STUDIES IN THE TERPENOID FIELD.

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Margaret Stewart Henderson.

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CHAPTER I.

INTRODUCTION

The diterpenoid lactone, marrubiin (1), a bitter
principle of the White horehound (Marrubium vulgare L)
was first isolated in 1842 by Mein and, sent to Harms[1] for
investigation. It was later examined by Kroymeyer[2],
Hertel[3], Morrison[4], and Matusow[5] all of whom employed
different methods for the isolation of the compound.
Matusow's method, using acetone as solvent, was found to
be the most convenient for extraction on a large scale.
This method was further improved upon by Gordin[6] who
obtained marrubiin m.p. 154-155° after repeated
crystallisations from alcohol. However it was not
obtained in a high state of purity until 1932[7].

The chemistry of marrubiin was first examined by
Gordin[6] who proposed the formula $C_{21}H_{28}O_4$ from analytical
data. Gordin recognised that marrubiin contained a
lactone since on hydrolysis a monobasic acid was formed
which he called marrubic acid (2a). This acid was found
to be reconverted into marrubiin either on heating in
vacuo or on treatment with alcoholic hydrochloric acid.

No further work on the constitution of marrubiin was
done until 1939 when two groups of workers, Hollis,
Richards and Robertson[8] and Lawson and Eustice[9]
independently found that their analytical results and
molecular weight determinations were in agreement with
the formula $C_{20}H_{28}O_4$ rather than $C_{21}H_{28}O_4$ as previously

suggested. Determination of active hydrogen indicated
that marrubiin contained one hydroxyl group and since the
compound did not form any acyl derivatives under the
usual conditions it was concluded that it was tertiary.
Treatment with the dehydrating agents, thionyl chloride or
phosphorus trichloride afforded anhydromarrubiin (3a).
The remaining oxygen atom was unreactive and was assumed
to be present in an ether linkage. That marrubiin
contains two double bonds was shown by the fact that it
could be hydrogenated over platinum black in acetic acid
to give a tetrahydro-derivative. When ethyl acetate was
used as solvent no hydrogenation took place and these
findings suggested to Lawson and Eustice that the double
bonds must be present in the cyclic part of the structure.
Dehydrogenation with selenium gave a good yield of
1, 2 , 5 trimethylnaphthalene (4) and from this it was
concluded that marrubiin is a hydroxy diterpene lactone
of the manoyl oxide (5), sclareol (6) type. On the basis
of these findings and the isoprene rule Lawson and Eustice
proposed the part structure (7) for marrubiin.
Marrubiin, however, differed from the manoyl oxide type
of diterpene in that no tricyclic derivatives could be
formed.

In 1947 Ghigi[10] began work on the chemistry of
marrubiin and found that oxidation with chromium trioxide
in acetic acid gave a neutral compound m.p. 162°
analysing for $C_{17}H_{22}O_4$ which could be hydrolysed by base
to an acid $C_{17}H_{24}O_5$ m.p. 222°.

Neither of these degradation products gave a positive tetra-nitromethane test, indicating that the three carbon atoms eliminated in the first stage of the oxidation are those which carry the double bonds. This was confirmed by Cocker[11] and his co-workers who corrected the formula of the oxidation product from $C_{17}H_{22}O_4$ to $C_{17}H_{24}O_4$. Since both double bonds and the inert ethereal oxygen were lost these results are best accomodated by cleavage of a furan ring. The infra red and ultra violet absorption maxima and colour reactions of marrubiin reinforced this conclusion. An absorption at 1740 cm^{-1} in the i.r. was assumed to be due to a γ-lactone. The C_{17} acid obtained from hydrolysis of the oxidation product displayed no furan absorption and lacked the tertiary hydroxyl band. However it showed a strong carbonyl band characteristic of a butanolide indicating that the oxidation product was a dilactone. From these results Cocker tentatively suggested the formulae (8) or (9).

However, when Hardy and Rigby[12] studied the i.r. spectrum of marrubiin they found a band at 1780 cm^{-1} characteristic of a γ-lactone. Ghigi's C_{17} compound showed only one carbonyl frequency, at 1778 cm^{-1}, corresponding to two γ-lactone groups, the original γ-lactone and one derived from degradation of the side chain. It was then realised that the tertiary hydroxyl must be in the γ position with respect to the point of attachment of the furan ring, since it readily undergoes lactonisation with the carboxyl group derived by cleavage

of the furan. Ozonolysis of anhydromarrubiin gave a keto
lactone $C_{14}H_{20}O_3$ in which the entire side chain was
removed. The i.r. spectrum of this compound showed that
the original γ-lactone was present along with a six
membered ring ketone. Further, since the hydroxy acid
obtained by hydrolysis did not readily lose carbon dioxide
it was not a β-keto acid. Consequently, of the three
possible positions C-4, C-8 and C-10[13] for the attachment
of the carboxyl group to the bicyclic nucleus, the last
two must be excluded and thus the carboxyl group of this
compound and of marrubic acid must be at C-4. Since
marrubiin was known to be a γ-lactone C-2 and C-6 are
the only possible positions of attachment of the oxygen
atom. Methyl marrubate (2*b*) on chromic acid oxidation
lost three carbon atoms with concomitant formation of the
γ-lactone and oxidation of the hydroxyl (derived from
hydrolysis of the original lactone) to a ketone. This
keto acid (10) was cyclised with acetic anhydride to an
enol-lactone which could have been either (11) or (12).
The product reacted rapidly with bromine and potassium
permanganate and on hydrogenation was reduced to a
saturated acid in keeping with an enol-lactone formulation.
A structure in which the ether oxygen was attached to C-2
could be ruled out since formation the enol lactone (13)
would be an infringement of Bredt's rule. That the enol
lactone (11) was the correct structure was shown by
ozonolysis which afforded an aldehyde (positive Schiff
and Tollen's tests).

The reactions of marrubiin were compatible with its formulation as (1) but no correlation with known compounds had been made until Burn and Rigby[14] succeeded in converting it into a known degradation product (14) of ambrein. The starting material for this conversion was the enol-lactone (11) which on hydrogenation gave the acid (15a). Treatment of this acid with thionyl chloride followed by Rosenmund reduction furnished the aldehyde (15b) which on Huang-Minlon reduction gave the compound (15c). This was identical with one of the isoambreinolides prepared by Collin-Asselineau[15] by the action of 70% sulphuric acid on ambreinolide (14). However the major product of the reduction was the unsaturated acid (16) which had also been prepared from ambreinolide.

The structure of marrubiin having been determined work began on the elucidation of its stereochemistry. The stereochemistry shown in (17) was proposed by Cocker[16] who based his arguments on Klyne's molecular rotation studies of diterpenes. Marrubiin was converted by a sequence of reactions which could not affect the stereochemistry of the A/B ring junction into (18) and the shift in molecular rotation studied. This suggested a trans A/B junction and an equatorial environment for the lactone carbonyl group. According to these authors the stability of the lactone in the keto-lactone (19) could only be explained if the carbonyl group and the oxygen atom had a diequatorial arrangement since otherwise the lactone would be impossibly strained.

The C-8 methyl group in the keto-lactone (19) and
therefore in marrubiin was assumed to be in the stable
equatorial conformation since it was not epimerised by
boiling in alkali and since it was formed from marrubiin
under conditions unlikely to epimerise this centre.
Further, since dehydration of marrubiin afforded a
compound with an exocyclic double bond this was taken as
evidence for an equatorial hydroxyl group. On further
study of the rotational data for the configuration at
C-6 Cocker[17] modified the stereochemical assignments to
that shown in (20) with lactone ring β oriented at both
points of attachment to the skeleton. Wheeler,[18] on the
other hand, on the basis of some preliminary reduction
studies proposed that the lactone was ∝ , ∝ fused.

Burn and Rigby[14] criticised Cocker's arguments,
rejecting as inadequate the reasoning used for
positions 4, 6, 8 and 9. Rigby's work on the conversion
of marrubiin into an isoambreinolide showed that the
C-10 angular methyl was β and axial and suggested that
the ring junction was trans (later confirmed by O.R.D.
studies). This co-relation with isoambreinolide prompted
the conclusion that a knowledge of the stereochemistry at
C-8 and C-9 in this lactone would allow the assignment
of stereochemistry at these centres in marrubiin.

Recently, during work on the stereochemistry of
grindelic acid (21), Mangoni[19] was able to prepare the
lactone and deduce the stereochemistry at these centres.

The hydroxy-ketone (22) derived from sclareol (6) by
permanganate oxidation was converted into the unsaturated
ketone (23) by teatment with iodine in benzene.
Oxidation of this compound with perphthalic acid gave the
epoxy-acid (24). Subsequent hydrolysis resulted in the
formation of two crystalline lactones (25) and (26) due to
the trans diaxial opening of the epoxide followed by
lactonisation. That the two lactones (25) and (26) had
identical configurations at C-8 and C-9 was confirmed by
the transformation of (25) into (26) by hydrolysis
followed by acidification. Reaction of (26) with thionyl
chloride in pyridine gave the unsaturated lactone (27).
The double bond was shown to be endocyclic from
spectroscopic evidence. Since under these conditions no
exocyclic olefin was formed it was taken as evidence that
the C-8 hydroxyl was axial and thus assuming the two
hydroxyl groups to be trans diaxially related the one at
C-9 must be α oriented. The reaction of osmium
tetroxide[15] with the unsaturated acid (16) gave as the
sole product a hydroxy-lactone (28) which was then
dehydrated with thionyl chloride in pyridine to afford
the unsaturated lactone (29), the exomethylene grouping
being clearly visible in the n.m.r. spectrum. Since
dehydration took place exo to the ring the C-8 hydroxyl
group must have been equatorial. Catalytic reduction of
(27) furnished a mixture of two saturated lactones,
epimeric at C-8. The most abundant product, which was
identical to the γ -lactone obtained by isomerisation of

ambreinolide-was-assigned-the structure (15C) with the

C-8 methyl group β since hydrogenation was assumed to

take place from the less hindered α -face of the molecule.

Hydrogenation of the lactone (29) however produced (30)

as the major product which differed considerably from

(15C) in its physical properties. As a result of these

findings it was claimed that marrubiin has a β oriented

C-9 side chain and a ¢ -oriented C-8 methyl group.

However it has since been pointed out [20,21] that it is

impossible to predict with any certainty which face of the

molecule is more accessible to hydrogenation and therefore

the assignment of stereochemistry at C-8 in marrubiin on

the basis of the above arguments was invalid. In a later

paper Mangoni[22] modified the stereochemistry at this

centre to that having the methyl group in an α -

orientation.

A synthetic route to marrubiin proposed by Moody[23]

was based on the conversion of the keto-ester (31) via

the diene-lactone (32) to the keto-lactone (19) which can

be derived from anhydromarrubiin (3a) or

anhydrotetrahydromarrubiin (33) by ozonolysis. This

scheme had to be abandoned because the intermediates

underwent unexpectedly facile rearrangements. Attempted

alkylation of the keto-lactone (19) with Grignard

reagents and lithium alkyls gave no adducts but sodium

acetylide gave a 40% yield of the ethynol (34). The

structure of this compound was confirmed by hydrogenation

over Adams catalyst to (35).

Attempted carboxylation of the sodio derivative of the ethynol gave neither a crystalline product nor the starting material.

Marrubium vulgare is the main source of marrubiin but it has also been isolated[24] from Ballota foetida. More recently Rivett[25] has isolated it from Leonotis leonuris R. Br. along with two related compounds. Despite its close relationship botanically to Marrubium vulgare a Yugoslavian sample of M. incanum was found[26] to contain very little marrubiin. The main constituent of this plant was a crystalline substance $C_{20}H_{26}O_5$ whose physical properties corresponded to those reported for peregrinine a compound isolated[27] from M. peregrinum. That this diterpene was 3-keto-marrubiin (36) was shown by its conversion into the olefin (37) which on catalytic hydrogenation afforded marrubiin.

DISCUSSION

The Stereochemistry of Marrubiin.

Since only the stereochemistry at C-5[14,17] C-9[19] and C-10[14,17] appeared acceptable a spectroscopic study of marrubiin derivatives was undertaken in order to determine the stereochemistry at the remaining asymmetric carbon atoms.

That the δ -lactone function was β , β fused to the skeleton was deduced from a study of the n.m.r. spectra of marrubiin (1), tetrahydromarrubiin (38) and the ether (39). In these compounds the C-6 proton resonates at 5.25, 5.28 and 5.85 τ respectively as an ill-resolved triplet with a multiplet width of 10-14 c./sec. In marrubenol (2C), marrubanol (40a) and the monoacetate (2d) this proton resonates* as a broad singlet ($W_{\frac{1}{2}}$ = 6-8 c/sec.) at 5.78 , 5.78 and 5.66 τ respectively. The narrowness of these resonances is diagnostic of an equatorial proton at C-6 since C-5 and C-7 both carry an axial proton, the proton at C-6 displaying a band width compatible with one equatorial-equatorial and two axial-equatorial spin-spin couplings. The substituent at C-6 in marrubiin and the derivatives discussed above is* therefore axial (β).

Convincing evidence for the stereochemistry at C-4 was less readily obtainable. Normally with diterpenoids, n.m.r. shift values[29] for the protons in the functional groups $-CH_2OAc$, $-CH_2OH$ and $-CHO$ and/or pK^*_{MCS} measurements[30] for the corresponding carboxylic acid

allow the assignment of stereochemistry to oxygenated methyl groups at C-4. In the present case, when utilising compounds[*] readily derivable from marrubiin such data did not accord with either a normal axial or equatorial group. Thus the pK^*_{MCS} of marrubic acid (2a) and tetrahydro-marrubic acid (40b) were[31] below the values expected for either an axial or equatorial carboxyl group. N.m.r. studies were also of little use in distinguishing between the two possible orientations of attachment of the lactone ring to C-4. In the keto-aldehyde (2f) the aldehydic proton appears as a barely resolved doublet (separation lc./sec.) at -0.42 τ a value considerably lower than that expected[29] for either an axial (0.2 τ approximately) or an equatorial (0.7 τ approximately) aldehyde group at C-4. This downfield shift is caused by the carbonyl group at C-6. A similar shift was apparent in the spectrum of the keto acetate (2e) which shows a quartet (J = 12 c./sec.) centred at 5.32 τ which conforms[26] with neither an axial (5.70 - 5.90 τ) nor an equatorial (6.15 - 6.35 τ) primary acetate group at C-4.

[*]FOOTNOTE:-   Preliminary studies on the stereochemistry
                of marrubiin were carried out by
                Dr. J. W. B. Fulke[28].

In the monoacetate (2d) this methylene group appears as a quartet (J=12 c./sec.) at 5.44 τ, the downfield shift being induced by the C-6 axial hydroxy group. In this case the chemical shift would appear to be better rationalised as derived from an axial rather than an equatorial primary acetate group. Reasoning on these lines, however, led only to tentative conclusions and to resolve the problem the oxygen function at C-6 was removed by the following sequence.[14]

Hydrogenation of anhydromarrubiin (3a) in ethanol over Adams catalyst afforded the desoxytetrahydrolactone (42) $C_{20}H_{32}O_3$, m.p. 94-95°. Treatment of this lactone with potassium hydroxide in cellosolve and careful acidification furnished the corresponding hydroxy acid (41a) $C_{20}H_{34}O_4$, m.p. 224-226° which was oxidised to the keto acid (41b) $C_{20}H_{32}O_4$ m.p. 170-172° with Sarett's reagent. The keto-acid was converted into the unstable enol lactone (43) with refluxing acetic anhydride containing a large excess of fused sodium acetate. No spectroscopic evidence for the position of the double bond in this compound was available since it rapidly decomposed into the keto-acid during the work-up procedure. However it was assumed to be a Δ^6 rather than a Δ^5 double bond by analogy with related compounds.[17,20] Catalytic hydrogenation of this last compound (containing the keto-acid as an impurity) in acetic acid over 10% Pd-C gave as the more polar product the acid $C_{20}H_{34}O_3$, (41c) m.p. 99-101° produced by

hydrogenolysis of the vinylic oxygen atom and saturation of the double bond. The desoxy-lactone (42) was obtained as the other component, identified by direct comparison with an authentic sample. The presence of this compound can be explained in terms of the hydrogenation of the keto-acid from the α face of the molecule to form the hydroxy-acid (41a) which would rapidly lactonise under the acidic reaction conditions.

Methylation of the acid (41c) followed by lithium aluminium hydride reduction gave the primary alcohol (41d) which shows an AB quartet at 6.41 τ (2H, C-19). The corresponding acetate (41e) and the unstable oily aldehyde (41f) were prepared and a study of their n.m.r. spectra (5.90 τ; -C$\underline{H}_2$OAc in (41e) : 0.14 τ; -C$\underline{H}$O in (41f)) reinforced our conclusions concerning the axial nature of the C-4 functional group.

Similar results were obtained[28] for the series with the C-9 hydroxyl group present. Thus the oily monoacetate (40c) derived from the alcohol (40d) shows in the n.m.r. a quartet (J= 11 c./sec.) centred on 5.93 τ (-C$\underline{H}_2$OAc) a value which is acceptable[26] for an axial primary acetate at C-4. Furthermore oxidation of the alcohol (40d) with chromium trioxide in pyridine provided the unstable oily aldehyde (40e) the n.m.r. of which shows a resonance at 0.14 τ (1H singlet) as expected[26] for a C-4 axial aldehyde group.

The orientation of the lactone ring in marrubiin as cis and β has been advanced[17] but then refuted[18].

The validity of the β cis orientation, assigned in this discussion mainly on spectroscopic grounds gains some confirmation from chemical evidence. Thus (a) the ease of formation of marrubiin (1) from[32,14], marrubic acid and the ether (39) on attempted[28] p-bromo-benzenesulphonation of marrubenol (2c) would be rationalised since in each case a 1,3 diaxial non-bonded interaction is being removed; (b) the observation[14] that the olefin (44) is obtained in appreciable yield (approximately 50%) from treatment of the hydroxy acid (45) with toluene-p-sulphonyl chloride-pyridine would indicate a smooth trans-diaxial (5 ;6) elimination of toluene-p-sulphonic acid from the intermediate ester; (c) the secondary hydroxy group in marrubenol (2c) is fairly resistant to acetylation, the product of acetylation under mild conditions being the mono-acetate (2d) which is however readily oxidised to the keto-acetate (2e) i.e. reactivity typical of an axial secondary alcohol.

The assignment of stereochemistry at C-8 based on the evidence presented below involves the assumption that the compounds discussed have ring B in the chair (or half chair) conformation. The major factor liable to lead to a preference for a ring B boat conformation would be the 1,3 diaxial interaction between a C-8 β methyl group and the C-10 β methyl group. However from models it seems likely that downward rotation of C-8 would eventually produce even more severe steric interactions. Assuming a ring B chair conformation it would be expected[33] that if the secondary methyl group at C-8 were axial, the

conversion of the mono-acetate (2d) into the keto-acetate (2e) would produce an upfield shift of about 15 - 20c./sec. for the resonances of the C-8 and C-10 methyl groups. Although the observed upfield shift (22 c./sec.) of the necessarily axial C-10 methyl group does indeed accord reasonably well with expectation, the secondary methyl group at C-8 suffers a downfield shift (3.5c/sec.) and is therefore probably equatorial (α). The resonances of the C-4 and C-10 methyl groups in the keto-acetate were identified by recording its n.m.r. spectra after progressive additions of benzene to a deuterochloroform solution and application of the "plane rule".[34] In the original spectrum the methyl groups appear at 8.94 (s) (3H, C-18), 8.97 (d) (3H, C-17 ; J = 6.5 c./sec.) and 9.09 τ (s) (3H , C-20) and shift progressively in benzene to a final value of 8.76, 9.34 and 9.29 τ respectively i.e. $\Delta \, C_6 H_6^{CDCl_3}$ -0.18, +0.37 and 0.20 p.p.m.

The products of dehydration of marrubiin with a large excess of phosphoryl chloride in pyridine at reflux for five hours reinforce this conclusion. Substantial quantities (approximately 90%) of marrubiin can be recovered even after treatment with a large excess of warm (60°) phosphoryl chloride-pyridine for two hours.

On the assumption of a β (axial) orientation for the hydrogen atom at C-8 the β (equatorial) orientation for the C-9 hydroxy group was originally[35] suggested very tentatively with the proviso that the slow rate of

dehydration might be due to the steric exclusion of reagents rather than an unfavourable orientation for trans diaxial elimination. Indeed Mangoni's[19] work on grindelic acid (21) presents convincing evidence for the assignment of the α configuration for the C-9 oxygen atom in this compound and in marrubiin. However a careful n.m.r. study of the phosphoryl chloride – pyridine dehydration product (forcing conditions-see later) suggests that the mixture consists of two compounds, namely $\Delta^{8(9)}$ olefin (46) (70%) and its $\Delta^{9(11)}$ isomer (3a) (30%). Formation of a substantial proportion of the product with an endo olefinic bond probably indicates the presence of an 8 β - H and a 9 β -OH group. These configurational assignments gain further support from the conversion (albeit in low yield) of ambreinolide (14) into isoambreinolide (15c) which is also derivable from marrubiin. The isomerisation of ambreinolide can be effected by treatment with sulphuric acid[15] probably via the unsaturated acid (16) protonation at C-8 and relactonisation at C-9 being expected to proceed in a trans diaxial fashion to furnish an equatorial methyl group at C-8 and an equatorial side chain at C-9.

Similar conclusions concerning the stereochemistry at these centres were arrived at independently by Wheeler[21] who based his arguments on reduction studies. Sodium borohydride and lithium in liquid ammonia reduction of the tetrahydro keto-acid (40f) both rather surprisingly gave tetrahydromarrubic acid (40b).

Treatment of the keto-acid (40a) with borohydride

afforded marrubic acid (2a) while the use of lithium-

liquid ammonia produced a mixture of narrubic acid (2a)
epimer
and its C-6/(47). Lithium aluminium hydride reduction

of the ester (2h) followed by acetylation afforded

marrubenol diacetate (2i) whereas treatment with lithium

liquid ammonia formed the isomeric triol (48) isolated

as its diacetate (49). A study of the spectroscopic

properties of these compounds supported the

stereochemistry shown in (1) for marrubiin.

Hydrogenation of Marrubiin and its derivatives.

Previous workers have described the catalytic

hydrogenation of marrubiin. Using platinum black in

acetic acid Lawson and Eustice[9] obtained tetra-

hydromarrubiin (38) m.p. 134° whereas the use[36] of acetic

acid containing both 10% Pd-C and Adams catalyst

furnishes, in addition to the tetrahydro derivative (60%)

m.p. $123-5^{\circ}$, two hexahydro compounds (40%) (50a, 50d)

which had m.p. 80° and 154°. These compounds were

separated by crystallisation but no evidence was

advanced which would allow the correct choice between the

alternative assignments. These compounds are derived

from the different modes of opening of the furan ring.

When marrubiin is hydrogenated over 10% Pd-BaSO$_4$ as

catalyst in either ethanol[25] or acetic acid[37] only tetra-

hydromarrubiin is formed. Since hydrogenation can take

place from both sides of the furan ring there arises the

possibility of the two epimers being formed. The great variations in the reported melting points of tetra-hydromarrubiin (38) led Boyle[37] to separate these isomers (epimeric at C-13). He ultimately obtained the two tetrahydro compounds m.p. 139° and 116°.

In our hands hydrogenation of marrubiin in ethanol over Adams catalyst yielded, in addition to the compounds previously described, the desoxy compound* $C_{20}H_{34}O_3$ (50c) m.p. 88-89°. This compound is the product of complete hydrogenolysis of the furan ring. The oily hydrogenation mixture was separated into its components by careful column chromatography over acidic alumina, complete separation of the two hexahydro compounds requiring repeated preparative thin layer chromatography.

The less polar compound* failed to crystallise and was characterised as its acetate (50b) $C_{22}H_{36}O_5$ m.p. 121-123° while the more polar* had m.p. 150-152°. The former* displays in its n.m.r. spectrum an ill-resolved doublet at 6.44 τ (2H-16 ; $W\frac{1}{2} = 6$ c./sec.) due to the CH -C$\underline{H}_2$ -OH group. On acetylation the resonance of these protons moves downfield and appears as a doublet at 6.06 τ (2H-16 ; $J = 6$ c./sec.). Hexahydromarrubiin A* can thus be formulated as (50a). Hexahydromarrubiin B*, on the

FOOTNOTE:- This and later compounds marked with an asterisk were presumably epimeric mixtures at C-13 but no attempt was made to separate the individual components.

other hand, shows a triplet at 6.32 τ (2H-15 ; J = 6
c./sec.) due to the CH_2 - CH_2 - OH group and therefore
can be represented as in (50d).

The least polar hydrogenation product, the desoxy
compound* (50c) shows in its n.m.r. spectrum the typical
C-6 ill-resolved triplet at 5.35 τ (J = 6 c./sec.) as
the only absorption below 7.5 τ . A singlet at 8.76
integrating for six protons is attributable to the C-18
and C-20 tertiary methyl groups while signals from the
secondary methyl groups appear as doublets at 9.05
(J = 5 c./sec.) and 9.12 τ (J = 5 c./sec.). The
primary methyl group in the saturated side chain gives
rise to a triplet at 9.10 τ (J = 5 c./sec.).

Anhydronarrubiin (3a) on hydrogenation under
similar conditions gave the corresponding desoxy series
of compounds, namely the waxy bisdesoxy compound* (51a)
$C_{20}H_{34}O_2$, desoxyhexahydronarrubiin A* (51b) $C_{20}H_{34}O_3$ m.p.
96-97°, desoxyhexahydronarrubiin B* (51d) $C_{20}H_{34}O_3$, m.p.
86-88° and desoxytetrahydronarrubiin* (42) $C_{20}H_{32}O_3$, m.p.
94-95°.

The resonance of the C-6 lactone proton in the
bisdesoxy compound* appears as two overlapping triplets
centred on 5.17 τ (J = 5 c./sec.) and 5.25 τ (J= 5
c./sec.) while in the desoxy tetrahydro compound*(42)
it appears as a broad multiplet at 5.22
($W_{\frac{1}{2}}$ = 16 c./sec.). The methyl signals in this compound
are observed at 8.74 τ (s) 9.04 τ (s) and 8.94 τ (d).

The two desoxy hexahydro derivatives* were eluted
together as a waxy solid but after separation by
preparative t.l.c. both crystallised. The less polar of
the two, desoxyhexahydromarrubiin A* displays a doublet
at 6.48 τ (2H-16 ; J = 4 c./sec.) due to the CH - CH$_2$ - OH
group while the more polar exhibits a triplet at
6.38 τ (2H - 15 ; J = 6 c./sec.) due to the CH$_2$ - CH$_2$ - OH
group. This therefore allows the assignment of
constitutions (51b) and (51d) respectively to the two
compounds. Both hexahydro derivatives were treated with
acetic anhydride in pyridine but the products failed to
crystallise. The n.m.r. of acetate A* (51c) shows a
doublet at 6.05 τ (2H-16 ; J = 4 c./sec.) while that of
acetate B* (51e) has a triplet at 5.90 τ (2H - 15 ;
J = 6 c./sec.).

Dehydration of Marrubiin

Previous workers have treated marrubiin with the
dehydrating agents thionyl chloride[9] or phosphorus
trichloride[9,36] in benzene and have reported only one
crystalline product, anhydromarrubiin (3a). This result
was taken as evidence[16] supporting an equatorial
assignment for the C - 9 hydroxyl group since the
hydrogen atom at C - 8 is axially oriented. However it
was pointed out[14] that this conclusion was unsound since
the yield (maximum 40%) of crystalline anhydromarrubiin
was so small. The dehydration of marrubiin with
phosphorus trichloride in refluxing benzene was repeated
and in our hands it was found that the n.m.r. of the

total oily product, after removal of traces of polar
material by chromatography, was identical even in detail
with that of crystalline anhydromarrubiin. The
difficulty experienced in recovering even moderate yields
of crystalline material from the oily product may be due
to one or both of the following. (a) Both geometric
isomers (3a, 3b) are produced in the dehydration and only
one is crystalline. This explanation is unsatisfactory
in that the product appears homogeneous on the basis of
both t.l.c. and n.m.r. behaviour. (b) Anhydromarrubiin
will not crystallise from moist solvent. This appears
more acceptable since crystallisation of the product
from dry methanol gives appreciably higher yields (63%)
of crystalline material than those reported and also the
m.p. of this material falls rapidly on exposure to
atmospheric moisture (95 - 96° to 56 - 58°in five hours).

Since dehydration exo to the ring takes place
exclusively and the 8 - H and 9 - OH are both axially
oriented then it is suggested that under these conditions
dehydration is cisoid and possibly proceeds by a cyclic
mechanism for otherwise it is difficult to rationalise
the fact that no endo elimination is observed. The first
stage of the reaction with phosphorus trichloride in
neutral solution is the formation of an alkyl
phosphorodichloridate[38] (52) which can then proceed
through a five membered ring transition state (see 53)
to the unsaturated dehydration product. The formation of
an exocyclic double bond in anhydromarrubiin produces a

substituted allylic group in the molecule. Such a
system has a form of steric hindrance associated with it.[39]
If one examines a model of anhydronarrubiin with ring B
in a chair conformation (54) it is seen that the C - 11
side chain and the C - 8 equatorial methyl group will
interfere with each other drastically. Relief of this
strain (known as $\Lambda^{(1,3)}$ strain since it arises from
substituents on the 1 and 3 positions of an allylic
system) can be attained most easily by conformational
inversion to the boat form. That $\Lambda^{(1,3)}$ strain has indeed
been relieved by a downward displacement of C - 8 and a
consequent upward rotation of C-7 producing a quasi -
boat ring B conformation (55) can be seen from a careful
study of the n.m.r. spectrum of anhydronarrubiin. All
other narrubiin derivatives containing the C - 4, C - 6
lactone ring show a collapsed triplet in their n.m.r.
spectra at about 5.30 τ attributable to H-6. In
anhydronarrubiin however this resonance is shifted
downfield to 4.97 τ and has a much wider spread (sextet;
$J_{H-5, H-6} = 5$ and $J_{H-6, 2H-7} = 8$ c./sec.). The dihedral
angles between the protons at C-5, C-6, C-7 and C-8 in the
boat form would be expected to result in spin - spin
coupling constants of approximately the magnitude found
(see figure 1).

Under conditions which are known to lead to transoid
elimination, phosphorus trichloride or phosphorus
oxychloride in pyridine, the major product is the endo-
olefin (46) as would be expected since H - 8 and the

C - 9 hydroxyl group are both axial. The oily mixtures
obtained ran as one symmetrical spot on thin layer
chromatography and no separation could be effected either
on silica gel or on silica gel impregnated with silver
nitrate. However an estimate of the compositions of the
mixtures was made on the basis of their n.m.r. spectra.
Careful integration of the resonance of the β - furan
proton versus that of the H - 6 plus H - 11 protons gave
a ratio of nearly exactly 1 : 2 for anhydronarrubiin but
1 : 1.3 for the reaction with phosphorus oxychloride -
pyridine and 1 : 1.25 for that with phosphorus trichloride-
pyridine. The proportion of olefins (46) : (3a)
present was therefore approximately 7 : 3 and 3 : 1
respectively. In an attempted partial separation of these
isomers the phosphoryl chloride - pyridine product was
subjected to preparative t.l.c. The resulting apparently
homogeneous band was halved with respect to polarity and
the two extracts subjected to analysis by n.m.r. However
their composition appeared to be almost identical
(see table [1]). Furthermore treatment of this mixture
with dry hydrogen chloride in chloroform produced very
little isomerisation (n.m.r. evidence). The possibility
of rearrangement of a first formed $\Delta^{9(11)}$ olefin into
its $\Delta^{8(9)}$ isomer under the dehydration conditions
was considered. However, anhydronarrubiin m.p. 95 - 96°
(reported[9] value 98°) was recovered apparently unchanged
(as seen from its n.m.r. spectrum) from treatment with
phosphoryl chloride in moist pyridine at reflux.

Tetrahydromarrubiin (38) on treatment with phosphorus
trichloride in refluxing benzene afforded the
corresponding anhydro compound (33) m.p. 124° which in
its n.m.r. spectrum exhibits a sextet at 5.00 τ ($W_{\frac{1}{2}}$ =
18 c./sec.) from the C-6 proton. However reaction with
redistilled phosphoryl chloride in dry refluxing pyridine
failed to give the mixture of endo and exo olefins as
expected by analogy with marrubiin. This reaction was
repeated several times under varying conditions but in
no case could any product be isolated.

Further Constituents of Marrubium vulgare

An acetone extract of the whole horehound plant was
partially separated into its components by column
chromatography over alumina. The early fractions
contained the hydrocarbon waxes described by Burn and
Rigby[14]. Marrubiin was eluted next along with
chlorophyll and after several crystallisations from
ethyl acetate - light petroleum was obtained as
colourless needles m.p. 159 - 160°. Two further
compounds were eluted and ultimately separated by
repeated preparative thin layer chromatography.

The less polar compound (56a) was obtained as a
dark coloured oil which could not be induced to
crystallise and as a result no satisfactory analysis
figures were obtained. A mass spectrometric molecular
weight determination corresponded to a molecular formula
of $C_{20}H_{30}O_5$. In keeping with its chromatographic
polarity the compound contains a hydroxyl group as seen

from the frequencies at 3610 and 3530 cm^{-1} in its i.r.

spectrum. The peak at 1760 cm^{-1} indicated that the

γ-lactone group of marrubiin was also present (1778

cm^{-1} in marrubiin). None of the characteristic furan

peaks were present and this suggested that the main

difference between marrubiin and this compound lay in the

nature of the side chain.

These findings were confirmed by a study of its n.m.r.

spectrum. The C-6 proton appears as the typical ill-

resolved triplet at 5.30 τ with a multiplet width of

10 c./sec. (5.25 τ ; J = 6 c./sec. in marrubiin). The

signals from the proton adjacent to the hydroxyl group

appear as broad singlets at 4.38 τ ($\frac{1}{3}$ H) and 4.56 τ ($\frac{2}{3}$ H),

at lower field than expected for a secondary hydroxyl

group suggesting a hemi-acetal hydroxyl, later confirmed

by its chemical behaviour. The two protons on the carbon

atom adjacent to the ethereal hemi-acetal oxygen give

rise to a very diffuse multiplet at 5.7 - 6.4 τ . The

fifth oxygen atom could not be detected by spectroscopic

methods and was assumed to be present as an ether linkage

(cf the diether (57) from Solidago canadensis)[40]. Methyl

groups give rise to resonances at 8.66 τ (singlet ;

tertiary methyl), 8.87 τ (broad singlet ; tertiary

methyl) and 9.04 τ (doublet ; J = 6 c./sec., secondary

methyl).

This compound was readily oxidised with Sarett's[41]

reagent to the corresponding crystalline dilactone (56b)

$C_{20}H_{28}O_5$, m.p. 179-185°, $[\alpha]_D$ + 9°. In the i.r. there

are carbonyl frequencies, at 1797 and 1778 cm^{-1}. The
latter corresponds to the original γ lactone, the former
to the lactone formed by oxidation of the hemi-acetal ring,
the high value being caused by the oxygen atom attached to
the β carbon atom. The n.m.r. spectrum exhibits signals
from one secondary (9.05 τ; 3H) and two tertiary (8.86
and 8.63 τ, 3H each) methyl groups. Also apparent, in
addition to the triplet at 5.28 τ due to the C-6 proton
are two diffuse quartets, one centred at 5.68 τ (2H-16 ;
J=10 c./sec.) and the other at 7.28 τ (2H-14 ; J = 17 c./
sec.). The diffuse nature of these quartets is
explicable in terms of a C-13 epimeric mixture. The
dilactone can thus be formulated as (56b) and the parent
alcohol as (56a). The n.m.r. spectra of these compounds
suggested that the hemi-acetal is in fact a mixture of
epimers at one or more centres (C-13 and C-15 ?).

It is of interest that Rivett[25] has isolated from
<u>Leonotis leonuris</u>, marrubiin and one of the epimers of
the dilactone. In an attempt to separate these dilactone
isomers the mixture was subjected to repeated t.l.c. over
the greater length of a 20 X 500 cm plate. The resulting
apparently homogeneous band was quartered with respect to
polarity. All four extracts were crystallised from ethyl
acetate - light petroleum and had, from least polar through to
most polar, m.p. 211 - 214°, 183 - 184°, 180 - 182°,
179 - 182° respectively. The first extract was
recrystallised and had m.p. 225 - 230°. Direct
comparison of this isomer with an authentic sample of the

dilactone from Leonotis leonuris revealed that the two

compounds were in fact identical (see Experimental

section).

Firm support for the conclusions concerning the

constitution of the hemi-acetal came from its rapid

conversion into marrubiin. This was carried out by

heating the compound with toluene-p-sulphonyl chloride

in pyridine. The marrubiin thus obtained was

identified by direct comparison with an authentic sample.

That the more polar compound m.p. 139-140° was in

fact marrubenol (2c) the product of lithium aluminium

hydride reduction of marrubiin was shown by direct

comparison with an authentic sample of marrubenol and by

its conversion into and direct comparison with authentic

samples of marrubenol monoacetate (2d) the keto aldehyde

(2f) and the ether (39) m.p. 124-125°. Marrubenol was

obtained as an oil and was crystallised with difficulty

from ether - light petroleum. In its n.m.r. spectrum

are signals from one secondary (9.08 τ (d) ; J = 6c./sec.)

and two tertiary methyl (8.99 (s) and 8.74 τ (s)) groups. The

geminal $-C\underline{H}_2OH$ resonances appear as two doublets with a

separation in excess of 1 p.p.m. (at 5.68 and 6.82 τ

(1H each); J = 12 c./sec.). This large separation is

caused by the interaction of the $-C\underline{H}_2OH$ protons with the

C-20 methyl group. Marrubenol on treatment with Sarett's

reagent gave the keto aldehyde (2f) n.p. 110-111° which

shows two carbonyl frequencies in the i.r. at 1713 and

1704 cm^{-1}. In the n.m.r. the aldehyde proton appears

at -0.42 τ as a doublet with a separation of 1 c./sec.,
the singlet at 6.74 τ being attributable to the C-5 proton.
Marrubenol, on acetylation under mild conditions gave the
oily monoacetate (2d). In its n.m.r. spectrum it exhibits
an AB quartet centred at 5.44 τ due to the $C\underline{H}_2$-OAc grouping
and a triplet at 5.66 τ from the proton adjacent to the
C-6 hydroxyl function. However on treatment with acetic
anhydride-pyridine at room temperature for three days the
oily diacetate (2i) (reported[21] m.p. 102-103°) was formed.
On attempted p-bromo-benzenesulphonation the other (39)
m.p. 124-125° was obtained as the sole product.

Previous published[6,10] procedures for the isolation of
marrubiin have all involved the use of rather vigorous
conditions: namely Soxhlet extraction of the plant with
acetone, dissolution of an extract in refluxing ethanol or
column chromatography over alumina. However under much
milder conditions (shaking with cold acetone for 30 minutes)
the dark green oil obtained shows a significant difference
in t.l.c. behaviour. Thus normally, the major Ehrlich-
active spot is that arising from marrubiin but under these
milder conditions this spot is absent and is replaced by
one of lower polarity. This new compound has been
isolated by exceedingly careful preparative t.l.c. but
failed to crystallise. The analytical figures indicated
a molecular formula of $C_{20}H_{28}O_4$, showing that the new
diterpene, named premarrubiin (58), was isomeric with
marrubiin. In its i.r. spectrum it exhibits

absorption at 1778 cm^{-1} characteristic of a γ·lactone but
significantly there are no peaks attributable to either a
hydroxyl group or a β substituted furan ring. The n.m.r.
spectrum has certain features in common with that of
narrubiin, namely resonances arising from one secondary
(doublet at 9.13 γ ; J = 6 c./sec.) and two tertiary
methyl groups (singlets at 8.85 and 8.98 γ) while that
from H - 6 appears as the typical broadened triplet at
5.44 γ (J = 5c./sec.). However the characteristic signals
from one β and two γ protons on the furan ring are notably
absent and are replaced by resonances from four protons
which give rise to two AB quartets, one from an enol ether
at 3.64 and 4.95 γ (J = 2c/sec.) and the other from
-C$\underline{H}_2$ O - at 5.67 and 6.03 (J = 10c/sec.). These data are
consistent with a structure (58) containing two ethereal
groups. Proof for this structure follows from its ready
conversion into narrubiin by distillation in vacuo, heating
in refluxing solvents or by dissolution in chloroform.
In contrast to the analogous spiro-ethers from $\underline{S}$.
$\underline{canadensis}$[40] and the hemi-acetals described above
prenarrubiin is, on the basis of its n.m.r. spectrum, not
a mixture of C - 13 epimers.

The isolation of compounds of the type (56a) and (58)
might indicate a biogenetic pathway to bicyclic diterpenoids
with a C - 9 tertiary hydroxyl function and a β - substituted
furan ring in the side chain. A possible biogenetic scheme
is outlined in figure 2 . Side chain oxygenation
representing all stages, except the hydroxy - aldehyde have

been found in diterpenoids of natural provenance.

Introduction of oxygen into the allylic position in the

side chain derived from geranyl - linalool affords a diol.

A compound with such a grouping in the side chain is methyl

sciadopate (59), isolated[42] from Sciadopitys verticillata,

a plant from which several furanoid diterpenes have been

obtained. Further oxidation produces the hydroxy-aldehyde

which on cyclisation affords the hemi - acetal.

Dehydration furnishes the dihydro - furan ring, a system

which has been obtained from both Marrubium vulgare and

Solidago canadensis, the source of the marrubiin - related

compound, solidagenone (60). Both these furan precursors

have a C - 13, C - 9 ether linkage, as do also grindelic

acid (21) and its congeners, isolated[43] from the rosin of

Grindelia robusta. In addition this system is found in the

dilactone (56b) from Leonotis leonuris and lagochilin (61),

the tetrol from[44] Lagochilus inebrians.

Attempted synthesis of "compound Y".

While preparing compounds required for the elucidation

of the structure from Solidago sero tina (vide infra) it

was found that certain allylic and homoallylic alcohols,

acetates and methyl esters on treatment with chromium

trioxide - pyridine at 20° react to form $\alpha\beta$-unsaturated

ketones by the introduction of an oxygen atom into an

allylic position. As an extension of this work it was

considered that oxidation of a suitable marrubiin

derivative might afford the Δ^5 - 7 - keto function

found in "compound Y" (62a) one of the diterpenoids
isolated[45] from the leaves of <u>Leonotis leonuris</u>. Since the
stereochemistry at all the asymmetric centres is the same
in compound Y as in marrubiin this oxidative step could
form the basis of a synthesis of "Y" from marrubiin.

The initial scheme envisaged the conversion of the
known* mono-acetate (2d) into the olefin (63a) by treatment
with toluene-p-sulphonyl chloride in pyridine at room
temperature, a method described earlier for the hydroxy-acid
(45) by Burn and Rigby[14]. These mild conditions, however,
left the mono-acetate unreacted. When the reaction was
carried out in refluxing pyridine the major product was the
crystalline acetoxy - tosylate (2j) $C_{29}H_{40}SO_7$, m.p. 110°
while the required oily olefin (63a) $C_{22}H_{32}O_4$ accounted for
only 6% of the mixture. The n.m.r. spectrum of the tosylate
exhibits resonances at τ 4.77 (1H, C - 6 ; $W_{\frac{1}{2}}$ = 7 c./sec.)
and a quartet

* A minor product obtained in the acetylation of
marrubenol was the crystalline hydroxy-acetate $C_{22}H_{34}O_5$
m.p. 179° which can be formulated as (2k). In its n.m.r.
spectrum the resonances of the two C - 19 primary hydroxyl
protons appear as a quartet centred at τ 6.29 (J = 11 c./sec.)
while the C - 6 proton of the secondary acetate function
resonates as a multiplet at τ 4.4 ($W_{\frac{1}{2}}$ = 7 c./sec.).

at Υ 5.53 and 6.2 (2H, C - 19 ; J = 10 c./sec.) ; that of

the olefin has a triplet at Υ 4.29 (1H, C - 6 ; J = 3 c./sec.)

and a quartet centred at 6.00 (1H, C - 19 ; J = 11 c./sec.).

Treatment of the tosylate (2j) with refluxing pyridine,

collidine or pyridine containing toluene-p-sulphonyl chloride

failed to eliminate toluene-p-sulphonic acid.

Reduction with either lithium aluminium hydride or

sodium borohydride of the acetoxy - tosylate (2j) afforded

as the major product a crystalline compound m.p 123 - 124°

whose n.m.r. spectrum was identical to that of the ether (39)

formed[28] previously from treatment of marrubenol with p-bromo-

benzene sulphonyl chloride. The formation of this compound

can be rationalised in terms of a nucleophilic displacement

of the secondary tosylate function by the newly formed

primary alcohol.

Since methyl esters appear to be as efficient as

acetoxy groups in aiding the introduction of an allylic

ketone the preparation of the corresponding olefinic ester

was undertaken with a view to subjecting it to chromium

trioxide - pyridine oxidation. The starting material for

this synthesis was marrubic acid (2a) which was converted

into the olefin by treatment with toluene-p-sulphonyl

chloride in pyridine. The temperature at which this reaction

was carried out proved to be critical since different products

were formed under different conditions. When the reaction

was carried out at 20° for four days the mixture of acids

obtained was immediately esterified with diazomethane and

the product chromatographed over alumina. The least polar

compound was the required oily olefinic-ester $C_{21}H_{30}O_4$
(63b) in approximately 48% yield (of the 52% yield of
Burn and Rigby[14]). In its n.m.r. spectrum the C - 6
vinylic proton resonates as a triplet at τ 4.17 (J = 3 c./sec.)
The compound of intermediate polarity proved to be methyl
marrubate (2b) (n.m.r.). The final fractions crystallised
spontaneously and contained only marrubiin. In a further
experiment marrubiic acid (2a) in warm (70°) pyridine was
treated with a large excess of toluene-p-sulphonyl chloride
for 65 hours, followed by diazomethylation as before. In
addition to the olefin and marrubiin a third major product
was formed. Crystallisation afforded this furano - sulphoxide
(64) $C_{27}H_{34}SO_6$ as a sharp melting solid m.p. 129°. That it
still contains the C - 9 tertiary hydroxyl function and the
γ -lactone is evident from the absorption at 3610, 3520,
and 1772 cm^{-1} in the i.r. In its n.m.r. spectrum the typical
pattern of the three furan protons is absent and is replaced
by two doublets at τ 2.53 and 3.63 (J = 2 c./sec.) indicating
that the substituent must be attached to C - 16 rather than
C - 15. Methyl marrubate (2b) was found to be converted
quantitatively into the olefin (63b) when kept for seven days
at 20° with toluene-p-sulphonyl chloride in pyridine. When
this experiment was repeated using refluxing pyridine for
12 hours the amount of olefinic - ester recovered was very
much less (approximately 72% : based on recovered material)
and the product required to be purified by preparative t.l.c.

The ester (63b) was transformed into the oily enone
(62b), $C_{21}H_{28}O_5$ in approximately 53% yield (based on material
recovered) by reaction with chromium trioxide in pyridine at
room temperature for 10 days. In its n.m.r. spectrum the
resonance of the C - 6 olefinic proton has moved downfield
to τ 3.82 and is now a sharp singlet as expected since the
adjacent methylene protons have been replaced by a carbonyl
function. The enone absorption is clearly visible in its
i.r. spectrum at 1680 cm^{-1}, the ester grouping appearing at
1730 cm^{-1}. Reduction with lithium aluminium hydride afforded
a mixture of two triols, in approximately equal amounts which
on Sarett oxidation were converted into one oily aldehyde
(62c) $C_{20}H_{26}O_4$. The signals from the C - 6 olefinic proton
and the aldehydic proton appear as singlets at τ 3.85 and
0.77 respectively, while in the carbonyl region of its i.r.
spectrum there are peaks at 1730 and 1680 cm^{-1} as expected.

The penultimate step in the synthesis was to have been
the conversion of the keto-aldehyde (62c) into the thio-
acetal, Raney nickel reduction of which would have yielded
the desired compound. However, conditions have not yet been
found whereby this thio-acetal can be produced. In several
experiments only non-furanoid material was recovered.

As a result this route was discontinued and as an
alternative the following scheme was devised in the hope
that the C - 9 hydroxyl group would assist in oxygen insertion at
C - 7. The ketone[40] (65a) was prepared from marrubiin via the
keto-aldehyde (2f) by reduction of the derived oily thio-
acetal with Raney nickel in acetone. Reduction with lithium

aluminium hydride or sodium borohydride of the ketone furnished as the major product the oily alcohol (65b) $C_{20}H_{32}O_3$. The axial nature of the C - 6 hydroxyl function was deduced from the half-band width (7 c./sec.) of the multiplet in its n.m.r. spectrum at τ 5.7. Treatment of this alcohol with methane sulphonyl chloride in pyridine at room temperature (conditions used previously[46] for the preparation of solidag-5-ene) afforded the required olefin (63c) $C_{20}H_{30}O_2$ m.p. 133 - 135°, which shows in its n.m.r. spectrum the resonance of the C - 6 proton as a triplet at τ 4.35 (J = 3 c./sec.).

Treatment of this compound with excess chromium trioxide - pyridine for 25 days furnished mainly one compound which did not react with Ehrlich's reagent indicating that it no longer contains a furan ring. This was confirmed by its i.r. spectrum in which the typical sharp band at about 875 cm^{-1} is absent as is any hydroxyl absorption. Instead, in the carbonyl region there are peaks at 1787, 1713, 1677 and 1657 cm^{-1} indicative of a γ -lactone and an $\alpha\beta$ -unsaturated ketone. The mass spectrum shows a molecular ion at m/e = 276 corresponding to a molecular formula of $C_{17}H_{24}O_3$. Thus the constitution of this enone can be represented by (66) which is the product of allylic oxidation and cleavage of the furan ring to form an acid which subsequently lactonises with the C - 9 tertiary hydroxyl group. A similar oxidation has been reported[10,11] for several marrubiin derivatives using either potassium permanganate or chromium trioxide in acetic acid.

Although these reactions have failed to produce the required "compound Y" the above oxidation of the olefin (63c) indicates that it is possible to introduce the Δ^5 - 7 - keto system even when C - 19 is lacking an oxygen function. Perhaps, the reaction time was too long since in the other (shorter) oxidation of the methyl ester (63b) there was very little, if any, lactonic material in the product. No further work in this direction has yet been done.

Experimental

General details.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations refer to chloroform solutions at room temperature. Infra red solution spectra were recorded on Perkin Elmer 257 and 225 Grating spectrometers. Microanalyses were by Mr. J.M.L. Cameron and his staff. Nuclear magnetic resonance spectra were recorded on the Perkin Elmer R 10 and Varian Associates T - 60 and HA - 100 spectrometers in deuterochloroform or carbon tetrachloride using tetra-methylsilane as internal standard. Mass spectra were run on A.E.I. M.S. 9 and M.S. 12 double focussing instruments. Woelm grade 1 alumina, deactivated to the appropriate grade according to Brockmann, was used for column chromatography. For analytical and preparative thin layer chromatography (t.l.c.) chromatoplates were made by the method of Stahl using Kieselgel G (Merck). Hydrogenations were carried out in a Sloping-Manifold hydrogenator at atmospheric pressure and temperature.

Extraction of Marrubium vulgare L.

(a) The coarsely chopped dried whole plant (5 Kg) was extracted with acetone (20 l) for 48 hours in a Soxhlet apparatus. The acetone solution was evaporated and the resulting oil (80 g) digested in benzene. The supernatant liquid was decanted and the residue digested with benzene twice more. The combined solutions were reduced in volume and chromatographed over alumina (2 Kg ; Spence grade O). Marrubiin (1) was eluted with chlorophyll in chloroform - light petroleum (1 : 1). The crude marrubiin thus obtained (12g) was crystallised several times from ethyl acetate-light petroleum and had m.p. 159 - 160°; $[\alpha]_D$ = 33° (c = 1.5); ν $\max^{CCl_4}$ 3620, 3585, 1778, 1740, 873 cm^{-1}; λ $\max^{EtOH}$ 214 mu (log ϵ = 3.93); n.m.r. signals at 5.31 τ (t)(1 H, C- 6 ; J = 6 c./sec.). Methyl protons (3 H each) appeared at 8.72 τ (s) (C - 20), 8.94 (s) (C - 18) and at 9.03 (d) (C - 17 ; J = 6 c./sec.). Elution with chloroform - light petroleum (3 : 1 approximately) afforded two further compounds which were separated by repeated preparative thin layer chromatography (chloroform containing 3% methanol). The less polar compound, the hemi-acetal (56a) was obtained as a dark coloured oil which could not be induced to crystallise; m/e = 350 (M); ν $\max^{CCl_4}$ 3610, 3530, 1780 cm^{-1}; n.m.r. signals at 4.38 τ (broad singlet) ($\frac{1}{3}$ H), 4.56 (broad singlet) ($\frac{2}{3}$ H), 5.30 τ (t) (1H, C - 6 ; $W_{\frac{1}{2}}$ = 10 c./sec.) and a very diffuse multiplet at 5.7 - 6.4 τ (2H, C- 16). Methyl protons (3 H) appeared at 8.66 τ (s)(C - 20), 8.87 τ (s) (C - 18) and at 9.04 τ (d)(C - 17 ; J = 6 c./sec.):

The more polar compound, marrubenol (2c) was obtained as an oil which crystallised from diethyl ether - light petroleum and had m.p. 139 - 140°; $\nu_{max}^{CCl_4}$ 3630, 3600, 3450, 3200, 872 cm^{-1}. In the n.m.r. it exhibited a pair of doublets (1 H each, C - 19 ; J = 12 c./sec.) at 5.75 and 6.88 τ. Methyl signals appeared at τ = 8.74 (s)(C - 20), 8.99 (s)(C - 18) and 9.08 (d)(C - 17 ; J = 6c./sec.). This compound was identical (t.l.c., m.p., mixed m.p., i.r., and n.m.r.) with an authentic sample of marrubenol obtained by lithium aluminium hydride reduction of marrubiin. A chloroform solution of marrubenol was allowed to stand for several days in bright sunlight and at the end of this time it was found that it had decomposed completely into a large number (t.l.c.) of compounds more polar than marrubenol itself. The n.m.r. spectrum of this mixture showed no evidence of furan absorption.

(b) The chopped whole horehound plant (60g) was shaken with cold acetone at room temperature for 30 minutes and after removal of solvent furnished a dark green oil (0.7g). Preparative t.l.c. (prewashed plates, redistilled solvents, ethyl acetate - light petroleum 3 :7) gave as the major component the oily ether (58 : 88 mg); $[\alpha]_D$ = - 41°(c = 0.6 ; EtOH); $\nu_{max}^{CCl_4}$ 1778 cm^{-1}. (Found: C = 72.10, H = 8.39 ; $C_{20}H_{28}O_4$ requires C = 72.26, H = 8.49%)

Conversion of the ether (58) into marrubiin.

The above ether was converted into marrubiin, m.p. 155 - 157°, $[\alpha]_D$ = + 33° (c = 0.95) by distillation in vacuo, heating for three hours in refluxing ethanol or dissolution in chloroform.

Reduction of Marrubiin (1).

Marrubiin (1 : 2g) and excess lithium aluminium hydride were heated in dry refluxing tetrahydrofuran (100 ml) for 24 hours. The excess reagent was decomposed by the cautious addition of a saturated sodium sulphate solution and the complex aluminium salts filtered off. Evaporation of the solvent afforded crude marrubenol (1.9g) as an oil which crystallised from diethyl ether - light petroleum and had m.p. $143.5 - 144.5^{\circ}$ (reported[11] 138°).

Acetylation of Marrubenol (2c).

Marrubenol (2c : 1.2g) in dry pyridine (50 ml) was treated at room temperature for 12 hours with acetic anhydride (50 ml). The reaction mixture was poured on to ice, extracted with ethyl acetate and washed with brine. Evaporation of the solvent afforded an oil (1.23 g) which was separated into its three components by preparative t.l.c. (chloroform). The least polar compound was the oily diacetate (2i : 125 mg); $\nu_{max}^{CCl_4}$ 3630, 3550, 1740, 1235, 875 cm^{-1}. The major product, the monoacetate A (2d : 933 mg) was also an oil, $[\alpha]_D = -6^{\circ}$ (c = 0.8); $\nu_{max}^{CCl_4}$ 3625, 3590, 3565, 1752, 1738, 1237, 873 cm^{-1}. It exhibited an AB quartet centred at τ 5.48 (2H, C - 19 ; J = 12 c./sec.), and a triplet at 5.65(1H, C - 6 ; $W_{\frac{1}{2}}$ = 6 c./sec). Methyl protons (3 H) appeared at τ 8.73 (s) (C - 20), 8.97 (s)(C - 18) and 9.00 (d) (C - 17 ; J = 6 c./sec.). Crystallisation of the most polar component (2k : 30 mg) from diethyl ether - light petroleum furnished the monoacetate B as very fine needles, m.p. 179°; $\nu_{max}^{CHCl_3}$ 3610, 3500, 1727, 872 cm^{-1}; n.m.r. signals at τ 4.4 (m)(1H, C - 6 ; $W_{\frac{1}{2}}$ = 7c./sec.)

6.29 (q)(2H, C - 19 ; J = 11c./sec.), 7.95 (s)(OAc), 8.78
and 8.97 (s) (3H each, 2 x C - $C\underline{H}_3$) and 9.07 (d) (3H, C - 17 ;
J = 6c./sec.). (Found: C = 69.60, H = 9.00 ; $C_{22}H_{34}O_5$
requires C = 69.81, H = 9.05%).

