stirred with anhydrous copper sulphate (30 g.) for 3 days, and the red oil (71 g.), remaining after removal of copper sulphate and acetone adsorbed from light petroleum on silica gel (1.5 kg.). Elution with ether-light petroleum (1:19) afforded the mixed acetonides (32.5 g.) of the diols X, Y and Z, and the same solvents (1:4) eluted the acetonides (10 g.) of triols P and Q. Elution with methanol-ether (1:9) furnished the tetracyclic diol.

Chromatography of this mixture (10 g.) of the acetonides of triol P and triol Q acetate on alumina (500 g., Grade H) afforded on elution with ether-light

petroleum (1:24) triol Q acetate acetonide, (B45) (6.21g.), prisms from methanol, m.p. 111-113°, $[\alpha]_D$ - 17° (c 1.32); $\nu_{max.}^{CCl_4}$ 1740 and 1246 (acetate), 860 (acetonide) cm.$^{-1}$; mass-spectral peaks at m/e 404 (P), 389 (P-15), 344 (P-60, 35%), 101 ($C_5H_9O_2$, 70%), and 60 (CH_3CO_2H, 100%); n.m.r. signals at τ 9.84, 9.48 (1H doublets; J = 4.8 c./sec., cyclopropyl H's), 9.09, 9.02, 9.00 (3H singlets; tertiary methyls), 8.68, 8.62 (3H singlets; acetonide methyls), 8.08 (3H, singlet, $O.CO.CH_3$), and 5.07 (1H quartet; J = 10, 6 c./sec.; $>CH\text{-}OAc$) (Found: C, 74.0; H, 9.8. $C_{25}H_{40}O_4$ requires C, 74.2; H, 9.95%).

Elution with ether-light petroleum (1:9) eluted triol P acetonide, (B44), (275 mg.), prisms from light petroleum, m.p. 142-143°, $[\alpha]_D$ + 31° (c 0.91), $\nu_{max.}^{CCl_4}$ 3625 (hydroxyl) and 860 (acetonide) cm.$^{-1}$; mass-spectral peaks at m/e 364 (P), 349 (P-15), 346 (P-18), and 101 ($C_5H_9O_2$); n.m.r. signals at τ 9.14, 9.10, 9.06, 8.98 (3H singlets; tertiary methyls), 8.64, 8.58 (3H singlets; acetonide methyls), and 6.18 (3H multiplet; acetonide H's) (Found: C, 75.6; H, 11.0. $C_{23}H_{40}O_3$ requires C, 75.75; H, 11.05%).

Elution with methanol-ether (1:1) afforded more polar materials (2.1 g.) that were not further investigated.

Triol Q Acetonide (B46)

A solution of triol Q acetonide acetate (B45) (380 mg.) and lithium aluminium hydride (200 mg.) in dry ether (15 ml.) was refluxed for 1 hr. Addition of saturated aqueous sodium sulphate and evaporation of solvent from the dried ethereal solution left triol Q acetonide (B46) (310 mg.), prisms from aqueous methanol, m.p. 115-116° $[\alpha]_D$ + 5° (c 0.86); $\nu_{max.}^{CCl_4}$ 3617 (free hydroxyl), 3051 (cyclopropane), and 866 cm.$^{-1}$ (acetonide); mass-spectral peaks at m/e 362 (P; 95%), 347 (P-15), 344 (P-18; 12%), and 101 ($C_5H_9O_2$; 100%) (Found: C, 75.95; H, 10.8. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%).

Triol Q Acetate (B32)

Triol Q acetate acetonide (B45) (50 mg.) was refluxed in aqueous dioxan (1:5; 10 ml.) with Amberlite 120 I.R. (150 mg.) for 2 hr. Filtration and evaporation of solvent yielded a residue (45 mg.) which after purification by preparative t.l.c. afforded triol Q acetate (B32), (24 mg.) as a colourless oil, $[\alpha]_D$ -14° (c 1.49); $\nu_{max.}^{CCl_4}$ 3640, 3610 (free hydroxyl), 3470 (bonded hydroxyl), 3048 (cyclopropane), 1730 and 1238 cm.$^{-1}$ (acetate); n.m.r. signals at τ 9.86, 9.46 (1H doublets; J = 4.8 c./sec.; cyclopropyl H's),

9.05 (3H), 8.98 (6H; tertiary methyls), 6.2 - 6.9 (5H multiplet; CH_2OH,CHOH, 2OH), and 5.17 (1H quartet; J = 10.2, 6.6 c./sec.; CH.OAc) (Found: C, 72.3; H, 9.85. $C_{22}H_{36}O_4$ requires C, 72.5; H, 9.95%).

Triol Q (B47)

Triol Q (B47) was regenerated from triol Q acetonide acetate (B45) (100 mg.) by refluxing it with aqueous acetic acid (1:19) for 4 hr., removal of acetic acid in vacuo, and reaction of the product, dissolved in tetrahydrofuran, with an excess of lithium aluminium hydride to destroy any acetates initially formed. Triol Q (B47) (65 mg.) thus obtained crystallised in needles from ethyl acetate, m.p. 181-183°, $[\alpha]_D$ -10° (c 0.81, EtOH); n.m.r. signals at τ 9.87, 9.43 (1H doublets; J = 4.8 c./sec.; cyclopropyl H's), 9.17, 9.02, 8.96 (3H, singlets; tertiary methyls), 6.35 (4H multiplet; >CH.OH) (Found: C, 74.15; H, 10.5. $C_{20}H_{34}O_3$ requires C, 74.5; H, 10.65%).

Attempted regeneration of Triol P (B35) from its Acetonide (B44).

Reaction of triol P acetonide (B44) (30 mg.) with aqueous

acetic acid (1:19) for 4 hr. at reflux, followed by removal of solvent in vacuo and reduction of the product in tetrahydrofuran with lithium aluminium hydride, afforded an oily product (21 mg.), n.m.r. signals at τ 9.36, 9.10, 8.94 (3H singlets, tertiary methyl), 4.47 (1H multiplet; vinylic proton). This material was acetonised in the usual way, and the product analysed by g.l.c. (1% SE 30 at 175° with C-20 and C-24 n-hydrocarbons as standards). It consisted of two components, the olefins (B63) (17%) and (B62) (83%). Olefin (B62) crystallised on standing, m.p. and mixed m.p. 84-86° with olefin (B62) obtained from dehydration of triol P acetonide (see p. 96).

The Ketone (B48)

Triol Q acetonide (B46) (200 mg.) and AnalaR chromium trioxide (350 mg.) in AnalaR pyridine (10 ml.) were kept at 20° for 48 hr. The single product, (t.l.c.) obtained in the usual way, afforded, from aqueous methanol, the ketone (B48) (160 mg.), m.p. 92-93°, $[\alpha]_D$ + 124° (c 1.10); $\nu_{max.}^{CCl_4}$ 1704 (cyclohexanone) cm.$^{-1}$; $\lambda_{max.}^{EtOH}$ 296 mμ (ε 55); mass-spectral peaks at m/e 360 (P), 345 (P-15), 101 ($C_5H_9O_2$, acetonide residue); n.m.r. signals in $CDCl_3$

at τ 9.92, 9.42 (1H doublets; J = 5 c./sec.; cyclopropyl H's), 9.12, 8.97, 8.82 (3H singlets; tertiary methyls), 8.62, 8.58 (3H singlets; acetonide methyls), 7.08, 8.23 (1H doublets, J = 13 c/sec.; C-12 hydrogens) and in benzene at τ 10.0, 9.48, 9.26 8.98, 8.93 8.70, 8.63, 7.10, 8.10 with the same assignments; rotatory dispersion (MeOH); $[\phi]_{400}$ + 950, $[\phi]_{312}$ + 2800°, $[\phi]_{276}$ + 1560°, $[\phi]_{217}$ + 6350° (Found: C, 76.9; H, 9.8. $C_{23}H_{36}O_3$ requires C, 76.6 H, 10.05%).

The dihydroxy-ketone (B49), obtained from the above acetonide by aqueous acetic acid (1:19) treatment, had (from light petroleum) m.p. 167-169°, mass spectroscopic M.W. 320 ($C_{20}H_{32}O_3$ requires 320); $\nu_{max.}^{CCl_4}$ 1704 (cyclohexanone), 3041 (cyclopropane), 3631 (free hydroxyl), and 3580 (bonded hydroxyl) cm.$^{-1}$.

Deuterium Exchange of Ketone (B48)

The ketone (B48) (60 mg.) was dissolved in dry dioxan (10 ml.) and deuterium oxide (3 ml.). To this solution was added sodium (100 mg.) in small pieces under nitrogen, and the solution stirred for 96 hr. at 60° in a nitrogen atmosphere. The solvents were removed in vacuo, the

residue extracted with dry ether (3 x 10 ml.), and the combined extracts washed with deuterium oxide (2 x 2 ml.), dried, and the ether removed. The crystalline residue (46 mg.) had by mass spectrometry, 16% d_0, 61% d_1, 13% d_2, and 0% d_3. In the n.m.r. spectrum the doublet centred at τ 7.08 (12α-H,?) had virtually disappeared.

Huang-Minlon Reduction of the Ketone (B48)

The ketone (B48) (40 mg.) and sodium (100 mg.) in dry ethanol (2 ml.), with added hydrazine hydrate (0.3 ml.) and triethylene glycol (5 ml.) were kept at 200° for 1 hr. in a nitrogen atmosphere. The product (28 mg.), obtained in the usual way, purified by preparative t.l.c., crystallised from methanol-ether to afford diol X acetonide, (B41) (12 mg.), m.p. and mixed m.p. 87-89°. Mass, n.m.r. and i.r. spectra and t.l.c. behaviour on silver nitrate-silica gel were indistinguishable from those of authentic material.

Sodium Borohydride Reduction of the Ketone (B48)

The ketone (B48) (210 mg.) and sodium borohydride (250 mg.) were kept in aqueous methanol (1:19; 20 ml.) at 20° for 3½ hr. Dilution with water and ether extraction

afforded an oil (140 mg.). Adsorption from benzene on to activated alumina (neutral, III) and elution with benzene-chloroform (1:1) afforded the alcohol (B51) (105 mg.), m.p. (from methanol) 113-115°, $[\alpha]_D$ + 36° (c 0.86); $\nu_{max.}^{CCl_4}$ 3632 (free hydroxyl), 3050 (cyclopropane), and 864 (acetonide) $cm.^{-1}$; mass-spectral peaks at m/e 362 (P), 347 (P-15), 344 (P-18), 101 (acetonide residue) (Found: C, 76.35; H, 10.7. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%)

Oxidation of the alcohol (B51) with the Sarett reagent under the usual conditions afforded the ketone (B48) as the sole product.

The Acetate (B50)

The alcohol (B51) obtained in the previous experiment (30 mg.) was kept in AnalaR pyridine (2 ml.) and AnalaR acetic anhydride (3 ml.) at 20° for 16 hr. Removal of solvent in vacuo and isolation of the product by preparative t.l.c. afforded the acetate (B50) (26 mg.), m.p. (from methanol) 119-121, $[\alpha]_D$ + 34° (c 0.83); $\nu_{max.}^{CCl_4}$ 1743 and 1243 (acetate) $cm.^{-1}$; n.m.r. peaks at τ 9.84, 9.47 (two 1H doublets; J = 4.7 c./sec.; cyclopropyl protons), 9.16, 9.02, 8.97 (three 3H singlets; tertiary methyls),

8.67, 8.62 (two 3H singlets; acetonide methyls), 7.94 (3H singlet; $OCO.CH_3$), 5.12 (1H triplet, J = 3 c./sec.; CH.OAc) (Found: C, 74.2; H, 10.0. $C_{25}H_{40}O_4$ requires C, 73.9; H, 9.9%).

Unsuccessful Attempts to React the Ketone (B48)

The ketone (B48) was recovered substantially unchanged from the following experiments:

(a) Ketalisation. Excess of ethylene glycol and benzene in the presence of β-naphthlene-sulphonic acid under reflux.

(b) Diosphenolation. Under conditions[62] which converted the ketone (B67) and α-onocerindione[63] into the corresponding diosphenols.

(c) Reaction with benzaldehyde. Under conditions[64] that were effective with α-onocerindine.

(d) Enol acetylation. With acetic anhydride-pyridine, unchanged ketone was the sole product. Acetic anhydride-toluene-p-sulphonic acid afforded the 16,17-diacetate, and isopropenyl acetate-toluene-p-sulphonic acid a mixture of ketone acetonide and ketone diacetate.

(e) α-Acetylation.[65] The only identifiable product was the 17-nor-16 aldehyde formed by removal of the acetonide with BF_3 and cleavage by lead tetra-acetate of the glycol formed.

Dehydration of Alcohol (B51)

The alcohol (B51) (70 mg.) was kept in AnalaR pyridine (10 ml.) and redistilled thionyl chloride (1 ml.) at 20° for 20 min. Working up in the usual way afforded a residue (55 mg.) consisting of one major product (70% by g.l.c. on 2% 20M PEG at 200°) and two minor products. Isolation of the major product by extraction with cold chloroform saturated with nitrogen from silver nitrate-silica gel chromatoplate, afforded the olefin (B52) (20 mg.) as a colourless oil; n.m.r. signals at τ 9.90, 9.42 (1H doublets, J = 4.2 c./sec.; cyclopropyl H's) 9.15 (3H), 8.96 (6H) (tertiary methyls), 8.68, 8.60 (3H singlets, acetonide methyls), 4.69 (1H quartet, J = 9.6; <1 c./sec.), 4.03 (1H doublet; J = 9.6 c./sec.) olefinic protons) (Found: C, 80.1; H, 10.75. $C_{23}H_{36}O_2$ requires C, 80.2; H, 10.55%).

One of the two minor dehydration products (B53 ?), separated by preparative t.l.c. on silver nitrate-silica gel, had n.m.r. peaks at τ 9.15, 8.92 (3H singlets, tertiary methyls), 8.98 (3H doublet; J = 6 c./sec.; secondary methyl), 8.66, 8.58 (3H singlets; acetonide methyls), and 6.12 (3H multiplet; acetonide H's).

Hydrogenation of the Olefin (B52)

The olefin (B52) (5 mg.) in ethanol (15 ml.) was hydrogenated over 10% palladium-charcoal (25 mg.) in a microhydrogenator for 2 hr. The mixture obtained after removal of solvent was compared on g.l.c. (2% 20M PEG at 200° with C_{24} and C_{30} n-hydrocarbons as standards) with olefin (B52) and diol X acetonide (B41) with the following results: Olefin (B52); R_t 12.15 min. [$R_t/R_t(C_{30})$ 0.476]; Diol X acetonide; R_t 9.65 min. [$R_t/R_t(C_{30})$ 0.512]; Hydrogenation product; R_t 9.45 min. [$R_t/R_t(C_{30})$ 0.511].

Dehydrogenation of Alcohol (B46)

Alcohol (B46) (200 mg.), was dehydrated as for alcohol (B51) above and the product recovered as before. This (165 mg.) consisted of one major (90% by g.l.c. on 2% 20M PEG at 200°) and two minor components. The major

product was again unstable in solutions containing oxygen and was therefore recovered from a silver nitrate-silica gel chromatoplate with cold oxygen-free chloroform, affording the olefin (B54), (115 mg.), as a colourless oil; n.m.r. signals at τ 10.04, 9.56 (1H doublets; J = 4.8 c./sec.; cyclopropyl H's), 9.02, 8.91 (3H singlets; tertiary methyls), 8.64, 8.58 (3H singlets; acetonide methyls), 6.17 (3H multiplet; acetonide H's), 4.17 (2H doublet; J = 2.4 c./sec.; = CH_2) (Found: C, 79.8; H, 10.4 $C_{23}H_{36}O_2$ requires C, 80.2; H, 10.55%).

The Ketone (B55)

The olefin (B54) (55 mg.) and osmium tetroxide (70 mg.) in dry ether (3 ml.) and pyridine (1.5 ml.) were kept at 0° for 18 hr. in the dark. The solution was saturated with hydrogen sulphide, the osmium sulphide removed by filtration, and the residue (45 mg.) obtained after solvent removal, purified by t.l.c. The mixed diols (32 mg.) so obtained were kept with sodium metaperiodate (100 mg.) in methanol (3 ml.) and water (1 ml.) at 20° for 36 hr. The product, obtained as usual, was separated by preparative t.l.c. into unreacted diols (14 mg.) and the ketone (B54) (13 mg.),

colourless plates, from methanol-chloroform, m.p. 142-143°, $[\alpha]_D$ + 67° (c 1.05); $\nu_{max.}^{CCl_4}$ 1696 cm.$^{-1}$; n.m.r. signals at τ 10.04, 9.34 (1H doublets; J = 4.2 c./sec.; cyclopropyl H's), 9.05, 8.90 (3H singlets; tertiary methyls), 8.66, 8.60 (3H singlets; acetonide methyls), 6.08 (3H multiplet; acetonide H's); mass-spectral peaks at 346 (P), 331 (P-15), 288 (100%; P-C_3H_6O) (Found: C, 76.2; H, 10.0. $C_{22}H_{34}O_3$ requires C, 76.25; H, 9.9%).

Deuterium Exchange of Ketone (B55)

The ketone (B55) (5 mg.) was treated with sodium in deuterium oxide-dioxan and the product recovered as described for the ketone (B48) above, after 48 hr. The process was repeated on the same sample for a further 24 hr. Mass spectrometry of the crystalline product showed the following incorporations:-

after 48 hr., 20% d_0; 30% d_1; 50% d_2; 0% d_3:

after 72 hr., 11% d_0; 18% d_1; 71% d_2; 0% d_3.

Isomerisation of Ketone (B55) with a Solution of Hydrogen Chloride in Chloroform

Dry hydrogen chlordie was passed into the ketone (B55) (6 mg.), in AnalaR chloroform (5 ml.) for 10 min. and the solution kept at 20° for 1 hr. Solvent and hydrogen chloride were removed in vacuo and the residue was stirred with anhydrous copper sulphate in AnalaR acetone for 2 hr. at 20°. Filtration and evaporation yielded an oil (4.5 mg.), homogeneous by t.l.c., but g.l.c. (2%M PEG at 200°) revealed the presence of two compounds (B56) and (B57) (9:1), differing from starting material. The i.r. spectrum of the mixture had bands at 1700 (ketone), 1670 (unsaturated ketone) and 870 (acetonide) $cm.^{-1}$; $\lambda_{max.}$ 254 mμ ($\varepsilon \sim 1000$) (4 mg. oil in 10 ml. EtOH).

Dehydration of Alcohol (B44)

The alcohol (B44) 40 mg.) was dehydrated with thionyl chloride and pyridine and the product recovered as in the dehydration of alcohols (B46) and (B51) above. G.l.c. analysis of the product (31 mg.) (1% SE 30 at 175°) showed it to consist of the olefin (B62) (88%) and the isomeric olefin (B63) (12%).

The olefin (B62) (20 mg.) crystallised from the oil and had, recrystallised from methanol, m.p. 85-86°, $[\alpha]_D$ -29° (c 0.68); n.m.r. signals at τ 9.35, 9.10, 9.00, 8.94 (3H singlets; tertiary methyls), 8.65, 8.60 (3H singlets; actonide methyls), 6.21 (3H multiplet; acetonide H's), 4.52 (1H multiplet; vinylic proton) (Found: C, 79.3; H, 11.35. $C_{23}H_{38}O_2$ requires C, 79.7; H, 11.05%).

The minor product had the same retention time as the known[46] olefin (B63) on 1% SE 30 at 175°.

Isomerisation of Olefin (B62)

Dry hydrogen chloride was passed through a solution of the olefin (B62) (5 mg.) in dry chloroform at 20% for 5 min., and the solution kept for 20 hr. The solvent and hydrogen chloride were removed at 20°, and the residue dissolved in AnalaR acetone (10 ml.) and shaken with anhydrous copper sulphate (20mg.) for 2 hr. at 20°. The oily product consisted (g.l.c. on 1% SE 30 at 175°) of olefin (B62) (53%), olefin (B63) (34%), and two unknown isomers.

Ozonolysis of the Acetonide (B41)

The actonide (B41) (1.00 g.) in methylene chloride (50 ml.) and dry pyridine (25 ml.) was ozonised for 3 hr. at -70°. Water (25 ml.) was added and the mixture kept at 20° for 16 hr. Working up in the usual way furnished an oily residue (820 mg.) consisting (t.l.c.) of starting material and two more polar products. Preparative t.l.c. afforded, in order of increasing polarity, recovered starting material (400 mg.), the hydroxy ketone (B70) (145 mg.) and the ketone (B67) (200 mg.).

The hydroxy ketone (B70), crystallised from petroleum, had m.p. 82-84°; $\nu_{max.}^{CCl_4}$ 1705 (carbonyl), 3049 (cyclopropane), 3484 (bonded hydroxyl) cm.$^{-1}$; n.m.r. signals at τ 9.45 (1H doublet; one of the cyclopropyl H's), 9.22, 8.99, 8.78 (3H, singlets; tertiary methyls), 5.57 (2H singlet; $CO.CH_2OH$); mass-spectral bands at m/e 304 (P), 289 (P-15), 245 (95%; P-59; loss of side chain) (Found: C, 78.7; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%). Acetylation of the hydroxy ketone (B70) under the usual conditions afforded the known[46] acetate (B71), m.p. and mixed m.p. 93-95°; 103-104°; i.r. (solution), mass, and n.m.r. spectra were indistinguishable from those of authentic material; $\nu_{max.}^{CCl_4}$ 1728

(ketonic carbonyl), 1756 and 1236 (acetate), 3046 (cyclopropane) $cm.^{-1}$; mass spectral peaks at m/e 346 (P), 331 (P-15), 245 (P-101; 70%; loss of side chain); n.m.r. signals at 9.88, 9.47 (1H doublets; J = 5 c./sec.; cyclopropyl H's), 9.22, 8.98, 8.74 (3H singlets; tertiary methyls) 7.84 (3H singlet; acetate methyl), 5.10 (2H singlet; $CO.CH_2OAc$) (Found: C, 76.05; H, 9.65, Calc. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.9%).

The ketone (B67) had (from aqueous acetone) m.p. 125-126°, $\nu_{max.}^{CCl_4}$ 1683 (α-cyclopropyl-cyclohexanone) $cm.^{-1}$; mass-spectral peaks at m/e 360 (P), 345 (P-15) and 101 ($C_5H_9O_2$); n.m.r. signals in $CDCl_3$ at τ 9.25 (1H doublet, J = 5 c./sec.; one of the cyclopropyl H's), 9.18, 9.07, 8.79 (3H singlets; tertiary methyls), 8.65, 8.60 (3H singlets; acetonide methyls) and in benzene at τ 9.75, 9.38, 9.12, 8.55, 8.72, 8.64; with the same assignments (Found: C, 76.8; H, 9.8. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.05%).

Deuterium Exchange of Ketone (B67)

The conditions were those used for ketone (B48), Mass spectroscopic analysis showed:

after 48 hr.; 4% d_0, 16% d_1, 80% d_2, 0% d_3;

after 72 hr.; 2% d_0, 6% d_1, 91% d_2, 1% d_3.

Huang-Minlon Reduction of Ketone (B67)

Under the conditions used for ketone (B48), ketone (B67) afforded as the only major product, material identical (mixed t.l.c. on silver nitrate-silica gel and g.l.c. on 2% 20M PEG at 200° with authentic diol X acetonide.

Enol Acetate (B68) of Ketone (B67)

The ketone (90 mg.) and a trace of toluene-p-sulphonic acid were refluxed in redistilled isopropenyl acetate (5 ml.) for 6 hr. Preparative t.l.c. afforded the enol acetate (B68) (50 mg.), m.p. (from methanol) 110-111°; $\nu_{max.}^{CCl_4}$ 1759, 1215 (acetate), 1680 (olefinic double bond) $cm.^{-1}$; n.m.r. signals at τ 9.46 (1H doublet; one of the cyclopropyl H's), 9.20, 9.08, 8.93 (3H singlets; tertiary methyls), 8.67, 8.61 (3H singlets; acetonide methyls), 7.89 (3H singlet; acetate methyl), 5.12 (1H quartet; vinyl H) (Found: C, 74.4; H, 9.8. $C_{25}H_{38}O_4$ requires C, 74.6; H, 9.5%).

The Diosphenol (B69)

The ketone (B67) (50 mg.) in 1N-potassium t-butoxide in t-butyl alcohol (10 ml.) was shaken in 1 atm.

oxygen in a hydrogenation apparatus for 3 hr. Dilution, acidification, and extraction afforded the product (45 mg.), which on preparative t.l.c. afforded the diosphenol (B69) (26 mg.), m.p. (from methanol) 168-170°, $\lambda_{max.}^{EtOH}$ 268 mμ (ε 3500) 240 mμ (ε 3650); $\lambda_{max.}^{0.1N-NaOH/EtOH}$ 314 mμ (ε 3130); $\nu_{max.}^{CCl_4}$ 1653 (olefinic double bond), 1673 (enone carbonyl), 3448 (bonded hydroxyl) $cm.^{-1}$; n.m.r. signals in $CDCl_3$ at τ 9.20, 9.08, 8.70 (3H, singlets; tertiary methyls), 8.69, 8.62 (3H singlets; acetonide methyls), 7.62 (1H doublet; J = 3.2 c./sec.; H-10), 4.35 (1H doublet; J = 3.2 c./sec.; H-1), and in benzene at τ 9.44, 9.19, 8.58, 8.74, 8.67, 8.17, 4.50 with the same assignments. (Found: C, 73.45; H, 9.15. $C_{23}H_{34}O_4$ requires C, 73.75; H, 9.15%).

REFERENCES

1. L. Ruzicka, Proc. Chem. Soc., 1959, 341.

2(a). A.R. Penfold, R. Robinson and J.L. Simonsen, J. Chem. Soc., 1939, 87,

(b) R. Robinson, The Structural Relations of Natural Products, Clarendon, Oxford, 1955, p. 12.

3. A. Eschenmoser and H. Heusser, Experientia, 1953, 9, 357.

4. R. B. Woodward and K. Bloch, J. Amer. Chem. Soc., 1953, 75, 2023.

5. W.G. Dauben, S. Abraham, S. Hotta, I.L. Chaikoff, H.L. Bradlow and A.H. Soloway, J.Amer.Chem.Soc., 1953, 75, 3038.

6. K. Bloch, Vitamins and Hormones, 1957, 15, 119.

7. R.G. Langdon and K. Bloch, J. Biol. Chem., 1953, 200,129.

8. A.J. Birch, R.W. Richards, H. Smith, A. Harris and W.B. Whalley, Proc. Chem. Soc., 1958, 223.

9. J.J. Britt and D. Arigoni, Proc.Chem.Soc., 1958, 224.

10. A.J. Birch, R.W. Richards and H. Smith, Proc.Chem.Soc., 1958, 192.

11. J.W. Cornforth, G.D. Hunter and G. Popjak, Biochem.J., 1953, 54, 597.

12. J.W. Cornforth, I.Y. Gore and G. Popjak, Biochem. J., 1957, 65, 94.

13. K. Folkers, D.E. Wolf, C.H. Hofmann, P.E. Aldrich, H.R. Skeggs and L.D. Wright, J.Amer.Chem.Soc., 1956, 78, 4499.

14. P.A. Tavormina, M.H. Gibbs and J.W. Huff, J. Amer. Chem. Soc., 1956, 78, 4498, 6210.

15. D. Arigoni, Experientia, 1958, 41, 153.

16. L. Gugliemetti, Ph.D. Thesis, Zurich, 1962.

17. A.J. Birch, D.W. Cameron, C.W. Holzapfel and R.W. Richards, Chem. and Ind., 1963, 374.

18. T.T. Tchen, J. Biol. Chem., 1958, 233, 1100.

19. W.D. Loomis and J. Battaile, Biochim. Biophys. Acta., 1963, 67, 54.

20. K. Markley and E. Smallman, Biochim. Biophys. Acta., 1961, 47, 327.

21. H.R. Levy and G. Popjak, Biochem. J., 1959, 72, 35P.

22. S. Chaykin, J. Law, A.H. Phillips, T.T.Tchen and K. Bloch, Proc. Nat. Acad. Sci., U.S.A., 1958, 44, 998.

23. A.H. Phillips, T.T. Tchen and K. Bloch, Fed. Proc., 1958, 17, 289.

24. K. Bloch, S. Chaykin, A.H. Phillips and A. de Waard, J. Biol. Chem., 1959, 234, 2599.

25. H. Hellig and G. Popjak, J. Lipid Res., 1961, 2, 235.

26. F. Lynen, H. Eggerer, U. Henning and I. Kessel, Angew. Chem., 1958, 70, 738.

27. A. de Waard, A.H. Phillips and K. Bloch, J.Chem.Soc., 1959, 81, 2913.

28. F. Lynen, B.W. Agranoff, H. Eggerer, U. Henning and E.M. Moslein, Angew. Chem., 1959, 71, 657.

29. S. Chaykin, J. Law, A.H. Phillips, T.T. Tchen and K. Bloch, Proc.Nat.Acad.Sci., U.S.A., 1958, 44, 998.

30. H. Rilling and K. Bloch, J.Biol.Chem., 1959, 234, 1424.

31. J.D. Connolly, R. McCrindle, R.D.H. Murray and K.H. Overton, Tetrahedron Letters, 1964, 1983.

32. A.I. Scott, G.A. Sim, G. Ferguson, D.W. Young and F. McCapra, J.Amer.Chem.Soc., 1962, 84, 3197.

33. A.J. Birch, R.W. Richards, H. Smith, A. Harris and W.B. Whalley, Tetrahedron, 1959, 7, 241.

34(a) D. Arigoni, Biosynthesis of Terpenes and Steroids, Churchill, London, 1959, p.231.

(b) D. Arigoni, Gazetta, 1962, 92, 884.

35. E. Wenkert, Chem. and Ind., 1955, 282.

36. W.G. Dauben, W.F. Thiessen and P.R. Resnick, J. Amer. Chem. Soc., 1962, 84, 2015.

37. H. Grotman, T. Noris, M. Sumimoto and A. Morrison, Tetrahedron Letters, 1964, 3879.

38. M.C. Woods, K. Nakanishi and N.S. Bhaccicca, Tetrahedron, 1966, 22, 243.

39. M. Shiro, T. Sato, H. Koyama, Y. Moki, K. Nakanishi and S. Uyeo, Chem. Comm., 1966, 97.

40. J.D. Connolly, D.M. Gunn, R. McCrindle, D.H.R. Murray and K.H. Overton, Tetrahedron Letters, 1966, 2109.

41. J.D. Connolly, D.M. Gunn, R. McCrindle, D.H.R. Murray and K.H. Overton, J. Chem. Soc., 1967(C), 668.

42. R.C. Gupta and M.S. Muthana, J.Indian Inst. Sci., 1954, 36A, 122.

43. R.D.H. Murray and R. McCrindle, Chem. and Ind., 1964, 500.

44. D.M. Gunn, B.Sc. Thesis, Glasgow, 1964.

45. J.D. Connolly, R. McCrindle, R.D.H. Murray and K.H. Overton, Tetrahedron Letters, 1964, 859.

46. J.D. Connolly, R. McCrindle, R.D.H. Murray, A.J. Renfrew, K.H. Overton and A. Melera, J.Chem.Soc., 1966(C), 268.

47. A.H. Kapadi and Sukh Dev, Tetrahedron Letters, 1964, 1171; ibid., 1964, 1902.

48. D.C. de Jongh and K. Biemann, J.Amer.Chem.Soc., 1964, 86, 67.

49. D.H. Williams, J.M. Wilson, H. Budzikiewicz and C. Djerassi, J.Amer.Chem.Soc., 1963, 85, 2091.

50. E.L. Eliel, "Stereochemistry of Carbon Compounds" McGraw-Hill, 1962, p.241.

51. N.S. Bhacca, J.E. Gurst and D.H. Williams, J.Amer.Chem.Soc., 1965, 87, 302.

52. L.H. Sarett, M. Feuer and K. Folkers, J.Amer.Chem.Soc., 1951, 73, 1777.

53. S. Bernstein, R.H. Lenhard and J.W. Williams, J.Org.Chem., 1953, 18, 1168.

54. W.S. Johnson, M. Neeman, S.P. Birkeland and N.A. Fedoruk, J.Amer.Chem.Soc., 1962, 84, 989.

55. G. Snatzke, B. Zech and E. Muller, Tetrahedron Letters, 1963, 1425.

56. E.L. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, "Conformational Analysis, Interscience, New York, 1966, p.291.

