PICROTOXININ AND RELATED SUBSTANCES

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I. INTRODUCTION

Fifteen or so years ago, the suggestion of an epoxide group as a structural feature in a natural product would have provoked immediate scepticism. It was a rarity to say the least. Since then many substances have been found in nature which possess this feature and can be added to the list of a few outstanding examples, such as scopolamine, which were known then to possess this grouping. The substances covered in this review give ample evidence of the widespread occurrence of the epoxide group in nature since nine out of the sixteen compounds possess at least one epoxide group, and some contain two.

The majority of these substances contain only carbon, hydrogen, and oxygen and, owing to the nature of their carbon skeletons, are classed in the realm of sesquiterpenes of abnormal structure. The smaller group of substances contains a tertiary nitrogen atom in the place of an oxygen atom, and thus falls in the class of alkaloids. The basic carbon skeleton remains unchanged throughout both groups.

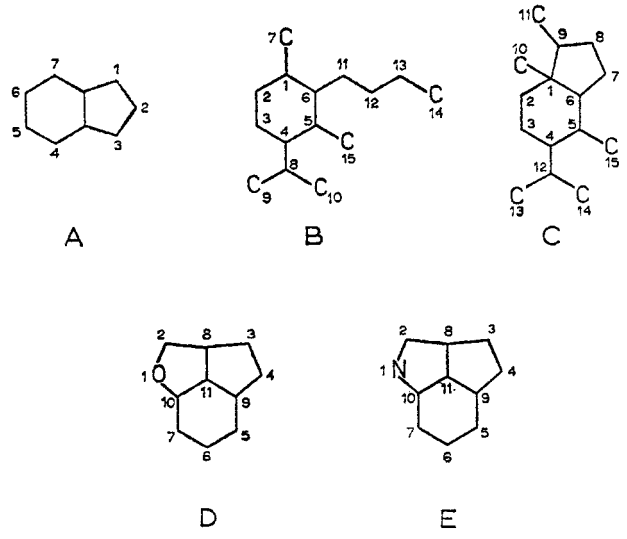


Figure 1.

Some of the compounds covered in this review have been surveyed earlier, notably picrotoxinin and picrotin, and coriamyrtin and tutin. However, the structures proposed for coriamyrtin and tutin were incorrect. In the case of picrotoxinin and picrotin, they were correct as far as they were covered, but many new substances have been studied since then, and some earlier material has been repeated to facilitate discussion (85). The survey of the literature pertaining to this review was completed December 1966.

Nomenclature of the carbon skeleton has presented difficulties in view of the bulkiness of fully systematic names. Most workers have avoided this by use of trivial names for the parent compounds and their derivatives. *Chemical Abstracts* indexes them under the trivial name, and, in the case of the terpenes, with a cross-reference based on their systematic nomenclature as derivatives of hexahydroindan, as shown in A of Figure 1. Some recent workers, especially in the Japanese group, have based skeletal numbering on this systematic name. Earlier workers, however, used a numbering system based on a hypothetical open-chain partial structure, devised before the true ring structure was known. It is extremely confusing, as shown in B of Figure 1, when applied to the true ring structure. It is therefore proposed, for the purpose of this discussion, to base the numbering of the carbon skeleton on a hypothetical picrotoxane, numbered as shown in C of Figure 1. This system will be used for all compounds. It is further proposed that, in addition to a systematic nomenclature based on hexahydroindane for the two-ring systems, systematic names be based on the new ring systems, decahydroindeno[7,1-*bc*]-furan and decahydrocyclopenteno[*cd*]indole, to cover the compounds, terpenoid and alkaloidal, respectively, that contain three fused rings. These two new rings are shown and numbered in D and E of Figure 1 (87, 118).

These substances all possess powerful physiological activity and have been, in some cases, the objects of intensive research along these lines. It is therefore fitting that a section of this review be devoted to a reasonably thorough coverage of this phase of the literature on the group. It is felt, however, that a chemical review journal is not the place for a detailed discourse in pharmacology. The coverage of the pharmacology of these substances is therefore meant to be representative, rather than exhaustive, to provide chemists with such interests a guide to the voluminous literature on the subject.

These sixteen substances represent a new carbon skeleton of rather widespread occurrence in nature. A small section of the discussion will thus be devoted to a phylogenetic treatment of the plant genera in which the substances occur. Proposed biogenetic pathways will also be mentioned.

II. Compounds without Nitrogen

A. Picrotoxinin and Picrotin

1. General History

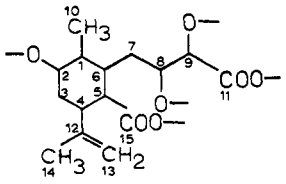
The chemical history of these two compounds began in the early 19th century when a bitter substance called picrotoxin, $C_{30}H_{34}O_{13}$, was isolated from a specie of poisonous plant from the family *Menispermaceae*, or moonseed family, native to regions of India (8). To date it has been found in *Cocculus indicus*, *Anamirta cocculus*, and *Menispermum cocculus*. Nearly three-quarters of a century later picrotoxin was shown to be two substances, picrotoxinin (XXI), $C_{15}H_{16}O_6$, and picrotin (XXXI), $C_{15}H_{18}O_7$ (4, 117). The first separation was done by solvent extraction and recrystallization. It was later replaced by a chemical separation (48, 97), which remained the only method of separation used until a recent chromatographic method was devised (64). Melting point–composition studies have shown that picrotoxin is a molecular compound of picrotoxinin and picrotin, with the components present in a 1 : 1 molar ratio (38).

Both picrotoxinin and picrotin contain two γ-lactones (19, 50). That picrotoxinin contains a terminal methylene group was shown on the basis of bromination (48, 97), hydrogenation (95, 101), ozonization experiments (39, 51, 95), and infrared spectra (19). Picrotin is saturated and neither compound gives carbonyl derivatives.

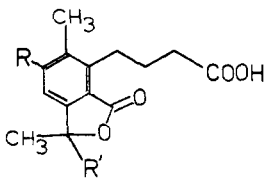
Acetylation experiments (97) and Zerewitenov determinations (11, 41, 50, 95, 97) suggested that picrotoxinin contained one hindered tertiary hydroxyl group and picrotin contained two tertiary hydroxyl groups, although the data were often ambiguous and conflicting. The remaining oxygen atom in both substances was assumed to be in an ether link (95).

2. *Picrotoxinin*

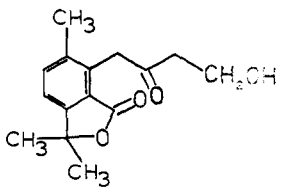
The partial carbon skeleton (I) for picrotoxinin was proposed (39, 96) to account for the formation of the substances picrotic acid (II) and picrotonol (III) formed by acid-catalyzed aromatization of picrotoxinin (3, 102). Picrotoxinin gives on ozonization formalde-



I



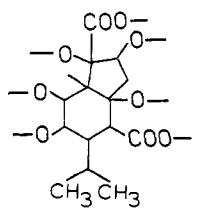
II; R=H, R'=CH_3
IV; R=H, R'=H
V; R=OH, R'=H



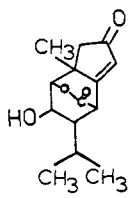
III

hyde and a ketone, α-picrotoxinone, $C_{14}H_{14}O_7$ (51). Reaction of α-picrotoxinone with hydrogen iodide and red phosphorus gives norpicrotic acid (IV), hydroxynorpicrotic acid (V), and a phenolic ketone, $C_{13}H_{16}O_2$ (39). These observations suggested the position in picrotoxinin of the terminal methylene (at C-12, -13) and provisionally located the remaining oxygen functions (at C-2, -8, -9, -11, -15) as shown in I.

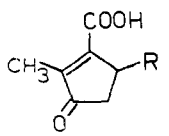
The partial structure for picrotoxinin was extended to VI on the basis of the formation of picrotoxinide (VII), formed when dihydro-α-picrotoxininic acid



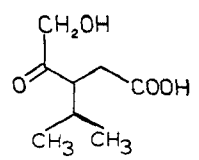
VI



VII



VIII; R=OH
X; R=H



IX

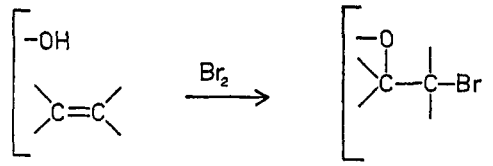
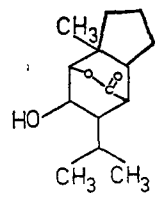


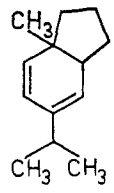
Figure 2.

(XV, discussed below) is heated above its melting point (19). The formation of VIII, IX, and X, when α-dihydropicrotoxinin is heated with aqueous bases, supports this extension (135).

Hydrogenation of picrotoxinide followed by removal of the ketone by desulfurization of the ethylene mercaptal derivative with Raney nickel produced tetrahydrodesoxypicrotoxinide (XI). That the hydroxyl and isopropyl groups in VII are *trans* to each other is shown by the ready pyrolysis of the benzoate of XI to produce carbon dioxide, benzoic acid, and picrotoxadiene (XII) (19). Picrotoxadiene readily forms a



XI



XII

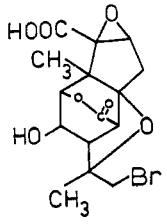
malonic anhydride adduct, supporting the homoannular diene structure and suggesting the rings were *cis*-fused. The structure of picrotoxadiene was confirmed by synthesis (20).

Bromination of picrotoxinin gives a mixture of two sparingly soluble isomeric monobromo derivatives, α- and β-bromopicrotoxinin, $C_{15}H_{15}O_6Br$, from either of which the parent compound can be quantitatively regenerated by reduction with zinc and ammonium chloride (48, 97). Picrotin does not react with bromine.[1] That the hydroxyl group of picrotoxinin is involved in this bromination, as shown in Figure 2, is suggested by the disappearance of the hydroxyl group. This is confirmed by chemical and spectral evidence (101). Alkaline hydrolysis of α-bromopicrotoxinin gives α-bromopicrotoxininic acid, $C_{15}H_{17}O_7Br$, which possesses a free carboxyl group, a δ-lactone, and a single secondary hydroxyl group (40, 48, 97), and which affords, by debromination with zinc and ammonium chloride, α-picrotoxininic acid, $C_{15}H_{18}O_7$,[2] possessing one free carboxyl group, a δ-lactone, and a secondary and a hindered tertiary hydroxyl group.

(1) This distinction is the basis of the chemical separation of picrotoxinin and picrotin.

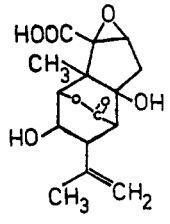
(2) In the bromopicrotoxinins and the bromo acids, α and β refer to isomerism of the $-CH_2Br$ about C-12. In the picrotoxininic acids, α and β refer to the absence or presence, respectively, of a new ether bridge which involves loss of a molecule of water. Thus it must be clearly understood which series is concerned lest confusion arise.