Oxidation of Marrubenol (2c).

Marrubenol (2c : 430 mg) in dry pyridine (15 ml) was
treated with chromium trioxide (500 mg) at room temperature
for 14 hours. Methanol (5 ml) was added and the mixture
allowed to stand for 15 minutes. Water (25 ml) and ethyl
acetate (30 ml) were then added and the solution allowed
to stand for a further two hours. The solution was filtered
through celite, extracted with ethyl acetate, washed with
brine, dried over anhydrous sodium sulphate and evaporated.
The crude product (418 mg) was chromatographed over neutral
alumina (grade 3 : 50 g) and furnished the keto - aldehyde
(2f) which crystallised from cholorform - light petroleum
as needles, m.p. 110 - 111°; $\nu \ _{max}^{CCl_4}$ 3620, 3580, 1712, 1705
cm^{-1}; aldehydic proton at τ - 0.42 (d ; separation 1 c./sec.).

Marrubiin ether (39).

Marrubenol (2c : 50 mg) in dry pyridine (5 ml) was
treated at room temperature for 15 hours with
p-bromobenzenesulphonyl chloride (50 mg). Work-up afforded
the crude product (52 mg) from which the ether (39 : 43 mg)
was obtained by preparative t.l.c. (chloroform).
Crystallisation from chloroform - light petroleum gave
needles, m.p. 124 - 125°; $[\alpha]_D$ = + 12.4°(c = 0.9); $\nu \ _{max}^{CCl_4}$
3628, 3588, 873 cm^{-1}; n.m.r. signal at τ 5.85 (m)
(1H, C - 6 ; band width 14 c./sec.).

Dehydration of Marrubenol mono-acetate (2d).

Marrubenol monoacetate (2d : 900 mg) was heated in dry refluxing pyridine (25 ml) for 18 hours with excess p-toluenesulphonyl chloride. The dark red oil obtained (945 mg) after work up was subjected to preparative t.l.c. (2 x 20% ethyl acetate - light petroleum) and two bands extracted. The less polar band (52 mg) which failed to crystallise was the olefinic - acetate (63a). Purification was effected by distillation at $130^{\circ}/0.05$ mm; max^{CCl_4} 3520, 1728 and 882 cm^{-1}; n.m.r. signals appeared at 4.29 (t) (1H, C - 6 ; J = 4 c./sec.), 6.00 (q) (2H, C - 19 ; J = 11 c./sec.), 7.97 (s) (3H, OAc), 8.90 (s) (6H, C - 18 and C - 20) and 9.00 (d) (3H, C - 17 ; J = 6 c./sec.). (Found : C = 73.15, H = 8.92; $C_{22}H_{32}O_4$ requires C = 73.30, H = 8.95%). Crystallisation of the more polar extract (689 mg) from ethyl acetate - light petroleum afforded the acetoxy - tosylate (2j), m.p. 110°; max^{CCl_4} 1730 and 882 cm^{-1}. Signals appeared in the n.m.r. at 4.77 (m)(1H, C - 6 ; $W_{\frac{1}{2}}$ = 7 c./sec.) 5.86 (q)(2H, C - 19 ; J = 10 c./sec.) and 8.07 (s)(3H, OAc). (Found: C = 65.13, H = 7.59 ; $C_{29}H_{40}SO_7$ requires C = 65.39, H = 7.57%)

Reduction of Acetoxy - Tosylate (2j).

The acetoxy - tosylate (2j : 50 mg) in dry refluxing tetrahydrofuran (5 ml) was treated for 18 hours with excess lithium aluminium hydride. T.l.c. showed the presence of one major compound, less polar than the starting material. Preparative t.l.c. (ethyl acetate - light petroleum, 1 : 3) furnished this compound (38 mg) which crystallised from ethyl acetate - light petroleum and had m.p. 123 - 124°.

is was identical (t.l.c., mixed m.p. and n.m.r.) to the ether (39). The minor, more polar component (4 mg) was marrubenol (2c).

Oxidation of the Hemi-acetal (56a).

The hemi-acetal (56a : 200 mg) was treated at room temperature for 14 hours with excess chromium trioxide in pyridine. Work up as described previously afforded the crude dilactone (56b ; 193 mg) from which the coloured impurities were removed by preparative t.l.c. (benzene - chloroform, 1 : 9). Crystallisation from ethyl acetate - light petroleum yielded a mixture of needles and cubes, m.p. 179 - 185°; $[\alpha]_D = + 9.1°$ (c = 1.1) ; $\nu_{max}^{CCl_4}$ 1797, 1778 cm^{-1}. In the n.m.r. it exhibited a triplet at τ 5.28 (1H, C - 6 ; J = 5 c./sec.) and two AB quartets centred at τ 5.68 (2H, C - 16 ; J = 10 c./sec.) and 7.28 (2H, C - 14 ; J = 17 c./sec.). Methyl groups (3H each) appeared at τ 8.63 (s)(C - 20), 8.86 (s)(C - 18) and 9.05 (d)(C - 17 ; J = 6 c./sec.) (Found: C = 69.07, H = 8.20 ; $C_{20}H_{28}O_5$ requires C = 68.94, H = 8.10%). In an attempted partial separation of the isomers of the dilactone the mixture was subjected to repeated preparative t.l.c. over the greater length of a 20 x 500 cm plate (ethyl acetate - light petroleum 1 : 1). The resulting apparently homogeneous band was quartered with respect to polarity and all four extracts crystallised from ethyl acetate - light petroleum. From least polar to most polar they had m.p. 210 - 214°, 183 - 184°, 180 - 182°, 179 - 182°. The least polar fraction was recrystallised and had m.p. 225 - 232°. This high melting sample was compared directly with an authentic sample of the lactone X

from Leonotis leonuris which had m.p. 230 - 240°. A
mixture of the two compounds had m.p. 225 - 235°. On
t.l.c. (hexane - ethyl acetate, 2 : 3) both compounds had
R_f 0.47 and could not be separated, the plate being sprayed
with 30% chlorosulphonic acid in acetic acid, heated at 100°
and viewed under u.v. light.

Conversion of the Hemi-acetal (56a) into marrubiin.

The hemi-acetal (56a : 54 mg) and p-toluenesulphonyl
chloride (50 mg) were heated for two hours in dry refluxing
pyridine under an atmosphere of nitrogen. Work up afforded
the crude product (49 mg) which when purified by preparative
t.l.c. (chloroform) furnished marrubiin as needles m.p. 158 -
159°, after crystallisation from ethyl acetate - light
petroleum $[\alpha]_D$ = + 27.5° (c = 1.1), identical (t.l.c., m.p.,
mixed m.p., $[\alpha]_D$, and n.m.r.) with an authentic sample of
marrubiin.

Hydrogenation of marrubiin (1).

Marrubiin (1 : 963 mg) in ethanol (40 ml) was
hydrogenated over Adams catalyst (400 mg). The uptake of
hydrogen stopped at 253 ml. The catalyst was filtered off
and the solution evaporated affording an oil (960 mg) shown
by t.l.c. to be a mixture of four components. These were
separated by chromatography over acid alumina (100 g ; grade 3)
using benzene as eluent. The early fractions contained the
desoxy-compound (50c) as a waxy solid (15 mg) which
crystallised from light petroleum as needles, m.p. 88 - 89°;
$[\alpha]_D$ = + 30° (c = 1.1); $\nu_{max}^{CCl_4}$ 3630, 1780 cm^{-1}; signals in
the n.m.r. at τ 5.35 (t)(1H, C - 6 ; J = 5 c./sec.).

(Found: C = 74.43, H = 10.76; $C_{20}H_{34}O_3$ requires C = 74.49,

H = 10.63%). The major component, tetra-hydromarrubiin (38)

was eluted next and crystallisation from ethyl acetate -

light petroleum furnished needles (856 mg), m.p. 125°;

$\nu\, ^{CCl_4}_{max}$ 3630, 1780 cm^{-1}; triplet centred at τ 5.26 (1H,

C - 6 ; J = 6 c./sec.). Methyl protons (3H) appeared at

τ 8.65 (s)(C - 20), 8.89 (s)(C - 18) and 9.02 (d) (C - 17 ;

J = 6c./sec.). The final components (80 mg) were eluted

together with almost no separation of one from the other.

They were eventually separated by repeated preparative t.l.c.

(ethyl acetate - light petroleum, 1 : 1) to give as the less

polar component, hexa-hydromarrubiin A (50a : 29 mg) which

failed to crystallise. In the n.m.r. it exhibited a triplet

at τ 5.28 (C - 6 ; J = 6c./sec.) and an ill-resolved doublet

at τ 6.44 (2H, C - 16 ; $W_{\frac{1}{2}}$ = 6c./sec.). The more polar

component, hexahydromarrubiin B (50d : 44 mg) was crystallised

from ethyl acetate - light petroleum as needles, m.p. 150 - 152°

(reported[36] 154°); $[\alpha]_D$ = 17° (c = 1.2); in the n.m.r. it

exhibited a triplet at τ 6.32 (2H, C - 15; J = 6c./sec).

(Found: C = 70.84, H = 9.95 ; $C_{20}H_{34}O_4$ requires C = 70.97,

H = 10.13%).

Acetylation of Hexahydromarrubiin A (50a).

Hexahydromarrubiin A (50 a : 20 mg) in dry pyridine (5 ml)

was treated at room temperature for 12 hours with acetic

anhydride (5 ml). Work up in the usual manner afforded the

crude acetate, crystallised from ethyl acetate - light

petroleum as needles, m.p. 121 - 128°; max^{CCl_4} 3620, 3540, 1775,

1745, 1240 cm^{-1}. In the n.m.r. it exhibited signals at τ 5.28

(t)(1H, C - 6 ; J = 5 c./sec.) and τ 5.99 (d)(2H, C - 16 ;
J = 5 c./sec.). (Found: C = 69.84, H = 9.65 ; $C_{22}H_{36}O_5$
requires C = 69.44, H = 9.54%).

Hydrogenation of Anhydromarrubiin (3a).

Anhydromarrubiin (3a : 4.994 g) in ethanol (40 ml) was
hydrogenated over Adams catalyst (1 g). Filtration of the
catalyst and evaporation of the solvent furnished an oil
(4.857 g) shown by t.l.c. to be a mixture of four compounds,
separated by chromatography over acidic alumina (500 g : grade 3)
using benzene as eluent. The early fraction contained the
bisdesoxy - compound (51a) as a waxy solid (433 mg) which
failed to crystallise, ν $_{max}^{CCl_4}$ 1775 cm^{-1}. In the n.m.r. it
showed two overlapping triplets centred at τ 5.17 and 5.25
(1H, C - 6 ; J = 5 c./sec.). (Found: C = 78.16, H = 10.98 ;
$C_{20}H_{34}O_2$ requires C = 78.38, H = 11.18%). The major product
was eluted as an oil (2.165 g) and crystallisation from ethyl
acetate - light petroleum furnished desoxytetrahydro-marrubiin
(42) as needles, m.p. 93.5 - 95°; ν $_{max}^{CCl_4}$ 1775 cm^{-1}. In the
n.m.r. it displayed a triplet at τ 5.22 (1H, C - 6 ; J = 5c./sec.)
Methyl resonances (3H each) appeared at τ 8.74 (s)(C - 20),
9.04 (s)(C - 18) and 8.94 (d)(C - 17 ; J = 6 c./sec.).
(Found: C = 74.84, H = 9.90 ; $C_{20}H_{32}O_4$ requires C = 74.96,
H = 10.06%). The final fractions contained a waxy solid
(1.90 g ; two components by t.l.c.) a sample of which (167 mg)
was separated by repeated t.l.c. (ethyl acetate - light
petroleum, 1 : 1). The less polar compound, desoxyhexa -
hydromarrubiin A (51b : 80 mg) crystallised from ethyl
acetate - light petroleum as needles, m.p. 96 - 97° ;

$\nu \, ^{CCl_4}_{max}$ 3640, 3530, 1775 cm^{-1}; doublet at τ 6.48

(2H, C - 16 ; J = 4c./sec.). (Found: C = 74.57, H = 10.42;

$C_{20}H_{34}O_3$ requires C = 74.49, H = 10.63%). Crystallisation

of the more polar compound from ethyl acetate - light

petroleum afforded desoxyhexahydromarrubiin B (51d : 78 mg)

as needles, m.p. 86 - 88°; $\nu \, ^{CCl_4}_{max}$ 3640, 3530, 1775 cm^{-1};

triplet at τ 6.38 (2H, C - 15 ; J = 6c./sec.). (Found: C =

74.76, H = 10.40; $C_{20}H_{34}O_3$ requires C = 74.49, H = 10.63%).

Acetylation of the Desoxyhexahydro-compounds.

The above desoxyhexahydro-derivatives (51a and 51b) in

dry pyridine were acetylated in the usual fashion to afford

the corresponding acetates, neither of which was obtained

crystalline. The n.m.r. of acetate A (51c) showed a doublet

at τ 6.05 (2H, C - 16 ; J = 4c./sec.) while that of

acetate B (51e) had a triplet at 5.90 τ (2H, C - 15 ; J =

6c./sec.).

Dehydration of marrubiin (1).

(a). Phosphoryl chloride in pyridine.

Marrubiin (1 : 100 mg) and freshly distilled

phosphoryl chloride (500 mg) were heated in dry refluxing

pyridine (5 ml) for five hours. After pouring on to ice

the product was taken up in ethyl acetate, washed with

brine, dried over anhydrous sodium sulphate and the solvent

evaporated. The oily residue (91 mg) appeared as a single

spot on t.l.c., however n.m.r. indicated the presence of two

components, namely the $\Delta^{8(9)}$ (70%) and $\Delta^{9(11)}$ (30%)

olefins. In an attempted partial separation of these isomers

the mixture was subjected to preparative t.l.c. on silica -

gel and on silica - gel impregnated with silver nitrate
(9 : 1). In the former case, after developing with chloroform,
the resulting apparently homogeneous band was halved with
respect to polarity and the corresponding extracts subjected
to analysis by n.m.r. : the product composition appeared to
be nearly identical in each case.

(b) Marrubiin (1 : 100 mg) in dry pyridine (5 ml) was treated
with redistilled phosphoryl chloride (500 mg) for two hours at
60°. The reaction mixture was poured on to ice and extracted
with ethyl acetate. Evaporation of the solvent afforded an
oil (90 mg) which was shown by t.l.c. to consist of two
components. These were separated by preparative t.l.c.
(chloroform - benzene 9 : 1) and afforded 9 mg of the olefin
mixture (n.m.r. evidence) and marrubiin (75 mg).

(c) Treatment of olefin mixture with hydrogen chloride.

The phosphoryl chloride dehydration mixture (50 mg) in
chloroform (25 ml) was treated with dry hydrogen chloride for
15 minutes until the solution was saturated. A careful study
of the reaction product showed that no significant isomerisation
had taken place (n.m.r. evidence).

(d) Phosphorus trichloride in benzene.

Marrubiin (1 : 6 g) and phosphorus trichloride (12 ml)
were heated for two hours in dry refluxing benzene (240 ml).
After the addition of water, the benzene layer was separated,
washed with sodium bicarbonate dried over anhydrous sodium
sulphate and then evaporated. Purification of the crude
product /by column chromatography over neutral alumina
(600 g : grade 3) using benzene as eluent. The anhydromarrubiin
obtained (4.99 g) was an oil which crystallised from dry

methanol as needles (3.14 g; 63%). After drying at room

temperature for three days under vacuum it had m.p. 95 - 96°

(reported[9] 98°); 56 - 58° after five hours exposure to

atmospheric moisture. $\sqrt{}$ $_{max}^{CHCl_3}$ 1772, 875 cm^{-1}. N.m.r.

signals for material m.p. 95 - 96° appeared at τ 4.64 (t)

(1H, C - 11), 4.97 (sextet) (1H, C - 6), 6.82 (d)(2H, C - 12),

6.95 (diffuse multiplet)(1 H,C - 8), 7.72 (q)(2H, C - 7),

8.02 (d)(1H, C - 5) and 8.78 (d)(3H, C - 17); $J_{H-5,H-6}$ =

5c./sec., $J_{H-6,H-7}$ = 8c./sec., $J_{2H-7, H-8}$ = 3.5 c./sec.,

$J_{H-8, 3H-17}$ = 7c./sec., and $J_{H-11, 2H-12}$ = 7c./sec.

(e) Teatment of anhydromarrubiin with phosphoryl chloride in

moist pyridine.

Anhydromarrubiin (3a : 72 mg) in pyridine (5 ml)

containing a trace of water (4 mg) was heated at reflux with

phosphoryl chloride (360 mg) for five hours. The reaction

was worked up as previously described to afford the product

(70 mg) the n.m.r. of which was very similar to that of the

starting material.

(f) Phosphorus trichloride in pyridine.

Marrubiin (1 : 148 mg) and phosphorus trichloride

(0.3 ml) were heated for two hours in dry refluxing pyridine.

The reaction was worked up in the usual manner and afforded

the crude product (134 mg) which failed to crystallise. A

careful integration study in the n.m.r. showed the presence

of the $\Delta^{8(9)}$(75%) and $\Delta^{9(11)}$(25%) olefins.

(g) Phosphorus trichloride in carbon tetrachloride.

Marrubiin (1 : 130 mg) and phosphorus trichloride (0.3 ml)

were heated for two hours in refluxing carbon tetrachloride

(6 ml). This afforded, on work up, the crude product (125 mg)

from which polar impurities were removed by preparative
t.l.c. (chloroform containing 10% benzene) to give the
dehydration product (80 mg) shown by n.m.r. to consist
exclusively of the Δ 9(11) isomer.

(h) Phosphoryl chloride in benzene.

Marrubiin (1 : 125 mg) and redistilled phosphoryl
chloride (600 mg) were heated for five hours in dry refluxing
benzene (5 ml). Work up in the normal fashion afforded a very
non polar oil which was not investigated further.

Dehydration of tetrahydromarrubiin (38).

(a) Phosphorus trichloride in benzene.

Tetrahydromarrubiin (38 : 63 mg) and phosphorus
trichloride (0.1 ml) were heated for two hours in dry
refluxing benzene (2 ml). Work up afforded the crude product
(61 mg) purified by repeated preparative t.l.c. (chloroform -
benzene, 1 : 1). Anhydrotetrahydro - marrubiin (33)
crystallised from ethyl acetate - light petroleum as needles,
m.p. 124° (reported[36] 125 - 126°); $\nu_{max}^{CCl_4}$ 1780 cm^{-1}. In the
n.m.r. it exhibited signals at τ 4.83 (t)(1H, C - 11 ; J =
5c./sec,), and τ 5.00 (sextet) (1H, C - 6 ; $W_{\frac{1}{2}}$ = 18 c./sec.).
(Found: C = 75.30, H = 9.50 ; $C_{20}H_{30}O_3$ requires C = 75.43,
H = 9.50%).

(b) Phosphoryl chloride in pyridine.

Tetrahydromarrubiin (38 : 60 mg) and redistilled
phosphoryl chloride (300 mg) were heated for eight hours in
dry refluxing pyridine. The reaction was worked up in the
normal manner but no dehydration products were obtained.
This reaction was repeated several times but in all cases the

results were the same.

Hydrolysis of desoxytetrahydronarrubiin (42).

Desoxytetrahydronarrubiin (42 : 2.165 g) was heated in refluxing ethoxy-ethanol (50 ml) containing potassium hydroxide (1 g) and water (1 ml) for two hours. The hot reaction mixture was poured on to ice and after adjusting the pH of the aqueous layer to 12, neutral products were extracted with ethyl acetate. The aqueous layer was made just acid to Congo red with 1N hydrochloric acid and extracted with ethyl acetate. Evaporation of the solvent afforded an oil (2.34 g) which was chromatographed on silica gel to afford the hydroxy - acid (41a : 1.8 g) crystallised from ethyl acetate - light petroleum as needles which sublimed at 224 - 226°; $\nu \, ^{CCl_4}_{max}$ 3590, 3400, 2720 and 1725 cm^{-1}; broadened singlet at τ 5.52 (1H, c - 6 ; $W_{\frac{1}{2}}$ = 8 c./sec.). (Found: C = 71.04, H = 10.23; $C_{20}H_{34}O_4$ requires C = 70.97, H = 10.13%).

Oxidation of hydroxy - acid (41a).

The above hydroxy - acid (41a : 1.75 g) in dry pyridine (30 ml) was treated with chromium trioxide (1.5 g) at room temperature for 16 hours. Work up afforded an oil (1.72 g) from which coloured impurities were removed by preparative t.l.c. (chloroform) to furnish the keto-acid (41b) which on crystallisation from ethyl acetate - light petroleum afforded needles, m.p. 170 - 172°; $\nu \, ^{CCl_4}_{max}$ 3060, 2740, 1780, 1745 and 1685 cm^{-1}; signals at τ = - 2.75 (s) (COOH), 7.44 (s)(1H, c - 5). (Found: C = 71.39, H = 9.62; $C_{20}H_{32}O_4$ requires C = 71.39, H = 9.59%).

Lactonisation of the keto-acid (41b).

The keto - acid (41b : 1.05g) was heated in refluxing acetic anhydride (50 ml) under nitrogen for an hour and then for a further two hours after the addition of fused sodium acetate (2 g). The solution was poured on to ice and extracted with ethyl acetate. Evaporation of the solvent afforded the enol - lactone (43 : 830 mg) which rapidly decomposed into the keto - acid (41b) on standing (t.l.c.) $\nu_{max}^{CCl_4}$ 1800, 1705 cm^{-1}.

Hydrogenation of enol - lactone (43).

The enol lactone (43 : 830 mg) containing the keto - acid as an impurity was hydrogenated in glacial acetic acid (40 ml) over 10% Pd/C (500 mg). The product (800 mg) was a mixture of two compounds (t.l.c.) which were separated by preparative t.l.c. using chloroform containing 2% methanol as solvent. This afforded desoxytetrahydromarrubiin (42 : 400 mg) as the least polar component, identified by m.p., mixed m.p., i.r., and n.m.r. The other component (305 mg) was the bisdesoxy - acid (41c) which crystallised from light petroleum as needles, m.p. 99 - 101°; $\nu_{max}^{CCl_4}$ 3520, 1780, 1740 and 1695 cm^{-1}. (Found: C = 74.64, H = 10.48 ; $C_{20}H_{34}O_3$ requires C = 74.49, H = 10.63%).

Methylation and reduction of bisdesoxy - acid (41c).

An etheral solution of the bisdesoxy - acid (41c : 100 mg) was esterified with an etheral solution of diazomethane and the methyl ester in dry refluxing diethyl ether treated for two hours with excess lithium aluminium hydride. The oily alcohol obtained (41d : 75 mg) had $\nu_{max}^{CCl_4}$ 3640 cm^{-1}. and

quartet centred at τ 6.41 (2H, C - 19 ; J = 11c./sec.).

Acetylation of the desoxy - alcohol (41d)

The desoxy - alcohol (41d : 30 mg) was acetylated in the normal manner to afford the corresponding acetate (41e : 27mg) which crystallised from ethyl acetate - light petroleum and had m.p. 76 - 77°, $[\alpha]_D$ = + 23.5° (c = 2.0); $\nu_{max}^{CCl_4}$ 1742 cm^{-1}; m/e = 290 (M - 60); In the n.m.r. it showed an AB quartet at τ 5.90 (2H, C - 19; J = 11c./sec.). (Found: C = 75.25, H = 11.3 ; $C_{22}H_{38}O_3$ requires C = 75.4, H = 10.9%).

Oxidation of the bisdesoxy - alcohol (41d).

The bisdesoxy - alcohol (41d : 12 mg) in dry pyridine (5 ml) was treated at room temperature for 14 hours with chromium trioxide. Work up yielded the unstable (t.l.c.) oily aldehyde (41f : 9 mg); $[\alpha]_D$ = + 13° (c = 0.8); $\nu_{max}^{CCl_4}$ 1718 cm^{-1}; m/e = 306 (M); singlet at τ 0.14 (1H, C - 19).

Thioketalisation and reduction of marrubenol keto-aldehyde (2f)

Marrubenol keto-aldehyde (2f : 330 mg) in diethyl ether (25 ml) containing freshly distilled boron trifluoride diethyl etherate (2 ml) was treated at room temperature for 70 hours with ethane dithiol (2 ml). The ethereal solution was washed with dilute (4N) sodium hydroxide and evaporated to afford an oil, an acetone solution of which was added to a suspension of Raney nickel in acetone. The mixture was allowed to reflux for 18 hours and the catalyst and solvent removed to afford an oil (295 mg) which was chromatographed over neutral alumina (grade 3 : 50 g). Elution with ethyl acetate - light petroleum (1 : 19) furnished the ketone

(65a: 176 mg) which crystallised from ethyl acetate - light petroleum and had m.p. 84 - 86° (reported[40] 89 - 90°). $\nu_{max}^{CHCl_3}$ 1700, 870 cm^{-1}. n.m.r. signal at τ 7.17 (s) (1H, C - 5).

Reduction of ketone (65a).

The above ketone (65a: 176 mg) in dry refluxing diethyl ether was treated for 18 hours with excess lithium aluminium hydride to afford an oil (182 mg) from which the major product, the axial <u>alcohol</u> (65b: 88 mg) was obtained by column chromatography over neutral alumina (grade 3 : 25 g) on elution with light petroleum containing 10% ethyl acetate. The alcohol failed to crystallise and was purified by distillation at 155°/0.05 mm. $\nu_{max}^{CCl_4}$ 3610, 3390, 865 cm^{-1}; n.m.r. resonances appeared at τ 5.7 (m)(1H, C - 6; $W_{\frac{1}{2}}$ = 7c./sec.). Methyl groups (3H each) appeared at τ 8.75, 8.78, 9.02 (all s)(tertiary C - CH_3) and τ 9.05 (d)(C - 17 J = 6 c./sec.). (Found: C = 74.73, H = 10.03; $C_{20}H_{32}O_3$ requires C = 74.96, H = 10.06%).

Dehydration of alcohol (65b).

The diol (65b : 66 mg) in dry pyridine (2 ml) was treated at room temperature for 70 minutes with methane sulphonyl chloride (1 ml). The oil obtained (72 mg) was subjected to preparative t.l.c. (5% ethyl acetate in light petroleum) and afforded the olefin (63c : 57 mg) which crystallised as needles m.p. 133 - 135°. $\nu_{max}^{CCl_4}$ 3560, 878 cm^{-1}; n.m.r. signals at τ 4.35 (t)(1H, C - 6 ; J = 3c./sec.).

Oxidation of olefin (63c).

The olefin (63c : 50 mg) in dry pyridine (3 ml) was allowed to stand at room temperature for 25 days with chromium trioxide (100 mg) and after work up the oil obtained (15 mg) was subjected to preparative t.l.c. (chloroform). Further purification of the lactone (66 : 7mg) was effected by distillation in vacuo; $\nu \, _{max}^{CCl_4}$ 1787, 1713, 1677, 1657 cm^{-1}; m/e = 276 (M) corresponding to $C_{17}H_{24}O_3$.

Reduction of Dehydromethyl marrubate (63b).

The olefinic ester (63b : 67 mg) in dry refluxing diethyl ether was treated for 12 hours with lithium aluminium hydride and after preparative t.l.c. (chloroform) afforded the alcohol (63d : 45 mg). After further purification by distillation in vacuo it had $\nu \, _{max}^{CCl_4}$ 3615, 880 cm^{-1}; n.m.r. signals at τ 4.3 (m)(1H, C - 6 ; $W_{\frac{1}{2}}$ = 6 c./sec.) and a multiplet centred at τ 6.53 (2H, C - 19 ; multiplet width = 28 c./sec.). (Found : C = 75.13, H = 9.27 ; $C_{20}H_{30}O_3$ requires C = 75.43, H = 9.50%).

Hydrolysis of marrubiin (1).

Marrubiin (1 : 2.2. g) in refluxing ethoxy-ethanol (3 ml) was treated for 30 minutes with potassium hydroxide (2 g). The solution was acidified by the careful addition of dilute (1N) hydrochloric acid and the precipitated solid taken up in ethyl acetate. The organic layer was washed with water and evaporated in vacuo to afford narrubiic acid (2a : 2.3 g) m.p. 190° (reported [6] 205°); $\nu \, _{max}^{Nujol}$ 3700, 3400 - 2700, 1675, 883 cm^{-1}.

Dehydration and Methylation of Marrubiic acid (2a).

(a) Marrubic acid (2a : 1.56 g) in dry pyridine (10 ml) was
treated at room temperature for four days with p-toluene
sulphonyl chloride (2 g). After removal of the reagent and
solvent the red oil was dissolved in methanol and treated with
an ethereal solution of diazomethane. The product (1.63 g)
was chromatographed over neutral alumina (grade 3 : 200 g)
and elution with light petroleum containing 5% ethyl acetate
furnished the oily olefin (63b : 693 mg) which was distilled
at 130°/0.02 mm). $\nu\ \substack{CCl_4 \\ max}$ 3660, 1722, 882 cm^{-1} ; n.m.r.
signals at τ 4.17 (t)(1H, C - 6 ; J = 3 c./sec), 6.37 (s)
(3H, O - CH$_3$), 8.7 and 9.07 (s)(3H each; tertiary C - CH$_3$)
and 9.00 (d)(3H, C - 17 ; J = 6 c./sec.). (Found : C = 72.61,
H = 8.62 ; C$_{21}$H$_{30}$O$_4$ requires C = 72.80, H = 8.73%). Continued
elution afforded methyl marrubate (2b : 282 mg) identified by
its n.m.r. spectrum where there were signals at τ 4.3 (s)
(1H, OH), 5.67 (m)(1H, C - 6 ; W$_{\frac{1}{2}}$ = 8 c./sec.), 6.3 (s)
(3H, O - CH$_3$), 8.7 and 8.97 (s)(3H each, tertiary C - CH$_3$)
and 9.05 (d)(3H, C - 17 ; J = 6 c./sec.). The final fraction
contained marrubiin (1 : 291 mg) which crystallised
spontaneously and was identified by t.l.c. and n.m.r.

(b) A further sample of marrubiic acid (2a : 600 mg) in warm
(70°) pyridine was treated for 65 hours with excess p-toluene
sulphonyl chloride. The crude product was dissolved in
methanol and treated with diazomethane as described above.
Chromatography of the product over neutral alumina (grade
3 : 30 g) furnished three fractions, the least polar of which
was not investigated further. The intermediate fraction

contained the required olefin (63b : 241 mg) identified by

n.m.r. The most polar fraction (295 mg) was a mixture of

two compounds of very similar polarity and was separated by

preparative t.l.c. (chloroform) to afford as the less polar

compound, the tosylate (64 : 92 mg) which crystallised from

ethyl acetate - light petroleum as needles m.p. 129° ;

$\nu_{max}^{CCl_4}$ 3610, 3520, 1772 cm^{-1}; n.m.r. signals at 2.53 (d)

(1H, C - 15 ; J = 2 c./sec.), 3.63 (d)(1H, C - 14 ; J = 2 c./sec.)

and 5.3 (t)(1H, C - 6 ; J = 6 c./sec.). The more polar component

(90 mg) was marrubiin (1).

Dehydration of Methyl marrubate (2b).

(a)   Methyl marrubate (2b : 421 mg) in dry pyridine was treated

at room temperature for seven days with excess p-toluene

sulphonyl chloride. Removal of the excess reagent and solvent

afforded an oil (414 mg) which consisted of only one compound,

the olefin (63b).

(b)   Methyl marrubate (2b : 521 mg) in dry refluxing pyridine

was treated for 14 hours with p-toluene sulphonyl chloride as

described above, to afford an oil (417 mg) which consisted of

mainly one compound, the olefin (63b). After preparative t.l.c.

(chloroform) the olefin (63b : 300 mg) was obtained as an oil

which could not be induced to crystallise.

Oxidation of Olefinic - ester (63b).

The above ester (63b : 750 mg) in dry pyridine (3 ml) was

treated at room temperature for ten days with chromium trioxide

(500 mg). Work up in the usual way afforded the crude

material (687 mg) separated by column chromatography over

neutral alumina (grade 3 : 60 g). The early fractions containing the unreacted ester (63b : 320 mg) were eluted with ethyl acetate - light petroleum (1 : 19). The enone (62b : 360 mg) was eluted next (3 : 17) as an oil which could not be induced to crystallise. $\nu^{CCl_4}_{max}$ 1730, 1680, 878 cm^{-1}; n.m.r. signals at τ 3.82 (s)(1H, C - 6) and 6.38 (s)(3H, O - C$\underline{H}_3$).

Reduction of Enone (63b).

The above enone (63b : 340 mg) in dry refluxing diethyl ether was treated for 12 hours with excess lithium aluminium hydride. Work up gave an oil (298 mg) seen from t.l.c. to consist of a mixture of two compounds.

Oxidation of Triols.

The mixture of alcohols obtained above (298 mg) was dissolved in dry pyridine (2 ml) and was treated at room temperature for 40 hours with chromium trioxide (100 mg). Work up gave an oil (272 mg) from which coloured polar material was removed by column chromatography over neutral alumina (grade 3 : 25 g). Elution with ethyl acetate - light petroleum (3 : 17) afforded the aldehyde (62c) which was further purified by distillation in vacuo. $\nu^{CCl_4}_{max}$ 1720, 1670, 882 cm^{-1}; n.m.r. signals at τ 0.77 (s)(1H, C - 19), 3.85 (s) (1H, C - 6), 8.59 (d)(3H, C - 17 ; J = 7 c./sec.) and 8.8 and 8.75 (s)(3H each, two C - C$\underline{H}_3$). (Found : C = 72.66, H = 8.01 ; $C_{20}H_{26}O_4$ requires C = 72.70, H = 7.93%).

Attempted thioacetalisation of the Aldehyde (62 c).

The above aldehyde (62c : 50 mg) in anhydrous diethyl ether (250 ml) was treated at room temperature for four hours

with redistilled boron trifluoride diethyl etherate (1 ml)
and ethane dithiol (1 ml). T.l.c. of the product after
work up showed the absence of the aldehyde without any
furanoid product.

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NMR single and double resonance spectra at 100 Mc./s of Anhydromarrubiin.
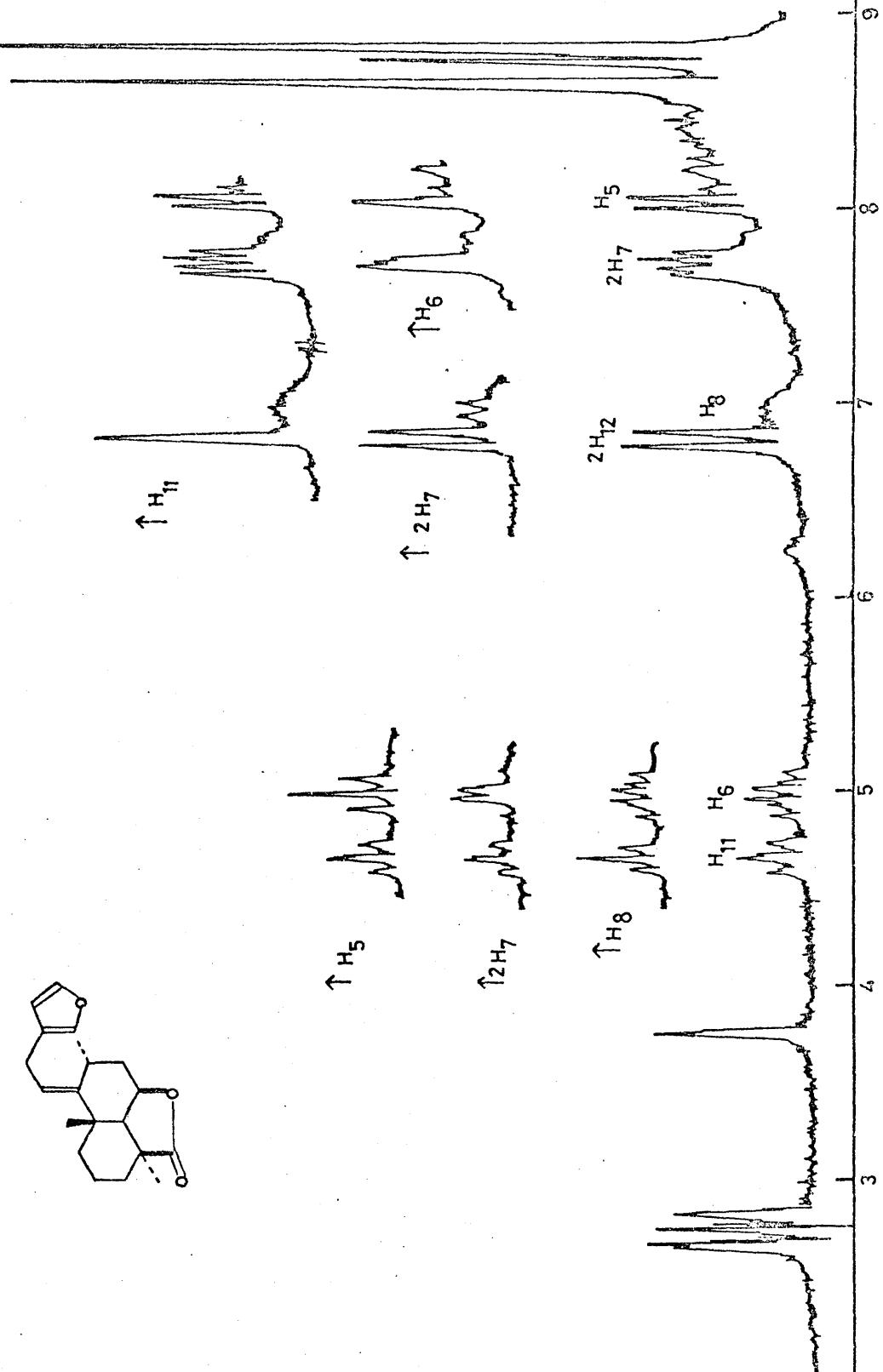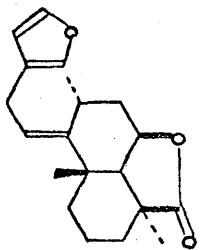
Figure 1

Dehydration of Marrubiin

Reaction	τ value of C-11 Proton	Integration of			% EXO Isomer	% ENDO Isomer
		C-11 Proton (scale units)	Furan Proton (scale units)	C-11 Proton (Protons)		
Marrubiin POCl$_3$-Py (Total)	4.67	4.0	13.0	0.3	30	70
Marrubiin POCl$_3$-Py (Band 1)	4.68	0.25	0.75	0.33	33	67
Marrubiin POCl$_3$-Py (Band 2)	4.66	0.37	1.0	0.37	37	63
POCl$_3$ mixture HCl-CHCl$_3$	4.67	2.0	5.0	0.4	40	60
Marrubiin PCl$_3$-Py	4.66	20	80	0.25	25	75
Marrubiin PCl$_3$- ▱ (Total)	4.75	6.25	6.25	1.0	100	–
Marrubiin PCl$_3$-CCl$_4$ (Total)	4.74	7.0	7.0	1.0	100	–
Anhydro-marrubiin POCl$_3$-H$_2$O	4.69	6.0	6.0	1.0	100	–
Marrubiin POCl$_3$- ▱	No Dehydration.					

Table 1

Postulated Biogenetic Pathway

Grindelia
robusta

Lagochilus
inebrians

Leonotis
leonuris

Marrubium
vulgare

Solidago canadensis

Marrubium vulgare

Figure 2

1

2
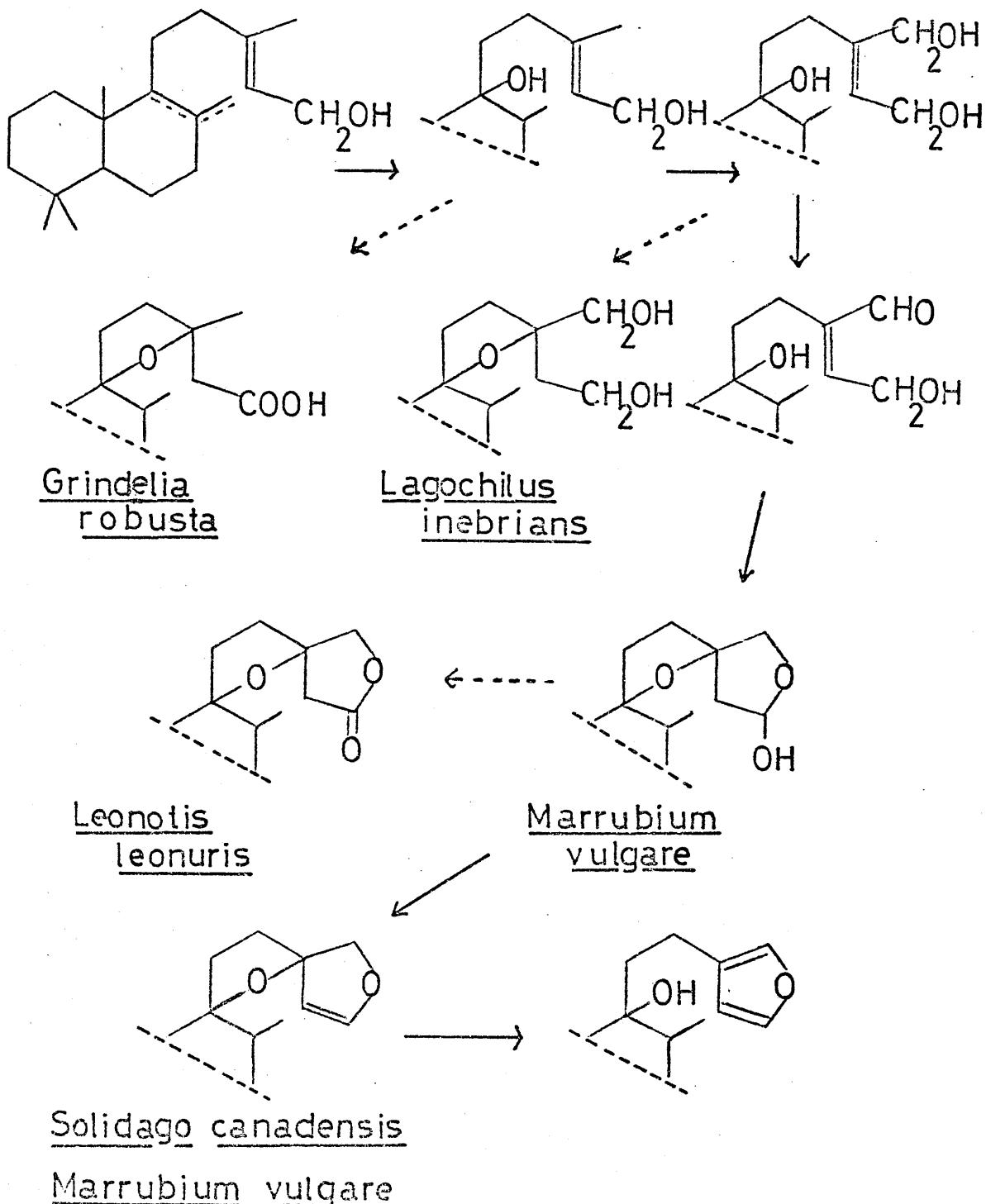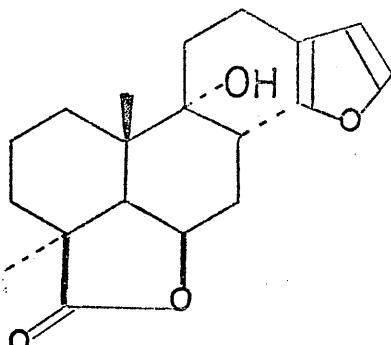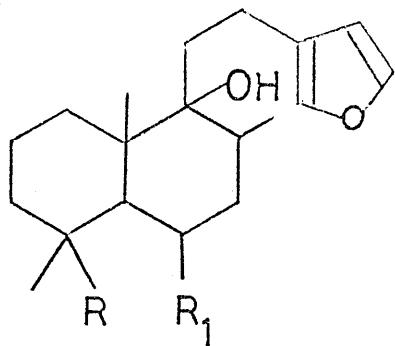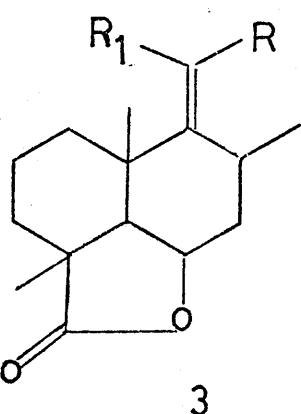
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b : R= CO$_2$CH$_3$: R$_1$= H,OH
c : R= CH$_2$OH : R$_1$=H,OH
d : R= CH$_2$OAc: R$_1$= H,OH
e : R= CH$_2$OAc: R$_1$= O
f : R= CHO : R$_1$= O
g : R= CO$_2$H : R$_1$= O
h : R= CO$_2$CH$_3$: R$_1$= O
i : R= CH$_2$OAc: R$_1$= OAc
j : R= CH$_2$OAc: R$_1$= OTs
k : R= CH$_2$OH : R$_1$= OAc

3

a : R = CH$_2$βFuran:R$_1$= H
b : R= H : R$_1$= CH$_2$βFuran
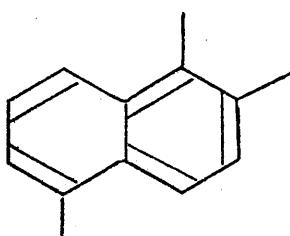
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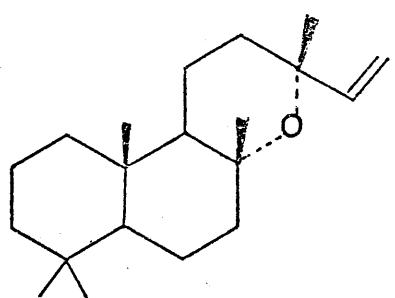
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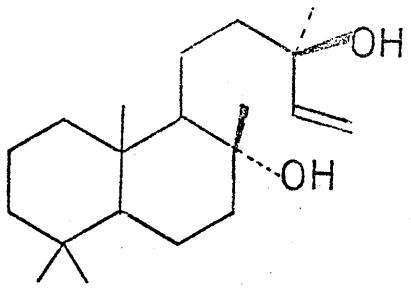
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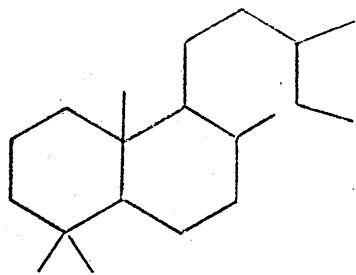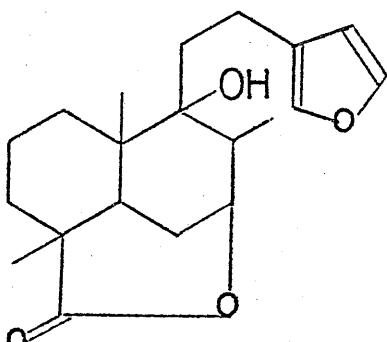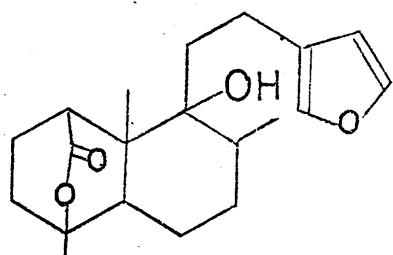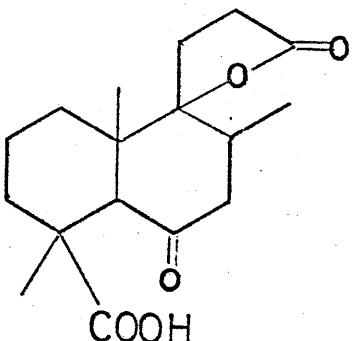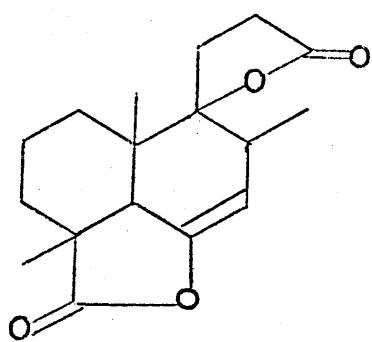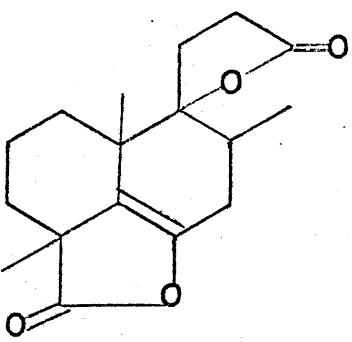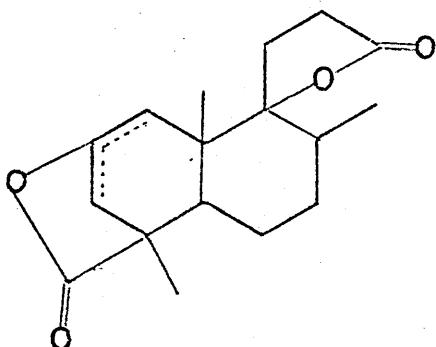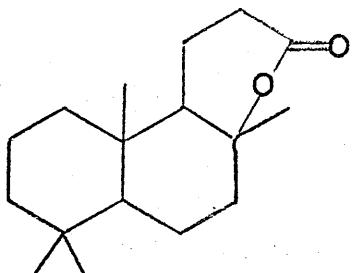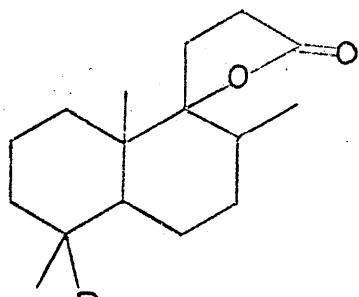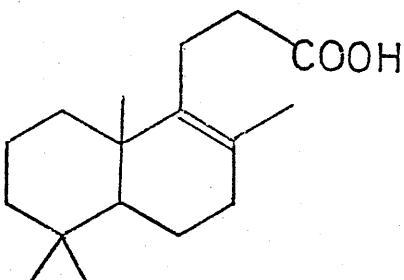
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c : R = CH₃

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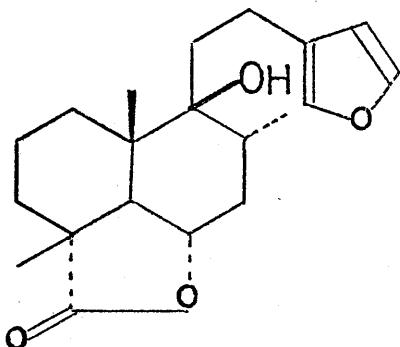
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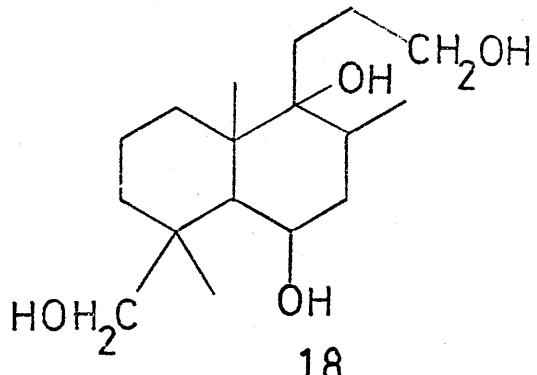
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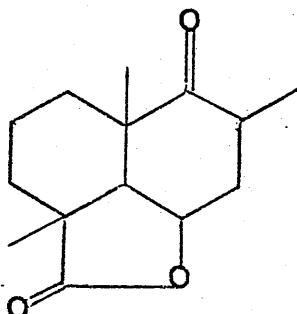
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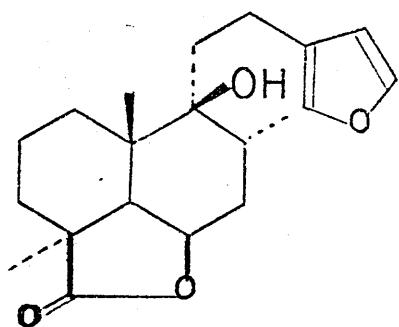
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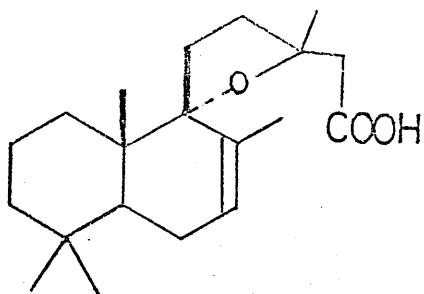
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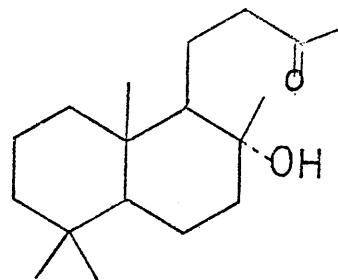
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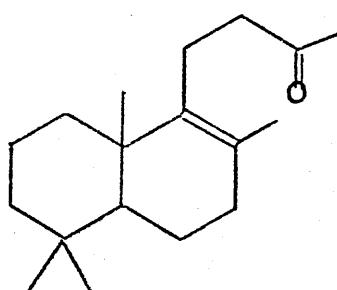
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CH_2

