STUDIES ON SWIETENOLIDE AND RELATED COMPOUNDS

by

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Thanks are also due to the Government of India and to the Government of West Bengal for the award of a scholarship.

CONTENTS

INTRODUCTION

This thesis presents an account of the chemistry of swietenine and swietenolide, extractives from the seeds of Swietenia macrophylla King. The Meliacea family to which this plant belongs, comprises about forty-five genera and seven hundred and fifty species[1] which are widely distributed in tropical regions. Meliacea plants are of considerable interest from a chemical and physiological point of view. A number of plants belonging to this family have been used medicinally[2] and in this connection Melia azadirachta which practically plays the role of a village dispensary in India, deserves special mention. The seeds of Meliacea plants are generally bitter and astringent; some are toxic, stimulant or emetic. The family also includes a number of valuable trees from which high grade timbers are obtained, some of which are bitter, resistant to decay and unattacked by larvae and termites.

The realisation of the potentialities of this plant family has recently stimulated much chemical work, which has shown that the Meliacea provide natural products of considerable interest. However, the literature on these compounds is widely scattered and it therefore seems desirable to make a brief survey of those Meliacea plants, including Swietenia macrophylla King, which are of interest from a chemical and medicinal point of view. This survey, which forms the first part of the introduction to this thesis, shows that much of the chemical work on these plants is of a preliminary nature and it is clear that the more detailed

investigation of many of the compounds would be of considerable interest.

The second part of the introduction is devoted to other natural products which are structurally related to swietenolide and swietenine.

Natural Products derived from the Meliacea family.

1) Cedrela toona Roxb.[2-3] is widely distributed in Australia, South America and India. It is a tall tree which is often referred to as "Indian Mahogany". Its bark, which contains tannins, bitter resins and citric acid, is of value in the treatment of chronic dysentery. The presence of quercetin in its leaves has been reported. From its flower a red colouring matter, $C_{15}H_{18}O_3$, m.p. 285-87°, has been isolated[4]. Its seeds also contain a red dye. On steam distillation the finely powdered, bitter wood yields a sweet smelling essential oil (0.44%) which contains (-)copaene, cadinene and (-)cadinol[5]. The wood was later re-examined by Dutta and Parihar[6] who isolated a reddish-yellow colouring matter, m.p. 256°, and a lactone, $C_{15}H_{30}O_5$, m.p. 204°, in addition to the essential oil. A preliminary investigation of the lactone by the above authors showed that it contains one ethylenic double bond, one keto group, one phenolic hydroxyl group and a lactone ring.

2) Carapa guianensis Aubl.[2-3]: There are five important species of Carapa, Carapa guianensis Aubl. and Carapa procera DC which grow in West Africa and tropical Asia have been shown to contain bitter alkaloids and other principles of therapeutic importance, but no pure compounds have been isolated.

3) The Desoxylon genus[3] includes several species of which Desoxylon fraseranum Benth. is the most important. Its wood, the famous "rose wood" also known as "Australian Mahogany", is resistant to larvae and is valued for furniture. Recently Combie[7] has isolated β-sitosterol, (+)-catechin and a small amount of an impure but crystalline ketonic compound from the heartwood and bark of Desoxylon spectable Hook.

4) Aglaia odoratissima Blume Bijd[2,8] is distributed in Ceylon, Burma and India. Its root, bark and seed are used in the classical Indian system of medicine. The essential oil isolated from its seeds, was investigated by Baslas[8] who found that it contains aromadendrene, cineol, α-terpinene, citral and a compound $C_{15}H_{24}$ which is probably a sesquiterpene.

5) Soymida febrifuga Juss.[2-3] grows in Ceylon and India. Its bark is acrid and has a therapeutic effect on ulcers and dysentery. No pure compounds have yet been isolated from it.

6) Melia azadirachta Linn (Synon.: Melia indica Braudis and azadirachta indica A. Juss.) grows plentifully in India and is known as "Nim". All parts of the plant possess medicinal properties and contain bitter principles. The oil of the seeds and leaves is sold in India as "Nim oil"; it possesses antiseptic properties and is widely used in therapeutics. The so-called "margosic acid" isolated from the oil by Chatterjee[9] in 1919, which was alleged to be the bitter and active principle of M. azadirachta was shown by Watson and his associates[10] to be mainly a mixture of fatty acids and bitter resins. These workers isolated a crystalline bitter acid "Margosopicrin", $C_{24}H_{26}O_5$, $3H_2O$

and amorphous bitter acids. Later on Quadrat-i-Khuda and his coworkers[11] reported the isolation of a sulphur-containing oil and an amorphous water-soluble bitter principle from an aqueous extract of "nim oil". More recently Siddique and Mitra[12] isolated the following bitter components from "nim oil".

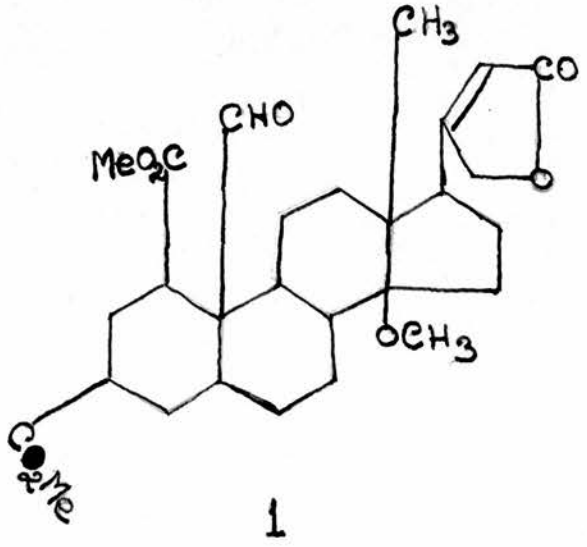
(a) Nimbidin: This is a sulphur-containing amorphous lactone, m.p. 90-100°, $[\alpha]_D^{24}$ +65°. No definite molecular formula has been suggested for it. On hydrolysis it yields a crystalline neutral product, neonimbidin, m p. 222°, a crystalline acid, nimbidic acid, m p. 235° and an amorphous acid, nimbidinic acid. Both nimbidin and sodium nimbidinate have been found to stimulate uterine contraction.

(b) Nimbin, m p. 205°, $[\alpha]_D^{24}$ +170°. This is further discussed below.

(c) Nimbinin, $C_9H_{10}O_3$, m p. 192°.

(d) Nimbidol: This is a liquid, $[\alpha]_D^{24}$ +61°, which is probably a mixture.

Nimbin has been investigated by three groups of workers but unfortunately the results are to some extent contradictory. Mitra[13] suggested that nimbin has the formula, $C_{28}H_{38}O_8$ and the structure (I)



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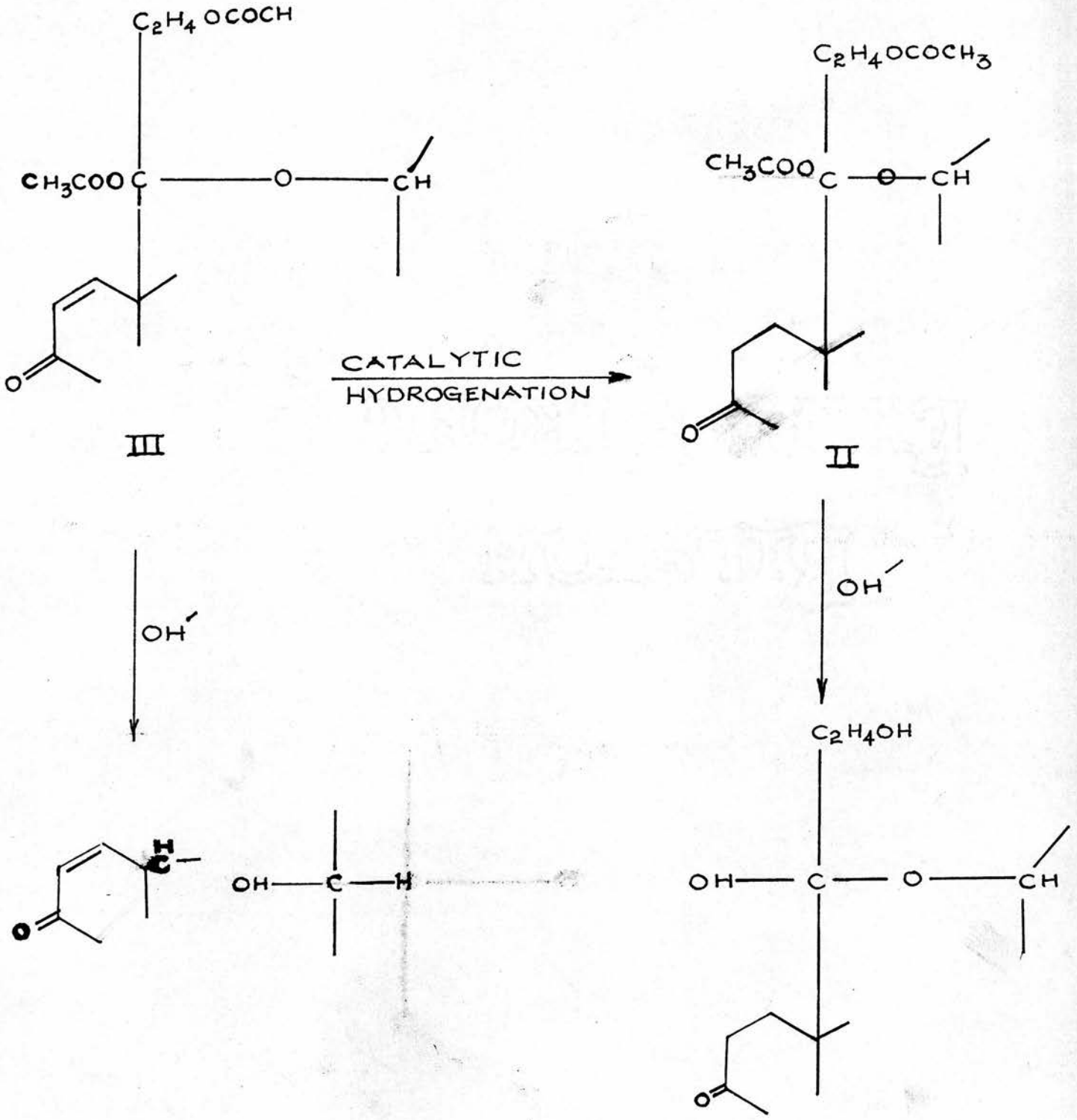
However this structure is not justified by the evidence which consists of colour reactions and inconclusive chemical work. Furthermore subsequent work by Narasimhan[14] has shown that nimbin does not contain an aldehyde group or an $\alpha\beta$-unsaturated lactone ring. According to Narasimhan, analyses and an X-ray molecular weight determination show that nimbin has the formula, $C_{30}H_{36}O_9$. Sengupta and his coworkers[15] favour the formula, $C_{29}H_{36}O_9$. This difference represents a discrepancy of about 0.8% between the carbon contents of both nimbin and dihydronimbin as determined by the two groups of workers.

Both Narasimhan and Sengupta et al. agree that nimbin contains a furan ring (Infra-red evidence) and an $\alpha\beta$-unsaturated ketonic function. The presence of the latter is evident from the difference between the ultraviolet and infra-red spectra of nimbin and its hydrogenated product, dihydronimbin, in which the $\alpha\beta$-unsaturation is absent.

The evidence concerning the other functional groups depends on the products obtained by alkaline hydrolysis of nimbin under various conditions. Here the experimental results obtained by Narasimhan and by Sengupta and his coworkers, appear to be incompatible. By hydrolysis of nimbin with cold methanolic potassium hydroxide, Narasimhan obtained a C_{26}-dibasic acid, which could be reconverted to nimbin by methylation followed by acetylation. This indicates the presence of two carbomethoxy groups and one acetoxy group; the remaining oxygen is assigned to a methoxyl group because the C_{26}-acid still contains methoxyl. On the other hand, Sengupta and his associates claim that nimbin contains one carbomethoxy group and two acetoxy groups, the


C2H4OCOCH
CH3COO
O
CH
III
CATALYTIC
HYDROGENATION
C2H4OCOCH3
CH3COO
O
CH
II
OH⁻
OH⁻
OH
C
H
C2H4OH
OH
C
O
CH

remaining oxygen atom being present as an oxide ring and not as a methoxyl group. They have found that the action of hot methanolic potassium hydrogen carbonate on nimbin results in the loss of one acetoxyl and of the ester methoxyl; the resulting monobasic acid can be converted into nimbin by methylation and acetylation. More vigorous hydrolysis is said to result in the loss of a further acetoxy group and of three additional carbon atoms. When dihydronimbin (II) is subjected to vigorous hydrolysis only the ester methoxyl group and two acetoxyl groups are lost. Sengupta and his coworkers have concluded from this that nimbin contains the system (III).

In Sengupta's view nimbin therefore contains only one methoxyl group. However the methoxyl content obtained analytically by both groups of workers is at least twice that required by the presence of one methoxyl group. Sengupta et al. have ascribed this discrepancy to the furan ring. It may be noted in this connection that swietenolide which also contains a furan ring does not give an abnormal methoxyl value.

Further work is obviously required before the position regarding the functional groups of nimbin can be regarded as settled. The production of C_{26}-dibasic acid by Narasimhan raises the interesting possibility that nimbin may be related to the C_{26}-furan-containing lactones, limonin and obacunone which will be discussed later and also to the C_{27}-lactone methyl ester, swietenolide. Nimbin, limonin and swietenolide all give alkyl napthalenes on dehydrogenation. Unfortunately, however, the C_{26}-dibasic acid from nimbin, unlike limonin and the C_{26}-acid obtained by hydrolysis of swietenolide, appears to contain methoxyl.

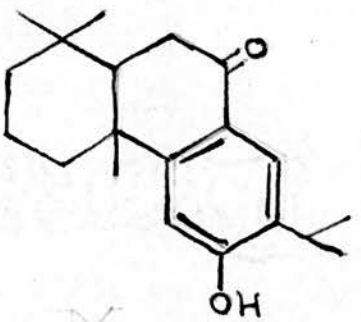
The bark of M. azadirachta Linn. has been examined by Sengupta and his coworkers[19] who have isolated the following products:

(a) Nimbin.

(b) β-sitosterol.

(c) A neutral compound, $C_{26}H_{54}O$, m.p. 82-83°. The authors give no information about the function of the oxygen atom but it seems possible that the compound is ceryl alcohol, $C_{26}H_{53}OH$, m.p. 79.5°.

(d) Two phenolic compounds namely sugiol (IV)[20] and nimbiol, $C_{18}H_{24}O_2$, m.p. 244°, $[\alpha]_D$ +32.3°. Like sugiol nimbiol contains a phenolic hydroxyl group and a ketonic carbonyl. The close similarity between the ultraviolet absorption curves of nimbiol and sugiol in neutral ethanol as well as in alkali suggest that the relative positions of the hydroxyl and ketonic groups are similar in two compounds.



IV

Nimbiol acetate, $C_{20}H_{26}O_3$, on catalytic hydrogenation yields deoxonimbiol acetate, $C_{20}H_{28}O_2$, which on alkaline hydrolysis followed by selenium dehydrogenation affords a phenanthrol which has not yet been fully characterised.

Nim blossoms are reported to have therapeutic value as a tonic after fever and in the treatment of dyspepsia. Mitra and his coworkers[16] have isolated the following products from a cold alcoholic extract of nim blossoms:

(a) Nimbosterol, $C_{28}H_{34}O$, m.p. 137°.

(b) Nimbosterin, m.p. 294°, which yields nimbosterol and an unidentified sugar component on hydrolysis with 5 per cent hydrochloric acid.

(c) A flavone, nimbicetin, $C_{15}H_{10}O_6$, 0.5 H_2O, m.p. 272°.

(d) Fatty acids, namely palmitic and oleic with smaller amounts of stearic, linolic, behenic and arachidic acids.

(e) Nonacosane.

(f) A sesquiterpene essential oil (0.5%), which is a mixture of an ester and acid.

Nim gum, a typical plant gum exudate, has been in pharmaceutical use in India for many centuries[17]. Mukherjee and Srivastava[18] have shown that it is a salt of a complex acidic polysaccharide. Nim gum on hydrolysis yields L-arabinose, L-fucose, D-galactose and D-glucuronic acid. The aldobiuronic acid obtained by graded hydrolysis of the gum has been shown to be 4-O-(D-glucuronosyl)-D-galactose.

(7) Trichila emetica Vahl: The oil of the seeds of Trichila emetica has been found to contain an acidic bitter principle which has not been further investigated.[21]

(8) The genus Swietenia:

One important member of the Meliacea family which had attracted little attention from the chemists prior to the present investigation is the genus Swietenia, which was first discovered by Gerard Van Swieten (1700-1772), a Dutch Botanist. It includes ten different species[22] distributed in tropical regions of the world. Swietenia mahogany is widely planted in India, particularly

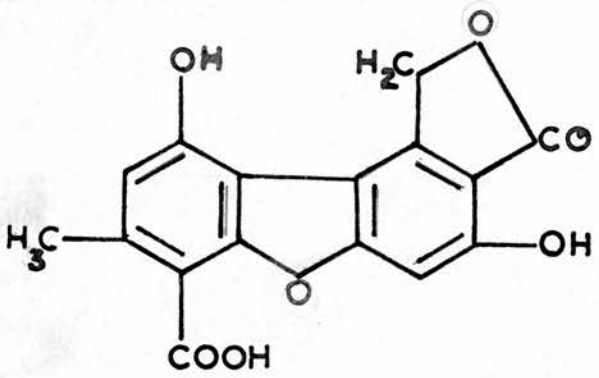
in the Bengal plain as avenue trees. The wood of Swietenia mahogany is bitter and is unattacked by larvae and termites. It is highly prized for the manufacture of furniture. Guha Sircar and Latif[23] have obtained an amorphous bitter principle from the seeds of this species but this has not been further investigated.

Swietenia macrophylla, which was first described by Sir George King in 1886[24], also grows widely in tropical regions and is one of the most majestic and beautiful of trees. Its fruits, bark and leaves taste extremely bitter. In 1951 the author and Guha Sircar[25] isolated a bitter and a nonbitter component designated as swietenolide and swietenine respectively, from the seeds. Swietenine was later investigated in collaboration with A. Chatterjee[26]; the results of this work are discussed later.

The present thesis reports an investigation of the chemistry of swietenolide as well as additional work on swietenine which has led to the revision of its molecular formula. The chemical background of this work is reviewed in the next section.

Other Natural Products Related to Swietenolide and Swietenine.

