# LACTONIC ALKALOIDS

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*Received May 4, 1964*

CONTENTS



## I. INTRODUCTION

A lactone ring was firmly established as a feature of several of the "older" alkaloids many years ago, and more recent researches have shown that the group is present in several unrelated alkaloidal families. In this review an attempt has been made to summarize recent developments in the chemistry of lactonic alkaloids, with literature coverage up to the end of 1963 and including some references in 1964.

For the purpose of the review, an alkaloid is defined as a naturally occurring basic compound, containing a basic, heterocyclic nitrogen atom. It is further understood that an alkaloid is a plant product, so that no attempt has been made to include lactonic bases of animal origin.

The review is concerned with the chemistry of lactonic alkaloids and does not include their pharmacological and physiological properties. Methods of extraction of the alkaloids from plant material have, in general, not been included. Earlier investigations on the alkaloids have not been described, but references to well-known authoritative works have been given.

A lactone group is defined, for the purpose of the

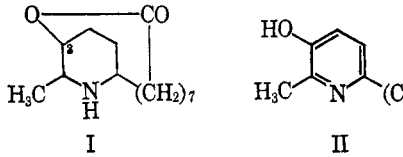
review, as a heterocyclic ring containing several carbon atoms and one oxygen atom, in the form of an internal ester. Hydrolysis of the lactone leads to the corresponding hydroxy acid, which can in most cases be relactonized to furnish the original lactonic alkaloid. The *Senecio* alkaloids, therefore, some of which are cyclic diesters formed from diols and dicarboxylic acids, have not been included because hydrolysis causes cleavage of the alkaloid molecules into two separate fragments.

Lactonic alkaloids, the structural chemistry of which has not been explored, have not been covered, and no attempt has been made to list newly discovered sources of known alkaloids.

## II. Pyridine–Piperidine Group

### A. CARPAINE

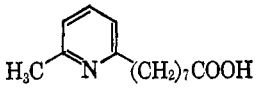
Extensive investigations into the chemistry of carpaine, a lactonic alkaloid occurring in the leaves of *Carica papaya* L., have led to the formulation of the base as I (63, 96, 98). This constitution has been



I

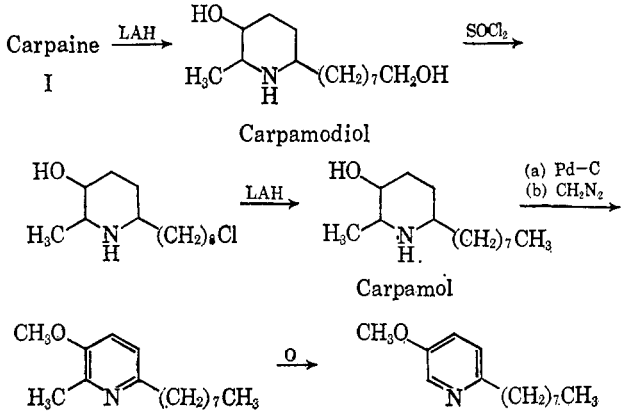


II



III

verified by the synthesis of ethyl carpyrinate (II) (49, 51, 54), obtained earlier by dehydrogenation of ethyl carpamate, the ethyl ester of the hydroxy acid derived from carpaine. Carpyrinic acid has also been synthesized (138). Further confirmation of the structure of carpaine has been provided by the following sequence of transformations (50).

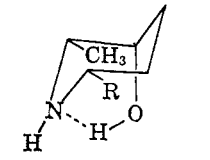


Carpamodiol

Carpamol

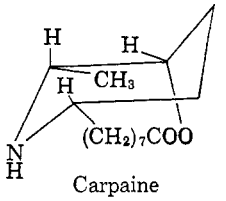
The final product proved to be identical with synthetic 5-methoxy-2-(*n*-octyl)pyridine.

The stereochemistry of carpamic acid has been investigated by Govindachari and Narasimhan (48). Catalytic hydrogenation of deoxycarpyrinic acid (III) in acid medium yielded a single product, racemic deoxycarpamic acid. Reduction of 2,6-disubstituted pyridines under these conditions is known to give *cis*-2,6-disubstituted piperidines, so that in deoxycarpamic and carpamic acids the methyl and caprylic acid substituents are *cis*, and both are presumably equatorial to the chair piperidine ring. Carpamic acid is resistant to dehydration, and its ethyl ester is not epimerized by prolonged base treatment. Further, the hydroxyl group of ethyl N-methylcarpamate undergoes easy nucleophilic replacement by chlorine. These observations led to the suggestion (48) that the hydroxyl group is equatorial and therefore *trans* to the 2- and 6-substituents. This view has been contested by Tichý and Sicher (168), who on the basis of infrared hydrogen bonding studies have concluded that the hydroxyl group in methyl carpamate (IV) is axial and *cis* to the 2- and 6-substituents. Carpaine therefore has the all-*cis* structure V.



R = $(CH_2)_7COOCH_3$

IV

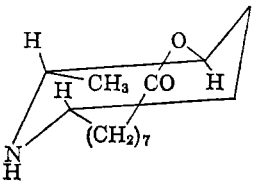


Carpaine

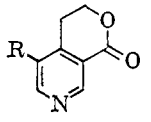
V

### B. PSEUDOCARPAINE

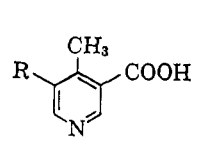
An additional base, isomeric with carpaine, has been isolated from *Carica papaya* L. The new base is closely similar in chemical properties to carpaine and affords deoxycarpyrinic acid (III) on dehydrogenation. On hydrolysis and esterification with ethanol, ethyl carpamate and ethyl pseudocarpamate are formed, separable as their hydrochlorides; dehydrogenation of the latter affords ethyl carpyrinate (II). Lithium aluminum hydride (LAH) reduction of pseudocarpaine gives pseudocarpamodiol, isomeric with carpamodiol. Pseudocarpaine evidently differs from carpaine only in the configuration at position 3 in formula I, and must be the *cis*, *trans*, *trans* isomer of carpaine, stereoformulated as VI, in which all the substituents are equatorial. The formation of both carpamic



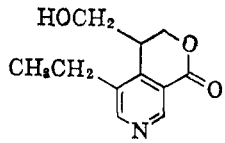
VI



VII, R = $CH{=}CH_2$
VII, R = $CH_2CH_3$



IX, R = $CH_2CH_3$
X, R = $CH{=}CH_2$



XI

and pseudocarpamic acids on hydrolysis of the alkaloid may be accounted for either by alkyl–oxygen fission during cleavage of the lactone ring, or partial epimerization of pseudocarpamic acid under the hydrolysis conditions. A single product, pseudocarpamodiol, results from lithium aluminum hydride reduction, there being no inversion of configuration at C-3 on lactone cleavage by this reagent (52).

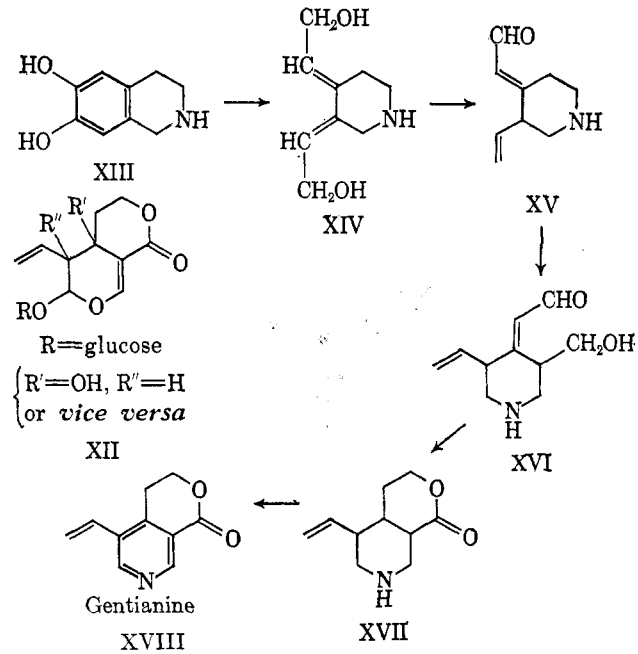
### C. GENTIANINE

The alkaloid gentianine was first isolated from *Gentiana kirilowi* (131, 134) and subsequently from *Enicostemma littorale* Bl. (45), *Dipsacus azureus* Schrenk. (137), *Gentiana lutea* L., *G. asclepiadea* L., *Menyanthes trifoliata* L. (165), and *G. tianschanica* (147). The base erythricine, found in *Erythraea muehlenbergii* Griseb. (*E. centaurium* Pers.) (38) is probably identical with gentianine.

Gentianine, $C_{10}H_9NO_2$, is a crystalline, optically inactive base which forms a series of crystalline salts. The nitrogen atom is tertiary, but the alkaloid contains neither N- nor C-methyl groups. A lactone ring is present, as evidenced by the behavior of gentianine towards alkali. Infrared studies show the lactone is six-membered and $\alpha,\beta$-unsaturated. Dihydrogentianine, obtained by catalytic hydrogenation, is also an $\alpha,\beta$-unsaturated lactone, so that additional unsaturation is present in the gentianine molecule. Ozonolysis of the alkaloid afforded formaldehyde, and permanganate oxidation, a lactonic acid $C_9H_7NO_4$. The additional unsaturation is therefore present as a vinyl group (45).

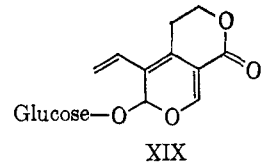
Vigorous oxidation of gentianine yielded pyridine-3,4,5-tricarboxylic acid. The lactonic acid $C_9H_7NO_4$, on hydrolysis, decarboxylation, and oxidation, afforded isonicotinic acid. The most acceptable structure for the alkaloid on this evidence is VII (45, 132, 133). Proof of this structure has been supplied by the synthesis of dihydrogentianine (VIII) by reaction of the sodium salt of 5-ethyl-4-methylnicotinic acid (IX) with formaldehyde; the use of the free acid led to the formation of the hydroxymethyl base XI, identical with the product from the condensation of dihydrogentianine and formaldehyde (45). More recently (46) gentianine itself has been synthesized by an analogous condensation between formaldehyde and the sodium salt of 4-methyl-5-vinylnicotinic acid (X).

Gentianine has also been isolated from *Swertia japonica* Makino, and it has been suggested that the glycoside swertiamarin (XII), which occurs in the same plant, may be a precursor in the biogenesis of the alkaloid. This view has been substantiated by mild treatment of swertiamarin acetate with ammonia, which yielded an amorphous glycoside; mild acid hydrolysis afforded gentianine (87). Another suggestion concerning biogenesis involves a Woodward fission of 1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline




(XIII) to the piperidinediol XIV, convertible by oxidation, reduction, and dehydration to XV. Attack of the allylic position in XV by formaldehyde would lead to XVI, and thence to XVII by lactonization, and to gentianine (XVIII) by aromatization (47). Other workers have proposed a biogenesis based on simple transformations starting with shikimic acid (174).

The conversion of the bitter principle gentiopicrin (XIX) into gentianine by treatment with ammonia has been reported (25, 86).



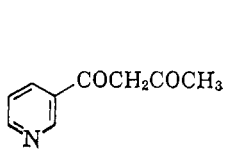

XIX

### D. ANIBINE

The wood of South American rosewood trees (genus *Aniba*) contains an alkaloid anibine, purified by crystallization and sublimation (103–105).