33

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OH

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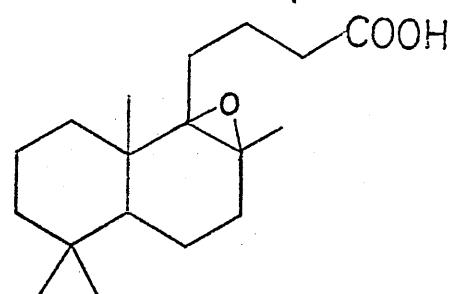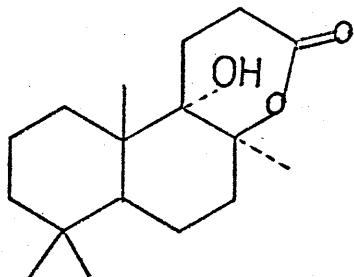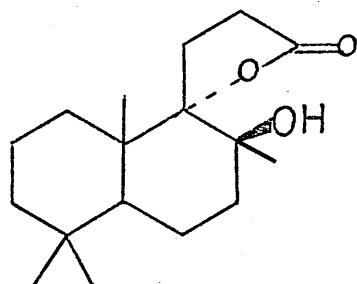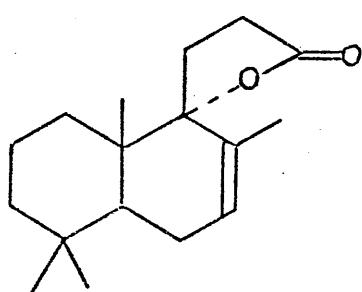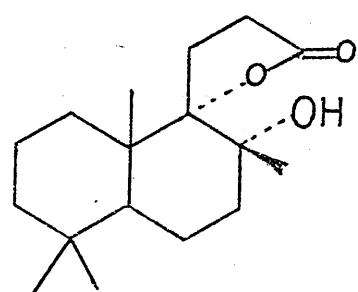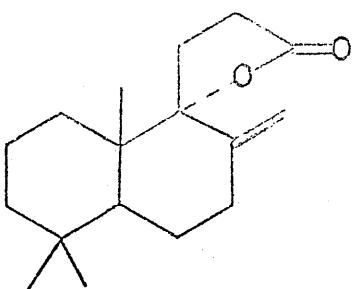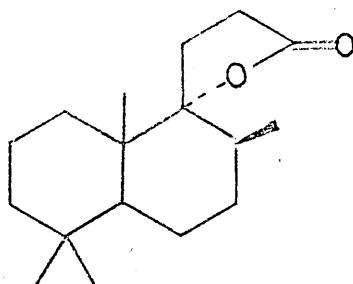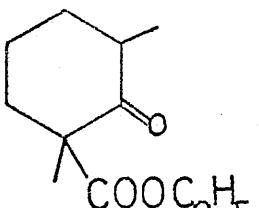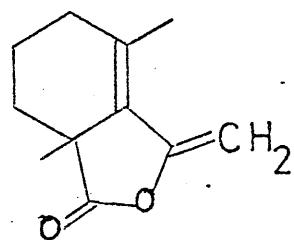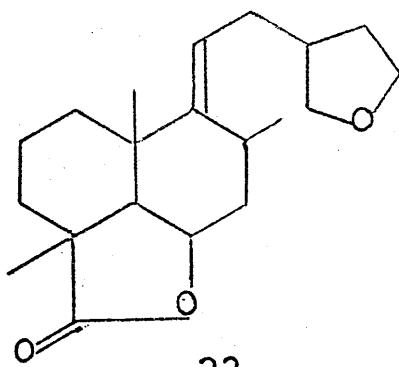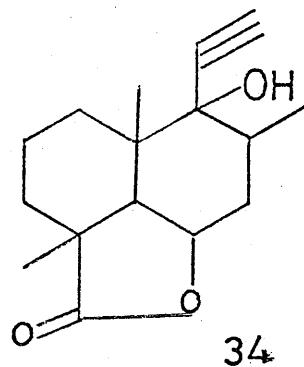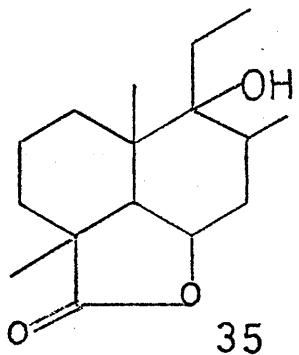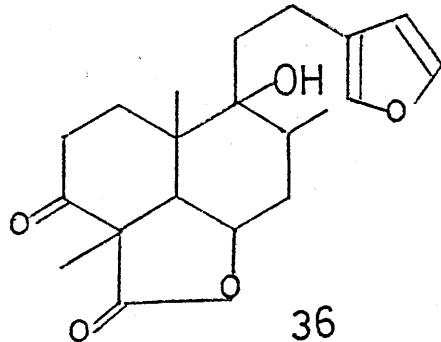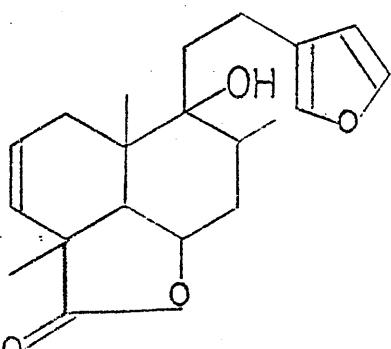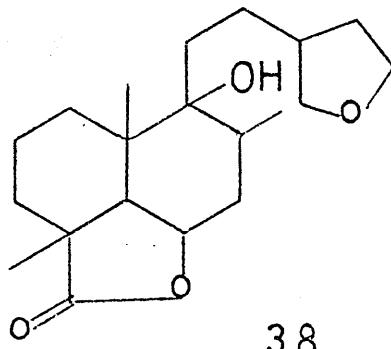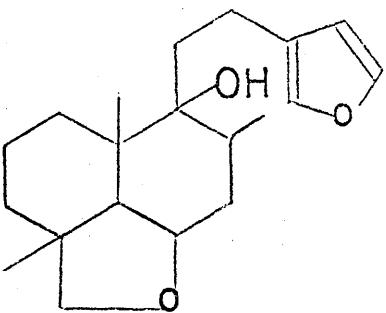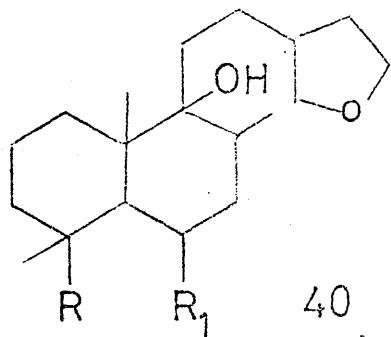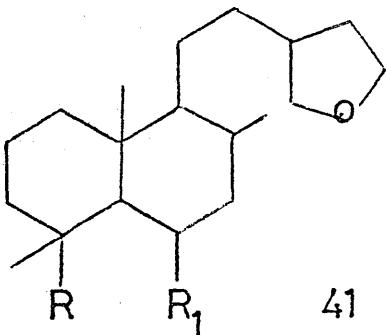
a : R= CH$_2$OH : R$_1$=H,OH

b : R= COOH :   R$_1$ = H,OH

c : R=CH$_2$OAc : R$_1$ = H$_2$

d : R= CH$_2$OH : R$_1$=H$_2$

e : R=CHO : R$_1$=H$_2$

f : R= COOH : R$_1$= O

41

a: R=COOH : R$_1$ =H,OH

b: R=COOH : R$_1$=O

c: R =COOH : R$_1$=H$_2$

d: R= CH$_2$OH : R$_1$=H$_2$

e: R=CH$_2$OAc : R$_1$ =H$_2$

f: R =CHO : R$_1$=H$_2$

g: R= COOCH$_3$: R$_1$=H$_2$

42

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48   R= H

49   R= Ac

50
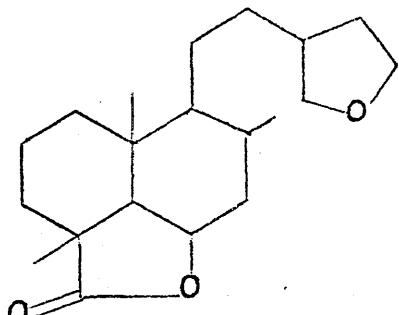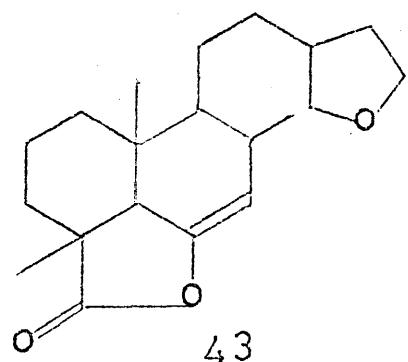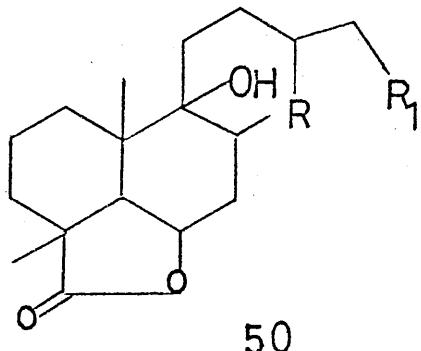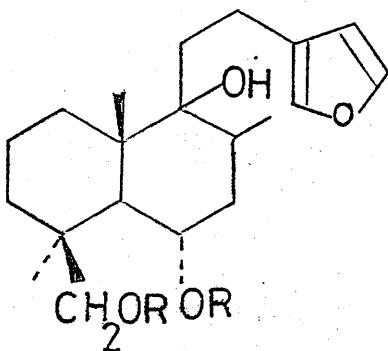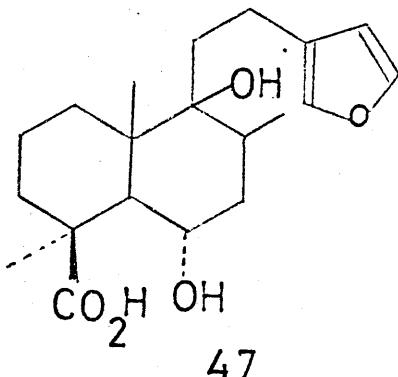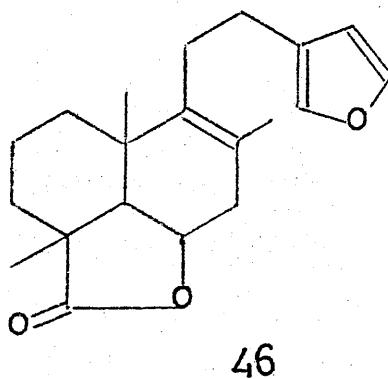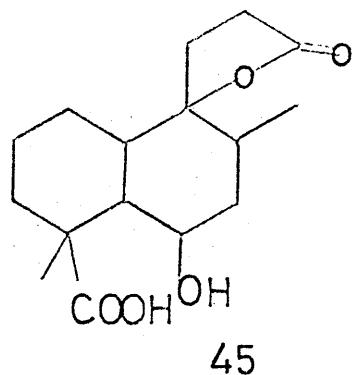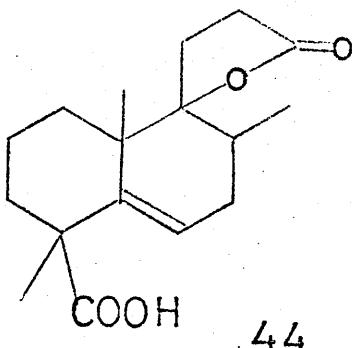
a : R= CH₂OH : R₁= CH₃
b : R= CH₂OAc : R₁= CH₃
c : R= R₁= CH₃
d : R= CH₃ : R₁= CH₂OH

51
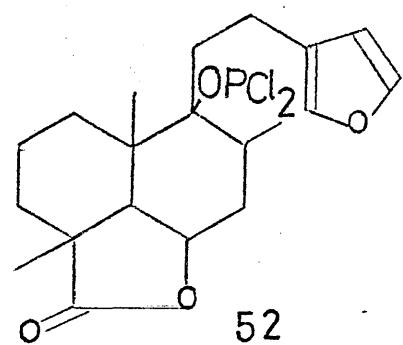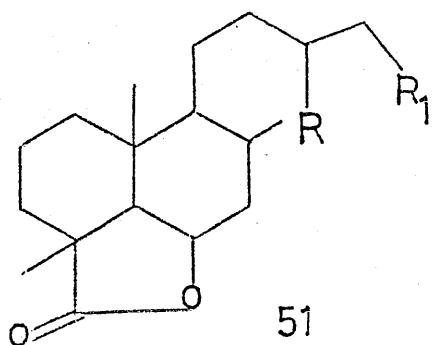
a : R = R₁ = CH₃

$a : R = R_1 = CH_3$

$b : R = CH_2OH : R_1 = CH_3$

$c : R = CH_2OAc : R_1 = CH_3$

$d : R = CH_3 : R_1 = CH_2OH$

$e : R = CH_3 : R_1 = CH_2OAc$

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$a : R = H, OH$

$b : R = O$

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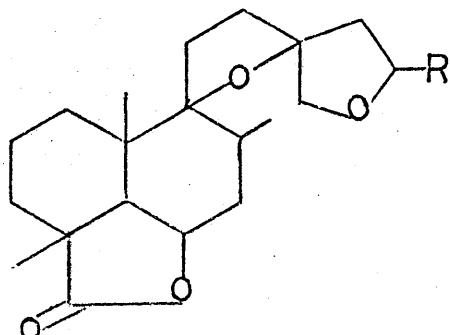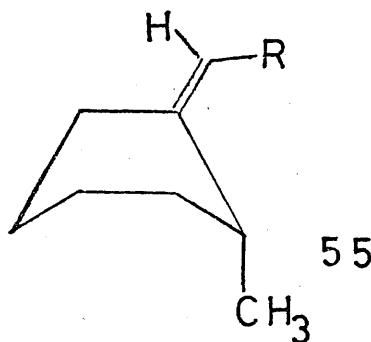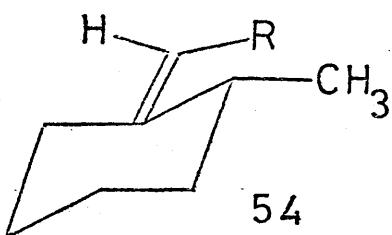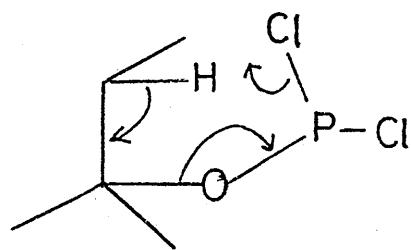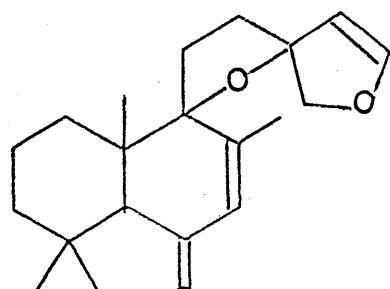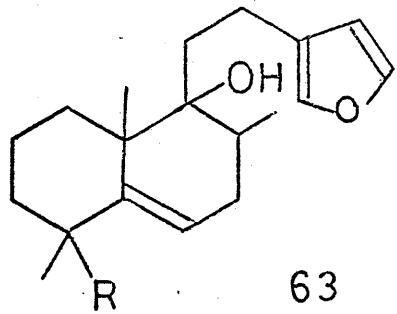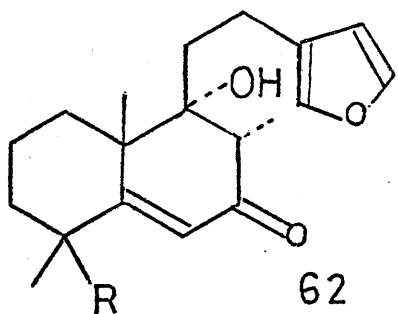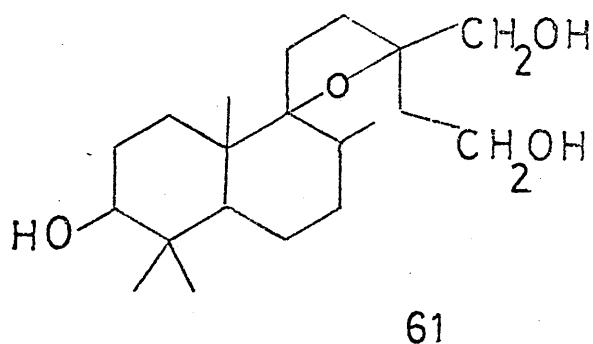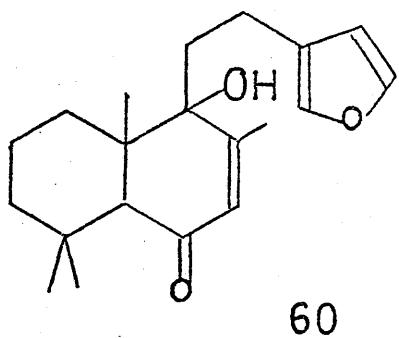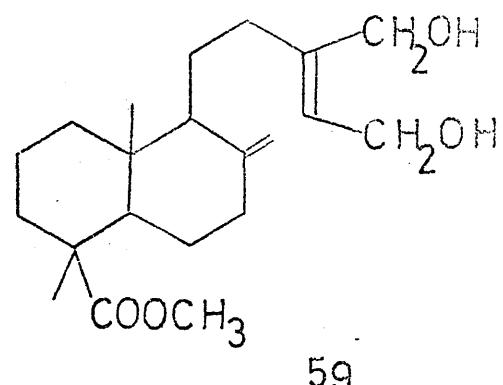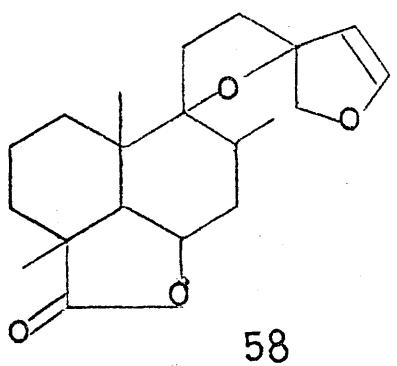
a : R = CH₃

b : R = COOCH₃

c : R = CHO

63

a : R = CH₂OAc

b : R = COOCH₃

c : R = CH₃

d : R = CH₂OH
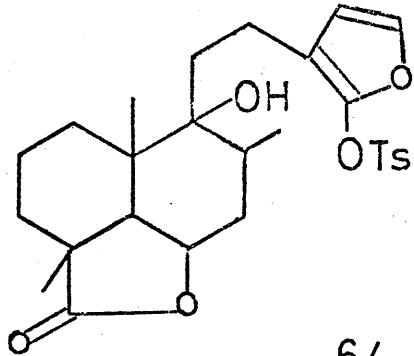
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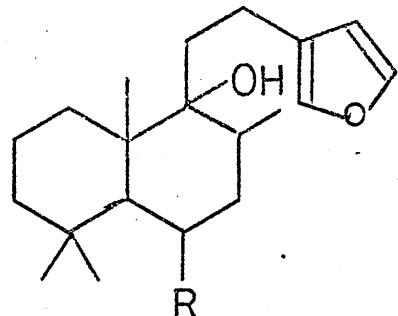
65

a : R = O

b : R = H, OH

66

Chapter 2.

Rearranged Labdanes.

In recent years a rapidly expanding class of
diterpenoids with a rearranged labdane skeleton has been
intensively investigated. These compounds can be envisaged
as arising from the cyclisation of a geranyl-geraniol or
geranyl-linalool" precursor followed by a series of concerted
1, 2 methyl and hydride ion migrations (see figure ι). If
the migrating axial groups were to retain their configurational
integrity this would result in the stereochemistry shown in
figure ι for a precursor with the 10 β methyl labdane
configuration. In many members of this class the resulting
backbone stereochemistry, established in some cases by X-ray
analysis, is indeed in accord with a concerted rearrangement
of this type.

Clerodin (1) the bitter principle of Clerodedron
infortunatum was first isolated[1] in 1936 but the correct
structural formula was not obtained until 1961 when the
constitution and stereochemistry were established by an
X-ray crystallographic study[2] of the derived bromo-lactone
(2). Before these results were available partial structures[3]
had been advanced on the basis of chemical and spectroscopic
evidence. Preliminary investigation showed that clerodin had
two acetoxy groups, one secondary and the other primary, in
a cis 1,3 relationship since deacetyltetrahydroclerodin (3)
could be converted into a cyclic carbonate on treatment with
ethyl chloroformate. The other functionalities in the
molecule consisted of an enol ether system contained in a

five membered ring, a 1,1 disubstituted epoxide and a
relatively inert ethereal oxygen atom which was shown to be
attached to the carbon atom carrying the oxygen of the
cyclic vinyl ether. The steric relationship of the epoxide
and the 1,3 glycol system was demonstrated chemically and
by n.m.r. experiments. The absolute configuration was
based on the optical rotatory dispersion curves of the
keto-tosylate (4) and the keto-acid (5) which were
enantiomeric with respect to that of a 6-keto trans A/B
steroid.

It has been suggested[4] that colombo root probably
contains only one compound of the composition $C_{20}H_{22}O_6$,
namely columbin (6) which is converted into its C - 8
epimer by treatment with alkali. The other naturally
occuring diterpenoids from this source[5] have the molecular
formula $C_{20}H_{22}O_7$ and are all epoxides. Jateorin (7) is
2,3 epoxy-columbin, chasmanthin (7a) is epimeric (at C - 12)
with jateorin while palmarin (7b) is the C - 8 epimer of
chasmanthin. 8 epi-jateorin may not occur naturally.
Palmarin was shown[6] to contain a β -substituted furan ring,
two δ lactone groups and a tertiary hydroxyl function.
The epoxide ring was shown to be located in a $\beta\alpha$ relationship
to the lactone in ring A of palmarin by careful analysis of
the nuclear magnetic double resonance experiments performed
on the derived keto-formate (8). Barton's original[7]
suggestion that columbin could arise biogenetically from a
labdane precursor by a series of methyl migrations would
indicate that columbin and its congeners had an A/B trans

ring fusion. Octahydroisocolumbinic acid (9) on hydrolysis
afforded the isolactone (10) which was converted into the
nor-ketone (11). A mixture of 1,4 ene-dione esters (12)
was obtained from the hydroxy-keto-ester (13) upon oxidation
with chromic acid and selenium dioxide. These results accord
only with an A/B cis fused ring junction. The absolute
configuration followed from the optical rotatory dispersion
curves and was confirmed by an X-ray analysis of the derived
iododiphenylnitrilimine (14).

Cascarilla bark is the source[8,9] of two furan-containing
diterpenes with the rearranged skeleton, namely cascarillin
A (15) and cascarillin, a mono-acetate (16a) which had been
known since 1896. The constitution and relative
stereochemistry of the latter as (16a) was determined from
the X-ray analysis of the iodoacetate (16b). This structure
superceded that shown in (17) which had been deduced from
extensive degradative and spectroscopic evidence. A
limitation on the location of the oxygen atoms was imposed
by the knowledge that both the acetoxy group and the
furfuryl-hydroxyl group were attached to carbon atoms δ to
the aldehyde function since acid treatment of deacetyl-
cascarillin (16c) gave the stable acetal (18). This acetal
was also isolated from similar treatment of cascarillin A,
indicating that it must have the same carbon skeleton as
cascarillin. In addition, the presence of an epoxide ring
and a secondary hydroxyl group in cascarillin A was deduced
from its n.m.r. spectrum. The absence of carbonyl
absorption in the i.r. was taken to indicate that the

aldehyde group was involved in hemi-acetal formation and confirmed by its oxidation to a keto- γ -lactone (19).

The oleoresin of <u>Hardwickia pinnata</u> has been shown[10] to consist of a series of sesquiterpenoids and a series of closely related diterpenoids. From the diterpenoid fraction five new compounds, three acids and two alcohols, were isolated. Hardwickiic acid, $C_{20}H_{28}O_3$ (20a) was seen from n.m.r. and i.r. evidence to contain a β -substituted furan ring, an $\alpha\beta$ -unsaturated acid and one secondary and two tertiary methyl groups. Hydrogenation over Rh-C afforded a tetrahydro-derivative, the n.m.r. of which still showed a resonance arising from an olefinic proton, while prolonged hydrogenation yielded a fully saturated hexahydro-compound indicating that hardwickiic acid has three ethylenic bonds and therefore must be bicyclic. Dehydrogenation over 10% Pd-C furnished a mixture of 1,2 dimethyl - and 1,2,5 trimethylnaphthalenes (21a and 21b respectively). From biogenetic considerations the structure (20a) was proposed for the acid. Dextrarotatory hardwickiic acid $[\alpha]_D = + 125^\circ$ has been isolated[11] from <u>Copaifera officinalis</u>. The melting point of a mixture of the two acids was 50° higher than the melting point of the individual components, behaviour typical of certain racemic compounds. The dicarboxylic acid, kolavic acid (22a), on dehydrogenation gave the same mixture of naphthalenes showing that it was closely related to hardwickiic acid. That both carboxyl groups were in conjugation with a double bond was deduced from the u.v. spectra of the acid and its methyl ester. Two moles of

hydrogen were taken up on hydrogenation over Pt indicating

the presence of only two double bonds and the attachment of

a methyl group to one of these bonds was deduced from the

presence of a doublet at 7.9 τ in the n.m.r. spectrum.

From this evidence kolavic acid was formulated as (22a) and

this was confirmed by a correlation with hardwickiic acid,

both compounds being converted into the same diacetate (23a).

The remaining acid, kolavenic acid (22b) was isolated as

its methyl ester. Spectral data indicated the presence of

one secondary, two tertiary and two vinylic methyl groups

in the acid and thus suggested a structure (22b) which was

confirmed by a direct interrelation with kolavic acid through

the hydrocarbon (23b). Hydride reduction of kolavenic acid

afforded an alcohol, kolavenol (22d) which was identical with

one of the naturally occuring alcohols from the oleoresin.

Kolavenyl acetate on selenium dioxide oxidation gave as the

main product, the compound (24) which was transformed into

methyl hardwickiate (20b) on shaking with Amberlyst-15.

The other alcohol, kolavelool (25)[12] was isomeric with

kolavenol and its structure proved by a partial synthesis

from this compound. The aldehyde (22c) obtained from

kolavenol by manganese dioxide oxidation, on treatment with

hydrogen peroxide furnished an epoxy-kolavenal. Reaction

with hydrazine hydrate and acetic acid afforded an allylic

alcohol (25) which proved to be indistinguishable from an

authentic sample of kolavelool.

Experimental support[13] for the positioning of the

angular methyl groups of hardwickiic acid as shown (20a)

came from degradative work which also led to the
elucidation of the absolute stereochemistry at the various
asymmetric centres. The two major products (26 and 27) of
ozonolysis of hardwickiic acid both showed in their n.m.r.
spectra that the resonance of one of the teriary methyl
groups had suffered a downfield shift to 8.8 τ , a value
acceptable for a methyl group adjacent to a carbomethoxy
function. This was taken to indicate the presence of a
C - 5 methyl group. Introduction of a double bond in
conjugation with the ketone of (27) furnished the compound
(28) whose n.m.r. spectrum showed the two olefinic protons
as an AB quartet with no further coupling indicating a
fully substituted C - 9 position. The triester (26) was
converted into a substituted cyclopentanone (29) with a
strong negative circular dichroism effect. Since this curve
was the mirror image of that of a normal 17-keto-steroid it
was concluded that the rings were trans fused but with the
opposite absolute stereochemistry. From the n.m.r. of the
derived keto-ester (30) it was seen that the ester function
had no shielding effect on the C - 5 methyl group and
therefore was β -oriented since in the alternative α
configuration the C - 5 methyl would have a 1,3 diaxial
relationship with the ester and lie in the shielding zone of
the ester carbonyl group. The diester (28) was converted
into the keto-ester (31) and in its n.m.r. spectrum the
C - 8 methyl resonance appeared as a doublet centred at
8.81 τ , having suffered a paramagnetic shift of about 21
c./sec. The C - 8 methyl group was therefore assigned the

equatorial configuration. The absolute stereochemistry of
the remaining naturally occuring compounds follows from
their relationship with hardwickiic acid.

A root and bark extract of Tinomiscium philippinense,
a plant of the same family as Jatorrhiza palmata from which
columbin (6) has been isolated furnished[14] a furanoid methyl
ester for which structure (32) was proposed. In the carbonyl
region of the infra-red spectrum were peaks characteristic of
an $\alpha\beta$ unsaturated ketone and ester and a δ lactone.
Reduction with zinc and acetic acid gave the saturated ketone
(33) as expected. In the high resolution n.m.r. spectrum in
benzene the C - 1 protons showed, in addition to the geminal
coupling, coupling to the C - 10 proton indicating the
absence of a methyl group at this position. However no
evidence was presented which would allow the assignment of
stereochemistry at either the ring junction or at any of
the remaining asymmetric centres.

From chemical and spectroscopic evidence the structure
(34a) was suggested[15] for olearin, a neutral diterpenoid
from Olearia heterocarpa. The presence of two $\alpha\beta$ unsaturated
carbonyl groupings was deduced from the i.r. and u.v.
absorption while the i.r. spectrum of the tetra-hydro
derivative (35a) indicated that both these functions are
present in γ lactone rings. That the remaining oxygen atom
is present as a secondary hydroxyl group was deduced from its
ready oxidation to the corresponding ketone (35b). Treatment
of this ketone with alkali gave formaldehyde by a
retro - aldol condensation showing that a newly formed

hydroxyl, from opening one of the lactone rings, must be in a β position to the keto group. The n.m.r. spectrum of olearin proved most informative showing resonances attributable to a β -substituted butenolide, two methyl groups, one secondary and the other tertiary, one vinyl proton adjacent to a methylene group and a - CH_2 O- attached to a fully substituted carbon atom. The protons of the trans double bond of anhydro-olearin (36) formed via the methane-sulphonate (34b) both appear as doublets showing no further coupling, consistent with olearin having a rearranged labdane skeleton. The relative stereochemistry of olearin implied in (35a) is based on biogenetic considerations.

A light petroleum extract of the heartwood of Plathymenia reticulata was found[16] to contain plathyterpol, an oily diterpenoid which was deduced to have the structure (37) from spectroscopic and degradative studies. The n.m.r. spectrum of the derived $\alpha\beta$ -unsaturated ketone (38) showed the protons α to the carbonyl function to be the AB part of an ABX system. Furthermore the C - 10 proton appeared to be equatorial to ring A and thus the A/B ring fusion was unexpectedly cis as in columbin. In order to resolve this problem the crystalline dibromoketone (39) was prepared and subjected[17] to X-ray analysis which confirmed the previous tentative stereochemistry at the ring junction.

An extract of the leaves and twigs of Croton lucidus, a member of the Euphorbiaceae, the family to which Croton eleuteria (the source of the cascarillins) also belongs, furnished[18] the norditerpenoid crotonin (40). The i.r.

spectrum lacked hydroxyl absorption but indicated the

presence of a ketone, a saturated γ lactone and a

β -substituted furan ring. The n.m.r. spectrum revealed

no further unsaturation while in the methyl region there

were two doublets from two secondary methyl groups.

Catalytic hydrogenation over Pd furnished the tetrahydro-

acid (41) showing that the ethereal oxygen atom in the

lactone is allylic to the furan ring. The n.m.r. spectrum

of the corresponding aldehyde showed this proton as a singlet

indicating that this group is attached to a fully substituted

carbon atom. The substitution pattern on the bicyclic

nucleus was deduced from the n.m.r. spectrum of the

methylated dehydrogenation product (42a) where the two

aromatic protons had a meta coupling. Oxidation of the ether

followed by treatment with furfuraldehyde furnished the

furfurylidene derivative (42b) whose n.m.r. spectrum showed

the C - 8 proton (now allylic) as a quartet at much lower

field.

An ethereal extract of <u>Dodonaea attenuata</u> gave[19] as the

major acidic constituent the hydroxy-acid (43a) whose n.m.r.

spectrum showed signals attributable to a β -substituted

furan ring, a tertiary methyl and an acetate group and an

$\alpha\beta$ enone system which includes a β carbon atom bearing a

proton and a methylene group. The steric relationship of

the acid and the primary hydroxyl functions was established

by the formation of an $\alpha\beta$ -unsaturated- γ -lactone on

treatment with dicyclo-hexylcarbodiimide. The n.m.r. spectrum

of this lactone showed the C - 19 protons as an AB system

indicating that this methylene group was attached to a fully saturated carbon atom. In the derived aldehyde (44a) the C - 17 proton appeared as a doublet showing that the adjacent carbon atom bears one proton. The relative positions of the acetoxy-methyl group and the β -substituted furan in (44b) were established by its conversion into the keto-lactone (45), the formation of a cyclopentanone indicating that there are four carbon atoms linking the primary acetate to the furan ring. In the product (46) of further degradation the vinyl proton resonated as a triplet and the C - 11 protons as a doublet, with no further coupling. Evidence for the decalin ring system was obtained by selenium dehydrogenation of (44c) which gave 1,2 dimethylnaphthalene. The relative stereochemistry shown in (43a) was assigned on the basis of chemical and spectroscopic evidence while the absolute configuration followed from the strong positive Cotton effect of the cyclopentanone (45) similar to that of 23,24-bisnor-Δ-(4)-nor-5 β (II)-lupan-3-one (47).

A methylated extract of D. attenuata A. Cunn. var. linearis Benth. after chromatography on alumina afforded[19] the lactone (48). Saponification furnished the hydroxy-acid (43b) which on sodium-ethanol reduction was converted into the saturated lactone previously prepared from the acetoxy-acid (43a) thus establishing the structure and stereochemistry of the lactone. The physical constants of the hydroxy-acid (43b) and the lactone (48) suggested that they are identical with hautriwaic acid (isolated in 1936[20] from D. viscosa) and its derived lactone.

<u>Teucrium polium</u>[21] has been a rich source of highly
oxygenated furanoid diterpenes with a rearranged labdane
skeleton, ten closely related crystalline compounds having
been isolated. Of these, complete structures have been
deduced for three and partial structures for five, only
insufficient material preventing pure samples of the
remaining compounds from being obtained. The major
component, picropolin (49a) was seen from its spectral
properties to contain a β -substituted furan ring, an α
ketol, a γ lactone, an epoxide and a primary acetate group.
Hydrogenolysis of picropolin over Pd furnished an acid (50)
which did not contain a lactone indicating that the lactone
ethereal oxygen atom was in an allylic position to the furan
ring. Hydride reduction of the lactone to a hexa-ol
followed by acetylation afforded a tetra-acetate (51a) and a
penta-acetate (51b) indicating the tertiary nature of the
sixth hydroxyl function. These results are consistent with
the opening of a primary-tertiary epoxide. Sodium carbonate
treatment of picropolin produced not desacetylpicropolin but
an isomer (52a) which on reacetylation gave isopicropolin
(52b) which was identical with one of the naturally occuring
acetates. A third compound, the diacetate (49b) was
obtained from picropolin by direct acetylation. The
remaining compounds, two monoacetates, one diacetate, and
two which do not contain acetoxy groups, all appeared to be
of similar structure, having a β -substituted furan ring
and a γ lactone.

Diosbulbins A, B and C (53a, 54 and 53b) from the
root tubers of <u>Dioscorea</u> <u>bulbifera</u> are the first terpenoids
reported[22] in Dioscoreaceae and the first furan-containing
diterpenoids in Monocotyledoneae. All three compounds, from
their analytical data, appeared to be norditerpenoids.
They had certain structural features in common, namely a
β -substituted furan ring, a γ lactone, an ether bridge
and one tertiary methyl group. Diosbulbin B, the main
constituent, had an additional γ lactone while C was a
hydroxy-acid, methylation of which gave a methyl ester
identical in all respects with compound A. Hydrolysis of
B with sodium hydroxide in aqueous pyridine afforded a
carboxylic acid which proved to be indistinguishable from
Diosbulbin C. Hydrogenation of B produced, in addition to
the corresponding tetrahydro-derivative, the tertiary
alcohol (55), the product of hydrogenolysis of the ether
linkage, thus establishing the relative positions of the
ether and the furan ring. The points of attachment (C-4 and
C-8) of the γ lactone rings to the bicyclic nucleus were
established from the product of selenium dehydrogenation.
The other points of attachment at C - 2 and C - 6
respectively were proved by further degradative work. The
secondary hydroxyl group in compounds A and C proved to be
sterically hindered resisting both acetylation and Sarett[23]
oxidation but it was converted into the corresponding
ketone using Snatzke's[24] conditions. The assignment of
stereochemistry was based largely on a careful study of a
series of optical rotatory dispersion curves which after

application of the lactone sector rule indicated that the
A/B ring system was trans fused, both lactones were cis
and α oriented, and the methyl group and the side chain
were β oriented. These findings were substantiated by
nuclear magnetic double resonance experiments. Saturation
of the β-furan proton signal gave rise to a 16% increase
in the tertiary methyl resonance while a similar experiment
on the latter produced a 20% increase in that of the furan
proton.

A novel bicyclic diterpene, portulal (56) which
contains a perhydro-azulene skeleton has been isolated[25]
from Portulaca grandiflora. Its spectral properties are
consistent with its containing a secondary and a vinyl
methyl group, two double bonds, three primary hydroxyl
groups and an isolated tertiary aldehyde. The molecular
structure, stereochemistry and absolute configuration were
determined from a three-dimensional X-ray diffraction study
of the derived brosylhydrazone. A biogenetic route to
portulal from a geranyl-geraniol precursor was suggested and
is as shown in figure 2 .

An extract of Fibraurea chloroleuca has been shown[26] to
contain the new columbin-type furanoid diterpene fibleucin
(57). The presence of two δ lactone rings was deduced from
its absorption in the i.r. while the similarity of its n.m.r.
spectrum to that of columbin indicated that one of the
lactones was present in ring A. Hydrogenation of fibleucin
furnished an unsaturated carboxylic acid (58) as expected
for a lactone in a position allylic to a furan ring.

In addition to the diterpenoids discussed above an alkaloid, thelepogine (59) which also has a rearranged labdane skeleton has been isolated[27] from the grass Thelepogon elegans. In this case however only a partial rearrangement has taken place in which the migration of the C - 4 methyl to C - 5 has not been followed by the hydride ion shift from C - 5 to C - 10. The structure was established[28] by an X-ray examination of the derived methiodide.

Diterpenoids from the Solidago Species.

Golden rod, the popular name for plants of the genus Solidago, is of the natural order Compositae. There are approximately 120 species, found chiefly in North America although a few do occur in Europe. The most common golden rod (S. canadensis) is a North American species, S. virgaurea being the only member of the genus native to Britain. Hybridisation between closely related species occurs freely in nature, making identification of species difficult.

Previous[29] chemical studies of various Solidago species have led to the isolation of a number of polyphenolic compounds while matricaria ester[30](60) and 8 cis αβ dihydromatricaria ester[31](61) have been obtained from S. virgaurea and S. sempervirens respectively. S. canadensis has been the object of several investigations. In 1947 Houston and Burrell[32] isolated, from the roots of this plant, a diterpene $C_{20}H_{28}O_3$ m.p. 80-90° but did not suggest a structure for the compound. The Czech workers Krepinsky and Herout[29] in 1962 reported the isolation of two alcohols, one a diterpene $C_{20}H_{34}O$ m.p. 169° and the other a triterpene $C_{30}H_{52}O_2$ m.p. 214-215° from an ethereal extract of the same plant. From S. canadensis and S. gigantea Gerlach[33] obtained the diterpene m.p. 131-132° previously isolated by Houston and Burrell and proposed the structure (62) which has a molecular formula $C_{20}H_{26}O_3$ despite the fact that his mass spectrometric determination

indicated a molecular weight of 316 corresponding to a

molecular formula of $C_{20}H_{28}O_3$.

During an examination of members of the Compositae

family for acetylenic compounds Anthonsen[34] also investigated

S. canadensis and isolated this diterpene in good yield.

From its spectral properties he recognised that it contains

a β-substituted furan ring. The presence of a hydroxyl

group was shown from the peak at M - 18 in the mass spectrum

but the intensity of this peak was much less than that of

the parent, an effect similar to that seen in the mass

spectrum of marrubiin[35]. The constitution of solidagenone as

(63) was proposed[36] on the basis of its spectroscopic and

chemical properties by members of this department working

in collaboration with Anthonsen. The presence of the $\alpha\beta$ -

unsaturated keto function was detected from the carbonyl

absorption at 1678 cm^{-1} in the i.r. spectrum, the enone

absorption in the u.v. being seen as a narrow band at 234 mu

after subtraction of the furan absorption of marrubiin.

That solidagenone contains a hydroxyl group was determined

from the n.m.r. spectrum where a concentration-dependent

one proton singlet at about 8 τ disappeared upon the

addition of heavy water. Since there was no resonance

attributable to a proton of the type $\underline{H}$ - C - OH it was

concluded that the hydroxyl is tertiary. These facts

readily explained the known[34] chemical properties. The

assignment[37] of stereochemistry was initially envisaged as

involving a correlation with marrubiin (64). It was hoped

that both compounds could be converted into the same

ketone (65) but solidagenone could not be reduced to the required compound. The dihydro derivative obtained by hydride or by catalytic reduction had a C - 8 axial methyl group (from n.m.r. evidence). However the $\beta\gamma$ unsaturated ketone (66) obtained from lithium-ammonia reduction of solidagenone was identical with the product of phosphoryl chloride - pyridine dehydration of the ketol (63) from narrubiin thus proving the stereochemistry at C - 5 and C - 10. The configuration at C - 9 was derived from the product of epoxidation (67) of the double bond in the $\beta\gamma$ unsaturated ketone. This epoxide was rapidly converted into solidagenone (63) indicating the formation of an α epoxide and ring opening to form a 9 α hydroxyl group.

It has been suggested[37] that solidagenone may in fact be an artefact since no solidagenone was obtained on concentration of a light petroleum extract of the plant. Instead a crystalline compound $C_{20}H_{28}O_3$ m.p. 108-109°(68) was isolated which on spectral evidence was apparently an approximately 1 : 1 mixture of two compounds epimeric at C - 13. These ethers were isomerised in high yield into solidagenone on heating in refluxing ethanol. These findings may explain the apparent change[32,33] in the melting point of solidagenone on recrystallisation.

An acetoxy monobasic carboxylic acid solidagonic acid $C_{22}H_{34}O_4$ (69a) has been isolated[38] from a root extract of <u>S. altissima</u>. The presence of several structural features was readily deduced from the n.m.r. spectrum of its methyl

ester (69b):   namely, a secondary acetate group (a one
proton signal at about 4.95 τ), a proton and a methyl
group attached to a double bond (a broad one proton signal
at 4.95 τ and a three proton singlet at 8.27 τ), two
tertiary methyl groups (singlets at 9.03 and 8.82 τ) and
one secondary methyl group (doublet centred at 9.09 τ).
That the carboxyl group was in conjugation with an olefinic
bond was seen from the u.v. absorption at 217.5 mu
(ϵ = 15400) and that this double bond also carries a
proton and a methyl group was deduced from the n.m.r.
resonances at 4.44 τ (one proton singlet) and 7.85 τ
(three proton doublet). The positions of the various
groups attached to the bicyclic nucleus were determined
from the products of selenium or 10% Pd/C dehydrogenation
of several derivatives. The structure (69a) involving a
rearranged labdane skeleton was proposed for this acid.
This was confirmed by a study of the n.m.r. spectrum of
the derived saturated ketone (70) which shows the presence
of three protons in positions α to the carbonyl function.
A quartet centred at 7.53 τ was assigned to a C - 8 proton
coupled only to the three protons in the secondary methyl
group while the two C - 6 protons appeared as two clean
doublets centred at 8.05 and 7.72 τ .

S. elongata Nutt. has been classified as a subspecies
of S. canadensis L. but it has been shown that these plants
are at least chemically distinct since the latter contains
diterpenoids which are considerably different from those
isolated[39] from the former by Anthonsen and McCrindle.

From an ethyl acetate extract these authors have obtained
a series of oily diterpenoids similar to those described
earlier from <u>Hardwickia pinnata</u>[10]. The polar fractions,
after treatment with diazomethane, furnished three methyl
esters one of which was identical to methyl kolavenate
(71a). The n.m.r. spectra of the other esters were similar
to that of methyl kolavenate but showed evidence of
additional ester functions, in one case a secondary
acetate group and in the other a secondary angelate group.
That these esters are located on the bicyclic nucleus and
not in the side chain was demonstrated from their mass
spectra where the most intense peaks result from cleavage
of either the C – 9, C – 11 or the C – 11, C – 12 bonds.
These peaks also occur in the spectrum of methyl
kolavenate. Positions 1 and 2 can also be eliminated
since in the derived ketone (71b) the $\triangle^3$ double bond is
not in conjugation with the carbonyl group nor does it
migrate into conjugation on treatment with basic alumina.
That the esters are located at C – 6 was deduced from
spectroscopic considerations. The considerable changes of
the chemical shift of the C –3 proton and the C – 4 methyl
group on conversion of the acetate (71c) into the alcohol
(71d) and the ketone (71b) can be explained by the
proximity of the substituent and the $\triangle^3$ double bond.
The width ($W_{\frac{1}{2}}$ = 6 c./sec.) of the C – 6 proton resonance was
taken to indicate an equatorial proton and an axial ester
group. Furthermore, in the mass spectrum of the ketone
(71b) the major peaks result from cleavage of the

C - 9, C - 10 and C - 5, C - 6 bonds as expected.

The neutral fraction furnished, in addition to five new butenolides (the "elongatolides") three alcohols of which two, kolavenol (22d) and kolavelool (25) have been obtained[10] previously. The third alcohol, an angeloyloxy-kolavelool was assigned the structure (72) on spectral and biogenetic grounds. The remaining five compounds (73 - 74) all contain a β -substituted $\alpha\beta$ butenolide group. Three of them form an alcohol - acetate - angelate series similar to that found in the methylated fraction. Conversion of the acetate (73b) into the ketone (75) yielded a compound suitable for the study of benzene induced shifts since it contains no additional carbonyl functions. The values obtained accord only with a C - 6 carbonyl group and suggest that ring B must be distorted into a twist - boat conformation.

Biogenesis of the Bicyclic Diterpenoids.
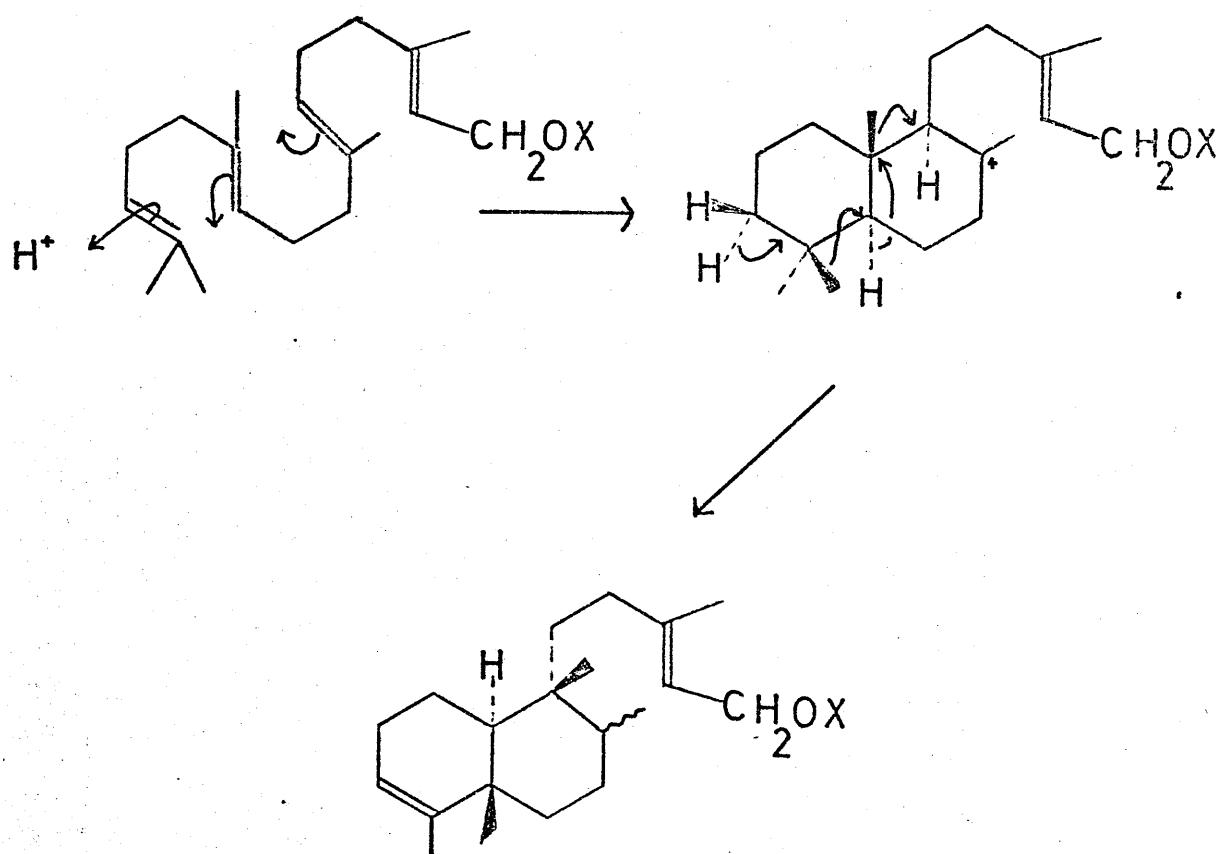

Figure 1

Postulated Biogenesis of Portulal.

Figure 2

1

2

3

4

5

6

7
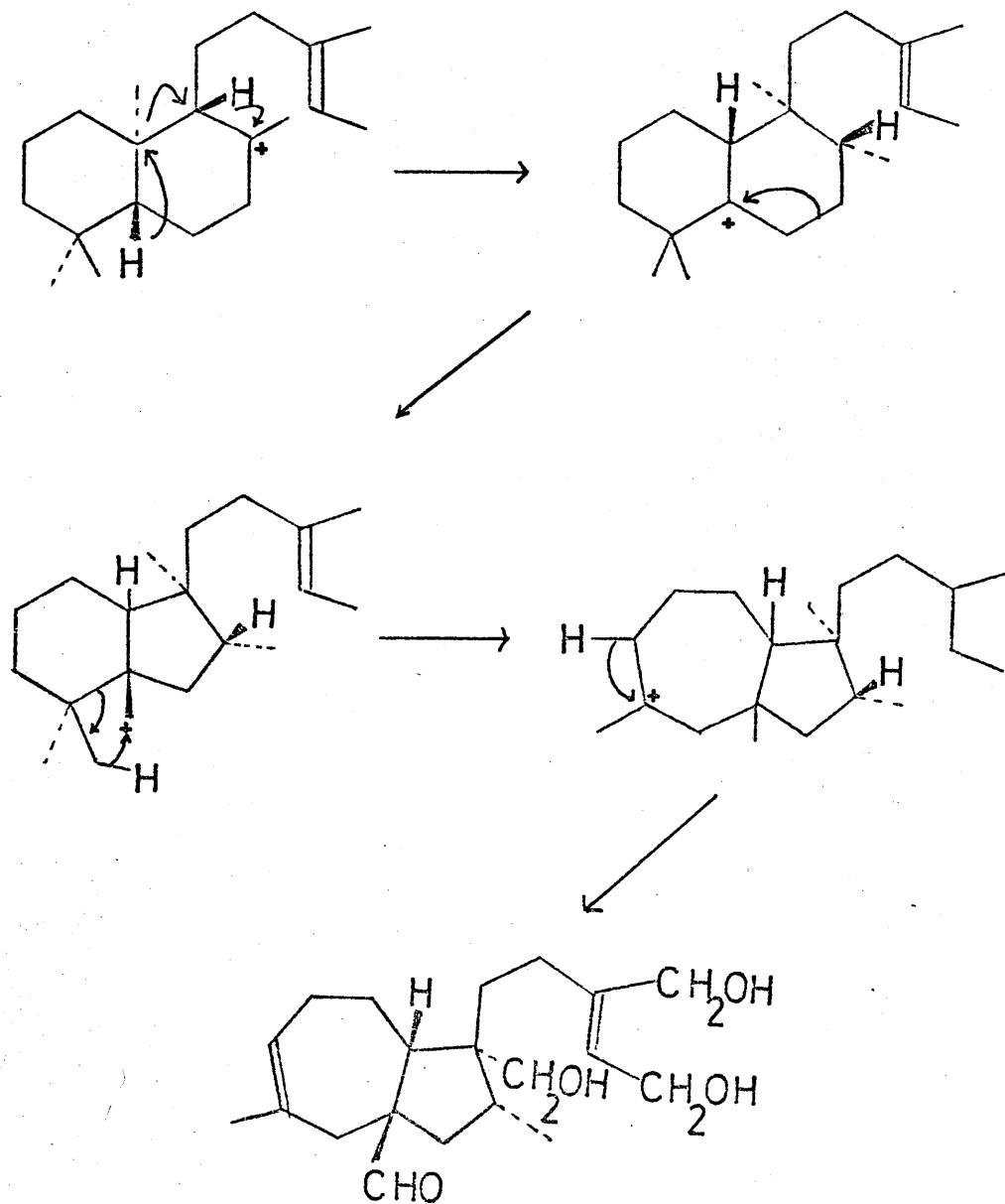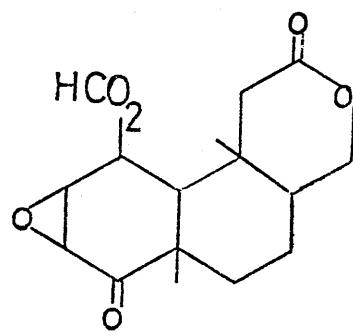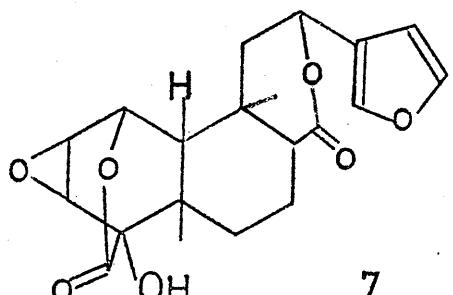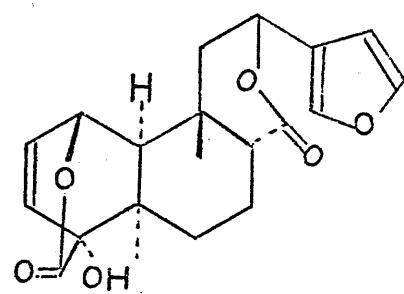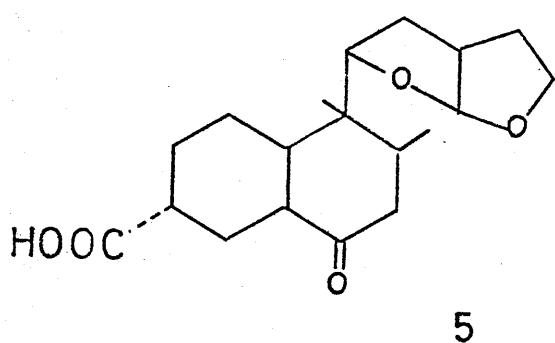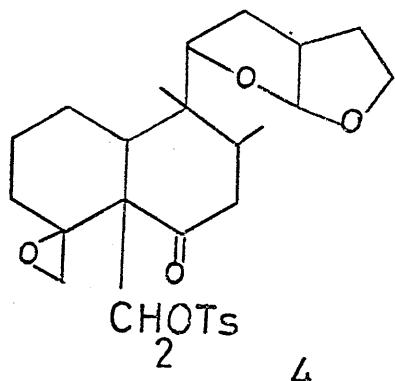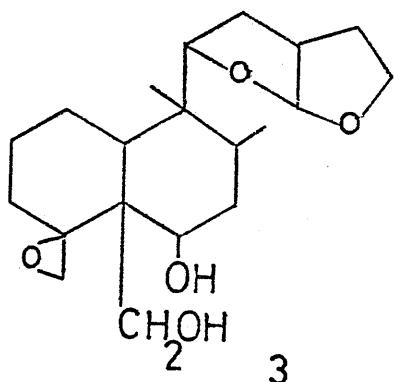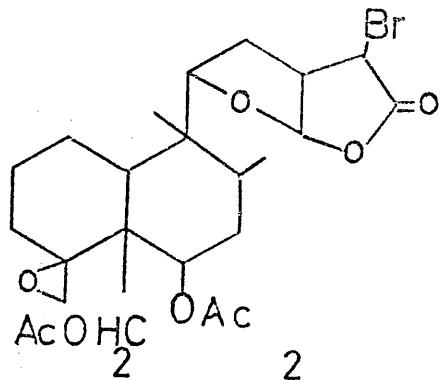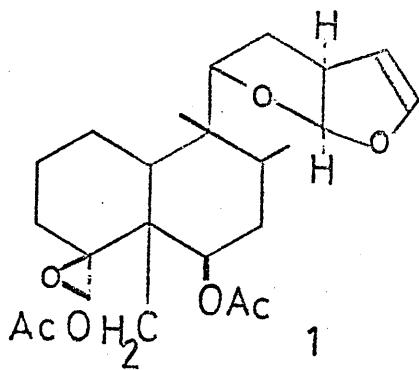
a   12 iso
b   12 iso : 8 iso

8
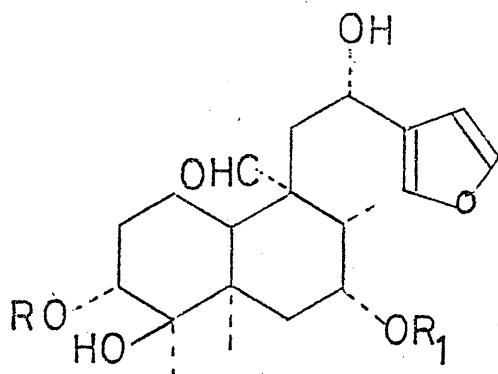
a   R = H : R₁ = Ac
b   R = JCH₂CO : R₁ = Ac
c   R = R₁ = H

16
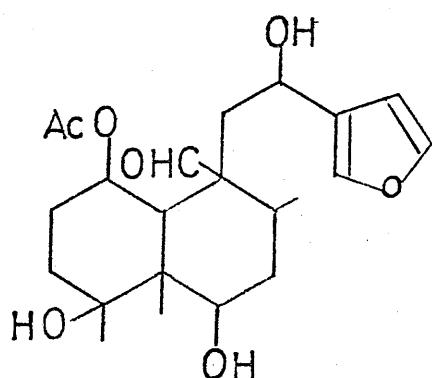
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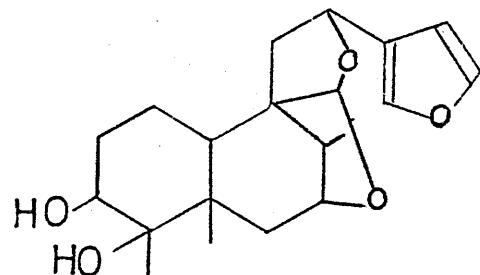
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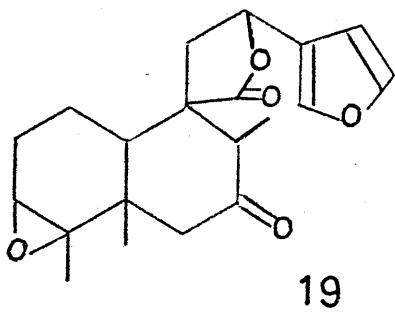
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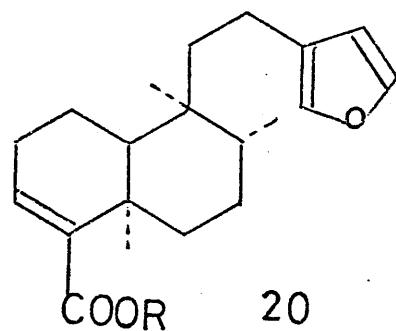
20

a   R = H
b   R = CH₃

21

a   R = H

b   R = CH₃

22
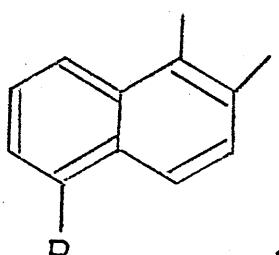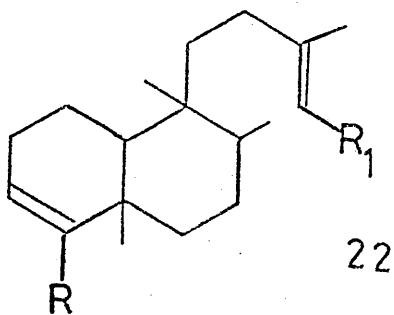
a R=COOH : R₁=COOH
b R=CH₃ : R₁=COOH
c R=CH₃ : R₁=CHO
d R=CH₃ : R₁=CH₂OH