57. J.D. Connolly, R. McCrindle, R.D.H. Murray and K.H. Overton, J. Chem. Soc., 1966(C), 273.

58. G. Hugel, L. Leds, J.M. Mellor and G. Ourisson, Bull. Soc. chim. France, 1965, 2894.

59. J.D. Connolly and R. McCrindle, Chem. and Ind., 1965, 379.

60. C.J. Timmons, Chem. Comm., 1965, 22, 576.

61. G. Ferguson, J.W.B. Fulke and R. McCrindle, Chem. Comm., 1966, 691.

62. D.H.R. Barton, S.K. Pradhan, S. Sternhell and J.F. Templeton, J.Chem.Soc., 1961, 255.

63. D.H.R. Barton and K.H. Overton, J.Chem.Soc., 1955, 2639.

64. D.H.R. Barton, A.J. Head and P.J. May, J.Chem.Soc., 1957, 935.

65. H.B. Henbest, D.N. Jones and G.P. Slater, J. Chem. Soc., 1961, 4472.

SECTION III

PEREGRINATIONS IN THE FIELD OF EPOXIDE CHEMISTRY

SUMMARY

This section commences with a review of epoxide isomerisation. The subsequent discussion describes the acid-induced isomerisations of erythroxydiol acetonides X and Y, and preparation and characterisation of the epoxides from the derived olefins. The final part deals with the effect of borontrifluoride etherate and grade I alkaline alumina on these and other ~~experiments~~ epoxides.

The α-epoxide derived from erythroxydiol Y acetonide showed an unusual ^{4}J coupling involving an epoxide proton.

REVIEW OF EPOXIDE ISOMERISATION

It has long been recognised that in many cases ethylene oxides tend to undergo isomerisation to carbonyl compounds, and even Wurtz[1] in his classical work on ethylene oxide stated that it was related to acetaldehyde. In summarising epoxide isomerisation, it is convenient to deal with three aspects separately; (a) thermal isomerisation, (b) acid-induced isomerisation and (c) base-induced isomerisation.

(a) Thermal Isomerisation

In 1903, Ipatieff and Leontovitch[2] achieved the conversion of ethylene oxide into acetaldehyde by passing the gas over alumina at 200-300°, or at 500° in the absence of catalyst. Propylene oxide has also been reported to undergo rearrangement mainly to propionaldehyde,[2] but more recently[3] it has been observed that at 555-650°, with Fuller's earth as catalyst, minor amounts of acetone and allyl alcohol were formed along with the major product, propionaldehyde. Allyl alcohol becomes the principal isomerisation product at lower temperatures and with a variety of catalysts.[4,5] Other catalysts can

lead almost exclusively to propionaldehyde.[6] The observed instability of epoxides on certain gas chromatographic columns is therefore to be expected. Crandall[7] has shown that norbornene oxide (C1) is isomerised on certain columns to 3-cyclohexene-1-carboxaldehyde (C2; 47%), norcamphor (C3; 43%) and nortricyclanol (C4; 10%). Pyrolysis of norbornene oxide on neutral alumina afforded,[7] in addition to the three previous products, the compounds (C5) and (C6), presumably formed by secondary oxidation-reduction processes.

Several other thermal rearrangements of epoxides are known[8-17] under a variety of conditions ranging from high temperature on a catalyst surface to gentle heating. Enol ester epoxides,[17] for example, require only gentle heat to rearrange them to acyloxy ketones, but fortunately most epoxides are more stable. Some of these thermal rearrangements have important uses in synthetic chemistry. The thermal decarboxylation of glycidic acids or glycidic salts obtained by hydrolysis of Darzens condensation products,[18] has application in the natural product field in synthetic approaches to vitamin A[19,20,21] and lysergic acid.[22]

(b) Acid-Induced Isomerisations

Acid isomerisations of epoxides have been known for some time and have been intensely studied[23] in certain fields. It is relevant here to consider especially the isomerisations brought about by acid, in particular boron trifluoride etherate, with steroidal and terpenoid epoxides.

Henbest and Wrigley[24] have studied the effect of born trifluoride on various steroidal epoxides. In all cases examined, hydride shifts, stereochemically controlled by Walden inversion at the site of the epoxide oxygen departure, took place in preference to ring contraction. The 4α,5α-, 9α,11α-, and 9β,11β- epoxy steroids were all smoothly isomerised to ketones in this way (Fig. I). Other epoxy steroids, such as 8α,9α-, 8α,14α- and 7α,8α-epoxides afforded dienes (Fig. II) rather than ketones, presumably by loss of a proton from the initially formed carbonium ion, followed by elimination of water from the allylic alcohol and then double-bond migration, all these processes being conceivable in the acidic medium.

Before considering the more interesting aspects of the reactions of variously substituted epoxides, it is relevant to note that, although the majority of boron

trifluoride-catalysed rearrangements have been carried out in benzene solution, the reaction is extremely solvent-dependent.[24] In the previously mentioned steroidal examples, a change of solvent to ether results in the formation of fluorohydrins instead of the expected ketones. Boron trifluoride in ether, which is more basic than benzene, is presumably unable to complex as effectively with the epoxide oxygen. House and Reif[25] also put forward this explanation to explain the greater effectiveness of boron trifluoride in cyclohexane, as compared with ether, for α,β-epoxy ketone isomerisation. Goldsmith[26] also found that the reactions of geraniolene monoepoxide with born trifluoride etherate in ether and in benzene do, in part, follow different courses, and suggests that the nature of the solvent may control the extent to which a carbonium ion transition state is developed, and that this should decide, in the absence of controlling steric factors, whether ketone or fluorohydrin is the initial product.

Henbest and Wrigley also examined the effect of boron trifluoride on various 5α,6α- and 5β,6β- epoxy steroids, with and without substituents at C-3, and interpreted their observations mainly in terms of a

long-range inductive effect of the C-3 substituent, and the avoidance of steric interactions involving bulky axial groups in the product. In two of the three substituted 5α,6α-epoxides, fluorohydrins are formed instead of ketones as in the unsubstituted compound. (see Fig. III). It has been suggested that in the production of ketone from a 5,6-epoxide the bond from oxygen to the more alkylated C(5) position should be appreciably ionised in the transition state. Thus as intramolecular electron-attracting groups have been shown to retard the rate of S_N1 solvolysis, the ionisation necessary for the formation of 6-ketones from the epoxides containing acetoxy- or chloro- groups at C-3 may be similarly inhibited. The alternative reaction, leading to fluorohydrin, involving dual attack of the Lewis acid and an external nucleophile, can then operate. Supporting this line of thought is the diaxial nature of the fluorohydrins, which are formed at slower rates than the 6-ketones from the unsubstituted epoxides.

Second, Henbest postulated[24] that reactions leading to less strained molecular conformations are favoured. Thus the 3α-acetoxy compound gives a higher yield of ketone than the unsubstituted 5α,6α-epoxide, the reaction

being assistes by the change of the acetate conformation from a xial to equatorial. The rate of reaction of the substituted epoxide was slower, in accordance with the general suggestion that ionisation of the C(5)-O bond would be more difficult. Also, formation of the diaxial fluorohydrin is probably discouraged because of increase of compression would be involved [C(3) axial -OAc —— C(5) axial -OH; C(6) axial -F —— (10) axial - Me]. In contrast, the 3β-acetoxy epoxide gave little ketone, the fluorohydrin being by far the major product. In this case, as with the 3β-chloro analogue, formation of ketone is inhibited by both conformational and electronic factors.

In the case of the 3β-acetoxy-5β,6β-epoxide, (see Fig. IV), the formation of both fluorohydrin and ketone can derive assistance from the change of the acetate conformation from axial to equatorial, and so the difficulty in ionising the C(5)-O bond necessary for the production of ketone is decisive in this case. Moreover the rate of reaction of the substituted epoxide is slower, in agreement with the postulate that the slower reaction leading to fluorohydrin formation becomes of importance only when the normal rapid " ionisation-hydrogen shift reaction" is inhibited.

Using this type of argument, Bowers[27] correctly predicted the influence of 3-oxo- and 3,3- ethylenedioxy groups on the reactivity of the 5α,6α-epoxy system and was able to obtain 6β-fluoro-5α-hydroxy steroids as intermediates in the preparation of 6-fluoro hormone analogues. In 3-oxo-5α,6α-epoxy steroids conformational effects can be regarded as virtually negligible, leaving the electron withdrawing influence of the carbonyl dipole as the dominant directive factor, and resulting in exclusive fluorohydrin formation (see Fig V). Subsequent authors have noted a large number of similar effects in the steroid field, and have advanced substantially identical rationalisations for them.[23]

As already illustrated in the case of unsubstituted steroidal epoxides, the major products of acid (boron trifluoride) treatment, are the corresponding ketones derived by stereospecific hydride migration. This is further exemplified by the work of Hartshorn and Kirk,[28] who could isolate only 5-methyl-5α-cholestan-4-one from boron trifluoride rearrangement of 4β,5β-epoxy-4α-methylcholestane, and 5-methyl-5β-cholestan-4-one from the 4α,5α-epoxide (see Fig. VI). Ketone formation in these cases is accompanied by stereospecific methyl migration

from C(4) to C(5). Treatment with aqueous acid of the diterpene, cascarillin A (C7),[29] afforded two previously known compounds, the diol (C8) and the ketone (C9), as well as the unsaturated alcohol (C10), which involves methyl migration and cannot be formed by a concerted mechanism. Unsaturated alcohols of this type have been formed in the present work and are discussed later.

House and Wasson[30] in studying the effect of boron trifluoride on substituted cyclohexene oxides, found that 2,3-epoxycyclohexanone and some of its derivatives rearrange on treatment with boron trifluoride to either cyclohexane-1,2-diones or ring contracted compounds, or a mixture of both, depending upon the presence of alkyl or phenyl substituents at C(2) or C(3). From their results, Table I, they suggest that as the stability of the carbonium ion (1), Fig. VII [the presumed intermediate in the formation of the keto-aldehyde (2)] decreases, the proportion of α-diketone (3) in the product increases. Such a result would be anticipated if the α-diketone (3) were formed by an acid catalysed elimination reaction [as (4)] which was competing with the formation of the intermediate (1). D.J. Collins[31] also found that the isomeric 4,5-epoxycholestan-3-ones behave in a similar

way giving cholestan-3,4-diones and A-nor-cholestan-3-one, the epoxy ketones proceeding via the two pathways. Similar products are obtained from some 3-substituted 4,5-epoxy-4-methylcholestanes with boron trifluoride.[29] Hartshorn and co-workers,[28,32-44] who in recent years have carried out an intense study of the effect of boron trifluoride on various substituted steroidal epoxides, have observed similar products, together with those arising from ring-expansion[39] and ring-cleavage.[38,39]

Perhaps the most interesting feature of Hartshorn's studies has been the observation of a novel "backbone" rearrangement[40,41] of the steroid nucleus. This was effected by treatment of a concentrated solution of 3β-acetoxy-5,6α-epoxy-5α-cholestane (C11) with boron trifluoride in benzne. The dimeric product (C12), obtained in 32% yield, has one normal steroid nucleus and one that has undergone complete "backbone" rearrangement. Subsequently Hartshorn and his colleagues[43] assigned structures, based on a "backbone" rearranged skeleton to the hydroxyolefins, obtained as minor products in their previous investigations. Their current studies are now directed to determine the factors which favour this type of skeletal rearrangement.

Other unexpected products arising from cleavage of steroidal epoxides have been isolated by Halsall and Jones and their colleagues,[45] These workers have investigated the reactivity, under acidic conditions, of 5,6-diols and 5,6-epoxides in the 4,4-dimethylcholestane and androstane series. Of particular interest is the participation of the hydroxyl group in these 5α,6α-epoxy-3β-hydroxy compounds (C13), leading to 6α-hydroxy-3-ketones (C14), by fission of the C(5)-O bond and very probably concerted trans-anti-parallel migration of the C(4) β-methyl and the C(3) α-hydrogen. Even more interesting is the case of the 3-oxo-5α,6α-epoxides (C15), where this type of participation cannot arise. With these compounds, spiro-hydroxy-ketones (C16) were obtained, instead of "backbone" rearrangement products for which these molecules appear to have the ideal stereochemistry. This observed rearrangement, involving cis migration of the C(1) - C(10) bond and proton loss from C(9), is unlikely to be concerted. In contrast, and unexpectedly, the corresponding 3-oxo-5β,6β-epoxides (C17), favour cis C(10) methyl group migration, affording the products (C18) with complete "backbone" rearrangement.

These facts are intriguing since, in the α-epoxides, the C(10) - C(19) bond is trans- and anti- parallel to the

C(5)-O bond, whereas, in the β-epoxides, it is the C(1) - C(10) bond that has this relationship. In other words, the observed results are precisely the reverse of what might have beenexpected. It must therefore be assumed that this rearrangement is a step-wise process, with initial C(5)-O bond fission and generation of a carbonium ion of finite lifetime, followed by subsequent step-wise or concerted methyl and hydride migration.

A review of acid-induced epoxide isomerisation would not be complete without reference to the recent, intriguing work on the acid catalysed cyclisation of epoxy olefins and their important bearing on the in vivo formation of polycyclic terpenoids.

The acid catalysed cyclisation of epoxy olefin systems as a model for terpenoid biogenesis has been accomplished in a number of cases. Goldsmith[46] in 1962 on treating geraniolene monoepoxide ( ) with boron trifluoride obtained some cyclic products. These products were the 1,4-endoxocyclohexane system (C20), and the cyclohexenol (C21). Also isolated from the reaction mixture were the acyclic ketone (C22) and the fluorohydrin (C23). Another Lewis acid, stannic chloride yielded only the cyclic compounds (C20) and (C21). The following year

van Tamelen[47] reported the non-enzymatic, selective terminal oxidation of trans, trans-farnesyl acetate (C24) and subsequent acid-induced, stereodirected cyclisation of this epoxide (C25) to the bicyclic diol monoacetate (C26), which duplicates, in respect to carbon framework, oxidation site and stereochemistry at all four asymmetric centres, the familiar 3-hydroxylated A/B ring system present in many polycyclic, di- and triterpenoid systems. With boron trifluoride, the monoepoxide (C25) is transformed into a mixture of cyclisation products consisting of the bicyclo diol monoacetate (C26) (85%) and its C-9 epimer (C27) (15%). Phosphoric acid affords a similar mixture. There is also substantial evidence for the presence, in the latter reaction mixture, of the bicyclic compound (C28).

From the boron trifluoride reaction there is evidence for another minor product, which appears to have structure (C29). This compound [c.f. the oxide (C20) isolated by Goldsmith] is of interest because of its close structural relationship to (±) farnesiferol C (C30). This undoubtedly prompted van Tamelen's biogenetic-type synthesis[48] of the farnesiferols A (C31) and C (C30). These were effected by reaction of the trans, trans-umbelliprenin

terminal epoxide (C32) with boron trifluoride in benzene affording (±) farnesiferol C, and reaction of trans-cis-umbelliprenin epoxide yielding (±) farnesiferol A.

Van Tamelen and co-workers again make use of this biogenetic-type oxidation-cyclisation sequence in their total synthesis of triterpenoid systems.[49] Their synthesis involves the coupling of sesquiterpenoid halves built up by oxidation-cyclisation of an acyclic precursor. The key bicyclic intermediate (C33) desired for entry into the C-30 series was produced most conveniently by a reaction sequence commencing with cyclisation of methyl trans, trans-farnesate-10,11-epoxide (C34) with boron trifluoride or phosphoric acid to the bicyclic compound (C35). This procedure is stereoselective, providing in one operation a bicyclic system, possessing the trans-anti- trans stereochemistry characteristic of polycyclic terpenes. Coupling of the intermediate (C33; X = Br) was effected with magnesium in ether, affording (±)-β-onocerin dibenzyl ether (C36) and the meso isomer (C37). Treatment of the derived (±)-β-onocerin diacetate with acetic-sulphuric acid, gave the pentacyclic product, (±)-γ-onocerin diacetate (C38), and since (±)-γ-onocerin

diacetate has been converted into hopenone-1 (C39), the outlined synthetic operations embrace the latter system as well.

Very recently van Tamelen[50] has effected the laboratory cyclisation of geranylgeranyl acetate terminal epoxide (C40) by exposing it to stannic chlordie in benzene. The tricyclic diol monoacetate (C41; 10%) was obtained, (along with the expected types of compound, i.e. cyclic ether, monocyclic ketone, acyclic terminal fluorohydrin), featuring six asymmetric centres specifically orientated in the relationship characteristic of the natural product series. The carbon skeleton obtained has however not been detected to date in naturally occurring diterepenoids. Several non-oxidative conversions of acyclic polyenes to tricyclic substances in the natural product category have been reported.[51]

This field received a great stimulus in 1966 when Corey[52] and van Tamelen[53] independently proved the intermediacy of 2,3-oxidosqualene (C42) in sterol biosynthesis, and in fact van Tamelen's synthetic route to terpenoids appears to simulate the actual biosynthetic pathways to these compounds. The role of the C-30 triterpenoid hydrocarbon, squalene (C43) as an intermediate in the bio-

synthesis of cholesterol and of the naturally occurring tetra- and pentacyclic triterpenes is well supported by experimental evidence. It has now been demonstrated[52,53] that 2,3-oxidosqualene is synthesised from squalene in the sterol-forming rat liver system, is a precursor of sterols and is, indeed, far more efficiently incorporated than is squalene under anaerobic conditions. Thus it seems likely that sterol biosynthesis, at least in rats and probably more generally, involves the intermediate, 2,3-oxidosqualene (C42) which is cyclised by a mechanism such as is depicted in Fig. VIII.

(c) Base-Induced Isomerisations

Until recently the base-induced rearrangement of ethylene oxides had received only limited attention in the literature, mainly due to the fact that epoxides undergo simple nucleophilic attack rather than isomerisation with most bases. By definition a base-induced epoxide isomerisation is strictly one in which the unitial step is direct proton abstraction from the oxide ring. This can now be followed by redistribution of bonding electrons in one of several possible ways to give ultimately one or more carbonyl compounds. For the purpose of

this discussion, however, the term "base-induced epoxide isomerisation" is given a somewhat broader meaning to include also certain rearrangements initiated by proton abstraction from carbon atoms not directly part of the oxide ring. These will be taken to include not only α-carbon atoms, but also, with certain alicyclic epoxides, transannular carbon atoms as well (although transannular proton abstraction is now known not to be the initial step).

It has been known for some time that benzalacetophenone oxide (C44) undergoes rearrangement[54] on ethanolic sodium hydroxide solution, giving 1,3-diphenylpropane-1,2-dione (C45). Several other methoxylated benzalacetophenones have likewise been isomerised to the corresponding 1,2-diones under alkaline conditions.[55-58] It is most likely that, in these cases, the benzoyl-activated proton is removed first, as indicated by the smooth isomerisation of trans-β-methylbenzalacetophene oxide, dypnone oxide (C46), in which no other dissociable proton exists.[59] Redistribution of electrons, followed by proton abstraction from the solvent, leads to the observed 1,2-dione products. However, the process might involve intramolecular proton transfer; but so far no distinguishing experiments have been published.

Activation of the epoxide proton by a neighbouring carbonyl function in base-induced isomerisation is not essential, as is shown[60] by the ready isomerisation of cyclooctatetrene oxide to 2,4,6-cyclooctatrienone in the presence of lithium diethylamide in non-polar media. In later work, Corey and his collaborators elucidated[61] the stereospecific character of the isomerisation of aryl-substituted ethylene oxides by identification of the products obtained from base-induced isomerisation of cis- and trans- stilbene oxides. Whereas the former affords only desoxybenzoin, the latter yielded diphenyl acetaldehyde exclusively. From the evidence it appears that, unlike acid catalysed migration to electron-deficient centres, the base-induced epoxide isomerisation in the above cases appear to involve cis migration and frontal attack upon an anionic centre (see Fig. IX).

In the cases so far described the epoxide protons, which are abstracted, are allylic, benzylic or α- to a ketonic function, and are thus activated to varying degrees. In 1949, two interesting examples of base-induced epoxide isomerisation, involving relatively non-labile epoxide protons were brought to light by Culvenor and co-workers,[62] The first consists of the rearrange-

ment of glucidonitrile (C47) to 3-cyanoallyl alcohol (C48); the second, the rearrangement of phenyl glycidyl sulphone (C49) to the corresponding allyl alcohol (C50), both in aqueous alkali. Here the initial step must be abstraction of one of the active methylene protons α- to the epoxide ring followed by electron redistribution and ring opening to yield the alcoholate anion. Protonation affords the allylic alcohol (see Fig. X). This activated β-proton abstraction process had already been invoked to explain the formation of 1-hydroxy-2-penten-4-yne (C51) on condensation of epichlorohydrin with sodium acetylide (see Fig. Xa), and, since then many examples of this β-proton abstraction, (the proton on the carbon α- to the epoxide ring), in the base-induced isomerisation of epoxides have been revealed.

Interesting observations, by Letsinger and co-workers[63], while attempting to add various alkyllithium reagents to cyclohexene oxide, illustrate two further aspects of base-induced epoxide isomerisations, (a) applicability to saturated epoxides and (b) catalysis by alkyllithium reagents. Methyllithium condenses normally with cyclohexene oxide to give 2-methylcyclohexanol, while n-propyllithium and n-butyllithium give mainly cyclohexene-3-ol,

along with small quantities of 2-methylcyclohexanol. Several similar alkyllithium-catalysed epoxide isomerisations are known.[64-66] These unexpected results must surely be attributed not only to the base strength of the reagent, but also to the ability of lithium to co-ordinate with the epoxide oxygen and thus assist oxide ring cleavage. The β-proton abstractions process, leading to allylic alcohol, in some cases might be more correctly regarded as a "push-pull" type mechanism, as appears to be the case in the alkyllithium rearrangement. This "pull" by co-ordination with the epoxide oxygen has a precedent. Certain alicyclic epoxides, when subjected to metallic sodium in refluxing benzene afford[67] the sodium enolates, which hydrolyse to the corresponding ketones.

More recently two good illustrations of base-induced epoxide isomerisations in which the activated proton, on a carbon atom α to the epoxide ring, is abstracted (i.e. β-elimination) have been described. When 1,2-epoxy-3-benzoyl-2-phenylcyclopenten-3-ol (C52) is treated with ethanolic sodium ethoxide the allylic alcohol, 1-benzoyl-2-phenylcyclopenten-3-ol (C53) is formed,[68] as shown in Fig. XI. A more interesting result arises on treatment of the β,γ-epoxy ester derivative (C54),[69] shown in

Fig. XII, with the base sarcosine, (the methyl ester of N-methylglycine), giving rise to the lactone (C55) instead of the expected nucleophilic addition product. In the terpene field also, several complex, epoxide isomerisations are known, and may be rationalised by use of the carbanion mechanism previously outlined. A typical example is the action of alkali on carophyllone oxide (C56).[70] The active proton at the ring junction α to the carbonyl group is abstracted, followed by transannular intramolecular nucleophilic attack on the epoxide by the generated carbanion, giving rise to the new tricyclic system of (C57) as shown in Fig. XIII.

More intensive base-catalysed epoxide rearrangements can involve the base-induced isomerisation steps already outlined. An example is the reaction of scopinone (C58) to yield m-hydroxybenzaldehyde (C59). Meinwald and Chapman suggest[71] that the first step is a proton abstraction from the activated methylene group, and this may be followed by intramolecular opening of the epoxide ring, and electron redistribution to give the observed aromatic product (Fig. XIV). A related base-induced rearrangement has been rationalised[72] by invoking participation by a pair of aromatic π-electrons instead of σ-electrons (see Fig. XV).

Perhaps the most interesting aspect of base-induced epoxide isomerisations is to be found in recent investigations of the transannular effects operating in medium-ring epoxides. Here a carbene type intermediate has been invoked in preference to the carbanion type mechanism previously discussed. As early as 1933, Huckel and Schnitzspahn reported[73] the base-catalysed intramolecular condensation of cyclodecane-1,6-dione, and although such condensations may depend to some extent upon the operation of a proximity effect, the condensations of a compound containing an active methylene grouping are well known and constitute a standard technique in the formation of five, six and seven membered ring compounds. However, transannular eliminations have been observed in which the labile hydrogen atom is activated only by a functional group on the opposite side of the ring. Such an example is the formation of a bicyclic unsaturated ketone (C60) on base treatment of the bromination products of cyclodecanone.[74]

Most of the work on the reaction with base on medium-ring epoxides has been carried out by Cope and his collaborators. The action of lithium diethylamide on cis-cyclooctene oxides (C61) results[75] in the formation

of an intramolecular alkylation product, endo-cis-bicyclo-[3,3,0]-octan-2-ol (C62), Δ^2-cyclooctenol (C63) being a minor product. The corresponding trans-epoxide (C64) yields exo-cis-bicyclo-[3,3,0]-octan-2-ol (C65), the minor products being cycloheptanecarboxyaldehyde (C66) and Δ^2 cyclooctenol (C63). Similar results (see Fig. XVI) have been observed[76] in the cis-and trans- cyclodecene oxides. The formation of the minor products can be rationalised by use of the carbanion mechanism already outlined; however, two alternative mechanisms can be postulated[77] to explain the formation of the bicyclic products. For example, in the case of cis-cyclodecene oxide the base could remove a proton from a carbon atom located across the ring from the epoxide ring with concerted epoxide ring opening by the carbanion formed, (see path 1; Fig. XVII), to give cis-cis-1-decalol (C67). Alternatively, carbanion attack at the other epoxide carbon atom would afford endo-cis-bicyclo-[5,3,0]-decan-2-ol (C68). In the second possible mechanism (path 2; Fig. XVII), removal by base of one of the epoxide protons, followed by heterolytic fission of the carbon-oxygen bond giving rise to a carbene intermediate, which can now form a bond to a carbon atom across the ring with concerted migration of

of hydride ion from this carbon to the electron-deficient carbon atom. Similar attack on C-7 would result in the formation of endo-cis-bicyclo-[5,3,0]-decan-2-ol (C68). Since the products are single stereoisomers, both mechanisms are thought to be fully concerted as illustrated.

It is possible to distinguish between paths 1 and 2 (see Fig. XVII), by deuterium tracer studies[78] with the deuterated epoxide (C69). If the reaction of (C69) with lithium diethylamide proceeds according to path 1, the bicyclic products should retain all the deuterium atoms that were present in the original epoxide. However, if the reaction proceeds via path 2, approximately 1.0 atom of deuterium per molecule would be lost in the bicyclic products. The reaction of this dideuterated epoxide (C69), in fact, was found to yield cis-cis-1-decalol and endo-cis-bicyclo-[5,3,0]-decan-2-ol containing 0.96 and 0.93 atom of deuterium per molecule respectively, implying that the concerted carbene mechanism (path 2) appears to be the route by which these bicyclic alcohols are formed. Further support[78] was obtained from the reaction of (C70) with lithium diethylamide. The endo-cis-bicyclo-[3,3,0]-octan-2-ol formed was found to contain approximately two atoms of deuterium per molecule, showing that no deuterium atoms were lost from C-5 or C-6 during the reaction.

In 1964, Crandall[7] obtained a very clean conversion of norbornene oxide (C1) into nortricyclanol (C4) on treatment with lithium diethylamide. In analogy with the work of Cope he also suggests that the transformation probably proceeds by base abstraction of an oxide ring proton, opening of the ring to a "carbenoid anion" intermediate and insertion of the carbene carbon into an opposing carbon-hydrogen bond. The formation of the carbene and its insertion are most likely compressed into one concerted process.

Now a stage has been reached where the products of base-induced isomerisation of epoxides can be rationalised in terms of one of two mechanistic approaches; (a)carbanion mechanism [α abstraction $\longrightarrow$ ketonic products: β abstraction $\longrightarrow$ allylic alcohols] and (b) concerted carbene mechanism [α elimination with carbenoid insertion — exemplified by the bicyclo products formed from medium-ring epoxides]. Very recently Crandall[79] and Chang have embarked upon an intensive study of the base-catalysed isomerisation of epoxides with a view to elucidating the factors influencing the course of reaction when a molecule has a choice between a carbanion or carbene type reaction course. Initial attention has been focussed on the part played by conformational effects in the selection of a mechanism. A study such as this will surely prove most interesting and informative.

DISCUSSION

Part A

(1) Acid-Induced Isomerisation of Erythroxydiols X and Y

Three naturally occurring isomeric erythroxydiols have been isolated[80,81] as their acetonides from the light petroleum extractive of the trunkwood of E. Monogynum (see Section II). Their individual isolation was initially achieved by column chromatography on silver nitrate-silica gel of the diol acetonide mixture, which consists of diol X acetonide (C71) (76%), diol Z acetonide (C72) (2%) and diol Y acetonide (C73) (22%). In this work a relatively clean and more convenient separation of the acetonide mixture was obtained by use of preparative silver nitrate-Kieselgel G thin layer chromatography. The saturated diol X acetonide (C71) proved to be the least polar material, closely followed by the trisubstituted olefin, diol Z acetonide (C72), and finally the exomethylene diol Y acetonide (C73). Throughout this study of acid-induced isomerisation of erythroxydiol acetonides X and Y it was noticeable that, under the above conditions of chromatography, the mobility of the products was dependent upon the substitution of their olefinic bonds.

In earlier work,[80] treatment of both acetonides X and Y with chloroformic hydrogen chloride had led to the isolation inter alia of the tetrasubstituted olefin (C74). Acid-induced isomerisation, (which in all cases discussed in this section must be followed by replacement of the acetonide function), of the third naturally occurring erythroxydiol Z as its acetonide (C72), also led to the formation of olefin (C74). Dehydration of erythroxytriol P (see Section II) affords a fourth unsaturated diol acetonide (C75) along with olefin (C74) as a minor product, and this new olefin (C75) is readily isomerised exclusively to the tetrasubstituted olefin (C74). Thus, since this $\Delta^{5(10)}$- olefin (C74) has been converted[81] into the antipode of the diene (C76) derived from deoxyrosenonolactone (C77), the structures and absolute configurations of all five diol acetonides [(C71) - (C75)] are substantiated. At this stage pure samples of the five diol acetonides were available.

It was now essential to prepare larger amounts of the olefines (C72), (C74) and (C75) for the later epoxide work, (see Part B). The best source of these olefins was the acid isomerisation of the more abundant acetonides X and Y, and as a simpler reaction mixture was anticipated from the

isomerisation of diol Y acetonide (C73), this system was examined first. A pilot reaction sequence, with diol Y acetonide (C73) (20 mg./ml.) in a solution of chloroformic hydrogen chlordie, saturated at 20°, was initiated and aliquots, removed at intervals, were analysed by gas-liquid chromatography (g.l.c.). Initially the proportion of diol Y acetonide (C73) in the mixture decreased at the expense of one major product, the Δ^3-olefin (C72) and two minor products, the Δ^5- and $\Delta^{5(10)}$- olefins (C75) and (C74). After 2 hr. under similar preparative conditions, the Δ^3-olefin (C72) was conveniently obtained from the reaction mixture (45%) by preparative silver nitrate-thin layer chromatography and crystallisation. As the isomerisation proceeded the same four constituents are present in the mixture, their relative abundance varying as the olefins with rearranged skeletons (C74) and (C75) increased at the expense of the olefins (C72) and (C73), (see Table II). After 30 hr. the mixture consisted of one major product, the $\Delta^{5(10)}$ olefin (C74) (68%), easily isolated at this stage under preparative conditions.

A comprehensive analysis of the processes involved in such isomerisations is outwith the scope of this work. However it would appear that protonation of diol Y

acetonide (C73) affords the tertiary carbonium ion (1), (see Fig. XVIII), which can revert by proton loss to starting material or form the isomeric olefin (C72). If this ion (1) on the other hand undergoes methyl migration to ion (2), proton loss would then give rise to olefins (C74) and (C75) having the rearranged skeleton. All steps would be expected to be reversible, the predominant final product being, as expected, the thermodynamically most stable compound, the tetrasubstituted olefin (C74).

Reasoning on the above evidence, acid treatment of diol X acetonide (C71) could conceivably give rise to ten isomeric olefins, (see Fig. XIX), However, following as before a small scale isomerisation of diol X acetonide (C71) by g.l.c. only six products were observed. Four were the previously characterised olefins (C72), (C73), (C74) and (C75). The remaining two compounds could not be isolated by the techniques used, and were later isolated as the derived epoxides and shown to be the ring A-expanded olefins (C78) and (C79). Reminiscent of the observations with diol Y acetonide (C73), the abundance of the tetra-substituted products (C74) and (C78) increased with time at the expense of the olefins (C72), (C73), (C75) and (C79) respectively, (see Table III). Also when all starting

material had been consumed, by acid cleavage of the cyclopropane ring, it was apparent that the ratio of six-membered ring A products to seven-membered ring A products remained approximately constant at 3:2. Such a result implies that in this system, initial acid cleavage of the cyclopropane ring of diol X acetonide (C71) is irreversible, and the interconversion of ions possessing six- and seven-membered ring A systems, as shown in Fig. XIX, is inhibited.

It was now possible to obtain a product mixture from diol X acetonide (C71), the most abundant by far of the naturally occurring erythroxydiols, containing workable amounts of the required olefins (C72), (C74) and (C75) contaminated with the seven-membered ring A compounds. Partial separation of this mixture was effected by preparative thin layer chromatography on silver nitrate-Kieselgel G, affording three olefinic fractions. The most mobile fraction contained the tetrasubstituted olefins (C74) and (C78), the middle, the three trisubstituted olefins (C72), (C75) and (C79), and the least mobile, pure diol Y actonide (C73). The characterisation of the seven-membered ring A olefins (C78) and (C79) via their corresponding epoxides is dealt with below.

(2) Preparation and Characterisation of Epoxides.

