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A Thesis

entitled

"Studies in the Tetranortriterpenoid Series"

submitted to the

University of Glasgow

for the Degree of Doctor of Philosophy

in the Faculty of Science

by R. Henderson, B.Sc.

Chemistry Department

December, 1964.

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Contents.

The Modified Triterpenes

The three sections of this thesis describe the constitution and stereochemistry of the furanoid bitter principles swietenine[1] (B7), nimbin[2] (C1) and salannin[3] (D1). It will be observed that these compounds have a close biogenetic relationship with limonin (A1) and it seems appropriate to preface the thesis with a review of the modified triterpenes.

The structure of limonin was deduced simultaneously from the chemical work of three groups of investigators[4], and from an X-ray study[5].

From a biogenetic viewpoint[6] limonin can be derived from a precursor possessing the carbon-skeleton and stereochemistry of the tetracyclic triterpene euphol (A2). Cleavage of the side-chain between C_{23} and C_{24} followed by oxidative cyclisation of the remainder leads to the furan ring. The structure of flindissol[7] (A3) supports this proposal in that flindissol contains a potential furan ring with the rest of the side-chain intact and a carbon skeleton identical with that in euphol.

The migration of the methyl group from C_{14} to C_8 with the concomitant loss of a proton from C_{15} and the introduction of a ketone at C_7 finds precedent in the oxidation of dihydrobutrospermyl acetate (A4) to the 7-ketone[8] (A5). The intermediate (A6) has the requisite functionality for its conversion to any of the known modified triterpenes. Thus allylic oxidation at C_{16} followed by a Baeyer-Villager cleavage and epoxidation of the olefinic linkage

leads to the common epoxy-δ-lactone in ring D. Limonin also requires ring A of the triterpene skeleton to be oxidatively cleaved between C_3 and C_4 and the carboxyl function at C_3 lactonised onto the oxidised methyl at C_{19} and the hydroxyl group at C_4 to cyclise onto the olefinic linkage at C_1. Precedents for the C_3 - C_4 cleavage are to be found in the triterpenes dammarenolic[9] (A7) and nyctanthic acids[9,10] (A8).

Two compounds, obacunone (A9) and nomilin (A10) have been related[11] to limonin. Biogenetically, their structures are derived, as in limonin, from a cleaved ring A which has not cyclised onto the oxidised methyl group C_{19} but has formed a seven membered ring lactone in ring A.

One of the more novel reactions of limonin which has been important as a diagnostic test for assigning modified triterpenes, is the base catalysed limonol (A11) to merolimonol (A12) conversion. Limonin on Meerwein-Ponndorf reduction gives limonol (A11) which has an axial hydroxyl group in keeping with its mode of formation. On treatment with base, limonol undergoes a profound rearrangement with the loss of β-furfuraldehyde and the formation of merolimonol (A12). This reaction, peculiar to the axial hydroxyl, has been rationalised by postulating opening of the epoxide ring to give the trimethylene oxide (A13). This then undergoes base-catalysed loss of furfuraldehyde as shown with the formation of the hydroxy acid (A14) which lactonises on acidification. This reaction depends on the presence of a C_7 axial hydroxyl group and an epoxy-δ-lactone.

The 'merolimonol' reaction was used in the structural elucidation of khivorin[12] (A15) and gedunin[13] (A16). Khivorin, $C_{32}\ H_{42}\ O_{10}$, was

shown to contain three acetoxyl groups, a furan ring, an epoxide and a δ-lactone and must therefore be tricarbocyclic. The positive 'merolimonol' reaction places an α-acetate at C_7. Hydrolysis of deoxykhivorin (A17), the chromous chloride reduction product, results in a trisdeacetyl derivative which on oxidation afforded a triketone (A18) whose ultraviolet spectrum indicated that it was a β-diketone. This permitted the remaining two acetates to be placed at C_1 and C_3.

Two tetracarbocyclic compounds, cedrelone[14] (A19) and anthothecol[15] (A20) with ring D intact, a diosphenol function in ring B and an α,β unsaturated ketone in ring A have been isolated. The structure of cedrelone was determined by X-ray methods.[16] One of the most interesting reactions of cedrelone is its treatment with boron trifluoride etherate to afford isocedrelone (A21). This arises through acid catalysed cleavage of the epoxide ring with concomitant methyl migration from C_{13} to C_{14} and the placing of a double bond in conjugation with the furan ring.

The first example of a modified triterpene in which ring B is cleaved, is swietenine[1] (B7). Biogenetically swietenine is derived from a precursor of the type (A22) in which the C_7 - C_8 bond is cleaved, followed by a Michael addition of C_2 to C_{30}. For detailed discussion see page 27. Recently, two further examples, andirobin[17] (A23) and methyl angelensate[18] (A24) of ring B cleavages in C-26 compounds have been reported.

The first and, so far, only examples of ring C cleavages are provided by nimbin[2] (C1) and salannin[3] (D1). In both these compounds,

ring D is intact and the C_{12} - C_{13} bond has been broken to form an acetic acid side-chain on C_9. An additional point of interest is that they are the only modified triterpenes in which one of the C_4 gem dimethyls has been oxidised. Recently, a group of C-19, C-20 and C-25 compounds have been added to the modified triterpenes.

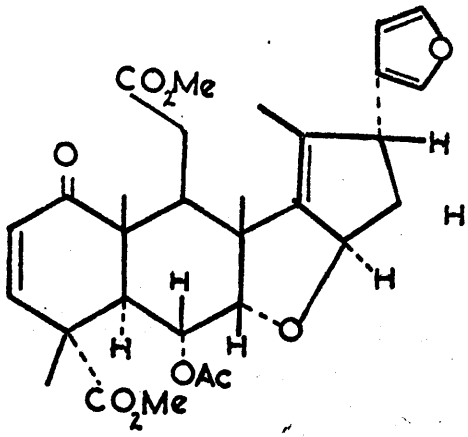
It had been proposed that quassin[19] (A25), a member of the simaroubaceae class was biogenetically derived from the diterpenoid pimarane (A26) skeleton by a series of C-methyl shifts and a shift of a two carbon fragment or by oxidative coupling of two identical C-10 units as shown in (A25).

It is now proposed[20,21] that C-26 terpenoids are the precursors of the C-20 bitter principles, and that they lose a C-5 fragment in a limonol to merolimonol type conversion followed by the loss of a methyl group at C_4 presumably through oxidation and decarboxylation of a precursor similar to nimbin. The compelling facts that support this proposal are the close structural resemblance and, more important, the stereochemical similarity of the merolimonol compounds to the simaroubaceae C-20 compounds.

Further proof that the simaroubaceae compounds are derived from a limonin type compound comes from the elucidation of the structure simarolide[22] (A27) which has a C-25 skeleton. The absolute stereochemistry of simarolide suggests that its precursor may be a tetracyclic triterpene of the euphol (A2) type from which a methyl group at C_4 has been oxidatively removed. The cleavage of the side-chain between C_{23} and C_{24} followed by lactonisation onto C_{20} leads to the γ-lactone.

The proposed biogenesis is then similar to that of limonin: migration of the C_{14} methyl group to C_8 with the formation of an alcoholic group at C_7 and conversion of ring D into the δ-lactone by way of a Baeyer-Villager oxidation on the C_{16} ketone group. Opening of the δ-lactone and relactonisation onto the hydroxyl group at C_7 followed by oxidation of the resulting hydroxyl group at C_{17} then leads to simarolide.

The C-20 structures of quassin (A25), chaparrin[23] (A28) and glaucarubin[24] (A29) are closely related to simarolide and may be formed by the cleavage of the C_{13} - C_{17} bond. The C-19 compounds samaderine[25] (A30) and cedronoline[26] (A31) are formed from the above by removal of C_{16}. Both contain oxygen functions at C_{13} suggesting a further oxidation at C_{17} in the precursor.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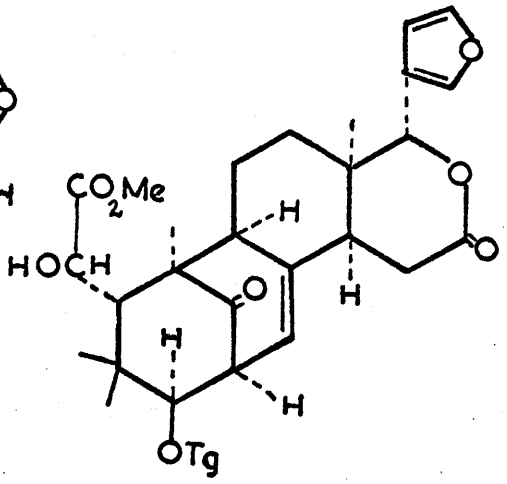
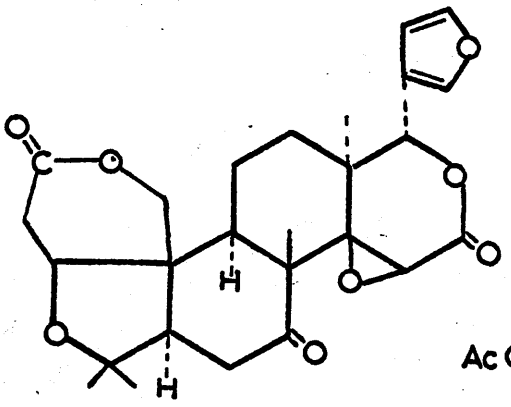
O
H
H
H
H
OAc
CO2Me

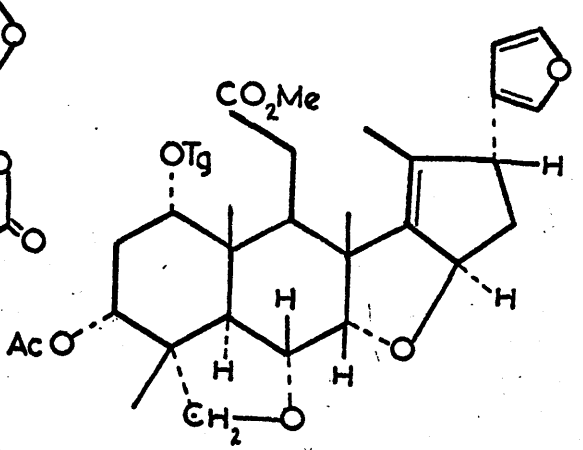
(C 1)


CO2Me
HOCH
H
O
H
H
H
OTg

(B 7)


O
O
O
H
O
H

(A 1)


CO2Me
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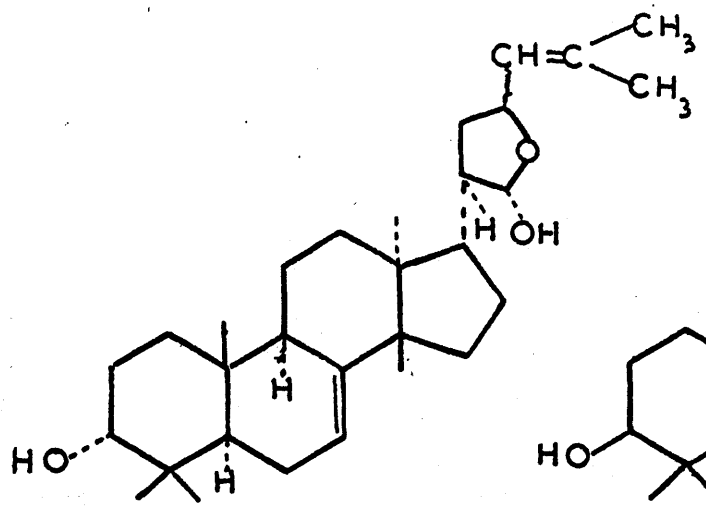
H
H
H
AcO
H
H
CH2
O

(D 1)



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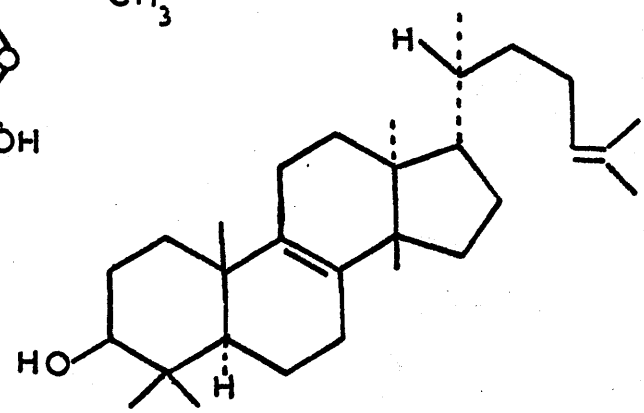

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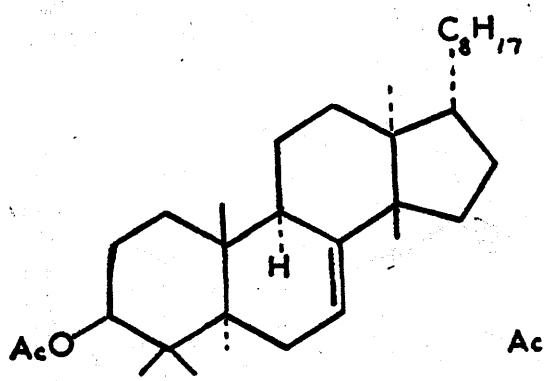

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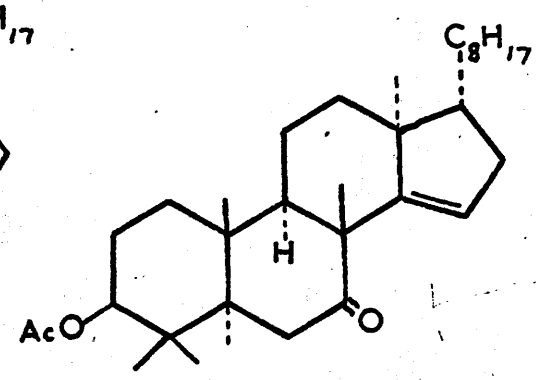

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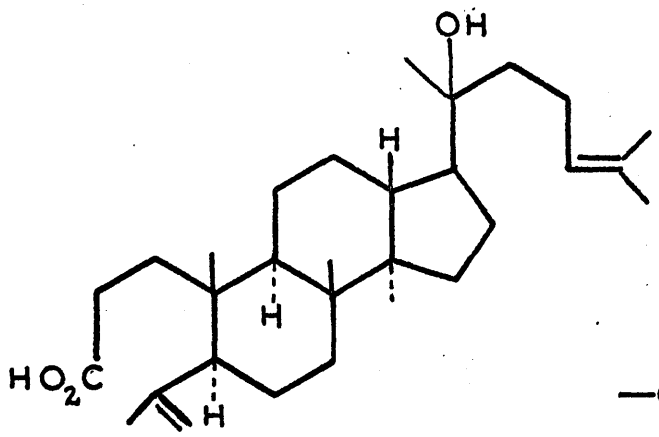

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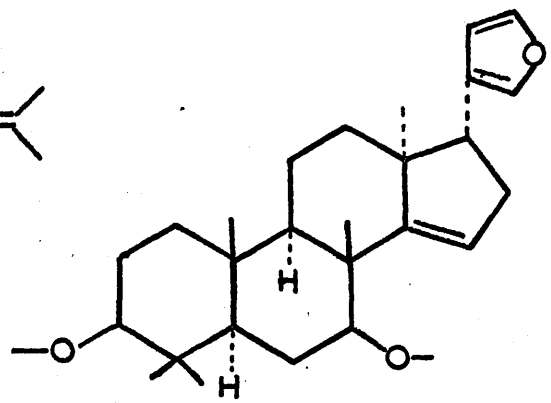

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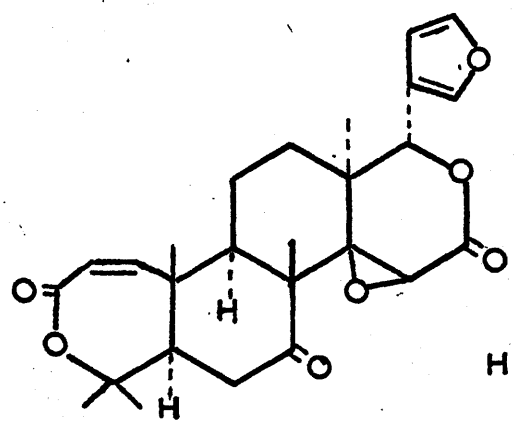

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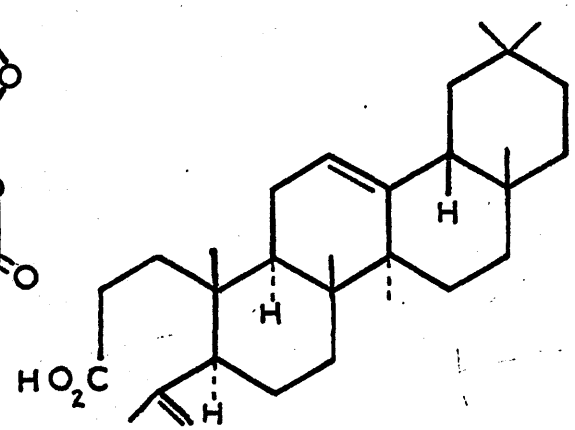

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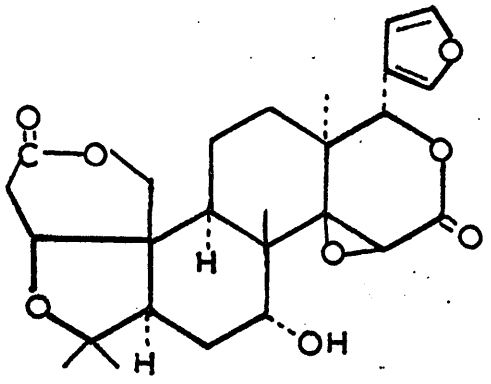

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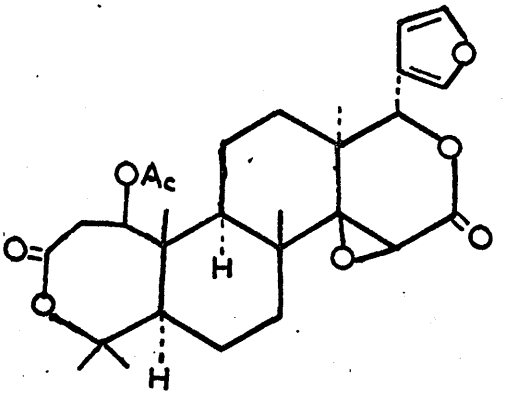

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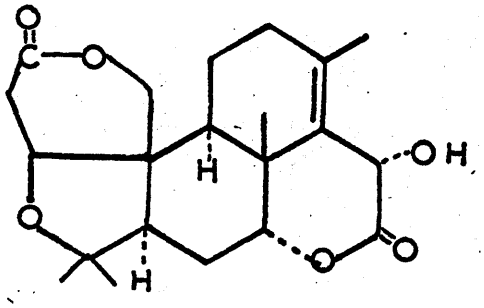

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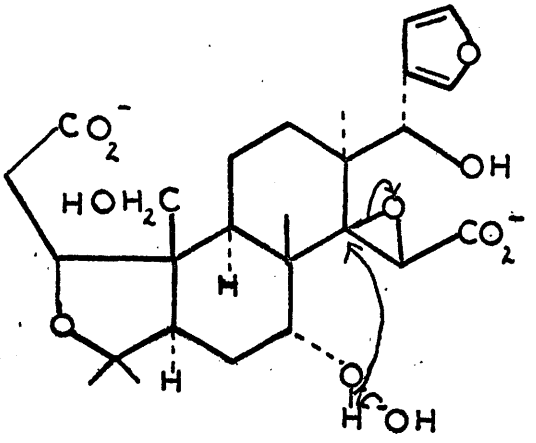
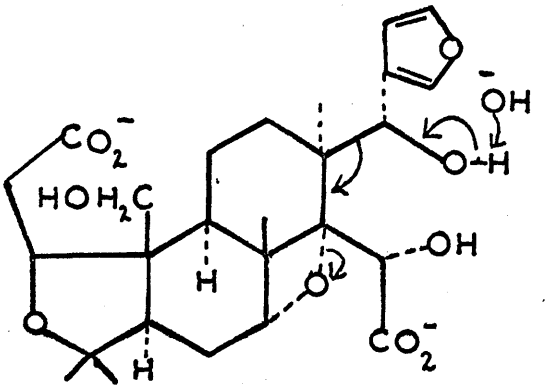
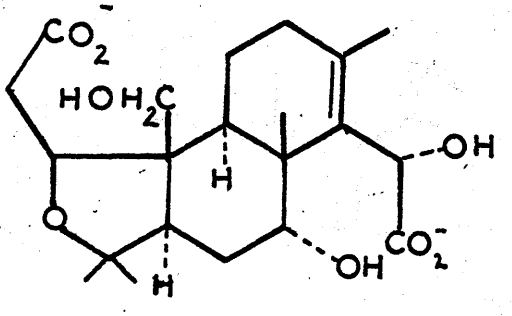




Limonol in Base. . (A 13)



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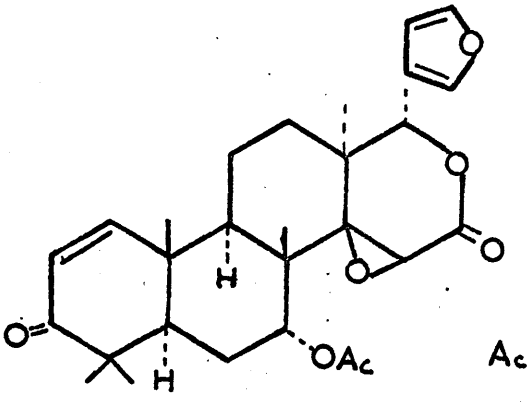

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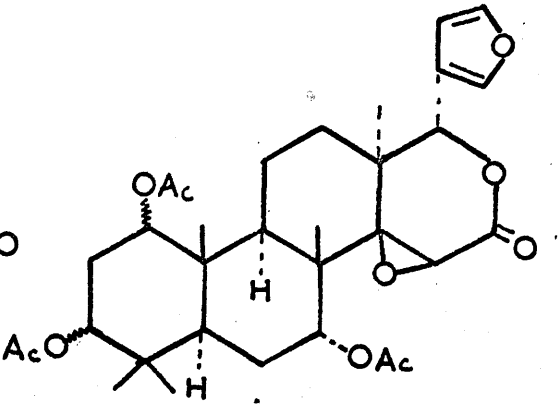

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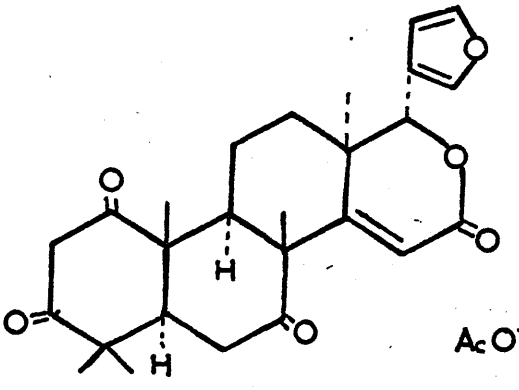

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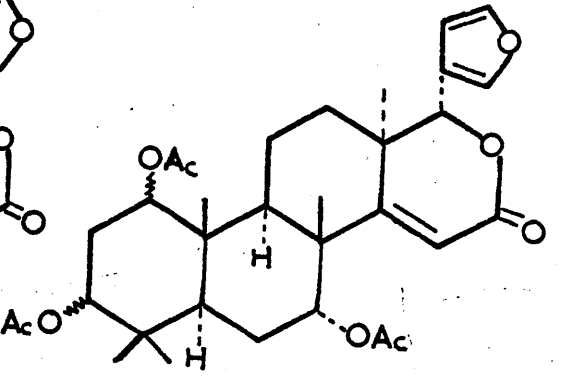

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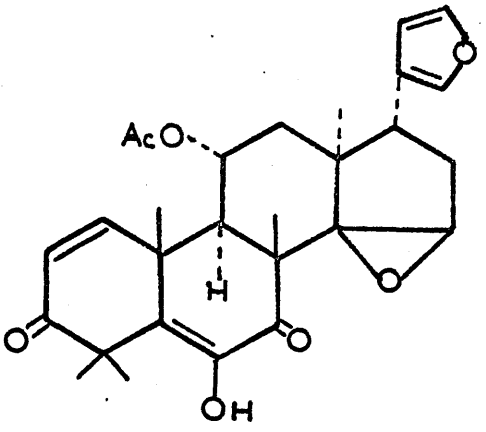

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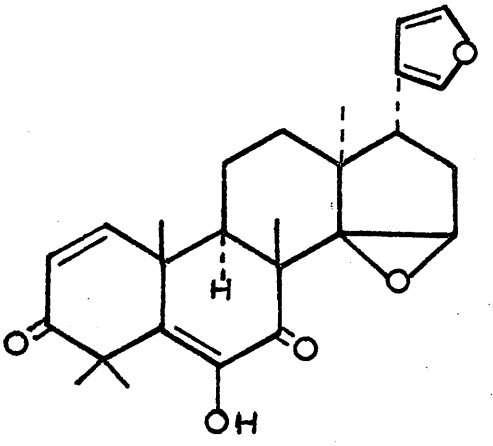

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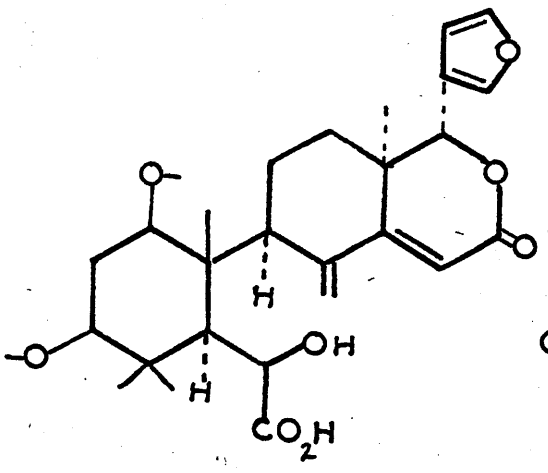

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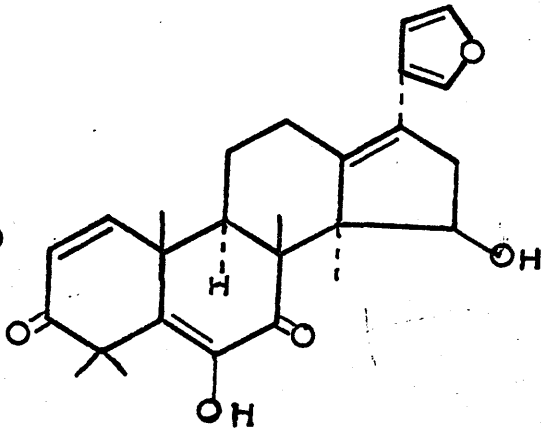

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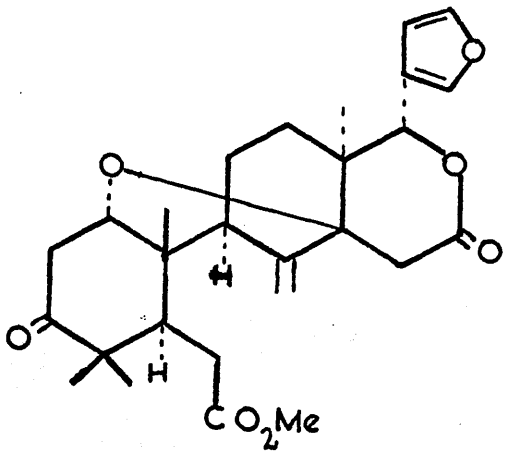

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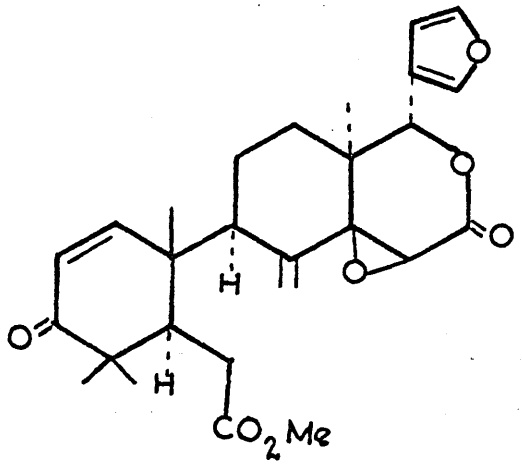

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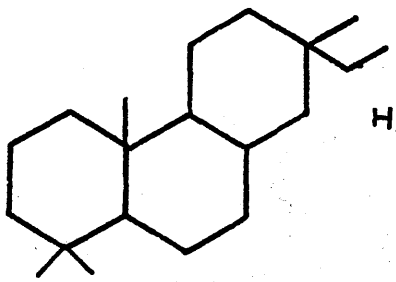