23

a R=OAc
b R=H

24

25

26

27

28

29

30

31

32

33

34

a   R = H,OH

b   R = H,OSO$_2$CH$_3$

35

a   R=H,OH

b   R= O

36

37

38

39

40

HOOC

41

CH₃O—
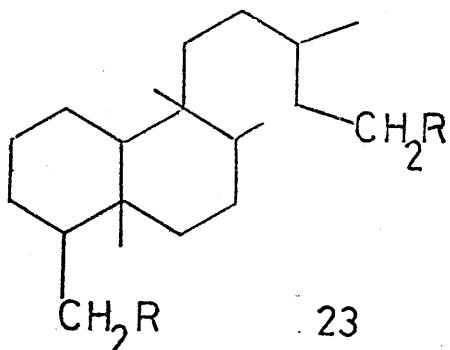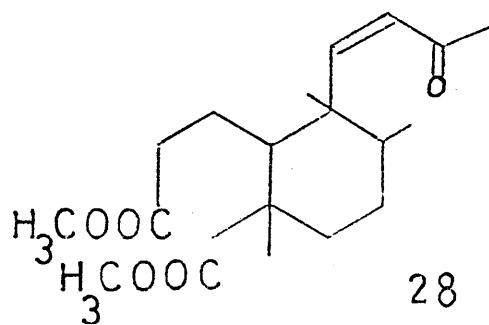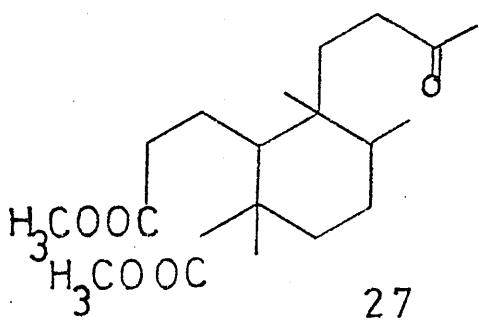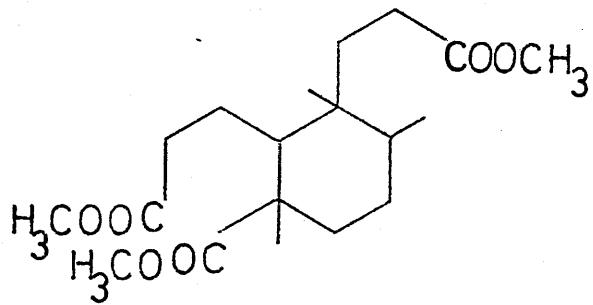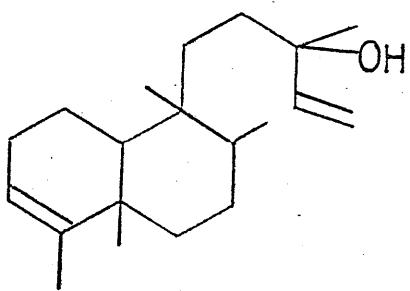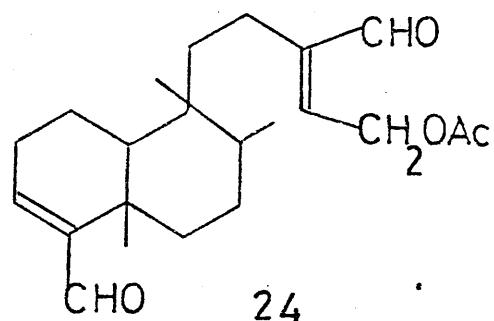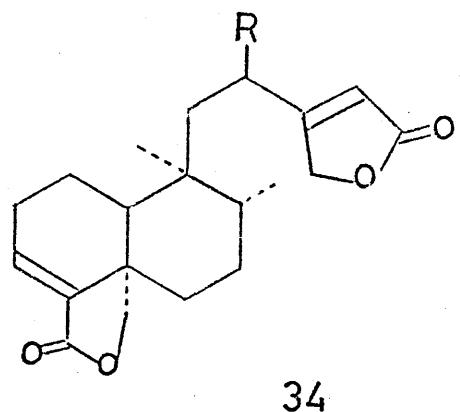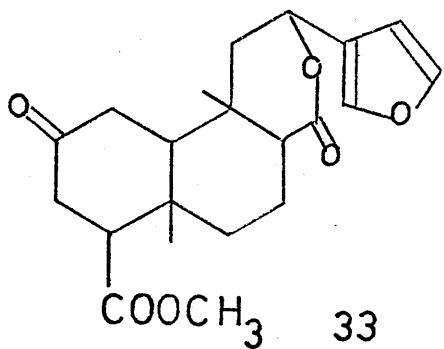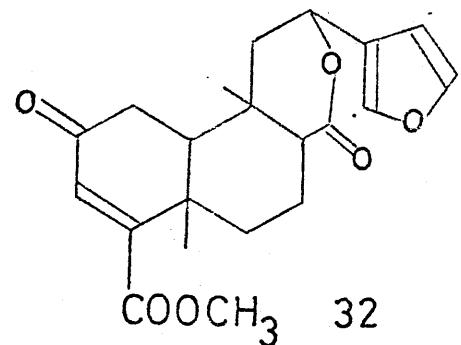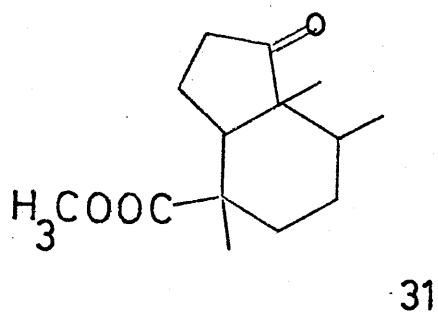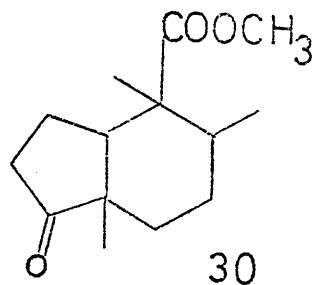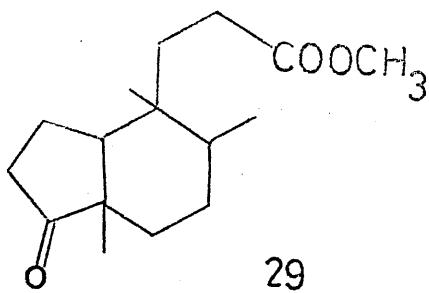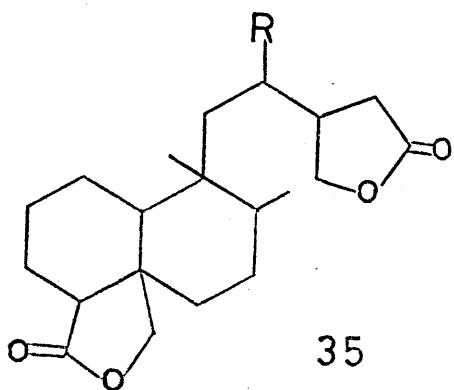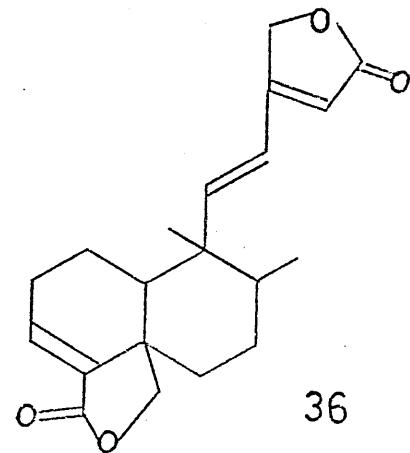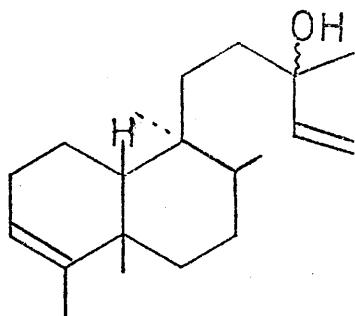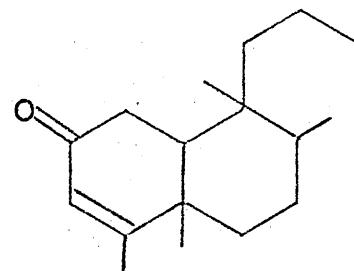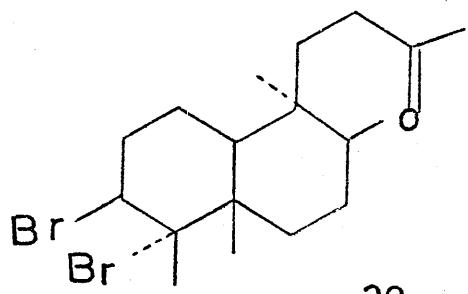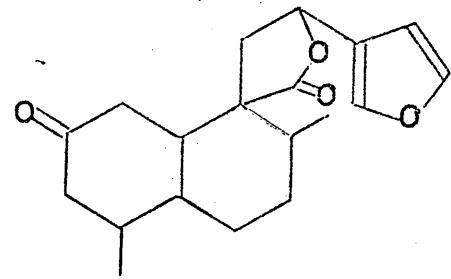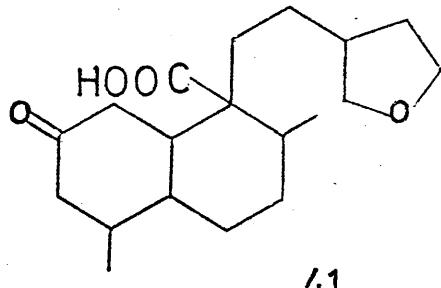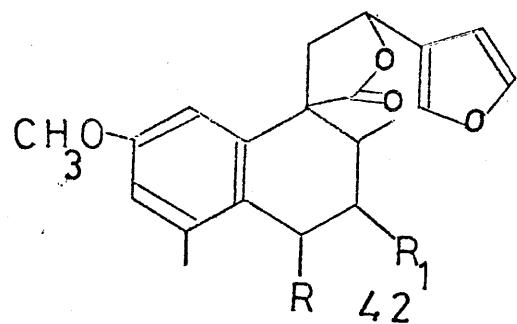
$$a \quad R = R_1 = H_2$$
$$b \quad R = O: R_1 = CH\text{-}Furan$$

42

HOOC CHOH
2

43

$$a \quad R = CHOAc$$
2

$$b \quad R = CH_3$$

44

a R = CHO

b R = CH$_2$OH

c R = CH$_3$

45

46 R = CH=C(Ph)$_2$

47

48

49

a R = H

b R = Ac

50

51

a R = H
b R = Ac

52

a R = H
b R = Ac

53

a R = CH₃

b R = H

54

55

56

57

R= COOH   58

59

$$H_3C - C \equiv C - C \equiv C - C \equiv C - CH = CH - CO_2CH_3 \quad 60$$

$$H_3C - CH = CH - C \equiv C - C \equiv C - CH = CH - CO_2CH_3 \quad 61$$
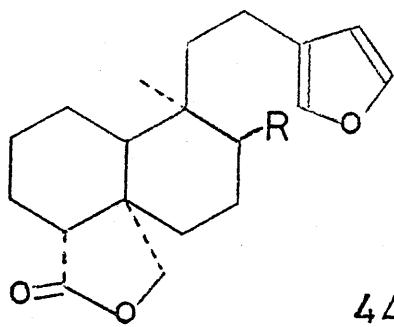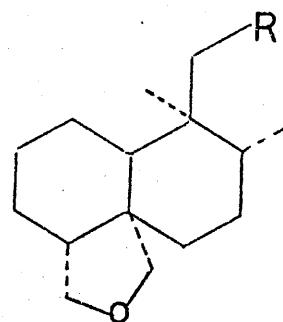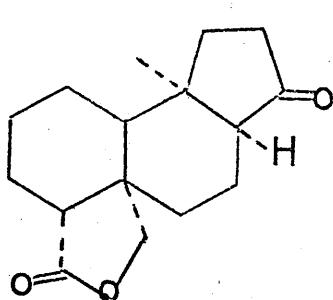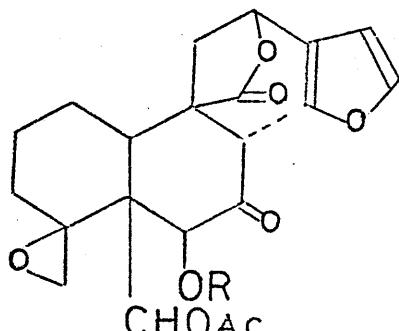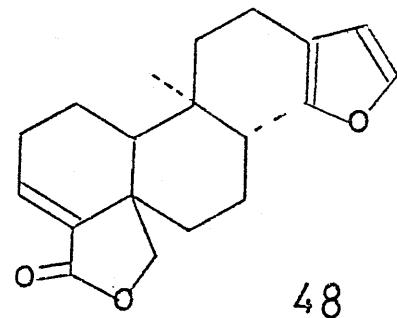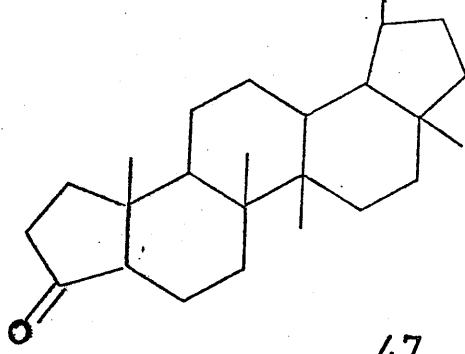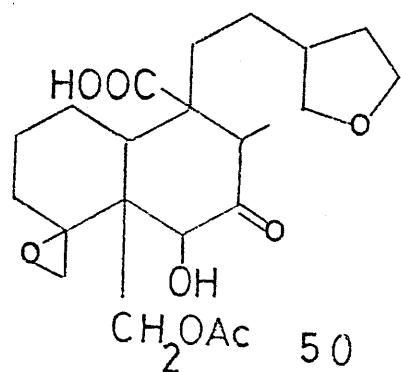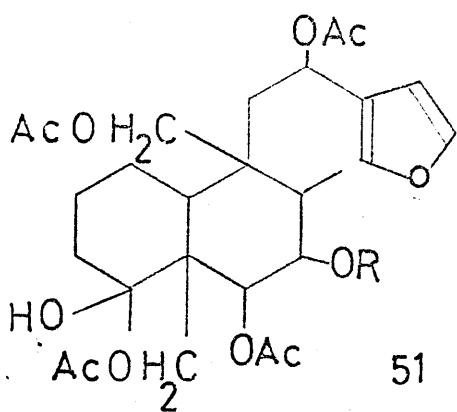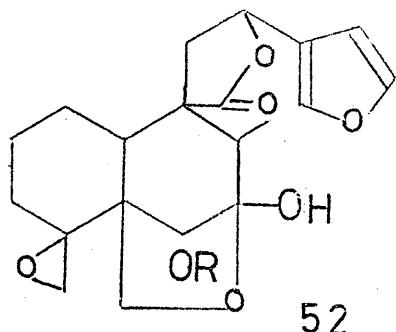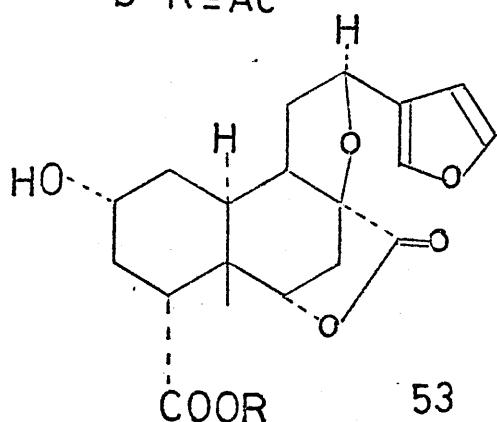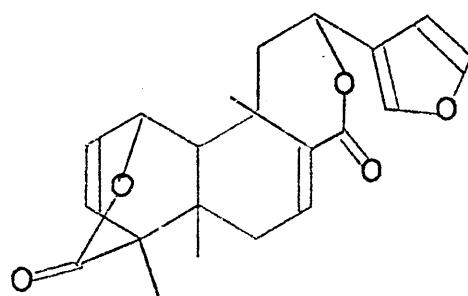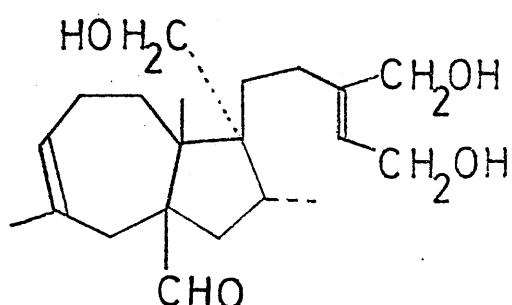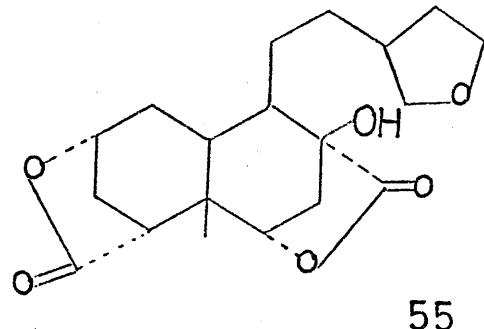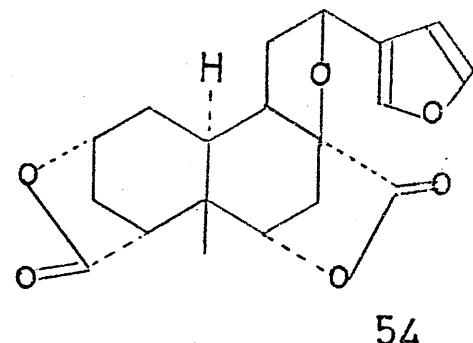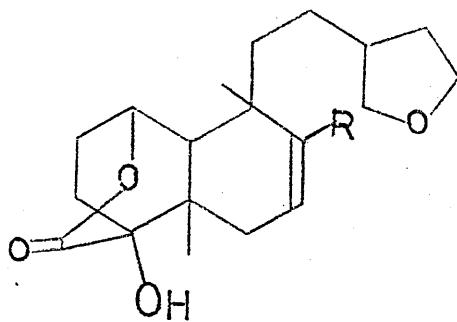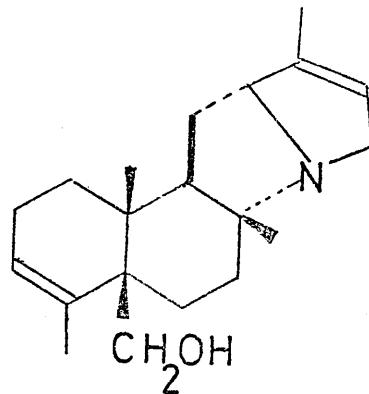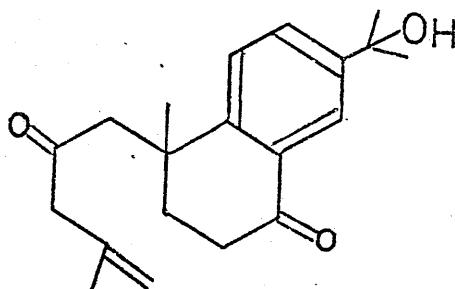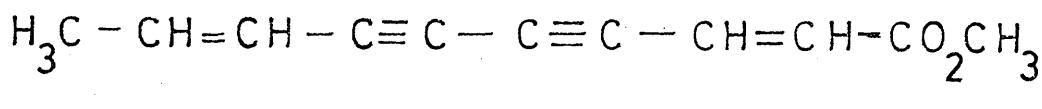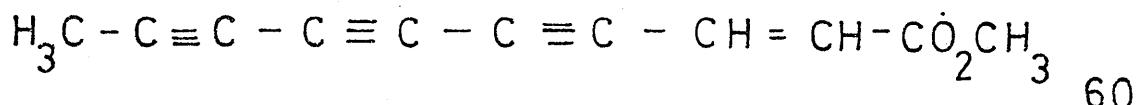
62

63

64

65

66

67

68

69

a : R = COOH

b : R = COOCH$_3$

70

71
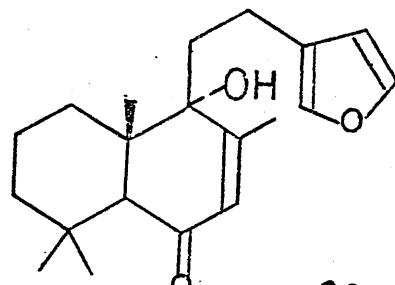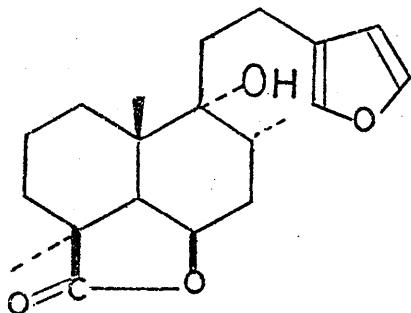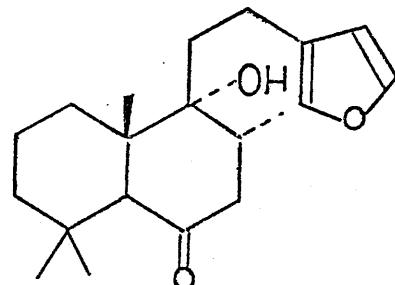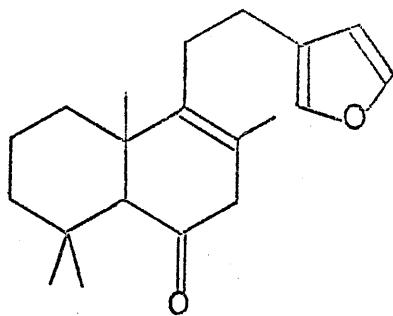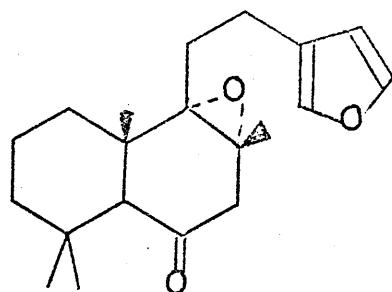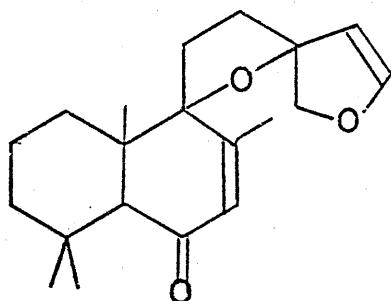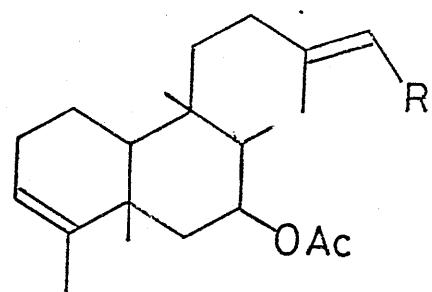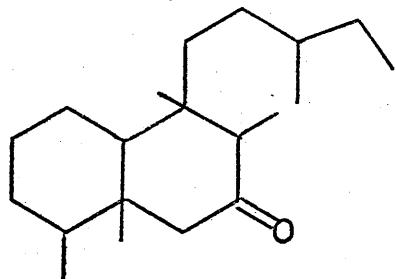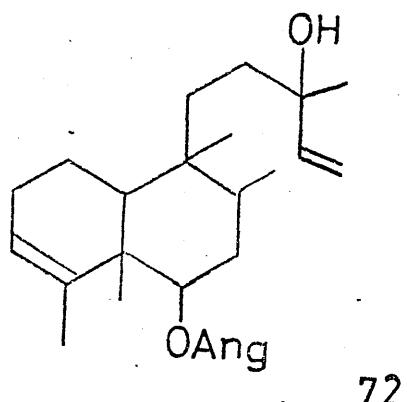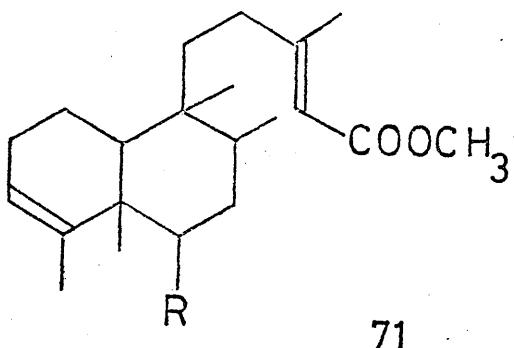
a : R = H$_2$

b : R = O

c : R = H, OAc

d : R = H, OH

72

73

a : R = OH

b : R = OAc

c : R = OAng

74

a : R = OAc

b : R = OAng

75
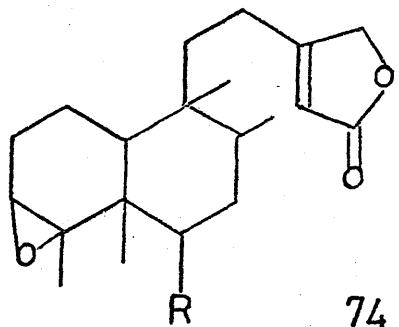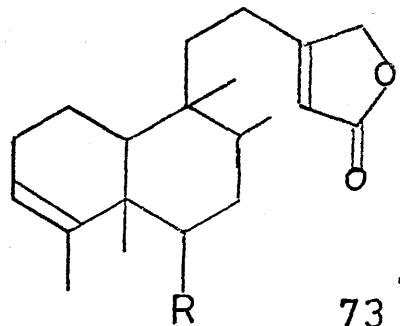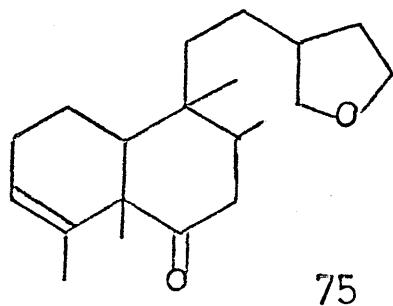
DISCUSSION.

Acidic Constituents of Solidago Serotina.

Since Solidago canadensis has been found[37] to contain
solidagenone (63) a diterpenoid related to marrubiin, a
chemical investigation of the readily available Solidago
serotina Ait. was undertaken in the hope that it might
contain biogenetically interesting compounds. Indeed, an
examination by t.l.c. of the chloroform - soluble fraction
of an ethyl acetate extract of dried root material contained
a large number of furanoid compounds which were detected by
their pink colouration with Ehrlich's reagent. In all, ten
diterpenoids have been isolated and their structures and
stereochemistry deduced on the basis of spectral and
chemical studies. A trial separation of this extract by
column chromatography over silica gel was only partially
successful since two of the neutral components were
contaminated with a major acidic constituent from which they
could not readily be separated by rechromatography over
silica gel. However, Woelm neutral alumina proved to be
more effective for separation of the extract and elution in
the normal manner furnished the neutral material. The
acidic compounds were obtained by washing the column with
ethyl acetate containing acetic acid (20%).

The acidic fraction after rechromatography, this time
over silica gel, furnished two crystalline acids, the less
polar of which was isolated in approximately 0.6% yield
(based on the weight of dried roots).

Analytical and mass spectral data indicated that this
compound, designated "solidagoic acid A" (76a) m.p.
169 - 171° has the molecular formula $C_{20}H_{28}O_3$. The sharp
i.r. band at 875 cm^{-1} taken in conjunction with the three
broadened singlets at γ 2.75, 2.94 and 3.82 in the n.m.r.
indicates the presence of a β - substituted furan ring.
That the remaining oxygen atoms are present in a carboxyl
group is confirmed spectroscopically by the broad absorption
between 3600 and 3100 cm^{-1} in the i.r. An olefinic proton
and a methyl group attached to the same double bond give rise
to an unresolved multiplet ($W_{\frac{1}{2}}$ = 11 c./sec.) at γ 4.45 and
a broadened singlet at γ 8.48 respectively. A three proton
singlet at γ 9.02 and doublet at γ 9.11 (J = 6 c./sec.) can
be attributed to two methyl groups, the former tertiary and
the latter secondary.

The derived methyl ester (76b), $[\alpha]_D$ = - 67.5° was
obtained as an oil which failed to crystallise. In its
n.m.r. spectrum the olefinic proton appears as an unresolved
multiplet at γ 4.51 ($W_{\frac{1}{2}}$ = 9 c./sec.) which on double
irradiation of the multiplet from the allylic methylene
protons collapses to a much narrower multiplet ($W_{\frac{1}{2}}$ = 5 c./sec.)
When the methylene envelope was irradiated at γ 8.14 the
doublet at γ 9.10 became a broad singlet confirming its
assignment as a secondary methyl group.

In order to transform it into the corresponding
primary alcohol (76c) the ester was treated with lithium
aluminium hydride in refluxing diethyl ether but even after
48 hours treatment a considerable amount of ester was left

unaffected.   For complete reaction the reduction required
to be carried out in refluxing tetrahydrofuran.   The oily
alcohol (76c), $[\alpha]_D = -38°$ thus obtained shows hydroxyl
absorption in the i.r. region at 3630 cm^{-1} while in its
n.m.r. spectrum the carbinol protons ($-C\underline{H}_2 - OH$) appear as
two doublets at τ 6.37 and 6.51 (J = 11 c./sec.).   The
proton and methyl group attached to the double bond give rise
to signals at τ 4.29 (m)($W_{\frac{1}{2}}$ = 9 c./sec.) and 8.33 (broad s)
respectively.

Oxidation of the alcohol with chromium trioxide -
pyridine furnished a mixture of three isolable compounds
which were separated by preparative t.l.c.   The least polar
was the aldehyde (76d) $C_{20}H_{28}O_2$, $[\alpha]_D = -161°$.   Peaks at
2690 and 1722 cm^{-1}, typical of an aldehyde function are
clearly visible in its i.r. spectrum while the $-C\underline{H}O$ aldehyde
proton resonates as a singlet at τ 0.54.   A doublet at τ
8.58 (J = 1.5 c./sec.) can be assigned to the vinylic methyl
group and the multiplet at τ 4.30 ($W_{\frac{1}{2}}$ = 10 c./sec.) to the
olefinic proton.   It is of significance that the resonances
of the $- C\underline{H}_2-OH$ and the $-C\underline{H}O$ protons show no vicinal spin -
spin coupling indicating that these groups must be attached
to a fully substituted carbon atom.   It was noted that the
least polar of the neutral components of the extract has
similar physical and spectral properties to this aldehyde.
Indeed, direct comparison of the two compounds indicated
that they were identical.

Furthermore, that the location of the carboxyl group
as γ to the olefinic bond in the parent follows from the

structure (77a) of the oxidation product of intermediate

polarity. This substance, $[\alpha]_D = -100°$ from mass spectral

and analytical figures has the molecular formula $C_{19}H_{26}O_2$.

Although its n.m.r. spectrum has no resonances attributable

to olefinic protons the vinylic methyl group is still present

and gives rise to a doublet at τ 8.31 (J = 1.5 c./sec.)

which shows long range coupling to one of the allylic protons.

In the methyl region of the spectrum the relative positions

of the secondary and tertiary methyl groups have interchanged,

the former now appearing as a doublet at τ 8.97 (J = 6 c./sec.)

and the latter as a singlet at τ 9.12. Support for the

structure (77a) for this compounds follows from the i.r.

band at 1675 cm^{-1} characteristic of an $\alpha\beta$ -unsaturated

ketone. The mechanism for the formation of this nor-enone

can be envisaged as attack by the O - Cr ester at the double

bond which then migrates into a tetrasubstituted position.

Similar results have been observed in the treatment of

certain drimenol derivatives with the same oxidant (see later).

The minor, most polar compound $C_{20}H_{26}O_3$, $[\alpha]_D = -197°$, from

n.m.r. evidence was an aldehyde - enone, the aldehyde proton

resonating as a singlet at τ 0.43, and the olefinic proton

now as a sharp singlet at τ 4.09 ($W_{\frac{1}{2}}$ = 3 c./sec.). The

signal from the vinylic methyl group also appears as a

sharp singlet at τ 8.29. The narrowness of these last two

signals indicates that a coupling to an additional

methylene group has been removed. That these protons have

been replaced by a carbonyl group is confirmed by the

downfield shift of the α olefinic proton resonance. The
i.r. spectrum shows two peaks in the carbonyl region at
1730 and 1680 cm^{-1} as expected.

These results require the system (78) to be present in
the acid but this cannot be accommodated in a normal bicyclic
diterpenoid skeleton. Assuming a clerodane skeleton, C(3) -
C(4) is the most favoured location of the double bond, on
biogenetic grounds. This would then require the carboxyl
group to be attached at C - 5. Since related Solidago
species have contained only diterpenoids with the normal
decalin ring system, only structures having this nucleus
have been considered. An alternative possibility is that
in which the double bond is in a $\triangle^7$ position with the
carboxyl group located at C - 9. Oxygenation of the methyl
group at C - 9 is less common than that at C - 5 although it
does occur in the cascarillin series. At this stage, however,
this structure appears unlikely since the n.m.r. of the
aldehydo - enone (79a) shows absorption from _two_ protons
α to the carbonyl of the enone system. Evidence will be
presented later which will completely eliminate this structure.

Additional evidence for the relationship of the double
bond and the carboxyl function followed from the product of
attempted chloroacetylation of the derived alcohol (76c).
Since the alcohol was recovered unchanged after being allowed
to stand for 15 hours at 20° with chloroacetic anhydride -
pyridine the experiment was repeated using refluxing
pyridine for several days. In this case an oily product

(77b), $[\alpha]_D = -32.5°$, less polar than the alcohol, was

obtained. In its n.m.r. spectrum it shows resonances from

three methyl groups at τ 9.13 (s)(tertiary methyl), 8.95

(d)(secondary methyl) and 8.35 (broadened s)(vinyl methyl)

and significantly, no resonance from an olefinic proton.

This nor-olefin (77b) is also formed when acid A is heated

at 200° in an evacuated tube. As observed in the spectrum of

the nor-enone (77a) the positions of the signals of the

tertiary and secondary methyl groups have interchanged and

this may indicate that the double bond, now exocyclic to

ring B causes this ring to take up a different conformation.

The second acidic component, solidagoic acid B (80a)

crystallised from ethyl acetate - light petroleum as needles

m.p. 134 - 135°. The analytical figures suggest a molecular

formula $C_{25}H_{36}O_5$ although the mass spectrum shows no peak

higher than m/e = 314 (which thus corresponds to a loss of a

five carbon unit). An infra - red band at 1695 cm^{-1} can be

assigned to an $\alpha\beta$ -unsaturated carbonyl grouping and that this

is contained in an ang·late ester is confirmed by an

examination of its n.m.r. spectrum. Thus there are resonances

at τ 3.96 (1H) and between 7.95 and 8.15 (6H) which are

characteristic[40] of this function. The remainder of the

spectrum shows a marked similarity to that of acid A

suggesting that the two compounds may be closely related.

A signal from the methylene protons of a -C$\underline{H}_2$ -O - group

appears as a singlet at τ 5.50 while a multiplet at τ 4.02

($W_{\frac{1}{2}}$ = 10 c./sec.) is assigned to an olefinic proton. Two

methyl groups, one tertiary, the other secondary give rise

to a singlet at τ 8.97 and a doublet at τ 9.09 (J = 6 c./sec.)
respectively. These assignments were confirmed by nuclear
magnetic double resonance experiments in which irradiation
of the singlet at τ 5.50 ($W_{\frac{1}{2}}$ = 4 c./sec.) caused the
resonance of the olefinic proton at τ 4.02 to collapse to a
triplet (J = 4 c./sec.). A similar experiment at τ 7.93
(the resonance of the C - 2 methylene protons) converted this
multiplet into a broad singlet ($W_{\frac{1}{2}}$ = 4 c./sec.) and the
singlet at τ 5.50 into a very sharp singlet ($W_{\frac{1}{2}}$ = 2.5 c./sec.),
confirming that the trisubstituted double bond has an allylic
methylene group adjacent to the carbon atom carrying the
vinylic proton while a - $C\underline{H}_2$ - O group is attached to the
other end. Irradiation at τ 8.42 caused the doublet at
τ 9.09 to collapse to a sharp singlet indicating that it
does indeed arise from a secondary methyl group. When the
olefinic proton of the angelate ester was doubly irradiated
the two methyl groups appeared as separate signals 0.08 ppm
apart. From this evidence it can be deduced that the vinyl
methyl group of acid A has been replaced by an allylic
primary alcohol present as its angelate ester.

Moreover, pyrolysis of this acid at 320° in an
evacuated tube furnished, in addition to an oily mixture of
compounds, a few crystals of angelic acid m.p. 45° (sealed
tube) which were collected in a cold trap. Comparison of
these crystals with an authentic sample of angelic acid,
prepared from tiglic acid by the method of Buckles and Mock[41],
was achieved by vapour phase chromatography (10% F.F.A.P. ;
125°), the three isomeric acids, dimethyl acrylic, tiglic and

angelic acids being well separated on this free acid phase.
Attempts to compare the acids as their methyl esters were
unsuccesful since no method of methylation on a microgram
scale could be devised. Diazomethylation was not practicable
since diazomethane is known to react with $\alpha\beta$ - unsaturated
acids to form pyrazoline derivatives.

The oily neutral material was seen from t.l.c. to
consist of two compounds of very similar polarity which were
only separated after repeated preparative t.l.c. The oily
less polar compound $C_{20}H_{26}O_3$ (81a), which was by far the
more abundant, shows a strong carbonyl frequency in the i.r.
at 1778 cm^{-1}, indicative of a γ - lactone. The allylic
methylene protons in this lactone resonate as a pair of
doublets at τ 5.31 and 5.60 (J = 12 c./sec.), the lower pair
showing further long range coupling. The minor compound
crystallised and had m.p. 145 - 147°. From i.r. and mass
spectral evidence it appeared to be an isomeric lactone
although insufficient material was obtained for an n.m.r.
spectrum, even at 100 Mc./s. The structure (82) is suggested
tentatively for this compound. The formation of these
lactones can be rationalised by a nucleophilic attack of the
carboxyl group at, in one case the allylic methylene group
carrying the ester, in the second at the other end of the
double bond with subsequent rearrangement of the double bond
into an exocyclic position, both processes being followed by
expulsion of angelic acid. Examination of models indicates
that the carboxyl group can approach sufficiently close to
C - 3 for the latter process to occur.

Careful treatment of acid B (80a) with diazomethane furnished the corresponding oily methyl ester (80b) $C_{26}H_{36}O_5$, $[\alpha]_D = -44^\circ$ which was separated from the diazomethane adducts by preparative t.l.c. The n.m.r. of this substance was very similar to that of the parent acid in that the two olefinic protons appear as multiplets at τ 3.97 (angelate proton) and 4.09 (H - 3).

Reduction of this methyl ester with lithium aluminium hydride led to the diol (80c), $[\alpha]_D = -36^\circ$. Mass spectral and analytical figures indicate the molecular formula $C_{20}H_{30}O_3$. The behaviour on t.l.c., rotation and spectral properties of this diol prompted a comparison with one of the more polar naturally occuring furanoid compounds and the physical and chemical properties of the two compounds were found to be identical. Its n.m.r. spectrum was of little diagnostic value due to the strong hydrogen bonding of the two hydroxyl functions which resulted in the individual signals being indistinguishable. However the n.m.r. of the derived diacetate (80d) $C_{24}H_{34}O_5$, $[\alpha]_D = -44^\circ$ was more informative since the two acetoxy methylene groups ($-\underline{CH}_2 - OAc$) give rise to two singlets, the one from the allylic group at τ 5.43, the other from the isolated acetate group at τ 6.01. This compounds was the least polar component of the mixture of acetates obtained when the diol was kept at 20° for 3 hours with acetic anhydride - pyridine. The compound of intermediate polarity was the monoacetate A (80e) $C_{22}H_{32}O_4$ whose n.m.r. shows resonances at τ 4.08 (m)(H - 3), 8.94 (s)(3H - 20) and

9.12 (d)(3H - 17). Two quartets appear at γ 5.53 (J = 12 c./sec.)
and 6.49 (J = 12 c./sec.). The former is assigned to the
methylene protons of an allylic primary acetate (-CH_2 - OAc)
and the latter to those of an isolated primary hydroxyl function.
The third component, the isomeric monoacetate B, $C_{22}H_{32}O_4$ can
therefore be assigned the constitution (80f) and this was
confirmed by its n.m.r. resonances at γ 5.50 (s)(allylic -CH_2-
OH) and 6.06 (s)(- CH_2 -OAc).

Hydrogenation of the diacetate (80d) in ethanol containing
triethylamine over 10% Pd - C for 40 minutes furnished material
which was seen from t.l.c. to consist of two compounds one of
which, the less polar, still contained a furan ring. The
n.m.r. of this compound (76e) $C_{22}H_{32}O_3$, $[\alpha]_D$ = - 44° shows a
multiplet at γ 4.53 from the olefinic proton indicating that
the double bond has remained intact. The singlet at 5.44 is
missing and is replaced by a broadened singlet at γ 8.35
from a vinylic methyl group suggesting that hydrogenolysis of
the allylic primary acetate group has taken place. The
protons of the remaining acetate group now appear as a quartet
at γ 6.05 (J = 11 c./sec.). Direct comparison of this
compound (by t.l.c., n.m.r. and $[\alpha]_D$) with a sample of the
monoacetate derived from the alcohol corresponding to acid A,
indicated that they were identical. The minor component of
the hydrogenation product was also an oil, analysing for
$C_{22}H_{36}O_3$. In its n.m.r. spectrum the three furan proton
singlets are absent but are replaced by two multiplets
assigned to the protons of a tetrahydro - furan ring. The
multiplet at γ 4.50 ($W_{\frac{1}{2}}$ = 9 c./sec.) is still present

indicating that the double bond has survived the hydrogenation and a methyl group attached to this double bond gives rise to a broad signal at γ 8.36. A singlet at γ 6.05 is attributed to the protons of a primary acetate group. From this evidence it can be deduced that this compound is the tetrahydro - derivative (84a) of alcohol A (76e).

The formation of these two acetates therefore confirms the earlier suggestion that the sole difference in the two acids lies in the nature of the function attached to the olefinic bond at C - 4. In A this is a methyl group and in B an allylic primary angelate ester.

<u>Neutral Constituents of Solidago serotina.</u>

The neutral fractions from the crude extract have furnished eight furan – containing diterpenoids seven of which have been interrelated with acid A (76a). The compounds will be discussed in the following order of increasing chromatographic polarity (on silica gel using ethyl acetate – light petroleum mixtures as eluent)

<u>Compound I.</u>

The least polar neutral constituent, an aldehyde (76d), is identical with one of the oxidation products of alcohol A (76c) (see preceeding section). In order to prepare the corresponding tetrahydro – derivative (84b) the aldehyde was hydrogenated in ethanol over Adams catalyst but furnished in all cases a hexahydro compound (85a) $C_{20}H_{34}O_2$, $[\alpha]_D = -15^o$ regardless of the reaction time. In its n.m.r. spectrum the signals from the olefinic and furan protons are absent and replaced by multiplets from the tetrahydro – furan ring. The aldehyde proton appears as a broad singlet at τ 0.65 ($W_{\frac{1}{2}}$ = 4 c./sec.), the breadth of the signal reflecting the asymmetry at C – 13.

In contrast to the behaviour of this aldehyde, when the methyl ester (76b) was hydrogenated over the same catalyst for 25 minutes a complex mixture of compounds was obtained. The least polar of these was the tetrahydro methyl ester (84c) $C_{21}H_{34}O_3$, $[\alpha]_D = -40^o$ which still shows evidence of an olefinic group in its n.m.r. spectrum. Thus there is a multiplet at τ 4.67 (1H – 3 ; $W_{\frac{1}{2}}$ = 9 c./sec.) and a broadened singlet at τ 8.60 (vinylic methyl). The next "component"

behaved on t.l.c. as a single compound but from n.m.r. data

was recognised to comprise the two possible hexahydro esters

(86a and 86b) $C_{21}H_{36}O_3$, formed by hydrogenolysis of the furan

ring. No attempt was made to separate the mixture into

individual components and it was characterised as the

mixture. It exhibits resonances at τ 4.63 (m)(H - 3) and 8.56

(broad s)(vinylic methyl) 6.32 and 6.38 (both s)(O - $C\underline{H}_3$) in

addition to the multiplet at τ 6.64 ($W_{\frac{1}{2}}$ = 6 c./sec.) from the

carbinol protons of the two primary alcohols. Hydride reduction

of the tetrahydro ester (84c) yielded the corresponding

alcohol (84d) $C_{20}H_{34}O_2$, $[\alpha]_D$ = - 16° whose n.m.r. spectrum

shows the carbinol protons (-$C\underline{H}_2$ - OH) as a quartet at

6.56 (J = 12 c./sec.) superimposed on the multiplets from

the tetrahydrofuran protons. Oxidation to the required aldehyde

(84b) $C_{20}H_{32}O_2$, $[\alpha]_D$ = - 88°, was accomplished by treatment

with Sarett's reagent in a large excess of pyridine to

minimise the possibility of allylic oxidation. The aldehydic

(-$C\underline{H}O$) proton appears in the n.m.r. as a doublet (separation

= 2 c./sec.) at τ 0.74, the two signals again reflecting the

asymmetry at C - 13.

Compound II.

The next two compounds were obtained as an oily mixture

which was separated into its components by repeated preparative

t.l.c. The less polar, the lactone (87a) $C_{20}H_{26}O_3$, $[\alpha]_D$ = +

11.7^o after distillation crystallised from light petroleum

and had m.p. 92 - 95°. Its formulation as a γ - lactone is

evident from the strong carbonyl absorption at 1772 cm^{-1} and

that this carbonyl group is in conjugation with a double bond

can be deduced from the u.v. maximum at 204 mu (ϵ = 21,000).
In its n.m.r. spectrum the olefinic proton now appears as a
triplet at τ 3.35 (J = 3 c./sec.) and only shows coupling to
the C – 2 methylene protons. This was confirmed by a nuclear
magnetic double resonance experiment in which irradiation of
the broad triplet at τ 7.77 (from 2H – 2) caused that of the
vinylic proton to collapse to a sharp singlet. On double
irradiation at τ 8.37 (1H – 8) the doublet at τ 9.10 (J =
6 c./sec.) became a sharp singlet allowing its assignment
as a secondary methyl group. In addition, a tertiary methyl
group appears as a sharp singlet at τ 8.97 and the two
protons adjacent to the ethereal oxygen atom of the δ –
lactone ring give rise to two doublets at τ 5.56 and 6.20
(J = 9 c./sec.) and show no vicinal coupling. Assuming this
lactone to have the same skeleton as the two acids its
constitution as (87a) accords with the above evidence. Its
correlation with the known compounds was accomplished by
reduction with lithium aluminium hydride to the diol (80c),
 acetylation of which afforded the corresponding diacetate
(80d) identical in all respects with the diacetate from
acid B.

If the above formulation for the lactone is correct then
this compound must be related to the lactone (48) m.p. 119 –
120°, $[\alpha]_D$ = – 156° isolated [19] from Dodonaea species.
However the physical constants of the two lactones are
markedly dissimilar suggesting that the difference may lie
in the stereochemistry at one or more of the asymmetric
centres (see later).

Compound III.

The third component (80g) was obtained as a solid which on crystallisation from ethyl acetate - light petroleum furnished needles, m.p. 103 - 105°. Analytical figures indicated that this compound, $[\alpha]_D = -49°$ has a molecular formula $C_{20}H_{26}O_3$, isomeric with the above conjugated lactone (87a). The presence of two aldehydo groups was recognised from the two n.m.r. singlets at τ -0.17 and 0.89, the one at lower field being assigned to that attached to the double bond, the vinylic proton of which resonates as a triplet at τ 3.16 (J = 4 c./sec.). The two carbonyl groups appear in the i.r. at 1720 (isolated aldehyde) and 1690 cm^{-1} ($\alpha\beta$ - unsaturated aldehyde). It was considered that reduction followed by acetylation should afford the diacetate (80d) and thus confirm the constitution (80g) and indeed when this was carried out the diacetate was identical to that obtained above.

Compound IV.

The next compound isolated, from i.r. evidence, was an alcohol. Since it could not be induced to crystallise it was distilled and afforded a colourless oil, $C_{20}H_{30}O_2$, $[\alpha]_D = -45°$. The n.m.r. spectrum indicated that it was closely related to the other diterpenoids discussed above. Thus, there are resonances at τ 4.26 (m)(H - 3) and in the methyl region at τ 8.82 and 8.97 (both s)(two tertiary methyl groups) and at 9.15 (d)(secondary methyl group). A two proton singlet at 5.84 can be attributed to the protons of a primary alcohol function, the downfield shift indicating its allylic nature. These assignments and hence the structure (88a) for this

alcohol gain some support from a series of spin - decoupling
experiments. Double irradiation of the multiplet from the
C - 2 protons causes the multiplet at τ 4.26 to become a
singlet and the τ 5.84 singlet ($W_{\frac{1}{2}}$ = 4 c./sec.) to collapse
to a much sharper singlet ($W_{\frac{1}{2}}$ = 2.5 c./sec.). Saturation of
the signal at τ 4.26 (olefinic proton) causes this singlet
to become a doublet (J = 1.5 c./sec.) and when the reverse
experiment is carried out the signal of the vinyl proton
becomes a triplet (J = 4 c./sec.). These results require
the system - CH_2 - CH = C - CH_2OH to be present and this
is accomodated in the postulated structure (88a).

Acetylation furnished an acetate (88b) $C_{22}H_{32}O_3$, $[\alpha]_D$
= - 34° whose n.m.r. spectrum shows the resonance of the
primary acetate protons as a singlet at τ 5.55. The remainder
of the spectrum is similar to that of the parent alcohol, the
three methyl groups giving rise to two singlets at τ 8.82 and
8.93 (tertiary methyl groups) and a doublet at τ 9.10 (J =
6 c./sec.)(secondary methyl group).

The first attempt to relate this alcohol with one of the
previously known compounds involved the preparation of the
aldehydo - acetate (80h) by oxidation of one of the mono-
acetates derived from the diol (80c). In one experiment when
the required mono - acetate A (80e) was treated for 12 hours
at 20° with chromium trioxide - pyridine the product consisted
of only one substance (83a), $C_{22}H_{30}O_5$. The i.r. shows peaks
at 2710, 1755, 1725 and 1230 cm^{-1} as expected for material
containing both an aldehyde and an acetate group. In its

n.m.r. spectrum the aldehyde (-C$\underline{H}$O) proton appears as a singlet at τ 0.05 while the -C$\underline{H}_2$-OAc protons appear as a pair of doublets at τ 6.07 and 6.42 (J = 12 c./sec.). However, the multiplet at about τ 4.2 is absent and is replaced by a broadened singlet at τ 6.97 assigned to the proton of an epoxide ring. This is possibly the first report of epoxidation during the course of an oxidation using the chromium trioxide – pyridine complex although the reaction occurs frequently when chromic acid is the oxidant.

When this experiment was repeated with a further sample of the monoacetate from the same source another substance was isolated which was less polar than the above epoxy – compound. This oily material (80h), $C_{22}H_{30}O_4$, $[\alpha]_D = - 89°$, from n.m.r. evidence, was the required olefinic – aldehyde. Thus it exhibits resonances at τ 0.53 (s), 4.03 (m) and 5.82 (s) which can be attributed to an aldehyde proton, a vinylic proton and the methylene protons of a primary acetate group, respectively.

The isomeric hydroxy – acetate B (80f) on similar oxidation furnished a mixture of compounds of which the less polar was by far the more abundant. The constitution of this acetoxy – aldehyde, $C_{22}H_{30}O_4$, $[\alpha]_D = - 21°$ as (80i) follows from the signals at τ 0.73 (s) from an aldehyde proton, a triplet at τ 3.29 (J = 4 c./sec.) from the β proton of an $\alpha\beta$ – unsaturated carbonyl function, and the pair of doublets at τ 5.48 and 5.80 (J = 12 c./sec.) ($\pm$C$\underline{H}_2$ – OAc). The minor component was not isolated in sufficient quantity for an n.m.r. spectrum to be recorded but a spectrum of the oxidation

mixture shows a peak at about γ 7 characteristic of an epoxide proton. These two oxidations appear to be isolated examples since no significant amount of any products of epoxidation has been observed in any of the other oxidations to be described.

Reduction of the epoxy – aldehyde (83a) with lithium aluminium hydride furnished, as the major product, an oily triol (89a), $[\alpha]_D = -27°$. Acetylation of this compound yielded a hydroxy – diacetate (89b), $[\alpha]_D = -16°$ whose i.r. spectrum shows hydroxyl absorption at 3590 and 3480 cm^{-1} and since there is no signal in the n.m.r. from a proton of the type –H –C –OH this group must be tertiary. The two methylene groups of the acetoxy functions give rise to a quartet at γ 5.71 (J = 13 c./sec.) and a singlet at γ 5.91. Because epoxide rings are known to open in a trans diaxial fashion when reduced with lithium aluminium hydride it follows that the hydroxyl group in (89a) must be axially (β) oriented and hence the epoxide ring in the parent compound must also have been β oriented at both points of attachment. In this example the insertion of oxygen has therefore taken place on the opposite face of the molecule from that of the hydroxyl function, deduced to be axial from biogenetic considerations. This contrasts with the behaviour of certain allylic alcohols towards chromic acid in which it was found[42] that epoxidation always takes place on the same side of the molecule as the hydroxyl group.

In order to convert the acetoxy – aldehyde (80h) into the acetate (88b) it was dissolved in methanol and treated

for 12 hours at 20° with 100% hydrazine hydrate whereupon a single product was isolated. From i.r. evidence this was an alcohol and not the required hydrazone and the n.m.r. spectrum was identical to the hemi - acetal (81b) of natural provenance which will be discussed in detail later.

After this, attention became focussed on attempts to prepare the hydrocarbon (88c) both from the allylic acetate (88b) and from acid A derivatives. Hydrogenolysis of the acetate (88b) in ethanol containing triethylamine for five minutes over 10% Pd - C furnished a mixture of two compounds one of which (the less polar) still retained the furan moiety. That the double bond in this compound (88c) $C_{20}H_{30}O$, $[\alpha]_D =$ $- 21^{\circ}$ had survived the hydrogenation is evident from the multiplet at τ 4.82 ($W_{\frac{1}{2}}$ = 9 c./sec.) arising from the olefinic proton. A vinylic methyl group appears as a broadened singlet at 8.50. The minor, more polar product was seen from mass spectral evidence to be a mixture of the tetrahydro and hexahydro - hydrocarbons.

In a further experiment the above acetate (88b) in basic solution was hydrogenated for 40 minutes over 10 % Pd - C - from the same source. The oil isolated consisted mainly of one compound, which was more polar than the hydrocarbons produced in the previous reaction and did not contain a furan ring. Mass spectral and analytical data indicated a molecular formula of $C_{20}H_{36}O$ (85b) corresponding to a hexahydro - compound. That indeed this is the case can be deduced from the n.m.r. spectrum which is lacking in absorption below 6.0 τ , the olefinic proton resonance

being completely absent and the furan signals having
been replaced by two multiplets at τ 6.3 and 6.8 typical
of a tetrahydrofuran ring.

One route from acid A to the hydrocarbon was considered
to be via the derived tosylate (76f). However when alcohol A
in chilled pyridine was treated with toluene-p-sulphonyl
chloride a mixture of one minor and two major products was
obtained, separation being effect by preparative t.l.c. on
silver nitrate – silica gel. The compound of intermediate
polarity was isolated as an oil and seen from n.m.r. data to
be a hydrocarbon instead of the required tosylate. The hydro-
carbon is presumably a product of ringexpansion. This
failure to form a tosylate function is perhaps not
surprising since the alcohol is contained in a substituted
neopentyl system with a double bond situated in a position
favourable for participation in a rearrangement process.

Two routes from the mono – aldehyde (76d) were explored.
In the first it was proposed to prepare the corresponding
thioacetal which could then be removed by reduction with
Raney nickel to afford the desired compound. However, the
aldehyde was recovered largely unaffected by treatment with
ethane dithiol. An alternative method consisted of
preparing, under mild conditions, the hydrazone (76g) which
could undergo a Huang – Minlon reduction to furnish the
hydrocarbon. When the aldehyde, in methanol, was treated at
20° with 100% hydrazine hydrate the product was a substituted
hydrazone (76h) $C_{22}H_{34}N_2O$. The n.m.r. spectrum of this

compound shows the two methyl groups attached to the nitrogen
atom as two singlets at τ 8.05 and 8.09. Multiplets at τ
2.77 and 4.52 can be assigned to a proton of the type
$\underline{H} - C = N$ and to the C - 3 olefinic proton respectively.

In a further experiment using more forcing conditions
the aldehyde in ethylene glycol was treated at 96° for 48
hours with hydrazine hydrate. The temperature was then raised
to 210° and the hydrazone decomposed by the addition of base.
The resulting oily material had $[\alpha]_D = - 19^{\circ}$ and was identical
in all respects with the hydrocarbon (88c) described above.
The corresponding tetrahydro - compound was prepared from
the tetrahydro - aldehyde (84b) using similar conditions.

Compound V.

The n.m.r. spectrum of the next substance (81b) $C_{20}H_{28}O_3$,
$[\alpha]_D = - 30^{\circ}$ showed a marked similarity to those of the less
polar compounds discussed above. Recognisable from the signals
at τ 4.52 (m), 9.03 (s) and 9.15 (d) are an olefinic proton
and two methyl groups, one tertiary and the other secondary.
Moreover, a multiplet at τ 6.65 which disappeared upon the
addition of deuterium oxide, can be assigned to a proton
$(O - \underline{H})$ of a hydroxyl group and that this group is contained
in a cyclic hemi - acetal ring can be deduced from the
singlet at τ 4.58 $(W_{\frac{1}{2}} = 5$ c./sec.) from the carbinol
proton. In addition the protons adjacent to the ethereal
oxygen atom appear as a broadened singlet at τ 5.79 $(W_{\frac{1}{2}} =$
6 c./sec.). Its constitution as (81b) and not the
alternative (87b) follows from some double resonance
experiments. When the resonance of the olefinic proton

was saturated the singlet at τ 5.79 became an ill – resolved
doublet $(W_{\frac{1}{2}} = 5 \text{ c./sec.})$ whereas on irradiation at τ 7.9
(from 2H – 2) it collapses to a sharp doublet $(J \approx 3 \text{ c./sec.})$.
These results require the system $- CH = C - CH_2 -$ to be
present as in (81b). The coupling of the carbinol proton to
the hydroxyl proton was demonstrated by irradiating at τ
6.65 whereupon the signal at τ 4.58 became a very sharp
singlet $(W_{\frac{1}{2}} = 2 \text{ c./sec.})$.