As will be seen later, swietenolide and swietenine are closely related. Both substances contain a lactone ring, a ketonic carbonyl group, a methyl ester function and a β-substituted furan ring (as well as other functional groups) and both can be degraded to alkyl naphthalenes. Swietenolide is the methyl ester of a C_{26}-acid and it seems probable that swietenine is the tiglate of



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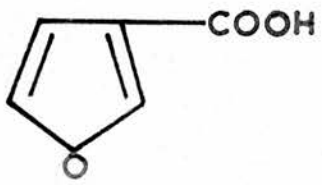
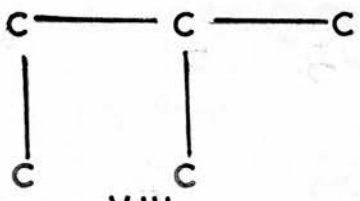
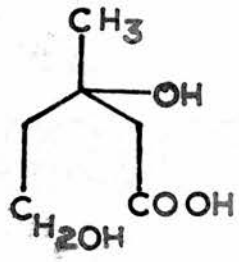


VII



VIII



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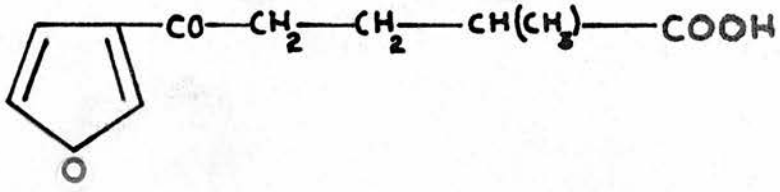

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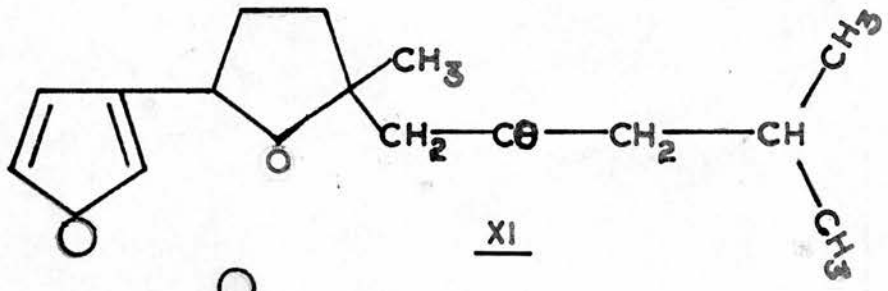

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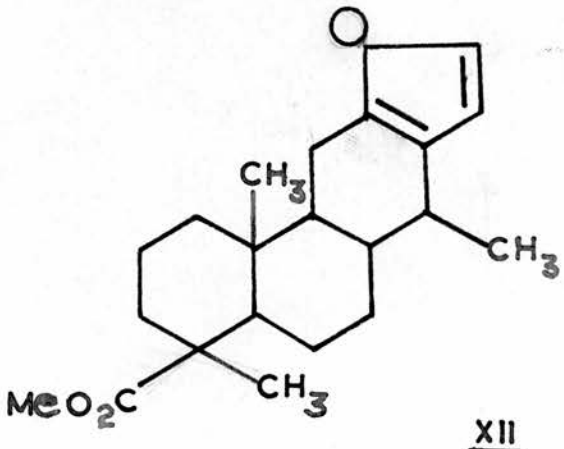


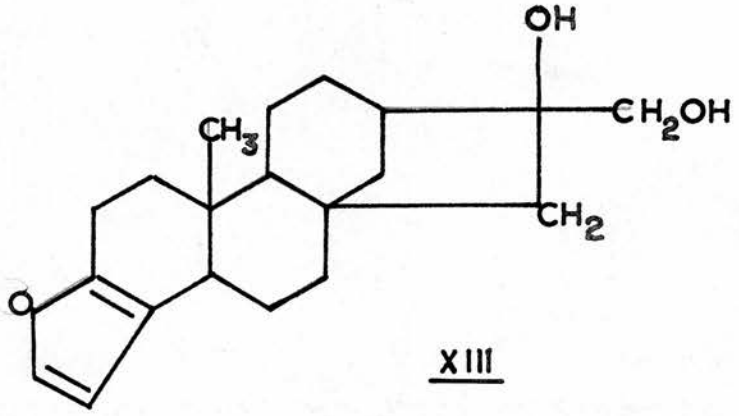
XII

a methyl ester derived from a closely related C_{26}-unit.

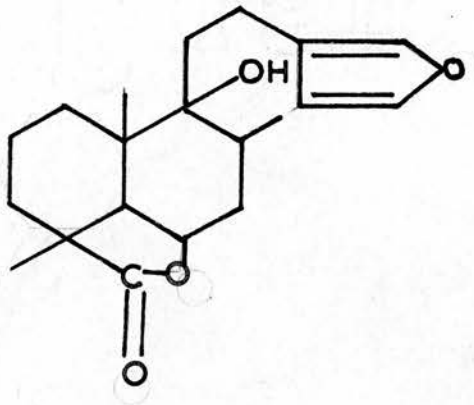
The presence of a β-substituted furan ring is perhaps the most striking feature of these molecules. Furan derivatives are widely distributed in nature[27] and they fall into a number of classes which differ fundamentally in structure and probably have different biogenetic origins. In some natural products the furan ring is fused to an aromatic ring, giving a benzofuran or dibenzofuran system, and these compounds are probably biosynthesised from acetate units along the pathway followed in the biosynthesis of other benzene derivatives.[28] Porphyrilic acid (VI) is an example of this class. Another class concists of simple α-substituted furans, e.g. α-methyl furan, and one is tempted to suggest that these may be related to the carbohydrates In the third major class of naturally occurring furan derivatives, the furan ring is β-substituted. This class contains a large number of compounds of varying molecular complexity, one of the simplest being furan-β-carboxylic acid (VII), which has been isolated from a number of natural sources[29]

Unlike the α-substituted furan system, the β-substituted furan system has an isoprene carbon skeleton (VIII) and it is therefore possible that, in nature, the β-substituted furan unit arises from mevalonic acid (IX), the biogenetic precursor of the terpenes.[30] In fact, examination of the structures of natural products containing a β-substituted furan ring shows that most of these are typical terpenes. Batatic acid (X), a monoterpene and ipomeamarone (XI), a sesquiterpene may be given as examples of furanoid terpenes with comparatively simple structures.

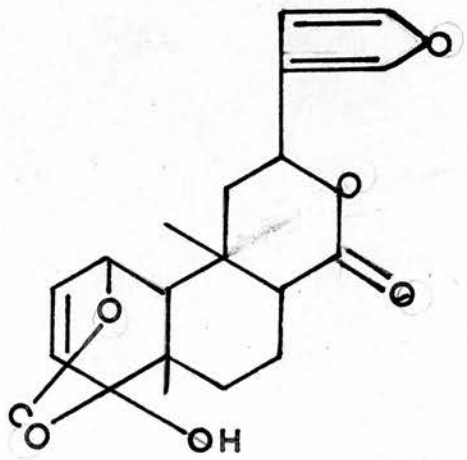
Two types of furanoid diterpenes have been encountered. In some compounds, e.g. methylvinhaticoate[31] (XII) and cafestol[32]



XIII



XIV



XV

(XIII), the furan ring is attached at the α- as well as the β-position. These compounds do not show any close similarities to swietenolide and will not be considered further. On the other hand, marrubiin[33] (XIV) and columbin[34](XV) both contain a simple β-substituted furan system. The former compound is of interest as it was the first diterpene in which the presence of the furan-system was recognised and the latter compound is of special significance because, as will be seen later, it contains several structural features which are also present in swietenolide.

Three other compounds which have recently been shown to contain β-substituted furan rings are of special interest in connection with the present work. These are the bitter principles limonin[35], $C_{26}H_{30}O_8$, nomilin[36a], $C_{28}H_{34}O_9$, and obacunone[36b], $C_{26}H_{30}O_7$. It seems likely that these three compounds, together with swietenolide, seietenine and possibly nimbin (p. 4-6), all belong to a new class of natural products involving a C_{26} carbon skeleton. Despite intensive work, the structures of these compounds have not yet been elucidated and the biological origin of the C_{26} unit which they contain is still uncertain. It is perhaps formed by degradation of a triterpene unit. Alternatively it may be formed from five molecules of mevalonic acid, the additional carbon atom being derived from formate as in the biosynthesis of the C_{31}-triterpene, eburicoic acid.[37]

The intractibility of this group of compounds can be ascribed to a number of factors. Firstly they contain a considerable number of oxygen functions, and reactions aimed at one point in the molecule often lead to amorphous mixtures because of side

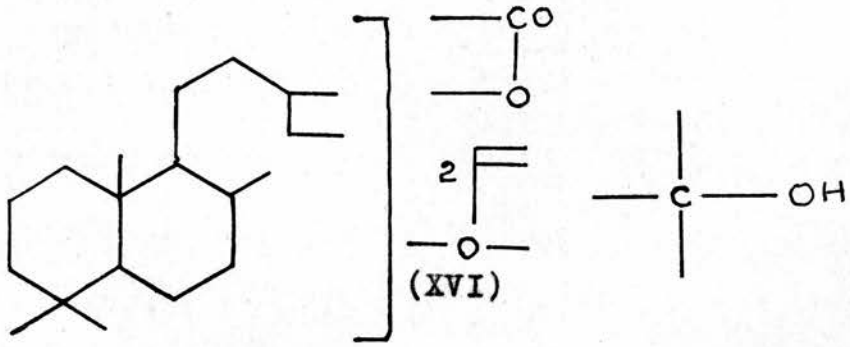
reactions; furthermore the characterisation of the individual functions by spectroscopic methods is more difficult than in simple compounds. Secondly the compounds retain solvents tenaciously and this causes analytical difficulties. Thirdly, because of the high molecular weight, the analytical changes produced by transformations of the functional groups are small. Finally it is not unlikely that the chemistry of these compounds is complicated by rearrangements. It is therefore not surprising that this group still remains one of the major unsolved problems of natural product chemistry.

In the following pages the furanoid lactones marrubiin, columbin, limonin, nomilin and obacunone will be discussed in detail, not only because of their relationship to swietenolide and swietenine but also because their chemistry provides excellent examples of the problems encountered in structural investigations and of the methods which are available for their solution.

Marrubiin

Marrubiin[33], the bitter principle of horehound (Marrubium vulgare) is a diterpenoid, $C_{20}H_{28}O_4$, m.p. 160°. Early work [33a] showed that the compound is a lactone which on hydrolysis gives marrubic acid, $C_{20}H_{30}O_5$. On catalytic hydrogenation marrubiin is converted to a tetrahydro-marrubiin which on dehydration gives tetrahydro-anhydromarrubiin. Marrubiin itself on dehydration affords anhydromarrubiin which on hydrogenation gives hexahydroanhydromarrubiin. It therefore contains one tertiary

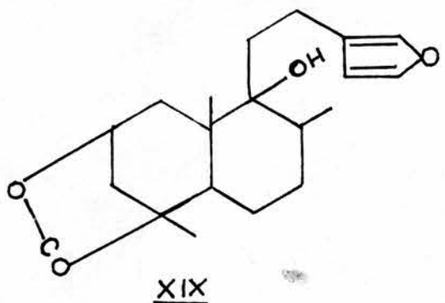
hydroxyl group and two double bonds. The inertness of the remaining oxygen atom suggests that it is present in an ether link. Dehydrogenation with selenium gives 1,2,5-trimethylnaphthalene. On the basis of these experimental results marrubiin may be represented by (XVI).



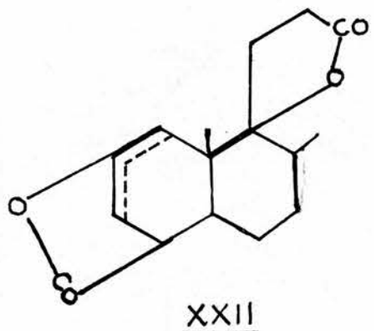
(XVI)

Further insight into the structure was obtained by oxidative degradation. Oxidation of marrubiin with chromic acid in acetic acid was found to result in the loss of three carbon atoms, the two double bonds and the inert oxygen atom. The product was formulated as $C_{17}H_{22}O_4$ by Ghighi[33b] but this formula was corrected to $C_{17}H_{24}O_4$ by Cocker et al.[33c] who recognised the compound as a dilactone and pointed out that its formation is best explained in terms of the oxidative destruction of a furan ring. The presence of a furan ring in marrubiin was confirmed by spectroscopic evidence and by colour tests. Infra-red spectroscopy also showed that the original lactone ring in marrubiin and the new lactone ring present in the dilactone are both five-membered. On the basis of the above evidence the partial structure of marrubiin can be elaborated to the expression (XVII).

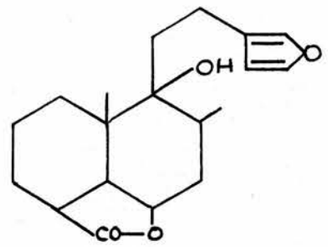
The next problem was the determination of the points of attachment of the lactone ring.



XIX



XXII



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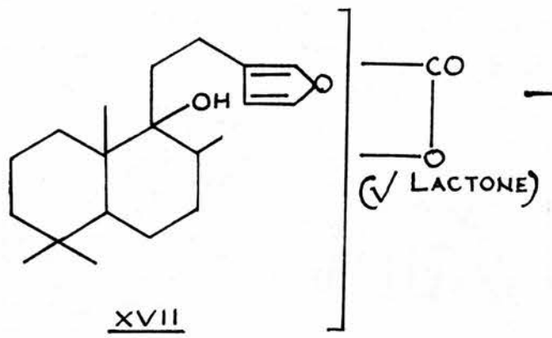
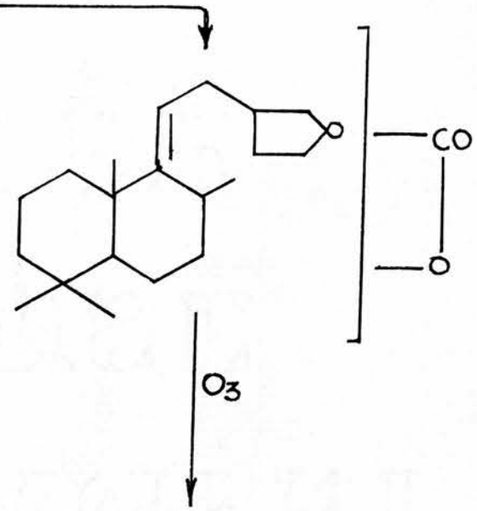
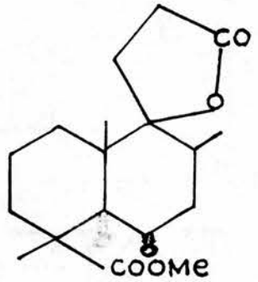


XVII





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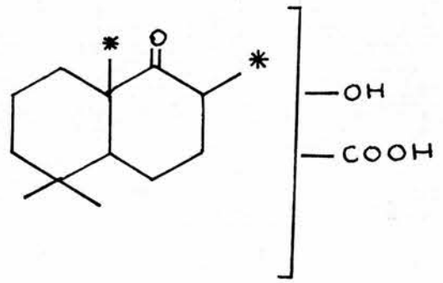
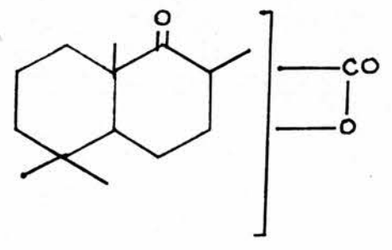
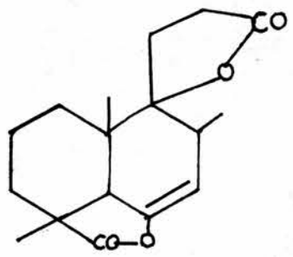


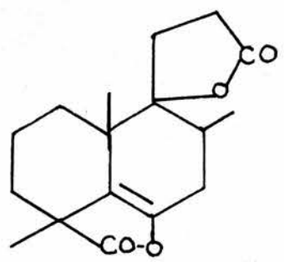


XVIII



XXIa

OR

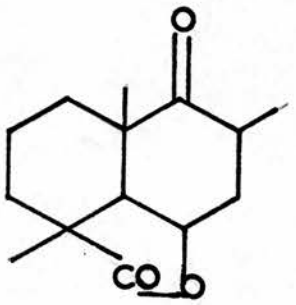


XXIb

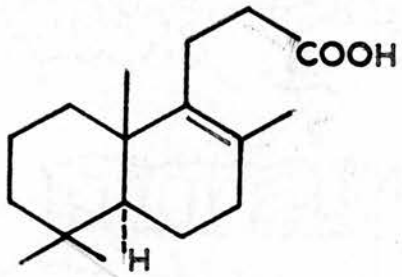
Anhydrotetrahydro-marrubiin on ozonolysis gave a keto-lactone, $C_{14}H_{20}O_3$ (XVIII) in which the entire side chain has been replaced by a carbonyl group, which was shown to be present in a six-membered ring by its absorption band at 1706 cm^{-1}. This confirms the above partial structure. The keto-lactone, which has also been obtained by oxidation of anhydromarrubiin with chromic acid, can be hydrolysed to a hydroxy acid, $C_{14}H_{22}O_4$, which does not lose carbon dioxide readily and is therefore not a β-keto acid. This shows that the carbon atoms marked with an asterisk cannot be carboxyl (both are β to the carbonyl group) and the carboxyl group must therefore be present at the geminal position. As the lactone ring in marrubiin is five-membered, the above evidence suggests (XIV) and (XIX) as the possible structures for marrubiin. Cocker et al. eliminated the latter possibility in the following way.

Oxidation of methyl marrubate with chromic acid destroyed the furan ring and converted the secondary hydroxyl group into a carbonyl giving a compound which can be formulated as (XX) on the basis of the structure (XIV) for marrubiin. The derived keto-acid could be cyclised to an enol lactone which can be formulated as (XXIa) rather than (XXIb) because it gives an aldehyde and not a ketone on ozonolysis[33d]. If marrubiin had the structure (XIX), the enol-lactone would have one of the structures represented by (XXII) and as both of these structures infringe Bredt's rule the structure (XIX) for marrubiin can be rejected.

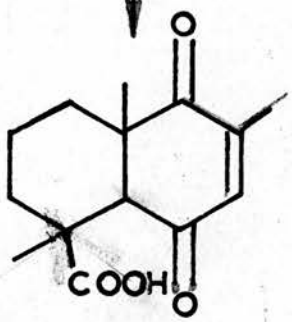
The formula (XIV) for marrubiin was confirmed by later work[33e]. Thus the C_{14} keto-lactone (XVIII) which can now be formulated as



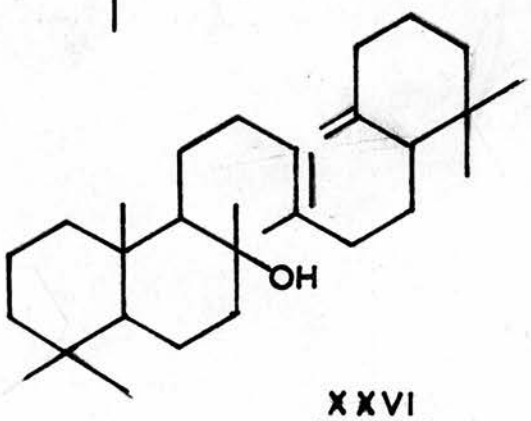
XXIII



XXV



XXIV



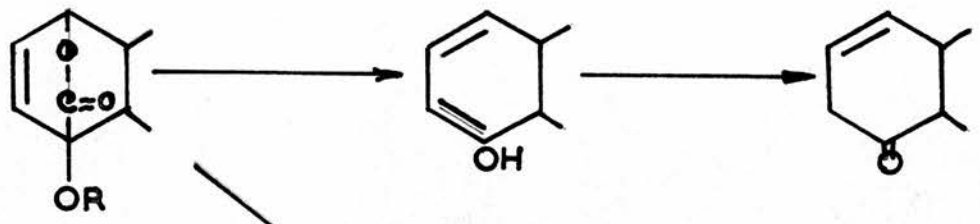
XXVI

(XXIII) is converted into the cisoid-dienone (XXIV) by oxidation of the derived hydroxy acid with chromium trioxide followed by selenium dioxide. This confirms the relative position of the two oxygen functions. The carbon skeleton of marrubiin was confirmed by conversion of enol lactone (XXI) into the compound (XXV)[33f] which has been obtained by degradation of ambrein (XXVI)[33g]. This also establishes the stereochemistry of the ring junction in marrubiin.

The chemistry of marrubiin is notable, firstly because it was the first diterpenoid in which the presence of the furan system was recognised and secondly because it provides a striking illustration of the value of oxidative degradation in structure determinations.

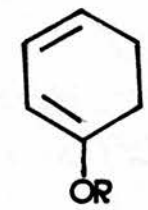
Columbin

The root of Jatrorrhiza palmata, Miers (Colombo-root) contains three neutral bitter principles; Columbin, $C_{20}H_{22}O_6$, chasmanthin, $C_{20}H_{22}O_7$ and the isomeric palmarin. These compounds were the subject of prolonged investigations by Wessely[34a] and by Feist[34b] and their respective collaborators but these workers were unable to reach any satisfactory structural conclusions. However, recent elegant work by Barton and Elad[34c] has elucidated the structure of columbin and has shown that this compound is of unusual complexity and interest. In view of the fact that some of the structural features of columbin are also present in swietenolide, the chemistry of columbin will be discussed in detail.

