A Thesis

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PART I

THE CONSTITUTION AND STEREOCHEMISTRY

OF DRIMENIN AND ISODRIMENIN

ACKNOWLEDGMENT

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INTRODUCTION

Three bicyclofarnesol sesquiterpenoid lactones, drimenin, isodrimenin and confertifolin have been isolated[3,30] from the South American Drimys species which previously yielded drimenol[2,29]. The structural elucidation of drimenin and isodrimenin forms the basis of this section of the present thesis. The discussion of the chemistry of drimenin and isodrimenin is prefaced by a review of sesquiterpene biogenesis, the acid-catalysed cyclisation of farnesol derivatives and the chemistry of the known bicyclofarnesol sesquiterpenoids, iresin, farnesiferols A, B and C, and drimenol.

SESQUITERPENOID BIOGENESIS

The biogenesis of terpenes was first systematised by the enunciation of the Biogenetic Isoprene Rule of Ruzicka[1] in 1953. The conspicuous absence, at that time, of a sesquiterpene with a bicyclofarnesol skeleton (1) led Ruzicka to the plausible assumption that the biogenesis of steroids, triterpenes and diterpenes differed in some fundamental detail from that of the sesquiterpenes and monoterpenes. Since then, however, a small group of natural bicyclofarnesol sesquiterpenes has emerged, which invalidate Ruzicka's assumption. In this group the alcohol drimenol (2)[2] and the lactones drimenin (3) isodrimenin (4) and confertifolin (5)[3] hold key positions since they are, at present, the only known bicyclofarnesol compounds having the absolute stereochemistry of the higher terpenes.

Ruzicka and his colleagues, in a discussion of the Biogenetic Isoprene Rule in its application to triterpenes, developed a scheme leading from squalene (6) to all the known cyclic triterpene groups in their full structural and configurational detail[4]. This scheme was based on a well defined set of idealised rules concerning the course of acid-catalysed cyclisation and rearrangements. The principal requirement is that of antiplanar addition which results in the newly formed bonds being parallel. In this way the relative stereochemistry of the product and the conformation of the cyclising molecule are defined. The latter point is illustrated by reference to the cyclisation of the 1,4-hexadiene (7) which reacts in a chair conformation (8) to give a trans-anti-trans product (9) and in a boat conformation (10) to a trans-syn-trans

system (11). The mechanistic requirements for antiplanar cyclisation are assumed to be synchronous bond formation, taking place without conformational reorganisation during the reaction or stepwise reaction via conformationally stable cation intermediates. It must be emphasised, however, that an identical steric result can arise via a conformationally unstable intermediate when the addition steps occur at a faster rate than conformational equilibration or when there is steric control in the unstable conformation. This demonstrates clearly the ambiguity which can arise in correlating the mechanism with the stereochemical outcome of a reaction. Further postulates in the cyclisation scheme of squalene are that Wagner Meerwein rearrangements and 1,2 eliminations only occur if the stereochemistry is correct i.e. trans-anti-parallel, and that carbonium ions are best represented by double bond complexes i.e. non classical ions.

The above stereomechanistic approach to biogenesis has been applied to sesquiterpenes by Hendrickson[5] to show how the manifold structural variations in this field can be derived from farnesol (12) using the same basic assumptions. Farnesol can arise by condensation of three molecules of mevalonic acid (13) the actual isoprenoid precursor used in terpene biosynthesis[6,7]. It is assumed that the central double bond of farnesol is trans and the biogenetic process commences by ionisation of the allylic hydroxyl group followed by cyclisation of one of the other double bonds to the allylic cation to yield a six-membered ring intermediate and a number of large ring intermediates. The concept of large ring species was introduced by Ruzicka in his original hypothesis[1]. Henrickson[5] considered

that trans-farnesol (22) and cis-farnesol (15), formed via anionotropic conversion through the corresponding allylic tertiary alcohol nerolidol (14), were reasonable precursors for cyclisation to all the cyclic sesquiterpenes. Thus by folding the cis or trans farnesol chain in such a way that the π electrons of one of the isolated double bonds can overlap with the allylic cation, the intermediate cations are obtained and some of their available reaction paths will now be considered briefly.

It is only in cis-farnesol (15) that the central double bond can be utilised via (16) to give the cations (17) and (18). The former (17) is electronically and sterically favourable and leads to the monocyclic six-membered ring sesquiterpenes e.g. bisabolene (26) by loss of a proton.

Interaction of the terminal double bond with the allylic cation in cis-farnesol (15) affords the intermediates (20) and (21) via (19) and in trans-farnesol (22) the intermediates (24) and (25) via (23). Models show that each has a unique conformation governed by π orbital overlap and steric factors in the course of its formation. However the eleven-membered ring cation (21) is sterically favoured over (20) and (24) is preferred to (25) on steric and electronic grounds. These two species (21) and (24) are intermediate in the formation of a large number of the sesquiterpenes.

The two double bonds in the trans cation (24) are in close proximity and favourably situated for concerted cyclisation. The alcohol resulting from hydration of the cationic centre can be written in the equivalent conformations (27 a-d) which undergo concerted cyclisation to

the eudesmol and guaiazulene skeletons (28) and (29). The intermediate (30) formed from (27b) by double bond isomerisation can cyclise concertedly to the β-vetivone series (31) and to the species (32) which leads as shown to the eremophilones, (33) to (35). Sesquiterpenes derived from (24) without further cyclisation are also known e.g. pyrethrosin (36).

In the cis cation (21) the double bonds are not closely situated and the hydrogen on C_1 is lying inside the ring. Deprotonation affords humulene (37) and attack of the C_{10} cationic centre by the 2,3 double bond leads directly to caryophyllene (38) with its known stereochemistry. 1,3-Migration of the C_1 hydrogen to (39) followed by cyclisation yields the bicyclic ion (40) which rearranges as shown to longifolene (42) via (41).

The case of the bicyclofarnesols fits well in the scheme of sesquiterpene biogenesis and they are, in fact, the simplest examples of farnesol cyclisation. Thus fully concerted cyclisation of trans-farnesol (43) leads directly to drimenol (44)[2] with the correct stereochemistry. It is probable that the lactones drimenin (3), isodrimenin (4) and confertifolin (5)[3] arise by secondary oxidation of a drimenol type precursor. The appropriate precursors for drimenol and iresin (47)[8] must have opposite absolute stereochemistries. The biogenesis of iresin is as depicted, (45) to (46), followed by secondary oxidation. It is interesting to note that the Drimys species has not, so far, yielded a sesquiterpene with an oxygen substituent on C_3 whereas the iresin family all possess this feature. Farnesiferol A[9], the remaining member of the bicyclofarnesol group, is also oxygenated on C_3

and like iresin has the opposite absolute stereochemistry to drimenol. It has been suggested that there is a correlation between absolute stereochemistry and introduction of a C_3 oxygen substituent in the process of biogenesis[39]*. Farnesiferol A (48) and its monocyclic isomers farnesiferols B (49) and C (50)[9,10] are very interesting from a biogenetic viewpoint in that their possible acyclic precursor, the umbelliferone ether umbelliprenine (51), has been isolated[11]. It is attractive to base the biogenesis of the farnesiferols on the concerted and non-concerted cyclisation of umbelliprenine. Since the stereochemistry at C_9 in a bicyclofarnesol is a direct reflection[12] of the cis or trans nature of the allylic double bond in the farnesol precursor, farnesiferol A must arise from cyclisation of cis-umbelliprenine, (52) to (53), in order to give the C_9 β-substituent (assuming that the assigned stereochemistry at C_9 is correct). In the formation of farnesiferol B and C the fully concerted cyclisation might be interrupted to yield the intermediate cation (54) which by loss of a proton (a) affords farnesiferol B or is transformed into farnesiferol C by internal attack of the C_3 hydroxyl on the cationic centre (b).

The fact that the Biogenetic Isoprene Rule was founded on purely theoretical considerations has led several workers, principally Eschenmoser and his colleagues, to seek in vitro support. Thus

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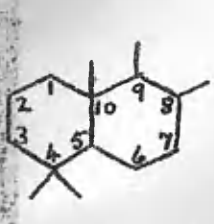
*This postulate appears to be invalidated by the recent isolation (subject to direct comparison) in this laboratory of enantio-isoiresin from Drimys winteri.

acid-catalysed cyclisations of a variety of farnesol derivatives have been carried out with some measure of success. In particular, Eschenmoser[13] has achieved a total synthesis of racemic drimenol in vitro from a farnesol precursor (see p. 14). The work which embodies this synthesis has a direct bearing on the present discussion and is summarised in the following section.



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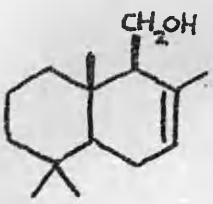

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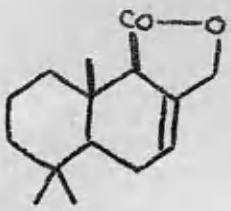

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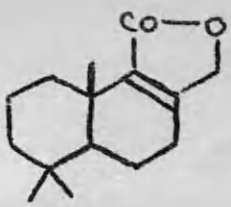

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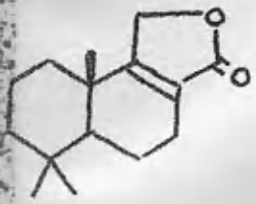

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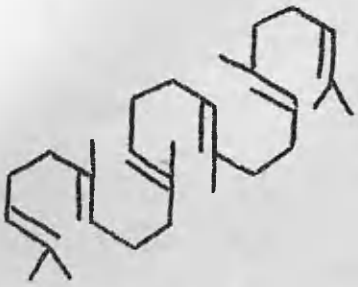

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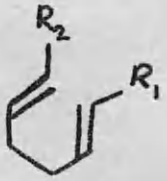

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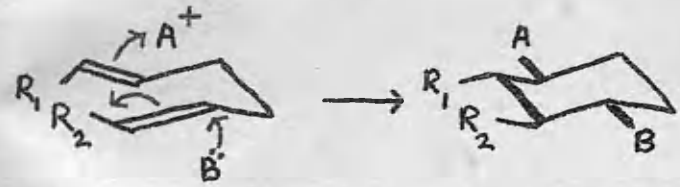

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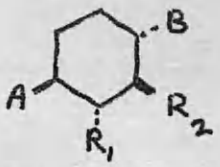

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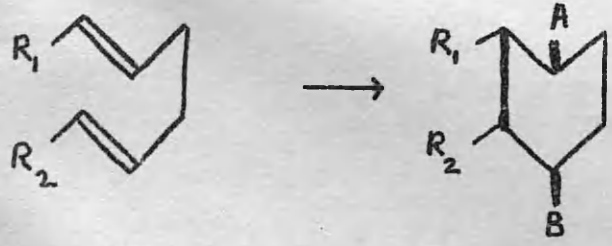

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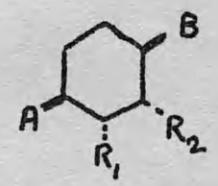

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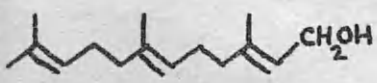

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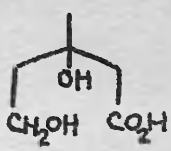

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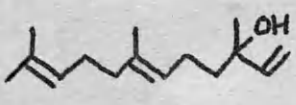

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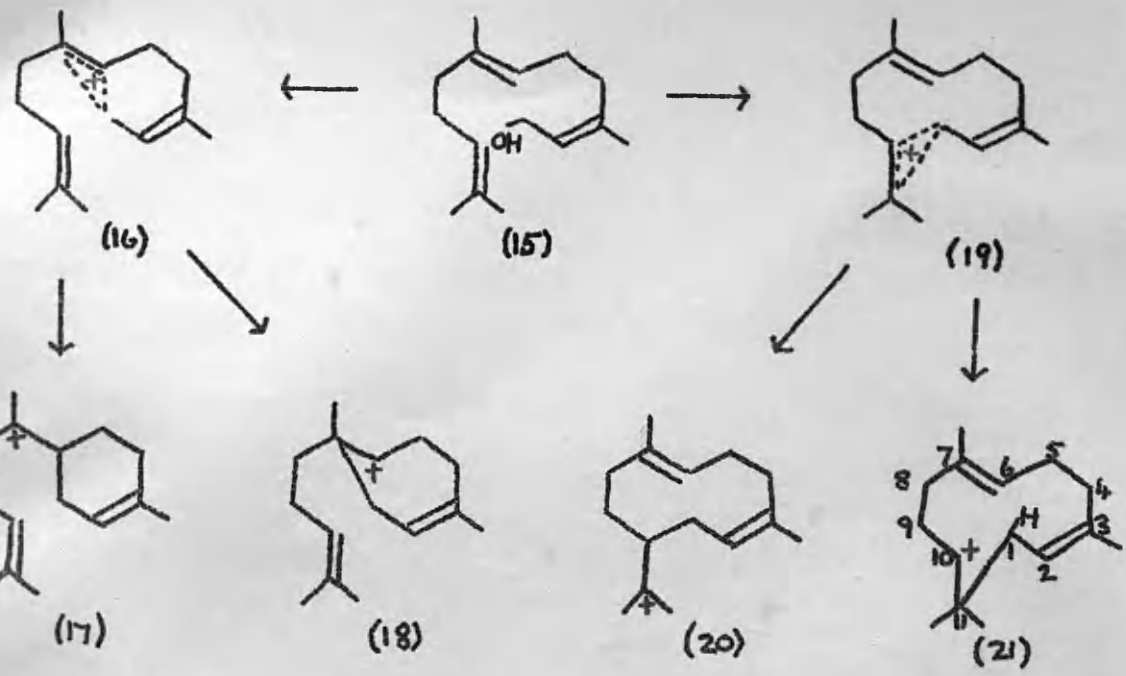
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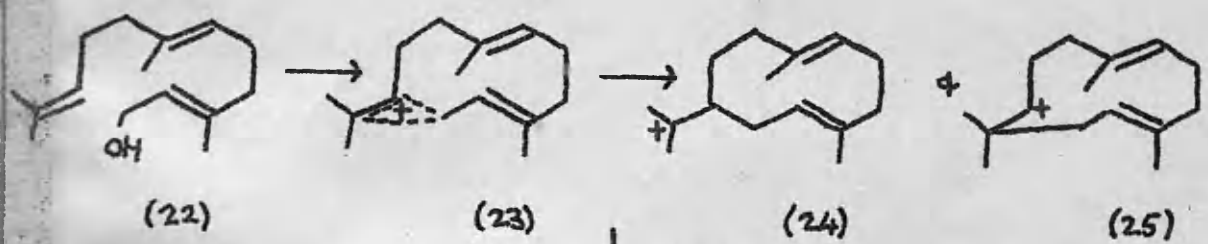
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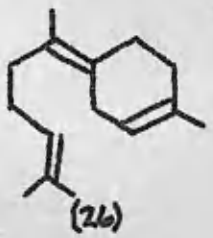
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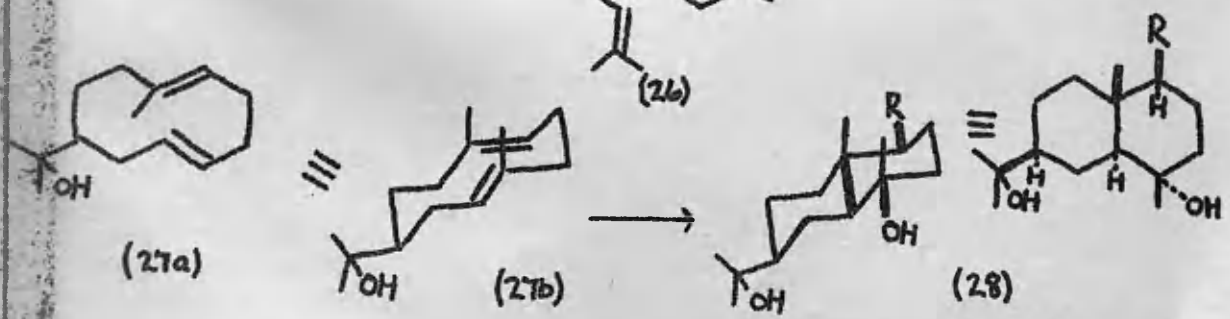
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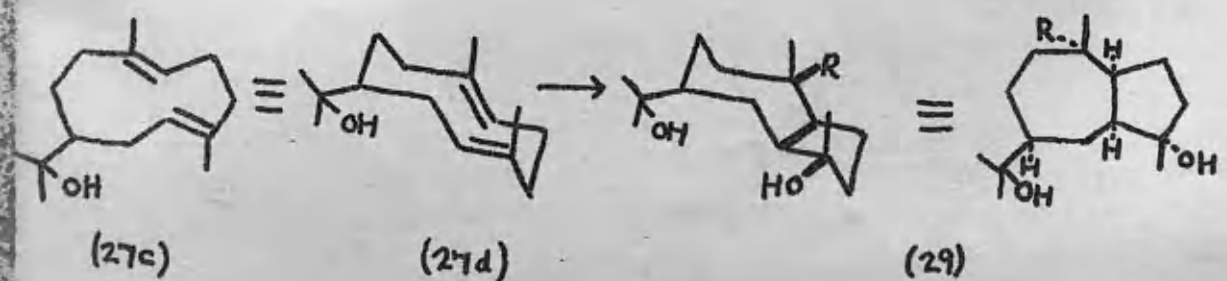
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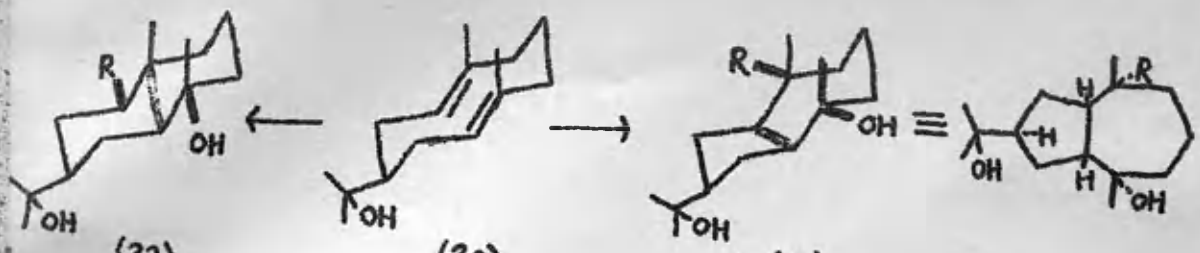

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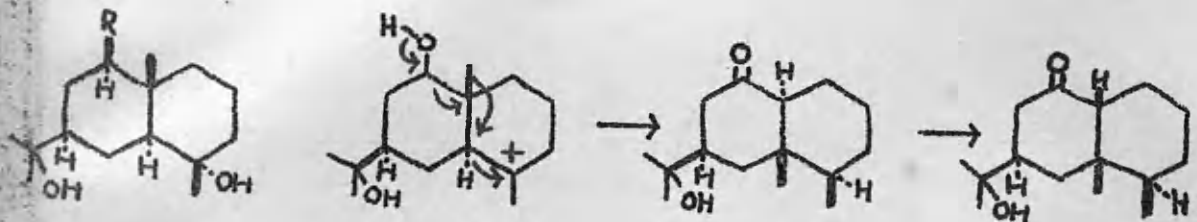

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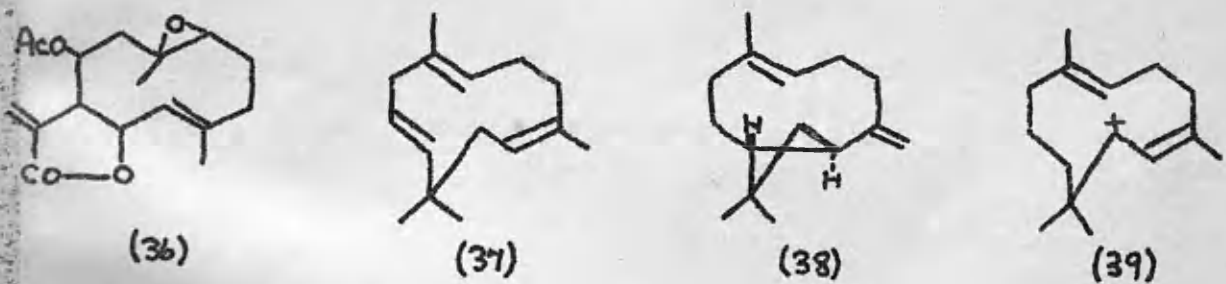

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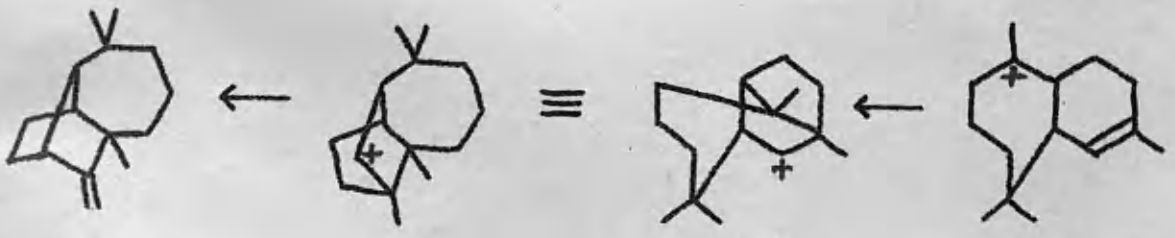

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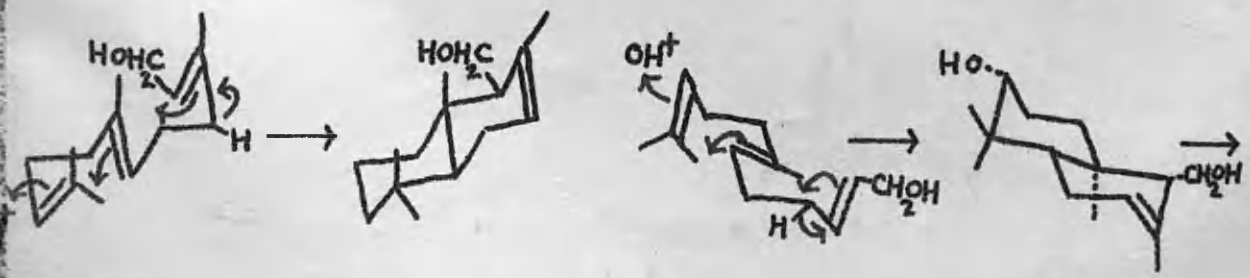

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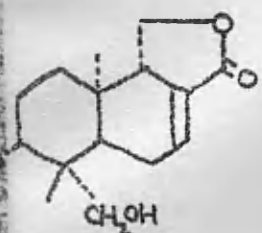

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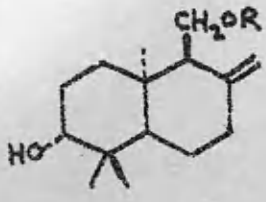

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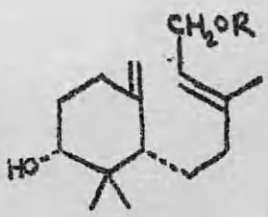

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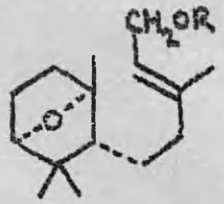

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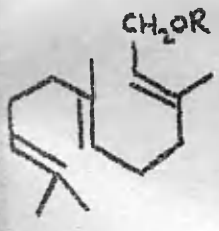

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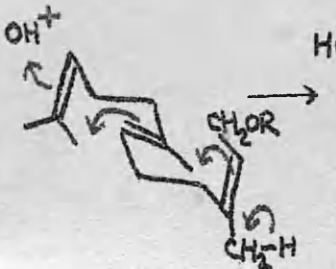

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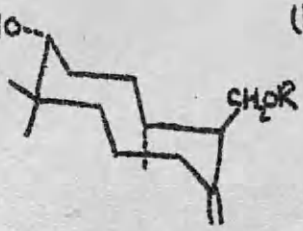

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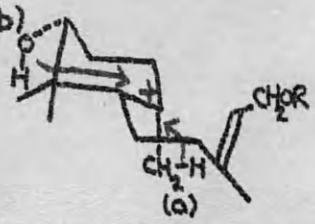

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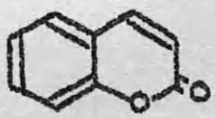
R = 

ACID-CATALYSED CYCLISATION OF FARNESOL DERIVATIVES

Cyclisation of farnesic acid (55)[12] in benzene with boron trifluoride etherate at less than 5° yielded two monocyclic acids which exhibited ultraviolet absorption characteristic of $\alpha\beta$-unsaturated acids. Dehydration of the hydroxy-acid (56) obtained from dihydro-β-ionone afforded the same two acids which must therefore be the geometrical isomers (57) and (58).

Treatment of the stable trans acid (57)[12] with boron trifluoride etherate at 40° gave, in 35% yield, a pure bicyclic acid (59) m.p. 131°. With formic acid-sulphuric acid a low yield of a second acid, the $\alpha\beta$-unsaturated isomer (60) m.p. 153-4°, was obtained. A third acid (61) m.p. 138° arose from the action of formic acid-sulphuric acid on the cis acid (58)[12]. The three acids all had the same basic octalin skeleton since hydrolysis of the acid chloride of (59) yielded the $\alpha\beta$-unsaturated isomer (60) and on treatment with base under equilibration conditions (61) was converted into the stable epimer (59).

Cyclisation of farnesic acid (55) originally with formic acid-sulphuric acid[14] and later with boron trifluoride etherate[12] at 30-35° led principally to the acid (59) but a small amount of the epimeric acid (61) was also isolated. In another experiment[15] with formic acid-sulphuric acid at 60° the $\alpha\beta$-unsaturated acid (60) was obtained. It is unlikely that the bicyclic acids are formed through the monocyclic acids since the latter are more difficult to cyclise.

The three bicyclofarnesic acids were assigned cis-octalin structures[12]

on the basis of the non-identity of their infrared solution spectra with that of the known optically active acid (62). Wolff and Lederer[16], however, converted the acid (59) into the bis-homo-acid which was identical with the acid (63) of known stereochemistry obtained from ambreinolide (64). The yield of (63) was very low and Stork[12] suggested that it had been derived from trans-octalin contaminant in the mainly cis octalin cyclisation product. He also proposed that the lack of trans-octalin product i.e. of concerted cyclisation was due to the lowering of the nucleophilic character of the double bond in conjugation with the carboxyl group. Thus farnesylacetic acid (65) would be expected to undergo concerted cyclisation to ambreinolide (64). In fact dl-ambreinolide was obtained in 3% yield by action of stannic chloride, stannic bromide or formic acid on (65). α- and β-monocyclic farnesylacetic acids (66) and (67) were synthesised from α- and β-ionone respectively and subjected to cyclisation conditions. The β-isomer, with stannic chloride or formic acid yielded 2% dl-ambreinolide and the α-isomer (66), with stannic chloride, ambreinolide and 8-epi-ambreinolide (68)[12].

These experiments seemed to support Stork's theory but the results of Wolff and Lederer[16] could not be ignored. This confused situation was resolved by the work of Eschenmoser and his colleagues who prepared trans- and cis-apofarnesic acids (69) and (70)[17]. The trans-isomer (69), on treatment with formic acid-sulphuric acid followed by mild base, yielded the hydroxy acid (71) which was oxidised to the corresponding keto-ester (72; R = Me). The latter was stable to potassium t-amylate

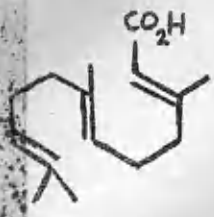
and was reduced by sodium borohydride or hydrogen over platinum to an epimeric hydroxy-acid (73). Cyclisation of the cis-isomer (70) afforded the hydroxy-acid (74) which was oxidised to the keto-acid (75). Treatment of the latter with potassium t-amylate resulted in epimerisation of the carboxyl group with formation of the keto-acid (72). Reduction of (75) with sodium borohydride yielded a mixture of hydroxy-acids, (74) and its C_8 epimer (76). The stereochemistry of the ring junction in the cyclisation products was settled by elimination of the methane sulphonyl derivative of the hydroxy-acid (73) to the $\alpha\beta$-unsaturated acid (77) followed by hydrogenation over platinum to the known saturated acid (78) previously obtained from manool and lanosterol[19]. These facts lead unequivocally to the stereochemistry, shown in (71) and (74), for the hydroxy-acid cyclisation products.

The hydroxy acid (71) was reduced with lithium aluminium hydride to the diol (79; R = H) whose acetate (79; R = Ac) was oxidised to the corresponding ketone (80) which reacted with methyl magnesium iodide to yield (81). Dehydration of the latter with formic acid afforded the unsaturated alcohol (82) whose infrared spectrum was identical with natural drimenol[2]. The acid (59) from cyclisation of farnesic acid also yielded racemic drimenol on lithium aluminium hydride reduction. Thus the stereochemistry at the ring junction of the three acids (59), (60) and (61) is unequivocally trans.

The cyclisation of α- and β-monocyclo-homofarnesic acids, (83) and (84), has also been investigated. Lucius[21], using formic acid-sulphuric acid,

isolated three stereoisomeric lactones in good yield. Two of them were shown to be trans-decalins by their identity with the lactone (85), obtained from sclareol, and its C_8 epimer (86). The third lactone was assigned the cis-decalin structure (87). Corey and Sauers[22] converted the lactone (85) into onocerin derivatives and pentacyclosqualene by electrolysis of the ammonium salt of the corresponding hydroxy-acid.

These results cannot be interpreted as being indicative of a fully concerted cyclisation process especially in view of the fact that cyclisation of farnesic acid with a cis-central double bond (88)[20], from which a cis-decalin system would be expected by antiplanar addition, also yields (71; R = H) with a trans-ring junction. The most probable conclusion to be drawn[20] is that the reaction proceeds stepwise through a common cationic intermediate e.g. (89) which equilibrates conformationally more quickly than it reacts with the side chain double bond. The formation of a trans-decalin would then be sterically controlled by the axial methyl group on C_4. It is evident, however, from the low yields of trans-decalin products obtained in vitro, that the cyclisation of farnesol precursors in nature is a highly specific process and is not readily reproducible in the laboratory.