Anibine, $C_{11}H_9NO_3$, is optically inactive, contains one methoxyl group, a tertiary basic nitrogen atom, and a lactone ring, but no N-methyl group, C-methyl group, or active hydrogen. Infrared studies support the lactonic nature of the base and reveal that the

alkaloid is a δ-lactone and is α,β-unsaturated. The presence of an enol ether grouping was also diagnosed; this was confirmed by the formation of a β-keto acid by alkaline hydrolysis of anibine. Decarboxylation of the acid yielded an amphoteric product $C_9H_9NO_2$, also formed by acid hydrolysis of the base. This product no longer contained a methoxyl group, but a Kuhn–Roth determination showed that a C-methyl group was present. The new C-methyl group must represent the point of attachment of the potential carboxyl group of anibine. The infrared spectrum of the $C_9H_9NO_2$ product was of the conjugate chelate type, and its chemical properties were typically enolic. These facts, coupled with the observations that nicotinic acid is a hydrolysis product of the compound and is also formed by nitric acid oxidation of anibine, sug-



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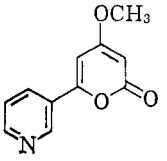
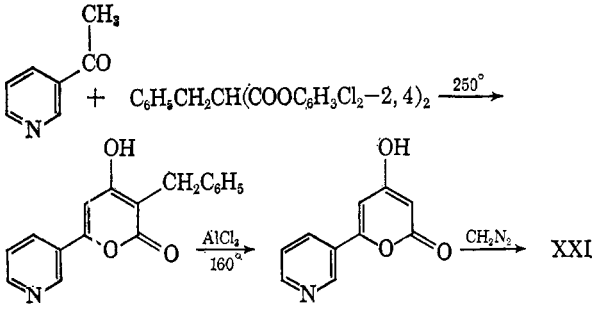


Anibine
XXI

gested that the $C_9H_9NO_2$ cleavage product was 3-acetoacetylpyridine (XX), and a direct comparison with a synthetic specimen proved this to be the case.

Anibine must therefore be formulated as 4-methoxy-6-(3-pyridyl)-2-pyrone (XXI); it appears to be the first alkaloid derived from α-pyrone (104). This formulation has been confirmed by the synthesis outlined below (183).



E. *Himantandra* ALKALOIDS

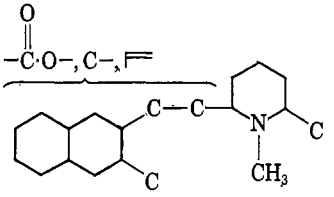
Several new alkaloids have been isolated from the bark of various *Himantandra* species, native to New Guinea and Australia; some of the bases are lactonic (23).

### 1. *Himbacine*

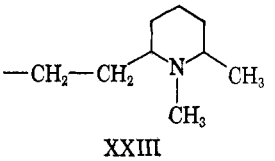
The alkaloid himbacine, $C_{22}H_{35}NO_2$, is one of the most abundant of the group (23). It is an optically active, strong base, containing a tertiary N-methyl group and two C-methyl groups. Spectral and chemical studies showed the presence of a saturated γ-lactone unit and a *trans* -CH=CH- double bond, not conjugated with the lactone carbonyl group (129).

Dehydrogenation of himbacine with palladium–carbon afforded a crystalline base $C_{21}H_{29}NO_2$, recognized on spectral grounds as a pyridine. Selenium dehydrogenation gave methylamine, 2,6-dimethylpyridine, 2-ethyl-6-methylpyridine, 2-ethyl-3-methylnaphthalene, and $C_{19}H_{16}$, a pyrene derivative, probably heterogeneous.

A careful examination of the acidic product of chromic acid oxidation revealed the formation of acetic acid only, unaccompanied by propionic acid, so that himbacine does not contain a terminal ethyl group. On the basis of these results, partial structure XXII was advanced for the alkaloid (129).

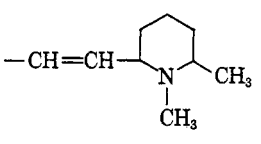


XXII

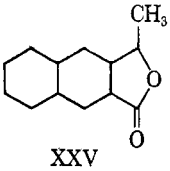


XXIII

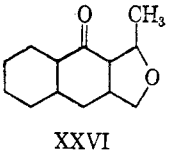
Exhaustive methylation studies on himbacine itself were not very rewarding. Better results were obtained with the dihydroanhydrodiol, $C_{22}H_{39}NO$, obtained by reduction of dihydrohimbacine with lithium aluminum hydride, followed by acid cyclization of the resulting diol. Hofmann degradation afforded a methine $C_{23}H_{41}NO$, containing a vinyl group. Reduction of the methine yielded the dihydromethine (-CH=$CH_2$ → $-CH_2CH_3$) which gave, in poor yield, trimethylamine and a mixture of two nitrogen-free products on Hofmann degradation. Hydroxylation of the mixture followed by periodate oxidation gave pentanal and hexanal, and two products which on oxidation with silver oxide yielded a pair of homologous acids $C_{16}H_{26}O_3$ and $C_{15}H_{24}O_3$. A study of the Barbier–Wieland degradation of these acids led to the conclusion that the unit XXIII was present in dihydrohimbacine, and confirmed the presence of the $C_2$ chain connecting the rings in XXII. Further Hofmann degradation studies, on the anhydrodiol $C_{22}H_{37}NO$, were effected and enabled the double bond in himbacine to be placed as in partial structure XXIV.



XXIV



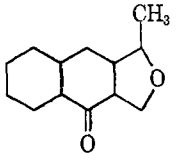
XXV



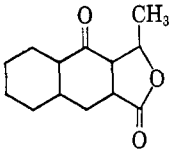
XXVI

Detailed oxidation experiments on himbacine were carried out, particular attention being paid to the structure of a lactonic acid $C_{14}H_{20}O_4$, so obtained. This acid on dehydrogenation yielded 2-ethylnaphthalene, and it thus became clear that the ethyl groups

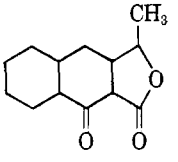
in the alkaloid dehydrogenation products, 2-ethyl-6-methylpyridine and 2-ethyl-3-methylnaphthalene, did not arise from the same two carbon atoms in the alkaloid. The point of attachment of the decalin and N-methylpiperidine fragments was not, therefore, as in XXII. The chemical properties of the lactonic acid led to the conclusion that himbacine contained the unit XXV, and the position of attachment of XXIV to the decalin system was settled by a consideration of the structures of a ketone $C_{13}H_{20}O_2$ and a ketolactone $C_{13}H_{18}O_3$, both oxidation products of the anhydrodiol. The former lacked a reactive methylene group and was formulated as either XXVI or XXVII; the latter was then XXVIII or XXIX. The last structure for the ketolactone was ruled out because



XXVII

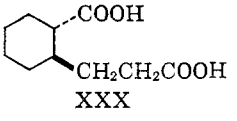


XXVIII

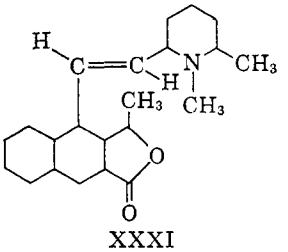


XXIX

of its lack of enolic properties, and confirmation of structure XXVIII was provided by a spectroscopic study of the behavior of the compound toward alkali. Conclusive proof of the presence of a decalin system was provided by degradation to the diacid XXX. It was concluded that himbacine was a vicinally substituted decalin, to be formulated as XXXI, in which the ethylenic bond has the *trans* configuration, the lactone ring is probably *cis* fused, and the



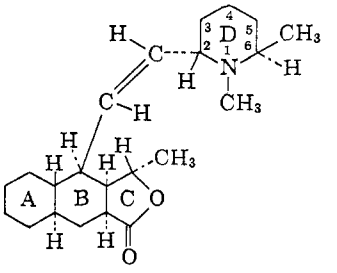
XXX



XXXI

decalin is probably *trans* (129).

This conclusion has been confirmed by an X-ray diffraction analysis of himbacine hydrobromide and the absolute configuration of the alkaloid shown to be XXXII (40).



XXXII

Rings A, B, and D are in the chair conformation, and between A and B is a *trans* union. The ethylenic bond is *trans*, and the substituents at positions 2 and 6 in the piperidine ring are, respectively, equatorial and axial (40).

### *2. Himbeline*

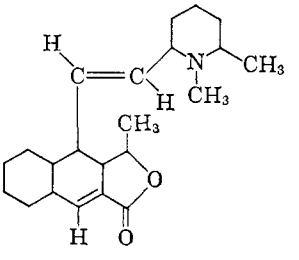
Himbeline, $C_{21}H_{33}NO_2$, is a secondary *Himantandra* base (23) which on methylation with formaldehyde–formic acid yielded himbacine (XXXI). It is therefore N-demethylhimbacine (129). The double bond in himbeline is considerably more reactive than that of himbacine, toward, for example, ozone, peracids, and catalytic hydrogenation (129). Demethylation of himbacine by reaction with cyanogen bromide, followed by catalytic hydrogenation, afforded himbeline (41).

### *3. Himandravine*

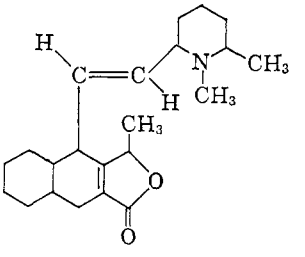
This alkaloid is also a secondary base (23), $C_{21}H_{33}NO_2$, which is readily oxidized by permanganate to the $C_{14}H_{20}O_4$ lactonic acid encountered during the oxidation of himbacine. Dehydrogenation affords dehydrohimbacine. Himandravine is a stereoisomer of himbeline, having a different configuration at one or both asymmetric centers in the piperidine ring (129).

### *4. Himgravine*

This lactonic base, $C_{22}H_{33}NO_2$ (23), contains an N-methyl group. Its spectral properties revealed that it is an $\alpha,\beta$-unsaturated $\gamma$-lactone ($\lambda_{max}$ 218 m$\mu$, $\nu_{max}$ 1684 and 1754 cm.$^{-1}$). Catalytic hydrogenation gave himbacine (XXXI); himgravine must therefore be formulated as either XXXIII or XXXIV (129). A decision between these structures was reached by n.m.r. spectral studies on himgravine and himbacine; the spectrum of the former showed a signal at 0.94 p.p.m. (from chloroform), absent in that of the latter



XXXIII



XXXIV

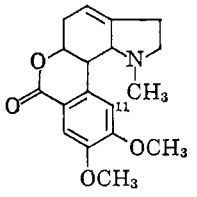
and ascribed to the $\beta$-proton of the conjugated lactone system in XXXIII, which therefore represents himgravine (1).