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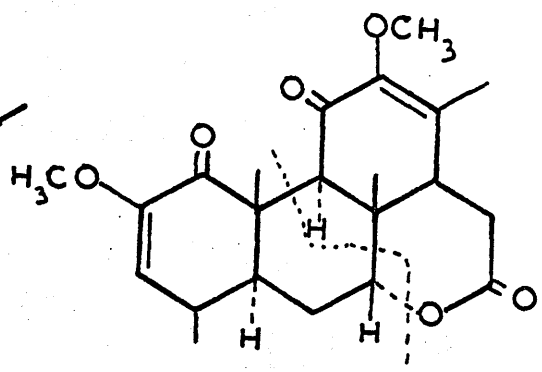

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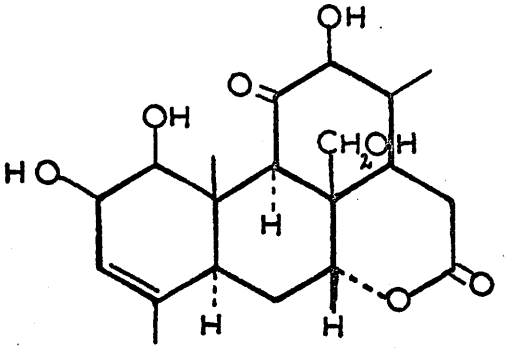

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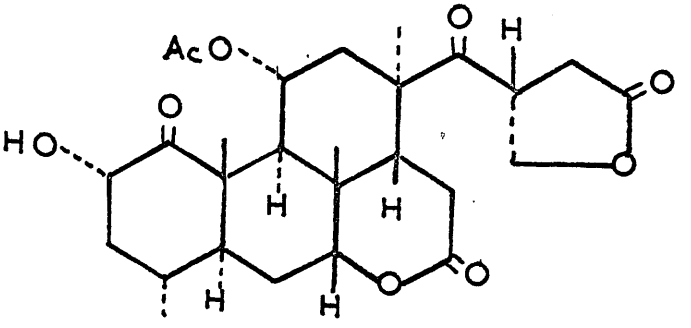

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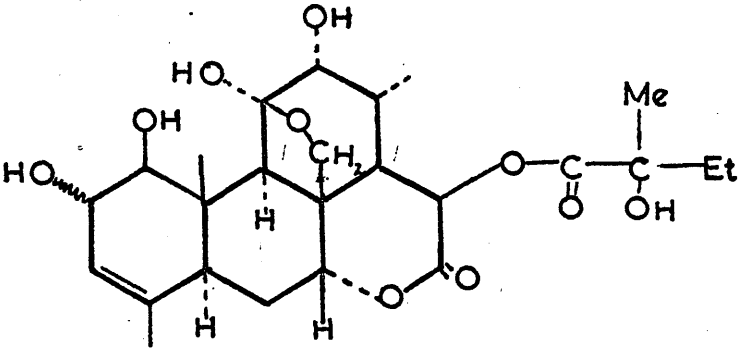

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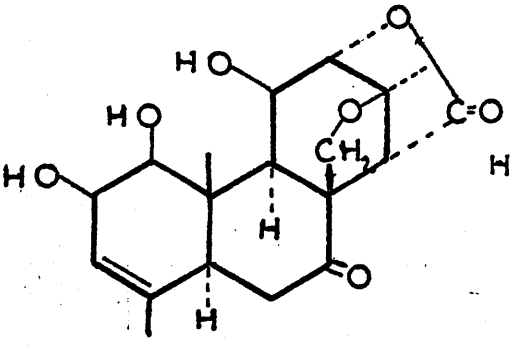

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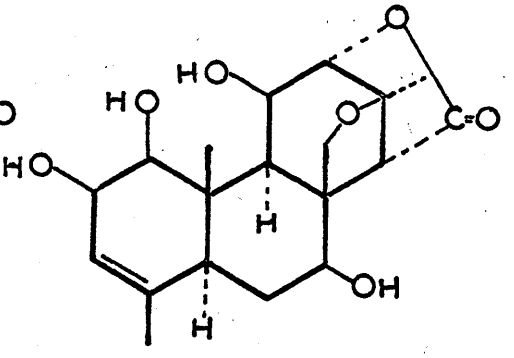

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PART I

THE CONSTITUTION OF SWIETENINE

The Constitution of Swietenine[1]

Swietenine, the non-bitter principle of Swietenia macrophylla King (Fam, Meliaceae) was first isolated by Sircar and Chakrabarthy[2] who concluded that it had the molecular formula $C_{18}H_{24}O_5$, a tertiary or inert hydroxyl group, a methoxyl group, a ketone and an α,β-unsaturated δ-lactone. Later investigations[3,4] were alleged to demonstrate that swietenine has an isolated double bond and is bicarbocyclic, since substituted napthalenes were isolated from dehydrogenation experiments. In a subsequent investigation, an X-ray molecular weight determination[5] (565) led the Indian workers to revise the molecular formula to $C_{32}H_{42}O_9$ and to suggest, on the basis of n.m.r. data, the presence of a β-substituted furan, five C-methyl groups and from the results of hydrolysis experiments, one tiglate and one methyl ester. On this basis they concluded that swietenine had the structure (B1).

We have reinvestigated the chemistry of swietenine with the following results.

The composition $C_{32}H_{40}O_9$ is established by the mass-spectrometric molecular weight (568) of swietenine (B7) and two of its derivatives and by combustion analyses of more than thirty derivatives.

Swietenine has three bands in the infrared (nujol) at 3160 w, 1505 w, and 877 s cm^{-1} and in the nuclear magnetic resonance spectrum, peaks at τ 2.4 - 2.6 (2H, multiplet) and τ 3.5 - 3.6 (1H, diffuse singlet) all characteristic of $\alpha\beta$-substituted furan system.

On treatment with base, tiglic acid sublimes from the acidified reaction mixture and can be characterised as its p-bromo-phenacyl ester. That swietenine is a secondary tiglate ester is confirmed by its nuclear magnetic resonance spectrum which shows peaks at τ5.3 (1H, doublet, J = 10 c.p.s.) and at τ 3 (1H, multiplet) and τ 8.2 - 8.3 (6H, 2 methyl groups). The multiplets observed at 100 Mc/S are highly characteristic of tiglate esters.

That swietenine is a methyl ester is shown in the nuclear magnetic resonance spectrum, one carbomethoxyl at τ6.2 (3H, singlet); and by a band in the infrared spectrum (carbon tetrachloride solution) at 1743 cm^{-1} (methyl ester).

Swietenine also contains a hydroxyl group as shown by the presence of infrared bands in chloroform solution at 3605 (free hydroxyl), 3540 (bonded hydroxyl) cm^{-1} and a peak at τ 5.5 (1H, doublet J = 1 c.p.s.) in the nuclear magnetic resonance spectrum which disappears on oxidation. Moreover, a concentration - and temperature - dependent signal (1H) between τ6.9 and 7.2 in the n.m.r. spectrum of swietenine in $CDCl_3$ solution (-OH) disappears on exchange with deuterium oxide. It would

appear that the alcohol is thus secondary and that its chemical shift can be accounted for by the deshielding effect of a carbonyl function situated α to the alcohol. This can be demonstrated by chemical means as indicated in the sequel.

In the infrared, swietenine also shows absorption at 1752 (δ-lactone) and 1716 (cyclohexanone) cm^{-1} in carbon tetrachloride solution. The presence of a saturated ketone in swietenine is further demonstrated by its optical rotatory dispersion which shows a negative Cotton curve. Although the ketone function in swietenine is too hindered to form derivatives under normal conditions, the octahydro acid (B8; see below) forms an oxime.

The above functional groups account for all the nine oxygen atoms present in swietenine.

Hydrogenation of swietenine over 10% palladium charcoal results in the uptake of four moles of hydrogen to yield a crystalline octahydro acid (B8) arising from hydrogenolysis of the lactone attached allylically to the furan ring, and saturation of the furan and tiglate double bonds. The nuclear magnetic resonance spectrum shows the disappearance of a sharp singlet which is present at τ 4.3 - 4.6 in all swietenine derivatives which retain the δ-lactone and furan functions and is therefore assigned to position 17 in swietenine.

The octahydro acid (B8) $C_{32}H_{48}O_9$, m.p. 153 - 154° $[\alpha]_D$ - 190°, had a pK value of 5.93 and the methyl ester (B9) $C_{33}H_{50}O_9$, m.p. 164 - 165° $[\alpha]_D$ - 179°, derived from the octahydro acid has absorption in the infrared at 1734 cm^{-1} (in carbon tetrachloride) which shows that

it is not an α-hydroxy, α-alkoxy or α,β - unsaturated carboxylic ester.

This leads to part-structure (B2) for swietenine.

The octahydro acid gave a positive tetranitromethane test and still retained end absorption in the ultra-violet λ_{max} 202 mμ (ε6,300) thus indicating the existence of an isolated double bond (τ4.63, 1H, multiplet) in swietenine which has survived hydrogenation. That the double bond was hindered was also shown by the fact that the octahydro acid methyl ester (B9) was inert when reacted with osmium tetroxide in dioxan for four days.

By refluxing the octahydro acid with hydroxylamine hydrochloride in pyridine for three days, a crystalline oxime $C_{32}H_{49}NO_9$ (B10) m.p. 251 - 254 was obtained (swietenine is unchanged under these conditions) affording further proof of the presence of an aldehyde or ketone function in swietenine.

Hydrogenation of swietenine over Adam's catalyst in ethyl acetate resulted in the uptake of one mole of hydrogen to yield crystalline dihydroswietenine (B11) $C_{32}H_{42}O_9$ m.p. 224 - 229° arising from the saturation of only the tiglate double bond. This can be shown in the nuclear magnetic resonance spectrum where the β-mono-substituted furan protons (τ 2.6, 2H, multiplet; τ 3.6, 1H, multiplet), olefinic proton (τ4.5, 1H, multiplet) and H_{17} (τ 4.3, 1H, singlet) are still present and the multiplet at τ 3.0 (1H, multiplet) of the tiglate olefinic bond has disappeared.

Allowing for the functional groups which have been accounted for, swietenine, $C_{32}H_{40}O_9$, must be tricarbocyclic.

If the contributions to the molecular formula of the tiglate and

methyl esters are subtracted from the molecular formula of swietenine, we arrive at the composition C_{26} H_{32} O_8 for destigloyl-desmethyl swietenine. This suggests a limonin-type[6] structure based on a modified euphol skeleton. Swietenine, however, like limonin contains only four C-methyl groups (apart from the tiglate ester) at τ 8.60 ($CH_3 - \overset{|}{C} - \overset{|}{C} = O$ and τ 8.96, 9.13, and 9.22 (quaternary methyls). The fifth methyl group of euphol must therefore be oxidised or incorporated in a carbocyclic ring.

Swietenine can be oxidised smoothly by either the Sarret or Jones reagents to dehydroswietenine C_{32} H_{38} O_9 (B12) m.p. 260 - 265°, $[\alpha]_D$ - 149°, $\nu_{max}^{CHCl_3}$ 1730 and 1705 cm^{-1}. The nuclear magnetic resonance spectrum shows the disappearance of the hydrogen atom on C_6, and the shift of H_B from τ6.5 in swietenine to τ4.97 in dehydroswietenine. This therefore represents oxidation of the α-hydroxy ester to an α-keto ester. Dehydroswietenine can be reduced back by either sodium borohydride or, in better yield, by zinc dust in refluxing acetic acid to swietenine, the second ketonic function remaining unaffected. This yields further proof that the hydroxyl group in swietenine is secondary and is also α to the methyl ester.

The alkaline hydrolysis of swietenine gives a complex mixture of acids (the derived methyl esters show nine spots on a chromatoplate) but by virtue of its insolubility in chloroform, the crystalline destigloyl-desmethyl-<u>iso</u>swietenine C_{26} H_{32} O_8 (B13) m.p. 246 - 248°, $[\alpha]_D$ - 67°, could be separated in 30% yield. This acid had a pK value of 4.85 which again suggests that one of the hydroxyl groups

is attached α to the carboxyl group. Methylation of this compound gave destigloyl-isoswietenine (B14) C_{27} H_{34} O_8, m.p. 243 - 246°, $[\alpha]_D$ - 67°, $\nu_{max}^{CHCl_3}$ 3604, 3530 and 1730 cm^{-1}. Tigloylation of destigloyl-isoswietenine (B14) with tigloyl chloride in pyridine yields isoswietenine (B15) C_{32} H_{40} O_9, m.p. 213 - 215°, $[\alpha]_D$ - 57°, isomeric with swietenine and containing the same functional groups. (Swietenine does not react with tigloyl chloride under the same conditions). This is demonstrated in the optical rotatory dispersion curves of swietenine and isoswietenine in methanol both of which show a negative Cotton effect, (Fig. V), isoswietenine having the smaller amplitude. In the infrared (nujol) spectrum, isoswietenine has bands at 3500 (hydroxyl), 3100, 1500, 879 (furan), 1705 (tiglate ester), 1725 (methyl ester, δ-lactone and cyclohexanone) cm^{-1}. In the nuclear magnetic resonance spectrum, the peaks are again very similar (Table I), the major points of difference being the chemical shift of the vinyl proton H_A at τ 3.88 (τ 4.63 in swietenine) and the methine proton H_M at τ 7.10 (τ 6.50 in swietenine). This can be accounted for by the postulate that in isoswietenine, the vinyl proton is deshielded and H_M is shielded by the carbonyl group of the tiglate ester.

Several situations can be visualised to account for the swietenine isoswietenine or more simply the destigloyl-swietenine destigloyl-isoswietenine change (see below - p 23)

i) Epimerisation α to the carbonyl an example (fig. I) of which is the transformation of the cis-decalone to the trans-decalone. This can be discounted since the oxidation of destigloyl-swietenine and destigloyl-isoswietenine yields the same triketone (see below) and

also the optical rotatory dispersion curves of destigloyl-isoswietenine and destigloyl-swietenine are similar only differing in their amplitude (fig. V). This latter argument also excludes ii) an intramolecular hydride transfer (fig. II) resulting in the transposition of the ketonic function and the hydroxyl group.

iii) Retroaldolisation and realdolisation of α,β-ketol system (fig. III) gives rise to the epimeric alcohol. This cannot involve the hydroxyl of the α-hydroxy acid since this would require the loss of a two carbon fragment (fig. IV).

It would seem, therefore, that the best situation to account for the swietenine→isoswietenine change is the retroaldolisation and realdolisation. An aldol condensation of the intermediate aldehydo-ketone to give a hydroxy-aldehyde can also be discounted since isoswietenine does not contain an aldehyde (n.m.r.)

Kupchan[7] tiglate cleavage using osmium tetroxide and periodic acid yields destigloyl-swietenine (B16) $C_{27}H_{34}O_8$ m.p. 200 - 204°, $[\alpha]_D$ - 62°. This is isomeric with destigloyl-isoswietenine and contains the same functional groups. The optical rotatory dispersion curves of destigloyl-swietenine and destigloyl-isoswietenine are shown in fig. V. The p-iodobenzoate of destigloyl-swietenine (B17) was submitted for X-ray[8] structural examination while the chemical work was in its final stages. Treatment of destigloyl-swietenine with base followed by methylation results in the formation of destigloyl-isoswietenine, identical with the destigloyl-isoswietenine obtained by the basic hydrolysis of swietenine followed by methylation.

Oxidation of destigloyl-swietenine and destigloyl-isoswietenine with the Jones reagent yields the same triketone (B18) $C_{27}H_{30}O_8$, m.p. 231 - 235°, $[\alpha]_D$ - 228°, $\nu_{max}^{CHCl_3}$ 1730, with a shoulder at 1742 cm^{-1}. This indicates that the hydroxyl group esterified with tiglic acid in swietenine is also secondary and, more important, that there is no skeletal rearrangement during the hydrolysis of swietenine.

The alkaline hydrolysis of dehydroswietenine (B12) gave in good yield dehydro-destigloyl-desmethyl-isoswietenine (B19) $C_{26}H_{30}O_8$, m.p. 264 - 267°, $[\alpha]_D$ - 61°, methylation of which gave dehydro-destigloyl-isoswietenine (B20), $C_{27}H_{32}O_8$, m.p. 242 - 246°, $[\alpha]_D$ - 74°, $\nu_{max}^{CHCl_3}$ 3612, 1730 cm^{-1} which on oxidation led to the same triketone (B18) as before.

Reduction of dehydro-destigloyl-desmethyl-isoswietenine by zinc dust in refluxing acetic acid for ten minutes yields destigloyl-desmethyl-isoswietenine (B13) (identical with the compound prepared in the basic hydrolysis of swietenine). Treatment for a longer period of time yields an acetate (B21) which failed to crystallise but which on the basis of its nuclear magnetic resonance spectrum (peaks at τ 7.92, 3H, singlet; τ 5.41, 1H, doublet, J = 1 c.p.s.; and τ 5.40, 1H, doublet, J = 1 c.p.s.) is considered to be the mono-acetate resulting from acetylation of the hydroxyl group not α to carbomethoxyl.

The above hydrolysis and oxidation-reduction reactions are summarised in flowsheet 1.

Further proof of the α-hydroxy-ester function in swietenine comes from the conversion of destigloyl-desmethyl-isoswietenine (B13) with

lead tetracetate into the hydroxy-keto-aldehyde (B22) C_{25} H_{30} O_6, m.p. 232 - 236°, $[\alpha]_D$ - 47° $\nu_{max}^{CCl_4}$ 3632, 1752, 1734, and 1721 cm^{-1}. The nuclear magnetic resonance spectrum shows a sharp doublet at τ 0.18 (1H, J = 6.5 c.p.s.). By spin decoupling, it was shown that this aldehydic proton couples with one proton at τ 7.25 which couples with no other. This suggests the system (B3). (It is also possible that there is a proton β to the aldehyde function but that the two protons have a dihedral angle of 90°).

When the hydroxy-keto-aldehyde (B22) is treated with acetic anhydride-pyridine, the acetoxy-keto-aldehyde (B23) C_{27} H_{32} O_7 m.p. 272 - 276°, $[\alpha]_D$ - 34°, $\nu_{max}^{CHCl_3}$ 1729 cm^{-1} is obtained. This compound was also formed together with the nor-aldehyde (B22) when destigloyl-desmethyl-isoswietenine was reacted with lead dioxide in refluxing acetic acid for three hours.

The hydroxy-keto-aldehyde (B22) also formed a toluene-p-sulphonate on reaction with toluene-p-sulphonyl chloride in pyridine but this resisted all attempts to eliminate the elements of toluene-p-sulphonic acid in refluxing collidine.

When the acetoxy-keto-aldehyde (B23) is treated with dry hydrochloric acid in methanol, a methyl ether, methyl ester (B25) C_{29} H_{38} O_8 m.p. 184 - 186°, ν_{max} (nujol), 1710, and 1730 cm^{-1} results. The compound had peaks in the nuclear magnetic resonance spectrum at τ 6.76 (3H, singlet, $-OCH_3$) and τ 6.26 (3H, singlet - CO_2 CH_3) and is considered to be formed by the mechanism indicated in fig. VI.

The relationship of the α-hydroxy-ester to the tiglate function in

swietenine could be established by exposure of the hydroxy-keto-aldehyde (B22) to methanolic sodium hydroxide when the isomeric γ-lactone (B26) $C_{25}H_{30}O_6$ m.p. 242 - 246°, $[\alpha]_D$ + 111°, $\nu_{max}^{CCl_4}$ 1782 (γ-lactone), 1745 (δ-lactone) and $\nu_{max}^{CHCl_3}$ 1770 (γ-lactone), 1732 (δ-lactone), 3620 (free hydroxyl), 3587 (bonded hydroxyl) cm^{-1} was obtained. A plausible way of accounting for the formation of this hydroxy-γ-lactone is by way of an intramolecular Cannizzaro reaction (Flowsheet 2). In this, the carboxyl group formed in the reaction cannot lactonise with the newly formed hydroxyl group since it is formed by a hydride transfer reaction and thus must be pointing in the "wrong" direction for lactonisation. Therefore, the carboxyl group must lactonise with the hydroxyl group already present in the hydroxy-keto-aldehyde (B22). This therefore means that the aldehyde function and the hydroxyl group present before hydride transfer are situated in an α - δ relationship with respect to one another (B4).

Also the alkali induced epimerisation at C_3 in the prepararation of <u>iso</u>swietenine from swietenine implies an α - γ relationship of the ketonic and tiglate ester functions in swietenine. Thus the part structure (B4) can be enlarged to (B5) which by spin-decoupling experiments, can be further extended to (B6) as follows:

The olefinic proton (A) at τ 4.63 in swietenine and dehydroswietenine and approximately τ 4.15 in all other derivatives (see Table I), is coupled to three other protons:

i) (M) which is at τ 6.50 in swietenine, τ 7.12 in destigloyl-<u>iso</u>swietenine and τ 6.22 when there is the β-diketone system (J_{MA} = 6 - 8.5 c.p.s.)
(M) in turn couples with one other proton (N) at τ 5.36 in swietenine

which can be assigned to the proton on the carbon atom which carries the tiglate ester (J_{MN} = 11 c.p.s.). This coupling disappears in the β-diketones and decreases in isoswietenine (J_{MN} = 1 c.p.s.).

ii) (X) and (Y) which are found at approximately τ 7.75 (allylic methine groups) (J_{MX} and J_{MY} = 1 - 2 c.p.s.). One of these protons (X) or (Y) in turn couples with a methylene group Z_2 at τ 7.1 (J_{XZ_2} or J_{YZ_2} = 3 - 5 c.p.s.) which from its position must be α to the carbonyl group of the ring D lactone.

In the γ-lactone (B26), which has a hydroxyl group instead of the ketone as explained above, the proton on this carbon atom, n, couples with M (J_{Mn} = 6 c.p.s.) and no others. This suggests that the carbon atom on the other side of n from M is fully substituted and we can thus join m and n. Further proof is given by the fact that in the triketone (B18), both cyclic ketones are cyclohexanones as judged by their infrared absorptions. Carbon atoms p and q are most probably identical since this then leaves two carbon atoms to form a cyclohexane ring C.

This leads to a bicyclo [3: 3: 1] system in swietenine (B7) which accounts for the non-conjugation of the isolated double bond in the triketone (B18) and also the non-enolisation of the β-diketones.

The stereochemistry of swietenine can be inferred from the biogenetic derivation of the compound (Flowsheet 3). The carbon skeleton of swietenine can be readily derived from a precursor of the type (B27) in which the C_7 - C_8 bond is cleaved which results in an exo-methylene group at C_8 and an α-hydroxy carboxylic acid at C_5. (The precise stage at which oxygenation occurs is uncertain). Rotation of ring A

about the 9 - 10 bond followed by Michael addition of the carbanion at C_Z to the exo-methylenic double bond at C_2 leads to the carbon skeleton of swietenine. This has the derived stereochemistry as shown in (B28) with an methyl group at C_{10}, an α-acetate side-chain at C_5, an α hydrogen atom at C_2 (it is impossible to close the bicyclo-system with a βH) and the normal orientations at C_9, C_{13}, and C_{17} (all α-orientated). Migrations of the double bond from the C_8 - C_{14} to the C_{30} - C_8 position gives the structure (B7) in which the only uncertainties (resolved by the X-ray analysis) are the stereochemistry of the tiglate at C_3 and the orientation of the hydroxyl group at C_6 (if we assume that the double bond in the C_8 - C_{14} position is protonated from the α-face).

These conclusions are fully supported by the results of the X-ray crystallographic analysis of the p-iodobenzoate (B17) of destigloyl-swietenine which also showed the tiglate to be β-orientated and the hydroxyl group at C_6 to be α.

With the constitution and stereochemistry of swietenine established, it now becomes possible to discuss its transformation products.

The γ-lactone derived from the aldehyde (B22) by reaction with alkali, was assigned the provisional structure (B26) in the arguments leading to the constitution of swietenine which have been presented above. However, certain properties of this γ-lactone were inconsistent with the proposed structure and a re-examination has led to the revised structure (B29). In particular, it could be shown by spin-decoupling that the methine proton H_B (τ 7.5) situated α to the carbonyl group of the γ-lactone was coupling with H_N (τ 5.35) and no other proton (J_{BN} = 7 c.p.s.).

The magnitude of this coupling constant is unprecedented for a ^4J coupling except under special circumstances[9].

An alternative structure for the γ-lactone (B29) which overcomes this difficulty can be derived in the following way. (Flowsheet 4). Cleavage of the C_2 - C_3 bond by a retroaldolisation (already invoked in the epimerisation of C_3 during the hydrolysis of swietenine, affords the intermediate dialdehyde (B30). Rotation about the C_5 - C_{10} bond brings C_6 and C_2 within interacting distance. However, there are serious interactions between the gem-dimethyl grouping attached to C_4 and the aldehyde with carbon atoms C_8 and C_9. Moreover, the resulting stereochemistry (if aldolisation did occur) would not permit subsequent Cannizzaro reaction. However, if the aldehydic function at C_5 epimerises before aldolisation, these interactions are relieved and the aldehyde and ketone are in appropriate positions for intramolecular hydride transfer. After lactonisation, this leads to structure (B29) for the γ-lactone with a cis-fused lactone and a bicyclo [3: 2: 1] octenol. The non-bonded interaction between the β-methyl group attached to C_2 and the methyl group at C_{10} can be relieved by lateral twist. H_C and H_B are vicinally coupled and the observed coupling constant (J_{BC} = 7 c.p.s.) is in accordance with the dihedral angle, θ_{BC} (30°).[10]

The γ-lactone (B29) readily forms an acetate (B31) $C_{27}H_{32}O_7$, m.p. 274 - 278°. ν_{max} (nujol) 1765, 1730 cm^{-1}. The nuclear resonance spectrum shows that the proton H_C couples with H_B (J_{BC} = 7 c.p.s.) but is not further coupled to H_M. This agrees with structure (B29) in which the dihedral angle between H_C and H_M is approximately 90°. It shows

the proton H_F (τ 5.04) of the secondary acetate to be coupled with H_M (J_{FM} = 5 c.p.s.) which is in accordance with the dihedral angle $\theta_{FM} = 40^\circ$. The stereochemistry of the hydroxyl group is shown below. (It is impossible to tell the stereochemistry from the dihedral angle since the other angle $\theta_{FM} = 50^\circ$).

Further support for the structure (B29) of the γ-lactone comes from the dehydro-γ-lactone (B32) $C_{25}H_{28}O_6$, m.p. 247 - 251° $[\alpha]_D$ + 190°, $\nu_{max}^{CHCl_3}$ 1781 (γ-lactone), 1762, 1735 (δ-lactone) cm^{-1} obtained by the chromic acid oxidation of the γ-lactone (B29). The new carbonyl band in the infrared spectrum of this compound at 1762 cm^{-1} is typical of a bridgehead carbonyl group in a bicyclo [3: 2: 1] octenone.[11]

Reduction of the dehydro-γ-lactone with sodium borohydride gave a mixture of two epimeric alcohols (B33), the γ-lactone (B29) being reformed as the major epimer (yield greater than 90%). In the infrared, the γ-lactone shows peaks at 3620 (free hydroxyl) and 3587 (bonded hydroxyl) cm^{-1} (in chloroform). The peak at 3587 cm^{-1} can be assigned to the hydroxyl group weakly bonded with the olefinic double bond. Thus it can be inferred that the hydroxyl group is directed towards the olefinic linkage. A similar effect is observed with the similarly constituted alcohol (B44) (see below).

The 1-epi-γ-lactone, which was obtained in very low yield and could not be obtained crystalline although homogeneous by thin-layer chromatoplate, showed peaks in the infrared (carbon tetrachloride) at 1757 (unsymmetrical broad band), 3620 with a very broad band below 3600 cm^{-1}. The low position of the carbonyl band and the hydrogen bonded hydroxyl can be attributed

to a weak hydrogen bond of the secondary hydroxyl group to the γ-lactone towards which the hydroxyl group is directed. Lack of time and material precluded the full characterisation of this compound.

Reaction of the dehydro-γ-lactone (B32) with aqueous sodium hydroxide in refluxing methanol, resulted in the formation of neutral and acidic materials. The neutral fraction was found to be unchanged dehydro-γ-lactone and the acidic material was methylated to give the hydroxy-methyl ester (B34) C_{26} H_{32} O_7, m.p. 209 - 212°, $[\alpha]_D$ + 120°, $\nu_{max}^{CHCl_3}$ 3614, 1750, 1731 cm^{-1}. The hydroxy-methyl ester has peaks in the nuclear magnetic resonance spectrum at τ4.44 (1H, H_A, vinyl proton, doublet) which was coupled with a proton at τ6.93 (1H, H_M, doublet, J_{AM} = 8 c.p.s.). The proton H_C was a quartet centred at τ5.50 which was coupled with H_B (1H, doublet, J_{BC} = 5 c.p.s.) at τ7.39 and also with H_M (J_{CM} = 8 c.p.s.). The above coupling constants are in agreement with the dihedral angles $\theta_{AM} = 10°$, $\theta_{MC} = 20°$, $\theta_{CB} = 120°$.