Since these olefin mixtures, described above, were not easily separable, it was decided to epoxidise the small quantities of pure olefins [(C72) - (C75)] available, characterise the derived epoxides, and thus isolate workable quantities of these epoxides by epoxidation of the olefinic fractions. All olefins and olefin mixtures were epoxidised with m-chloroperbenzoic acid in chloroformic solution for 24 hr.

Epoxidation of erythroxydiol Y acetonide (C73) afforded the α-epoxide (C80), $C_{23}H_{38}O_3$, m.p. 122-124°, $[\alpha]_D$ + 37°, and the β-epoxide (C81), $C_{23}H_{38}O_3$, m.p. 94-95°, $[\alpha]_D$ + 75° in the ratio of 1 to 3 (g.l.c.), and these were readily separable by column chromatography. The configurations of the two epoxides were established by lithium aluminium hydride reduction and dehydration, with phosphorous oxychloride and pyridine, of the tertiary alcohols resulting in each case. Thus the α-epoxide (C80) gave the α-alcohol (C82), $C_{23}H_{40}O_3$, m.p. 163-165°, $[\alpha]_D$ + 25°, which was dehydrated exclusively (g.l.c.) to the known exocyclic olefin (C73), while the β-epoxide (C81), gave the β-alcohol (C83), $C_{23}H_{40}O_3$, m.p. 99-100°, $[\alpha]_D$ + 30°, and then exclusively (g.l.c.) to the known endocyclic olefin (C72).

During the formation of these epoxides from erythroxydiol Y acetonide (C73), an interesting nuclear magnetic resonance $^{4}J_{HH}$ coupling in a sterically "unfavourable" situation involving an epoxide proton was observed.

In the majority of cases, observable long-range proton-proton coupling through four sigma bonds (H_1-C_1-C_2-C_3-H_2) is confined to the geometrical situation where the two interacting protons are situated at the terminal points of a letter W[82,83] and the H_1-C_1 and C_3-H_2 bonds are coplanar. In several recent instances,[84,85,86] all in the bicyclo-[2.2.1]-heptane and bicyclo-[2.2.1]-oxoheptane series appreciable (0.5-1 c./sec.) ^{4}J coupling has been noted where these conditions are not fulfilled. ^{4}J coupling involving epoxide protons have been previously observed. However in the case of epichlorohydrin (C84)[87] ($J_{H_1 - H_4}$ = -0.2 c./sec.; $J_{H_1 - H_5}$ = -0.1 c./sec.) the rotameric conformation of the chloromethyl group and hence the geometry of the interacting protons is not known, and in indene oxide (C85)[88] the observed long-range coupling ($J_{H_1 - H_3}$ = + 1.3 c./sec.) may well be homoallylic rather than involving the alternative four sigma bond path. In the epoxide (C80) a $^{4}J_{H-H}$ coupling of 2.3 c./sec. between two protons (H_1, H_2) of fixed geometry, see (C86), has been

observed, where the projected dihedral angle between the terminal C-H bonds of the W, H_1 - C_1 and C_3 - H_2 is probably more than 90° as judged by Dreiding models.

The nuclear magnetic resonance spectrum of the β-epoxide (C81) shows the epoxide protons, as expected, as two mutually coupled (nuclear magnetic double resonance) doublets (J = 4 c./sec.) centred at 7.24 and 7.69 τ. In the spectrum of the α-epoxide (C80) the corresponding protons appear as a quartet (J = 4.5; 2.3 c./sec.) at τ 6.94 and a doublet (J = 4.5 c./sec.) at τ 7.61. Irradiation at τ 7.61 reduces the quartet at τ 6.94 to a doublet (J = 2.3 c./sec.). This residual minor coupling is most probably due to long-range coupling with one C-3 proton. It disappears (a) on irradiation at τ 8.04; (b) in the 3,3-d_2-epoxide (C87), but is retained when only the equatorial C-3 proton is replaced by deuterium in the 3β-d_1-epoxide (C88). This demonstrates that the long-range coupling in the α-epoxide (C80) occurs between the epoxide proton at τ 6.94 and the axial 3α-proton (τ 8.04). This epoxide proton is tentatively identified as that pointing towards C-5, since this at least allows preservation of the W geometry [see (C86)].

The 3,3-d_2- and 3β-d_1-epoxides (C87) and (C88) were prepared from the corresponding nor-ketone (C89) and (C90). Ozonolysis of diol Y acetonide (C73) afforded[81] the nor-ketone (C91) from which the 3,3-dideuterio compound (C89) can be obtained by deuteration. The nuclear magnetic resonance spectrum of (C91) had the C-3 protons in the 7.3 to 8.0 τ region. The low field C-3 proton appeared to a first approximation as a broadened quartet centred at τ 7.53, and from its multiplicity and chemical shift[89] was assigned the axial configuration. The equatorial proton on the other hand appeared as a broadened doublet at τ 7.86.

When the deuteration of the nor-ketone (C91) was followed by nuclear magnetic resonance, it was apparent that the low field (i.e. axial) proton, at τ 7.53, was being exchanged preferentially, and this has a precedent[90]. After exposure of the nor-ketone (C91) to conditions (Na/D_2O/dioxan at 65° for 1 hr. and then recycled) that achieved maximum deuteration, 12% d_0, 18% d_1, 70% d_2, (isotopic abundances determined by mass spectrometry) the residual C-3 proton resonances could not be detected - (n.m.r.). Assuming that the axial proton was exchanged more rapidly, this 3,3-d_2-ketone (C89) would have an isotopic constitution of 88% axial D-3 and 70% equatorial D-3 (see Table IV).

Reaction now of this sample with the dimethylsulphonium methylide reagent in dimethylsulphoxide resulted in the formation of an α-epoxide (41% d_0, 37% d_1, 22% d_3), which had lost much of the original deuterium content. If the axial proton was being back exchanged preferentially in the methylsulphinyl carbanion solution before reaction, these isotopic contributions would represent 22% axial D-3 and 59% equatorial D-3 species. In the nuclear magnetic resonance spectrum of this sample of epoxide, the low field proton exists as a much broadened doublet, which, on double irradiation at 7.86 τ, collapses to a broad singlet, with a peak height of approximately 60% of the corresponding singlet obtained at 7.86 τ by irradiation at 7.53 τ. Such a spectrum would be consistent with an epoxide sample, having 78% of the molecules retaining the minor coupling and 22% with this coupling removed. This result would suggest that it is the axial C-3 proton that participates in the minor coupling.

To avoid this difficulty of back exchange, the preparation of a more completely dideuterated epoxide was attempted, by reaction of the ketone (C89), of the above isotopic distribution, with the methylide reagent in the presence of perdeuterio-dimethylsulphoxide [$(CD_3)_2SO$].

The α-epoxide (C87) obtained had the following isotopic analysis - 15% d_0, 16% d_1, 44% d_2 and 25% d_3, implying that 85% of the epoxide molecules possess axial D-3, and 69% equatorial D-3. The third deuterium atom was possibly introduced via a homo-enolisation process[91,92] and might be located at C-2. The nuclear magnetic resonance spectrum of (C87) revealed two distinct doublets, of approximately equal intensities, at 7.61 and 6.94 τ. This experiment gave conclusive evidence that the low field epoxide proton in the non-deuterated epoxide (C80) was interacting with one of the C-3 protons, most probably the axial one.

However, it was desirable to prepare a specifically mono-deuterated ketone and the derived epoxide to distinguish between the two C-3 protons. A difficulty was now anticipated, in that, if the 3α-d_1- ketone was prepared by mono-deuteration of (C91), it in turn would be susceptible to extensive deuterium loss in the methylsulphinyl carbanion solution, also further deuteration would result if the perdeuterio anion was used. It was thus decided to accept axial deuterium loss in the methylide reaction with the 3β-d_1- ketone, which, it was anticipated, would prove to be less destructive, isotopically.

The 3β-d_1- ketone (C90) was prepared by partial back exchange of (C89) (Na/H_2O/dioxan for 30 min. at 20°). This sample, (C90) with composition 22% d_0, 70% d_1, 8% d_2, implied 8% axial D-3 and 78% equatorial D-3, and a low field multiplet at ~τ 7.53 was observed in its nuclear magnetic resonance spectrum, signifying the reappearance of the C-3 axial proton. From the methylide reaction in dimethylsulphoxide of this ketone (C90), an epoxide (C88) of composition 74% d_0, 26% d_1 and 0% d_2 was obtained. As expected considerable back exchange had occurred. However, more than a quarter of the molecules in this epoxide (C88) contain equatorial D-3, and, if it is this proton in the original epoxide (C80) that is involved in the minor coupling, an effect (c.f. the effect of 22% axial D-3, above) would be visible in the nuclear magnetic resonance spectrum. On the other hand, the spectrum of this epoxide (C88) revealed the low field epoxide quartet fully reconstituted, giving definite proof, when taken in conjunction with the corresponding spectra of the above mentioned deuterated epoxides, that it is the axial C-3 proton which gives rise to the observable ^4J coupling.

The preparation and use of the dimethylsulphonium methylide reagent was first described[93] by Corey and Chaykovsky in 1965. However contrary to previous experience[93,94] the reactions described above were not stereospecific, affording the α- and β- epoxides in the ratio 3 to 7 (g.l.c.).

Epoxidation of the only other naturally occurring erythroxydiol olefin Z, as its acetonide (C72), afforded exclusively one epoxide, the β-epoxide (C92), $C_{23}H_{38}O_3$, m.p. 116-118°, $[\alpha]_D$ + 22°. The nuclear magnetic resonance spectrum of this epoxide revealed, as expected, four tertiary methyl signals (3H singlets at τ 9.28, 9.08, 8.92 and 8.80) as well as an epoxide proton (1H triplet; J = 2 c./sec.) at 7.18 τ which collapses to a singlet by irradiation at 8.02 τ. The configuration of this epoxide was determined by lithium aluminium hydride reduction, which produced an alcohol as the sole product, identical in all respects with the alcohol (C83) obtained by similar reduction of the epoxide (C81).

The Δ^5-olefin acetonide (C75), obtained by dehydration of triol P acetonide (C75), (see Section II), on epoxidation also gave rise to only one epoxide. This epoxide (C93), $C_{23}H_{38}O_3$, m.p. 91-92°, $[\alpha]_D$ + 8°, nuclear

magnetic resonance signals at τ 9.24, 9.13, 9.03, 8.85 (3H singlets; tertiary methyls) and 6.80 (1H triplet; J = 2 c./sec,; epoxide proton), was assigned the α-configuration, since lithium aluminium hydride reduction furnishes the acetonide of the naturally occurring erythroxytriol P [i.e. (C94)]. Thus an interconversion of erythroxytriol P and the erythroxydiols X and Y has been effected.

Again only one epoxide was formed during the epoxidation of the tetrasubstituted $\Delta^{5(10)}$ olefin (C74), isolated from the acid isomerisation of diol Y acetonide (C73) (see above). This epoxide (C95), $C_{23}H_{38}O_3$, m.p. 99-100°, $[\alpha]_D$ + 38°, has no epoxide proton resonances in its nuclear magnetic resonance spectrum. Signals at τ 9.11, 9.08, 9.02 and 8.97 (3H singlets) revealed the presence of four tertiary methyl groups. This epoxide from a nuclear tetrasubstituted olefin has been assigned the β-configuration (C95), since attack by peracid during its formation would be expected to occur more readily on the less hindered β-face of the $\Delta^{5(10)}$ olefin (C74), and since the epoxide, thus formed, is stable to lithium aluminium hydride reduction in either ether or tetrahydrofuran revealing its hindered nature.

The four olefins (C72), (C73), (C74) and (C75) thus gave rise to a total of five epoxides, which were characterised. To obtain workable amounts of these compounds, the olefin fractions obtained from acid-induced isomerisation of erythroxydiol X acetonide (C71), [see Part A (1)], were epoxidised and the resulting mixtures of epoxides were conveniently separated by column chromatography.

Epoxidation of the olefin fraction contining the diol acetonides (C74) and (C78), (see page 138), resulted in the formation of three epoxides, one of the epoxides (C95) being derived from the olefin (C74). Assuming that no rearrangement had occurred during epoxidation the other two could be derived only from the seven-membered ring A olefin (C78). In the formation of epoxides from olefin (C78) in contrast to epoxide formation from (C74), the α-face of the molecule would appear (models) to be less hindered, allowing attack on that face and leading to two epoxides in the ratio of 1 to 2. The minor epoxide (C96), $C_{23}H_{38}O_3$, m.p. 68-70°, $[\alpha]_D$ + 37°, revealed in its nuclear magnetic resonance spectrum two tertiary methyls at τ 9.20 and 9.14, one secondary methyl at τ 9.17 (J = 6 c./sec.) and no epoxide proton resonances, and was assigned the α-configuration by analogy with

epoxidation of the $^{5(10)}$ olefin (C74). The more predominant epoxide is formulated as the β-epoxide (C97), $C_{23}H_{38}O_3$, m.p. 116-118°, $[\alpha]_D$ + 51°. This has two tertiary methyl groups (3H singlets at 9.16 and 9.09 τ), one secondary methyl (3H doublet; J = 6 c./sec.; at 9.11 τ) and no epoxide proton resonances.

Epoxidation of the trisubstituted olefin fraction containing acetonides (C72),(C75) and (C79), again led to the formation of three epoxides, two of them, (C92) and (C93), already characterised. The third must therefore result from epoxidation of a trisubstituted olefin with a seven-membered ring A, (C79) or (C98). This epoxide (C99) $C_{23}H_{38}O_3$, m.p. 128-130°, $[\alpha]_D$ + 7°, had in its nuclear magnetic resonance spectrum a one proton broadened singlet at τ 7.07 (epoxide proton), which collapsed to a sharp singlet on irradiation at 8.68 τ, one secondary methyl group (3H doublet; J = 6 c./sec.) at 9.00 τ, which remained unchanged on irradiation at 8.68 τ but collapsed on irradiation at 8.33 τ. The spectrum also revealed two tertiary methyl groups at 9.28 and 9.06 τ. These observations are consistent with an epoxide formed from olefin (C79) but not from olefin (C98). This epoxide (C99) was assigned, without definite proof, the α-configuration by comparison with the epoxidation of the Δ^5 olefin (C75), The chemistry of these seven-membered ring A epoxides (C96), (C97) and (C99) was not further investigated.

PART B

(1) Boron Trifluoride induced isomerisation

Following the interesting acid-induced steroidal epoxide rearrangements, previously mentioned (see Review), it was hoped that some information regarding the ideal stereochemical requirements and possible concerted pathways could be obtained by born trifluoride treatment of the epoxides (C80) and (C81). The β-epoxide (C81) has the stereochemical requirements, 4β-oxide ring, 5α-axial methyl, 10β-axial proton and 9α-axial methyl, which would allow postulation of a concerted mechanism to a "back-bone" rearranged product, such as (C100). In the case of the α-epoxide (C80), however, such a rearrangement with C-5 methyl migration to C-4 with epoxide ring cleavage can only be envisaged as occurring via a step-wise process. Such "back-bone" rearrangements, if found, would constitute the reverse of the probable biogenetic route to the erythroxydiols (see Section II), which entails migration of the C-5 methyl to C-4 and the C-9 methyl to C-10.

The α- and β-epoxides, (C80) and (C81), were treated in turn with boron trifluoride etherate in benzene for (a) 15 mins. and (b) 5 hours. It was necessary following these conditions to replace the acetonide function before an examination of the products could be attempted. Reaction of the β-epoxide (C81), for 15 min., resulted in the complete transformation of this epoxide, into one major product (t.l.c.) more polar than the starting material. This compound (C101), $C_{23}H_{38}O_3$, obtained as an oil, M.W. 362, with infra-red bands at 3636 (free hydroxyl), and 857 (acetonide) $cm.^{-1}$, and nuclear magnetic resonance signals at τ 9.15, 9.11, 9.08 (3H singlets; tertiary methyls) and 6.84 and 6.39 (2H doublets; J = 10.5 c./sec.; $-C\underline{H}_2-OH$) as well as the expected acetonide resonances, was converted via its tosylate to the known $\Delta^{5(10)}$-olefin (C74). The boron trifluoride reaction also afforded a small amount of much less polar material. After 5 hours, the β-epoxide (C81) yielded only this less polar material, which was on silver nitrate-thin layer chromatography resolved into four components, one major, but all attempts at isolating the individual compounds failed, decomposition occurring. This latter mixture had an intense ultra-violet band at 246 mμ, ($\varepsilon \sim 8000$), and resonances in the olefinic

(multiplet approximate weight 1H at 4.57 τ) and vinylic methyl (singlet at τ 8.05 ~ 3H) regions of its nuclear magnetic resonance spectrum indicated the presence of a diene, such as (C102).

After short reaction, the α-epoxide (C80), is recovered mostly unchanged, together with the alcohol (C1C1) and a non-polar fraction, identical (g.l.c. and $AgNO_3$ - t.l.c.) with that obtained from the β-epoxide (C81). The reaction mixture also contained an unstable product, slightly less polar (by t.l.c.) than starting material, which gave a positive reaction with D.N.P. spray, and showed infra-red absorption at 1725 $cm.^{-1}$ and mass-spectral peaks at 362 [P] and 361 [P-1]. These facts are consistent with the presence of an aldehyde group. The product is therefore assigned structure (C103) and presumably arises via a hydride shift mechanism. Longer reaction of this epoxide yielded a similar mixture. No evidence (t.l.c. and i.r.) could be found for the presence of (C103) in the reaction mixture from the β-epoxide (C81).

It would appear therefore, that of these two epoxides, which could give rise by epoxide ring cleavage to the same intermediate carbonium ion (C104), the one with the C-5 trans methyl group, i.e. the β-epoxide (C81), readily

isomerises to the unsaturated alcohol (C101) as the sole product, and this undergoes further rearrangement probably with dehydration. Such smooth reaction is consistent with a concerted-type mechanism. However, in the case of the α-epoxide (C80), ionisation is essential before methyl migration, leading to a slow step-wise process for the formation of (C101). This process has also to compete with the alternative, potentially concerted hydride shift, giving rise to the aldehyde (C103). (see). Methyl migration in both cases is followed by proton loss from C-10, instead of the alternative C-10 hydride, C-9 methyl shifts followed by proton loss from C-8 resulting in the formation of the hydroxy olefin (C100). Presumably the increase in compression with an α-methyl at C-10 in (C100) disfavours this possibility.

Lack of time prevented more detailed studies with these compounds and their reactivity towards boron trifluoride. It was also hoped to induce isomerisation of the β-epoxide (C92), which could also give rise to a tertiary carbonium ion similar to that depicted in (C104).

An epoxide of the type (C92) should show a preference for methyl rather than proton migration [the latter leading to (C105a)], and thus (C92) would be expected to yield an unsaturated alcohol, such as (C105b).

(2) Alumina-induced isomerisation

During earlier work on the erythroxydiols it was decided to attempt the formation of a cyclopropane system, such as that present in diol X acetonide (C71), whose stereochemistry had been determined,[81,95,96] from the other naturally occurring erythroxydiols Y and Z, [as their corresponding acetonides, (C73) and (C72)]. The formation of such a system was visualised via base-induced isomerisation of the β-epoxides (C81) and (C92), as shown in Fig.XX for (C92). Although no evidence was obtained for the formation of a cyclopropane system from these epoxides, this work initiated a new and interesting study on the effect of alumina, more particularly grade I basic, on epoxides.

Reaction of the β-epoxide (C81) with grade I basic Woelm alumina in benzene at 20° for 8 hr. afforded two isomerisation products, the hydroxy olefins (C106), $C_{23}H_{38}O_3$, as an oil, M.W. 362, infra-red bands at 3632 (free hydroxyl) and 860 (acetonide) $cm.^{-1}$, nuclear magnetic resonance signals at 9.33, 9.10, 8.95 (3H singlets; tertiary methyls), 6.84, 6.36 [1H doublets; J = 10.2 c./sec.; with the proton at 6.36 showing further coupling (J = 2.5 c./sec.), probably with the C-3 axial proton; $-CH_2-OH$] and

4.38 τ (1H multiplet; olefinic proton), and (C107), $C_{23}H_{38}O_3$, also obtained as an oil, M.W. 362, infra-red bands at 3621 (free hydroxyl) and 858 (acetonide) $cm.^{-1}$, nuclear magnetic resonance signals at 9.24, 9.18, 8.92 (3H singlets; tertiary methyls), 5.90 (2H broadened singlet; $-CH_2OH$) and 4.42 τ (1H multiplet; olefinic proton). The final product from this reaction was the olefin (C108), $C_{22}H_{36}O_2$, M.W. 332, with nuclear magnetic resonance signals at 9.40, 9.08 (3H singlets; tertiary methyls) 8.68, 8.62, (3H singlets; acetonide methyls) 8.39 (3H singlet; vinylic methyl) 6.23 τ (3H multiplet; acetonide protons), absence of olefinic proton resonances. This olefin (C108) had been formed by a secondary process, loss of formaldehyde from the hydroxy-olefin (C106) (i.e. retro-Prins reaction) (see Fig. XXI). In attempting to relate the alcohol (C106) to the known Δ^5-olefin (C75), tosylation of (C106) only returned starting material and the olefin (C108). Further alumina treatment of alcohol (C106) also afforded only the olefin (C108). The formation of an unsaturated aldehyde (C109), $C_{23}H_{36}O_3$, M.W. 360, with intense ultra-violet adsorption at 231 mμ and infra-red bands at 2740 and 1688 $cm.^{-1}$, on manganese dioxide treatment of the unsaturated alcohol (C107), is consistent with its formulation.

The hydroxy olefin (C107) is presumably formed from the epoxide (C81) by straightforward β-proton abstraction and epoxide ring opening. However in the formation of (C106), methyl migration of the C-5 methyl occurs, with most likely concerted epoxide ring opening and proton abstraction since the epoxide (C81) has the ideal stereochemistry for such a rearrangement. This hydroxy olefin (C106) with methyl migration is not the same as the hydroxy olefin (C101) derived from boron trifluoride treatment, see above, of the same β-epoxide (C81). As a result, it is possible to make some qualitative comparison of the behaviour of these two catalysts. With boron trifluoride, the step of decisive importance is the complexing of boron trifluoride with the epoxide oxygen, which initiates and " pulls" the reaction to completion. On the other hand, it is to be expected that alumina, even grade I basic, contains both acidic and basic sites, and complexing of the basic epoxide oxygen to an acidic site is complemented by specific proton abstraction by a basic centre. The proton, being abstracted, would thus be, as expected, one occupying a relatively unhindered position — thus formation of the hydroxy olefin (C106), and not the alternative boron trifluoride product (C101), whose formation is probably controlled by the relative thermodynamic stability of its tetrasubstituted double bond.

The relatively hindered β-epoxide (C95) reacted smoothly with alumina to yield, as sole product, the heteroannular diene (C110), $C_{23}H_{36}O_2$, m.p. 92-93°, $[\alpha]_D$ - 110°, M.W. 344, with ultra-violet absorption bands at 233, 240 and 247 mμ, and nuclear magnetic resonance signals at 9.24, 9.12, 9.07, 8.93 (3H singlets; tertiary methyls) and 4.47 τ (2H multiplet; olefinic protons). Reaction of this epoxide (C95) with another base, potassium t-butoxide in t-butanol at 20° for 24 hr. resulted in the slow formation this diene (C110). This diene (C110) was also obtained by acid-induced epoxide cleavage (i.e. by reaction with either boron trifluoride or perchloric acid) of epoxide (C95). The similarity of the ultra-violet spectrum of this diene (C110) with that of euphatrine[97] (C111) gives further support for the stereochemistry at C-8 and C-9 in the erythroxydiols and triols, as shown in (C110). Formation of this heteroannular diene (C110) from the epoxide (C95) must result from initial base-induced isomerisation by abstraction of either a C-1 or C-6 proton and epoxide ring cleavage, followed by dehydration of the tertiary allylic alcohol thus formed. Dehydration of tertiary alcohols under these reaction conditions can occur as was shown by formation of only the Δ^5-olefin (C75) from erythroxytriol P acetonide (C94) [c.f. its relatively

more random thionyl chloride dehydration, Section II]. Thermal alumina-catalysed dehydrations are, however, well known.[99] Once again the product reflects the preference for proton abstraction at C-6 rather than C-10, presumably for steric reasons.

Isomerisation of the 5α, 6α-epoxide (C93) with basic alumina was not as effective, starting material (50%) being recovered. Three isomerisation products, however, were detected. The ketone (C112) or (C113), $C_{23}H_{38}O_3$, m.p. 138-140°, with carbonyl absorption at 1711 cm.$^{-1}$, and nuclear magnetic resonance signals at 9.12, 9.08, 8.93 and 8.89 τ (3H singlets; tertiary methyls) was assigned structure (C113) on the basis that the initially formed ketone (C112), by stereospecific hydride migration, would epimerise under the conditions used to the supposedly more stable trans-decalone. The two other isomerisation products present in low yield are most likely the allylic alcohols (C114) and (C115), since a fourth product, the heteroannular diene (C110) was also observed. Dehydration of these allylic alcohols, to the same homoannular diene (C116), would be expected to be followed by isomerisation to the more stable heteroannular diene system.

Lack of time prevented a detailed study of the reaction of the 3β,4β-epoxide (C92) with basic I alumina. By analogy with the above work, however, it would be expected that a hydroxy olefin with C-5 methyl migration, such as (C117), would be a principal isomerisation product. Similar reaction of the β-epoxide (C80) could prove informative, when compared with the reaction of the isomeric β-epoxide (C81). From comparison of their reaction paths it might be possible to draw some conclusions as to the stereochemical requirements of these alumina-induced isomerisations.

In the course of this work, it has been shown that basic I alumina can react with epoxides to induce β-proton abstraction, as well as methyl and hydride migration. In certain cases, the dehydration of alcohols have also been observed, and in one case the catalyst induced a retro-Prins reaction. It was now considered desirable to look at the possibility for "backbone" rearrangement and carbene insertion type isomerisations with this alumina catalyst.

The system chosen for the former study was 3β-acetoxy-5α,6α-epoxy-5α-cholestane (C11). Treatment of this epoxide, however, with grade I, basic alumina in

sodium dried benzene afforded no "backbone" rearranged material. Starting material was recovered in 25% yield, and the only isomerisation product obtained was the allylic alcohol (C118) m.p. 141-143°, $[\alpha]_D$ -23°, infra-red absorption bands at 3620 (free hydroxyl), 3020 (olefinic protons) and 1735 and 1245 (acetate) cm.$^{-1}$, and nuclear magnetic resonance signal at 4.42 τ (2H multiplet; olefinic protons). Also isolated from this reaction, as minor products, were the triol monoacetate (C119) and cholesterol α-oxide (C120)[98]. Abstraction of the less hindered β-proton appears to be the predominant mode of epoxide cleavage. The other products demonstrate two further possible reaction courses under the conditions employed (a) epoxide hydrolysis and (b) acetate hydrolysis.

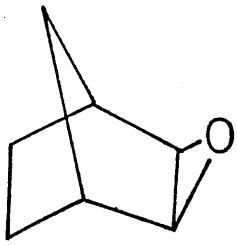
Crandall[7] effected smooth conversion of norbornene oxide (C1) to nortricyclanol (C4) with lithium diethylamide, and (see Review) he postulated a carbenoid-type reaction path (c.f. Fig. XVII, path 2). Treatment of norbornene oxide (C1), where the possibility of β-proton abstraction giving rise to allylic alcohol is inhibited, with basic alumina in benzene afforded four products. The major isomerisation product (57% by g.l.c.) was nortricyclanol (C4). $C_7H_{10}O$, m.p. 106-109° with free

hydroxyl absorption at 3622 cm.$^{-1}$ in the infra-red, and nuclear magnetic resonance signals at 6.18 (1H broadened singlet; $>C\underline{H}$-OH) and 7.93 τ (1H singlet; -O$\underline{H}$). Two other isomerisation products were identified as norcamphor (C3) and exo-norbornenol (C121). The latter compound being identified by comparison of its hydrogenation product (C122) with the major product from sodium borohydride reduction of norcamphor (C3). The fourth product was identified as 3-cyclohexene-1-methanol (C6), $C_7H_{12}O$, with infra-red absorption at 3638 (free hydroxyl) and 3022 (olefinic protons) cm.$^{-1}$, and nuclear magnetic resonance signals at 8.47 (1H singlet; -O$\underline{H}$), 6.41 (2H doublet; J = 5 c./sec; -C$\underline{H}_2$-OH) and 4.24 τ (2H broadened singlet; olefinic protons), arising probably via a secondary reduction pathway on the gas-liquid chromatography column used for preparative isolation.

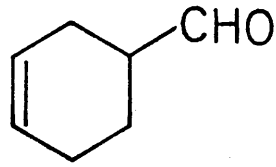
Table V illustrates the results of basic, neutral and acidic alumina (grade I) on this epoxide (C1). Neutral alumina yielded the same four products, as above, together with a small quantity of 3-cyclohexene-1-carboxaldehyde (C2), $C_7H_{10}O$. with infra-red bands at 3030 (olefinic protons) 2705 and 1732 (aldehydic function) on 1651 (C = C) cm.$^{-1}$, which is the probably precursor of (C6).

Acid alumina afforded a further unidentified component (C123) in low yield.

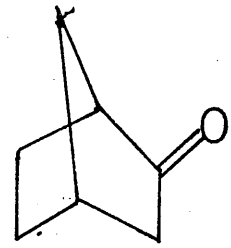
It would therefore appear that as the number of acidic sites or as the acidic nature of the alumina increases the proportion of carbenoid insertion product, nortricyclanol (C4), decreases, as would be expected.