Acetylation furnished an oily substance (81c) which in
its n.m.r. spectrum exhibited the resonance of the proton
adjacent to the acetate group $(\underline{H} - C - OAc)$ as a singlet
at τ 3.68 having shifted downfield by 0.9 ppm and that of
2H – 18 as a multiplet at τ 5.72 $(W_{\frac{1}{2}} = 12 \text{ c./sec.})$. This
acetate hydrolysed rapidly on standing, behaviour typical
of hemi – acetal acetates.

Hydroxylation of an ethereal solution of the hemi –
acetal (81b) for several days with osmium tetroxide
furnished, albeit in very small yield, an oily triol (90a)
(the overall amount of material recovered also being low).
Addition of pyridine to the brown suspension only resulted
in even lower yields. The formation of this triol is in
contrast to the behaviour of acid A and its derivatives
towards this reagent and towards hydroboration when only
starting material, with no trace of any polar material
was recovered (t.l.c.) even after extended reaction times.
The n.m.r. spectrum of this triol was rather complex but
was simplified by the addition of heavy water whereupon

multiplets at $\curlyvee$ 5.18, 5.56 and 6.82 were no longer visible.
The remaining peaks can therefore be assigned to protons of
the type $\underline{H}$ - C - OR. Those at $\curlyvee$ 4.51 ($W_{\frac{1}{2}}$ = 5 c./sec.) and
6.31 ($W_{\frac{1}{2}}$ = 6 c./sec.) arise from the protons adjacent to
the hemi - acetal hydroxyl and to the newly formed C - 3
hydroxyl and the narrowness of the latter signal is
diagnostic of an axial alcohol function, the equatorial
proton showing only an equatorial - equatorial and an
equatorial - axial coupling to the neighbouring methylene
group. From this it follows that the attack of the reagent
has been from the less hindered α face. As in the parent
compound the methine proton of the hemi - acetal group
shows coupling to the hydroxyl proton since in the spectrum
recorded before the addition of heavy water the signal
appears as a much broader multiplet ($W_{\frac{1}{2}}$ = 10 c./sec.). The
methylene protons of C - 18 are visible as a singlet ($W_{\frac{1}{2}}$ =
6 c./sec.) at $\curlyvee$ 6.12, at higher field since they are no
longer allylic.

The correlation of the hemi - acetal (81b) with a
known compound was achieved by treating it with sodium
borohydride and the diol (80c) thus obtained was
immediately acetylated to afford the diacetate (80d), $[\alpha]_D$
= - 56°, identical in all respects with that prepared
previously. Further confirmation of the location of the
hemi - acetal ring was obtained from an examination of the
n.m.r. spectrum of the corresponding deuterated diacetate
(80j) prepared from the hemi - acetal by reduction with
lithium aluminium deuteride followed by acetylation. This

spectrum was identical to that of the diacetate except that the peak at τ 6.08 now integrates for only one proton showing that the methylene group and not the methine proton is attached to the double bond.

All attempts to oxidise the hemi - acetal ring to the corresponding γ - lactone were unsuccessful. A large number of oxidising agents were tried but either the compound was recovered or else no isolable product was obtained.

Compound Vl.

The next compound (91a) $C_{20}H_{28}O_4$, $[\alpha]_D = -47°$ was obtained as an oil which slowly crystallised on cooling to $0°$ but melted just below room temperature. In keeping with its chromatographic polarity it shows evidence of hydroxyl absorption in the i.r. at 3600 and 3400 cm^{-1}. That this group is contained in a cyclic hemi - acetal ring can be deduced from the singlet in its n.m.r. spectrum at τ 4.49. Also visible is a quartet at τ 5.96 (J = 10 c./sec.) from an ethereal methylene group. The multiplet at about τ 4.4 present in the spectra of the naturally occuring diterpenoids discussed above, is absent and replaced by a singlet at τ 6.71 ($W_{\frac{1}{2}}$ = 4 c./sec.) diagnostic of a proton attached to an epoxide ring. This evidence would seem to suggest that the compound is the epoxy - analogue of the above hemi - acetal. However, all attempts to prepare this epoxide by treatment of compound V with $\underline{m}$ - chloroperbenzoic acid in various solvents led either to the recovery of the unreacted hemi - acetal or to non - furanoid material.

Its correlation with the diol (80c) was carried out as

follows. Reduction with lithium aluminium hydride furnished

a mixture of two triols of very similar polarity. After

separation by preparative t.l.c. the less polar component,

which was by far the major product, was obtained as a

colourless oil (89a), $C_{20}H_{32}O_4$, $[\lambda]_D = -12^{\circ}$. The n.m.r.

spectrum of this compound shows the hydroxyl protons as a

broad unresolved multiplet between τ 5.4 and 6.6.

Acetylation afforded a hydroxy - diacetate (89b) $C_{24}H_{36}O_6$,

$[\lambda]_D = -13^{\circ}$ which shows i.r. absorption at 3590 and

1745 cm^{-1} from the hydroxyl and acetate functions. The

methylene protons of the acetate groups appear as a

quartet centred at τ 5.63 (J = 13 c./sec.) and a broad

singlet at ν 5.83. The failure of the third hydroxyl group

to acetylate and the lack of a resonance attributable to a

carbinol proton in the product is taken to indicate the

formation of an axial tertiary hydroxyl function during

reduction of the epoxide ring. In the parent compound the

epoxide ring must therefore be β oriented as   is the

epoxide formed by oxidation of the mono - acetate (80h)

and indeed direct comparison showed the products of reduction

of both compounds to be identical. Treatment of the hydroxy -

diacetate with phosphoryl chloride in pyridine, conditions

known to effect trans diaxial elimination, gave mainly

one compound, the known diacetate (80d).

Although these reactions confirm the presence of an

epoxide and a hemi - acetal ring they do not distinguish

between the two alternative structure (91a) and (92). To

determine this the above sequence of reactions was repeated

using deuterated material. The more abundant product of

reduction with lithium aluminium deuteride was the triol

which on acetylation furnished the deuterio - diacetate (93)

the mass spectrum of which indicated the presence of two

deuterium atoms. In the n.m.r. spectrum the two proton

singlet at τ 5.84 is still present but the quartet centred

at τ 5.63 has now collapsed to a one - proton singlet at τ

5.35 indicating that the proton giving rise to the upfield

doublet has been replaced by a deuterium atom. Dehydration

as described above furnished the diacetate obtained from the

olefinic hemi - acetal confirming that both compounds have

the hemi - acetal ring attached to the skeleton in the same

fashion. These results enable assignments to be made for the

signals between τ 5 and 6 in the n.m.r. spectrum of the

hydroxy - diacetate (89b). The singlet at τ 5.83 derives

from the C - 18 acetate function, shifting downfield to τ

5.52 on dehydration since it is now allylic and the singlet

at τ 5.35 from the C - 19 group which moves upfield to

6.08 in the diacetate (80d).

Reduction of (91a) with sodium borohydride left the

epoxide ring unaffected. The epoxy - diol (83b), $C_{20}H_{30}O_4$,

$[\alpha]_D$ = - 5° shows strong hydroxyl absorption in the i.r.

at 3630 and 3380 cm^{-1} and in its n.m.r. spectrum the carbinol

protons appear as an unresolved multiplet between τ 6.0 and

6.6. On the other hand, in the derived diacetate (83c),

$C_{24}H_{34}O_6$ the protons of the primary acetate functions appear

as two quartets centred at τ 5.82 (J = 12 c./sec.) and at

5.89. In addition the proton on the epoxide ring is visible
as a doublet at $\curlyvee$ 6.89 (J = 3 c./sec.) and the acetoxy methyls
as two singlets at $\curlyvee$ 7.97 and 7.99.

The behaviour of the hydroxyl group in this epoxy hemi –
acetal (91a) parallels that of the hemi – acetal (81b) ․․ ․
discussed above in that acetylation affords an easily
hydrolysed acetate (91b), the n.m.r. spectrum of which exhibits
signals at $\curlyvee$ 3.62 (s) from the proton adjacent to the acetate
function, 6.14 (q) from the methylene group attached to an
oxygen function and 6.71 (s) from the proton of the epoxide
ring. Furthermore, the resistance of the hydroxyl group to
oxidation to the corresponding $\curlyvee$ – lactone was very similar
to that encountered with the hemi – acetal (81b).

Compound V11.

The neutral component penultimate in polarity was the
diol (80 c), $[\alpha]_D = -36^o$ to which all the above mentioned
compounds have been related. On cooling this compound to 0°
it slowly crystallised as rosettes of needles, m.p. 60 – 63°.

By analogy with the reaction of marrubenol with p–
bromobenzene sulphonyl chloride in pyridine to form an ether,
the above diol was treated with the same reagent. The product
isolated was very much less polar than the starting material
and analytical and mass spectral evidence indicated a molecular
formula $C_{20}H_{28}O_2$, (94). Its i.r. spectrum significantly shows
no peaks attributable to either a hydroxyl or a carbonyl
function. In its n.m.r. spectrum the ethereal methylene groups
appear as two quartets, one centred at $\curlyvee$ 5.88 from the two

protons in the allylic position at C - 18 and the other at τ
6.28 from 2H - 19.

Oxidation of the diol with Sarett's reagent using a large
excess of chromium trioxide over pyridine furnished as the
major product a lactone (95) $C_{20}H_{24}O_4$, $[\alpha]_D = - 8^o$ which
crystallised from ethyl acetate - light petroleum as plates
m.p. 148 - 149°. The i.r. shows two carbonyl bands at 1779
and 1690 cm^{-1} characteristic of a γ -lactone and an $\alpha\beta$ -
unsaturated ketone respectively. That the double bond is also
in conjugation with the carbonyl group of the lactone can
be deduced from the presence of a very sharp singlet in its
n.m.r. spectrum, at τ 3.56 from an olefinic proton showing
no further coupling. The upfield region of the spectrum is
relatively simple, showing as the main features, a pair of
doublets at τ 5.49 and 6.04 (J = 12 c./sec.) from the
methylene protons of C - 19, a singlet at τ 9.03 from a
tertiary methyl and a doublet at τ 9.10 (J = 6 c./sec.)
from a secondary methyl group. When the reaction was repeated
using a much smaller amount of chromium trioxide a mixture
of two lactones was obtained, the more polar, minor
component of which was the above product of allylic
oxidation. The major product in this second experiment was
the lactone (87a), $[\alpha]_D = + 5.3^o$ which crystallised from
ethyl acetate - light petroleum and had m.p. 93 - 95° and
direct comparison with the lactone of natural provenance
suggested that the two compounds were identical. No trace
of any non - conjugated lactones was observed in the product

from which it can be deduced that oxidation of the allylic primary alcohol must be the initial step in the reaction, followed by cyclisation to form a hemi - acetal with subsequent oxidation to the γ - lactone.

In order to prepare the corresponding tetrahydro - lactones it was first necessary to make the tetrahydro - diol (84f), the major product from hydrogenation of the diol (80c) in ethanol over either Adams platinum oxide catalyst or palladium - charcoal. After preparative t.l.c. the oily tetrahydro - diol (84f), $C_{20}H_{34}O_3$, $[\alpha]_D = -47^o$ was obtained as an oil. N.m.r. data indicated the retention of the double bond. A multiplet at 4.22 ($W_{\frac{1}{2}}$ = 7 c./sec.) can be assigned to the olefinic proton but the carbinol ($-CH_2 - OH$) region again appears as a broad multiplet between τ 5.6 and 6.8. However, the n.m.r. spectrum of the derived diacetate (84g) $C_{24}H_{38}O_5$ is more informative. In it, the primary acetate methylene groups appear as singlets at τ 5.49 (C - 18) and τ 6.06 (C - 19) in addition to a multiplet at τ 4.11 ($W_{\frac{1}{2}}$ = 6 c./sec.) from the vinylic proton.

Oxidation of the tetrahydro - diol (84f) as described above using the forcing condition, furnished in low yield, a number of products (t.l.c. evidence) of which the major were the two of lowest polarity. The least polar component was the lactone (96a) $C_{20}H_{30}O_3$ which shows the C - 3 olefinic proton as a triplet at τ 3.41 (J = 3 c./sec.) again indicating that the double bond is in a position $\alpha\beta$

to the carbonyl group of the lactone function. The C - 19

methylene group is seen as a doublet at τ 5.64 (J = 8 c./sec.),

the higher field signal being superimposed on multiplets

from the tetrahydrofuran ring protons. The second component

(96b), $C_{20}H_{28}O_4$, $[\alpha]_D = - 4^\circ$ from its i.r. bands at 1775

and 1693 cm^{-1} in the carbonyl region is the enone - lactone.

Its n.m.r. spectrum (in CCl_4) shows the olefinic proton as

a singlet at τ 3.64 and the C - 19 protons as a pair of

doublets at τ 5.57 and 6.12 (J = 8 c./sec.) while the

C - 1 methylene protons appear as a multiplet at τ 7.71.

This spectrum was also recorded using benzene as solvent

and will be discussed in the following section.

The formation of these enone - lactones led to an

investigation of the possibility of introducing an

oxygen atom into C - 2 in molecules not containing an

oxidisable function. To do this a number of derivatives

of acid A were treated with chromium trioxide - pyridine

at 20° for several days. Thus when the mono - acetate (76e),

diacetate (80d) and the methyl ester (76b) were reacted

under similar conditions it was found that all three

compounds had had an additional oxygen atom inserted into

the allylic position. The enone acetate (79b), $C_{22}H_{30}O_4$

$[\alpha]_D = - 88^\circ$ had bands in the i.r. at 1740 and 1660 cm^{-1}

(in $CHCl_3$)characteristic of an acetate and an $\alpha\beta$ -

unsaturated ketone. In its n.m.r. spectrum the olefinic

proton resonates as a broadened singlet at τ 4.07 ($W_{\frac{1}{2}}$ =

4 c./sec.) and shows coupling to the vinylic methyl group at

τ 8.28. The spectral properties of the enone - diacetate
(79d) $C_{24}H_{32}O_6$ are very similar to those of the above
acetate (79b) in that the olefinic proton appears as a
singlet at τ 4.05. As in the spectra of the two nor -
compounds (77a and 77b) the relative positions of the
resonances of the two methyl groups have been inter-
changed indicating a distortion in the ring systems. In the
spectrum of the enone - methyl ester (79c) $C_{21}H_{28}O_4$ the
olefinic proton gives rise to a broadened singlet at τ 4.23
($W_{\frac{1}{2}}$ = 3 c./sec.) coupled to the vinylic methyl group
which is visible as a doublet (J = 1 c./sec.) at τ
8.29. The remaining methyl groups appear at their normal
positions, the tertiary at τ 9.07 and the secondary as an
ill - resolved doublet at τ 9.12 (J = 6 c./sec.).

Compound Vlll.

The most polar furanoid compound (90b) $C_{20}H_{30}O_5$, $[\alpha]_D$
= - 18° was obtained as an oil which slowly crystallised
and had m.p. 135 - 137°. The n.m.r. spectrum shows no trace
of olefinic absorption but a broad multiplet between. τ
5.6 and 6.6 from hydroxyl functions, while a multiplet
at τ 4.5 can be assigned to the carbinol proton of a
cyclic hemi - acetal ring. Acetylation afforded as the
major product an oily diacetate (90c) which from i.r.
evidence still contains a hydroxyl group, assumed
to be tertiary. The n.m.r. spectrum was more useful for
determining the structure of this compound than that of the
parent compound. Thus, the proton adjacent to the hemi -
acetal acetate has moved downfield and appears as a

a singlet Υ 3.28. A triplet at Υ 5.18 (J = 6 c./sec.) can be

assigned to the proton of a secondary equatorial acetate

function having two neighbouring protons. The ethereal

methylene group of the hemi - acetal ring gives rise to a

quartet at Υ 5.87 (J = 10 c./sec.). Assuming the Δ^{3} double

bond to have been replaced by a 1,2 diol system then the

constitution (90b) follows for the parent compound and

(90c) for the derived acetate. The location of the hemi -

acetal is by analogy with the previous compounds. The

difference in stereochemistry at C - 3 in this compound and

the triol obtained from hydroxylation of the hemi - acetal

(81b), assigned on the basis of n.m.r. evidence was

reflected in the difference in polarity of the two

compounds on t.l.c. The small amount of this substance

available prevented any interrelation with the known

compound and as a result the structure (90b) is only

tentatively suggested.

The Stereochemistry of Solidagoic acid A and its Congeners.

The constitution of acid A and its congeners having been established the remaining problem is the assignment of stereo-chemistry at the four asymmetric centres, C - 5, C - 8, C - 9 and C - 10. Since attempts to form a heavy atom derivative for for an X - ray crystallographic analysis met with little success our attention was turned to the preparation of suitable derivatives whose spectral properties could be compared with those of compounds of known configuration. As observed earlier, diterpenoids derived from an acyclic precursor by cyclisation and a series of concerted methyl and hydride ion migrations should have a trans ring fusion. Those columbin - type compounds which have a cis fusion are assumed to arise from addition across the ring to a $\triangle^{1 \, (10)}$ double bond formed from a trans fused precursor.

That the solidagoic acids do indeed possess the expected stereochemistry at the ring junction follows from a careful examination of the n.m.r. spectra of the tetrahydro derivatives (96b) and (97). For this investigation it was deemed desirable to remove the furan ring by hydrogenation since otherwise the signals from the two C - 1 protons were obscured by those of the protons at C - 12. Allylic oxidation by Sarett's reagent in the tetrahydro series of compounds was less successful than when applied to the corresponding furanoid derivatives and in the acid A group no enones could be prepared. Allylic oxidation by the more common reagents, selenium dioxide, di-tert butyl chromate or sodium chromate also failed to produce the required compound. However, the tetrahydro - enone lactone (96b) was

isolated, although in low yield, from the mixture of compounds
obtained when the tetrahydro - diol (84f) was treated with
chromium trioxide - pyridine. An n.m.r. spectrum of this
compound in CCl_4 showed the two C - I protons as a multiplet
centred at τ 7.71 from which J_{AB} (17 c./sec.) was obtained by
inspection. When the spectrum was recorded in benzene this
region appeared as the AB part of a deceptively simple ABX
system in which only three lines are visible. After the addition
of chloroform the two protons became magnetically equivalent
and appear as a doublet. Double irradiation of the methylene
envelope at τ 8.38 caused these signals to collapse to a
broad singlet indicating that this methylene group is not
isolated but attached to a carbon atom bearing a proton. This
evidence therefore eliminates the structure having the double
bond located in a Δ^7 position. A calculation of the
individual coupling constants was made and the results $J_{AX} =$
3.75 and $J_{BX} = 14.25$ c./sec. obtained. However, from an
examination of models of both cis and trans fused compounds it
was seen that the lactone ring produces a constraint in the
system which in both cases leads to a marked decrease in
conformational preference. In brief it appeared that no firm
deduction of stereochemistry could be made.

Since introduction of an enone system into a tetrahydro-
compound could not be effected the reverse procedure was adopted
in which the oxygen atom was inserted first and then the furan
ring carefully hydrogenated. In this way the acid (97) was
formed whose n.m.r. spectrum (in CCl_4) shows the olefinic
proton as a broad singlet ($W_{\frac{1}{2}} = 2.5$ c./sec.) at τ 4.20. Its

coupling to a vinylic methyl group (broadened singlet at τ 8.23) was demonstrated by nuclear magnetic double resonance experiments. Irradiation at τ 8.23 caused the former signal to collapse to a sharp singlet while in the reverse experiment a similar effect was observed for the resonance at τ 8.23. In the 7.7 - 7.9 τ region the two C - 1 protons give rise to a similar pattern as that observed in the spectrum in benzene of the lactone, namely a three line system. Assuming J_{AB} to be 17 c./sec. it can be calculated that J_{AX} = 16 c./sec. and J_{BX} = 4 c./sec. corresponding to dihedral angles of approximately 180° and 125° respectively. An examination of a model of the compound with a trans fused ring system indicates that this conformation would result in coupling constants of approximately the magnitude observed. On the other hand, the most favoured conformation of the corresponding cis compound would be expected to give rise to angles of approximately 90° and 120° for which the coupling constants would be considerably different from those calculated. These results can be taken as evidence for a trans ring fusion in accord with biogenetic predictions.

To confirm these results the spectra of two model compounds were examined, one having a trans and the other a cis fusion. In the former, the enone ($_{114}$) derived from confertifolin diacetate, the two C - 6 protons appear (in $CDCl_3$) as the AB portion of an ABX system in which the central lines of both quartets are visible. However, all eight lines can be observed when the spectrum is recorded in benzene. By inspection J_{AB} was found to be 17 c./sec. while by calculation there are two

possible values for J_{AX} (3.5 or 7.75 c./sec.) and J_{BX} (13.5 or 16.75 c./sec.). The enone (38) derived from the anomalous plathyterpol (37) was known[17] to possess a cis ring junction from X - ray evidence. The spectrum* in $CDCl_3$ was very similar in the 7.2 - 7.4 τ region to those described previously in that it consists of three lines while in benzene these become a doublet. However, taking J_{AB} to be 17 c./sec. J_{AX} was calculated to cb 0.75 and J_{BX} to be 9.25 c./sec., coupling constants markedly different to those found in the Solidago compounds.

The isolation of the alcohol (88a) made direct comparison with its stereoisomer hardwickiol* (98a) possible. Although the physical constants and the t.l.c. behaviour of the two compounds were identical there are small but significant differences in the n.m.r. spectra. Thus there are differences in the position of the resonances of the secondary methyl and one of the tertiary methyl groups (9.20 and 9.29 τ respectively in hardwickiol ; 9.15 and 8.97 in the Solidago alcohol). In addition, the doublet from the secondary methyl group in hardwickiol is much less sharp than that in the above compounds behaviour typical of an equatorial methyl group. This would suggest that this group is therefore axial in the solidago series. Careful hydrogenation of hardwickiol acetate (98b)

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* The spectra of plathyterpol were kindly supplied by Dr. T. J. King of the University of Nottingham and samples of (+) ethyl hardwickiate and (-) hardwickiol by Professor W. Cocker and Dr. Sukh Dev respectively.

in ethanol containing triethylamine over 10% Pd – C furnished the oily hydrocarbon (98c) $C_{20}H_{30}O$ which again had an n.m.r. spectrum similar to that of the known hydrocarbon (88c) except for the position of the signal of the secondary methyl group (τ 9.13). The low field regions of the two spectra were almost identical from which it may be taken that the sole difference lies in the stereochemistry of the C – 8 methyl group. This is taken as evidence for the stereochemistry shown in (76a) for solidagoic acid A. That of the other naturally occuring compounds follows from their proven relationship with acid A.

Solidago juncea.

The roots of Solidago juncea were extracted with ethyl acetate in the manner described for S. serotina and the major Ehrlich - active compound was isolated as an oil, in approximately 1% yield, based on dried plant material, by preparative t.l.c. From its behaviour on t.l.c. it was deduced to be acidic and this was confirmed by the broad absorption between 3400 and 3000 cm^{-1} in the i.r. A mass spectrometric molecular weight determination indicated a molecular formula of $C_{20}H_{28}O_3$ showing that the compound, "junceaic acid" is isomeric with solidagoic acid A (76a).

The presence of a β -substituted furan moiety is evident from the absorption at 877 cm^{-1} in its i.r. spectrum and the three characteristic singlets at τ 2.63, 2.74 and 3.70 in its n.m.r. spectrum. The remainder of its n.m.r. spectrum is similar to that of acid A in that there are resonances from an olefinic proton (an unresolved multiplet at τ 4.72 ; $W_{\frac{1}{2}}$ = 8 c./sec.), a methyl group attached to a double bond (a broadened singlet at τ 8.40), a tertiary methyl group (a singlet at τ 9.04) and a secondary methyl group (an ill-resolved doublet at τ 8.83). It was noted, however, that the signal from the olefinic proton appears at higher field than in acid A (τ 4.46)(cf the high value found (τ 4.82) in the derived hydrocarbon (88c) in which the oxygen functions at C - 5 have been replaced by a methyl group). Furthermore the resonance of the secondary methyl group appears at lower field than that of acid A and its

derivatives (about γ 9.1). In contrast to both the acids
from S. serotina junceaic acid distilled in vacuo with no
decomposition (t.l.c. evidence) suggesting that in this
compound the carboxyl function is not homoallylic.

Reaction with diazomethane furnished the corresponding
oily methyl ester the n.m.r. of which showed resonances
from the olefinic proton as a multiplet at γ 4.83, the
secondary methyl group as a doublet at γ 8.88, and the
tertiary methyl group as a singlet at γ 9.2. That the
doublet centred at γ 8.8 does indeed arise from a secondary
methyl group was confirmed by nuclear magnetic double
resonance experiments in which irradiation at γ 8.34 caused
the doublet to collapse to a sharp singlet. Similar
irradiation of the olefinic proton caused a sharpening of
the broadened signal at γ 8.45 attributed to the methyl
group attached to the double bond (see figure γ).

In the derived alcohol, readily prepared from the
methyl ester by reduction with lithium aluminium hydride,
the primary hydroxyl protons resonate as a singlet at γ
6.37, significantly showing no vicinal spin-spin coupling.
The n.m.r. also exhibits signals from the secondary methyl
group as a doublet at γ 9.10 (having shifted upfield by
approximately 0.22 p.p.m.).

This evidence appears to indicate a rearranged labdane
skeleton and assuming the compounds to have a bicyclic
nucleus containing a Δ^3 olefinic bond as found in the
diterpenoids described earlier there are several possible
structures for junceaic acid. Its chemical behaviour and

its spectral properties appear to eliminate C - 5 as a
possible point of attachment of the carboxyl group to the
trans decalin ring system. This therefore leaves C - 9 as
an alternative site for the location of the carboxyl
function. The equatorial orientation of the C - 8 secondary
methyl group follows from the ill - resolved nature of the
doublet in the n.m.r. spectra of the acid and its derivatives.
The assignment of stereochemistry at the remaining asymmetric
centres is by analogy with acid A. From this evidence the
structure (99a) is suggested very tentatively for this acid
and hence (99b) and (99c) for the derived ester and alcohol
respectively. In order to confirm this structure it was
proposed to prepare the corresponding aldehyde and treat it
under Wolff - Kishner reduction conditions. Assuming the
acid to have the same clerodane skeleton as the other
diterpenoids from S. serotina this reaction should have
furnished one or other of the known hydrocarbons (88c) or
(98c), thus establishing the stereochemistry at all the
asymmetric carbon atoms, and at C - 8 in particular. However
Sarett oxidation failed to produce the desired aldehyde and
although the experiment was repeated several times this
result was reproducible. This lends support to the suggestion
that the primary hydroxyl function is not located at C - 5
since alcohol A (76c), under similar conditions, was
readily oxidised to the corresponding aldehyde. Additional
work on junceaic acid must await further supplies of plant
material.

Solidago glaberina.

A steam distillate of Solidago glaberina,[*] after
preparative t.l.c., furnished a crystalline diterpenoid
(100), m.p. 92 - 94°, $[\alpha]_D = - 50°$, the mass spectrum of
which clearly shows a molecular ion at 290 corresponding
to a molecular formula of $C_{20}H_{34}O$. In its i.r. spectrum
there are no peaks attributable to either hydroxyl or
carbonyl functions suggesting that the oxygen atom is
present as an ether bridge. Significantly, it exhibits a
sharp peak at 3083 cm^{-1} indicative of at least one olefinic
bond. From this it can be concluded that the compound is
probably tricyclic. Three sharp three - proton singlets
from tertiary methyl groups are visible at τ 9.17, 9.25
and 9.30 in its n.m.r. spectrum. Two tertiary methyl groups
attached to carbon atoms adjacent to oxygen give rise to
additional signals at τ 8.81 and 8.90. In the low field
region of the spectrum three olefinic protons give rise to
resonances which form a typical ABC pattern, the downfield
C - 14 proton appearing at τ 3.98 as a quartet from which
J_{trans} and J_{cis} are seen to be approximately 18 c./sec. and
10 c./sec. respectively. The two C - 15 protons H_C and H_B
resonate as doublets at τ 5.05 and 5.11 respectively
indicating that the geminal coupling is negligible.

These findings are consistent with this compound being

(-) 13 epinanoyl oxide. Indeed, its physical properties are

identical to those of the diterpene isolated from Gibberella

fujikuroi by Cross, Galt and Hanson.[43] These authors have

compared their compound with a sample of olearyl oxide, a

monounsaturated ether of unknown structure isolated earlier

from Olearia paniculata by McLean and Slater[44] and have

found them to be identical in all respects.

Allylic oxidation by Chromium (Vl).

Introduction

The first examples of allylic oxidation by chromium (Vl) were reported by Treibs and Schmidt[45] who were able to convert cyclohexene into cyclohexenone using a solution of chromium trioxide in a mixture of acetic anhydride and carbon tetrachloride. This same oxidation was effected by Whitmore and Pedlow[46] during an ivestigation of the oxidation of alkenes by chromic acid. These authors found that allylic oxidation by chromic acid is a relatively minor reaction with straight chain alkenes but can take place to a considerable extent in a number of steroidal alkenes. A similar allylic oxidation using di - tert - butyl chromate was discovered by Oppenauer and Oberrauch[47] who used a solution of the reagent in a non-polar solvent to which was added acetic anhydride. With it they were able to convert cyclohexene into cyclohexanone in 40% yield and cholesteryl acetate into its 7-keto derivative in 90% yield. Following this, several groups of Japanese workers[48] used this reagent for the oxidation of certain monoterpenes and found that oxidation usually occurs at both ends of the double bond, which contrasts with allylic oxidation by mercuric acetate or selenium dioxide. The nature of the reagent has not been fully investigated but is thought to be diacetyl chromate formed by the reaction of tert-butyl chromate with the acetic anhydride in the solvent.

Two types of mechanisms have been postulated for chromium (Vl) allylic oxidation. In the first, a hydrogen atom (or hydride ion) is abstracted from the alkene to form an allylic

free radical (or carbonium ion) which is then converted into the unsaturated ketone. This mechanism predicts that the products should contain a mixture of double bond isomers as is indeed found in the reactions of many steroidal alkenes. The second mechanism involves oxidation at the double bond leading to a ketol derivative which, after elimination of water, forms the enone system. Evidence for the first mechanism followed from the chromic acid oxidation of cyclohexene labeled with C^{13} at the double bond when it was found that one quarter of the original total label appeared at the carbonyl carbon atom. No mechanistic studies on allylic oxidation by chromyl acetate and di - tert - butyl chromate have as yet been carried out but it is assumed that their mode of attack is similar to that of chromic acid.

In addition, the chromium (Vl) oxidation of alkenes in an acidic medium may also lead to formation of epoxides, ketols and even acids or ketones derived by either cleavage of the double bond or a rearrangement. The product obtained differs according to the solvent used. When the reaction is carried out in acetic acid with a deficiency of the oxidant the product is commonly an epoxide. A number of steroidal alkenes give mixtures formed by allylic oxidation and the epoxides derived from the ketones. In the case of the $\Delta^{8(9)}$ steroids double bond migration occurs before epoxidation leading to mixtures of epoxy ketones.

Reactions carried out in aqueous acid solution are much more complex since considerable skeletal rearrangement occurs.

It has been suggested that an epoxide may be the intermediate in many reactions and a large number of rearrangement products which have been observed can be rationalised in terms of an acid catalysed pinacol - type rearrangement of an intermediate epoxide. The possibility of the intermediate being a glycol was considered but discounted since for an intermediate glycol the rate of oxidation or cleavage would be faster than the rate of rearrangement. An alternative mechanism was proposed to account for those examples which could not be explained by epoxide formation, in which the initial step is the electrophilic addition of $O - Cr (Vl)$ to the double bond. The intermediate could either decompose to the epoxide by loss of chromium (Vl) or lead directly to the rearranged products without involving the epoxide. It is not known whether the electrophilic attack at the double bond is similar to the addition of bromine to an alkene in a polar medium or involves simultaneous addition to both sides of the double bond in a similar manner to that of permanganate. Either of these steps could account for the formation of epoxides and the other products observed. (see figure **8**).

The occurrence of rearrangement products in both the chromic acid and chromyl acetate oxidations of alkenes indicates that a carbonium ion may be formed at some stage during the reaction. This could occur in the opening of the epoxide ring or from a chromium - containing intermediate which precedes the formation of an epoxide. However there is insufficient data available which would allow a decision to be made between the two possibilities.

While preparing compounds required for the elucidation of the structure of a steroidal lactone Glotter, Greenfield and Lavie [42] found it necessary to oxidise some allylic alcohols with Jones [49] reagent. Since the products were not the expected enones but instead epoxy-ketones these authors investigated other allylic alcohol systems to discover the requirements for, and the limitations of such a reaction. It was observed that whereas the equatorial alcohols were always oxidised to the corresponding $\alpha\beta$ unsaturated ketones their axial isomers were either oxidised to enones or underwent epoxidation of the double bond in addition to the oxidation of the hydroxyl function to form epoxy-ketones. In the examples studied epoxidation only occurred under acidic conditions, pyridine solution [23] producing only the corresponding enones. In those axial allylic alcohols in which the rate of oxidation of the secondary alcohol is faster than that of epoxidation of the double bond it was noted that enones were formed whereas epoxy-ketones were produced from those in which the relative rates of the two processes are reversed. Furthermore, unsaturated alcohols which give transoid enone systems belong to the former group while those which would result in cisoid enones give epoxy-ketones. Epoxidation was stereospecific and took place on the same side of the molecule as the hydroxyl function, as in the case of epoxidation by per-acids. From this evidence it was assumed that the epoxidation of the double bond involved the initial formation of a chromate ester followed by transfer of an oxygen atom from the ester to the double bond.

The oxidations discussed above have all been carried out in an acidic medium, making them unsuitable for use with compounds containing additional acid-sensitive functional groups. This problem was overcome by the introduction, as an oxidising agent, of the fairly stable chromium trioxide - pyridine complex which had previously been prepared[50] by the cautious addition of chromium trioxide to anhydrous pyridine. This reagent was successfully applied to a series of steroidal alcohols by Sarett[23] who found that it smoothly converted primary and secondary alcohols into the corresponding carbonyl compounds, the yields of ketones from monohydric secondary alcohols being almost theoretical. In the examples studied the complex did not attack double bonds or thioethers. No further investigation into the scope of the reagent, or the mechanism of the oxidation has as yet been carried out.

Additional chromium trioxide - pyridine oxidations.

As noted above, the chromium trioxide - pyridine complex has until now been used more or less exclusively as an oxidising agent for compounds which are acid-labile and in the majority of cases only the expected oxidation products have been reported. It has been observed however, during the course of the present investigation, that this reagent is a much more versatile oxidising agent. In addition to the examples discussed above further work on the oxidation of some readily available sesquiterpenoids and steroids was carried out in order to investigate its potential uses.

Previous workers[51] have treated drimenol (101a), the

sesquiterpene alcohol isolated from the bark of _Drinys_
winteri with chromic acid and potassium dichromate in
aqueous acetic acid and have isolated a crystalline nor-
enone for which the structure (102a) was first proposed and
then revised [52] to the isomeric enone (103). However on
treatment of drimenol with the chromium trioxide - pyridine
complex the keto acid (102b) was formed, [51] albeit in low
yield. As an extension to this the corresponding oily acetate
(101d) was prepared and in its n.m.r. spectrum it shows the
resonance of the C - 7 olefinic proton as a multiplet at
4.5 ($W_{\frac{1}{2}}$ = 8 c./sec.) and that of the methyl group attached to
a double bond as a broadened singlet at γ 8.34 ($W_{\frac{1}{2}}$ = 4 c./sec.).
The methylene protons adjacent to the acetate function appear
as the AB part of an ABX system at γ 5.75 and 5.87 (J_{AX} =
J_{BX} = 4 c./sec. and J_{AB} = 12 c./sec.)(calc.). This acetate
on being allowed to stand for 16 days with chromium trioxide
in pyridine furnished as the more polar product an oil (102c)
$C_{17}H_{26}O_3$ which slowly crystallised on cooling to 0° and had
m.p. 48 - 50°. Significantly, in its n.m.r. spectrum there is
no resonance from an olefinic proton, the methyl group
attached to the double bond appearing as a very sharp singlet
at γ 8.24 showing no further coupling as expected for a
methyl group adjacent to a carbonyl function. Furthermore,
the protons of the primary acetate group appear as a quartet
at γ 5.28 (J = 13 c./sec.) having moved downfield by
approximately 0.53 ppm to a value acceptable for an allylic

primary acetate indicating that the $\triangle^7$ double bond has migrated into the tetrasubstituted position. The i.r. spectrum shows in addition to the acetate peak at 1745 cm^{-1} a peak at 1677 cm^{-1} characteristic of a cyclohexenone. The formation of this compound can be rationalised by an electrophilic attack by O - Cr (VI) on the double bond followed by its rearrangement into the $\triangle^{8(9)}$ position. A similar result was found[53] in the triterpene field in the conversion of alnusadienol (*104*) into the dienedione (*105*).

In order to examine the effect, if any, of the reagent on a compound containing no oxygen functions two hydrocarbons were subjected to oxidation under similar conditions. The sesquiterpene hydrocarbon drimene (101b) $C_{15}H_{26}$ was prepared from drimenol (101a) via the thermally unstable tosylate (101c) $C_{22}H_{32}SO_3$. The n.m.r. spectrum of this compound had certain features in common with that of the corresponding acetate (101d):- a multiplet at γ 4.52 ($W_{\frac{1}{2}}$ = 8 c./sec.) from the olefinic proton, a broadened singlet at γ 8.44 from the C - 12 methyl group, a six-proton singlet at γ 9.18 and a three-proton singlet at γ 9.28 from three tertiary methyl groups. In addition, the four aromatic protons resonate as a pair of doublets at γ 2.20 and 2.66 (J = 9 c./sec.). The two magnetically non-equivalent primary tosylate protons being the AB part of an ABX system appear as two quartets at γ 5.85 and 5.95 (J_{AX} = 4 c./sec., J_{BX} = 8 c./sec. and J_{AB} = 10 c./sec.)(calc.).

This tosylate on hydrogenolysis with lithium aluminium hydride furnished as the major product, the oily hydrocarbon, drimene ($101b$), the n.m.r. of which exhibits a multiplet at Υ 4.57 ($W_{\frac{1}{2}}$ = 8 c./sec.) and a broadened singlet at Υ 8.38 attributable respectively to a proton and a methyl group, both attached to a double bond. The oxidation of this compound afforded no isolable product (t.l.c. evidence) while similar treatment of cholest-5-one ($106a$) for 23 days and work up produced only starting material (n.m.r.) and slight traces of more polar compounds.

A further investigation of the stem barks of South American Drimys species furnished [54] an unsaturated lactone, confertifolin (107) shown to be related to drimenol. Under our conditions confertifolin itself was resistant to oxidation but certain of its derivatives proved to be susceptible. Previous workers[54] have also noted that while drimenin (108) and isodrimenin (109) were transformed into oxoisodrimenin (110) at similar rates with either Beckmann's mixture or chromium trioxide in 95% acetic acid confertifolin did not yield the corresponding oxo-lactone and was recovered largely unchanged.

Hydride reduction of the lactone furnished a crystalline diol ($111a$) in which the protons from the two primary allylic hydroxyl functions resonate as two singlets at Υ 5.83 and 5.9. That the low field signal arose from the C - 11 protons was deduced from the spectrum of the deuterated diol ($111d$), prepared by reduction with lithium aluminium deuteride, where

the signal at Υ 5.9 from the C - 12 hydroxyl group is absent. The diol was converted by treatment with the reagent for 15 hours at 20° into an oily mixture of compounds. The less polar component, which was the only one to stain up with Ce^{4+} failed to crystallise but after distillation analysed for $C_{15}H_{22}O$. In its n.m.r. spectrum the signals from the three tertiary methyl groups (at Υ 8.81, 9.08 and 9.10) are clearly seen while in the low field region there is a two proton singlet at Υ 2.93 characteristic of $\propto$ furan protons. From this evidence it follows that this compound must be a β , β -disubstituted furanoid compound of the structure (112). The other two products were of very similar polarity and after crystallisation the less polar had $150 - 152^{\circ}$ and proved to be isodrimenin. The more polar, obtained in approximately the same yield, on crystallisation had m.p. 127° and was identical in all respects with the isomeric lactone confertifolin (108). The reaction can be envisaged as proceeding through the hemi-acetals (*113 a* and *b*) via the hydroxy-aldehydes (*111b* and *c*). Further oxidation leads to the lactones, the furanoid compound arising from dehydration. The aldehydes are produced in approximately equal amounts since in the diol (111a) the two hydroxyl groups are chemically much more nearly equivalent than those of the diol (80d) from <u>S</u>. <u>serotina</u>.

In the n.m.r. spectrum of the corresponding diacetate (111e) $C_{19}H_{30}O_4$ the signals from the acetate groups at C - 11 and C - 12 appear as singlets at Υ 5.37 and 5.4. Treatment with the oxidising reagent transformed it into the product of

allylic oxidation, the oily keto-diacetate $(_{114})$ $C_{19}H_{28}O_5$ the n.m.r. of which has already been discussed (vide supra).

Cholesteryl acetate $(106b)$ has previously been converted into its 7 - keto derivative (115), in high yield, by the action of di - tert - butyl chromate and in this present investigation the reaction was repeated using chromium trioxide in pyridine. The major product obtained was the Δ^5-7 ketone (115) although in much lower yield. In cholesteryl acetate the olefinic proton appears as a multiplet at Υ 4.59 $(W_{\frac{1}{2}} = 8$ c./sec.$)$ and the proton at C - 3 adjacent to the acetate group as a broad multiplet centred at Υ 5.33 (multiplet width = 40 c./sec.). In the enone $(_{115})$ while the resonance of the C - 3 proton still appears at 5.33 that of the olefinic proton has moved downfield to τ 4.3 and is now a singlet as expected. Cholesterol $(106c)$ itself, on oxidation under similar conditions, yielded as the major products, cholest-4-ene, 3, 6-dione $(116a)$ and 6 hydroxy-cholest-4-ene-3-one $(116b)$ identified from their n.m.r. and i.r. spectra. These compounds have been isolated from the reaction of cholesterol with chromic acid.

Erythroxylol B acetate (117) a homoallylic acetate derived from one of the tetracyclic diterpene alcohols found [55] in <u>Erythroxylon monogynum</u> was also treated as described above. Since this compound has no methylene group adjacent to the double bond allylic oxidation to an enone is impossible as is attack by O - Cr (VI) at C - 15 with concomitant migration of the double bond. There remains the

possibility of epoxidation of the double bond. However, the acetate was recovered apparently unchanged (n.m.r. evidence) and showed no evidence of any epoxide formation.

In conclusion then, it may be noted that the reaction of chromium trioxide in pyridine is more complex than has previously been suggested, in that it can give rise to products of allylic oxidation, rearrangement, epoxidation and glycol cleavage. These reactions have until now only been reported for the action of chromium (Vl) in an acidic medium. It also appears to attack furan rings which may explain the poor yields experienced in the investigation of the furan-containing diterpenoids. At this stage, however, no suggestion as to the mechanisms of these various reactions can be made but it would appear that for the successful introduction of an allylic carbonyl function into an olefin the presence of an oxygen function elsewhere in the molecule is desirable.

EXPERIMENTAL.

Extraction of Solidago serotina roots.

The finely ground, dried roots of Solidago serotina (grown in the Glasgow area; gathered in August 1967)(500 g) were extracted for 24 hours with ethyl acetate in a Soxhlet apparatus. Evaporation of the solvent afforded the crude extract (27 g) shown by qualitative t.l.c. to consist of twelve major components, ten of which gave a positive Ehrlich test for furan-containing compounds.

Isolation of compounds from S.serotina extract.

The chloroform soluble portion of the above extract (24 g) was chromatographed over Woelm neutral alumina (grade 3 : 2 Kg) using as solvent, light petroleum - chloroform mixtures. Since no fraction was obtained completely pure further purification by column or preparative chromatography was necessary. For those compounds which were isolated as oils this was followed by distillation in vacuo.

Fraction A (4.3 g) eluted with chloroform - light petroleum (1 : 19) contained the non-polar material and was not investigated further since it did not appear to contain any furanoid compounds.

Fraction B (923 mg) was eluted with 10% chloroform in light petroleum and contained the mono-aldehyde (76d :471mg) as the major constituent. Distillation in vacuo furnished the aldehyde as a colourless oil which had $[\alpha]_D = -164°$ (c = 0.9)* ; $\nu_{max}^{CCl_4}$ 2690, 1722, 872 cm^{-1} ; n.m.r. signals at τ 0.54 (s)(1H, C - 19), 4.28 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 9 c./sec.), 8.57 (d)(3H, C - 18 ; J = 2c./sec.) (Found : C =

* In this section rotations refer to ethanol solutions unless otherwise stated

79.90, H = 9.38 ; $C_{20}H_{28}O_2$ requires C = 79.95, H = 9.39%);
m/e = 300 (M).

Fraction C (1.3 g) contained two compounds of very
similar polarity which were separated with considerable
difficulty by repeated preparative t.l.c. (6 x ethyl acetate -
light petroleum, 1 : 19). The resulting apparently
homogeneous band (water spray) was divided into four parts
with respect to polarity. The less polar quarter contained
the conjugated lactone (87a : 311 mg) which after
distillation crystallised from light petroleum as needles,
m.p. 92 - 95°, $[\alpha]_D$ = + 11.7° (c = 0.65) ; $\nu_{max}^{CCl_4}$ 1772,
874 cm^{-1} ; λ_{max}^{EtOH} 204 mu (ϵ = 21,300); n.m.r. signals
at τ 3.35 (t)(1H, C - 3 ; J = 3 c./sec.), 5.88 (q)(2H,
C - 19 ; J = 9 c./sec.), 8.97 (s)(3H, C - 20) and 9.10 (d)
(3H, C - 17 ; J = 6 c./sec.). (Found : C = 76.44, H = 8.41 ;
$C_{20}H_{26}O_3$ requires C = 76.40, H = 8.34%); m/e = 314 (M).
The two extracts of intermediate polarity contained the
lactone along with the dialdehyde (80g)(i.r. and n.m.r.
evidence). The pure dialdehyde (80g : 472 mg) was
obtained from the most polar band and crystallised as needles
from ethyl acetate - light petroleum and had m.p. 103 - 105°;
$[\alpha]_D$ = - 49° (c = 0.7) ; $\nu_{max}^{CCl_4}$ 1720, 1690, 878 cm^{-1} ;
n.m.r. signals at τ -0.17 (s) (1H, C - 18), 0.89 (s)
(1H, C - 19), 3.16 (t) (1H, C - 3 ; J = 4 c./sec.), 9.04 (s)
(3H, C - 20) and 9.15 (d)(3H, C - 17 ; J = 6 c./sec). (Found·
C = 76.52, H = 8.43 ; $C_{20}H_{26}O_3$ requires C = 76.40, H = 8.34%);
m/e = 314 (M)

Fraction D (928 mg) contained only one component, the

<u>alcohol</u> (88_a : 671 mg) which since it could not be

induced to crystallise, was purified by distillation at

$120^{\circ}/0.01$ mm, $[\alpha]_D = -45^{\circ}$ (c = 0.6) ; $\nu \, ^{CCl_4}_{max}$ 3620, 3400,

875 cm^{-1}. The n.m.r. showed resonances at τ 4.36 (m)(1H,

C - 3 ; $W_{\frac{1}{2}}$ = 8c/sec.), 5.99 (s)(2H, C - 18), 7.86 (s)(-O<u>H</u>),

8.80 and 8.93 (s)(3H each, 2 tertiary methyl groups) and

9.10 (d)(3H, C - 17 ; J = 6 c./sec). (Found : C = 79.30, H =

9.94 ; $C_{20}H_{30}O_2$ requires C = 79.42, H = 10.00%) ; m/e = 302 (M).

Fraction E (4.3 g) contained the hemi-acetal and a non-

furanoid sterol and after further separation by column

chromatography, the <u>hemi-acetal</u> was distilled in vacuo ;

$[\alpha]_D = -29.7^{\circ}$ (c = 1.1 ; CHCl$_3$) ; $\nu \, ^{CCl_4}_{max}$ 3600, 3390,

872 cm^{-1} ; n.m.r. signals at τ 4.51 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 10

c./sec.), 4.58 (broad s)(1H, C - 19), 5.79 (broad s)(2H, C -

18 ; $W_{\frac{1}{2}}$ = 7 c./sec.), 6.67 (m)(-O<u>H</u>), 9.03 (s)(3H, C - 20) and

9.15 (d)(3H, C - 17 ; J = 6 c./sec.). (Found : C = 75.91, H =

9.03 ; $C_{20}H_{28}O_3$ requires C = 75.91, H = 8.92%) ; m/e = 316

(M). Crystallisation of the sterol from ethyl acetate - light

petroleum gave needles, m.p. 161 - 163° ; $\nu \, ^{CCl_4}_{max}$ 3600 cm^{-1};

m/e = 412 ($C_{29}H_{48}O$). These physical properties are similar

to those reported for stigmasta - 8 (14), 22-dien-3 β -ol

recently isolated [56] from "rayless goldenrod"(<u>Aplopappus</u>

<u>heterophyllus</u>).

Fraction F (3.2 g) contained the <u>epoxy-hemiacetal</u>

(91_a : 1.9 g) as the main component, separation from the

minor components being effected by column chromatography

over alumina (grade 3) followed by preparative t.l.c. (ethyl

acetate - light petroleum, 1 : 3). It was obtained as a colourless oil which slowly crystallised on cooling, m.p. c 18°; $[\alpha]_D = -47°$ (c = 0.8); $\nu_{max}^{CCl_4}$ 3600, 3400, 872 cm^{-1}; n.m.r. signals at τ 4.49 (s)(1H, C - 19), 6.11 (q) (2H, C - 18 ; J = 10 c./sec.). 6.71 (s) (1H, C - 3, $W_{\frac{1}{2}} =$ 4 c./sec.) and 7.03 (m)(1H, -O$\underline{H}$).(Found : C = 72.33, H = 8.64; $C_{20}H_{28}O_4$ requires C = 72.26, H = 8.49%) ; m/e = 332 (M).

Fraction G, eluted from the column with chloroform, contained the diol (80c : 2.9 g) as the sole constituent which after distillation in vacuo followed by cooling to 0° crystallised as rosettes, m.p. 60 - 62°; $[\alpha]_D = -36.1°$ (c = 0.7) ; $\nu_{max}^{CCl_4}$ 3620, 3300, 875 cm^{-1} ; n.m.r. signal at τ 4.11 (m)(1H, C - 3 ; $W_{\frac{1}{2}} =$ 8c./sec).(Found : C = 75.26, H = 9.30°, $C_{20}H_{30}O_3$ requires C = 75.43, H = 9.50%); m/e 318 (M).

The final neutral fraction (509 mg) was eluted with chloroform containing 5% methanol and contained the most polar compound, the triol (90b : 284 mg). Further column chromatography over neutral alumina (grade 5 : 50 g) and elution with diethyl ether - light petroleum (1 : 1) furnished the triol as an oil which after prolonged cooling at 0° crystallised as needles m.p. 135 - 137° ;$[\alpha]_D = -18°$ (c = 0.95) : $\nu_{max}^{CCl_4}$ 3425, 875 cm^{-1} ; n.m.r. resonance at τ 4.5 (m)(1H, C - 19 ; $W_{\frac{1}{2}}$ = 10 c./sec.) (Found : C = 68.42, H = 8.89 ; $C_{20}H_{30}O_5$ requires C = 68.54, H = 8.63%); m/e = 350 (M).

Further elution of the column with ethyl acetate - acetic acid (4 : 1) afforded the acidic fractions which were separated by further column chromatography over silica gel.

Elution with diethyl ether - light petroleum (1 : 9)
afforded as the major component, the less polar <u>solidagoic</u>
<u>acid A</u> (76a : 3.1 g) which crystallised as large plates
from ethyl acetate - light petroleum and had m.p. 169 - 171°;
$[\alpha]_D$ = - 57.7° (c = 0.9) ; $\nu_{max}^{CCl_4}$ 3600-3100, 1695, 875
cm^{-1} ; n.m.r. signals at τ 4.46 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.).
8.46 (s)(3H, C - 18), 8.99 (s) (3H, C - 20), and 9.09 (d)
(3H, C - 17 ; J = 6 c./sec.). (Found: C = 75.75, H = 8.58 ;
$C_{20}H_{28}O_3$ requires C = 75.91, H = 8.92%) ; m/e = 316 (M).
Continued elution with diethyl ether - light petroleum (1 : 4)
afforded another crystalline acid, <u>solidagoic acid B</u>
(80a : 371 mg) which on crystallisation from ethyl acetate
- light petroleum furnished needles, m.p. 134 - 135° ;
$[\alpha]_D$ = - 27.7° (c = 0.7 ; $CHCl_3$); $\nu_{max}^{CCl_4}$ 3600, 3100, 1720,
1695, 875 cm^{-1} ; λ_{max}^{EtOH} = 221 mu (log ϵ = 3.78); n.m.r.
signals at τ 3.96, 7.95 - 8.15 (1H and 6H respectively ;
angelate proton and methyl groups), 4.02 (m)(1H, C - 3),
5.50 (s)(2H, C - 13) and 8.97 (s)(3H, C - 20) and 9.09 (d)
(3H, C - 17 ; J = 6 c./sec.). (Found: C = 72.40, H = 8.55 ;
$C_{25}H_{34}O_5$ requires C = 72.43, H = 8.27%) ; m/e = 314 (M - 100).
The final fractions were oily and contained at least two
additional furanoid acids which were not investigated
further.

<u>Methylation of Acid A (76a)</u>.

Solidagoic A (76a : 1.53 g) in diethyl ether was
treated with an ethereal solution of diazomethane for 15
minutes. Evaporation of the solvent afforded the oily
methyl ester (76b : 1.58 g), $[\alpha]_D$ = -67.5° (c = 1.0);

$\sqrt{}$ max 1728, 873 cm^{-1}; n.m.r. signals at τ 4.51 (m)

(1H, C - 3 ; $W_{\frac{1}{2}}$ = 9c./sec.), 6.47 (s)(3H, -O -C$\underline{H}_3$), 8.47

(broad s)(3H, C - 18), 8.97 (s)(3H, C - 20) and 9.10 (d)

(3H, C - 17 ; J = 6c./sec.).

Reduction of Methyl ester A (76b).

The above methyl ester (76b : 1.58 g) was dissolved

in dry refluxing tetrahydrofuran (50 ml) and treated for 72

hours with excess lithium aluminium hydride. Work up gave

the crude alcohol (76c : 1.56 g) which also failed to

crystallise. $[\alpha]_D$ = - 37.5° (c = 1.0); $\sqrt{}$ max^{CCl_4} 3630, 875

cm^{-1} ; n.m.r. signals at τ 4.29 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 9c./sec.).

6.4 (q) (2H, C - 19 ; J = 11 c./sec.), 8.33 (broad s)(3H, C - 18

8.91 (s)(C - 20) and 9.10 (d)(3H, C - 17 ; J = 6c./sec.).

Oxidation of Alcohol A (76c).

Acid A alcohol (76c : 725 mg) in dry pyridine (10 ml)

was treated at room temperature for 14 hours with chromium

trioxide (800 mg) and the crude material obtained (782 mg)

was seen to consist of three major components separated by

preparative t.l.c. (ethyl acetate - light petroleum, 1 : 9).

The least polar component (76d : 480 mg) had $[\alpha]_D$ = -161°

(c = 0.85); $\sqrt{}$ max^{CCl_4} 2690, 1722, 872 cm^{-1} and was identical

($[\alpha]_D$, i.r., n.m.r. and t.l.c.) with the mono-aldehyde of

natural provenance. The compound of intermediate polarity

the nor-enone (77a : 35 mg) was obtained as an oil from

which the dark colour was removed by distillation at 160°/

0.02 mm; $[\alpha]_D$ = - 100° (c = 0.7); $\sqrt{}$ max^{CCl_4} 1675, 872 cm^{-1} ;

n.m.r. signals at τ 8.31 (d)(3H, C - 18 ; J = 2c./sec.),

8.97 (d) (3H, C - 17 : J = 7c./sec.) and 9.12 (s)(3H, C -20).

(Found: C = 79.58, H = 9.15; $C_{19}H_{26}O_2$ requires C = 79.68, H = 9.15%); m/e = 286 (M). The most polar of the major compounds was the <u>aldehydo-enone</u> (79a   : 25 mg) further purified by distillation at $140°/0.03$ mm; $[\alpha]_D = -197°$ (c = 0.86); $\nu_{max}^{CCl_4}$ 2700, 1730, 1680, 873 cm^{-1} ; n.m.r. signals at τ 4.09 (s)(1H, C - 3), 0.43 (s)(1H, C - 19), 8.29 (s)(3H, C - 18), 9.04 (s)(3H, C - 20) and 9.16 (d) (3H, C - 17 ; J = 6 c./sec.). (Found : C = 76.48, H = 8.40; $C_{20}H_{26}O_3$ requires C = 76.40, H = 8.34%) ; m/e = 314 (M).