The formation of the hydroxy-methyl ester (B34) can be rationalised by base catalysed cleavage of the γ-lactone and epimerisation of the resulting hydroxyl group by a retro- and re-aldolisation previously discussed. This results in the hydroxy-acid (B35) which cannot lactonise. The proportions of γ-lactone to hydroxy-methyl ester (1: 2) presumably represents the equilibrium proportions of hydroxy-acid anions.

When the hydroxy-keto-aldehyde (B22) is oxidised with either the Sarret or Jones reagent, a diketo-aldehyde (B36), C_{25} H_{28} O_6, m.p. 213 - 217°, $[\alpha]_D$ - 186°, $\nu_{max}^{CCl_4}$ 1751, 1722 cm^{-1} is obtained. This compound had peaks in the nuclear magnetic resonance spectrum at

τ0.13 (aldehydic proton, doublet, J = 6 c.p.s.) which was coupled to the proton H_B at τ 7.00. All attempts to oxidise the aldehydic function failed.

Treatment of the diketo-aldehyde (B36) with aqueous base resulted in the formation of a hydroxy-acid. Methylation of this compound gave the enone-methyl ester (B37) C_{26} H_{32} O_7, m.p. 285 - 287°, $[\alpha]_D$ + 25°, $\nu_{max}^{CHCl_3}$ 1737 (methyl ester and δ-lactone), 1687 (conjugated enone), 3620 (free hydroxyl), 3583 (bonded hydroxyl) cm^{-1}.

We envisage the formation of this compound in the following manner (Flowsheet 5): β-diketone cleavage yields the keto-carboxylate anion (B38) whose isolated olefinic linkage then isomerises to form the conjugated enone (B39). The C_8 carbanion can then undergo a vinylogous aldol condensation with the aldehyde which on acidification yields the hydroxy-enone-acid (B40). There are minor interactions between the gem-dimethyls and the carbonyl group with the α-methyl at C_{10} and the hydrogen atoms at C_{11} but whether they are so severe as to cause the aldehyde to epimerise before the aldol condensation, is difficult to ascertain. The structure of the enone-methyl ester derived from the epimerised aldehyde is free from the above interactions.

The nuclear magnetic resonance spectrum provides further support for this structure (B37). There are two doublets centred at τ3.05 and τ3.98 (J = 9 c.p.s.) which are assigned to the β - and α-vinylic protons respectively of the α,β-unsaturated ketone. That the β-proton is not further split supports the proposal that C_8 is tetrasubstituted and therefore the new bond formed in the aldol condensation must

terminate at this carbon atom. There is also a multiplet at τ5.1 which simplifies to a doublet ($J \doteq 7$ c.p.s.) when the solution is equilibrated with deuterium oxide. This shows that this is the proton, H_C, of the secondary alcohol. This proton is coupled with the methine proton H_B centred at τ 7.7. That the proton H_C is not further split suggests that the carbon atom α to the alcohol is also quaternary which agrees with structure (B37). The position of the proton H_C (τ5.1) is very low and must presumably be deshielded by the lactonic carbonyl.

The configuration of the hydroxyl group cannot be deduced from the coupling constant of H_C and H_B since the dihedral angles are 0° and 135° which give approximately the same coupling constant (8 c.p.s.). The hydroxyl group is probably endo to the double bond since in the infrared there is weakly bonded hydroxyl which cannot be to either the methyl ester or δ-lactone both of which are at their normal unbonded positions at 1733 cm^{-1}. It seems probable that the hydrogen bond is to the olefinic linkage since this also provides the necessary geometry for the deshielding of the proton H_C at τ5.1 by the lactonic carbonyl. If the hydroxyl group is endo, the proton H_C is in the plane of the lactonic carbonyl if the assumption is made that the δ-lactone is in the twist-boat conformation where carbon atoms C_{17}, C_{16} and the oxygen are coplanar. This conformation was found in swietenine by the X-ray analysis. A Dreiding model of this compound shows the hydroxyl to be severely hindered, and this is reflected in its failure either to acetylate or oxidise.

Another interesting sequence of reactions concerns the treatment of the triketone ester (B18) with base. This results in the formation of an acid whose methyl ester (B41) $C_{27}H_{30}O_8$ m.p. 297 - 299°, $[\alpha]_D$ + 43°, is isomeric with the starting material. The methyl ester has absorptions in its chloroform solution spectrum at 1787 (γ-lactone), 1764 (bicyclo [3: 2: 1] octenone and α-acyloxy-ester) and 1735 (δ-lactone) cm^{-1}. These peaks are very similar in position to the bands in the dehydro-γ-lactone (B32), the only difference being the higher intensity of the 1764 cm^{-1} peak. This is assigned, as before, to the bridge-head carbonyl group of the bicyclo [3: 2: 1] octenone and the enhanced intensity is due to the additional α-acyloxy-ester[12]. In the nuclear magnetic resonance spectrum, the clean doublet H_M τ6.88 (J_{AM} = 8 c.p.s.) couples only with the olefinic proton H_A τ4.41 which in turn has a small coupling with H_X and H_Y (J_{AX} and J_{AY} = 1 - 2 c.p.s.). The triketone ester (B18) has a negative Cotton curve (322.5 mμ) - 12,200, (270 mμ) + 4,860 (see fig. V) whereas the isotrione (B41) has a positive Cotton curve (310 mμ) + 18,450, (270 mμ) - 17,650, both in chloroform.

The above evidence strongly indicates that the isotrione has the structure (B41) and this can be rationalised as follows (flowsheet 6): β diketone cleavage as in the diketo-aldehyde (B36) first gives the diketo-carboxylate anion (B42). Intramolecular aldol condensation, as shown in the diagram, then leads to the bicyclo [3: 2: 1] octenone structure which on acidification and methylation yields the isotrione in which the carbomethoxyl group is α. The severe interactions between the gem-dimethyls and the hydrogens of C_{11} can be reduced by lateral twist.

An alternative structure (B42a) for the isotrione can be derived by the same scheme as above if the α-keto acid is epimerised before the aldol condensation takes place. This also contains a cis-fused γ-lactone and the carbomethoxyl is in the β orientation. In this structure, the interactions are not so severe but the structures of the reduction products, discussed below, of the isotrione suggest that the alternative structure (B42a) is incorrect.

When the isotrione is treated with an excess of sodium borohydride, two isomeric alcohols $C_{27}H_{32}O_8$ (B43) and (B44) result. The less polar and crystalline alcohol A (B43), m.p. 316 - 321°, $[\alpha]_D$ - 72°, shows bands in the infrared (chloroform solution) at 3618 (small peak corresponding to unbonded hydroxyl), 3465 (strong peak, very broad, corresponding to bonded hydroxyl) 1783 (γ-lactone) and 1720 (δ-lactone and bonded methyl ester) cm^{-1}. The fact that the hydroxyl is bonded to the methyl ester strongly suggests that structure (B41) is correct since in the alternative structure (B42a) it is impossible for the bridge-head hydroxyl group to bond to the methyl ester.

Alcohol B, which failed all attempts at crystallisation although it was homogeneous as judged by thin-layer chromatography and gave a crystalline acetate, shows bands in the infrared at 3620 (free hydroxyl) and 3575 (bonded hydroxyl) cm^{-1}. The bonding in this case is very similar to that formed in the γ-lactone (B29) (see page 30) and can be attributed to a weak hydrogen bond to the isolated olefinic linkage towards which the hydroxyl group is oriented. In the carbonyl region, there is absorption at 1783 (γ-lactone), a shoulder at 1756 (α acyloxy-

ester) and 1732 (δ-lactone) cm^{-1} (chloroform solution).

Alcohol A formed, with difficulty, an acetate (B45), $C_{29}H_{34}O_9$, m.p. 141 - 144°, $[\alpha]_D$ - 82°, $\nu_{max}^{CHCl_3}$ 1783 and 1739 cm^{-1}. The nuclear magnetic resonance spectrum of acetate A shows peaks at τ4.32 (1H, H_A, olefinic proton, doublet, J = 8 c.p.s.) which was coupled with H_M τ6.93 (J_{MA} = 8 c.p.s.), not itself otherwise coupled. The proton H_F of the carbon which carries the secondary acetate is at τ5.21 (1H, singlet). This agrees very well with the structure (B43) for alcohol A, which has a bonded methyl ester in which the dihedral angles θ_{MA} is 10° and θ_{MF} is 90°.

Alcohol B readily formed a crystalline acetate (B46) $C_{29}H_{34}O_9$, m.p. 236 - 239°, $[\alpha]_D$ - 13°, $\nu_{max}^{CHCl_3}$ 1783 (γ-lactone), 1739 (δ-lactone, acetate and methyl ester) cm^{-1}. The nuclear magnetic resonance spectrum of acetate B shows the proton H_F of the carbon which carries the secondary acetate to be a doublet centred at τ5.03 (1H, J_{FM} = 5 c.p.s.) which couples with H_M at τ6.8 (1H, quartet) which in turn is coupled with the olefinic proton H_A τ4.64 (1H, doublet, J_{MA} = 8 c.p.s.). This agrees with the structure of alcohol B in which the hydroxyl group is bonding to the double bond and the dihedral angles θ_{MA} is 10° θ_{MF} is 40°.

Both the acetates A and B could be hydrolysed back to the respective alcohols without methyl ester hydrolysis indicating that the methyl ester is hindered. The alcohols in turn could be oxidised back to the isotrione (B41) proving that there is no skeletal rearrangement in either the reduction or acetylation reactions.

Reduction of the triketone ester (B18) with zinc dust in refluxing

acetic acid leads to the dihydrotriketone (B47) C_{27} H_{32} O_8, m.p. 221 - 223°, $[\alpha]_D$ - 254°, $\nu_{max}^{CHCl_3}$ 3611 (free hydroxyl), 3538 (bonded hydroxyl), 1739 (methyl ester and δ-lactone) 1716 (cyclohexanones) cm^{-1}. The dihydrotriketone could be reconverted by the Jones reagent to the triketone (B18). The nuclear magnetic resonance spectrum shows that it is the ketone function α - to the methyl ester which has been reduced: H_B moves from τ5.32 (sharp singlet) in the triketone to τ6.80 (J = 1 c.p.s.) in the dihydro compound. Also present in the dihydrotriketone is the proton H_C on the carbon atom bearing the secondary alcohol group at τ5.32 (J = 1.c.p.s.). The above reaction is analagous to the reduction of dehydroswietenine with zinc dust in refluxing acetic acid to swietenine.

Reaction of the dihydrotriketone (B47) with base yields an acid whose methyl ester (B48), C_{27} H_{32} O_8, m.p. 257 - 263°, $[\alpha]_D$ + 113° has absorption in the infrared at 1783 (γ-lactone) 1738 (methyl ester and δ-lactone) and 1717 (cyclohexanone) cm^{-1} in chloroform solution. There are no bands above 3,000 cm^{-1} showing the absence of hydroxyl groups. The dihydrotriketone has a negative Cotton curve (320 mμ) - 26,200; (270 mμ) + 25,400 whereas the isodihydrotrione has a positive Cotton curve (330 mμ) + 5,200; (275 mμ) + 300. The disappearance of the hydroxyl and the presence of the 1783 cm^{-1} band can best be explained by a β-diketone cleavage to give the keto-acid which lactonises with the hydroxyl group to give the γ-lactone. Hydroxide attack on the carbonyl at C_3 leads to structure (B48) whereas attack on the bridge-head carbonyl yields the alternative

structure (B49). However, the high frequency ascribed to the carbonyl function in the infrared spectrum suggests that the cyclo-octenone structure (B49) is less likely.

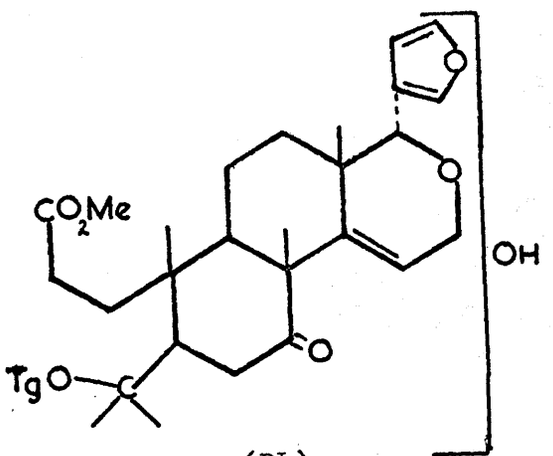
The nuclear magnetic resonance spectrum shows an olefinic proton H_A at τ4.61 and a singlet at τ 5.1 which would be assigned to the proton H_C, the proton α - to the carbomethoxyl but if the structure is correct, it should be further downfield at approximately τ4.1.[13] Also present are multiplets between τ6.3 and τ8.0 which from integration correspond to eight protons. However, the spectrum is so complex that more secure assignments will have to await the use of nuclear magnetic resonance spectroscopy at 100 Mc/s and double irradiation. The structure (B48) is also open to the objection that an α -acyloxy-ester should have infrared absorption at 1760 cm^{-1} instead of the observed ester carbonyl band at 1738 cm^{-1}.

When dehydroswietenine (B12) is treated with alkali under the same conditions as in the preparation of the isotrione (B41), desmethyl dehydroswietenine (B50), m.p. 272 - 276° was obtained. This suggests that more strongly basic conditions are required to remove the tiglate ester function and, more important, that no cleavage takes place until this function is hydrolysed.

It is of some interest to consider the cleavage reaction of the bicyclononenone system of swietenine discussed in the preceding pages. In all the cases studied, this comes about through fission of the C_2 - C_3 bond either by β -dicarbonyl cleavage or dealdolisation, depending on whether a ketonic or hydroxylic group is present at C_3.

There is no evidence of β-dicarbonyl fission occurring through hydroxide ion attack at the bridge-head carbonyl group. The factors which determine the subsequent fate of the initial cleavage product are not always easily discerned on the available evidence. For instance, it is a matter of very considerable interest why in the arrangements of the tricarbonyl compounds (B18) and (B36) the reaction apparently takes an entirely different course.

However, the answer to these questions must await the results of further chemical work on these transformation products, and also the verification of their structures by X-ray crystallography which is being undertaken with a number of selected derivatives.



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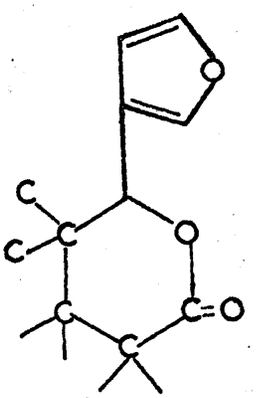

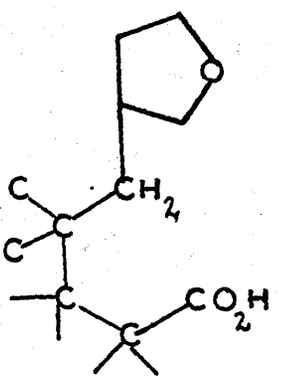

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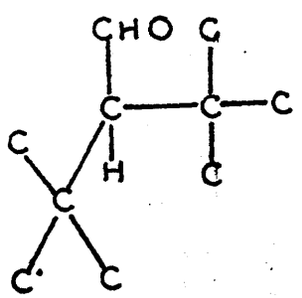

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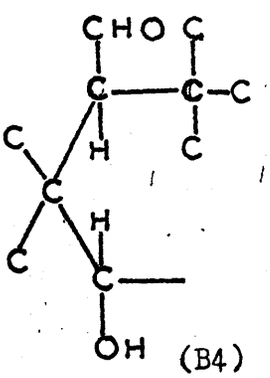

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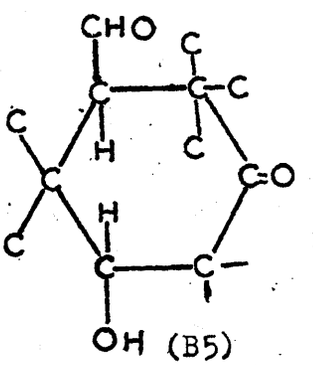

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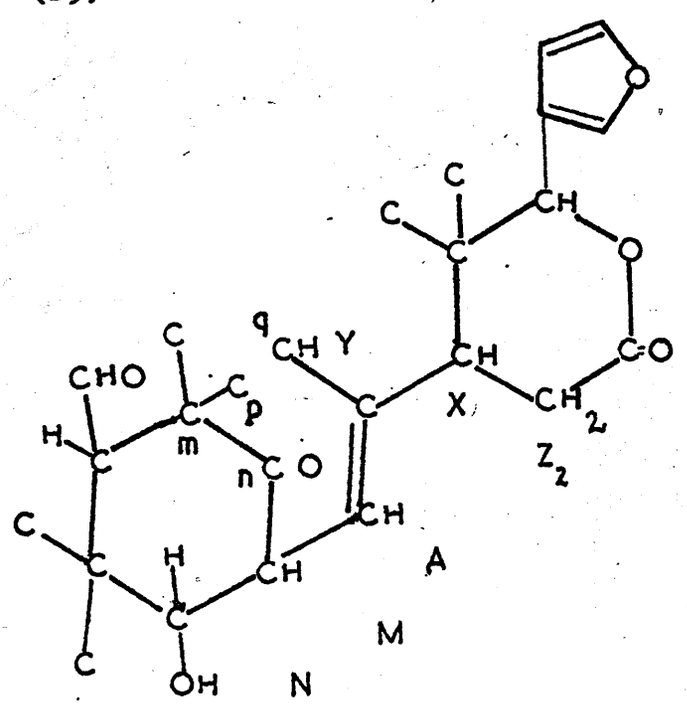

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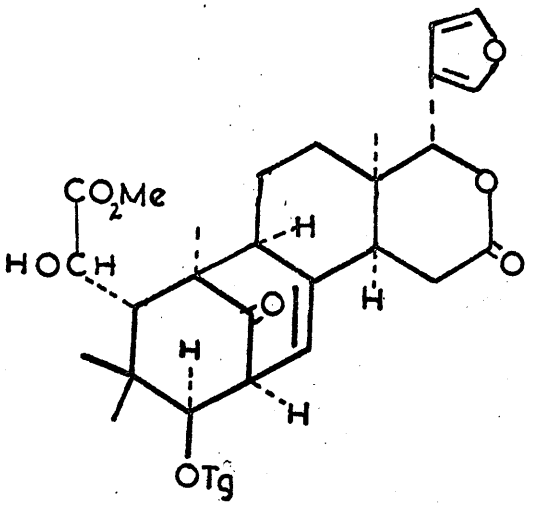

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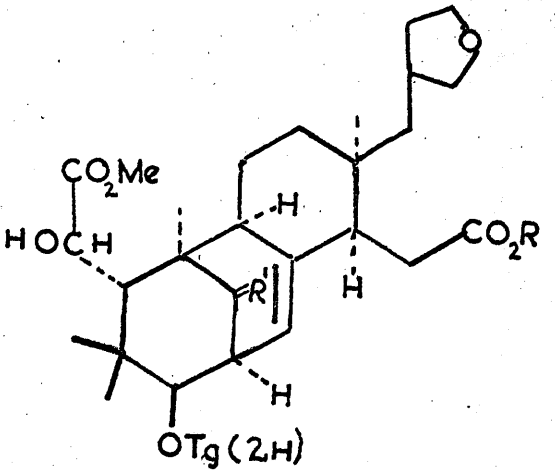
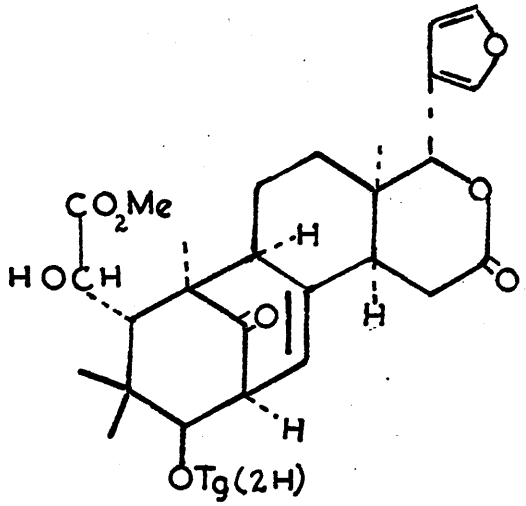


(B 8) R = H; R^1 = O.
(B 9) R = CH_3; R^1 = O.
(B 10) R = H; R^1 = NOH.



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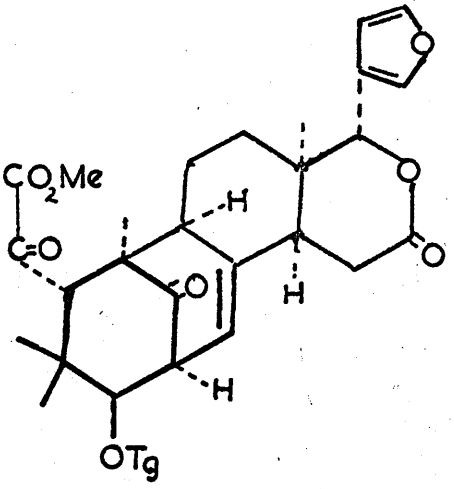

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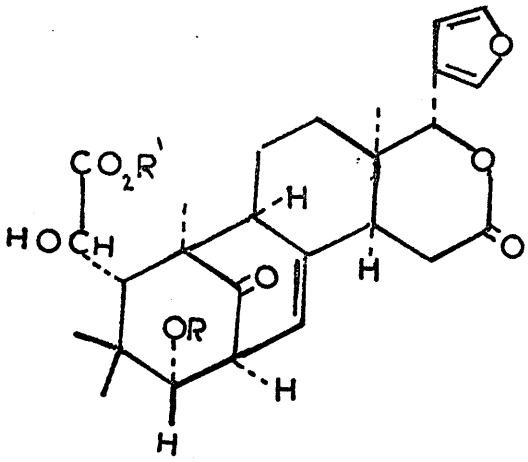
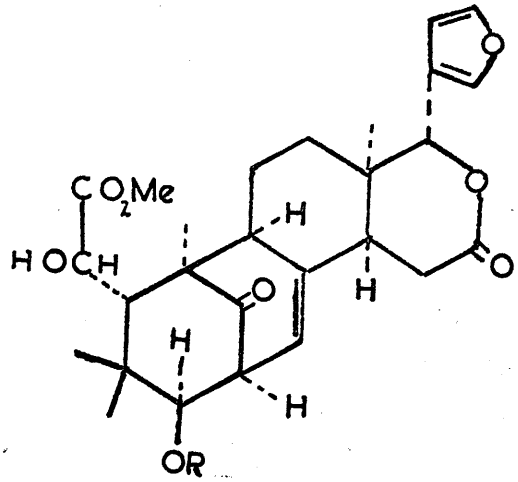
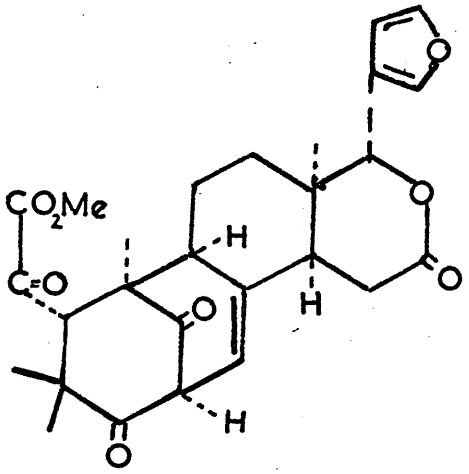


(B 13) R^1 = H; R = H.
(B 14) R^1 = Me; R = H.
(B 15) R^1 = Me; R = Tg.



(B 16) R = H.
(B 17) R = p - COC_6H_4I



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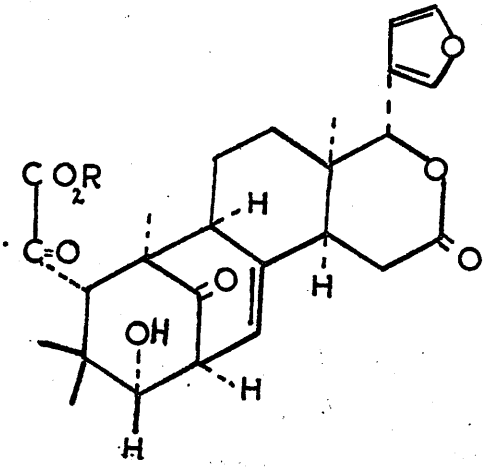
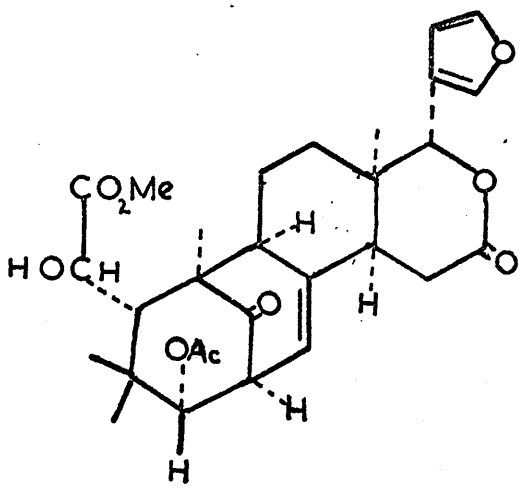


(B 19) R = H.
(B 20) R = Me.



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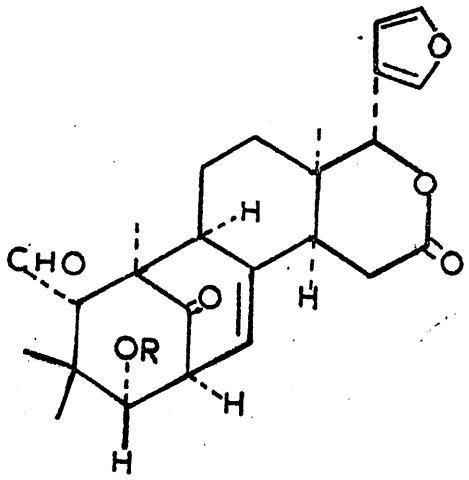
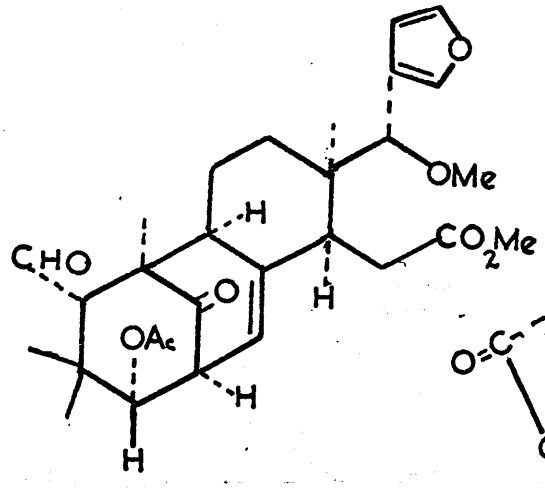


(B 22) R = H.
(B 23) R = Ac.
(B 24) R = Ts.