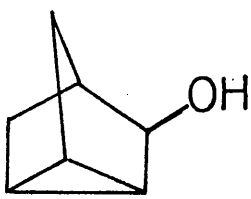
C1



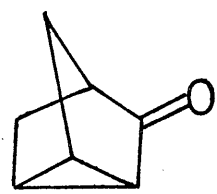
C2



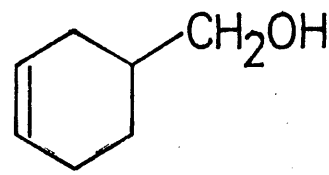
C3



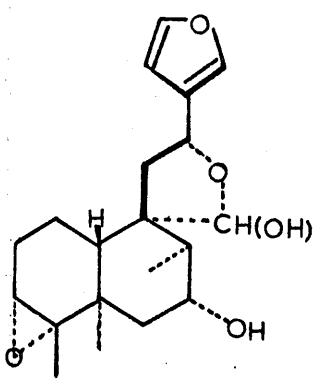
C4



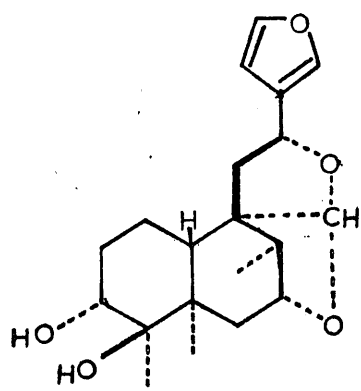
C5



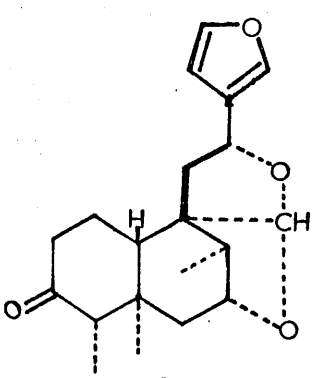
C6



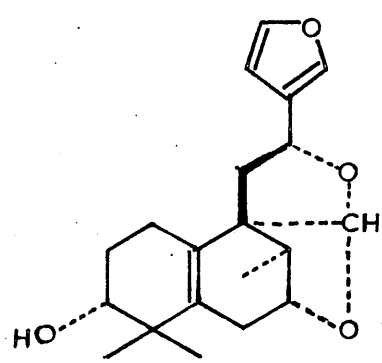
C7



C8



C9



C10

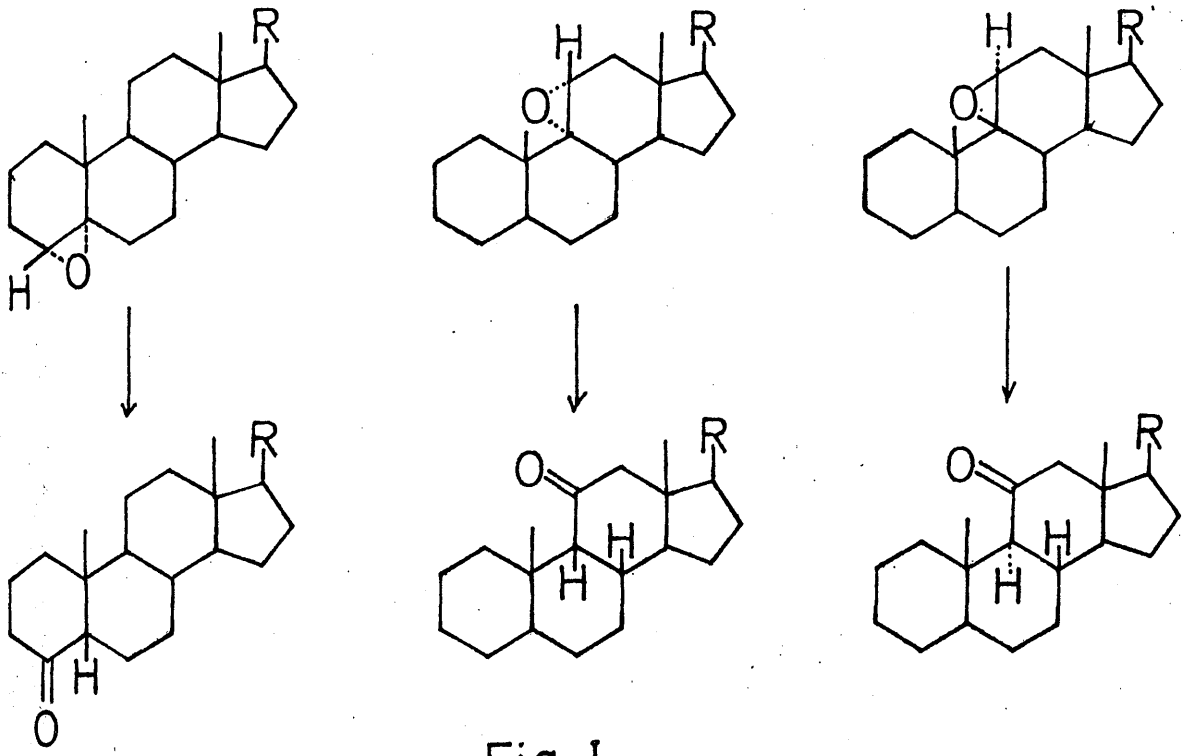


Fig I

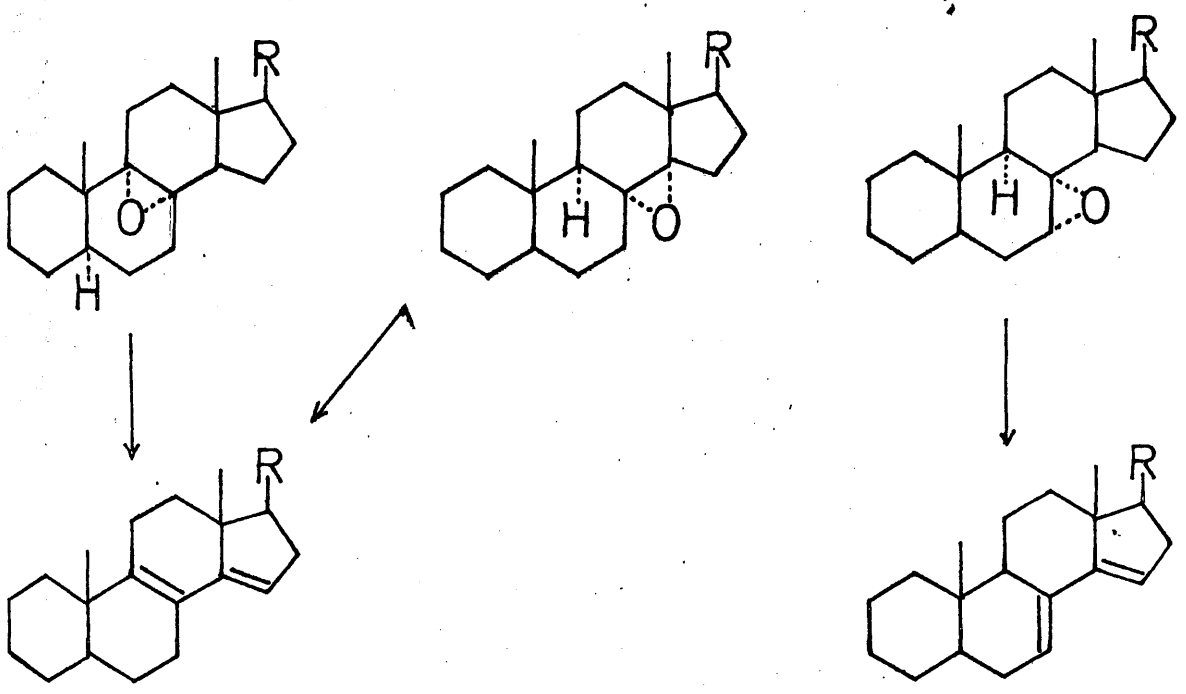


Fig II

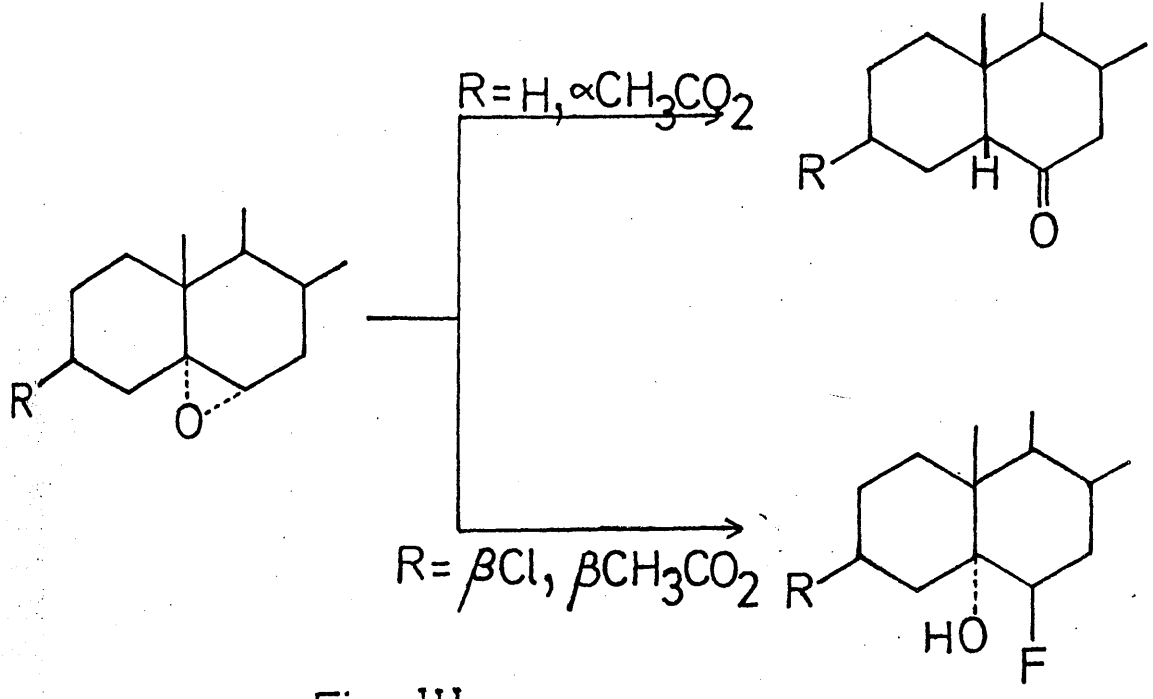


Fig III

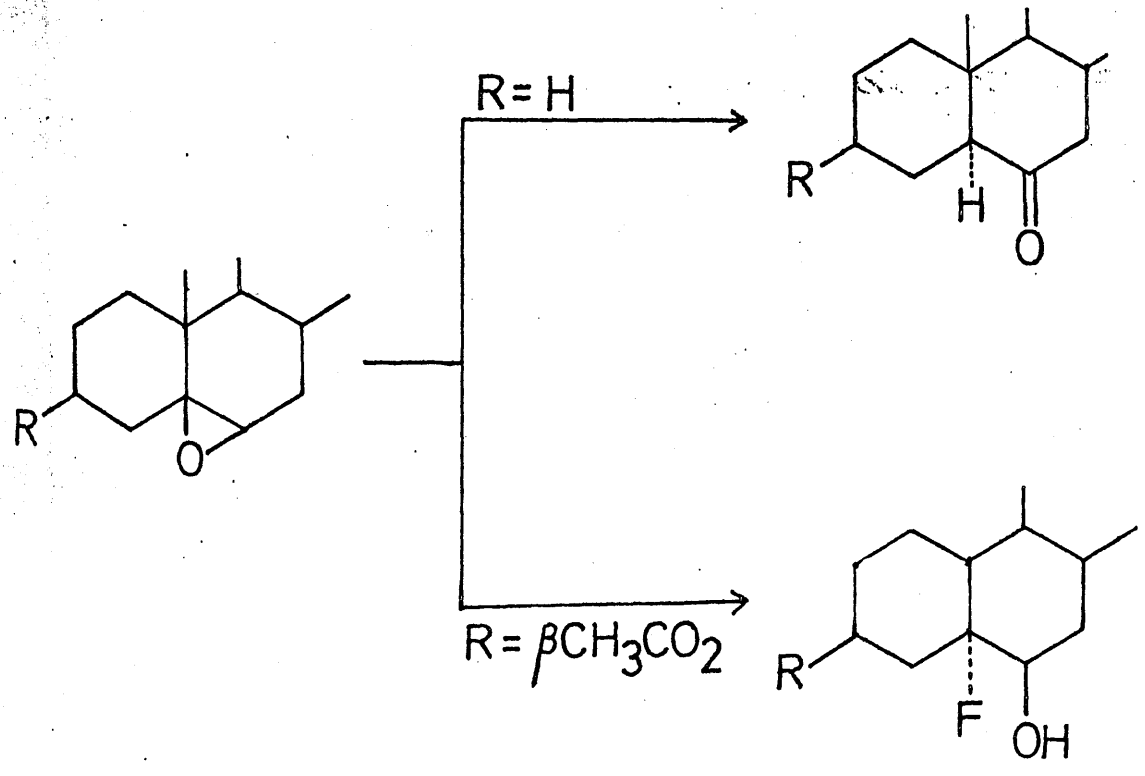


Fig IV

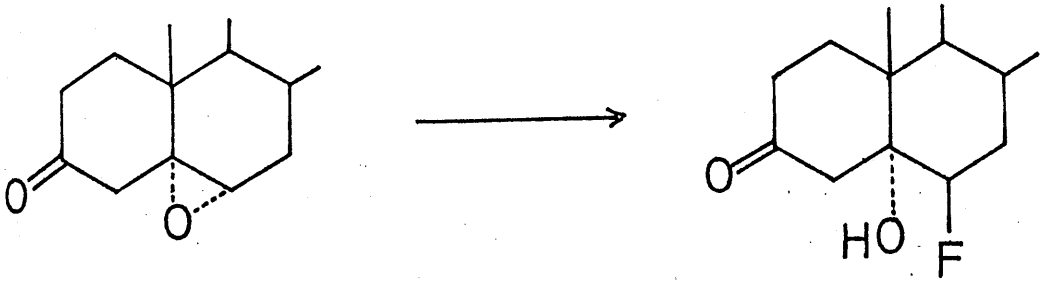
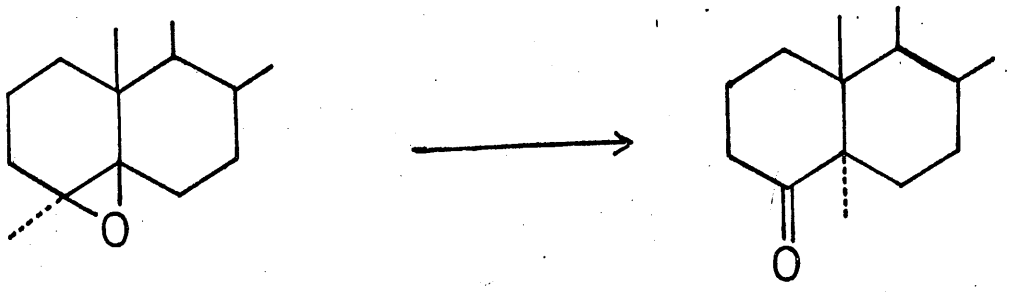


Fig V



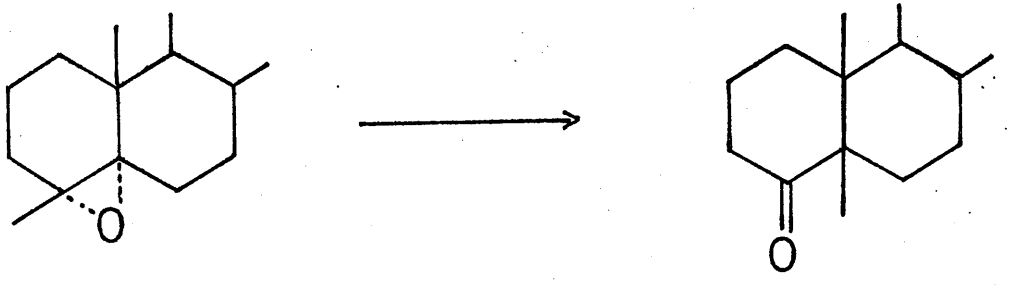
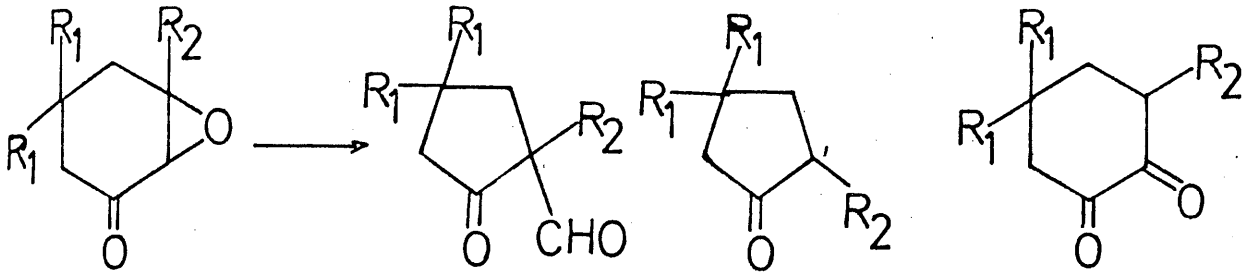


Fig VI



$R_1 = R_2 = CH_3$.	33%	28%	3%
$R_1 = CH_3$; $R_2 = Ph$.	-	68%	-
$R_1 = R_2 = H$.	-	25%	56%

Table I

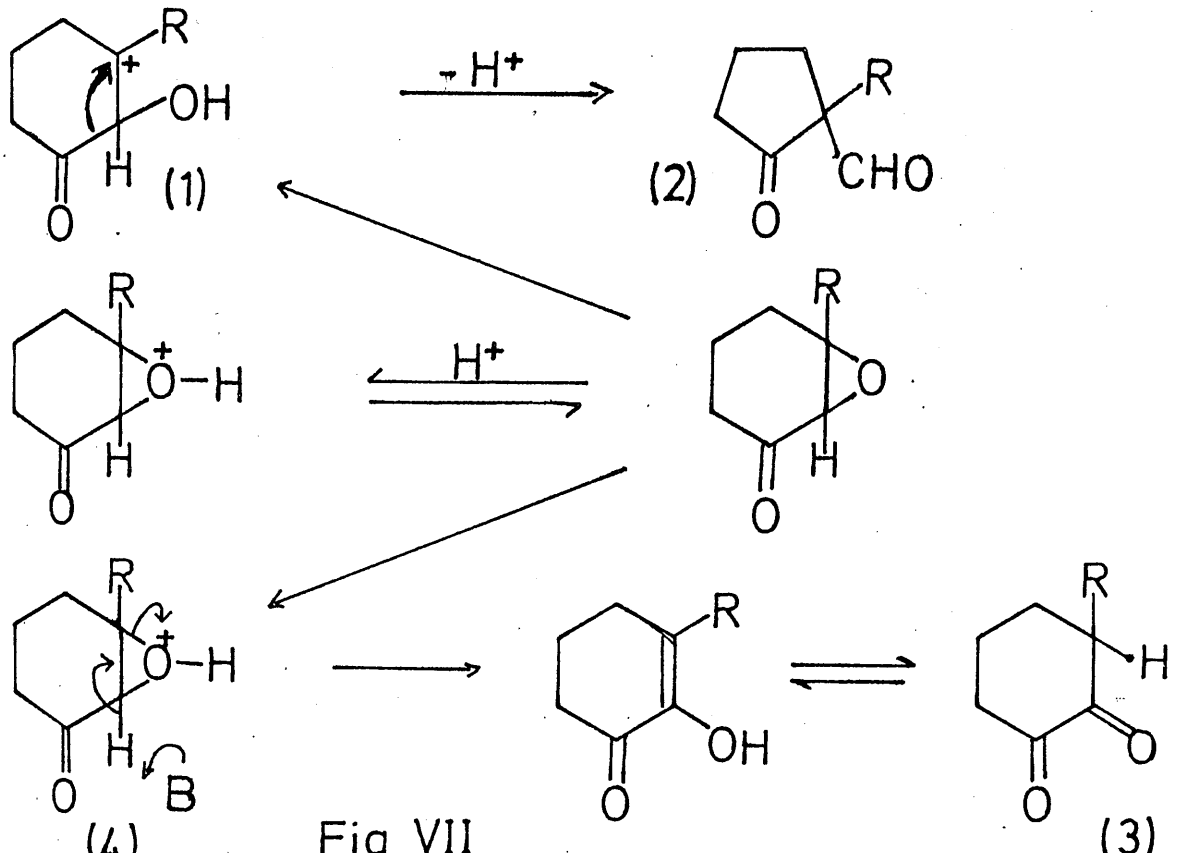
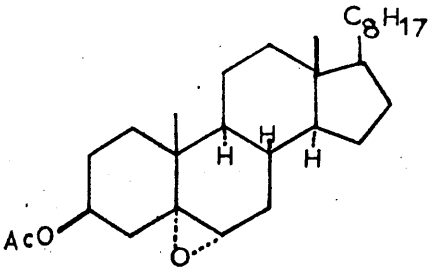
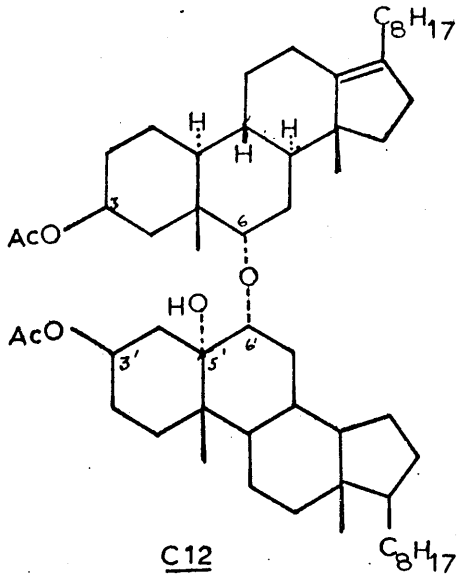


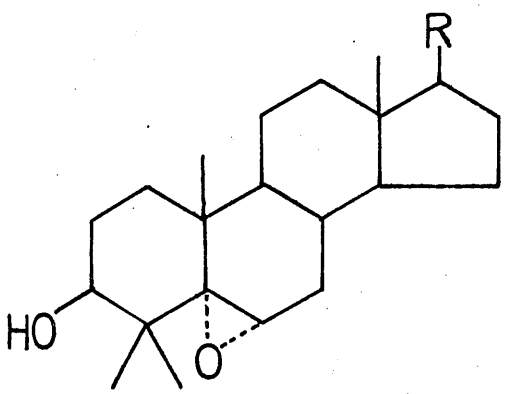
Fig VII



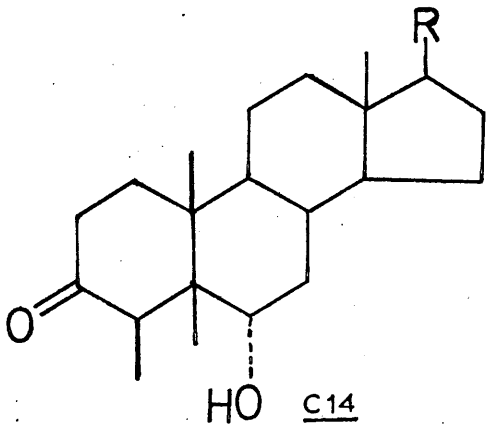
C 11



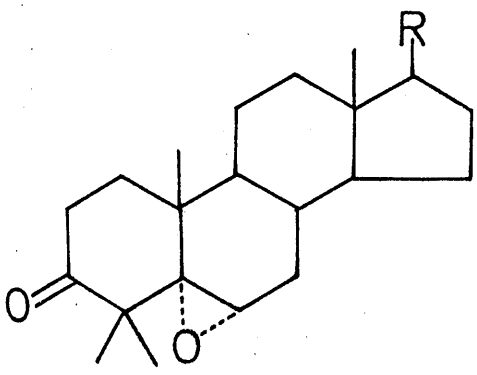
C 12



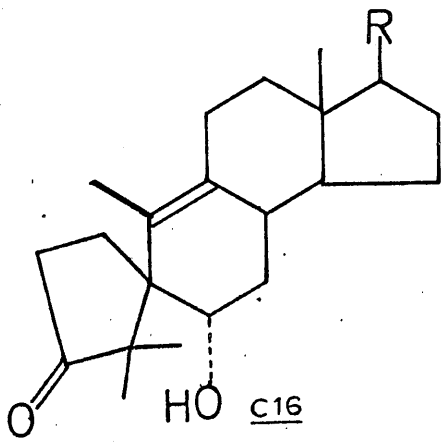
C 13



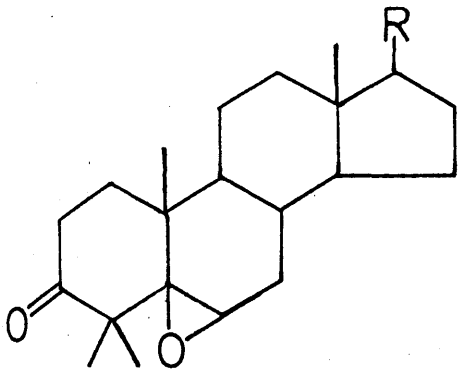
C 14



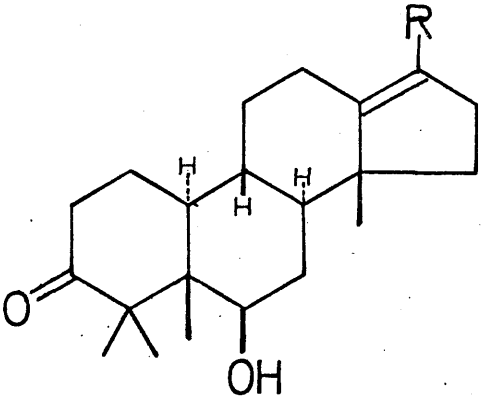
C 15



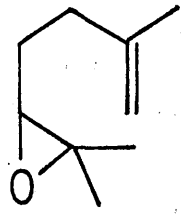
C 16



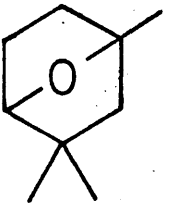
C 17



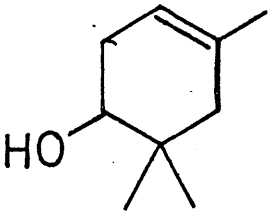
C 18



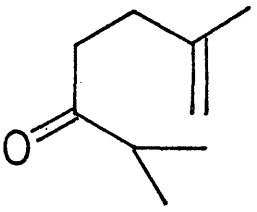
C 19



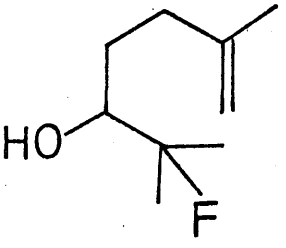
C 20



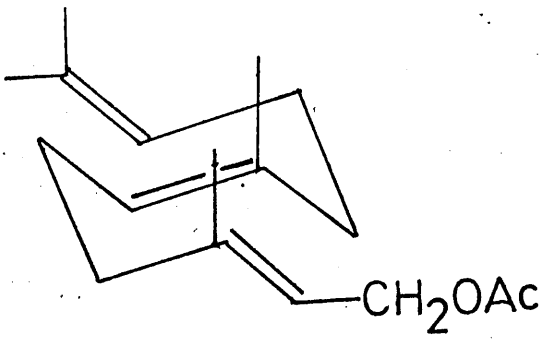
C 21



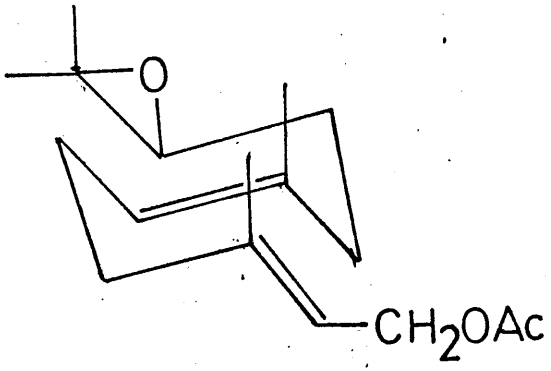
C 22



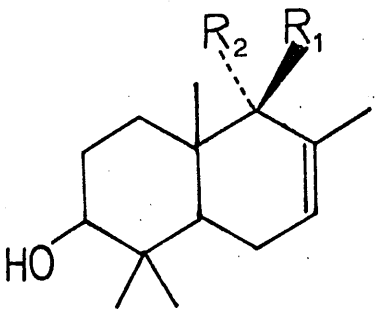
C 23



C 24

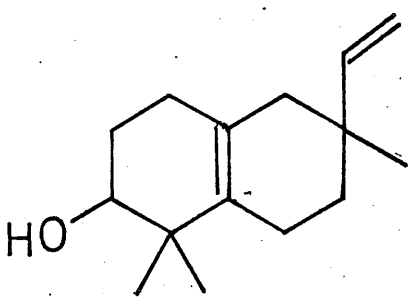


C 25

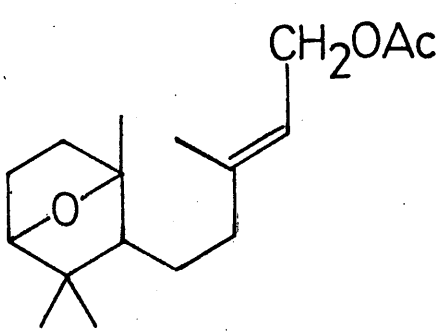


C 26 $R_1 = CH_2OAc$; $R_2 = H$.

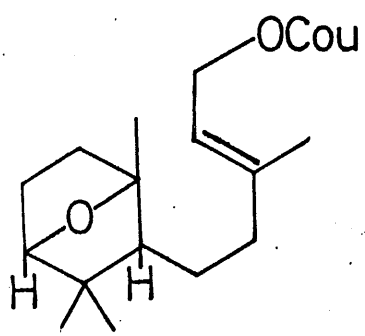
C 27 $R_1 = H$; $R_2 = CH_2OAc$.