The tertiary hydroxyl group in picrotoxinin was thus placed at C-6 where it is near enough to participate in the bromination of the double bond, and where it is needed in the dealdolization reactions observed in some derivatives (135). In α-picrotoxininic acid, C-11 was selected for the free carboxyl group and C-15 for the six-membered lactone carbonyl group, since C-11 must be lost in the formation of picrotoxinide. Spectral evidence supports these assignments. That the bromopicrotoxininic acids possess a secondary hydroxyl group is shown by the formation of a ketone with chromic anhydride, from which dihydro-α-picrotoxininic acid can be produced by reduction, and formation of an acetyl compound and an acid chloride (of the acetyl compound) with thionyl chloride. This evidence establishes structure XIII for α- and β-bromopicrotoxininic acids, with uncertainty still remaining concerning which atom, C-13 or C-14, bears the bromine atom in the α and β compounds, respectively.

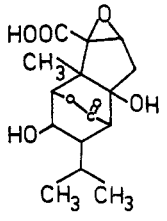


XIII

Structure XIII also accounts for the consumption of 1 mole of periodate after warming with alkali and is the least strained of two alternatives (21). Since the bromine-free α-picrotoxininic acid is obtained by mild reduction that should involve no skeletal changes, structures XIV and XV represent α-picrotoxininic acid and its dihydro derivative, respectively. The



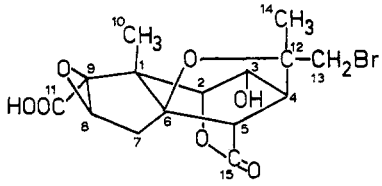
XIV



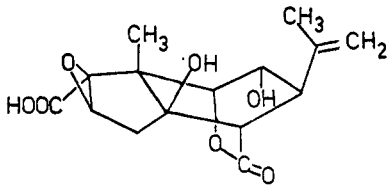
XV

formation of picrotoxinide from dihydro-α-picrotoxininic acid thus becomes the thermal decomposition of a glycidic acid to a ketone and carbon dioxide, followed by loss of water from the β-hydroxylactone.

The production of picrotoxadiene (XII) by an elimination reaction on the benzoate of tetrahydrodesoxypicrotoxinide (XI) establishes a relative *trans* relationship between the C-3 hydroxyl group and the C-4 isopropyl group, and a similar relative *trans* relation between the C-3 hydroxyl group and the bromo ether bridge must also exist. The transannular lactone ring must also be *trans* to the bromo ether bridge since any other configuration is not possible sterically. Assuming a *cis*-locked epoxide bridge, the possible stereochemical forms for the bromopicrotoxininic acids are reduced to four, of which XVI is chosen since only in this configuration can all the possible derivatives be allowed which involve a lactone bridge between C-11 and the C-2 hydroxyl group. The structure of α-picrotoxininic acid becomes XVII.



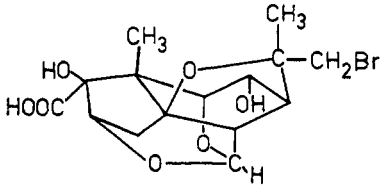
XVI



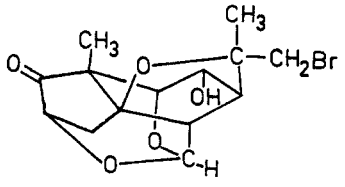
XVII

The formulation of an epoxide in these compounds prompted considerable dispute (5, 45), since no clear-cut reactions, whose starting materials and products bear the relation of epoxide to halohydrin, have been found, with one possible exception (128). Examination of structure XVI shows the rear side of the epoxide ring is strongly shielded by the lactone ring, and this effect is augmented by the rigid caged structure. Abnormal behavior toward epoxide reagents might thus be expected.

The reduction of the bromopicrotoxininic acids provided additional support for the proximity of the epoxide ring and lactone groupings and for the selection of XVI as the stereochemical representation of the bromo acids. Reduction of bromopicrotoxininic acid with sodium borohydride gives XVIII, which possesses only a carboxyl carbonyl group, gives a diacetate, and on reaction with lead oxide in acetic acid gives, quantitatively, carbon dioxide and XIX, which gives a monoacetate and carbonyl derivatives. Spectral evidence supports these assignments (21).

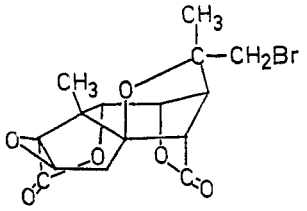


XVIII

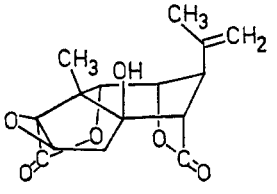


XIX

The structure of the bromopicrotoxinins cannot be the dilactone formed from bromopicrotoxininic acid by formation of a lactone between C-11 and the C-3 hydroxyl group in XVI, since this structure is sterically impossible. This and spectral evidence (22) suggests that formation of bromopicrotoxininic acid from bromopicrotoxinin involves opening of both lactones of the latter followed by transesterification to the more stable six-membered lactone found in bromopicrotoxininic acid. Bromopicrotoxinin then has structure XX, and picrotoxinin, derived from the bromo compound by a mild, reversible reaction, has structure XXI. The difference in the lactone systems of XX



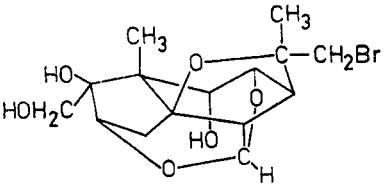
XX



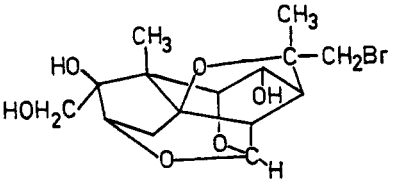
XXI

and XVI explains the difference in the lithium aluminum hydride reduction products of the two, XX giving XXII and XVI giving XXIII (23, 67).

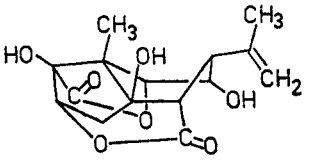
In contrast to β-bromopicrotoxininic acid itself, a prior warming of the acid with excess alkali and neutralization affords a water-miscible syrup which consumes 3 moles of periodate and which is converted to apopicrotoxininic dilactone (XXIV) by reduction with zinc and ammonium chloride. Treatment with base opens the lactone of the bromo acid, but steric restrictions require that the bromo ether bridge be broken by reduction prior to formation of a new boat cyclohexane ring and subsequent relactonization as shown in XXIV.



XXII



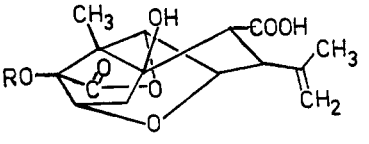
XXIII



XXIV

The two new lactone rings are coplanar, previously eclipsed centers at C-1 and C-6 become staggered, and the isopropenyl and angular methyl groups become equatorial in the process (21).

Treatment of picrotoxinin with alkali or hot dilute acid produces picrotoxic acid (XXV), which contains an alcoholic hydroxyl group methylated by diazomethane (22, 48–50). This reaction is analogous to the formation of apopicrotoxininic dilactone, since both processes involve intramolecular epoxide opening to form an α-hydroxy acid. "Compound C" (XXVI), a third substance of this type, is produced from XXV



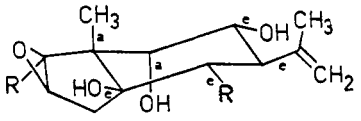
XXV; R=H

XXVI; R= CH_3

by treatment with diazomethane, or directly from picrotoxinin by reaction with diazomethane in the presence of alkali (136).

In addition to picrotoxic acid, picrotoxinindicarboxylate (XXVII) is formed from picrotoxinin by treatment with alkali. That XXVII possesses no new ether

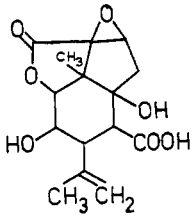
bridge is shown by its periodate reaction. Picrotoxinindicarboxylate reacts with sodium methoxide to give the dimethyl ester (XXVIII), which also reacts with periodate. It cannot be converted to picrotoxic acid or a monocarboxylic acid and can be formed as the sole product from α-picrotoxininic acid by treatment with excess alkali. The dicarboxylate and its ester are exceptions to the series, since the cyclohexane



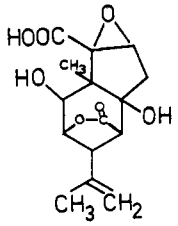
XXVII; R=COOH

XXVIII; R=$COOCH_3$

ring can be represented in the chair, rather than boat or pseudo-boat form, allowing equatorial positions for the large carboxyl, isopropenyl, and the C-3 hydroxyl groups. This equatorial position of the C-3 hydroxyl group makes impossible the opening of the epoxide ring as in the formation of picrotoxic acid. Nowhere in the literature do the two substances XXIX and XXX appear, corresponding to the simple opening of one or the other of the lactone rings of picrotoxinin.



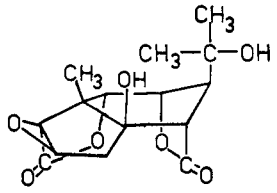
XXIX



XXX

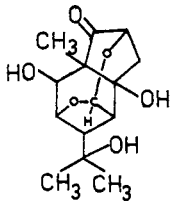
3. Picrotin

Picrotin (XXXI) occurs in the plant with picrotoxinin and possesses the same structure as picrotoxinin except for the formal addition of the elements of water across the isopropenyl double bond of picrotoxinin, forming a second tertiary hydroxyl group. The evidence supporting this relationship of picrotin to picrotoxinin was indirect until the same substance could be obtained from both compounds.

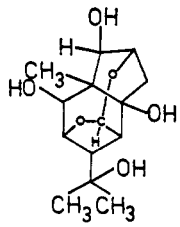


XXXI

When picrotin (XXXI) is reduced with lithium aluminum hydride and then oxidized with periodic acid, XXXII is obtained, which gives XXXIII on hydrogenation over Raney nickel or reduction with lithium aluminum hydride. Picrotoxinin (XXI) gives

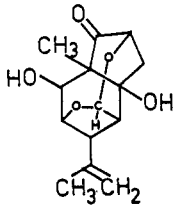


XXXII



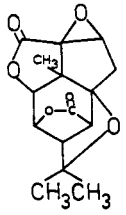
XXXIII

XXXIV on reduction with lithium aluminum hydride followed by oxidation with periodic acid and mild alkaline hydrolysis. XXXIII is then obtained by reacting XXXIV with perbenzoic acid, followed by reduction with lithium aluminum hydride (45).



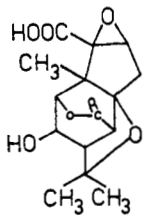
XXXIV

Treatment of picrotin with phosphorus pentachloride in chloroform gives the sparingly soluble anhydropicrotin (XXXV), which can also be formed from picrotoxinin by the action of dry hydrogen chloride in acetic acid at room temperature or by boiling 95% formic acid. The structure was assigned on the basis of the disappearance of all hydroxyl and double-bond absorption in the infrared spectrum and the existing precedent for such ether formation in the bromo compounds (46).