## III. INDOLE GROUP

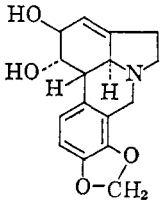
### A. HOMOLYCORINE

The earlier investigations on homolycorine, an Amaryllidaceae alkaloid, which lead to its formula-

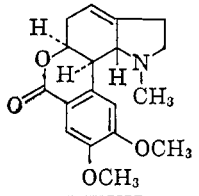
tion as XXXV, have been described elsewhere (28, 62, 126, 181). The most important recent development concerning the alkaloid is the determination of its stereochemistry. As a result of a careful, intricate study of di-, tetra-, and hexahydrohomolycorines,



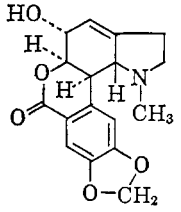
XXXV



XXXVI



XXXVII

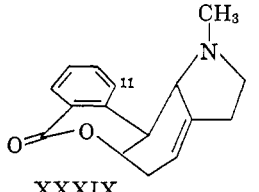


XXXVIII

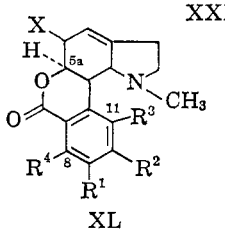
and the establishment of stereochemical correlations between them and derivatives of the closely related alkaloid lycorine, of absolute configuration XXXVI (108), it has been possible to assign to homolycorine the stereoformula XXXVII (83). An analysis of molecular rotation differences between the alkaloid and various hydro derivatives and closely related compounds suggests that XXXVII also represents the absolute configuration of the natural base (83).

Hippeastrine, a related lactonic alkaloid, has been correlated with lycorine (XXXVI) and is represented by the stereoformula XXXVIII (83).

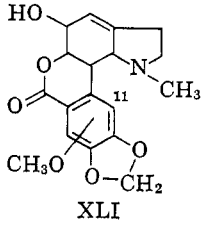
Two new methods of investigation of the aromatic oxygenation pattern in lactonic Amaryllidaceae alkaloids have been described. Inspection of models of these alkaloids show that one side of the nitrogen atom is hindered sterically by a substituent at position 11, as shown in XXXIX. Methiodide formation would



XXXIX



XL



XLI

therefore be expected to be more rapid in bases unsubstituted at this position, compared with alkaloids of the series carrying an alkoxyl group at C-11. This expectation has been substantiated by a comparison between, for example, neronine (XL; $R^1$, $R^2 = CH_2O_2$, $R^3 = OCH_3$, $R^4 = H$, X = OH), albomaculine (XL; $R^1 = R^2 = R^4 = OCH_3$, $R^3 = X = H$) and homolycorine (XXXV), which indicated that a measurement of the rate of methiodide formation could be used to ascertain the presence of an alkoxyl group at C-11. Nuclear magnetic resonance measurements have been used to decide whether there is a substituent at position 8 and have confirmed that the hydrogen atom at position 5a is $\alpha$ (formula XL) in neronine, albomaculine, and homolycorine (75).

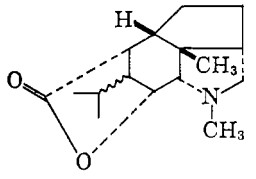
### B. CANDIMINE

Candimine, $C_{18}H_{19}NO_6$, is a newly discovered alkaloid of *Hippeastrum candidum*, containing a tertiary basic N-methyl group, a methoxyl group, and, on infrared evidence, a benzene ring. The base also contains a double bond, an allylic hydroxyl group, and a six-membered lactone ring, with the carbonyl group of the latter conjugated with a benzene ring. The allylic hydroxyl group is also attached to a six-membered ring, since oxidation of it with activated manganese dioxide afforded a cyclohex-2-en-1-one, on infrared evidence. Reduction of candimine with lithium aluminum hydride yielded tetrahydrocandimine, a triol in which two of the hydroxyl groups are vicinal. Catalytic hydrogenation afforded two epimeric dihydrocandimines, separable by chromatography. These observations, and the fact that candimine is an Amaryllidaceae alkaloid, lead to its formulation as XLI, with the methoxyl group probably located at C-11; candimine is therefore an *ar*-methoxyhippeastrine (34). The position of this group could doubtless be settled by a study of the rate of methiodide formation by the alkaloid.

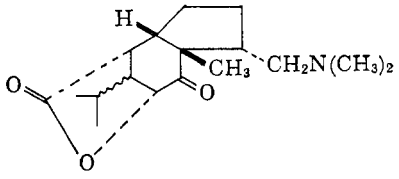
### C. DENDROBINE

The alkaloid dendrobine was first described in 1932, when it was extracted from the Chinese drug "chin-shih-hu" (*Dendrobium nobile*) (166). Preliminary examination of the base showed it to have a molecular formula $C_{16}H_{25}NO_2$, containing a lactone group and an N-methyl group (166, 167). Mass spectral studies confirmed a molecular weight of 263, and infrared measurements revealed that the alkaloid was a saturated $\gamma$-lactone. An analysis of its n.m.r. spectrum has enabled assignments to be made to $C(CH_3)_2$, $NCH_3$, and $CH(CH_3)_2$ groups, the presence of the last being confirmed by mass spectroscopy. Largely on spectral evidence the structure XLII has been advanced for the alkaloid (182). Alkaline hydrolysis followed by oxidation of dendrobine leads to a keto acid in which the keto group is in a six-membered ring. Reduction of the alkaloid with lithium aluminum hydride af-

forded a diol, convertible into a mono- and a diacetate. N.m.r. spectral studies on these and other derivatives have been used to determine the stereostructure of the base, expressed as in XLII. The over-all structure of dendrobine is confirmed by a comparison of its physical data with those of a nonalkaloidal base nobiline, occurring in the same plant and formulated as XLIII (182).



XLII

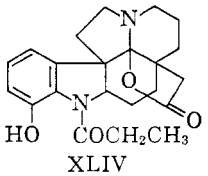


XLIII

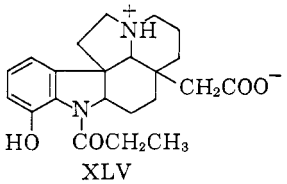
D. CIMICINE

Cimicine is an alkaloid of *Haplophyton cimicidum*, a Mexican shrub. It is dextrorotatory and has the molecular formula $C_{22}H_{26}N_2O_4$. Spectral and chemical evidence points to the presence of a lactone unit in the molecule. The n.m.r. spectrum of cimicine shows that there are neither $NCH_3$ nor $OCH_3$ groups, but that a strongly hydrogen-bonded hydroxyl group and an N-propionyl group are present. The infrared spectrum shows bands characteristic of a 7-hydroxy-N-acyldihydroindole unit. A study of spectral data and a consideration of the difference between the molecular formulas of cimicine and the nonlactonic alkaloid haplocine, $C_{22}H_{28}N_2O_3$, led to the suggestion that cimicine is XLIV. Catalytic hydrogenolysis leads to the betaine dihydrocimicine XLV.

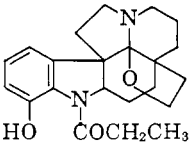
Cimicine is formed in low yield by oxidation of haplocine (XLVI) with chromic acid–pyridine (26).



XLIV



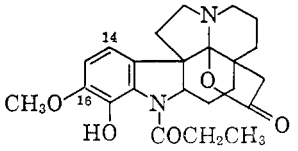
XLV



XLVI

E. CIMICIDINE

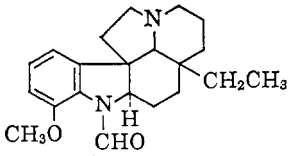
Cimicidine is an insecticidal alkaloid of *Haplophyton cimicidum* (142, 162, 163). Preliminary studies showed that the base $C_{23}H_{28}N_2O_5$ contained a methoxyl group. Infrared and n.m.r. spectral analyses suggested that cimicidine was 14- or 16-methoxycimicine, the latter structure XLVII being favored because of the frequent occurrence of aspidospermine-type alkaloids which are oxygenated at position 16 (26).



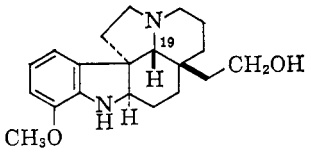
XLVII

F. DICHOTAMINE

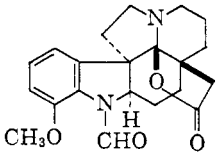
Dichotamine is a minor alkaloid of *Vallesia dichotoma* (68). Mass spectral measurements supported a molecular formula $C_{21}H_{24}N_2O_4$ (22) of two suggested earlier (68), and infrared spectral measurements suggested the presence of a $\gamma$-lactone group (22, 68) and an N-formyl group, both being confirmed by n.m.r. studies, which revealed three aromatic protons. The ultraviolet spectrum was almost identical with that of the alkaloid vallesine (XLVIII). The mass spectrum of dichotamine has been analyzed carefully, and the



XLVIII



XLIX



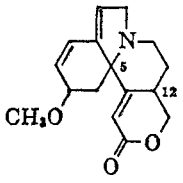
L

fragmentation pattern is consistent with the presence of an indole system containing a methoxyl group and associated with a lactone ring. Acid hydrolysis of the alkaloid yielded deformyldichotamine, the mass spectrum of which was also examined. Lithium aluminum hydride reduction of this product gave deacylcylindrocarpol (XLIX), a known compound, and its C-19 epimer. A similar reduction with lithium aluminum deuteride also gave two epimers, containing deuterium, which were duly examined mass spectroscopically. Structure L was proposed for dichotamine as accommodating all the observations (22).

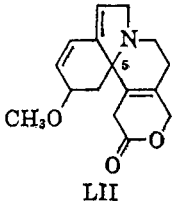
G. LACTONIC *Erythrina* ALKALOIDS

Details concerning the chemistry of $\alpha$- and $\beta$-erythroidine, the two lactonic alkaloids of this indole

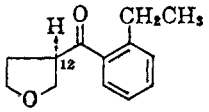
subgroup, have been summarized (17, 18, 97, 128) and shown to lead to structures LI and LII, respectively. Recent developments have been concerned with the relative and absolute stereochemistry of these bases.



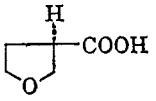
LI



LII



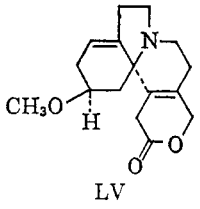
LIII



LIV

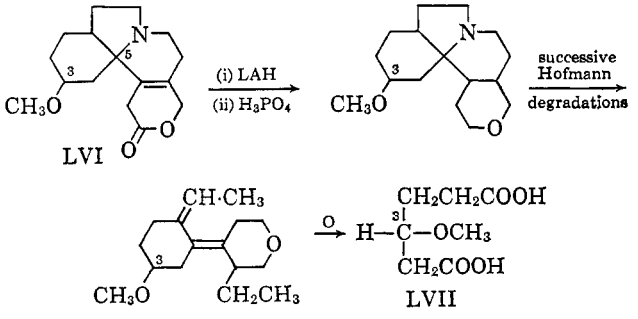
The absolute configuration at C-12 in $\alpha$-erythroidine (LI) has been settled by the synthesis of the (+)-ketone LIII from (+)-3-tetrahydrofuroic acid. The absolute configuration LIV for the latter has been proved by its correlation with (+)-methylsuccinic acid. The ketone LIII proved to be identical with the ketone obtained earlier (43) by stepwise degradation of $\alpha$-erythroidine, and a knowledge of its absolute configuration settles that of the alkaloid at position 12 (67).

The absolute configuration LV for dihydro-$\beta$-erythroidine has been established by X-ray analysis of its hydrobromide (58). In agreement with this is the stepwise degradation of tetrahydro-$\beta$-erythroidine



LV

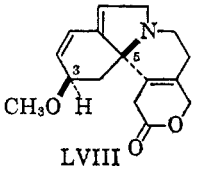
(LVI) to (−)-3-methoxyadipic acid (LVII) as shown.