<u>Treatment of Aldehyde A with Hydrazine hydrate.</u>

Aldehyde A (76d   : 50 mg) in methanol (2ml) was treated at room temperature for 16 hours with 100% hydrazine hydrate (2ml). The solution was extracted with ethyl acetate, washed with water and the organic layer dried over anhydrous sodium sulphate. Evaporation of the solvent furnished an oil from which the very minor, polar compounds were removed by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 3). The substituted <u>hydrazone</u> (32 mg) thus obtained was distilled at $140°/0.001$ mm; $\nu_{max}^{CCl_4}$ 875 cm^{-1}; n.m.r. signals at τ 4.52 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 10 c./sec.) 8.05 and 8.09 (s)(3H each, - N - C$\underline{H}_3$), 8.53 (broad s)(3H, C - 18), 9.04 (s)(3H, C - 20) and 9.13 (d)(3H, C - 17 ; J = 6 c./sec.). (Found: C = 77.11, H = 9.94, N = 8.20 ; $C_{22}H_{34}N_2O$ requires C = 77.14, H = 10.01, N = 8.18 %).

<u>Acetylation of Alcohol A (76c).</u>

Alcohol A (76c : 50 mg) in dry pyridine (2ml) was treated at room temperature for 14 hours with acetic

anhydride (2 ml). The <u>acetate</u> obtained (47 mg) failed to crystallise and after purification by preparative t.l.c. (benzene) followed by distillation in vacuo it had $[\alpha]_D$ = - 59.4° (c = 0.8); $\nu_{max}^{CCl_4}$ 1740, 1235, 872 cm^{-1} ; n.m.r. signals at $\tilde{\tau}$ 4.26 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.97 (q) (2H, C - 19 ; J = 12 c./sec.), 8.00 (s)(3H, OAc), 8.35 (broad s)(3H, C - 18), 8.91 (s)(3H, C - 20) and 9.10 (d) (3H, C - 17; J = 6 c./sec.). (Found : C = 76.99, H = 9.54 ; $C_{22}H_{32}O_3$ requires C = 76.70, H = 9.36 %); m/e = 344 (M).

<u>Attempted thioketalisation of Aldehyde A (76d).</u>

Aldehyde A (76d : 50 mg) in diethyl ether (50 ml) containing redistilled boron trifluoride diethyl etherate (2 ml) was treated at room temperature for 75 hours with ethane dithiol (3 ml). The ethereal solution was washed with dilute sodium hydroxide until the last traces of ethane dithiol had been removed. Evaporation of the solvent afforded an oily residue (53 mg) which was seen (t.l.c.) to consist mainly of the unreacted aldehyde with at least six more polar compounds none of which appeared to be in major yield.

<u>Wolff-Kishner reduction of Aldehyde A (76d).</u>

Aldehyde A (76d : 50 mg) in ethylene glycol (2 ml) was treated at 95° for 48 hours with 100% hydrazine hydrate (3 ml). Potassium hydroxide (100 mg) was added and the temperature of the mixture allowed to rise to 210° and remain there for 13 hours. After being allowed to cool the solution was acidified and then extracted with ethyl

acetate. The oil obtained (45 mg), after removal of the
solvent, was subjected to preparative t.l.c. (100% light
petroleum) and the major component isolated had $[\alpha]_D = -19°$
(c = 1.0) and was identical (t.l.c. and n.m.r. to the
hydrocarbon (88c) obtained previously.

Attempted hydroxylation of Acid A (76a).

To a solution of the acid in diethyl ether (21 mg in 5 ml)
was added an ethereal solution of osmium tetroxide (80 mg in
5 ml) and the resulting brown suspension allowed to stand at
room temperature for 20 hours. Hydrogen sulphide gas was
bubbled through the mixture for 30 minutes and after removal
of the precipitated sulphides the solvent was evaporated to
afford the crude material (18 mg) which from t.l.c. and n.m.r.
evidence was the unreacted acid.

Attempted hydroboration of Acid A (76a).

Freshly distilled boron trifluoride diethyl etherate
(0.2 ml) was added to a solution of the acid (17 mg) in
diethyl ether (1 ml) under nitrogen. Lithium aluminium
hydride in dry diethyl ether was added drop-wise over a
period of ten minutes with stirring. The mixture was then
stirred for a further two hours whereupon the excess reagent
was destroyed by the cautious addition of a saturated sodium
sulphate solution. After evaporation of the solvent the
residue was dissolved in 90% ethanolic sodium hydroxide (2 ml)
and 30% hydrogen peroxide added dropwise under nitrogen with
stirring and then the mixture was stirred for a further 12
hours. Extraction with ethyl acetate gave the product (16 mg)

seen from t.l.c. and n.m.r. to consist of the unreacted acid.

Attempted hydroxylation of Acetate A (76e).

The derived acetate (76e : 16 mg) was treated with osmium tetroxide in the manner described above but on work up the material was shown from t.l.c. and i.r. evidence to consist of the starting acetate.

Hydrogenation of Methyl Ester A (76b).

Methyl ester A (76b : 380 mg) in absolute alcohol (40 ml) was hydrogenated for 25 minutes over Adams catalyst (2 0 mg). Removal of the catalyst and solvent afforded an oil (401 mg) consisting of one major and several minor components. Separation by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 3) afforded the oily tetrahydro-methyl ester (84c : 215 mg) which distilled at $130^{\circ}/0.04$ mm; $\nu_{max}^{CCl_4}$ 1723 cm^{-1}; n.m.r. signals at τ 4.67 (m)(1H, C – 3; $W_{\frac{1}{2}}$ = 8c./sec.), 6.40 (s)(3H, -OCH$_3$). (Found: C = 75.62, H = 10.47 ; $C_{21}H_{34}O_3$ requires C = 75.40, H = 10.25%). The two hexa-hydro derivatives ($86a$ and 86b: 40 mg) were obtained with no separation of one from the other and the mixture had signals in the n.m.r. at τ 4.63 (m)(1H, C – 3 ; $W_{\frac{1}{2}}$ = 10 c./sec.) and two singlets at 6.32 and 6.38 (-OCH$_3$). (Found: C = 75.22, H = 10.90 ; $C_{21}H_{36}O_3$ requires C = 74.95, H = 10.78%).

Reduction of Tetrahydro-Methyl ester (84c).

The tetrahydro-methyl ester (84c : 60 mg) in dry refluxing diethyl ether was treated for 14 hours with excess lithium aluminium hydride. Work up gave the tetrahydro-

alcohol (84d : 57 mg) as an oil which distilled at $140^{\circ}/0.02$ mm ; $[\alpha]_D = -15.8^{\circ}$ (c = 1.2 : $CHCl_3$); n.m.r. signals at τ 4.42 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8c./sec.), 6.56 (q)(2H, C - 19 ; J = 12c./sec.), 8.36 (broad s)(3H, C - 18, 8.99 (s)(3H, C - 20) and 9.14 (d)(3H, C - 17; J = 6c./sec.). (Found : C = 78.52, H = 11.28 ; $C_{20}H_{34}O_2$ requires C = 78.38, H = 11.18%).

Oxidation of Tetrahydro-alcohol (84d).

The above alcohol (84d : 23 mg) in dry pyridine (2 ml) was treated at room temperature for 15 hours with chromium trioxide (100 mg). Work up gave the crude material (24 mg) from which the aldehyde (84b : 17 mg) was obtained by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 4). Distillation in vacuo afforded a colourless oil, $[\alpha]_D = -88^{\circ}$ (c = 1.2 : $CHCl_3$); ν max^{CCl_4} 1723 cm^{-1} ; n.m.r. signals at 0.74 (d)(1H, C - 19 ; separation 2c./sec.) and 4.36 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8c./sec.). (Found: C = 78.92, H = 11.05 $C_{20}H_{32}O_2$ requires C = 78.89, H = 10.59%); m/e = 304 (M).

Oxidation of Methyl ester A (76b).

Methyl ester A (76b : 152 mg) in dry pyridine (2 ml) was treated at room temperature for 18 days with chromium trioxide (500 mg). Work up in the usual manner afforded an oil (172 mg) which was subjected to preparative t.l.c. (ethyl acetate - light petroleum, 3 : 7). The less polar component (48 mg) was the unreacted ester while the compound of intermediate polarity was the enone-ester (79c : 63 mg) which was distilled in vacuo ; ν max^{CCl_4} 1725, 1675, 882 cm^{-1} ; n.m.r. signals at τ 4.23 (s)(1H, C - 3), 6.5 (s)(3H, -O$C\underline{H_3}$),

8.29 (d)(3H, C – 18 ; J = 1c./sec.), 9.07 (s)(3H, C – 20)

and 9.07 (d)(3H, C – 17 ; J = 5 c./sec.). (Found: C = 73.26,

H = 8.35 ; $C_{21}H_{28}O_4$ requires C = 73.22, H = 8.19%); m/e =

344 (M).

Hydrogenation of Aldehyde A (76d).

Aldehyde A (76d : 140 mg) in absolute alcohol (40 ml)

was hydrogenated for 30 minutes over Adams catalyst. The

catalyst was filtered off and the solvent evaporated to afford

an oil (133 mg) from which the major product, the hexahydro-

aldehyde (85a : 65 mg) was obtained by preparative t.l.c.

(2 x ethyl acetate - light petroleum, 1 : 4). Distillation at

$140^{\circ}/0.02$ mm afforded the aldehyde as a colourless oil, $[\alpha]_D$

$= -15^{\circ}$ (c = 0.74 : $CHCl_3$) ; $\nu \, \substack{CCl_4 \\ max}$ 1713 cm^{-1}. In the n.m.r.

the aldehydic proton appeared at τ 0.65 (s). (Found: C = 78.61,

H = 11.45 ; $C_{20}H_{34}O_2$ requires C = 78.38, H = 11.18 %).

Oxidation of Acetate A (76e).

The acetate from acid A (76e : 40 mg) in dry pyridine

(2 ml) was treated at room temperature for 17 days with

chromium trioxide (100 mg). The oil obtained (38 mg) was

separated by preparative t.l.c. (ethyl acetate - light petroleum,

2 : 3) to afford the acetate (17 mg) as the less polar

component. The polar product, the enone-acetate (79b : 12 mg)

was obtained as an oil which distilled at $140^{\circ}/0.04$ mm ; $[\alpha]_D$

$= -87.6^{\circ}$ (c = 0.8); $\nu \, \substack{CHCl_3 \\ max}$ 1740, 1660, 872 cm^{-1} ; n.m.r.

signals at τ 4.07 (s)(1H, C – 3), 6.01 (q)(2H, C – 19 ; J =

12 c./sec.), 8.0 (s)(3H, -OAc), 8.28 (broad s)(3H, C – 18 ;

$W_{\frac{1}{2}}$ = 5c./sec.), 8.97 (d)(3H, C – 17 ; J = 6 c./sec.) and

9.08 (s)(3H, C - 20). (Found: C = 73.83, H = 8.52 ; $C_{22}H_{30}O_4$
requires C = 73.71, H = 8.44%).

Wolff-Kishner reduction of Tetrahydro-aldehyde (84b).

Tetrahydro-aldehyde (84b : 35 mg) in ethylene glycol
(2 ml) was treated for 66 hours at 70° with 100% hydrazine
hydrate (2 ml). Potassium hydroxide (100 mg) was added and
the temperature raised to 190° and maintained there for 24
hours. The oil (27 mg) obtained after work up was subjected
to preparative t.l.c. (ethyl acetate - light petroleum, 1 : 4)
and afforded the oily tetrahydro - hydrocarbon (84e : 9 mg).
m/e = 290 (M).

Attempted chloroacetylation of Alcohol A (76c).

(a) Alcohol A (76c : 125 mg) in dry pyridine (2ml) was
treated at room temperature for 15 hours with excess
chloroacetic anhydride. T.l.c. of the product after work up
showed only starting material.

(b) The above alcohol was treated with chloroacetic anhydride
in refluxing pyridine for five days and the oily material was
seen from t.l.c. to consist of two compounds the more polar of
which was the unreacted alcohol (76c : 43 mg). Separation
was effected by preparative t.l.c. (light petroleum
containing 5% ethyl acetate) and afforded the nor-olefin
(77b : 24 mg) as the less polar component, $[\alpha]_D = -32.5^{\circ}$
(c = 1.0). In the n.m.r. it exhibited signals at τ 8.35 (s)
(3H, C - 18), 8.98 (d) (3H, C - 17 ; J = 6 c./sec.) and 9.1 (s)
(3H, C - 20); m/e = 272 (M).

Attempted chloroacetylation of acid A (76a).

Acid A (76a : 52 mg) in dry chilled benzene (2 ml) was treated for 40 minutes with excess chloroacetic anhydride. Redistilled boron trifluoride diethyl etherate was added and the mixture allowed to stand at room temperature for an hour. After the addition of water the solution was kept at room temperature for 24 hours. The crude material obtained on work up was seen from t.l.c. to consist of the unreacted acid with no trace of any non-furanoid material.

Treatment of Alcohol A with p-toluene sulphonyl chloride.

Alcohol A (76c : 65 mg) in dry pyridine (0.5 ml) was treated at 0° for 7 days with p-toluene sulphonyl chloride. T.l.c. of the product on silver nitrate - silica gel showed the presence of one minor and two major products, all of which were less polar than the starting material. Preparative t.l.c. on silver nitrate - silica gel afforded the compound of intermediate polarity (27 mg) as an oil which, since it was not the required tosylate, was not investigated further. The most polar component (23 mg) did not contain a furan ring and failed to crystallise.

Methylation of Acid B (80a).

Acid B (80a : 60 mg) in diethyl ether was treated for five minutes with an ethereal solution of diazomethane. Evaporation of the solvent afforded an oil (62 mg) from which the required methyl ester B was separated from the diazomethane adducts by preparative t.l.c. (ethyl acetate - light petroleum, 3 : 17). Distillation in vacuo afforded

the <u>methyl ester</u> (80b) as a colourless oil, $[\alpha]_D = -24.7°$
(C = 0.95 ; CHCl$_3$): $\nu_{max}^{CCl_4}$ 1728 cm^{-1} ; n.m.r. signals at
τ 3.97 (m)(angelate H), 4.09 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 9 c./sec.),
5.63 (s)(3H, C - 18), 6.52 (s)(3H, -OC$\underline{H}_3$), 9.05 (s)(3H, C - 20)
and 9.19 (d)(3H, C - 17 ; J = 6c./sec.). (Found: C = 73.32,
H = 8.49 ; C$_{26}$H$_{36}$O$_5$ requires C = 72.86, H = 8.47%) ; m/e =
428 (M).

Reduction of Methyl ester B (80b).

Methyl ester B (80b : 40 mg) in dry refluxing diethyl
ether was treated for 15 hours with lithium aluminium hydride.
Work up gave the crude diol (80c : 36 mg),$[\alpha]_D = -36.1°$,
which on treatment with acetic anhydride - pyridine (2 ml each)
furnished the corresponding diacetate (80d : 27 mg)
identical (t.l.c. and n.m.r.) with the diacetate prepared
from the naturally occuring diol by direct acetylation.

Pyrolysis of Acid B (80a).

Acid B (80a : 75 mg) was heated at 300° for five
minutes in an evacuated tube. A few crystals of angelic acid
m.p. 45° (sealed tube) collected in the cold part of the tube
and were identified by gas-liquid chromatography (10% F.F.A.P.
at 125°). The oily material obtained (49 mg) was
seen to consist of three compounds (t.l.c.), two of very
similar polarity and the other much more polar. This
compound was seen from t.l.c. to be unreacted acid B and was
separated from the neutral components by filtration through a
short column of neutral alumina. The non - polar compounds
were separated from each other by preparative t.l.c.

(ethyl acetate - light petroleum, 1 : 19) and the oily
lactone A (81a : 20 mg) obtained as the more abundant
component.   Distillation in vacuo was necessary to remove
the dark colour and then it had $[\alpha]_D$ = - 66.3° (C = 1.4);
$\nu_{max}^{CCl_4}$ 1778, 872 cm^{-1}; n.m.r. signals at τ 4.41 (m)
(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.45 (q)(2H, C - 18 ; J = 11 c./s.
8.96 (s)(3H, C - 20) and 9.13 (d)(3H, C - 17; J = 6c./sec.).
(Found: C = 76. 34, H = 8.48 ; $C_{20}H_{26}O_3$ requires C = 76.40,
H = 8.34%). The more polar lactone (82 : 6 mg) crystallised
from ethyl acetate - light petroleum and had m.p. 145 - 147° ;
$\nu_{max}^{CCl_4}$ 1785 cm^{-1}; m/e = 314 (M).

Acetylation of Diol (80c).

The diol (80c : 960 mg) in dry pyridine (20 ml) was
treated at room temperature for two hours with acetic
anhydride (0.35 ml). T.l.c. of the product (975 mg) showed
that it consisted of four compounds which were separated by
preparative t.l.c. (ethyl acetate - light petroleum, 3 : 17).
The least polar component (320 mg) was the oily <u>diacetate</u>
(80d), $[\alpha]_D$ = - 44.1° (c = 1.7) ; $\nu_{max}^{CCl_4}$ 1745, 1238, 875
cm^{-1}; n.m.r. signals at τ 4.06 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 7c./sec.),
5.43 (s)(2H, C - 18), 6.01 (s)(2H, C - 19), 7.98 (s)(6H, 2 x OAc)
8.93 (s)(3H, C - 20) and 9.08 (d)(3H, C - 17 ; J = 6 c./sec.).
(Found : C = 71.58, H = 8.72 ; $C_{24}H_{34}O_5$ requires C = 71.61,
H = 8.51%) ; m/e = 402 (M). The monoacetate A (80c : 175 mg)
was also an oil which after distilling at 120°/0.01 mm had
$[\alpha]_D$ = - 53.6° (c = 0.8) ; $\nu_{max}^{CCl_4}$ 3460, 1740, 1220, 872
cm^{-1} ; n.m.r. signals appeared at τ 4.08 (m)(1H, C - 3 ;
$W_{\frac{1}{2}}$ = 8 c./sec.), 5.53 (q)(2H, C - 18; J = 12 c./sec.),

6.49 (q) (2H, C - 19 ; J 12 c./sec.), 8.00 (s)(3H, OAc),

8.94 (s)(3H, C - 20) and 9.12 (d)(3H, C - 17 ; J = 6 c./sec.).

(Found: C = 73.20, H = 8.82; $C_{22}H_{32}O_4$ requires C = 73.30,

H = 8.95%). Similarly, the <u>monoacetate B</u> (80f : 170 mg)

was distilled at $150°/0.001$ mm ; ν max^{CCl_4} 3580, 1745, 1230,

878 cm^{-1} ; n.m.r. signals at ν 4.12 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ =

7 c./sec.), 5.50 (s)(2H, C - 18), 6.06 (s)(2H, C - 19),

8.03 (s) 3H, OAc), 8.92 (s)(3H, C - 20) and 9.16 (d) (3H,

C - 17 ; J = 6 c./sec.). (Found : C = 73.32, H = 8.73 ;

$C_{22}H_{32}O_4$ requires C = 73.30, H = 8.95%). The remaining

component was the unreacted diol (80c : 102 mg).

Oxidation of Diol (80c).

(a) The diol (80c : 50 mg) in dry pyridine (20 ml) was

treated at room temperature for 14 hours with chromium

trioxide (50 mg). After work up the oily product (55 mg)

was purified by preparative t.l.c. (ethyl acetate - light

petroleum, 1 : 19) to afford as the sole product the lactone

(87a : 37 mg) which crystallised from ethyl acetate - light

petroleum and had m.p. 89 - 90°, $[\alpha]_D$ = + 5.3° (c = 1.5) :

max^{CCl_4} 1772, 871 cm^{-1}. This compound was identical (m.p.,

mixed m.p., n.m.r., and t.l.c.) with a sample of the

naturally occuring lactone.

(b) The diol (80c : 75 mg) in dry pyridine (2 ml) was

treated at room temperature for 14 hours with a large excess

of chromium trioxide (500 mg). Under these conditions the

product was seen from t.l.c. to consist of two components,

the less polar of which corresponded to the lactone obtained

previously. Separation of the two compounds was effected by

preparative t.l.c. and afforded the lactone (87a : 11 mg)

as the minor component. The more polar, major product

(95 : 47 mg), the _enone-lactone_ crystallised from ethyl

acetate - light petroleum as plates, m.p. 148 - 149°, $[\alpha]_D$ =

- 8.4° (c = 1.2) ; $\nu_{max}^{CCl_4}$ 1779, 1690, 872 cm^{-1} ; n.m.r.

signals at τ 3.56 (s)(1H, C - 3), 5.76 (q)(2H, C - 19 ; J =

8c./sec.), 9.03 (s)(3H, C - 20), 9.10 (d)(3H, C - 17 ; J =

6 c./sec.). (Found : C = 73.11, H = 7.23 ; $C_{20}H_{24}O_4$ requires

C = 73.14, H = 7.37 %); m/e = 328 (M).

Hydrogenation of Diol (80c).

The diol (80c : 325 mg) in absolute alcohol (35 ml)

was hydrogenated over Adams catalyst (300 mg) for two hours.

Removal of the catalyst and solvent afforded an oil (320 mg)

which was seen from t.l.c. to consist of a complex mixture

of compounds none of which contained a furan ring (Ehrlich's

test). The major component, the tetrahydro - diol (84f:175 mg)

was obtained by preparative t.lc. (chloroform containing

5 % methanol). Distillation at 180°/0.035 mm gave a

colourless oil, $[\alpha]_D$ = - 46.5° (c = 0.77) ; $\nu_{max}^{CCl_4}$ 3620,

3320 cm^{-1} ; n.m.r. signals at τ 4.22 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ =

7c./sec.), 9.07 (s)(3H, C - 20) and 9.18 (d)(3H, C - 17 ; J

= 6 c./sec.). (Found : C = 74.20, H = 10.80 : $C_{20}H_{34}O_3$

requires C = 74.49, H = 10.63%).

Acetylation of Tetrahydro-diol (84f).

Tetrahydro-diol (84f : 30 mg) in dry pyridine (3 ml)

was treated at room temperature for 16 hours with excess

acetic anhydride to afford the corresponding _tetrahydro-diacetate_

(84g : 27 mg). Distillation at 175°/0.04 mm furnished a colourless oil, ν max^{CCl_4} 1745, 1235 cm^{-1} ; n.m.r. signals at τ 4.11 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 6c./sec.), 5.49 (s)(2H, C - 18), 6.06 (s)(2H, C - 19), 8.00 (s)(6H, 2 x OAc), 8.99 (s)(3H, C - 20) and 9.10 (d)(3H, C - 17 ; J = 6 c./sec.). (Found: C = 70.66, H = 9.51 ; $C_{24}H_{38}O_5$ requires C = 70.90, H = 9.42%)

Oxidation of Tetrahydro-diol (84f).

The tetrahydro-diol (84f : 101 mg) in dry pyridine (2 ml) was treated at room temperature for 14 hours with chromium trioxide (500 mg). The product (98 mg) after work up was seen to be a mixture of compounds, the two major ones being of very similar polarity. These were separated by from the minor components by preparative t.l.c. (4 x ethyl acetate - light petroleum, 3 : 17). Distillation of the less polar one at 155°/0.015 mm afforded the <u>tetrahydro-lactone</u> (96a : 27 mg) as a colourless oil, $[\alpha]_D$ = + 25.4° (c = 1.1), ν max^{CCl_4} 1775 cm^{-1} ; n.m.r. signals at τ 3.41 (t)(1H, C - 3 ; J = 3 c./sec.), 9.11 (s)(3H, C - 20) and 9.18 (d)(3H, C - 17 ; J = 6 c./sec.). (Found : C = 75.67, H = 9.47 ; $C_{20}H_{30}O_3$ requires C = 75.43, H = 9.50%) ; m/e = 318 (M). The more polar <u>enone-lactone</u> (96b : 43 mg) also failed to crystallise and was purified by distillation in vacuo, $[\alpha]_D$ = - 4.2° (c = 0.9) ; ν max^{CCl_4} 1783, 1694 cm^{-1} ; n.m.r. signals at τ 3.64 (s)(1H, C - 3), 5.84 (q)(2H, C - 19; J = 8 c./sec.). (Found: C = 72.03, H = 8.28 ; $C_{20}H_{28}O_4$ requires C = 72.26, H = 8.49 %); m/e = 332 (M).

Formation of Ether (94).

The diol (80c : 50 mg) in dry refluxing pyridine (5 ml) was treated for 15 hours with p-bromobenzene sulphonyl chloride. After working up in the usual manner an oil (46 mg) was obtained from which the major product was obtained by preparative t.l.c. (ethyl acetate - light petroleum, 3 : 17). Extraction furnished the ether (94 : 32 mg) as an oil which was distilled at $150^{\circ}/0.03$ mm ; $[\alpha]_D = -30^{\circ}$ (c = 0.65); $\nu_{max}^{CCl_4}$ 872 cm^{-1}; n.m.r. signals at τ 4.57 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 7 c./sec.), 5.88 (q)(2H, C - 18 ; J = 11 c./sec.), 6.28 (q)(2H, C - 19 ; J = 8 c./sec.), 9.01 (s)(3H, C - 20) and 9.16 (d)(3H, C - 17 ; J = 6 c./sec.). (Found: C = 79.88, H = 9.52 ; $C_{20}H_{28}O_2$ requires C = 79.95, H = 9.39 %) ; m/e = 300 (M).

Oxidation of Monoacetate A (80e).

(a) Mono-acetate A (80e : 130 mg) in dry pyridine (2 ml) was treated at room temperature for 12 hours with chromium trioxide (500 mg). From the crude product (145 mg) the epoxy-aldehyde (90 mg) was obtained by preparative t.l.c. (chloroform - light petroleum, 1 : 9). Distillation at $150^{\circ}/0.015$ mm afforded a colourless oil, $[\alpha]_D = +2.3^{\circ}$ (c = 1.3) ; $\nu_{max}^{CCl_4}$ 2710, 1755, 1722, 1230, 878 cm^{-1} ; n.m.r. resonances appeared at τ 0.05 (s) (1H, C - 19), 6.25 (q)(2H, C - 18 ; J = 12 c./sec.), 6.97 (broad s)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 4 c./sec.), 8.04 (s)(3H, OAc), 9.13 (s)(3H, C - 20) and 9.25 (d) (3H, C - 17 ; J = 6 c./sec.). (Found: C = 70.21, H = 7.89 ; $C_{22}H_{30}O_5$ requires C = 70.56, H = 8.08 %) ; m/e = 374 (M).

(b) Mono-acetate A (80e : 45 mg) in dry pyridine (20 ml)
was treated at room temperature for 12 hours with chromium
trioxide (50 mg). The crude product (49 mg) was seen from
t.l.c. to consist of only one compound, less polar than that
obtained in the previous experiment. Purification by
preparative t.l.c. (chloroform - light petroleum, 4 : 1)
followed by distillation at $160^{\circ}/0.04$ mm furnished the
<u>aldehyde</u> (80h) as colourless oil, $[\alpha]_D = - 89.4^{\circ}$ (c = 0.8);
$\nu_{max}^{CCl_4}$ 2690, 1745, 1725, 1230, 878 cm^{-1}; n.m.r. signals at
τ 0.53 (s)(1H, C - 19), 4.03 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 9 c./sec.),
5.82 (s)(2H, C - 18), 8.08 (s) (3H, OAc), 9.02 (s)(3H, C - 20)
and 9.23 (d)(3H, C - 17 ; J = 6 c./sec.). (Found : C = 73.86 ;
H = 8.47 ; $C_{22}H_{30}O_4$ requires C = 73.71, H = 8.44%). m/e =
358 (M).

Oxidation of Mono-acetate B (80f).

Mono-acetate B ($80f$: 50 mg) in dry pyridine (2 ml) was
treated as described above with chromium trioxide (50 mg).
Work up gave the crude product (52 mg) which consisted of two
compounds, the more polar one being the more abundant.
Preparative t.l.c. (ethyl acetate - light petroleum, 1 : 3)
afforded the <u>acetoxy-aldehyde</u> (80i : 37 mg) as an oil which
was distilled at $155^{\circ}/0.025$ mm ; $[\alpha]_D = - 21^{\circ}$ (c = 0.88); $\nu_{max}^{CCl_4}$
2710, 1745, 1695, 1235, 874 cm^{-1} ; n.m.r. signals at
τ 0.73 (s)(1H, C - 18), 3.29 (t)(1H, C - 3 ; J = 4 c./sec.),
5.64 (q)(2H, C - 19 ; J = 12 c./sec.), 8.14 (s)(3H, OAc), 8.97
(s)(3H, C - 20) and 9.16 (d)(3H, C - 17 ; J = 6 c./sec.).
(Found : C = 73.70, H = 8.42 ; $C_{22}H_{30}O_4$ requires C = 73.71,
H = 8.44 %) ; m/e = 358 (M).

Treatment of Aldehyde (80h) with Hydrazine Hydrate.

The acetoxy-aldehyde (80h : 50 mg) in methanol (5 ml) was treated at room temperature for 15 hours with 100% hydrazine hydrate (3 ml) to afford an oil (47 mg) from which the major product (81b : 32 mg) was obtained by preparative t.l.c. (chloroform). It had $[\lambda]_D$ = - 73.8° (c = 1.08) and was identical (n.m.r., i.r. and t.l.c.) with the hemiacetal (81b) of natural provenance.

Hydrogenolysis of Diacetate (80d).

The diacetate (80d : 60 mg) in absolute alcohol (30 ml) containing triethylamine (5 ml) was hydrogenated for 40 minutes over 10% Pd-C. Removal of the catalyst and solvent afforded an oil (62 mg) which was seen to contain two compounds, one of which still contained a furan ring. These compounds were separated by preparative t.l.c. (benzene) to afford the acetate (76e : 37 mg) as the less polar component, $[\lambda]_D$ = - 43.7° (c = 1.2), $\nu_{max}^{CCl_4}$ 1740, 1235, 872 cm^{-1}. This acetate was (i.r., n.m.r. and t.l.c.) indistinguishable from the acetate prepared from acid A. The other compound, the corresponding tetrahydro-acetate (84a : 14 mg) after distillation at 150°/0.04 mm had $[\lambda]_D$ = + 27.5° (c = 1.2); $\nu_{max}^{CCl_4}$ 1740, 1235 cm^{-1}; n.m.r. signals at τ 4.50 (1H, C - 3; $W_{\frac{1}{2}}$ = 9c./sec.), 6.05 (s)(2H, C - 19), 8.01 (s) (3H. OAc), 8.36 (broad s)(3H, C - 18), 8.97 (s)(3H, C - 20) and 9.12 (d)(3H, C - 17 ; J = 6 c./sec.) (Found: C = 75.86, H = 10.20 ; $C_{22}H_{36}O_3$ requires C = 75.81, H = 10.41%).

Reduction and acetylation of Epoxy-aldehyde (83a).

The epoxy-aldehyde (83a : 60 mg) in dry refluxing diethyl ether was treated with excess lithium aluminium hydride. Work up gave an oily mixture (57 mg) of compounds of which the less polar compound was the most abundant. Separation was effected by preparative t.l.c. (chloroform containing 3 % methanol) and afforded the triol (89a : 35 mg), $[\alpha]_D = -27^\circ$ (c = 0.91). Acetylation in the usual fashion furnished the hydroxy-diacetate (89b : 33 mg), $[\alpha]_D = -15.8^\circ$ (c = 1.0) which was identical (t.l.c., i.r. and n.m.r.) with the diacetate prepared from the naturally occuring epoxy-hemiacetal (91a).

Reduction of (+) Ethyl hardwickiate (98d).

Ethyl hardwickiate (98d : 55 mg) in dry refluxing diethyl ether (5 ml) was treated with excess lithium aluminium hydride for 19 hours. Work up gave the crude product (57 mg) which was seen from t.l.c. to consist of two components of very similar polarity, the less polar of which was the more abundant. Separation by preparative t.l.c. (2 x chloroform) afforded the oily hardwickiol (98a : 37 mg). In the n.m.r. it showed resonances at τ 4.45 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.93 (s)(2H, C - 18), 8.95 and 9.29 (s) (3H each, 2 tertiary methyl groups) and 9.20 (d)(3H, C - 17 ; J = 5 c./sec.); m/e = 302 (M).

Acetylation of Hardwickiol (98a).

Hardwickiol (98a : 30 mg) in dry pyridine (2 ml) was treated at room temperature for 14 hours with acetic anhydride

to afford the corresponding acetate (98b : 31 mg).

Hydrogenation of Hardwickiol acetate (98b).

Hardwickiol acetate (98b : 25 mg) in absolute alcohol (20 ml) containing triethylamine (5 ml) was hydrogenated for five minutes over 10% Pd - C. The oil (27 mg) obtained was purified by preparative t.l.c. (light petroleum) to afford the oily hydrocarbon (98c: 22 mg) which was distilled in vacuo. In the n.m.r. it exhibited resonances at τ 4.86 (m) (1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 8.41 (d)(3H, C - 18 ; J = 2 c./sec.), 8.97 and 9.22 (s)(3H each ; 2 tertiary methyl groups) and 9.13 (d)(3H, C - 17 ; J = 6 c./sec.), (Found : C = 83.87, H = 10.62 ; $C_{20}H_{30}O$ requires C = 83.86, H = 10.56%); m/e = 286 (M).

Acetylation of Epi-hardwickiol (88a).

The alcohol (88a : 100 mg) in dry pyridine (2 ml) was treated at room temperature for 15 hours with acetic anhydride to afford a mono-acetate (88b : 98 mg) which was purified by preparative t.l.c. (chloroform). Distillation in vacuo furnished a colourless oil, $[\alpha]_D$ = - 33.5° (c = 1.4); $\nu_{max}^{CCl_4}$ 1740, 1230, 878 cm^{-1} ; n.m.r. signals at τ 4.34 (m) (1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.55 (s)(2H, C - 18), 8.05 (s) (3H, OAc), 8.82 and 8.93 (s)(3H each, 2 tertiary methyl groups) and 9.10 (d)(3H, C - 17 ; J = 6 c./sec.).(Found : C = 76.95, H = 9.34 ; $C_{22}H_{32}O_3$ requires C = 76.70, H = 9.36%).

Hydrogenation of Epi-hardwickiol acetate (88b).

(a) The above mono-acetate (88b : 50 mg) in absolute alcohol (25 ml) containing triethylamine (5 ml) was hydrogenated for five minutes over 10% Pd-C. Removal of catalyst and solvent

afforded an oil which appeared to consist of two compounds, one of which (the less polar) still contained a furan ring. Preparative t.l.c. (light petroleum) afforded the <u>hydrocarbon</u> (88c : 31 mg) as the major component and after distillation it had $[\measuredangle]_D = -21^\circ$ (c = 1.08); $\nu\ max^{CCl_4}$ 872 cm^{-1}; n.m.r. signals at γ 4.28 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 8.50 (s) (3H, C - 18), 8.96 and 9.05 (s)(3H each, two tertiary methyl groups) and 8.23 (d)(3H, C - 17 ; J = 6 c./sec.)(Found: C = 83.82, H = 10.75 ; $C_{20}H_{30}O$ requires C = 83.86, H = 10.56%); m/e = 286 (M). The minor "compound" appeared, from mass spectrometric evidence, to be a mixture of the tetrahydro- and hexahydro-hydrocarbons; m/e = 290 (292).

(b) In a separate experiment the above acetate (88b : 45 mg) in absolute alcohol containing triethylamine was hydrogenated for 40 minutes over 10% Pd-C. Work up gave an oil (40 mg) seen from t.l.c. to consist of mainly one compound, not containing a furan ring which was more polar than the hydrocarbon obtained above. Preparative t.lc. (ethyl acetate - light petroleum, 1 : 19) afforded the <u>hexahydro-compound</u> (85b : 28 mg) as an oil which was distilled at 100°/0.05 mm ; $[\measuredangle]_D = -7^\circ$ (c = 0.7 ; $CHCl_3$).(Found: C = 81.95, H = 12.23 ; $C_{20}H_{36}O$ requires C = 82.12, H = 12.40%); m/e = 292 (M).

<u>Acetylation of the Hemi-acetal (81c).</u>

The hemi-acetal (81c : 20 mg) in dry pyridine (2 ml) was treated at room temperature for 15 hours with acetic anhydride. The unstable oily acetate (81c : 19 mg) obtained had $\nu\ max^{CCl_4}$ 1740, 882 cm^{-1} ; n.m.r. signals at

τ 3.68 (s)(1H, C - 19), 4.44 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 10 c./sec.

and 5.72 (m)(2H, C - 18 ; $W_{\frac{1}{2}}$ = 12 c./sec.).

<u>Reduction of the Hemi-acetal (81b).</u>

(a) The hemi-acetal (81b : 60 mg) in absolute alcohol (5 ml)
was treated at room temperature for 15 hours with a large
excess of sodium borohydride. The solution was diluted with
water and extracted with ethyl acetate. Evaporation of the
dried (Na_2SO_4) solvent afforded the diol (86c :54 mg) as the
sole product, $[\lambda]_D$ = - 52° (c = 1.2). Acetylation of this
diol in the usual manner furnished the diacetate (80d),
$[\lambda]_D$ = - 55.6° (c = 0.8) which was indistinguishable (i.r.,
n.m.r. and t.l.c.) from the diacetate formed from the
naturally occuring diol by direct acetylation.

(b) The hemi-acetal (81b : 50 mg) in dry refluxing diethyl
ether was treated for 14 hours with excess lithium aluminium
deuteride. The deutero-diol   (47 mg) obtained after
work up was acetylated in the usual manner with acetic
anhydride - pyridine to afford the corresponding deutero-
diacetate (80j : 39 mg). In its n.m.r. spectrum it
exhibited resonances at τ 4.12 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 8 c./sec.
5.50 (s)(2H, C - 18), 6.08 (s)(1H, C - 19), 8.03 (s)(6H, 2 x
OAc), 8.93 (s)(3H, C - 20) and 9.07 (3H, C - 17 ; J = 7c./sec.).

<u>Hydroxylation of the Hemi-acetal (81b).</u>

The hemi-acetal (81b : 450 mg) in anhydrous diethyl
ether was treated for four days with osmium tetroxide (500 mg).
Working up as described previously gave the crude product
(430 mg) which was seen from t.l.c. to consist of two compound

which were separated by preparative t.l.c. (chloroform
containing 5% methanol). The less polar (350 mg) was the
unreacted hemi-acetal while the minor product (89a : 40 mg)
was the required diol, ν max 3500, 880 cm^{-1}; n.m.r. signals
at τ 4.51 (m)(1H, C - 19; $W_{\frac{1}{2}}$ = 10 c./sec.), 6.14 (s)(2H,
C - 18) and 6.33 (s)(1H, C - 3). Hydroxyl protons resonated
at τ 5.18 (m), 5.56 (s) and 6.82 (m) and disappeared upon
the addition of heavy water. m/e = 350 (M).

Attempted epoxidation of the Hemi-acetal (81b).

(a) The hemi-acetal (81b : 15 mg) in chloroform was treated
at room temperature for 90 minutes with m-chloroperbenzoic acid
(20 mg) in chloroform (1 ml). Filtration through a short
column of neutral alumina afforded an oil (13 mg) which was
seen from t.l.c. to be the unreacted hemi-acetal.

(b) The hemi-acetal (81b : 12 mg) was treated as described
above for 15 hours. In this case, after filtration through
alumina no isolable product was obtained.

Attempted oxidation of the Hemi-acetal (81b).

(a) The hemi-acetal (81b : 10 mg) in diethyl ether was
stirred at room temperature for 16 hours with activated
manganese dioxide but after removal of the reagent t.l.c.
showed the oil obtained to consist solely of the unreacted
starting material. This experiment was repeated using
different grades of manganese dioxide but in all cases the
result was the same.

(b) The hemi-acetal was treated at room temperature for
15 hours with Sarett's reagent with the same result as found
above.

<u>Reduction of the Epoxy-Hemiacetal (91_a).</u>

(a) The epoxy-hemiacetal (91a : 50 mg) in absolute alcohol (10 ml) was treated at room temperature for 15 hours with a large excess of sodium borohydride. Work up afforded an oil (47 mg) which was seen from t.l.c. to consist of one major component, from which minor impurities were removed by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 1). Further purification of the <u>epoxy-diol</u> was achieved by distillation at $150°/$ 0.035 mm and the resulting colourless oil had $[\nu]_D = -5.3°$ (c = 1.5); $\nu_{max}^{CCl_4}$ 3630, 3380, 875 cm^{-1}; (Found : C = 71.89, H = 9.12 ; $C_{20}H_{30}O_4$ requires C = 71.82, H = 9.04 %).

(b) The epoxy-hemiacetal (91a : 50 mg) in dry refluxing tetrahydrofuran was treated for 15 hours with excess lithium aluminium hydride. The product (43 mg) obtained consisted of two polar compounds of very similar polarity which were separated by preparative t.l.c. (ethyl acetate - light petroleum, 3 : 1). The major, less polar component, <u>triol A</u> (89a : 21 mg) was an oil which distilled at $180°/0.1$ mm ; $[\alpha]_D = -11.8°$ (c = 0.75) ; $\nu_{max}^{CCl_4}$ 3420, 880 cm^{-1} ; (Found: C = 71.33, H = 9.60 ; $C_{20}H_{32}O_4$ requires C = 71.39, H = 9.59%).

(c) The epoxy-hemiacetal (91_a : 50 mg) in dry refluxing diethyl ether was treated for 17 hours with lithium aluminium deuteride and the oily deutero-triol A isolated as described above.

<u>Acetylation of the Epoxy-diol (83b).</u>

The above epoxy-diol (83^b : 30 mg) was acetylated using acetic anhydride - pyridine and the resulting <u>epoxy-diacetate</u>

(83c : 27 mg) was distilled at $180^{\circ}/0.02$ mm and had $[\lambda]_D =$ -11° (c = 0.6); $\nu_{max}^{CCl_4}$ 1745, 1235, 875 cm^{-1} ; n.m.r. signals at τ 5.82 (q)(2H, C - 18 ; J = 12 c./sec.), 5.89 (q) (2H, C - 19 ; J = 7 c./sec.), 6.89 (d)(1H, C - 3 ; J = 3 c./sec.), 8.97 and 8.99 (s)(3H each, 2 x OAc), 8.97 (s)(3H, C - 20), and 9.14 (d)(3H, C - 17 ; J = 6 c./sec.). (Found: C = 69.04, H = 8.39 ; $C_{24}H_{34}O_6$ requires C = 68.86, H = 8.19%).

Acetylation of Triol A (89a).

(a) Triol A (89a: 50 mg) was acetylated in the usual manner to afford the _hydroxy-diacetate_ (89b : 45 mg) as an oil which was distilled at $75^{\circ}/0.01$ mm ; $[\lambda]_D = -12.5^{\circ}$ (c = 1.0) ; $\nu_{max}^{CCl_4}$ 3590, 3480, 1745, 1240, 875 cm^{-1} ; n.m.r. signals at τ 5.63 (q)(2H, C - 19 ; J = 13 c./sec.), 5.83 (s)(2H, C - 18), 8.00 and 8.13 (s)(3H each, 2 x OAc), 9.07 (s)(3H, C - 20) and 9.18 (d)(3H, C - 17 ; J = 6 c./sec.). (Found: C = 68.74, H = 8.86 ; $C_{24}H_{36}O_6$ requires C = 68.54, H = 8.63%).

(b) The corresponding deuterated diacetate (80j) was prepared in a similar manner and showed n.m.r. resonances at τ 5.35 (s)(1H, C - 19) and 5.84 (s)(2H, C - 18) ; m/e = 422 (M).

Dehydration of the Hydroxy-diacetate (89b).

(a) The hydroxy-diacetate (89b : 15 mg) in dry pyridine was heated for 3 hours with redistilled phosphoryl chloride (0.5 ml). The reaction mixture was poured on to ice and extracted with ethyl acetate to afford the crude material (17 mg) which was seen from t.l.c. to consist of two compounds. Separation by preparative t.l.c. (ethyl acetate - light

petroleum, 1 : 4) furnished the oily diacetate (80d: 10 mg)
as the major, more polar component. It had $[\alpha]_D$ = - 57.3^o
(c = 1.0). This compound was identical (n.m.r. and t.l.c.)
to that obtained previously by direct acetylation of the
diol (80c).

(b) The deuterated hydroxy-diacetate (93 : 17 mg) was
treated in a similar manner and in its n.m.r. spectrum it
showed resonances at ν 4.13 (m)(1M, C - 3 ; $W_{\frac{1}{2}}$ = 5 c./sec.),
5.52 (s) (2H, C - 18), 6.08 (s)(1H, C - 19), 8.03 (s) (6H,
2 x OAc), 8.93 (s)(3H, C - 20) and 9.07 (d)(3H, C - 17 ; J
= 7 c./sec.) ; m/e = 407 (M).

Reduction and acetylation of the dialdehyde (80g).

The dialdehyde (80g : 50 mg) in dry refluxing diethyl
ether was treated for 24 hours with a large excess of lithium
aluminium hydride. Work up in the usual fashion afforded
an oily residue (45 mg) from which the diol (80c : 27 mg)
was isolated by preparative t.l.c. (chloroform containing
3% methanol). This compound, $[\alpha]_D$ = - 51° (c = 1.3) was
acetylated with acetic anhydride - pyridine to afford the
diacetate (80d : 25 mg); $[\alpha]_D$ = - 45.5^o (c = 0.9) which
was identical (n.m.r. and t.l.c.) with an authentic sample
of the diacetate (80d).

Oxidation of Diacetate (80d).

The diacetate (80d : 50 mg) in dry pyridine (2 ml) was
treated for 17 days with chromium trioxide and after work up
afforded the crude material (51 mg) from which the enone –
diacetate (79d : 16 mg) was obtained by preparative t.l.c.

(ethyl acetate – light petroleum, 2 : 3). Distillation at $150°/0.03$ mm afforded an oil. ν $\max^{CCl_4}$ 1753, 1675, 1220, 875 cm^{-1}; n.m.r. signals at τ 4.05 (s)(1H, C – 3), 5.28 (m) (2H, C – 18), 5.99 (q)(2H, C – 19 ; J = 11 c./sec.), 7.91 and 8.02 (s)(3H each, OAc), 8.99 (d)(3H, C – 17 ; J = 7 c./sec.) and 9.12 (s)(3H, C – 20). (Found : C = 69.21, H = 7.72 ; $C_{24}H_{32}O_6$ requires C = 69.21, H = 7.74 %).

Extraction of Solidago juncea roots.

The ground dried roots of Solidago juncea (9 g) were extracted continuously for four hours with ethyl acetate in a Soxhlet apparatus. Evaporation of the solvent afforded the extract (282 mg) which was seen (on t.l.c.) from its staining pattern with Ehrlich's reagent to consist of one major furanoid compound with traces of at least three other minor ones.

Chromatography of S. Juncea extract.

The above extract (282 mg) was subjected to preparative t.l.c. (ethyl acetate - light petroleum, 3 : 7) and the major furanoid compound was extracted to afford the acid (99a : 80 m₉, as an oil which was purified by distillation in vacuo. It had $[\alpha]_D = -59°$ (c = 0.84 ; $CHCl_3$); ν max^{CCl_4} 1748, 1700, 877 cm^{-1} ; n.m.r. signals at τ 4.72 (m)(1H, C – 3 ; $W_{\frac{1}{2}}$ = 8c./sec.), 8.40 (broad s)(3H, C – 18), 8.83 (d)(3H, C – 17 ; J = 6 c./sec.), and 9.04 (s)(3H, C – 19); m/e = 316 (M).

Methylation of acid (99a).

The acid (99a : 70 mg) in diethyl ether was treated for 15 minutes with excess diazomethane. Evaporation of the solvent afforded the corresponding methyl ester (99b : 72 mg) which distilled at 160°/0.02 mm, $[\alpha]_D = -53.5°$ (c = 1.57 ; $CHCl_3$); ν max^{CCl_4} 1735, 878 cm^{-1} ; n.m.r. resonances at τ 4.83 (m) (1H, C – 3; $W_{\frac{1}{2}}$ = 7 c./sec.), 6.47 (s)(3H, – O$\underline{CH_3}$), 8.45 (broad s)(3H, C – 18), 8.88 (d)(3H, C – 17; J = 6c./sec.) and 9.2 (s)(3H, C – 19); m/e = 330 (M).

Reduction of Methyl ester (99b).

The above methyl ester (99b : 60 mg) in dry refluxing diethyl ether was treated for 15 hours with excess lithium aluminium hydride and furnished the alcohol (99c : 57 mg) which since it failed to crystallise was distilled in vacuo and had $[\alpha]_D$ = - 48.8° (c = 1.03 ; CHCl$_3$); $\sqrt{}$ max^{CCl_4} 3650, 3460, 877 cm^{-1} ; resonances in the n.m.r. at τ 4.86 (m) (1H, C - 3; $W_{\frac{1}{2}}$ = 7 c./sec.), 6.37 (s)(2H, C - 20), 8.43 (broad s)(3H, C - 18), 9.0 (s)(3H, C - 19) and 9.1 (d) (3H, C - 17 ; J = 6 c./sec.); m/e = 302 (M).

Attempted oxidation of alcohol (99c).

The alcohol (90c : 18 mg) was treated for 14 hours with Sarett's reagent but no isolable product (t.l.c.) was obtained. This experiment was repeated three times but in all cases the result was the same.

Reduction of Confertifolin (108).

Confertifolin (108 : 187 mg) in dry refluxing diethyl ether (10 ml) was treated for 90 minutes with excess lithium aluminium hydride and after work up afforded the diol (111a : 190 mg) which crystallised from ethyl acetate - light petroleum and had m.p. 123° (reported [54] 121 - 123°); n.m.r. signals at τ 5.83 and 5.9 (s)(4H, C - 11 and C - 12), 9.0, 9.1 and 9.15 (all s)(3H each, 3 tertiary methyl groups).

Oxidation of Confertifolin diol (111a).

The above diol (111a : 150 mg) in dry pyridine (2 ml) was treated for 14 hours with excess chromium trioxide and afforded the crude material (146 mg) seen from t.l.c. to consist of three components. Separation was effected by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 19) and afforded the least polar component, the β , β' - disubstituted furan (112 : 57 mg) as the major constituent. $\sqrt{}$ max^{CCl_4} 889 cm^{-1} ; n.m.r. signals at τ 2.93 (s)(2H, C - 11 and C - 12), 8.81, 9.08 and 9.10 (s)(3H each, C - 13, C - 14 and C - 15). (Found: C = 82.40, H = 10.12; $C_{15}H_{22}O$ requires C = 82.51, H = 10.16%). The minor components were of very similar polarity and were seen from n.m.r. to be confertifolin (108 : 34 mg) m.p. 150-152° and isodrimenin (109 : 37 mg) m.p. 125 - 127° (reported [54] m.p. 152° and 131 - 132° respectively).

Acetylation of Drimenol (101a).

Drimenol (101a : 98 mg) in dry pyridine was treated at room temperature for 15 hours with excess acetic anhydride

to afford the oily acetate (101d), ν max^{CCl_4} 1740, 1235 cm^{-1};

n.m.r. signals at τ 4.5 (m)(1H, C - 7 ; $W_{\frac{1}{2}}$ = 8 c./sec.),

8.00 (s)(3H, OAc), 9.13 (s)(6H, C - 13 and C - 14), 8.34

(s)(3H, C - 12 ; $W_{\frac{1}{2}}$ = 4c./sec.) and 9.20 (s)(3H, C - 15).

Oxidation of Drimenyl acetate (101d).

Drimenyl acetate (101d : 70 mg) in dry pyridine (2 ml)

was treated at room temperature for 16 days with excess

chromium trioxide to afford the crude product (77 mg) which

was separated into its two components by preparative t.l.c.

(ethyl acetate - light petroleum, 3 : 17). The less polar

band (23 mg) was identical with drimenyl acetate. The more

polar compound, the enone-acetate (102c : 33 mg) was obtained

as an oil which slowly crystallised on being allowed to stand

at 0° and had m.p. 48 - 50°; ν max^{CCl_4} 1745, 1677, 1228 cm^{-1};

n.m.r. signals at τ 5.28 (q)(2H, C - 11 ; J = 13 c./sec),

7.97 (s)(3H, OAc), 8.24 (s)(3H, C - 12), 8.91, 9.10 and 9.13

(s)(3H each, 3 tertiary methyl groups). (Found: C = 73.10,

H = 9.40 ; $C_{17}H_{26}O_3$ requires C = 73.34, H = 9.41%).

Acetylation of Confertifolin Diol (111a).

Confertifolin diol (111a: 90 mg) was acetylated in the

usual manner with acetic anhydride - pyridine to furnish the

oily diacetate (111e : 92 mg) which was purified by

distillation at 100°/0.05 mm; ν max^{CCl_4} 1743, 1225 cm^{-1};

n.m.r. signals at τ 5.37 and 5.4 (s)(2H each, C - 11

and C - 12), 7.93 and 7.97 (s)(3H each, 2 x OAc), 8.97

9.03 and 9.10 (s)(3H each, 3 tertiary methyl groups). (Found:

C = 71.05, H = 9.55; $C_{19}H_{30}O_4$ requires C = 70.77, H = 9.38%).

Oxidation of Confertifolin diacetate (111e).

Confertifolin diacetate (111e : 80 mg) was treated as described above with Sarett's reagent. The oily mixture (84 mg) obtained after work up was subjected to preparative t.l.c. (ethyl acetate - light petroleum, 1 : 3) and afforded the unreacted diacetate (111e : 23 mg) as the less polar component. The more polar compound, the enone-diacetate (114 : 47 mg) failed to crystallise and was purified by distillation in vacuo ; $\sqrt{\ }_{max}^{CCl_4}$ 1750, 1685 and 1230 cm^{-1}; n.m.r. signals at τ 5.16 (s)(4H, C - 11 and C - 12), 7.95 and 8.00 (s)(3H each, 2 x OAc), 8.81, 9.06 and 9.08 (s) (3H each, three tertiary methyl groups).(Found: C = 68.26, H = 8.47; $C_{19}H_{28}O_5$ requires C = 67.83, H = 8.39%); m/e = 336 (M).

Tosylation of Drimenol (101a).

Drimenol (101a: 153 mg) in dry chilled (0°) pyridine was treated at 0° f-r 90 hours with a solution of p-toluenesulphonyl chloride in pyridine. Work up gave the oily tosylate (101c : 157 mg); n.m.r. signals appeared at τ 4.52 (m)(1H, C - 7; $W_{\frac{1}{2}}$ = 6 c./sec.), 8.44 (s)(3H, C - 12), 9.18 (s)(6H, C - 13 and C - 14) and 9.28 (s)(3H, C - 15). (Found: C = 70.42, H = 8.79 ; $C_{22}H_{32}SO_3$ requires C = 70.18, H = 8.57%).

Reduction of Drimenyl tosylate (101c).

Drimenyl tosylate (101c : 85 mg) in dry refluxing tetrahydrofuran was treated for 15 hours with excess lithium aluminium hydride. The crude product (83 mg) obtained was

separated by preparative t.l.c. (light petroleum) to

afford drimene (101b: 73 mg) as the less polar component.

Since it failed to crystallise it was purified by

distillation at $45^{\circ}/0.005$ mm to afford a very mobile

colourless oil. In the n.m.r. it showed resonances at τ

4.57 (m)(1H, C - 7 ; $W_{\frac{1}{2}}$ = 8 c./sec.) and 8.38 (broad s)

(3H, C - 12; $W_{\frac{1}{2}}$ = 5 c./sec.). (Found: C = 87.08, H = 12.58;

$C_{15}H_{26}$ requires C = 87.30, H = 12.70%).

Attempted oxidation of Drimene (101b).

Drimene (101b : 40 mg) was treated for 14 days with

excess Sarett's reagent but after work up no isolable

Product (t.l.c.) was obtained.

Attempted oxidation of Confertifolin (107).

Confertifolin (107 : 52 mg) was treated for 22 days

with Sarett's reagent and after work up afforded the crude

material (50 mg) from which the coloured impurities were

removed by filtration through a short column of alumina.

Crystallisation of the product from ethyl acetate - light

petroleum afforded needles, m.p. 148 - 150° identical with

confertifolin.

Attempted oxidation of Erythroxylol B acetate (117).

Erythroxylol B acetate (117 : 14 mg) was treated for

17 days with Sarett's reagent to afford the crude product

(14 mg) which was identical (t.l.c. and n.m.r.) with the

starting material and showed no trace of any polar material

Acetylation of Cholesterol (106c).

Cholesterol (106c : 350 mg) was acetylated with acetic anhydride-pyridine in the usual manner and afforded cholesteryl acetate (106b: 354 mg) which crystallised from chloroform - light petroleum and had m.p. 119° (reported

111 - 116°). In the n.m.r. signals appeared at 4.59 τ (m)(1H, C - 6 ; $W_{\frac{1}{2}}$ = 10 c./sec.) and 5.33 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 16 c./sec.).

Oxidation of Cholesteryl acetate (106b).

Cholesteryl acetate (106b : 330 mg) was treated for 14 days with excess Sarett's reagent. The product (340 mg) obtained after work up was subjected to preparative t.l.c. (ethyl acetate - light petroleum, 3 : 17) and two major bands extracted. The less polar was the acetate (106b : 130 mg Crystallisation of the other band (68 mg) from light petroleum afforded 3 β acetoxy-cholest-5-ene-7one as plates, m.p. 154° (reported 155 - 163°); ν $_{max}^{CCl_4}$ 1740, 1682 cm^{-1}. In the n.m.r. it showed signals at $\sim$ 4.3 (s)(1H, C - 6; $W_{\frac{1}{2}}$ = 2 c./sec.) and 5.33 (m) (1H, C - 3, multiplet width 20 c./sec.).