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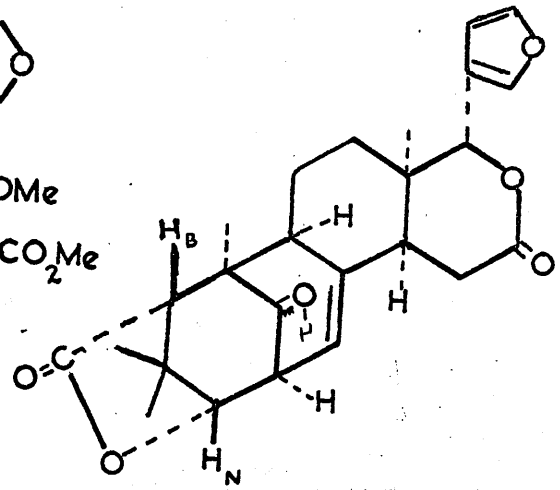

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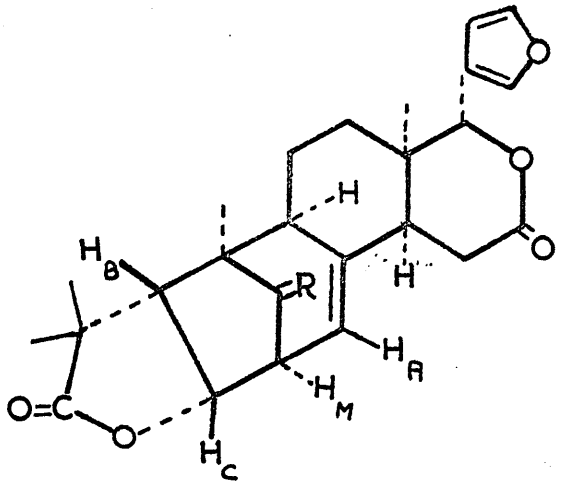
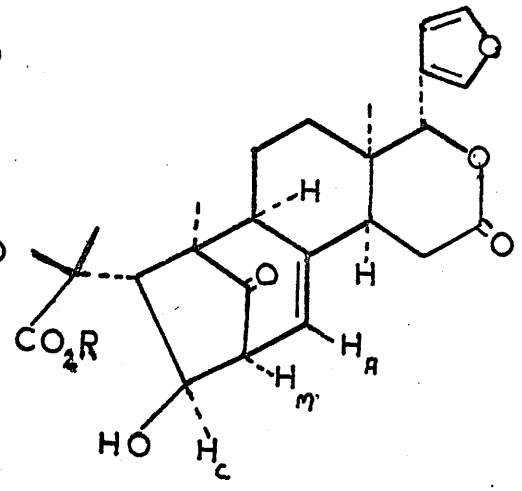
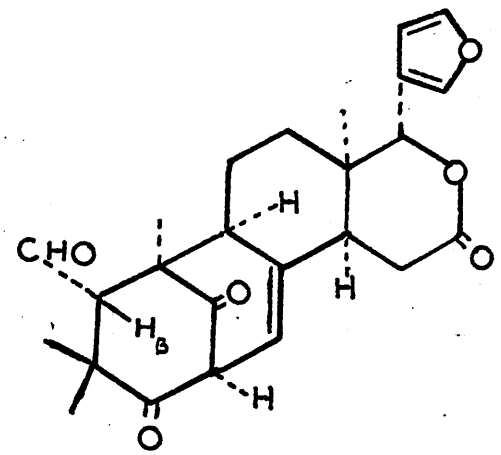


(B 29) R = H, OH.
(B 31) R = H, OAc.
(B 32) R = O.
(B 33) R = OH, H.



(B 34) R = Me.
(B 35) R = H.



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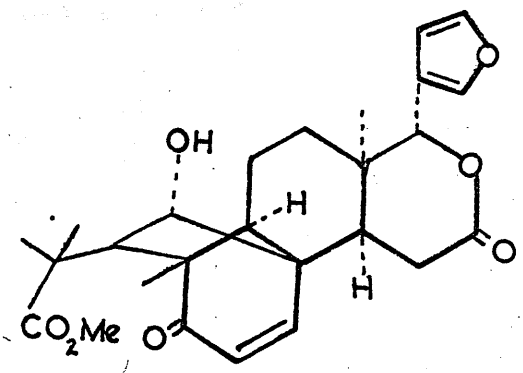

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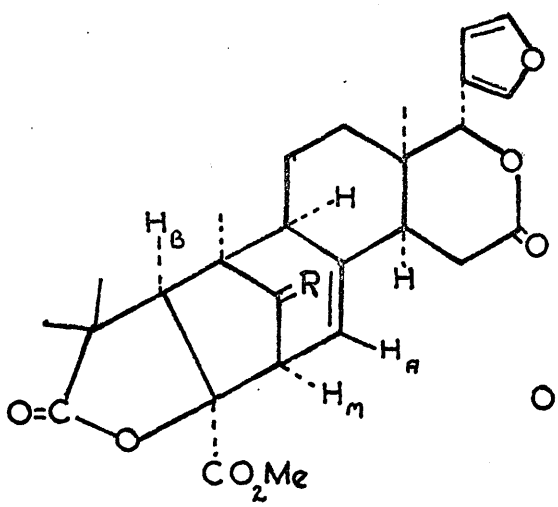
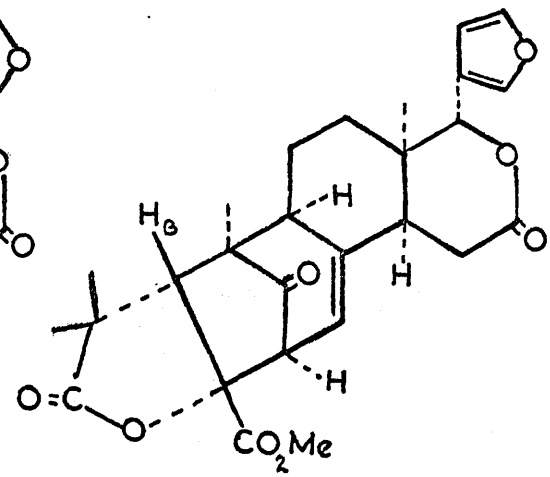


(B 41) R = O.
(B 43) R = H, OH
(B 44) R = OH, H.
(B 45) R = H, OAc.
(B 46) R = OAc, H.



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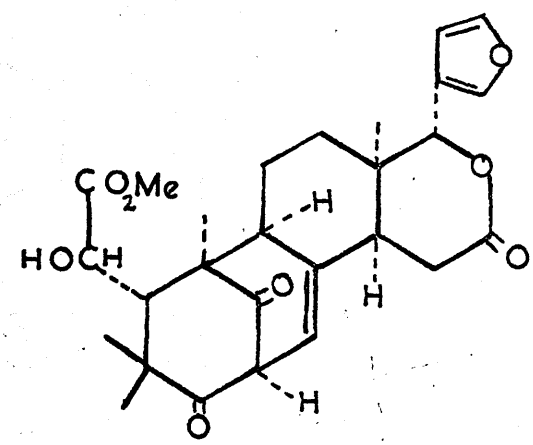

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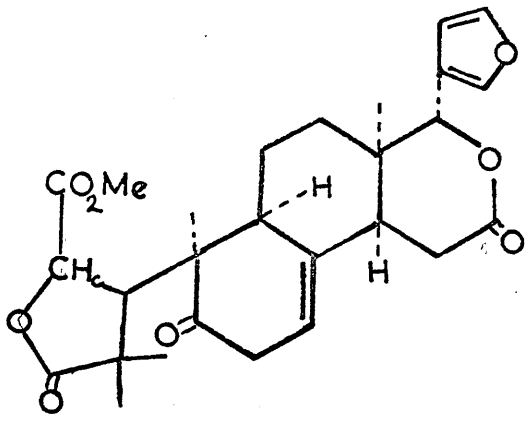

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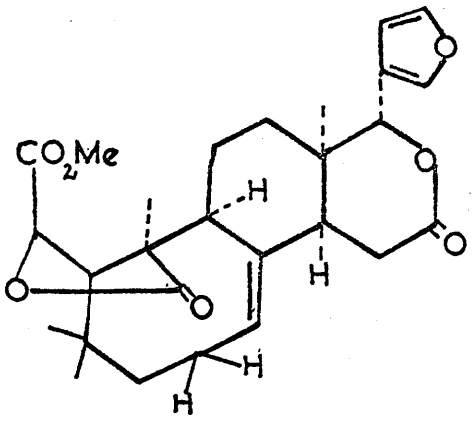

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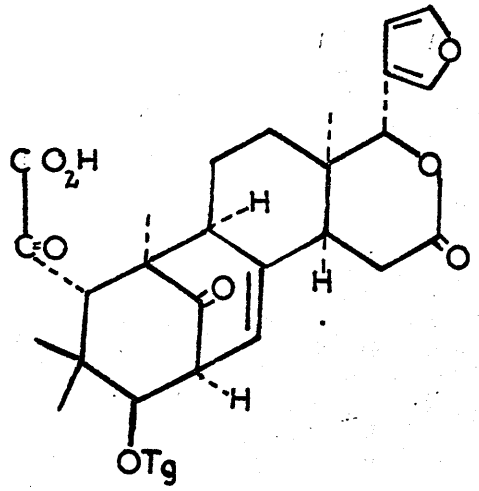
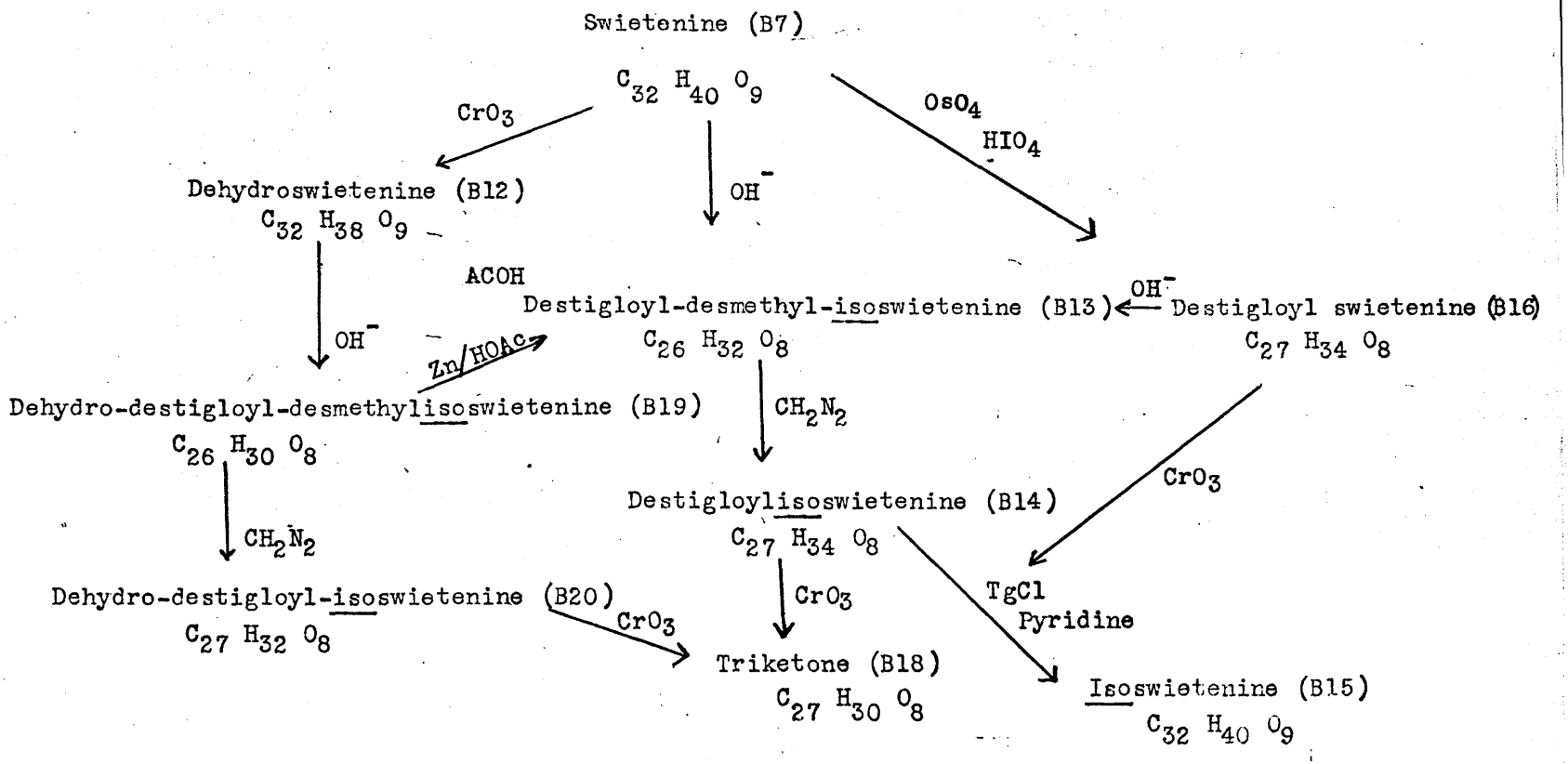
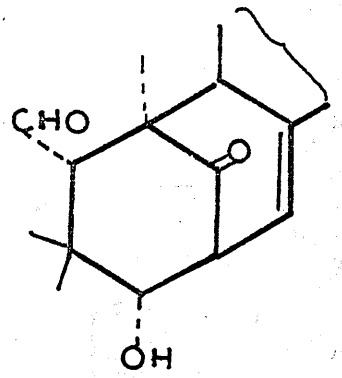


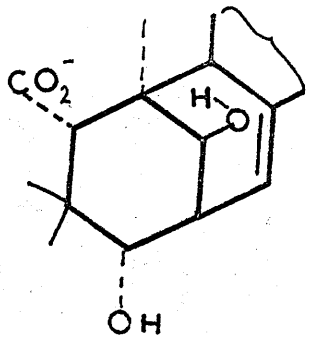
(B 50)

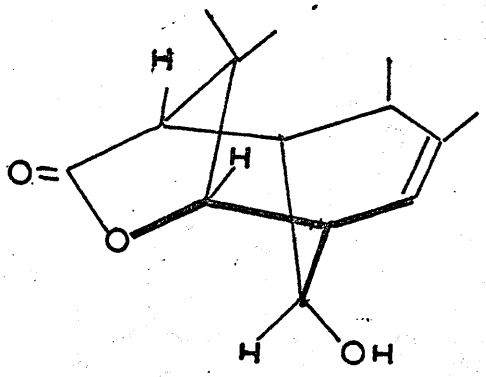
Flowsheet 1

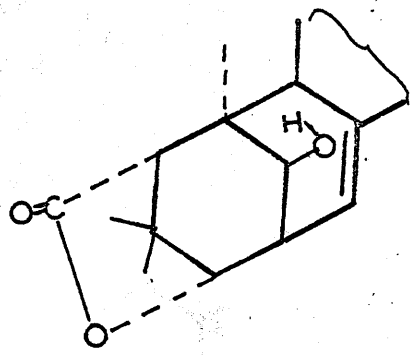

Swietenine (B7)
$C_{32}H_{40}O_9$
CrO_3
OH^-
OsO_4
HIO_4
Dehydroswietenine (B12)
$C_{32}H_{38}O_9$
ACOH
Destigloyl-desmethyl-isoswietenine (B13)
$C_{26}H_{32}O_8$
OH^-
Destigloyl swietenine (B16)
$C_{27}H_{34}O_8$
OH^-
Zn/HOAc
Dehydro-destigloyl-desmethylisoswietenine (B19)
$C_{26}H_{30}O_8$
CH_2N_2
Destigloylisoswietenine (B14)
$C_{27}H_{34}O_8$
CrO_3
CH_2N_2
Dehydro-destigloyl-isoswietenine (B20)
$C_{27}H_{32}O_8$
CrO_3
CrO_3
TgCl
Pyridine
Triketone (B18)
$C_{27}H_{30}O_8$
Isoswietenine (B15)
$C_{32}H_{40}O_9$

Flowsheet 2

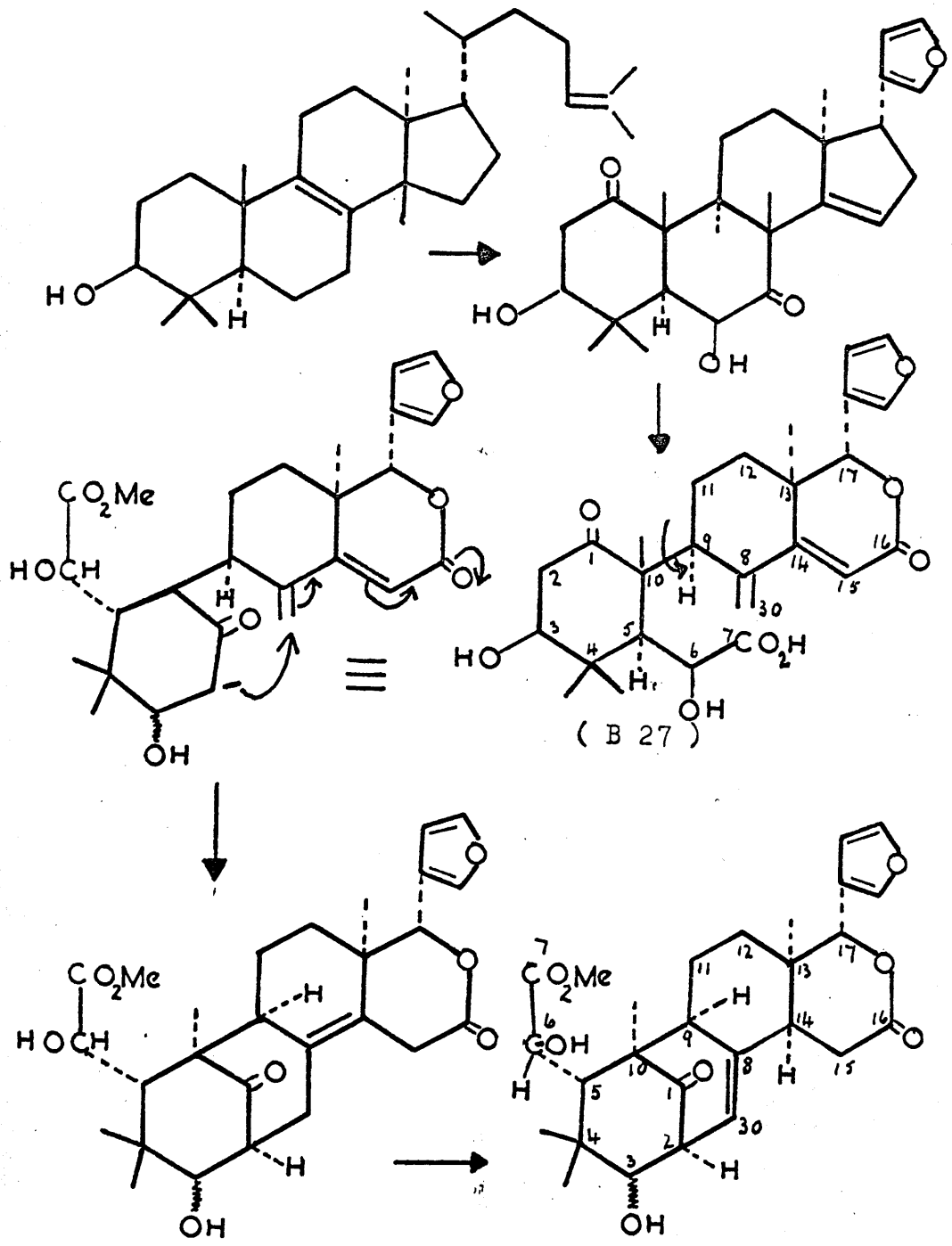








Flowsheet 3
Biogenesis of Swietenine.

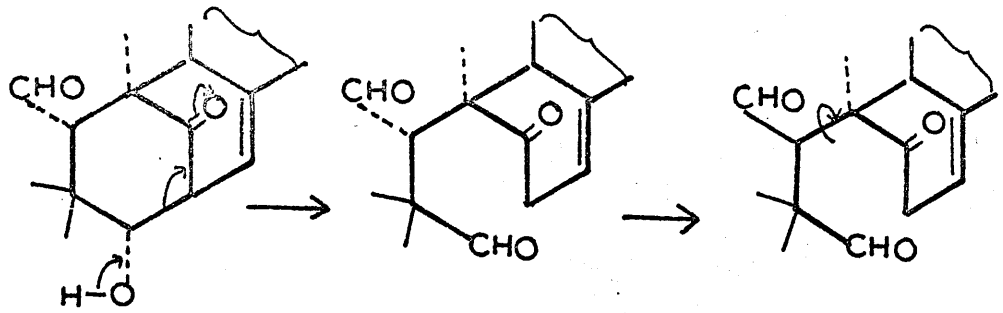


(B 28)

(B 7)

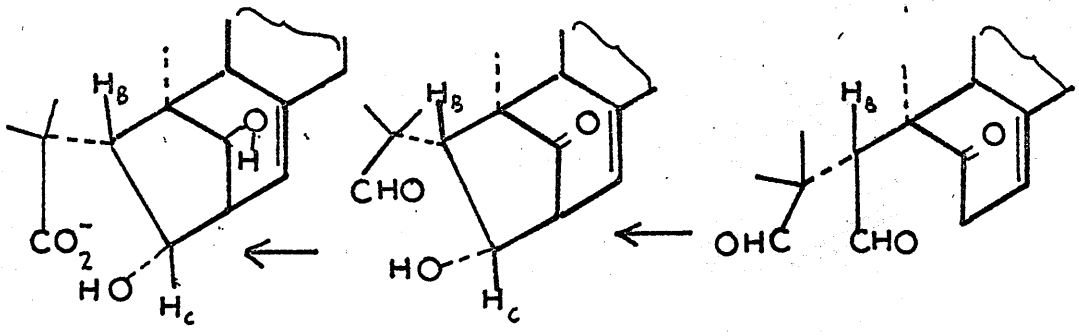
Flowsheet 4

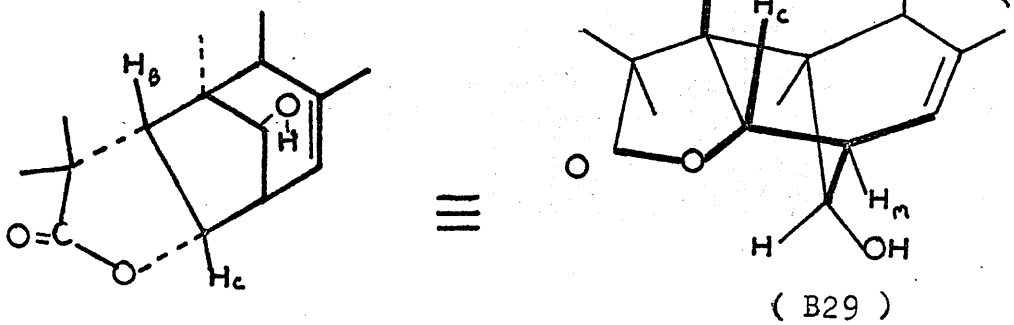
Preparation of the γ-Lactone (B29)



(B22) (B30)

|||

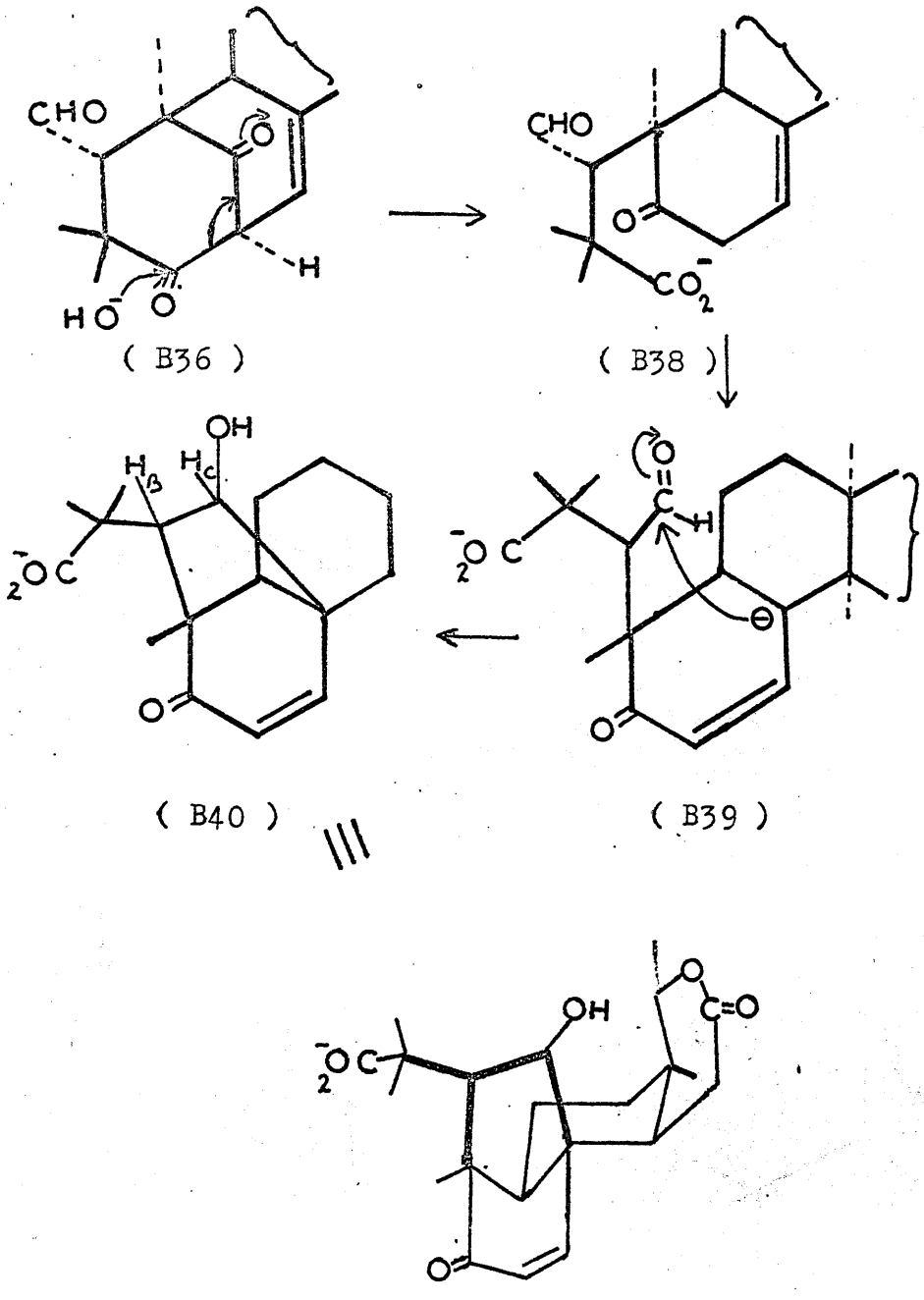




(B29)

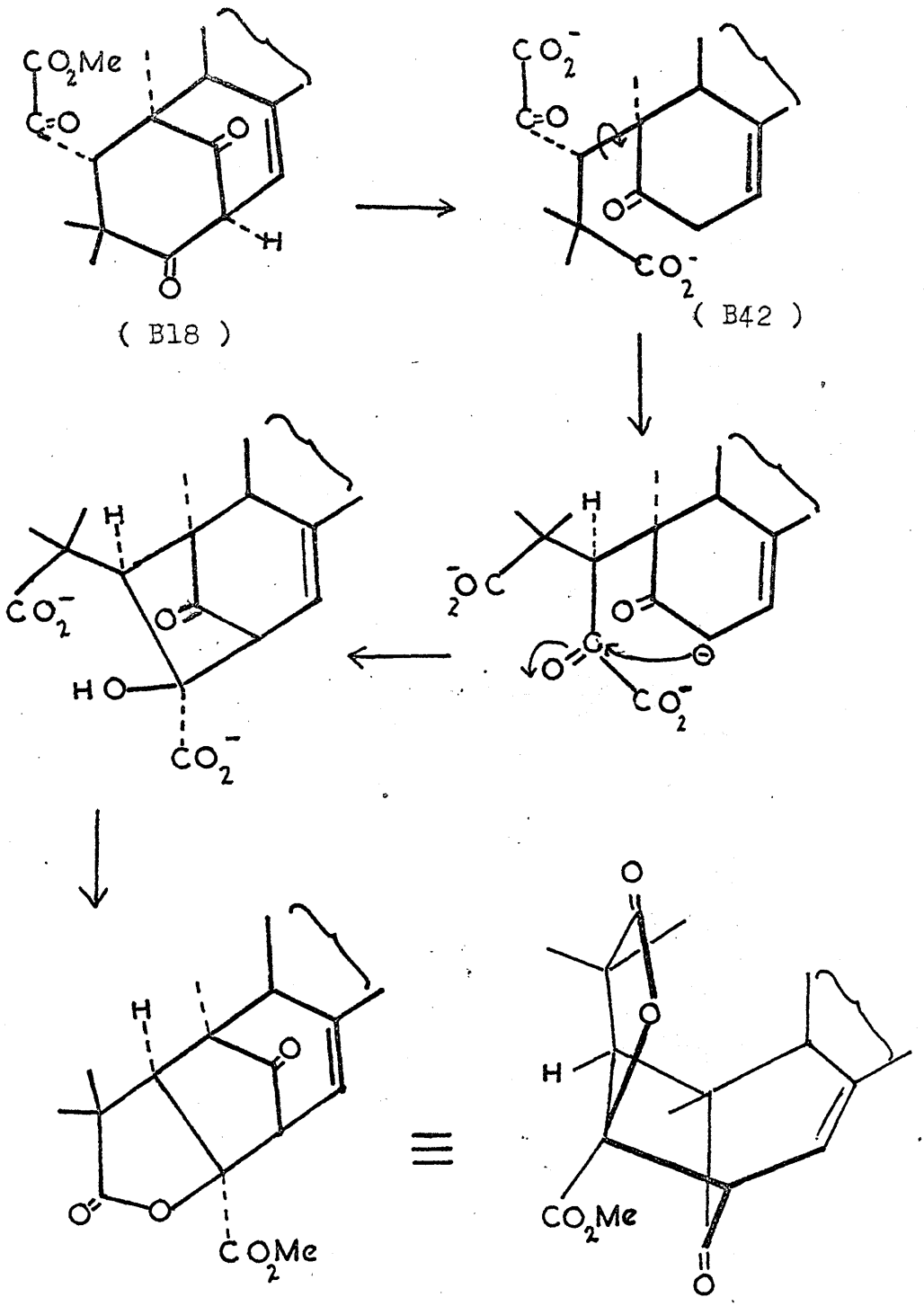
Flowsheet 5

Preparation of the Enone Methyl Ester (B37)