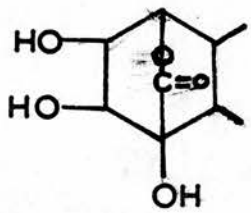


XXVII

XXVIII



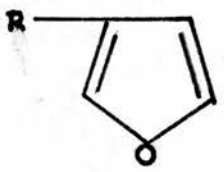
XXIX



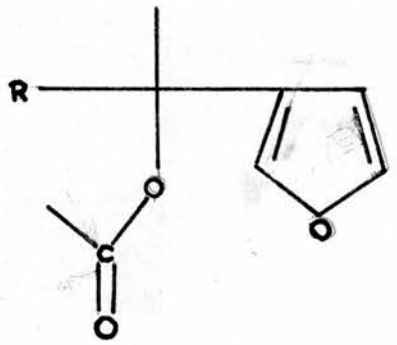
XXX

Columbin, $C_{20}H_{22}O_6$, is easily isomerised by base to <u>iso</u>-columbin. Both substances behave as dilactones toward alkali and both give the same monoacetyl derivative, <u>iso</u>columbin acetate with acetic anhydride-sodium acetate. They therefore contain one hydroxyl group. This is somewhat acidic as it can be methylated easily with methyl sulphate and sodium hydroxide; however it is not enolic or phenolic. Columbin and <u>iso</u>columbin both lose one molecule of carbon dioxide on melting, giving the monolactones decarboxycolumbin, $C_{19}H_{22}O_4$ and decarboxy<u>iso</u>columbin respectively. These cannot be acylated or methylated and the decarboxylation therefore involves the destruction of the hydroxyl group. However <u>iso</u>columbin acetate and O-methyl <u>iso</u>columbin both decarboxylate to products which still contain an acetyl and a methoxyl group respectively. On the other hand, dihydro-columbin which can be prepared by careful hydrogenation of columbin over palladised calcium carbonate, does not decarboxylate. These reactions can be explained in terms of the partial structure (XXVII, R = H) for columbin. The spectra of decarboxycolumbin (XXVIII), decarboxy<u>iso</u>columbin acetate (XXIX, R = Ac) and de-carboxy-O-methyl<u>iso</u>columbin (XXIX, R = Me) are in agreement with the structure indicated. Further confirmation of the partial structure (XXVII, R = H) was obtained by oxidation of <u>iso</u>columbin with osmium tetroxide. As expected the product (XXX) consumed two molecules of lead tetraacetate.

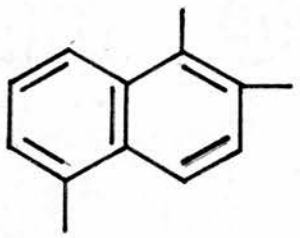
The partial formula (XXVII, R = H) contains three of the oxygen atoms of columbin. Two further oxygens are involved in the second lactone ring and the remaining oxygen is inert. Columbin, like marrubiin was very sensitive to chromic acid oxidation and ozonolysis of dihydrocolumbin gave an acid, $C_{17}H_{22}O_7$, with the loss of three carbon atoms, two double bonds and the inert oxygen



XXXI



XXXII

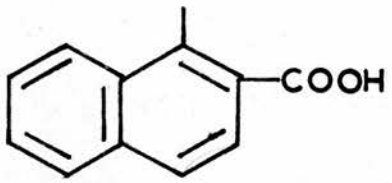


XXXIII

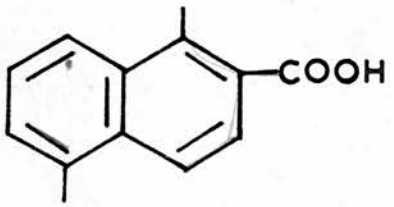
atom. This suggests the presence of a furan ring; the β-substituted formulation (XXXI) is confirmed by proton magnetic resonance[34d] and by the use of the Alder-Rickert decomposition[34e].

As mentioned above, careful hydrogenation of columbin gives dihydrocolumbin. Further hydrogenation brings about hydrogenolysis of a lactone ring and also saturates the furan ring, the product being octahydrocolumbinic acid. Decarboxycolumbin also undergoes hydrogenolysis giving decarboxyoctahydrocolumbinic acid and the lactone ring which is hydrogenolysed is therefore not the one represented in the partial structure (XXVII). These results suggest that the remaining lactone ring is attached as indicated in the partial structure (XXXII).

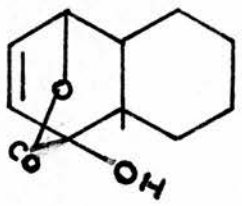
This summarises briefly the evidence to support the characterisation of the oxygen functions in columbin. Early degradative work showed that columbin and isocolumbin both give o-cresol and 1,2,5-trimethylnaphthalene (XXXIII) on zinc dust distillation. Fusion with caustic potash gave 2,4-dimethylbenzoic acid and 2-methylterephthalic acid. This early evidence was insufficient to complete the elucidation of the carbon skeleton. Later Barton and Elad found that decarboxyoctahydrocolumbinic acid also gave 1,2,5-trimethyl naphthalene on reduction with lithium aluminium hydride followed by selenium dehydrogenation. Furthermore octahydrocolumbinic acid when submitted to the same treatment, gave the same trimethylnaphthalene and not a tetramethylnaphthalene as expected. This clearly showed that the formation of the trimethylnaphthalene from decarboxyoctahydrocolumbinic acid must involve migration of a methyl group from a quaternary position. Confirmation of this was obtained by dehydrogenation of decarboxyoctahydrocolumbinic



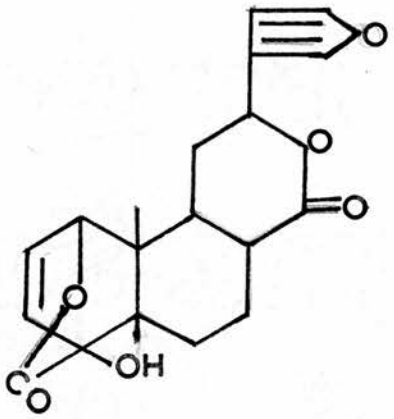
XXXIV



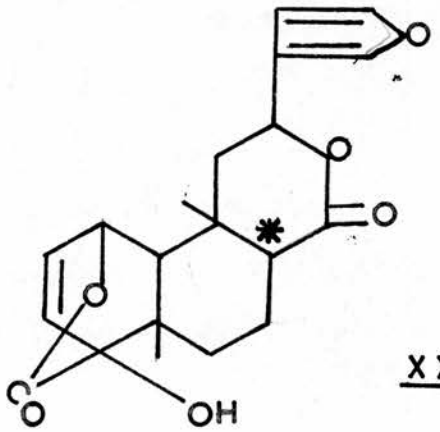
XXXV



XXXVI



XXXVII



XXXVIII

acid after removal of the carbonyl by Wolff-Kishner reduction; the product was 1-methyl-2-naphthoic acid (XXXIV). The absence of a substituent at C_5 shows that in this case migration is absent. On the other hand, reduction of the carbonyl to hydroxyl, giving decarboxydecahydrocolumbinic acid, and dehydrogenation gave 1,5-dimethyl-2-naphthoic acid (XXXV) in which the methyl migration has taken place. Migration, as expected, therefore only takes place when an oxygen function is present to provide a carbonium ion by elimination. The above evidence shows that a quaternary methyl group is present β to the lactone carboxyl and that the lactone carboxyl is attached at C_5. This gives for columbin the partial formula (XXXVI).

The production of (XXXIV) shows that the side-chain bearing the furan ring must be attached at C_1 and that the carboxyl group of the second lactone is at C_2. This and the earlier evidence, together with the fact that columbin contains two C-methyl groups, allows two possible structures for columbin, namely (XXXVII) and (XXXVIII). (XXXVIII) is preferred because it explains the degradations to O-cresol and 2,4-dimethyl-benzoic acid better than (XXXVII) which might be expected to give 2,3-dimethyl-phenol and 3,4-dimethyl-benzoic acid.

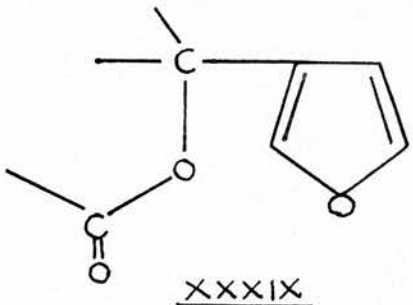
The stereochemistry of columbin remains to be elucidated; it seems probable that the columbin-isocolumbin transformation involves inversion at the carbon atom marked with an asterisk.

Limonin

The bitter principle limonin was first isolated from citrus fruits by Bernay[35a] in 1841. Since then, it has been investigated in many laboratories but, for reasons which have already been discussed above (p.11-12), progress in the elucidation of its structure has been slow. Although a number of structural features can be regarded as firmly established, many of the reactions of limonin are difficult to interpret and some of the partial structures which have been invoked are so tentative that it seems unprofitable to discuss them until further experimental evidence is available. The present review is therefore confined to a summary of the most important reactions of limonin, and structural conclusions are only drawn in those cases where the evidence is unambiguous.

Limonin[35] has the formula, $C_{26}H_{30}O_8$. It contains two lactone rings which are easily opened by alkali; the corresponding dibasic acid has not been isolated as such, as it readily lactonises. Potentiometric titration of the sodium salt indicates that a strongly acidic carboxyl group is present (pK_1 2.7, pK_2 4.7). The presence of a ketonic group is demonstrated by the formation of an oxime and a 2,4-dinitrophenylhydrazone and by the presence of an absorption maximum at ca. 280 mμ, log ε , 1.5. The infrared spectrum shows that no hydroxyl functions are present and, as alkoxyl functions are also absent, the remaining oxygens are considered to be involved in oxide rings. The ultraviolet[35c], infrared[35d] and proton magnetic resonance spectra[34d] suggest that one of the oxide rings is a β-substituted furan ring; this has

been confirmed by photo-oxidation[35c] and by the application of the Alder-Rickert decomposition[35d]. On hydrogenation, limonin gives tetrahydrolimonin (in which the furan ring has been saturated) as well as hexahydrolimoninic acid $C_{26}H_{36}O_8$, pK 2.7[35b]. This behaviour is reminiscent of columbin and suggests that one of the lactone rings is attached as in the partial structure (XXXIX)



XXXIX

The high acidity of hexahydrolimoninic acid suggests that the carbon atom α to the carboxyl group probably carries an electron-attracting oxygen function.

Reduction of the keto group in limonin gives two epimeric alcohols, limonol and epi-limonol[35c]. On alkaline degradation the former loses the furan ring and one additional carbon atom to give merolimonol, $C_{21}H_{28}O_6$, a dilactone. Tetrahydrolimonol also gives merolimonol on alkaline degradation. Limonin itself undergoes alkaline degradation under more vigorous conditions to give a mixture of products from which two C_{21}-methyl esters were isolated after methylation. These do not contain a furan ring and and the degradation therefore involves the loss of the furan ring and of two additional carbon atoms. These degradation products should prove to be useful stepping stones in the elucidation of the structure of limonin.

Limonin on oxidation with sodium hypoiodite gives limonilic acid, $C_{26}H_{30}O_9$, pK ca. 4.4, which contains a free hydroxyl group

as shown by the band at 2.8μ in the infrared spectrum of methyl limonilate[35b]. Limonilic acid is a monolactone and alkaline hydrolysis gives the sodium salt of a dibasic acid which has pK, ca. 3.0. These results suggest that the lactone ring opened in the oxidation is not the one which is opened by hydrogenolysis. In confirmation of this, hexahydrolimoninic acid, $C_{26}H_{36}O_8$, gives a dibasic acid, $C_{26}H_{36}O_9$, on oxidation with hypoiodite.

The reduction of limonin with hydroiodic acid gives citrolin[35b] which probably has the formula $C_{26}H_{28}O_6$ and contains four double bonds.

The molecular formula of limonin together with the above evidence regarding the functional groups suggests that the compound contains two carbocyclic rings. This view is supported by the production of 1,2,5-trimethylnaphthalene by selenium dehydrogenation of the volatile product obtained by fusion of limonin with potassium hydroxide[35e]. Merolimonol also gives a naphthalene derivative on dehydrogenation but this has not yet been identified.[35c]

It is clear that the elucidation of the structure of limonin will be a significant milestone in the progress of natural product chemistry.

Nomilin and Obacunone

Nomilin, $C_{28}H_{34}O_9$[36a] and obacunone, $C_{26}H_{30}O_7$[36b] are two keto-dilactones which, like limonin, occur in citrus fruits. Although they have been less thoroughly studied than limonin, it is clear that the three compounds belong to the same group of natural products.

On alkaline hydrolysis, both nomilin and obacunone give

obacunoic acid, $C_{26}H_{32}O_8$, the former yielding acetic acid at the same time. Furthermore nomilin is converted into obacunone by boiling with γ-picoline[36c]. Both obacunone and obacunoic acid show high intensity absorption at 209 mμ, while nomilin absorbs much less intensely. These results suggest that one of the lactone rings in nomilin carries a β-acetoxyl group, obacunone being the corresponding αβ-unsaturated lactone.

The absence of hydroxyl functions and alkoxy groups in nomilin and obacunone suggests that the two oxygen atoms not accounted for by the above functional groups, are present in oxide rings. Infrared spectra[36c] and application of the Alder-Rickert decomposition[35d] suggest that one of these oxide rings is a β-substituted furan, as in limonin. A further analogy with limonin is provided by the fact that both nomilin and methyl obacunoate undergo catalytic hydrogenolysis with the liberation of a strongly acidic carboxyl group. However the hydrogen uptakes suggest that nomilin and methyl obacunoate contain one and two ethylenic linkages respectively (in addition to the furan ring); if the above views on the molecular formulae and functional groups of nomilin and obacunone are correct, these compounds can therefore contain only one carbocyclic system, unlike limonin which probably contains two.

THE CHEMISTRY OF SWIETENOLIDE

Isolation of Swietenolide.

Through the kind co-operation of the Superintendent of the Indian Botanic Garden, Calcutta, a generous supply of the authentic seeds of Swietenia macrophylla, King was available. Chloroform extraction of the decorticated, dried and defatted seeds gave a semi-solid gum (7%). This partly solidifies on treatment with ethanol giving the non-bitter principle, swietenine, which has been the subject of previous work by the writer[25, 26]. The alcoholic mother-liquor has an extremely bitter taste which indicates that a second substance is present. Evaporation of the mother-liquor gives a gum which fails to crystallise even after chromatography over alumina. A crystalline bitter principle, swietenolide, was finally obtained on treatment of the alcoholic mother-liquor with barium hydroxide as described in the experimental section. After chromatography it has m.p. 220°. The yield was variable (ca. 0.1% calculated on the basis of dried decorticated crushed seeds); a smaller yield was obtained when old, partly decomposed seeds were used.

It is possible that swietenolide may not be present as such in the original extract, but that it is formed from a precursor by hydrolysis or rearrangement under the alkaline conditions used in the isolation. Attempts to demonstrate the presence of swietenolide in the crude extract by paper chromatography were inconclusive.

Swietenolide is very soluble in chloroform, fairly soluble in alcohol and ethyl acetate, and somewhat less soluble in ether

and benzene. It is optically active, $[\alpha]_D$ - 126° (C, 2.09 in chloroform). It gives a pink coloration which fades after a few minutes with N-potassium hydroxide in methanol. Colour tests with certain other reagents are described below. Other more informative colour tests are discussed later.

Reagent	Coloration
1. Liebermann-Burchard[38] reaction	Sulphuric acid layer turns greenish yellow, then orange, then red and after standing 20 minutes a blue fluorescence appears.
2. Salkowski's reaction.[39]	Sulphuric acid layer becomes pink, changing to reddish brown.

THE MOLECULAR FORMULA OF SWIETENOLIDE

Variability in the analytical results obtained for swietenolide and its derivatives during the first nine months of this work was a great handicap to progress. Carbon and hydrogen analyses obtained for swietenolide during this period by Weiler and Strauss (Oxford) are given in Table 1A. It is apparent that the variation in the results cannot be related to the drying conditions or to the solvent used for the final crystallisation.

A clue to these erratic results was finally provided by Dr. J.W. Minnis of the Biochemistry Department, University of Edinburgh, who kindly undertook to analyse a sample of swietenolide. Dr. Minnis noted that swietenolide is hygroscopic, a sample which has been dried to constant weight in vacuo at 100° increased in weight by 3.2% after exposure to the atmosphere overnight. The increase in weight suggests that a monohydrate is formed. This was confirmed by subsequent work which also showed that the rate of hydration is quite high, e.g. after three hours exposure to the atmosphere the weight of a dried sample increased by ca. 1%. It therefore seems likely that the erratic results obtained by Weiler and Strauss are due to rehydration of the compound after drying.

The carbon and hydrogen values shown in Table 1B were obtained by Dr. Minnis by correcting the analyses of the rehydrated sample for its water content. Similar results (Table 1C) were obtained by Pascher, Microanalytisches Laboratorium, Bonn, by direct analysis of a dried sample. This analyst takes special precautions to avoid rehydration of dried samples.

Although swietenolide does not give a positive result in the sodium fusion test for nitrogen, Dumas microanalyses by Weiler and Strauss and by Dr. Minnis gave low and variable nitrogen values (N = 3.5, 0.6, 1.2%). These results may be due to the evolution of methane.[41] Microanalyses kindly carried out by Dr. Colson of I.C.I. with special precautions to avoid errors due to methane indicated that nitrogen was absent (< 0.1%). This was confirmed by Pascher. The analytical oxygen content of swietenolide also showed that it contains only carbon, hydrogen and oxygen.

Attempts to determine the molecular weight of swietenolide by the Rast method gave variable results. A determination of the molecular weight of swietenolide hydrate by the X-ray method, kindly carried out by Dr. C.A. Beevers, gave M.W. 490. The specimen used in this determination was obtained by slow crystallisation from ethyl acetate followed by solvent removal at 100° under reduced pressure and hydration by exposure to the atmosphere. The resulting crystals were slightly cloudy and the molecular weight obtained must therefore be treated with some reservation. However, as will be seen later, titrimetric equivalent weights determined on swietenolide and its derivatives also give a molecular weight of ca. 500 for swietenolide hydrate. On the basis of these results $C_{27}H_{32}O_8$, $C_{27}H_{34}O_8$ and $C_{28}H_{36}O_8$ are the most likely formulae for swietenolide. The analytical data for swietenolide and some of its derivatives (see Table II) on the whole favours the C_{27}-formulae. It is difficult to decide between $C_{27}H_{32}O_8$ and $C_{27}H_{34}O_8$; the former is favoured by the carbon contents and the latter by the hydrogen contents. In the present thesis $C_{27}H_{34}O_8$ has been chosen as a working hypothesis.

TABLE I

A) Weiler and Strauss

Samples dried in vacuo at 50° by the analyst.		Samples dried in vacuo at 100° by the analyst.	
% carbon	% hydrogen	% carbon	% hydrogen
66.5	7.1*	67.7	7.1
66.2	7.1*	64.0	7.1
64.1	6.5	64.6	7.0
		64.5	7.1
		64.7	7.3*
		64.5	7.4*

Values marked with an asterisk were obtained from samples which had been crystallised from ethyl acetate - light petroleum; in all other cases the solvent for the final crystallisation was aqueous ethanol.

B) Biochemistry Department, University of Edinburgh.

% carbon	% hydrogen
67.15	7.04
66.85	6.96

C) Pascher, Mikroanalytisches Laboratorium, Bonn.

% carbon	% hydrogen
66.85	7.19
66.68	7.25

TABLE II

	$C_{27}H_{32}O_8$ (Calc.)	$C_{27}H_{34}O_8$ (Calc.)	$C_{28}H_{36}O_8$ (Calc.)
Swietenolide (dried to const. wt. at 100°in high vacuo. Loss in wt.: 2.9%)			
C: 66.85; 66.68; 67.15; 66.85	66.92	66.65	67.18
H: 7.19; 7.25; 7.04; 6.96	6.66	7.04	7.25
O: 26.34; 26.12	26.42	26.31	25.57
Swietenolide hydrate			
C: 64.52	64.53	64.27	64.85
H: 7.10	6.82	7.19	7.39
M.W.: 490 (X-ray method)	484.5	486.5	500.6
Swietic Acid (Dried to const. wt. at 140° in high vacuo. Loss in wt. : 3.22%).			
C: 65.82	66.37	66.08	66.65
H: 6.68	6.43	6.83	7.04
Swietic acid hydrate			
C: 64.03	63.92	63.66	64.27
H: 6.77	6.60	6.99	7.19
Hexahydroswietenolic acid Dried to const. wt. at 100° in high vacuo.)			
C: 66.07; 65.91	66.1	65.83	66.38
H: 8.30; 8.18	7.81	8.19	8.36
Dehydroswietenolide (Dried to const. wt. at 100° in high vacuo.)			
C: 66.98	67.20	66.92	67.45
H: 6.59	6.27	6.66	6.87
Lithium aluminium hydride reduction product (Dried to const. wt. at 100° in high vacuo.)			
C: 66.95	67.51	67.21	67.75
H: 8.31	8.28	8.68	8.85
Crystalline acetate (A) (Dried to const. wt. at 100° in high vacuo).			
C: 68.55; 68.32.	68.49	68.22	68.68
H: 6.86; 6.98.	6.34	6.71	6.92

THE FUNCTIONAL GROUPS OF SWIETENOLIDE

As indicated in the previous section, it is probable that swietenolide has the molecular formula, $C_{27}H_{34}O_8$. The high oxygen content suggests that it might be glycoside, but this was disproved by showing that it does not give any sugar on treatment with dilute acid. Furthermore the Keller-Killiani reaction[42] for 2-deoxyglycosides was negative. The possibility that swietenolide belongs to one of the many classes of polyoxygenated natural products (e.g. flavones) which contain oxygen attached to an aromatic ring is excluded by its ultraviolet absorption spectrum (details of ultraviolet, infrared and proton magnetic resonance spectra are given in an appendix). Swietenolide does not give any colour with alcoholic ferric chloride solution and a test[43] for the methylenedioxy group was negative. Kuhn-Roth oxidation shows that it contains three C-methyl groups.