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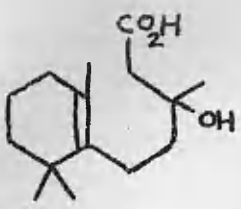

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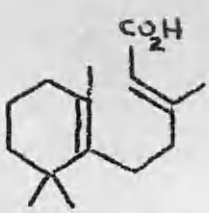

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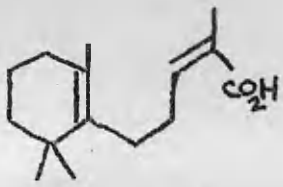

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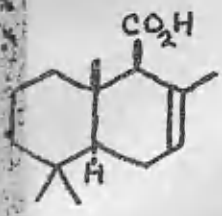

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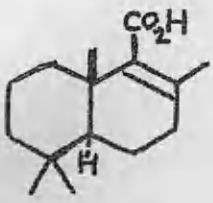

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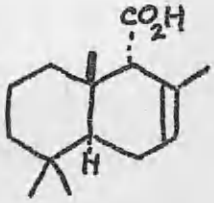

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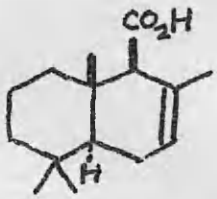

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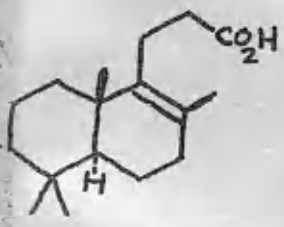

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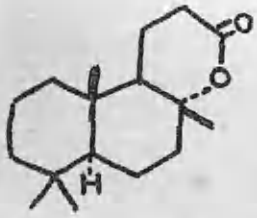

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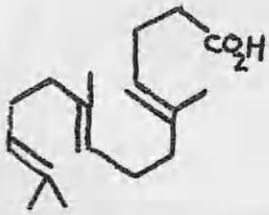

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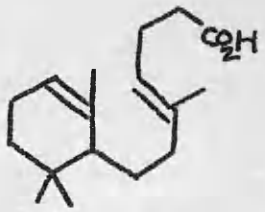

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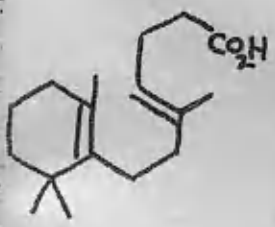

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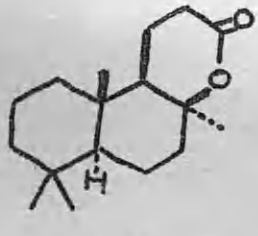

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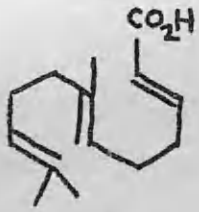

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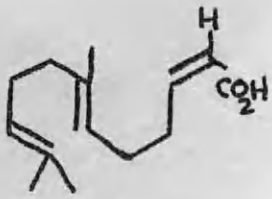

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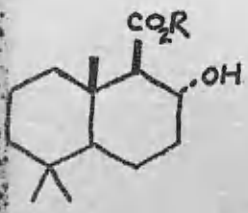

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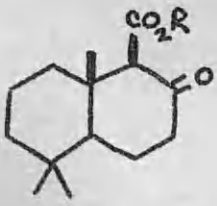

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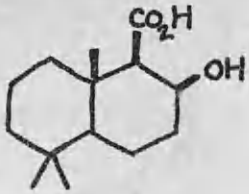

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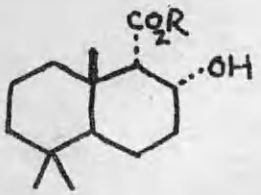

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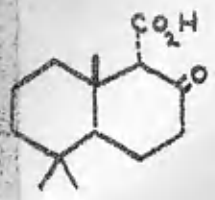

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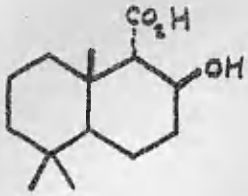

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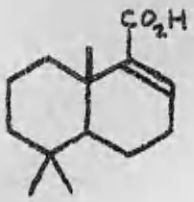

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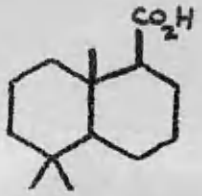

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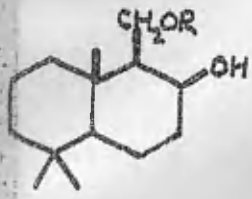

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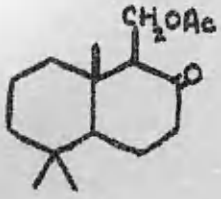

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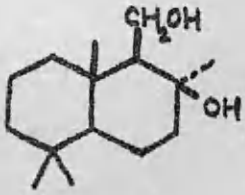

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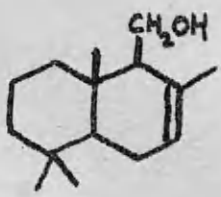

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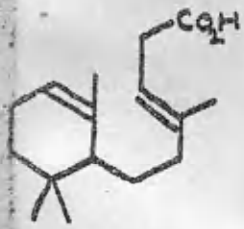

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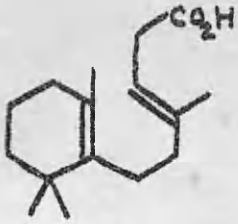

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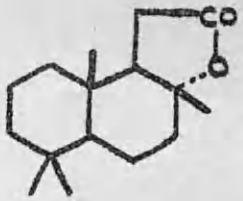

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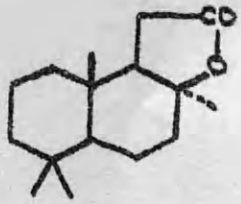

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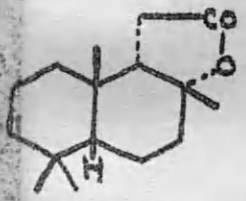

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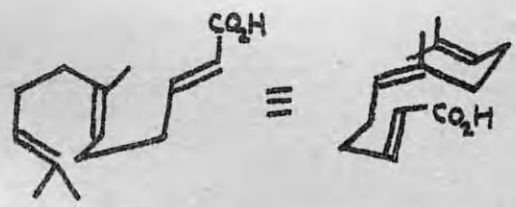

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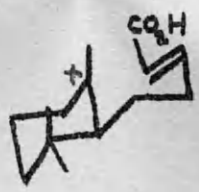


(89)

REVIEW OF THE BICYCLOFARNESOL SESQUITERPENOIDS

(a) Iresin[8]:- The first natural bicyclofarnesol derivative to have its structure elucidated was iresin, $C_{15}H_{22}O_4$, (90; R = R' = H) which was isolated from the Mexican shrub Iresine celosioides L. Its spectroscopic properties $[\lambda_{max.}$ 224 m.μ. (ε 14,500); $\nu_{max.}$ 3469, 1752, 1690 cm.$^{-1}]$ indicated the presence of an α,β-unsaturated γ-lactone and one or more hydroxyl groups. Under mild acetylation conditions iresin formed a diacetate (90; R = R' = Ac) which could be easily hydrolysed back to iresin, and hydrogenation over a palladium catalyst furnished dihydroiresin (91; R = R' = H). On mild base hydrolysis of dihydroiresin diacetate (91; R = R' = Ac) or mild base treatment of dihydroiresin itself, isodihydroiresin (92; R = R' = H) was obtained. That simple opening of the lactone and relactonisation with another hydroxyl was not involved in this change was shown by lithium aluminium hydride reduction of iresin (90) and dihydroiresin (91) to the same tetrol (93) and of isodihydroiresin to a different tetrol (94). Lithium aluminium hydride reduction of iresin results in reduction of the α,β-unsaturated γ-lactone system.

Treatment of iresin with benzaldehyde (or acetone) in presence of zinc chloride yielded a benzylidine (or acetylidine) derivative which could be hydrogenated and isomerised in base to the corresponding isodihydroiresin (92). This series of reactions indicates clearly that the hydroxyl groups of iresin cannot be involved in the base-induced isomerisation of the dihydro-series, which must therefore involve epimerisation α to an enolisable centre.

Dehydrogenation of iresin afforded 1,5-dimethyl-naphthalene (95) and 1,5-dimethyl-2-naphthol (96), novel dehydrogenation products in the sesquiterpene field. These products immediately suggested a new type of skeleton for iresin. The isolation of the phenol was particularly useful since it fixed the position of one oxygen function. It was also reminiscent of dehydrogenation of pentacyclic triterpenes, e.g. β-amyrin, with a 3-hydroxy-4,4-dimethyl system. On the assumption that iresin obeyed the isoprene rule there were only two C skeletons, (97) and (98) that needed to be considered. The system with the C_5 methyl was excluded by the following experiments. Oxidation of isodihydroiresin (92) with chromium trioxide in pyridine yielded the keto-aldehyde (99) which underwent a retro-aldol fission in hot ethanolic hydrochloric acid to give 13-nor-3-dehydro-isodihydroiresin (100). Treatment of the latter with bromine resulted in formation of the 2,6-dibromo-enone (101) which was dehydrobrominated to the 1,4,6-trienone (102). The spectroscopic characteristics of (101) and (102) were typical of those of the corresponding steroidal compounds. The 1,4,6-trienone system is only possible in iresin if C_{10} and not C_5 bears the angular methyl group.

Ozonolysis of iresin proved to be a very informative experiment. The product (103) had not the expected aldehyde group but showed spectroscopic properties consistent with an α-ketobutanolide. The loss of the original hydroxyl groups suggested that internal acetal formation had taken place. Confirmation of this was provided by the observation that ozonolysis of acetylidine iresin (90; R and R' = $(CH_3)_2C<$) yielded

the aldehydo-α-ketobutanolide (104), which cyclised immediately to (103) on treatment with acid to remove the protecting acetylidine grouping. The formation of the internal acetal (103) requires that the C_3-hydroxyl, the C_4-hydroxymethylene and the C_5-C_6 bond be cis.

Oxidation of iresin with chromium trioxide in pyridine led to a mixture of products. The less polar product analysed for loss of CH_4O and was assigned the 13-nor-3-dehydro structure (105). This must have arisen via an intermediate β-keto-aldehyde or β-keto-acid thus requiring the presence of a primary hydroxyl in iresin. The second product was the hydroxy-aldehyde (106). Oxidation of the trityl ether of iresin followed by acid cleavage of the resultant keto-trityl ether was accompanied by retro-aldol fission with formation of formaldehyde (characterised as its dimedone derivative) and the nor-ketone (105). This series of reactions confirmed the presence of a primary-secondary 1,3-glycol system.

The reactions of the glycol system were investigated with a view to removing the oxygens. The trityl ether of 3-dehydro-isodihydroiresin (107) was treated with ethane dithiol in presence of boron trifluoride. The trityl group was removed during the reaction and the resultant thio-acetal was desulphurised with Raney-Nickel to yield 3-deoxy-isodihydroiresin (108). The primary alcohol was removed by oxidation to the aldehyde, formation of the thio-acetal and desulphurisation with Raney-Nickel to the bisdeoxy-lactone (109) (see p. 45).

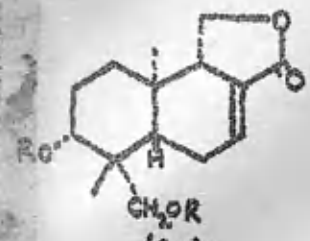
The ozonolysis of iresin fixed the relative stereochemistry of the

glycol system and the C_5 hydrogen. Since hydrogenation of isoiresin (110) (see below) yielded dihydroiresin (91) and addition of hydrogen must occur from the less hindered face (i.e. β), the relative stereochemistry at C_9 in iresin is revealed. The nature of the ring junction and absolute stereochemistry were derived by optical rotatory dispersion. The curve of the 13-nor-3-ketone (100) exhibited a negative Cotton effect in contrast to the positive effect of 4-methyl-3-keto-5α-steroids and the curve of the dibromo-ketone (101) was antipodal to that of 2α,6β-dibromo-4-methyl-testosterone acetate. Thus iresin possesses the opposite absolute stereochemistry to that of the steroids and higher terpenes. The facts given above lead unequivocally to the structure and absolute stereochemistry (90; R = R' = H) for iresin. This was subsequently confirmed by an X-ray study of iresin di-p-bromobenzoate[38].

Several other related compounds were isolated from Iresine celosioides L. Dihydroiresone, $C_{15}H_{22}O_4$, (111) showed only weak absorption in the ultraviolet ($\lambda_{max.}$ 290 mμ). Its infrared spectrum indicated the presence of a hydroxyl group, a γ-lactone and a ketonic function. Treatment of (111) with boiling acid caused retro-aldolisation to occur with formation of 13-nor-3-dehydro-dihydroiresin (112) which was transformed in base to the known 13-nor-3-dehydro-isodihydroiresin (100). Sodium borohydride reduction of dihydroiresone afforded dihydroiresin (91) which was also isolated in very small amounts from the plant.

During hydrogenation of crude iresin over palladium it was noticed that some material was not absorbing hydrogen. This observation led to

the isolation of isoiresin (110) which was hydrogenated slowly over platinum in acetic acid to yield dihydroiresin (91). Since isoiresin still has an $\alpha\beta$-unsaturated γ-lactone system it must be the 8,9-double bond isomer of iresin.



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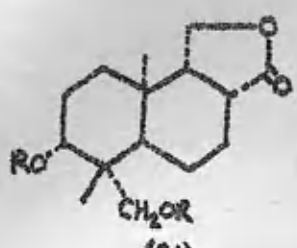

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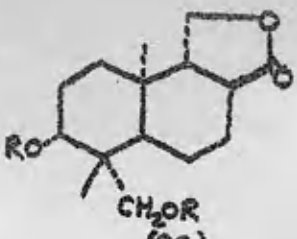

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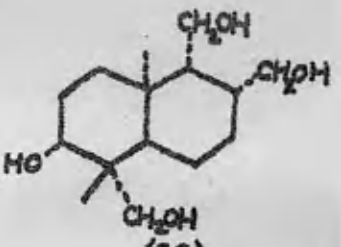

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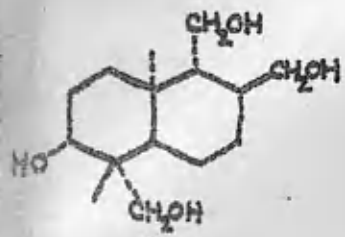

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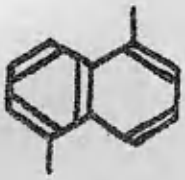
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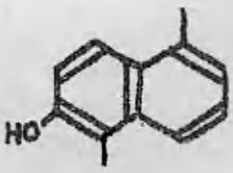

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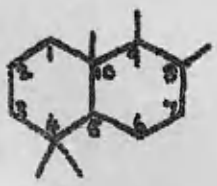
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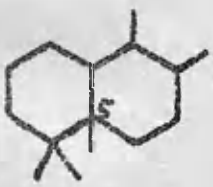

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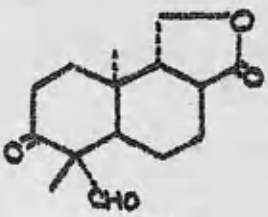

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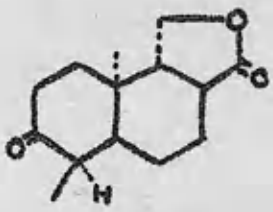

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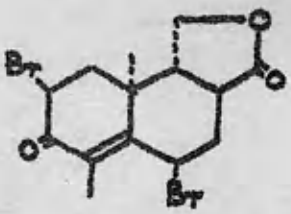

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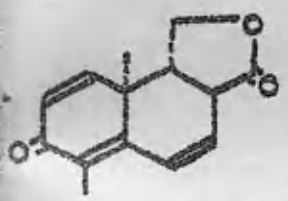

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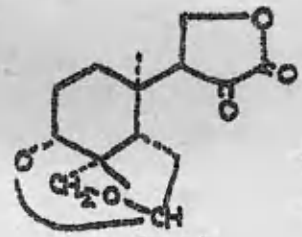

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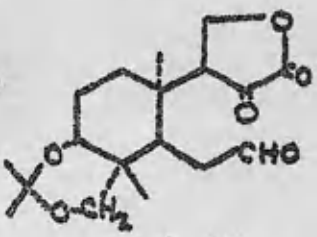

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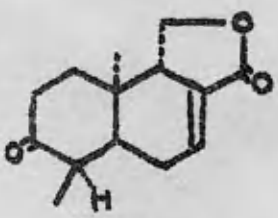

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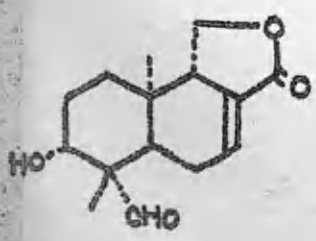

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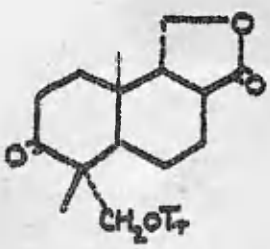

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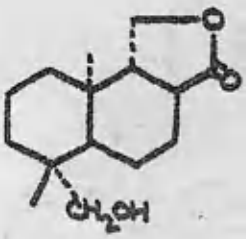

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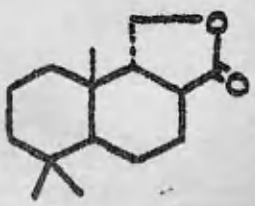
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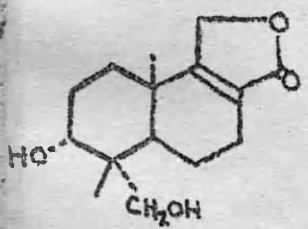

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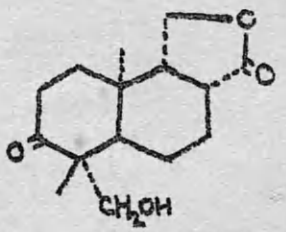

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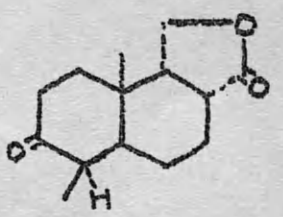


(112)

(b) Farnesiferols A, B and C:- Three isomeric compounds, $C_{24}H_{30}O_4$, were isolated[9] from the neutral non-volatile fraction of the ether extract of Asa foedita. They were designated farnesiferol A, B and C and proved to be of considerable interest in the scheme of sesquiterpene biogenesis.

Farnesiferol A (113; R = H) was shown to be a mixed ether of umbelliferone (114) with a bicyclofarnesol sesquiterpene moiety[9]. Thus it had characteristic coumarin absorption in its ultraviolet spectrum and bands in the infrared at 3590 (hydroxyl) 1725 and 1615 (coumarin) and 1645 and 890 (exomethylene) cm.$^{-1}$. Umbelliferone (114) was obtained on vigorous acid hydrolysis of farnesiferol A and the action of acetic anhydride in pyridine afforded a monoacetate (113; R = Ac) which could be readily hydrolysed with mild base back to the parent compound. The hydroxyl group was shown to be secondary by its oxidation to a ketone, $C_{24}H_{28}O_4$ (115) $\nu_{max.}$ 1730, 1712, 1615 (cyclohexanone and coumarin) cm.$^{-1}$. On reduction of (115) with sodium borohydride farnesiferol A was obtained.

Hydrogenation of the acetate (113; R = Ac) over palladised charcoal led to the uptake of two moles of hydrogen with formation of the tetrahydro-acetyl derivative, $C_{26}H_{36}O_5$ (116) $\nu_{max.}$ (KBr disc.) 1775 (dihydro-coumarin) and 1725 (acetate) cm.$^{-1}$. This indicated the presence of a double bond in the non-aromatic fragment since one mole was required for the $\alpha\beta$-unsaturated lactone of umbelliferone. Confirmation of the presence of a double bond was obtained by oxidation of farnesiferol A with perbenzoic acid when an epoxide, $C_{24}H_{30}O_5$ (117) was formed. On the above evidence it was clear that the sesquiterpene fragment, $C_{15}H_{25}O$-,

contained a secondary hydroxyl group and an exocyclic ethylenic linkage and was therefore bicyclic.

Dehydrogenation experiments proved to be very informative. Selenium dehydrogenation of the ketone (115) yielded a mixture of products identified as 1,2,5,6-tetramethyl-naphthalene (118) and 1,5,6-trimethyl-2-naphthol (119). The former was probably formed by a retro-pinacolic rearrangement, of a type familiar in triterpene chemistry. Farnesiferol A gave 1,2,5,6-tetramethyl-naphthalene in good yield on dehydrogenation. The formation of these aromatic compounds was fully consistent with a 3-hydroxy-bicyclofarnesol system in farnesiferol A.

It was now necessary to isolate the C_{15} fragment for complete identification and this was done by forcing hydrogenation over platinum. Six moles of hydrogen were absorbed with hydrogenolysis of the coumarin-ether bond to yield the saturated diol, $C_{15}H_{28}O_2$ (120), characterised as its diacetate. Oxidation of (120) with Kiliani's mixture afforded the keto-acid, $C_{15}H_{24}O_3$(121). Since the secondary hydroxyl group was present in the original farnesiferol system at C_3, the formation of a keto-acid indicated that the coumarin residue was attached through an ether linkage with the primary hydroxyl group in (120). The methyl ester of the keto-acid (121) was neither identical nor enantiomeric with the known keto-ester (122) from oleanolic acid[23]. Wolff-Kishner reduction of (121) yielded the desoxy-acid, $C_{15}H_{26}O_2$ (123), whose melting point was depressed on admixture with the desoxy-acid (124) corresponding to (122)[23]. This showed that the difference between (121) and (122) did

not lie simply in the position of the ketonic function.

Proof of the diastereoisomeric relationship of (121) and (122) was obtained in the following manner. The methyl ester of (121) was reduced with sodium borohydride to the hydroxy acid, $C_{15}H_{26}O_3$ (125; R = H). The corresponding acetate (125; R = Ac) was converted to the acid chloride and treated with cadmium dimethyl to give the methyl ketone, $C_{18}H_{30}O_4$ (126). Baeyer Villiger oxidation of (126) with perbenzoic acid followed by acetylation resulted in the formation of the diacetate (127; R = Ac) which was hydrolysed with base to the nor-diol, $C_{14}H_{26}O_2$ (127; R = H). The corresponding diketone (128) was stable to base and proved to be the enantiomer of the known diketone (129) obtained from α-amyrin[24]. The infrared spectra of (128) and (129) were identical but their optical rotatory dispersion curves were antipodal. This showed conclusively that farnesiferol A has the opposite absolute stereochemistry to that of the higher terpenes.

The assignment of the relative stereochemistry at C_9 in farnesiferol A was based on the following argument: the desoxy-acid (123), on treatment with base under equilibrating conditions, did not yield the optical antipode of (124) (from oleanolic acid)[23] whereas the two ketones (128) (from farnesiferol A) and (129) (from α-amyrin)[24], with the C_8 methyl group in the more stable equatorial configuration, were antipodal (see above). Thus (123) and (124) must differ at least in the relative configurations of their C_8 methyl groups and since the C_8 and C_{10} methyls are cis in the known acid (124) they must be trans in the acid (123) from farnesiferol A.

Hydrogenation of farnesiferol A (113) therefore yields the equatorial C_8 methyl group and this is in contrast to the hydrogenation of manool (130) which affords the C_8 axial methyl group (131)[25]. To account for this apparent anomaly, the authors assigned the β-configuration to the C_9 substituent in farnesiferol A. It is questionable, however, whether manool is a valid model compound in the present case and the assignment of the axial configuration at C_9 in farnesiferol A seems to require more rigorous proof.

Additional evidence for the structure of the bicyclofarnesol moiety was available from vigorous oxidation of (113) with chromium trioxide in acetic acid. This resulted in formation of an unsaturated keto-acid, $C_{15}H_{22}O_3$ (132) $\nu_{max.}$ (in chloroform) 1700 (acid and cyclohexanone) 1645 and 905 (exomethylene) cm.$^{-1}$ which still retained the exomethylene double bond. Ozonolysis of (132) was accompanied by decarboxylation of the initially formed β-keto-acid and the bisnor-diketone, $C_{13}H_{20}O_2$ (133) was isolated.

Farnesiferol B was shown to have the structure (134)[10]. It yielded umbelliferone on acid hydrolysis and also on pyrolysis which therefore required the presence of an allylic ether grouping. On hydrogenation of (134) over palladised charcoal three moles of hydrogen were taken up and oxidation with perbenzoic acid afforded a bis-epoxide. This indicated that the C_{15} fragment contained two double bonds and was monocyclic. Formaldehyde was identified from the ozonolysis of (134) and from the rest of the product, after treatment with base, an $\alpha\beta$-unsaturated ketone,

$C_{12}H_{18}O_2$ (135) [$\lambda_{max.}$ 243 mμ (ε 15,900)] was obtained. The latter was oxidised with chromium trioxide to the corresponding diketone, $C_{12}H_{16}O_2$ (136) [$\lambda_{max.}$ 242 mμ (ε 15,900); $\nu_{max.}$ (in carbon tetrachloride) 1715 (cyclohexanone) 1680 and 1615 (cyclohexenone) cm.$^{-1}$] which was stable to base thus excluding all but position 3 for the original hydroxyl group.

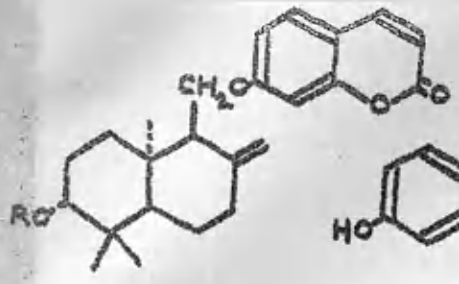
Seven moles of hydrogen were absorbed when the hydrogenation was carried out over platinum. After saponification of the product, the diol (137) was isolated, oxidised with chromic acid and methylated to the corresponding keto-ester, $C_{16}H_{28}O_3$ (138) [$\nu_{max.}$ (in chloroform) 1730 (ester) and 1700 (cyclohexanone) cm.$^{-1}$].

Reductive cleavage of the allylic ether (134) with sodium in liquid ammonia gave the doubly-unsaturated alcohol (139) which was converted by chromium trioxide in pyridine into the non-conjugated unsaturated ketone (140) [$\nu_{max.}$ (in chloroform) 1710 cm.$^{-1}$ (cyclohexanone)]. Wolff-Kishner reduction afforded the hydrocarbon (141) [$\nu_{max.}$ 1645 and 890 (exomethylene)] which, on treatment with osmium tetroxide followed by lead tetra-acetate, produced formaldehyde, acetaldehyde and the diketone (142). The latter cyclised on alumina to the hydroxy-ketone (143) which is the partially racemised optical antipode of the hydroxy-ketone (144) from ambrein (145)[26a]. The structure (144) was proved by action of methyl magnesium bromide to yield the known diol (146)[26b]. The absolute stereochemistry of (143) was assigned as shown from optical rotatory dispersion comparisons with analogous 3-keto-5α-steroids.

Farnesiferol C (147) showed no hydroxyl absorption in the infrared

and yielded umbelliferone (114) on pyrolysis thus confirming the presence of an allylic ether system. A mono-epoxide was obtained on perbenzoic acid oxidation. Hydrogenolysis of the allylic ether linkage with sodium in liquid ammonia afforded a singly unsaturated compound $C_{15}H_{26}O$ (148) with no hydroxyl or carbonyl absorption in the infrared. Hydroxylation of (148) with osmium tetroxide and lead tetra-acetate oxidation of the resultant diol gave acetaldehyde and a ketone, $C_{13}H_{22}O_2$ (149) which gave a positive iodoform test.

These facts fit the biogenetically plausible structure (147) for farnesiferol C. Further support was forthcoming from the nuclear magnetic resonance spectrum of farnesiferol C which was in full agreement with the proposed structure (147).



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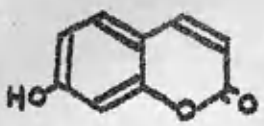

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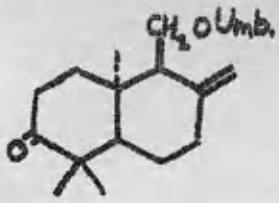

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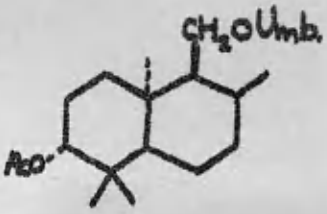

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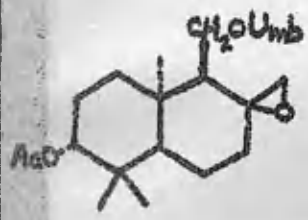

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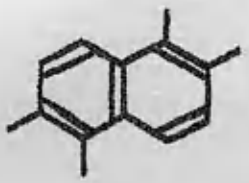

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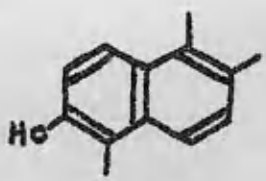

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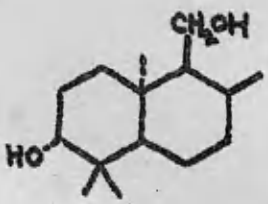

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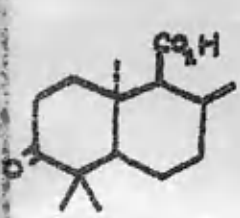

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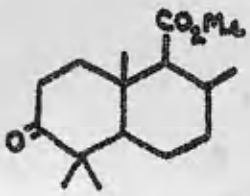

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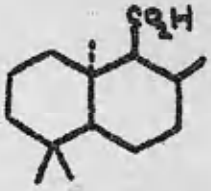

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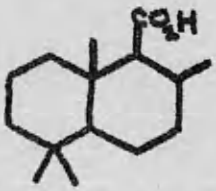

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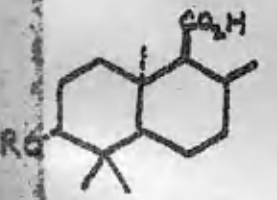

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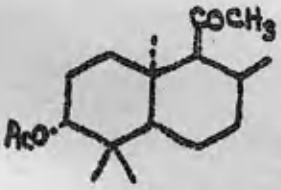

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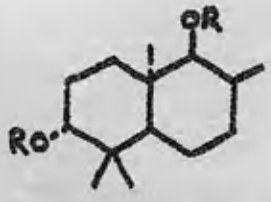

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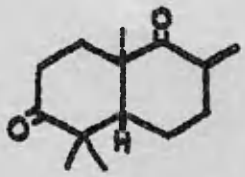

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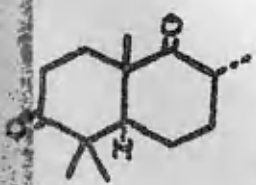

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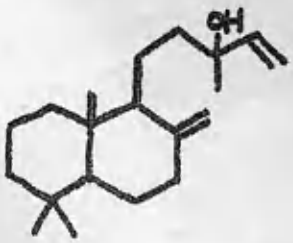

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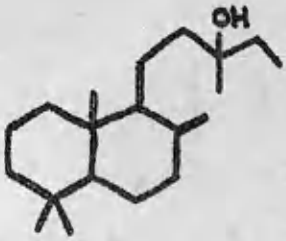

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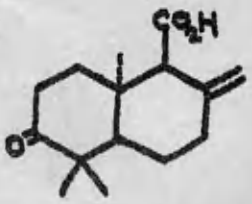

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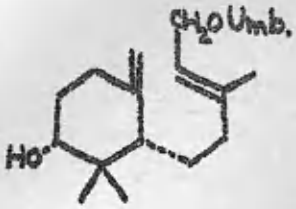

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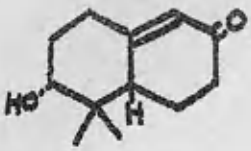

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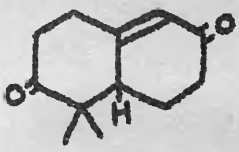

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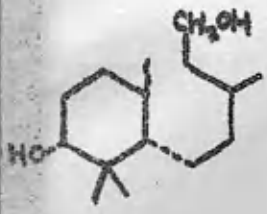

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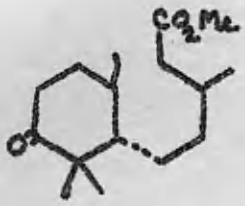

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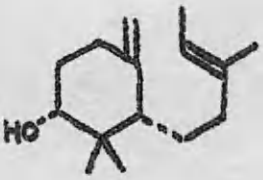

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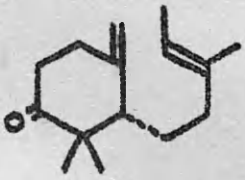

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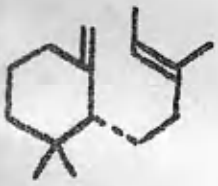

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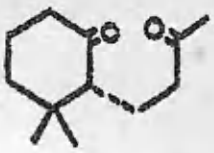

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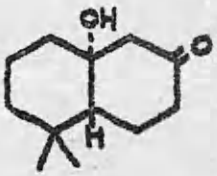

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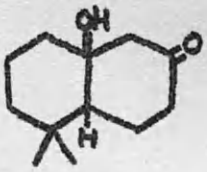

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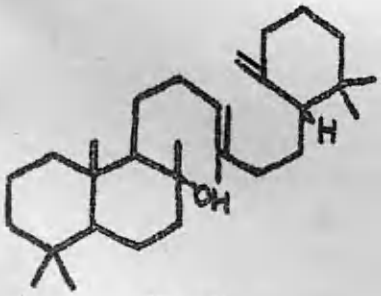

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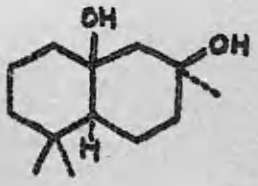

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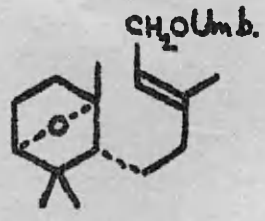

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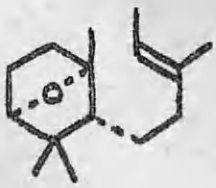

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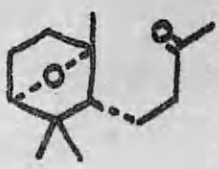


(149)

(c) Drimenol[2]:- The investigation of the constituents of the stem bark of the South American Drimys winteri Forst. was initiated by Appel and his colleagues and resulted in the isolation of drimenol, $C_{15}H_{26}O$ (150)[29]. It gave a yellow colour with tetranitromethane, on hydrogenation yielded the saturated alcohol, drimanol, $C_{15}H_{28}O$ (151) and consumed one mole of peracid to give the saturated epoxy-alcohol, drimanol α-oxide (152). The spectroscopic properties of drimenol revealed that it was an alcohol [$\nu_{max.}$ (in carbon disulphide) 3570 (free hydroxyl) and 3450 (bonded hydroxyl) cm.$^{-1}$] and the ethylene linkage was trisubstituted [$\varepsilon_{210\ m\mu}$ 2140; $\varepsilon_{215\ m\mu}$ 950; $\varepsilon_{220\ m\mu}$ 250; $\nu_{max.}$ (in Nujol 814 cm.$^{-1}$]. These facts indicated that drimenol was a mono-olefinic bicyclic alcohol and failure to react with manganese dioxide suggested that there was no allylic alcohol present. On dehydrogenation with palladium charcoal drimenol yielded 1,2,5-trimethyl-naphthalene consistent with a bicyclofarnesol skeleton. In order to accommodate the evidence presented below drimenol was assigned the structure and absolute stereochemistry (150).

