CHAPTER I - INTRODUCTION
CHAPTER I

INTRODUCTION

TRITERPENOID BITTER PRINCIPLES

All the known triterpenoid bitter principles are of plant origin. Their complete structures have been elucidated only during the last six years. Chemical and physical methods particularly PMR spectral and X-ray crystallographic studies have been used to determine the complex structures of this group of compounds. This chapter will summarise the chemical transformations and diagnostic PMR studies done in this group of compounds which helped in the elucidation of their individual structures.

The nineteen presently known triterpenoid bitter principles with their physical constants and sources are enumerated in Table 1. Limonin (I) is perhaps the oldest known member of this type of compounds. The constitution of limonin\(^1,2\) has recently been fully determined by the brilliant collaborative work of Arigoni, Barton, Corey, Jeger and their collaborators. Its structure was confirmed and stereochemistry determined by an X-ray investigation by J.M. Robertson and his co-workers. The structure
determination of limonin has led to the determination of the structures of a number of related triterpenoid bitter principles. Besides, extensive work on limonin has enriched the chemical literature with a series of interesting and sometimes intriguing chemical transformations. Some of the more important of these are detailed below.

1. Limonin (I) on treatment with hydriodic acid or chromous chloride, gets rid of the epoxide \( \alpha \) to the lactone carboxyl and affords an \( \alpha\beta \)-unsaturated lactone viz. deoxylimonin (II).

2. Reduction of limonin (I) by Meerwein-Ponndorf method gives the axial alcohol limonol (III) which on treatment with five percent aqueous sodium hydroxide yields merolimonol (IV) and furan-3-aldehyde, possibly by an assistance with the backside attack of the anion of the \( C_7 \)-hydroxyl group at the \( C_{14} \)-carbon, consequent cleavage of the epoxide ring to a \( C_{15} \)-alcohol, followed by cleavage of the \( C_{13}-C_{17} \) bond to form a \( C_{13},C_{14} \)-double bond and the furan-3-aldehyde. The free carboxyl group of the lactone now lactonises with the \( C_7 \)-hydroxyl group.

3. Merolimonol(IV) on treatment with 2% barium hydroxide in a sealed tube at 150-200\(^\circ\)C gives an acid which on esterification gives an ester (V). In this case, probably the five membered ether in ring A
1) CHROMOUS CHLORIDE OR HYDRIODIC ACID 2) MEERWEIN-PONNDORF REDUCTION
3) REFLUXING WITH AQUOUS 5% SODIUM HYDROXIDE 4) 20% Aq. Ba(OH)₂ AT 150-200° 5) Pt/H₂ IN ACETIC ACID 6) DIOXAN-HYDROCHLORIC ACID.

CHART - 1.
opens up by a \( \beta \)-elimination from \( C_2 \), forming a \( C_1, C_2 \)-double bond, the lactone ring opens up and the \( C_3 \)-hydroxyl then recloses with the \( C_1, C_2 \)-double bond forming an acid, epimeric at \( C_1 \), whose stereochemistry is now unfavourable for relactonisation.

4. Limonin itself with barium hydroxide undergoes a similar rearrangement giving limoclastic acid, (VI), but in this compound there is a hydrogen atom at \( C_{10} \) in place of the original primary hydroxyl group. In this case, the first step is considered to be a hydride transfer from \( C_{19} \) to the top of \( C_7 \)- to give the \( C_7\alpha \)-alcohol and a \( C_{19} \)-aldehyde. Opening of the \( A \) ring ether and removal of \( C_{19} \) aldehyde as a molecule of formic acid and further changes as formulated before, leads to limoclastic acid (VI).

5. The action of hydrochloric acid-acetic acid on hexahydrolimoninic acid (VII) (obtained by catalytic hydrogenation of limonin) gives a neutral isomer containing a \( \delta \)-lactone ring (VIII) probably by a concerted reaction as shown in formula (VII).

Nomilin\(^{2,3} \) (IX) and obacunone\(^{2,3} \) (X) are correlated to limonin (I) by converting them to common degradation products. Nomilin and obacunone on mild treatment with alkali give obacunoic acid (XI).

Obacunoic acid on reduction with chromous chloride
affords deoxybacunoic acid (XII). PMR spectrum of methyl obacunoate (XIII) showed five quaternary methyl groups (at 1.09; 1.13; 1.2; 1.23 and 1.46), a proton at 3.63 \( (C_{15}) \) another at 5.36 \( (C_{17}-\text{proton}) \), an AB quartet centred at 5.96, 5.66. \( J=13 \) cps. \( (C_1, C_2-\text{protons}) \) and \( \beta \)-substituted furan protons at 7.31 and 6.3. Structures of nomilin and obacunone were fully established by correlating an obacunoic acid derivative with a limonin derivative as detailed below.

Obacunoic acid (XI) on treatment with barium hydroxide for a short time afforded epi-isoobacunoic acid (XIV) which is different from the known isoobacunoic acid (XV) obtained by long treatment with barium hydroxide. This acid (XIV) lacked the \( \alpha\beta \)-unsaturated acid function of obacunoic acid (XI) and also the hydroxyl group. Epi-isoobacunoic acid (XIV) is also converted to isoobacunoic acid (XV) on long treatment with barium hydroxide and they are found to be epimeric at \( C_1 \).