Swietenolide is neutral to litmus and does not liberate carbon dioxide from sodium bicarbonate solution. The absence of a carboxylic acid group can also be deduced from its proton magnetic resonance spectrum. However, swietenolide reacts readily with dilute alkali in the cold, consuming one equivalent of alkali. On acidification of the resulting solution with dilute hydrochloric acid (but not with carbon dioxide) swietenolide is reformed. A lactone ring which is easily opened and closed is therefore present.

Analysis by the conventional titrimetric Zeisel procedure[44] shows that swietenolide contains one alkoxy group. This was identified as methoxyl by use of a Zeisel technique in which the alkyl iodide is determined in the gas phase by quantitative infrared measurement.[45]

On hydrolysis of swietenolide with aqueous-alcoholic alkali under reflux for five hours two equivalents of alkali are consumed. Acidification yields a crystalline acid, designated as swietic acid, $C_{26}H_{32}O_8$, m.p. 180-181°. Swietic acid does not contain methoxyl and titrates as a monobasic acid. On methylation with diazomethane it yields swietenolide. This clearly shows that swietenolide is the methyl ester of swietic acid. Like swietenolide, swietic acid rapidly absorbs water from the air giving a monohydrate. Solid swietic acid does not liberate carbon dioxide from aqueous sodium bicarbonate (presumably owing to its insolubility); however aqueous sodium bicarbonate readily extracts swietic acid from chloroform solution.

Swietic acid consumes two equivalents of alkali on standing with dilute aqueous-alcoholic alkali in the cold; it can be recovered unchanged on acidification. This indicates that the lactone ring in swietic acid, like that in swietenolide, is readily opened and closed.

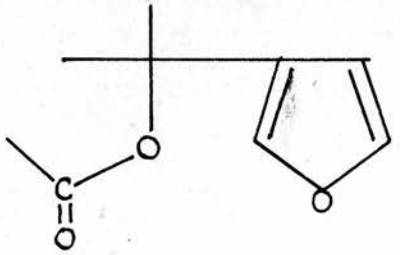
No condensation product of swietenolide with hydroxylamine, semicarbazide or 2,4-dinitrophenyl-hydrazine could be isolated. However swietenolide, swietic acid and hexahydroswietenolic acid (see below) all show an absorption peak near 284-288 mμ, ε = ca. 50, characteristic of an isolated carbonyl group. Further evidence for the presence of a carbonyl group in swietenolide is given below. Attempts to reduce the carbonyl group selectively with borohydride gave amorphous products.

Swietenolide does not reduce Fehling's solution or ammoniacal silver nitrate solution. This suggests that the carbonyl function

is a keto-group rather than an aldehyde-group. The absence of an aldehyde group is confirmed by the proton magnetic resonance spectrum.

The infrared spectra (Nujol Mull) of swietenolide and swietic acid both showed peaks at 3100 - 3200, ca. 1505, 1025, 875 and 800 cm^{-1}, suggesting the presence of a furan ring[46, 33c, 36c]. This is confirmed by the proton magnetic resonance spectrum which furthermore indicates that the furan ring is β-substituted as in limonin and columbin[34d].

The presence of a furan ring is also shown by the catalytic hydrogenation of swietenolide in glacial acetic acid in the presence of palladised charcoal. Three molecules of hydrogen are slowly consumed giving hexahydroswietenolic acid, $C_{27}H_{40}O_8$, m.p. 202 - 203°. This titrates as a monobasic acid and does not show the infrared peaks characteristic of the furan ring. The above behaviour is reminiscent of columbin[34], limonin[35], nomilin and obacunone[36] and suggests that hydrogenation involves hydrogenolysis of the lactone ring as well as saturation of the furan. Hydrogenolysis requires, in general, allylic or vinylic attachment to a double bond. In this case vinylic attachment can be excluded since the hydrolysis of the lactone ring is readily reversible. Therefore the most likely explanation is that swietenolide, like the above mentioned compounds contains the system:



The ultraviolet absorption spectra of swietenolide and swietic acid have ε = 13,500 at $\lambda_{max.}$ 209 mμ, while hexahydroswietenolic acid has ε = 6,500 at this wavelength. The difference between these extinctions is also consistent with the presence of a furan ring in swietenolide[33c, 34c, 36c]. A number of positive colour reactions for furan are described in the experimental section.

Hexahydroswietenolic acid, like swietenolide and swietic acid, is hygroscopic. Methylation with diazomethane gave a dimethyl ester which could not be crystallised. On hydrolysis of hexahydroswietenolic acid with 0.1N-sodium hydroxide, two equivalents of alkali were consumed, but the resulting dibasic acid also resisted attempted crystallisation.

Swietenolide could not be hydrogenated in presence of Raney nickel catalyst. With Adam's catalyst it absorbed 3.6 molecules of hydrogen giving a product which could not be crystallised.

It was noted above that hexahydroswietenolic acid has strong end-absorption (apparent maximum at 208 mμ, ε = 6500) and that swietenolide itself absorbs more intensely in this region than would be expected from a furan ring. Furthermore, hexahydroswietenolic acid gives a yellow colour with tetranitromethane. This suggests that hexahydroswietenolic acid and swietenolide contain at least one ethylenic double bond. The ultraviolet and infrared spectra of these compounds exclude the presence of an αβ-unsaturated ketone function, but the possibility of conjugation with one of the carboxyl functions must be seriously considered. Although most αβ-unsaturated esters, lactones and acids have $\varepsilon_{max.} > 10,000$, some compounds containing these systems have somewhat lower

extinctions[47]. However the presence of an αβ-unsaturated carboxyl system in swietenolide was excluded in the following way.

Reduction of swietenolide with lithium aluminium hydride gave a small yield of a crystalline product; an attempt to obtain more of this by repeating the reduction under apparently identical conditions gave only amorphous material. The crystalline compound did not absorb in the carbonyl region of the infrared and its analysis was in good agreement with the formula $C_{26}H_{40}O_7$ expected on the basis of complete reduction of the ester, lactone and ketone functions. It showed log ε = 4.28 at 211-212 mμ (apparent maximum). The presence of an αβ-unsaturated carboxyl system is therefore excluded, as in this case the lithium aluminium hydride reduction product would be expected to absorb much less intensely. The light absorption of hexahydroswietenolic acid is therefore probably due to a tetrasubstituted double bond[48]; the extinctions of swietenolide and the lithium aluminium hydride reduction product also include a contribution due to the furan ring.

Swietenolide does not give Legal test nor does it reduce ammoniacal silver nitrate, but it readily reduces Tollens' reagent.[49] However an alkaline solution of swietenolide which has been allowed to stand for ca 20 minutes to allow hydrolysis of the lactone ring no longer reduces Tollens' reagent. Hexahydroswietenolic acid does not reduce Tollens' reagent, but its amorphous methyl ester does. This suggests that the lactonic carboxyl group is intimately associated with the reduction of Tollens' reagent and, to account for the reducing power, this group must be in close proximity to some other function, perhaps a βγ-double bond. (It is interesting

to note that crotonic acid and fumaric acid do not reduce Tollens' reagent while their ethyl esters do).

It is possible that the lactone carboxyl is also involved in the chromophoric system responsible for the faint pink colour which swietenolide gives with alkali; it is tempting to speculate that the fairly rapid fading of this colour is due to the hydrolysis of the lactone ring.

The carbomethoxy group, the lactone ring, the keto group and the furan ring account for six of the eight oxygen atoms in the molecule of swietenolide. As a Zerewitinoff determination gave 2.3 active hydrogens per molecule, it seemed probable that the remaining oxygen atoms are present as hydroxyl groups. This is confirmed by infrared evidence. In chloroform solution, carefully dried swietenolide showed a sharp maximum at 3628 cm^{-1}, $\varepsilon = 169$, an inflection at 3610 cm^{-1}, $\varepsilon = 89$, and a broad maximum at 3535 cm^{-1}, $\varepsilon = 57$. This is in good agreement with the presence of two hydroxyl groups, one of which is unassociated while the other is partly hydrogen-bonded.

To obtain further information about the hydroxyl groups, oxidative experiments were carried out. Hexahydroswietenolic acid, with which there is no danger of complications due to oxidation of the furan ring, was investigated first. Oxidation of this compound with ca. 0.07 N-chromium trioxide in acetic acid was very rapid and gave no useful quantitative information, although under the same conditions the oxidation of menthol was very slow after the rapid uptake of one atom of "oxygen". With ca. 0.07 N-potassium dichromate (three atoms of "oxygen" per molecule of hexahydroswietenolic acid) in acetic acid, hexahydroswietenolic acid was oxidised more

slowly but no sharp break was observed in a graph of the uptake. Swietenolide behaved in a very similar way under the same conditions.

Preparative experiments on the oxidation of swietenolide with potassium dichromate in acetic acid indicated that a crystalline neutral product was produced. When the oxidation was stopped after one atom of "oxygen" had been consumed, the crystalline product was obtained in ca. 45% yield after purification. It is therefore probable (though not entirely certain) that the formation of the crystalline compound involves the consumption of one atom of "oxygen". The analysis of the compound, which has been called dehydroswietenolide, is in good agreement with the formula $C_{27}H_{32}O_8$. Dehydroswietenolide was also obtained when swietenolide was oxidised with chromium trioxide in pyridine or with sodium hypobromite. The latter oxidising agent also gave an amorphous acidic product which yielded dehydroswietenolide on treatment with diazomethane.

Dehydroswietenolide reduces Tollens' reagent and ammoniacal silver nitrate solution. It does not give a colour with ferric chloride. It still contains a furan ring (peaks at 3160, 1507, 1023 and 870 cm^{-1}). The infrared spectrum in dry chloroform shows a fairly sharp band at 3597 cm^{-1}, $\varepsilon = 80$, and a broad maximum at 3525 cm^{-1}, $\varepsilon = 51$. Comparison of this with the infrared spectrum of swietenolide indicates that the formation of dehydroswietenolide involves oxidation of the "unassociated" hydroxyl group in swietenolide, presumably to a keto group. The presence of an additional carbonyl group in dehydroswietenolide is confirmed by other evidence. Thus the peak at 1710 cm^{-1} in the spectrum of dehydroswietenolide in

carbon tetrachloride solution is more intense (relative to the other carbonyl peaks) than the corresponding peak (1721 cm^{-1}) in the spectrum of swietenolide. Furthermore in the ultraviolet spectrum dehydroswietenolide has $\varepsilon_{max.}$ = 102 at 288-289 mμ, compared with $\varepsilon_{max.}$ = 54 at 288 mμ for swietenolide.

Dehydroswietenolide, unlike swietenolide, swietic acid and hexahydroswietenolic acid, is not hygroscopic. It seems likely that the hygroscopic nature of swietenolide and the above derivatives can be ascribed to the "unassociated" hydroxyl group revealed in the infrared spectrum of swietenolide in dry chloroform; in dehydroswietenolide this hydroxyl group is absent.

All the above evidence supports the view that swietenolide contains two hydroxyl groups, one of which is secondary. The nature of the second hydroxyl group is not exactly known. As will be seen later, both the hydroxyl groups seem to be appreciably sterically hindered.

Detailed examination of the ultraviolet absorption spectrum of dehydroswietenolide gave very interesting results. When the compound was dissolved in ethanol which had been acidified with dilute sulphuric acid, it showed $\lambda_{max.}$ 288-289 mμ, log ε = 2.01 and end absorption log ε = 4.22 at 210 mμ. These values were unchanged after the solution had been allowed to stand for 24 hours. However, when the compound was dissolved in unacidified ethanol, the maximum at ca. 288 mμ was appreciably higher (log ε = 2.84) and on standing it increased further in intensity (log ε = 3.39 after 24 hours). When a fresh solution in ethanol was treated with a drop of dilute alkali, the spectrum immediately showed intense absorption (log $\varepsilon_{max.}$ = 4.54) at 288-289 mμ, as well

as end absorption, log ε = 4.04 at 220 mμ. These values were unchanged after 24 hours. On acidification of the alkaline solution the maximum at 288 mμ was shifted to 262-264 mμ and decreased in intensity (log ε = 4.38). This behaviour is strongly reminiscent of enolised β-diketones[50]. These show a peak characteristic of the enolate ion in alkaline solution; the free enol which is produced on acidification absorbs at a lower wavelength and with somewhat smaller intensity. The above results can therefore be explained by the assumption that dehydroswietenolide is a β-diketone which enolises on addition of alkali. It is however very surprising that this diketone does not enolise spontaneously in acidified ethanol, especially as the stability of the spectrum of the enol shows that it does not revert to the diketone in this solvent. The possibility that dehydroswietenolide contains a marked β-diketone system which is only liberated under mildly alkaline conditions cannot be entirely excluded.

Attempts to isolate the above enol gave an amorphous product, $\lambda_{max.}$ 286-288 mμ, log ε = 4.46 which, on methylation with diazomethane gave a non-crystalline compound. The latter showed $\lambda_{max.}$ 262-264 mμ, log ε = 4.26: this is in good agreement with its formulation as the methyl ether of an enolised β-diketone.

If dehydroswietenolide is a β-diketone, swietenolide itself must be a β-hydroxyketone and therefore would be expected to eliminate water readily. However attempts at dehydration gave unpromising results. With thionyl chloride in pyridine at room temperature for 18 hours swietenolide yielded two crystalline compounds in a very small yield, namely (a) a dark-red compound m.p. 240°, and (b) a colourless compound m.p. 115°, which was

only obtained in the first of two experiments carried out under apparently identical conditions. In both cases the quantity of material obtained was insufficient for a satisfactory analysis.

The dark red compound contained nitrogen indicating that pyridine had been incorporated into the molecule. A blank experiment verified that it was not produced in the absence of swietenolide. The infrared spectrum (Nujol) of the compound showed three peaks in the carbonyl region (1745, 1707 and 1685 cm^{-1}) and three strong peaks at 1582, 1560 and 1540 cm^{-1}. In the ultraviolet it had three strong absorption peaks of roughly equal intensity ($E^{1\%}_{1\ cm}$ = 2.24, 2.28 and 2.36) at 494, 295 and 260 mμ respectively.

The colourless compound (b) showed $\lambda_{max.}$ 263-265 mμ, log ε = 4.10, suggesting conjugation. However no peak corresponding to αβ-unsaturated ketone (1685-1665 cm^{-1}) was found in an infrared spectrum done on less than 1 mg. of the compound in chloroform solution.

Because of the low yields obtained neither of these compounds was further investigated. No crystalline products were obtained when the above dehydration was carried out with a 15 minutes reaction time.

Although the above attempts at dehydration did not give satisfactory results, dehydration did occur when swietenolide was boiled under reflux with acetic anhydride and sodium acetate. A crystalline monoacetate (A) was obtained which analysed satisfactorily for $C_{29}H_{34}O_8$, i.e. swietenolide monoacetate minus water. In agreement with the view that both of the hydroxyl groups in swietenolide had reacted, the above acetate did not show any absorption in the hydroxyl stretching region of the infrared.

Before this acetate is further discussed, other acetylation products which are unfortunately less well characterised must be considered.

Attempted acetylation of swietenolide with acetic anhydride-perchloric acid led to the recovery of the starting material. This suggests that both of the hydroxyl groups in swietenolide are relatively hindered. Swietenolide was also recovered from an attempted tosylation with p-toluenesulphonyl chloride in pyridine at room temperature. When swietenolide was heated on the water bath for 30 minutes with acetic anhydride in pyridine, an amorphous acetate (B) was obtained. Acetylation with acetic anhydride-sodium acetate on the water bath for one hour gave an acetate (C), which also could not be crystallised. Acetyl analysis shows that both (B) and (C) contain one acetyl group and infrared spectra confirm that one of the hydroxyl groups of swietenolide remains unacetylated. The infrared spectra of (B) and (C) are very similar and the two products are possibly identical. In the ultraviolet both show end absorption, log ε = ca. 4.08 at 215 mμ and a peak at 280 mμ, log ε = ca. 3.2 which may be due to impurity (e.g. ca. 10% of the acetate (A)).

Swietenolide gave two further amorphous acetylation products (D) and (E), with zinc chloride-acetic anhydride and acetic acid-trifluoroacetic anhydride respectively. Analysis showed that these are both diacetates and identity of their infrared spectra suggests that they are probably identical. The infrared spectra of (D) and (E), unlike those of swietenolide and of (C) and (D) show an intense peak at 1685 cm^{-1} (conjugated carbonyl). The presence of an extended conjugated system in (D) and (E) is

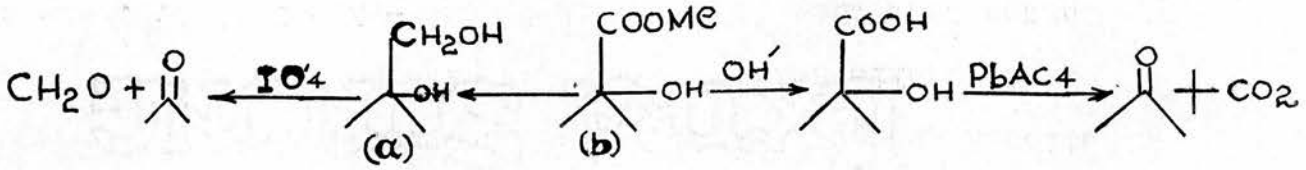
supported by their ultraviolet spectra which have $\lambda_{max.}$ 271 mμ, log ε = 4.1 as well as end absorption, log ε = 3.97 at 215 mμ. The exact nature of this conjugated system is uncertain.

The ultraviolet and infrared spectra of the crystalline acetate (A) suggest that this compound contains a similar conjugated system ($\lambda_{max.}$ 276 mμ, log ε = 4.18; strong peak at 1685 cm^{-1} in Nujol Mull). However (D) and (E) show a pronounced minimum at ca. 240 mμ (log ε = 3.6) while the crystalline acetate (A) has only a shallow minimum ($\lambda_{min.}$ 250 mμ, log ε = 3.97) and shows a shoulder at ca. 235 mμ. This suggests that the crystalline acetate (A) contains additional conjugation presumably related to the elimination involved in its formation.

The above results provide additional evidence for the presence of two hydroxyl groups in swietenolide and lend some support to the view that one of these is situated β with respect to the keto group.

Further evidence concerning the relative position of the functional groups will now be considered. Swietenolide and hexahydroswietenolic acid do not react with sodium periodate which indicates that they do not contain an α-glycol system. In confirmation of this, swietenolide and hexahydroswietenolic acid react only slowly with lead tetraacetate; this also shows that hexahydroswietenolic acid is not an α-hydroxy acid. However swietic acid consumed lead tetraacetate much more rapidly, the rate of reaction being slightly faster than that of 1-hydroxycyclohexane carboxylic acid. This suggests that swietic acid is an α-hydroxy acid and one of the hydroxyls in swietenolide must therefore be α to the carbomethoxy group. Confirmation of this

was obtained from the observation that the amorphous lithium aluminium hydride reduction product of swietenolide consumed 1.4 molecule of periodate, yielding formaldehyde which was distilled from the reaction mixture and detected by its colour reaction with chromotropic acid.[51] The formation of formaldehyde indicates the presence of the system (a) presumably formed by reduction of (b). The system (b) would also account for the internal hydrogen bonding observed in the infrared spectra of swietenolide and dehydroswietenolide.