That the alcoholic function of drimanol was primary was shown by its oxidation with Beckmann's mixture without loss of carbon to driman-11-oic acid, $C_{15}H_{26}O_2$, which proved to be identical with the known acid (153) from oleanolic acid and ambrein[23]. This established the structure and absolute stereochemistry of drimenol as (150).

The configuration of the methyl group at position 8 in drimanol (151) was assigned on the grounds that hydrogenation would occur from the less

hindered α-face as in cativic acid (154)[27] and on the similar molecular rotation changes associated with hydrogenation of drimenol to drimanol ($\Delta[M]_D + 73^\circ$) and cativic acid to dihydrocativic acid (155) ($\Delta[M]_D + 98^\circ$).

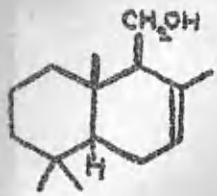
Drimenol was oxidised with Beckmann's mixture to 11-nordrim-8-en-7-one, (nordrimenone) $C_{14}H_{22}O$ [$\lambda_{max.}$ 235 mμ (ε 6,500): $\nu_{max.}$ (in carbon tetrachloride) 1670 cm.$^{-1}$] which was assigned the structure (156) on account of its spectroscopic properties, its genesis (see (157)), and its further oxidation with Beckmann's mixture or ozone to a dicarboxylic acid, drimic acid, $C_{12}H_{20}O_4$, identical with the known acid (158) from onocerin and abietic acid[28]. This provided additional confirmation of the absolute stereochemistry of drimenol. The acetic acid formed in the ozonolysis of nordrimenone was identified as its p-bromophenacyl ester.

Oxidation of drimenol with chromium trioxide in pyridine afforded, in low yield, an unsaturated keto-acid, 7-oxodrim-8-en-11-oic acid, $C_{15}H_{22}O_3$ (159) [$\nu_{max.}$ (in carbon tetrachloride) 2800-2300 (acid hydroxyl) 1748 (carboxyl) and 1685 ($\alpha\beta$-unsaturated cyclohexenone): $\lambda_{max.}$ 247 mμ (ε 8,500) (neutral ethanol), 260 mμ (ε 11,600) (0.0001 N ethanolic potassium hydroxide)]. The acid (159) was reduced with zinc in acetic acid to 7-oxo-8α-driman-11-oic-acid, $C_{15}H_{24}O_3$ (160) [$\lambda_{max.}$ 282 mμ (ε 40): $\nu_{max.}$ (in carbon tetrachloride) 1752 (carboxyl) 1710 (cyclohexanone) and 3525 (hydroxyl of carboxyl group) cm.$^{-1}$]. The configuration at position 8 in (160) was confirmed by its preparation by another route. Thus drimenol α-oxide (152) was reduced with lithium aluminium hydride to

8α-driman-7α-11-diol (161). The production of a secondary alcohol from this reaction is in full agreement with the assignment of the α-configuration to the oxide (152) and the methyl group at position 8 in (161). Oxidation of the diol (161) with chromium trioxide in acetic acid afforded 7-oxo-8α-driman-11-oic-acid (160). The latter could not be oxidised to the dehydro-acid (159) with selenium dioxide. It is clear that the initial cis-addition product in the zinc reduction of (159) is readily isomerised to the more stable 8α-epimer (160). A small amount of the 8β-epimer was isolated as its methyl ester.

Drimenol α-oxide (152) was treated with boron trifluoride in ether in the hope of obtaining the keto-alcohol (162). The product isolated was, however, an oily hydroxy-aldehyde, $C_{15}H_{26}O_2$ (163) [$\nu_{max.}$ (in carbon tetrachloride) 1728 and 2700 (aldehyde) 3480 and 3600 (bonded and free hydroxyl) cm.$^{-1}$: $\lambda_{max.}$ 280 mμ (ε 12)]. This was oxidised with silver oxide to the hydroxy acid, $C_{15}H_{26}O_3$ (164), which was converted with chromium trioxide in acetic acid to the diacid (165) characterised as its dimethyl ester [$\nu_{max.}$ (in carbon tetrachloride) 1743 cm.$^{-1}$]. Efforts to obtain a lactone from (164) or an anhydride from (165) failed. This is consistent with the stereochemistry of (163) assigned on the basis of its mode of formation from drimenol α-oxide by ring contraction. Wolff-Kishner reduction of the hydroxy-aldehyde (163) yielded isodrimanol (166; R = H) which was not identical with drimanol (151) or 8α-drimanol, the minor product from hydrogenation of drimenol. Isodrimanol acetate (166; R = Ac) was pyrolysed to give isodrimene (167).

$\lceil \nu_{max.}$ (film) 1645 and 880 (exomethylene) cm.$^{-1}\rfloor$ which on ozonolysis afforded isonordrimanone (168) $\lceil \nu_{max.}$ 1738 (cyclopentanone) cm.$^{-1}\rfloor$. These results are in full accordance with the proposed structure (163) of the hydroxy-aldehyde and further confirmation was obtained by examination of the infrared spectra of drimanol (151) and isodrimanol (166) in carbon tetrachloride solution in the region associated with the symmetrical CH deformation mode of methyl groups. This clearly indicated the presence of two gem-dimethyl groupings in isodrimanol.



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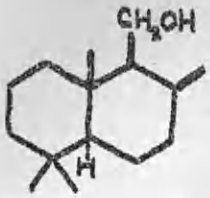

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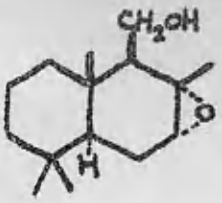

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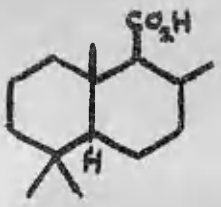

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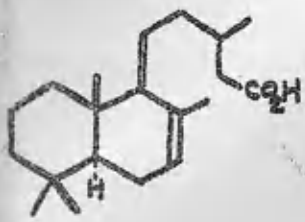

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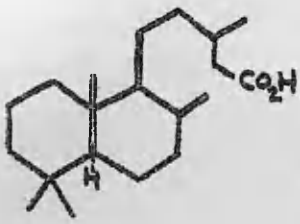

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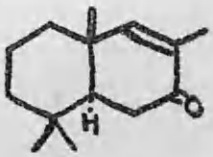

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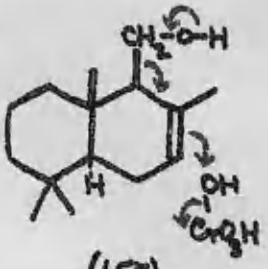

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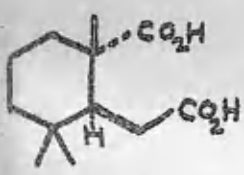

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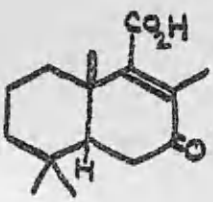

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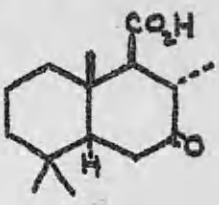

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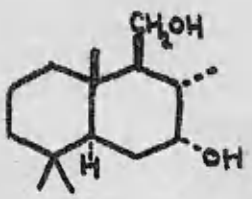

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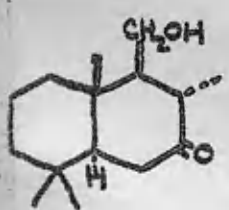

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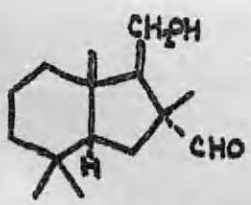

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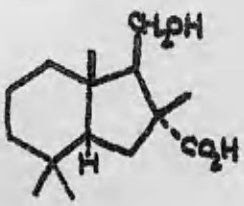

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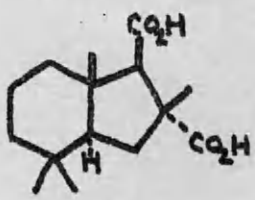

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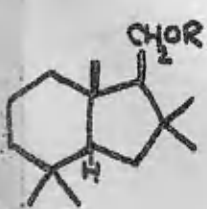

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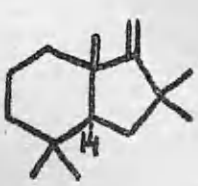

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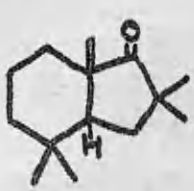


(168)

THE CONSTITUTION AND STEREOCHEMISTRY OF DRIMENIN AND ISODRIMENIN[3]

Subsequent investigation of the constituents of the stem bark of the South American Drimys species revealed the presence of three isomeric sesquiterpene lactones, drimenin[30], isodrimenin and confertifolin[30]. The discussion which follows, concerns the elucidation of the structure and absolute stereochemistry of drimenin and isodrimenin.

Drimenin, $C_{15}H_{22}O_2$ (169), was isolated from bark specimens of Drimys winteri Forst., which did not contain drimenol. It gave a yellow colour with tetranitromethane. The functional groups present were shown spectroscopically to be a butanolide $\nu_{max.}$ (in carbon tetrachloride) 1780 cm.$^{-1}$ and a trisubstituted ethylenic linkage $\nu_{max.}$ 1670 and 808 cm.$^{-1}$. It followed from this that drimenin was tricyclic. The presence of a gem-dimethyl grouping in the infrared $\nu_{max.}$ (in carbon tetrachloride) 1366 and 1389 cm.$^{-1}$ and the biogenetically significant fact that drimenol was not present in the bark with drimenin suggested that we were dealing with a bicyclofarnesol system. By analogy with iresin the γ-lactone might be expected to arise from oxidation of the carbon atoms at positions 11 and 12 in drimane and the double bond to be located in position 7,8 as in (169). In fact this was shown to be correct.

On treatment with 10% ethanolic potassium hydroxide at room temperature for one hour drimenin was transformed into isodrimenin (170) $\lambda_{max.}$ 218 mμ (ε 10,000): $\nu_{max.}$ (in carbon tetrachloride) 1766 and 1671 cm.$^{-1}$ which clearly contains an $\alpha\beta$-unsaturated γ-lactone system.

Oxidation of either drimenin (169) or isodrimenin (170) with Beckmann's

mixture afforded oxoisodrimenin, $C_{15}H_{20}O_3$, which was assigned the structure (171) on its spectroscopic properties $\lambda_{max.}$ 247 mμ (ε 10,600) (in neutral ethanol) and 259 mμ; rising to a maximum (ε 5,600) after $\frac{2}{3}$ hour (in 0.01 N ethanolic potassium hydroxide): $\nu_{max.}$ (in carbon tetrachloride) 1774 (αβ-unsaturated γ-lactone) and 1690 (αβ-unsaturated cyclohexenone) cm.$^{-1}$ and by analogy with the corresponding acid (172) from drimenol. It was found (following the oxidation by the appearance in the ultraviolet of the maximum at 247 mμ (see experimental)) that drimenin and isodrimenin were transformed into oxoisodrimenin at similar rates by either Beckmann's mixture or chromium trioxide in acetic acid. In contrast methyl 19-oxo-olean-12-enolate acetate was readily oxidised with chromium trioxide to methyl 12,19-diketo-olean-13,(18)-enolate acetate whilst the conjugated ester methyl-19-oxo-olean-13,(18)-enolate acetate was inert to this reagent[31].

Oxoisodrimenin (171) was reduced with zinc in refluxing acetic acid to dihydro-oxodrimenin, $C_{15}H_{22}O_3$ (173) $\lambda_{max.}$ 282 mμ (ε 30): $\nu_{max.}$ (in carbon tetrachloride) 1781 (butanolide) and 1716 (cyclohexanone) cm.$^{-1}$. The cis-fusion of the lactone ring in (173) is shown by its ready dehydrogenation by selenium dioxide to the dienone lactone, dehydro-oxoisodrimenin, $C_{15}H_{18}O_3$ (174) $\lambda_{max.}$ 248 mμ (ε 14,800): $\nu_{max.}$ (in carbon tetrachloride) 1773 (αβ-unsaturated butanolide) 1682 and 1651 (cyclohexadienone) cm.$^{-1}$. The spectroscopic properties of dehydro-oxoisodrimenin compare very favourably with those of the analogous ester (175) obtained from methyl cativate[32], particularly in the appearance

of an intense band near 1650 cm.$^{-1}$ in the infrared. Dehydro-oxoisodrimenin, which was also obtained by selenium dioxide oxidation of oxoisodrimenin (171), did not show the bathochromic shift in basic solution observed with the compounds (171) and (172). Preliminary observations on selected analogous compounds suggest that the shift is probably due to enolisation of the ketonic carbonyl group[33].

The stability of the cis-lactone, dihydro-oxodrimenin (173) in comparison with 7-oxo-8β-driman-11-oic acid (176), in the drimenol series[2], which is readily isomerised during work-up to the 8α-epimer, is worthy of comment. An examination of molecular models shows that in the acid (176) the 8β-methyl group is axial and this results in 1,3,5-triaxial non-bonded interaction with the methyl groups at positions 4 and 10. Relief of this strain is achieved by epimerisation at position 8 to give the more stable 8α-epimer. In the lactone (173), however, the 8β-substituent is held in a quasi-equatorial conformation by virtue of its inclusion in the butanolide ring. Thus the non-bonded interaction is less intense and the need for isomerisation to the 8α-lactone less compelling.

When dihydro-oxodrimenin (173) was kept in 1% ethanolic potassium hydroxide at room temperature for 16 hours in an attempt to epimerise the C_8 substituent an acid, $C_{17}H_{28}O_4$ $\nu_{max.}$ (in chloroform) 3504 (hydroxyl of acid monomer) 1740 (acid monomer) and 1705 (cyclohexanone and acid dimer) cm.$^{-1}$ was recovered. It was considered that this acid had the structure (177; R = Et) and was formed by β-elimination of the lactonic

alkyl oxygen with addition of ethanol to the resulting α-methylene ketone (178). In support of this, the action of 1% methanolic potassium hydroxide on dihydro-oxodrimenin yielded the corresponding methoxy acid (177; R = Me). The acids (177; R = Me or Et) when heated above their melting points afforded a compound $(C_{15}H_{22}O_3)_n$ $\lambda_{max.}$ 205 mμ (ε 5,400) (Hilger Uvispek); $\nu_{max.}$ 3505 (hydroxyl of acid monomer) 1746 (acid monomer) and 1706 (cyclohexanone and acid dimer)] which gave a yellow colour with tetranitromethane and had a mass-spectroscopic molecular weight of 506 ± 10. This was formulated as the dimer (179) on the basis of its spectroscopic properties, molecular weight and probable mode of genesis by pyrolytic β-elimination of methanol or ethanol and dimerisation of the resultant α-methylene ketone (178). The dimerisation of the exomethylene ketone (180) was used by Eschenmoser and his colleagues[18] in a synthesis of onoceran-8,8'-diol (181). The dimer (179) did not show the expected enol ether band in the infrared.

The dienone-lactone chromophore of dehydro-oxoisodrimenin can only be accommodated in the drimane skeleton as in (174) and thus drimenin must have the constitution drim-7-en-11,12-olide (169). This assignment was confirmed by the following experiments which also defined the absolute stereochemistry of drimenin.

First, ozonolysis of oxoisodrimenin (171) in ethyl acetate at -70° and decomposition of the ozonide with aqueous sodium hydrogen carbonate in presence of hydrogen peroxide furnished drimic acid (182) in low yield. Constant ether extraction of the aqueous mother liquors yielded

glycollic acid.

Secondly, when the methoxy-keto-acid (177; R = Me) was refluxed with zinc in acetic acid 7-oxo-8α-drimanoic acid (183) was obtained. This was presumably formed from (177) by acid induced β-elimination followed by reduction of the ethylenic linkage through the 8,9-double bond isomer.

Thirdly, reduction of drimenin with lithium aluminium hydride in ether afforded the diol (184) which gave a yellow colour with tetranitromethane and had the spectroscopic characteristics of a trisubstituted ethylenic linkage [$\nu_{max.}$ 834 cm.$^{-1}$: $\varepsilon_{208\ m\mu}$ 2000; $\varepsilon_{212\ m\mu}$ 920; $\varepsilon_{220\ m\mu}$ 1257]. On hydrogenation over Adam's catalyst in acetic acid the diol (184) was rapidly hydrogenolysed and hydrogenated to drimanol (185) identical in all respects [melting point, infrared spectrum, specific rotation and 3,5-dinitrobenzoate] with natural material[2]. This proved unequivocally that drimenin and isodrimenin have the same absolute stereochemistry as drimenol[2].

Reduction of drimenin (169) over Adam's catalyst in acetic acid or ethyl acetate resulted in the formation of a 1:1 mixture of dihydrodrimenin (186) [$\nu_{max.}$ (in carbon tetrachloride) 1780 (butanolide) cm.$^{-1}$] and isodrimenin (170). Drimenin was unchanged after treatment with Adam's catalyst in acetic acid in the absence of hydrogen and thus the transformation to isodrimenin must have occurred during hydrogenation. The migration during catalytic reduction of an ethylenic double bond, initially exocyclic to a butanolide, to a tetrasubstituted endocyclic position is not unknown. The sesquiterpene lactone

ambrosin (187) yields the corresponding dihydro-derivative (188) on hydrogenation[34]. Van Tamelen found a similar migration occurring during hydrogenation of protolichesterinic acid (189)[35]. In this case, as in drimenin, the double bond is moving into conjugation with the lactonic carbonyl group, thus providing an additional driving force for the migration. A mechanism has been proposed involving hydrogen deficient centres on the catalyst surface[35].

Dihydrodrimenin (186) was reduced with lithium aluminium hydride to the cis-diol (190) whose stereochemistry follows from identity with the necessarily cis-diol obtained from confertifolin (191; see p. 45) by hydrogenation and lithium aluminium hydride reduction and from the known stereochemistry at position 9 in drimenin (169). Catalytic hydrogenation of drimenin thus occurs from the more accessible α-face, as is the case with drimenol. Treatment of the diol (190) with toluene-p-sulphonyl chloride in pyridine yielded the corresponding ditoluene-p-sulphonate derivative and a second product, $C_{15}H_{26}O$, which was formulated as 11,12-epoxy-8β,9β-drimane (192) on the basis of its infrared spectrum [$\nu_{max.}$ (in Nujol) 1069 (cyclic ether) cm.$^{-1}$].

Dihydrodrimenin (186) was recovered unchanged after 24 hours in 5% methanolic potassium hydroxide, conditions which readily transform dihydroiresin (193) into the corresponding trans-lactone, isodihydroiresin[8]. The stability of the cis-lactone in (186) was readily rationalised by reference to molecular models. Inversion at position 9 to give the trans-lactone required ring B to adopt a boat

conformation and was therefore not favoured. A similar conformational argument was invoked in the assignment of stereochemistry at C_9 in the lactone (194) obtained from sclareol[36].

Isodrimenin (170) was isolated from a specimen of Drimys winteri Forst., and is probably not an artefact since drimenin was substantially unchanged when subjected to the isolation procedure. Attempts to hydrogenate isodrimenin even in presence of perchloric acid were unavailing. It is worth noting that when drimenin was hydrogenated under these conditions there was no hydrogenolysis of the allylic lactone. Isodrimenin was reduced with lithium aluminium hydride to the unsaturated diol, drim-8-en-11,12-diol (195) which gave a yellow colour with tetranitromethane.

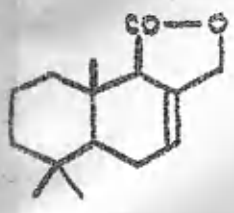
In the infrared spectra (in Nujol) of isodrimenin (170), oxoisodrimenin (171), dehydro-oxoisodrimenin (174) and confertifolin (191) there is an intense band at 783 cm.$^{-1}$. The significance of this band is not understood and it is hoped to investigate it further.

It seems appropriate that the chemistry of the closely related lactone, confertifolin (investigated by R. P. M. Bond in this laboratory) should be summarised at this juncture. Confertifolin was first isolated[30] from Drimys confertifolia Phil., and subsequently in much higher yield from Drimys winteri Forst. It did not give a colour with tetranitromethane and its spectroscopic properties $\lambda_{max.}$ 217 mμ (ε 11,750); $\nu_{max.}$ (in carbon tetrachloride) 1769 (αβ-unsaturated butenolide) and 1677 (conjugated ethylenic linkage) cm.$^{-1}$ closely resembled those of isodrimenin (170) and

isoiresin (196)[8]. This suggested for confertifolin the constitution of drim-8-en-12,11-olide (191) either directly or enantiomerically related to iresin. Lithium aluminium hydride reduction of confertifolin yielded the unsaturated diol (195) obtained from isodrimenin (170) thus showing that confertifolin belonged to the same absolute stereochemical series as drimenin (169). Like isoiresin (196) but unlike isodrimenin, confertifolin was smoothly hydrogenated over Adam's catalyst in acetic acid to dihydroconfertifolin (197) $[\nu_{max.}$ (in carbon tetrachloride) 1784 (butanolide) cm.$^{-1}]$ which was reduced with lithium aluminium hydride to the cis-diol (190) previously obtained from dihydrodrimenin (186). Thus addition of hydrogen occurs from the less hindered α-face. The difference in behaviour during hydrogenation of isodrimenin (170) and confertifolin (191) can be rationalised if the reduction is supposed to proceed via the 7,8-double bond isomer; with confertifolin and isoiresin (196) conjugation with the carbonyl is retained in the intermediate whereas this would not be the case with isodrimenin. It is not without significance that (196) and (191) did not hydrogenate in ethyl acetate but required acetic acid.

As expected by analogy with the iresin series [8], dihydroconfertifolin was readily converted to the trans-lactone, isodihydroconfertifolin (198) $[\nu_{max.}$ (in carbon tetrachloride) 1792 (butanolide) cm.$^{-1}]$ with methanolic potassium hydroxide at room temperature. The physical constants of the trans-lactone (198) did not agree with those published[8] for the enantiomeric lactone (199), obtained from iresin, which was not available

for comparison. There was, however, satisfactory correspondence between the molecular rotation changes associated with the transformations isoiresin diacetate (196; R = Ac) → isodihydroiresin diacetate (200) ($\Delta[M]_D$ + 245°) and confertifolin (191) → isodihydroconfertifolin (198) ($\Delta[M]_D$ - 216°). Lithium aluminium hydride reduction of isodihydroconfertifolin (198) yielded the new trans-diol (201). Confertifolin was recovered unchanged from chromic acid oxidation in contrast to the behaviour of drimenin (169) and isodrimenin (170).



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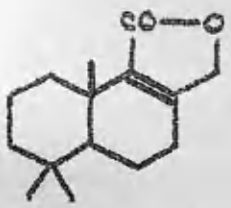

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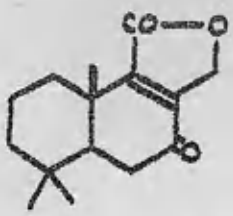

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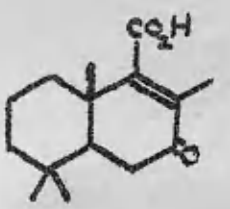

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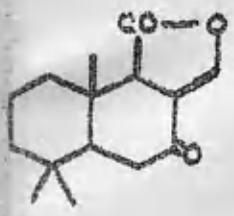

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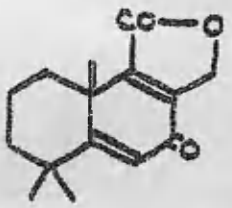

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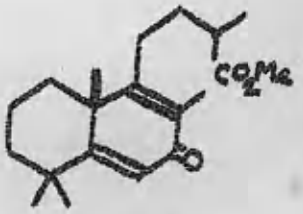

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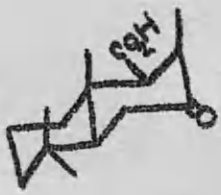

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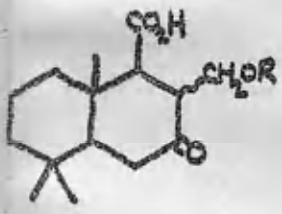

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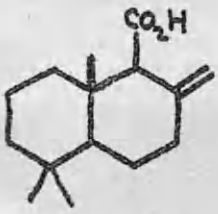

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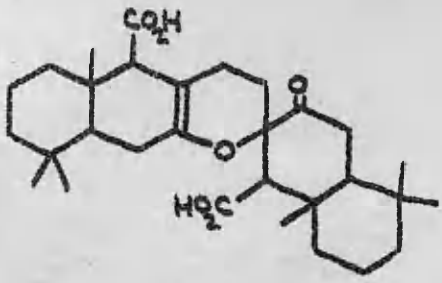

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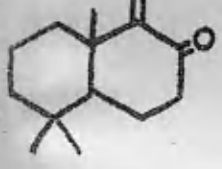

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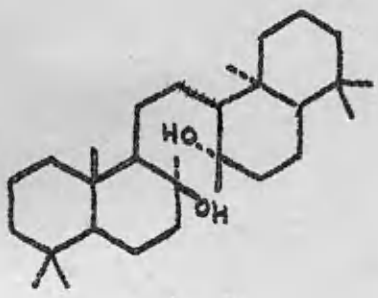

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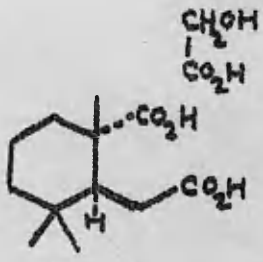

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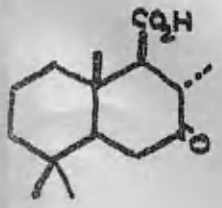

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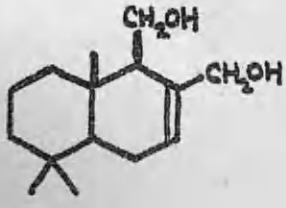

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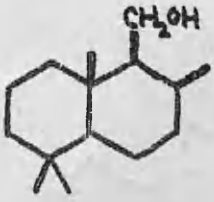

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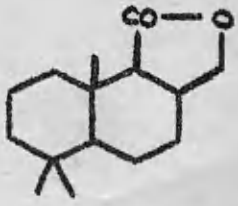

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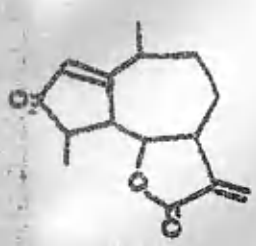

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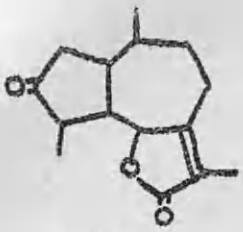

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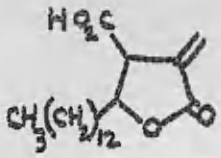

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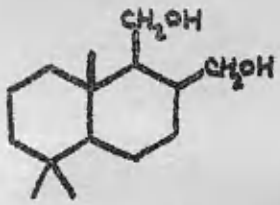

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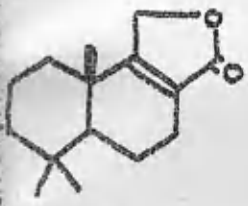

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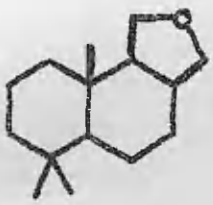

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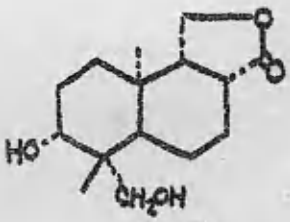

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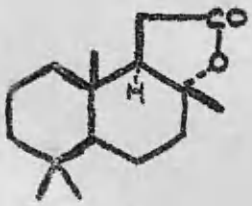

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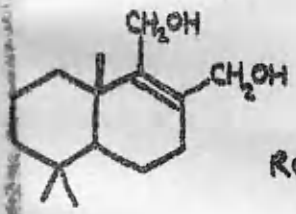

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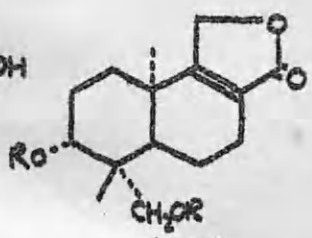

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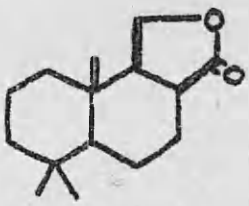

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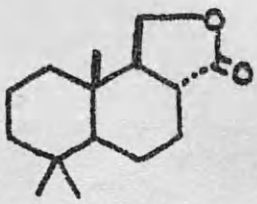

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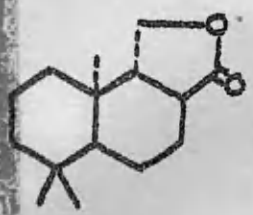

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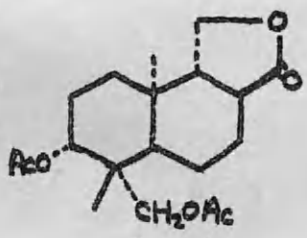

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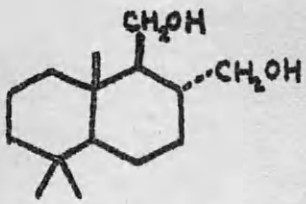

(201)

EXPERIMENTAL

M.p.s were determined on the Kofler block. Infrared solution and KCl disc spectra were kindly recorded by Mrs. F. Lawrie with a Unicam S.P. 100 double-beam infrared spectrometer and are accurate to $\pm$ 1 cm.$^{-1}$; Nujol spectra were taken with a Perkin-Elmer 13 spectrometer, ultraviolet spectra with a Unicam S.P.500 spectrometer for solutions in ethanol unless stated to the contrary. Microanalyses are by Mr. J. M. L. Cameron and his staff. Chromatographic alumina was prepared and standardised by Brockmann's procedure[37]. The light petroleum used was of b.p. 60-80° unless stated to the contrary. Extractions of plant material were kindly carried out by Sr. J. Olivares.

Extraction of Drimenin, Isodrimenin:- The dried powdered bark was in each case exhaustively extracted with light petroleum (b.p. 70-80°) in a Soxhlet apparatus. Removal of solvent, distillation in vacuo of the residue, and working up of the appropriate fractions then afforded the lactones as follows.

Drimenin (169). From Drimys winteri Forst. (Loncoche). Obtained by washing of the fraction of b.p. 160-185°/8 mm. with a little cold methanol, drimenin (2% by weight of the extract) crystallised from methanol and sublimed at 110°/0.1 mm., then having m.p. 133°, $[\alpha]_D$ - 42° (c 0.76 in C_6H_6) (Found: C, 77.2; H, 9.5%. Calc. for $C_{15}H_{22}O_2$: C, 76.9; H, 9.45%).

Isodrimenin (170). From Drimys winteri Forst. (Loncoche). Obtained from the fraction of b.p. 195-210°/3 mm. in 0.56% yield based on the

extract. Crystallised from n-hexane and sublimed at 100°/0.1 mm., it had m.p. 131-132°, $[\alpha]_D$ + 87° (c 2.02 in $CHCl_3$), + 78° (c 0.80 in C_6H_6) (Found: C, 76.55; H, 9.5%).