Meerwein-Ponndorf reduction of methyl epi-isoobacunolate (XVI) in isopropyl alcohol afforded isopropyl epi-isoobacunolate (XVII) which on treatment with sodium hydroxide, under the condition needed to transform limonol (III) to merolimonol (IV), yielded epi-meroobacunolic acid (XVIII). Dehydration of methyl-epi-meroobacunolate (XIX) afforded anhydro-epi-
XVIII $R = H$
XIX $R = CH_3$

1 ALKALI
2 CHROMOUS CHLORIDE
3 $Ba(OH)_2$ BRIEF PERIOD
4 $Ba(OH)_2$ LONG PERIOD
5 MEERWEIN-PONNDORF REDUCTION
6 REFLUX WITH 5% Aq. NaOH
7 $POCl_3$ / PYRIDINE
8 Pd/c HYDROGENATION

CHART - 2.
meroobacunolate (XX) which on catalytic hydrogenation gave methyl tetrahydroanhydro-epi-meroobacunolate (XXI).

Methyl isoobacunolate (XXII) was also subjected to the same series of reactions to get the corresponding iso-compounds.

From limonin also a corresponding compound was made by the following series of reactions. Limonin (I) was reduced to limonol (III) which on treatment with alkali gave merolimonol (IV) and this on dehydration with phosphorus oxychloride was converted to anhydromerolimonol (XXIII) which on catalytic reduction afforded tetrahydroanhydro-merolimonol (XXIV). Tetrahydroanhydromerolimonol (XXIV) when hydrolysed with barium hydroxide under drastic conditions gave a lactonic hydroxy acid (XXV).

In this reaction, the lactone ring A is opened irreversibly. Structure (XXV) was assigned to this compound having the acetic acid side-chain at C_1 in the α-configuration, which is considered to be the more stable one in limonin. The methyl ester (XXVI) of the lactonic acid (XXV) was then mesylated at C_19 which on treatment with sodium iodide at 180° afforded an acid which on methylation with diazomethane followed by treatment with zinc and acetic acid gave a crystalline ester (XXVII). This product (XXVII) was found to be identical with methyl tetrahydroanhydro-epi-meroobacunolate (XXII) by melting point, mixed melting point and infrared spectra.
Hence obacunone (X) has the same configuration at C_5^-, C_8^-, C_9^- and C_{10}^- positions as in limonin. Barton and collaborators found that treatment of the methyl ester acid (XXVIII) obtained by complete hydrogenation of methyl obacunoate (XIII), with dioxan-hydrochloric acid, under the conditions needed to transform hexahydro-limoninic acid (VII) into its rearranged isomer (VIII), gives an acidic product (XXIX) which from its infrared spectrum (1785 cm\(^{-1}\)) contains a \(\gamma\)-lactone. Therefore the C, D-ring fusion of obacunone must be \textit{trans} as in limonin. Further it can be concluded that the 14-15 epoxy group of obacunone has the \(\beta\)-configuration because of the transformation of (XVII) to (XVIII); for in this, assistance by a backside attack of the C_7-hydroxyl group at C_{14}-carbon is envisaged. Thus the structure and stereochemistry of obacunone and nomilin were established as in (IX) and (X).

Veprisone,\(^5\) a natural product isolated from Vepris biloculares, has been characterised by its physical and chemical properties as methyl epi-isoobacunoate (XVI) a known derivative of obacunone (X).
1. REFLUX WITH 5% AQ. ALKALI
2. POCI₃ - PYRIDINE
3. Pd/H₂
4. Ba(OH)₂ AT 150-220°C
5. i) MeSO₂Cl, ii) NaI AT 180°C, iii) CH₂N₂, iv) Zn IN ACETIC ACID
6. DIOXAN - HYDROCHLORIC ACID

CHART - 3
Gedunin showed absorption maxima in the ultraviolet at $\lambda_{\text{max}}$ 215 $\mu$m and 333 $\mu$m ($\log \epsilon$ 4.12 and 1.8 respectively) and in the infrared at 1686, 1502 and 875 cm$^{-1}$ consistent with the presence of an $\alpha\beta$-unsaturated ketone and a furan ring. The maximum at 215 $\mu$m is due to the combined absorption of the $\alpha\beta$-unsaturated ketone and the furan ring. When the ultraviolet absorption of dihydrogedunin (obtained by partial hydrogenation of gedunin) which still has the furan ring intact, (1502 and 875 cm$^{-1}$) is subtracted from that of gedunin, the maximum for the unsaturated ketone appeared at 227 $\mu$m ($\log \epsilon$ 4). Dihydrogedunin on ozonolysis gave an acid, which on saponification consumed three moles of alkali. The methyl ester of this acid was reduced with sodium borohydride to an alcohol which on treatment with phosphorous pentachloride and then ozonolysis gave acetone and a cyclopentanone derivative. This reaction sequence is characteristic of 4,4-dimethyl 3-oxo-terpenoids with rings A and B trans fused.