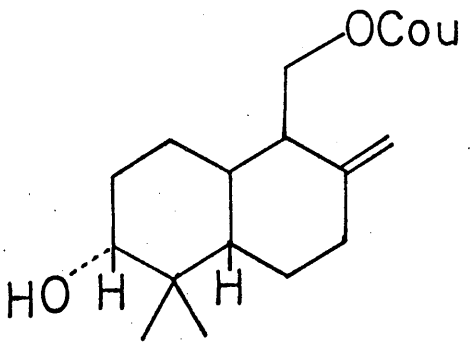
C 28



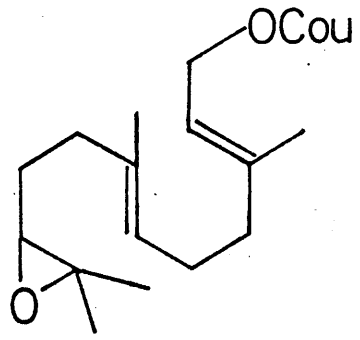
C 29



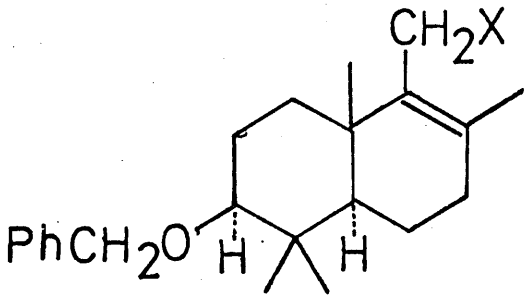
C 30



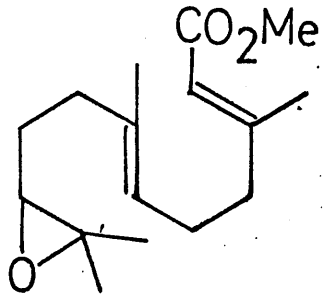
C 31



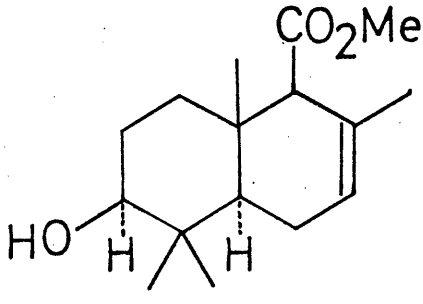
C 32



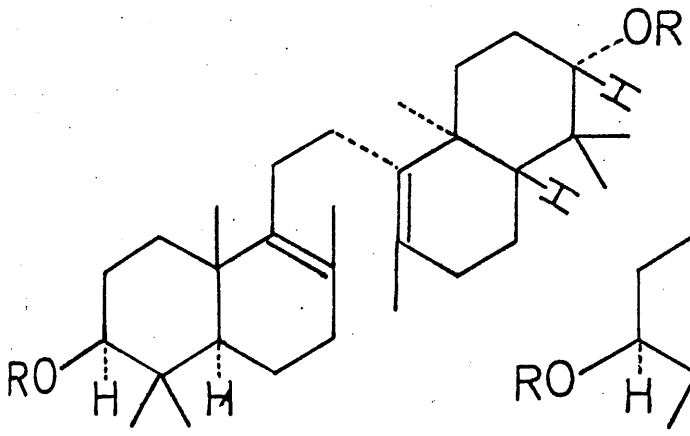
C 33



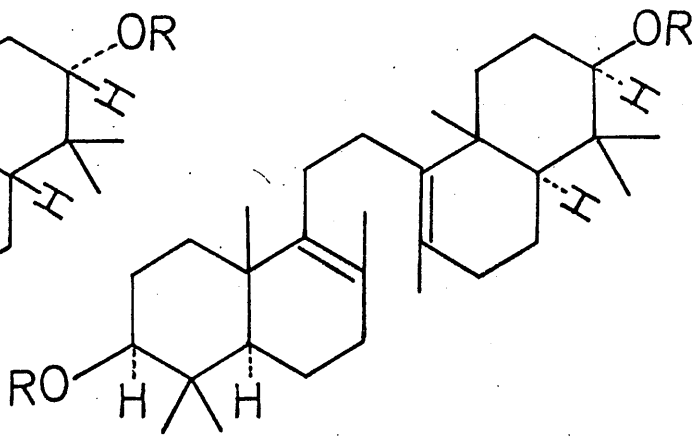
C 34



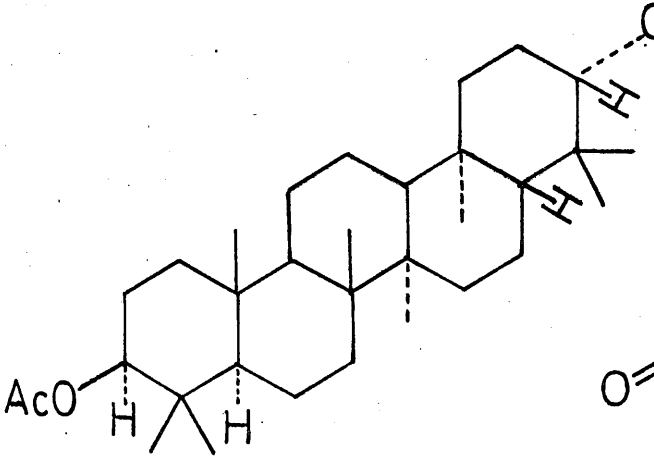
C 35



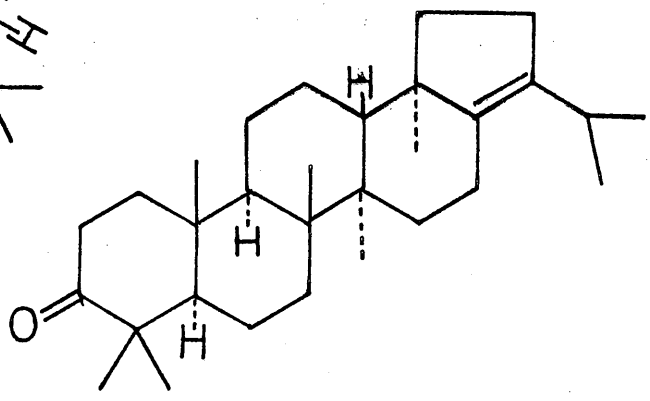
C 36



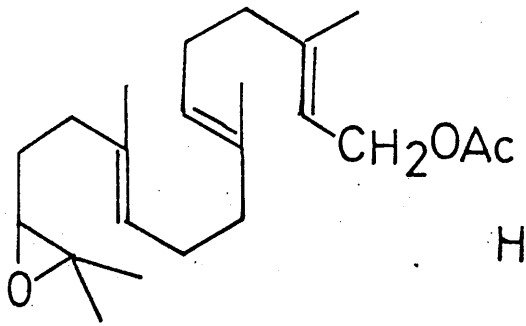
C 37



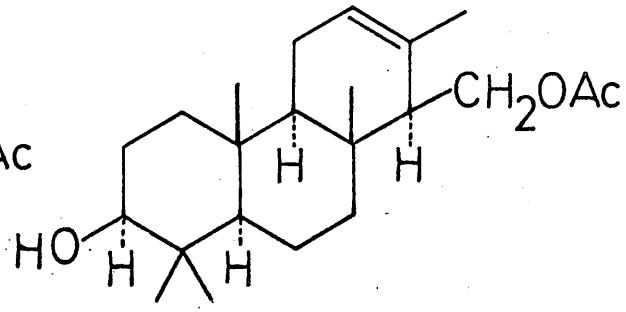
C 38



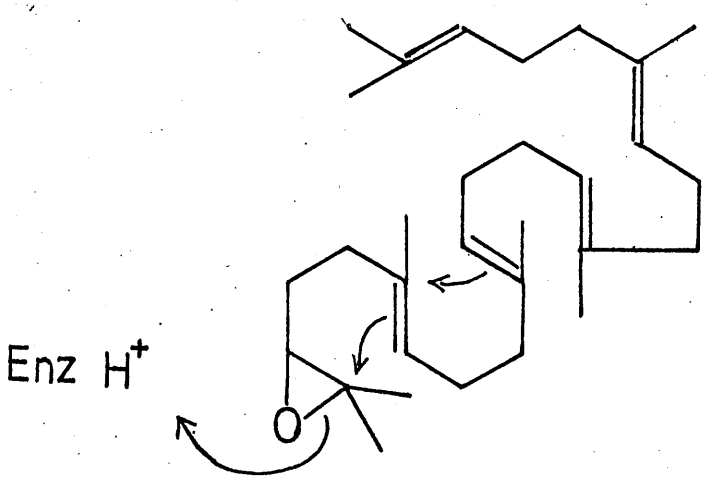
C 39



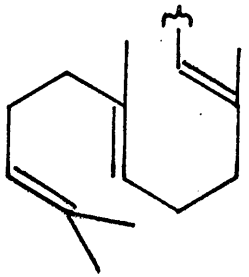
C 40



C 41

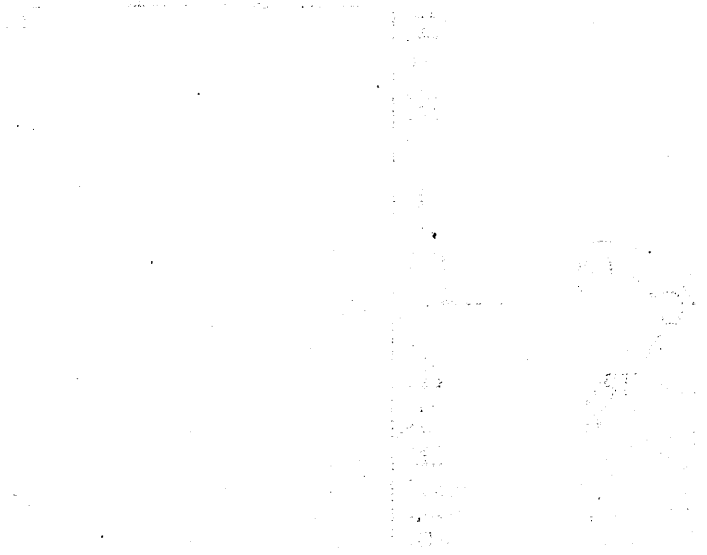


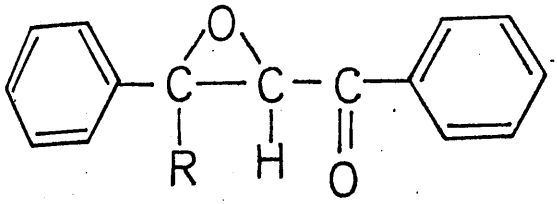
C 42



C 43

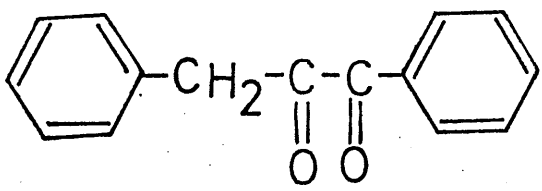
Fig VIII





C 44 R = H

C 46 R = Me



C 45

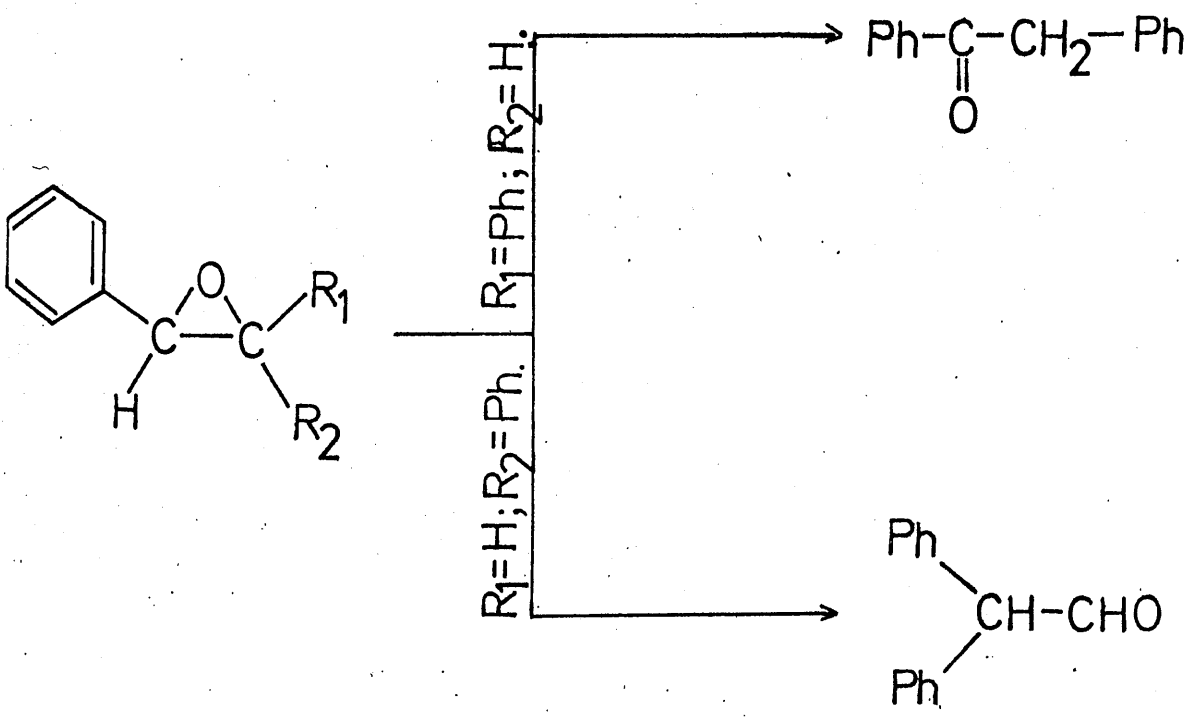
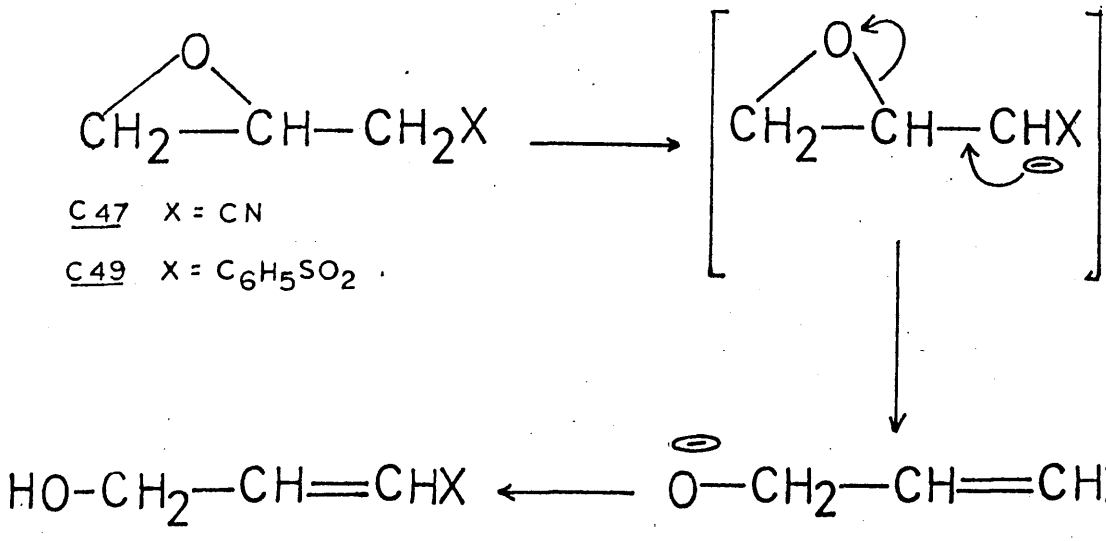


Fig IX



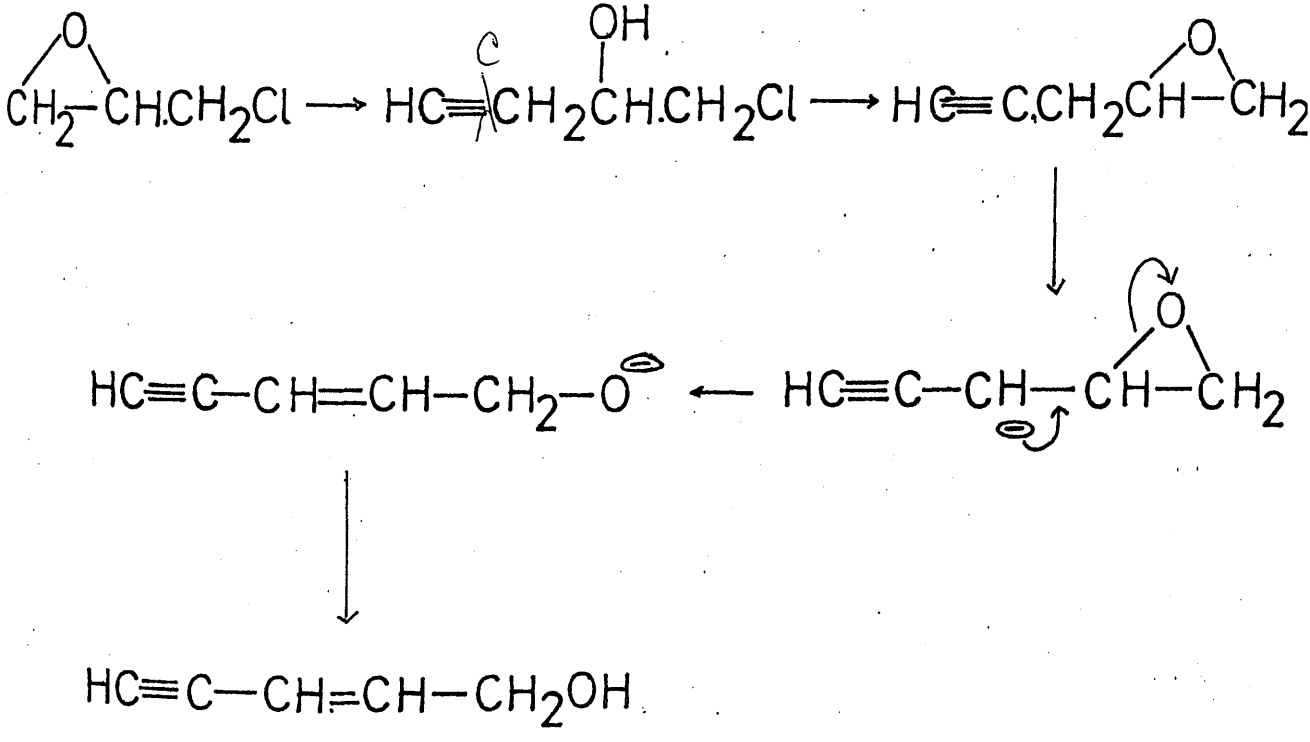
C 47 X = CN

C 49 X = $C_6H_5SO_2$

C 48 X = CN

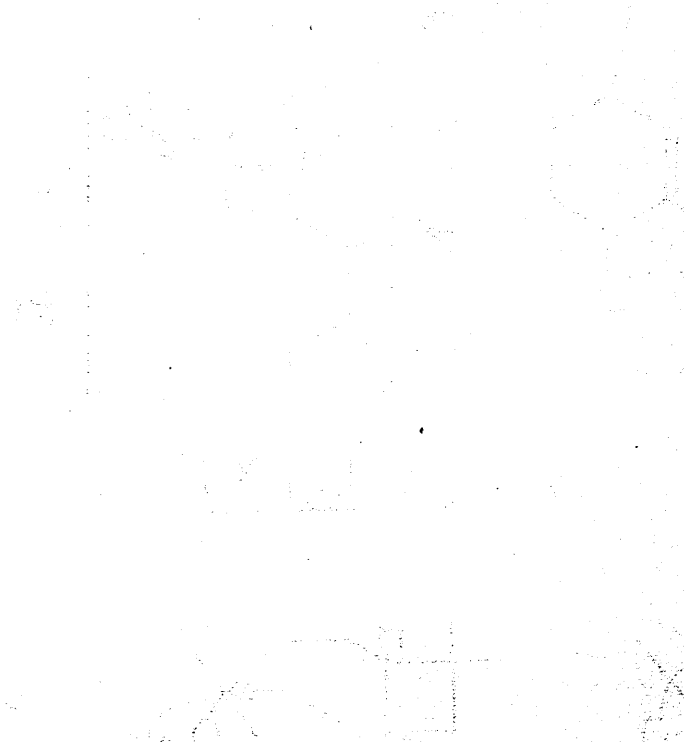
C 50 X = $C_6H_5SO_2$

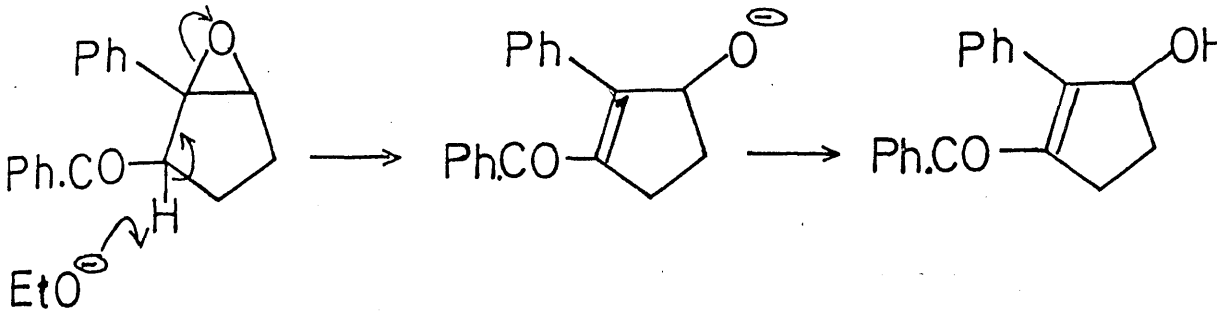
Fig X



C 51

Fig Xa

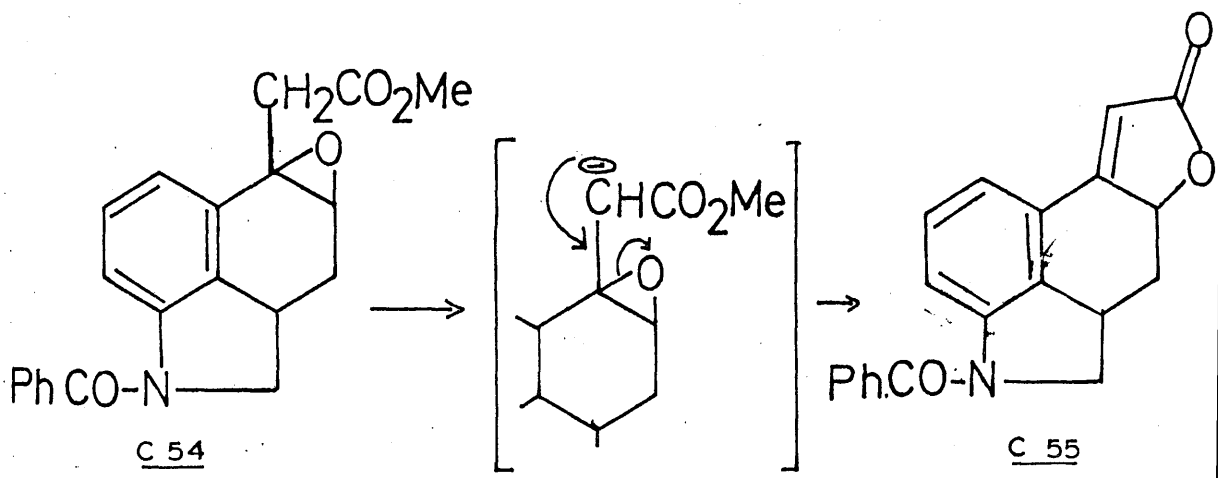




C 52

Fig XI

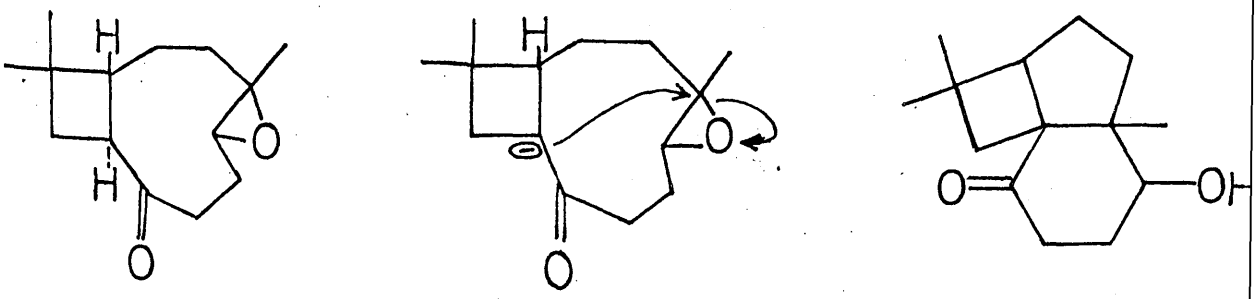
C 53



C 54

C 55

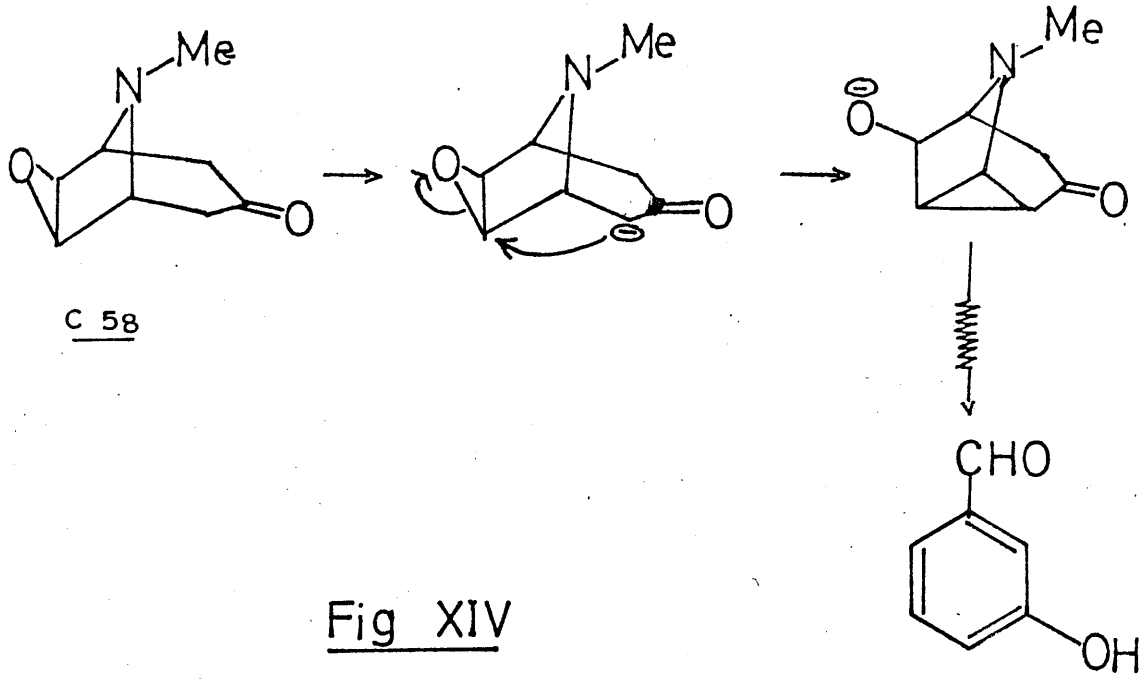
Fig XII



C 56

C 57

Fig XIII



C 58

C 59

Fig XIV

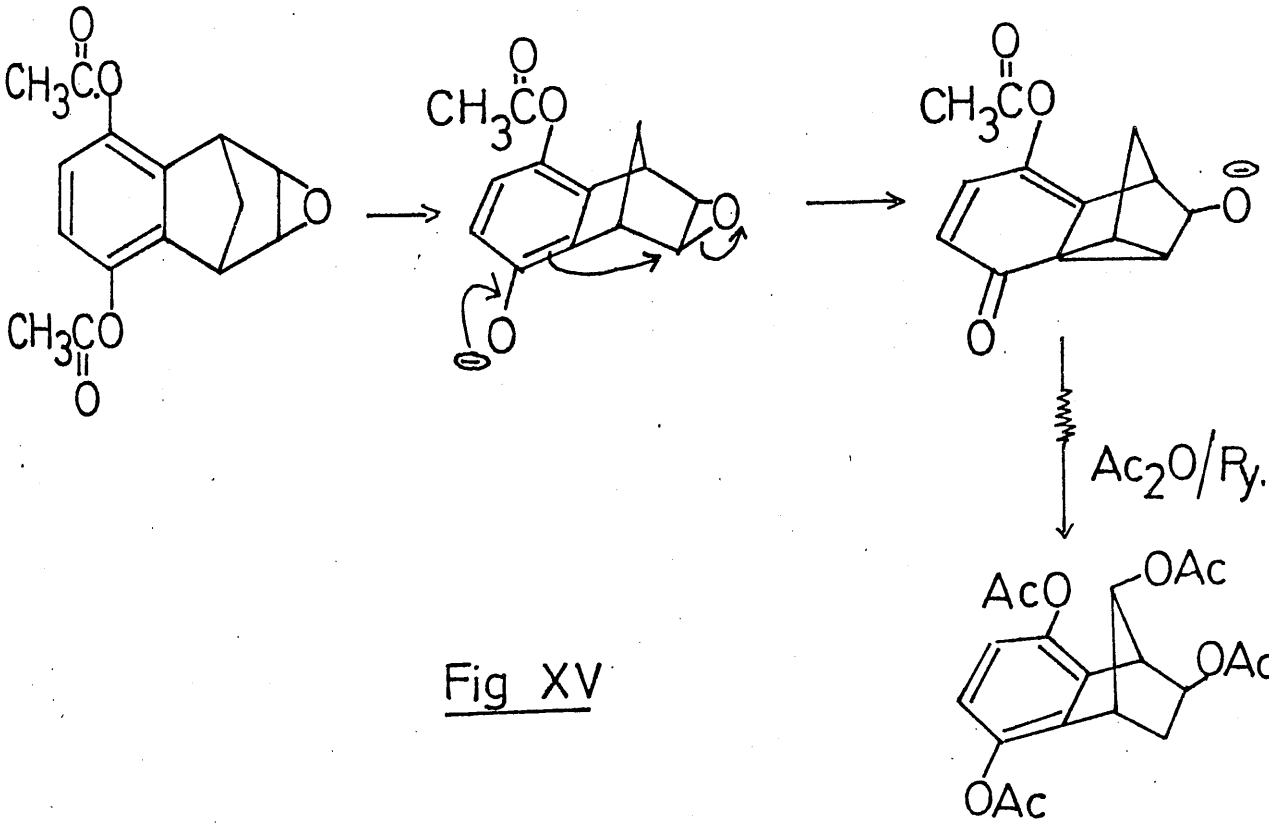
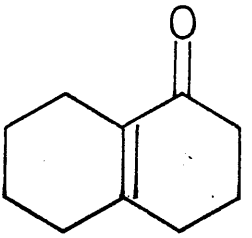
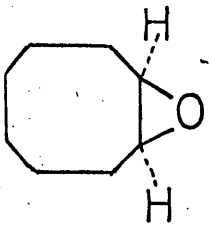


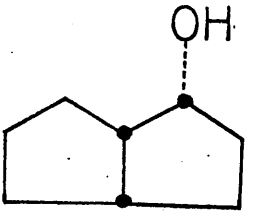
Fig XV



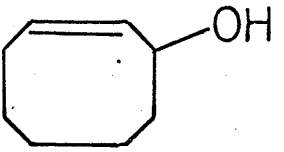
C 60



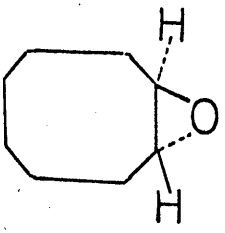
C 61



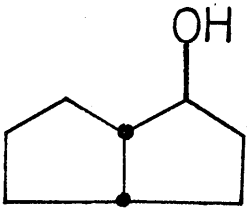
C 62



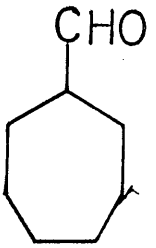
C 63



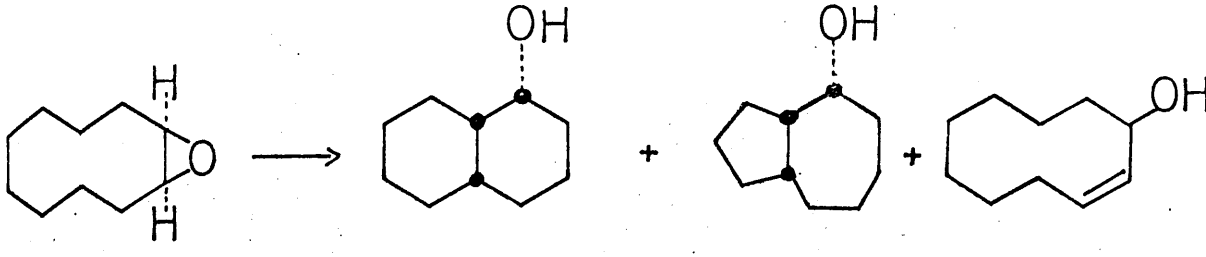
C 64



C 65



C 66



C 67 C 68

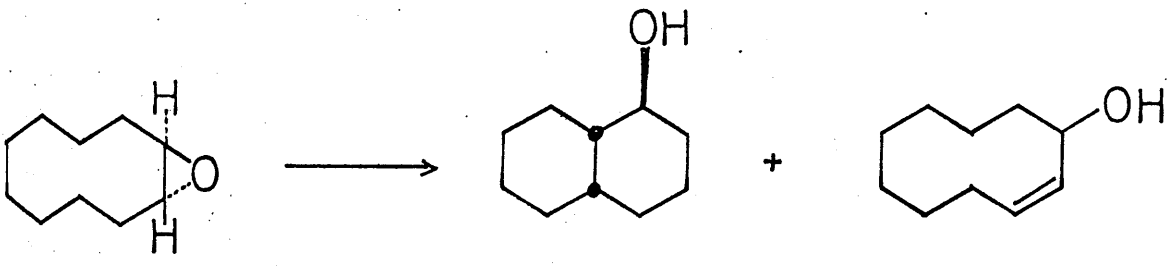
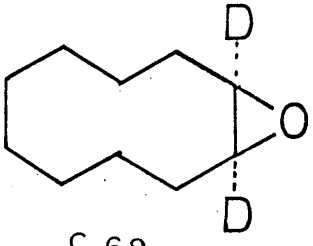
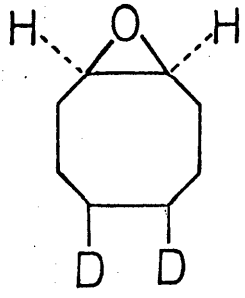


Fig XVI



C 69



C 70

cis-cyclodecene oxide

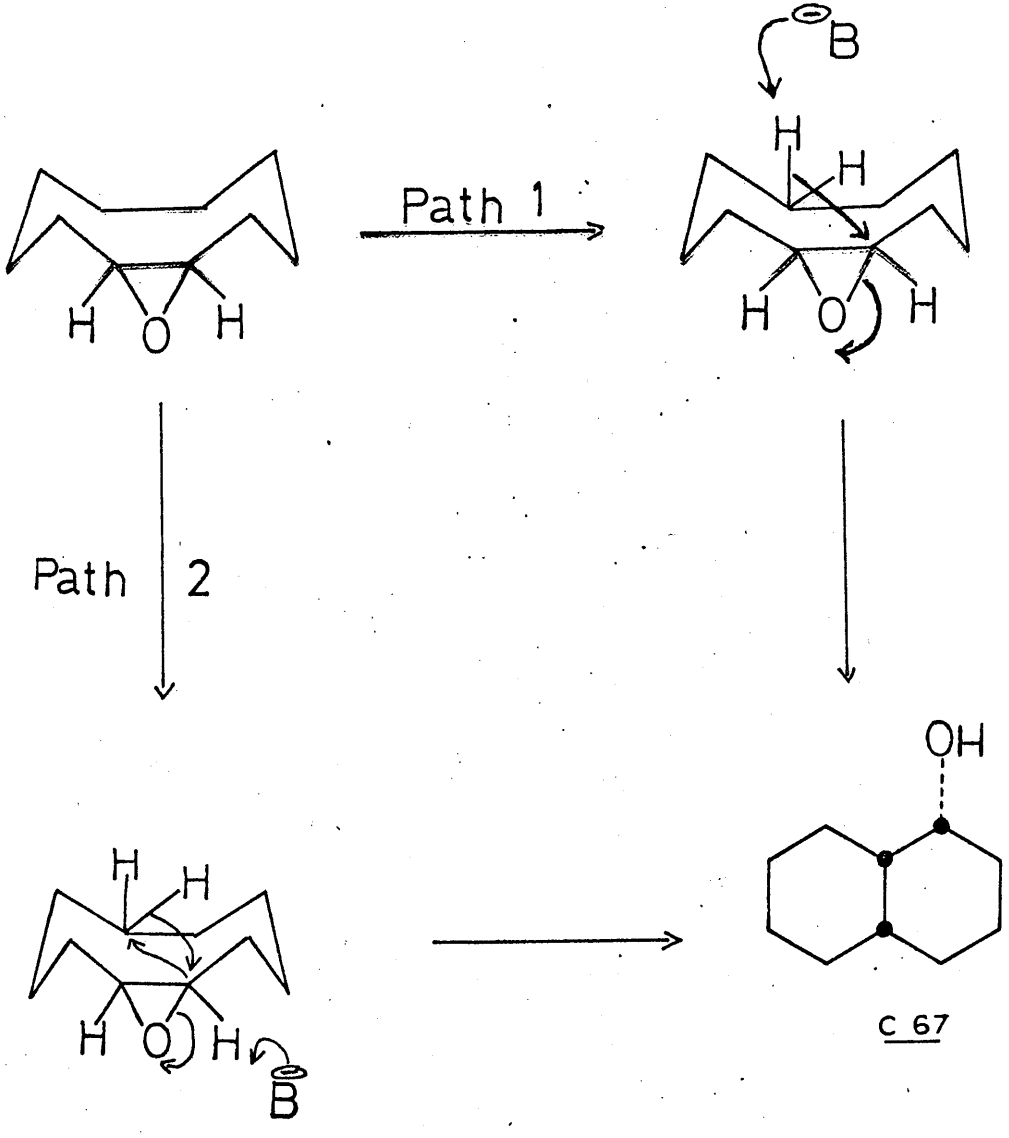
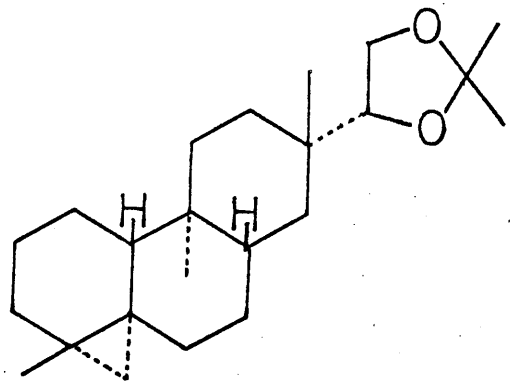
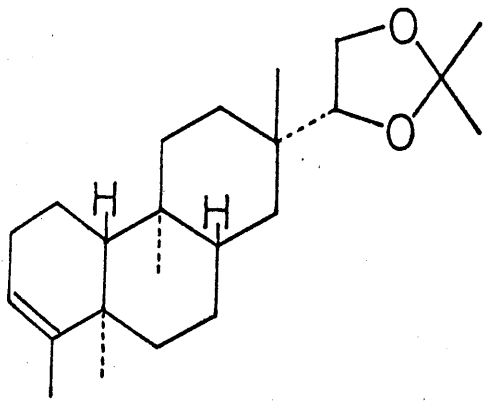