Isomerisation of Drimenin:- Drimenin (40 mg.) was dissolved and kept in 10% ethanolic potassium hydroxide (2 ml.) at 20° for 1 hr. Acidification, dilution, and extraction into ether afforded isodrimenin (170) (36 mg.) which, crystallised (rods) from n-hexane and sublimed at 115°/0.1 mm., had m.p. 129-131°, $[\alpha]_D$ + 79° (c 1.03 C_6H_6); it was identical in m.p., mixed m.p. and infrared spectrum with isodrimenin isolated from D. winteri Forst. (see above) and by hydrogenation of drimenin (see below).

Oxidation of Drimenin and Isodrimenin with Beckmann's Mixture:- (A) Drimenin (200 mg.) in "AnalaR" acetic acid (8 ml.) and Beckmann's mixture (2 ml.) was kept at 20° for 24 hr. Dilution, extraction into ether, washing of the ether extract successively with saturated aqueous sodium hydrogen carbonate and water, and chromatography over alumina (activity III; 6 g.) in benzene, afforded oxoisodrimenin (172) (120 mg.), plates (from n-hexane), m.p. 112-113°, $[\alpha]_D$ + 52° (c 1.89 in C_6H_6).
(B) Isodrimenin (200 mg.), oxidised in the same manner, afforded oxoisodrimenin (160 mg.), identical in m.p., mixed m.p., and infrared spectrum with material obtained as in (A).

Relative Rates of Oxidation of Drimenin, Isodrimenin with (a) Beckmann's Mixture and (b) Chromium Trioxide in 95% Acetic Acid:- The compound (100 mg.) in (a) acetic acid (4 ml.) and Beckmann's mixture (1 ml.)

or (b) acetic acid (2 ml.) containing chromium trioxide (43 mg., 1.5$\hat{0}$) was kept at 20° for 16 hr. The total neutral product obtained in the usual way was examined in the ultraviolet region. Drimenin: (a) the neutral product (80 mg.) had $\lambda_{max.}$ 247 mμ (ε 5,600); (b) 93 mg. $\lambda_{max.}$ 247 mμ (ε 4,200). Isodrimenin: (a) 95 mg., $\lambda_{max.}$ 219 (ε 7000), 247 mμ (ε 5500); (b) 95 mg., $\lambda_{max.}$ 219 (ε 7400), 247 mμ (ε 5000).

Reduction of Oxoisodrimenin with Zinc and Acetic Acid:- Oxoisodrimenin (70 mg.) was refluxed with zinc dust (1.5 g.) in glacial acetic acid (20 ml.) for 3 hr. Removal of zinc and solvent left a residue (60 mg.) of dihydro-oxoisodrimenin (173) which, thrice crystallised from benzene-n-hexane (needles), had m.p. 124-126°, $[\alpha]_D$ - 115° (c 1.0 in C_6H_6), $\lambda_{max.}$ 282 mμ (ε 29) (Found: C, 71.8; H, 8.8. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%).

12-Ethoxy-7-oxodriman-11-oic Acid (177; R = Et):- Dihydro-oxoisodrimenin (56 mg.), dissolved in 1% ethanolic potassium hydroxide (6 ml.), was kept at 20° for 16 hr. The acidic product (59 mg.), obtained in the usual way, afforded needles (50 mg.) of 12-ethoxy-7-oxodriman-11-oic acid from acetone-light petroleum; these had m.p. 175-179° and resolidified at 230-245° (see below). Sublimed at 130°/10^{-3} mm. and recrystallised from the same solvents, this acid had m.p. 182-184°, $[\alpha]_D$ + 21° (c 1.17 in $CHCl_3$) (Found: C, 68.9; H, 9.5. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%).

The corresponding methoxy-acid (177; R = Me) obtained in the same way with methanolic alkali had (from the same solvent) m.p. 170-171°,

$[\alpha]_D$ + 12° (c 1.17 in $CHCl_3$) (Found: C, 68.2; H, 9.4. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.3%).

7-Oxo-8α-driman-11-oic Acid (183):- The methoxy-acid (177; R = Me) (7 mg.) in "AnalaR" acetic acid (2 ml.) was refluxed with zinc dust (35 mg.) for 3 hr. Removal of zinc and solvent afforded 7-oxo-8α-driman-11-oic acid (6 mg.), prisms (from ether-hexane), m.p. 200-202° alone and mixed with the acid obtained by reduction of 7-oxodrim-8-en-11-oic acid, and of identical infrared spectrum.

Dimer (179):- (a) The above ethoxy-acid (31 mg.), heated in nitrogen at 200° until gas evolution ceased (2-3 min.), solidified on cooling to afford the dimer. Crystallised from acetone-benzene (needles) (12 mg.), this had m.p. 258-260°; a second crop (10 mg.) had m.p. 254-258°. The dimer had a mass-spectroscopic molecular weight 506 ± 10 (calc., 500), (kindly determined by Dr. R. I. Reed and his colleagues on a Metropolitan-Vickers Ltd. M.S. 2 Mass-spectrometer) (Found: C, 71.45; H, 8.3. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%). (b) Pyrolysis of the methoxy-acid afforded the dimer, m.p. alone and mixed 255-260°, and identical in infrared spectrum with that obtained as in (a).

Oxidation of Dihydro-oxoisodrimenin and Oxoisodrimenin with Selenium Dioxide:- (i) Dihydro-oxoisodrimenin (15 mg.) and selenium dioxide (100 mg.) were refluxed in glacial acetic acid (3 ml.) for 2 hr. Removal of solids and solvent and filtration of the residue in benzene through alumina (activity V; 1 g.) afforded a yellow oil (12 mg.). Crystallisation from hexane furnished dehydro-oxoisodrimenin (174) as rods

m.p. 98-100°, contaminated with red selenium.

(ii) Oxoisodrimenin (25 mg.) was oxidised with selenium dioxide (100 mg.) as in (i). The crude product in benzene (10 ml.) was shaken with precipitated silver for 4 hr., and the benzene solution filtered through silver and alumina (activity III; 1 g.). The residue obtained on removal of solvent from the eluate was dissolved in benzene-hexane (1 : 5) and chromatographed over alumina (activity III; 1 g.), affording selenium-free dehydro-oxoisodrimenin (174) (18 mg.) which crystallised spontaneously. Recrystallised from hexane this had m.p. 100-102° and was identical in mixed m.p. and infrared spectrum with material obtained as in (i). The product has $[\alpha]_D$ + 21° (c 1.95 in C_6H_6) and $\lambda_{max.}$ 248 mμ (ε 15,800) in EtOH and 0.001 N ethanolic KOH (Found: C, 73.45; H, 7.25. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35%).

Ozonolysis of Oxoisodrimenin:- (i) Oxoisodrimenin (100 mg.) in ethyl acetate (10 ml.) was treated with ozonised oxygen at -70° until the absorption peak at 247 mμ had disappeared (2¾ hr.). The solution was allowed to warm to 20°, saturated aqueous sodium hydrogen carbonate (5 ml.) was added, and the ethyl acetate removed by distillation in vacuo. 30% Hydrogen peroxide (2 ml.) was then added and the solution kept at 20° for 10 hr. Acidification, saturation with ammonium sulphate, and extraction with ether afforded a clear oil (90 mg.) which was adsorbed from benzene on chromatographic silica gel (B.D.H.; 6 g.). Elution with 4 : 1 benzene-ether furnished the only semicrystalline fractions (41 mg.), which on sublimation at 140°/0.1 mm. gave drimic

acid[2] (182), m.p. alone and mixed with material prepared from nordrimenone[2], 165-167°, and of essentially identical infrared spectrum.

(ii) Oxoisodrimenin (150 mg.) was ozonised for 3¾ hr. as in (i), and the ozonide was decomposed without hydrogen peroxide. Saturation with ammonium sulphate of the aqueous solution and hand-extraction with ether afforded a colourless oil (155 mg.) which was not further investigated. Continuous extraction with ether for 36 hr. furnished a crystalline acid (17 mg.) which, recrystallised from ether-benzene, had m.p. 76-77°, alone and mixed with glycollic acid, and of correct infrared spectrum.

Reduction of Drimenin with Lithium Aluminium Hydride:- Drimenin (100 mg.) in ether (5 ml.) was added dropwise to lithium aluminium hydride (200 mg.) in ether (10 ml.), and the suspension was stirred for 4 hr. The product obtained in the usual way was a clear oil (87 mg.), showing only residual carbonyl absorption in the infrared spectrum. Absorption on alumina (activity V; 3 g.) from benzene-hexane (1 : 1) and elution with benzene afforded drim-7-ene-11,12-diol (184) (53 mg.), rods (from hexane), m.p. 73.5-74.5°, $[\alpha]_D$ - 7° (c 1.38 in C_6H_6), giving a yellow colour with tetranitromethane (Found; C, 75.6; H, 11.25. $C_{15}H_{26}O_2$ requires C, 75.6; H, 11.0%).

Hydrogenation of the Diol:- The above diol (25 mg.) in glacial acetic acid (5 ml.) was hydrogenated with Adam's catalyst (23 mg.) at 20°/1 atm.; 2.2 mol. hydrogen were absorbed in 30 min. The crystalline product (26 mg.), twice crystallised from hexane, had m.p. 109-110° alone and mixed with drimanol[2] (185) (identical infrared spectrum) and

$[\alpha]_D$ + 18° (c 0.39 in C_6H_6). The derived 3,5-dinitrobenzoate had m.p. 138-139° alone and mixed with drimanyl 3,5-dinitrobenzoate.

Hydrogenation of Drimenin:- Drimenin (600 mg.) in ethyl acetate (120 ml.) was hydrogenated with Adam's catalyst (270 mg.) at 20°/1 atm.; 1.18 mol. hydrogen were absorbed in 40 min. The crude product was adsorbed on alumina (activity III; 18 g.) from light petroleum. Elution with 1 : 9 benzene-light petroleum afforded dihydrodrimenin (186) (347 mg.), rods (from hexane), m.p. 71-73°, $[\alpha]_D$ - 79° (c 1.14 in C_6H_6) (Found: C, 76.4; H, 10.2. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.25%). Elution with benzene-light petroleum (1 : 4 to 1 : 0) afforded isodrimenin (170) (207 mg.), rods (from benzene-hexane), m.p. 131-132°, $[\alpha]_D$ + 79° (c 1.03 in C_6H_6).

Drimenin was recovered after treatment with acetic acid at 70° or with Adam's catalyst and acetic acid at 20°.

When drimenin in acetic acid was hydrogenated in presence of 10 N hydrochloric acid or perchloric acid the hydrogen uptake was 1-1.1 mol. and there was no acidic product.

Dihydrodrimenin was recovered after 24 hr. in 5% methanolic potassium hydroxide.

Isodrimenin (20 mg.) in acetic acid (5 ml.) and perchloric acid (1 drop) did not consume hydrogen during 72 hr. and was recovered.

Reduction of Dihydrodrimenin and Isodrimenin with Lithium Aluminium Hydride:- 8β,9β-Drimane-11,12-diol (190) Dihydrodrimenin (100 mg.) was reduced with excess of lithium aluminium hydride in refluxing ether (10 ml.)

for 1.5 hr. The diol (190) (93 mg.) obtained in the usual way, crystallised from chloroform in rods, m.p. 151-152°, $[\alpha]_D$ + 27° (c 0.98 in $CHCl_3$) (Found: C, 75.15; H, 11.9. $C_{15}H_{28}O_2$ requires C, 74.95: H, 11.8%).

The diol (22 mg.) and toluene-p-sulphonyl chloride (27 mg.) were kept in dry pyridine (7 ml.) for 16 hr. The product (22 mg.) obtained in the usual way was adsorbed on alumina (1.5 g.; activity III) from 1 : 1 benzene-hexane. Elution with the same solvent afforded 11,12-epoxy-8β,9β-drimane (192) (10 mg.). Sublimed at 25°/0.1 mm., this had m.p. 38-38.5°, $\nu_{max.}$ (in Nujol) 1069 cm.$^{-1}$ (cyclic ether) (no OH or CO band) (Found: C, 81.35; H, 11.5. $C_{15}H_{26}O$ requires C, 81.0; H, 11.8%). Elution with benzene furnished 8β,9β-drimane-11,12-diol ditoluene-p-sulphonate (8 mg.), needles (from ether-hexane), m.p. 143-145°, $\lambda_{max.}$ 225 mμ (ε 24,000) (Found: C, 63.3; H, 7.15. $C_{29}H_{40}O_6S_2$ requires C, 63.5; H, 7.35%).

Drim-8-ene-11,12-diol (195):- Isodrimenin (30 mg.) was reduced with excess of lithium aluminium hydride in ether (7 ml.) for 2 hr. Working up in the usual way afforded drim-8-ene-11,12-diol (195) (27 mg.), plates (from benzene), m.p. 123-124°, $[\alpha]_D$ + 118° (c 1.03 in C_6H_6), giving a yellow colour with tetranitromethane, $\varepsilon_{205\ m\mu}$ 10,150, $\varepsilon_{210\ m\mu}$ 5900, $\varepsilon_{215\ m\mu}$ 2650, $\varepsilon_{220\ m\mu}$ 850 (Found: C, 75.9; H, 10.9. $C_{15}H_{26}O_2$ requires C, 75.6; H, 11.0%).

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PART II

THE CONSTITUTION AND STEREOCHEMISTRY OF THE LACTONE $C_{10}H_{16}O_4$ OBTAINED IN THE PERACID OXIDATION OF CAMPHOR

INTRODUCTION

In 1899 Baeyer and Villiger[1] reported the formation of a lactone $C_{10}H_{16}O_4$ as a by-product in the peracid oxidation of camphor. The constitution (12; R = R' = OH) has been assigned to this lactone[24] on the evidence to be presented below. Discussion of this evidence is preceded by a summary of the action of peracid on camphor and its congeners, and it is shown that the formation of (12; R = R' = OH) can be accommodated as part of the general mechanistic picture that applies to the peroxidation of camphor.

THE ACTION OF PERACIDS ON CAMPHOR AND ITS CONGENERS

In 1899 Baeyer and Villiger[1] showed that the oxidation of the alicyclic ketones menthone, tetrahydrocarvone and camphor with persulphuric acid (Caro's acid) gave rise to lactones. The reaction has since been found to be of wide applicability and has been used extensively in both synthetic and degradative chemistry[2]. It can be represented by the general equation:-

$$R.CO.R' \xrightarrow{OH^+} R.CO.OR'$$

The mechanism of this reaction has received considerable attention. Baeyer and Villiger[1] suggested that it proceeded through a simple "oxoxide" intermediate (1) which rearranged as shown (scheme 1) to the lactone or ester. Wittig and Pieper[3] proposed a linear peroxide (2) as the initial step in the reaction (scheme 2). The mechanism which has been most favourably received was postulated by Criegee[4] in 1948. He assumed initial addition of peracid to the carbonyl group to form a hydroxyperester (3) which decomposed heterolytically via an intermediate oxonium ion (4) to the lactonic product (scheme 3). Friess[5] suggested a concerted rearrangement of the oxonium ion (4) with migration of the more electronegative group R' and concluded that the rate-determining step in the reaction was addition to the carbonyl group. Doering and Speers[6] preferred a non-concerted process tending towards the carbonium ion species (5) to account for the observed migratory aptitudes.

Hawthorne, Emmons and McCallum[7] have reinvestigated the mechanism of peracid cleavage of ketones using trifluoroperacetic acid and have concluded that there is a fast and reversible formation of hydroxyperester followed by acid catalysed decomposition with concerted migration and elimination of the carboxylate leaving group (6). Since trifluoroperacetic acid reacts faster than peracetic acid by a factor of two hundred in the oxidation of cyclohexanone, the above authors consider that the rate determining step in the reaction must be the acid catalysed decomposition of the hydroxyperester. The difference in reaction rate is explained by the superiority of trifluoro-acetate over acetate as a leaving group.

As a general rule in Baeyer Villiger oxidations the more fully substituted alkyl group migrates i.e. the group which can best support a positive charge. It is implied in the concerted mechanism proposed above [see (6)] that the migrating species carries a pair of bonding electrons. This is inconsistent with the experimentally observed migration aptitudes which suggest that in the transition state the migrating group bears a partial positive charge. The situation is perhaps best represented by a non-classical cation (7).

The Criegee mechanism (scheme 4) (a) received support from perbenzoic acid oxidation of O^{18} enriched benzophenone[8] when the carbonyl group of the derived phenyl benzoate was found to be enriched in O^{18}. If the mechanisms of Baeyer and Villiger[1](b) or Wittig and Pieper[3](c) played a part in the reaction, the isotopic oxygen would not be detected

exclusively in the carbonyl oxygen of the phenyl benzoate.

There is one well documented exception to the rule of migratory aptitude in the Baeyer Villiger reaction, namely the oxidation of camphor (8). Baeyer and Villiger found that the principal product was α-campholide (9) which arises by migration of the less substituted carbon atom. It should be noted that apocamphor (10) behaves similarly[9] to yield the lactone (11) while carvone camphor (11a) reacts normally[38]. The formation of these products is not easily rationalised in terms of a comprehensive mechanistic interpretation. A number of recent publications[10,11,12,13] have attempted to illuminate this subject and these are discussed below.

The Baeyer Villiger reaction was originally thought to be controlled by purely electronic factors[6] and this led to the rule of migratory aptitudes which is highly satisfactory for most cases with the notable exceptions of camphor and apocamphor. Murray, Johnson, Pederson and Ott[11] while investigating the peracid oxidation of 17-keto-steroids (13) which had been reported[14] to give the anomalous ring D lactone (14), suggested that steric factors in the transition state could also affect the course of the reaction especially in fused alicyclic systems. They showed conclusively that the lactone obtained by action of peracid on 17-keto-steroids had the structure (15) i.e. it arose by migration of the fully substituted C_{13}. It is interesting to note that thermal decomposition of the equivalent 17-gem-dihydroperoxy steroid (16)[15] yields two ring D lactones (15) and (17) epimeric at C_{13}. This is not

unexpected since the decomposition presumably proceeds by a free radical equivalent of the Criegee mechanism (scheme 5). It has been shown conclusively that the Baeyer Villiger reaction occurs with retention of configuration[16,17,18].

Murray and his colleagues assumed addition of peracid to the C_{17} carbonyl group from the less hindered α-face of the molecule by analogy with a multitude of stereospecific attacks on the steroid nucleus. Migration of C_{13} to an α-oriented electron deficient substituent on C_{17} leads to a highly favoured transition state with the expanded ring D in the chair conformation [scheme 6(a)] whereas migration of C_{16} would result in a higher energy transition state with ring D in the boat conformation [scheme 6(b)]. When this conformational treatment is applied to camphor one finds, assuming addition of peracid to the less hindered endo-face[20], that migration of C_3 leads to the observed product [α-campholide (9)] via a favoured chair transition state [scheme 7(a)] whereas migration of C_1 via a boat transition state is less favourable on conformational grounds [scheme 7(b)].

This conformational treatment was extended by Ourisson[12] and Meinwald[13] to norcamphor (18). The peracid oxidation product was predicted on the assumption that attack of peracid would occur preferentially from the exo-side[19]. Thus the hydroxyperester (19) can breakdown via a chair transition state to the lactone (20) whose formation is favoured both electronically and conformationally. The epimeric hydroxyperester (21) whose formation is sterically less favoured,

can break down via a chair transition state only by migration of C_3, the less substituted carbon atom, affording the lactone (22). In fact both Meinwald and Ourisson isolated (20) in high yield from the peroxidation of norcamphor in a strongly acidic medium. When the reaction was carried out in a buffered medium a trace of a second product, possibly the lactone (22) was detected. Ourisson[12] suggested the existence, in buffer, of an equilibrium between the epimeric hydroxyperester anions (scheme 8) to account for the possible formation of (22).

Sauers[10] carried out the peracid oxidation of camphor in buffer and obtained in 80% yield the lactone (23), dihydro-α-campholenolactone. Although the formation, in small amounts, of α-campholide (9) cannot be excluded, none was isolated. In accordance with its proposed structure, (23) isomerised on treatment with acid to dihydro-β-campholenolactone (24) and on reduction with lithium aluminium hydride followed by acetylation and dehydration yielded the unsaturated acetate (25) identical with that obtained from α-campholenic acid (26) by reduction and acetylation.

It would seem that the formation of both α-campholide (9) and dihydro-α-campholenolactone (23) on peroxidation of camphor, depending on the reaction conditions, can be rationalised in the following manner:- In buffer, although initial attack of peracid on the ketone is under steric control and must occur from the endo-face with formation of (27), equilibration results in the existence of the exo-hydroxyperester (28) whose break down to dihydro-α-campholenolactone (23) is electronically and conformationally favoured (scheme 9). The decomposition of the

endo-hydroxyperester to α-campholide (9) is unfavourable on electronic grounds since it requires migration of the less substituted carbon atom.

In an acid medium equilibration of the epimeric hydroxyperester anions is not possible and no exo-hydroxyperester (28) is formed. Thus α-campholide arises in 30% yield by the electronically less favoured pathway [scheme 7(a)]. We consider that (27) can break down to α-campholenic acid (26) by an alternative mechanism analogous to the formation of α-campholenonitrile (29) in the Beckmann rearrangement of camphor oxime[21]. This conclusion appears to be supported by the mechanism which we later invoke for the formation of the dihydroxy-lactone (12; R = R' = OH) (see p. 70). Under the reaction conditions α-campholenic acid undergoes further rearrangement to dihydro-β-campholenolactone and the dihydroxy-lactone (12). It is possible also that this alternative break down can occur in a buffered medium when α-campholenic acid may exist and survive as dihydro-α-campholenolactone (23).

Several other bicyclic ketones have been subjected to peracid oxidation under acidic and buffered conditions by Meinwald[13,22]. Bicyclo [2,2,2] octanone (30) reacted according to prediction and formed the lactone (31) in high yield. This is completely analogous to the behaviour of bicyclo [2,2,1] heptanone (norcamphor) (18) and shows that the additional carbon atom in the bridge does not affect the course of the reaction.

In the case of the two βγ-unsaturated ketones bicyclo [2,2,2]

oct-5-en-2-one (32) and bicyclo [2,2,1] hept-5-en-2-one (dehydro-norcamphor) (33) there is the possibility of competition between epoxidation of the isolated double bond and Baeyer Villiger oxidation of the ketonic function. In both these ketones the double bond is inert to epoxidation due to spacial interaction with the carbonyl group which is favourably situated to deactivate the double bond to electrophilic attack by withdrawal of electrons. An example of the phenomenon of spacial interaction in $\beta\gamma$-unsaturated carbonyl systems can be found in the synthesis of reserpine[23] where the $\beta\gamma$-double bond of lactone (34) is inert to peracid attack.

On peracid oxidation dehydronorcamphor yielded the lactone (35) from normal bridgehead migration and also the allylic isomeric lactone (36) presumably formed through an intermediate of the type (37). Bicyclo [2,2,2] oct-5-en-2-one (32) was converted solely into the more stable allylic isomeric lactone (38).

Thus in all the bicyclic ketones examined, with exception of camphor and apocamphor, normal bridgehead migration occurs on peracid oxidation. This has been satisfactorily rationalised in terms of electronic and conformational factors. Camphor and apocamphor owe their unique position to the steric compression caused by the gem-dimethyl grouping on C_7 which reverses the stability of the epimeric hydroxyperester intermediates and allows alternative break-down mechanisms to come into operation. By involving one of the C_7 methyl groups in a cyclobutane ring in the case of carvone camphor (11a) the steric compression is sufficiently reduced to allow peracid oxidation to proceed by normal bridgehead migration[38].

CONSTITUTION AND STEREOCHEMISTRY OF THE LACTONE $C_{10}H_{16}O_4$ (12: R=R'=OH)[24]

In the oxidation of camphor with Caro's acid Baeyer and Villiger[1] isolated, in minor yield, a lactonic product $C_{10}H_{16}O_4$ in addition to α-campholide (9). The only published contribution to the chemistry of this lactone was made by Locquin[25] who pyrolysed it in acid and obtained a tetramethyl cyclopentenone to which he ascribed the structure (39). We undertook an investigation of the lactone $C_{10}H_{16}O_4$ and have deduced for it the constitution and stereochemistry (12; R = R' = OH) on the evidence presented below.

The lactone was obtained from either persulphuric or more conveniently peracetic acid oxidation of camphor. The molecular formula was confirmed as $C_{10}H_{16}O_4$ and Kuhn-Roth oxidation indicated the presence of two C-methyl groups. The lactone consumed one equivalent of base within two minutes at 95°. The infrared spectrum of (12; R = R' = OH) had bands (in Nujol) at 1393 and 1379 (gem-dimethyl) and (in chloroform) at 3628 (free hydroxyl) 3524 (bonded hydroxyl) and 1773 (γ-lactone) cm.$^{-1}$. Mild acetylation of (12; R = R' = OH) in pyridine with acetic anhydride afforded a monoacetate, $C_{12}H_{18}O_5$ (12; R = OAc, R' = OH) which still retained hydroxyl absorption in the infrared and more vigorous acetylation with refluxing acetyl chloride, a diacetate, $C_{14}H_{20}O_6$ (12; R = R' = OAc). Oxidation of (12) with chromium trioxide in acetic acid yielded the hydroxy-cyclopentanone, $C_{10}H_{14}O_4$ (40) $\nu_{max.}$ (in carbon tetrachloride) 1787 (γ-lactone), and 1747 (cyclopentanone) and 3600

(free hydroxyl) cm.$^{-1}$] which formed a monobenzylidine derivative. Thus of the four oxygens in the molecule, one is present as a secondary hydroxyl group flanked by at least one methylene group and attached to a five-membered ring, the second probably as a tertiary hydroxyl group and the remaining two as part of a γ-lactone system.

The carbon skeleton of the diol-lactone (12; R = R' = OH) and the relative positions of the functional groups were revealed in an unexpectedly simple manner. When the ketone (40) was refluxed with decinormal ethanolic potassium hydroxide the product obtained was the hydroxy-cyclopentenone, $C_9H_{14}O_2$ (41) [$\lambda_{max.}$ 222 mμ (ε 12,000); $\nu_{max.}$ (in carbon tetrachloride) 3570 (free hydroxyl) 1710 (cyclopentenone) and 1620 (conjugated ethylenic linkage) cm.$^{-1}$] which was reduced with zinc in refluxing acetic acid to the deoxy-ketone $C_9H_{14}O$ (42). To account for these transformations the hydroxyl group in (41) must be attached α (or vinylogously α) and the lactone carbonyl group in (40) β (or vinylogously β) to the ketone [i.e. the secondary hydroxyl group in (12; R = R' = OH)]. Dehydration of the dihydroxy-lactone with phosphorus oxychloride in pyridine gave the diene-lactone, $C_{10}H_{12}O_2$ (43) [$\lambda_{max.}$ 262 mμ (ε 11,900); $\nu_{max.}$ (in carbon tetrachloride) 1769 and 1749 (lactone carbonyl) and 1637 (conjugated ethylenic linkage) cm.$^{-1}$] which on hydrogenation over Adam's catalyst absorbed two moles of hydrogen with formation of the known dihydro-β-campholenolactone (24) characterised as the crystalline diol[37] (44) obtained by lithium aluminium hydride reduction.

The constitution of the dihydroxy-lactone as (12; R = R' = OH) follows unambiguously from the above experiments. The base catalysed transformation of the ketone (40) proceeds by β-elimination of the tertiary hydroxyl group with subsequent decarboxylation of the vinylogous β-keto lactonic carbonyl group. The resultant hydroxy-cyclopentenone is a vinylogous α-hydroxy ketone and was therefore reduced with zinc in acetic acid to the tetramethyl cyclopentenone (42) (scheme 10).

The tetramethyl cyclopentenone obtained by action of hot mineral acid on (12; R = R' = OH) was formulated by Locquin[25] as (39) on the basis of its degradation via a trimethyl laevulic acid to trimethyl succinic acid. This sequence of reactions was repeated and the formation of trimethyl succinic acid confirmed. Whereas this does not distinguish between the alternative tetramethyl-cyclopentenone structures (39) and (42), the pyrolysis product was found to be different from (42) and identical with a synthetic cyclopentenone of established structure (39) [direct comparison of the semicarbazones][27]. A possible mechanism for the formation of (39) from (12; R = R' = OH) involving acid-induced dehydration, decarboxylation and methyl migration is shown (scheme 11).

There are two possible pathways for the formation of the dihydroxy-lactone (12; R = R' = OH). The first finds analogy in the Beckmann rearrangement of camphor oxime which yields α-campholenonitrile (29) as the major product[21]. Normally the Beckmann rearrangement of alicyclic ketoximes gives rise to lactams[28] but in the case of camphor oxime the

expected ring expansion to the lactam (45) or (46) apparently does not take place. The alternative ring fission to the nitrile occurs possibly because of the favourable trans-anti parallel stereochemistry (scheme 12). By analogy the hydroxyperester species (27) from camphor can break down to α-campholenic acid (26) the desired intermediate in the formation of the dihydroxy-lactone (12; R = R' = OH) (scheme 13).

Alternatively α-campholenic acid (26) can arise by the previously discussed route leading to dihydro-α-campholenolactone (23) (scheme 9) which will be in equilibrium with α-campholenic acid. The existence of an equilibrium between (23) and (26) (scheme 14) is consistent with the isomerisation of (23) on treatment with acid[10] to dihydro-β-campholenolactone (24). This second pathway to α-campholenic acid is must less attractive than the first since in acid conditions little or no exo-hydroxyperester of camphor will be formed.

It is considered that the diol-lactone (12; R = R' = OH) is formed from α-campholenic acid (26) by a mechanism similar to that which operates in the acid isomerisation of the latter to dihydro-β-campholenolactone (scheme 15) with subvention, in presence of peracid, of OH^+ instead of H^+ as the cationic species (scheme 16). Attack of OH^+ on (26) with migration of a methyl group gives rise to the carbonium ion intermediate (47) which can either lactonise to (48) or lose a proton to give (49). Since (48) and (49) are in equilibrium the acid (49) undergoes further attack of OH^+ with lactonisation (probably concerted) to give the dihydroxy-lactone.

α-Campholenic acid was oxidised with peracid to the dihydroxy lactone (12; R =R' = OH) in higher yield than was camphor under similar conditions thus bearing out its claims as an intermediate. Further support for the proposed pathway was realised when peracid oxidation of dihydro-β-campholenolactone (24) gave rise to a monohydroxy-lactone, $C_{10}H_{16}O_3$ (50) $\nu_{max.}$ (in carbon tetrachloride) 3618 (free hydroxyl) 1778 (γ-lactone) cm.$^{-1}$. The structure of this new lactone followed simply from the following observations. It was resistant to acetylation with acetic anhydride in pyridine. Dehydration with phosphorus oxychloride in pyridine yielded an oily αβ-unsaturated lactone, $C_{10}H_{14}O_2$ (51) $\lambda_{max.}$ 219-220 mμ (ε 11,700) which was converted by hydrogenation, with uptake of one mole, to dihydro-β-campholenolactone (24), characterised as the diol (44).

The monohydroxylactone (50) can arise from dihydro-β-campholenolactone via β-campholenic acid (52) by a pathway analogous to the formation of the dihydroxy-lactone (scheme 17). The lactone (50) was also isolated in low yield from 5% peracetic acid oxidation of either camphor or α-campholenic acid when no dihydroxy-lactone was found. In this case the concentration of peracid was probably too low to compete with the acid-catalysed isomerisation of α-campholenic acid to dihydro-β-campholenolactone which could then be attacked by peracid to form (50). Unlike the dihydroxy-lactone, the monohydroxy-lactone is optically inactive. This is not unexpected when one considers its mode of genesis.

The dihydroxy-lactone is partially racemic. This implies that the

initial attack of OH^+ on α-campholenic acid is under some steric control. When the oxidation is carried out in a homogeneous medium (peracetic acid) the product from both camphor and α-campholenic acid has the same rotation, $[\alpha]_D$ + 40°, which can be raised by several crystallisations to + 60°. The optically pure dihydroxy-lactone, $[\alpha]_D$ + 60°, forms a mono-(+)-camphorsulphonate, $[\alpha]_D$ + 67°. When, however, the oxidation is carried out in a two-phase system with persulphuric acid, the extent of racemisation varies unpredictably depending on whether camphor or α-campholenic acid is the substrate. The dihydroxy-lactone obtained from the latter has $[\alpha]_D$ + 30°, which can be raised by crystallisation to + 60°, but the product from camphor is almost completely racemised $[\alpha]_D$ + 8° (unchanged on crystallisation). An effort was made to resolve this racemic mixture via the (+)-camphorsulphonate. Several crystallisations of the crude ester led to the same diasterioisomer, $[\alpha]_D$ + 67°, as was obtained from optically pure diol-lactone. All attempts to hydrolyse the (+)-camphorsulphonate failed, only unsaturated material being produced.