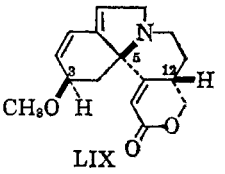

LVI

LVII

Combination of this result, which establishes the absolute configuration at C-3 in $\beta$-erythroidine, with a logical interpretation of the configuration at C-5, and with the above evidence (67) relating to position 12 in $\alpha$-erythroidine, indicates that $\beta$-erythroidine is 3*R*,5*S* (LVIII) and $\alpha$-erythroidine is 3*R*,5*S*,12*S* (LIX) (175). This result for $\beta$-erythroidine is at variance in the configuration at C-5 with an absolute



LVIII

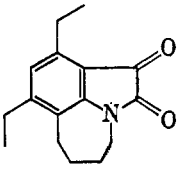


LIX

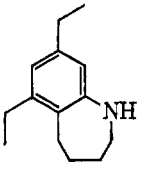
configuration deduced from optical rotatory dispersion measurements on $\beta$-erythroidine and its hydro derivatives. The explanation of this discrepancy may be the need for a reinterpretation of O.R.D. studies on *transoid* dienes (171).

### H. TUBEROSTEMONINE

Preliminary studies (36, 64, 81, 94) on tuberostemonine, the major alkaloid of *Stemona tuberosa* and other *Stemona* species, pointed to a molecular formula $C_{22}H_{33}NO_4$, with a tertiary basic nitrogen atom and two $\gamma$-lactone rings as functional groups. Dehydrogenation of the alkaloid afforded an oxygen-free product "tuberostemonane," $C_{20}H_{29}N$, which was clearly an indole on spectral and chemical evidence. Oxidation of the product yielded an isatin derivative, identified as 1,7-butano-4,6-diethylisatin (LX) by synthesis. More vigorous oxidation afforded an aldehyde $C_{20}H_{29}NO_2$ and

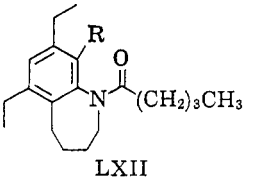


LX

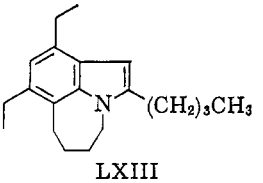


LXI

the corresponding acid $C_{20}H_{29}NO_3$. Hydrolysis of the latter effected breakdown into *n*-valeric acid and an amine, $C_{14}H_{21}N$. The latter contained a 1,2,3,5-tetrasubstituted benzene ring on infrared spectral evidence, and was formulated as LXI, confirmed by synthesis. The aldehyde and acid were formulated as LXII (R = CHO) and LXII (R = COOH), respectively, and "tuberostemonane" as LXIII (151).



LXII

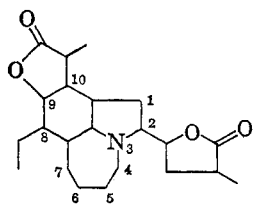


LXIII

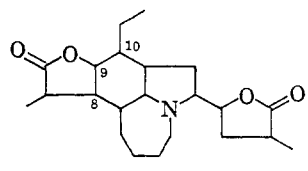
The n.m.r. spectrum of tuberostemonine revealed the presence of three C-methyl groups, and a modified Kuhn–Roth oxidation yielded acetic and propionic acids, identified as their methyl esters by gas chromatography. Two of the C-methyl groups are deshielded and therefore placed $\alpha$ to lactone carbonyl groups.

The spectrum also showed the absence of N-methyl groups and unsaturation, and a consideration of the molecular formula led to the view that tuberostemonine contained two nitrogen heterocycles (44).

A series of transformations on tuberostemonine has led to its formulation as either LXIV or LXV (44). A careful study of the n.m.r. spectrum of bisdehydrotuberostemonine (LXVI) has established that the alkaloid is correctly formulated as LXIV (35). The spec-

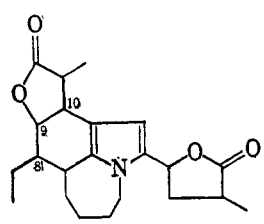


LXIV

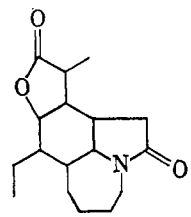


LXV

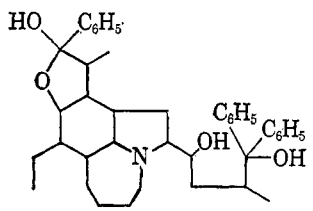
trum showed two apparent triplets at $\tau$ 5.45 and 6.9, the former being assigned to the proton at C-9 in LXVI. The similarity in the splitting of both signals suggested that the hydrogens responsible are on adjacent carbon atoms; if this were so, the signal at $\tau$ 6.9 would be that of the hydrogen at C-10, which would be deshielded by the pyrrole ring and nearby oxygen atoms. The simplicity of this signal is not consistent with a structure corresponding to LXV, since here the C-10 hydrogen



LXVI



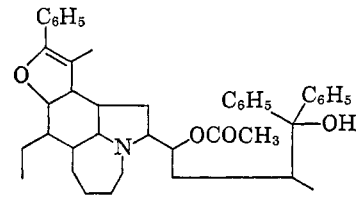
LXVII



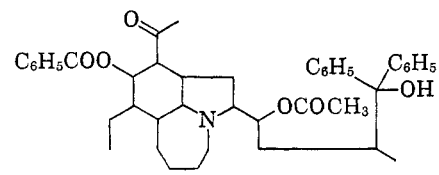
LXVIII

would give rise to at least a four-line multiplet. A spin decoupling technique was used to verify that the hydrogens responsible for the two signals are on adjacent carbon atoms. Under these conditions the upper side band of the $\tau$ 5.45 signal and the lower side band of the $\tau$ 6.9 signal were reduced to doublets, with the same coupling constants, and there was no sign of other decoupling in the vicinity of these signals, proving that the hydrogen atoms responsible are indeed attached to neighboring carbon atoms, that bisdehydrotuberostemonine is LXVI, and that tuberostemonine is LXIV (35).

Degradative studies (44) on tuberostemonine are now to be interpreted as follows. Permanganate oxidation of the alkaloid afforded (−)-methylsuccinic acid and a neutral compound containing $\gamma$-lactone and $\gamma$-lactam groups, formulated as LXVII, on spectral evidence. Reaction of tuberostemonine with three molecules of phenylmagnesium bromide gave a triol LXVIII, which was dehydrated and esterified to LXIX by acetic anhydride, the structure being supported by spectral study. Chromic acid oxidation of LXIX yielded the

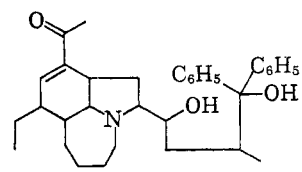


LXIX

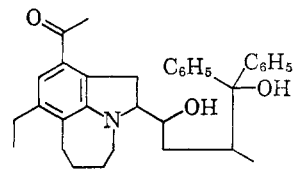


LXX

ketone LXX, which lost benzoic acid with great facility, with simultaneous hydrolysis, to give LXXI. Aerial

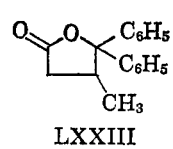


LXXI

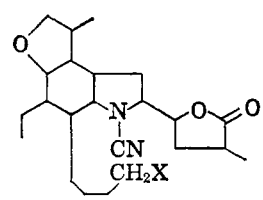


LXXII

oxidation of LXXI gave the dihydroindole LXXII, the n.m.r. spectrum pointing to the presence of a single proton in the aromatic ring, and $\gamma,\gamma$-diphenyl-$\beta$-methylbutyrolactone (LXXIII) (44).



LXXIII

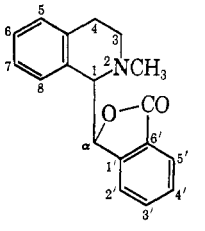


LXXIV

The n.m.r. spectrum of bisdehydrotuberostemonine (LXVI) shows that the alkaloid contains a 2,3,5-trisubstituted pyrrolidine ring. Von Braun degradation of tuberostemonine yields the cleavage product LXXIV (X = Br), the n.m.r. spectrum of which has been analyzed satisfactorily in terms of this structure. A three-proton signal at $\tau$ 6.66 is shifted downfield to *ca.* $\tau$ 6.0 by conversion of LXXIV (X = Br) to the corresponding acetate (LXXIV, X = OAc) and is therefore due to one of the protons $\alpha$ to the cyanamide group and the two hydrogens of the $-CH_2X$ group (44).

## IV. PHTHALIDE–ISOQUINOLINE GROUP

An important subgroup of the large family of isoquinoline alkaloids comprises bases with a framework formed by union of 1,2,3,4-tetrahydroisoquinoline and phthalide units, *via* the 1-position of the former and the α-position of the latter, as in LXXV. The alkaloids



LXXV

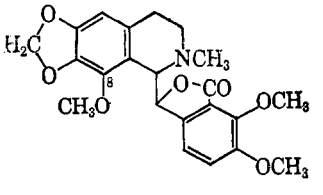
differ from one another in the nature and position of oxygenated substituents in the two aromatic rings. These substituents may be hydroxyl, methoxyl, or methylenedioxy groups, or combinations of these, and may be located at positions 6, 7, 8, 4′, and 5′ (61, 125, 164).

An important chemical property of the alkaloids is the facility with which they are cleaved by mild oxidation, reduction, or hydrolysis into two fragments, derived, respectively, from 1,2,3,4-tetrahydroisoquinoline and phthalide (or a closely related compound). These fragments together contain all the carbon atoms and the nitrogen atom of the original alkaloid, and their identification provides nearly all the information necessary for structural elucidation.

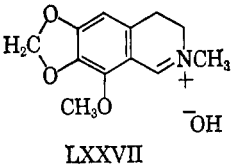
### A. NARCOTINE

The chemistry of narcotine, one of the first alkaloids to be discovered, has been given detailed treatment in several authoritative works (61, 125, 164), and reviewed (20). Its structure has been established as LXXVI by degradation and synthesis.

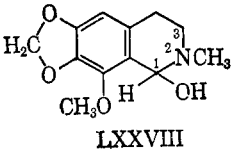
A somewhat unexpected source of the alkaloid is *Rauwolfia heterophylla* Roem. and Schult (19, 32). Narcotine has been separated from opium by paper chromatography (29, 74) and thin layer chromatography (33). Variation in the narcotine content of different parts of *Papaver somniferum* with the time of day



LXXVI



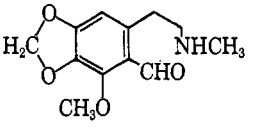
LXXVII



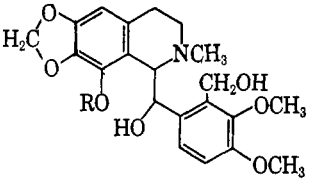
LXXVIII

(66, 84) and of year (65) have been investigated.

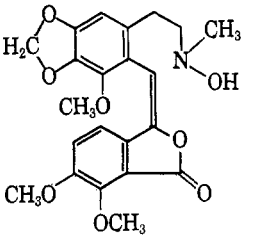
Ultraviolet absorption and electrometric titration studies confirm that cotarnine, one of the principal cleavage products of narcotine, is present in aqueous solution as the quaternary ammonium form LXXVII. Addition of alkali causes conversion into the pseudobase form LXXVIII (161). No evidence for the free existence of the aldehyde form LXXIX has emerged, and it is interesting to note that "N-methylcotarnine" [LXXIX, $NHCH_3$ replaced by $N(CH_3)_2$] is not formed by methylation of cotarnine, though it can be prepared by indirect methods (11).