Flowsheet 6

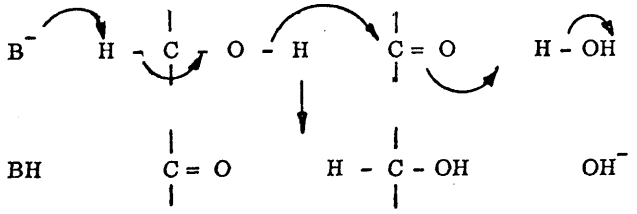
Preparation of the Isotrione (B41)



(B41)

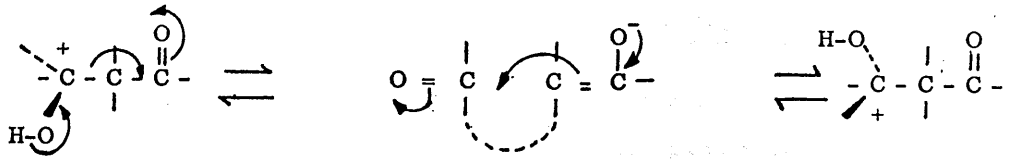
Fig. I Epimerisation α to C = O

II Intramolecular H^- Transfer



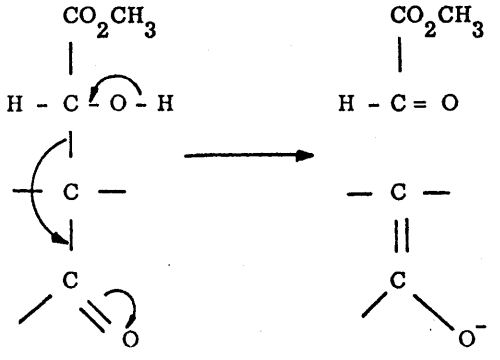
Interchange of -OH and CO

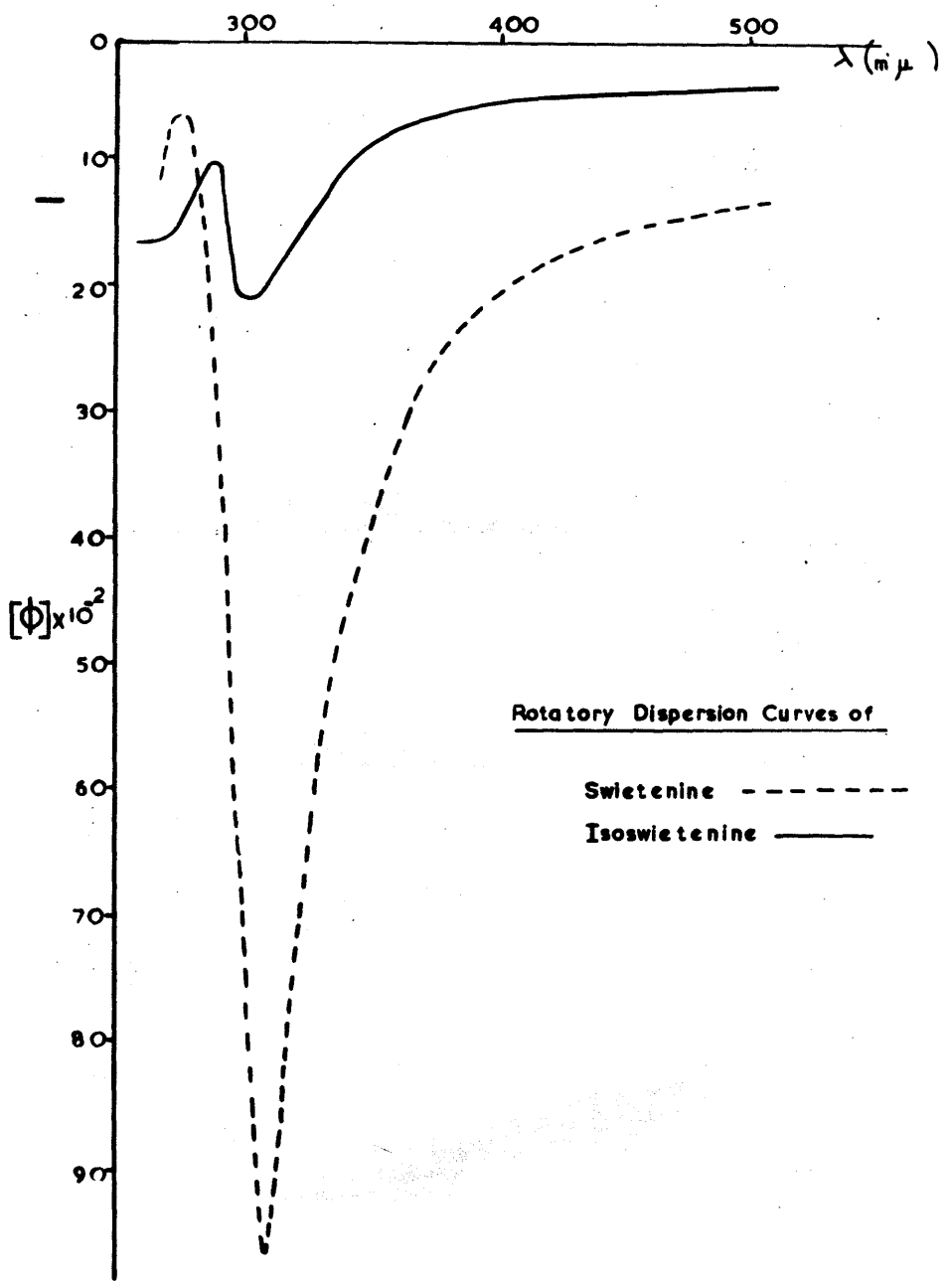
III Retroaldolisation and Realdolisation



Epimerisation at C_+

Fig. IV





Rotatory Dispersion Curves of

Swietenine - - - - - - -

Isoswietenine ———

Fig. V.

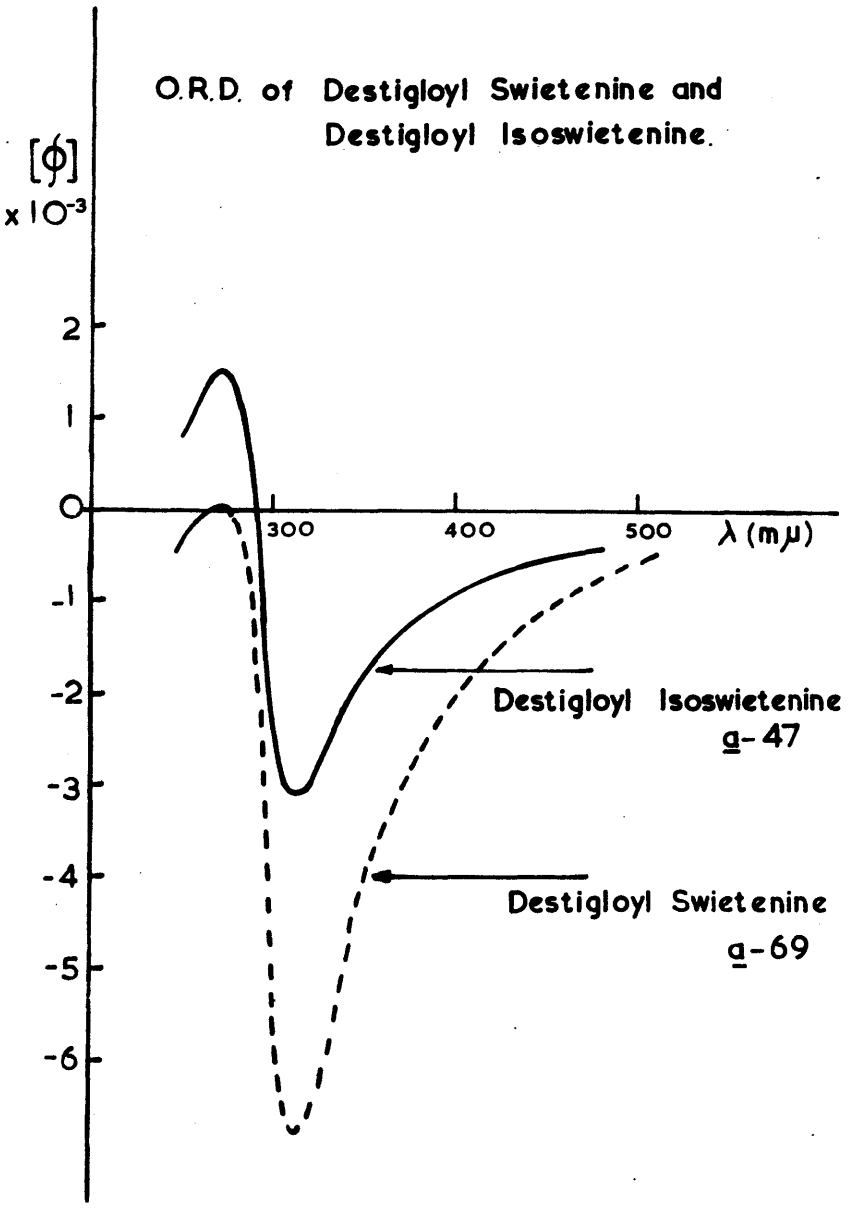

O.R.D. of Destigloyl Swietenine and
Destigloyl Isoswietenine.
[ϕ]
x 10⁻³
2
1
0
-1
-2
-3
-4
-5
-6
300
400
500
λ (mμ)
Destigloyl Isoswietenine
a-47
Destigloyl Swietenine
a-69

Fig. V

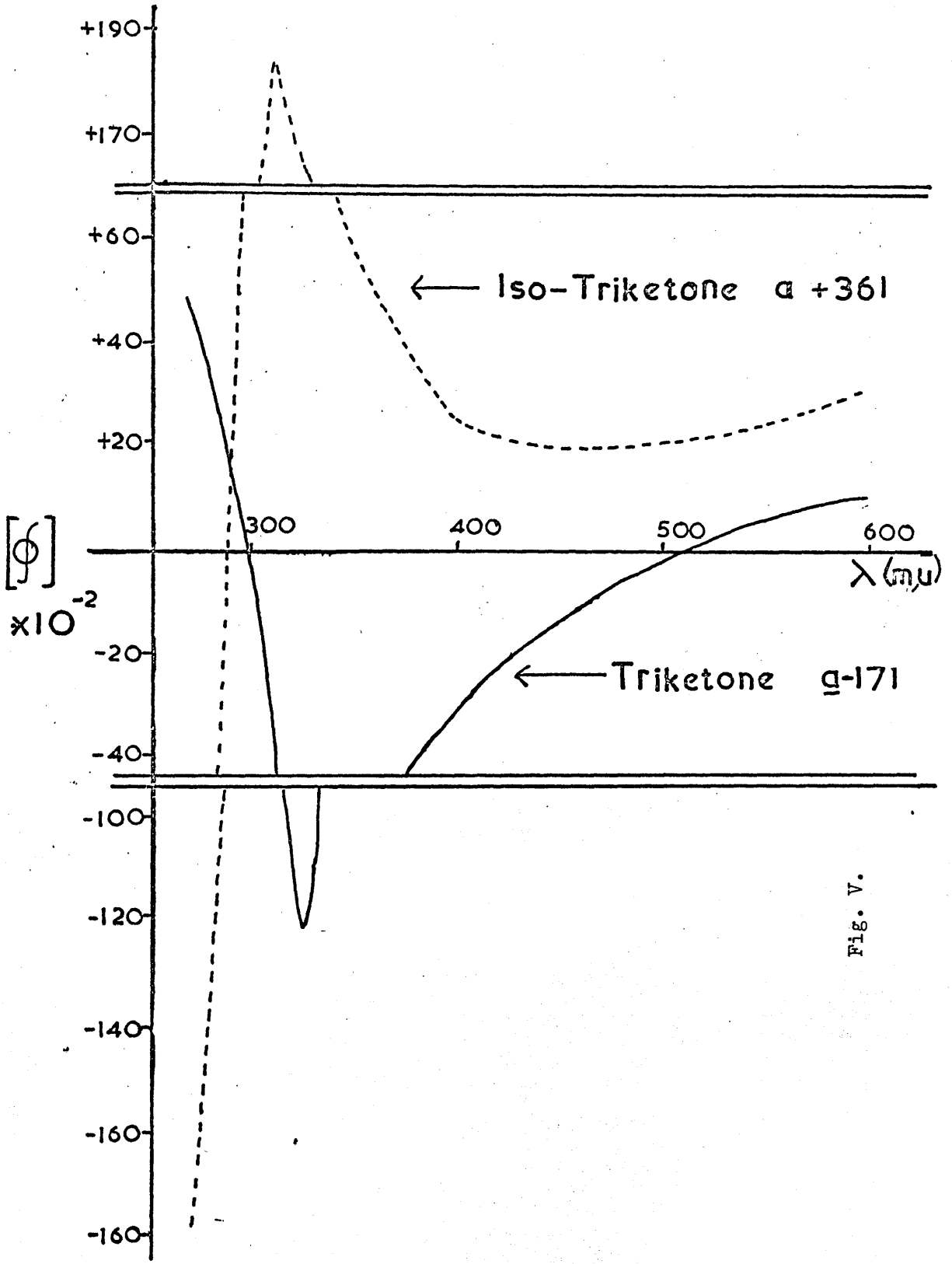

+190
+170
+60
+40
+20
-20
-40
-100
-120
-140
-160
-160
300
400
500
600
λ (mμ)
[φ]
×10^-2
← Iso-Triketone a +361
← Triketone a-171

Fig. V.

Fig. VI

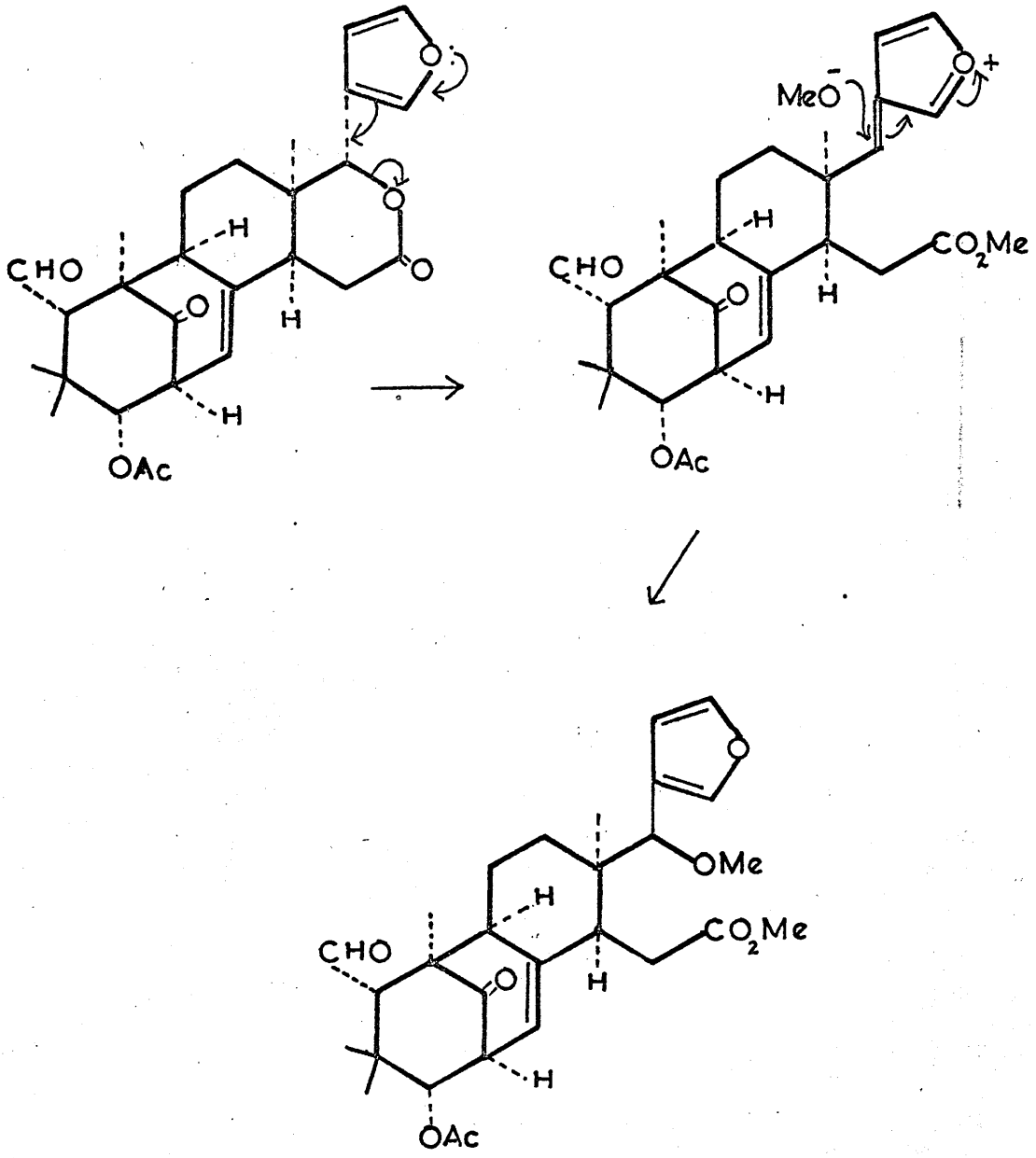
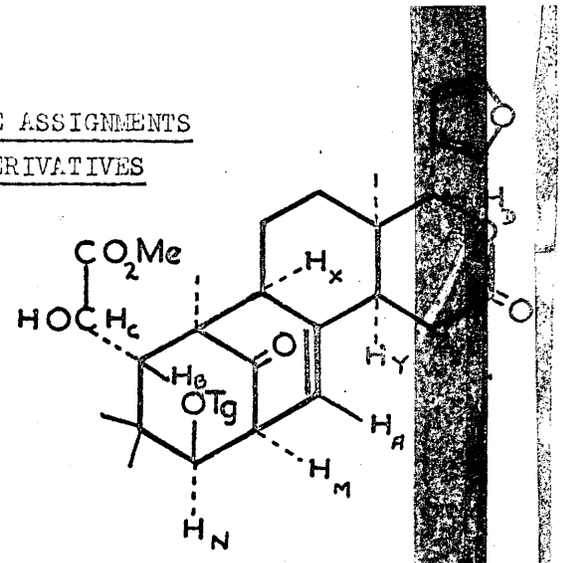


Table 1

NUCLEAR MAGNETIC RESONANCE ASSIGNMENTS OF SWIETENINE AND ITS DERIVATIVES

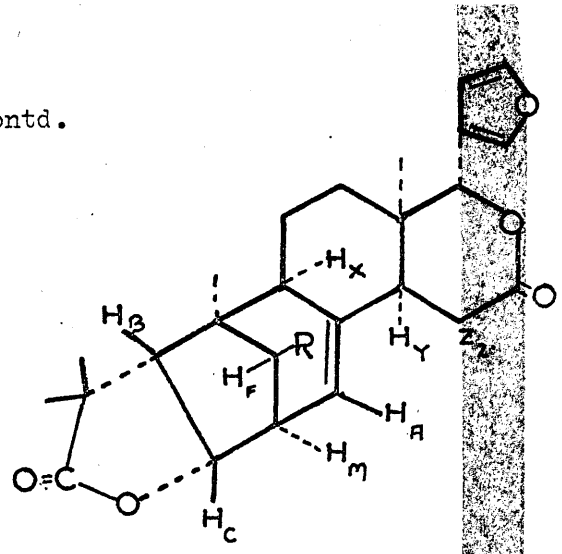


Compound	Furan	D	A	N	C	Methyl ester	B	M	Z_2	X & Y	Methyls	
B 7	2.43 2.56 3.61	4.43	4.63	5.36	5.47	6.25	6.50	6.50	7.24	7.72 7.82	8.56 8.88 9.02 9.12	OH 7.10 H of tiglate 3.03 CH_3 x 2 " 8.20
B 15	2.43 2.53 3.54	4.33	3.88	5.24	5.34	6.16	6.63	7.10	6.98	7.62	8.44 8.76 8.96 x2	H of tiglate 3.12 CH_3" " 8.17 (6H)
B 14	2.45 2.54 3.59	4.33	4.29	6.50	5.42	6.27	6.50	6.50	7.08	7.65	8.58 8.98 9.00 9.10	OH 6.92
B 16	2.50 2.57 3.63	4.44	4.08	6.37	5.43	6.27	6.37	7.10	7.10	7.74	8.55 9.00 9.02 x2	
B 21	2.42 2.50 3.60	4.40	3.92	5.41	5.40	6.28	6.31	7.15	7.07	7.76	8.53 8.89 9.00 9.08	OAc 7.92
B 12	2.27 2.57 3.55	4.32	4.56	5.08	-	6.02	4.97	6.40	7.15	7.80 (2 protons)	8.77 8.91 8.97 9.07	H of tiglate 2.93 CH_3 x 2 " 8.15

Table 1 contd.

Compound	Furan	D	A	N	C	Methyl ester	B	M	Z_2	X & Y	Methyls	
B 20	2.32 2.57 3.55	4.37	4.08	6.18	-	6.08	5.58	7.10	7.10	7.30 7.72	8.76 8.92 8.97 9.12	
B 18	2.32 2.57 3.47	4.49	4.24	-	-	6.07	5.32	6.22	7.08	7.65	8.72 8.86 8.91 9.00	
B 47	2.45 2.55 3.58	4.52	4.22	-	5.32	6.27	6.80	6.40	7.07	7.60	8.42 8.82 8.90 8.98	
B 22	2.34 2.56 3.53	4.59	4.16	6.25	0.18	-	7.25	7.10	7.10	7.68	8.63 8.87 8.92 8.95	
B 36	2.36 2.56 3.53	4.73	4.32	-	0.13	-	7.00	6.22	7.10	7.65 8.15	8.58 8.75 8.83 8.92	
B 23	2.31 2.51 3.47	4.56	4.01	5.35	0.13	-	7.15	7.15	7.04	7.80	8.63 8.80 8.93 9.00	OAc 7.91
B 25	2.2 2.56 3.51	5.76	4.18	5.29	0.23	6.26	6.98	6.98	7.12	7.7	8.98 8.93 8.74 8.59	OMe 6.76 OAc 7.8
B 9	-	-	4.96	5.43	5.51	6.16 6.38	6.63	6.70	7.64	7.74	9.18 9.08 8.98	OH 7.17 T.H.F. α 6.2 β 8.3
B 11	2.53 2.64 3.60	4.32	4.5	5.22	5.36	6.2	6.46	6.50	7.07	7.80		OH 7.07

Table 1 contd.



Compound	Furan	D	A	F	C	Methyl ester	B	M	Z_2	X ? Y	Methyls		
B 29	2.58 3.62	4.78	4.45	5.04	5.35	-	7.50	6.88	7.12	7.68	8.94 8.79 8.66 8.61	OAc	7.97
B 32	2.58 3.56	4.58	4.18	-	5.09	-	7.40	6.90	7.12	7.64	8.94 8.73 8.70 8.60		
B 34	2.56 3.58	4.30	4.44	-	5.50	6.32	7.39	6.93	7.16	7.65	9.04 8.96 8.83 8.67		
B 41	2.27 2.57 3.53	4.56	4.41	-	-	6.16	7.18	6.90	7.22	7.82	8.88 8.73 8.67 8.50		
B 46	2.27 2.56 3.53	4.60	4.64	5.03	-	6.13	7.26	6.78	7.12	7.60	8.88 8.82 8.72 8.53	OAc	7.99
B 45	2.27 2.56 3.56	4.54	4.32	5.21	-	6.20	7.72	6.93	7.14	7.60	8.91 8.80 8.70 8.55	OAc	7.93

Experimental.

M.p.s. were determined on a Kofler block. Specific rotations refer to chloroform solutions at room temperature, unless otherwise specified. Infrared solution spectra were kindly recorded by Mrs. F. Lawrie on the Unicam S.P. 100 Mark II spectrophotometer with a prism grating monochromator, and operated with evacuated optics, Nujol spectra were obtained from a Perkin-Elmer "Infracord" spectrophotometer. Microanalyses are by Mr. J.M.L. Cameron and his staff. Woelm Grade I alumina deactivated according to the Brockmann[14] scale of activity was used for chromatography. Chromatoplates were prepared by the method of Stahl[15] using Keiselguhr G (Merck). R.f. values are not recorded but where necessary known compounds were run concurrently for comparison purposes. Rotatory Dispersion Curves were measured by Professor W. Klyne to whom we express our thanks. Nuclear magnetic resonance spectra were recorded by Dr. N.C. Bhacca, Varian Associates, Palo Alto (swietenine), Dr. A. Melera, Varian Associates, Zurich (salannin) on Varian H.R. 100 spectrometers and by Dr. D.W. Turner, Imperial College, London (nimbin) on a Varian 4311 spectrometer operating at 56.4 Mc/sec adapted for double resonance experiments in which the single-band technique developed by Turner[16] was used.

Octahydro-Swietenine (B8).

Swietenine (2 gms) in "Analar" acetic acid (200 ml) was hydrogenated over 10% palladium-charcoal (2 gms) for 12 hours at atmospheric pressure. The uptake of hydrogen was 385 ml (3.8 moles). The solution was filtered and the solvent removed in vacuo. Separation into acid and neutral fractions using methylene chloride and saturated sodium hydrogen carbonate gave crude an acid (1.680 gms) and a neutral (310 mgs) fraction. The acid fraction was crystallised from ether-light petroleum to give octahydro-swietenine (B8) (650 mgs), m.p. 153-4°, $[\alpha]_D$ - 190° (C 0.81 in chloroform), pK ~ 5.2, ν_{max} (nujol) 1730 cm^{-1}, λ_{max} 202 mμ (ϵ 6,300). (Found C, 64.63; H, 8.41. $C_{32}H_{48}O_9$ (H_2O) requires C, 64.62; H, 8.47%).

Methyl Ester of Octahydro Swietenine (B9).

The residue obtained by removal of solvent from the mother liquors (1.2 gms) in the above experiment was dissolved in ether and an excess of ethereal diazomethane added. The product was adsorbed on Grade III acid alumina (25 gms). Benzene-ether (4:1 - 7:3) eluted the crystalline methyl ester of octahydro-swietenine (B9) (880 mgs) which, recrystallised from ether-light petroleum, had m.p. 164 - 165°, $[\alpha]_D$ - 179°, (C, 1.22 in chloroform), λ_{max} 204 mμ (ϵ 5,670), $\nu_{max}^{CCl_4}$ 3610, 3527, 1734 cm^{-1}. (Found C, 66.58; H 8.42. $C_{33}H_{50}O_9$ requires C, 66.41; H, 8.71%).

Pure octahydro-swietenine (84 mgs) was dissolved in ether and an excess of ethereal diazomethane added. The product, crystallised as above, was identical with the above methyl ester of octahydro-swietenine (m.p., m.m.p.).

Attempted Osmylation of the Methyl Ester of Octahydro-Swietenine

The methyl ester of octahydro-swietenine (B9) (98mgs) was dissolved in dioxan (2 ml) and to this was added a solution of osmium tetroxide (47 mgs) in ether (2 ml). This was kept in the dark at room temperature for three days. Excess hydrogen sulphide was passed into the solution which was then filtered through a celite pad. The removal of solvent gave unchanged methyl ester of octahydro-swietenine (85 mgs) m.p. 164 - 165° (identical m.p., m.m.p.).

Octahydro Swietenine Oxime (B10)

Octahydro-swietenine (200 mgs) and hydroxylamine hydrochloride (460 mgs, 18 moles) were dissolved in ethanol and pyridine (8 ml) and solution refluxed for 36 hours. The removal of solvents and extraction with chloroform give octahydro-swietenine oxime (B10) which crystallised in needles from chloroform-benzene, m.p. 251 - 254°. (Found C, 63.22; H, 7.83. C_{32} H_{51} O_{10} N requires C, 63.03; H, 8.43%).