On the assumption that the extended Hudson Lactone rule[29,30] can be applied to systems with an angular methyl group, the enantiomer formed in excess can be tentatively assigned the absolute configuration (12; R = R' = OH) on the basis of the large positive ΔM_D value ($[M]_D$ lactone/ethanol - $[M]_D$ lactone/N ethanolic potassium hydroxide + 124°).

It now remains to consider the relative stereochemistry of the three asymmetric centres in the molecule. The cis-nature of the ring fusion

is assigned on stereomechanistic grounds. The product appears to be sterically uniform and this implies stereospecific lactonisation which is best visualised as being concerted with and trans to peracid attack on the double bond of the intermediate (49) (scheme 18). Such concertion is sterically favoured and has good analogy in the literature[31,32]. It would necessarily result in the proposed cis-fusion of the two five-membered rings. The optical rotatory dispersion (see page 87) of the hydroxy-ketone (40) is in harmony with such a proposal.

The relative stereochemistry of the two hydroxy groups is not easily predicted and was difficult to confirm by chemical means. In our preliminary publication[24] we assigned a cis relationship on the basis of hydrogen bonding in the hydroxyl region of the infrared spectrum at low concentration. Recently intermolecular hydrogen bonding[33] has been shown to persist at concentrations (0.002M) below those normally regarded[34] as limiting for such bonding. While the diol-lactone (12; R = R' = OH) still showed bonded hydroxyl absorption in carbon tetrachloride at 0.003M concentration, this however eventually disappeared on further dilution and cannot therefore result from intramolecular bonding. It is evident that the geometry of the diol-lactone is such as to favour molecular association by hydrogen bonding in very dilute solution.

Chemical evidence supporting a trans relationship of the two hydroxyl groups is twofold. First, attempts to involve the hydroxyl groups in a cyclic derivative proved entirely fruitless. Though the increase in oxygen-oxygen distance in cyclopentane-1,3-diols as compared

with the diaxial cyclohexane derivatives makes the formation of acetonides and cyclic carbonates less likely, a p-nitrobenzylidine derivative of cyclopentane-1,3-diol has been reported[36]. Efforts to condense the diol-lactone with acetone, benzaldehyde and diethyl carbonate were unsuccessful.

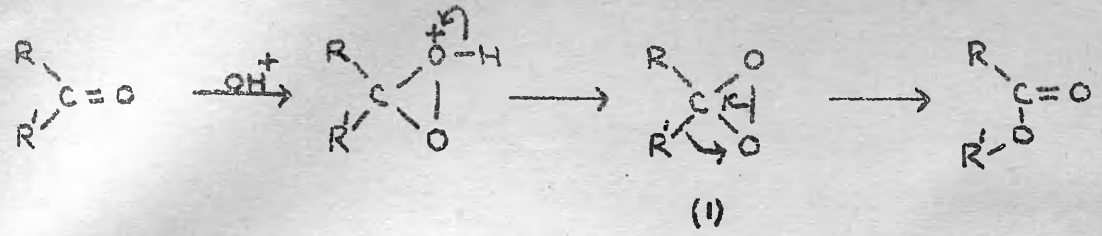
Construction of a cyclic oxalate without distortion of bond angles is perfectly feasible for a cis (but not a trans) cyclopentane-1,3-diol. When the diol-lactone was refluxed with oxalyl chloride no cyclic oxalate (53) but a good yield of oily half-acid chloride (54; R = Cl) was obtained. This was characterised as the crystalline half-methyl ester (54; R = OMe) which showed no intramolecular hydrogen bonding in the hydroxyl region of its infrared solution spectrum. The monoacetate (12; R = OAc, R' = OH) likewise showed no bonded hydroxyl absorption. The half-acid chloride was refluxed in pyridine to effect ring closure but only unsaturated material was recovered. Attempts to cyclise the half-acid (54; R = OH) using dicyclohexylcarbodiimide proved equally unsuccessful.

Second, efforts to obtain the epimeric secondary hydroxyl by reduction of the hydroxy-ketone (40) with sodium borohydride afforded only the known diol-lactone apart from minor amounts of material arising from reduction of the lactone. Such stereospecificity is explicable if reduction is supposed to occur by intramolecular hydride transfer from an initially formed borate complex (55) of a kind discussed by Henbest[35] for reduction of $\beta\gamma$-epoxy-cyclohexanols. The resulting diol must then necessarily be trans-oriented. Catalytic reduction of (40) over Adam's

catalyst resulted in a mixture of the known diol-lactone and unchanged ketone. Solvolysis of the diol-lactone mono-toluene-p-sulphonate (12; R = $C_7H_7O_3S$, R' = OH) using fused sodium acetate in acetic acid under a variety of reaction conditions yielded only unchanged mono-toluene-p-sulphonate and unsaturated material.

The apparently exclusive formation of the trans-diol in the peracid oxidation may be due to steric control over the direction of attack of the second mole of peracid. In the intermediate (49), attack of OH^+ leading to a cis-diol is hindered by two β-substituents whereas attack leading to a trans-diol is hindered by only one β-substituent and might consequently be favoured.

SCHEME 1



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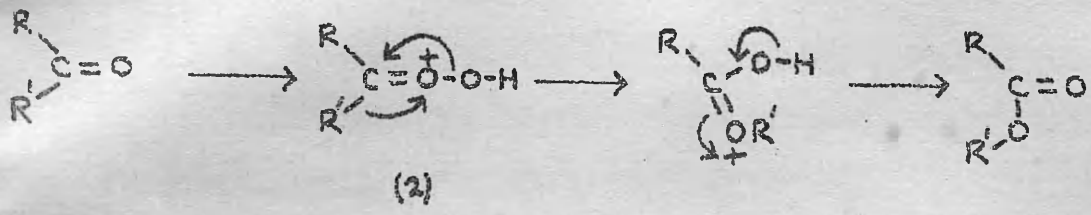

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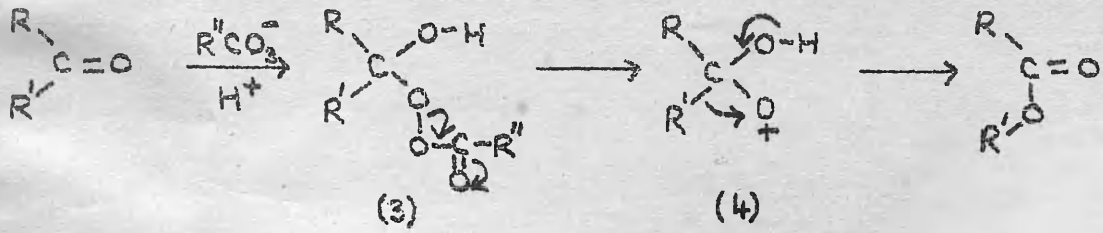

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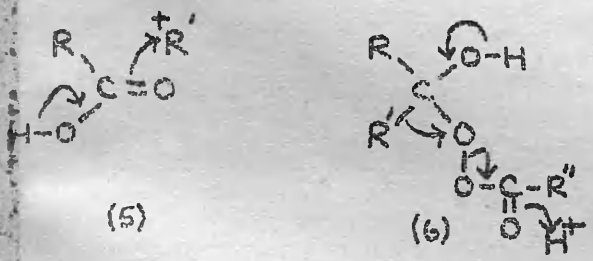

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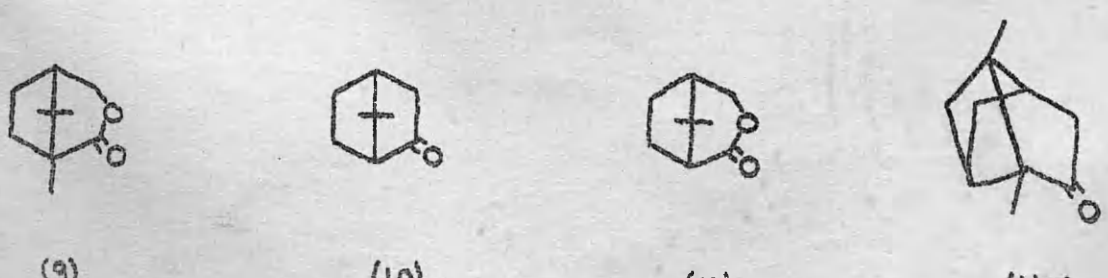

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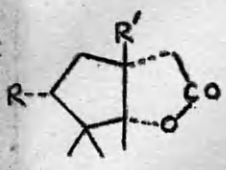

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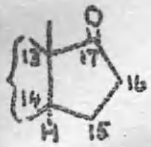

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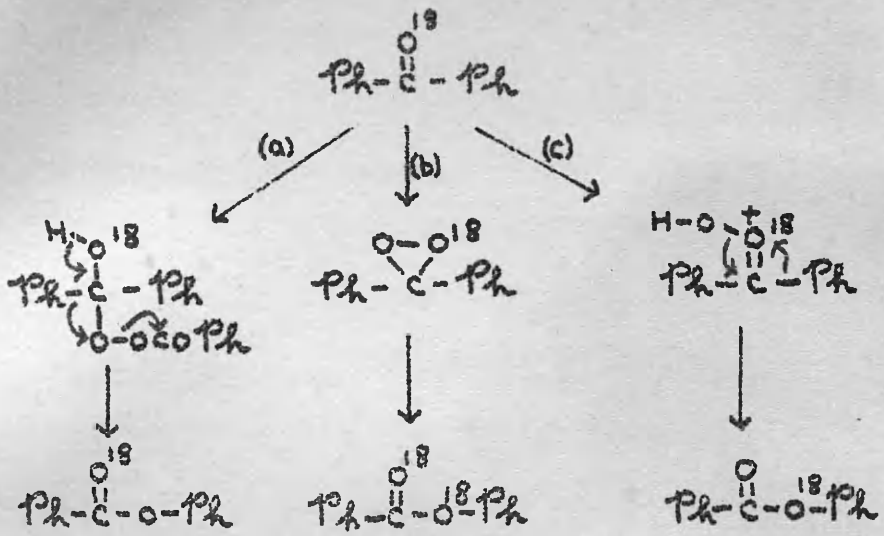

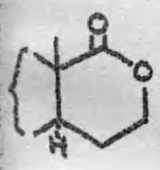

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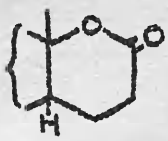

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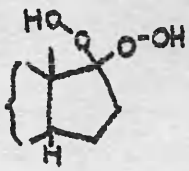

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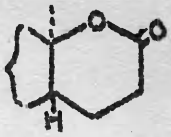

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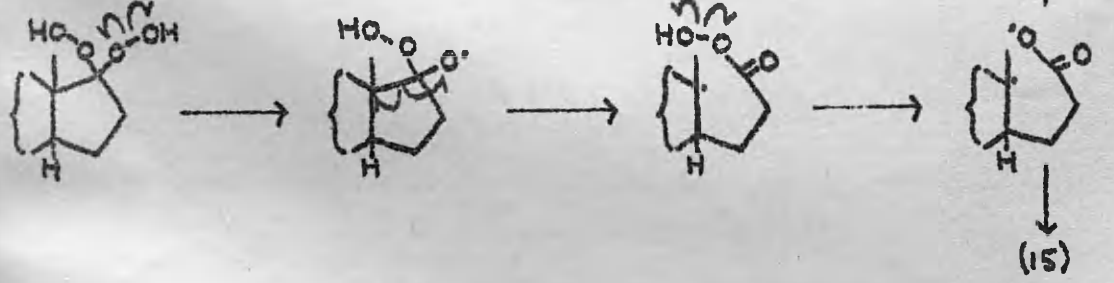

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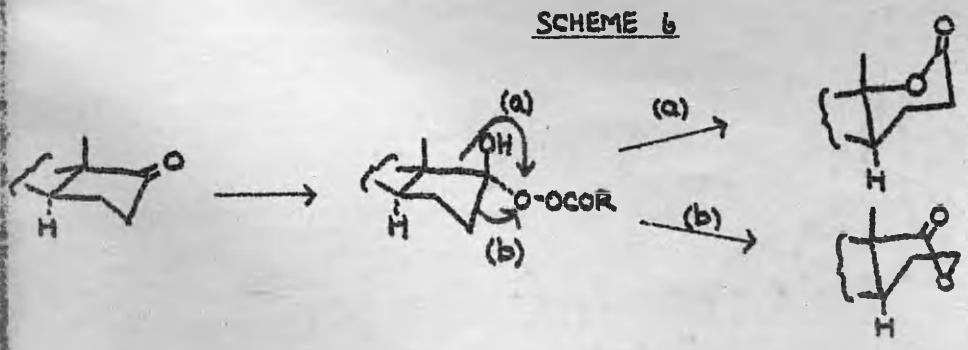

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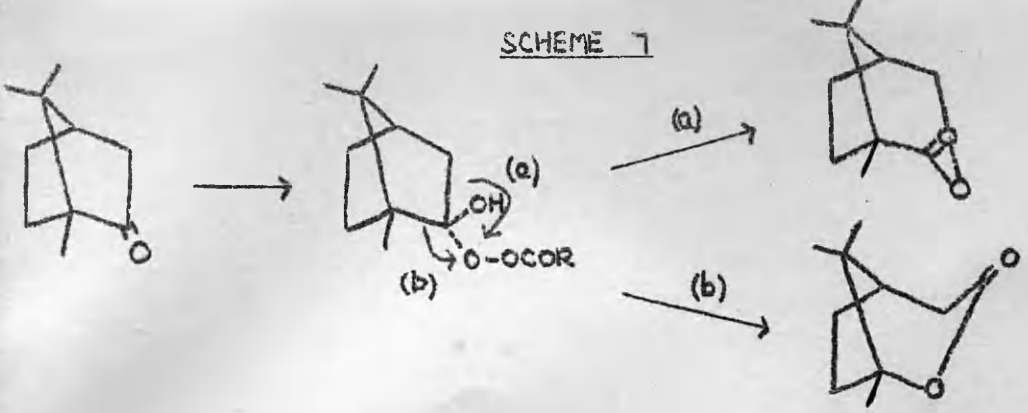

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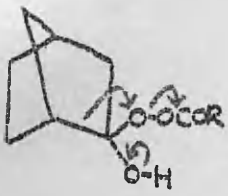

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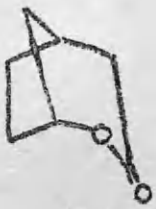

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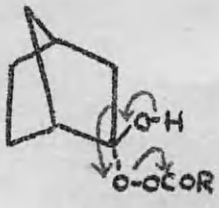

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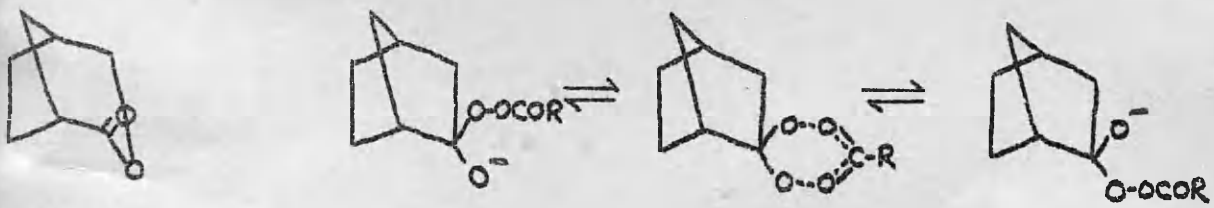

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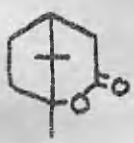

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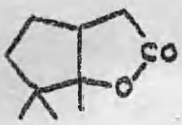

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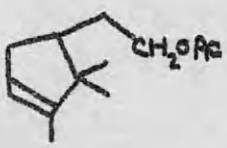

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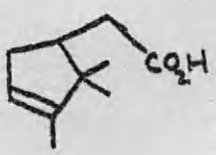

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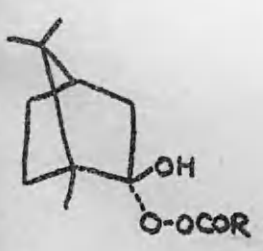

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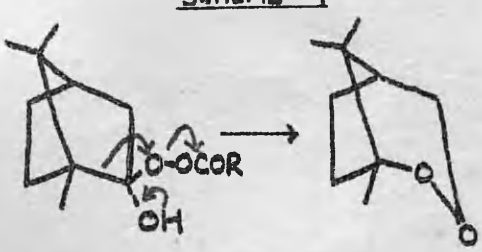

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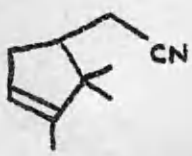

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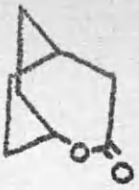

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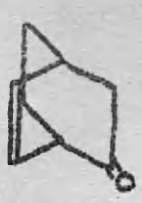

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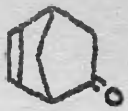

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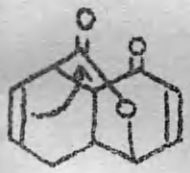

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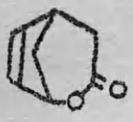

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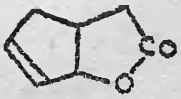

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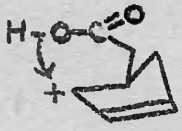

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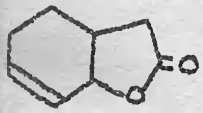

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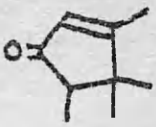

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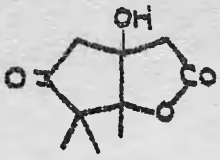

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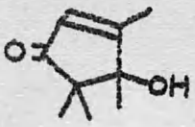

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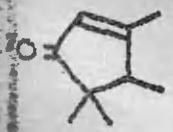

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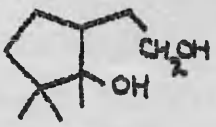

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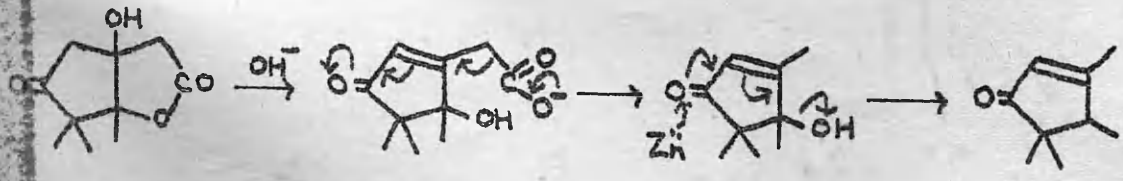

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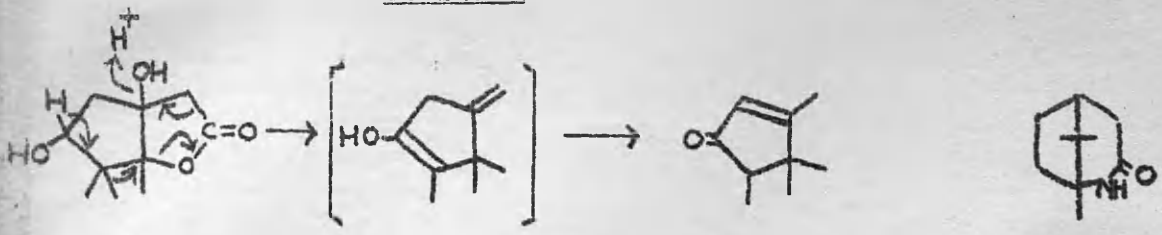

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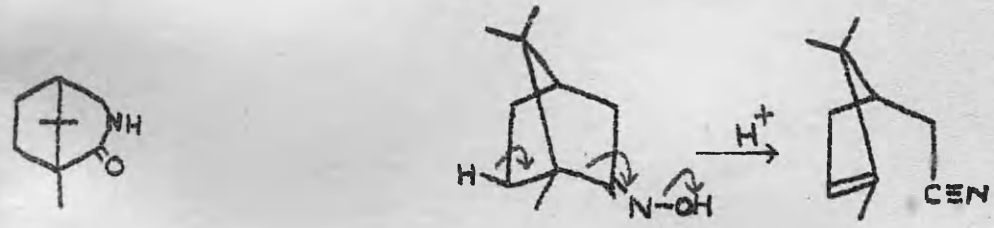

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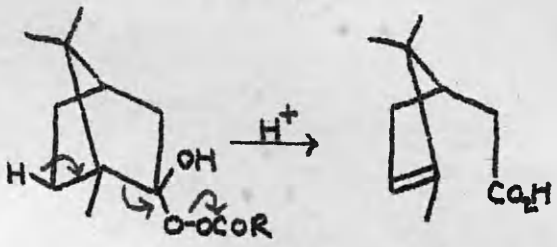

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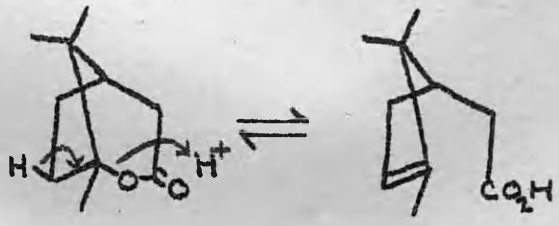

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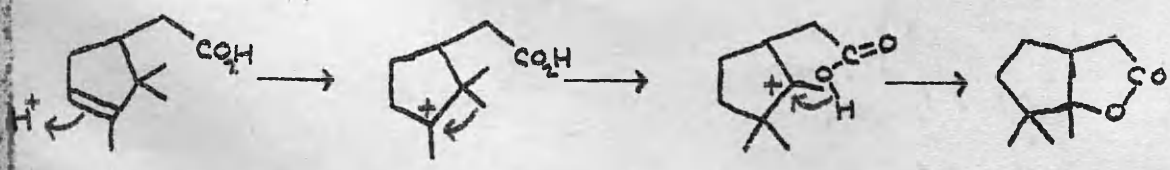

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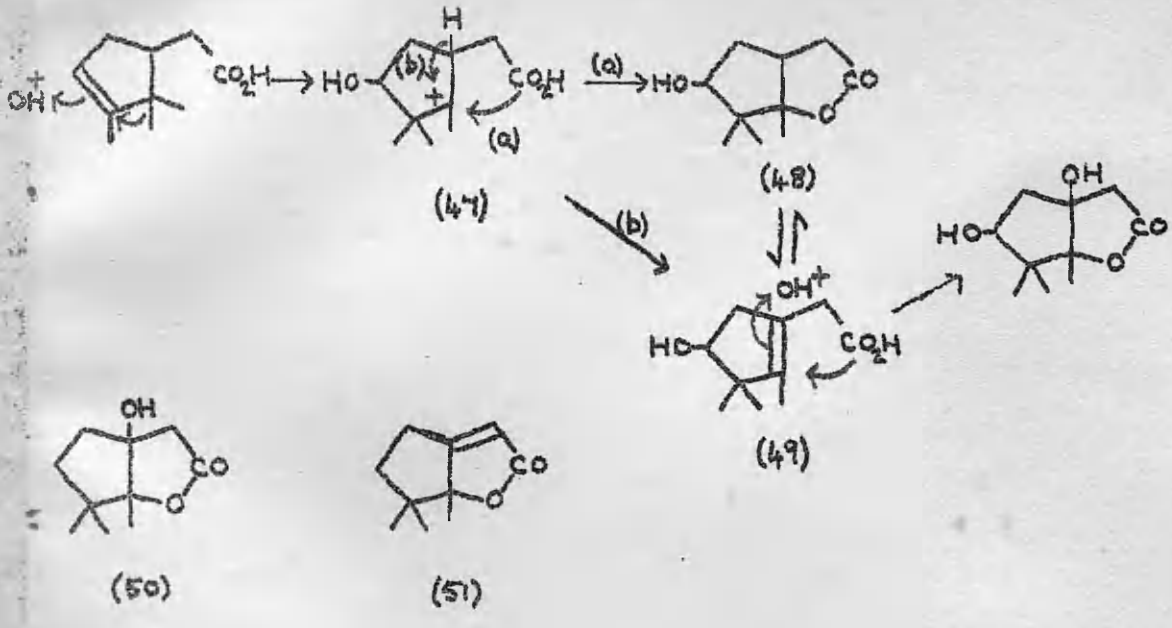

(47) (48) (49) (50) (51)

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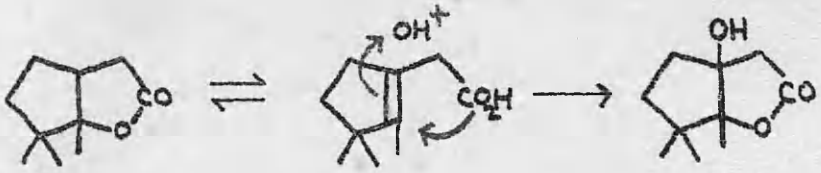

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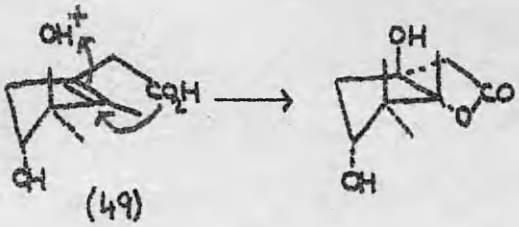

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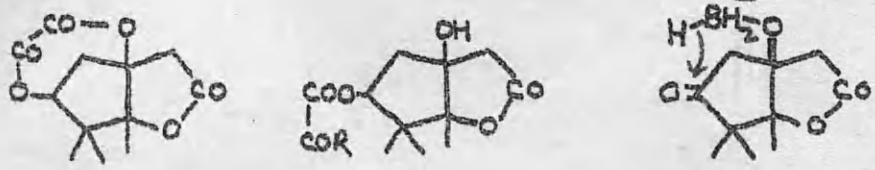

(53) (54) (55)

EXPERIMENTAL

For general experimental procedures see p. 49.

The Dihydroxylactone (12; R = R' = OH)

(a) From (+)-Camphor (i) (+)-Camphor($[\alpha]_D$ + 44° (ethanol); 75g.) in light petroleum (120 ml.) was added dropwise over two hours to potassium persulphate (600 g.) suspended in water (360 ml.) and concentrated sulphuric acid (990 ml.); the camphor solution was dropped on the disc of a vibro-mixer, placed near the surface and the reaction temperature maintained at 20° by external cooling. Agitation was continued for a further 1/2 hr., the reaction poured into ice and neutralised (pH5) with ammonia gas. The brown, gummy cake containing ammonium sulphate and α-campholide was removed and the aqueous filtrate continuously extracted with ether for 16 hr. The yellow, semi-crystalline residue obtained on removal of ether, purified by chromatography over alumina (grade V) in benzene/ethyl acetate (1:1), furnished the diol (12; R = R' = OH) (10.0 g.) prisms (from acetone-benzene) m.p. 192-193°, $[\alpha]_D$ + 8° (c 0.90 in acetone) not appreciably raised by successive crystallisations (Found: C, 59.85; 60.1; H, 7.95, 8.2; OMe, 14.15. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.2; OMe (2) 15.0%).

Hydrolysis of the lactone (5.00 mg.) with 0.1 N sodium hydroxide (~4 mol.) for 2 min. at 95° gave on back-titration an equivalent weight of 207 (Calc. 200).

(ii) (+)-Camphor ($[\alpha]_D$ + 44° (ethanol); 20 g.) in "AnalaR" acetic acid (100 ml.) was added dropwise to a stirred, cooled mixture of

sulphuric acid (40 ml.) and peracetic acid (43%; 50 ml.) then kept at 20° for five days, poured into ice, saturated with sodium chloride, extracted with ether (3 x 150 ml.) and the combined extracts washed with saturated sodium bicarbonate and water. Chromatography of the product over alumina (grade III) afforded successively (benzene) α-campholide, (ethyl acetate-benzene; 1:2) non-crystalline hydroxy-lactonic material and (ethyl acetate) dihydroxy-lactone [12; R = R' = OH] (1.6 g.), prisms from acetone-benzene, m.p. 180-192°; $[\alpha]_D$ + 45° (acetone), raised on two crystallisations from acetone to m.p. 192-194°; $[\alpha]_D$ + 60° (c 1.01 in acetone). In ethanol this had $[M]_D$ + 156° (c 0.8) and in 1 N ethanolic potassium hydroxide $[M]_D$ + 32° (c 0.8).

(b) <u>From (+)-α-Campholenic Acid</u>. (i) (+)-α-Campholenic acid ($[\alpha]_D$ + 11° (acetone); 11 g.), oxidised and worked as in (a) (i) afforded the dihydroxy-lactone (3.4 g.), m.p. 190-192°; $[\alpha]_D$ + 30° (acetone). Repeated crystallisation from acetone raised this to m.p. 192-193°; $[\alpha]_D$ + 63° (c 1.80 in acetone).

(ii) (+)-α-Campholenic acid ($[\alpha]_D$ + 11°; 920 mg.) was oxidised as in (a) (ii), and the product chromatographed over alumina (grade V), affording dihydro-β-campholenolactone (600 mg.; benzene), monohydroxy-lactonic material (benzene-ethyl acetate, 2:1) and dihydroxy-lactone (150 mg.; ethyl acetate). Crystallised twice from acetone, this had m.p. 192-194°; $[\alpha]_D$ + 59° (c 1.48 in acetone).

Attempts to condense the dihydroxy-lactone with (a) acetone (in presence of either HCl gas or anhydrous copper sulphate - H_2SO_4), (b) diethyl carbonate or phosgene in presence of base and (c) benzaldehyde in presence of acid, gave in each case quantitative recovery of unchanged dihydroxy-lactone.

Attempts to form the Cyclic Oxalate (53). (i) With Oxalyl Chloride.

The dihydroxy-lactone (500 mg.) was refluxed with excess freshly distilled oxalyl chloride for 10 hr. The half acid chloride (54; R = Cl) obtained by removing unreacted oxalyl chloride in vacuo was hydrolysed with water, and the half acid (54; R = OH) characterised as the methyl ester obtained with ethereal diazomethane. Needles (from acetone-benzene-n-hexane) m.p. 138-139°. (Found: C, 54.55; H, 5.95. $C_{13}H_{18}O_7$ requires C, 54.55; H, 6.35%). $\nu_{max.}$ (in carbon tetrachloride) 3615 (free OH; no bonded OH), 1787, 1805 (shoulder) (γ-lactone), 1753 (oxalate) $cm.^{-1}$.

The half acid (54; R = OH) (150 mg.) in dry tetrahydrofuran (10 ml.) was kept with dicyclohexylcarbodiimide (40 mg.) for 3 days. The product after removal of solvent was separated into acidic /75 mg.; unchanged half-acid (I.R.)/ and neutral (120 mg.) fractions. The latter afforded dicyclohexyl urea (insoluble in ether) (m.m.p. and I.R.) and on careful chromatography of the remainder (alumina; grade V) only hydroxylic fractions (I.R.) but no cyclic oxalate.

The half acid (70 mg.) and dicyclohexylcarbodiimide (25 mg.)

were kept in dry pyridine (5 ml.) for 16 hr. Dilution with ether and successive extractions with dilute hydrochloric acid and aqueous sodium hydrogen carbonate gave back unchanged acid (62 mg.).

The half-acid chloride (55 mg.) was kept in dry pyridine (7 ml.) for 1 hr. and then refluxed for 1 hr. more. Dilution with ether and work-up in the usual way gave no acidic material. The neutral fraction (40 mg.) was hydroxylic and unsaturated (I.R.); chromatography did not reveal the cyclic oxalate (53).

Mono-(+)-Camphorsulphonate (12; R = $C_{10}H_{15}O_4S$, R' = OH)

The dihydroxy-lactone ($[\alpha]_D$ + 62°; 650 mg.) and (+)-camphorsulphonyl chloride (1 mol.) were kept in pyridine for 16 hr. Chromatography of the products, obtained as usual, over alumina (grade V) gave (up to 40% ethyl acetate-benzene) the mono-(+)-camphorsulphonate (400 mg.), followed by unchanged diol (320 mg.). The ester, twice crystallised from ethyl acetate, had m.p. 181-183°, $[\alpha]_D$ + 67° (c 0.73 in acetone) (Found: C, 58.25; H, 7.25. $C_{20}H_{30}O_7S$ requires C, 57.95; H, 7.3%).