Hydrolysis of gedunin under mild conditions gave desacetyl gedunin (unaffected by acetic anhydride and pyridine but giving back gedunin by treatment with acetic anhydride and p-toluene sulphonic acid. This suggested that gedunin is the acetate of a
(1) Pd/H₂
(2), (5) O₃
(3) NaBH₄
(4) PCl₅
(6) REFLUX WITH 5% AO. NaOH
tertiary or sterically hindered secondary alcohol.

Alkaline hydrolysis of gedunin gave a \( \delta \)-lactone (XXXVII) and furan-3-aldehyde like merolimonol from limonol. This establishes the presence of a 7\( \alpha \)-hydroxy group and an \( \beta \)-epoxy-\( \delta \)-lactone group in gedunin in the environments present in the B, C, D rings of limonin. The structure (XXX) was therefore proposed for it.

The product obtained by oxidising desacetyl gedunin (XXXVI) with chromic acid in acetone is characterised as 7-oxo-gedunin\(^8\). This 7-oxogedunin (XXXVIII) was found to be identical with a naturally occurring product isolated from Cedrela adrorata.

Structures assigned to the naturally occurring products, gedunin\(^6\), 7-desacetyl-7-oxogedunin\(^8\) and dihydrogedunin\(^7\) were fully confirmed by the X-ray investigation of 3 \( \beta \)-iodoacetate of dihydrogedunol.

Khivorin

Spectral evidence of khivorin (XXXIX)\(^8\) showed the presence of a furan ring. Khivorin on hydrolysis with alkali gave furan-3-aldehyde and a hydroxy lactone-\( \delta \) khivol (XL)\( \nu_{\text{max}} \) 1765 and 3300 cm\(^{-1}\). If khivorin contains three acetoxy groups then all its carbon atoms can be accounted. Khivorin (C\(_{32}\)H\(_{42}\)O\(_{10}\))

\[ + 3\text{H}_2\text{O} \rightarrow \text{Furan-3-aldehyde (C}_5\text{H}_4\text{O}) + \text{khivol (C}_{21}\text{H}_{32}\text{O}_5\text{)} + 3(\text{CH}_3\text{COOH}) \]

This hydrolysis is analogous to that of limonol. If three acetoxy groups, a furan ring,
an epoxy group, and a lactone grouping are considered as present in khivorin, its formula is consistent with the presence of three carbocyclic rings.

Chromous chloride reduction of khivorin gave deoxykhivorin (XLI) whose ultraviolet spectrum was in keeping with the presence of both a furan ring and an αβ-unsaturated-γ-lactone. Ozonolysis of deoxykhivorin led to attack on the furan ring and formation of an acid (XLII) with a change of -121° in ($\Delta$D)**. Two acetoxy groups are placed at C₁ and C₃ positions in ring A on biogenetic grounds. Hydrolysis of deoxykhivorin gave a tridesacetyl derivative (XLIII). Oxidation of the tridesacetyl derivative gave an endocyclic triketone (XLIV) with ultraviolet absorption $\lambda_{max}$ 253 μm (ε 16,100) in ethanol changing to $\lambda_{max}$ 285 μm (ε 24100) on addition of alkali. These results are consistent with a 1,3 diketone chromophore in the product.

Khivorin was added to a solution of sodium in dry methanol and the suspension refluxed for three hours, to give tridesacetyl khivorin. Tridesacetyl khivorin is acetylated to get the 1,3-diacetate which on oxidation with chromic acid in acetone gave 7-desacetyl-7-oxo khivorin® - the natural product (XLV).

** Dihydrogedunin (XXXI) on ozonolysis also gives an acid with a change of -113° in ($\Delta$D).
1 REFLUX WITH 5% Aq NaOH
2 CHROMOUS CHLORIDE
3 O₃
4 ALKALI
5 JONE'S REAGENT
From mass spectrometric investigations, cedrelone (XLVI) was found to have the molecular formula $C_{26}H_{30}O_5$. Two of the five oxygen atoms must be located in a diosphenol system as shown by the positive test with ferric chloride, ($\nu_{\text{max}}$ 3420, 1678, 1655 cm$^{-1}$) $\lambda_{\text{max}}$ 279 µm ($\varepsilon$ 9100) shifted by base to 327 µm ($\varepsilon$ 5550) as well as by the preparation of a monoacetate (XLVII) ($\nu_{\text{max}}$ 1770, 1732 cm$^{-1}$). PMR spectrum of cedrelone shows the presence of five tertiary methyl groups in a substituted furan ring ($\delta$ 7.36, 7.14 and 6.17), an AB quartet centred at $\delta$ 6.9 and 6.1 ($J = 10$ cps.), and a proton on a carbon bearing an ether oxygen at $\delta$ 3.78.

Catalytic hydrogenation of cedrelone under mild conditions yielded the dihydroderivative (XLVIII) in which the double bond in ring A has saturated.