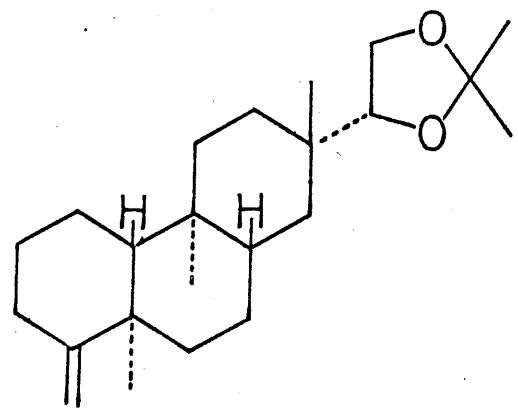
Fig XVII



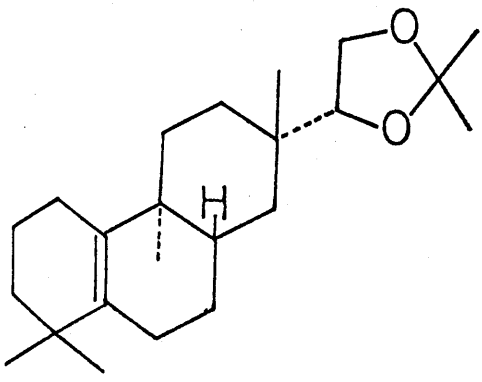
C 71



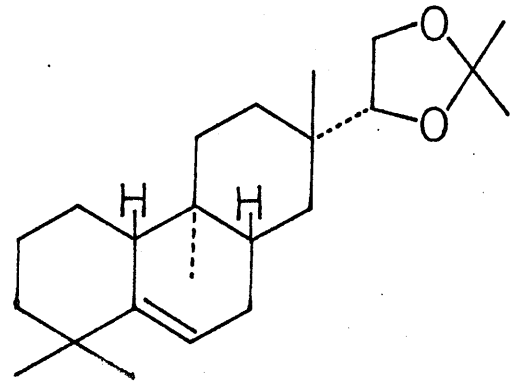
C 72



C 73



C 74



C 75

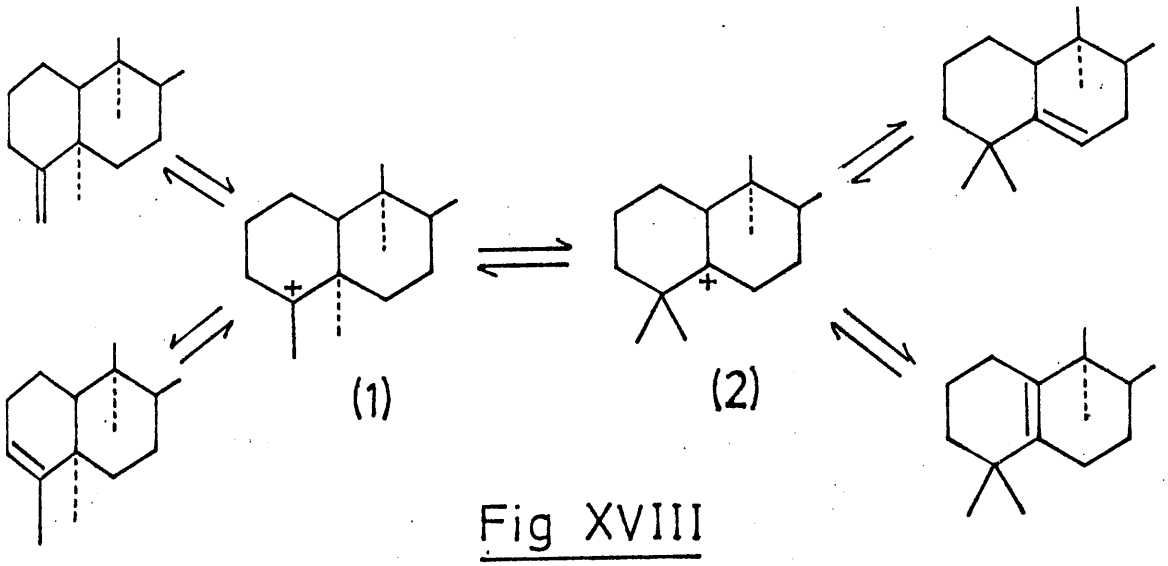


Fig XVIII

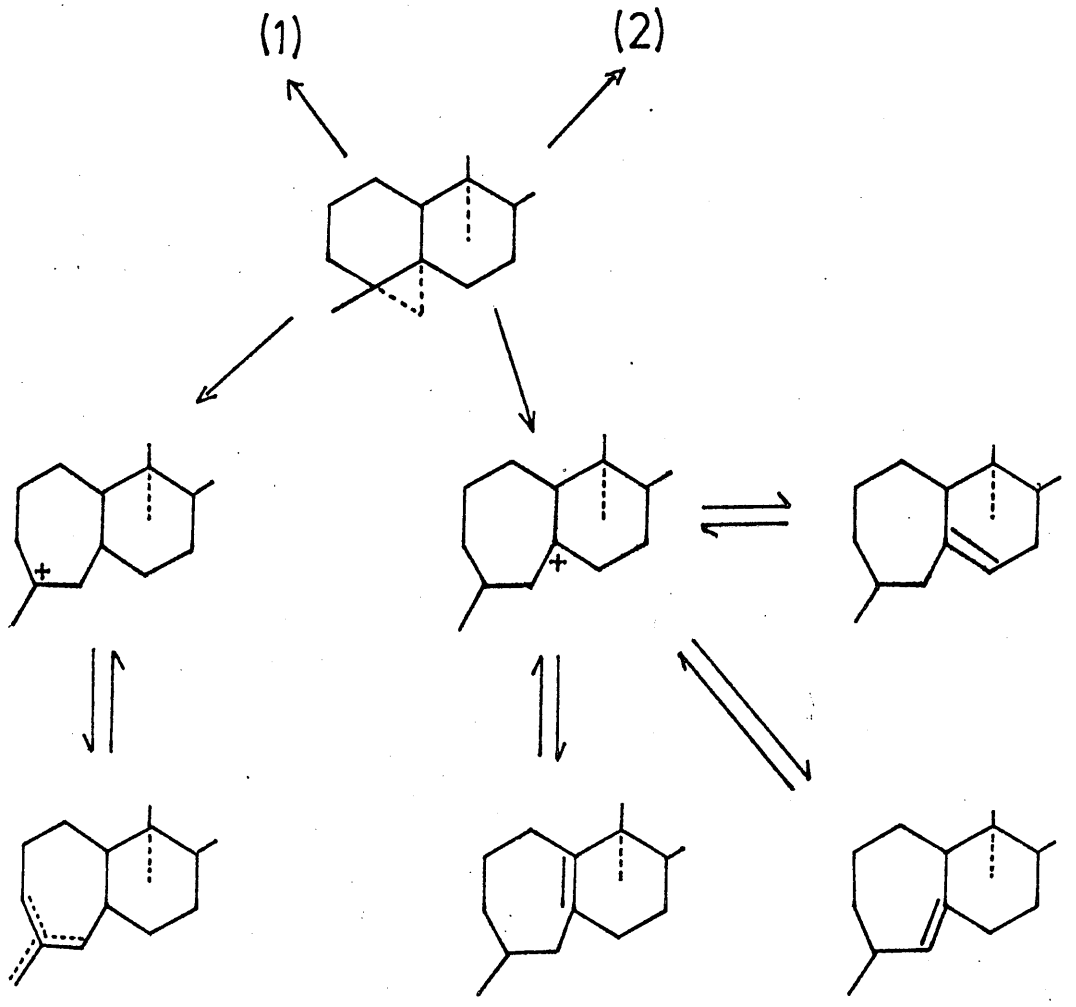
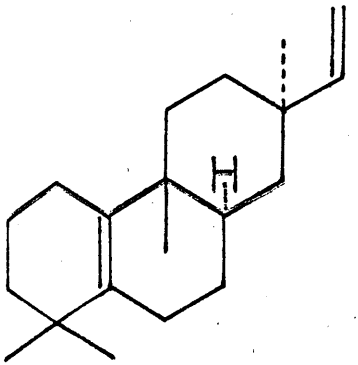
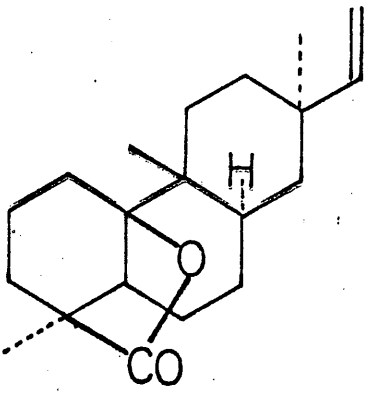


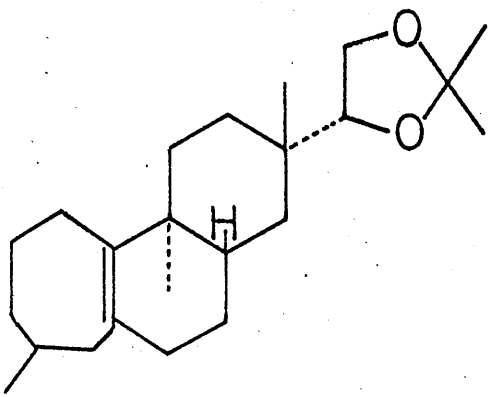
Fig XIX



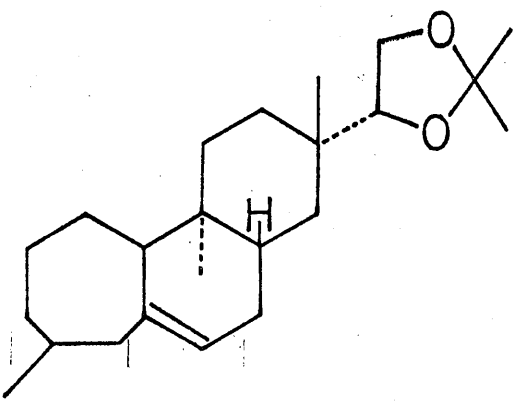
C 76



C 77



C 78



C 79

Table II

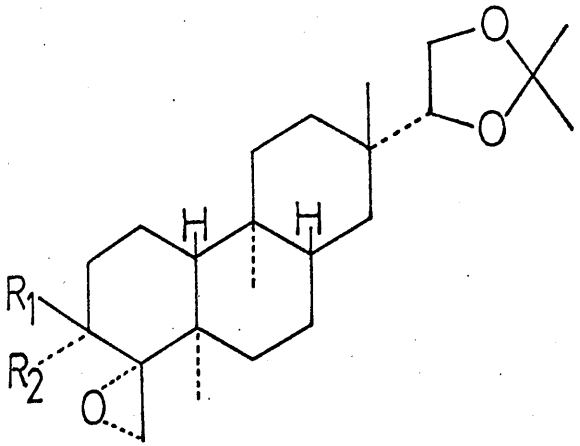
C73 Reaction Mixture — Composition/Time

Time (hr.)	C73	C72	C74	C75
2	27	45	21	7
12	18	35	35	12
18	13	29	42	16
30	4	8	68	20

Table III

C71 Reaction Mixture — Composition/Time

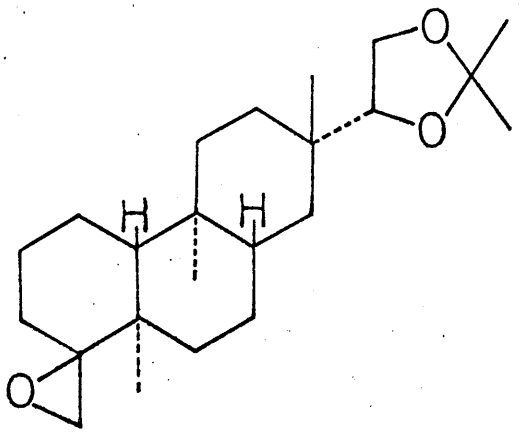
Time (hr.)	C71	C72	C73	C74	C75	C78	C79
1	27	15	7	10	18	8	15
3	9	21	12	9	21	11	17
5	-	28	4	13	13	16	26
8	-	19	3	21	16	20	21
12	-	15	3	31	14	23	14
24	-	10	-	42	12	29	7



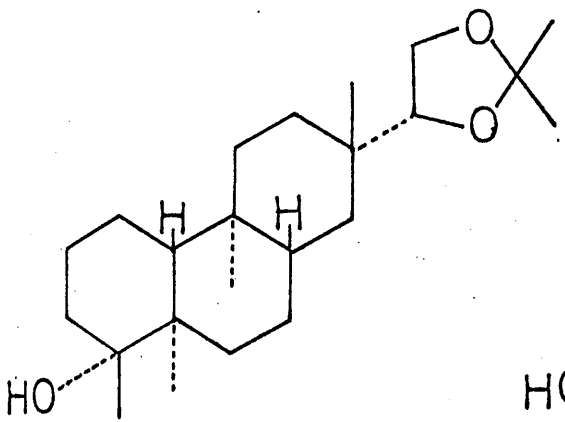
C 80 $R_1 = R_2 = H$.

C 87 $R_1 = R_2 = D$.

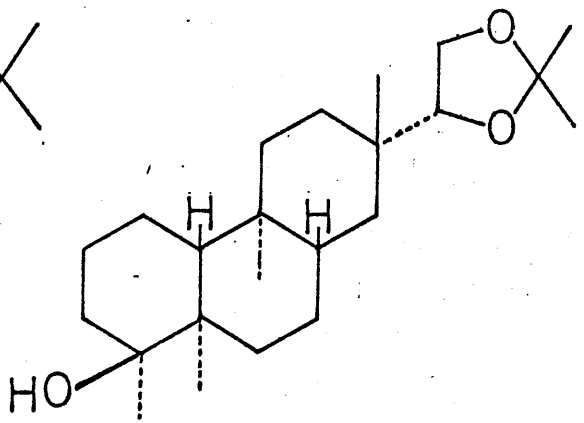
C 88 $R_1 = D$; $R_2 = H$.



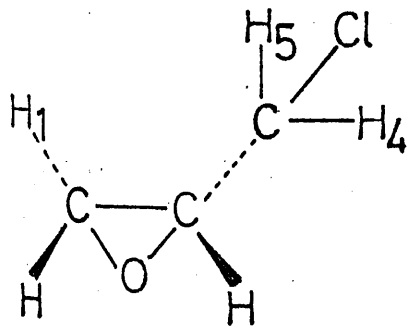
C 81



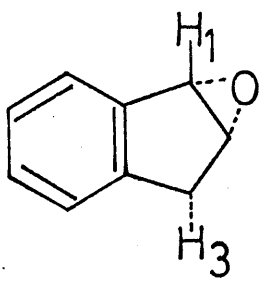
C 82



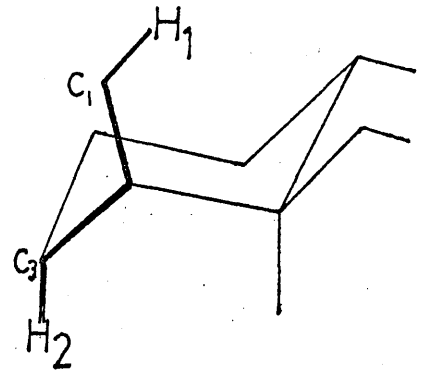
C 83



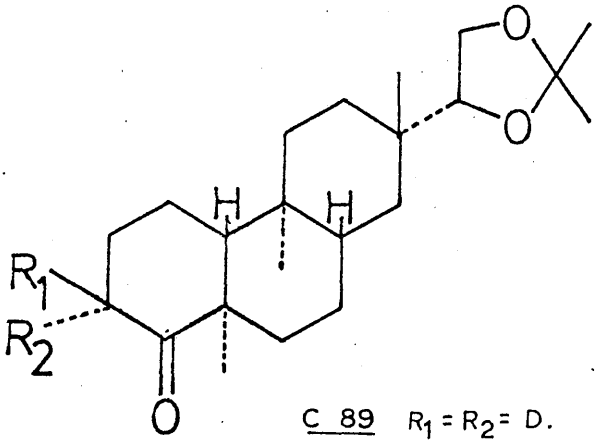
C 84



C 85



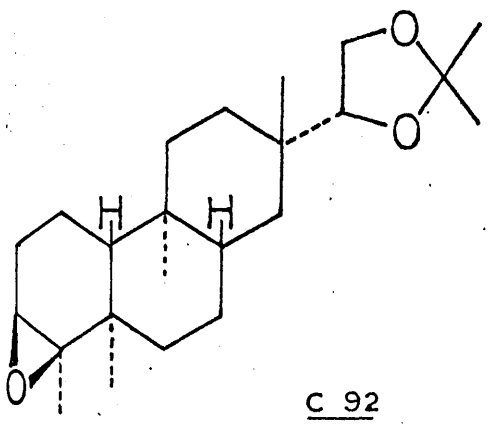
C 86



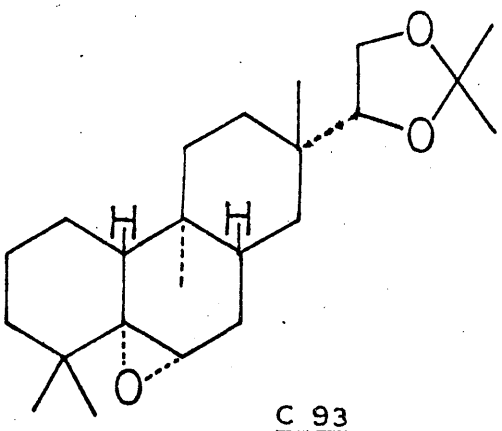
C 89 $R_1 = R_2 = D$.

C 90 $R_1 = D$; $R_2 = H$.

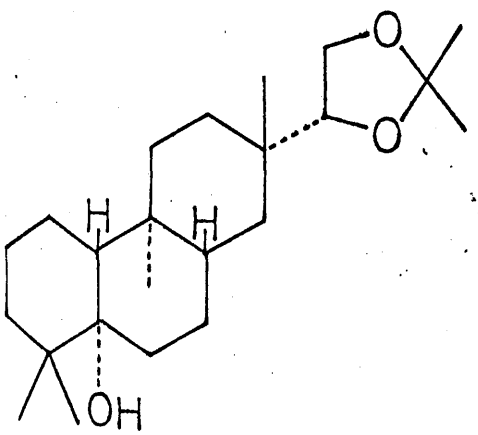
C 91 $R_1 = R_2 = H$.



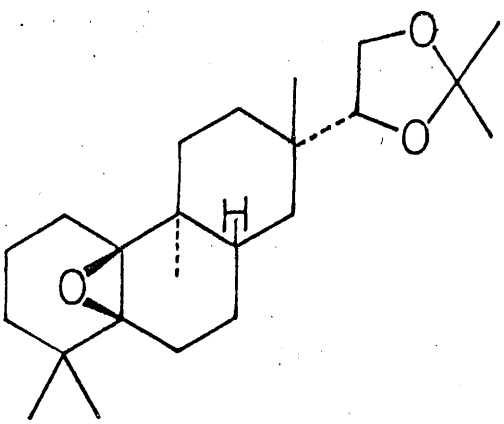
C 92



C 93



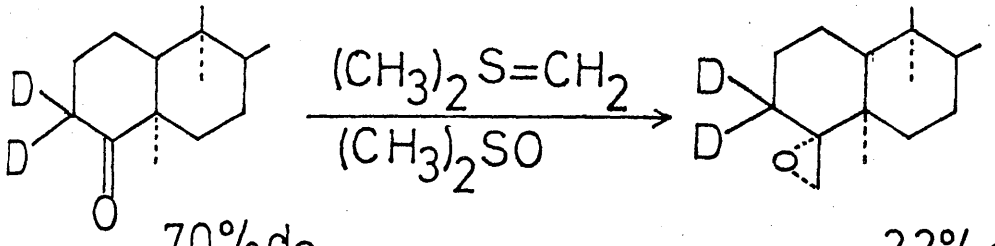
C 94



C 95

Table IV

Preparation of the Deuterated Epoxides



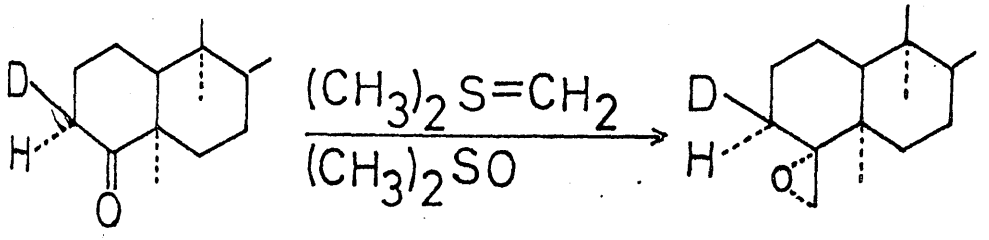
70% d_2
18% d_1
12% d_0

22% d_2
37% d_1
41% d_0

$(CH_3)_2S\ CH_2$
$(CD_3)_2SO$

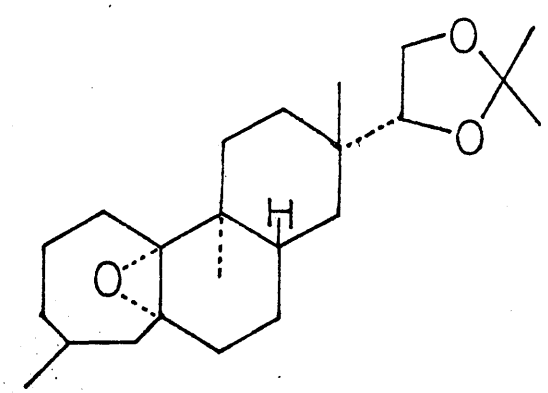
C 87

25% d_3
44% d_2
16% d_1
15% d_0

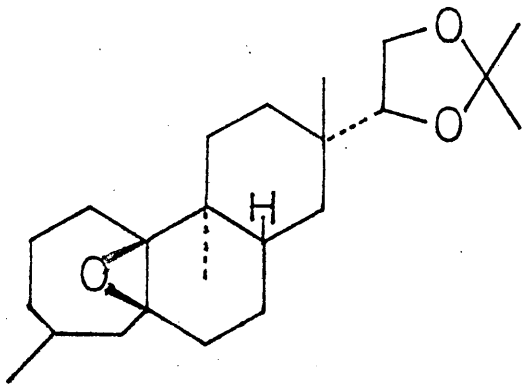


8% d_2
70% d_1
22% d_0

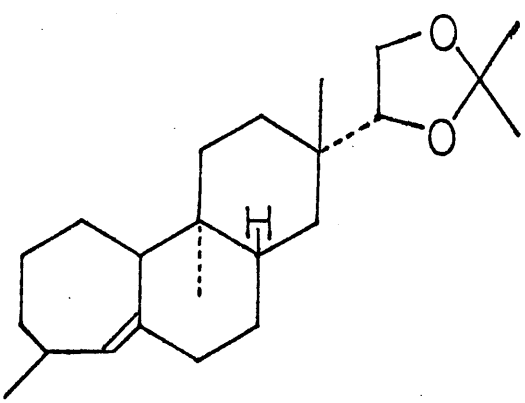
0% d_2
26% d_1
74% d_0



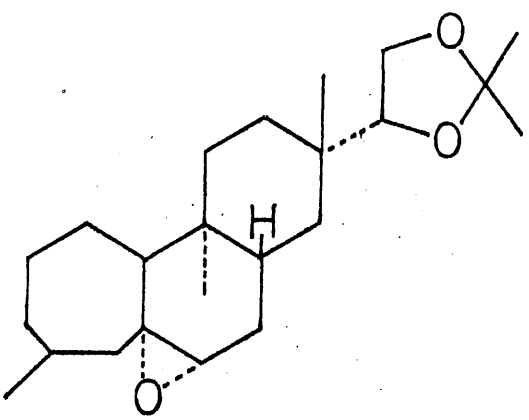
C 96



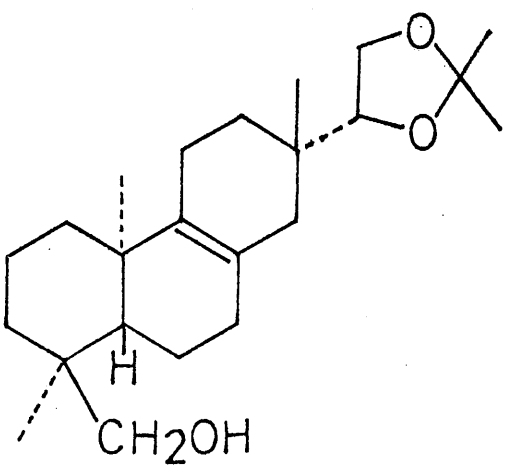
C 97



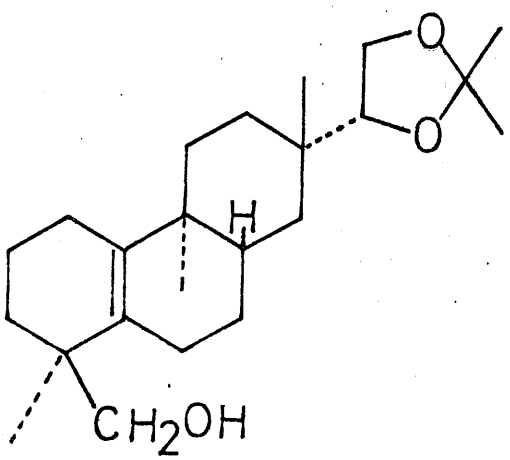
C 98



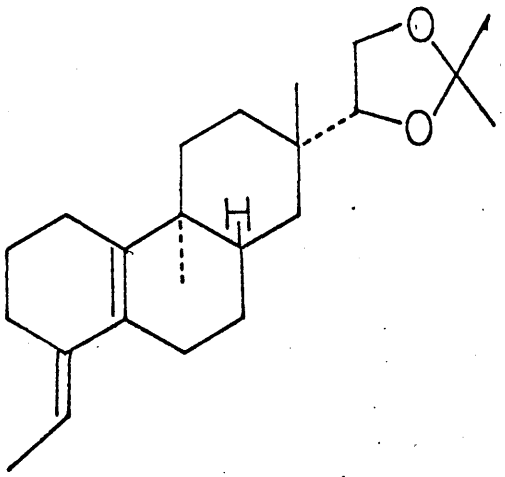
C 99



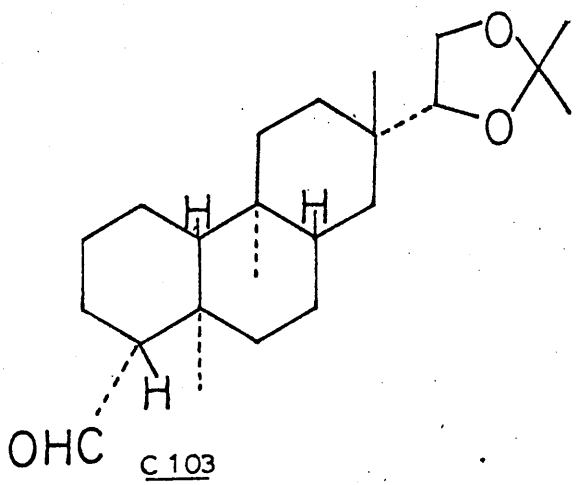
C 100



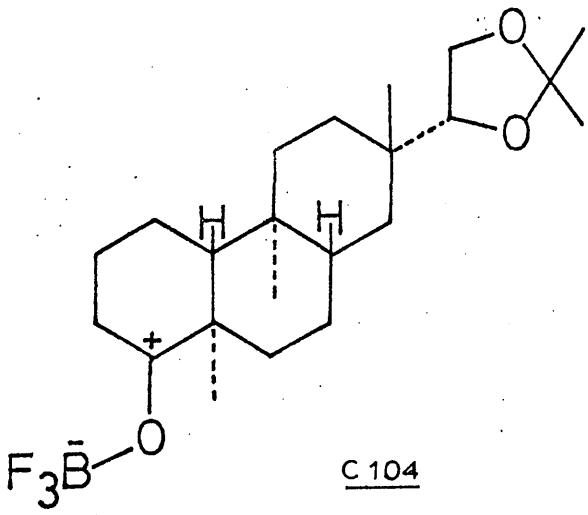
C 101



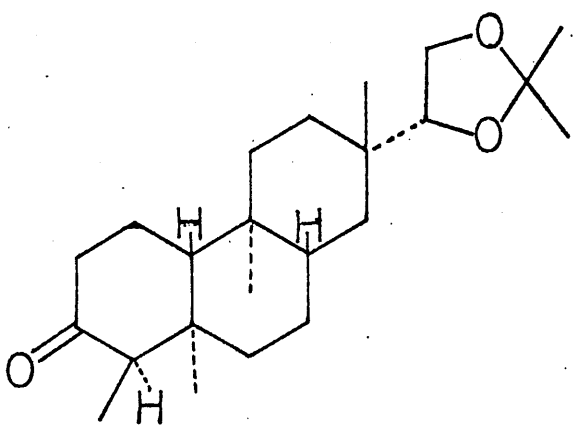
C 102



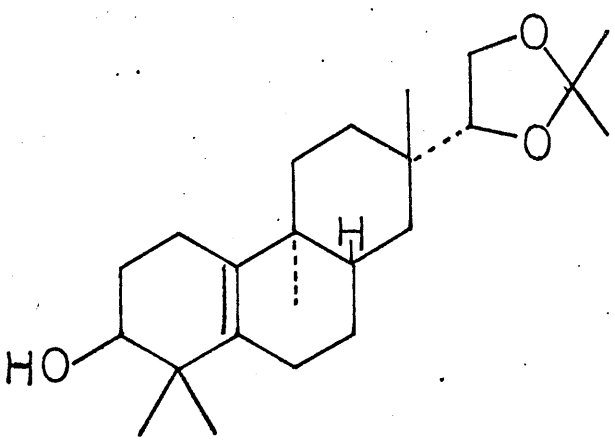
C 103



C 104



C 105a



C 105b

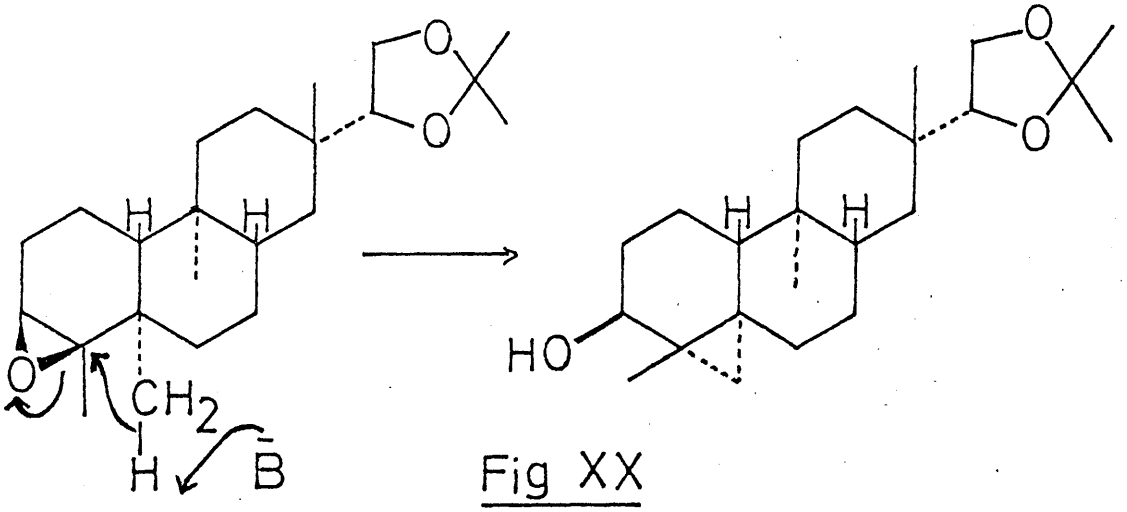
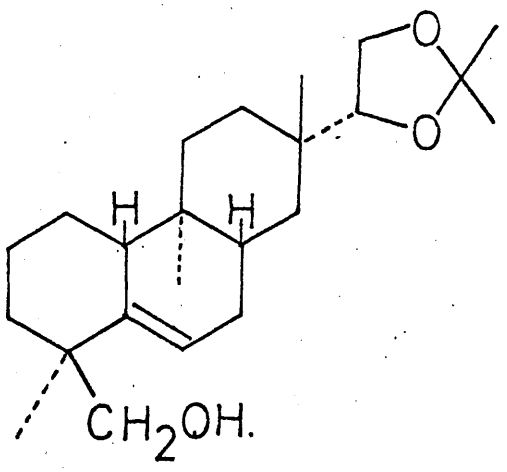
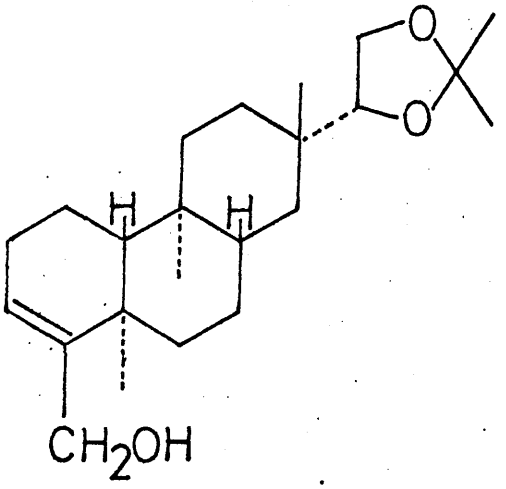