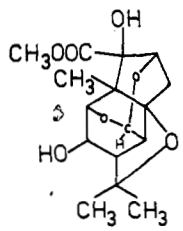
XXXV

Treatment of anhydropicrotin with dilute aqueous sodium hydroxide gives anhydropicrotic acid (47), which was shown to be identical with β-picrotoxininic acid (XXXVI) (49), obtained from α-picrotoxininic acid by reflux with dilute sulfuric acid. On reduction with lithium aluminum hydride, the methyl ester of XXXVI gives XXXVII, which affords carbon dioxide and the ketone XXXVIII on treatment with

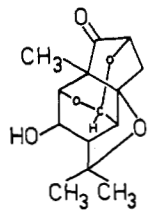


XXXVI

lead dioxide, analogous to the formation dihydro-β-bromopicrotoxininic acid (XVIII) by reduction of β-bromopicrotoxininic acid (XVI) with sodium borohydride.



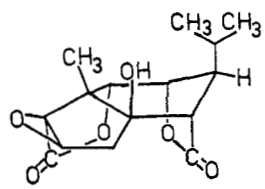
XXXVII



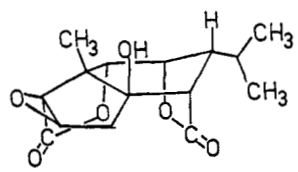
XXXVIII

Early workers made many attempts to make picrotoxinin from picrotin by dehydration, and to make picrotin from picrotoxinin by hydration of the double bond. None of these direct efforts were successful, however, affording such substances as anhydropicrotin (XXXV) and picrotoxic acid (XXV). In one attempt, picrotoxinin was allowed to react with performic acid to produce hydroxypicrotoxinin formate, which afforded the free hydroxypicrotoxinin on hydrolysis in formic acid. When picrotoxinin is treated with perbenzoic acid, however, picrotoxinin epoxide is produced, which is hydrolyzed to form a stable dihydroxypicrotoxinin. Acetylneopicrotoxinin reacts with either reagent to give acetyloxyneopicrotoxinin. These transformations are summarized in Figure 3 (67).

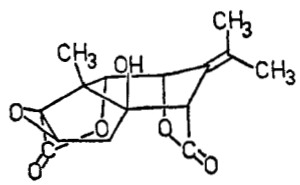
Hydrogenation of picrotoxinin over platinum catalysts gives only α-dihydropicrotoxinin (XXXIX)



XXXIX



XL



XLI

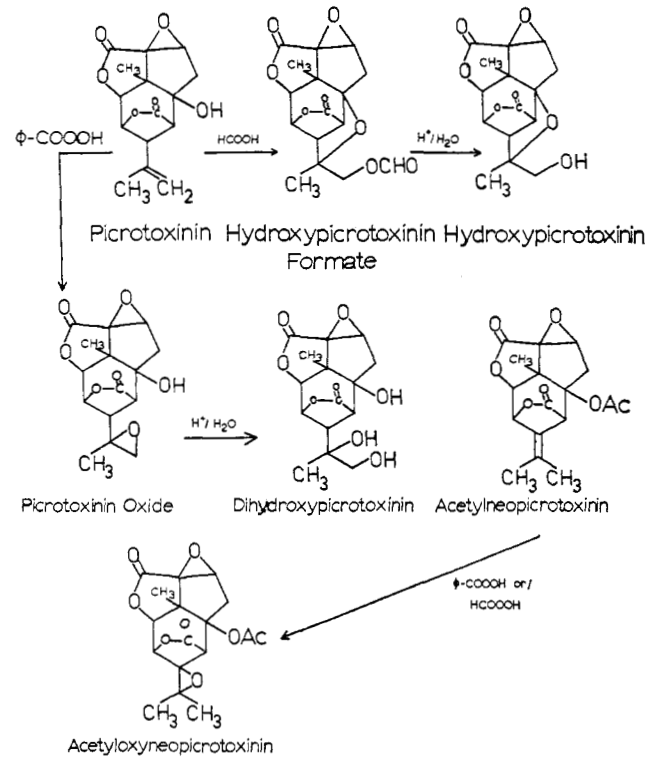
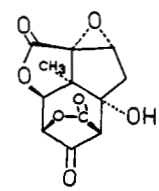


Figure 3.

(46). When the hydrogenation is carried out over a palladium–charcoal catalyst, however, three products result: α-dihydropicrotoxinin, β-dihydropicrotoxinin (XL), and neopicrotoxinin (XLI), the last being the double-bond isomer of picrotoxinin (67, 101, 131).

The acetate and benzoate of neopicrotoxinin can be obtained by refluxing anhydropicrotin with acetic anhydride and ferric chloride, or benzoyl chloride, respectively. The conditions favoring the isomerization of picrotoxinin to neopicrotoxinin seem to require hydrogen, a trace of acid, and a weak hydrogenation catalyst, although the relative amounts of the three substances produced varies greatly with the reaction. Ozonolysis of neopicrotoxinin acetate gives a stable ozonide[3] which gives acetone and the ketone XLII on hydrogenation over a platinum catalyst.

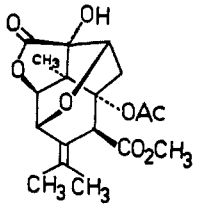


XLII

β-Dihydropicrotoxinin has the isopropyl group *cis* to the lactone rings and is distinguished from the α isomer by being resistant to hot dilute sulfuric acid.

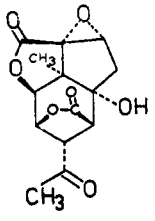
(3) It can be recrystallized without decomposition from ethyl acetate.

The α-dihydro isomer gives dihydropicrotoxic acid under these conditions. That the isopropyl group strongly hinders the tertiary hydroxyl group at C-6 in the compounds where it is *trans* to the lactone rings is seen in the ease with which β-dihydropicrotoxinin and neopicrotoxinin can be acetylated. The β-dihydro isomer is thought to be formed by addition of hydrogen to neopicrotoxinin from the least hindered (upper) side. Hydrolysis of neopicrotoxinin acetate with dilute sodium hydroxide gives a crystalline acid which forms methyl neopicrotoxate (XLIII) on esterification with diazomethane.

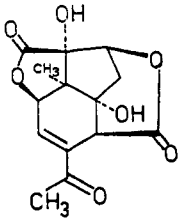


XLIII

Ozonolysis of picrotoxinin gives formaldehyde and α-picrotoxinone (XLIV), which forms β-picrotoxinone (XLV), when heated under reduced pressure or on long boiling in water (10). This isomerization is best done

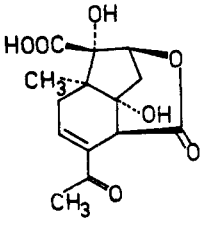


XLIV

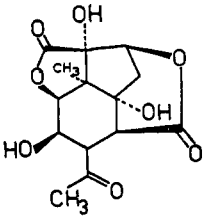


XLV

in methanol containing a trace of sodium methoxide. Early objections to structure XLIV for α-picrotoxinone on the basis of its discrepant ultraviolet spectrum are explained by the probable contamination with small amounts of the β isomer, which is nearly impossible to avoid. Hydrogenolysis of XLV gives XLVI. Moreover, ozonolysis of apopicrotoxininic dilactone (XXIV) gives XLVII, which forms the C-9 acetoxy derivative of XLV when dehydrated and acetylated with acetic anhydride in pyridine. The C-9 acetoxy compound is also formed by direct acetylation of XLV.

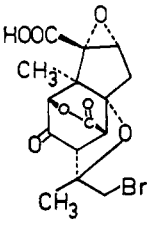


XLVI

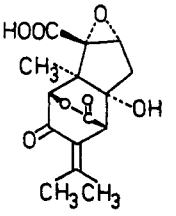


XLVII

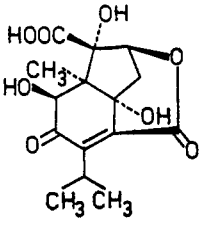
β-Bromopicrotoxininic acid can be oxidized with chromic acid in acetone to give β-bromooxopicrotoxininic acid (XLVIII) which affords XLIX and L on debromination with zinc and ammonium chloride. Treatment of XLIX with the same reagents also produces L. The methyl ester of β-bromopicrotoxininic



XLVIII

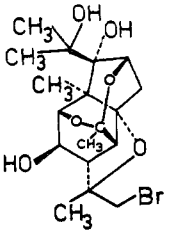


XLIX

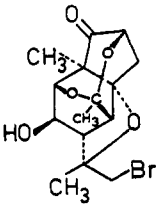


L

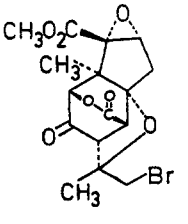
acid reacts with methylmagnesium iodide to form the carbonyl-free polyhydroxy derivative LI, which can be oxidized with lead tetraacetate to form the cyclopentanone derivative LII. Similarly to the free acid, methyl β-bromopicrotoxinate can be oxidized to the ketone LIII with chromic acid in acetone (14).



LI



LII

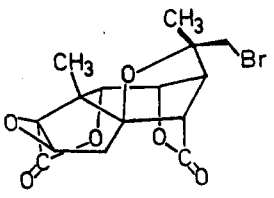


LIII

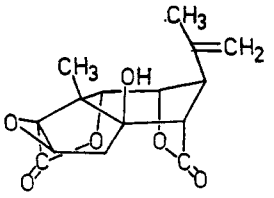
4. Absolute Configurations

The absolute configuration of α-bromopicrotoxinin has been established by X-ray analysis. This shows that α-bromopicrotoxinin is represented by LIV, and thus LV follows for picrotoxinin (25). Earlier workers have drawn picrotoxinin and its derivatives in the enantiomorphic form to that represented by LIV and LV.

The bromination of picrotoxinin has long been known to give a mixture of two isomers, arbitrarily assigned the names α-bromopicrotoxinin (LIV) and β-bromo-

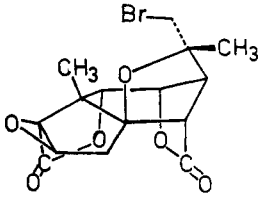


LIV



LV

picrotoxinin (LVI). The mixture can be separated into its components by fractional crystallization from ethanol, and structures have been assigned on the basis of nuclear magnetic resonance (nmr) studies which support the assignment by X-ray analysis (13).



LVI

The two isomers are formed in the bromination to the extent of 14% α isomer and 86% β isomer.

B. CORIAMYRTIN AND TUTIN

1. *General History*

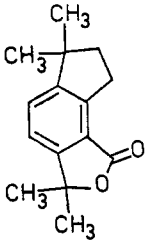
Since coriamyrtin and tutin occur as the principal toxic substance in two distinct species found in separate parts of the world, their chemical histories are independent of one another, at least in the early phases. They are both amaroids found in plants of the family *Coriariaceae*, or "tanners bush," native principally in countries and islands of the southern and western Pacific Ocean and areas adjacent to the Mediterranean Sea.

Near the turn of the century tutin (LXVII), $C_{15}H_{18}O_6$, was first isolated from the three New Zealand *Coriaria* species, *Coriaria ruscifolia* L., *C. thymifolia*, Humb. and Bonp., and *C. augustissima*, Hook., in which coriamyrtin was later found as a minor constituent. Tutin has recently been found also in the fruits of *Hyenancha globosa*, *Euphorbiaceae* (70). Tutin is a bitter, toxic lactone, consuming 1 mole of hydrogen and forming a monobromo derivative involving a hydroxyl group, from which tutin can be regenerated by reduction with zinc and ammonium chloride, as in picrotoxinin (28, 130). That tutin has two hydroxyl groups is shown by formation a mono- and a diacetate (12, 105).