The curve obtained by the subtraction of the ultraviolet absorption of dihydrocedrelone from that of cedrelone had $\lambda_{\text{max}}$ 225 µm ($\varepsilon$ 8100). This is the contribution of the enone-chromophore in ring A to the total ultraviolet absorption of cedrelone. Its complete structure and stereochemistry have been established as (XLVI) by an x-ray investigation of the iodoacetate of cedrelone (XLVIIa). Ring A in cedrelone and dihydrocedrelone is in a half-boat form and boat form.
respectively as shown by X-ray study and chemical reactions. The high hindrance of the C₂-ketone to oxime formation and reduction is consistent with this conformation. Thus on sodium borohydride reduction surprisingly the C₁, C₂ conjugated double bond is reduced, leaving the ketone intact. Two interesting chemical transformations of cedrelone are summarised.

(1) Cedrelone acetate (XLVII) on treatment with boron trifluoride-etherate yielded isocedrelone acetate (XLIX), comparison of whose infrared and ultraviolet spectra with those of cedrelone acetate established that a new hydroxyl and a new chromophore had been introduced. Subtraction curve of cedrelone acetate from that of isocedrelone acetate had \( \lambda_{max} 242 \text{ nm} \ (\varepsilon 13230) \), which is assigned to the substituted vinylfuran. The downfield shift of two of the furan protons in the PMR spectrum of this compound supported the presence of a double bond conjugated with the furan. Also, this compound gave a reddish brown colour to tetra nitromethane. Thus the reaction with BF₃-etherate is envisaged as the opening up of the axial C₁₄-oxygen linkage, followed by a concerted migration of the C₁₃-\( \alpha \)-methyl group and the elimination of the C₁₇-\( \beta \)-proton to form the C₁₃, C₁₇ double bond in isocedrelone acetate (XLIX).
(2) Treatment of cedrelone with aqueous potassium hydroxide under reflux and further treatment with acid afforded an isocedrelonic acid (L). This acid is stable to boron trifluoride etherate. The ultraviolet absorption of isocedrelonic acid at $\lambda_{\text{max}} 235 \text{ mu}$ ($\epsilon 23,000$), unaltered in base, suggested that the diosphenol was no longer present and that the epoxide has opened up in the same manner as in isocedrelone acetate. Hence isocedrelonic acid is assigned structure (L). Thus cedrelone has to undergo a benzilic acid rearrangement also, to give this product. This reaction does not take place with dihydrocedrelone. Hence the reaction sequence is envisaged as the addition of an $\alpha$-hydroxyl group at $C_1$, ketonisation of the $C_6$-enol to the cis A/B rings, ketalisation of the $C_1 \alpha$-OH and the $C_6$-ketone, followed by benzilic acid rearrangement and subsequent opening up of the epoxide leading to the formation of (L).

From the infrared spectra of cedrelone, intramolecular hydrogen bonding in the diosphenol (low carbonyl absorption 1673, 1685 cm$^{-1}$) was observed. This was confirmed by determining the infrared spectra of the $C_6$-acetate, when the $C_7$-carbonyl absorbs at the normal position of 1702 cm$^{-1}$ and $C_6$-enol acetate at 1770 cm$^{-1}$.
1  Pd/C OR NaBH₄
2  BF₃ - ETHERATE
3  ALKALI, H⁺

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Anthothecol (LI) is an acetoxyl derivative of cedrelone (XLVI). Spectral properties and chemical transformations of anthothecol are similar to those of cedrelone. Mild alkaline hydrolysis gives a desacetyl derivative (LII) which on oxidation gives a ketone (LIII). Hence the alcohol in desacetyl anthothecol (LII) is a secondary one. Functional groups of anthothecol left one oxygen atom unaccounted for. This oxygen atom may be present as an oxide. If anthothecol contained an oxide ring, it should be reduced by chromous chloride to a deoxy-compound as in the other epoxy bitter principles. This was investigated on the ketone (LV) obtained by chromic acid oxidation of desacetyl dihydro anthothecol (LIV). Reduction of this compound with chromous chloride gave a deoxy-compound (LVI) but having spectral properties similar to those of the starting material. This shows that the compound (LV) contains an epoxide group but that it is not adjacent to an unsaturated function or carbonyl group, since the deoxy-compound (LVI) shows no spectral evidence of new conjugated unsaturation.

The position of the acetoxyl group may be at C_{11}-C_{12} or C_{16} since it is found to be the acetate of a secondary hydroxyl. It is not at C_{1} or C_{2} since hydrolysis does not give an \alpha or \beta diketone. If the acetoxyl group were at 16, then hydrolysis and oxidation
would give an $\alpha\beta$-epoxy ketone, which would be expected on reduction with chromous chloride to give an unsaturated ketone. As the ultraviolet absorption spectrum of the chromous chloride reduction product (LVI) of desacetyl dehydrodihydroanthothecol (LV) shows no new $\alpha\beta$-unsaturated ketone, the acetoxy cannot be at C$_{16}$. Moreover, its infrared spectrum is consistent with the new carbonyl in a six-membered ring before and after the chromous chloride reduction.