Dihydroxy-lactone of $[\alpha]_D$ + 8° gave after six crystallisations (+)-camphorsulphonate m.p. 181-183°; $[\alpha]_D$ + 65° (c 1.4 in acetone).

Attempts to hydrolise the (+)-camphorsulphonate using oxalic acid in aqueous dioxan or water at reflux were unsuccessful, affording unchanged ester and unsaturated hydroxy-lactone (infrared) respectively.

Mono-Toluene-p-Sulphonate (12; R = $C_7H_7O_3S$, R' = OH).

The mono-toluene-p-sulphonate, obtained in the usual way, had (from benzene-light petroleum) m.p. 110-112°; $\lambda_{max.}$ 226 mμ (ε 11,400). (Found: C, 57.8; H, 6.3. $C_{17}H_{22}O_6S$ requires C, 57.6; H, 6.25%).

Attempts to replace the toluene-p-sulphonate by acetate with inversion under a variety of conditions resulted either in elimination or recovery of unchanged material.

Monoacetate (12; R = OAc, R' = OH). The dihydroxy-lactone (100 mg.), acetylated with pyridine and acetic anhydride at 20° in the usual way afforded the monoacetate, rods (80 mg.) from benzene, m.p. 80-82°, $[\alpha]_D$ + 66° (c 1.92 in acetone). $\nu_{max.}$ (in carbon tetrachloride) 3615 (OH), 1784 (γ-lactone) and 1747 (acetate) cm.$^{-1}$. (Found: C, 59.55; H, 7.5. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%).

Diacetate (12; R = R' = OAc). The diol when refluxed with acetyl chloride for 2 hr. afforded the diacetate, plates from ethyl acetate-light petroleum, m.p. 105-106°. $\nu_{max.}$ (in carbon tetrachloride) 1790 (γ-lactone), 1748 (acetate) cm.$^{-1}$. (Found: C, 59.05; H, 6.8. $C_{14}H_{20}O_6$ requires C, 59.15; H, 7.1%).

Hydroxy-ketone (40). The diol (150 mg.) in "AnalaR" acetic acid, was treated with chromium trioxide (75 mg.; 1.5Ô) in aqueous acetic acid (1:19) at 20° for 16 hr., affording the hydroxy-ketone (40), rods (132 mg.) from chloroform-benzene, m.p. 160-162°. (Found: C, 60.85; H, 6.85. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%). Hydroxy-ketone obtained from diol of $[\alpha]_D$ + 62° (acetone) had a

positive Cotton curve (c 0.28 in $CHCl_3$): (600 mμ) + 292°; (589) + 340°; (320) + 2332°; (300) + 1,000°. The derived acetate obtained with refluxing acetyl chloride separated as needles from ether-n-hexane, m.p. 123-125°. $\nu_{max.}$ (in carbon tetrachloride) 1790 (γ-lactone) and 1747 (acetate and cyclopentanone) cm.$^{-1}$. (Found: C, 59.85; H, 6.5. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%).

The ketone (50 mg.) in 0.1 N ethanolic KOH (10 ml.), containing freshly distilled benzaldehyde (250 mg.), was kept for 10 min. Extraction of the acidified solution with ether (bisulphite wash) gave the mono-benzylidine derivative as plates from ethyl acetate-benzene, m.p. 150-151°; $\lambda_{max.}$ 302 mμ (ε 22,600). (Found; C, 71.2; H, 6.4. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%).

Borohydride Reductions of the Ketone (40)

The ketone (100 mg.) and sodium borohydride (100 mg.) were kept in methanol (10 ml., containing a few drops of water) for 3 days at 20°. The product (95 mg.) obtained with ether from the acidified reaction, afforded on chromatography over alumina (grade V) the dihydroxy-lactone (12; R = R' = OH) (80 mg.; 1:1 benzene-ethyl acetate) and a crystalline compound, m.p. 145° (7 mg.; 1:2 benzene-ethyl acetate) which showed no carbonyl absorption in the I.R. and was not investigated further.

When water was used as the solvent, the more polar product was obtained in excess (5:2) of the diol.

Changes in the proportion of sodium borohydride and substitution

of potassium borohydride did not afford any of the epimeric diol-lactone.

Catalytic Reduction of the Ketone (40)

The ketone (20 mg.) and Adam's catalyst (25 mg.) in ethyl acetate (4 ml.) were shaken in hydrogen until no more was absorbed (3 days; 1.2 ml. 0.58 mol.). Chromatography of the product over alumina (grade V) gave unchanged ketone (14 mg.: 9:1 benzene-ethyl acetate) and the dihydroxy-lactone (12; R = R' = OH; 4 mg.; 1:1 benzene-ethyl acetate).

Action of Alkali on the Hydroxy-Ketone (40)

The ketone (420 mg.) in dry ethanol (5 ml.) containing potassium hydroxide (3 mol.) was kept under nitrogen for $\frac{1}{2}$ hr. at 80°. Potassium carbonate (190 mg.) separated during the reaction. Dilution with water and ether extraction afforded the cyclopentenone (41) as a colourless oil which spontaneously crystallised, affording plates, from benzene-light petroleum, m.p. 62-63°. (Found: C, 70.15; H, 8.9. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%).

The derived semicarbazone, prisms from aqueous methanol, had m.p. 216-218° (decomp.); $\lambda_{max.}$ 275 mμ (ε 15,000). Found: C, 57.0; H, 7.75; N, 19.95. $C_{10}H_{17}O_2N_3$ requires C, 56.85; H, 8.1; N, 19.9%).

Reduction of the Cyclopentenone (41) with Zinc and Acetic Acid.

The cyclopentenone (200 mg.) and zinc dust (1.5 g.) in "AnalaR" acetic acid were refluxed for 72 hr. Neutralisation with

4 N sodium hydroxide, saturation with sodium chloride and ether extraction furnished the deoxy-ketone (42), b.p. 78°/10 mm., n_D^{20} 1.4730; $\lambda_{max.}$ 228 mμ (ε 12,900). $\nu_{max.}$ (film) 1697 (cyclopentenone) and 1615 (conjugated ethylenic linkage) cm.$^{-1}$.

The derived 2:4-dinitrophenylhydrazone, orange needles from chloroform-methanol, had m.p. 200-201°; $\lambda_{max.}$ 380 mμ (ε 27,800). (Found: C, 56.9; H, 5.5; N, 17.55. $C_{15}H_{18}O_4N_4$ requires C, 56.6; H, 5.7; N, 17.6%).

Diene-Lactone (43)

The dihydroxy-lactone (750 mg.) in pyridine (20 ml.) and phosphorus oxychloride (1 ml.) (both freshly distilled), was refluxed for 2 hr. The product obtained in the usual way was eluted from alumina (grade III) by light petroleum, affording the diene-lactone (535 mg.), b.p. 77-80°/0.7 mm., n_D^{22} 1.5129. (Found: C, 72.9; H, 7.05. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.35%).

Dihydro-β-Campholenolactone and the Diol (44).

The diene-lactone (16 mg.) in ethyl acetate over platinum oxide absorbed 1.8 mol. hydrogen in 7 hr. The product (identical by infrared spectrum with authentic dihydro-β-campholenolactone). afforded on reduction with lithium aluminium hydride the diol (44), plates from benzene, m.p. 142-144°, identical with an authentic specimen by m.p., m.m.p. and infrared spectrum.

Cyclopentenone (39). The dihydroxy-lactone (1 g.) was heated with phosphoric acid (20%; 20 ml.) in a sealed tube for 6 hr.

The neutral fraction of the product afforded the cyclopentenone (39), b.p. 78-80°/12 mm., n_D^{20} 1.4750; $\lambda_{max.}$ 228 mμ (ε 12,800).

The derived 2:4-dinitrophenylhydrazone, orange needles from chloroform-methanol, had m.p. 202-203°, m.m.p. with the 2:4-dinitrophenylhydrazone of (42) 184-188°, $\lambda_{max.}$ 385 mμ (ε 24,800). (Found: C, 56.45; H, 5.95; N, 17.55. $C_{15}H_{18}O_4N_4$ requires C, 56.6; H, 5.7; N, 17.6%). The derived semicarbazone, m.p. 176-178°, was identical by m.p., m.m.p. and infrared spectrum with an authentic specimen[27].

αββ-Trimethyl Laevulic Acid Semicarbazone

The cyclopentenone (39) (500 mg.) in dry methylene chloride (20 ml.) was treated at -70° with ozonised oxygen, until $\lambda_{max.}$ 228 mμ had disappeared (½ hr.). Decomposition of the ozonide with water (10 ml.) at 95°, afforded on ether extraction trimethyl laevulic acid (426 mg.) as a yellow oil.

The derived semicarbazone plates from aqueous methanol had m.p. 175-177°. (Found: C, 50.5; H, 8.1; N, 19.4. $C_9H_{17}O_3N_3$ requires C, 50.2; H, 7.95; N, 19.5%).

Trimethyl Succinanil

Trimethyl laevulic acid (100 mg.) was added to bromine (350 mg.) and sodium hydroxide (225 mg.) in water (4 ml.). The solution was kept for 10 min., reduced to 1 ml. at the water pump and acidified with hydrochloric acid. The crude trimethyl succinic acid obtained with ether (60 mg.; m.p. 144-154°) was

refluxed with aniline (300 mg.) for 1 hr. The product, worked up as usual, afforded from aqueous ethanol needles of trimethyl succinanil m.p. 131-132° after sublimation. (Found: C, 72.2; H, 7.05; N, 6.75. $C_{13}H_{15}O_2N$ requires C, 71.85; H, 6.95; N, 6.45%).

The Hydroxy-lactone (50)

Dihydro-β-campholenolactone (1.6 g.) was oxidised by the procedure (a) (i) used for (+)-camphor. Chromatography of the product over alumina (grade V) afforded (benzene) unchanged dihydro-β-campholenolactone (1.4 g.) and [ethyl acetate-benzene; (1:9)] the hydroxy-lactone (80 mg.), rods from benzene-light petroleum, m.p. 143-145° (sublimed at 90°/0.5 mm.). (Found: C, 65.2; H, 8.8 $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%).

The hydroxy-lactone was unchanged when treated with acetic anhydride-pyridine at 20°.

The hydroxy-lactone (250 mg.) was dehydrated with phosphorus oxychloride in pyridine and the product, dissolved in light petroleum, filtered through alumina, affording the unsaturated lactone (51) (176 mg.), b.p. 88°/0.8 mm.; $\lambda_{max.}$ 219 mμ (ε 11,700). (Found: C, 71.75; H, 8.25. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.5%).

Hydrogenation over platinum oxide in ethyl acetate gave dihydro-β-campholenolactone, which was converted to the diol (44), identical with material obtained from the diene-lactone (43).

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PART III

THE CHEMISTRY OF SWIETENINE

AND SWIETENOLIDE

INTRODUCTION

Recent years have seen the emergence of a new group of natural products, triterpenes with a modified euphol structure. The chemistry of this group has been advanced considerably by the beautiful structural elucidation of limonin[1] followed by the structures of nomilin and obacunone[2,7] and the X-ray work on cedrelone[9]. Swietenine, $C_{32}H_{42}O_9$, and swietenolide, $C_{27}H_{34}O_8$, constituents of the seeds of Swietenia macrophylla King, appear from their functional groups and molecular size to be further members of this series and the investigation of these compounds forms the basis of this section of the present thesis. It is appropriate, therefore, to preface the discussion of swietenine and swietenolide with a brief survey of the chemistry of the known modified triterpenes with particular emphasis on limonin.

REVIEW OF THE CHEMISTRY OF THE LIMONIN-TYPE MODIFIED TRITERPENES

Limonin, $C_{26}H_{30}O_8$, is the characteristic bitter principle of the citrus species. Its structural elucidation provided a great challenge to the organic chemist and was eventually achieved by the work of three groups of investigators[1,2] in conjunction with an X-ray study[3] which confirmed the chemical conclusions and revealed the stereochemistry. Thus limonin was shown to have the structure (1).

From a biogenetic viewpoint limonin can be derived from a tetracyclic triterpene of the euphol (2) type from which four carbons at the end of the side chain have been removed and C_{20} to C_{23} converted into a furan ring. By analogy with nyctanthic (3)[4,5] and dammarenolic (4)[4] acids ring A has been oxidatively cleaved between C_3 and C_4 and the resultant C_3 carboxyl group cyclised oxidatively on to C_{19}. The migration of a methyl group from C_{14} to C_8 and the introduction of the ketone at C_7 and the epoxide finds precedent in the oxidation of dihydrobutyrospermyl acetate (5) to the 7-ketone (6)[6]. The 15,16 double bond in (6) can be oxidised in the C_{16} allylic position, followed by epoxidation of the double bond and Baeyer Villiger cleavage of ring D to give the required partial structure for limonin. The limonin skeleton is numbered in accordance with its proposed biogenesis. The rotatory dispersion curve of limonin exhibits a strong negative Cotton effect, corresponding in type to that of a 7-keto-steroid and thus confirming the absolute stereochemistry as in (1).

Limonin was shown to contain two δ-lactones which could be opened reversibly, a mono-β-substituted furan ring, a ketonic oxygen and two ethereal oxygens. Hydrogenation afforded tetrahydrolimonin (9) arising from saturation of the furan ring and hexahydrolimoninic acid (11) from prior hydrogenolysis of the lactonic ether oxygen attached β to the furan ring. The nuclear magnetic resonance spectrum of limonin confirmed the presence of a mono-β-substituted furan ring as did treatment of limonol (the 7α-hydroxy compound obtained from limonin by Meerwein Ponndorff reduction) with alkali which afforded furan-3-aldehyde and merolimonol, $C_{21}H_{28}O_6$, (7). Dehydrogenation of limonin yielded 1,2,5-trimethylnaphthalene.

The fact that hexahydrolimoninic acid (11) was a strong acid suggested that there was an oxygen function attached α to the carboxyl group. The existence of a 1,2-epoxide in conjugation with the ring D lactone in limonin was confirmed by the formation of desoxylimonin (8) by the action of hydriodic acid or chromous chloride on limonin. In addition, pyrolysis of hexahydrolimoninic acid (11) yielded an aldehydic product as would be expected from pyrolysis of a glycidic acid. Treatment of tetrahydrolimonin (9) with hydrochloric acid-acetic acid afforded the enol-lactone (10) whereas desoxytetrahydrolimonin was stable under the same conditions of acidity. When hexahydrolimoninic acid (11) was treated with acid as above, it rearranged with a methyl group migration to the α-hydroxy-γ-lactone (12) which was oxidised to the corresponding α-keto-γ-lactone (13) in which the new ketone could not be enolised.

The environment of the ketone in ring B of limonin was readily disclosed by deuteration experiments when two atoms of deuterium were rapidly incorporated and a third more slowly. This was confirmed in a beautifully simple manner by treatment of limonin with potassium-t-butoxide in presence of oxygen when one mole of oxygen was rapidly taken up with formation of the diosphenol (14). Analogous diosphenols were obtained from tetrahydrolimonin (9) and desoxylimonin (8). Ozonolysis of tetrahydrolimonin diosphenol produced the nor-acid (15) which, on treatment with alkali, gave formaldehyde by a reversed aldol-type elimination. This is consistent with the CH_2-O-CO- grouping attached at C_{10}.

Desoxylimonin (8), under mild alkaline conditions, afforded desoxylimonic acid (16), arising from cleavage of ring B. The ketone is necessary for this change since desoxylimonin oxime was stable under the same conditions. Desoxytetrahydrolimonin (17) gave the analogous desoxytetrahydrolimonic acid (18) which reacted with one mole of chlorine to give an unstable adduct which on heating in vacuo yielded two crystalline diene-acids, the cisoid diene (19) and the transoid diene (20). The formation of these two compounds demonstrates chemically the presence of the C_8 methyl group and the C_9 hydrogen and the relationship between the ring D lactone and the ring B ketone.

Merolimonol (7) was readily dehydrated to the conjugated diene-lactone (21) and on ozonolysis yielded the keto acid (22) which gave a positive iodoform test. Oxidation of merolimonol with manganese dioxide in chloroform or benzene proved to be an interesting reaction. In

addition to the expected ketone (23), a decarbonylated product, the $\alpha\beta$-unsaturated γ-lactone (24), was obtained. The infrared spectrum of the dihydro-derivative (25) showed clearly the presence of a γ-lactone. Hydrogenation of merolimonol followed by oxidation with chromium trioxide in pyridine also yielded (25). The γ-lactone (24), on ozonolysis, afforded the α-keto-lactone (26) in which the ketone could not be enolised and which gave a positive iodoform reaction. These reactions of merolimonol clearly define the relationship between positions 7 and 8 and 12,13,14,15, 16 and 18 in limonin.

Treatment of merolimonol (7) with barium hydroxide resulted in irreversible opening of the ring A lactone with formation of the hydroxy-acid (27) which was oxidised with manganese dioxide to the γ-lactone (28). This, on further oxidation with chromium trioxide yielded the aldehyde (29) which is important evidence that the ring A lactone terminus is on the C_{19} methyl group.

Under more vigorous alkaline conditions than were required for the limonol-merolimonol change, limonin was transformed into limoclastic acid (30) the chemistry of which parallels that of merolimonol in many respects. Thus it was dehydrated to a conjugated diene lactone (as 21), oxidised with manganese dioxide to the nor-compound (31; R = H) which on oxonolysis afforded the corresponding α-keto-γ-lactone (as 26). The relationship between merolimonol and limoclastic acid was established by barium hydroxide treatment of the aldehyde (29) which resulted in formation of the lactone-ester (31; R = Me). The formation of

limoclastic acid is considered to proceed from limonin by alkali-induced intramolecular hydride transfer to give a limonol type (32); this undergoes the merolimonol change to (33) which permits conventional deformylation to occur giving (34), followed by hydration of the $\alpha\beta$-unsaturated acid and lactonisation to yield limoclastic acid. The formation of limoclastic acid also requires that ring A of limonin be a δ-lactone with at least one α-hydrogen to permit reversible elimination of the β-ethereal oxygen.

Oxidation of limonin with alkaline potassium permanganate or preferably treatment with alkaline hypoiodite afforded limonilic acid (35) which was shown to retain intact the furan, ring D lactone and the epoxide. The ketone group in limonilic acid, however, did not undergo autoxidation to the diosphenol and its spectroscopic properties suggested the presence of an axial ether oxygen in the α-position. In agreement with the formulation (35) reduction of limonilic acid with aluminium amalgam gave back limonin.

Vigorous treatment of limonin with hydriodic acid yielded citrolin which was also obtained by the action of hydrobromic acid on desoxylimonin (8). The structure (36) was assigned to citrolin principally on ultraviolet evidence.

Two minor bitter principles of the citrus species are nomilin (37) and obacunone (38)[2,7]. Nomilin, a β-acetoxy-lactone, was readily converted into the $\alpha\beta$-unsaturated lactone, obacunone, by hot α-picoline[19]. Obacunone contained two lactone rings, one of which did not open

reversibly, a hindered ketone, a furan ring and an ethereal oxygen. Obacunone behaved in an analogous manner to limonin on hydrogenation, reduction with chromous chloride, base cleavage of desoxyobacunoic acid (39) and acid transformation of octahydro-obacunoic acid (40) into a γ-lactone. In the last case the tertiary hydroxyl group was eliminated and the product of acid treatment was formulated as (41).

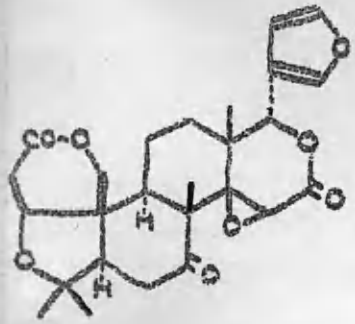
By the action of mild alkali both nomilin and obacunone were converted into obacunoic acid (42; R = H). Methyl obacunoate (42; R = Me), on mild treatment with sodium methoxide, yielded the biogenetically significant iso-obacunoic acid (43), lacking the $\alpha\beta$-unsaturated acid and the hydroxyl group. Iso-obacunoic acid gave the diosphenol acid (44) whereas obacunoic acid afforded the diosphenol lactone (45).

The chemical behaviour of nomilin and obacunone is consistent with the same gross structural features as limonin with the exception of ring A. It is attractive to consider them as biogenetic precursors of limonin, the process having been interrupted at the ring A cleavage stage with the isolation of the seven-membered lactones. The formation of iso-obacunoic acid (43) lends support to this theory.

Another interesting member of the group of modified triterpene bitter principles is cedrelone (46), from Cedrela toona,[8] whose structure has recently been established by an X-ray study[9]. Cedrelone is of significance in the biogenetic scheme for the modification of euphol. Ring A remains intact and there is no ring D lactone possibly because

epoxidation of the 15,16 double bond in the precursor has occurred before oxidation of C_{16}. In addition the cedrelone precursor has undergone further oxidation in ring B with formation of the diosphenol system. It is interesting to notice how facile is the introduction of the diosphenol system in the limonin series.

From the information at present available[10] it appears that nimbin, $C_{29}H_{36}O_9$, a bitter principle from Melia azadirachta Linn., is a further member of this series.



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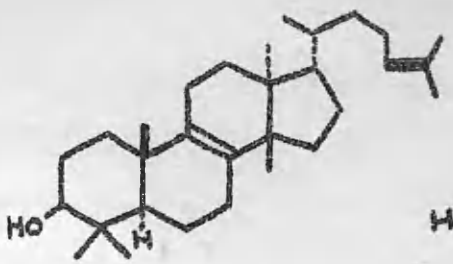

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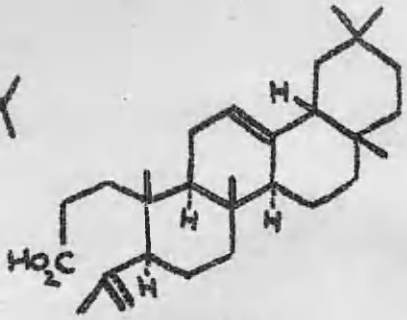

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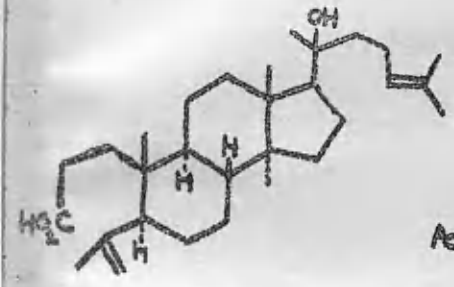

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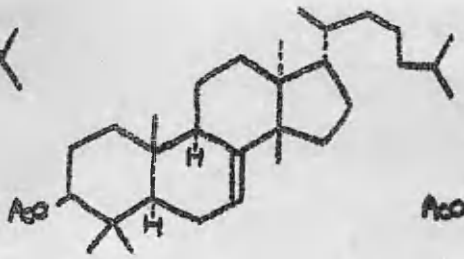

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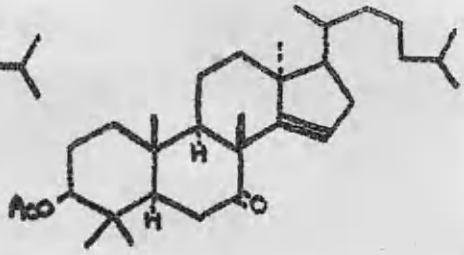

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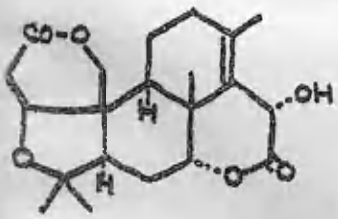

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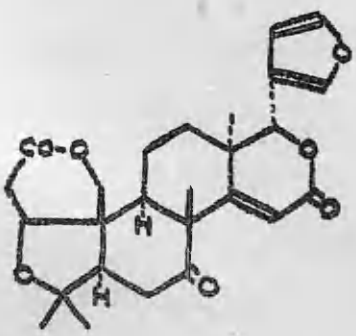

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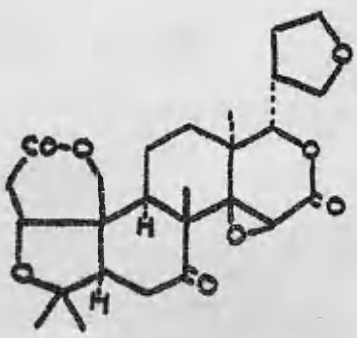

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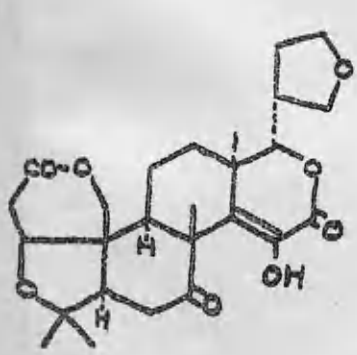

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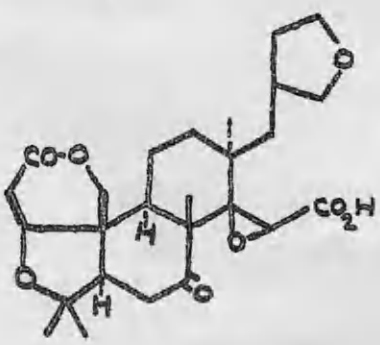

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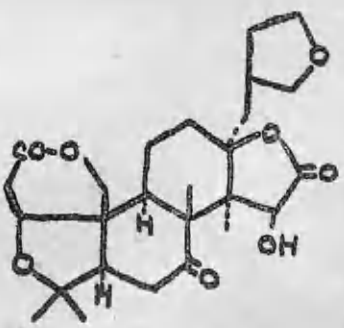

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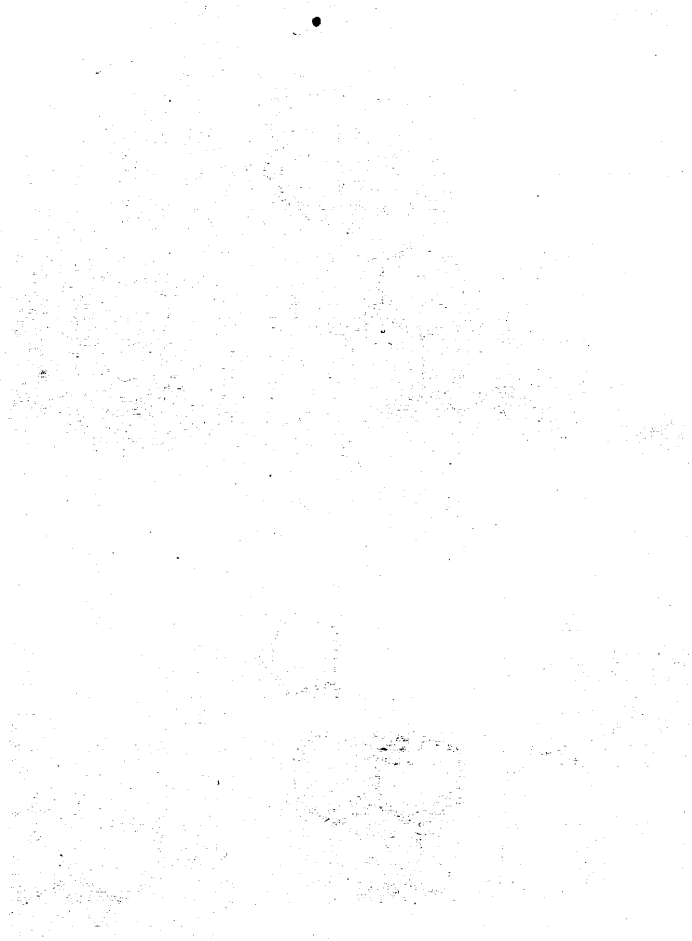

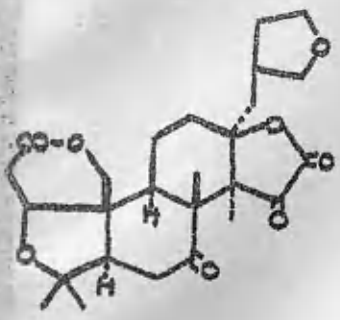

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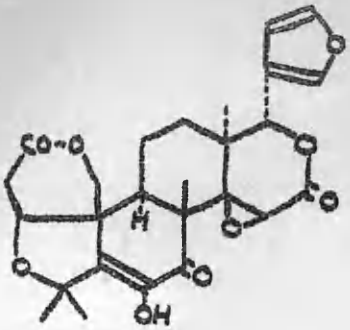

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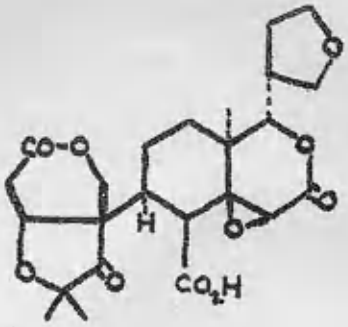

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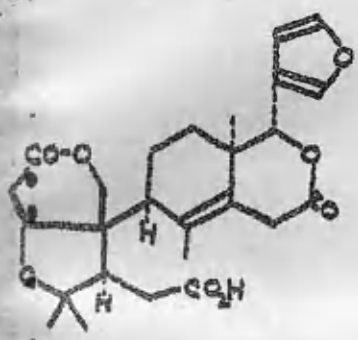

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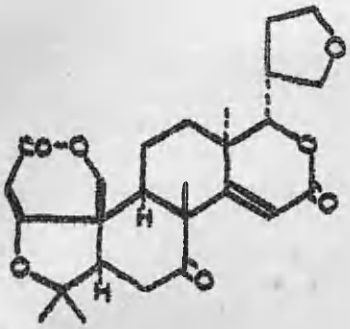

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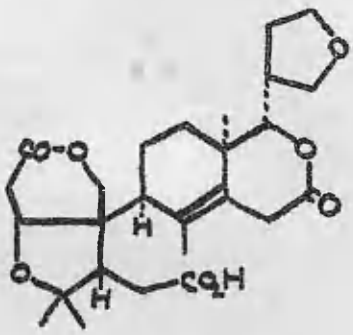

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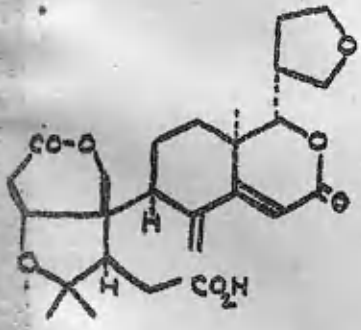

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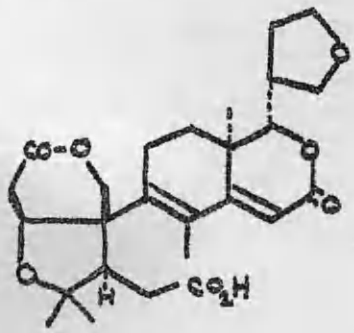

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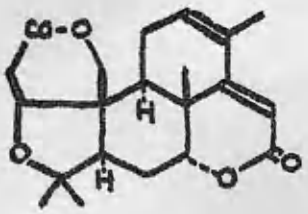

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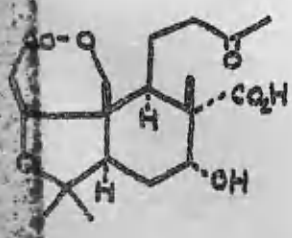

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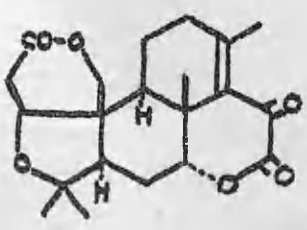

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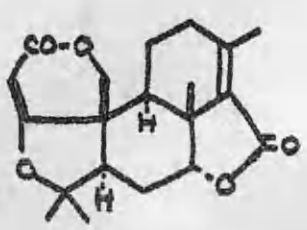

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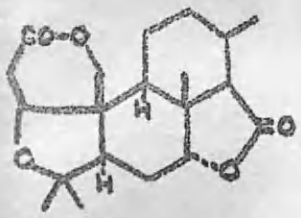