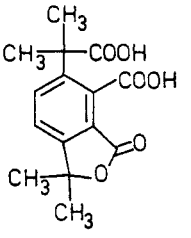
Coriamyrtin (LXV), $C_{15}H_{18}O_6$, was first isolated from the European *Coriaria* specie, *Coriaria myrtifolia*, nearly 40 years before tutin (125). It was later found to be the major constituent of the Japanese *Coriaria* specie, *Coriaria japonica*, along with smaller amounts of tutin. Coriamyrtin is a bitter, toxic lactone which consumes 1 mole of hydrogen and forms a monobromo derivative involving a hydroxy group, as in tutin and picrotoxinin. No acetate derivative could be formed, although other evidence suggested the presence of a tertiary hydroxyl group (73, 76, 108).

2. *Coriamyrtin*

When coriamyrtin is boiled with hydrogen iodide, a small amount of crystalline coriaria lactone (LVII) is formed, which produces acetone on fusion with potassium hydroxide, has no double bond, and gives coriaric acid (LVIII) on permanganate oxidation.

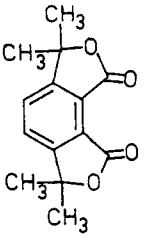


LVII

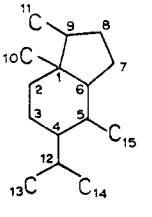


LVIII

Upon treatment with boiling dilute sulfuric acid containing a small amount of potassium permanganate, coriaric acid affords coriaria dilactone (LIX), which also gives acetone on fusion with potassium hydroxide (75, 77). The structure of coriaria dilactone, and thus coriaria lactone, was proved by synthesis (74, 78, 79). The carbon skeleton of coriamyrtin was proposed to be LX by analogy with picrotoxinin. The above data also suggest the spacial arrangement of an isopropenyl group, a tertiary hydroxyl group, and a γ-lactone on the cyclohexane ring in a like manner to that found in picrotoxinin.



LIX



LX

On heating in dilute sulfuric acid, dihydrocoriamyrtin gives isohydrocoriamyrtin (LXI). That LXI contains a new conjugated aldehyde is shown by the formation of a carbonyl derivative and spectral evidence. The presence of an angular methyl group, as shown by nmr evidence, indicates the five-membered ring has not been opened in the isomerization. Isohydrocoriamyrtin (LXI) is hydrogenated to give hexahydrocoriamyrtin, which affords a diacetate that still has a free hydroxyl group. Sodium borohydride reduces LXI to

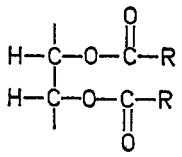
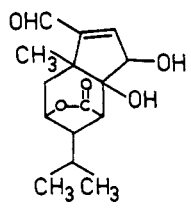
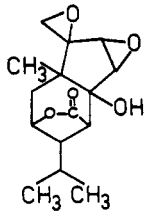


Figure 4.

a crystalline material that also gives a diacetate still having an unacetylated hydroxyl group and forms an isopropylidene derivative. LXI consumes 1 mole of periodate. This establishes structure LXI for isohydrocoriamyrtin, and structure LXII for dihydrocoriamyrtin follows from this.

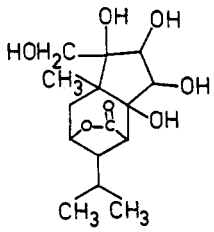


LXI

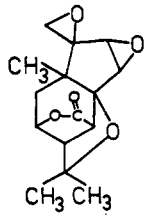


LXII

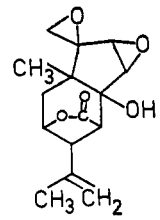
Treatment of dihydrocoriamyrtin with hot sodium carbonate solution affords a polyhydroxy lactone LXIII, which forms a triacetate that still possesses a free hydroxyl group. The nmr spectrum of the triacetate suggests the partial structure shown in Figure 4, presumed to be located at C-7 and C-8. Another isomer, apocoriamyrtin (LXIV), is formed when coriamyrtin is dissolved in concentrated hydriodic acid and then diluted with water. Spectral evidence suggests that this has resulted from the formation of a new ether link between C-6 and C-12 analogous to the formation of anhydropicrotin from picrotoxinin. The above transformations establish LXV as the structure of coriamyrtin. Structure LXVI is considered the only conformational form of LXV which can provide sufficient shielding against backside attack at the epoxides to account for their unusual stability, comparable to that in picrotoxinin (108). That coriamyrtin does not form a more stable derivative comparable to the bromopicrotoxininic acids is explained by the lack of the required oxygen at C-2.



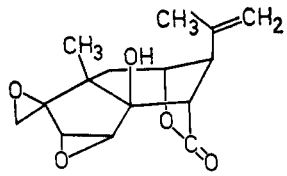
LXIII



LXIV



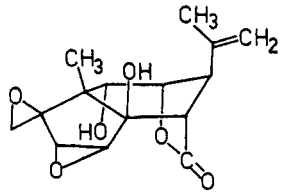
LXV



LXVI

3. *Tutin*

Since the first isolation of both substances, tutin was considered to be a hydroxycoriamyrtin, bearing an additional secondary hydroxyl group, but, as was the case with the believed relation between picrotoxinin and picrotin initially, the evidence was indirect. That tutin is indeed a hydroxycoriamyrtin was shown chemically by the following transformations which showed tutin to have structure LXVII (110).



LXVII

Since attempts at direct removal of the 2-hydroxyl group of tutin to form coriamyrtin were prevented by the apparent steric hindrance at this position, tutin was ozonized to give the norketone LXVIII. Comparison of the nmr spectrum of LXVIII with that of tutin showed that all the relative stereoconfigurations had been retained. A similar ozonolysis of coriamyrtin gave the corresponding norketone LXIX. A trace of sodium methoxide in methanol isomerized LXVIII to LXX, which gave a methoxyl derivative LXXI with methanol and perchloric acid. A similar treatment of LXIX afforded LXXII. The methoxyl derivative LXXI was then converted to LXXIII by zinc-dust reduction in refluxing acetic acid, which gave LXXIV on catalytic hydrogenation. The ketone LXXIV was also obtained from LXXII by hydrogenation or zinc-dust reduction in acetic acid. That the ketones LXXIV, made by the two different routes, were indeed identical was demonstrated by physical methods. Direct conversion of LXXIII to LXXII was done in refluxing ethanol containing potassium acetate. Figure 5 summarizes these transformations of coriamyrtin and tutin.

That isomerization of the lactone groups of LXVIII and LXIX removes protection of the epoxide rings is shown by the ready cleavage of the lactone isomers by dilute hydrochloric acid in acetic acid or water to form the chlorohydrins LXXV and LXXVI, respectively.

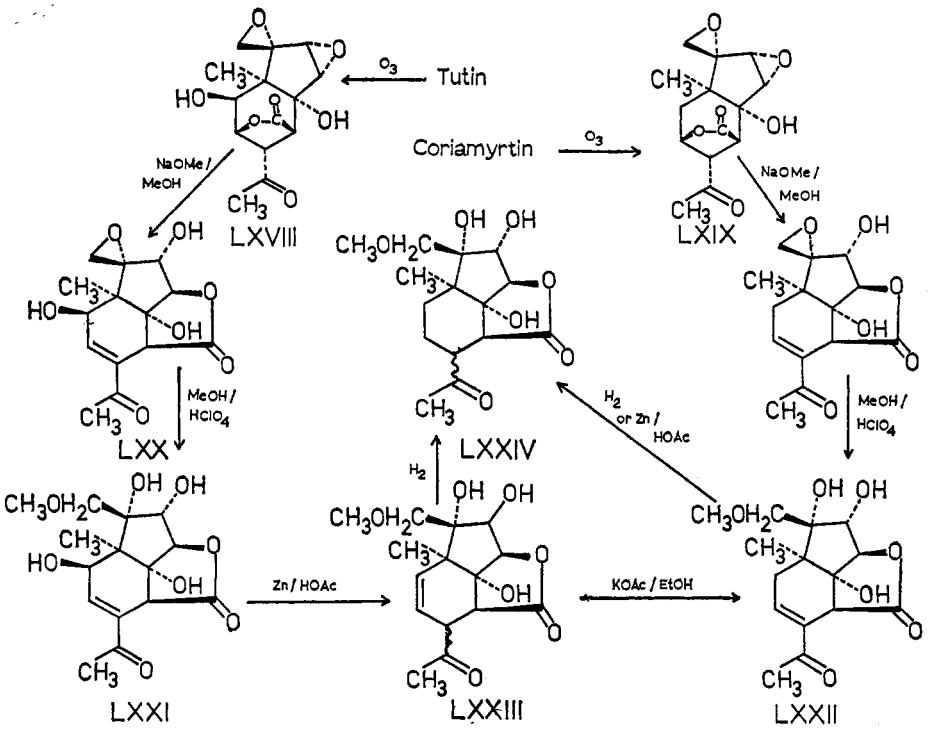
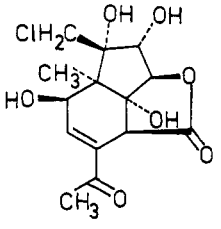
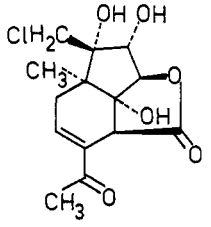


Figure 5.

These chlorohydrins were also formed in the attempted hydrogenation of the lactone isomers over a palladized charcoal in acetic acid containing some hydrochloric acid. No hydrogen was consumed. The isomerization of the lactone ring is similar to the formation of β-picrotoxinone from α-picrotoxinone.

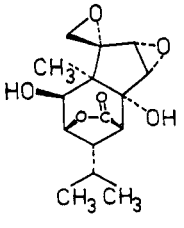


LXXV

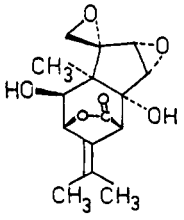


LXXVI

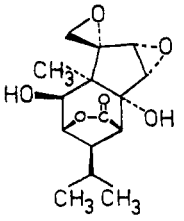
Tutin seems to suffer the same sensitivity toward hydrogenation conditions as picrotoxinin. Thus, while hydrogenation of tutin with platinum oxide in acetic acid gives simply dihydrotutin (LXXVII) (105), hydrogenation with palladium–charcoal in the presence of acid affords neotutin (LXXVIII) (12, 33, 66) and dihydroneotutin (LXXIX). The latter compound can also be produced by direct hydrogenation of neotutin and presumably differs from dihydrotutin only in the stereochemistry of the isopropyl group at C-4. That both neotutin and dihydroneotutin readily form diacetates supports the contention that the hydroxyl group at C-6 is strongly hindered by the isopropyl group in those compounds in which the two groups have a relative *cis* configuration.