If the acetoxy group were at position 12, then the rearranged benzilic acid (LVII) and isoanthothecol (LVIII) would be allyl alcohol derivatives, and it seems unlikely that these would survive the conditions of formation without dehydration to a furylbutadiene. The spectral properties expected for such a compound would also be different from those found. Moreover if the acetoxy group were at position 12, then the compound (LV) obtained by hydrogenation of (LI) and oxidising the hydroxyl to a ketone, would be expected to rearrange under acid conditions to a compound in which the furan ring is conjugated through the C$_{13}(17)$-double bond with the 12 carbonyl group. Such a conjugated system would be expected to show an absorption maximum at ~314 nm, similar to that shown by furfurylecene acetone. In fact, acidic rearrangement of compound (LV) gave an isocompound (LIX) having an absorption maximum similar to isoanthothecol (LVIII) and the benzilic ester (LVII). For these reasons, the
1 ALKALI
2 HYDROGENATION
3 CHROMOUS CHLORIDE
4, 5 ACID
6 ALKALI

CHART - 7.
positions 16 or 12 are ruled out for the acetoxy function and hence is assigned to the remaining position 11. As the acetate is easily hydrolised and the liberated hydroxyl could also be easily reacetylated, its configuration at C\textsubscript{11} is considered as α.

Andirobin\textsuperscript{16} C\textsubscript{27}H\textsubscript{32}O\textsubscript{7}

The PMR spectrum of andirobin (LX) showed the presence of a β-substituted furan ring (\(\delta\) 7.56) (two α protons), 6.38 (one β proton), an AB quartet characteristic of an αβ-unsaturated carbonyl grouping centred at \(\delta\) 7.2 and 6.12; \(J = 10\) cps.) four protons as singlets (\(\delta\) 5.53; 5.45, 5.33 and 4.08) one carbomethoxy group (\(\delta\) 3.75) and four tertiary methyl groups (\(\delta\) 1.12, 1.12, 0.99 and .95).

The sharp AB quartet suggested the presence of a cis-disubstituted double bond and a tertiary γ-carbon atom. Biogenetic analogy and comparison of the PMR spectrum of andirobin with that of dihydrogedunin (XXXI) suggested that the singlets at \(\delta\) 5.53 and 4.08 could be assigned to two protons at C\textsubscript{15} and C\textsubscript{17} respectively. The presence of an epoxy-\(\delta\)-lactone was fully confirmed by its smooth reduction with chromous chloride to deoxyandirobin (LXII).

Hence structures (LX) or (LXI) were suggested for, andirobin, on the above evidences. The singlets at \(\delta\) 5.45 and 5.33 could be assigned to two protons of the exocyclic methylene group. The γ-β-location of
1) CHROMUS CHLORIDE
2) Pd/C H₂

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the vinyl double bond with respect to the 
\( \alpha\beta \) epoxy-\( \alpha \)-lactone carbonyl in andirobin was clearly 
indicated by subtraction of the UV spectrum of 
andirobin from that of deoxyandirobin (LXII) 
(\( \lambda_{\text{max}} 257 \mu \text{m} \leq 8300 \)) compare UV of the derivative 
(LXIII) from limonin (\( \lambda_{\text{max}} 255 \mu \text{m}, \leq 7800 \)). 
Comparison of the chemical shift of the \( C_{17} \) proton 
in andirobin and its derivatives with those of 
dihydrogedunin showed that the \( C_{17} \) proton was not 
allylically placed with respect to the vinyl group.

From the above data, structure (LX) was 
preferred for andirobin. Andirobin on catalytic 
hydrogenation gave the dihydro compound (LXIV) the 
PMR spectrum of which showed the presence of a new 
vinyl methyl group and the absence of exocyclic methylene 
group. This confirms the presence of the exocyclic 
methylene group which has been found before as at \( C_8 \).

The Structure of Methyl Angolensate

Methyl angolensate \( C_{27} H_{34} O_{7} \) (LXV) showed the 
presence of a keto group \( \lambda_{\text{max}} 287 \mu \text{m} (\varepsilon 26) \). 
Spectral data showed a \( \beta \)-substituted furan, and two 
ester or \( \alpha \)-lactone groups, or one ester and one 
\( \alpha \)-lactone group. Reduction of the keto group 
with potassium borohydride gave an alcohol which could 
be reoxidised to methyl angolensate. With phosphorous 
pentachloride the alcohol underwent a retropinacolinic 
rearrangement to give a product, which gave acetone and a
cyclopentanone derivative on ozonolysis. This indicates a typical triterpene ring \( A \) with a 3-oxo group.

Reduction of methyl angolensate with lithium aluminium hydride gave a mixture of two triols

\[
\begin{align*}
\text{C} & \rightarrow \text{CHOH} ; \quad \text{CO}_2\text{Me} \rightarrow \text{CH}_2\text{OH} ; \quad \text{CO} - \rightarrow \text{CH(OH)} - 0 \\
\text{and a diol} & \quad \text{C} = 0 \rightarrow \text{CHOH} ; \quad \text{CO}_2\text{Me} \rightarrow \text{CH}_2\text{OH}.
\end{align*}
\]

On oxidation the triols gave angolensic acid. On Oppenaur oxidation the diol gave a hydroxy aldehyde, the aldehydic proton of which appeared as a triplet \( (\delta 9.95) \) indicating the presence of \( \text{CH}_2\text{CHO} \) and hence of \( \text{CH}_2\text{COOMe} \) in methyl angolensate.