Attempted oxidation of cholest-5-ene (106a).

Cholest-5-ene (106a: 46 mg) was treated at room temperature for 23 days with chromium trioxide in pyridine Work up gave the crude material from which the colouring matter was removed by filtration through a short column of alumina. T.l.c. and n.m.r. of the product showed it to be identical to the olefin with only very small traces of more

polar material.

Oxidation of Cholesterol ([106c]).

Cholesterol (106c: 262 mg) was treated at room temperature for 15 hours with chromium trioxide in pyridine and afforded an oily mixture (268 mg) of three compounds which were separated by preparative t.lc. (chloroform). The least polar band, cholest-4-ene, 3, 6, dione (116a : 139 mg) crystallised from chloroform - light petroleum and had m.p. 113 - 115° (reported 122°), $\nu\ _{max}^{CCl_4}$ 1685 cm^{-1}; n.m.r. signal at τ 3.85 (s)(1H, C - 4). The compound of intermediate polarity was cholesterol (106c : 70 mg) while the most polar compound was 6 β - hydroxy-cholest-4ene-3-one (116b:42 mg) which crystallised from ethyl acetate - light petroleum and had m.p. 179 - 180° (reported 191 - 193°); $\nu\ _{max}^{CCl_4}$ 3550, 1675 cm^{-1} ; n.m.r. signals at τ 4.2 (s)(1H, C - 4) and 5.46 (m) (1H, C - 6 ; $W_{\frac{1}{2}}$ = 7c./sec.).

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NMR spectrum at 60 Mc/s of Solidagoic acid A.
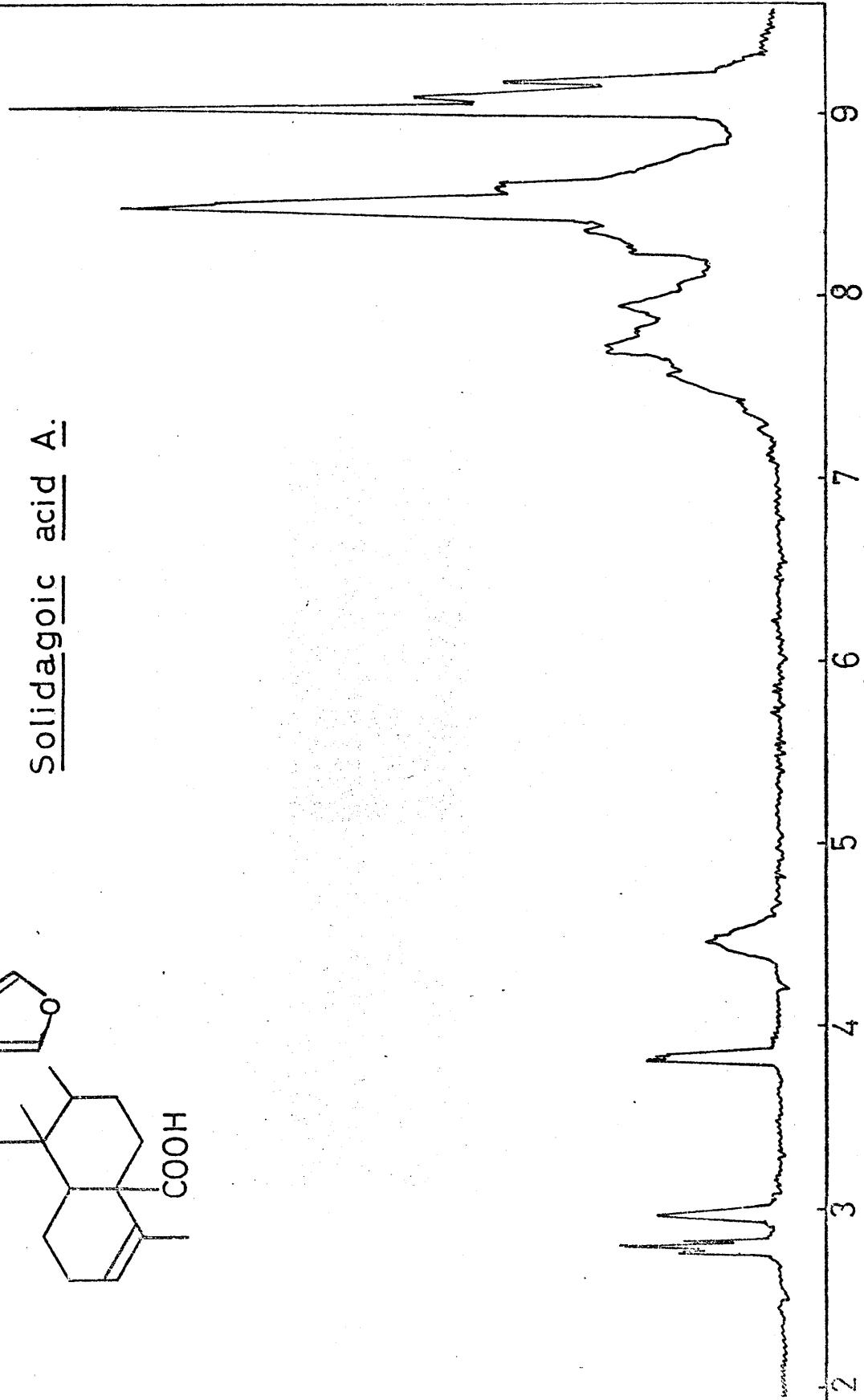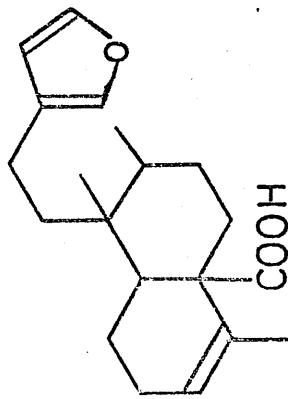
Figure 3
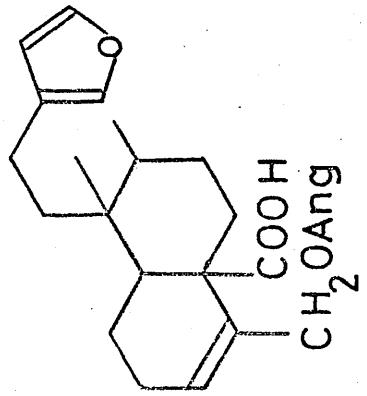
NMR spectrum at 60 Mc/s of

Solidagoic acid B.

Figure 4

Figure 5

HARDWICKIOL

$^2H_{18}$

H_3

Figure 6

NMR spectrum at 60 Mc/s of

Methyl

junceate.
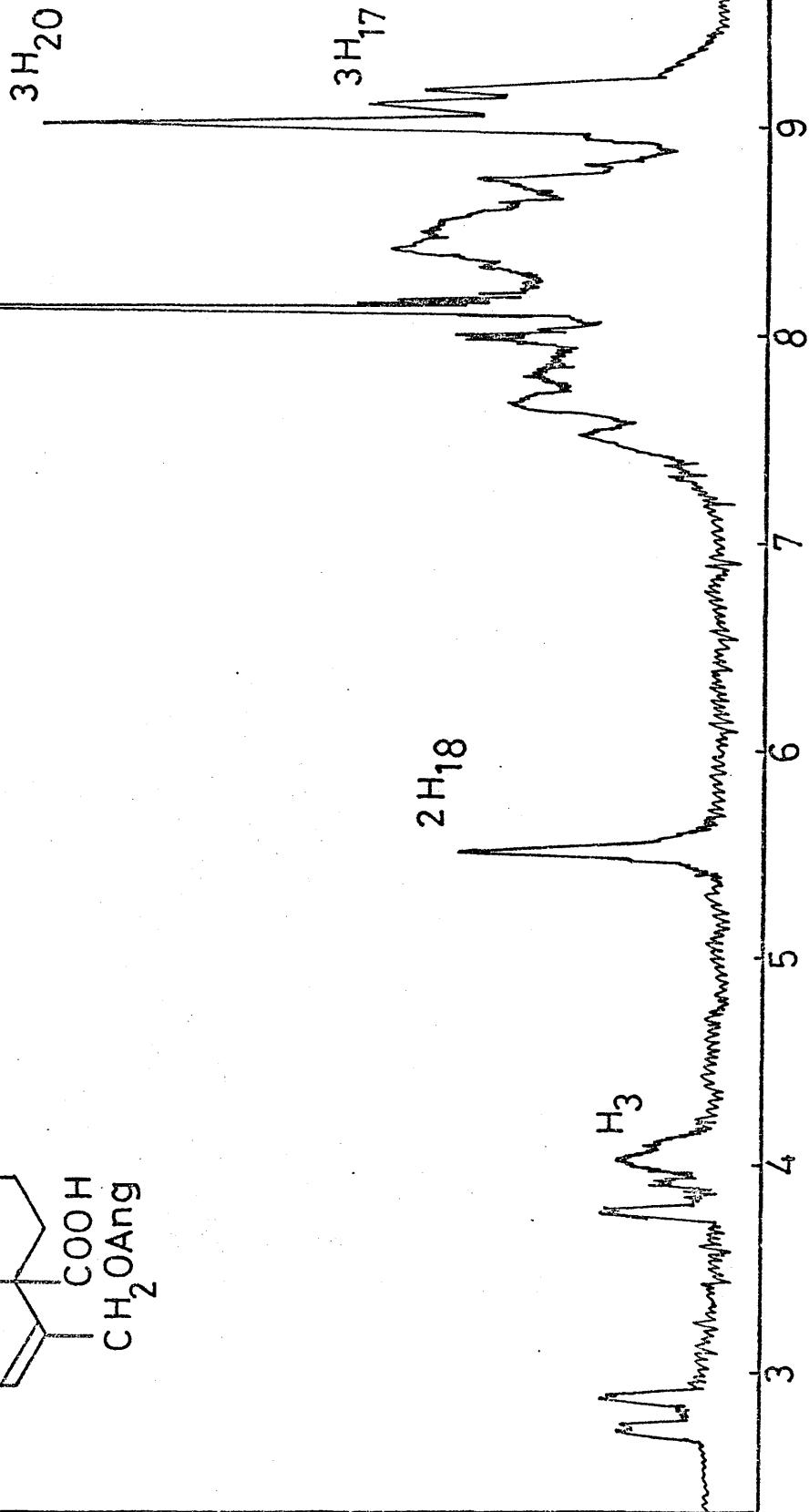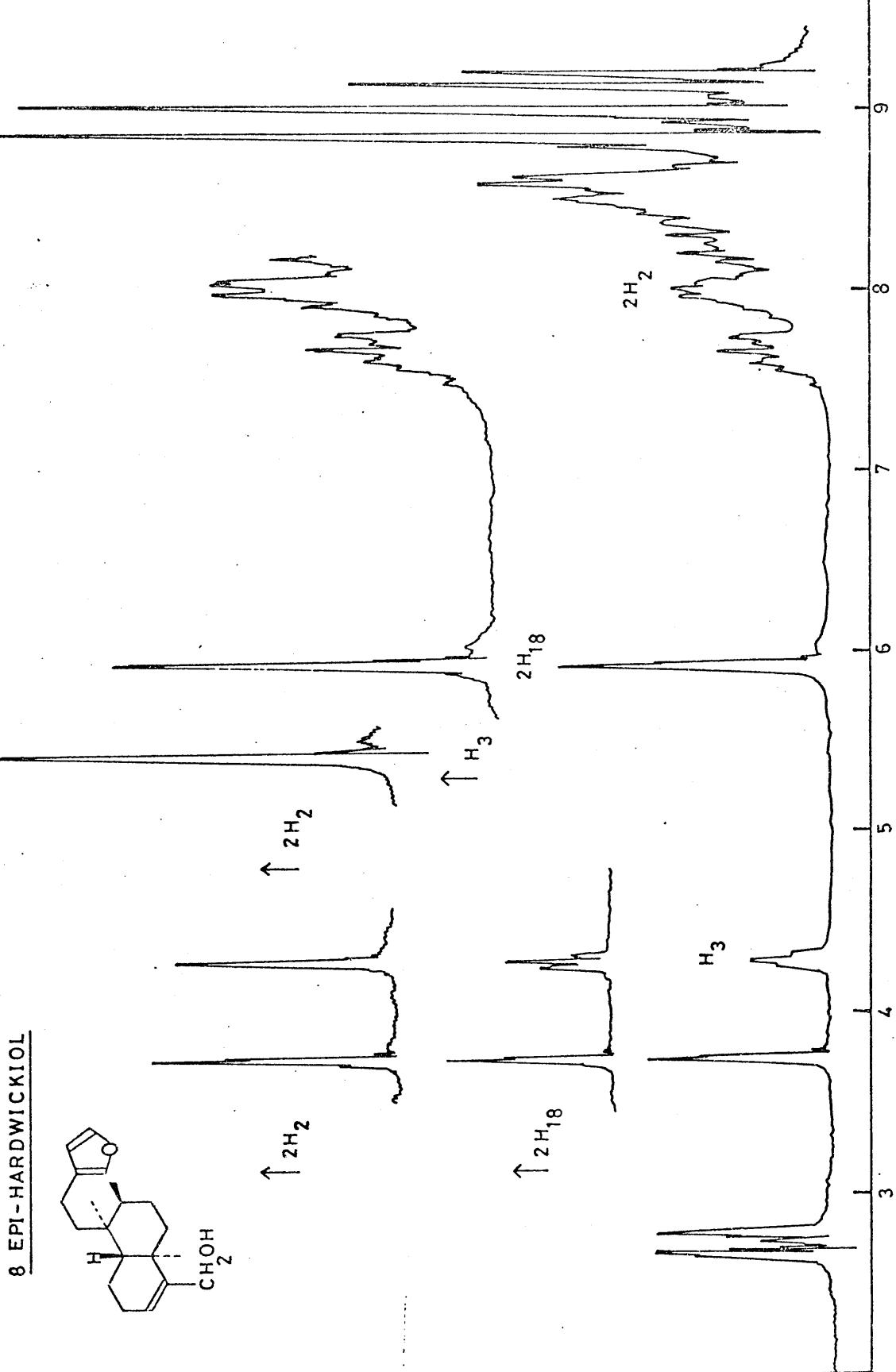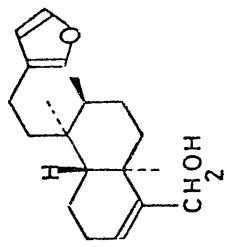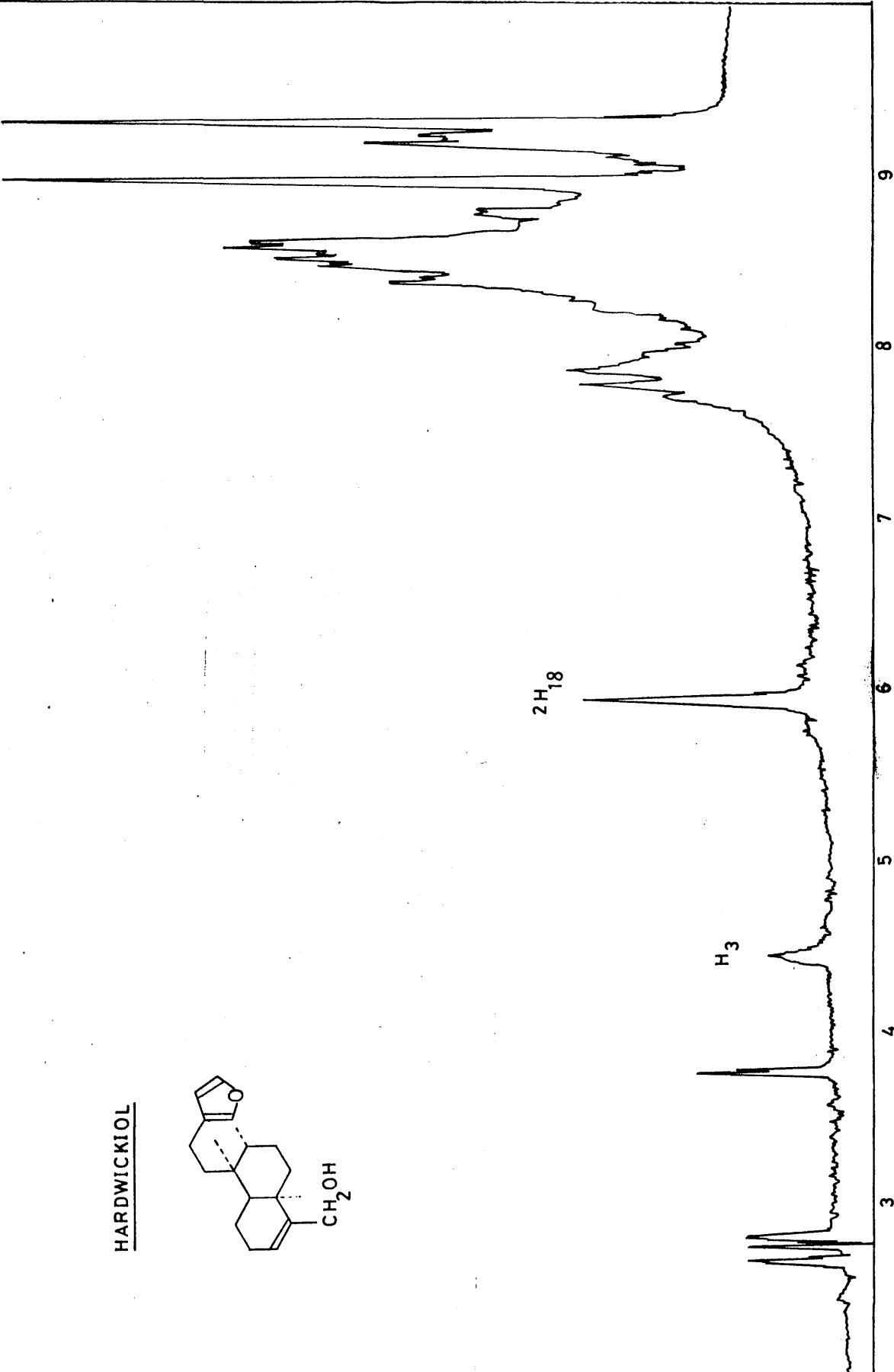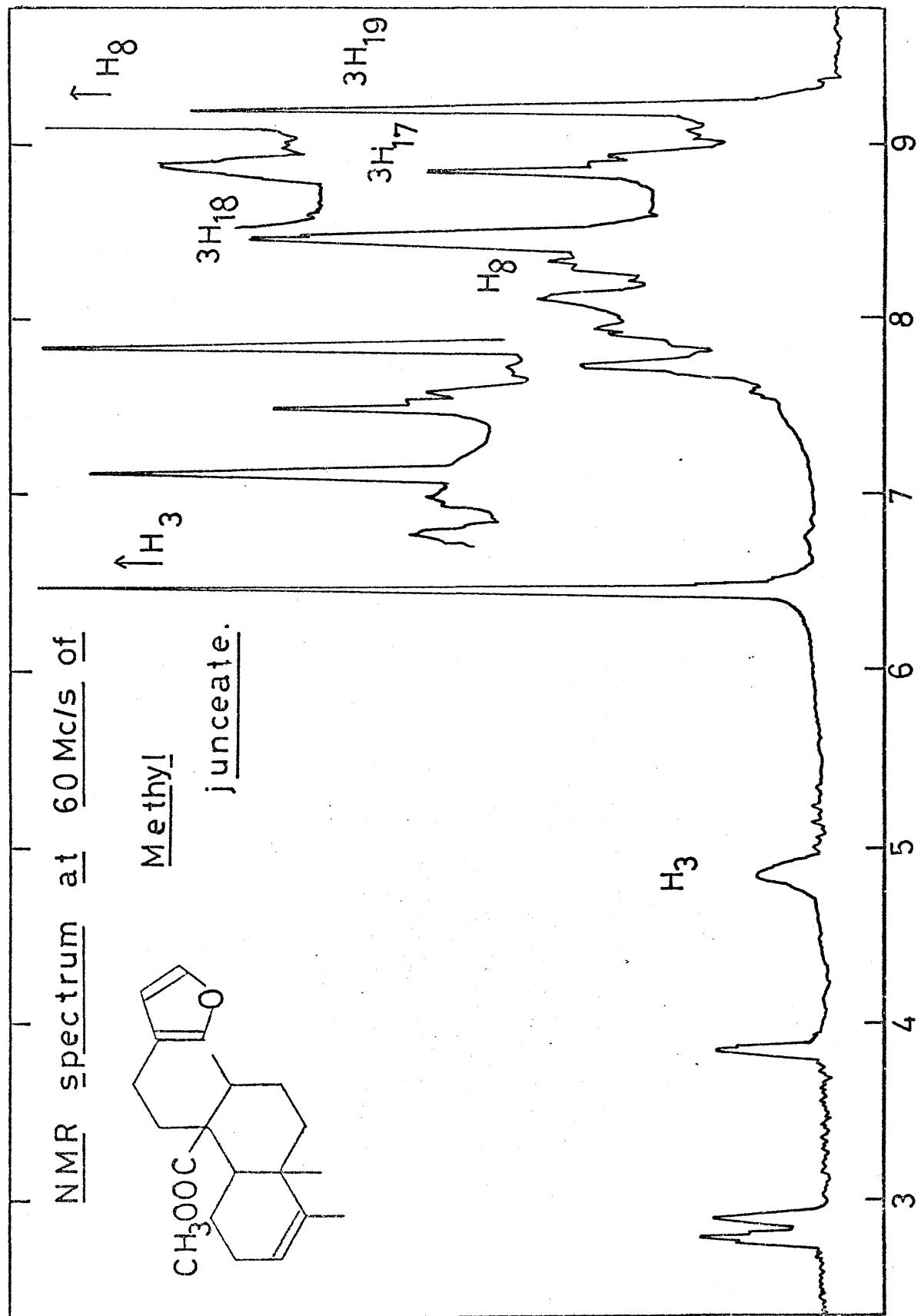
Figure 7

Diterpenoids from Solidago serotina

No.	Molecular Formula	Melting Point	$[\alpha]_D^{20}$(EtOH)	$\nu_{max}^{CCl_4}$ (cm^{-1})
76a	$C_{20}H_{28}O_3$	169–171°	− 58°	3100–3600, 1695, 875.
80a	$C_{25}H_{34}O_5$	134–135°	− 28°	3100–3600, 1720, 1695.
80d	$C_{20}H_{28}O_2$	oil	− 164°	2690, 1722, 875.
87a	$C_{20}H_{26}O_3$	92–95°	+ 12°	1772, 874.
80g	$C_{20}H_{26}O_3$	103–105°	− 49°	1720, 1690, 878.
81b	$C_{20}H_{28}O_3$	oil	− 28°	3600, 3390, 872.
91a	$C_{20}H_{28}O_4$	c. 18°	− 47°	3600, 3400, 872.
88a	$C_{20}H_{30}O_2$	oil	− 45°	3620, 3400, 875.
80c	$C_{20}H_{30}O_3$	60–62°	− 36°	3620, 3340, 875.
90b	$C_{20}H_{30}O_5$	135–137°	− 18°	3425, 875.

Table 1

Oxidation by Chromium (VI)

Mechanism A
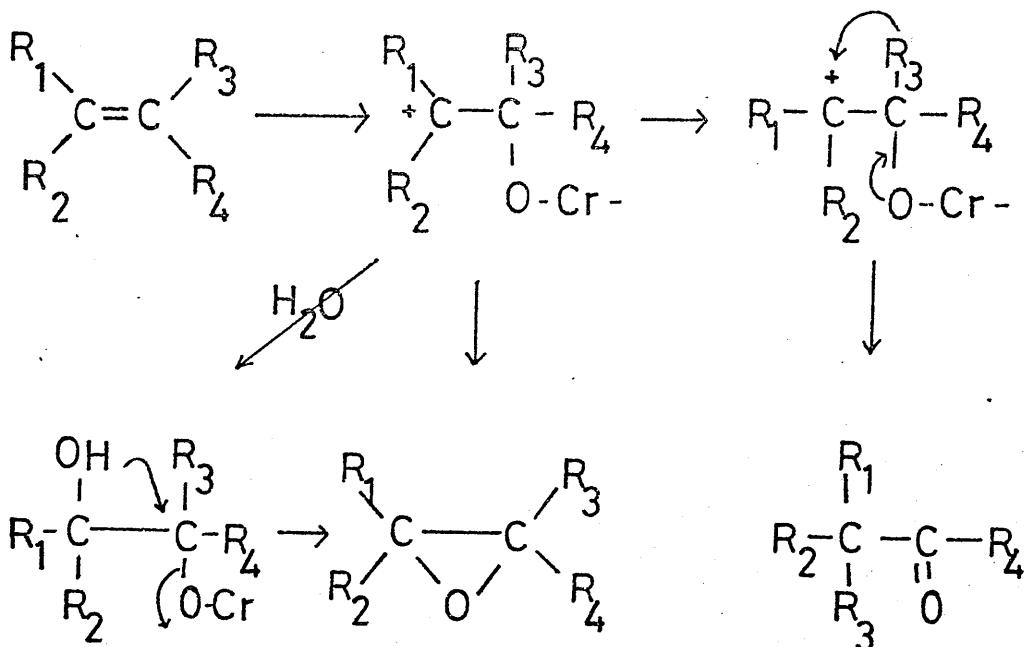
Mechanism B

Figure 8

76
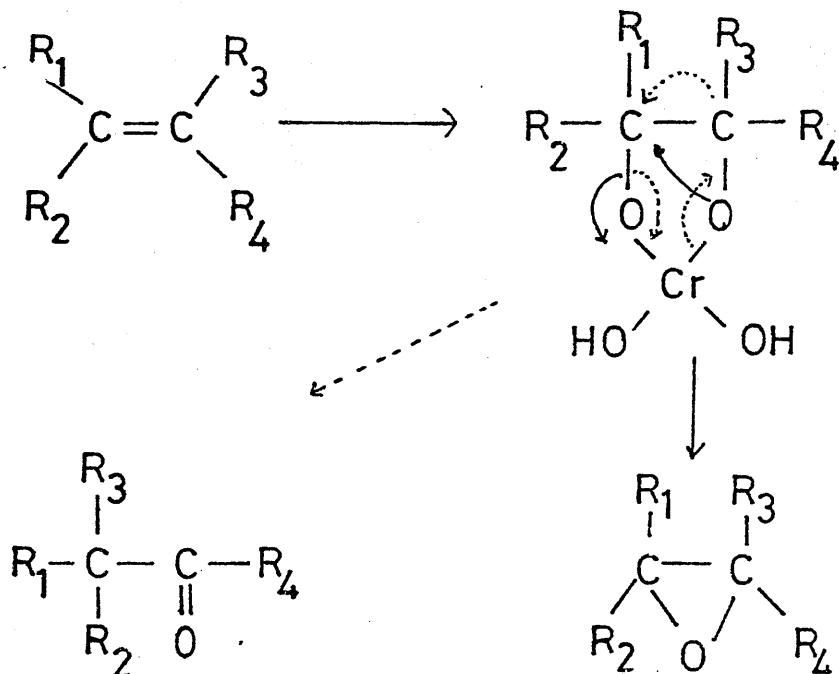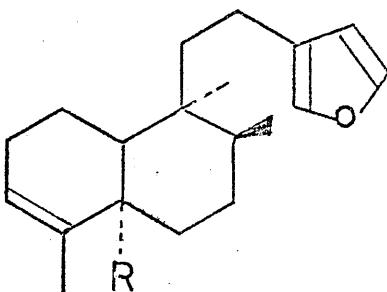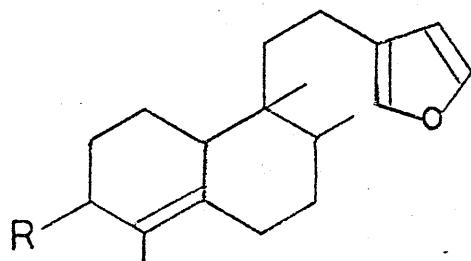
a : R=COOH
b : R=COOCH$_3$
c : R=CH$_2$OH
d : R=CHO
e : R=CH$_2$OAc
f : R=CH$_2$OTs
g : R=CH=N-NH$_2$
h : R=CH=N-N(CH$_3$)$_2$

77

a: R= O
b : R= H

78

79
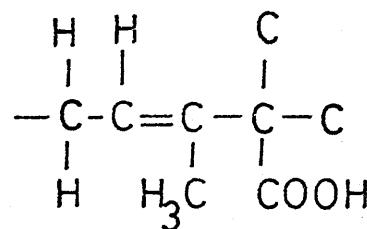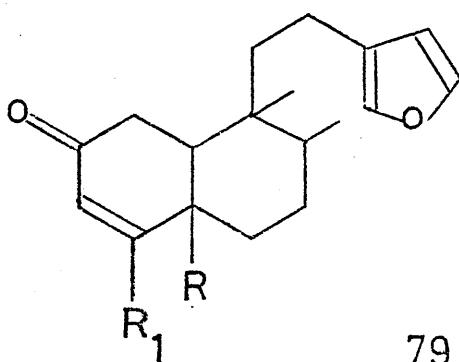
a : R = CHO : R$_1$= CH$_3$
b : R = CH$_2$OAc : R$_1$= CH$_3$
c : R = CO$_2$CH$_3$: R$_1$= CH$_3$
d : R = R$_1$= CH$_2$OAc

80
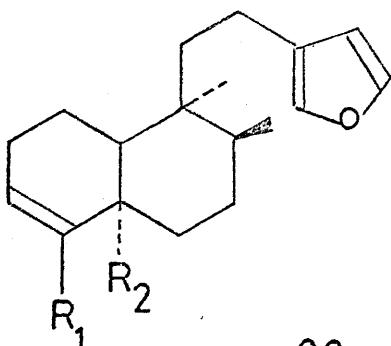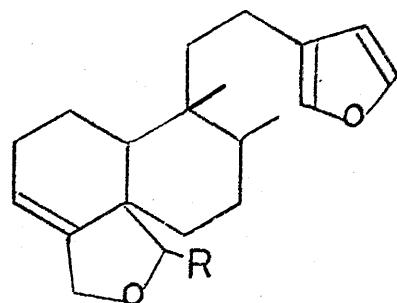
a : $R_1 = CH_2OAng$: $R_2 = COOH$

b : $R_1 = CH_2OAng$: $R_2 = CO_2CH_3$

c : $R_1 = R_2 = CH_2OH$

d : $R_1 = R_2 = CH_2OAc$

e : $R_1 = CH_2OAc$: $R_2 = CH_2OH$

f : $R_1 = CH_2OH$: $R_2 = CH_2OAc$

g : $R_1 = R_2 = CHO$

h : $R_1 = CH_2OAc$: $R_2 = CHO$

i : $R_1 = CHO$: $R_2 = CH_2OAc$

j : $R_1 = CH_2OAc$: $R_2 = CHDOAc$

81

a : $R = O$

b : $R = H, OH$

c : $R = H, OAc$

82
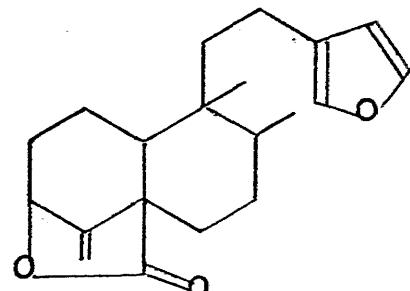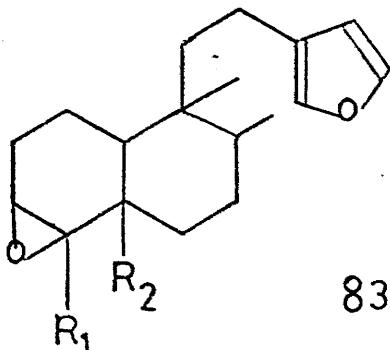
a : $R_1 = CH_2OAc$: $R_2 = CHO$

b : $R_1 = R_2 = CH_2OH$

c : $R_1 = R_2 = CH_2OAc$

83
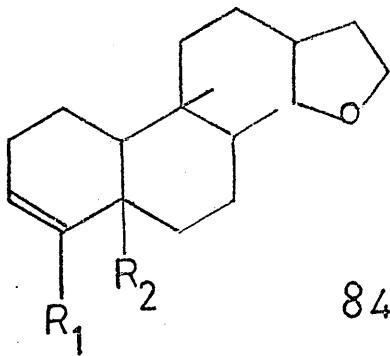
84

a : $R_1 = CH_3$: $R_2 = CH_2OAc$

b : $R_1 = CH_3$: $R_2 = CHO$

c : $R_1 = CH_3$: $R_2 = COOCH_3$

d : $R_1 = CH_3$: $R_2 = CH_2OH$

e : $R_1 = R_2 = CH_3$

f : $R_1 = R_2 = CH_2OH$

g : $R_1 = R_2 = CH_2OAc$
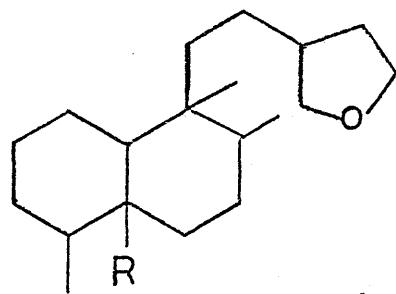
85

a : $R = CHO$

b : $R = CH_3$

86
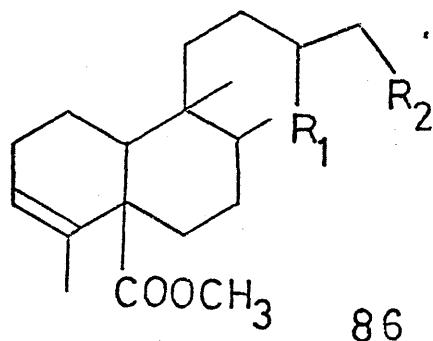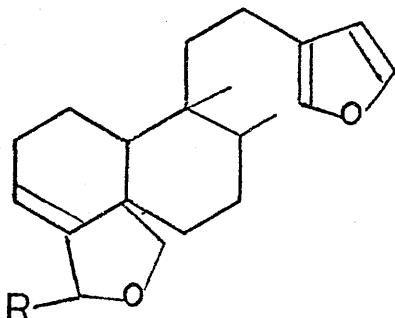
a : $R_1 = CH_2OH$: $R_2 = CH_3$

b : $R_1 = CH_3$: $R_2 = CH_2OH$

a : $R = O$

b : $R = H, OH$

87

88

a : R = CH₂OH

b : R = CH₂OAc

c : R = CH₃

89

a : R = CH₂OH

b : R = CH₂OAc

90

a : R = αOH

b : R = ßOH

c : R = ßOAc

91

a : R = H,OH

b : R = H,OAc

92

93
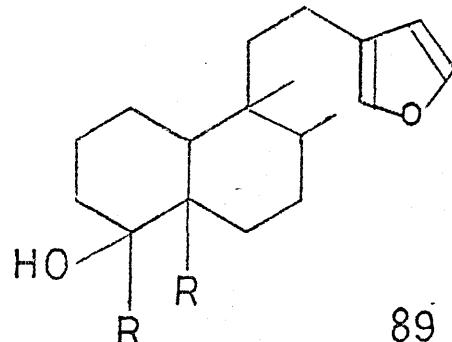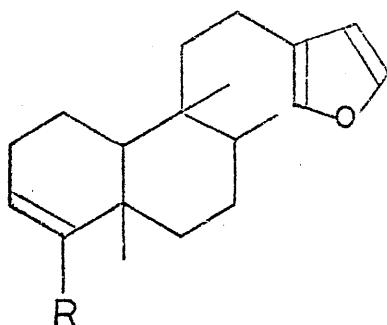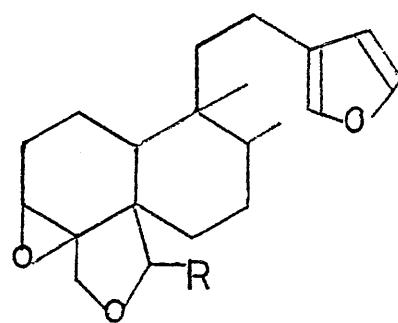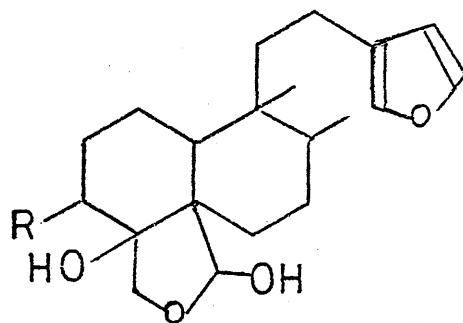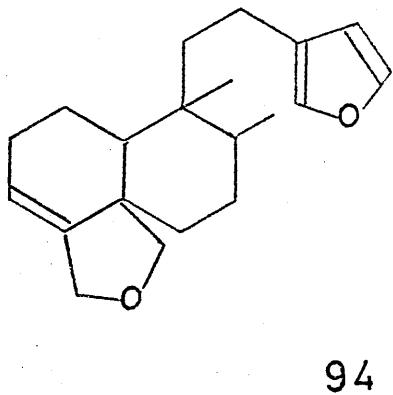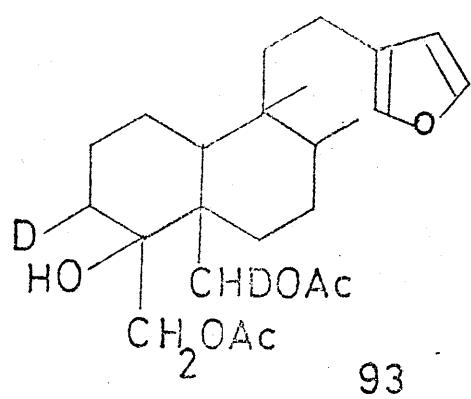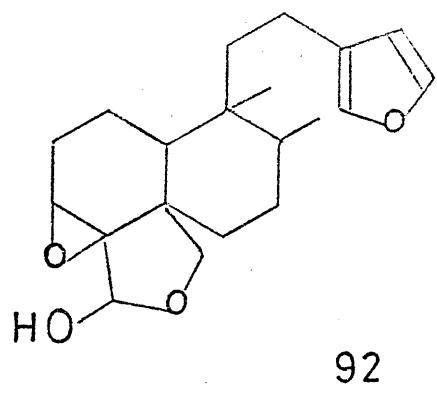

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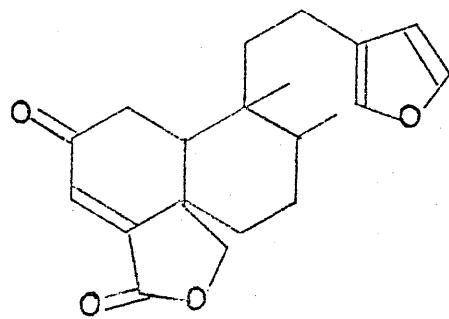
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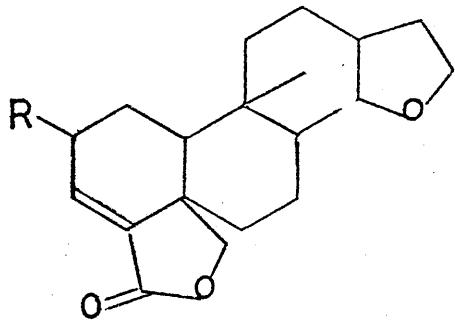
a : R = H$_2$

b: R = O

96
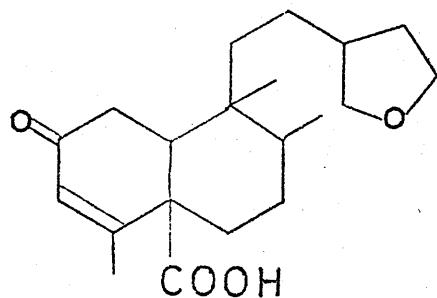
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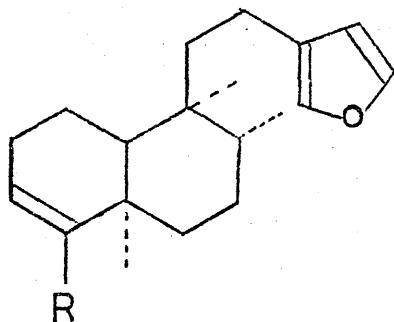
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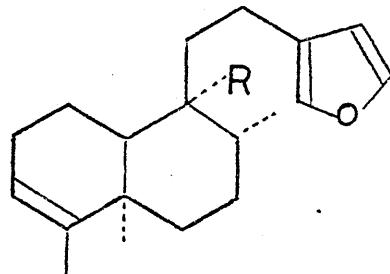
99

a : R = CH$_2$OH

b : R = CH$_2$OAc

c : R = CH$_3$

d : R = COOC$_2$H$_5$

a : R = COOH

b : R = COOCH$_3$

c : R = CH$_2$OH

100

101
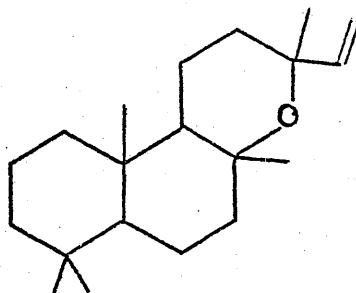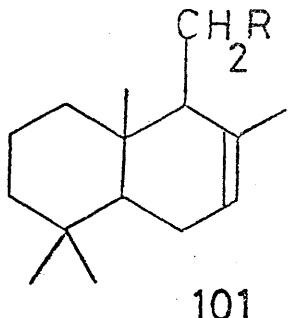
a : R = OH
b : R = H
c : R = OTs
d : R = OAc

102
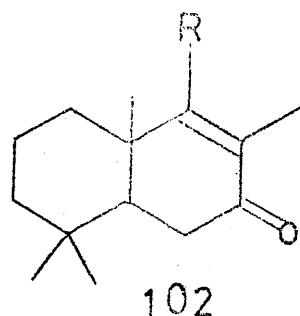
a : R = H
b : R = COOH
c : R = CH₂OAc

103

104

105

106
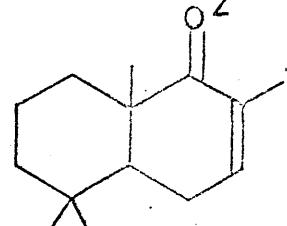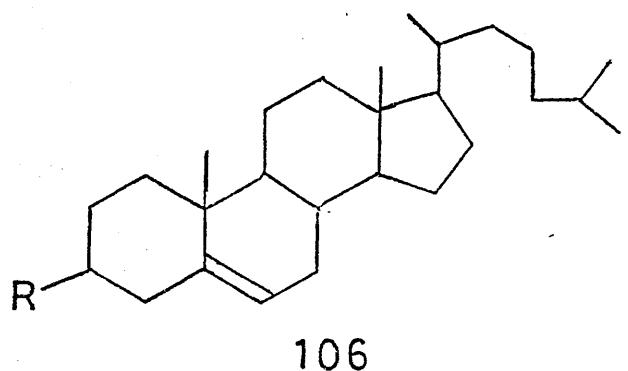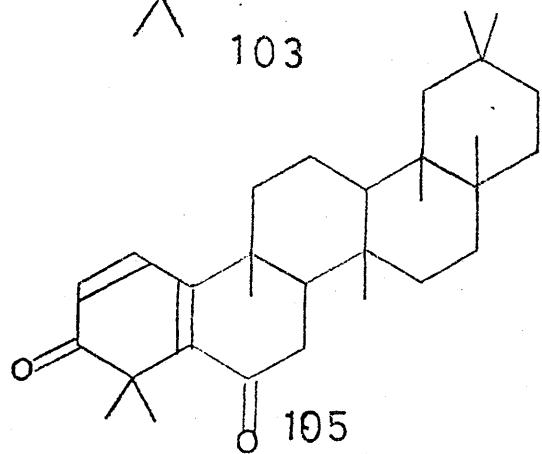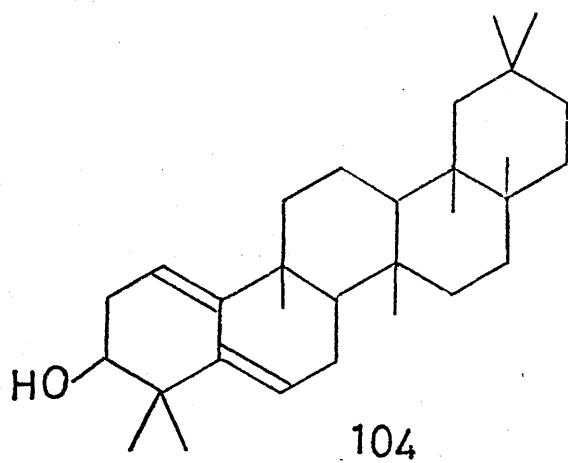
a : R = H
b : R = OAc
c : R = OH
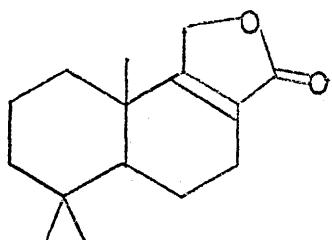
107

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112
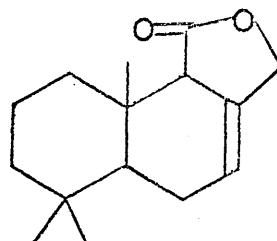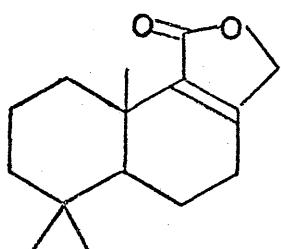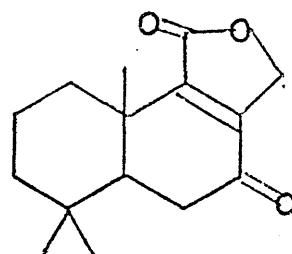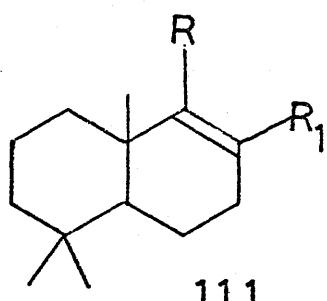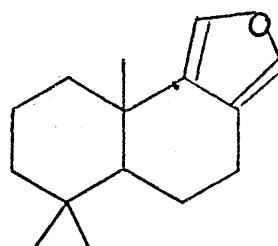
a : R = R$_1$ = CH$_2$OH

b: R = CHO : R$_1$ = CH$_2$OH

c : R = CH$_2$OH : R$_1$ = CHO

d : R = CH$_2$OH : R$_1$ = CD$_2$OH

e : R = R$_1$ = CH$_2$OAc

113

a R = H$_2$: R$_1$ = H,OH

b R = H,OH : R$_1$ = H$_2$
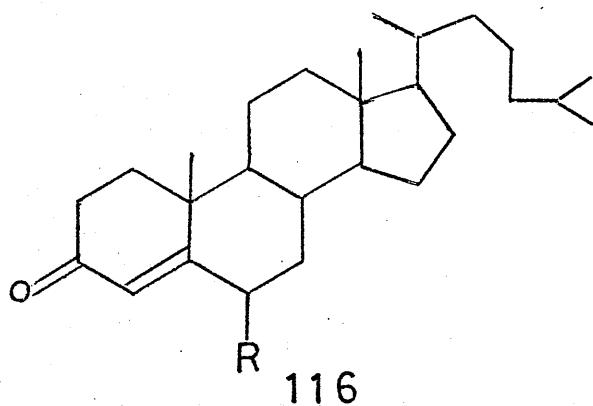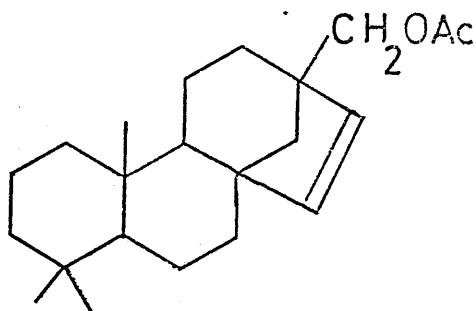
114

115

116

a : R = O

b : R = H, OH

117

Chapter 3 .

Introduction.

Since members of the Meliaceae family have been a rich source of modified triterpenes an examination of the heartwood of _Guarea glabra_ was undertaken in a search for biogenetically related compounds. From an ethyl acetate extract Dr. J.W.B. Fulke[1] has isolated seven tetracyclic triterpenoids and from chemical and spectroscopic evidence has suggested tentative structures for five of them.

The least polar compound, glabral I (1a) was seen from its mass spectrum to be a mixture of compounds of molecular formulae $C_{37}H_{56}O_7$ and $C_{36}H_{54}O_7$. The i.r. and n.m.r. spectra indicated the presence of an acetoxy group and an unsaturated ester. In addition, in its n.m.r. spectrum, were resonances from a proton of the type - O - CH - OH in a cyclic hemiacetal, and from a further proton on the carbon atom which is the other terminus of the ethereal linkage. This latter proton showed coupling to an epoxide proton. The conclusion was reached that glabral I has a side chain similar to that of turraeanthin (2)[2]. Sarett oxidation furnished a δ -lactone (1b) confirming the presence of a cyclic hemi-acetal in the parent. The absence of the expected double bond in the nucleus was accounted for by the doublets centred at τ 9.66 and 9.34, typical of a methylene group in a cyclopropane ring which was tentatively assigned a 9,10 fusion as in the cycloartanol (3) group of triterpenoids where the cyclopropane ring is β fused.

The resonance of the proton adjacent to the secondary acetate group (-C$\underline{H}$ · OAc) appeared in the n.m.r. spectra of glabral I and its derivatives as an ill-resolved triplet at Υ 4.98 which suggested that this proton has two neighbours. In the part structure (4) there are only four possible positions for this proton, viz. C - 1, C - 11, C - 12 and C - 15 and since the acetate was found to be resistant to base hydrolysis, this eliminated C - 1 and C - 15. From biogenetic considerations the hindered position at C - 11 was suggested for the location of the acetate function. The stereochemistry of this group followed from the small coupling observed ($W_{\frac{1}{2}}$ = 6 c./sec.) which is indicative of an axial group. Since all naturally occuring triterpenoids of the lanostane - euphane group have oxygenation at C - 3, this is the probable point of attachment of the $\alpha\beta$ unsaturated ester grouping. The adjacent proton appeared in the n.m.r. as a triplet at Υ 5.31, with a half band width of only 7 c./sec., indicating that this ester is also in an axial orientation.

In the members of the lanostane series containing a cyclopropane ring the C - 8 proton is β corresponding to addition of hydrogen to the double bond from the sterically less hindered β face. Since glabral I is assumed[1] to belong to the euphol series the C - 8 proton is assigned the α orientation as the α face is the less hindered in this case.

The second compound, glabral II (5a) had the molecular formula $C_{32}H_{48}O_6$ and from its i.r. spectrum was seen to contain a hydroxyl group, an acetate and a six membered ring ketone. The presence of a cyclopropane ring and the hemiacetal -

epoxide side chain was deduced from its n.m.r. spectrum.
From this evidence the structure of glabral II was proposed
as (5a).

Glabral III (6a) was assigned the molecular formula
$C_{37}H_{58}O_8$ from analytical data and a mass spectrometric
molecular weight determination. Its spectral properties
indicated the presence of the hemiacetal - epoxide side
chain and oxidation furnished a δ -lactone as expected.
In addition to the signals in the n.m.r. from an equatorial
proton adjacent to the acetoxy group (- C$\underline{H}$OAc) and the
cyclopropyl methylene group there appeared a broadened
singlet at τ 5.22 (H - 3) and a resonance at about τ
9.10 from two secondary methyl groups. A multiplet at
τ 6.05 collapsed to a sharp doublet when the sample was
shaken with heavy water. Nuclear magnetic double resonance
experiments indicated that this doublet arose from coupling
of the carbinol proton of a secondary hydroxyl function with
a proton in the methylene envelope. Such a system cannot
be accomodated on the tetracyclic nucleus and therefore had
to be located in the five carbon ester function which proved
to be a 3-methyl-2-hydroxybutyrate by comparison with the
n.m.r. spectrum of ethyl lactate.

The oily glabral IV (5b), $C_{32}H_{50}O_6$, in common with
the three less polar compounds had a hemiacetal - epoxide
side chain, a cyclopropane ring and an axial secondary
acetate group. A multiplet at τ 6.55 ($W_{\frac{1}{2}}$ = 7 c./sec.)
and the absorption at 3626 cm^{-1} in the i.r. indicated the
presence of a secondary hydroxyl group, the small coupling

being diagnostic of an equatorial proton.   Oxidation

furnished a keto- γ -lactone (5c) which was identical

in all respects to the oxidation product of glabral II.

The most polar compound, glabral VIII was obtained as

an oil after repeated preparative t.l.c. and its i.r.

spectrum showed the presence of an acetate group, a six

membered ring ketone and two hydroxyl functions, one primary

and the other secondary, possibly in a 1,4 relationship.

Multiplets at τ 6.20 (1H), 6.38 (2H) and 6.62 (1H) in its

n.m.r. spectrum were assigned to $-C\underline{H}$ -OH, $-C\underline{H}_2$ -OH and $-C\underline{H}$ - OR

protons respectively while in the methyl region there

were singlets from six tertiary methyl groups.   Sarett

oxidation furnished a crystalline compound in which the

hydroxyl absorption had disappeared and was replaced by a

new peak at 1790 cm^{-1} characteristic of a δ -lactone.   The

n.m.r. of this compound was most informative, the two protons

of the cyclopropane ring being clearly visible as doublets at

τ 9.64 and 9.35 (J = 6 c./sec.).   Nuclear magnetic double

resonance experiments showed that the methylene group adjacent

to the carbon atom bearing the axial secondary acetate function

was also attached to a fully substituted carbon atom.

Assuming the skeleton to be the same as that of the other

triterpenoids there are only two possible locations for the

acetoxy group, at C - 11 and C - 12.   C - 11 was chosen as the

more likely site of attachment from biogenetic considerations.

In the low field region of the spectrum there were resonances

from two mutually coupled protons which appeared as triplets,

one at $\curlyvee$ 6.02 (J = 8 c./sec.) and the other at $\curlyvee$ 5.64
(width = 26 c./sec.). Irradiation at $\curlyvee$ 6.02 caused the
multiplet at $\curlyvee$ 5.64 to collapse to a quartet while the
reverse experiment caused the triplet at $\curlyvee$ 6.02 to collapse
to a doublet. The proton at $\curlyvee$ 5.64 was further coupled to a
proton at $\curlyvee$ 7.54 and that at $\curlyvee$ 6.02 to two protons at $\curlyvee$ 7.72
which suggested that the system (7) must be present. Since
the hemiacetal - epoxide side chain of the less polar compounds
appeared to be absent this grouping was assumed to constitute
the side chain and from this evidence the structure (8)
which contains the required $\curlyvee$ -lactone, was suggested. The
formation of this system from the precursor, glabral VIII
(9) can be envisaged as involving the oxidation of the
primary alcohol to a hydroxy-aldehyde, which after cyclisation
to a hemiacetal would be oxidised to the corresponding -
lactone.

No conclusions concerning the structures of the remaining
compounds were made since only very small amounts of material
were available and thus the quality of the n.m.r. spectra was
poor and of little value in structure determination. However,
from the i.r. spectra it was seen that these compounds were
considerably different from those described above.

DISCUSSION.

If the conclusions reached above concerning the nature of the C - 3 ester functions are correct then removal of this moiety from glabral I and glabral III should afford glabral IV and thus relate the four major triterpenoids from the extract, glabral II and IV having previously[1] been interrelated. In fact, the oxidised forms of the compounds have been used for the following interrelations since the parent compounds are mixtures of the two possible epimeric hemi-acetals. In their n.m.r. spectra this is reflected in the resonance of the C - 24 epoxide proton which appears as a pair of doublets in the hemi-acetals but as a single doublet in the corresponding γ -lactones.

An ethereal solution of glabral 1 lactone (1b), prepared from glabral I by Sarett oxidation, was treated with osmium tetroxide and afforded an oily mixture of two compounds which were easily separated by preparative t.l.c. using plates 0.3 mm in thickness. On thicker plates the boundaries of the two compounds were indistinct and led to mixtures. The less polar diol A (10a) $C_{37}H_{56}O_9$ after crystallisation from ethyl acetate - light petroleum had m.p. 218 - 220°. The molecular ion at m/e = 644 is clearly visible in its mass spectrum which shows no trace of any lower homologues. In the carbonyl region of its i.r. spectrum there are only two peaks, one at 1777 cm^{-1} from the γ -lactone and the other a broad peak at 1731 cm^{-1} from the acetate and the ester function, the peak at 1717 cm^{-1} from the $\alpha\beta$ -unsaturated ester grouping having disappeared. The hydroxyl absorption appears at 3583 and 3514

In its n.m.r. spectrum the low field olefinic protons are absent and are replaced by a quartet centred at τ 5.82 (J = 7 c./sec.) from the proton (-C$\underline{H}$ -OH) of a secondary hydroxyl function which is spin - spin coupled to a methyl group. The C - 3 and C - 11 equatorial protons appear as unresolved multiplets at τ 5.24 ($W_{\frac{1}{2}}$ = 7 c./sec.) and 4.98 ($W_{\frac{1}{2}}$ = 6 c./sec.) while the C - 23 and C - 24 protons appear as a multiplet at τ 6.4 (multiplet width = 30 c./sec.) and a doublet at τ 7.2 (J = 7 c./sec.) respectively. The methyl signal of the acetate group appears as two singlets at τ 7.98 and 8.01 indicating a mixture of diastereoisomers as expected upon the formation of two additional asymmetric centres.