LXXVII

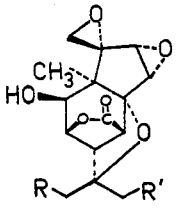


LXXVIII



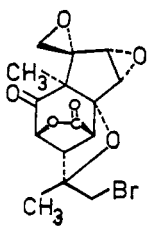
LXXIX

As is the case with picrotoxinin, bromination of tutin affords a mixture of two isomeric monobromo derivatives, α- and β-bromotutin (LXXX and LXXXI, respectively; see below), which both regenerate tutin on debromination with zinc and ammonium chloride. Oxidation of α-bromotutin with chromic acid in acetone or pyridine produces α-bromotutinone (LXXXII), which affords tutinone (LXXXIII) on debromination.



LXXX; R=H, R'=Br

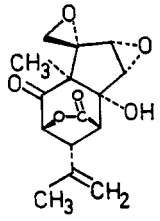
LXXXI; R=Br, R'=H



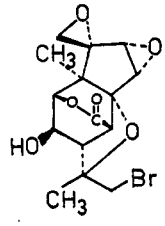
LXXXII

Treatment of α-bromotutin with alkali converts it to the isomeric δ-lactone LXXXIV, α-bromoisotutin, which

is converted to α-bromoisotutinone by oxidation with chromic acid in acetone or pyridine (12).

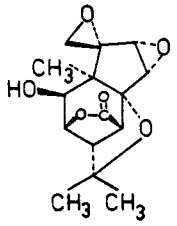


LXXXIII

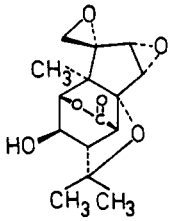


LXXXIV

Reaction of tutin with hot, normal hydrochloric acid converts it to β-tutin (LXXXV), which affords γ-tutin (LXXXVI) on reaction with sodium methoxide in methanol or diazomethane containing a few drops



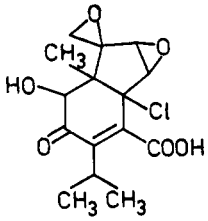
LXXXV



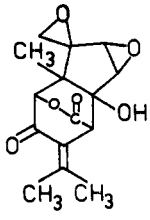
LXXXVI

of alkali (33, 66). The formation of LXXXV and LXXXVI from tutin is analogous to the formation of anhydropicrotin and β-picrotoxininic acid, respectively, from picrotoxinin.

Attempted debromination of α-bromoisotutinone followed by a work-up with hydrochloric acid produces a chloro compound which was assigned structure LXXXVII, making appropriate changes regarding the epoxide rings. LXXXVII reacts with 1 mole of lead tetracetate. If the time of debromination is shortened and the work-up done in sulfuric acid, LXXXVIII results. These structures were assigned mainly on the basis of spectra, analyses, and analogy to the debromination of β-bromopicrotoxininic acid (66).



LXXXVII

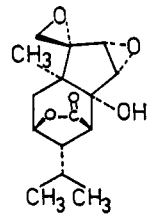


LXXXVIII

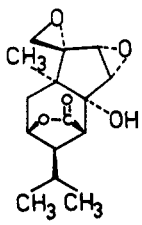
Reaction of α-bromoisotutinone with dilute alkali affords a substance, $C_{15}H_{17}BrO_7$, for which no structure has been given, and which gives a monomethyl ester methyl ether on treatment with diazomethane.

On reaction with dilute alkali followed by acidification, tutin affords a substance corresponding to $C_{15}H_{18}O_6$, which forms a monomethyl ester with diazomethane, gives a triacetate with hydroxyl absorption in the infrared, and can be converted to a di-*p*-bromophenacyl ester by reaction with *p*-bromophenacyl bromide and alkali. Tutin also affords a substance fitting $C_{16}H_{22}O_7$, thought to be tutin monomethyl ester, which affords a triacetate with acetic anhydride in pyridine and decolorizes diazomethane. No structures have been proposed for these substances (12).

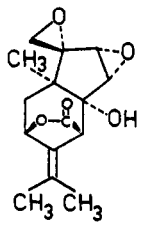
Like the other substances in this series, coriamyrtin too is sensitive to hydrogenation conditions. Catalytic hydrogenation over platinum produces α-dihydrocoriamyrtin (LXXXIX). If, however, the hydrogenation is carried out over a palladium–charcoal catalyst in the presence of mineral acid, β-dihydrocoriamyrtin (XC) results. Hydrogenation over a palladium–charcoal catalyst without mineral acid affords a complex mixture, thought to contain both dihydrocoriamyrtins and neocoriamyrtin (XCI) by analogy to picrotoxinin (106). Methanolysis of coriamyrtin at room temperature gives methyl coriamyrtate (XCII) (107).



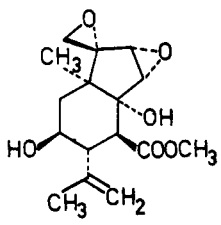
LXXXIX



XC

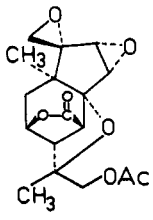


XCI

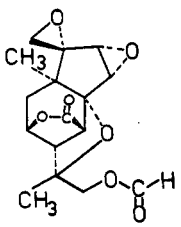


XCII

Oxidation of coriamyrtin with lead tetraacetate affords the acetoxyl derivative XCIII (72, 111), which was also prepared by a route analogous to the formation of hydroxypicrotoxinin formate and hydroxy-



XCIII

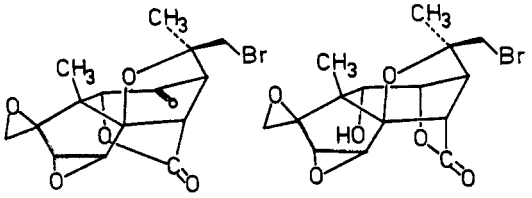


XCIV

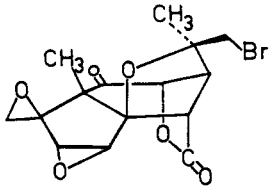
picrotoxinin from picrotoxinin. Coriamyrtin was treated with performic acid to give XCIV, which was hydrolyzed and acetylated to form XCIII.

4. *Absolute Configurations*

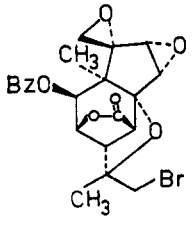
The X-ray analyses of α-bromoisotutinone (88), α-bromotutin, and α-bromotutinone (24) established structures XCV–XCVII, respectively, for these substances. Studies of the nmr spectra, optical rotatory dispersion (ORD) curves, and molecular rotations of α-bromotutin, benzoyl-α-bromotutin (XCVIII), α-bromoisotutin, tutin, and benzoyltutin (XCIX) support these assignments (109).

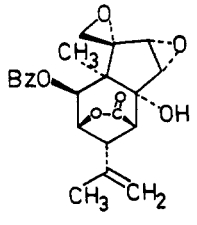


XCV XCVI



XCVII





XCVIII XCIX

C. MELLITOXIN

1. *General History*

Mellitoxin (C), $C_{15}H_{18}O_7$, is an insect metabolite first isolated from the honey of bees. The insect *Scolypopa australis*, the "passion vine hopper," which feeds on the leaves and stems of *Coriaria arborea* Lindsay (*C. ruscifolia* L.), was identified as the source of the toxin. In feeding on the plant, *S. australis* leaves anal excretions on the surface of the leaves, and the bees incorporate this into their honey. Mellitoxin is, thus, perhaps not a separate plant product but rather a metabolite of tutin. It will, nonetheless,

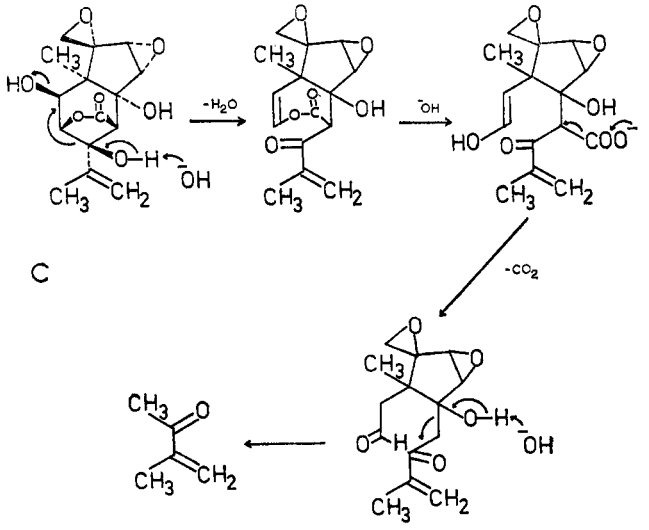


Figure 6.

be covered in this discussion. That mellitoxin was indeed an oxygenated tutin was initially suspected on the basis of its mode of formation, molecular formula, and biological activity (115, 134).

Mellitoxin possesses a double bond, three hydroxyl groups, and a strained lactone. That the double bond, which is absent in dihydromellitoxin, lies in a similar relation with a hydroxyl group as that found in tutin and picrotoxinin is shown by formation of a monobromomellitoxin. Bromomellitoxinone, formed by oxidation of bromomellitoxin with chromic anhydride, has hydroxyl and ketone carbonyl absorption in its infrared spectrum which indicates two of the hydroxyl groups are in a similar environment to those in tutin and the third is probably tertiary (44).

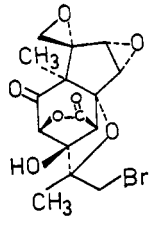
2. *Mellitoxin*

Mellitoxin is unreactive toward periodate, and both mellitoxin and dihydromellitoxin react with alkali to give methyl isopropenyl ketone and methyl isopropyl ketone, respectively. Tutin gives no volatile products under these conditions. A mechanism for these transformations is suggested in Figure 6.

The assignment of structure C to mellitoxin and the placement of the additional hydroxyl group at C-4 was made on the above evidence and by comparison of the mass spectra of tutin and mellitoxin. An ion at *m/e* 294 established the molecular weight of tutin, which also forms an ion of *m/e* 296 upon deuterium exchange, due to the two hydroxyl groups. Mellitoxin showed no parent peak, but the molecular weight was calculated to be 310 from the appearance of a peak at *m/e* 279 and a metastable peak at *m/e* 251.1 due to the transition ($310^+ \rightarrow 279^+ + 31$). Both the spectra of tutin and mellitoxin had peaks at M − 15 ($-CH_3$) and M − 18 ($-H_2O$). Extensive analysis

of the mass spectra of the two substances accounted for the stronger peaks in both spectra.

The mass spectrum of bromomellitoxinone (CI) showed its molecular weight to be 386 and confirmed the presence of one bromine atom as $-CH_2-Br$ and one hydroxyl group.



CI

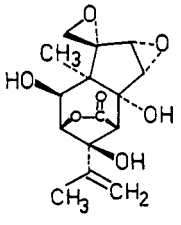
D. CONSTITUENTS OF *Hyenancha globosa*

1. General History

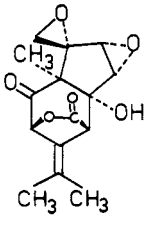
In comparison to the histories of the preceding substances of this discussion, the constituents of *Hyenancha globosa* are relative newcomers to the group of amaroids of the picrotoxinin type. They also extend the occurrence of the group to include the family *Euphorbiaceae*, or "spurge" family.