Dehydroswietenine (B12)

To swietenine (1 gm) dissolved in "Analar" acetone (40 ml) was added an excess of 7.5 N chromic acid at 0°. The solution was allowed to warm to room temperature. Work up in the usual way gave a gum (980 mgs) which crystallised from chloroform-ether to give dehydroswietenine (638 mgs) (B12), m.p. 257 - 262°, $[\alpha]_D$ - 149° (C 1.88 in chloroform),

$\nu_{max}^{CHCl_3}$ 1705, 1730 cm^{-1}. This was identical (m.p., I.R.) with a sample prepared by chromium-trioxide oxidation of swietenine by Dr. J.D. Connolly[17].

Reduction of Dehydroswietenine to Swietenine.

Dehydroswietenine (22 mgs) was refluxed with zinc dust (290 mgs) in "analar" acetic acid (2 ml) for 10 minutes. The removal of the zinc dust and the solvent gave a gum (24 mgs) which had the same Rf. value on a chromatoplate as swietenine. Filtration through Grade IV acid alumina using chloroform as eluent gave swietenine (16 mgs), m.p. 271 - 274° (from chloroform-light petroleum). (Identical I.R., m.p., m.m.p.).

Alkaline Hydrolysis of Dehydroswietenine (B12)

a) Dehydro-Desmethyl-Swietenine (B50)

Dehydroswietenine (B12) (24 mgs) in dioxan (0.4 ml) was hydrolysed with 5% methanolic potassium hydroxide (0.4 ml) at room temperature for 0.5 hour. The solution was acidified with 6N hydrochloric acid and diluted with water until a crystalline precipitate appeared. Recrystallisation from chloroform-ether afforded dehydro-desmethyl-swietenine (B50), (18 mgs), m.p. 272 - 276°. Treatment with an excess of ethereal diazomethane in methanol gave dehydro-swietenine m.p. 255 - 260° (identical I.R., m.p., m.m.p.).

b) Dehydro-Destigloyl-Desmethyl-Isoswietenine (B19)

Dehydroswietenine (B12) (1 gm) was hydrolysed with 2½% ethanolic

potassium hydroxide (100 mls) at 100° under nitrogen for 10 minutes. Water was added and the solution acidified with 6N hydrochloric acid. The crystalline dehydro-destigloyl-desmethyl-isoswietenine (B19) (594 mgs), m.p. 258 - 265° was filtered. A further crop of crystalline acid (250 mgs) was obtained by extraction of the aqueous mother liquors with ethyl acetate. Treatment with excess ethereal diazomethane in methanol afforded dehydro-destigloyl-isoswietenine (B20), m.p. 238 - 244° (from chloroform-ether) α_D - 74° (C 1.21 in chloroform) $\nu_{max}^{CHCl_3}$ 3612, 1730 cm^{-1}. (Found C, 67.03; H, 6.65. $C_{27}H_{32}O_8$ requires C, 66.92; H, 6.66%).

Destigloyl-Desmethyl-Isoswietenine (B13)

Dehydro-destigloyl-desmethyl-isoswietenine (680 mgs) was refluxed for 2 hours with zinc dust (7.4 gms) in "Analar" acetic acid (150 ml). The solution was filtered and solvent removed in vacuo. Work-up in the usual manner afforded a gum (670 mgs) which crystallised from chloroform. A portion of this material (100 mgs) was dissolved in ethyl acetate and treated with an excess of ethereal diazomethane. The product showed a mixture of two compounds on a chromatoplate and was chromatographed on Grade IV acid alumina (10 gms). Chloroform-benzene (3: 7) eluted a gum which failed to crystallise but which is considered to be 3-acetoxy-destigloyl-isoswietenine (B21) from its N.M.R. spectrum (Table 1) and chloroform eluted destigloyl-isoswietenine (B14) (identical Rf. value with destigloyl-isoswietenine prepared by Dr. J.D. Connolly

by the alkaline hydrolysis of swietenine).

By shortening the time of reflux to 10 mins. destigloyl-desmethyl-isoswietenine was prepared without contamination by the acetate.

Isoswietenine (B15)

Destigloyl-isoswietenine (B14) (56 mgs) was dissolved in "Analar" pyridine (2 ml) and tigloyl chloride (1 ml b.p. 45° - 50° / 17 m.m.) added in the cold and left at 0° for 12 hours. The solution was poured into ice and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate and water in succession. Removal of solvent gave a black tar which was chromatographed on Grade IV acid alumina (2 gms). Chloroform-benzene (1: 9) eluted crystalline isoswietenine (B15) (45 mgs), m.p. 213 - 215° (from ethyl acetate - light petroleum), $[\alpha]_D$ - 57° (C, 1.22 in chloroform), ν_{max} (nujol) 3500 (hydroxyl) 3100, 1500, 879 (furan), 1705 (tiglate ester), 1725 (methyl ester, δ-lactone, cyclohexanone) cm^{-1} (Found C, 67.20; H, 7.10. C_{32} H_{40} O_9 requires C, 67.59; H, 7.09%).

Hydroxy-Keto-Aldehyde (B22)

Destigloyl-desmethyl-isoswietenine (B13) (290 mgs) and lead tetracetate (400 mgs) were dissolved in "Analar" acetic acid (20 ml) and left in the dark for 3 days at room temperature. Water was added, solution filtered, extracted with chloroform and separated into acid (20 mgs) and neutral (260 mgs) fractions. Crystallisation

from chloroform-light petroleum of the neutral fraction afforded hydroxy-keto-aldehyde (B22) (225 mgs) m.p. 230 - 237°, $\nu_{max}^{CCl_4}$ 3632, 1752, 1734, 1721 cm^{-1}. This was identical in I.R., m.p., m.m.p. with material prepared by Dr. J.D. Connolly by the cleavage of the α-hydroxy-acid by lead dioxide in refluxing acetic acid.

Keto-Aldehyde-Acetate (B23)

The hydroxy-keto-aldehyde (B22) (40 mgs) was acetylated in acetic anhydride (1 ml) and pyridine (2 ml) at room temperature for 12 hours. Work up in the usual manner afforded the keto-aldehyde-acetate (B23) (37 mgs) m.p. 274 - 279° (from chloroform-light petroleum). This was identical with material prepared directly by Dr. J.D. Connolly in the above lead dioxide reaction.

Keto-Aldehyde-Tosylate (B24)

The hydroxy-keto-aldehyde (B22) (58 mgs) was dissolved in pyridine (2 ml) and p-toluene-sulphonyl chloride (63 mgs) was added and left at room temperature for 24 hours. The usual work up gave a gum which showed a mixture of starting material and a less polar product on a chromatoplate. The mixture was chromatographed on Grade IV neutral alumina (3 gms), light-petroleum-benzene (1: 1) eluting keto-aldehyde-tosylate (B24) (31 mgs) which solidified on long standing ν_{max} (nujol) 1590, 1360 cm^{-1}.

The tosylate (B24) was refluxed under nitrogen in redistilled

collidine (5 ml) for 6 hours. The solution was poured into water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate and water. The product was run on a chromatoplate which showed only starting material.

Methyl Ether, Methyl Ester of the Hydroxy-Keto-Aldehyde

The hydroxy-keto-aldehyde (B22) (90 mgs) was treated with 0.1N dry methanolic hydrochloric acid (1.5 ml) on the steam-bath under reflux for 20 minutes. The methanol was removed and the product chromatographed on Grade V neutral alumina (5 gms). Benzene eluted material (53 mgs) which, although it was one spot on a chromatoplate, failed to crystallise.

The Methyl Ether, Methyl Ester of the Acetoxy-Keto-Aldehyde (B25)

The above gum (53 mgs) was dissolved in "Analar" pyridine (1 ml) and acetic anhydride (1 ml) added and left at room temperature for 12 hours. The usual work-up gave the product (55 mgs) which was chromatographed on Grade IV acid alumina (3 gms). Benzene eluted the crystalline methyl ether, methyl ester of the acetoxy-keto-aldehyde (B25) (35 mgs), m.p. 184 - 186°, ν_{max} (nujol) 1710, 1740 cm^{-1} (Found C, 67.92; H, 7.61. $C_{29}H_{38}O_8$ requires C, 67.68; H, 7.44%).

The same product was obtained by the treatment of the keto-aldehyde-acetate (B23) with 0.1N methanolic hydrochloric acid.

γ -Lactone (B29)

The hydroxy-keto-aldehyde (B22) (116 mgs) was dissolved in ethanol (7 ml), 0.5N sodium hydroxide solution (7 ml) added and refluxed under nitrogen on the steam-bath for 1 hour. The solution was acidified with 6N hydrochloric acid and extracted with ethyl acetate. Evaporation of the solvent gave a gum which showed two spots on a chromatoplate but which could not be separated by chromatography. The mixture was separated by preparati: T.L.C. using 2% methanol-chloroform as solvent and spraying with water to show the bands. Extraction of the more polar band gave γ-lactone (B29) (70 mgs), m.p. 242 - 246° (from chloroform-petrol), $[\alpha]_D$ + 111° (C, 1.02 in chloroform), $\nu_{max}^{CHCl_3}$ 3620, 3587, 1770 and 1732 cm^{-1}. (Found C, 67.87; H, 7.52. C_{25} H_{30} O_6 (H_2O) requires C, 67.55; H, 7.26%). Extraction of the other band gave a gum (40 mgs) which although it was one spot on a chromatoplate, failed to crystallise. The acetate of this compound, prepared in the usual way, also failed to yield a crystalline compound.

γ-Lactone Acetate (B31)

The γ-lactone (10 mgs) was dissolved in "Analar" pyridine (1 ml) and acetic anhydride (1 ml) was added and left at room temperature for 12 hours. The usual work-up gave γ-lactone acetate (B31) (9 mgs) m.p. 274 - 278° (from chloroform-ether), ν_{max} (nujol) 1730, 1770 cm^{-1}. (Found C, 68.77; H, 6.85. C_{27} H_{32} O_7 requires C, 69.21; H, 6.88%).

Dehydro-γ-Lactone (B32)

To the γ-lactone (180 mgs) dissolved in "Analar" acetone (5 ml) was added an excess of 7.5N chromic acid at 0°C. The solution was allowed to warm to room temperature. Work-up in the usual manner and washing with sodium bicarbonate solution afforded dehydro-γ-lactone (B32) (120 mgs), m.p. 247 - 251° (from chloroform-ether), $[\alpha]_D$ + 190° (C 0.92 in pyridine) $\nu_{max}^{CHCl_3}$ 1735, 1762, 1781 cm^{-1}. (Found C, 70.14; H, 6.35. $C_{25}H_{28}O_6$ requires C, 70.74; H, 6.65%).

Reduction of Dehydro-γ-Lactone.

Dehydro-γ-lactone (B32) (29 mgs) was treated with an excess of sodium borohydride (15 mgs) in methanol (10 ml) for 1.5 hours. The solution was acidified with dilute hydrochloric acid and extracted with chloroform. The crude gum, thus obtained, showed two spots on a chromatoplate. The mixture was separated by preparative T.L.C., extraction of the more polar band giving γ-lactone (B29) (25 mgs) m.p. 240 - 245°. Extraction of the other band afforded 1-epi-γ-lactone (B33) (3 mgs) which failed to crystallise $\nu_{max}^{CHCl_3}$ 1758, 3200 cm^{-1}.

Treatment of Dehydro-γ-Lactone with Base

Dehydro-γ-lactone (B32) (52 mgs) was dissolved in ethanol (3.5 ml) and treated with 0.5N sodium hydroxide solution (3.5 ml) on the steam-bath under nitrogen for one hour. Water was added, solution acidified

with dilute hydrochloric acid, extracted with chloroform and separated into acid (34 mgs) and neutral (17 mgs) fractions. The acidic fraction was dissolved in methanol and treated with ethereal diazomethane. Filtration through Grade IV acid alumina in chloroform afforded crystalline hydroxy-methyl-ester (B34) (25 mgs), m.p. 209 - 212°, (from chloroform-light petroleum), $[\alpha]_D$ + 120° (C 1.1 in chloroform) $\nu_{max}^{CHCl_3}$ 3614, 1750, 1731 cm^{-1}. (Found C, 68.31; H, 7.12. $C_{26}H_{32}O_7$ requires C, 68.40; H, 7.07%). Crystallisation of the neutral fraction from chloroform-light petroleum afforded dehydro-γ-lactone (B32) (15 mgs), m.p. 247 - 251°. (Identical m.p., m.m.p., I.R., and Rf value).

Diketo-Aldehyde (B36)

The hydroxy-keto-aldehyde (B22) was oxidised in the usual way with an excess of 7.5N chromic acid at 0°C. The product was a gum (70 mgs) which was chromatographed on Grade IV acid alumina (3 gms). Benzene eluted the diketo-aldehyde (B36) (44 mgs), m.p. 218 - 221° (from chloroform-ether), $\nu_{max}^{CCl_4}$ 1751, 1722 cm^{-1}. The same compound was obtained by Dr. J.D. Connolly by the action of chromium trioxide in pyridine on the hydroxy-keto-aldehyde.

Enone Methyl Ester (B37)

The diketo-aldehyde (B36) (71 mgs) was dissolved in ethanol (3 ml) and treated with 0.5N sodium hydroxide solution (3 ml) on the steam-bath for one hour. Water was added, solution acidified with 6N hydrochloric

acid, extracted with ethyl acetate and separated into acid and neutral fractions. The acid fraction (60 mgs) was dissolved in methanol and treated with an excess of ethereal diazomethane. Removal of solvents afforded a gum which was chromatographed on Grade IV acid alumina (3 gms). Chloroform-benzene (3: 7 - 2: 3) eluted the crystalline enone-methyl ester (B37) (48 mgs), m.p. 285 - 287° (from chloroform-ether), $[\alpha]_D$ + 25°. (C 0.56 in chloroform), $\nu_{max}^{CHCl_3}$ 3620, 3583, 1733, 1687 cm^{-1}. (Found C, 67.19; H, 7.16. $C_{26}H_{32}O_7$ ($\frac{1}{2}H_2O$) requires C, 67.10; H, 7.15%).

Attempt to Oxidise Enone Methyl Ester (B37)

The enone methyl ester (8 mgs) was dissolved in "Analar" acetone (2 ml) and an excess of 7.5N chromic acid added to the ice-cold solution. The solution was allowed to warm to room temperature and extraction with chloroform afforded crystalline enone methyl ester m.p. 285 - 287° (identical m.p., m.m.p., I.R., and Rf value with starting material).

Attempt to Acetylate Enone Methyl Ester (B37)

The enone methyl ester (11 mgs) was dissolved in acetic anhydride, fused sodium acetate (60 mgs) added and solution refluxed for one hour. The solvent was removed in vacuo and the usual work-up afforded a gum which was chromatographed on Grade IV acid alumina. Chloroform-benzene (2: 5) eluted the enone methyl ester m.p. 284 - 287° (identical m.p., m.m.p., Rf value with starting material).

Attempt to Dehydrate Enone Methyl Ester (B37)

The enone methyl ester (4 mgs) was dissolved in pyridine (o.5 ml), phosphorous oxychloride (4 drops) added and left at room temperature for 3 days. The usual work-up afforded the enone methyl ester (identical m.p., m.m.p., Rf value with starting material).

Borohydride Reduction of the Enone Methyl Ester (B37)

The enone methyl ester (13 mgs) and sodium borohydride (30 mgs) were kept in methanol (2 ml) at 20° for 12 hours. The product obtained with ethyl acetate from the acidified reaction showed a mixture of six compounds on a chromatoplate.

Triketone (B18)

Dehydro-destigloyl-*iso*swietenine (460 mgs) was oxidised in the usual manner with 7.5N chromic acid. Usual work-up gave the triketone (B18) (316 mgs) m.p. 231 - 235° (from chloroform-ether), $\nu_{max}^{CHCl_3}$ 1730 with a shoulder at 1742 cm^{-1}. This was identical to the triketone obtained by Dr. J.D. Connolly by the action of chromium trioxide-pyridine on destigloyl-*iso*swietenine (B14).

Isotriketone (B41)

The triketone ester (B18) (200 mgs), dissolved in dioxan (4 ml), was treated with 5% methanolic pctassium hydroxide (4 ml) at room

temperature for 30 minutes. The usual work-up afforded an acid which was methylated with an excess of ethereal diazomethane to afford the isotriketone (B41) (155 mgs), m.p. 297 - 299° with previous sublimation (from chloroform-ether), $[\alpha]_D$ + 43° (C 1.08 in chloroform) $\nu_{max}^{CHCl_3}$ 1787, 1764, 1735 cm^{-1}. (Found C, 66.04; H, 6.29. $C_{27}H_{30}O_8$ ($\frac{1}{2}H_2O$) requires C, 65.99; H, 6.33%). The mother liquors from the crystallisation of the isotriketone showed strong enone absorption in the I.R. (1680 cm^{-1}) but no crystalline enone could be obtained.

Treatment of the Isotriketone with Zinc and Acetic Acid

The isotriketone (B41) (11 mgs) was refluxed with zinc dust (158 mgs) in "Analar" acetic acid (1 ml) for 3 hours. The usual work-up gave a gum which had the same Rf value on a chromatoplate as the isotriketone. The crude material was filtered through Grade IV acid alumina in chloroform to give isotriketone (10 mgs) m.p. 297 - 299° (identical I.R., m.p., m.m.p. with authentic sample).

Borohydride Reduction of the Isotriketone

The isotriketone (B41) (150 mgs) and sodium borohydride (450 mgs) were kept in methanol (35 ml) for 12 hours. The product (145 mgs) obtained with chloroform from the acidified reaction, showed two more polar spots on a chromatoplate. The mixture was chromatographed on Grade III acid alumina (6 gms). Elution with chloroform-benzene (3: 7 - 2: 3) afforded the alcohol A (B43) (56 mgs), m.p. 313 - 317°

(from chloroform-petrol), $[\alpha]_D$ - 72° (C 1.00 in pyridine), $\nu_{max}^{CHCl_3}$ 3465, 1783, 1720 cm^{-1}. (Found C, 66.73; H, 6.63. $C_{27}H_{32}O_8$ requires C, 66.92; H, 6.66%).

Elution with chloroform-benzene (1: 1 - 3: 2) gave the alcohol B (B44) (84 mgs) which, although it was homogeneous as judged by thin-layer chromatography, failed to crystallise $\nu_{max}^{CHCl_3}$ 3620, 3575, 1783, 1756, 1732. cm^{-1}.

Acetate A (B45)

The alcohol A (B43) (50 mgs) was dissolved in pyridine (1 ml), "Analar" acetic anhydride (1 ml) added and the solution left at room temperature for 12 hours. The usual work-up gave a mixture which was chromatographed on Grade III acid alumina. Chloroform-benzene (1: 9) eluted the acetate A (B45) (35 mgs), m.p. 141 - 144° (from chloroform-petrol), $[\alpha]_D$ - 82° (C 1.22 in chloroform) $\nu_{max}^{CHCl_3}$ 1780, 1737 cm^{-1}. (Found C, 65.33; H, 6.57. $C_{29}H_{34}O_9$ ($\frac{1}{2}H_2O$) requires C, 65.05; H, 6.58%).

Acetate B (B46)

The alcohol B (B44) (44 mgs) was dissolved in pyridine (1 ml), "Analar" acetic anhydride (1 ml) added and the solution was left at room temperature for 12 hours. The usual work-up afforded the acetate B (B46) (35 mgs), m.p. 259 - 262° (from chloroform-petrol), $[\alpha]_D$ - 13° (C 1.12 in chloroform), $\nu_{max}^{CHCl_3}$ 1783, 1739 cm^{-1}. (Found C, 65.60; H, 6.47. $C_{29}H_{34}O_9$ ($\frac{1}{2}H_2O$) requires C, 65.05; H, 6.58%. After prolonged drying at 100° for 60 hours: Found C, 66.04; H, 6.40, $C_{29}H_{34}O_9$ requires C, 66.14; H, 6.51%).

Hydrolysis of Acetates A and B to Alcohols A and B

The acetates A and B (10 mgs) were in turn hydrolysed with 5% methanolic potassium hydroxide (1 ml) at room temperature for one hour. The usual work-up afforded alcohols A and B without methylation (same Rf values on a chromatoplate).

Oxidation of Alcohols A and B to the Isotriketone.

The alcohols A and B were in turn oxidised by 7.5N chromic acid to afford the isotriketone, m.p. 297 - 299° (no depression with authentic isotriketone).

Dihydrotriketone (B47)

The triketone ester (B18) (110 mgs) was refluxed with zinc dust (1.2 gm) in "Analar" acetic acid for 2 hours. The usual work-up afforded a gum (110 mgs) which was filtered through Grade IV acid alumina in chloroform to give the dihydrotriketone (B47) (78 mgs), m.p. 221 - 223° (from ethyl acetate-petrol), $[\alpha]_D$ - 254° (C 1.63 in chloroform) $\nu_{max}^{CHCl_3}$ 3611, 3538, 1739, 1716 cm^{-1}. (Found C, 66.46; H, 6.93. $C_{27}H_{32}O_8$ requires C, 66.93; H, 6.66%).

Oxidation of the Dihydrotriketone (B47) to the Triketone (B18)

The dihydrotriketone (B47) (10 mgs) was oxidised in the usual manner with 7.5N chromic acid. The usual work-up afforded the triketone

(B18), m.p. 227 - 231° (identical with authentic sample in I.R., m.p., m.m.p., and Rf value).

Isodihydrotriketone

The dihydrotriketone (B47) (42 mgs) in dioxan (0.8 ml) was treated with 5% methanolic potassium hydroxide (0.8 ml) for 30 minutes at room temperature. The usual work-up afforded an acid which was dissolved in methanol and treated with an excess of ethereal diazomethane. The product was chromatographed on Grade IV acid alumina. Chloroform-benzene (1: 4) eluted crystalline isodihydrotriketone (30 mgs), m.p. 259 - 263°, (from chloroform-petrol), $[\alpha]_D$ 113° (C 0.91 in chloroform) $\nu_{max}^{CHCl_3}$ 1783, 1738, 1717 cm^{-1}. (Found C, 65.89; H, 6.80. $C_{27}H_{32}O_8$ ($\frac{1}{2}H_2O$) requires C, 65.72; H, 6.74%).

The Attempted Oxidation of Isodihydrotriketone

The isodihydrotriketone (6 mgs) was oxidised in the usual manner with 7.5N chromic acid. The usual work-up afforded isodihydrotriketone, m.p. 257 - 263° (identical m.p., m.m.p. and Rf value).

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PART II

THE CONSTITUTION OF NIMBIN

The Constitution of Nimbin[1]

Nimbin isolated[2] from various parts of the nim tree (Melia azadirachta Linn) has been previously investigated by Narasimhan[3] and by Sengupta et al[4] who concluded that it had the molecular formula $C_{29}H_{36}O_9$ or $C_{30}H_{36}O_9$, contained a furan ring, a methoxyl, two carbomethoxyl, one acetate groups, an α,β unsaturated ketone and is bicarbocyclic since 1, 2, 5 trimethyl-naphthalene was isolated from dehydrogenation experiments of a lithium aluminium hydride reduction product. The products of alkaline degradation and pyrolytic experiments established that nimbin had the part structure (C2) or (C3). The molecular formula, $C_{30}H_{36}O_9$,[5] has recently been confirmed by mass-spectrometry.

We have re-examined the above evidence and on the basis of additional chemical and nuclear magnetic resonance (spin-decoupling[6]) studies conclude that nimbin (C1) is a novel tetranortriterpenoid in which ring C is cleaved.

The nuclear magnetic resonance spectrum has confirmed the functional groups in nimbin. It shows the presence of three quaternary methyl groups (τ 8.73, 3H, singlet, and τ 8.66, 6H, singlet), and one vinyl methyl (τ 8.33, 3H, doublet, J = 2 c.p.s.), one acetate group (τ 7.98, 3H, singlet), two carbomethoxyl groups (τ 6.38 and τ 6.28, 3H each, singlet) and one β-substituted furan ring (τ 2.72, 2H, multiplet and τ 3.68, 1H, diffuse singlet). In the infra-red, nimbin shows absorptions at 1739 (ϵ, 1,260) (two carbomethoxyl, one acetate groups), and 1688 (ϵ, 632) (α,β unsaturated ketone) cm^{-1} in carbon tetrachloride solution. Nimbin does not contain a hydroxyl group (absence in the infrared of bands above 3,000 cm^{-1}) which

suggests that the remaining oxygen function is present as an ether. This can be confirmed by the nuclear magnetic resonance spectrum (see sequel).

The above functional groups account for all the nine oxygen atoms present in nimbin.

Hydrogenation[3] of nimbin over 10% palladium charcoal results in the uptake of three moles of hydrogen to yield crystalline hexahydro-nimbim (C4), m.p. 202 - 206° which from its nuclear magnetic resonance (vinyl methyl, τ8.2, 3H, doublet, J = 2 c.p.s.) and its ultraviolet spectra (λ max 213 mμ, ϵ 4,900) must contain an isolated double bond. Nimbin is therefore tricarbocyclic and its basic C_{26} carbon skeleton, the β-substituted furan ring and its five C-methyl groups (three at quaternary carbon atoms, one on an olefinic linkage, and one oxidised to a carbomethoxyl group), suggests a biogenetic relation to limonin[7].

Mild hydrolysis[3,4] of nimbin affords nimbic acid in which both the carbomethoxyl and the acetate groups have been hydrolysed. The treatment of nimbic acid with diazomethane yields desacetyl nimbin (C5), m.p. 206 - 210 $\nu_{max}^{CCl_4}$ 1687 (α,β unsaturated ketone), 1743 (carbomethoxyls) cm^{-1}. When nimbin is treated further with base, a mixture of acids was obtained whose derived methyl esters were separated by chromatography using gradient elution. It has been proved[4] that these esters A, B, and C are isomeric, $C_{26}H_{32}O_6$, formed by the ready decarboxylation of nimbic acid. Ester A (C6), m.p. 138 - 142°, is the $\beta.\gamma$ unsaturated ketone ν_{max} (nujol) 3500 (hydroxyl) 1735 (carbomethoxyl) 1710 (cyclohexanone) cm^{-1} and ester B, m.p. 153 - 155° and ester C, m.p. 148 - 153° (C7) are the α,β unsaturated

ketones which are epimeric at the carbon atom γ to the ketone, ν_{max} (nujol) 3500 (hydroxyl), 1740 (carbomethoxyl), 1690 (α,β unsaturated ketone) cm^{-1}. The decarboxylation does not occur when hexahydronimbin (C4) is treated with alkali.

The above experiments can be explained if nimbin has the part structure (C8). This can be confirmed by nuclear magnetic resonance spectroscopy. Nimbin contains an α,β unsaturated ketone with the carbon atom γ to the ketonic function fully substituted. This follows since the vinyl protons of nimbin form a typical A B quartet (τ 3.68, τ 4.15, 2H, doublets, J_{AB} = 10 c.p.s.) and are not further coupled. In the nuclear magnetic resonance spectrum of the acetate of the above ester B (C9), m.p. 178 - 180°, $[\alpha]_D$ + 178°, the vinyl protons still form an A B quartet (τ 3.52, τ 4.20) but now are further coupled with the new proton at C_4 which itself couples with the new secondary methyl group (τ 8.73). This confirms the previously inferred[4] substitution at position C_4 and if we assume a euphol-derived[7] structure, places the enone and one carbomethoxyl group in ring A.

The relation of the second methoxy-carbonyl group to the enone system emerges from the constitution of pyronimbic acid[3,4] (C10), $C_{25}H_{28}O_5$, m.p. 252-3°, $\nu_{max}^{CHCl_3}$ 1652 (olefinic linkage), 1747 (enol δ-lactone) cm^{-1}, λ max 280 mμ (ϵ9,500), the neutral pyrolysis product of nimbic acid. The nuclear magnetic resonance spectrum of this compound shows an A B quartet arising from H_2 and H_3 consisting of a sharp doublet (H_2; τ4.49, 1H, J_{AB} = 7 c.p.s.) and a multiplet (H_3; τ4.20) attributable to coupling with H_2, H_5 (τ7.12) and the vinyl methyl group at C_4 (τ 7.83). C_{10} is therefore tetrasubstituted and C_5 trisubstituted. The absence of the

ketonic and carboxyl groups and the formation of the enol-δ-lactone suggest the ketone and the carboxyl group are situated in an α, δ relationship with respect to one another and thus ring C must be cleaved to provide the carboxyl function for enol-lactone formation.