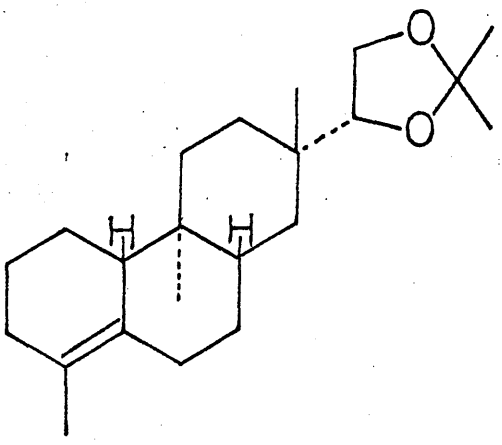
Fig XX



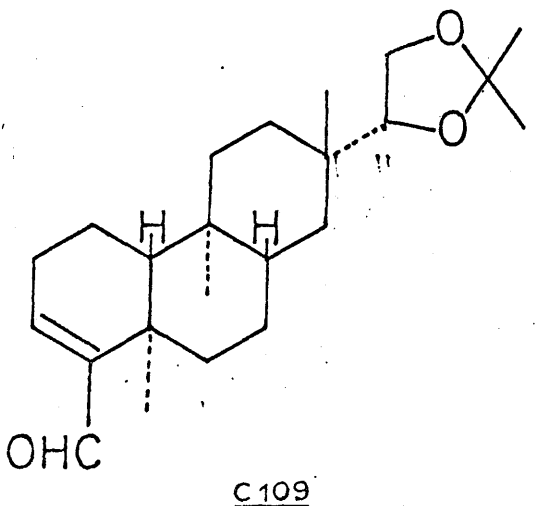
C 106



C 107



C 108



C 109

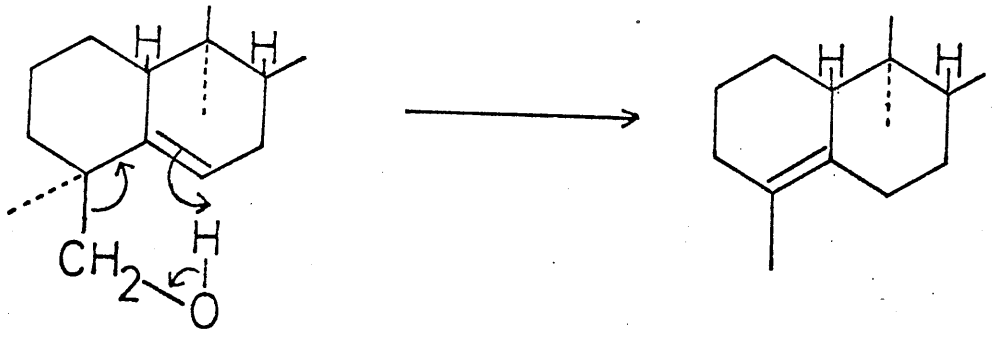
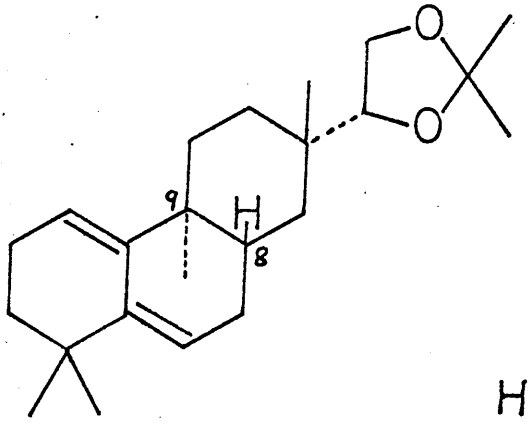
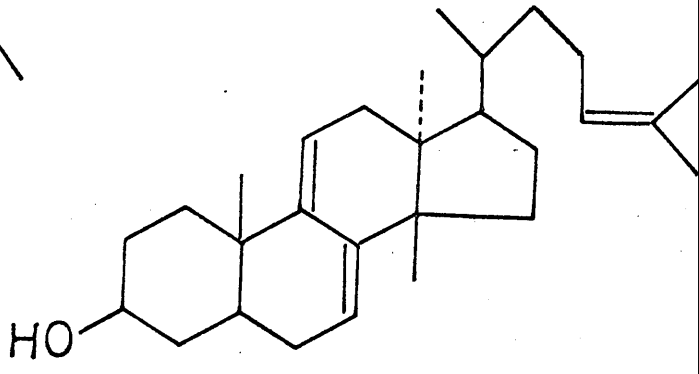


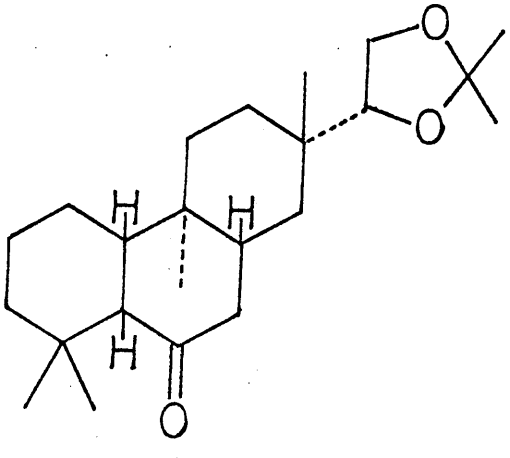
Fig XXI



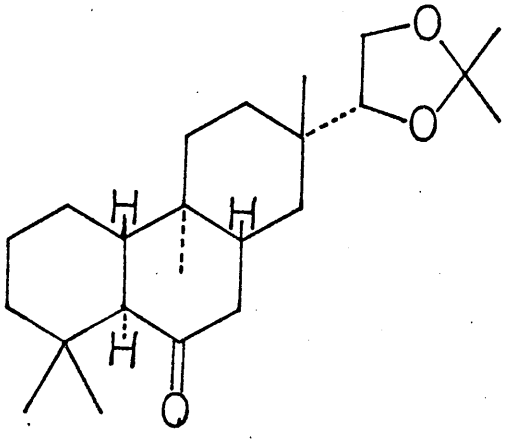
C 110



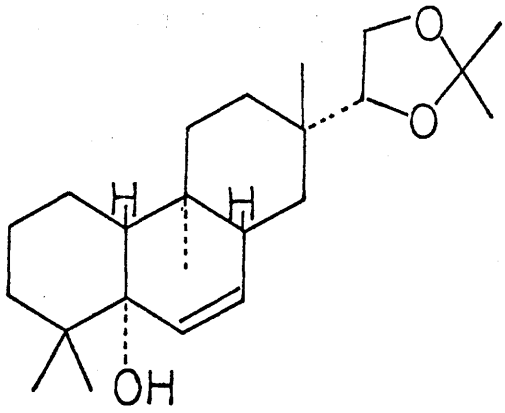
C 111



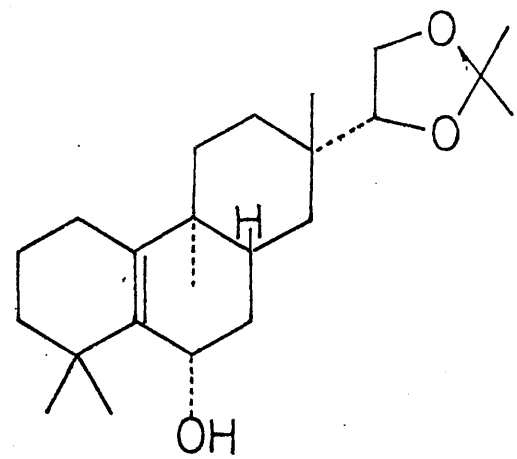
C 112



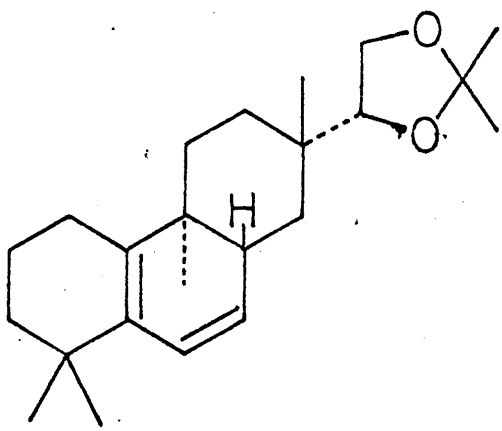
C 113



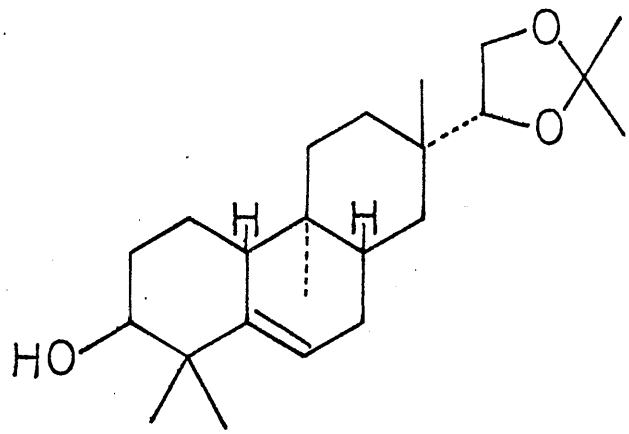
C 114



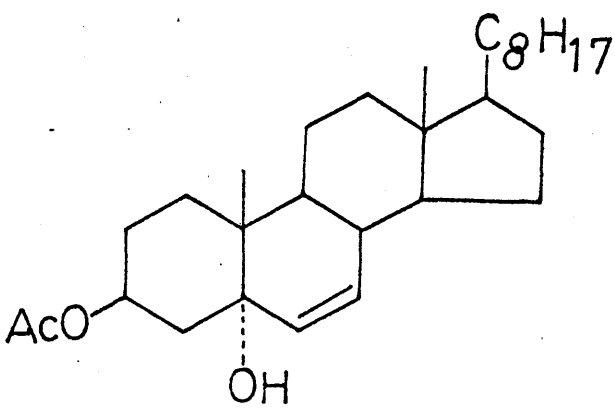
C 115



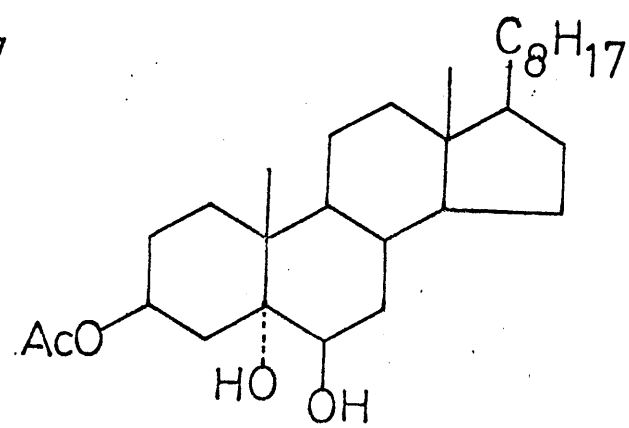
C 116



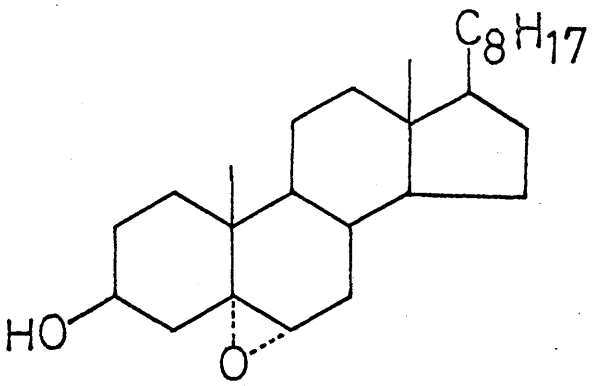
C 117



C 118



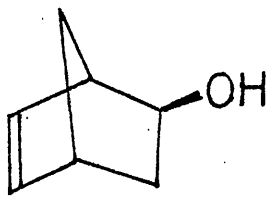
C 119



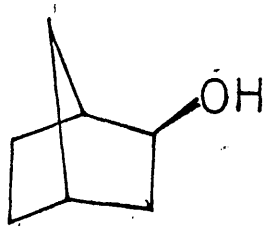
C 120

ALUMINA	C2	C121	C3	C4	C123	C6
Basic		19	16	57		8
Neutral	5	19	36	36		4
Acidic	5	17	37	19	7	15

Table V



C 121



C 122

EXPERIMENTAL

Isolation of Erythroxydiol Acetonides from the Acetonide Mixture.

For previous isolation see Ref. 81

Diol acetonide mixture (see page 83) (6.1 g.) was chromatographed on five preparative 1 m.m. silver nitrate (10%) - Kieselgel G meter plates in ethyl acetate-petrol (3:97). The chromatographed compounds were detected by iodine spray and extracted with chloroform. The most mobile fraction, diol X acetonide (C71) (3.3 g.) crystallised spontaneously, mixed m.p. 89-91°, $[\alpha]_D$ + 16° (c. 0.55). Crystallisation of the least mobile fraction afforded diol Y acetonide (C73) (823 mg.), mixed m.p. 143-145°; $[\alpha]_D$ + 81° (c. 0.41). An intermediate fraction afforded a small quantity of material (91 mg.) which on further purification yielded diol Z acetonide (C72) (65 mg.) mixed m.p. 107-109°, $[\alpha]_D$ -20° (c. 0.33) The n.m.r. spectra of these compounds were identical with those previously reported.[81]

Acid-Induced Isomerisation of Diol Z Acetonide (C72).

Diol Z acetonide (60 mg.) in a solution of chloroformic hydrogen chloride (10 ml.), saturated at 20° for

15 min., was kept at 20° for 8 hr. Work up by removal of solvent, was followed by treatment with anhydrous copper sulphate in acetone for 3 hr. at 20°. Filtration and removal of solvent furnished an olefinic residue, consisting of (by g.l.c. on 1% SE 30 at 175°) diol Z acetonide (C72) (5%), olefin (C75) (11%) and the $\Delta^{5(10)}$ olefin (C74) (84%). Silver nitrate - t.l.c. of this residue afforded the olefin (C74) (25 mg.) m.p. 105-109°, $[\alpha]_D$ + 78°, and identical n.m.r. spectrum to that reported.[81]

Dehydration of Erythroxytriol P Acetonide

See Section II, page 96

Acid-Induced Isomerisation of Olefin (C75)

See Section II, page 97

Acid-Induced Isomerisation of Erythroxydiol Y Acetonide (C73).

(a) Analytical Scale - Diol Y acetonide (C73) (60 mg.) was added to a solution (3 ml.) of chloroform that had been saturated with hydrogen chloride gas for 15 min. at 20°. Aliquots (0.5 ml.) were removed at intervals, taken to dryness, redissolved in AnalaR acetone (5 ml.)

and stirred with anhydrous copper sulphate (20 mg.) for 3 hr. Filtration and evaporation yielded olefin acetonide mixtures that were analysed on g.l.c. (on 1% SE 30 and 1% CHDMS at 175°). The results are illustrated in Table II.

(b) Preparative Scale - Diol Y acetonide (300 mg.) in a saturated hydrogen chloride solution (15 ml.) was kept at 20° for 2 hr. Half of this solution (7.5 ml.) was removed and worked up as above. This residue (121 mg.) was run twice on $AgNO_3$ - t.l.c. in ethyl acetate-petrol (3:97). The plate was sprayed with iodine, and the most intense band (Rf ~ 0.6) was extracted affording the olefin (C72) (33 mg.) which on crystallisation from methanol had m.p. and mixed m.p. 106-109, $[\alpha]_D$ - 20°. Similar work up of the remainder of the solution, after 30 hr., gave a residue (108 mg.) which chromatographed as above (Rf ~ 0.8) yielded the olefin (C74) (44 mg.), m.p. (from methanol) 108-110°, $[\alpha]_D$ + 82°

Acid-Induced Isomerisation of Diol X Acetonide (C71)

(a) Analytical Scale - Diol X acetonide (C71) (100 mg.) was added to a saturated solution of chloroformic hydrogen

chloride (10 ml.) and aliquots (0.5 ml.) were removed at intervals, worked up and analysed as before, affording the results depicted in Table III.

(b) Preparative Scale - Diol X acetonide (C71) (3.3 g.) was kept in a saturated hydrogen chloride solution (330ml.) at 20° for 8 hr. Removal of solvent, and replacement of acetonide function with anhydrous copper sulphate in AnalaR acetone as above, resulted in an oil (2.97 g.). Preparative $AgNO_3$ - t.l.c. in ethyl acetate-petrol (3:97), effected a separation of this residue into three fractions. The most mobile (1.1 g.) consisted (g.l.c.) of the olefins (C74) (57%) and (C78) 43%), next fraction (610 mg.) a mixture of the trisubstituted olefins, (C72) (25%), (C75) (41%) and (C78) (34%), and least mobile (95 mg.) of diol Y acetonide (C73).

Epoxidation of Diol Y Acetonide (C73)

Diol Y acetonide (C73) (300 mg.) in AnalaR chloroform (30 ml.) was treated with m-chloroperbenzoic acid (500 mg.) in chloroform (16 ml.) and kept at 20° for 24 hr. The solution was washed with water (3 x 50 ml.), sodium hydrogen carbonate solution, (3 x 50 ml.), water (3 x 50 ml.), dried over anhydrous sodium sulphate and the

solvent removed. The residue (350 mg.) was adsorbed on Grade H alumina (30 g.) deactivated with 5% of 10% acetic acid.

Elution with petroleum ether-benzene (20:3) afforded the β-epoxide (C81) (210 mg.) m.p. (from aqueous methanol) 95-96°, $[\alpha]_D$ + 75° (c. 0.67); $\nu_{max.}^{CCl_4}$ 3046 (epoxide protons), 865 (acetonide) cm.$^{-1}$; mass spectral peaks at m/e 362 (P), 347 (P-15), and 101 (acetonide residue); n.m.r. signals at 9.30, 9.13 8.92 (3H singlets; tertiary methyls), 8.70, 8.64 (3H singlets; acetonide methyls) 7.69, 7.24 (1H doublets, J = 4 c./sec.; epoxide protons) and 6.30 τ (3H multiplet; acetonide protons). (Found: C, 76.19; H, 10.35. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Continuing elution, petroleum ether-benzene (5:1) gave the α-epoxide (C80)(95 mg.), m.p. (from methanol) 122-124°, $[\alpha]_D$ + 37° (c. 1.46); $\nu_{max.}^{CCl_4}$ 3047 (epoxide proton) 865 (acetonide) cm.$^{-1}$ mass spectral peaks at 362 (P), 347 (P-15), and 101 ($C_5H_9O_2$); n.m.r. signals at 9.23, 9.10, 8.87 (3H singlets; tertiary methyls), 8.68, 8.62 (3H singlets; acetonide methyls), 7.61 (1H doublet; J = 4.5 c./sec.; epoxide proton), 6.94 (1H quartet; J = 4.5; 3.2 c./sec.; epoxide proton), and 6.26 τ (3H multiplet; acetonide protons), (Found: C, 76.21; H, 10.28. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Lithium Aluminium Hydride Reduction of Epoxide (C81).

Epoxide (C81) (45 mg.) was refluxed in dry ether (10 ml.) with lithium aluminium hydride (50 mg.) for 0.5 hr. Addition of saturated aqueous sodium sulphate and evaporation of solvent from the dried ethereal solution afforded the alcohol (C83) (38 mg.), m.p. (from aqueous methanol) 99-100°, $[\alpha]_D$ + 30° (c. 1.36); $\nu_{max.}^{CCl_4}$ 3628 (free hydroxyl), 862 (acetonide) cm.$^{-1}$; mass spectral peaks at 364 (P), 349 (P-15), 346 (P-18), 101 ($C_5H_9O_2$); n.m.r. signals at 9.27, 9.10, 9.04, 8.94 (3H singlets; tertiary methyls), 8.69, 8.63 (3H singlets; acetonide methyls), 6.30 (3H multiplet; acetonide protons), (Found: C, 76.17; H, 11.21. $C_{23}H_{40}O_3$ requires C, 75.77; H, 11.06%).

Lithium Aluminium Hydride Reduction of Epoxide (C80).

Epoxide (C80), was treated with lithium aluminium hydride (20 mg.), in dry ether (10 ml.) for 0.5 hr. at reflux. Working up in the usual way afforded, as sole product, the alcohol (C82) (18 mg.), m.p.)from aqueous methanol) 163-165°, $[\alpha]_D$ + 25° (c. 0.65); $\nu_{max.}^{CCl_4}$ 3621 (free hydroxyl) 865 (acetonide) cm.$^{-1}$; mass spectral peaks at 364 (P), 349 (P-15), 346 (P-18) and 101 ($C_5H_9O_2$); n.m.r. signals at 9.20, 9.15, 8.98, 8.89 (3H singlets; tertiary methyls) 8.70, 8.64 (3H singlets; acetonide methyls)

6.28 (3H multiplet; acetonide protons), (Found: C, 75.75; H, 11.14. $C_{23}H_{40}O_3$ requires C, 75.77; H, 11.06%).

Dehydration of Alcohols (C82) and (C83).

The alcohols (C82) and (C83), (5 mg.) were treated in turn with dry pyridine (1 ml.) and phosphorous oxychloride (10 drops) under reflux for 1 hr. The reaction mixtures were poured into water, and the respective products ether extracted, and compared with authentic diol Y acetonide (C73) and diol Z acetonide (C72) on g.l.c. (1% SE 30 at 175° with C_{20} and C_{24} n-hydrocarbons as standards) yielding the following results:-

Diol Y acetonide (C73); R_t 5.14 min. [R_t/R_t (C_{24}) 0.825].

Diol Z acetonide (C73); R_t 5.37 min. [R_t/R_t (C_{24}) 0.880].

Dehydration Product from Alcohol (C82); R_t 5.16 min. [R_t/R_t (C_{24}) 0.828].

Dehydration Product from Alcohol (C83); R_t 5.44 min. [R_t/R_t (C_{24}) 0.878].

The Nor-ketone (C91).

Diol Y acetonide (500 mg.) in AnalaR ethyl acetate (50 ml.) was ozonised at -70° for 2 hr. Reductive work up with zinc and acetic acid afforded one major product (t.l.c.). Crystallisation of this product (430 mg.) from

methanol furnished the nor-ketone acetonide (C91), m.p. 138-140°; $[\alpha]_D$ + 45° (c. 0.49); $\nu_{max.}^{CCl_4}$ 1710 (cyclohexanone), 863 (acetonide) cm.$^{-1}$; n.m.r. signals at 9.20, 9.12, 8.88 (3H singlets; tertiary methyls) 8.68, 8.62 (3H singlets; acetonide methyls) 7.85 (1H, broadened doublet; equatorial C-3H) 7.53 (1H multiplet; axial C-3H) and 6.26 τ (3H multiplet; acetonide protons), (Found: C, 75.7; H, 10.6. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%).

The 3,3-d_2-Nor-ketone (C89).

The nor-ketone (C91) (480 mg.) was dissolved in dry dioxan (8 ml.) and deuterium oxide (8 ml.). To this solution was added sodium (200 mg.) in small pieces under nitrogen, and the solution stirred for 1 hr. at 65° in a nitrogen atmosphere. The solvents were removed in vacuo, the residue extracted with dry ether (3 x 10 ml.), and the combined extracts washed with deuterium oxide (2 x 2 ml.), dried and the ether removed. The crystalline material was subjected to the above conditions once more. The product, the 3,3,-d_2-nor-ketone (C89) (468 mg.) had by mass spectrometry: 13% d_0, 18% d_1, 69% d_2. C-3 proton signals could not be detected in the n.m.r. spectrum of this material.

The 3β-d_1-nor ketone (C90)

A sample of the 3,3-d_2-nor-ketone (C89) (250 mg.) was dissolved in dioxan (5 ml.) and water (5 ml.) and, after the introduction of sodium (100 mg.) in small pieces, was stirred at 20° for 30 min. in a nitrogen atmosphere. Work up as above afforded the 3β-d_1-nor-ketone (C90) (231 mg.), which had by mass spectrometry: 22% d_0, 70% d_1, 8% d_2. In the n.m.r. spectrum, the reappearance of a low field multiplet at ~ τ 7.53, (acial C-3H) was observed.

The 3,3-d_2-Epoxide (C87)

Sodium hydride (50% mineral oil dispersion; 200 mg.) was placed in a three necked 25 ml. conical flask, and washed with light petroleum (3 x 5 ml.) by swirling and decanting the liquid portion. The system was evacuated at the water pump to remove residual traces of light petroleum. Perdeuterio-dimethylsulphoxide [$(CD_3)_2$ SO] (3 ml.) was added in a nitrogen atmosphere, and the flask with condenser, drying tube and rubber stopper set up stirring at 65° for 45 min. The perdeuterio-methylsulphinyl carbanion solution was cooled to 20°, diluted with dry tetrahydrofuran (5 ml.) and then cooled in a salt-ice bath. A compensated dropping funnel replaced the drying tube, and,

after the system had been evacuated and flushed several times with nitrogen, its contents - trimethylsulphonium iodide (500 mg.) in perdeuterio-dimethylsulphoxide (1.3 ml.)- were added with stirring over 3 min. After a further 1 min. stirring, the 3,3-d_2-nor-ketone (C89) (115 mg.) was introduced in tetrahydrofuran (1 ml.) by hypodermic syringe via the rubber stopper. Stirring was continued at ice-salt temperature for 0.5 hr. and then for 1 hr. at 20°.

The reaction mixture was diluted with water (10 ml.) and ether extracted (3 x 10 ml.). The combined ether extracts were washed with water (3 x 20 ml.), dried and the solvent removed. The residue (128 mg.), containing only epoxide product (t.l.c.), was chromatographed on Grade H alumina deactivated with 5% of 10% acetic acid. Elution with petroleum ether-benzene (20:3) afforded the 3,3-d_2-β-epoxide (78 mg.) and petroleum ether-benzene (5:1) yielded the desired 3,3-d_2-epoxide (C87) (26 mg.) with isotopic composition (by mass spectrometry): 15% d_0, 16% d_1, 44% d_2, 25% d_3; n.m.r. spectrum shows the epoxide proton at τ 6.94 as a doublet (J = 4.5 c./sec), which collapsed to a singlet by irradiation at 7.61 τ.

* the epoxide mentioned on page 143 was prepared by this method, with dimethylsulphoxide replacing perdeuterio -d,m,s.o.

The 3β-d_1- Epoxide (C88)

The method outlined above was repeated with the 3β-d_1-nor-ketone (C90) except that dimethylsulphoxide was used instead of the perdeuterio compound. Reagents: sodium hydride (400 mg.); dimethylsulphoxide (6 ml.); tetrahydrofuran (10 ml.); trimethylsulphonium iodide (1g.) in dimethylsulphoxide (3 ml.); and 3β-d_1-nor-ketone (200 mg.).

Work up as before and chromatography afforded, as well as the isomeric epoxide (123 mg.), the required 3β-d_1-epoxide (C88) (49 mg.) which had by mass spectrometry: 74% d_0, 26% d_1, 0% d_2; n.m.r. spectrum revealed the epoxide proton at τ 6.94 as a quartet (J = 4.5; 2.3 c./sec.).

Epoxidation of Diol Z Acetonide (C72)

Diol Z acetonide (C72) (50 mg.) in AnalaR chloroform (10 ml.) was treated with m-chloroperbenzoic acid (80 mg.) in chloroform (5 ml.) and kept at 20° for 24 hr. Usual work up afforded the β-epoxide (C92) (41 mg.), as the sole product, m.p. (from aqueous methanol) 116-118°; $[\alpha]_D$ + 22° (c. 0.91); $\nu_{max.}^{CCl_4}$ 861 (acetonide) cm.$^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.28, 9.08, 8.92, 8.80 (3H singlets; tertiary methyls), 8.66, 8.60 (3H singlets; acetonide methyls) 7.18 (1H triplet; J = 2 c./sec.) and 6.24 τ (3H multiplet; acetonide protons), (Found: C, 76.17; H, 10.47. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Lithium Aluminium Hydride Reduction of Epoxide (C92).

Epoxide (C92) (33 mg.) was refluxed with lithium aluminium hydride (60 mg.) in dry ether (10 ml.) for 45 min. Usual work up furnished product (18 mg.) which had from aqueous methanol, m.p. and mixed m.p. 97-99°, and was identical in all respects with the alcohol (C83) obtained above.

Epoxidation of Olefin Acetonide (C75)

The olefin (C75) (50 mg.) was epoxidised under conditions used for the olefin (C72), above. Usual work up afforded only one product, the epoxide (C93) (43 mg.) m.p. (from aqueous methanol) 91-92°, $[\alpha]_D$ + 8° (c. 0.59), $\nu_{max.}^{CCl_4}$ 856 (acetonide) cm.$^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.24, 9.13, 9.03, 8.85, (3H singlets; tertiary methyls) 8.60, 8.54 (3H singlets; acetonide methyls) 6.80 (1H triplet; J = 3 c./sec.; epoxide proton) and 6.20 τ (3H multiplet; acetonide protons); (Found: C, 76.02; H, 10.52. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Lithium Aluminium Hydride Reduction of Epoxide (C93)

On treatment of the epoxide (C93) (30 mg.) with lithium aluminium hydride (50 mg.) in ether (10 ml.) for

1 hr. at reflux, and after usual work up, only starting material was recovered. Under similar conditions with tetrahydrofuran as solvent, a crystalline alcohol (C94) m.p. (from petrol) 141-143° $[\alpha]_D$ + 29° (c. 0.81), was obtained, identical in all respects with erythroxytriol P acetonide (see Section II).

Epoxidation of Olefin Acetonide (C74)

The olefin (C74) (45 mg.) was epoxidised under the conditions used for olefin (C72), above. Usual work up afforded one epoxide (C95) m.p. (from aqueous methanol) 99-100°, $[\alpha]_D$ + 38° (c. 1.17); $\nu_{max.}^{CCl_4}$ 865 (acetonide) $cm.^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.11, 9.08, 9.02, 8.97 (3H singlets; tertiary methyls), 8.66, 8.60 (3H singlets; acetonide methyls) and 6.25 τ (3H multiplet; acetonide protons), (Found: C, 75.9; H, 10.7. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Attempted Lithium Aluminium Hydride Reduction of Epoxide (C95).

Only starting material was recovered when the epoxide (C95) was treated with lithium aluminium hydride at reflux in ether (3 hr.) or in tetrahydrofuran (8 hr.).

Epoxidation of Most Mobile Olefin Fraction (see page 197).

The most mobile olefin fraction (1.1 g.) in AnalaR chloroform (100 ml.), after addition of a solution of m-chloroperbenzoic acid (1.3 g.) in chloroform (30 ml.), was kept at 20° for 24 hr. The reaction mixture was washed with saturated sodium bicarbonate solution (3 x 100 ml.), water (3 x 100 ml.) dried over anhydrous sodium sulphate and the solvent removed, The residue (853 mg.) was adsorbed on Spence's grade H alumina (80 g.) deactivated with 5% of 10% acetic acid. Elution with benzene-petrol (3:20) afforded the epoxide (C96) (105 mg.) m.p. (from aqueous methanol) 68-70°, $[\alpha]_D$ + 37° (c. 0.34); $\nu_{max.}^{CCl_4}$ 867 (acetonide) $cm.^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.20, 9.14 (3H singlets; tertiary methyls) 9.17 (3H doublet; J = 6 c./sec.; secondary methyl), 8.70, 8.64 (3H singlets; acetonide methyls) and 6.30 (3H multiplet; acetonide protons). (Found: C, 76.21; H, 10.5. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%). Continuing elution with benzene-petrol (1:5) yielded the already isolated epoxide (C95) (421 mg.). Elution with benzene-petrol (1:4) gave the final component, the epoxide (C96) (230 mg.), m.p. (from methanol) 116-118°, $[\alpha]_D$ + 51° (c 0.81), $\nu_{max.}^{CCl_4}$ 860 (acetonide); mass spectral M.W. 362,

n.m.r. signals at 9.16, 9.09 (3H singlets; tertiary methyls) 9.11 (3H doublet; J = 6 c./sec.; secondary methyl), 8.68, 8.63 (3H singlets; acetonide methyls) and 6.30 τ (3H multiplet; acetonide protons). (Found: C, 76.05; H, 10.54. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Epoxidation of the Trisubstituted Olefin Fraction (see page 197).