2. Hyenanchin

Hyenanchin (CII), $C_{15}H_{18}O_7$, was the first substance to be identified from the extracts of *H. globosa* and was shown to be identical with mellitoxin by comparison of derivatives and infrared nmr and spectra. It consumes 1 mole of hydrogen, can be brominated to form the customary monobromo ether, so characteristic of this group of substances, and contains a γ-lactone. Hyenanchin itself is inert to periodate but consumes 2 to 3 moles in alkaline solution (68). Hyenanchin is converted to neotutinone (CIII) by hydrogenation followed by dehydration with phosphorus oxychloride in pyridine, establishing the relationship between the two substances (70).



CII



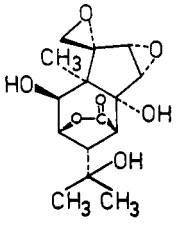
CIII

3. Isohyenanchin

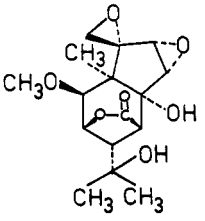
A second substance, isohyenanchin (CIV), has also been isolated from the crude plant extracts. This isomer of hyenanchin possesses a γ-lactone, forms a diacetyl derivative, and does not react with periodate. Oxidation of isohyenanchin followed by reaction with phosphorus oxychloride affords neotutinone (CIII), which can also be formed by the isomerization of tutinone with *p*-toluenesulfonic acid in pyridine. Tutin also occurs in the fruits of *H. globosa* (71).

4. "Substance D"

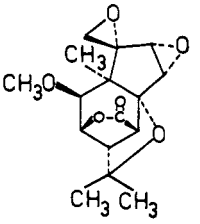
The third substance isolated from the crude extracts has not yet been named and is referred to as "substance D" (CV), $C_{16}H_{22}O_7$. It forms a monoacetate (of the hydroxyl group at C-12) and an anhydro compound (CVI) like anhydropicrotin upon treatment with phosphorus oxychloride in pyridine (72).



CIV



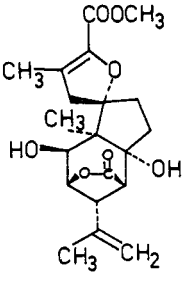
CV



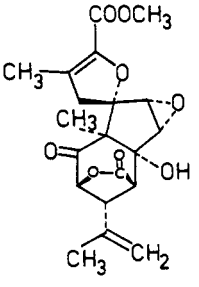
CVI

5. Capenicin

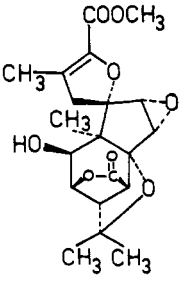
The fourth substance from this plant is capenicin (CVII), $C_{20}H_{24}O_8$, which forms a monoacetate (of the hydroxyl group at C-2) and is oxidized by chromic anhydride to a monoketone (CVIII), which produces a dihydro derivative on hydrogenation. A substance termed isocapenicin (CIX) has also been formed. These structures were demonstrated by degradation experiments and analysis of the ultraviolet, infrared, and nmr spectra of the products (69).



CVII



CVIII



CIX

III. COMPOUNDS CONTAINING NITROGEN

A. CONSTITUENTS OF *Dendrobium nobile*

1. General History

So far the nitrogen-containing compounds of this type have been found only in a single plant, and their structures contain a tertiary nitrogen atom at C-11 of the picrotoxane skeleton, in place of the oxygen atom born at this position in the nonnitrogenous

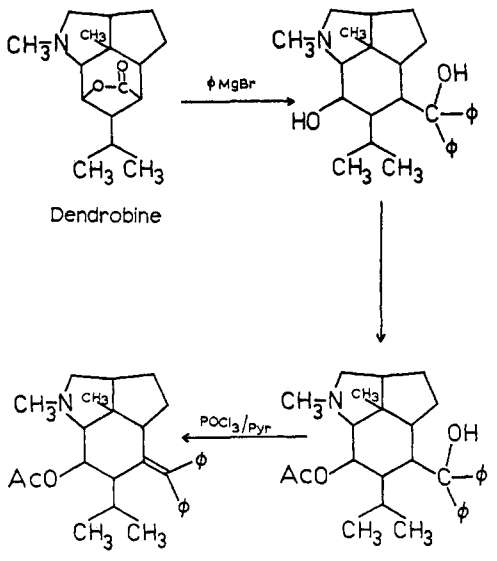
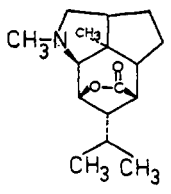


Figure 7.

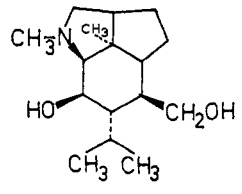
members of the class. The alkaloids have one other feature in common that distinguishes them from the terpenes: none of them so far possess an epoxide ring. They all possess one five-membered lactone and, thus, represent the addition of several more compounds to the ranks of lactonic alkaloids (119) and extend the occurrence of this carbon skeleton to the family *Orchidaceae*. They are the basic constituents of some samples of a Chinese herbal preparation, "Chin-Shih-Hu." Not all Chin-Shih-Hu samples purchased commercially contain alkaloids, and taxonomic study of the individual samples shows considerable species variation. However, the specie responsible for the alkaloid content is probably the ornamental orchid, *Dendrobium nobile* Lindl.

2. *Dendrobine*

Dendrobine (CX), $C_{16}H_{25}NO_2$, was first isolated from Chin-Shih-Hu samples more than 30 years ago and was shown to possess a γ-lactone and a tertiary N-methyl group (54, 137, 138). Dehydrogenation of dendrobine

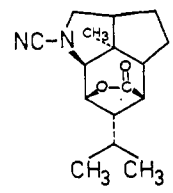


CX

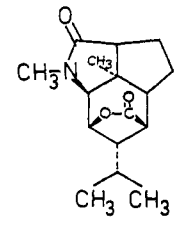


CXI

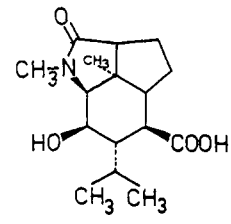
and its lithium aluminum hydride (LAH) reduction product, dendrobinediol (CXI), afforded, along with ammonia and various alkylbenzenes, 4-isopropyl-2-pyridone, which structure was verified by synthesis (58, 59, 112). Treatment of dendrobine with cyanogen bromide gives cyanonordendrobine (CXII), from which dendrobine can be regenerated by hydrolysis with dilute acid followed by reaction with nitrous acid, then treatment with formaldehyde, and catalytic reduction. When dendrobine is oxidized with a potassium permanganate–magnesium sulfate mixture there results oxodendrobine (CXIII), from which dendrobinediol can be formed by reduction with $LiAlH_4$. Reaction of oxodendrobine with alkali gives oxodendrobinic acid (CXIV), which affords the ketoester CXV upon treatment with diazomethane, followed by oxidation with chromic acid in pyridine. That dendobine possesses



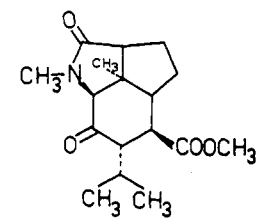
CXII



CXIII



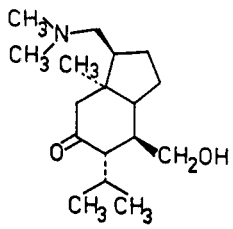
CXIV



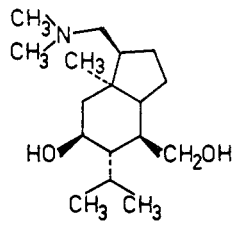
CXV

an isopropyl and a bridgehead methyl group is shown by the formation of acetic and isobutyric acids upon oxidation with chromic acid in sulfuric acid. Treatment of dendrobine with phenylmagnesium bromide opens the lactone ring to give a diphenyldiol, which forms a monoacetate that can be dehydrated with phosphorus oxychloride in pyridine. These transformations are confirmed by spectral evidence and summarized in Figure 7.

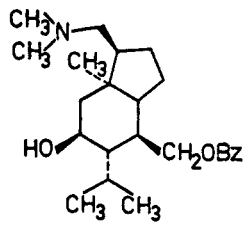
Hofmann degradation of dendrobinediol gives the nitrogen-containing keto alcohol CXVI, from which the diol CXVII can be formed by $LiAlH_4$ reduction. Benzoylation of the methine base CXVI and sodium borohydride reduction gives CXVIII, which affords the olefin CXIX with phosphorus oxychloride. Attempts to make a nitrogen-free compound by further Hofmann degradation of CXVI or CXVII were unsuccessful. *cis* elimination of the N-oxide of CXVII diacetate, however, affords CXX, which forms the cyclopentanone derivative CXXI upon osmolation and lead tetraacetate oxidation. Bromination of CXXI affords a bromo ketone which gives CXXII upon dehydrobromination with lithium chloride–lithium carbonate in dimethyl-



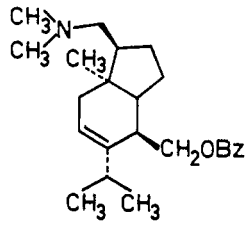
CXVI



CXVII

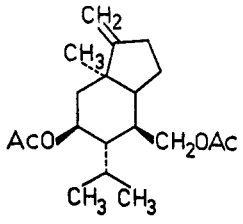


CXVIII

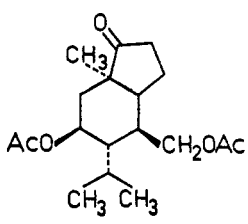


CXIX

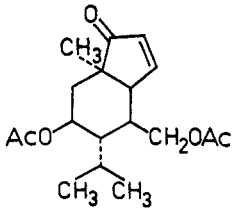
formamide. Hydrogenation of CXXII regenerates CXXI (57).



CXX

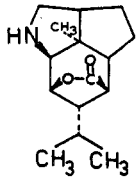


CXXI

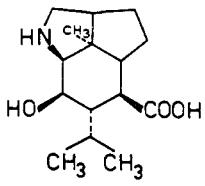


CXXII

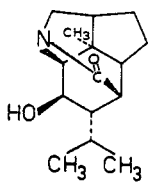
Nordendrobine (CXXIII), formed by treatment of cyanonordendrobine (CXII) with dilute acid followed by nitrous acid, gives upon reaction with barium hydroxide, nordendrobinic acid (CXXIV), which can be cyclized thermally to nordendrobinic acid lactam (CXXV) (59). Methyl oxodendrobinate (CXXVI),



CXXIII

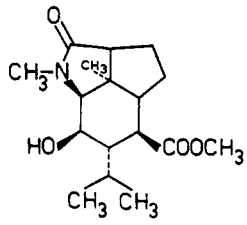


CXXIV

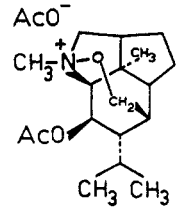


CXXV

formed from oxodendrobine (CXIII) by basic hydrolysis and treatment with diazomethane, can be recyclized to oxodendrobine by reaction with sodium methoxide. Lithium aluminum hydride reduction of dendrobine (CX), oxodendrobine (CXIII), methyloxodendrobinate (CXXVI), and the ketoester CXV, all afford the same compound, dendrobinediol (CXI) (150). Treatment of dendrobinediol under drastic conditions with acetic anhydride and pyridine gives a monoacetoxy acetate salt (CXXVII) (55).