LXXIX



LXXX



LXXXI

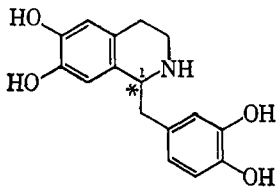
The lithium aluminum hydride reduction of narcotine has been described. Two groups (101, 150) have observed that reduction occurs as expected, to the corresponding diol LXXX (R = $CH_3$). Another group has reported that in tetrahydrofuran, partial demethylation occurs simultaneously, leading to the phenol LXXX (R = H), itself the LAH reduction product of narcotoline (8-demethylnarcotine) (6). The reduction is inhibited by pyridine (100).

The pyrolysis of narcotine N-oxide yields the enol–lactone LXXXI (12), the same compound being formed by heating a chloroform solution of the oxide (130). The pyrolysis of narcotine itself leads to an unidentified base (140).

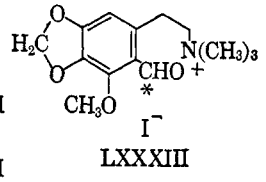
The nuclear magnetic resonance (148) and infrared spectra (21) of narcotine have been recorded, with special interest in the spectral characteristics of the methylenedioxy group. X-Ray powder photographic data on the alkaloid have been published (8).

Tracer experiments have substantiated the original suggestion (141) that narcotine, as a typical phthalide–isoquinoline alkaloid, is biosynthesized from a benzylisoquinoline residue and a one-carbon unit. Uniformly labeled tyrosine has been shown to be incorporated into narcotine (85), and (±)-[2-$^{14}$C]-tyrosine, when fed to *Papaver somniferum* plants, yielded radioactive narcotine. The latter was degraded to active cotarnine (LXXVIII) and inactive opianic acid.

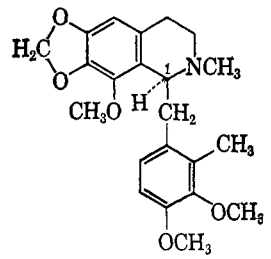
Degradation of the former revealed that the molecule was equally labeled at positions 1 and 3, the activity in each position being one-half that of the labeled alkaloid. [1-$^{14}$C]-Norlaudanosoline (LXXXII) was also incorporated; degradation of the radioactive narcotine to the methiodide LXXXIII was effected and the latter shown to be labeled at the aldehyde group only, the



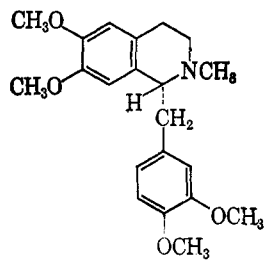
LXXXII



LXXXIII



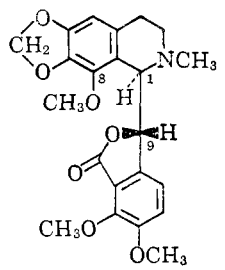
LXXXIV



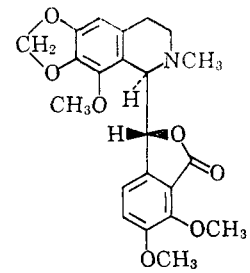
LXXXV

activity there being equal to that of the narcotine. Sodium [$^{14}$C]-formate was also incorporated, with labeling of the lactone carbonyl group (9).

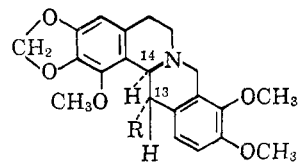
The narcotine structure LXXVI contains two asymmetric centers and is therefore capable of existence in two racemic ($\alpha$- and $\beta$-gnoscopine) and four optically active forms [(+)- and (−)-$\alpha$-narcotine, and (+)- and (−)-$\beta$-narcotine]. Marshall, Pyman, and Robinson (99) have shown that (+)- and (−)-$\alpha$-narcotines are epimerized by alkali to (+)- and (−)-$\beta$-narcotines, and considered that inversion had occurred at the phthalide asymmetric center only. It was concluded that (+)-$\alpha$-narcotine and (+)-$\beta$-narcotine differed at the phthalide center only. This view has been confirmed (115) by the reduction of both (−)-$\alpha$- and (−)-$\beta$-narcotine with lithium aluminum hydride to the corresponding diols LXXX (R = $CH_3$). Acetylation of the diols gave the diacetates, hydrogenolysis of which afforded a common product, the 1-benzyltetrahydroisoquinoline LXXXIV, proving that the two narcotines have the same configuration at C-1. The absolute configuration of LXXXIV was settled by optical rotatory dispersion comparison with (−)-laudanosine, of known absolute configuration, LXXXV. The two showed Cotton effects of opposite sign, so that the absolute configuration of LXXXIV is as depicted. The absolute configuration at the other (phthalide) asymmetric center in narcotine was settled by a similar comparison with hydrastine (see below). It had been suggested earlier (99) that the natural alkaloids were not stereochemically parallel, but it has now been established that they do in fact have the same configuration at both centers of asymmetry, their O.R.D. curves (in dilute acid) both showing a negative Cotton effect. Similarly (−)-$\beta$-narcotine and (−)-$\alpha$-hydrastine are configurationally related, having positive Cotton effects (115). The absolute configurations of natural (−)-$\beta$-hydrastine and of (−)-$\alpha$-hydrastine having been elucidated (see below) (114), it follows that (−)-$\alpha$-narcotine is LXXXVI and (−)-$\beta$-narcotine is LXXXVII (115). These absolute configurations have also been proved by conversion of (−)-$\alpha$-narcotine by several steps into the (−)-tetrahydroprotoberberine LXXXVIII (R = H), of known



LXXXVI



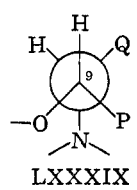
LXXXVII



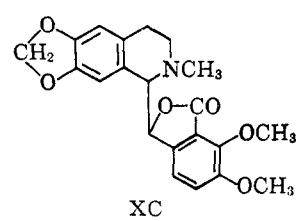
LXXXVIII

absolute configuration at C-14. The relative configuration at C-13 in the penultimate product LXXXVIII (R = OH) was deduced from n.m.r. spectroscopic measurements, leading to LXXXVI for the alkaloid. (−)-$\beta$-Narcotine similarly yielded LXXXVIII (R = OH, and opposite configuration at C-13) and must therefore have the absolute configuration LXXXVII (10).

The n.m.r. spectrum of narcotine has been analyzed and found to be in agreement with the representation of the alkaloid as LXXXVI or its mirror image. It has been deduced that, because of the methoxyl group at C-8, the most important conformation of the base is the staggered one LXXXIX (Q = isoquinoline benzene ring; P = phthalide benzene ring) (143).



LXXXIX



XC

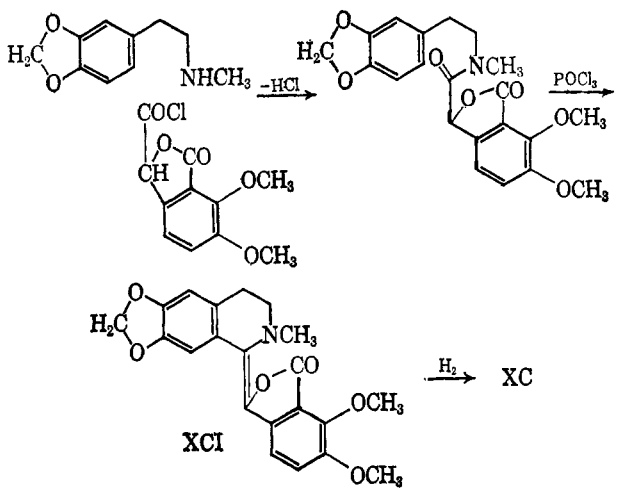
B. NARCOTOLINE

Tyrosine labeled generally with carbon-14 has been fed to *Papaver somniferum* plants. Radioactive narcotoline (8-demethylnarcotine) was isolated and cleaved

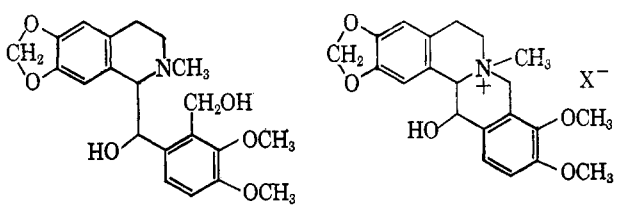
to cotarnoline (LXXVIII, $OCH_3$ replaced by OH) and meconine, both of which had activities consistent with the use of the carbon skeletons of two tyrosine molecules in the biosynthesis of narcotoline (85).

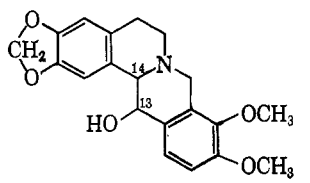
### C. HYDRASTINE

The constitution XC has been assigned to hydrastine (61, 125, 164), the chemistry of which is closely parallel to that of narcotine. The two racemates corresponding to this structure have been synthesized and separated in improved yield by the following route (59).

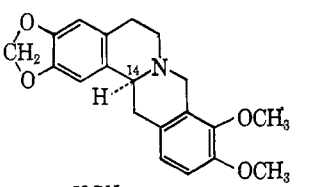


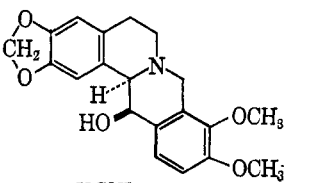

Catalytic hydrogenation of the penultimate product, dehydrohydrastine (XCI), yielded a separable mixture of two racemates, one of which, (±)-β-hydrastine, yielded to attempts to resolve it, the (−)-enantiomorph proving identical with natural (−)-hydrastine (59, 60). The other racemate, (±)-α-hydrastine, resisted attempts at resolution, but (−)-α-hydrastine has been prepared by alkaline epimerization of natural (−)-β-hydrastine (99), the epimerization involving the phthalide asymmetric carbon atom (99). Reduction of natural (−)-β-hydrastine and (−)-α-hydrastine with lithium aluminum hydride afforded two diols XCII, one crystalline and one a sirup. These were converted into

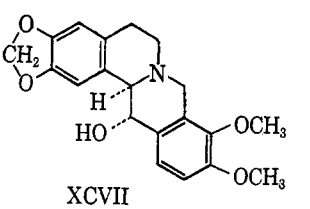


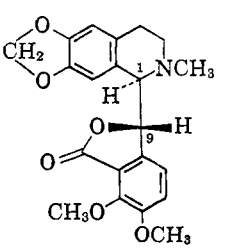

their monotosylates, the less hindered primary alcoholic group being esterified. The esters underwent spontaneous quaternization to the salts XCIII (X = OTs), convertible to the corresponding methiodides and methochlorides (XCIII, X = Cl). The methochlorides on pyrolysis yielded (−)-13-epiophiocarpine and (−)-ophiocarpine (XCIV), respectively. Acetylation gave the epimeric ophiocarpine acetates (XCIV, HO replaced by AcO), which were subjected to catalytic hydrogenolysis. Both yielded (−)-canadine (with racemic canadine), the absolute configuration XCV of which has been settled. This correlation confirms that in (−)-α- and (−)-β-hydrastines the configuration at the isoquinoline asymmetric center is the same, and establishes the ab-

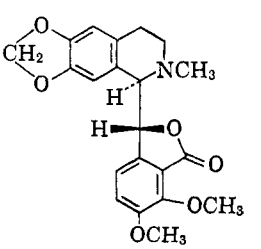


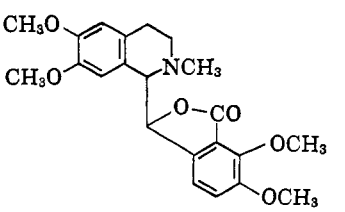




solute configuration as in XCV. Infrared studies on ophiocarpine and epiophiocarpine (XCIV) at high dilution show that in the former case only is there evidence of intramolecular hydrogen bonding. The hydroxyl group in ophiocarpine must therefore be quasi-axial; this assignment has been confirmed by basic strength studies and by n.m.r. spectral measurements. (−)-Ophiocarpine and (−)-epiophiocarpine are therefore stereoformulated as XCVI and XCVII, and natural (−)-β-hydrastine and (−)-α-hydrastine as XCVIII and XCIX, respectively (114).