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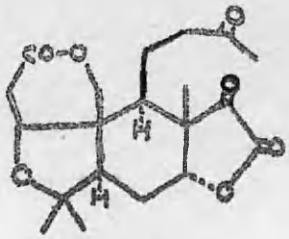

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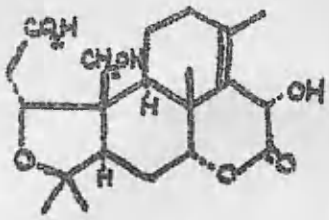

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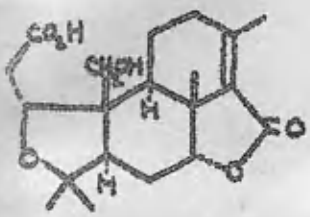

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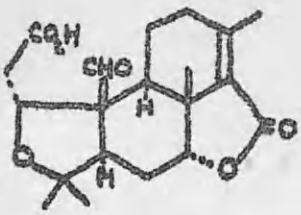

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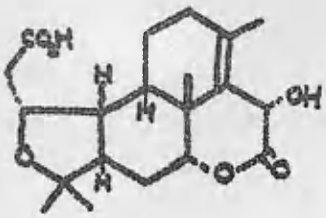

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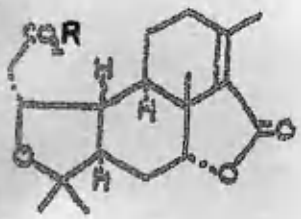

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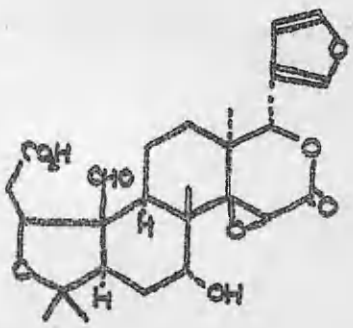

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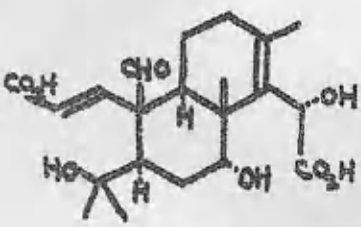

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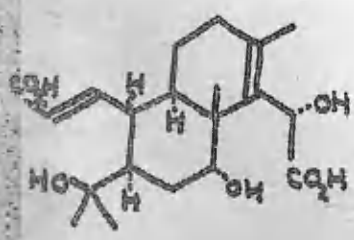

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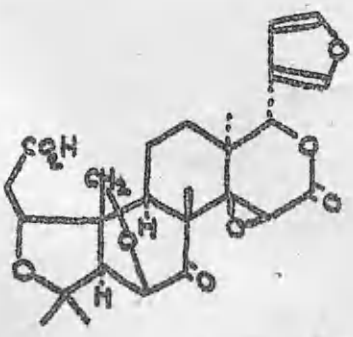

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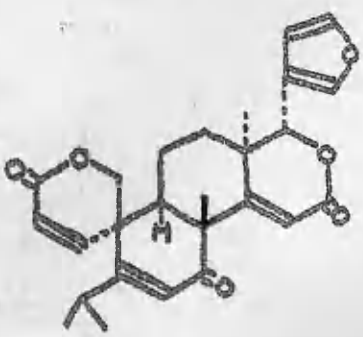

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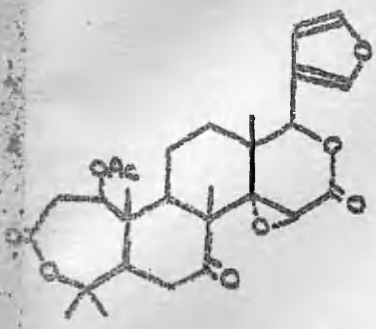

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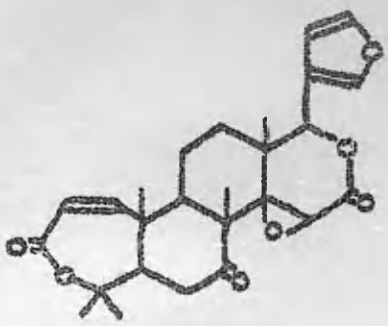

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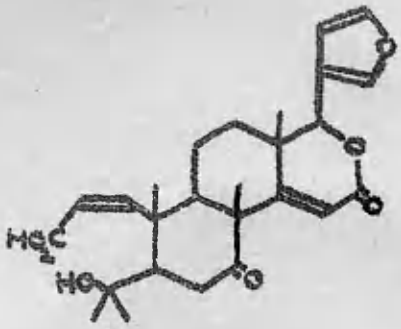

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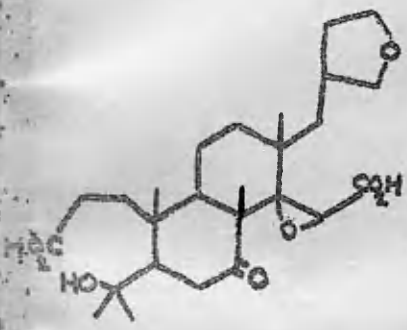

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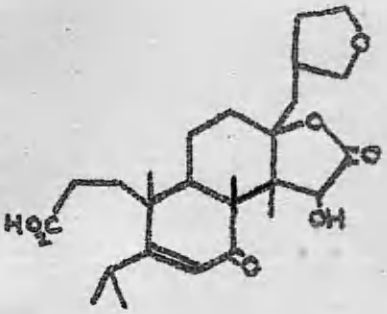

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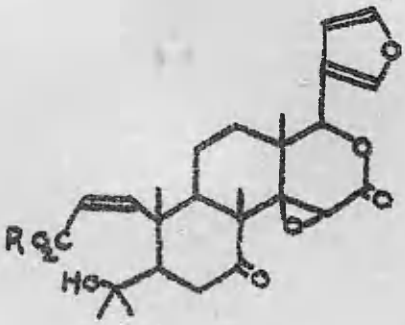

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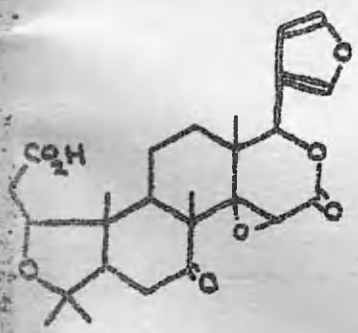

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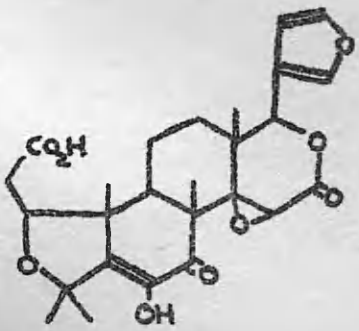

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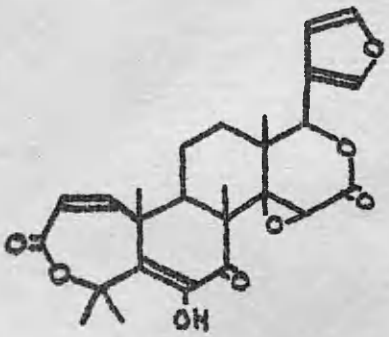
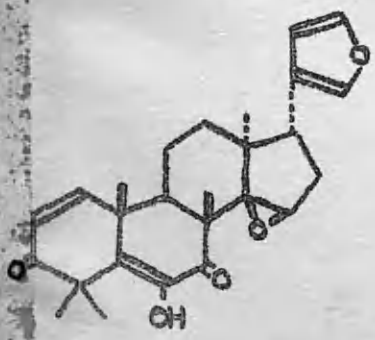


(45)



(46)

THE CHEMISTRY OF SWIETENINE

Swietenine, the non-bitter principle of Swietenia macrophylla, was isolated by Chakrabartty and Sircar[11] who concluded that it had the molecular formula $C_{18}H_{24}O_5$ and contained an $\alpha\beta$-unsaturated δ-lactone, a ketonic function, a hydroxyl and a methoxyl group. Chakrabartty and his colleagues[12,13,14] obtained an unidentified polyalkylnaphthalene, $C_{16}H_{20}$ (trinitrobenzene adduct m.p. 152-153°) and 1,2,5-trimethylnaphthalene on selenium dehydrogenation of swietenine and isolated tiglic acid from caustic fusion experiments. Later work[15] showed that swietenine had a molecular weight of approximately 565 and on this basis, in conjunction with analytical data, the molecular formula $C_{32}H_{42}O_9$ was proposed. The Indian workers, however, were unable to isolate any crystalline transformation products of swietenine to confirm this molecular formula and the functional groups revealed spectroscopically. In view of the interesting nature of swietenine and its possible relation to limonin we undertook this investigation and the results of some preliminary experiments are disclosed below.

Swietenine (47)* has bands in its infrared spectrum (in carbon tetrachloride) at 1752 (δ-lactone), 1743 and 1734 (methyl ester and tiglate ester), and 1716 (cyclohexanone) cm.$^{-1}$. These functional groups account for seven of the nine oxygens in the molecule and infrared

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*The experimental observations which follow are summarised in flowsheet I on p. 119

absorption (in chloroform) at 3605 (free hydroxyl), 3540 (bonded hydroxyl) and (in Nujol) at 3160, 1506 and 877 (furan ring) cm.$^{-1}$, reveals the character of the remaining two. Zerewitinoff determination gave 1.3 atoms of active hydrogen consistent with the presence of a hydroxyl group and Kuhn-Roth oxidation indicated the presence of five C-methyl groups. Hydrogenation of swietenine resulted in the uptake of four moles of hydrogen to yield a crystalline octahydro-acid (48), arising from hydrogenolysis of the lactonic ether oxygen attached allylically to one of the furanic double bonds, and saturation of the furan and tiglate double bonds.* The presence of a mono-β-substituted furan was confirmed by nuclear magnetic resonance (see p. 113). The octahydro-acid still retained end absorption in its ultraviolet spectrum [$\lambda_{max.}$ 203 mμ (ε 6,200)] thus indicating the existence of an isolated double bond, probably trisubstituted, in swietenine whose untraviolet spectrum [$\lambda_{max.}$ 213 mμ (ε 18.800)] must be due to the furan ring, the tiglate ester, and an isolated double bond.

Initially our attention was directed to the alkaline hydrolysis of swietenine. This proved to be a complex reaction giving rise to a mixture of products. Tiglic acid, characterised as its p-bromophenacyl ester, was readily isolated but the remainder of the reaction mixture was very reluctant to yield any crystalline material. By carefully defining

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*This reaction is analogous to the hydrogenation of limonin, obacunone[1,2] and columbin[20].

the hydrolysis conditions a crystalline hydroxy-acid, destigloylswieteninic acid $C_{26}H_{32}O_8$ (50) could be separated in about 30% yield, by virtue of its insolubility in chloroform. Analysis showed that this had arisen from hydrolysis of the methyl and tiglate esters (subsequent rearrangements are of course not precluded). Destigloylswieteninic acid $[\nu_{max.}$ (in Nujol) 3500-2500 (hydroxyl and associated acid hydroxyl), 1750 (δ-lactone), 1705 (ketone and acid), 1500 and 877 (furan) cm.$^{-1}]$ was characterised as its methyl ester $C_{27}H_{34}O_8$ (51) $[\nu_{max.}$ (in Nujol) 3530 (hydroxyl), 1725 (unresolved lactone, ester and ketone), 3100, 1500, 877 (furan) and (in chloroform) 3605 and 3530 (hydroxyl) and 1729 (broad unresolved carbonyl) cm.$^{-1}$: $\lambda_{max.}$ 208 mμ (ε 10,480)]. Under normal acetylation conditions (acetic anhydride in pyridine) methyl destigloylswieteninate formed a non-crystalline monoacetate (infrared). That methyl destigloylswieteninate still retained the mono-β-substituted furan-lactone system was demonstrated by its hydrogenation over palladised charcoal to an acidic compound (infrared) which was not characterised. On one occasion a second crystalline ester, $C_{29}H_{36}O_7$ (51a) m.p. 245-250°, was isolated from the neutral fraction of a hydrolysis reaction. It had bands in the infrared (in Nujol) at 3570 and 3500 (hydroxyl), 1740 and 1705 (lactone, ester and ketone), 1500 and 877 (furan) and (in chloroform) 1720 (unresolved carbonyl) cm.$^{-1}$, and ultraviolet absorption $\lambda_{max.}$ 209 mμ (ε 10,320). An acidic product was obtained from hydrogenation of this ester over palladised charcoal. The relationship between this second ester and swietenine has not been established.

Destigloylswieteninic acid had a pK value of approximately 4.85 which suggested that one of the hydroxyl groups is attached α to the carboxyl group (under identical conditions the octahydro-acid from swietenine had pK 5.93). This was confirmed by cleavage of the α-hydroxy-acid by lead dioxide in refluxing acetic acid. Two crystalline products, easily separable by chromatography, were formed in this reaction. The major product, $C_{25}H_{32}O_6$ $\nu_{max.}$ (in chloroform) 3610 (free hydroxyl), 1726 and 1719 (lactone and ketone), and (in Nujol) 1500 and 877 (furan) cm.$^{-1}$ (which was later obtained in good yield and more cleanly by oxidation of destigloylswieteninic acid with lead tetra-acetate in the cold) was not aldehydic and was assigned a hemiacetal structure (52) since it was smoothly oxidised with chromium trioxide in pyridine to a crystalline bislactone, $C_{25}H_{30}O_6$ (54) $\nu_{max.}$ (in carbon tetrachloride) 1753 and 1748 (δ-lactones), 1722 (ketone) and (in chloroform) 1744 and 1720 cm.$^{-1}$ which took up two moles of base on titration. The new lactone ring was not reversibly opened with base and from the titration experiment a new crystalline hydroxy-acid (55) was recovered on acidification (see p. 112). On hydrogenation over palladised charcoal the bislactone absorbed three moles of hydrogen and yielded principally an acidic product $\nu_{max.}$ (film) 1740 (δ-lactone) and 1720 (ketone and acid) cm.$^{-1}$. This was methylated with diazomethane and afforded a mixture of two esters $\nu_{max.}$ (in chloroform) 1735 and 1723 cm.$^{-1}$ respectively. Lack of time and material prevented full characterisation of these esters.

The second product of the lead dioxide oxidation of destigloylswieteninic acid analysed for the molecular formula $C_{27}H_{34}O_7$ and on its spectroscopic properties $\nu_{max.}$ (in chloroform) no hydroxyl, 1730 (unresolved lactone, ester and ketone), and (in Nujol) 1500 and 877 (furan), and 1240 (acetate C - O) cm.$^{-1}$ was presumed to be the hemiacetal acetate (53).

The Indian workers[12] claimed that the hydroxyl group in swietenine was probably tertiary because of its resistance to oxidation. In our hands, oxidation of swietenine with chromium trioxide in pyridine yielded a mixture of at least three components, one of which was unchanged swietenine. This mixture was readily resolved by chromatography which resulted in the isolation, in good yield, of dehydroswietenine, $C_{32}H_{40}O_9$ (57) $\nu_{max.}$ (in Nujol) no hydroxyl, 1738 sh., 1720 and 1703 sh. (lactone, ester and ketone), 3100, 1643, 1502, 877 (furan) cm.$^{-1}$ which, on reduction with sodium borohydride, afforded swietenine. Thus the hydroxyl group present in swietenine is secondary. A more polar product was obtained from the oxidation of swietenine in small yield and in a semi-crystalline state. It had bands in the infrared (in Nujol) at 3350, 1765, 1700, 1660, 1620, 1595, 1500 and 877 cm.$^{-1}$. There was not sufficient time available to purify and characterise this product. Dehydroswietenine was observed to change spontaneously on standing in air. Chromatography of an old sample of dehydroswietenine afforded the product of spontaneous change as a gum $\nu_{max.}$ (film) 3520 (hydroxyl), 1720, 1660 and 877 cm.$^{-1}$. Time again did not permit investigation of this important compound.

Hydrolysis of dehydroswietenine with 2½% ethanolic potassium hydroxide on the steam bath for ten minutes gave a good yield of dehydro-destigloylswieteninic acid, $C_{26}H_{30}O_8$ (58) $\nu_{max.}$ (in Nujol) 3380 (hydroxyl), 2650 (associated acid hydroxyl), 1740 and 1720 sh. (lactone, ketone and acid), 1500 and 880 (furan) cm.$^{-1}$ which with diazomethane afforded the corresponding methyl ester, $C_{27}H_{32}O_8$ (59) $\nu_{max.}$ (in Nujol) 3590 (hydroxyl), 1725 (unresolved lactone, ester and ketone), 1500 and 880 (furan) cm.$^{-1}$. Methyl dehydro-destigloylswieteninate was oxidised smoothly with chromium trioxide in pyridine to a crystalline triketone, $C_{27}H_{30}O_8$ (60) $\nu_{max.}$ (in Nujol) no hydroxyl, 1720 (unresolved carbonyl), 1500 and 880 (furan) cm.$^{-1}$. This indicates that the hydroxyl group carrying the tiglate ester is also secondary, assuming that no rearrangement has occurred during its hydrolysis. All the above compounds in the dehydro-series were unstable and changed spontaneously in air. The nature of this change has not yet been investigated but it seems likely that it involves the carbonyl group created by oxidation of the free hydroxyl in swietenine.

Oxidation of destigloylswieteninic methyl ester (51) with chromium trioxide in pyridine yielded a mixture of products from which the above triketone (60) could be separated by chromatography. A second pure crystalline component $\nu_{max.}$ (in Nujol) 3480 (hydroxyl), 1730 and 1700 (lactone, ester and ketone), 1500 and 880 (furan) cm.$^{-1}$ was isolated but lack of material prevented further investigation. The remainder of the product was a more polar, crystalline solid which was still obviously a mixture.

Dehydro-destigloylswieteninic acid, on oxidation with lead dioxide in refluxing acetic acid, afforded a mixture of acidic products, the major component of which, was found, after methylation, to be identical in behaviour on a chromatoplate with the methyl ester (56) of the hydroxy-acid (55) obtained by hydrolysis of the bislactone (54). The reason for the reluctance of the second lactone ring in the bislactone to close back after alkaline hydrolysis is not yet known but it may be due to a conformational change in the molecule arising from a shift of the isolated double bond. This could also account for the failure to isolate any bislactone from lead dioxide oxidation of dehydro-destigloylswieteninic acid.

The above experimental results reveal the relative positions of the carbomethoxyl, the secondary hydroxyl and the secondary tiglate ester in swietenine as in part structure (68) (Flowsheet III, page 121). The formation of a hydroxy-acid (75) on lead dioxide oxidation of dehydro-destigloylswieteninic acid requires that the tiglate grouping be on the hydroxyl group which is not α to the carbomethoxyl. Dehydro-destigloylswieteninic acid is therefore an α-keto-acid (74; R = H) and dehydroswietenine an α-keto-ester (73). It seems probable from the infrared spectrum that the new lactone ring in the bislactone is δ-constituted and thus the hydroxyl bearing the tiglate group in swietenine must be on the ε-carbon atom with respect to the original carbomethoxyl. This allows part-formulation of the bislactone (71), the hemiacetal (70), destigloylswieteninic acid (69; R = H) and the

triketone (72; R = Me).

Proton magnetic resonance measurements on swietenine, methyl destigloylswieteninate and the octahydro-ester provide additional evidence for the structural features present in the molecules. The peaks to which definite assignments can be made are shown in Table I on page 118. The presence of a mono-β-substituted furan is clearly indicated in swietenine (τ 2.37, 2.58, 3.62) and its hydrolysis product (τ 2.45, 2.56, 3.62). The uncoupled proton (τ 4.43) is equivalent to the C_{17} proton in limonin[2] and since it is absent in the octahydro-ester one can conclude that swietenine has the partial structure (76) (Flowsheet IV, page 122). All three compounds have a proton (τ 5.39, 5.38, 5.51) attached to a carbon atom bearing a hydroxyl group and α to a carbomethoxyl group. Since this proton does not show any coupling the adjacent carbon atom must be fully substituted (77). In swietenine and the octahydro-ester there is a proton (τ 4.67, 5.04) coupling with other protons, attached to a carbon atom bearing an acyl group (tiglate and isovalerate). This confirms the chemical evidence that the esterfied hydroxyl group in swietenine is secondary (78). The methyl group of the methyl ester also shows up clearly (τ 6.22). Methyl destigloylswieteninate has a proton (τ 6.32) attached to a carbon atom bearing a hydroxyl group. In limonin[2] three uncoupled protons (τ 8.6) have been assigned to the C_{13} angular methyl group, the change in τ value being attributed to the proximity of the furan ring. These three protons are also present in swietenine, methyl destigloyl-swieteninate and the octahydro-ester (τ 8.6, 8.55, 8.58). The fact that

they are present in the latter excludes the effect of the furan ring and suggests that the assignment to a C_{13} methyl group is incorrect. The τ value is consistent with that of a methyl group attached to a fully substituted carbon atom α to a ketone, e.g. the C_8 methyl group in limonin. The partial structure for swietenine can now be extended to (79). It is biogenetically plausible to place the ketone at C_7 in swietenine (limonin numbering) and support for this is found in the optical rotatory dispersion measurements on swietenine which show a negative Cotton curve like limonin. The protons of at least three angular methyl groups can be seen (τ 8.96, 9.13, 9.22). There is one proton (τ 6.91, 7.14 sh., 6.97) in the spectra of all three compounds and it seems likely that this is situated in the allylic position to the isolated double bond which survives hydrogenation of swietenine. The character of this double bond is not yet known.

All the information on the structure of swietenine, derived by physical and chemical methods is summarised in (80). It is noteworthy that swietenine lacks the epoxide function present in limonin and its congeners and does not have an $\alpha\beta$-unsaturated ring D lactone. The ketonic function in swietenine appears to be much more hindered than the C_7 ketone in limonin and has so far failed to react cleanly with sodium borohydride or hydroxylamine hydrochloride. The available evidence, however, still suggests a relationship between limonin and swietenine and it is to be hoped that the structural elucidation of swietenine will throw more light on the biogenetic processes available for the modification of triterpenoid precursors.

THE CHEMISTRY OF SWIETENOLIDE

Swietenolide, $C_{27}H_{34}O_8$, the bitter principle[11] of Swietenia macrophylla, has the same functional groups as swietenine with the exception of the tiglate ester. Some preliminary experiments were done on swietenolide by Chakrabartty[15,16]. During the course of our work on swietenine we repeated his experiments and, in some cases, found wide discrepancies between the physical constants of our products and those reported by him. In addition two new compounds have been isolated.

Swietenolide (61) (Flowsheet II, p. 120) on hydrogenation over palladised charcoal, absorbed three moles of hydrogen to yield hexahydroswietenolic acid, $C_{27}H_{40}O_8$ (62) [$\nu_{max.}$ (in Nujol) 3480 (hydroxyl), 2600 (associated acid hydroxyl), 1725 (ester), 1695 (acid and ketone) cm.$^{-1}$] characterised as its previously unreported crystalline methyl ester, $C_{28}H_{42}O_8$ (63) [$\nu_{max.}$ (in Nujol) 3500 (hydroxyl), 1725 (unresolved ketone and ester) cm.$^{-1}$]. The ultraviolet absorption of hexahydroswietenolic acid [$\lambda_{max.}$ 205 mμ (ε 5,700)] indicated the presence of a residual double bond resistant to hydrogenation.

Acetylation of swietenolide with fused sodium acetate in refluxing acetic anhydride for one hour afforded a new product, acetate II, $C_{29}H_{36}O_9$ (65) [$\nu_{max.}$ (in Nujol) 3550 (hydroxyl), 1740 (acetate, ester and lactone), 1710 (ketone), 1500 and 877 (furan) cm.$^{-1}$: $\lambda_{max.}$ 208 mμ (ε 10,400)]. When the reaction was allowed to proceed for five hours the previously described[15] acetate I, $C_{29}H_{34}O_8$ (64) [$\nu_{max.}$ (in Nujol) 1750, 1700, 1675, 1620 and 1590 and also 1500 and 877 (furan) cm.$^{-1}$:

$\lambda_{max.}$ 280 mμ (ε 15,300)] was isolated.

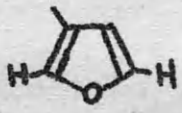
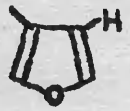
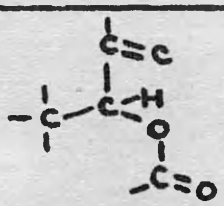
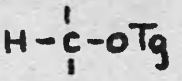
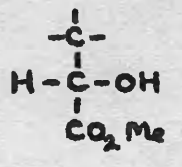
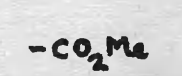
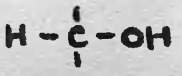
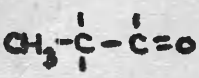
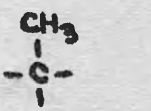
Oxidation of swietenolide with potassium dichromate in acetic acid resulted in the formation of dehydroswietenolide (66) and two other compounds which were not isolated in a pure state. Dehydroswietenolide, $C_{27}H_{32}O_8$ (66) [$\nu_{max.}$ (in Nujol) 3500 (hydroxyl), 1725 (lactone and ester), 1700 (ketone), 3120, 1500 and 870 (furan) cm.$^{-1}$] still retains hydroxyl absorption in the infrared and since the other products of oxidation are less polar it is possible that their formation involves oxidation of the other hydroxyl group in swietenolide which had previously been assumed to be tertiary[15,16].

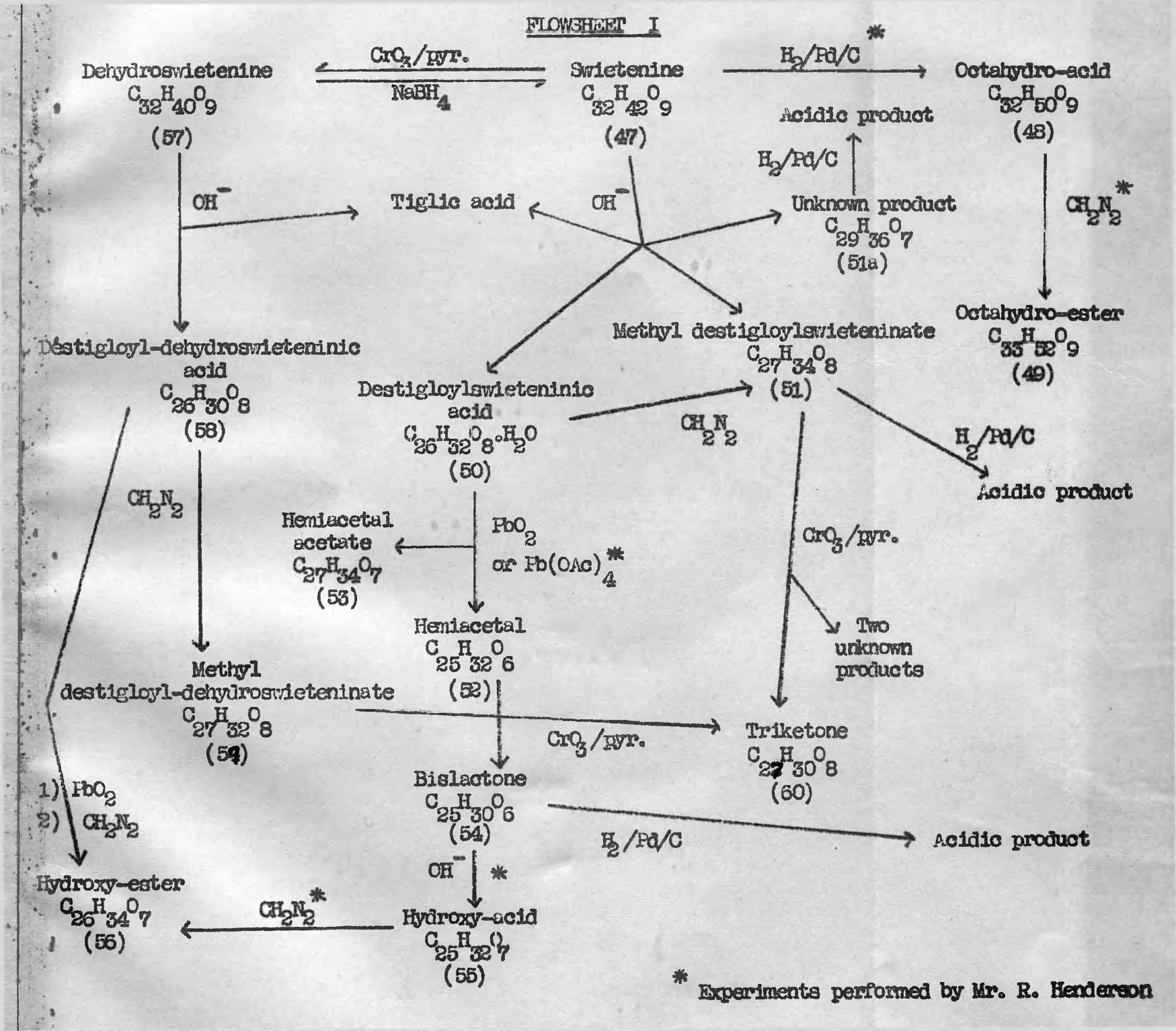
Swietenolide was hydrolysed with 5% ethanolic potassium hydroxide under reflux for one hour and from the reaction, after acidification, a crystalline acid, swietic acid (67), was isolated. Swietic acid has pK 4.68 which suggests that there is an α-hydroxy-acid grouping present.

The proton magnetic resonance spectrum of methyl hexahydroswietenolate provided further evidence for the structural features of swietenolide which had been revealed chemically. The protons of the tetrahydrofuran ring (τ 6.3) and the carbomethoxyl groups (τ 6.18) show up clearly. There is one proton (τ 5.42) attached to a carbon atom bearing a hydroxyl group and α to a carbomethoxyl group. This is consistent with the suggested α-hydroxy acid grouping in swietic acid. The protons of at least three angular methyl groups can be seen (τ 9.2). As in limonin, obacunone and swietenine there is a methyl group (τ 8.67) attached to a saturated carbon atom α to a ketone.

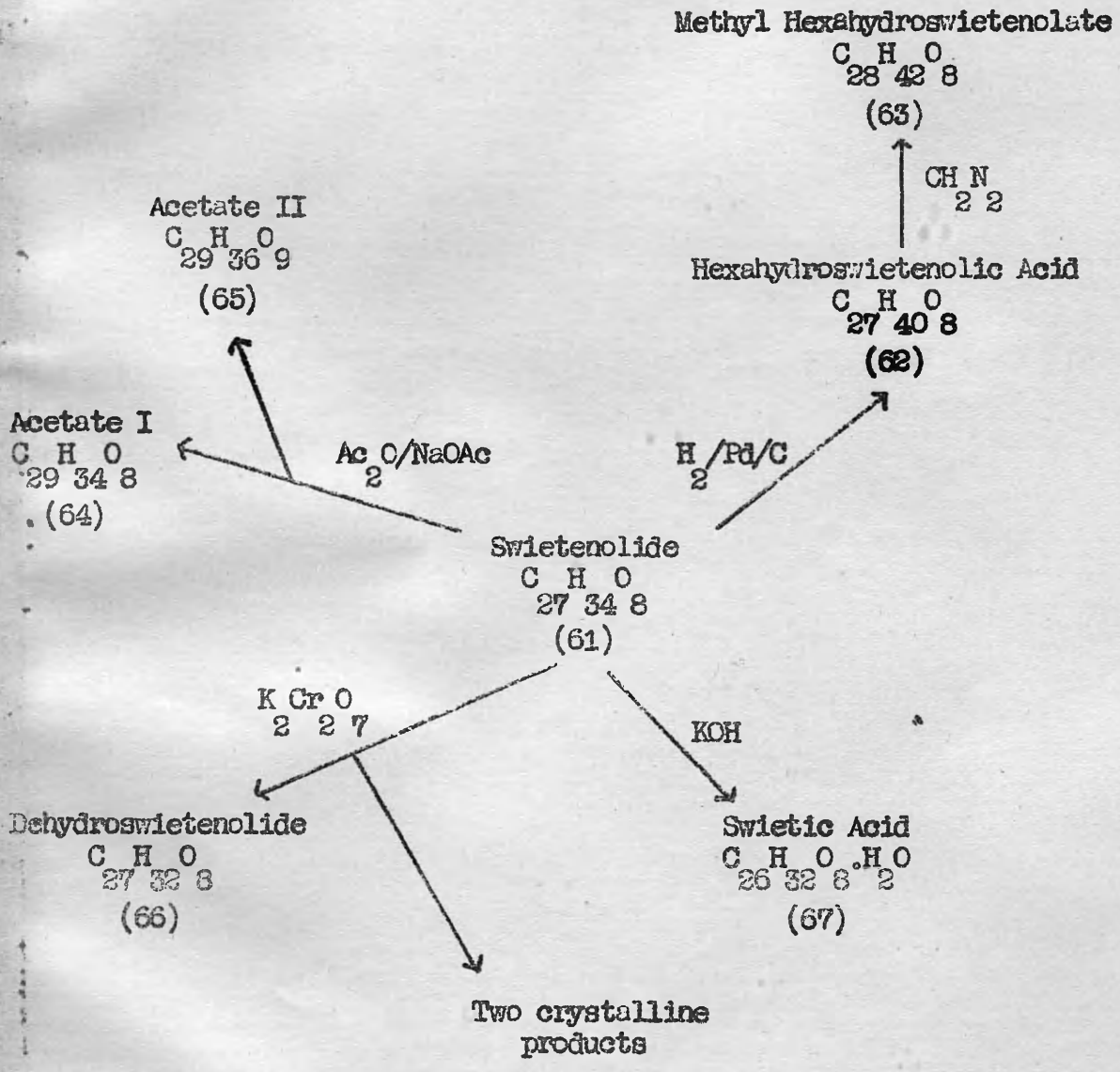
The available evidence indicates that swietenine and swietenolide have many structural similarities. It was initially suggested[15] that swietenine was the tiglate ester of swietenolide but the isolation of methyl destigloylswieteninate disproves this. Swietenolide and hexahydroswietenolic acid have negative Cotton curves but the amplitudes of the curves are much larger (10^{-2}a -186 and -161 respectively) than those of tetrahydrolimonin (10^{-2}a -79) and the octahydro-acid from swietenine (10^{-2}a -85). It seems likely from these results, that the relationship between swietenine and swietenolide is not a simple one.