This trisubstituted olefin fraction (610 mg.) was epoxidised under conditions used above, and after work up, the residue (563 mg.) was adsorbed on deactivated alumina. Elution with benzene-petrol (1:10) gave the epoxide (C93) (180 mg.), and the same solvent mixture (3:20), the epoxide (C92) 130 mg.). Further elution with benzene-petrol (1:5) afforded the epoxide (C99) (160 mg.) m.p. (from methanol) 128-130°, $[\alpha]_D$ + 7° (c. 0.56); $\nu_{max.}^{CCl_4}$ 857 (acetonide) cm.$^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.28, 9.06 (3H singlets; tertiary methyls), 9.00 (3H doublet; J = 6 c./sec.; decoupled by irradiation at 8.33 τ) 8.58, 8.52 (3H singlets; acetonide methyls) 7.07 (1H broadened singlet; epoxide proton; decoupled by irradiation at 8.68 τ) and 6.20 τ (3H multiplet; acetonide protons). (Found: C, 75.9; H, 10.41. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%).

Reaction of Epoxide (C81) with Boron Trifluoride

(a) Short reaction - Epoxide (C81) (150 mg.) was dissolved in benzene (15 ml.) and born trifluoride etherate (0.6 ml.) added. After 15 min. at 20°, the reaction was quenched with sodium bicarbonate solution and ether extracted. The residue was dissolved in AnalaR acetone (10 ml.) and stirred with anhydrous copper sulphate for 2 hr. Filtration through celite and evaporation of solvent gave a residue (98 mg.), from which was isolated by preparative t.l.c. one major component, more polar than starting material, the unsaturated alcohol (C101)(63 mg.) as an oil, $\nu_{max.}^{CCl_4}$ 3636 (free hydroxyl) and 857 (acetonide) $cm.^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.15, 9.11, 9.08 (3H singlets; tertiary methyls) 8.66, 8.60 (3H singlets; acetonide methyls) 6.84, 6.39 (2H doublets; J = 10.5 c./sec.; $-CH_2-OH$) and 6.20 τ (3H multiplet; acetonide proton), (Found: C, 76.0; H, 10.58. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%), as well as less polar material, which was made up of four components, one major, by g.l.c. and $AgNO_3$ - tlc.

(b) Long reaction - After similar reaction of the epoxide (C81) for 5 hr. the only product was the less polar material mentioned above. Attempted separation of the four

components by preparative $AgNO_3$ - t.l.c. with cold oxygen-free chloroform extraction resulted in decomposition. The mixture, had one major compound present (~80%) and had $\lambda_{max.}$ 246 mμ (ε = 8,500); n.m.r. signals at 8.05 (~3H singlet; vinylic methyl) at 4.5 τ (multiplet; approximate weight one proton; olefinic proton). Typical acetonide resonances were also present.

Correlation of Alcohol (C101) with Olefin (C74)

The alcohol (C101) (10 mg.) in dry pyridine (1 ml.) at 0° was added to a solution of tosyl chloride (20 mg.) in dry pyridine at 0°. The reaction mixture was kept at 0° for 1 hr. and then at 20° overnight. The solution was poured on to ice and ether extracted, yielding a residue which (t.l.c.) consisted of starting material and one slightly less polar product. This residue (8 mg.) with lithium aluminium hydride was refluxed for 3 hr. in tetrahydrofuran (5 ml.). Usual work up afforded a mixture of starting material and one very much less polar compound. This latter material was isolated by t.l.c. and shown to be homogeneous and identical with the olefin (C74) by g.l.c. (1% SE 30 at 175°).

Reaction of Epoxide (C80) with Boron Trifluoride

(a) Short time - Epoxide (C80) was reacted under identical conditions to those used for epoxide (C81). A complex reaction mixture (78 mg.) was obtained, from which was isolated by preparative t.l.c., starting material (35 mg.), a slightly less polar, comparatively unstable compound (C103) (10 mg.), $\nu_{max.}^{CCl_4}$ 1725 (aldehydic carbonyl) cm.$^{-1}$; mass spectral peaks at 362 (P), 361 (P-1), 101 ($C_5H_9O_2$); and giving a positive reaction with D.N.P. spray. Also isolated was the unsaturated alcohol (C101) (15 mg.) and a non-polar fraction (6 mg.) identical (t.l.c. and g.l.c.) with that obtained above.

(b) Long reaction - The epoxide (C80) under the longer reaction conditions (5 hr.) afforded a similar reaction product.

Reaction of Epoxide (C81) with Alumina)

The epoxide (C81) (100 mg.) was stirred with basic grade I Woelm alumina (2 g.) in benzene (5 ml.) for 8 hr. Filtration, followed by washing of the alumina with methanol-chloroform (1:1), and removal of solvent afforded an oil (88 mg.), consisting of three components that could be conveniently separated by preparative t.l.c. (15%

ethyl acetate-petrol) yielding the olefin acetonide (C108) (20 mg.) as a colourless oil, n.m.r. signals at 9.40, 9.08 (3H singlets; tertiary methyls), 8.68, 8.62 (3H singlets; acetonide methyls), 8.39 (3H singlet; vinylic methyl) and 6.23 τ (3H multiplet; acetonide protons). (Found: M.W. 332, $C_{22}H_{36}O_2$ requires 332), the unsaturated alcohol (C106) (33 mg.), as a colourless oil, $\nu_{max.}^{CCl_4}$ 3632 (free hydroxyl) 860 (acetonide) $cm.^{-1}$; mass spectral M.W. 362; n.m.r. signals at 9.33, 9.10, 8.95 (3H singlets; tertiary methyls), 8.64, 8.58 (3H singlets; acetonide methyls), 6.86, 6.36, (1H doublets; J = 10.2 c./sec.; proton at 6.36 τ further coupled J = 2.5 c./sec.; $-C\underline{H}_2-OH$), 6.18 (3H multiplet; acetonide protons) and 4.38 τ (1H multiplet; olefinic proton). (Found: C, 76.05; H, 10.80. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.57%), and the hydroxy olefin (C107) (22 mg.), as an oil, $\nu_{max.}^{CCl_4}$ 3622 (free hydroxyl) 858 (acetonide) $cm.^{-1}$, mass spectral M.W. 362; n.m.r. signals at 9.24, 9.18, 8.92 (3H singlets; tertiary methyls) 8.65, 8.59 (3H singlets; acetonide methyls) 6.20 (3H multiplet; acetonide protons) 5.90 (2H broadened singlet; $-C\underline{H}_2OH$) and 4.42 τ (1H multiplet; olefinic proton), (Found: C, 75.94; H, 10.71. $C_{23}H_{38}O_2$ requires C, 76.19; H, 10.57%).

Attempted Correlation of Alcohol (C106) with Olefin (C75)

Tosylation of the unsaturated alcohol (C106) under the conditions used for alcohol (C101) resulted only in the recovery of starting material and olefin (C108).

Reaction of Alcohols (C106) and (C107) with Alumina

Alcohol (C106) (10 mg.) in benzene (1 ml.) was stirred with basic grade I alumina for 8 hr. Work up afforded the olefin (C108) (6 mg.) from preparative t.l.c. The alcohol (C107) (10 mg.) was recovered unchanged under these conditions.

Manganese Dioxide Oxidation of Alcohol (C107)

The alcohol (C107) (8 mg.) in AnalaR chloroform (4 ml.) and active manganese dioxide (50 mg.) was shaken at 20° for three days. Reaction mixture was filtered, solvent removed and purification by t.l.c. afforded the aldehyde (C109) (5 mg.), $\nu_{max.}^{CCl_4}$ 2740, 1688 (unsaturated aldehyde function) 1628 (C=C) and 875 (acetonide) $cm.^{-1}$, $\lambda_{max.}^{EtOH}$ 231 mμ (ε 11,500).

Reaction of Epoxide (C95) with Alumina

The epoxide (C95) (100 mg.) in benzene (5 ml.) was stirred with grade I basic alumina (2g) for 8 hr. Usual work up furnished, as sole product, the heteroannular

diene (C110) (76 mg.) m.p. (from methanol) 92-93°, $[\alpha]_D$ - 110° (c. 0.48); $\lambda_{max.}^{EtOH}$ 240 mμ (ε 14,600), (s) 233 mμ, (s) 247 mμ; mass spectral M.W. 344; n.m.r. signals at 9.24, 9.12, 9.07, 8.93 (3H singlets; tertiary methyls) 8.62, 8.57 (3H singlets; acetonide methyls) 6.16 (3H multiplet; acetonide protons) and 4.47 τ (2H multiplet; olefinic protons), (Found: C, 80.15; H, 10.50. $C_{23}H_{36}O_2$ requires C, 80.18; H, 10.53%).

Reactions of Epoxide (C95)

(a) Epoxide (C95) (10 mg.) was left standing at 20° for 12 hr. in a solution of 1N potassium t-butoxide in t-butanol (2 ml.). The solution was acidified and the product ether extracted. Starting material (~ 80%) was recovered along with the diene (C110).

(b) Epoxide (C95) (10 mg.) was treated with the boron trifluoride conditions previously outlined for 2 hr. Starting material was consumed and the only identifiable product was the diene (C110).

(c) Epoxide (C95) (10 mg.) in AnalaR acetone (0.4 ml.) containing perchloric acid (0.4 ml.; 1.54 s.g.) was left at 20° for 1 hr. The solution was diluted with water and ether extracted. The residue (7 mg.) crystallised from methanol and had m.p. and mixed m.p. 90-92° with diene (C110).

Reaction of Erythroxytriol P Acetonide with Alumina

Triol P acetonide (C94) (5 mg.) in benzene (1 ml.) and grade I basic alumina (300 mg.) was stirred at 20° for 16 hr. Working up in the usual way gave a reaction product consisting of starting material (85%) and a sole dehydration product (15%) identical on g.l.c. (1% SE 30 and 1% CHDMS at 175°) with the previously obtained olefin acetonide (C75).

Reaction of Epoxide (C93) with Alumina

Epoxide (C93) (100 mg.) was treated under identical alumina conditions to those used on epoxide (C95). Preparative t.l.c. (15% ethyl acetate-petrol) furnished the already characterised diene (C110) (12 mg.), starting material (46 mg.), ketone (C113) (27 mg.) m.p. (from methanol) 138-140°, $\nu_{max.}^{CCl_4}$ 1715 (carbonyl) 860 (acetonide) $cm.^{-1}$; n.m.r. signals at 9.12, 9.08, 8.93 and 8.89 (3H singlets; tertiary methyls) 8.67, 8.60 (3H singlets; acetonide methyls) and 6.24 τ (3H multiplet; acetonide protons), and traces of two compounds of alcohol polarity.

Reaction of the 3β-Acetoxy-5α,6α-Epoxy-5α-Cholestane C11 with Alumina

The epoxide (C 11) (150 mg.) was stirred with basic grade I alumina (3 g.) in dry benzene (10 ml.) at 20° for

48 hr. Work up by filtration, and evaporation of solvent afforded a mixture (t.l.c.) that could be conveniently resolved into its components by preparative t.l.c. (15% EtOAc/petrol). Starting material was recovered in 25% yield. The major product (45%) was the allylic alcohol (C118) (67 mg.) m.p. (from aqueous methanol) 141-143°, $[\alpha]_D$ -23° (c. 0.57); $\nu_{max.}^{CCl_4}$ 3620 (free hydroxyl), 3020 (olefinic protons), 1735 and 1245 (acetate) cm.$^{-1}$; n.m.r. signals at 8.03 (3H singlet; $C\underline{H}_3$-CO_2-), 4.83 (1H multiplet; C<u>H</u>-OAc) and 4.42 τ (2H multiplet; olefinic protons), (Found: C, 78.04; H, 10.7. $C_{29}H_{58}O_3$ requires C, 78.32; H, 10.88%). The minor products from the reaction were identified as the triol monoacetate (C119) (7 mg.) m.p. (from ether/petrol) 207.5-209°, $[\alpha]_D$ - 17° (c. 0.46); $\nu_{max.}^{CCl_4}$ 3630, 3595 (free hydroxyls), 1734 and 1245 (acetate) cm.$^{-1}$, and cholesterol α-oxide (C120) (14 mg.) m.p. (from petrol) 141-142°, $[\alpha]_D$ -47° (c. 0.63); $\nu_{max.}^{CCl_4}$ 3620 (free hydroxyl) cm.$^{-1}$.

Epoxidation of Norbornene

A chloroform solution (150 ml.) with m-chloroperbenzoic acid (10.3 g.) was added slowly to solid norbornene (5 g.) producing a strongly exothermic reaction. The addition was completed with cooling and the resulting

solution kept at 0° for 48 hr. The reaction mixture was washed with 4N sodium hydroxide solution (3 x 200 ml.), water (3 x 200 ml.), dried and the chloroform removed by distillation at atmospheric pressure. Atmospheric sublimation of the crude product (4 g.) at 150-158° gave exo-2,3-epoxynorbornene (C1), m.p. (from hexane) 121-125° homogeneous on g.l.c. [10% APL at 75° and 20% 1,2,3-tris-(2-cyano)-ethoxypropane at 100°] n.m.r. signals at 9.32 (1H doublet; J = 10 c./sec.; H-7 syn proton), 7.57 (2H broadened singlet; H-1 and H-4) and 6.96 τ (2H singlet; epoxide protons; H-2 and H-3).

Reaction of Norbonene Oxide (C1) with Alumina

(a) Pilot reactions - Small scale reactions with norbornene oxide (100 mg.) and grade I alumina (1) basic, (2) neutral and (3) acidic were carried out in turn with stirring in pentane (3 ml.) for 20 hr. at 20°. After filtration the reaction mixtures were examined on g.l.c. [1,2,3-tris-(2-cyano)-ethoxypropane at 100°] revealing the presence of four, five and six compounds respectively, as shown in Table V.

(b) Preparative alumina reaction - Norbornene oxide (1g.) was stirred with grade I neutral alumina (100 mg.) in pentane (100 ml.) for 48 hr. at 20°. Work up as before, followed by atmospheric distillation of excess pentane, afforded an oily residue (923 mg.) which had (g.l.c.) five components.

Separation of this mixture was achieved by preparative g.l.c. on a 25% 1,2,3-tris-(2-cyano)-ethoxypropane column at 150° yielding 3-cyclohexene-1-carboxaldehyde (C2), as a volatile oil, $\nu_{max.}^{CCl_4}$ 3030 (olefinic protons), 2705 and 1732 (aldehydic function) and 1651 (C=C) cm.$^{-1}$; (Found: M.W. 110; $C_7H_{10}O$ requires 110), exo-norbornenol (C121), as a colourless soild, $\nu_{max.}^{CCl_4}$ 3575 (free hydroxyl), 3060 (olefinic protons) and 1640 (C=C) cm.$^{-1}$; n.m.r. signals at 9.10 (1H doublet; J = 7 c./sec.; one of C-7 protons) 7.26 (2H broadened singlet, bridgehead protons, 6.24 (1H broadened singlet; >C<u>H</u>-OH) and 3.92 (2H broadened singlet; olefinic protons), (Found: M.W. 110; $C_7H_{10}O$ requires 110, norcamphor (C3) as a white solid; $\nu_{max.}^{CCl_4}$ 1755 (carbonyl) cm.$^{-1}$, (Found: M.W.110; $C_7H_{10}O$ requires 110); nortricyclanol (C4), as a white solid, m.p. 106-109°, $\nu_{max.}^{CCl_4}$ 3622 (free hydroxyl), 3060 (cyclopropyl protons) cm.$^{-1}$, n.m.r. signals at 7.93 (1H singlet;

-OH) and 6.18 (1H broadened singlet; >CHOH), (Found: M.W. 110. $C_7H_{10}O$ requires 110), and 3-cyclohexene-1-methanol (C6) as a colourless oil, $\nu_{max.}^{CCl_4}$ 3638 (free -OH) and 3022 (olefinic protons) $cm.^{-1}$; n.m.r. signals at 8.47 (1H singlet; -OH) 6.41 (2H doublet; J = 5 c./sec.; $-CH_2OH$) and 4.24 τ (2H broadened singlet; olefinic protons). (Found: M.W. 112, $C_7H_{12}O$ requires 112).

When norbornene oxide (C1) was isomerised on grade I acidic alumina, a mixtures resulted consisting of these five products together with another unidentified component, which was not separable from nortricyanol on preparative g.l.c.

Sodium Borohydride Reduction or Norcamphor (C3).

Norcamphor (C3) (100 mg.) and sodium borohydride (200 mg.) were kept in aqueous methanol (1:19; 20 ml.) at 20° for 5 hr. Dilution with water and ether extraction afforded an oil, consisting of two components by g.l.c., exo-norbornanol (C122) (82%) and the endo isomer (18%).

Hydrogenation of Exo-Norbornenol (C121)

The hydroxy olefin (C121) (20 mg.) in ethyl acetate (5 ml.) was hydrogenated over 10% palladium charcoal

(80 mg.) in a microhydrogenator for 2 hr. The reaction mixture was filtered, and the product analysed on g.l.c. which revealed starting material (15%) and one other compound (85%) identical with exo-norbornanol (C122).

REFERENCES

1. A. Wurtz, Compt. rend., 1859, 48, 101.
2. V. Ipatieff and V. Leontovitch, Ber., 1903, 36, 2016.
3. M.O.Robeson and R.A. Springer, U.S.Pat., 2,660,609.
4. G.W. Fowler and J.T. Fitzpatrick, U.S.Pat., 2,426,264.
5. L.G. Lunsted and E.C. Jacobs, U.S. Pat., 2,479,632.
6. E.C. Jacobs and L.G. Lunsted, U.S. Pat., 2,600,654; 2,600,655.
7. J.K. Crandell, J. Org. Chem., 1964, 29, 2830.
8. G. Büchi and E.M. Burgess, J.Amer.Chem.Soc., 1962, 84, 3104.
9. E.P. Kohler, N.K. Richtmeyer and W.R. Hester, J. Amer. Chem. Soc., 1931, 53, 205.
10. R. Pointet, Compt. rend., 1909, 148, 417.
11. M. Tiffeneau and J. Levey, Anales. soc. quim.argentina, 1928, 16, 144.
12. E. Troell, Ber., 1928, 61, 2497.
13. V.I. Pansevich-Kolyada, Chem. Abs., 1956, 50, 8584.
14. V.I. Pansevich-Kolyada and V.A. Ablova, Chem. Abs., 1955, 6173.
15. E.G.E. Hawkins, J.Chem.Soc., 1955, 3288.
16. H.O. House and R.L. Wasson, J. Amer. Chem. Soc., 1956, 78, 4394.

17. A.L. Droper, W.J. Heilman, W.E. Schaefer, H.J. Shine and J.N. Shoolery, J. Org. Chem., 1962, 27, 2727.

18. (a) M.S. Newman and B.J. Magerlein, Org. Reactions, Vol. V., p. 413-440, John Wiley and Sons, Inc., New York, 1949.

(b) M. Ballister, Chem. Rev., 1955, 55, 283.

19. I. Heilbron, A.W. Johnson, E.R.H. Jones and A. Spinks, J. Chem. Soc., 1942, 727.

20. O. Isler, W. Huber, A. Ronco and M. Kofler, Helv. Chim. Acta., 1947, 30, 1911.

21. N.A. Milas, S.W. Lee, E. Sakal, H.C. Wohlers, N.S. MacDonald, F.X. Grossi and H.F. Wright, J. Amer. Chem. Soc., 1948, 70, 1584.

22. E.C. Komfeld, E.J. Fornefeld, G.B. Kline, M.J. Mann, D.E. Morrison, R.G. Jones and R.B. Woodward, J. Amer. Chem. Soc., 1956, 78, 3087.

23. A. Weissberger, Heterocyclic Compounds with three and four membered Rings, Part I, Interscience, John Wiley and Sons, Inc., 1964.

24. H.B. Henbest and T.I. Wrigley, J.Chem.Soc., 1957, 4596, 4765.

25. H.O. House and D.J. Reif, J.Amer.Chem.Soc., 1954, 76, 1235; 1955, 77, 6525.

26. D.J. Goldsmith, J. Org. Chem., 1962, 27, 3913.

27. A.Bowers, L.C. Ibanez and H.J. Ringold, Tetrahedron, 1959, 7, 138.

28. M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1964,20,559.

29. T.G. Halsall, A.W. Oxford and W. Rigby, Chem. Comm., 1965, 218.

30. H.O. House and R.L. Wasson, J. Amer. Chem. Soc., 1957, 79, 1488.

31. D.J. Collins, J. Chem. Soc., 1959, 3919.

32. J.M. Coxon, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1964, 20, 2351.

33. J.M. Coxon, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1964, 20, 2547

34. J.M. Coxon, M.P. Hartshorn and D.N. Kirk, Aust. J. Chem., 1965, 18, 759.

35. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1965, 21, 559.

36. M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1965,21, 1547.

37. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 1966, 2125.

38. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Chem. Comm., 1965, 545.

39. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1966, 22, 1421.

40. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Chem. Comm., 1966, 160.

41. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1966, 22, 3195.

42. M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 1966, 3913.

43. J.W. Blunt, J.M. Coxon, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1967, 23, 1811.

44. J.M. Coxon, M.P. Hartshorn and D.N. Kirk, Tetrahedron, 1967, 23, 3511.

45. T.G. Halsall, E.R.H. Jones, E.L. Tan and G.R. Chaudhry, J.Chem.Soc., 1966 (C), 1374.

46. D.J. Goldsmith, J.Amer.Chem.Soc., 1962, 84, 3913.

47. E. E. van Tamelen and B. Pappas, J.Amer.Chem.Soc., 1963, 85, 3295.

48. E.E. van Tamelen and R.M. Coates, Chem.Comm., 1966,413.

49. E.E. van Tamelen, M.A. Schwartz, E.J. Hessler and A. Storni, Chem. Comm., 1966, 409.

50. E.E. van Tamelen and R.G. Nadeau, J. Amer. Chem. Soc., 1967, 89, 176.

51. E.E. van Tamelen and E.J.Hesler, Chem.Comm., 1966, 411.

52. E.J. Corey, W.E. Russey and P.R. Ortiz de Montellano, J. Amer. Chem. Soc., 1966, 88, 4750.

53. E.E. van Tamelen, J.D. Willett, R.B. Clayton and K.E. Lond, J. Amer. Chem. Soc., 1966, 88, 4752.

54. W.G.H. Lake and S. Peat, J.Chem.Soc., 1939, 1069.

55. W. Baker and R. Robinson, J.Chem.Soc., 1932, 1798.

56. C.J. Collins and O.K. Neville, J. Amer.Chem.Soc., 1951, 73, 2471.

57. E.C. Hendley and O.K. Neville, J.Amer.Chem.Soc., 1953, 75, 1995.

58. O.K. Neville, J. Amer. Chem. Soc., 1948, 70, 3499.

59. H.H. Wasserman and M.J. Gorbunoff, J. Amer. Chem. Soc., 1958, 80, 4568.

60. A.C. Cope and B.D. Tiffany, J. Amer. Chem. Soc., 1951, 73, 4158.

61. A.C. Cope, G.A. Berchtold, P.E. Peterson and S.H. Sharman, J. Amer. Chem. Soc., 1960, 82, 6366.

62. C.C.J. Culvenor, W. Davies and W.E. Savige, J. Chem. Soc., 1949, 2198.

63. R.L. Letsinger, J.G. Traynham and E. Bobko, J. Amer. Chem. Soc., 1952, 74, 399.

64. W. Rave and L.W. Fine, J.Amer.Chem.Soc., 1964, 86, 880.

65. D.F. Hoeg, J.E. Forrette and D.I. Luck,
Tetrahedron Letters, 1964, 2059.

66. J. Bornstein, M.A. Joseph and J.E. Shields,
J. Org. Chem., 1965, 30, 801.

67. M. Mousseron, R. Richard, R. Granger, F. Winternitz,
G. Combes, E. Canals, L. Souche and P. Froger,
Bull. soc. chim., France, 1946, 629.

68. H.H. Wasserman and M.J. Gorbunoff,
J. Amer. Chem. Soc., 1958, 80, 4568

69. E.C. Kornfeld, E.J. Fornefeld, M.J. Mann, . .
D.E. Morrison, R.G. Jones and R.W. Woodward,
J. Amer. Chem. Soc., 1956, 78, 3087.

70. D.H.R. Barton and P. de Mayo, Quart. Rev., 1957,11,189.

71. J. Meinwald and O.L. Chapman, Tetrahedron, 1958, 3,311;
J. Amer. Chem. Soc., 1959, 81, 5800.

72. J. Meinwald, H. Nozaki and G.A. Wiley,
J. Amer. Chem. Soc., 1957, 79, 5579.

73. W. Hückel and L. Schnitzpahn, Annalen, 1933, 505, 274.

74. K. Schenker and V. Prelog,
Helv. Chim.Acta., 1953, 36, 896.

75. A.C. Cope, H.H. Lee and H.E. Petree,
J. Amer. Chem. Soc., 1958, 80, 2849.

76. A.C. Cope, M. Brwon and H.H. Lee,
J. Amer. Chem. Soc., 1958, 80, 2855.

77. A.C. Cope, M.M. Martin and M.A. McKeney,
Quart. Rev., 1966, XX, 119.

78. A.C. Cope, G. A. Berchtold, P.E. Peterson and
S.H. Sharman, J.Amer.Chem.Soc., 1960, 82, 6370.

79. J.K. Crandall and Luan-Ho Chang,.
J. Org. Chem., 1967, 32, 435; 532.

80. J.D. Connolly, R. McCrindle. R.D.H. Murray and
K.H. Overton, Tetrahedron Letters, 1964, 1859.

81. J.D. Connolly, R. McCrindle, R.D.H. Murray,
A.J. Renfrew, K.H. Overton and A. Melera,
J. Chem. Soc., 1966 (C), 268.

82. (a) J. Meinwald and A. Lewis,
J. Amer. Chem. Soc., 1961, 83, 2769.
(b) A. Rassat, C.W. Jefford, J.M. Lehn and
B. Waegell, Tetrahedron Letters, 1964, 233.

83. S. Sternhell, Rev. Pure and Applied Chem., 1964,14,15.

84. G. Chatier, A. Rassat and A. Rousseau,
Bull. soc. chim., France, 1966, 428.

85. M. Moriarty, H. Gopal, H.G. Walsh, K.C. Ramey
and D.C. Lini, Tetrahedron Letters, 1966, 4555.

86. E. Payo, L. Cortes, J. Monteconi and C. Riesmanti,
J. Org. Chem., 1966, 31, 1888.

87. C.A. Reilly and J.D. Swalen, J.Chem.Phys., 1961, 35, 1522.

88. D.D. Elleman, S.L. Manatt and C.D. Pearce, J. Chem. Phys., 1965, 42, 650.

89. (a) N.S. Bhacca and D.H. Williams, Applications of N.M.R. Spectroscopy in Organic Chemistry, Holden-Day, Inc., 1964 Chapter 4.
(b) N.S. Bhacca, J.E. Gurst and D.H. Williams, J. Amer. Chem. Soc., 1965, 87, 302.

90. (a) D.H. Williams, J.M. Wilson, H. Budzikiewicz and C. Djerassi, J.Amer.Chem.Soc., 1963, 85, 2091.
(b) E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, 1962, p. 241.

91. A. Nickon and J.L. Lambert, J. Amer. Chem. Soc., 1962, 84, 4604.

92. A. Nickon, J.H. Hammons, J.L. Lambert and R.O.Williams, J. Amer. Chem. Soc., 1963, 85, 3713.

93. E.J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 1965, 87, 1353.

94. C.E. Cook, R.C. Corley and M.E. Wall, Tetrahedron Letters, 1965, 891.

95. J.D. Connolly, D.M. Gunn, R. McCrindle, R.D.H. Murray and K.H. Overton, J. Chem. Soc., 1967 (C), 668.

96. G. Ferguson, J.W.B. Fulke and R. McCrindle, Chem. Comm., 1966, 691.

97. M.C. Dawson, T.G. Halsall and R.E.H. Swayne, J. Chem. Soc., 1953, 590.

98. L.F. Fieser and M. Fieser, Steroids, Reinhold, N.Y., 1959.

99. K. Watanabe, C.N. Pillai and H. Pines, J. Amer. Chem. Soc., 1962, 84, 3934.

STUDIES IN NATURAL PRODUCT CHEMISTRY.

By Donald M. Gunn.

SUMMARY

This thesis entitled "Studies in Natural Product Chemistry" can be divided into three distinct sections.

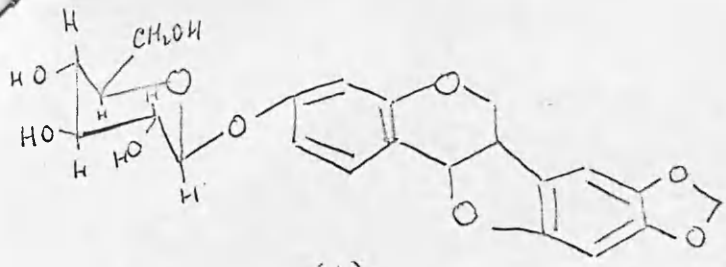
Section I deals with the structural elucidation of two glycosides, isolated from the acetylated Ononis spinosa L. root extract. These compounds were identified as the tetra-acetates of inermin 7-β-D-glucoside (1) and homoinermin 7-β-D-glucoside (2), on the basis of spectroscopic evidence and by enzymatic hydrolysis of their corresponding free glucosides. The discussion of these glucoside acetates is prefaced by a brief review of the naturally occurring pterocarpans, and a discussion of their probable biogenesis.

Section II is concerned with the structural elucidation of the diterpenoids, erythroxytriol P (3) and erythroxytriol Q acetate (4), which occur in the heartwood of Erythroxylon monogynum Roxb. Their structures are suggested on the basis of spectroscopic and chemical evidence. During this study, ozonolysis of diol X acetonide (5) was shown to lead to the formation of an α-cyclopropyl ketone and unexpectedly to an α-ketol. The discussion is preceded by a review of relevant

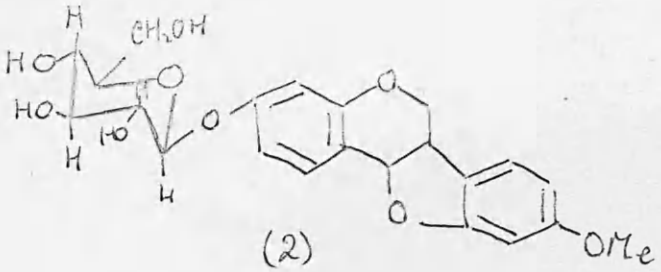
diterpene biogenesis.

The third section commences with a review of epoxide isomerisation, with special reference to acid-induced (boron trifluoride) and base-induced isomerisations. The subsequent discussion describes the acid-induced isomerisations of erythroxydiol acetonides X and Y (5 and 6), and preparation and characterisation of the epoxides from the derived olefins. The final part of this section deals with the effect of boron trifluoride and alkaline grade I alumina on these and other epoxides. Under acid catalysis, diterpenoid epoxides with and without the supposedly ideal sterical requirements for concerted "backbone" rearrangement were compared, with a view to elucidating further the factors involved in such rearrangements. These results were contrasted with those obtained from alkaline alumina treatment. The acid-base catalytic action of alumina did not effect "backbone" rearrangement in the steroidal system, but where β-elimination was inhibited carbene insertion products could be obtained.

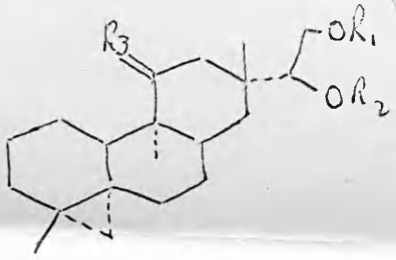
The α-epoxide (7) derived from erythroxydiol Y acetonide showed an unusual ^{4}J coupling involving an epoxide proton. The other interacting proton involved was shown to be the axial C-3 proton by deuteration experiments on the nor-ketone (8) followed by reaction of these deuterated ketones with the Corey methylide reagent to afford specifically deuterated α-epoxides.

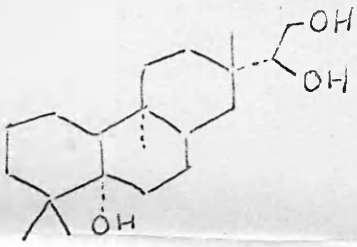


(1)



(2)

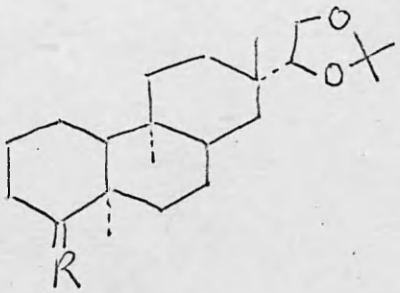


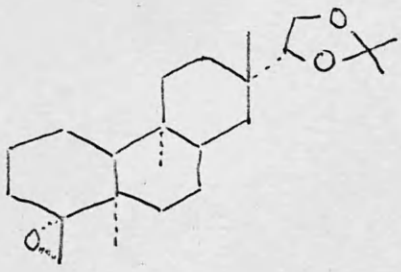


(3)

(4) $R_1 = R_2 = H$; $R_3 = \alpha OH, \beta H$.

(5) $R_1 + R_2 = Me_2C{=}$; $R_3 = H_2$





(7)

(6) $R = CH_2$

(8) $R = O$