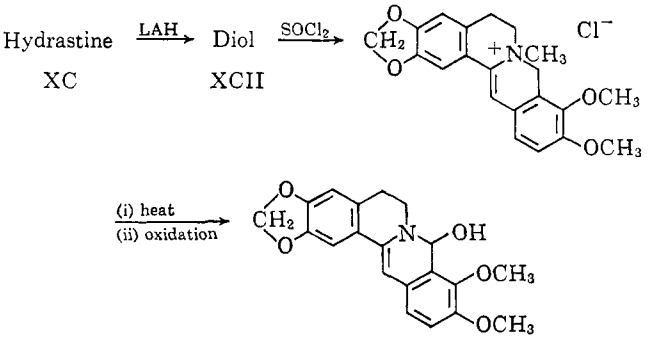


The nuclear magnetic resonance spectrum of hydrastine has been measured (16). An analysis of the spectrum leads to the conclusion that natural hydrastine has the configuration XCVIII or its mirror image and shows that hydrastine, narcotine, bicuculline, and corlumine are stereochemically parallel, but adlumine differs from these at the configuration of the phthalide asymmetric center. Some deductions about the contributions of possible conformations of XCVIII about the C-1–C-9 bond to the structure of the alkaloid have been made (143).

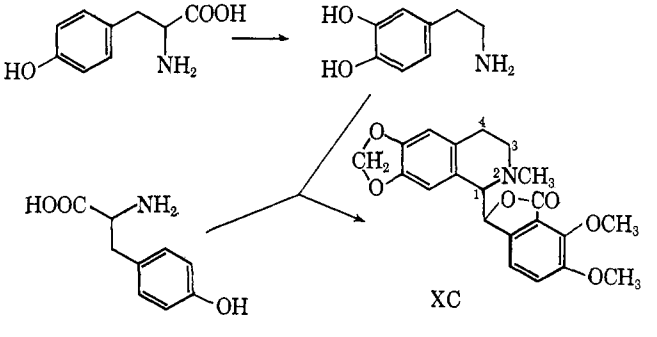
Hydrastine has been converted into berberine by the following route (101).




Berberine

The pyrolysis of hydrastine N-oxide leads to an enol-lactone of structure analogous to LXXXI, similarly obtained from narcotine N-oxide (12).

The biosynthesis of hydrastine has been investigated by Gear and Spenser (42), who have fed carbon-14 labeled compounds to *Hydrastis canadensis* plants. Hydrastine has been found to be derived specifically from two molecules of tyrosine; one molecule of dopamine was also incorporated. These results are consistent with the classical hypothesis concerning the biosynthesis of the alkaloid (141) and are not in agreement with an alternative scheme based on prephenic acid (172, 173). Degradation of hydrastine derived from (±)-[2-$^{14}$C]-tyrosine showed that the activity was located exclusively at carbon atoms 1 and 3 of the hydrastine skeleton, while feeding of [1-$^{14}$C]-dopamine led to labeling only at position 3. Present knowledge of the biosynthesis of hydrastine may thus be summarized as follows (42).

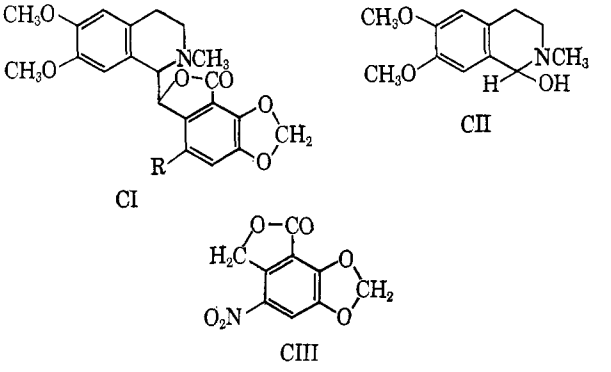



### D. CORDRASTINE

The constitution assigned to cordrastine (C) is based principally upon the expectation that the tetramethoxy analog of hydrastine would be found in nature (61, 125, 164). The two racemates corresponding to C have been synthesized (59) by a route analogous to the synthesis of hydrastine (see above), but neither racemate could be resolved.

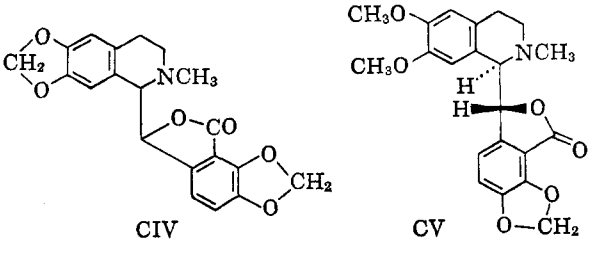
### E. CORLUMINE

The chemical behavior of corlumine is so closely similar (61, 125, 164) to that of adlumine that it was evident that the alkaloids were epimers of structure CI (R = H). Groenewoud and Robinson (53), in an attempt to synthesize adlumine, condensed lodal (CII) with 3,4-methylenedioxy-6-nitrophthalide (CIII) and obtained a racemic nitro base CI (R = $NO_2$), which was reduced to the corresponding amino base CI (R = $NH_2$). A reinvestigation of this partial synthesis, and its completion by replacement of the amino group by hydrogen, yielded a racemic base CI (R = H), resolution of which afforded (+)- and (−)-corlumine. 6-Iodo-3,4-methylenedioxyphthalide also condensed with lodal stereospecifically to give only (±)-iodocorlumine, which on hydrogenation furnished (±)-corlumine. No products having the epimeric adlumine configuration were encountered (176). The infrared and n.m.r. spectra of corlumine have been recorded (37) (see below).




### F. BICUCULLINE

The constitution CIV for bicuculline (61, 92, 125, 164) has been confirmed by a synthesis which follows the same lines as one used for other alkaloids of the group, leading ultimately to (±)-bicuculline, which was resolved with tartaric acid (53, 60). The infrared and



n.m.r. spectra of bicuculline have been recorded (37); analyses of the latter and of the n.m.r. spectrum of corlumine reveal that these two alkaloids are stereochemically parallel to narcotine (LXXXVI) and hydrastine (XCVIII), their absolute configurations being represented by structures analogous to these, or their mirror images (143).

### G. ADLUMIDINE AND CAPNOIDINE

These bases are optical enantiomorphs, $C_{20}H_{17}NO_6$, and have been shown to have the same structure as bicuculline (91, 125, 164), since all three alkaloids yield the same hydrolytic oxidation products (92). Adlumidine has been found in *Corydalis incisa* (Thumb.) Pers. On admixture the bases yield a racemate which is one of the two corresponding to structure CIV (92).

### H. ADLUMINE

The n.m.r. spectrum of adlumine (91, 125, 164) has been studied, and it has been concluded from it that the natural alkaloid is not stereochemically parallel to narcotine, hydrastine, corlumine, and bicuculline. It differs from these bases in the configuration of the phthalide asymmetric carbon atom and is therefore represented by CV or its mirror image (143).

## V. INDOLIZIDINE GROUP

### A. SECURININE AND VIROSECURININE

As will be noted in the sequel, securinine and virosecurinine have been shown to be optical enantiomorphs and so are conveniently considered together.

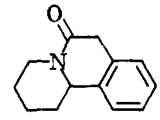
Securinine is an alkaloid found in the leaves of *Securinega suffruticosa* Rehd. (106, 107, 146) and in the roots, stems, and leaves of *Phyllanthus discoides* (15, 116). It is strychnine-like in its physiological action, stimulating the central nervous system and increasing the blood pressure (169).

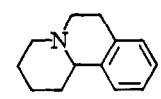
Securinine, $C_{13}H_{15}NO_2$, is a crystalline, highly levorotatory base which forms a series of crystalline salts. Preliminary studies showed that it was a tertiary base containing a lactone system, with no OH, $NCH_3$, $OCH_3$, or $CCH_3$ groups. Ultraviolet absorption studies ($\lambda_{max}^{EtOH}$ 256 m$\mu$, $\epsilon$ 18,200) showed that the lactone was $\alpha,\beta$-unsaturated, with an additional ethylenic bond extending the conjugation (72, 106, 107, 146, 149). Infrared absorption measurements confirmed that the lactone ring was $\alpha,\beta$-unsaturated and showed it to be five-membered (split carbonyl bands at 1792 and 1764 cm.$^{-1}$) (72, 106, 107, 146, 149).

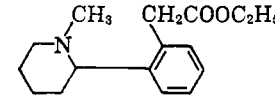
Stepwise catalytic hydrogenation of securinine led firstly to dihydrosecurinine, $C_{13}H_{17}NO_2$, $\lambda_{max}^{EtOH}$ 215 m$\mu$ ($\epsilon$ 17,700), $\nu_{max}$ 1810 and 1767 cm.$^{-1}$, an $\alpha,\beta$-unsaturated $\gamma$-lactone lacking the additional conjugated ethylenic linkage of the parent alkaloid. Further reduction gave tetrahydrosecurinine, $C_{13}H_{19}NO_2$, $\nu_{max}$ 1789 cm.$^{-1}$, transparent in the ultraviolet region, and recognized as a saturated $\gamma$-lactone. Securinine is therefore tetracyclic (72, 106, 146, 149). The ultimate reduction product was hexahydrosecurinine, $C_{13}H_{21}NO_2$, m.p. 223–225°, which was shown, on spectral evidence, to be a hydroxylactam (146, 149). Another (stereoisomeric) hydroxylactam, m.p. 184–184.5°, was formed by reduction of securinine with Raney nickel and alkali (146).

Reduction of dihydrosecurinine with lithium aluminum hydride afforded an oily diol, ozonolysis of which gave glycollic aldehyde and an $\alpha$-ketol $C_{11}H_{17}NO_2$, the hydroxyl group of which proved to be tertiary (149).

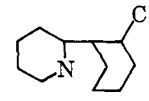
Treatment of securinine with zinc and alcoholic sulfuric acid caused a deep-seated transformation, to a lactam $C_{13}H_{15}NO$, which on oxidation yielded phthalic acid. The lactam, which was also obtained from virosecurinine by the same procedure (109), was shown by degradation and spectral study to be the oxobenzoquinolizidine CVI (149). On reduction with lithium aluminum hydride CVI afforded the benzoquinolizidine CVII, identical with an authentic sample (109). Securinine methiodide is also partially aromatized under the same conditions to an ester formulated as CVIII on spectral groups (149).