Mild hydrolysis of hexahydronimbin affords hexahydronimbic acid. An attempt was made to acetylate the acid which resulted in the formation of a neutral enol-lactone, γ-lactone (C11), $C_{26}H_{32}O_6$, m.p. 252 - 254°, $[\alpha]_D$ +13°, $\nu_{max}^{CCl_4}$ 1650, 1768 (γ-lactone), 1797 (enol-δ-lactone), formed by the lactonisation of the two carboxyl groups with the enol of the C_1 ketone and with the hydroxyl formed by the hydrolysis of the original acetate. This fixes the position of the hydroxyl group γ to the C_4 carboxyl group at C_6. The nuclear magnetic resonance spectrum of the dilactone shows the proton H_6 to be a quartet centred at τ 5.44 which is coupling with H_5 (τ 7.18, 1H, doublet, J_{5-6} = 12 c.p.s.) and H_7 (τ 5.68, 1H, doublet, J_{6-7} = 3 c.p.s.) neither H_5 nor H_7 being otherwise coupled.

These observations demonstrate the configuration of the protons attached to C_5, C_6, C_7 (axial, axial, equatorial) and the absence of hydrogen atoms at C_8 and C_{10} and the location of oxygen functions at C_6 (lactone) and C_7 (ether). This XAB system is clearly present in several nimbin derivatives; the X component appears at remarkably low field in nimbin (τ 6.34) where it is "hidden" by the carbomethoxyl, and in the diethyl ester (τ 6.3), (C12), $C_{32}H_{40}O_9$, m.p. 174 - 176°, $[\alpha]_D$ +106° prepared by ethylation and acetylation of nimbic acid but moves upfield (τ 7.15) in pyronimbic acid and in the decarboxylated derivative (C9) (τ 7.75).

Further support for the structures of rings A and B emerges from the hydrogenation of hexahydronimbin over Adam's catalyst in acetic acid. This results in the formation of the fully saturated δ-lactone (C13), $C_{29}H_{42}O_8$, m.p. 269 - 271°, $[\alpha]_D \pm 0$, $\nu_{max}^{CCl_4}$ 1755 (δ-lactone), 1738 (carbomethoxyl and acetate) whose formation supports the acetic acid side-chain at C_9 in nimbin. This also follows from the nuclear magnetic resonance spectrum of the 1,6-dione (C14), m.p. 155 - 157°, $[\alpha]_D$ +139°, ν_{max}(nujol) 1680 (α,β unsaturated ketone), 1730 (cyclohexanone, carbomethoxyls) cm^{-1} prepared by the oxidation of desacetyl nimbin (C5) with chromium trioxide in pyridine. The nuclear magnetic resonance spectrum shows the multiplet (2H) centred at τ6.8 from the C_{11} methylene group collapses to a narrow band on irradiation of H_9 (τ 7.62).

Thus the portion $C_{24}H_{29}O_9$ (allowing for the β-substituted furan) has been accounted for leaving the portion C_6H_7 which contains the isolated double bond still to be assigned.

Originally, it was thought that the olefinic linkage in nimbin was trisubstituted (τ 8.33, 3H, doublet,, J = 2 c.p.s., vinyl methyl; τ 4.42, 1H, multiplet, vinyl proton). By spin-decoupling experiments of the hexahydro dilactone (C11) and pyronimbic acid (C10) it was shown that the downfield proton (τ4.42) was coupling to the vinyl methyl group (τ 8.20) and with a methylene group (τ 7.80) which in turn couples with a proton at τ6.20 which from its chemical shift was thought to be the proton on the carbon atom having an oxygen (ether) function on it. This leads to part structure (C15) which in turn suggests formula (C16) for nimbin. It is difficult to derive a biogenetic pathway for this compound and

attempts were made to perform chemical reactions on the olefinic linkage.

The isolated double bond in nimbin is hindered as shown by the failure of hexahydronimbin either to osmylate or to react with diborane. The reaction of diborane on nimbin results in a mixture of acids (caused by the alkaline work-up) which on further treatment with base and re-methylation affords the diol (C17), m.p. 125 - 129° formed by the reduction of the enone system. This is proved by the disappearance of the α,β unsaturated ketonic group in the infrared and by its reappearance on oxidation.

While our work on the chemistry of nimbin was proceeding, papers[8,9] by a group at the National Research Laboratory, Poona, appeared which agreed with the proposed structure of rings A and B but suggested that the olefinic linkage was tetrasubstituted and that H_{15} (τ 4.42) was coupling with the methylene group at C_{16} (τ 7.80), with the vinyl C_{26} methyl group (τ8.20) and with the methine proton H_{17} (τ 6.20). The last two are long-ranged or homoallylic couplings. Although the H_{15} proton is very low, the Indian workers gave analogous values for protons in similar environments[10].

In the light of our more extensive nuclear magnetic resonance studies with Salannin (see part III) in which the molecular fragment under discussion also features, we concur with the conclusions reached by the Indian group, so far as this portion of the molecular is concerned.

Thus nimbin has the structure (C1) in which the only uncertainty is the configuration at C_4. The Indian workers suggested[9] that the carbomethoxyl group is axial, β, on the grounds that the methyl group at C_4 is deshielded by the hydroxyl group in desacetyl nimbin which would

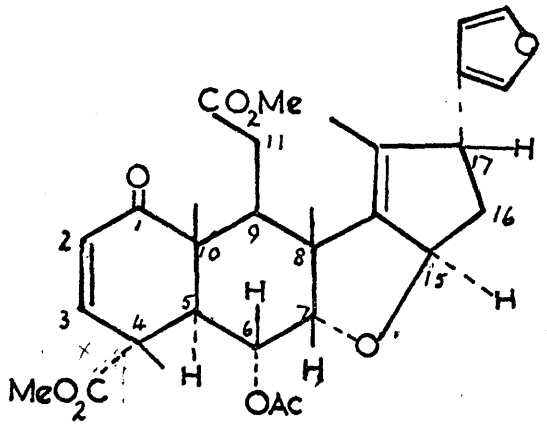
require a 1,3 diequatorial disposition of the two groups. We prefer the carbomethoxyl group to be e (equatorial) since in the easy formation of the enol-lactone-γ-lactone (C11) a cis γ-lactone is produced. This is confirmed in the similarly constituted salannin (part III) where reasons ar are given for a cis-fused ether ring.

During the course of the investigations into the chemistry of nimbin, two reaction products were obtained to which no structure can reasonably be assigned on the available chemical evidence.

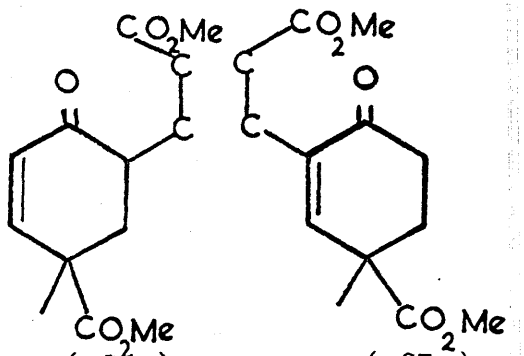
Treatment of desacetyl nimbin (C5) with phosphorous oxychloride, resulted in the formation of an acid whose derived methyl ester, m.p. 202 - 205°, showed absorptions in the infrared at 1687, 1740 cm^{-1} which suggests that the α, β unsaturated ketone group is still present. The nuclear magnetic resonance spectrum confirms this since the vinyl protons form the typical A B quartet (τ3.60, τ4.11; J_{AB} = 10 c.p.s.). Also shown are two quaternary methyl groups (τ 8.74, 8.66, 3H each, singlets), one vinyl methyl (τ8.48, 3H, doublet, J = 1.5 c.p.s.) and three carbomethoxyl groups (τ6.36, 3H, singlet; τ6.30, 6H, singlet). This suggests the loss of a quaternary methyl group but more secure assignments will have to await the use of nuclear magnetic resonance spectroscopy at 100 Mc/s and double irradiation.

The second unassigned product arises from the treatment of hexahydro-nimbin with β-naphthalene sulphonic acid. This results in the formation of a diene, m.p. 265 - 267°, (λ_{max} 298 mμ). The compound analysed for C_{29} H_{36} O_7 which was confirmed by mass spectrometry (mol. wt. 496.2461). Thus the compound is formed by the elimination of the elements of methanol

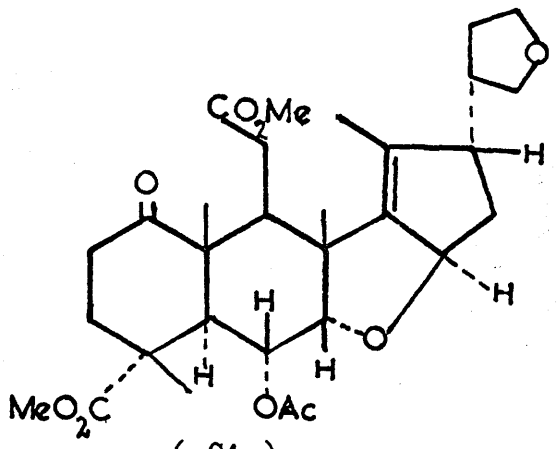
and water to form a lactone $\nu_{max}^{CCl_4}$ 1662, 1717, 1732, 1751, 1797 cm^{-1}. The nuclear magnetic resonance spectrum shows only one carbomethoxyl at τ 6.62 and methyl groups at τ 8.71 (3H, singlet), τ 8.54 (6H, singlet), τ 7.98 and τ 7.88. That the compound is a lactone was confirmed by the hydrolysis of the diene and remethylation. The infra-red of the hydrolysis product showed the disappearance of the 1797 cm^{-1} band and the nuclear magnetic resonance spectrum confirmed the presence of two carbomethoxyls (τ 6.48, τ 6.29. 3H, singlets). The mode of formation of the diene is uncertain and will have to await the results of further chemical work.



(C1)



(C2) (C3)



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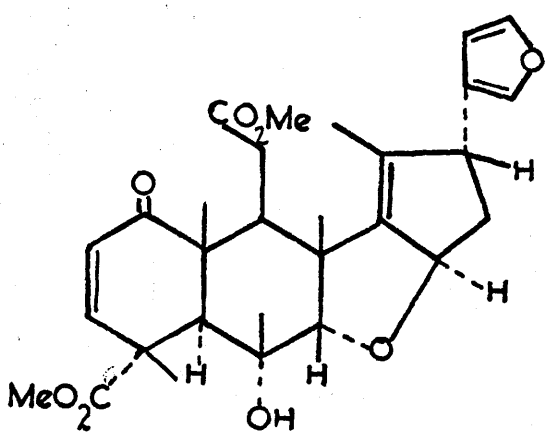
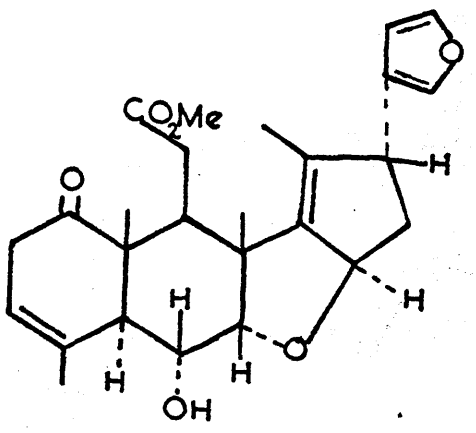
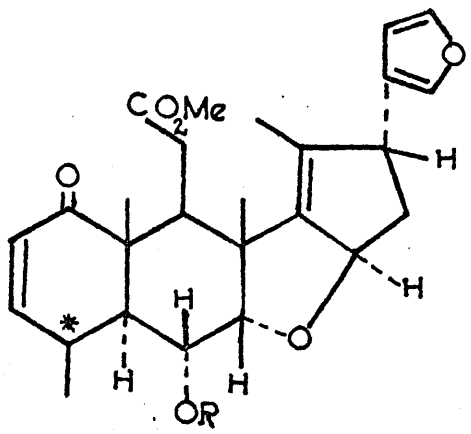


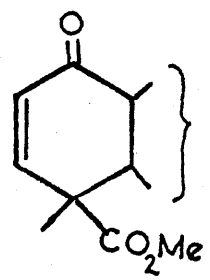
(C 5)



(C6)



(C7) R H
(C9) R Ac



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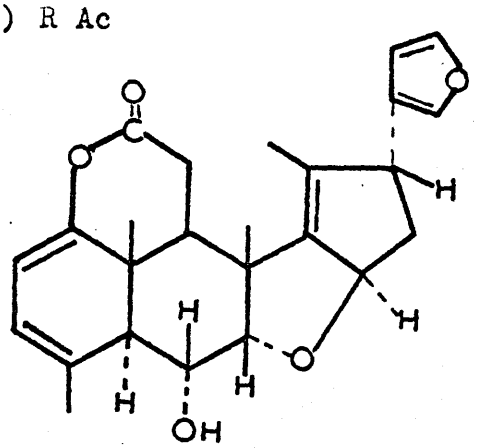
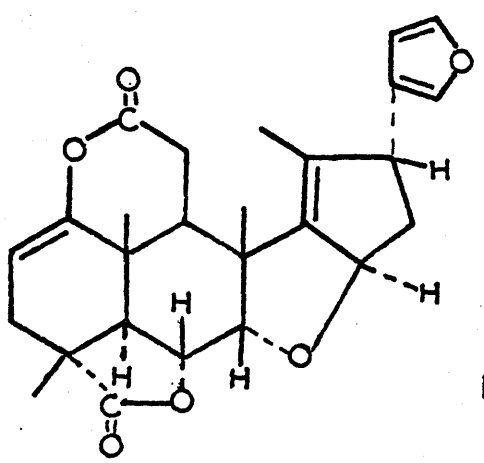


(C10)



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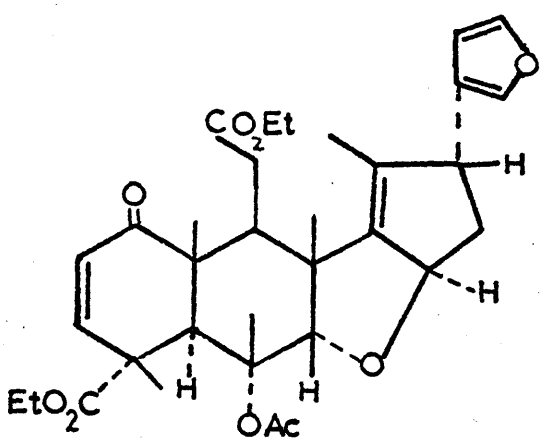

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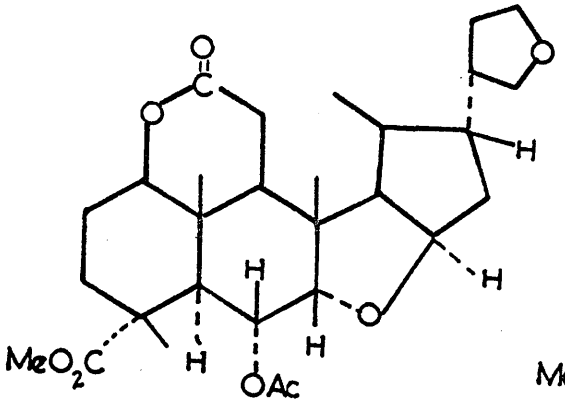

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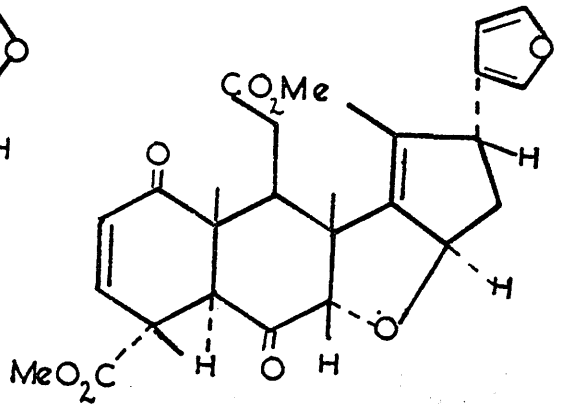

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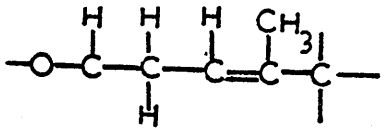

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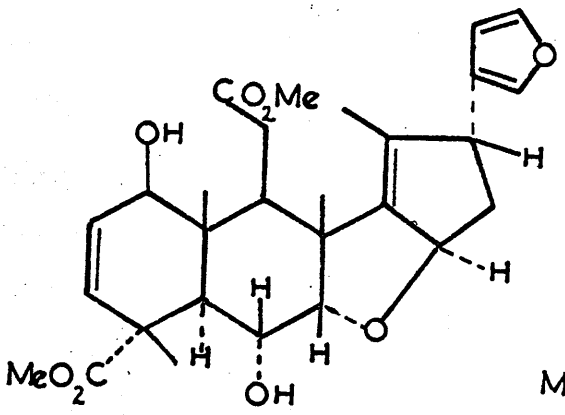

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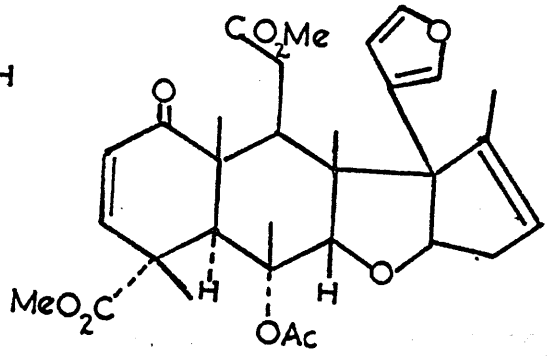

(C16)

Experimental

Isolation of Nimbin and Salannin

Nim-oil (1 Kg.) was dissolved in benzene-petrol (1: 3) (1 litre) and chromatographed over alumina (3 Kgs deactivated with 240 ml of 10% acetic acid in water. The column was washed with petrol (4 litres) which eluted fats and then ether-petrol (1: 9 - 9: 1) to afford nimbin (540 mgs). The residue obtained by removal of solvent from the mother liquors (170 gms) was rechromatographed on Spence alumina (3 Kgs.) deactivated as above. The column was eluted with petrol, ether-petrol (1: 9) and finally by gradient elution ether (3 litres) into ether-petrol (1: 5) (3 litres). The crystallisation of the earlier fractions from methanol afforded nimbin (1.9 gms) m.p. 201 - 204° (reported 205°[2]) $\nu_{max}^{CCl_4}$ 1739 (carbomethoxyls and acetate) 1688 (α,β unsaturated ketone) cm^{-1}.

Crystallisation of the later fractions from ethyl acetate-petrol afforded salannin (9.45 gms) m.p. 167 - 170°, $[\alpha]_D$ + 167° (C 1.2 in chloroform) $\nu_{max}^{CCl_4}$ 1710 (tiglate ester), 1743 (acetate and carbomethoxyl) cm^{-1}. (Found C, 68.48; H, 7.51. $C_{34}H_{44}O_9$ requires C, 68.44; H, 7.43%).

Hexahydronimbin (C4)

A solution of nimbin (520 mgs) in ethyl acetate (20 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-charcoal (315 mgs) for 12 hours at atmospheric pressure. The uptake of hydrogen was 69 ml. The solution was filtered and the solvent removed in vacuo

to afford hexahydronimbin (C4) (510 mgs) which was crystallised from ethyl acetate-petrol (350 mgs), m.p. 202 - 206° λ_{max} 213 mμ. (ε4,900).

Hydrolysis of Nimbin

Nimbin (485 mgs) was hydrolysed with 10% potassium hydroxide in 90% aqueous methanol (5 ml) at room temperature for 2 hours. The solution was acidified with 6N hydrochloric acid and the crystalline nimbic acid (380 mgs), m.p. 149 - 152° was filtered. The mother liquors were extracted with ethyl acetate to afford a further crop of nimbic acid (90 mgs).

Desacetyl Nimbin (C5)

Nimbic acid (20 mgs) was dissolved in methanol and an excess of ethereal diazomethane added. The removal of solvent afforded desacetyl nimbin (18 mgs), m.p. 206 - 210° (from ethyl acetate-petrol) $\nu_{max}^{CCl_4}$ 1687 (α,β unsaturated ketone), 1743 (carbomethoxyls) cm^{-1}.

Diethyl Nimbin (C12)

Nimbic acid (138 mgs) was dissolved in ethanol, an excess of ethereal diazoethane added and solution left at room temperature for 12 hours. The removal of solvent gave a gum which was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) for three hours at 95°. The removal of solvent gave a gum which was chromatographed on Grade IV acid alumina.

Benzene eluted material (120 mgs) which crystallised from ethyl acetate-petrol to afford diethyl nimbin (C12) (70 mgs), m.p. 174 - 176°, $[\alpha]_D$ +106° (C, 1.2 in chloroform). (Found C, 67.82; H, 7.34. $C_{32}H_{40}O_9$ requires C, 67.59; H, 7.09%).

Oxidation of Desacetyl Nimbin

To a solution of desacetyl nimbin (80 mgs) in pyridine (2 ml) was added a solution of chromium trioxide (200 mgs) in pyridine (4 ml). After two hours, methanol (0.5 ml) was added and the mixture was worked-up in the usual way to afford a yellow oil which was chromatographed over Grade IV acid alumina (3.5 gms). Benzene eluted, first, a colourless "jelly" (20 mgs) which was not further investigated and finally the crystalline 1,6 dione (C14) (35 mgs), m.p. 154 - 157° (from ethyl acetate-petrol), $[\alpha]_D$ +139° (C 1.4 in chloroform). ν_{max} (nujol) 1680 (α,β unsaturated ketone), 1730 (cyclohexanone, carbomethoxyls) cm^{-1}. (Found C, 67.70; H, 6.79. $C_{28}H_{32}O_8$ requires C, 67.73; H, 6.50%).

Decarboxylation of Nimbic Acid

Nimbin (1 g) in 5% methanolic potassium hydroxide solution (50 ml) was refluxed under nitrogen for one hour. The usual work-up afforded a yellow gum (910 mgs) which was dissolved in methanol and methylated with an excess of diazomethane. The mixture of esters was chromatographed on Grade III acid alumina. The column was eluted with petrol-benzene (1: 1) and then by gradient elution ether (2 litres) into ether-petrol

(1: 19, 1.5 litres) , 50 ml fractions being taken. The fractions 27 - 29 contained ester A (C6) (57 mgs), m.p. 138 - 142° (from ether-petrol), ν_{max} (nujol) 3500 (hydroxyl), 1735 (carbomethoxyl), 1710 (cyclohexanone) cm^{-1}.

The fractions 33 - 35 contained ester B (C7) (72 mgs), m.p. 153 - 155° (from ether-petrol), ν_{max} (nujol) 3500 (hydroxyl), 1740 (carbomethoxyl), 1690 (α,β unsaturated ketone) cm^{-1}.

The crystallisation of fraction 36 from ether-petrol afforded ester C (C7) m.p. 148 - 153°, ν_{max} (nujol) 3500 (hydroxyl), 1740 (carbomethoxyl), 1690 (α,β unsaturated ketone) cm^{-1}.

Acetate of Ester B

Ester B (72 mgs) was dissolved in pyridine (1 ml), acetic anhydride (1 ml) added and the solution was heated under nitrogen on the steam-bath for 1.5 hours. The removal of solvent afforded a gum which was chromatographed on Grade IV acid alumina. Benzene eluted the acetate of ester B which on crystallisation from chloroform-petrol had m.p. 178 - 180° (with previous sublimation at 165-8°) (57 mgs), $[\alpha]_D$ + 178° (C, 2.0 in chloroform). (Found C, 69.74; H, 7.26. $C_{28}H_{34}O_7$ requires C, 69.69; H, 7.10%).

Pyronimbic Acid (C10)

Crystalline nimbic acid (72 mgs) was sublimed at 200° and 2 m.m. pressure. The sublimed material was recrystallised from methanol

to afford pyronimbic acid (C10), (37 mgs), m.p. 252-3° $\nu_{max}^{CHCl_3}$ 1747 (enol-ζ-lactone) cm^{-1}. λ_{max} 280 mμ(ϵ, 9,500).

Preparation of Hexahydronimbin Dilactone (C11)

Hexahydronimbin (200 mgs) was hydrolysed with 10% methanolic potassium hydroxide at room temperature for 5 hours. The solution was acidified with 6N hydrochloric acid and extracted with ethyl acetate. The removal of solvent afforded a gum (195 mgs) which was treated with acetic anhydride-pyridine (3: 4.5 ml) for two hours at 110°. The removal of solvent gave a gum which was chromatographed on Grade IV acid alumina. Benzene-chloroform (1: 1) eluted a yellow gum (130 mgs) which crystallised from ethyl acetate to give the hexahydronimbin dilactone (C11) 105 mgs) m.p. 252 - 254°, $[\alpha]_D$ + 13° (C, 1.4 in chloroform), $\nu_{max}^{CCl_4}$ 1797 (enol-δ-lactone), 1768 (γ-lactone) cm^{-1}. (Found C, 70.66; H, 7.74. C_{26} H_{32} O_6 requires C, 70.89; H, 7.32%).

Hydrogenation of Hexahydronimbin

Hexahydronimbin (155 mgs) was dissolved in acetic acid (20 ml), Adam's catalyst (360 mgs) added and the solution shaken in an atmosphere of hydrogen at atmospheric pressure for 16 hours at room temperature. The solution was filtered and the solvent removed in vacuo to give the fully saturated lactone (C13), m.p. 269 - 271° (from ethyl acetate-ether) $\nu_{max}^{CCl_4}$ 1755 (δ-lactone), 1738 (carbomethoxyl and acetate) cm^{-1}. (Found C, 66.80; H, 8.36. C_{29} H_{42} O_8 requires C, 67.16; H, 8.16%).

Reaction of Diborane on Nimbin

Diborane, generated from the addition of a solution of sodium borohydride (254 mgs) in diglyme (5 ml) to a solution of boron-trifluoride etherate (2.2 ml) in diglyme (3 ml) was passed into the reaction flask containing nimbin (255 mgs) in dry tetrahydrofuran (10 ml) in an atmosphere of nitrogen at 0 - 1°C. The reaction mixture was stirred for 2 hours at room temperature. To the mixture was added methanol (2 ml), 10% aqueous sodium hydroxide (2 ml) and 30% hydrogen peroxide (2 ml) and stirred for 2 hours. The alkaline solution was acidified with dilute hydrochloric acid and worked-up in the usual way to afford an acid which was treated with diazomethane. Crystallisation from ether-petrol gave the diol (C17) (180 mgs), m.p. 125 - 129°. Oxidation of the diol in the usual manner afforded the 1,6 dione (C14) (identical I.R.).

The Reaction of Phosphorous Oxychloride on Desacetyl Nimbin

Desacetyl nimbin (57 mgs) was dissolved in pyridine (5 ml) to which redistilled phosphorous oxychloride (0.5 ml) was added in the cold and the mixture was kept at 0° for 1 hour. The solution was poured into cold sodium bicarbonate solution and extracted with chloroform. The bicarbonate solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate which on evaporation afforded acidic material (35 mgs). The acidic material was methylated with diazomethane to afford crystalline trimethylester

(29 mgs), m.p. 202 - 205° (from ethyl acetate-petrol), $\nu_{max}^{CCl_4}$ 1687, 1740 cm^{-1}. (Found C, 59.32; H, 6.34%).

Hexahydronimbin Diene.

β-naphthalene sulphonic acid (15 mgs) in "Analar" benzene was heated in a Dean and Stark apparatus for 15 mins. The solution was allowed to cool, hexahydronimbin (60 mgs) added and solution refluxed in the dark for 3 hours. The reaction mixture was filtered, benzene removed and the product separated on a preparative chromatoplate, chloroform being used as solvent. Hexahydronimbin diene (33 mgs) crystallised from ethyl acetate-petrol. m.p. 265 - 267°, λ_{max} 298 mμ $\nu_{max}^{CCl_4}$ 1662, 1717, 1732, 1751, 1797. (Found C, 70.42; H, 7.48. $C_{29}H_{36}O_7$ requires C, 70.14; H, 7.31%).

Hydrolysis of Hexahydronimbin Diene

Hexahydronimbin diene (25 mgs) was hydrolysed with 10% methanolic potassium hydroxide at room temperature for 2 hours. The usual work-up afforded an acid which was methylated with diazomethane to afford crystalline material (17 mgs), m.p. 189 - 191°, $[\alpha]_D$ + 81° (C, 2.2 in chloroform), λ_{max} 290 mμ, $\nu_{max}^{CCl_4}$ 3572, 1746, 1719, 1663 cm^{-1}. (Found C, 67.75; H, 7.79. $C_{30}H_{40}O_8$ requires C, 68.16; H, 7.63%).

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PART III

THE CONSTITUTION AND STEREOCHEMISTRY OF SALANNIN

The Constitution and Stereochemistry of Salannin.[1]

During the isolation of nimbin from nim oil, the seed oil of Melia azadirachta, a new related "modified triterpene" was obtained, which has been called salannin and for which the constitution and stereochemistry (D1) is proposed on the following basis.