Swietic acid remains unchanged on boiling with aqueous alcoholic sulphuric acid. This shows that it is not a β-keto acid and that neither of the two hydroxyl groups is in a position suitable for lactonisation.

The infrared spectrum of swietenolide in carbon tetrachloride shows three peaks in the carbonyl region which can be tentatively assigned as follows: 1751 cm^{-1} (6 ring lactone), 1740 cm^{-1} (COOMe), 1721 cm^{-1} (side chain or 6 ring ketone). However, detailed interpretation of the modifications undergone by these peaks in derivatives of swietenolide will not be attempted. Swietenolide is a novel compound and it is well known that the characteristic frequencies of groups vary somewhat from one class of natural products to another[52]. Furthermore, complications due

to interactions between the many functional groups in swietenolide are not unlikely.

For reference purposes, the most important bands in the infrared spectra of swietenolide and its derivatives, together with some tentative structural assignments, are given in an appendix. It is interesting to note that the bands in the carbonyl region are usually better resolved in carbon tetrachloride solution than in chloroform solution. This seems to be largely due to the fact that the band at ca. 1750 cm^{-1} in carbon tetrachloride is shifted to lower frequencies in chloroform. Such shifts are not uncommon.[53]

DEGRADATIVE EXPERIMENTS ON SWIETENOLIDE.

Attempts to obtain a clue to the carbon skeleton of swietenolide by dehydrogenation met with considerable difficulties. Direct selenium dehydrogenation of swietenolide in a sealed tube at 320-330° for 25 hours gave a product which was separated into a neutral fraction and a phenolic fraction by extraction with alkali. Treatment of the distilled neutral fraction with alcohol gave a very small amount of a crystalline product, m.p. 185-187°. Mass spectrometric molecular weight determination, kindly carried out by Dr. W. Sneddon and Dr. R.I. Reid gave molecular weight ca. 510. The compound showed $\lambda_{max.}$ 294 mμ, log ε 3.84; 285 mμ, log ε 3.84; 258 mμ, log ε 4.35 and 210 mμ (apparent maximum) log ε 4.87. $\lambda_{min.}$ 288 mμ, log ε 3.81; 276 mμ, log ε 3.72 and 237 mμ, log ε 4.00. This suggests that the compound is aromatic but it is not certain whether it is a hydrocarbon. With trinitrobenzene the mother liquor from the crystalline product yielded a very small quantity of a red crystalline trinitrobenzene adduct. Both of the above compounds were obtained in quantities insufficient for further investigation. The phenolic fraction which showed strong blue fluorescence in alkaline solution, did not yield any crystalline product although it coupled with benzenediazonium chloride giving a red precipitate.

In view of these unpromising results, attempts were made to dehydrogenate derivatives of swietenolide in which the ketonic group had been reduced. However, dehydrogenation of a crude potassium borohydride reduction product and of a crude lithium

aluminium hydride reduction product also gave poor results, no crystalline product being obtained. It is interesting to note, however, that in these cases the alkaline extracts of the etherial solutions of the crude dehydrogenation products did not show any fluorescence and did not yield any material which coupled with benzenediazonium chloride. It therefore seems likely that the formation of the crude phenolic material obtained from swietenolide is related to the presence of a six-membered cyclic ketone function in the molecule of swietenolide.

The above results suggest that swietenolide contains a structural unit which does not dehydrogenate smoothly. Swietenolide was therefore fused with potassium hydroxide in the hope that preliminary degradation would give material which would be more susceptible to dehydrogenation.

Fusion of swietenolide with potassium hydroxide as described in the experimental section gave a small quantity of a volatile oil and a non-volatile residue. The volatile oil had a characteristic terpenoid odour and gas chromatography showed that it contained at least three components, none of which could be identified. An infrared spectrum of the oil showed peaks at 1710 and 1685 cm^{-1} which indicated that ketonic material was present. This was confirmed by the formation of a precipitate with 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid but the yield of this was too small to allow purification.

The non-volatile product from the potassium hydroxide fusion was subjected to dehydrogenation with selenium and the product was again separated into a neutral fraction and a phenolic fraction.

The latter gave red precipitate with benzenediazonium chloride but no crystalline phenol could be isolated. The former yielded an orange-yellow trinitrobenzene adduct, m.p. 150-152°, the analysis of which was in agreement with that of a tri- or tetra-methylnaphthalene derivative (ethyl methylnaphthalenes etc. would, of course, also satisfy the analytical data). The spectrum of the hydrocarbon (Obtained by subtracting the spectrum of trinitrobenzene from that of the adduct [54]) had λ_{max} 327 mμ, log ε 2.98; 283 mμ, log ε 3.73; 231 mμ, log ε 4.88. This absorption is similar to that shown by alkyl naphthalenes.[55] An attempt to obtain the hydrocarbon by decomposition of 30 mg. of the adduct on alumina was unfortunately unsuccessful, only traces of material having $\lambda_{max.}$ 327 mμ, 287-288 mμ and 230 mμ being obtained. This failure may be ascribed to the unsuspected volatility of the hydrocarbon.

The neutral fraction from a second dehydrogenation under the same conditions yielded an orange crystalline picrate. After several crystallisations this had m.p. 130-132° and analysed satisfactorily for the picrate of a trimethyl naphthalene. Unfortunately the quantity obtained was insufficient for the isolation of the hydrocarbon to be attempted. However material (m.p. ca. 124°; satisfactory analysis for the picrate of a trimethyl naphthalene) from the combined mother liquors, was decomposed with sodium carbonate giving an oily product. Gas chromatography (kindly carried out by Dr. G. Eglinton) showed that this contained at least two major components. Its ultraviolet spectrum ($\lambda_{max.}$ 324 mμ, log ε 2.91; 283 mμ, log ε 3.81 and 230 mμ, log ε 4.97) was characteristic of alkyl naphthalenes.

These results indicate that dehydrogenation of the non-volatile product from the potassium hydroxide fusion of swietenolide yields alkyl naphthalenes. However in view of the difficulty of separating hydrocarbons by crystallisation of their adducts, it seems unsafe to assume that the picrate, m.p. 130-132°, and the trinitrobenzene derivative, m.p. 150-152° are pure. It is also uncertain if both are derived from the same hydrocarbon. Further investigation was unfortunately precluded by a shortage of swietenolide.

In the early stages of this work an attempt was made to aromatise swietenolide by treatment with 50% sulphuric acid for 20 hours at 50°. This gave a very small amount of crystalline material which did not give a colour with ferric chloride and did not couple with benzenediazonium chloride, showing that a phenolic system was absent. Furthermore the ultraviolet and infrared spectra indicated the absence of an aromatic ring. The infrared spectrum had two distinct peaks in the carbonyl region (one of these must be due to carbomethoxy as the compound still contains methoxyl) and also showed that the furan ring has been destroyed. The compound was not further investigated because of its very poor yield.

THE CHEMISTRY OF SWIETENINE

During the course of the work on swietenolide, a few experiments were carried out with the non-bitter principle, swietenine, although a systematic investigation was not possible because of a shortage of material. The results of these experiments are recorded in the present section.

Swietenine has been previously investigated by the author in collaboration with Guha Sircar[25] and later with Chatterjee.[26] The results of these studies can be briefly summarised as follows. Swietenine is a neutral, colourless, crystalline compound, m.p. 260° (dec.), which does not reduce Fehling's solution or ammoniacal silver nitrate but reduces Tollens' reagent. Analyses, molecular weight determination by the Rast method and saponification data suggested the molecular formula $C_{18}H_{24}O_5$. Saponification gave an amorphous hydroxy-acid, swietenic acid, which on treatment with dilute acid yielded a crystalline neutral compound isoswietenine. The presence of a lactone ring was therefore postulated and this was considered to be αβ-unsaturated on the basis of the ultraviolet spectrum. The ultraviolet spectrum also suggested that an unconjugated keto group was present and this was confirmed by the formation of a 2,4-dinitrophenylhydrazone. The infrared spectrum and acetylation experiments indicated that a hydroxyl group was present. Zeisel analysis showed that the compound contained a methoxyl group, although the methoxyl content was surprisingly low. Selenium dehydrogenation gave an aromatic hydrocarbon, $C_{16}H_{20}$, which gave a trinitrobenzene adduct, m.p. 152-153°, and which was characterised as a polyalkylnaphthalene

by its ultraviolet absorption spectrum. Caustic fusion of swietenine gave tiglic acid.

The present reinvestigation was prompted by the fact that a determination of the molecular weight of swietenine by the X-ray method, which was kindly carried out by Dr. C.A. Beevers, gave molecular weight 565.

This molecular weight is in agreement with the methoxyl content and indicates that the molecule of swietenine is considerably larger than had been previously supposed. In view of the fact that no satisfactory crystalline derivatives of swietenine have been prepared, it seems unwise to decide on a molecular formula. However the formula $C_{32}H_{42}O_9$ which is in agreement with the analytical data and the molecular weight determination may be considered as a possibility.

Spectroscopic observations suggest that swietenine is probably closely related to swietenolide. Bands at 3160, 1506, 1030, 877 cm^{-1} in the infrared spectrum (Nujol) suggest that swietenine contains a furan ring and the proton magnetic resonance spectrum shows that this is a β-substituted, as in swietenolide. In dry chloroform, swietenine has bands at 3605 cm^{-1}, ε = ca. 58 and 3540 cm^{-1}, ε = ca. 72; which may be ascribed to a partly hydrogen-bonded hydroxyl group; similar bands are observed in the spectrum of swietenolide and dehydroswietenolide. The presence of a hydroxyl group is confirmed by a Zerewitinoff determination which gave 1.3 atoms of active hydrogen. It is interesting to note that unlike swietenolide but like dehydroswietenolide, swietenine is not hygroscopic; this may be associated with the

absence of the unassociated hydroxyl group present in swietenolide. The absence in swietenine of one of the two hydroxyl groups of swietenolide, is also indicated by the fact that on oxidation with potassium dichromate in acetic acid, swietenine consumes 'oxygen' much more slowly than swietenolide.

In carbon tetrachloride, swietenine shows four peaks in the carbonyl region. By analogy with swietenolide, three of these may be tentatively assigned as follows: 1752 cm^{-1} (six ring lactone; 1743 or 1734 cm^{-1} (carbomethoxy) and 1716 cm^{-1} (side chain or six ring ketone). These functions together with the furan ring and the hydroxyl group account for the seven of the nine oxygens in swietenine. On hydrolysis with dilute sodium hydroxide, swietenine consumes 2.5 equivalents of alkali giving tiglic acid and an amorphous product ('swietenic acid'), equivalent weight 443, which contains only 1.42% methoxyl. This supports the presence of a carbomethoxy group and a lactone ring and suggests that the fourth carbonyl peak (1743 or 1734 cm^{-1}) in the infrared spectrum of swietenine and the two remaining oxygens may be ascribed to a tiglate ester group. The presence of an acyl group is also confirmed by a conventional analytical 'acetyl' determination. It is interesting to note that swietenine contains five C-methyl groups while swietenolide only contains three; the two additional C-methyl groups may be ascribed to the tiglate ester function.

Attempts to crystallise 'swietenic acid' and to repeat the preparation of '<u>iso</u>swietenine' were unsuccessful. It is possible that in the earlier work hydrolysis was incomplete and that '<u>iso</u>swietenine' may have been unchanged swietenine.

The above results raise the interesting possibility that swietenine might be a tiglate ester of swietenolide. However, this is unlikely for several reasons. Firstly, methylation of the amorphous product obtained on hydrolysis of swietenine did not give swietenolide. Secondly, attempted tiglylation of swietenolide with tiglyl chloride in pyridine did not give swietenine, although this would have been easy to isolate because of its insolubility. Thirdly if swietenolide is $C_{27}H_{34}O_8$, its tiglate ester will have the formula $C_{32}H_{40}O_9$ and this requires a carbon content which is somewhat higher than that of swietenolide (see experimental section). Fourthly swietenolide and swietenine show certain interesting differences which are described below.

Nomilin, a β-acetoxy lactone which was discussed in the introductory section, gives the corresponding αβ-unsaturated lactone, obacunone, on boiling with dry γ-picoline. An attempt to remove the tiglyl group of swietenine in a similar way gave an amorphous acidic product (equivalent weight, 525) with a low methoxyl content (0.3%). On methylation with diazomethane this gave swietenine. The γ-picoline treatment therefore removes the ester methoxyl with the formation of the corresponding acid. Surprisingly, swietenolide could be recovered unchanged after treatment with γ-picoline under the same conditions. Methyl cinnamate and ethyl-m-nitrobenzoate, two esters which are fairly easily hydrolysed, were also recovered unchanged after boiling with γ-picoline. The above reaction of swietenine therefore seems most remarkable.

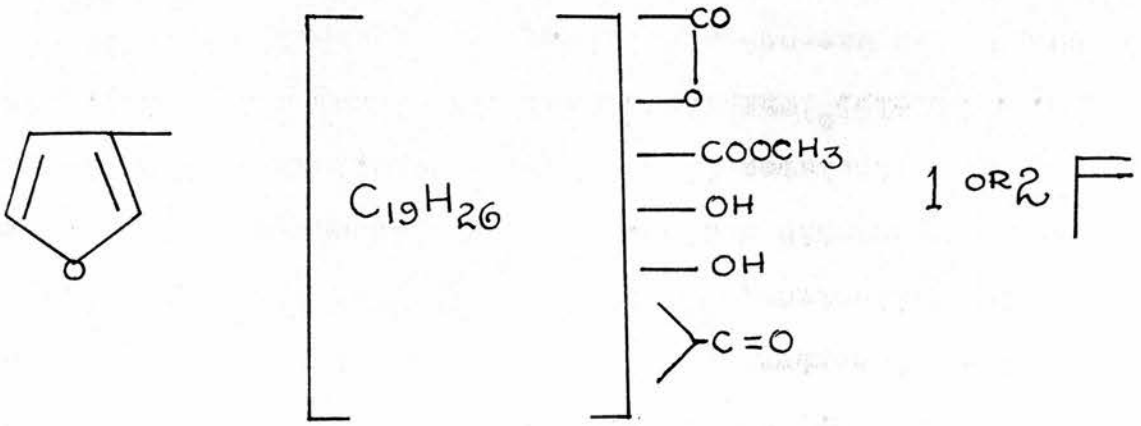
Swietenine and swietenolide also differ in their behaviour on

dehydrogenation. The earlier work on swietenine showed that this gave a good yield of aromatic hydrocarbon on direct dehydrogenation with selenium. However as indicated in the previous section, swietenolide gives an extremely poor yield under these conditions, although it gives better results if the dehydrogenation is preceded by caustic fusion. The trinitrobenzene adduct, m.p. 150-152°, which was isolated in the latter case, may be identical with that (m.p. 152-153°) previously obtained from swietenine, but direct comparison was not possible.

The above results suggest that swietenine is the tiglate ester of a compound related to swietenolide (perhaps a dihydroswietenolide). However it is clear that the above suppositions about the molecular formula and the nature of the functional groups require further confirmation before they can be entirely accepted.

DISCUSSION

The evidence which has been detailed in the previous sections shows that swietenolide contains a lactone ring, a carbomethoxy group, a ketocarbonyl group, a β-substituted furan ring and two hydroxyl functions, one of which is partly hydrogen-bonded. If it is assumed that the molecular formula $C_{27}H_{34}O_8$ for swietenolide is correct, then eleven 'double bond equivalents' must be present. Seven of these are accounted for by the above functional groups. As it is known that at least one ethylenic double bond is present, the four remaining double bond equivalents may be composed of one ethylenic linkage with a tricyclic carbon skeleton or two ethylenic linkages with a bicyclic carbon system. The formation of a naphthalene by selenium dehydrogenation of the potassium hydroxide fusion product of swietenolide is of interest in this connection, but does not provide unambiguous evidence concerning the number of rings in swietenolide, as ring opening may have occurred during the caustic fusion. The structural position may thus be summarised in the expression (XL).

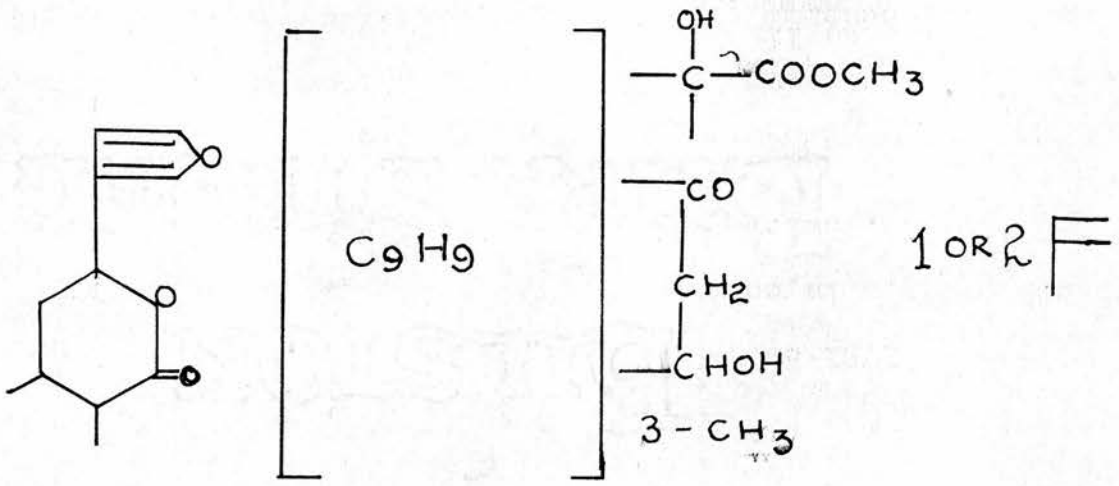


XL

It is clear from the above that swietenolide belongs to the group of furanoid bitter principles having a C_{26} skeleton which was discussed in the introduction. Thus the functional groups of limonin, the most important member of this group, are similar to those of swietenolide except that limonin has a lactone ring instead of the carbomethoxy group and two oxide rings instead of the hydroxyl groups. Furthermore, like the related but simpler compound columbin, both limonin and swietenolide contain a lactone ring which is readily hydrogenolysed. Analogy with limonin and columbin therefore suggests that the lactone ring in swietenolide is also allylic to the furan ring. Furthermore the lactone ring in swietenolide is probably six-membered, despite the rather high frequency (1751 cm^{-1}) of its infrared band, as the six-membered lactone rings in columbin and limonin also absorb in this region. Like limonin, swietenolide contains three C-methyl groups and both compounds give naphthalenes on caustic fusion followed by dehydrogenation.

It is also likely that swietenolide and limonin have certain stereochemical similarities. Thus both compounds have high negative rotations (swietenolide, -126° (chloroform); limonin, -128° (acetone)) while the rotations of the derived hexahydroacids are much less negative (hexahydroswietenolic acid, -46° (chloroform); hexahydrolimoninic acid, -6.5° (acetone)).[35c] A similar shift is observed when the rotations of the two parent compounds are determined in alkaline solution (swietenolide, -44°; limonin, + 32.6; in both 0.25N-sodium hydroxide in 50% aqueous ethanol).[56]

Columbin contains an α-hydroxy lactone ring in addition to the lactone ring which is hydrogenolysed. It is therefore interesting to note that, in swietenolide, one of the hydroxyl groups (probably the one which is partly hydrogen-bonded) appears to be α to the carbomethoxy group. As indicated earlier, it is probable that the hydroxyl group which is not hydrogen-bonded is situated β to the keto group although further evidence on this point is desirable. The expression (XL) for the structure of swietenolide can therefore be elaborated to (XLI)



XLI

The relation between swietenolide and swietenine has already been discussed. It is clear that both of these compounds provide structural problems of the greatest interest and it may be hoped that these will appear less formidable once the structure of limonin has been elucidated.

EXPERIMENTAL

General

All melting points are uncorrected and were determined in an oil bath unless otherwise stated.

For chromatography the fractional elution technique was invariably employed. Alumina (Spence Type H) was washed with dilute nitric acid followed by boiling distilled water and was then washed with methanol as described by Lederer[57], reactivated at 200° and standardised according to Brockmann[58]. The material to be purified was dissolved in benzene or benzene-light petroleum, adsorbed on 20 to 40 times its weight of alumina and eluted with benzene, benzene containing increasing proportion of ether, ether and finally ether containing increasing proportion of ethanol.

In volumetric determinations of alkali or oxidant uptakes, blank determinations on the solvent were always carried out.

Solvents were evaporated under reduced pressure on a water bath below 50° unless otherwise stated.