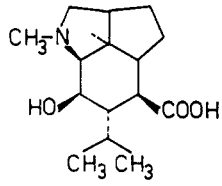


CXXVI

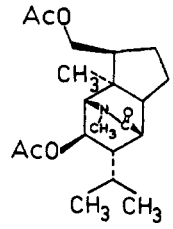


CXXVII

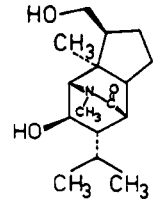
Dendrobinic acid (CXXVIII), formed from dendrobine by alkaline hydrolysis, reacts reversibly with acetic anhydride to form a small amount of dendrobine and a neutral amorphous lactam (CXXIX), which gives the crystalline diol CXXX upon mild methanolysis (60). The above transformations establish that, in all the above derivatives of dendrobine, the five- and six-membered rings are *cis*-fused, and the substituents at carbons 2, 3, 4, 5, and 9 have the relative configurations as shown in structure CXXXI for dendrobine.



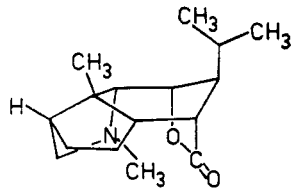
CXXVIII



CXXIX



CXXX



CXXXI

3. *Methyldendrobinium Salt*

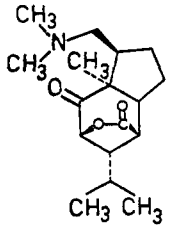
A quaternary base, the N-methyldendrobinium salt, has been isolated from aqueous fractions of the plant

extracts. The structure was confirmed by a partial synthesis (54).

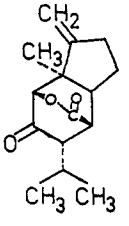
4. *Nobilonine*

The second most abundant alkaloid in extracts of Chin-Shih-Hu is nobilonine (CXXXII), $C_{17}H_{27}NO_3$, which has also been termed nobiline by some workers (150). Preliminary studies showed it to possess a γ-lactone, a six-membered ketone, a bridgehead methyl group, an isopropyl group, and an N-dimethyl group (150).

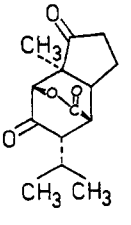
Hofmann degradation of nobilonine gives trimethylamine and deaminonobilonine (CXXXIII), in which the γ-lactone of nobilinine has been isomerized to a δ-lactone in the process. Ozonolysis of CXXXIII affords formaldehyde and the diketone CXXXIV.



CXXXII



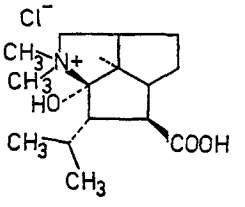
CXXXIII



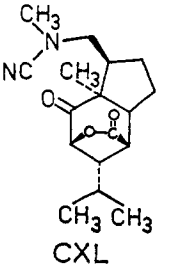
CXXXIV

Mild treatment of nobilonine with alkali and acidification produces isonobilonine (CXXXV). Reduction of nobilonine with $LiAlH_4$ affords an amorphous triol (CXXXVI), which consumes 1 mole of lead tetraacetate in acetic acid, while reduction with sodium borohydride gives hydroxynobilonine (CXXXVII), which is converted to hydroxyisonobilonine (CXXXVIII) by the action of mineral acid. That the bridgehead methyl group is located as shown in CXXXII is supported by the fact that the ketone in nobilonine cannot be enolized. Drastic treatment of nobilonine with potassium hydroxide followed by acidification affords the hydroxy acid CXXXIX as the salt. The detailed analysis of the mass spectra of the above derivatives supports these assignments (150).

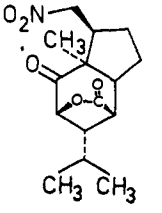
Reaction of nobilonine with cyanogen bromide gives cyanonornobilonine (CXL), which regenerates nobilonine upon mild catalytic reduction and affords dendrobine with more vigorous reduction. Treatment of dendrobine with ozone in acetone produces some nitronobilone (CXLI), which also gives dendrobine on catalytic reduction, along with nordendrobine (CXXIII). Catalytic reduction of CXLI in the presence of formaldehyde affords nobilonine (113).



CXXXIX



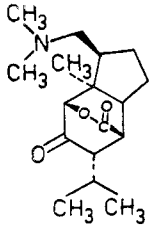
CXL



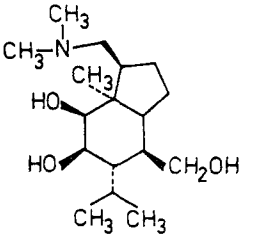
CXLI

5. *Dendrine*

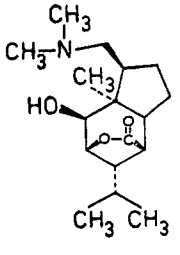
Yet another minor alkaloid, dendrine, $C_{19}H_{29}NO_4$ (CXLII), has been isolated from extracts of Chin-Shih-Hu. Reaction of dendrine with methylmagnesium bromide affords the alcohol CXLIII, which can be produced from dendrobine by the following sequence of transformations. Oxidation of dendrobine with N-bromosuccinimide gives the immonium salt CXLIV, which regenerates dendrobine on reduction with sodium borohydride. Chromatography of CXLIV on neutral alumina with acetone affords the ketone CXLV, which gives CXLIII on treatment with methylmagnesium bromide (56).



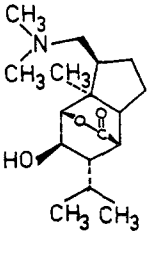
CXXXV



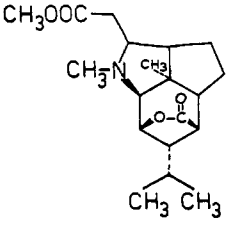
CXXXVI



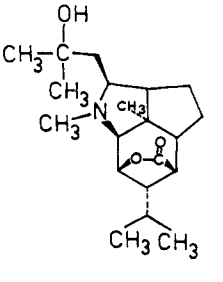
CXXXVII



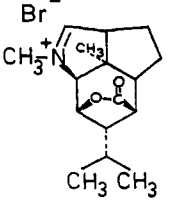
CXXXVIII



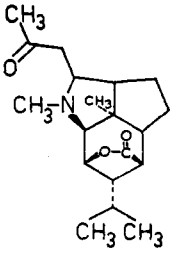
CXLII



CXLIII



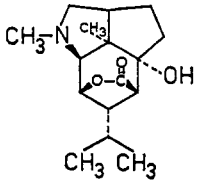
CXLIV



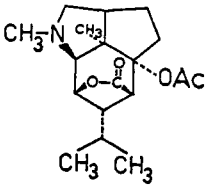
CXLV

6. *Dendramine*

A preliminary study of dendramine (CXLVI), $C_{16}H_{25}NO_3$, another minor alkaloid from Chin-Shih-Hu extracts, shows it to contain a γ-lactone, an N-methyl group, a bridgehead methyl group, two secondary methyl groups, and a hindered hydroxyl group. Dendramine gives starting material with acetic anhydride in pyridine, but affords acetyldendramine (CXLVII), on treatment with acetic anhydride in the presence of *p*-toluenesulfonic acid (61, 103).

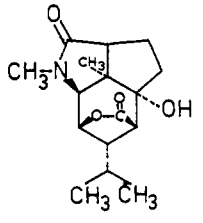


CXLVI

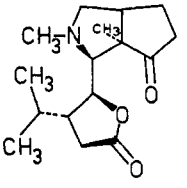


CXLVII

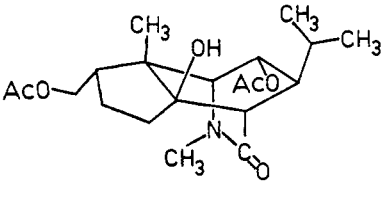
Oxidation of dendramine with potassium permanganate affords the lactam oxodendramine (CXLVIII), whereas no reaction results on treatment with chromic acid. Oxodendramine affords an acetyl derivative on treatment with acetic anhydride and *p*-toluenesulfonic acid. Refluxing alcoholic potassium hydroxide converts dendramine to CXLIX, which gives CL on treatment with acetic anhydride. Spectral evidence supports these structural assignments.



CXLVIII



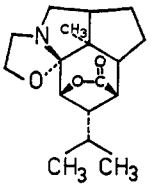
CXLIX



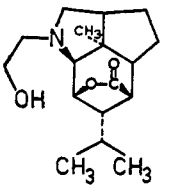
CL

7. *Dendroxine*

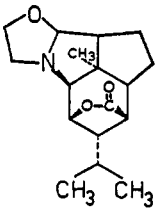
Initial investigation of dendroxine (CLI), $C_{17}H_{25}NO_3$, obtained in small amounts from Chin-Shih-Hu extracts, indicates the presence of a γ-lactone, two secondary methyl groups, one bridgehead methyl group, no hydroxyl group, and no N-methyl group (104). Catalytic reduction of dendroxine affords the amorphous base CLII, which can also be formed from nordendrobine by treatment with ethylene oxide in methanol. Reaction of CLII with osmic acid affords an isodendroxine (CLIII).



CLI



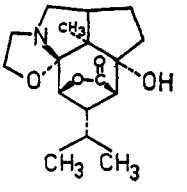
CLII



CLIII

8. *6-Hydroxydendroxine*

A sixth, minor Chin-Shih-Hu alkaloid, 6-hydroxydendroxine (CLIV), $C_{17}H_{25}NO_4$, possesses a γ-lactone and a hydroxyl group. The structure was assigned on the basis of spectral evidence by comparison to dendramine and dendroxine (103).



CLIV

IV. PHARMACOLOGY OF THE GROUP

A. PICROTOXININ AND PICROTIN

1. *History*

The pharmacognostic history of picrotoxin goes much farther into the past than does its chemical history and is proportionately harder to trace with accuracy. It is, nonetheless, reasonably safe to say it goes back at least to the 16th century (147). Its first practical uses were to stun fish and kill body lice (7).

2. *General Discussion*

In the earlier parts of this century, picrotoxin's extreme potency and the nature of its physiological action caused it to be included in nearly every study of convulsant drugs, but with few conclusive results. It was found to produce muscle excitation (36) and to increase the irritability of the respiratory center (62) and the excitability of the vomiting center in cats (148). It was also found to activate yeast cultures (100), to be a central acting glycogenolytic agent in subconvulsive doses (140), and to render pain centers more sensitive (heat–cold) (2). Some early work gave a small sampling of its later implications in studies on the central nervous system (CNS). Thus, it was

suggested that picrotoxin was a medullary convulsant, causing seizures similar to those of epilepsy (120), and it was found to stimulate the nerve cord of the earthworm, *Lumbricus terrestris* (99).

In the late twenties, picrotoxin was found to antidote chloral hydrate poisoning (149), which information more than likely led to the discovery of its therapeutic efficacy as an analeptic drug in severe barbiturate intoxication (63, 92, 93, 98, 124). It was following this discovery that picrotoxin began to enjoy great notoriety and became the object of an even more intensive study, wherein all earlier work was repeated in an effort to gain insight into the extent and mode of its activity. It was thus found to produce convulsions by its action in the midbrain rather than on the medulla or spinal cord (127), and it was included in a study of coumarin fish poisons (132). The dried fruits of *Anamirta cocculus* L. are called "fish berries" in some areas (153). Its hyperglycemic action was studied again (84), and it was found to alter the phosphocreatine portion of the carbohydrate metabolism of the brain (82). Picrotoxin was also shown to increase visceral activity (1, 6, 114, 152) and glandular secretions (40, 139), all by a central mechanism.