Hydrogenation of methyl angolensate in acetic acid over palladised charcoal gave an octahydro acid (LXVI). This reaction indicates the presence of the grouping (LXVII) in the molecule. The \( pK_a \) of this acid showed that it is not an \( \alpha \) oxy-acid as in the epoxy bitter principles. These functional groups account for six out of the seven oxygen atoms. The NMR spectrum of methyl angolensate had a band at \( \delta 3.47 \) (one proton) indicative of \( \gamma\text{CHO} \). This suggested that the seventh oxygen atom was in a cyclic ether. The analytical data indicate three carbocyclic rings or double bonds in methyl angolensate.

The PMR spectrum of methyl angolensate showed four tertiary methyl groups instead of the five in gedunin (XXX) and three apparently singlet protons at \( \delta 5.66, 5.15 \) and 4.90. The one at \( \delta 5.66 \) is assigned
to the \( C_{17} \)-proton by comparison with the spectra of gedunin and its derivatives. The other two protons could be in an exocyclic methylene group. This was established by the PMR spectrum of the acid (LXVI) which no longer showed the singlet protons but had bands due to five methyl groups one of which appeared as doublet and hence is a \( >CH,Me \) group.

The presence of the \( CH_2COOMe \) group and \( >C = CH_2 \) group in methyl angolensate can be explained if ring B or C of gedunin skeleton has been opened by oxidation of a grouping \( \overset{0}{C} -Me \) to \( \overset{0}{C} -O-C -Me \) and to \( \text{COOH} + C = CH_2 \) on biogenetic considerations. The methylene group could be at \( C_8 \) or \( C_{13} \). On mild hydrogenation methyl angolensate gave an inseparable mixture of two dihydro compounds. If it were at \( C_{13} \) then in the dihydro product the extra hydrogen at \( C_{13} \) would split \( C_{17}-H \) into doublet, if it were at \( C_8 \) this would not happen. The \( C_{17} \) proton appears as a singlet in the dihydro compounds thus indicating \( C_8 \) as the site of the exo methylene group.

This evidence together with biogenetic considerations leads to partial structure (LXVII) for methyl angolensate (LXVIII). When angolensic acid was stirred at 25° with sodium isobutoxide in toluene, an \( \alpha \beta \)-unsaturated ketonic acid (LXIX) was formed presumably by a base catalysed \( \beta \)-elimination. Its methyl ester
1) pd/c in acetic acid H₂
2) Sodium isobutoxide in toluene

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had $\lambda_{\text{max}}$ 236 mp ($e$ 11000) and $\nu_{\text{max}}$ 3425 (OH) and 1745, 1730 and 1664 cm$^{-1}$. Its PMR spectrum had no band due to a proton attached to $\text{-C-OH}$ but had two doublets at 7.68 and 5.95 (J = 11) indicative of $\text{-C\text{-CH\text{-CH\text{-C}}}$ grouping. On treatment with acid the unsaturated ester recylised to methyl angolensate. These results show that one end of the ether linkage is at $\text{C}_1\beta$ to the ketone group. The other end must be at one of the tertiary centres $\text{C}_5$, $\text{C}_9$ or $\text{C}_{14}$. Steric and biogenetic considerations point to $\text{C}_{14}$.

Structure (LXV) is related to the gedunin group of compounds. A possible precursor of gedunin and methyl angolensate is (LXX), $\beta$ elimination of the $\text{C}_1$-hydroxyl acetylation at $\text{C}_7$ and epoxidation at $\text{C}_{14}$-$\text{C}_{15}$ would give gedunin. Oxidation at $\text{C}_7$ to the $\text{C}_7$-ketone and further oxidation to the $\text{se-co-ring B}$ exocyclic methylene acid followed by $\beta$-addition of the hydroxy group at $\text{C}_1$ to $\text{C}_{14}$ would give angolensic acid.

Swietenine

Swietenine has been assigned the molecular formula $\text{C}_{32}\text{H}_{42}\text{O}_9$ from its mass-spectrum. Its constitution and stereochemistry have been established as (LXXI) by an X-ray investigation of the p-iodobenzoate of dehydroxydugloyl swietenine (LXXII). Some chemical transformations have been summarised which are consistent with this structure.
Catalytic reduction of swietenine afforded an octahydroacid (LXIII) in which the $\gamma$-lactone has been hydrogenolised but an isolated trisubstituted double bond has survived. In this compound the $C_{17}$-proton at $\delta$ 5.7 has disappeared. Thus the hydrogenolysis leads to a partial structure (LXVII) for swietenine.

Alkaline hydrolysis of swietenine afforded a complex mixture of acidic products. However from this mixture there was isolated by virtue of its insolubility in chloroform demethyldetigloylisoswietenine (LXXIV). Methylation gave detigloylisoswietenine (LXXV) and further tigloylation gave isoswietenine (LXXVI). The PMR spectrum of isoswietenine (LXXVI) shows the same functional groups as swietenine. The additional change then occurs during conversion of detigloylswietenine (LXXVII) into detigloylisoswietenine (LXXV). Three simple interpretations can be given for this change, (i) epimerisation to the ketonic or carboxyl function, (ii) intramolecular (conceivably intermolecular) hydride transfer between the ketone and hydroxyl function, resulting in their positional interchange, (iii) dealdolisation and realdolisation involving the hydroxyl and ketonic functions and resulting in their epimerisation at the carbinol carbon atom. The third alternative was favoured since optical rotatory dispersion and circular dichroism curves of the pairs of
swietenine and isoswietenine and the corresponding detigloyl derivatives differ only in amplitude but not in the sign or positions of their extreme. Alternatives (i) and (ii) would be reflected in more strikingly different optical properties.