Isolation of Swietenine and Swietenolide

The decorticated, dried and crushed seeds of Swietenia macrophylla (1 Kg.) were defatted by Soxhlet extraction with petroleum ether (40-60°) and the residue was extracted with chloroform. After concentration, the extract was precipitated with petroleum ether, giving a yellowish gummy mass (yield ca. 7% calculated on the basis of dried decorticated seeds). The crude gummy product (ca. 30 g.) was warmed with ethanol (200 c.c.) when

crude swietenine separated out, which was filtered from the mother liquor (A). The swietenine was purified by crystallisation from acetic acid or by chromatography over alumina and then had m.p. 260° (dec.), $[\alpha]_D^{20}$ - 168° (c, 1.99 in chloroform), yield 1%. Found (in a sample dried to constant weight in high vacuo at 100°): C, 66.98, 67.08; H, 7.18, 7.19; Acetyl, 10.51. $C_{32}H_{42}O_9$ requires C, 67.35; H, 7.42; one acetyl, 7.54; $C_{32}H_{40}O_9$ requires C, 67.59; H, 7.09; one acetyl, 7.56%.

The alcohol mother liquor (A) was shaken with saturated barium hydroxide solution (40 c.c.) and then filtered. On acidification with ice-cold dilute hydrochloric acid the filtrate gave a light yellow flocculent precipitate, m.p. ca. 120°. Three crystallisations from ethyl acetate gave crystalline swietenolide, m.p. 214-216°. This was further purified (yield, ca. 0.5 g) by crystallisation from aqueous ethanol or chromatography over alumina (grade III) and then had m.p. 220° (dec.), $[\alpha]_D^{19}$ - 126° (c, 2.09 in chloroform), $[\alpha]_D^{19}$ - 114° (c, 1.28 in methanol), $[\alpha]_D^{19}$ - 44° (c, 2.03 in 0.25N sodium hydroxide in 50% aqueous ethanol). Drying under reduced pressure at 100° for 3-4 hours gave anhydrous swietenolide, which had the same melting point. On exposure to the atmosphere this rapidly rehydrated to swietenolide hydrate.

X-ray molecular weight determinations

These were kindly done by Dr. C.A. Beevers who reported as follows:

Swietenolide

The crystals are monoclinic (pseudo tetragonal) with axial dimensions a = 11.69 Å, b = 8.85 Å, c = 11.73 Å and a mono-

clinic angle $\beta = 90.0^{\circ}$. The volume of this cell is 1214 $\AA^3$. The density (by flotation) was 1.340 gm./c.c. so that the weight of the cell converted (on the molecular wt. scale) is 980.

The space group is P_{2_1} or P_{2_1}/a so that the number of molecules per cell is 2 or 4. Hence the molecular weight is 490 or 245.

Swietenine

The crystals are clear tablets with a parallel extinction. The unit cell dimensions were found from an oscillation and a Weissenberg photograph which gave axial lengths of 15.92 x 9.85 x 18.38 A (± 1% each) the lattice being orthorhombic. Hence the cell volume is 2883 $\AA$. Taking the number of molecules per cell as 4 and the density as 1.301, we obtain a molecular weight of 565 ± 20.

C-methyl Determinations (Kuhn-Roth).

Swietenolide: (anhydrous) 3.58, 4.40 and 4.59% (Weiler and Strauss); 3.38, 1.85% (Pascher); 7.83% (J.M.L. Cameron, Glasgow).

Swietenine: 7.27% (Weiler and Strauss); 4.89% (Pascher); 11.61% (J.M.L. Cameron, Glasgow).

Mr. J.M.L. Cameron found that both substances were rather insoluble in the oxidation mixture and suggested that the low and variable results obtained by the other analysts were due to this. In his determinations the substances were dissolved in a small amount of concentrated sulphuric acid prior to addition of the oxidation mixture. His results suggest the presence of 2.5, i.e. 3 C-methyl groups in swietenolide and 4.3, i.e. 5 C-methyl groups in swietenine.

Methoxy Determinations.

Values marked (A) and (P) were determined by the conventional titrimetric Zeisel procedure by the authors and Pascher respectively. Values marked (I) were kindly determined by J.L. Duncan using a spectroscopic Zeisel technique[45]; this showed that the alkyl groups were methoxyl groups.

Swietenolide (hydrated): 6.42, 6.32% (A); 5.81% (P); 5.92% (I).
$C_{27}H_{34}O_8$ requires 6.16% on the basis of one methoxy group.

Swietenine: 5.36, 5.37% (I); 5.07% (P).
$C_{32}H_{42}O_9$ requires 5.43% on the basis of one methoxyl group.

Active Hydrogen Determinations.

Swietenolide (anhydrous): 0.465%.
$C_{27}H_{34}O_8$ requires 0.412% on the basis of two active hydrogens.

Swietenine (dried): 0.236%.
$C_{32}H_{42}O_9$ requires 0.175% on the basis of one active hydrogen.

Alkaline Hydrolysis of Swietenolide.

(a) With 0.05N-sodium hydroxide solution at room temperature.

Swietenolide hydrate (0.0557 g.), ethanol (5 c.c.) and aqueous sodium hydroxide solution (0.1N, 5 c.c.) were allowed to stand for 15 minutes at room temperature. Back titration with 0.1N-sulphuric acid using phenolphthalein (1.13 c.c. 0.1N-alkali consumed), gave equivalent weight, 493; $C_{27}H_{34}O_8.H_2O$ requires 504. The

alcohol was then removed under reduced pressure at 35° and acidification with ice-cold dilute hydrochloric acid afforded a precipitate which from aqueous alcohol gave swietenolide (ca. 50 mg.) identified by its mixed m.p. Under similar conditions back-titration after one hour and five hours gave equivalent weights of 494 and 420 respectively. In each case swietenolide was recovered (yields: 85% and 50% respectively).

(b) With 0.1N-sodium hydroxide solution for five hours under reflux. The preparation of swietic acid.

Swietenolide hydrate (0.1685 g.) in ethanol (5 c.c.) and 0.2N-sodium hydroxide (5 c.c.) was refluxed for five hours. Back titration with 0.1N-sulphuric acid using phenolphthalein (6.50 c.c. 0.1N-alkali consumed), gave equivalent weight 259, $C_{27}H_{34}O_8$, H_2O requires 252 (one lactone ring and one ester grouping). Alcohol was then removed in vacuo at 35°. Acidification with ice-cold dilute hydrochloric acid gave a brownish precipitate (0.16 g.), m.p. 150-160°. This was dissolved in chloroform and then extracted with sodium bicarbonate solution. The bicarbonate extract was acidified with ice-cold dilute hydrochloric acid and extracted with chloroform, and the extract was dried and concentrated. Treatment with petroleum ether gave a light brown precipitate (0.14 g.), m.p. 170° (with preliminary shrinking at 160°). This was crystallised from aqueous alcohol, m.p. 180-181° (Kofler block), yield 0.11 g.

(i) Found (in a sample dried in high vacuo to constant weight at 140°: C, 65.82; H, 6.68. $C_{26}H_{32}O_8$ requires C, 66.08; H, 6.83%.

(ii) Found (in a sample dried in high vacuo to constant weight at 100°): C, 65.18; H, 6.71; OMe, none. $C_{26}H_{32}O_8\ \frac{1}{2}H_2O$ requires C 64.80; H, 6.80%.

(iii) Found (in a sample dried in high vacuo to constant weight at 100° and then rehydrated at room temperature until the weight is constant): C, 64.03; H, 6.77 $C_{26}H_{32}O_8, H_2O$ requires C, 63.66; H, 6.99%. $[\alpha]_D^{19}$ - 129° (c, 0.9275 in chloroform).

Alkaline Hydrolysis of Swietic Acid.

(a) Direct titration with 0.01N-sodium hydroxide solution.

Swietic acid hydrate (0.0184 g.) in ethanol (5 c.c.) was directly titrated with 0.01N-sodium hydroxide solution using phenolphthalein as indicator (3.65 c.c. required). This gives equivalent weight, 504; $C_{26}H_{32}O_8, H_2O$ requires 490 (one carboxyl group).

(b) With dilute sodium hydroxide solution at room temperature for five hours.

Swietic acid (0.0784 g.) in ethanol (10 c.c.) and 0.1N-sodium hydroxide (5 c.c.) was allowed to stand at room temperature for five hours. Back titration with 0.1N-sulphuric acid using phenolphthalein as indicator (3.16 c.c. 0.1N-alkali consumed), gave equivalent weight 248; $C_{26}H_{32}O_8\ H_2O$ requires 245 (one lactone ring and one carboxyl group). The alcohol was then removed in vacuo at 35° and the solution on acidification with ice-cold dilute hydrochloric acid gave colourless precipitate (0.075 g.), m.p. 175-180° (dec.). Crystallisation from aqueous

alcohol gave swietic acid in flakes (ca. 0.060 g.), m.p. 180-181°, (Kofler block) not depressed by an authentic sample.

Action of dilute sulphuric acid on swietic acid.

Swietic acid (0.1 g.) was refluxed for one hour with 50% ethanol (6.c.c.) and N-sulphuric acid (6 c.c.). When the ethanol was distilled off in vacuo a colourless precipitate appeared, yield 0.09 g., m.p. 172-174°. It was crystallised from aqueous alcohol giving prisms (0.065 g.) m.p. 180-181°, not depressed by authentic swietic acid.

Action of diazomethane on swietic acid.

Swietic acid (70 mg.) was dissolved in the minimum volume of methanol and treated with an excess of etherial diazomethane for one hour at room temperature. The yellow gummy product (ca. 70 mg.) on crystallisation from aqueous alcohol, gave swietenolide (25 mg.), identified by its m.p., mixed m.p. and infrared spectrum.

Acetylation Experiments on Swietenolide..

(i) With boiling acetic anhydride and fused sodium acetate for five hours. Preparation of acetate (A).

Swietenolide (0.3 g.) was boiled under reflux with acetic anhydride (9 c.c.) and fused sodium acetate (1.2 g.) for five hours on an oil bath. Excess of acetic anhydride was removed under reduced pressure and the residue was shaken with water when a brown gummy mass separated. This was taken up in chlorcform

and the extract was washed with sodium bicarbonate solution and then with water, dried and concentrated. The crude product was dissolved in benzene and chromatographed over alumina (10 g., grade III). Elution with benzene containing 30% and 50% ether (7 fractions) afforded non-crystalline material m.p. 90-100°. This was twice crystallised from aqueous alcohol giving prisms, m.p. 130° (Kofler block), yield, 0.1g. (Found (in a sample dried to constant weight in high vacuo at 100°): C, 68.55, 68.32; H, 6.86, 6.98; acetyl, 7.89. $C_{27}H_{31}O_6(OCOCH_3)$ requires C, 68.22; H, 6.71; one acetyl, 8.43%).

(ii) With acetic anhydride and pyridine at 100° for 30 minutes.

Preparation of acetate (B).

A mixture of swietenolide (0.2 g.), acetic anhydride (0.8 c.c.) and pyridine (3 c.c.) was heated on a water bath for 30 minutes. After cooling, the excess of acetic anhydride was decomposed by the addition of a few drops of water. Pyridine was then removed under reduced pressure. After the addition of water the crude product was extracted with chloroform and the extract was washed, dried and concentrated. On precipitation with light petroleum, it afforded a non-crystalline product (0.11 g.), m.p. 110° (not sharp), which could not be crystallised. On chromatography over alumina (5 g., grade III), elution with ether containing 3% alcohol (two fractions) afforded amorphous material (ca. 0.06 g.), m.p. 105° (with preliminary shrinking) which failed to crystallise. (Found: acetyl 9.8; $C_{27}H_{33}O_7(OCOCH_3)$ requires 8.1%).

(iii) With acetic anhydride and fused sodium acetate at 100° for one hour. Preparation of acetate (C).

A mixture of swietenolide (0.1 g.), acetic anhydride (2 c.c.) and fused sodium acetate (0.3 g.) was heated on a steam bath for one hour. The excess of acetic anhydride was then removed in vacuo at 35°. On addition of water a gummy mass separated. Attempted crystallisation from aqueous alcohol gave amorphous material, m.p. 100° (not sharp), yield, 0.08 g. The amorphous product was then dissolved in carbon tetrachloride with warming and the brown gummy matter (small amount) which remained insoluble, was filtered off. The filtrate on standing overnight deposited a non-crystalline product, m.p. 109-111°, yield, ca. 30 mg. It was again dissolved in aqueous alcohol and allowed to stand at room temperature for a month, when a colourless precipitate was obtained, m.p. 164-166° (with preliminary shrinking at 144°), yield ca. 10 mg. (Found: acetyl, 6.6; $C_{27}H_{33}O_7$ ($OCOCH_3$) requires 8.1%).

(iv) With acetic anhydride and fused zinc chloride at room temperature for 20 hours. Preparation of acetate (D).

A mixture of swietenolide (0.3 g.), acetic anhydride (8 c.c.) and fused zinc chloride (0.1 g.) was kept in a well-stoppered flask for 20 hours at room temperature. The excess of acetic anhydride was decomposed by adding water (3 c.c.) with continuous shaking. After ½ hour excess of water was added and the solution was concentrated in vacuo at ca. 35°. The amorphous product was filtered and then dissolved in aqueous alcohol. On standing overnight a

light brownish precipitate appeared, m.p. 140° (with preliminary shrinking at 110°), yield, 0.31 g. It could not be crystallised. On chromatography over alumina (10 g., grade III), elution with ether containing 4% alcohol (two fractions) afforded a white amorphous solid (0.24 g.) It was dissolved in a small volume of alcohol and a few drops of water were added. On standing overnight a colourless precipitate appeared, m.p. 125° (with preliminary shrinking), yield, 0.14 g. (Found: acetyl, 14.40, 13.98. $C_{27}H_{32}O_6(OCOCH_3)_2$ requires 15.09%).

(v) With trifluoracetic anhydride and acetic acid at room temperature for one hour. Preparation of acetate (E).

A mixture of swietenolide (0.2 g.), trifluoracetic anhydride (3 c.c.) and acetic acid (1 c.c.) was allowed to stand for one hour at room temperature when the solution became deep brown in colour. It was then poured into a saturated solution of potassium bicarbonate (5 g.). Chloroform was then added and the chloroform extract was washed with sodium bicarbonate and water and then dried. Concentration and precipitation with light petroleum gave a brown precipitate (0.17 g.), m.p. 120-140°. It could not be crystallised. On chromatography over alumina (7 g., grade III), elution with ether containing 1% alcohol (8 fractions) afforded a microcrystalline product (0.1 g.), m.p. 130° (with preliminary shrinking). (Found: acetyl, 15.63. $C_{27}H_{32}O_6(OCOCH_3)_2$, requires 15.09%).

(vi) With acetic anhydride and perchloric acid at room temperature for one hour.

Swietenolide (0.1 g.) was allowed to react with acetic anhydride (0.5 c.c.) in acetic acid (2 c.c.) in the presence of perchloric acid (one drop) for one hour at room temperature. More than 50% of unchanged swietenolide was isolated from the reaction mixture.

Attempted Dehydration of Swietenolide.

1. With thionyl chloride and pyridine for 18 hours at room temperature.

(a) A solution of anhydrous swietenolide (0.3 g.) in pyridine (Analar, 4 c.c.) was placed in an ice bath and freshly distilled thionyl chloride (0.6 c.c.), was added with shaking. The solution was allowed to stand at room temperature for 18 hours when it had become deep brown. The excess of thionyl chloride was decomposed by adding some ice chips and then water was added. The solution was then extracted with chloroform and the extract washed with N-sulphuric acid, followed by sodium bicarbonate solution and dried. Evaporation of the solvent gave a deep red gummy solid (0.17 g.). On chromatography over alumina (25 g., grade III), elution with benzene-ether (1:1) and crystallisation from ethyl acetate afforded colourless prisms (ca. 5 mg.), m.p. 115° (Kofler block). Elution with alcohol gave a red gum which on crystallisation from chloroform gave a red crystalline compound, m.p. 240°, (Kofler block).

(b) The above experiment was repeated under the identical conditions. On concentration of the deep red chloroform solution, the red crystalline compound (ca. 10 mg.), m.p. 240°, separated out. It was recrystallised from chloroform, yield, 5 mg., m.p. 240°. (Found: N, 2.3%). The mother liquor was evaporated to dryness and the product was dissolved in benzene and chromatographed over alumina (10 g., grade III). On elution with ether containing 3% alcohol, a pale yellow material (ca. 20 mg.), m.p. 120-130°, was obtained which did not yield to crystallisation. Further elution with alcohol gave a trace of the above red compound, m.p. 240°.

2. With thionyl chloride in pyridine for 15 minutes at room temperature.

A solution of swietenolide (0.1 g.) in pyridine (Analar, 4.5 c.c.) was placed in an ice bath and freshly distilled thionyl chloride (0.66 c.c.) was added drop by drop with shaking. After 15 minutes the solution was worked up as above. On chromatography over silica gel, elution with benzene-ether (4:2) gave an amorphous product (ca. 50 mg.), m.p. 150° (not sharp), which could not be crystallised.

Attempted Preparation of a Tosyl Derivative of Swietenolide.

(a) Swietenolide (0.25 g.) was dissolved in pyridine (5 c.c.) and p-toluenesulphonyl chloride (0.4 g.) was added at 0°. The mixture was allowed to stand at room temperature for 48 hours. It was then poured into ice water, extracted with chloroform and the extract was washed with N-sulphuric acid and dried. Evaporation

of the solvent gave brown material (0.3 g.), m.p. 190° (not sharp). Chromatography over alumina and elution with ether containing 3% alcohol afforded unchanged swietenolide (0.16 g.), m.p. 220°, not depressed by an authentic sample.

(b) A mixture of swietenolide (0.12 g.) and pyridine (3 c.c.) containing p-toluenesulphonyl chloride (0.2 g.) was heated on a boiling water bath for one hour. Isolation as described above gave a pale brown crystalline product (60 mg.), m.p. 200°, which did not contain sulphur and is possibly impure swietenolide.

Action of Carbonyl Reagents on Swietenolide.

(a) 2:4-dinitrophenylhydrazine.

A solution of swietenolide (0.1 g.) in ethyl alcohol (5 c.c.) containing 2:4-dinitrophenylhydrazine (60 mg.) and concentrated hydrochloric acid (two to three drops) was heated under reflux for 15 minutes and then allowed to stand overnight at room temperature. Dilution with water followed by chromatography of the product gave several gummy fractions and orange crystals (5 mg.), m.p. 216-217° (Found: N, 0.86%) which were probably impure swietenolide.

(b) Semicarbazide hydrochloride.

Semicarbazide hydrochloride (0.11 g.) and sodium acetate (0.16 g.) were dissolved in the minimum quantity of water (2 c.c.) A solution of swietenolide (0.17 g.) in alcohol (10 c.c.) was added and the mixture was heated under reflux for 30 minutes. Evaporation of the solvent and addition of water gave a crude product (0.15 g.) which did not contain nitrogen. On crystallisation swietenolide (80 mg.) was recovered.

(c) Hydroxylamine hydrochloride.

Swietenolide (0.2 g.) was heated under reflux for four hours with hydroxylamine hydrochloride (0.2 g.) in pyridine (4 c.c.) and ethanol (3 c.c.). Evaporation of the solvents and treatment with water gave a brown gummy mass which did not contain nitrogen. Crystallisation gave swietenolide (0.1 g.).

Attempted reaction with hydroxylamine hydrochloride and sodium acetate in aqueous alcohol gave similar results.

Catalytic Hydrogenation of Swietenolide.

1. With 5%-Palladised charcoal. Preparation of hexahydroswietenolic acid.

5% Palladised charcoal (0.2 g.) in acetic acid (Analar, 15 c.c.) was shaken with hydrogen until saturated and then swietenolide hydrate (0.2928 g.) was dropped into the mixture. Hydrogen uptake appeared to be complete after shaking for 29 hours at 20°/748 mm. when 39 c.c. of hydrogen (2.8 mols.) had been consumed. The catalyst was filtered off and washed with acetic acid. The combined filtrates were concentrated to a small volume under reduced pressure and the product precipitated with water. The crude product was dissolved in chloroform which was then extracted three times with sodium bicarbonate solution. The chloroform solution left no residue on evaporation. The aqueous layer was acidified with dilute hydrochloric acid, extracted with chloroform, washed, dried and concentrated. Crystallisation from aqueous alcohol gave small needles of

hexahydroswietenolic acid (0.24 g.), m.p. 202-203°, $[\alpha]_D^{20}$ - 46° (c, 1.92 in chloroform). (Found (in a sample dried to constant weight at 100°): C, 66.07, 65.91; H, 8.30, 8.18; OMe, 6.10, 6.10. $C_{27}H_{40}O_8$ requires C, 65.83; H, 8.19; OMe, 5.95%).