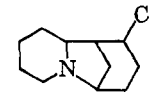

CVI

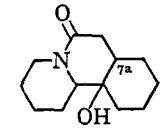

CVII

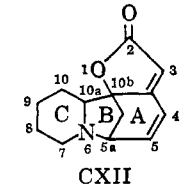

CVIII

The hydroxylactam, hexahydrosecurinine, afforded 2-*o*-tolylpyridine on dehydrogenation, indicating that in securinine the nitrogen atom and twelve of the thirteen carbon atoms are united in the expression CIX.


CIX

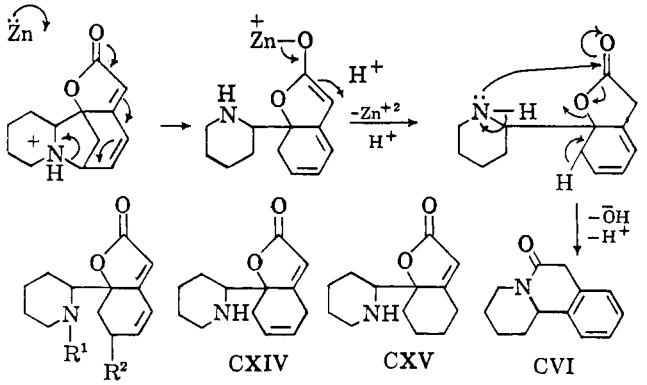

CX


CXI


CXII

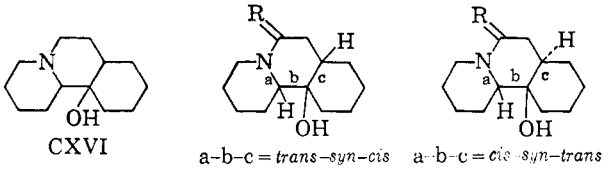
The formation of phthalic acid by permanganate oxidation of tetrahydrosecurinine was in agreement, and the formation of *p*-toluidine by dehydrogenation of securinine allowed CIX to be expanded to CX (146). On treatment with acid, hexahydrosecurinine was transformed into a $\gamma$-lactone, reconverted into the hydroxylactam by base. Together with spectral interpretations, these observations allowed hexahydrosecurinine to be for-

mulated as CXI and securinine as CXII. The n.m.r. spectrum of the alkaloid has been satisfactorily interpreted in terms of this structure (146, 149). The formation of the lactam CVI from securinine has been explained by an electron transfer from zinc to the nitrogen atom *via* the conjugated system, causing rupture of the N–C bond; acid-catalyzed lactam formation follows, with final dehydration to an aromatic ring (159).



CXIII CXIV CXV CVI

The formulation CXII for securinine has been confirmed by a von Braun degradation of the alkaloid, leading first to CXIII ($R^1$ = CN, $R^2$ = Br), which on hydrogenation afforded CXIII ($R^1$ = CN, $R^2$ = H). Acid hydrolysis of the latter yielded CXIII ($R^1$ = $R^2$ = H), which could also be obtained by the direct hydrogenation of securinine in wet ether to CXIV, followed by thermally induced double bond shift. Catalytic hydrogenation of both CXIII ($R^1$ = $R^2$ = H) and CXIV gave CXV, also obtained as a minor product in the catalytic hydrogenation of securinine. Reduction of CXV with Raney nickel and alkali yielded the hydroxylactam CXI, m.p. 184–185° (hydroxylactam A), while catalytic hydrogenation (Pt) afforded a stereoisomeric hydroxylactam, m.p. 223–225° (hydroxylactam B; hexahydrosecurinine). Reduction of the two hydroxylactams with lithium aluminum hydride afforded two hydroxyquinolizidines, A and B (CXVI). A study of molecular models of the eight possible optically active isomers of CXVI suggested that infrared spectral

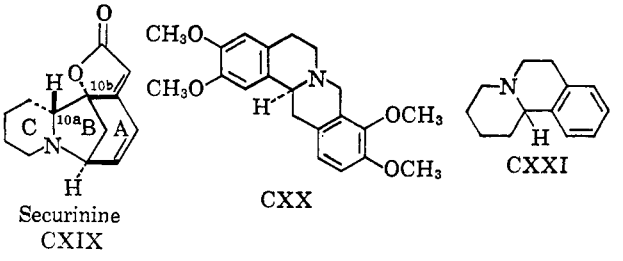


CXVI

a-b-c = *trans-syn-cis* CXVII

a-b-c = *cis-syn-trans* CXVIII

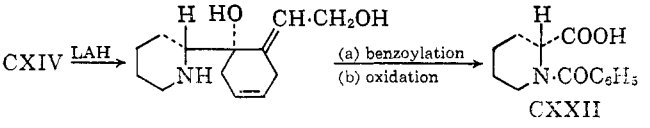
measurement might be used to settle the relative configuration of the two hydroxyquinolizidines. Compound A (m.p. 163–165°) showed in its spectrum bands associated with a *trans*-quinolizidine system, while there was no evidence of intramolecular hydrogen bonding. Compound B, on the other hand, had no bands characteristic of a *trans*-quinolizidine, but showed evidence of intramolecular hydrogen bonding. Quinolizidine A was therefore represented by CXVII (R = $H_2$) and B by CXVIII (R = $H_2$), or their mirror images. Hydroxylactam A was thus CXVII (R = O) and hydroxylactam B, CXVIII (R = O). The synthesis of racemic hydroxylactam B and quinolizidine B by a stereospecific route has been described. The stereochemistry of securinine is therefore depicted by CXIX, where the



Securinine CXIX CXX CXXI

relative configuration of positions 10a and 10b remained to be settled. A study of models suggested strongly that only the configuration as depicted in CXIX could give rise to the two epimeric hydroxylactams, so that securinine is CXIX or its mirror image (144, 145).

The absolute configuration of securinine has been shown to be CXIX by optical rotatory dispersion and molecular rotation studies. The O.R.D. curve of the quinolizidine CVII derived from securinine was found to be opposite in sign to that of (−)-tetrahydropalmatine (CXX), so that the absolute configuration CXXI can be written for CVII; molecular rotation measurements enabled the same conclusion to be reached. It followed that securinine was represented by the absolute configuration CXIX. Confirmation was provided by the degradation of securinine to (+)-N-benzoylpipecolic acid, of absolute configuration CXXII, by the following route (69, 70, 144)



CXXII

Two of the three possible conformations of CXIX are regarded as more favorable than the third, on ultraviolet spectral evidence (70).

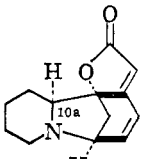
Virosecurinine, an alkaloid of *Securinega virosa* Pax., has been shown to be the optical enantiomorph of securinine, and its chemistry is consequently closely similar to that of securinine. It is formulated as the mirror image of structure CXIX and has been degraded to (−)-N-benzoylpipecolic acid (109–113). The relative configuration has been confirmed by n.m.r. studies on virosecurinine and its hydro derivatives (113).

Dihydrosecurinine has been found to be a minor alkaloid of *Securinega suffruticosa* (71).

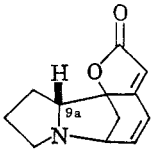
### B. ALLOSECURININE

Allosecurinine is a minor alkaloid of *S. suffruticosa*. It is isomeric with securinine and has closely similar

physical and chemical properties, the two being separable as their oxalates. The action of zinc and sulfuric acid on allosecurinine yielded a lactam CVI, antipodal with that obtained from securinine, and the same as that derived similarly from virosecurinine. Evidently allosecurinine and virosecurinine have the same configuration at position 10a (see formula CXIX), opposite to that in securinine (110, 112, 149). Since the absolute configuration of virosecurinine has been proved to be the mirror image of CXIX, it is apparent that allosecurinine must differ from virosecurinine in the stereochemistry of the methylene bridge and have the absolute configuration CXXIII (110–113, 149).



CXXIII



CXXIV

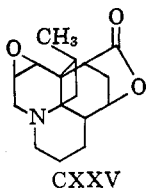
### C. NORSECURININE

An alkaloid, norsecurinine, has been found in the roots of *Securinega virosa*. Norsecurinine, $C_{12}H_{13}NO_2$, is lactonic, but contains no $NCH_3$, $OCH_3$, $CCH_3$, or OH groups. The nitrogen atom is tertiary. Mass spectral investigations confirm the molecular formula, and the fragmentation pattern suggests that a six-membered heterocyclic nitrogen ring is not present. N.m.r. spectral studies and mass spectral measurements are consistent with the structure CXXIV for the base, with the hydrogen atom at position 9a $\beta$. The configuration of the $CH_2$ bridge has not yet been settled. The alkaloid can be reduced in a stepwise manner to dihydro and tetrahydro bases, and spectral measurements on all three lactones have been made (73). The alkaloid is actually related to pyrrolizidine, but is conveniently discussed here.

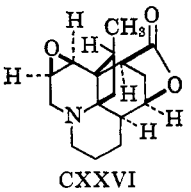
## VI. QUINOLIZIDINE GROUP

### A. ANNOTININE

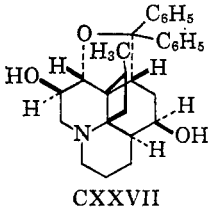
Earlier investigations on the structure of annotinine, $C_{16}H_{21}NO_3$, the principal *Lycopodium* alkaloid, leading to the structure CXXV, have been summarized in reference works (93, 95, 127). Full experimental details of an earlier preliminary communication (177), in which



CXXV



CXXVI

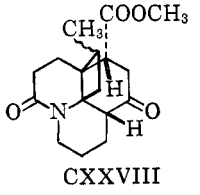


CXXVII

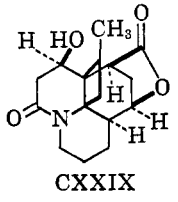
structure CXXV was advanced, have been published (179), and the structure has been corroborated by X-ray analysis of annotinine bromohydrin (135, 136). This investigation led to CXXVI as the relative configuration of annotinine.

Recent developments have been concerned with confirmation of this relative configuration and the determination of the absolute configuration of annotinine (178). Reaction of annotinine with phenyllithium afforded the diol CXXVII (119). The established relative configuration of the lactone ring in annotinine and the known geometric requirements for a concerted epoxide ring cleavage suggest that the phenyl ketone, formed initially, epimerizes at the $\alpha$-carbon atom and then reacts with another phenyllithium molecule to yield a diphenylcarbinol, which interacts with the epoxide group to give CXXVII. Models show that for this concerted intramolecular attack the four-membered ring must be *cis* to the epoxide ring in annotinine (178).

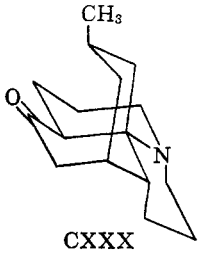
The absolute configuration of annotinine has been investigated by optical rotatory dispersion studies on the keto ester CXXVIII, derived from the alkaloid (170). Application of the octant rule to the Cotton



CXXVIII



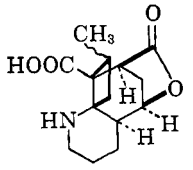
CXXIX



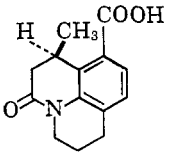
CXXX

effect shown by the O.R.D. curve leads to the absolute configuration CXXVIII for the ester. This configuration has been checked by application of Hudson's lactone rule to annotinine hydrate [CXXVII, $C(C_6H_5)_2$ replaced by CO]. A second confirmation was provided by an application of the Prelog procedure to the alcohol CXXIX, also obtainable from annotinine (170): the phenylglyoxylate ester of this alcohol, on treatment with methylmagnesium iodide gave, after hydrolysis, mainly (−)-atrolactic acid, which points to the absolute configuration CXXIX for the alcohol (178).