The discovery of a temperature-lowering effect in dogs produced by picrotoxin (81) was perhaps instrumental in the postulate of a temperature-lowering center in the brain (126).

Picrotoxin is rapidly absorbed from the blood by the body tissues and excreted unchanged later (27). It is partly detoxified by a microsomal strychnine metabolizing enzyme (80). Sources differ concerning whether picrotoxin does (9), or does not (121), enhance the learning process.

The extensive study to which picrotoxin was subjected failed to bring to light any additional clinical and therapeutic uses, other than its use as an analeptic in barbiturate intoxication. And even this has fallen into disuse with most groups because of its extreme toxicity (*viz.*, convulsions) and its relatively unfavorable therapeutic index. Indeed, due to these limitations the clinical use of picrotoxin was never legalized in some European countries.

The principal feature in the action of picrotoxin is its ability to produce a general and extreme CNS excitation. This initiated an ever-intensified search for the mechanism by which it produces this excitation and led to the emergence of picrotoxin as a useful research tool in the study of the pharmacology of the central nervous system. In an attempt to localize its action in the brain, further studies were made which showed that picrotoxin lowers the threshold of excitability in dogs with electrodes implanted in the cerebral cortex (31) and causes a small decrease in the brain γ-aminobutyric acid (GABA) (94). The evidence concerning the effect of picrotoxin on the concentration of brain acetylcholine (Ach) is conflicting (29, 142).

The complexity of the human and other vertebrate CNS anatomies led workers to study the action of picrotoxin in simpler, anatomically more suitable organisms. Extensive studies were made of picrotoxin's effect on crayfish claw muscle, in which it causes an apparent blockade of the inhibitory nerve (146). It was later suspected that this blockade was caused by picrotoxin's competitive inhibition of GABA, a suspected agonist, or transmitter at inhibitory nerve synapses (145). The role of picrotoxin as a true competitive inhibitor was questioned (42), and the role of GABA as a CNS agonist was extensively studied (43, 144). Picrotoxin's effect was also studied on the CNS of the centipede and other annelid species (34) and mice (123), and extensive microelectrode studies have been performed on the cat brain, where a similar relation involving picrotoxin and GABA was found (65, 122). Insight into modern approaches to the pharmacology of the CNS may be obtained from a number of review articles on the subject (26, 37, 141).

Picrotin was initially believed to be physiologically inactive, and independent studies were therefore not carried out on this substance, which behaved more or less as a diluent in the picrotoxin preparations, wherein the active substance was felt to be picrotoxinin alone. More recent work, however, has shown picrotin to have nearly identical effects as picrotoxinin, only at about 100 times the dose level.

B. CORIAMYRTIN AND TUTIN

1. *History*

The effect on Western man of at least one of these substances, tutin, may be traced back to the 18th century. Tutin is more than likely responsible for the death of many of the cattle brought to New Zealand by Captain Cook. Tutin is the main toxic principle in the New Zealand *Coriaria* plant which the Maiori call "tutu" or "toi-toi," and, since this plant is very succulent, cattle find it most desirable. Hence the frequent death of cattle in a "tutu" area is to be expected; hence also the name tutin for this amaroid (28).

2. *General Discussion*

The actions of coriamyrtin and tutin are nearly identical and parallel exactly that of picrotoxin, though tutin is slightly more toxic than coriamyrtin or picrotoxinin but less enduring (32, 35). Coriamyrtin and tutin cause stimulation of the respiratory, vasomotor, and cardioinhibitory centers in the brain (89, 90) 129) and seem to produce identical symptoms in fish, frogs, mice, rabbits, and guinea pigs (86). Both substances antidote barbiturate poisoning in the same manner as picrotoxin (17, 91, 133), but they have not

been studied in anything approaching the same thoroughness as picrotoxin regarding their analeptic effect or CNS stimulant activity.

C. MELLITOXIN

The physiological activity of mellitoxin is the same as that of tutin, causing death by convulsions. It is about one-fifth as potent as tutin (18, 116).

D. COMPONENTS OF *Hyenancha globosa*

To date the only member of this group for which pharmacological data have appeared in the literature is hyenanchin (identical with mellitoxin) which was shown to have a pharmacological action similar to tutin (18).

E. COMPONENTS OF *Dendrobium nobile*

1. History

Having its roots, so to speak, in China, the history of Chin-Shih-Hu will more than likely remain obscure to Westerners. The first appearance of Chin-Shih-Hu in the Western chemical literature following the initial Japanese work on the structure of dendrobine must mark these historical beginnings for the Western world. *Dendrobium* species including *D. nobile* are also used medicinally in Japan, where they bear the name "Sekkuko" (83). This preparation is used as a tonic and sweet-voice in both Japan and China.

2. General Discussion

The pharmacological action of the only member of this group so far studied, dendrobine, is nearly identical with that of picrotoxin and the others. Dendrobine has slight but demonstrable analgesic and antipyretic actions, much weaker than those of aminopyrine; it produces moderate hyperglycemia, diminishes cardiac activity, lowers blood pressure, suppresses respiration, and inhibits isolated rabbits' intestines. Large doses cause death preceeded by convulsions of central origin. Five to seven times the dosage for picrotoxinin is required to produce comparable effects (15). Dendrobine also has analeptic action and is effective in antidoting barbiturate intoxication (16).

V. PHYLOGENETIC AND BIOSYNTHETIC IMPLICATIONS

A. PHYLOGENY OF THE GROUP

The field of the phylogeny of plants is currently in a high state of flux, perhaps even greater than that in chemistry. Not only is the knowledge of detail being broadened, but even the basic concepts concerning the principles one should follow in arranging families and orders of plants in a manner that will represent true evolutionary pathways is changing. And there is considerable variation at any one time among various authors. A simple statement, however, of the apparent nearest neighbors to each of the four families under discussion is given, with mention of the variation among some of the current authors.

The family *Menispermaceae,* containing the genera *Cocculus, Anamirta,* and *Menispermum,* producing picrotoxinin and picrotin, is placed in the order *Berberidales* by some authors (52). This is a primitive order, also containing the families *Sargentodoxaceae, Lardizabalaceae, Nandinaceae, Circaeasteraceae,* and *Berberidaceae.* Other authors place *Menispermaceae* in the suborder *Ranunculineae* of the order *Ranunculales* (30). Other families of the same suborder are *Ranunculaceae, Berberidaceae, Sarqentodoxaceae,* and *Lardizabalaceae.* The only other suborder in *Ranunculales* is *Nymphaeineae,* containing the family *Nymphaeaceae.*

The genus *Coriaria,* elucidating coriamyrtin and tutin, is in the family *Coriariaceae,* which is placed in the order *Coriariales* by some authors, and its position is doubtful. It is also a primitive order. Other authors place *Coriariaceae* alone in the suborder *Coriariineae* of the order *Sapindales,* with no other closely related families. The other suborders of the *Sapindales* are *Anacardiineae* and *Balsamiineae.*

The genus *Hyenancha,* which elucidates the terpenes related to hyenanchin, is in the family *Euphorbiaceae.* This family is the sole member of the order *Euphorbiales,* according to some authors. It is an evolutionarily advanced order. Other authors place *Euphorbiaceae* in the suborder *Euphorbiineae* of the order *Geraniales.* The only other closely related family of the *Euphorbiineae* is *Daphniphyllaceae.* The other suborders of *Geraniales* are *Limnanthineae* and *Geraniineae.*

The genus *Dendrobium,* elucidating the only alkaloids of this type so far found, belongs in the family *Orchidaceae* and has been a popular ornamental orchid among horticulturists.

The family *Orchidaceae* is placed in the order *Orchidales* by some authors and is the only monocot of the group. The *Orchidales* is a highly advanced order (53). Other authors place *Orchidaceae* in the order *Microspermae* with no other closely related families.

An outline of many of the modern classification systems can be found in Engler's "Syllabus der Pflanzenfamilien" (30), cited above, on pp 13–26.

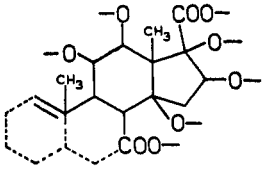
One might profitably search in other genera of the above four families for this carbon skeleton, and perhaps a search of the other families of the respective orders and suborders might be useful, as well as the other suborders of the same order, where this applies. However, in view of the large changes that can occur within families and suborders, not to mention between orders, and the current state of flux in classification, a further widening of a systematic search would be unwise. The seemingly endless variation of the substances already found in some of the above families, such as

Menispermaceae and *Berberidaceae*, to mention only a couple, will serve to illustrate the point. And perhaps, when one is dealing with any attempted chemical taxonomy that may reach farther than from one genus to another in the same family, an attitude of cautious attention would be best. It will certainly be interesting, however, to see if this carbon skeleton occurs elsewhere in the realm of plants, and if this occurrence might become of some chemical-toxonomic significance.

B. BIOGENESIS

As soon as a reasonably sound picture of the chemical structure of the various members of the group emerged, postulates were often made regarding their mode of formation in the plants. Picrotoxinin and picrotin were the first to receive such consideration.

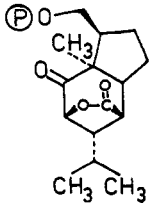
Early suggestions regarding the biogenesis of picrotoxinin and picrotin pictured them as representing an intermediate in phytosterol biosynthesis or a biological oxidation product of a steroid as shown in CLV, in spite of nonconformity to the isoprene rule (20). This



CLV

was later elaborated into a discrete off-shoot of steroid biosynthesis (143).

The only actual experimental evidence supports a new terpene pathway. Feeding labeled mevalonic acid to *Dendrobium nobile*, Lindl. affords active dendrobine. The incorporation and labeling pattern has led to the suggestion that dendrobine might be derived from a bisabolane- (or cadalane-) type precursor, by cleavage of the C-5–C-6 bond (151), as shown in Figure 8. It has also been suggested that dendrobine, nobilonine, and dendroxine may have the same biological precursor (CLVI) (104).



CLVI

No other biogenetic proposals have been made so far for the other substances possessing this new carbon skeleton.

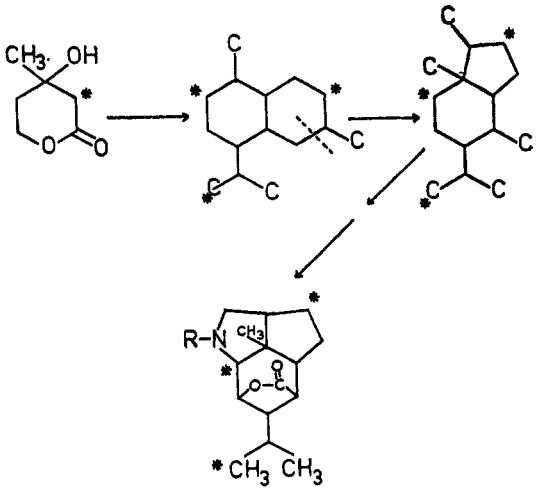


Figure 8.

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