2. With Adams' platinum oxide.

Swietenolide (0.3829 g.) was added to Adams' catalyst (0.28 g.) previously saturated with hydrogen in acetic acid (Analar, 25 c.c.) and the mixture was shaken in a hydrogen atmosphere at 16°/752 mm. After 4 hours 66.5 c.c. of hydrogen had been absorbed (3.6 mols.) and the hydrogen uptake appeared to be complete. The catalyst was filtered off and washed with acetic acid. The combined filtrates were concentrated and precipitated with water. The amorphous product had m.p. 114-116° (not sharp), and could not be recrystallised.

3. With Raney/nickel.

Swietenolide in methanol did not absorb hydrogen in the presence of Raney/nickel catalyst at ordinary temperature and pressure.

Alkaline Hydrolysis of Hexahydroswietenolic Acid

(1) Direct titration with 0.01N-sodium hydroxide.

Hexahydroswietenolic acid (0.0185 g.) in ethanol (5 c.c.) was directly titrated with 0.01N-sodium hydroxide solution using phenolphthalein as indicator (3.60 c.c. required) giving equivalent weight, 514, $C_{27}H_{40}O_8, H_2O$ requires 510.

Colour Tests given by Swietenolide and its Derivatives

Name of Compound	Ammoniacal silver-nitrate solution[49]	Tollens' reagent[49]	Tetranitromethane in Chloroform	Fehling's Solution
Swietenolide	No reduction	Rapid reduction	Yellow	No reduction
Swietic acid	No reduction	Rapid reduction	Yellow	No reduction
Hexahydroswietenolic acid	No reduction	No reduction	Yellow	No reduction
Methyl hexahydroswietenolate (amorphous)	No reduction	Rapid reduction	-	-

	Ehrlich Reagent[59]	Shear's Colour Reaction[60]	Vanillin and concentrated hydrochloric acid (alcoholic)[40]
Swietenolide	Pink orange colour changing to greenish blue	Amber colour with red brown tinge	Bluish violet colour on heating
Swietic acid	Pink orange colour changing to greenish blue	Amber colour with red brown tinge	-
Hexahydroswietenolic acid	Faint pink colour appeared but vanished within one minute	No coloration	-

Colour Tests given by Swietenolide and its Derivatives (Contd.)

Name of Compound	N-potassium hydroxide in methanol[61]
Swietenolide	Pink colour which disappeared on standing or warming.
Swietic acid	Pink colour which disappeared on standing or warming.
Hexahydroswietenolic acid . .	No colour appeared.
Andrographolide[61]	Intense pink colour which became slightly brown after one hour.

(2) With excess sodium hydroxide solution at room temperature.

A mixture of hexahydroswietenolic acid (0.0850 g.) in ethanol (10 c.c.) and 0.1N-sodium hydroxide (5 c.c.), was allowed to stand at room temperature for five hours. Back titration with 0.1N-sulphuric acid, using phenolphthalein (1.70 c.c. 0.1N-alkali consumed), gave equivalent weight, 500; $C_{27}H_{40}O_8$, H_2O requires 510 (one carboxyl group). The alcohol was then evaporated and the solution, on acidification with ice-cold dilute hydrochloric acid, gave a colourless precipitate (0.075 g.), m.p. 195°. Crystallisation from aqueous alcohol gave hexahydroswietenolic acid (ca. 0.06 g.), m.p. and mixed m.p. 202-203°.

(3) With excess dilute sodium hydroxide solution at 100°.

Hexahydroswietenolic acid (0.0937 g.) and 0.1N-sodium hydroxide solution (5 c.c.) were heated on the steam bath for five hours. Back titration with 0.1N-sulphuric acid (3.84 c.c. 0.1N-alkali consumed) gave equivalent weight 244, $C_{27}H_{40}O_8$, H_2O requires 255 (one carboxyl and one ester grouping). Acidification, after evaporation of the alcohol, gave an amorphous product, m.p. 240° (preliminary shrinking begins at 110°), which could not be crystallised. The product (0.0509 g.) in ethanol (5 c.c.) was titrated with 0.01N-sodium hydroxide using phenolphthalein as indicator (1.96 c.c. required) giving equivalent weight 260.

Action of diazomethane on hexahydroswietenolic acid.

Excess of an etherial solution of diazomethane was added to hexahydroswietenolic acid (0.15 g.) in methanol (3 c.c.) at room temperature. After an hour the solvent was evaporated giving a yellow gummy product. This was dissolved in ethyl acetate and filtered. After concentration the filtrate was precipitated with petroleum ether giving amorphous material (0.12 g.), m.p. 60-80°. This could not be crystallised. (Found: OMe, 10.75, 10.47%. Hexahydroswietenolic acid methyl ester, $C_{28}H_{42}O_8$ requires 12.25%).

Reduction of Swietenolide with Lithium Aluminium Hydride

Anhydrous swietenolide (1 g.) in an extraction thimble was placed in a Soxhlet extractor. Finely powdered lithium aluminium hydride (2 g.) and anhydrous ether (150 c.c.) were taken in a flask. The ether was maintained at a moderate rate of boiling in a hot water bath for 23 hours when all the swietenolide in the thimble had completely dissolved. After cooling, ethyl acetate was cautiously added with stirring to decompose the excess of lithium aluminium hydride. Then water (20 c.c.) was added, followed by dilute hydrochloric acid to decompose the aluminium hydroxide. The ether layer was separated and the aqueous layer was extracted several times with chloroform. The organic layers were then dried and combined together, and the solvents were distilled off. Treatment of the resulting syrup with light petroleum gave an amorphous solid, m.p. 90-115° (with preliminary shrinking), yield, 0.8 g. It was insoluble in benzene or ether but soluble in alcohol. Crystallisation from alcohol gave long prisms (ca. 10 mg.). Found (in a sample dried to constant weight in high vacuo at 100°): C, 66.95; H, 8.31. $C_{26}H_{40}O_7$ requires C, 67.21; H, 8.68%). From the mother liquor only amorphous material was obtained. When the lithium aluminium hydride reduction of swietenolide was repeated under the above conditions no crystalline compound was isolated.

Reduction of Swietenolide with Potassium Borohydride

Swietenolide (0.2 g.) in methanol (10 c.c.) was treated with potassium borohydride (0.14 g. in 10 c.c. of water). The mixture was kept for one hour at room temperature with occasional shaking.

Excess borohydride was then decomposed with water (10 c.c. containing 0.5 c.c. glacial acetic acid). Extraction with chloroform and concentration of the washed extract gave a syrup which on treatment with petroleum ether gave amorphous material (0.14 g.), m.p. ca. 120°. This was dissolved in benzene and chromatographed over alumina (7 g., grade III). Elution with ether containing 3% alcohol afforded a colourless amorphous product (ca. 10 mg.) which could not be crystallised. Further elution with ether containing 20% alcohol (three fractions) gave amorphous material (70 mg.) (m.p. 160-161° with preliminary shaking), which also resisted crystallisation. (Found (in a sample dried to constant weight in high vacuo at 100°): C, 64.05; H, 7.24%. $C_{27}H_{36}O_8$, H_2O requires C, 64.01; H, 7.56%).

Lead Tetraacetate Oxidation

Lead tetraacetate (ca. 0.3 g.) was dissolved in acetic acid (10 c.c.; purified by refluxing with acetic anhydride and chromic acid followed by distillation).[62a] The samples (0.04 millimol.) dissolved in acetic acid (2 c.c.) were mixed with the lead tetraacetate solution (2 c.c.) and the volumes were adjusted to 5 c.c. with acetic acid. Blank solutions were prepared in the same way. The solutions were then kept in an incubator at 36° and at intervals 1 c.c. samples were withdrawn and added to 3 c.c. of a solution prepared by dissolving 0.5 g. sodium iodide and 5 g. sodium acetate in 25 c.c. water, the liberated iodine being titrated with 0.02N-thiosulphate solution. Titration of a blank indicated that the solutions initially contained 3 molecules

of lead tetraacetate per molecule of substance. The blank titre decreased slightly when the lead tetraacetate solutions were allowed to stand at 36° and the appropriate blanks were used in calculating the uptakes which are recorded below:

Name of Compounds	Number of molecules of lead tetra-acetate consumed per molecule of substance		
	8 hrs.	21 hrs.	48 hrs.
Swietenolide	0.1	0.2	0.4
Hexahydroswietenolic acid	0.05	0.1	0.2
Swietic acid	1.0	1.3	1.7
1-hydroxy cyclo-hexane carboxylic acid	0.6	0.9	1.2

Oxidation of Hexahydroswietenolic Acid with Chromium Trioxide in Acetic Acid.

Anhydrous hexahydroswietenolic acid (81·1 mg., 0.165 millimols) in acetic acid (5 c.c.; purified as in the lead tetra-acetate oxidation)[62a] was treated with ca. 0.1N-chromium trioxide in acetic acid (10 c.c.). The colour of the solution turned red. A blank solution was prepared in the same way. Periodically 1 c.c. portions were withdrawn and added to 0.3M-potassium iodide (4 c.c.) containing sodium bicarbonate (0.1 g.). After

addition of N-sulphuric acid (2 c.c.) and standing for 10 minutes the liberated iodine was titrated with 0.02N-thiosulphate solution. Appropriate blanks were used in calculating the uptakes. Titration of a blank indicated that the solution initially contained 3.06 atoms of "oxygen" per molecule of hexahydroswietenolic acid. The uptakes of "oxygen" per molecule of hexahydroswietenolic acid were found to be: 2.07 atoms (15 mins.); 2.29 atoms (60 mins.); 2.32 atoms (90 mins.); 2.36 atoms (135 mins.); 2.46 atoms (5 hours); 2.47 atoms (6 hours); 2.47 atoms (7 hours); 2.63 atoms (24 hours).

Under similar conditions menthol gave the following results: 0.96 atoms (15 mins.); 0.98 atoms (45 mins.); 0.99 atoms (60 mins.); 0.99 atoms (90 mins.); 1.8 atoms (28 hours).

Quantitative oxidation of Swietenolide, Hexahydroswietenolic Acid, and Swietenine, with Potassium Dichromate in Acetic Acid.

The compounds (0.16 millimols) dissolved in acetic acid (5 c.c.) were treated with ca. 0.1N-potassium dichromate in acetic acid (10 c.c.). Uptakes of "oxygen" were determined as above. The initial solutions contained 3.15 atoms of oxygen per molecule of compound. The uptakes were as follows:

Swietenolide: 0.91 atoms (15 mins.); 1.23 atoms (1 hour); 1.44 atoms (2 hours); 1.63 atoms (3 hours); 1.70 atoms (4 hours); 1.81 atoms (5 hours); 1.87 atoms (6 hours); 1.91 atoms (7 hours); 2.00 atoms (8 hours); 3.02 atoms (24 hours).

Hexahydroswietenolic acid: 0.76 atoms (15 mins.); 1.25 atoms (1 hr.); 1.50 atoms (2 hours); 1.70 atoms (3 hours); 1.76 atoms (4 hours); 1.91 atoms (6 hours); 1.93 atoms (7 hours); 1.99 atoms (8 hours); 2.00 atoms (9 hours); 2.45 atoms (24 hours).

Swietenine: 0.34 atoms (15 mins.); 0.58 atoms (1 hour); 0.79 atoms (2 hours); 0.89 atoms (3 hours); 1.00 atoms (4 hours); 1.14 atoms (6 hours); 1.19 atoms (7 hours); 1.41 atoms (24 hours).

Preparative Oxidation of Swietenolide with Potassium Dichromate in Acetic Acid.

A mixture of swietenolide (0.24 g.), acetic acid (10 c.c.) and 0.1N potassium dichromate in acetic acid (30 c.c.) was allowed to stand at room temperature. After 8 hours the excess of oxidising agent was discharged with methanol and the solution was concentrated at 35°. It was then diluted with water (40 c.c.) and extracted with chloroform. The extract was washed with sodium bicarbonate solution, dried and evaporated. Crystallisation from ethyl acetate - light petroleum afforded dehydroswietenolide (0.085 g.), m.p. 246-248°. It reduced Tollens' reagent and ammoniacal silver nitrate solution but not Fehling's solution. It gave yellow coloration with tetranitromethane in chloroform. It did not couple with diazotised aniline. (Found (in a sample dried to constant weight in high vacuo at 100°): C, 66.98; H, 6.59; $C_{27}H_{32}O_8$ requires C, 66.92; H, 6.66%).

From the mother liquor a colourless amorphous solid (0.07 g.), m.p. 110-120°, was obtained.

Repetition of the oxidation allowing reaction times of 15 minutes or one hour gave slightly larger yields (ca. 0.11 g.) of dehydroswietenolide.

Oxidation of Swietenolide with Chromium Trioxide in Pyridine.

The reagent was prepared by adding chromium trioxide to pyridine (not vice versa).[62b]

Swietenolide (0.2 g.) in pyridine (3 c.c.) was thoroughly mixed with chromium trioxide (0.15 g.) in pyridine (3 c.c.) at 0°. After standing overnight at room temperature the solution was poured into water (30 c.c.) and extracted with chloroform. The chloroform extract was washed successively with dilute hydrochloric acid and sodium bicarbonate solution. Evaporation of the dried extract furnished a brown solid (0.21 g.), m.p. 170-180°, which was twice crystallised from ethyl acetate - light petroleum to yield a crystalline product (0.03 g.), m.p. 245-247°. This did not depress the melting point of dehydroswietenolide and gave an identical infrared spectrum.

From the mother liquor a light yellow solid (0.12 g.), m.p. 100-150°, was obtained which could not be crystallised.

Oxidation of Swietenolide with Sodium Hypobromite.

A mixture of swietenolide (0.3 g.), methanol (15 c.c.) and sodium hydroxide solution (0.1N, 12 c.c.) was allowed to stand at room temperature. After one hour methanol was removed by careful distillation under reduced pressure. The solution was then treated with 10 c.c. sodium hypobromite solution (0.5 g. bromine dissolved in 10 c.c. of 4% sodium hydroxide solution at 0°) and the clear yellow solution was left at room temperature for 45 minutes. A small amount of sodium sulphite was

added and the solution was then acidified with dilute hydrochloric acid. After 30 minutes the colourless precipitate (0.2 g.), m.p. 126° (not sharp), was filtered and dried. This was dissolved in chloroform and extracted three times with sodium bicarbonate solution. The neutral chloroform extract on concentration furnished a syrupy liquid which crystallised from ethyl acetate (30 mg.), m.p. 240°. Further crystallisation from ethyl acetate - light petroleum gave material which had m.p. 246-248°, not depressed by dehydroswietenolide . Identity was confirmed by the infrared spectrum. (Found (in a sample dried to constant weight in high vacuo at 100°): C, 66.53; H, 6.76; OMe 6.5. $C_{27}H_{32}O_8$ requires C, 66.92; H, 6.66; OMe 6.4%).

The bicarbonate solution (vide supra) was acidified with ice-cold dilute hydrochloric acid and extracted with chloroform. The extract yielded a colourless amorphous product (0.15 g.), m.p. 150-160°, which could not be crystallised. (Found equivalent weight 555; OMe, 2.3%).

This (0.1 g.) was dissolved in methanol (2 c.c.) and treated with excess of etherial diazomethane for one hour at room temperature. After evaporation of the solvent and two crystallisations from chloroform-ethyl acetate, the product (30 mg.) had m.p. 246-248°, not depressed by dehydroswietenolide.

Preparation and Methylation of the Enol from Dehydroswietenolide.

A mixture of dehydroswietenolide (0.0414 g.), ethanol (19 c.c.) and sodium hydroxide solution (0.2N, 1 c.c.), was

allowed to stand at room temperature. After one hour the solution showed the characteristic U.V. absorption spectrum of the enol ($\lambda_{max.}$ 286-287 mμ), logϵ 4.00). The solution was then concentrated at 20° in a rotatory evaporator and the resulting syrupy liquid was cooled in an ice bath and then acidified with dilute sulphuric acid. Extraction with chloroform and evaporation of the solvent furnished an amorphous enolic product (ca. 35 mg.), m.p. 130° (dec.), $\lambda_{max.}$ 286-288 mμ, logϵ 4.46, which could not be crystallised. In alkaline solution this reacted with diazotised aniline to give a light orange precipitate. It did not give a coloration with alcoholic ferric chloride.

The enol (25 mg.) was dissolved in the minimum volume of methanol and treated with an excess of etherial diazomethane. After two hours at room temperature the ether was distilled off and the residue was taken up in ethyl acetate. The solution was filtered and then concentrated. Precipitation with light petroleum gave an amorphous product (18 mg.), m.p. 170° (with preliminary shrinking), $\lambda_{max.}$ 262-268 mμ, log ϵ 4.26. It did not yield to crystallisation. (Found: OMe, 10.3. $C_{26}H_{28}O_6$ $(OCH_3)_2$ requires 12.4%).

Sodium Periodate Oxidation of Crude Lithium Aluminium-Hydride Reduction Product of Swietenolide.

The sample (0.034 g., i.e. 0.075 millimols) dissolved in 2 c.c. of ethanol, was mixed with sodiumperiodate solution (2 c.c., 0.1M) and the volume was adjusted to 5 c.c. with water. At intervals 1 c.c. samples were pipetted into a flask containing

3 c.c. of 0.5M-phosphate buffer (pH 7) and 1 c.c. of 10% potassium iodide solution, the liberated iodine being titrated with 0.05N-arsenite solution. The oxidation was run at room temperature in the dark and appropriate blanks were run for each determination. Uptake of periodate per molecule of substance: 1.4 mols. (18 hours); 1.4 mol. (36 hours).

After destroying the periodate in the remaining solution by reaction with buffered potassium iodide and sodium arsenite, the solutions were combined together and distilled under slightly reduced pressure (bath temperature ca. 50°) into a trap cooled in ice and salt, ca. 10 c.c. distillate being collected. This was tested for formaldehyde using the chromotropic acid method[51] which indicated that 1 c.c. of the distillate contained ca. 7 mols. of formaldehyde. An attempt to obtain the crystalline dimedone derivative of formaldehyde from the remainder of the above distillate was unsuccessful.

Attempted Sodium Periodate Oxidation of Swietenolide.

Following exactly the same method as described above (except that ethanol was used to make the solution up to 5 c.c.), it was found that sodium periodate did not react with swietenolide at room temperature even on standing for 48 hours.

Reaction of Swietenolide with 50% Sulphuric Acid at 50°.

Swietenolide (0.2 g.) was added to 4.9 c.c. of 50% sulphuric acid and the solution was stirred at 50° for twenty hours. The colour of the solution changed to pink within ten

minutes and ultimately to dark brown. After cooling it was poured into cold water (20 c.c.) and then extracted with chloroform which was washed with sodium bicarbonate solution, filtered, dried and evaporated, yielding a brown gummy product. This was taken up in ethyl acetate and the solution was filtered to remove insoluble material. Concentration yielded crystals (ca. 40 mg.), m.p. 212°, not depressed by swietenolide. The above insoluble material on repeated crystallisation from Chloroform-light petroleum afforded colorless crystals, (6 mg.), m.p. 300° (Kofler block). The compound did not reduce Tollens' reagent. (Found: C, 61.94, 62.46; H, 7.37, 6.69; OMe, 6.93, 6.83%). Although the analyst (Weiler and Strauss) dried the sample, no precautions were taken to prevent uptake of atmospheric moisture before analysis.

Selenium Dehydrogenation of Swietenolide.

A mixture of swietenolide (3.25 g.) and powdered selenium (6.5 g.) was kept at 320-330° for 25 hours in a sealed tube. The product was extracted with ether in a Soxhlet apparatus for 14 hours. The filtered etherial solution was shaken with N-sodium carbonate solution, 2N-sodium hydroxide and water, and then dried and evaporated leaving a brown gummy residue which on high vacuum distillation at 170-190°/0.01 mm. gave an orange viscous oily product (0.15 g.). Treatment with alcohol gave needles which were recrystallised from the same solvent to yield a very small amount of material (ca. 2 mg.), m.p. 185-187° $\lambda_{max.}$ 294 mμ , log ε 3.84; 285 mμ , log ε 3.84; 258 mμ , log ε 4.35 and apparent maximum at 210 mμ , log ε 4.87.