The conclusion emerges that the change from detigloylswietenine (LXXVII) to detigloylisoswietenine (LXXV) proceeds through mechanism (iii), involving the ketonic carbonyl group and the secondary hydroxyl group that is tigloylated in swietenine, and results in epimerisation of the latter, showing that these functions must bear a 1-3 relationship one to the other. This conclusion is borne out by the change in coupling constant between the C₃-proton and its only neighbour C₂-proton from 11 cps. in swietenine to 2 cps. in isoswietenine.

As indicated above, alkaline hydrolysis leads to demethyldetigloylisoswietenine (LXXIV). Oxidation of this α-hydroxy acid with lead tetra acetate or with lead dioxide led to nor-aldehyde (LXXVIII). The C₅-H at $\int 2.77$ is coupled (J = 6 cps.) with the aldehydic proton at $\int 9.82$. The coupling pattern of C₅-H suggests that carbon atoms flanking C₅ do not bear hydrogen. This is supported by the fact that in dehydroswietenine (LXXIX), H-5 ($\int 5.03$) appears as a sharp singlet. The aldehyde function resists oxidation under normal conditions.
LXXI $R = \text{Tigloyl}; \ R' = \text{Me}$
LXXII $R = \text{p-CO}_2 \text{C}_6 \text{H}_4 \text{I}, \ R' = \text{Me}$
LXXVII $R = \text{H}; \ R' = \text{Me}$

1. ALKALINE HYDROLYSIS
2. $\text{CrO}_3/\text{Py}$ OR JONES REAGENT
3. $\text{Pb(OAc)}_4$ OR $\text{PbO}_2$
4. $0.25\text{N}\text{NaOH}$
On treatment with alkali, the aldehyde (LXXVIII) afforded an isomeric-$\gamma$-lactone (LXXX). Aldolisation between $C_2$ and $C_6$ cannot occur until configuration at $C_5$ has inverted. However as soon as epimerisation at $C_5$ has taken place, hydride transfer between $C_3$ and $C_1$ becomes possible. In the lactone (LXXX), the two mutually coupled protons $H-5$ ($\delta 7.48$, $J = 7$ cps.) and $H-6$ ($\delta 5.33$, $J = 7$ cps.), are vicinal and coplanar.

The complete structure and stereochemistry of swietenine as mentioned before as disclosed by the X-ray investigation, can readily be rationalised on its biogenesis from apoeuphol. Fission of ring B between $C-7$ and $C-8$ of a precursor related to the natural khivorin (XXXIX) and additionally oxygenated at $C-6$, could lead to the intermediate diene-lactone (LXXXI). Rotation about $C-9$, $C-10$, and intramolecular michael addition of $C-2$ to $C-3$ would result in the formation of the bicyclononanone system of swietenine.

Swietenolide$^{20}$ and Maxicanolide$^{21,22,23}$

Swietenolide (LXXXII) and Maxicanolide (LXXXIII) are two bitter principles related to swietenine (LXXI). Swietenolide is the 3-destiglyol $\Delta^{8(14)}$-isomer of swietenine (LXXII). Maxicanolide (LXXXIII) and 3-dehydro swietenolide (LXXXIV) have comparable PMR and
UV spectra. Maxicanolide had in neutral ethanol 
\( \lambda_{\text{max}} 239 \ \text{m} \) \( \mu \) \( (\varepsilon 10,850) \) which changed on addition of 
alkali to \( \lambda_{\text{max}} 287 \ \text{m} \) \( \mu \) \( (\varepsilon 31,701) \). This further changed 
on acidification to \( \lambda_{\text{max}} 264 \ \text{m} \) \( \mu \) \( (\varepsilon 29,803) \).

3-Dehydrosiwanenolide (LXXXIV) has also shown similar 
changes in the ultraviolet. These changes reflect the 
cleavage of \( C_9^- \), \( C_{10}^- \) bond and the formation of 
diene-lactone as (LXXXV) and (LXXXVI). Attempts to 
directly correlate siwanenolide either to maxicanolide 
or siwenenine have so far been unsuccessful. However 
they are related thus.