Salannin m.p. 167 - 170°, $[\alpha]_D$ + 167°, analysed for $C_{34}H_{44}O_9$. Its nuclear magnetic resonance spectrum showed the presence of three quaternary methyl groups (τ 9.0, 8.77, and 8.68; 3H each, singlets) and one vinyl methyl group (τ 8.31; 3H, doublet, J = 1.5 c.p.s.), one carbomethoxyl group (τ 6.72; 3H, singlet), one acetate group (τ 8.02; 3H, singlet), one tiglate ester (τ 3.0; 1H, multiplet and τ 8.0 - 8.25; 6H, characteristic multiplets at 100 Mc/s), and one β-substituted furan ring (τ 2.7; 2H, multiplet and τ 3.67; 1H, diffuse singlet).

In the infrared, salannin showed absorptions in carbon tetrachloride solution at 1710 (ϵ 480, tiglate ester), 1743 (ϵ 1,045 acetate and methyl ester) and 1653 (olefinic linkage) cm^{-1}. Salannin does not contain a hydroxyl group (absence of infrared bands above 3000 cm^{-1}) or a ketone or aldehyde function (quantitative evaluation of the carbonyl absorptions in the infrared) so that the two remaining oxygen atoms are probably present as ethers.

Alkaline hydrolysis of salannin leads, after methylation, to a mixture of two compounds, a hydroxy-tiglate (D3), $C_{32}H_{42}O_8$, m.p. 213 - 216°, $[\alpha]_D$ + 137°, $\nu_{max}^{CCl_4}$ 3600 (free hydroxyl), 1742 (methyl ester) and 1717 (tiglate ester) cm^{-1} in which only the acetate function

has been hydrolysed and a diol (D2), $C_{27}H_{36}O_7$, m.p. 201 - 205°, $[\alpha]_D$ + 135°, $\nu_{max}^{CCl_4}$ 3465 (bonded hydroxyl), 1718 (bonded methyl ester) cm^{-1} in which both the tiglate ester and the acetate group have been hydrolysed. Prolonged treatment of the diol (D2) with acetic anhydride - pyridine results in the diacetate (D4) $C_{31}H_{40}O_9$, m.p. 230 - 234°, $[\alpha]_D$ + 126°, $\nu_{max}^{CCl_4}$ 1743 (acetates and methyl ester) cm^{-1}.

The common botanical source and the similarity of several functional groups suggested a close structural relationship between nimbin and salannin.

In particular, two features present in nimbin could easily be discerned in the 100 Mc/s nuclear magnetic resonance spectrum (Fig. I) of salannin diacetate (D4). First, the structure of rings C and D were fully supported as follows: H_{15} is coupled equally with the two protons of the methylene group at C_{16} (J_{15-16} = 7 c.p.s.), with the vinyl (C26) methyl group ($J_{15,26}$ = 2 c.p.s.) and with the methine proton H_{17} ($J_{15,17}$ = 2.5 c.p.s.). The last two are homoallylic couplings[2].

This follows from the observations that H_{15}, a diffuse multiplet centred at τ 4.51 (τ 4.42 in nimbin) simplifies to a triplet of doublets upon irradiation at the C_{26} vinyl methyl group at τ 8.35 (τ 8.4 in nimbin). Removal of the major ($J_{15,16}$ 7 c.p.s.; $\theta_{H_{15}\,H_{\alpha 16}}$ = 20°; $\theta_{H_{15}\,H_{\beta 16}}$ = 140°) coupling by irradiation at τ 7.82 (C_{16} methylene) left H_{15} as a very narrowly spaced quartet.

Second, the C_5 - C_6 - C_7 carbon chain resembles that of nimbin in the following manner. The proton H_6 (a quartet centred at τ6.0) is coupled, as in nimbin, to two neighbours: H_5 (τ 7.22, J_{5-6} = 13 c.p.s.) and H_7 (τ 5.82, J_{6-7} = 3 c.p.s.) neither H_5 nor H_7 being otherwise coupled.

These observations demonstrate the configurations of the protons attached to C_5, C_6, C_7 (axial, axial, equatorial) and the absence of hydrogen atoms at C_8 and C_{10} and the location of ether oxygen atoms at C_6 and C_7.

The second ether ring, (that not present in nimbin) would terminate most probably at C_{23}. In fact, the C_{23} methylene group gives rise to a AB quartet (τ 6.25, 6.42, 2H, J = 8.5 c.p.s.) at the expected position. The A branch (τ 6.25) has a small (less than 1 c.p.s.) ^4J coupling[3] with the methyl group at C_{22} (τ 8.78).

On the assumption that ring C is cleaved as in nimbin to generate an acetate side chain attached at C_9 [H_9 (τ 7.30 couples with one proton (τ 7.82) at C_{11}], the two ester functions (acetate and tiglate) must be located between C_1 and C_3 in salannin. They cannot be on adjacent carbon atoms since the α protons are not coupling with each other but couple individually with an intermediate methylene group at C_2 (τ 7.56, J_{AX_2} = J_{BY_2} = 3 c.p.s.). The tiglate must be at C_1 and the acetate group at C_3, rather than the reverse, for the following reason. The methyl ester $\underline{CH_3}$ resonances are abnormally high in salannin D1 (τ 6.72) and the hydroxy-tiglate D3 (τ 6.78) but normal (τ 6.40) in the diol D2, suggesting the tiglate function shields the methyl ester protons and must therefore be at C_1. In the diacetate the $\underline{CH_3}$ resonance is again abnormally high (τ 6.68) suggesting it is the carbonyl group and not the olefinic linkage of the tiglate which is shielding the methyl ester protons.

Confirmation comes from i) the fact that the methyl ester carbonyl group is unbonded in dilute solution in the hydroxy-tiglate (D3) $\nu_{max}^{CCl_4}$ 1742 cm^{-1} but is hydrogen-bonded in the diol (D2), $\nu_{max}^{CCl_4}$ 1718 cm^{-1} and

ii) the preferential hydrolysis of the less hindered acetate at C_3.

Thus, the structure D1 for salannin has been derived and there only remains for discussion the configuration at C_4, C_1, C_3, and C_{15}.

The C_4 stereochemistry can be such as to produce a cis- or a trans-fused ether ring with the α - (equatorial) hydroxyl at C_6, corresponding respectively to the oxidation of the equatorial or axial methyl group of the gem-dimethyls of C_4. A cis-fused ether ring is preferred for the following reasons. The diol D2 is oxidised to a ketol (D5) $C_{27}H_{34}O_7$, m.p. 253 - 255°, $[\alpha]_D$ +160°, $\nu_{max}^{CHCl_3}$ 1719 (hydrogen bonded methyl ester and cyclohexanone) cm^{-1}, formed by oxidation of only the C_3 hydroxyl group. Comparison of the methyl group resonances of this hydroxy-ketone with these in the diol (D2) shows that the newly introduced carbonyl group exerts a marked deshielding effect on the C_{22} and C_{24} methyl groups. A trans-fused C_6 - C_{23} ether ring would impose a quasi-boat conformation on ring A. In the most stable form of this (Dreiding model) the C_{24} methyl group would be strongly shielded[4] by the C_3 carbonyl group, contrary to the observations. With a cis-fused ether ring, the C_{24} methyl group is in the plane of the C_3 carbonyl group and therefore negatively shielded, as observed. On this basis, and consequently assumption of a chair ring A, the ester functions at C_1 and C_3 must both be axial to account for the small coupling constants (7 c.p.s.)[5] of the C_1 and C_3 proton multiplets in the nuclear magnetic resonance spectrum of the diacetate D4 (fig. I).

The C_{15} configuration can be inferred from the C_{25} methyl group resonance in salannin and its derivatives. This is consistently the most

deshielded (τ 8.62 - 8.72, table I) of the quaternary methyl groups and must owe its large paramagnetic shift to the isolated C_{13} - C_{14} tetrasubstituted double-bond.[6] The optimum geometry for such a large shift (methyl group in plane of olefinic double bond) results when the C_{15} hydrogen has the α configuration. Thus the structure and stereochemistry of salannin is as shown in D1.

Because of the marked similarity between salannin and nimbin, an attempt was made to correlate them. The method envisaged for this was to oxidise the methylene group of the tetrahydrofuran in salannin to the γ-lactone and to form the α,β-unsaturated ketone in ring A.

First, an attempt was made to oxidise the tetrahydrofuran of salannin to the corresponding γ-lactone with chromium trioxide in acetic acid. This resulted in a mixture of six compounds from which by chromatography a more polar compound, $\nu_{max}^{CCl_4}$ 1650, 1710, 1740, 1760, 1795 cm^{-1} could be isolated which was reasonably pure, as judged by thin layer chromatography. Unfortunately, this compound failed to crystallise and was not further investigated.

Secondly, the method envisaged to form the α,β unsaturated ketone in ring A was to treat the diol (D2) with toluene-p-sulphonyl chloride to form the monotosylate (D6) at the less hindered C_3 position, to oxidise the alcohol at C_1 to the ketonic function and, finally, to eliminate the elements of toluene-p-sulphonic acid by refluxing the keto-tosylate in collidine to form the enone function.

Since the oxidation of the tetrahydrofuran had failed to yield the desired product, it was decided to reduce nimbin with lithium

aluminium hydride to afford the tetrol (D7) which on treatment with toluene-p-sulphonyl chloride would readily form the primary toluene-p-sulphonates at C_4 and C_{11}. This intermediate would be expected[7] to eliminate the elements of toluene-p-sulphonic acid readily with formation of the tetrahydrofuran ring involving carbon atoms C_4 and C_6. The enone derived from salannin on lithium aluminium hydride reduction and attempted tosylation would be expected to afford the same product (D8).

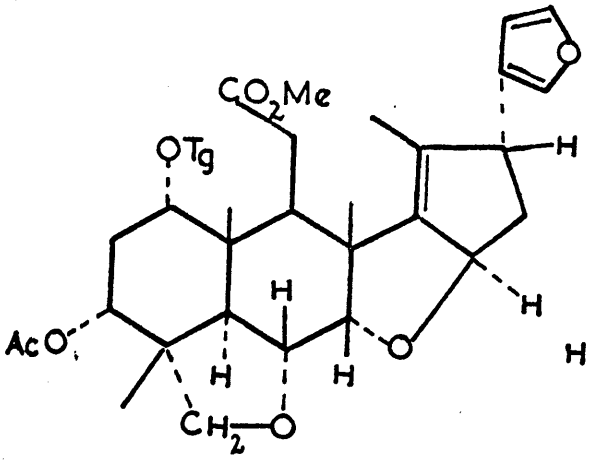
The treatment of the diol with toluene-p-sulphonyl chloride afforded the monotosylate (D6), $C_{34}H_{42}O_9$ m.p. 165 - 167°, ν_{max} (nujol) 3380, 1730, 1370, 1180 cm^{-1}. The monotosylate had bands in the nuclear magnetic resonance spectrum at τ 2.2 - 2.7 (4H, aromatic protons, multiplet), τ5.3 (1H, triplet, H - $\underset{|}{\overset{|}{C}}$ - OTs) and τ7.58 (3H, singlet, aromatic $\underline{CH_3}$).

The product of chromium trioxide-pyridine oxidation of the monotosylate showed, in the nuclear magnetic resonance spectrum, the disappearance of the tosylate group and the presence of doublets at τ 2.92 and τ 4.1 (2H, doublets, J = 10 c.p.s.). The infrared confirmed the loss of the tosylate group and showed absorption in the carbonyl region at 1730 and 1675 cm^{-1}. These observations can best be accounted for by the oxidation of the alcohol at C_1 to the ketonic group and the facile removal of the elements of toluene-p-sulphonic acid to form the α,β unsaturated ketone (D9) in ring A. Unfortunately, this compound could not be induced to crystallise and these studies were not further pursued.

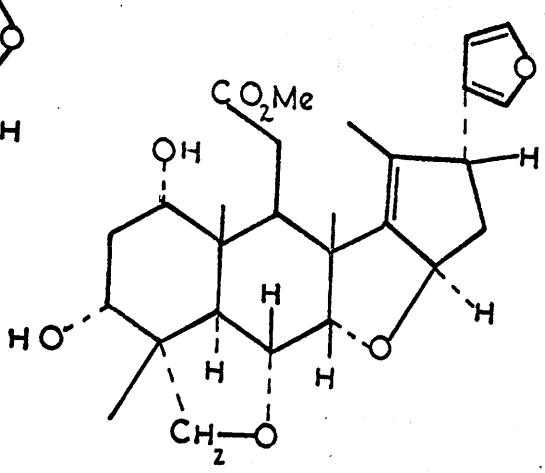
Table I

Resonances (τ) of Angular Methyl Groups in the Nuclear Magnetic Resonance Spectra of Salannin and its Derivatives.

Compound	D1	D2	D3	D4	D5
C_{25}	8.67	8.72	8.70	8.70	8.62
C_{22}	8.77	8.89	8.85	8.80	8.70
C_{24}	9.01	9.11	9.05	9.06	8.88


CO2Me
OTg
H
AcO
H
H
H
H
CH2
O

(D1)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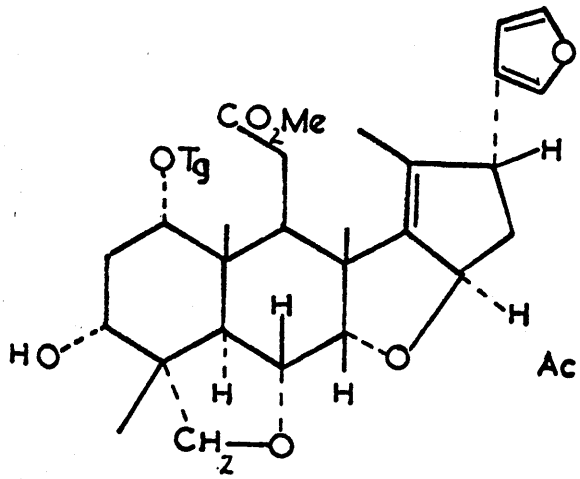
OH
H
HO
H
H
H
H
CH2
O

(D2)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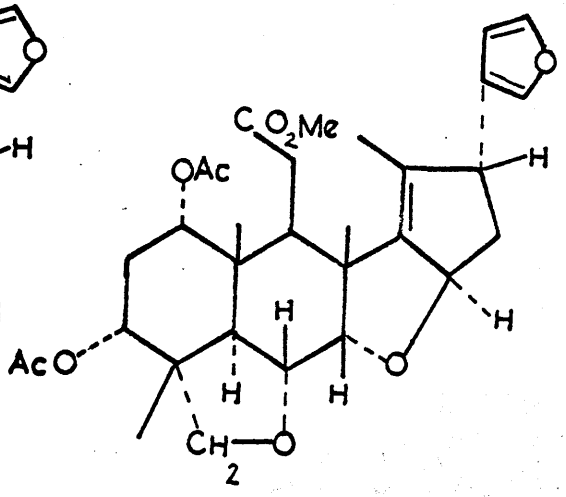
OTg
H
HO
H
H
H
H
CH2
O

(D3)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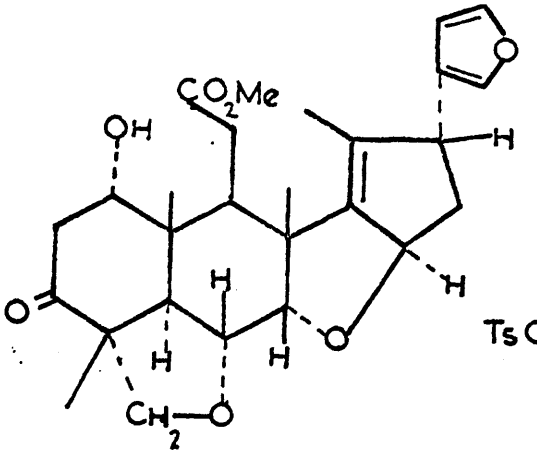
H
AcO
H
H
H
H
CH2
O

(D4)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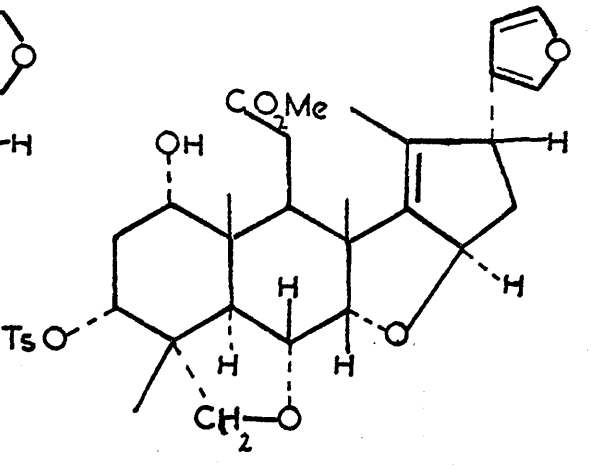
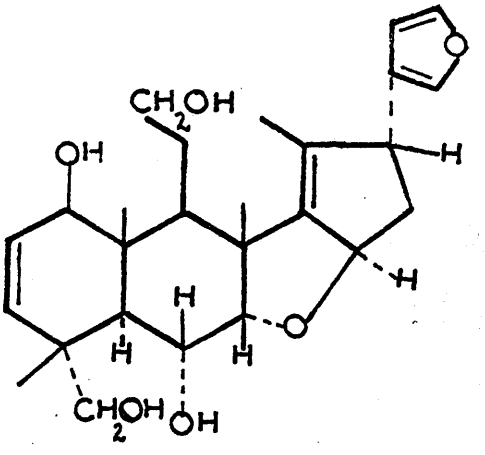
OH
H
H
H
H
H
O
CH2
O

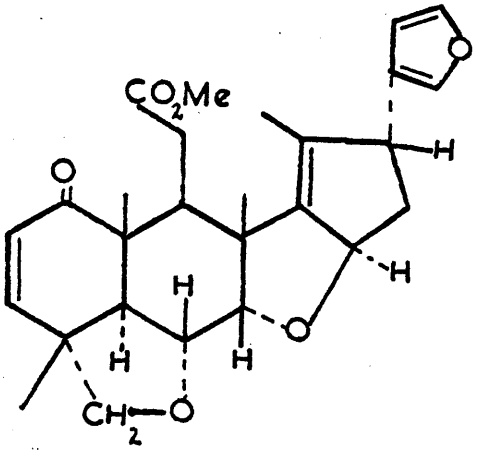
(D5)


CO2Me
OH
H
H
H
H
H
Ts
O
CH2
O

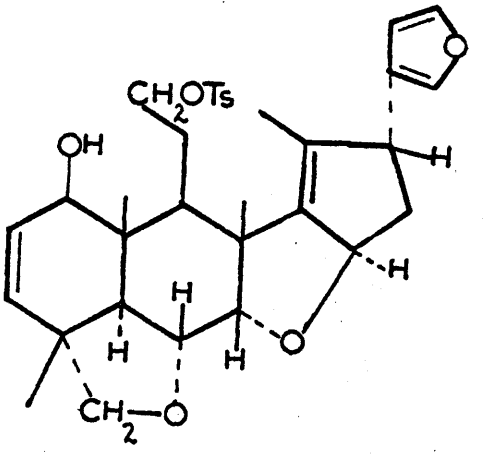
(D6)


CH2OH
OH
H
H
H
H
CH2OH
OH

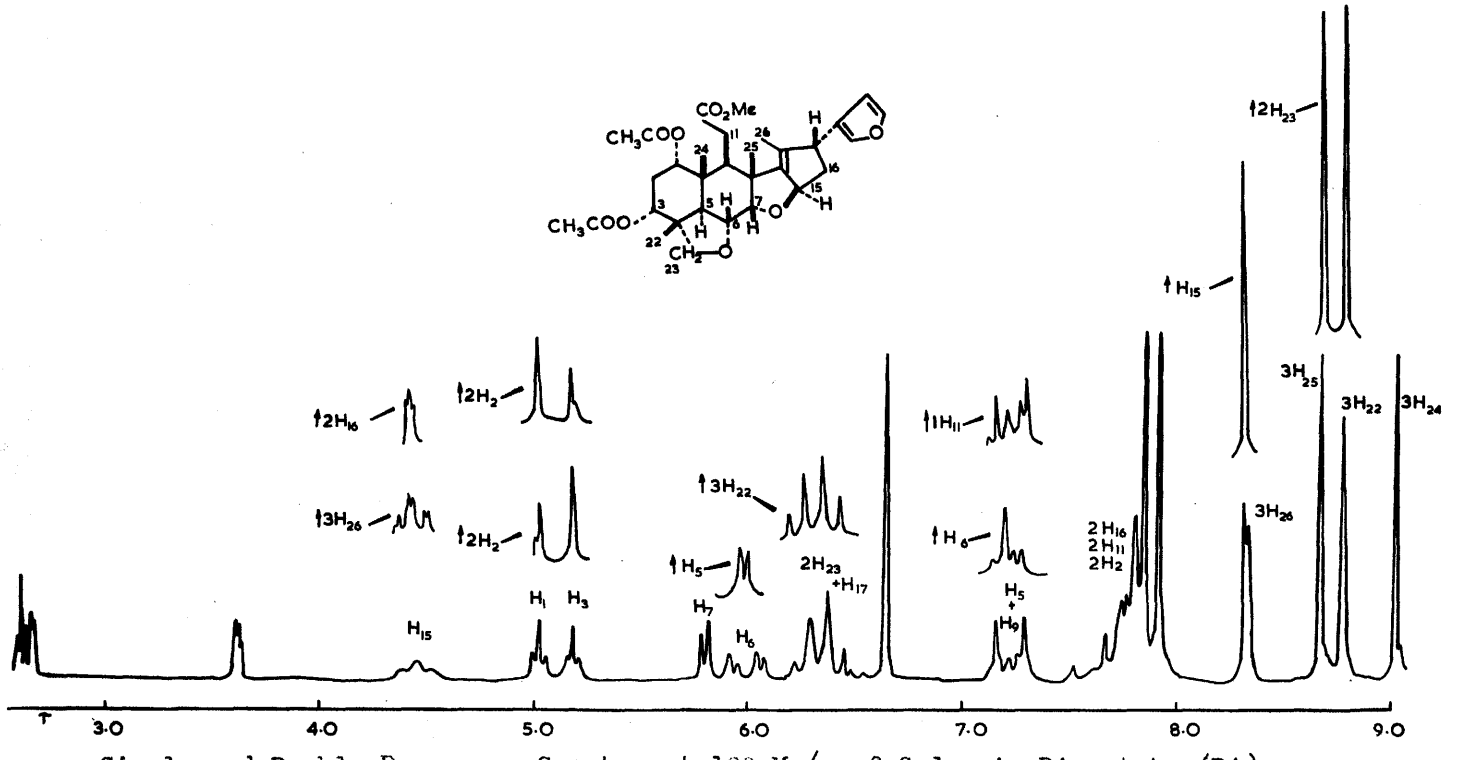
(D7)


CO2Me
O
H
H
H
H
H
CH2
O

(D9)


CH2OTs
OH
H
H
H
H
H
CH2
O

(D8)



Single and Double Resonance Spectra at 100 Mc/s of Salannin Diacetate (D4)

Fig. I.

Experimental

The isolation of salannin C_{34} H_{44} O_9, m.p. 167 - 170°, $[\alpha]_D$ + 167° (C 1.2 in chloroform) $\nu_{max}^{CCl_4}$ 1710, 1743 cm^{-1}, is described on page

Hydrolysis of Salannin.

a). Salannin (400 mgs) was dissolved in 5% methanolic potassium hydroxide and the solution was left at room temperature for two hours. The solution was diluted with water and the acidified reaction mixture was extracted with ethyl acetate. The removal of solvent, gave a gum (390 mgs) which on methylation with diazomethane showed it to be a mixture of starting material and two more polar compounds (thin-layer chromatoplate). The mixture of methyl esters was chromatographed on Grade IV acid alumina (20 gms). Benzene eluted salannin (165 mgs), m.p. 165 - 168°. Chloroform-benzene (3: 17) eluted hydroxy-tiglate (D3) (130 mgs) m.p. 213 - 215° (from ethyl acetate-petrol), $[\alpha]_D$ + 137° (C, 0.94 in chloroform), $\nu_{max}^{CCl_4}$ 3600 (free hydroxyl), 1742 (methyl ester) and 1717 (tiglate ester) cm^{-1}. (Found C, 69.26; H, 7.68. C_{32} H_{42} O_8 requires C, 69.29; H, 7.63%). Chloroform-benzene (1: 1) eluted the diol (D2) (80 mgs), m.p. 201 - 205° (from ethyl-acetate-petrol), $[\alpha]_D$ + 135° (C, 1.13 in chloroform), $\nu_{max}^{CCl_4}$ 3465 (bonded hydroxyl), 1718 (bonded methyl ester) cm^{-1}. (Found C, 68.71; H 7.50. C_{27} H_{36} O_7 requires C, 68.62; H, 7.68%).

b). Salannin (460 mgs) was treated with 10% methanolic potassium hydroxide for 18 hours at room temperature. The solution was diluted with

water, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The removal of solvent gave a glass (405 mgs) together with tiglic acid m.p. (identical with authentic material in m.p., m.m.p., and I.R.), which had sublimed from the ethyl acetate solution. The acid was dissolved in methanol and excess ethereal diazomethane added to yield the diol (380 mgs) m.p. 201 - 205 (identical with the diol prepared as above.).

Diacetate (D4)

The diol (D2) (230 mgs) was dissolved in "Analar" pyridine (2 ml), "Analar" acetic anhydride (2 ml) added and the solution left at room temperature for three days. Water was added and the solution was extracted with ethyl acetate. The usual work-up gave a gum (225 mgs) which was chromatographed on Grade III acid alumina (8 mgs). Ether-benzene (3 : 1) eluted the diacetate (D4) (180 mgs), m.p. 230 - 234° (from ethyl acetate-petrol), $[\alpha]_D$ +126° (C, 1.1 in chloroform), $\nu_{max}^{CCl_4}$ 1743 (acetates and methyl ester) cm^{-1}. (Found C, 66.83; H, 7.28; $C_{31}H_{40}O_9$ requires C, 66.89; H, 7.24%).

Oxidation of the Diol

Salannin diol (D2) (110 mgs) was dissolved in "Analar" pyridine (1 ml), chromium trioxide (400 mgs) in pyridine (5 ml) added and solution was left at room temperature for 18 hours. The usual work-up gave a red gum which was chromatographed on Grade IV acid alumina (10 gms).

Chloroform eluted the ketol (D5) (40 mgs), m.p. 253 - 255° (from ethyl acetate) $[\alpha]_D$ + 160° (C, 0.5 in chloroform), $\nu_{max}^{CHCl_3}$ 3450 (bonded hydroxyl), 1719 (bonded methyl ester) cm^{-1}. (Found C, 67.83; H, 7.11. $C_{27}H_{34}O_7$ requires C, 68.92; H, 7.28%).

Oxidation of Salannin

Salannin (10 mgs) was dissolved in acetic acid (0.5 ml) and to this was added a solution (4 ml) of chromium trioxide in acetic acid chromium trioxide (50 mgs) in acetic acid (50 ml) and solution heated at 60° for 5 mins. Methanol was added and the solution was extracted with ethyl acetate. The usual work-up gave a gum which showed six spots on a chromatoplate. The gum was chromatographed on Grade IV acid alumina. Benzene-chloroform (1: 4) eluted material (6 mgs) $\nu_{max}^{CCl_4}$ 1650, 1710, 1740, 1760, 1795 cm^{-1} which, although it was reasonably pure as judged by thin-layer chromatography, failed to crystallise.

Monotosylate (D6)

Salannin diol (D2) (190 mgs) was dissolved in pyridine (3 ml) and toluene-p-sulphonyl chloride (1 gm) was added and left at room temperature for 36 hours. The usual work-up gave a gum (230 mgs) which was chromatographed on Grade IV acid alumina (15 gms). Chloroform-benzene (1: 19 - 1 - 9) eluted the monotosylate (D6) (145 mgs), m.p. 165 - 167° (from aqueous methanol), ν_{max} 3380, 1730, 1370, 1180 cm^{-1}. (Found C, 64.49; H, 6.40. $C_{34}H_{42}O_9$ requires C, 65.15; H, 6.75%). Elution

with chloroform-benzene (1: 1) eluted unchanged diol (55 mgs) m.p. 198 - 203° (identical in I.R., m.p., m.m.p. with authentic sample).

Oxidation of Monotosylate (D6)

The tosylate (50 mgs) was dissolved in pyridine (3 ml), chromium trioxide (250 mgs) was added and the solution left at room temperature for 18 hours. The usual work-up afforded a gum (48 mgs) which was chromatographed on Grade IV acid alumina (11 gms). Chloroform-benzene (3: 17 - 1: 4) eluted material (30 mgs) ν_{max} (nujol) 1730, 1675 which although it was pure as judged by thin-layer chromatography failed to crystallise.

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