$\lambda_{min.}$ 288 mμ, log ε 3.81; 276 mμ, log ε 3.72, and 237 mμ, log ε 4.00.

From the mother liquor a small amount of a red crystalline trinitrobenzene adduct (4 mg.), m.p. 148° was prepared.

The above aqueous sodium hydroxide extract exhibited a blue fluorescence. Acidification with dilute hydrochloric acid afforded a brown gummy product which did not yield to crystallisation. It coupled with benzenediazonium chloride giving a red precipitate. An attempt to isolate a crystalline trinitrobenzene derivative was unsuccessful.

No useful results were obtained when swietenolide was subjected to dehydrogenation with selenium in a sealed tube at 310-320° for 10 hours or with palladised charcoal (5%) in an open tube at 280-310° for 15 hours. Attempted dehydrogenation of the crude lithium aluminium hydride reduction product and the crude potassium borohydride reduction product of swietenolide with selenium in a sealed tube at 320-330° for 25 hours gave no crystalline products.

Fusion of Swietenolide with Potassium Hydroxide.

Swietenolide (1.5 g.) was placed in a 25 ml. distilling flask with potassium hydroxide (3 g.) and water (2 c.c.). The mixture was heated in a Wood's metal bath in the course of 30 minutes to 300-310° (bath temperature). The distillate (A) was collected in a trap cooled in an ice-salt mixture. The cold melt was extracted with water, filtered and then acidified with dilute hydrochloric acid when a dark brown gummy mass

separated. It was taken up in ether and the etherial layer was washed, dried and concentrated, yielding thereby a brown pasty product (B), (ca. 0.9 g.) with a smell of fatty acid. High vacuum distillation of a portion at 75-80°/0.01 mm. gave a gummy product which could not be crystallised.

The distillate (A) was steam distilled giving a suspension of a colourless oil with a peculiar smell. It did not reduce Tollens' reagent or ammoniacal silver nitrate solution. With Brady's reagent it gave an amorphous precipitate, m.p. 80-90°.

Selenium Dehydrogenation of the Nonvolatile Potassium Hydroxide Fusion Product (B).

3.3 g. of the pasty mass (B) were mixed with powdered selenium (6.6. g.) and the mixture was heated in a sealed tube at 320-330° for 25 hours. The sticky reaction mixture was then extracted with ether in a Soxhlet apparatus for 18 hours. The filtered etherial solution was washed with N-sodium carbonate, 2N-sodium hydroxide and water and then dried and evaporated leaving a gummy residue which on high vacuum distillation (bath temperature, 120-150°/0.01 mm.) gave a viscous oil (C), (0.35 g.).

Preparation of the Picrate.

The product (C), (0.35 g.) in alcohol was treated with an alcoholic solution of picric acid (0.17 g.) and the orange crystals (0.14 g.), m.p. 120-124°, which separated, were collected. Repeated crystallisation from alcohol gave an orange crystalline

picrate (30 mg.), m.p. 130-132°. (Found (in a sample dried to constant weight in high vacuo at room temperature): C, 57.15; H, 4.21; N, 10.63. $C_{13}H_{14}$, $C_6H_3N_3O_7$ requires C, 57.14; H, 4.29; N, 10.52%).

Material from the combined mother liquors was once crystallised and then had m.p. ca. 124°, (0.1 g.). (Found (in a sample dried to constant weight in high vacuo at room temperature): C, 57.07; H, 4.17; N, 10.69. $C_{13}H_{14}$, $C_6H_3N_3O_7$ requires C, 57.14; H, 4.29; N, 10.52%).

Preparation of the Trinitrobenzene Derivative.

The product (C), (0.2 g.) in alcohol was treated with an alcoholic solution of trinitrobenzene (0.1 g.) and the orange crystals were collected. On repeated crystallisation from alcohol the trinitrobenzene adduct was obtained as long orange yellow needles (ca. 0.1 g.), m.p. 150-152°. (Found (in a sample dried to constant weight in high vacuo at room temperature): C, 60.27; H, 4.50; N, 10.95. $C_{13}H_{14}$, $C_6H_3(NO_2)_3$ requires C, 59.53; H, 4.47; N, 10.96 and $C_{14}H_{16}C_6H_3(NO_2)_3$ requires C, 60.45; H, 4.82; N, 10.58%).

An attempt was made to isolate the hydrocarbon by decomposing the trinitrobenzene derivative (30 mg.) on alumina but only a very small amount of an oily hydrocarbon ($\lambda_{max.}$ 327 mμ, 287-288 mμ and 230 mμ and $\lambda_{min.}$ 322 mμ and 250 mμ) was obtained thereby.

U.V. Absorption Spectra

Trinitrobenzene adduct		Trinitrobenzene		Difference
$\lambda_{max.}$ (mμ)	log ε	λ (mμ)	log ε	log ε
327	3.10	327	2.49	2.98
283	3.81	283	3.03	3.73
231	5.01	231	4.43	4.88
$\lambda_{min.}$ (mμ)	log ε	λ (mμ)	log ε	log ε
322	3.04	322	2.51	2.89
250	4.21	250	4.15	3.32

Decomposition of the Picrate (m.p. ca. 124°).

The picrate (80 mg.) was dissolved in ether and shaken with two portions of 10% sodium carbonate solution. The ether was washed with water until the washings were colourless and then dried and evaporated to give an oily product. It showed $\lambda_{max.}$ 324, 283 and 230 mμ (log ε 2.91, 3.81 and 4.97 respectively), $\lambda_{min.}$ 320 and 248 mμ (log ε 2.76 and 3.26 respectively). Gas chromatography showed that it contained at least two major components.

12 mg. of the above oily hydrocarbon mixture was then converted into its trinitrobenzene adduct, m.p. 150-152°, not

depressed by the trinitrobenzene derivative obtained directly from the hydrocarbon product (C).

Attempted Isolation of Phenolic Product.

The 2N-sodium hydroxide solution (vide supra) was acidified with dilute hydrochloric acid and then extracted with ether yielding a brown gummy mass. High vacuum sublimation at 220°/ 0.05 mm. gave a semi-solid product (ca. 50 mg.) which did not yield to crystallisation. It gave red coloration with alcoholic ferric chloride solution and coupled with benzenediazonium chloride giving red precipitate.

Isolation of Tiglic Acid

Swietenine (0.4 g.) in ethanol (25 c.c.) containing sodium hydroxide solution (0.1N, 25 c.c.) was refluxed for five hours. (Titration of solution prepared under identical conditions showed that 2.5 equivalent of alkali had been consumed). The alcohol was then evaporated and the concentrated solution was acidified with dilute hydrochloric acid and then extracted with ether. The extract was dried, concentrated, precipitated with light petroleum and then filtered. The amorphous product was then shaken with hot petroleum ether and filtered. The above two filtrates on concentration and crystallisation from light petroleum yielded colourless crystals (ca. 30 mg.), m.p. 64°, not depressed by authentic tiglic acid.

Preparation of Acyl-Urea of Tiglic Acid.

10 mg. of tiglic acid (obtained from the alkaline hydrolysis of swietenine) in ether was treated with an etherial solution

of carbodiimide (30 mg.). The solution was allowed to stand at room temperature overnight yielding crystals which were recrystallised from acetone, m.p. 138-139° (Kofler block), not depressed by the authentic acyl-urea of tiglic acid.

Reaction of Swietenine with γ-picoline

A mixture of swietenine (0.2 g.) and freshly distilled γ-picoline (10 c.c.) was refluxed in an oil bath when the colour of the solution turned brown. After one hour the γ-picoline was removed in vacuo and the resulting dark gummy mass was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid and then with sodium bicarbonate solution. Evaporation of the chloroform followed by crystallisation from chloroform-light petroleum gave swietenine (40 mg.), m.p. 260°, not depressed by authentic sample.

The sodium bicarbonate extract was acidified with dilute hydrochloric acid and then extracted with chloroform. The extract gave a colourless amorphous product (90 mg.), m.p. 190-200° (with preliminary shrinking) (Found: OMe, 0.3%).

Action of Diazomethane on the Acidic Product Obtained from Swietenine by Reaction with γ-picoline.

An excess of etherial diazomethane was added to the amorphous acid (0.15 g.) dissolved in the minimum volume of methanol. After one hour at room temperature the ether was evaporated. After several crystallisations from chloroform-ethyl acetate-light petroleum, the product (0.1 g.) had m.p. 260° (dec.) undepressed by swietenine.

Attempted Reaction of Methyl Cinnamate and ethyl-m-dinitrobenzoate with γ-picoline.

γ-picoline was allowed to react with methyl cinnamate and also with ethyl-m-dinitrobenzoate for three hours under the conditions given in the case of swietenine. In both cases unchanged material was obtained and nothing was isolated from the sodium bicarbonate extract.

Attempted Reaction of Swietenolide with γ-picoline.

A mixture of swietenolide (0.2 g.) and freshly distilled γ-picoline (10 c.c.) was refluxed in an oil bath. After one hour the γ-picoline was removed in vacuo and the dark gummy product was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid, and then with sodium bicarbonate solution. Evaporation of the chloroform gave a yellowish amorphous product (ca. 0.14 g.), m.p. 130-160°. On chromatography over alumina (15 g., grade III), elution with ether containing 3% alcohol gave unchanged swietenolide (ca. 70 mg.), m.p. 216-218° not depressed by an authentic sample. The sodium bicarbonate extract was acidified with dilute hydrochloric acid and then extracted with chloroform, dried, concentrated and precipitated with light petroleum ether, when an amorphous material (< 2 mg.), m.p. 180-190° (with preliminary shrinking) was obtained.

Attempted Reaction of Swietenolide with Tiglyl Chloride.

Tiglyl chloride was prepared from tiglic acid and phosphorus trichloride as described by Berger et al.[63]

A solution of swietenolide (0.2 g.) in pyridine (Analar, 3.5 c.c.) was placed in an ice bath and tiglyl chloride (0.15 g.) was added drop by drop with shaking. After standing overnight at room temperature the solution became dark brown. The excess of tiglyl chloride was decomposed by adding a few drops of water. After some time more water was added and the mixture was extracted with chloroform. The extract was washed successively with N-sulphuric acid and with sodium bicarbonate solution and on concentration afforded brown material (ca. 0.1 g.), m.p. 70-120°. Neither swietenine nor any other crystalline product could be obtained from this by attempted crystallisation or chromatography over alumina.

APPENDIX

INFRARED LIGHT ABSORPTION SPECTRA

Bands marked (H) were kindly determined by Dr. D.M.W. Anderson using a Hilger H 800 double beam spectrophotometer. Values marked (U) were determined by Dr. G. Eglinton and his associates (Glasgow University) using a Unicam S.P. 100 grating spectrophotometer. The author is most grateful to Dr. Eglinton for his generous help. For carbon tetrachloride solution spectra, filtered saturated solutions were used as the compounds were only very sparingly soluble. Intensity measurements were made using dilute (ca. 0.01 M) solutions of carefully dried samples in dry chloroform. At the low concentrations used, intermolecular hydrogen bonding can probably be neglected. Frequencies of peaks are given in cm^{-1}, $\Delta\nu_{\frac{1}{2}}$ is the band width in cm^{-1} at half of the peak intensity and ϵ is the "apparent molecular extinction coefficient."[64]

Swietenolide

Nujol Mull, H: 3160, 1505, 1025, 875 and 800 (all furan).

Carbon tetrachloride solution U: 1751 (six ring lactone), 1740 (COOMe) and 1721 (side chain or six ring ketone).

Chloroform solution, U:

ν	ε
3628	169 (unassociated OH)
3610 (Shoulder)	89 (unassociated OH)
3535	57 (associated OH)
1736	990 (lactone and COOMe)
1718 (Shoulder)	- (ketone)

Swietic Acid

Hexachlorobutadiene Mull H: 3500 (hydroxyl), 3140 (furan)

Nujol Mull, H: 3460 (hydroxyl), 3150 (furan), 1715 (broad); 1505, 1029, 879 and 808 (all furan).

Hexahydroswietenolic Acid

Nujol Mull, H: 3480 (hydroxyl), 1750 (COOMe and COOH), 1700-1710 (side chain or six ring ketone) and 1640 (unsaturation), no furan peaks.

Dehydroswietenolide

Nujol Mull, H: 3160, 1507, 1023, 870, 802 (all furan).

Carbon tetrachloride solution, U:

ν	Δν½		
1755	16	...	lactone
1739	12	...	COOMe
1710	13	...	ketone

Chloroform solution, U:

ν	Δν½	ε	
3597	32	80	partly hydrogen bonded hydroxyl
3525	broad	51	
1738	29	1230	... lactone and COOMe
1708	16	810	... ketone

Crystalline Monoacetate (A)

Nujol Mull, H: Ca. 1730 (very broad); 1685 (conjugated ketone); 1505, 1028, 873 and 800 (all furan).

Carbon tetrachloride, U:

ν	Δν½	
1756	21	... lactone, COOMe and acetate
1728	22	
1680	15	... conjugated ketone

Chloroform solution, U:

ν	Δν½	ε	
1749	32	803	...lactone, COOMe and acetate
1710	26	903	
1676	26	519	...conjugated ketone
1629	19	110	...unsaturation
1597	14	85	

No hydroxyl.

Amorphous Monacetyl Derivative (B) (Ac_2O-pyridine)

Nujol Mull, H: 3500 (hydroxyl); 3160, 1505, 1025, 875 and 800 (furan); 1737 (broad and strong; COOMe, lactone, ketone and acetate); 1600 (unsaturation).

Amorphous Monacetyl Derivative (C) (Ac_2O - NaOAc)

HeB, H: 3520 (hydroxyl); 3170, 1507, 1027, 875 and 800 furan; 1735 (broad and strong, COOMe, lactone, ketone and acetate); 1605 (unsaturation).

Amorphous Diacetyl Derivative (D) ($Zncl_2$ - Ac_2O)

Nujol Mull, H: 3160, 1510 (furan); 1745 (lactone, COOMe and acetate); 1685 (conjugated ketone) and 1600 (unsaturation). No strong furan peaks at ca. 875 or ca. 800, suggesting that the furan ring may have been modified.

Carbon tetrachloride, U: 1750, 1733, 1720 (lactone, COOMe, acetate); 1688 (conjugated ketone).

Amorphous Diacetyl Derivative (E) (trifluoroacetic anhydride-acetic acid).

Nujol Mull, H: 3160, 1507, (furan); 1745 (lactone, COOMe and acetate); 1684 (conjugated ketone) and 1600 (unsaturation). No strong furan peak at ca. 875 or ca. 800, suggesting that the furan ring may have been modified.

Lithium Aluminium Hydride Reduction Product of Swietenolide (crystalline).

Nujol Mull, H: 3520 and 3430 (hydroxyl); 3200, 1510, 1028 and 875 (all furan); no carbonyl.

50% Sulphuric Acid Reaction Product of Swietenolide (crystalline).

Nujol Mull, H: 3500 (hydroxyl); 1750; 1725; no furan peaks.

Red Crystalline Product (a) Obtained From Swietenolide with Thionyl Chloride and pyridine.

Nujol Mull, H: 3430; 1745; 1707; 1687 (conjugated ketone); 1582, 1560 and 1540 (strong; heterocyclic unsaturation).

Swietenine.

Nujol Mull, H: 3160, 1506, 1030, 877 and 815 (all furan).

Carbon tetrachloride solution, U: 1752 (six ring lactone); 1743 and 1734 (COOMe and tiglate functions); 1716 (side chain or six ring ketone).

Chloroform solution, U:

ν	ϵ	
3605	58	... partly hydrogen bonded hydroxyl.
3540	72	
1735	1444	... lactone and esters.
1708 (Shoulder)	-	... ketone.
1650	135	... unsaturation.

Proton Magnetic Resonance Spectrum

These were kindly determined by Dr. C.F.H. Tipper and Dr. Lee (Liverpool University) using methylene chloride solutions under the conditions described by Corey[34d].

Swietenolide gave peaks at -116 and -69 cycles per sec. relative to water, the former being about twice as intense as the latter. This indicates the presence of a β-substituted furan ring[34d]. There are no peaks with shifts more negative than -116, and CHO or COOH functions are therefore absent.[65]

In swietenine the furan peaks were at -112 and -60 cycles per sec., the former having twice the intensity of the latter; peaks with more negative shifts were again absent.

Ultraviolet Light Absorption Spectra.

Unless otherwise stated, the spectra were determined in ethanol using a Unicam S.P. 500 spectrophotometer. The ethanol was purified as described by Bladon et al.[48] Some of the maxima observed near 210mμ are probably apparent maxima due to the effect of stray light.[48] In the case of swietenolide the Optica CF 4 grating spectrophotometer which is claimed to have less stray light than prism instruments also gave a maximum in this region.

Swietenolide	λ (mμ)	log ϵ (Unicam)	log ϵ (Optica)
maximum	288	1.72	not determined.
end absorption	220	4.00	3.99
"	215	4.08	4.07
"	210	4.13	4.09
apparent maximum	209	4.133	4.09
Swietic Acid			
maximum	288	1.72	
end absorption	220	4.01	
"	215	4.09	
"	210	4.14	
apparent maximum	209	4.14	
Hexahydroswietenolic Acid			
maximum	284	1.70	
end absorption	220	3.66	
"	215	3.74	
"	210	3.80	
apparent maximum	208	3.81	
Lithium Aluminium Hydride Reduction Product of Swietenolide (crystalline).			
end absorption	220	4.12	
"	215	4.24	
apparent maximum	211-212	4.28	

Crystalline Monoacetate (A)

	λ(mμ)	log ε
maximum	276	4.18
minimum	250	3.97
shoulder	230-232	4.09
end absorption	220	4.14
apparent maximum	216	4.16

Monacetyl Derivative (B)

maximum	280	3.12
end absorption	220	4.02
"	215	4.08
apparent maximum	212	4.11

Monoacetyl Derivative (C)

maximum	280	3.27
end absorption	220	4.03
"	215	4.08
apparent maximum	212	4.10

Diacetyl Derivative (D)

maximum	271	4.08
minimum	242	3.64
end absorption	220	3.95
"	215	3.97

Diacetyl Derivative (E)

maximum	271	4.10
minimum	242	3.64
end absorption	220	3.95
"	215	3.97

Red Crystalline Product (a) Obtained from swietenolide with thionyl chloride and pyridine.

$\lambda_{max.}$ (mμ)	$E_{1\ cm.}^{1\%}$
494	2.24
295	2.28
260	2.36

Dehydroswietenolide

In ethanol after 15 to 20 minutes:

$\lambda_{max.}$ 288 mμ, log ε 2.84; end absorption 220 mμ, log ε 4.00 and 215 mμ, log ε 4.10; apparent maximum, 210 mμ, log ε 4.14.

In ethanol after 24 hours:

$\lambda_{max.}$ 286-288 mμ, log ε 3.39.

In acidified ethanol after 15 to 20 minutes:

$\lambda_{max.}$ 288-289 mμ, log ε 2.01; end absorption 220 mμ, log ε 4.08 and 215 mμ, log ε 4.16; apparent maximum 210 mμ, log ε 4.22. The values were unchanged after 24 hours.

In alkaline ethanol after 15 to 20 minutes:

$\lambda_{max.}$ 288-289 mμ, log ε 4.54; end absorption 220 mμ, log ε 4.04 and 215 mμ, log ε 4.16; apparent maximum 208 mμ, log ε 4.36. The values were unchanged after 24 hours.

Alkaline ethanol again acidified; reading after 15 to 20 minutes:

$\lambda_{max.}$ 262-264 mμ, log ε 4.38; end absorption 220 mμ, log ε 4.01 and 215 mμ, log ε 4.05; apparent maximum 210 mμ, log ε 4.07. The values were unchanged after 24 hours.

Enol from dehydroswietenolide

	λ(mμ)	log ε
maximum	286-288	4.46
end absorption	220	3.96
apparent maximum	210-214	4.05

Methyl ether of above enol:

	λ(mμ)	log ε
maximum	262-264	4.26
end absorption	220	4.04
"	215	4.10
apparent maximum	210	4.15

Swietenine

shoulder	279-282	1.79
end absorption	220	4.18
"	215	4.27
apparent maximum	208	4.32

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