Diol B (10b) $C_{36}H_{54}O_9$ also crystallised from ethyl acetate - light petroleum but as very fine needles, m.p. 203 - 205°. That this compound contains only a C_4 ester group can be deduced from the presence of the molecular ion at m/e = 630 in its mass spectrum which shows no peaks from higher molecular weight material. Its i.r. spectrum is very similar to that of diol A in that the absorption from the hydroxyl groups appears at 3585 and 3518 cm^{-1} and that from the carbonyl functions at 1781 and 1727 (broad) cm^{-1}. In its n.m.r. spectrum it exhibits an ill-resolved quartet at τ 6.4 (J = 9 c./sec.) attributable to the methylene protons of a primary hydroxyl group. Furthermore, the acetoxy methyl group again resonates as two singlets at τ 8.0 and 8.04 refelcting the inhomogeneity of this substance.

Sodium metaperiodate treatment of diol A afforded a crystalline compound (11) $C_{35}H_{50}O_8$ m.p. 180 - 182° which in its i.r. spectrum shows three carbonyl peaks at 1782, 1730 and 1722 cm⁻¹. The latter arises from the pyruvate, the lower value being caused by the introduction of an additional carbonyl function to form an α-keto-ester. This is confirmed by the presence in its n.m.r. spectrum of a singlet at τ 7.61 from a methyl group attached to an α-dicarbonyl system. A compound identical in all respects was obtained from similar treatment of diol B (10b) which must therefore contain the HOH_2 C-$C(CH_3)(OH)$-C = O grouping since otherwise the product of periodate cleavage would be an aldehyde and not a methyl ketone.

From this chemical evidence it is seen that the original material, glabral I, must be, as previously suggested[1] on spectral grounds, a mixture of C_4 and C_5 $\alpha\beta$-unsaturated esters, although no separation on silica gel or on silver nitrate - silica gel could be effected. Of the six possible esters only the three with methyl groups attached to the α carbon atom need be considered since the others would not give a pyruvate ester on oxidation. That glabral I is a mixture of angelate, tiglate and methacrylate esters is confirmed by an examination of the olefinic region in the n.m.r. spectrum of both it and the lactone. A broad multiplet at τ 3.15 (multiplet width = 24 c./sec.) and an unresolved multiplet at τ 3.89 ($W_{\frac{1}{2}}$ = 4 c./sec.) are characteristic[3] of the olefinic protons in tiglate and angelate esters respectively while the exomethylene protons

of a methacrylate appear as multiplets at γ 4.48 ($W_{\frac{1}{2}}$ =

5 c./sec.) and 3.89, the cis proton being approximately 0.6

ppm lower than the trans proton.

Both diols A and B were treated with Sarett's reagent

and after preparative t.l.c. the major product in both cases

crystallised from ethyl acetate and had m.p. 179 - 181°.

The mass and n.m.r. spectra of both of these compounds were

identical to that of the α -keto ester previously obtained

by periodic acid cleavage. The minor product, from its

melting point and i.r. spectrum was deduced to be glabral IV

lactone (5c) produced by cleavage of the pyruvate ester in

basic solution followed by oxidation of the newly formed

hydroxyl to a cyclohexanone. Since both periodic acid and

chromium trioxide - pyridine oxidations have produced

identical products it appears possible that the intermediate

in the latter may be a cyclic chromate ester, decomposition

of which in a manner similar to that suggested for lead tetra-

acetate and periodic acid cleavages would afford the observed

product.

Glycol cleavage by chromic acid has previously been

reported [4,5] and the mechanism studied in some detail. The

suggestion of a cyclic intermediate followed from the fact

that the monomethyl ether of pinacol was not readily oxidised

and that cis 1,2-dimethyl-1,2-cyclopentanediol is oxidised to

2,6-heptanedione 17,000 times faster that the corresponding

trans isomer. No study of the chromium trioxide - pyridine

cleavage of cis glycols has been reported but there is no

obvious reason for the mechanism to be other than that

suggested for the reaction under acidic conditions.

Hydrolysis of the pyruvate (11) with a saturated aqueous solution of sodium bicarbonate furnished the alcohol (5d) $C_{32}H_{48}O_6$, m.p. 202 - 204° which on treatment with Sarett's reagent afforded a keto-lactone (5c) m.p. 215 - 217° identical in all respects with glabral IV lactone previously[1] prepared from glabral IV by direct oxidation. The i.r. spectrum of the hydroxy-lactone (5d) shows absorption at 3630 (non-bonded hydroxyl), 1779 (γ -lactone) and 1728 (acetate) cm^{-1} as expected. In its n.m.r. spectrum the C - 3 equatorial proton appears at the surprisingly high value of γ 6.60 as an unresolved multiplet ($W_{\frac{1}{2}}$ = 5 c./sec.) while H - 11 resonates as a multiplet at γ 5.00 ($W_{\frac{1}{2}}$ = 7 c./sec.), H - 23 as a multiplet at γ 5.84 (multiplet width = 28 c./sec.) and H - 24 as a doublet at γ 7.22 (J = 7 c./sec.).

Hydrogenation of glabral I over Adams catalyst in either ethanol or ethyl acetate furnished as the major product the oily dihydroglabral I (1c) whose n.m.r. spectrum shows no absorption below γ 4.5. That the hemi-acetal and the cyclopropane rings have remained intact can be deduced from the presence of a multiplet at γ 4.62 ($W_{\frac{1}{2}}$ = 6 c./sec.) and the pair of doublets at γ 9.35 and 9.66 (J = 6 c./sec.). By treatment with Sarett's reagent this substance was converted into the corresponding γ - lactone (1d) m.p. 190 - 191° which was an inseparable mixture of $C_{37}H_{56}O_7$ and $C_{36}H_{54}O_7$ (mass spectrum).

The hemi-acetal grouping could be reduced to the diol, by reaction of glabral I with sodium borohydride, which after crystallisation from ethyl acetate - light petroleum furnished the diol (12) as very fine needles m.p. 183 - 184°. Mass spectral and analytical data indicated that this material was a mixture of compounds of molecular formulae $C_{37}H_{56}O_7$ and $C_{36}H_{54}O_7$. In the n.m.r. the resonance at about γ 4.6 is notably absent and is replaced by a multiplet between τ 6.2 and 6.8 integrating for three protons. This can be assigned to the protons adjacent to the newly formed hydroxyl groups.

Oxidation of glabral III yielded a mixture of two lactones, the less polar of which after crystallisation had m.p. 209 - 210°. That this compound (6b) $C_{37}H_{54}O_8$ was the fully oxidised glabral III lactone was deduced from its i.r. spectrum which shows no hydroxyl absorption but instead a band at 1768 cm^{-1} (γ -lactone) and a very broad band at 1720 cm^{-1} from the acetate and the C - 3 ester. The proton adjacent to the α -dicarbonyl system appears in the n.m.r. as a septet at τ 6.82 (J = 7 c./sec.) showing coupling to two methyl groups which themselves give rise to a six-proton doublet at τ 8.84 (J = 7 c./sec.). Also visible are the signals from the C - 11 proton (multiplet at 5.02 ; $W_{\frac{1}{2}}$ = 6 c./sec.), the C - 3 proton (multiplet at τ 5.17 ; $W_{\frac{1}{2}}$ = 6 c./sec.), the C - 23 proton (multiplet at τ 5.87 ; width = 30 c./sec.) and the C - 24 proton (doublet at τ 7.24 ; J = 8 c./sec.). The more polar oxidation product (6c) crystallised from ethyl acetate - light petroleum and had m.p. 225 - 226°.

The mass spectral and analytical figures correspond to a molecular formula of $C_{37}H_{56}O_8$ indicating that only one of the hydroxyl groups had been oxidised. That it was the hemi-acetal hydroxyl group can be deduced from the presence of the characteristic δ -lactone absorption in the i.r. at 1779 cm^{-1}, the hydroxyl and the acetate appearing at 3535 and 1724 cm^{-1} respectively. The resonance of the HO -C -<u>H</u> proton appears at τ 5.94 as a doublet (J = 4 c./sec.) superimposed on the multiplet from H - 23 at τ 5.83 (multiplet width = 34 c./sec.). This hydroxyl group proved to be rather resistant to oxidation since after 18 hours treatment with the chromium trioxide complex considerable amounts of the half-oxidised product were obtained.

The corresponding acetoxy - lactone (6d) was prepared from glabral III by treatment with acetic anhydride - pyridine followed by hydrolysis to the acetoxy - hemiacetal on basic alumina. This compound was transformed by oxidation with Sarett's reagent into the δ -lactone (6d) crystallisation of which afforded needles, $C_{39}H_{58}O_9$, m.p. 204 - 205°. In its n.m.r. the signal from the extra-nuclear <u>H</u> - C - OAc proton had moved downfield by 0.85 ppm to 5.09 (d)(J = 4 c./sec.). The acetate methyl groups appear as separate singlets at τ 8.86 and 8.98.

Glabral III lactone (6b) being an α -keto ester was readily hydrolysed by an aqueous solution of sodium bicarbonate and gave as the major product the hydroxy - lactone (5d) m.p. 201 - 203° previously obtained by Kupchan cleavage of glabral I lactone as described above.

Sodium borohydride reduction of glabral IV lactone
(5c) furnished as the major product an oily triol (12b)
$C_{32}H_{52}O_6$ the spectral properties of which indicate that both
the cyclohexanone and the δ -lactone functions have been
reduced (peaks at about 1705 and 1780 cm^{-1} absent). The
retention of the acetate and the epoxide ring can be deduced
from its n.m.r. resonances at τ 5.01 (m)$(W_{\frac{1}{2}} = 5$ c./sec.) and
7.26 (d)(J = 9 c./sec.). The carbinol protons appear as a
multiplet (4H) between τ 6.2 and 6.9 in which the
individual signals cannot be distinguished. As a result it
is not possible to deduce the stereochemistry at C - 3 in
this compound but as reduction takes place from the less
hindered α face of the molecule the hydroxyl group should
have the opposite stereochemistry to that of glabral IV
itself. The 3 orientation of the oxygen functions, although
less common than the 3 orientation is not unknown in
compounds isolated from members of the Meliaceae (or the
related Rutaceae species). Indeed, it has been found[6] in
flindissol (13), a triterpenoid which also contains a
cyclic hemi-acetal in the side chain.

Treatment of glabral IV lactone (5c) with either
chloroacetic or bromoacetic acid in refluxing benzene
furnished in addition to the desired chloro- or bromoacetate
(see later) significant amounts of two other crystalline
compounds by opening of the epoxide ring. The least polar
component, the hydroxy - olefin (14a) m.p. 157 - 160°
analysed for $C_{32}H_{46}O_6$ isomeric with glabral IV lactone.

That the original ketone, acetate and lactone are still
intact can be seen from its i.r. spectrum. In addition there
is hydroxyl absorption at 3588 and 3445 cm^{-1}. The resonance
in the n.m.r. spectrum from H - 24 is absent and replaced by
a two proton multiplet at τ 4.97 (J = 6 c./sec.) assigned to
an exomethylene grouping. A methyl group attached to a double
bond gives rise to a broadened singlet at τ 8.23. In
addition, there is a doublet at τ 6.03 (J = 7 c./sec.) from
the (-C$\underline{H}$ - OH) proton of a secondary hydroxyl function which
is coupled to the lactone proton at C - 23. Acetylation of
this compound afforded very large needles (14b), m.p.
110 - 115°, 184° after crystallisation from chloroform -
light petroleum. Analytical figures indicated that the
compound contained a molecule of chloroform of crystallisation.
This was confirmed by recording its n.m.r. spectrum in
acetone when the C$\underline{H}$Cl$_3$ proton appears as a singlet at τ 1.95
(chloroform dissolved in acetone alone appears at τ 2.18).
In the remainder of the spectrum the signals from the
exomethylene protons and the two protons adjacent to the
acetoxy groups are superimposed on each other and cannot be
distinguished.

The second compound from the reaction was the
chloroacetate (15a) (or bromoacetate (15b)) which will
be discussed in detail in the following section. The most
polar compound was a diol, C$_{32}$H$_{48}$O$_7$ m.p. 198 - 200° whose
constitution as (15c) follows from its molecular weight
and its i.r. spectrum which shows peaks at 3565, 3515, 1782,
1734 and 1707 cm^{-1}.

From these results it is seen that all four compounds
have the same skeleton and only differ in the nature of the
oxygenated functions tentatively located at C - 3 on
biogenetic grounds. As yet no chemical evidence is available
for the correct positioning of the acetate group or the
cyclopropane ring.   The relationship of the hemi-acetal and
the epoxide ring has been demonstrated by nuclear magnetic
double resonance experiments and the positioning of these
groups in the side chain at C - 17 appears acceptable since
similar groups are found in flindissol[6] (13), aglaiol[7]
(16) and turraeanthin[2](2).

Unsuccessful X-ray Determination.

In order to determine the remaining structural and
stereochemical features of the Guarea glabra triterpenoids
it was decided that an X-ray crystallographic examination
of a heavy atom derivative was required. Only compounds
derived from glabral III or IV could be used since the
less polar compounds were known from mass spectrometric
evidence to be mixtures of homologues. Attempts to
functionalise the hydroxyl group of the hydroxy-lactone (5d)
with p-bromobenzene sulphonyl chloride, p-iodobenzoyl
chloride or 3,5 dibromobenzoyl chloride resulted in starting
material with only traces of less polar compounds. Similar
treatment of the hydroxy-ester (6c) obtained from glabral III
by Sarett oxidation failed to produce the desired derivative.

Experiments directed towards the opening of the epoxide
ring met with more success. Reaction of glabral IV lactone
(5c) with chloroacetic acid in benzene gave the chloroacetate
(15a) $C_{34}H_{49}O_8Cl$, m.p. 195-196° as one of the major
products. In its n.m.r. spectrum the doublet at about τ
7.3 (J = 6 c./sec.) attributable to the epoxide proton is
absent and is replaced by an ill-resolved doublet at τ 5.10
(J = 4 c./sec.) assigned to the proton adjacent to the newly
formed chloroacetate group, the methylene protons of which
appear as a singlet at τ 5.94. Although its i.r. spectrum
shows hydroxyl absorption at 3590 cm^{-1} there is no resonance
in the n.m.r. from a proton adjacent to a hydroxyl, indicating
an Anti-Markovnikoff opening of the epoxide ring to form a

secondary chloro-acetate and a tertiary hydroxyl group.

Treatment of the chloroacetate with sodium iodide in refluxing acetone furnished a compound of similar polarity which crystallised from diethyl ether - petroleum* in clusters of crystals which were unsuitable for X-ray analysis. Very slow recrystallisation of this iodoacetate (15d) $C_{34}H_{49}O_8I$ from chloroform - petroleum* afforded needles, m.p. 173-174°, of a size suitable for X-ray analysis. However on viewing these crystals under a polarising microscope it was seen that they were twinned and did not extinguish properly, thus making this derivative unsuitable for the X-ray determination. The n.m.r. spectrum of this compound was very similar to that of the corresponding chloroacetate in that the proton adjacent to the iodoacetoxy function appears as a doublet at τ 5.12 (J = 3 c./sec.), the multiplet at τ 4.97 ($W_{\frac{1}{2}}$ = 6 c./sec.) arising from the proton adjacent to the C - 11 acetate group. The protons of the iodoacetate give rise to a two proton singlet at τ 6.15.

The corresponding bromoacetate $C_{34}H_{49}O_8Br$ (15b) was prepared from glabral IV lactone by treatment with bromoacetic acid in dry refluxing benzene. The bromoacetate was isolated from the other hydrolysis products by preparative t.l.c. and obtained as needles m.p. 203-204° from chloroform-petroleum*. Slow crystallisation from a large volume of ethyl acetate - petroleum* afforded the large needles which fulfilled the physical conditions necessary for an X-ray analysis. In its n.m.r. spectrum the methylene bromoacetate protons appear as a singlet at τ 6.15, a value intermediate between that of

the chloroacetate (γ 5.94) and the iodoacetate (γ 6.25)
as expected. The carbonyl regions of the i.r. spectra of
these three halogen derivatives are identical, having
absorption at 1780cm^{-1} from the γ -lactone and a broad peak
at 1735 cm^{-1} from the two acetoxy groups.

Preliminary oscillation and equi - inclination Weissenberg
photographs taken with Cu - K$_\alpha$ radiation, of the
chloroacetate and the bromoacetate were identical indicating
that the crystals were isomorphous, both crystals belonging
to the orthorhombic system with cell dimensions of 7.27,
18.14 and 25.80 Å. Since the bromo derivative was more
suitable for an X - ray determination of a triterpene the
chloroacetate was not investigated further and the following
discussion refers to the bromoacetate. The absence of (0k0)
and (00l) (k and l both odd) reflexions in the zero layer
photographs indicated the presence of two 2 - fold screw axes
of symmetry parallel to b and c. The data were collected up
the a axis from layers (0kl) to (5kl) using the multi-film
technique, a total of 1457 reflexions being obtained. These
were estimated visually by comparison with a calibrated scale.
Unfortunately the high order reflexions necessary for a good
crystallographic structure were absent but it was considered
that there were sufficient reflexions for a gross structure,

* In this section petroleum marked with an asterisk refers
to that fraction having boiling range 100 - 120°.

without any refinements, to be obtained.

The observed intensities were converted into structure factors and a Patterson vector map obtained in order to determine the position of the heavy atom. Since the space group was not completely determined by the photographs, the Harker modification which simplifies the Patterson method by making use of the symmetry properties of the crystal was applied in order to detect the presence of the special vectors from a $P_{2_1 2_1 2_1}$ space group. This space group has the following equivalent positions:-

$$
\begin{array}{ccc}
x & y & z \\[4pt]
\tfrac{1}{2} - x & \bar{y} & \tfrac{1}{2} + z \\[4pt]
\tfrac{1}{2} + x & \tfrac{1}{2} - y & \bar{z} \\[4pt]
\bar{x} & \tfrac{1}{2} + y & \tfrac{1}{2} - z
\end{array}
$$

which give rise to vectors at

$$
\begin{array}{ccc}
\tfrac{1}{2} - 2x & -2y & \tfrac{1}{2} \\[6pt]
\tfrac{1}{2} & \tfrac{1}{2} - 2y & -2z \\[6pt]
-2x & \tfrac{1}{2} & \tfrac{1}{2} - 2z
\end{array}
$$

Since no peaks appeared at these positions it was concluded that there was no 2-fold screw axis parallel to the <u>a</u> axis. Similarly, the space group $P_{22_1 2_1}$ has equivalent positions:-

$$
\begin{array}{ccc}
x & y & z \\[4pt]
x & \bar{y} & \bar{z} \\[4pt]
\bar{x} & \tfrac{1}{2} + y & \tfrac{1}{2} - z \\[4pt]
\bar{x} & \tfrac{1}{2} - y & \tfrac{1}{2} + z
\end{array}
$$

0	2y	2z
2x	$\frac{1}{2}$	$\frac{1}{2} - 2z$
2x	$\frac{1}{2} - 2y$	$\frac{1}{2}$

Assuming this to be the correct space group the bromine atom was found to have co-ordinates:-

$$x = 0.250$$

$$y = 0.19587$$

$$z = 0.02154$$

These values were used for a three-dimensional Fourier summation. Even allowing for the complication of the pseudo-symmetry associated with this space group it was not possible to pick out peaks which would make chemical sense and this attempt had to be abandoned at this stage. This behaviour together with the absence of high order reflexions is typical of a disordered crystal in which the heavy atom does not have a definite position in the crystal. The co-ordinates found from the Patterson map did not, in fact, represent the true position of the bromine atom.

EXPERIMENTAL.

Isolation of triterpenoids from Guarea glabra.

The chloroform - soluble portion (70 g) of an ethyl acetate extract of the heartwood of Guarea glabra from which the non polar waxes had been removed was chromatographed over acidic alumina (Woelm grade 3 ; 2 Kg). Elution with chloroform - light petroleum (1 : 3) furnished the non polar material (6 g) which was not investigated further. Continued elution with the same solvents afforded Glabral I (1a : 10g) which crystallised from ethyl acetate - light petroleum and had m.p. 105 - 110°; $\nu_{max}^{CCl_4}$ 3611, 1732, 1715, 1652, 1635, 1249 cm^{-1}; n.m.r. signals at τ 4.49 (m)(1H, C - 21 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.03 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.35 (m) (1H, C - 3 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 6.23 (m)(1H, C - 23 ; multiplet width = 34 c./sec.), 7.16 and 7.33 (both d) (1H, C - 24 ; J = 7 c./sec.) and 8.01 (d)(3H, OAc ; separation = 2 c./sec.). Glabral II (5a : 6g) was obtained from the next fractions and after crystallisation from ethyl acetate - light petroleum had m.p. 130 - 133°; $\nu_{max}^{CCl_4}$ 3610, 1735, 1709, 1246 cm^{-1} ; n.m.r. signals at τ 4.75 (m)(1H, C - 21 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.04 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 4 c./sec.), 6.25 (m)(1H, C - 23 ; $W_{\frac{1}{2}}$ = 9 c./sec.), 6.4 (m)(O$\underline{H}$; $W_{\frac{1}{2}}$ = 6 c./sec. : disappeared on addition of D_2O), 6.66 (d)(1H, C - 24 ; J = 7 c./sec.) and 8.08 (s)(3H, OAc). Methyl signals appeared as singlets at τ 9.07 (6H), 9.04 (3H), 8.89 (3H) and 8.79 (6H). Further elution with ethyl acetate - light petroleum (1 : 1) furnished Glabral III (6a : 7g) which crystallised from

ethyl acetate - light petroleum and had m.p. 118 - 130°,
200° ; ν $_{max}^{CCl_4}$ 3610, 3540, 3430, 1730, 1250 cm^{-1} ; n.m.r.
signals at τ 4.64 (m)(1H, C - 21 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.05
(m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.29 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ =
5 c./sec.), 7.15 and 7.32 (both d)(1H, C - 24 ; J = 7 c./sec.)
and 8.00 (s)(3H, OAc). Hydroxyl protons (O$\underline{H}$) appeared at τ
6.15 (m) and 6.98 (d) and disappeared upon the addition of
D$_2$O. (Found : C = 70.39, H = 9.36 ; C$_{37}$H$_{58}$O$_8$ requires C =
70.44, H = 9.27 %). Glabral IV (5c : 3.5 g) was obtained as
an oil which could not be induced to crystallise; ν $_{max}^{CCl_4}$
3634, 3611, 3530, 1731, 1250 cm^{-1} ; n.m.r. signals at τ 4.63
(m)(1H, C - 21 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.03 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ =
6 c./sec.), 5.33 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 6.20 (m)
(1H, C - 23 ; multiplet width = 18 c./sec.), 7.17 and 7.35
(both d)(1H, C - 24 ; J = 8 c./sec.) and 7.90 (d)(3H, OAc ;
separation = 2 c./sec.). The polar compounds (22 g) were
eluted together as a dark oil which was not investigated
further.

Oxidation of Glabral I (1a).

Glabral I (1a : 425 mg) in dry pyridine (5 ml) was
treated for three days at room temperature with excess
chromium trioxide. Work up gave the crude lactone (1b : 442 mg)
which when filtered through a short column of neutral alumina,
crystallised from ethyl acetate - light petroleum and had
m.p. 200 - 202°. In the n.m.r. it exhibited signals at τ
5.00 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.34 (m)(1H, C - 3 ;
$W_{\frac{1}{2}}$ = 6 c./sec.), 5.85 (m)(1H, C - 23 ; multiplet width = 36 c./sec.
and 7.26 (d)(1H, C - 24 ; J = 7 c./sec.).

Hydroxylation of Glabral I lactone (1b).

Glabral I lactone (1b : 400 mg) in dry diethyl ether (20 ml) containing pyridine (5 ml) was treated for 24 hours at room temperature with osmium tetroxide (500 mg). The excess osmium tetroxide and the osmate ester were decomposed by precipitation as sulphide after the addition of hydrogen sulphide gas. Filtration through celite and evaporation of the solvents furnished a dark coloured oil (350 mg) shown by t.l.c. to consist of two major compounds of very similar polarity which were separated by repeated preparative t.l.c. (3 x ethyl acetate - light petroleum, 3 : 1). The less polar diol A (10a : 155 mg) crystallised from ethyl acetate - light petroleum as needles m.p. 218 - 220°, ν $_{max}^{CCl_4}$ 3584, 3515, 1780, 1732 cm^{-1} ; n.m.r. signals at τ 4.98 (m)(1H, C - 11, $W_{\frac{1}{2}}$ = 5 c./sec.), 5.24 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.82 (q)(1H, $\underline{H}$ - C - OH ; J = 7 c./sec.), 6.14 (m)(1H, C - 23 ; multiplet width = 40 c./sec.), 7.2 (d)(1H, C - 24 ; J = 7 c./sec.) and 7.98 and 8.01 (s)(OAc). (Found : C = 68.81, H = 8.77 ; $C_{37}H_{56}O_9$ requires C = 68.81, H = 8.75 %) ; m/e = 644 (M). The more polar diol B (10b : 160 mg) also crystallised from ethyl acetate - light petroleum but as very fine needles m.p. 203 - 205° ; ν $_{max}^{CCl_4}$ 3585, 3520, 1785, 1744, 1737 cm^{-1} ; n.m.r. signals at τ 5.01 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.29 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.90 (m)(1H, C - 23 ; multiplet width = 34 c./sec.) 6.40 (m)(2H, C$\underline{H}_2$ - OH ; multiplet width = 35 c./sec.), 7.25 (d)(1H, C - 24 ; J = 7 c./sec.) and 8.0 and 8.04 (s)(OAc). (Found : C = 66.68,

H = 8.48 ; $C_{36}H_{54}O_9 \cdot H_2O$ requires C = 66.64, H = 8.70 %);
m/e = 530 (M).

Periodate oxidation of Diol A (10a).

Diol A (10a : 40 mg) in methanol (1 ml) was treated at
room temperature for 12 hours with a saturated aqueous
solution of sodium metaperiodate. Filtration of the insoluble
material followed by extraction with chloroform and evaporation
of the solvent gave the crystalline product (11 : 35 mg).
Crystallisation from ethyl acetate - light petroleum afforded
the pyruvate as very fine needles, m.p. 189 - 192° ; $\sqrt{\ } \max^{CCl_4}$
1784, 1730, 1724 cm^{-1} ; n.m.r. signals at τ 5.03 (m)(1H,
C - 11 ; $W_{\frac{1}{2}}$ = 7 c./sec.), 5.26 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 6 c./sec.),
5.88 (q)(1H, C - 23 ; J = 7 c./sec.), 7.27 (d)(1H, C - 24 ;
J = 8 c./sec.), 7.61 (s)(3H, $C\underline{H}_3$ - C = O) and 8.01 (s)(OAc).
(Found : C = 68.44, H = 8.30 ; $C_{35}H_{50}O_8 \cdot H_2O$ requires C = 68.15,
H = 8.50 %) ; m/e = 598 (M).

Periodate cleavage of Diol B (10b).

Diol B (10b : 40 mg) in methanol was treated with
sodium metaperiodate in a similar manner and afforded needles
m.p. 180 - 182° ; $\sqrt{\ } \max^{CCl_4}$ 1783, 1730, 1723 cm^{-1} ; m/e = 598 (M).
This compound was identical with that obtained from diol A.

Oxidation of Diol A (10a).

Diol A (10a : 30 mg) in dry pyridine (5 ml) was
treated at room temperature for 15 hours with chromium
trioxide (50 mg). The product obtained on work up was seen
from t.l.c. to consist of two compounds which were separated

by preparative t.l.c. (2 x ethyl acetate - light petroleum,
1 : 1). The less polar compound (19 mg) crystallised from
chloroform - light petroleum and had m.p. 179 - 181°. m/e =
598 (M). It was identical (n.m.r. and m.s.) with the pyruvate
(11) obtained previously. The minor component (4 mg)
crystallised from ethyl acetate - light petroleum as very fine
needles, m.p. 213 - 215° and was identical (m.p., mixed m.p.
and i.r.) with a sample of glabral IV lactone.

Oxidation of Diol B (10b).

Diol B (10b : 28 mg) was treated with Sarett's
reagent as described above and after preparative t.l.c. of
the product the λ -keto-ester (11) crystallised from
light petroleum as rosettes m.p. 180 - 181°, identical
(n.m.r. and m.s.) with the above pyruvate.

Cleavage of λ Keto-ester (11).

The above keto-ester (11 : 82 mg) in methanol (50 ml)
was allowed to stir for four hours with a saturated aqueous
solution of sodium bicarbonate. The insoluble material was
filtered off, the filtrate reduced in volume and extracted
with chloroform. Evaporation of the solvent afforded the
crude hydroxy-lactone (5d : 70 mg) purified by preparative
t.l.c. (2 x ethyl acetate - light petroleum 1 : 1).
Crystallisation from ethyl acetate - light petroleum furnished
plates m.p. 202 - 204° ; $\nu_{max}^{CCl_4}$ 3630, 1779, 1728, 1244 cm^{-1};
n.m.r. signals at τ 5.02 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 8 c./sec.),
5.90 (m)(1H, C - 23 ; multiplet width = 36 c./sec.), 6.62 (m)

(1H, C - 3 ; $W_{\frac{1}{2}}$ = 7 c./sec.), 7.26 (d)(1H, C - 24 ; J =
7 c./sec.) and 8.01 (s)(3H, OAc). (Found : C = 70.36, H =
9.18 ; $C_{32}H_{48}O_6 \cdot H_2O$ requires C = 70.30, H = 9.22 %) ; m/e
= 528 (M).

Oxidation of Hydroxy-lactone (5d).

The above hydroxy-lactone (5d : 30 mg) in dry pyridine
(5 ml) was treated in the usual manner with a slurry of
chromium trioxide in pyridine. Chloroform extraction
afforded an oily product (27 mg) from which coloured impurities
were removed by preparative t.l.c. (ethyl acetate - light
petroleum, 1 : 1). The ketone (5c) thus obtained crystallised
from chloroform - light petroleum as very fine needles m.p.
215 - 218° ; ν $_{max}^{CCl_4}$ 1780, 1735, 1710, 1248 cm^{-1}; n.m.r.
signals at τ 4.93 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.88
(m)(1H, C - 23), 7.23 (d)(1H, C - 24 ; J = 8 c./sec.) and
8.0 (s)(3H, OAc). This compound was indistinguishable from
an authentic sample of glabral IV lactone.

Oxidation of Glabral III (6a).

Glabral III (6a : 141 mg) in dry pyridine was treated
at room temperature for 7 hours with excess chromium trioxide.
Work up afforded an oily mixture (139 mg) which was separated
into two components by preparative t.l.c. (ethyl acetate -
light petroleum, 1 : 1). The less polar compound, the keto-
lactone (6 b : 82 mg) crystallised from ethyl acetate -
light petroleum as needles m.p. 209 - 210° ; ν $_{max}^{CHCl_3}$ 1768,
1720 (broad) cm^{-1} ; n.m.r. signals at τ 5.02 (m)(1H, C - 11 ;

$W_{\frac{1}{2}}$ = 6 c./sec.), 5.17 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.87 (m)(1H, C - 23 ; multiplet width = 30 c./sec.), 6.82 (septet) (1H, $(CH_3)_2$-C - $\underline{H}$; J = 7 c./sec.), 7.24 (d)(1H, C - 24 ; J = 8 c./sec.) and 8.0 (s)(3H, OAc). (Found : C = 71.13, H = 8.70; $C_{37}H_{54}O_8$ requires C = 70.90, H = 8.68 %) ; m/e = 626 (M). The more polar constituent, the hydroxy - lactone (6c : 52 mg) crystallised from ethyl acetate - light petroleum as very fine needles m.p. 225 - 226° $\sqrt{}$ $\max^{CCl_4}$ 3535, 1779, 1724 cm^{-1} ; n.m.r. signals at Υ 5.00 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 8 c./sec.), 5.24 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 4 c./sec.), 7.23 (d)(1H, C - 24 ; J = 6 c./sec.) and 8.01 (s)(3H, OAc). (Found : C = 70.52, H = 9.10 ; $C_{37}H_{56}O_8$ requires C = 70.67, H = 8.98 %); m/e = 628 (M).

Cleavage of Keto-lactone (6b).

The keto-lactone (6b : 60 mg) in methanol (30 ml) was stirred for 15 hours with a saturated solution of sodium bicarbonate. Work up as described above gave the hydroxy - lactone (5d : 58 mg) as the major product. After being subjected to preparative t.l.c. (ethyl acetate - light petroleum, 1 : 1) it crystallised from ethyl acetate - light petroleum and had m.p. 202 - 204° and was identical in all respects with the material obtained from Kupchan cleavage of glabral I lactone.

Acetylation of Glabral III (6a).

Glabral III (6a : 92 mg) was acetylated at room temperature over two days with acetic anhydride - pyridine. Work up afforded a mixture of acetates (98 mg) which were

dissolved in anhydrous benzene and after the addition of basic alumina (Woelm grade 1 : 5 g) allowed to shake for 48 hours. The less polar major product was separated from the polar material by preparative t.l.c. (chloroform containing 2 % methanol) to afford the hydroxy - acetate (44 mg). Sarett oxidation furnished the lactone - acetate (6d : 37 mg) which crystallised from ice-cold ethyl acetate – light petroleum as needles, m.p. 204 - 205° ; $\nu_{max}^{CCl_4}$ 1782, 1737, 1248, 1232 cm^{-1}; n.m.r. signals at τ 5.01 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 9 c./sec.), 5.09 (d)(1H, $\underline{H}$ - C - OAc ; J = 4 c./sec.), 5.30 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 7 c./sec.), 7.23 (d) (1H, C - 24 ; J = 7 c./sec.), 8.86 and 8.98 (s)(3H each, 2 x OAc).(Found : C = 70.03, H = 8.76 ; $C_{39}H_{58}O_9$ requires C = 69.83, H = 8.71 %); m/e = 670 (M).

Reduction of Glabral IV lactone (5c).

Glabral IV lactone (5c : 70 mg) in absolute alcohol was treated at room temperature for 17 hours with excess sodium borohydride. The crude oil (65 mg) was seen from t.l.c. to be mainly one compound much more polar than the starting material. Preparative t.l.c. (2 x ethyl acetate - light petroleum, 3 : 1) afforded the oily triol (12b : 52 mg), $[\alpha]_D$ = - 5.4° (c = 1.8) ; $\nu_{max}^{CCl_4}$ 3620, 3520, 1735 cm^{-1} ; n.m.r. signals at τ 5.01 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 4 c./sec.), 6.2 - 6.9 (m)(4H, $\underline{H}$ - OH), 7.26 (d)(1H, C - 24 ; J = 9 c./sec.) and 7.99 (s)(3H, OAc). (Found : C = 72.03, H = 9.94 ; $C_{32}H_{52}O_6$ requires C = 72.14, H = 9.84 %).

Hydrogenation of Glabral I (1a).

Glabral I (1a : 70 mg) in ethyl acetate (35 ml) was hydrogenated for 60 minutes over Adams catalyst. Filtration of the catalyst and evaporation of the solvent afforded an oily residue (74 mg) from which the oily dihydro derivative (1c : 48 mg) was obtained by preparative t.l.c. (2 x chloroform containing 2 % methanol). It had ν max^{CCl_4} 3630, 3595, 3475, 1730, 1715 (s) cm^{-1}; n.m.r. signals at τ 4.62 (m)(1H, C - 21 ; $W_{\frac{1}{2}}$ = 6 c./sec), 5.04 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 5.48 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 6 c./sec.), 6.16 (m) (1H, C - 23 ; multiplet width = 30 c./sec.), 7.20 and 7.46 (both d)(1H, C - 24 ; J = 8 c./sec.) and 7.99 (s)(3H, OAc).

Oxidation of Dihydroglabral I (1c).

Dihydroglabral I (1c : 24 mg) was oxidised using Sarett's reagent and after work up afforded the crude lactone (28 mg) from which the coloured impurities were removed by preparative t.l.c. (chloroform containing 2 % methanol). Crystallisation of dihydroglabral I lactone (1d : 14 mg) from ice-cold ethyl acetate - light petroleum furnished very fine needles, m.p. 190 - 191°; n.m.r. signals at τ 5.01 (m) (1H, C - 11 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.35 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.90 (m)(1H, C - 23 ; multiplet width = 30 c./sec.), 7.21 (d)(1H, C - 24 ; J = 7 c./sec.) and 7.99 (s)(3H, OAc), (Found : C = . 72.49, H = 9.07 ; $C_{37}H_{56}O_7$ requires C = 72.51, H = 9.21 % ; $C_{36}H_{54}O_7$ requires C = 72.21, H = 9.09 %).

Reduction of Glabral I (1a).

Glabral I (1a : 91 mg) in absolute alcohol (20 ml) was treated at room temperature for 70 minutes with excess sodium borohydride and afforded after work up, an oily residue (83 mg) which was subjected to preparative t.l.c. (ethyl acetate - light petroleum, 3 : 1). Crystallisation of the _diol_ (12a) from ethyl acetate - light petroleum furnished very fine needles, m.p. 183 - 184° ; n.m.r. signals at τ 5.02 (m) (1H, C - 11 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 5.35 (m)(1H, C - 3 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 6.2 - 6.8 (m)(3H, $\underline{H}$ - OH), 7.31 (d)(1H, C - 24 ; J = 9 c./sec.) and 8.0 (s)(3H, OAc). (Found : C = 70.50, H = 9.45 ; $C_{37}H_{56}O_7 \cdot H_2O$ requires C = 70.44, H = 9.27 ; $C_{36}H_{54}O_7 \cdot H_2O$ requires C = 70.10, H = 9.15 %).

Acid hydrolysis of Glabral IV lactone (5c).

(a) Glabral IV lactone (5c : 207 mg) in anhydrous benzene was refluxed for four hours with chloroacetic acid (200 mg). The solution was filtered through a short column of neutral alumina (grade 3) to afford an oily mixture of four compounds (188 mg) which was separated by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 1). The least polar component (11 mg) was isolated as oil which distilled at 270°/0.04 mm and then solidified and had m.p. 85 - 90° ; ν $_{max}^{CCl_5}$ 1706, 1734, 1785 cm^{-1} ; n.m.r. signals at τ 4.94 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 7 c./sec.) and 7.99 (s)(3H, OAc). m/e = 526 (M)($C_{32}H_{46}O_6$). The second component was the _hydroxy - olefin_ (14a : 68 mg) which crystallised from ethyl acetate - light petroleum and had m.p. 157 - 160° ; ν $_{max}^{CCl_4}$ 3588, 3445, 3062, 1780, 1734, 1705

1240 cm^{-1} ; n.m.r. signals at $\mathcal{V}$ 4.97 (m)(2H, C - 26 and

1H, C - 11 ; $W_{\frac{1}{2}}$ = 5 c./sec.), 6.03 (d)(1H, C - 24 ; J =

7 c./sec.), 7.99 (s)(3H, OAc) and 8.23 (broad s)(3H, C - 27).

(Found : C = 73.21, H = 8.72 ; $C_{32}H_{46}O_6$ requires C = 72.97,

H = 8.80 %) ; m/e = 526 (M). The third compound, the

chloroacetate (15a : 79 mg) also crystallised from ethyl

acetate - light petroleum, as very long thin needles m.p.

195 - 196° ; $\mathcal{V}$ max^{CCl_4} 3590, 3480, 3065, 1780, 1735, 1708, 1242

cm^{-1} ; n.m.r. signals at $\mathcal{V}$ 5.00 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 6 c./sec.)

5.10 (d)(1H, C - 24 ; J = 4 c./sec.), 5.94 (s)(2H, CH_2 - Cl)

and 7.98 (s)(3H, OAc). (Found : C = 65.82, H = 7.95;

$C_{34}H_{49}O_8Cl$ requires C = 65.75, H = 7.89 %). m/e = 560 (M - 60).

A crystal suitable for X-ray analysis was mounted and

preliminary photographs taken but were identical to those

from the bromoacetate (16b) indicating that the two compounds

were isomorphous. The most polar compound, the diol

(15c : 18 mg) was crystallised from ethyl acetate - light

petroleum and after drying it had m.p. 198 - 200° ; $\mathcal{V}$ max^{CCl_4}

3565, 3520, 1707, 1723 and 1782 cm^{-1}. (Found : C = 67.40,

H = 8.83 ; $C_{32}H_{48}O_7$ 3/2H_2O requires C = 67.25, H = 8.93 %) ;

m/e = 484 (M - 60).

(b) Glabral IV lactone (5c : 150 mg) was treated in

refluxing benzene for 15 hours with bromoacetic acid as

described above. T.l.c. showed that the product consisted of

a similar series of compounds from which the major product,

the bromo-acetate (15b : 64 mg) was isolated by preparative

t.l.c. Crystallisation from chloroform - light petroleum

furnished needles m.p. 201 - 202°. A sample for X-ray
analysis was grown by dissolving it in a large volume of
ethyl acetate, followed by the addition of high boiling
petroleum (b.p. 100 - 120°) and allowing the solvents to
evaporate slowly. ν max^{CCl_4} 3590, 1765, 1724, 1700 cm^{-1} ;
n.m.r. signals at τ 4.98 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 7 c./sec.),
5.12 (d)(1H, C - 24 ; J = 3 c./sec.), 5.29 (m)(1H, C - 23 ;
$W_{\frac{1}{2}}$ = 21 c./sec.), 6.15 (s)(2H, $C\underline{H}_2$ - Br), and 8.02 (s)
(3H, OAc). (Found: C = 61.29, H = 7.37 ; $C_{34}H_{49}O_8Br$ requires
C = 61.36, H = 7.37 %) ; m/e = 665 (M).

Formation of Iodoacetate (15d).

The above chloroacetate (15 a : 75 mg) in acetone was
refluxed for 15 hours with excess sodium iodide in an
atmosphere of nitrogen. T.l.c. showed that the polarity of
the product was similar to that of the starting material.
After purification by preparative t.lc. (ethyl acetate -
light petroleum, 1 : 1) the iodo-acetate (15d : 56 mg)
crystallised from chloroform - light petroleum as needles
m.p. 173 - 174° ; ν max^{CCl_4} 3590, 1765, 1724, 1700 cm^{-1} ;
n.m.r. signals at τ 4.97 (m)(1H, C - 11 ; $W_{\frac{1}{2}}$ = 6 c./sec.),
5.12 (d)(1H, C - 24 ; J = 3 c./sec.), 6.25 (s)(2H, $C\underline{H}_2$ - I)
and 8.00 (s)(3H, OAc). (Found : C = 57.23, H = 7.05 ;
$C_{34}H_{49}O_8I$ requires C = 57.31, H = 6.89%). A sample was
grown for X-ray analysis as described above but formed
clusters of crystals unsuitable for an X-ray determination.
Recrystallisation furnished single crystals of a suitable size
but were found to be twinned when viewed under a polarising

microscope and were not further investigated.

Crystal Data.

Bromoacetate (15b), $C_{34}H_{49}O_8Br$, M = 665, Orthorhombic, a = 7.27, b = 18.14, C = 25.80 Å, u = 3402 Å^3, D_m not measured, Z = 4, D_c = 1.30.

The intensity data collection was by the equi - inclination Weissenberg method using Cu - K$_\alpha$ radiation with a small crystal rotating about the a axis. The reciprocal lattice nets (0kl) to (5kl) were surveyed using the multi - film technique, a total of 1457 reflexions being obtained. The intensities were estimated visually by comparison with a calibrated scale and appropriate corrections were made for Lorentz, polarisation and rotation factors. Since absorption was small no corrections were applied.

Acetylation of Hydroxy - Olefin (14a).

The hydroxy - olefin (14a : 26 mg) was treated at room temperature for 48 hours with acetic anhydride - pyridine and afforded the corresponding acetate (14b : 24 mg) from which minor impurities were removed by preparative t.l.c. (ethyl acetate - light petroleum, 1 : 1). Crystallisation from ice cold chloroform - light petroleum afforded the olefinic - acetate (14b) as very large needles, m.p. 110 - 115°, 184°; (Found : C = 60.99, H = 7.24 ; $C_{34}H_{48}O_7CHCl_3$ requires C = 61.09, H = 7.12 %).

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a : R = H,OH : $R_1 = C_5H_8O_2 + C_4H_6O_2$

b : R = O : $R_1 = C_5H_8O_2 + C_4H_6O_2$

c : R = H,OH : $R_1 = C_5H_{10}O_2 + C_4H_8O_2$

d : R = O : $R_1 = C_5H_{10}O_2 + C_4H_8O_2$
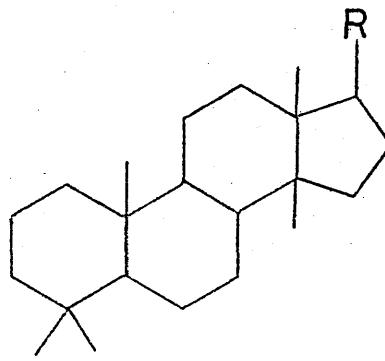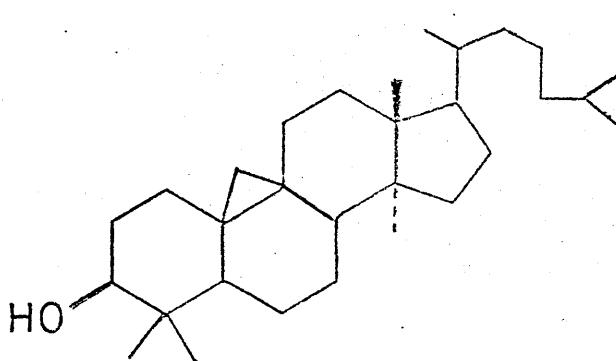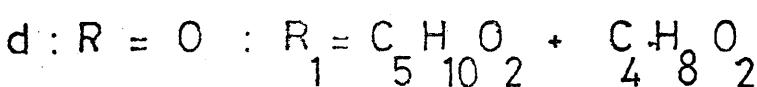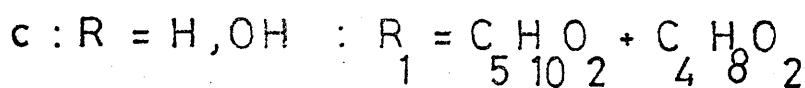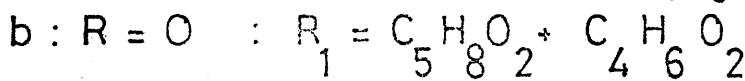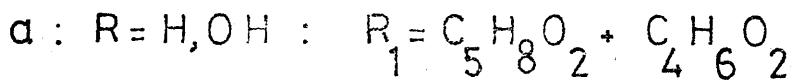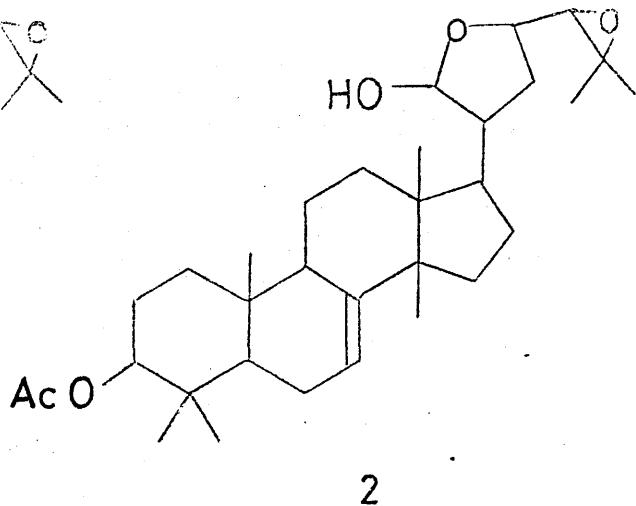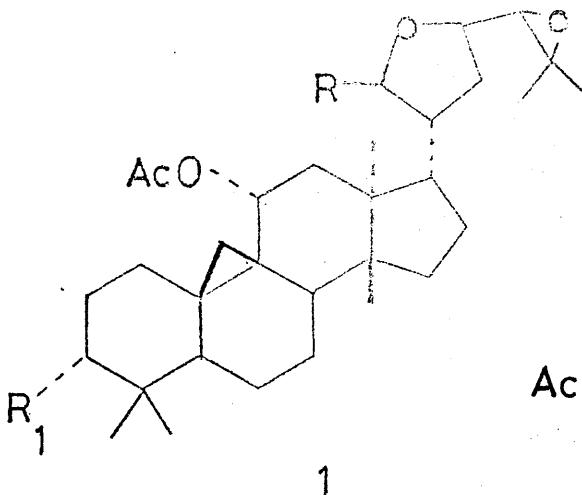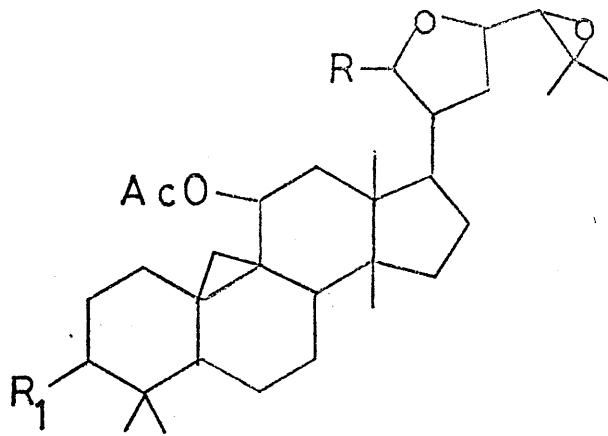
a : R= H,OH : R$_1$= O
b : R= H,OH : R$_1$=H,OH
c : R = O : R$_1$= O
d : R =O : R$_1$ = H, OH

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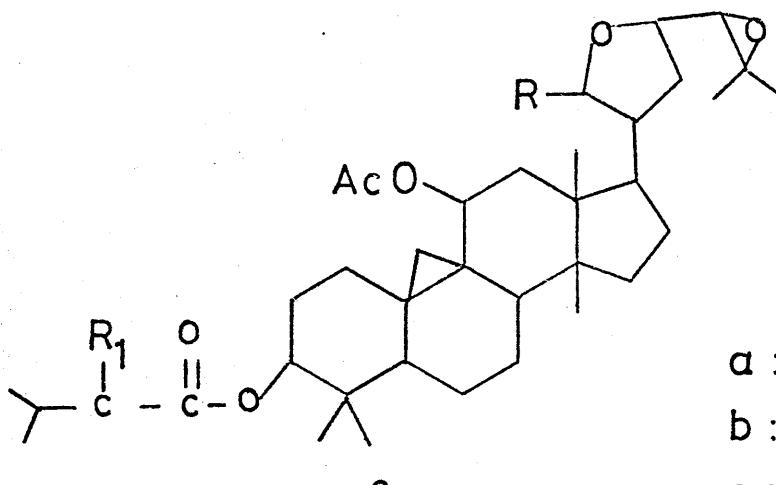
a : R= H, OH : R$_1$= H, OH
b : R = O : R$_1$= O
c : R = O : R$_1$ = H,OH
d : R = O : R$_1$ = H ,OAc

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$$H-\overset{\overset{H}{|}}{C}-\overset{\overset{H}{|}}{\underset{\underset{O}{||}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{O}{||}}{C}}-\overset{\overset{H}{|}}{C}-$$

7

8

9

a : R = CH₃

b : R = H
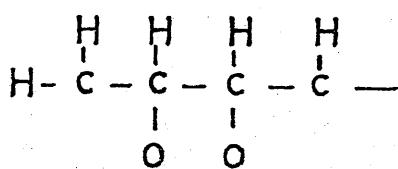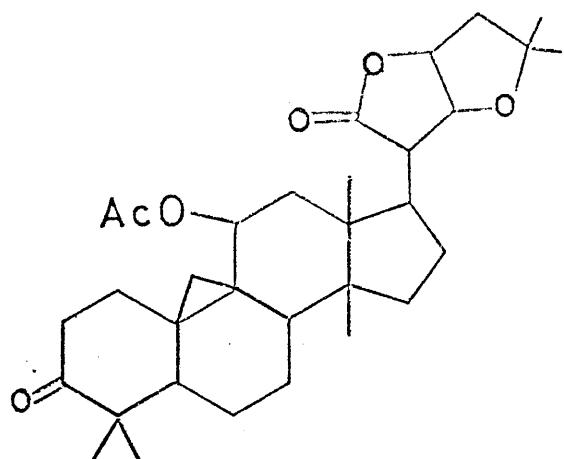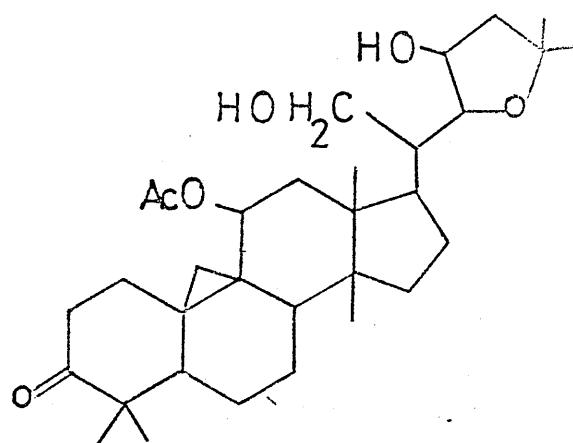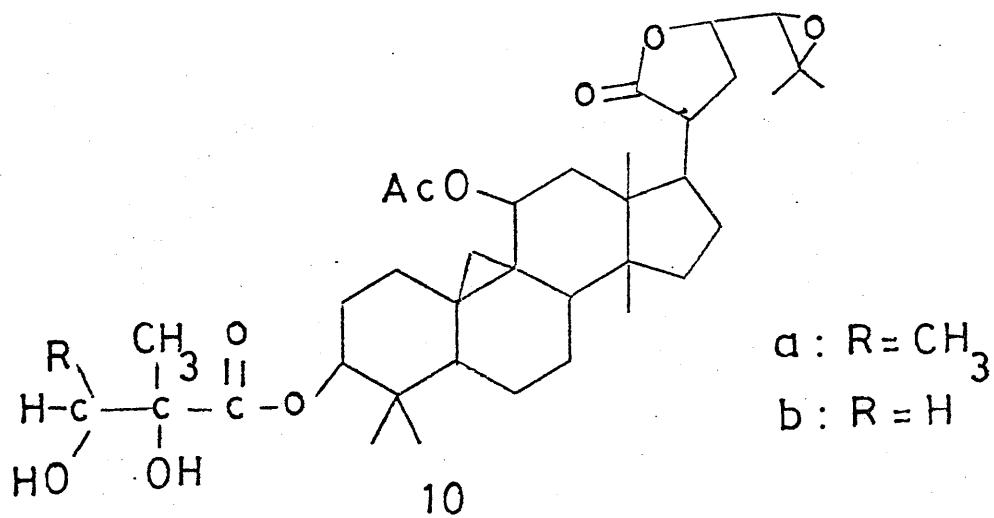
10
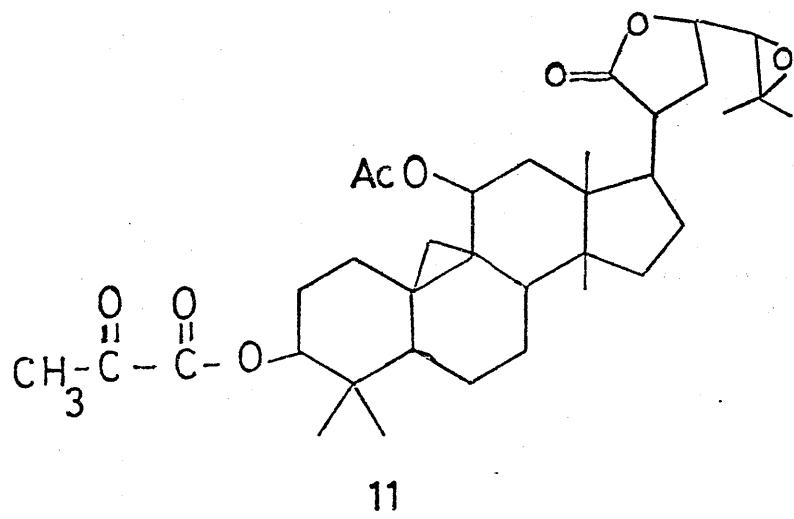
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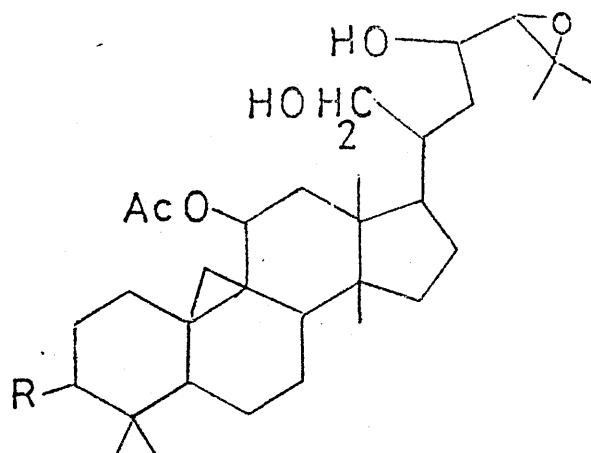
a : R = angelate,
    tiglate and
    methacrylate

b : R = H,OH

12

13

a : R = H,OH
b : R = H,OAc

14

15

a : R = -C-CH₂Cl
   ‖
   O

b : R = -C-CH₂Br
   ‖
   O

c : R = H

d : R = -C-CH₂I
   ‖
   O

16