TABLE I

Swietenine	Methyl destigloylswieteninate	Octahydro-ester	Protons	Assignments
τ	τ	τ		
2.37 2.58	2.45 2.56	-	2	
3.62	3.62	-	1	
4.43	4.43	-	1	
4.67	-	5.04	1	
5.39	5.38	5.51	1	
6.22	6.26	6.16	3,6	
-	6.32	-	1	
-	-	6.38	4	
6.91	7.14 sh.	6.97	1	Allylic proton
8.60	8.55	8.58	3	
8.96 9.13 9.22	8.99	8.94 9.01 9.13	9	


FLOWSHEET I
Dehydroswietenine
$C_{32}H_{40}O_9$
(57)
CrO_3/pyr.
$NaBH_4$
Swietenine
$C_{32}H_{42}O_9$
(47)
H_2/Pd/C *
Octahydro-acid
$C_{32}H_{50}O_9$
(48)
Acidic product
H_2/Pd/C
Unknown product
$C_{29}H_{36}O_7$
(51a)
CH_2N_2 *
Octahydro-ester
$C_{33}H_{52}O_9$
(49)
OH^-
Tiglic acid
OH^-
Destigloyl-dehydroswieteninic acid
$C_{26}H_{30}O_8$
(58)
Destigloylswieteninic acid
$C_{26}H_{32}O_8 \cdot H_2O$
(50)
Methyl destigloylswieteninate
$C_{27}H_{34}O_8$
(51)
CH_2N_2
H_2/Pd/C
Acidic product
CH_2N_2
Heniacetal acetate
$C_{27}H_{34}O_7$
(53)
PbO_2
or $Pb(OAc)_4$ *
CrO_3/pyr.
Heniacetal
$C_{25}H_{32}O_6$
(52)
Two unknown products
Methyl destigloyl-dehydroswieteninate
$C_{27}H_{32}O_8$
(59)
CrO_3/pyr.
Triketone
$C_{27}H_{30}O_8$
(60)
1) PbO_2
2) CH_2N_2
Bislactone
$C_{25}H_{30}O_6$
(54)
H_2/Pd/C
Acidic product
OH^- *
Hydroxy-ester
$C_{26}H_{34}O_7$
(56)
CH_2N_2 *
Hydroxy-acid
$C_{25}H_{32}O_7$
(55)
* Experiments performed by Mr. R. Henderson

FLOWSHEET II



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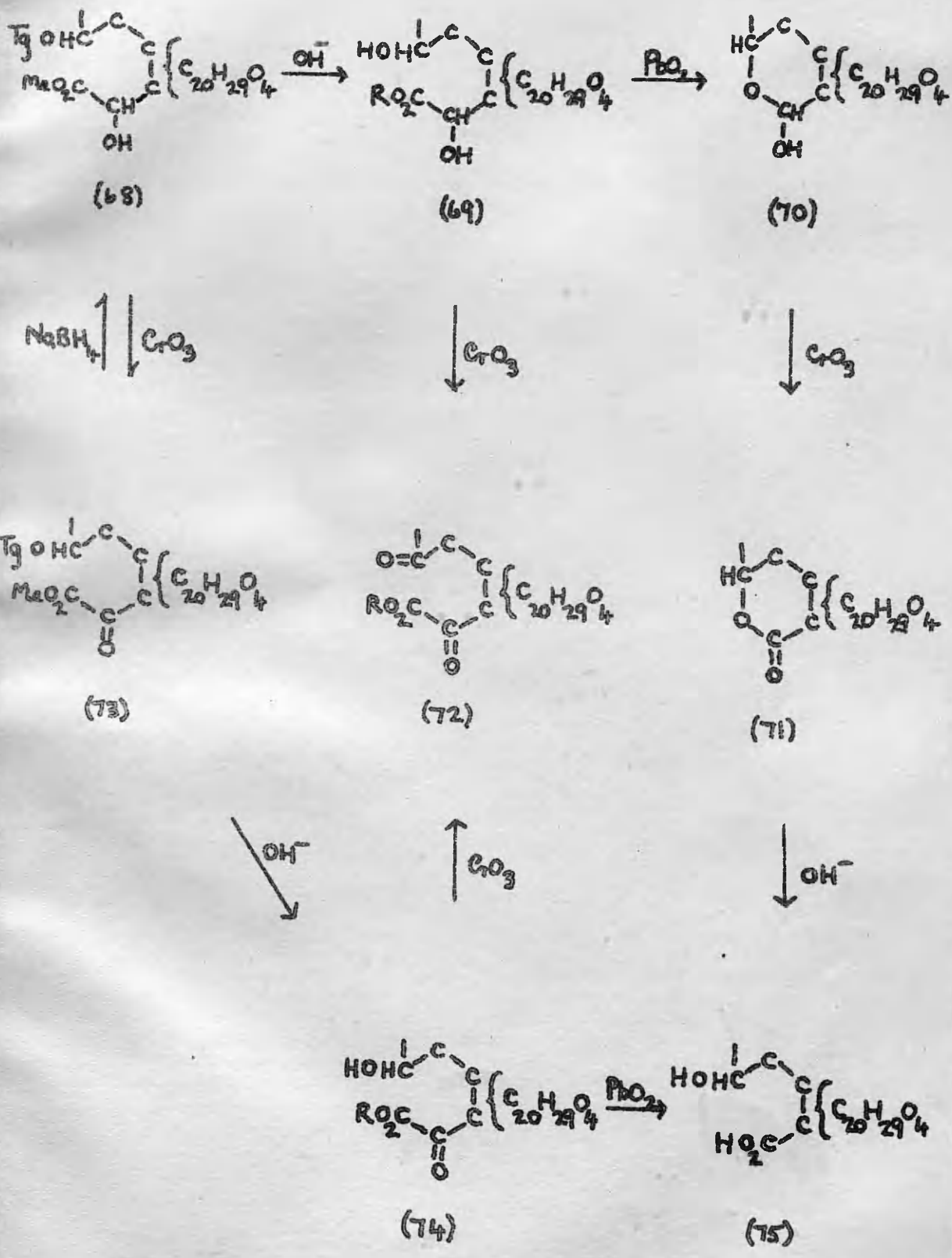

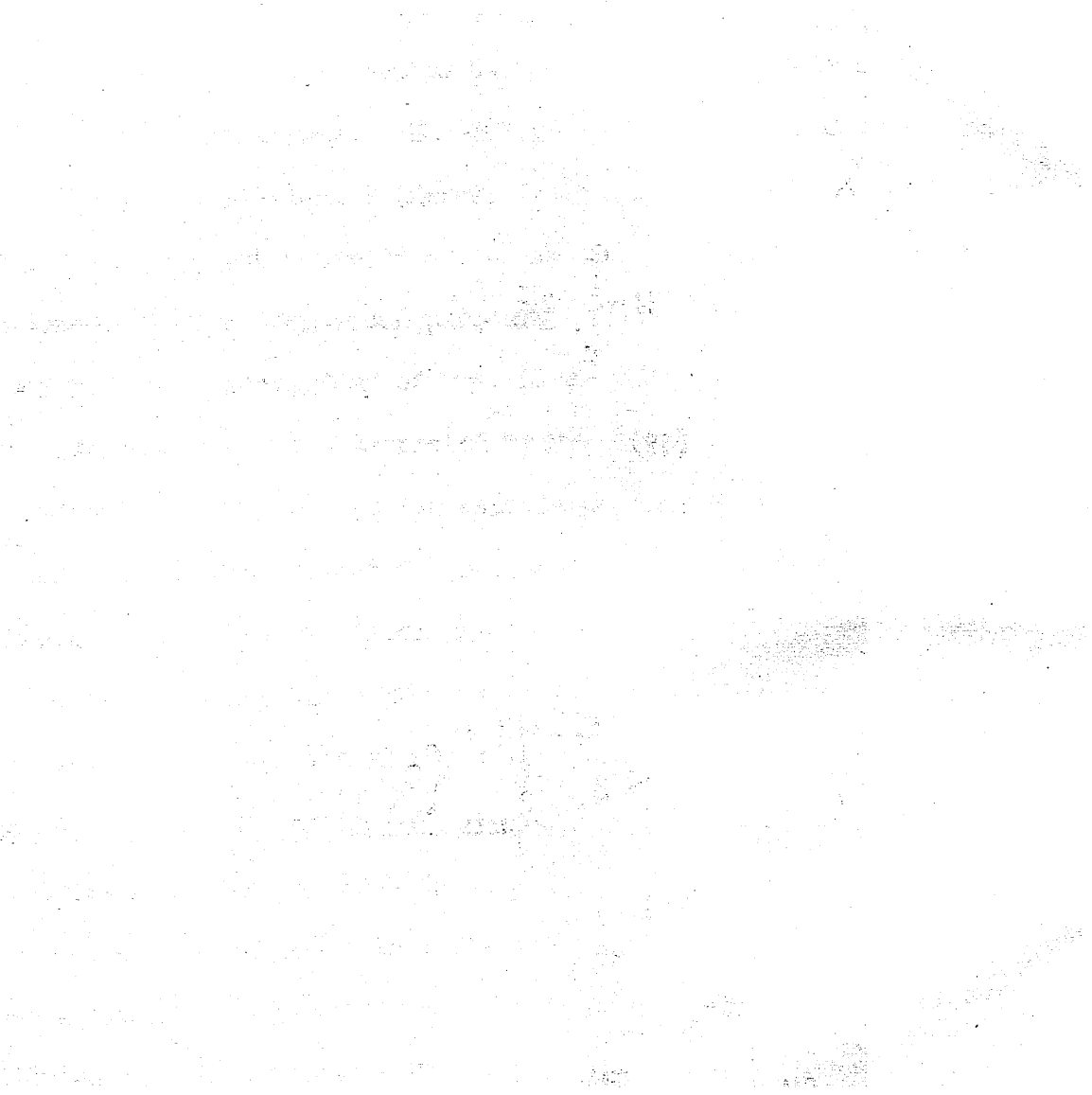

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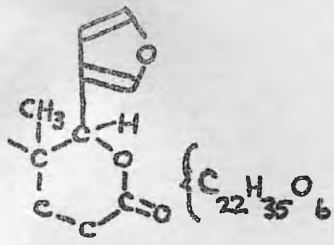
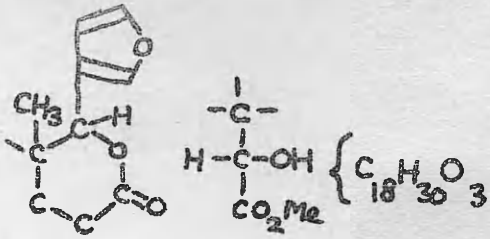


(76)



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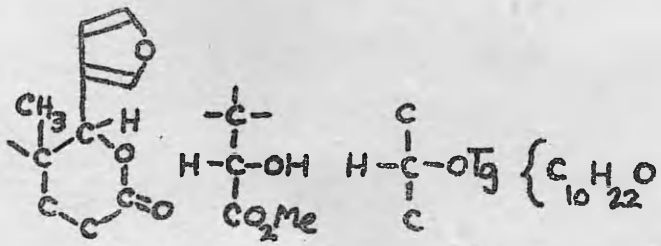

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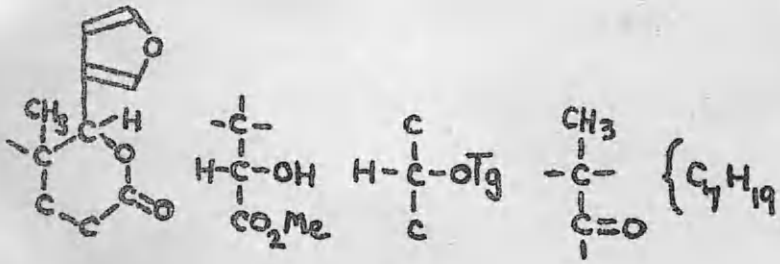

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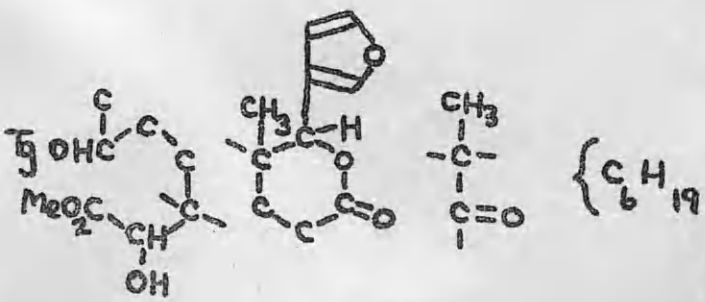

(80)

EXPERIMENTAL

For other general experimental procedures see p. 49. In this section Nujol spectra were taken with a Perkin Elmer Infracord Spectrometer and $\nu_{max.}$ values are approximate ($\pm$ 5 cm.$^{-1}$). Woelm Grade I acid alumina, deactivated according to the Brockmann[17] scale of activity, was used for chromatography. Chromatoplates were prepared by the method of Stahl[18] using Kieselgel G (Merck). Chloroform was used as an eluant; Rf. values are not recorded but where necessary known compounds were run concurrently for comparison purposes. Nuclear magnetic resonance spectra were obtained by courtesy of Drs. L. M. Jackman and J. W. Lown (Imperial College, London) and interpreted by Dr. A. L. Porte. The spectra were taken in $CDCl_3$ using a Varian Associates spectrometer model V.4311 at a fixed frequency of 56.445 Mc./sec. and with tetramethylsilane as internal reference. Rotatory dispersion curves were measured by Professors G. Ourisson and W. Klyne to whom we express our thanks. Assistance with extraction of seeds was kindly given by Mr. G. Milmine.

Extraction of Swietenine (47) and Swietenolide (61):- Milled seeds (8 kg.) of Swietenia macrophylla King were defatted by extraction with light petroleum (b.p. 40-60°) in a Soxhlet apparatus. The dried meal (3.7 kg.) was extracted with chloroform and the concentrated chloroform extract diluted with light petroleum when a yellow gummy material precipitated out. This was dissolved in warm ethanol and left overnight. Crude swietenine m.p. 190-240° (42 gm.) separated and was filtered off. One recrystallisation from chloroform light petroleum yielded swietenine (47)

m.p. 250-260° (21 gm.), $[\alpha]_D$ -182° (c 2.11 in $CHCl_3$).

Saturated aqueous barium hydroxide solution was added to the ethanolic mother liquors with resultant precipitation of a yellow gummy material. The supernatant aqueous solution was decanted and acidified with dilute hydrochloric acid to yield crude swietenolide (30 gm.) as a yellow amorphous powder. A portion (2 gm.) of this was crystallised from ethyl acetate and afforded crystalline swietenolide (61) (450 mg.) m.p. 215-222°. It had a negative Cotton curve: (310 mμ) -2,181°; (268) + 1656°.

Swietenine, as obtained above, still showed two spots on a chromatoplate even after several recrystallisations from chloroform-light petroleum. It was chromatographed on acid alumina (activity IV) in chloroform-benzene (1 : 9). Elution with this solvent mixture was continued until the fractions showed only one spot on chromatoplates and then chloroform-benzene (1 : 4) afforded pure swietenine (47) m.p. 272-276° (rods from chloroform-light petroleum). This had a negative Cotton curve (c 0.22 in $CHCl_3$): (600 mμ) -156°; (589) -167°; (312.5) -2255° (275) +64°. (Found: C, 66.95; H, 7.55. $C_{32}H_{42}O_9$ requires C, 67.35; H, 7.4%). Swietenine of m.p. 250-260°, $[\alpha]_D$ -182° was used in the following experiments.

Oxidation of Swietenine with Chromium Trioxide in Pyridine:- Swietenine (200 mg.) in dry pyridine (25 ml.) was left overnight at room temperature with chromium trioxide (100 mg.). The excess oxidant was destroyed with methanol and the solvents removed in vacuo at 100°. Water was added and

the solution extracted with chloroform to yield a crystalline product (190 mg.) which showed three distinct spots on a chromatoplate. Chromatography on acid alumina (activity IV) in benzene afforded dehydroswietenine (57) (119 mg.). Chloroform-benzene (1 : 9) eluted unchanged swietenine and chloroform a semi-crystalline product (10 mg.). Dehydroswietenine was recrystallised twice from chloroform-ether (rods) m.p. 260-265°, $[\alpha]_D$ -149° (c 1.88 in $CHCl_3$) (Found: C, 67.45; H, 6.6. $C_{32}H_{40}O_9$ requires C, 67.6; H, 7.1%).

Dehydroswietenine changed spontaneously on standing in air and after several weeks the analytical specimen had m.p. 115-140° and showed two spots on a chromatoplate. A sample (90 mg.), m.p. 120-220°, at least a week old, was chromatographed on acid alumina (activity IV). Unchanged dehydroswietenine was eluted with chloroform-benzene (1 : 9) and chloroform-benzene (1 : 1) yielded the desired spontaneous transformation product as a gum (15 mg.).

Dehydroswietenine was unchanged after two days with chromium trioxide in pyridine.

Dehydroswietenine (17 mg.) was treated with excess sodium borohydride in methanol at room temperature. After one hour the solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The crude gum, thus obtained, was chromatographed on acid alumina (activity IV). Chloroform-benzene (1 : 4) eluted crystalline material (5 mg.) identical with swietenine (I.R., m.p., m.m.p.). The rest of the product was not further investigated.

Dehydro-destigloylswieteninic Acid (58):- Dehydroswietenine (355 mg.) was hydrolysed with 2½% ethanolic potassium hydroxide (35 ml.) under nitrogen for 10 min., at 100°. The solution was acidified with 6N hydrochloric acid and diluted with water until a crystalline precipitate appeared. After several hours the crystalline dehydro-destigloylswieteninic acid (58) (233 mg.), m.p. 254-264°, was filtered off and recrystallised twice from acetone-ether-light petroleum in rods m.p. 264-267°, $[\alpha]_D$ -61° (c 1.32 in acetone) (Found: C, 65.90; H, 6.65. $C_{26}H_{30}O_8$ requires C, 66.35; H, 6.45%). Treatment with an excess of ethereal diazomethane in a little methanol gave the corresponding methyl ester m.p. 242-246° (rods from chloroform-ether), $[\alpha]_D$ -74° (c 1.21 in $CHCl_3$). (Found: C, 66.9; H, 7.8. $C_{27}H_{32}O_8$ requires C, 66.9; H, 6.65%). Extraction of the aqueous mother liquors with ethyl acetate yielded a crude acid product (100 mg.) which was esterified with diazomethane. The crude ester showed at least four spots on a chromatoplate and was set aside.

It was observed that, on standing, dehydro-destigloylswieteninic acid and its methyl ester both underwent spontaneous change, (m.p. drops; colour goes yellow).

Oxidation of Methyl Dehydro-destigloylswieteninate (59):- The methyl ester (20 mg.) was oxidised in the usual way with chromium trioxide (20 mg.) in dry pyridine. The product was a gum (18 mg.) which crystallised on addition of ether. Filtration through acid alumina (activity IV) in chloroform-benzene (1 : 19) afforded crystalline triketo-ester (60)

(15 mg.) m.p. 231-235° (from chloroform-ether), $[\alpha]_D$ -228° (c 1.12 in $CHCl_3$) (Found: C, 67.0; H, 6.35. $C_{27}H_{30}O_8$ requires C, 67.2; H, 6.25%).

As with the other compounds in the dehydro-series the triketo-ester was unstable and turned yellow on standing (m.p. 110-120°).

Lead Dioxide Oxidation of Dehydro-destigloylswieteninic Acid (58):- Dehydro-destigloylswieteninic acid (50 mg.) was refluxed for 2 hr. with lead dioxide (50 mg.) in glacial acetic acid. The acidic product (40 mg.) was esterified with ethereal diazomethane. Chromatoplates showed that several compounds were present but that the principal spot was identical with the hydroxy-ester (56) obtained by alkaline hydrolysis of the bislactone (54) followed by methylation.

Alkaline Hydrolysis of Swietenine (47):- Swietenine (100 mg.) was heated for 3 hr., at 100° with 10% ethanolic sodium hydroxide (10 ml.). The solution was acidified with 6N hydrochloric acid, diluted with water and distilled to separate any volatile acid. The aqueous distillate (60 ml.) which showed a maximum in the ultraviolet at 218 mμ., was concentrated, saturated with ammonium sulphate and extracted with ether. This yielded a crude crystalline acid (17 mg.) which was converted, in the usual way, into its p-bromophenacyl ester m.p. 67-68°, identical with the corresponding ester of tiglic acid (mixed m.p. 66-67°).

Swietenine (1 gm.) was hydrolysed with 5% ethanolic potassium hydroxide (100 ml.) under nitrogen for 10 min., at 100°. The solution was acidified with 6N hydrochloric acid, extracted with ethyl acetate and

separated into acid and neutral fractions. The acid fraction (850 mg.) crystallised on standing in chloroform. The crystalline acid (250 mg.) was filtered off and washed with chloroform. On recrystallisation from acetone-ether it yielded destigloylswieteninic acid (50) in clusters of rods m.p. 249-251°, $[\alpha]_D$ -75° (c 1.69 in acetone), pK~4.85. (Found: C, 64.2; H, 6.65. $C_{26}H_{32}O_8.H_2O$ requires C, 63.65; H, 7.0%). The pure acid, on treatment with excess ethereal diazomethane in a little methanol, yielded methyl destigloylswieteninate (51) m.p. 214-216° (from chloroform-ether), $[\alpha]_D$ -67° (c 1.04 in $CHCl_3$). (Found: C, 66.75; H, 6.9. $C_{27}H_{34}O_8$ requires C, 66.65; H, 7.05%). Methyl destigloylswieteninate (51) was also obtained in small yield from the acid mother liquors by methylation with diazomethane and chromatography (elution with 50-60% chloroform-benzene) and from the neutral fraction of the hydrolysis. Chromatoplates showed that the crude hydrolysis product was a complex mixture of at least six components.

The hydrolysis was carried out under varying conditions of time and base concentration but the yields of destigloylswieteninic acid (50) could not be raised.

In one experiment swietenine (1 gm.) was dissolved in 5% ethanolic potassium hydroxide (50 ml.) by heating for 5 min., and left for 80 hr., at room temperature. Chromatography of the neutral fraction (185 mg.) on acid alumina (activity IV) yielded a crystalline ester (30 mg.) m.p. 230-240° (elution with 50% chloroform-benzene) different from methyl destigloylswieteninate (51). It was recrystallised twice from

chloroform-ether, m.p. 243-246° (Found: C, 70.45; H, 7.55. $C_{29}H_{36}O_7$ requires C, 70.15; H, 7.3%). The compound had a mass-spectroscopic molecular weight 500 (calc., 496) (kindly determined by Mr. J. Wilson on a Metropolitan-Vickers Ltd., M.S. 2 Mass-spectrometer). This ester was also obtained in small yield by repeated crystallisation of crude methyl destigloylswieteninate (51) from the neutral fraction of a previous hydrolysis.

Small amounts of unchanged swietenine were isolated from both the acid and neutral fractions of some hydrolyses.

Oxidation of Methyl Destigloylswieteninate (51):- Methyl ester (34 mg.) was oxidised as usual with chromium trioxide (15 mg.) in dry pyridine. The product (31 mg.) showed at least three spots on a chromatoplate and was chromatographed on acid alumina (activity IV). Benzene and chloroform-benzene (1 : 19) eluted crystalline material (5 mg.) m.p. 226-230° (from chloroform-ether-light petroleum) identical with the triketo-ester (60) previously obtained from methyl dehydro-destigloyl-swieteninate (59). Chloroform-benzene (1 : 9) afforded a further crystalline compound (8 mg.) which was recrystallised from chloroform-ether-light petroleum m.p. 223-226°. Elution with chloroform yielded a third crystalline fraction (12 mg.) m.p. 160-200° which showed three spots on a chromatoplate and was set aside.

Lead Dioxide Oxidation of Destigloylswieteninic Acid (50):- Pure acid (120 mg.) was refluxed for 3 hr. with lead dioxide (B.D.H.; 90 mg.) in glacial acetic acid. The solvent was removed and the residue extracted

with chloroform and separated into acid and neutral fractions. The neutral product (106 mg.), a yellow gum, showed two spots on a chromatoplate and was chromatographed on acid alumina (activity IV). Benzene eluted crystalline hemiacetal acetate (53) (28 mg.), m.p. 272-276° (needles from chloroform-ether), $[\alpha]_D$ -34° (c 0.9 in $CHCl_3$) (Found: C, 69.45; H, 7.1. $C_{27}H_{34}O_7$ requires C, 68.9; H, 7.3%). Chloroform-benzene (3 : 17 - 1 : 3) afforded crystalline hemiacetal (52) (48 mg.) which was twice recrystallised from chloroform-benzene-light petroleum, m.p. 232-237° $[\alpha]_D$ -47° (c 1.2 in $CHCl_3$) (Found: C, 70.35; H, 7.2. $C_{25}H_{32}O_6$ requires C, 70.05; H, 7.5%).

As a blank experiment methyl destigloylswieteninate (51) was refluxed for 3 hr., with excess lead dioxide in glacial acetic acid. The product had lost most of the furanoid absorption in the infrared but chromatoplates showed that some of the ester was unchanged.

Oxidation of the Hemiacetal (52):- Hemiacetal (18 mg.) was oxidised as usual with chromium trioxide (20 mg.) in dry pyridine overnight. The product (14 mg.) crystallised spontaneously on addition of ether and was recrystallised twice from chloroform-ether-light petroleum to yield the bislactone (54) in needles, m.p. 213-217°, $[\alpha]_D$ -186° (c 1.36 in $CHCl_3$) (Found: C, 70.15; H, 6.75. $C_{25}H_{30}O_6$ requires C, 70.4; H, 7.1%).

Hydrogenation of the bislactone (10 mg.) in acetic acid over 10% palladised charcoal resulted in the rapid uptake of hydrogen (~3 mol.). The acidic product (7 mg.) was methylated and shown to be a mixture of two compounds by chromatography.

Hydrogenation of Methyl Destigloylswieteninate (51):- Ester (18 mg.) was hydrogenated over 10% palladised charcoal (18 mg.) in glacial acetic acid. The compound absorbed 2.15 ml. of hydrogen (~ 3 mol.) in 4 hr. The product was separated into acid (17 mg.) and neutral (6 mg.) fractions. The acid, after one crystallisation from chloroform-ether had m.p. 140-205°.

The other hydrolysis ester m.p. 246-248° (11 mg.) also yielded an acidic product m.p. ~ 140° (crude) on hydrogenation over palladised charcoal.

Swietenine was not unchanged after treatment with sodium borohydride or hydroxylamine hydrochloride but the reactions have so far failed to yield crystalline products.

Alkaline hydrolysis of the octahydro-acid (48) or the corresponding oxime afforded a complex mixture of products.

Hydrogenation of Swietenolide (61):- Swietenolide (500 mg.) in glacial acetic acid was shaken in an atmosphere of hydrogen with 10% palladised charcoal (87 ml. uptake). The acid product (500 mg.) crystallised on standing and pure hexahydroswietenolic acid (62) m.p. 232-235° was obtained in square prisms after several crystallisations from chloroform-ether. It had a negative Cotton curve: (310 mμ) -1,205°; (268) +2,097° $[\alpha]_D$ -59° (c 1.7 in $CHCl_3$), pK ~ 5.93. (Found: C, 65.3; H, 8.3. $C_{27}H_{40}O_8$ requires C, 65.8; H, 8.2%). The corresponding methyl ester (63) had m.p. 195-200° (from chloroform-ether), $[\alpha]_D$ -35° (c 1.48 in $CHCl_3$) (Found: C, 66.05; H, 8.4. $C_{28}H_{42}O_8$ requires C, 66.4; H, 8.35%).

Acetylation of Swietenolide:- (a) Swietenolide (300 mg.) was refluxed for 5 hr. with fused sodium acetate (1.3 gm.) in acetic anhydride (10 ml.). The solvent was removed in vacuo, water added and the aqueous solution extracted with chloroform. The product, a dark brown oil, was adsorbed on acid alumina (activity IV) in benzene. Elution with ether-benzene (1 : 9) yielded crystalline acetate I (64) (36 mg.) which was recrystallised twice from chloroform-ether, m.p. 198-201°, $[\alpha]_D$ +249° (c 1.06 in $CHCl_3$) (Found: C, 68.1; H, 6.5. $C_{29}H_{34}O_8$ requires C, 68.2; H, 6.7%). The remainder of the product was obtained as a dark oil which could not be crystallised.

(b) Swietenolide (98 mg.) was refluxed for 1 hr. with fused sodium acetate in acetic anhydride (5 ml.). The product was chromatographed on acid alumina (activity IV). Light petroleum-benzene (1 : 9) afforded crystalline acetate II (65) (26 mg.) m.p. 224-228° (square prisms from chloroform-ether),

$[\alpha]_D$ -129° (c 1.11 in $CHCl_3$) (Found: C, 65.3; H, 6.6. $C_{29}H_{36}O_9$ requires C, 65.9; H, 6.85%).

Oxidation of Swietenolide:- Crude amorphous swietenolide (770 mg.) in glacial acetic acid was left overnight with 0.1N potassium dichromate in acetic acid (50 ml.). The crude dark glass thus obtained was chromatographed on acid alumina (activity IV). Ether-benzene (1 : 9 - 1 : 4) eluted crystalline material (225 mg.) which showed three spots on a chromatoplate. It was re-adsorbed on acid alumina in benzene. Benzene (20 ml.) eluted crystalline material m.p. 180-190° (from chloroform-ether; one spot on plate); benzene (15 ml.) a further crystalline fraction m.p. 220-235° (from chloroform-ether; two spots on plate); finally benzene (20 ml.) more crystalline material (two spots on plate). Chloroform-benzene (1 : 19) afforded pure dehydroswietenolide (66) m.p. 242-248° (rods from chloroform-ether-light petroleum), $[\alpha]_D$ -127° (c 1.02 in $CHCl_3$) (Found: C, 66.65; H, 6.5. $C_{27}H_{32}O_8$ requires C, 66.9; H, 6.65%).

Hydrolysis of Swietenolide:- Swietenolide (100 mg.) was refluxed in 5% ethanolic potassium hydroxide (25 ml.) for 1 hr. The acid product (66 mg.) crystallised, on standing, from aqueous alcohol yielding swietic acid (67) m.p. 178-184°, pK~4.68.

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