Oxidative cleavage by sodium periodate 
of the diketone (LXXXV) and (LXXXVI) derived 
respectively from siwenenolide (LXXXII) and 
maxicanolide (LXXXIII) resulted in each case without 
the loss of carbon atoms in the formation of two 
fragments. Both the diones afforded after methylation 
of the oxidation products the same diene-lactone (LXXXVII) 
\( \text{C}_{17}\text{H}_{18}\text{O}_5 \) representing the common rings C and D which 
is characterised by physical methods. The fragment 
representing ring A and its substitutents differed 
in the two cases. Thus the dione from siwenenolide 
afforded the oily \( \gamma \)-lactone (LXXXVIII) and that from 
maxicanolide afforded the oily trimethyl ester (LXXXIX).
CHART - 11.
Carapin\textsuperscript{24} 

Carapin (XC) and maximanolide (LXXXIII) from carapa procera are separated by TLC. On alkaline hydrolysis carapin gave diketone (LXXXVI) and its PMR spectrum showed a singlet at $\delta$ 5.79 due to the $\alpha$-proton on a double bond conjugated with an ester or lactone. Carapin shows UV absorption at $\lambda$ max 213 nm ($\epsilon$ 16000), comparable to that of deoxykhivonin (XLI) $\lambda$ max 213 nm ($\epsilon$ 14000). Thus carapin is $\Delta^{14(15)}$ isomer of maximanolide hence the structure (XC) has been assigned to it.

The above structures of swietenolide, maximanolide and carapin are mainly based on X-ray structural evidence of swietenine. Later the structure of maximanolide has also been confirmed by X-ray crystallography.

Biogenesis

All the triterpenoid bitter principles containing a skeleton of twenty-six carbon atoms with a $\beta$-substituted furan ring can be considered to be derived from the triterpenoid apoeuphol (XCI). These bitter principles can be broadly classified into four groups according to their oxidative levels.
**Type I**

Rings A and D oxidised but none cleaved

Cedrelone and anthothecol form the two compounds of this type.

**Type II**

Rings A and D oxidised but at least one ring cleaved.

The compounds are limonin, nimbilin, obacunone, veprisone, gedunin, dihydrogedunin, 7-desacetyl-7-oxo gedunin, khivorin and 7 desacetyl-7-oxo-khivorin.

**Type III**

Compounds having ring C oxidised and cleaved - nimbin and salanjhin form this group.

**Type IV**

Ring B oxidised cleaved and further modified compounds of this group are andirobin, methyl angolensate, swietenine, swietenolide, maxicanolide and carapin. Of course, these compounds were not discovered in the order given above. Limonin, as stated before was the first of the series whose structure was fully elucidated. Nimbin was the first compound whose structure was elucidated amongst the IIIrd and IVth groups, and its structure elucidation was the forerunner for the elucidation of the structures of the IV group of compounds also.
Biogenesis of Limonin

Limonin is revealed as a triterpenoid of the apoeuphol (XCI) type from which the four carbon atoms at the end of the side-chain have been removed and carbon 20 to 23 then oxidised to form the furan ring. Ring A of the triterpenoid skeleton has been oxidatively cyclised into \( C_{19} \). The constitution of limonin requires an allylic oxidation at \( C_{16} \) to a ketone and bayer-villiger oxidation of ring D between \( C_{16} \) and \( C_{17} \) to give a \( \delta \)-lactone. Further oxidation has also taken place at \( C_{7} \) in limonin. Modifications of this and appropriate oxidations at other sites can give other eighteen compounds dealt with.
All values in ppm

<table>
<thead>
<tr>
<th>Compound</th>
<th>Methyis</th>
<th>C_{15}</th>
<th>C_{17}</th>
<th>Furan (2H)</th>
<th>Furan (1H)</th>
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</thead>
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<tr>
<td>Limonin(^4)</td>
<td>1.08, 1.16, 1.16, 1.3</td>
<td>4.03</td>
<td>5.45</td>
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<td>Nomilin(^4)</td>
<td>1.08, 1.18, 1.31, 1.41, 1.58</td>
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<tr>
<td>Obacunone(^4)</td>
<td>1.11, 1.25, 1.14, 1.51, 1.51</td>
<td>3.65</td>
<td>5.41</td>
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<td>6.35</td>
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<td>Veprisone(^5)</td>
<td>1.3 (9H(\delta)), 1.33 (3H), 1.4 (3H)</td>
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<td>Dihydrogedunin(^16)</td>
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<td>3.52</td>
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<td>Cedrelone(^11)</td>
<td>0.75, 1.12, 1.29, 1.5, 1.56</td>
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<td>Nimbin</td>
<td>1.29, 1.36, 1.37 (Vinyl)</td>
<td>5.58</td>
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<td>7.34</td>
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<td>Salanin(^15)</td>
<td>0.99, 1.23, 1.33, 1.7 (Vinyl)</td>
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<td>3.73</td>
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<td>Andirobin(^16)</td>
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<td>Methylangolensate(^17)</td>
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<td>Swietenin(^18)</td>
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<td>M.P in °C.</td>
<td>Rotation in °</td>
<td>Source</td>
<td>Ref</td>
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<td>1</td>
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<td>3</td>
<td>Obacunone</td>
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<td>6</td>
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<td>7</td>
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<td>7-Desacetyl-7-oxo khivorin</td>
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<tr>
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<td>Anthothecol</td>
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<td>Khaya anthotheca</td>
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<td>12</td>
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<td>14</td>
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<td>-do-</td>
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<td>19</td>
<td>Carapin</td>
<td>175-78°</td>
<td>+64°</td>
<td>Cedrela procasa</td>
<td>24</td>
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References


5. T. R. Govindachari, B. S. Joshi and V. N. Sunderasan Tetrahedron, 22, 2985 (1964)


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