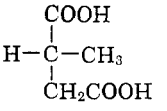
The stereochemistry of the alkaloid lycopodine, which occurs in the same plant as annotinine, has been deduced recently (5) and is represented by CXXX. It seems likely that, since the two bases differ in skeleton by one carbon atom only, they have the same absolute configuration. The optical rotatory dispersion of lycopodine has been studied and is consistent with the absolute configuration CXXX for the base; this is in agreement with an absolute configuration for annotinine as CXXVI (178), except for the configuration of the methyl group, which remains to be settled. An attempt was made to elucidate this by a dehydrogenation rearrangement of the amino acid CXXXI, derived from annotinine (179), which led to the lactam carboxylic



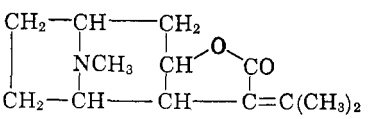
CXXXI



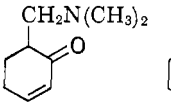
CXXXII



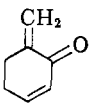
CXXXIII



CXXXIV



CXXXV



CXXXVI

acid CXXXII; a plausible mechanism for the change involves an inversion of the >CH·CH$_3$ group. Ozonolysis of the lactam carboxylic acid gave (+)-methylsuccinic acid (CXXXIII). It would appear from this that the methyl group in annotinine is *trans* to the lactone ring, whereas X-ray analysis of the alkaloid (135, 136) shows it to be *cis*. It is possible that this discrepancy can be explained in terms of an alternative mechanism for the conversion of CXXXI into CXXXII, involving a double inversion at the >CH·CH$_3$ group (178).

The mass spectrum of annotinine has been recorded. The spectrum is complex, but a peak at mass 42 can be explained by the fragmentation of the –CH$_2$·CH(CH$_3$)– bridge. Other peaks at masses 86 and 87 are probably due to elimination of the oxygens of the lactone ring as carbon dioxide. A peak at mass 42 is of importance from the structural viewpoint, since it differentiates annotinine from other *Lycopodium* alkaloids (90).

Some plausible speculations concerning the biogenesis of annotinine have been made. It has been suggested that the alkaloid might be formed by a condensation of two eight-carbon polyacetate straight-chain precursors, of the type believed to play a part in the biosynthesis of fatty acids and macrolide antibiotics. The grosser features of the structure can be accounted for by a union of two molecules of a 3,5,7-trioxooctanoic acid *via* an aldol-type condensation, followed by subsequent aldol condensations. All the oxygenated positions in the acids either take a direct part in the formation of the final skeleton or appear as oxygenated or unsaturated centers in the final alkaloid (27). Another biogenetic scheme proposes 3,5-dioxocaproic acid (derived from three acetate units) and mevalonic lactone as starting materials, the nitrogen atom being introduced at a later stage by a condensation with the iminodialdehyde HN(CH$_2$CH$_2$CHO)$_2$ (derived from aspartic acid) (89).

## VII. Isoquinuclidine Group

### A. Dioscorine

Early investigations on dioscorine, the alkaloid of *Dioscorea hispida* tubers, led to the formulation of the base as CXXXIV (124), derived from tropane. More recent studies have confirmed and extended the earlier work and forced the conclusion that the alkaloid is in fact related to isoquinuclidine.

The alkaloid has been shown by quantitative hydrogenation to contain one double bond, and its ultraviolet absorption ($\lambda_{max}$ 217 m$\mu$, $\epsilon$ 10,160) indicated that the double bond was conjugated with the lactone carbonyl group. Infrared studies showed that the lactone ring was six-membered or higher, and acetone was not formed as an ozonolysis or oxidation product. Structure CXXXIV was therefore untenable (120).

Additional studies (120) revealed that dioscorine contained one C-methyl group, and on treatment with alkali and then oxidation with permanganate it yielded oxalic acid. The $\alpha$-carbon atom of the lactone ring therefore carries a hydrogen atom. The ease with which the lactone ring was opened by alkali and reformed by acid suggested that dioscorine was a $\delta$-lactone.

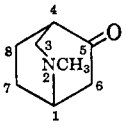
A reinvestigation of the exhaustive methylation of dioscorine (121) shows that the $C_{13}H_{21}N$ product was a mixture of bases, on ultraviolet spectral and chemical evidence. It was not aromatic, contained three double bonds, and when heated with palladized carbon afforded isobutylbenzene, $\beta,\beta$-dimethylstyrene, and trimethylamine. Hofmann degradation of the base to the highly unstable hydrocarbon $C_{11}H_{14}$ was confirmed; this product, too, was a mixture, containing four double bonds. The formation of *o*-toluic acid from it by degradation was confirmed.

Reduction of dioscorine with lithium aluminum hydride led to the crystalline diol dioscorinol, $C_{13}H_{23}NO_2$, which on ozonolysis afforded glycollic aldehyde and a saturated ketol, $C_{11}H_{19}NO_2$ (7, 24, 77, 78, 122, 123). Dioscorinol therefore contains the expression >C=CH·CH$_2$OH; on reduction with sodium in liquid ammonia it yielded deoxydioscorinol, $C_{13}H_{23}NO$ (=CH·CH$_2$·OH → =CH·CH$_3$), which furnished acetaldehyde on ozonolysis. Further reduction gave dihydrodeoxydioscorinol, $C_{13}H_{25}NO$, a saturated tertiary alcohol (122, 123).

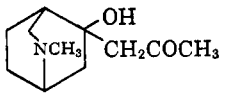
The ketol $C_{11}H_{19}NO_2$ was smoothly cleaved to acetone and an optically active keto base $C_8H_{13}NO$ (7, 24, 77, 78) by dilute alkali; it was therefore to be formulated as an aldol containing the grouping >C(OH)CH$_2$·COCH$_3$. In agreement, it gave a strongly positive iodoform test. The keto base was at first thought to be 2- or 6-oxotropane (7, 24), but direct comparison of it with synthetic specimens of these compounds showed that it was not identical with either (31, 77, 78).

The $C_8H_{13}NO$ base showed abnormally high carbonyl stretching absorption (1740 cm.$^{-1}$) in its infrared spectrum and formed a methiodide which underwent remarkably facile Hofmann degradation, catalyzed by sodium bicarbonate (24, 30, 78, 102). The products of this degradation were 6-(dimethylamino)methylcyclo-

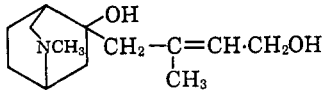
hex-2-en-1-one (CXXXV) and 6-methylenecyclohex-2-en-1-one (CXXXVI). The former was identified by its spectral properties and by synthesis, and the latter by its easy rearrangement to *o*-cresol (30, 102). The $C_8H_{13}NO$ base was therefore formulated as 2-methyl-5-oxoisoquinuclidine (CXXXVII), the abnormally high carbonyl stretching frequency being explained in part by the presence of the strongly basic nitrogen atom and in part by the strain in the bridged system. The ease of Hofmann degradation is explicable in terms of activation of hydrogen atoms $\beta$ to the nitrogen and also of strain. Confirmation of this formulation was provided by reduction of the keto base to 2-methylisoquinuclidine (102) and by synthesis and resolution of the keto base itself by two routes (117).




CXXXVII

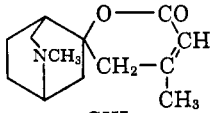



CXXXVIII

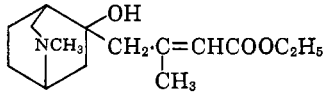



CXXXIX

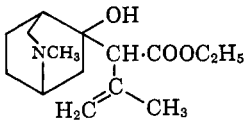
The aldol base $C_{11}H_{19}NO_2$ is therefore formulated as CXXXVIII, dioscorinol as CXXXIX, and dioscorine as CXL. The latter structure for the alkaloid has been confirmed by its synthesis from (+)-2-methyl-5-oxoisoquinuclidine, which in a Reformatsky reaction with ethyl $\gamma$-bromosenecioate afforded the hydroxy ester CXLI, but the major product was the isomeric ester CXLII, the result of an abnormal reaction. Hydrolysis and lactonization of CXLI afforded (−)-dioscorine (CXL) (117).




CXL

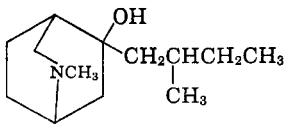



CXLI



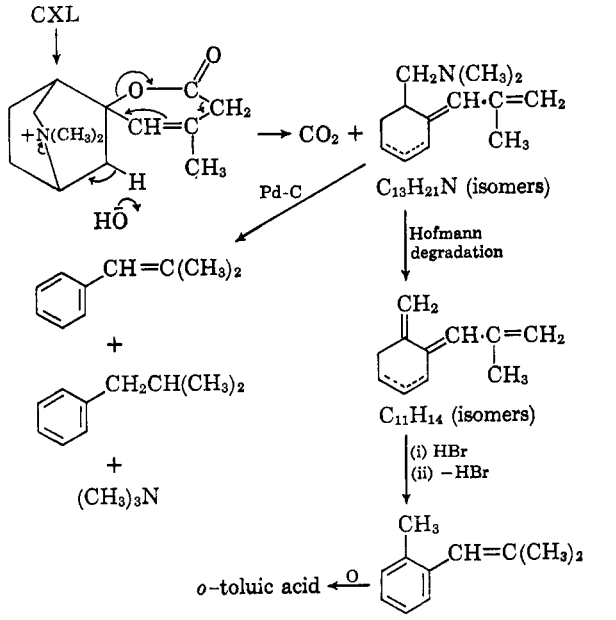

CXLII

The configuration of dioscorine cannot yet be regarded as settled. Infrared studies on dihydrodeoxydioscorinol (CXLIII) showed that there was no intramolecular hydrogen bonding in the molecule, which suggested that the nitrogen atom and the hydroxyl group are directed away from each other. However, study of a model of the epimer having these two groups directed toward each other shows that the oxygen and nitrogen atoms are too far apart (*ca.* 3.5 Å.) to permit hydrogen bonding, so that the matter cannot be settled by infrared study (102).




CXLIII

The exhaustive methylation of the alkaloid, and other reactions mentioned above, are pictured in outline below (117).




Reduction of (+)-2-methyl-5-oxoisoquinuclidine with potassium borohydride, lithium aluminum hydride, or by sodium-2-propanol yields crystalline 5-hydroxy-2-methylisoquinuclidine, as yet of undetermined configuration (7, 118).

Dioscorine has also been found in the tubers of *Dioscorea dumetorum* Pax. and of *Dioscorea sanzibarensis* (3, 4).

### B. DIOSCINE (DUMETORINE)

Dioscine, $C_{13}H_{21}NO_2$, has been isolated from tubers of *Dioscorea dumetorum* Pax., a common West African wild plant (3, 4, 13, 14). It is a liquid which has been shown by comparison of spectra and pharmacological properties to be almost certainly identical with dihydrodioscorine (14). Dioscine also occurs in the tubers of *Dioscorea sanzibarensis*, together with a compound believed to be the hydroxy acid corresponding to dioscorine (3).

## VIII. MONOTERPENOID GROUP

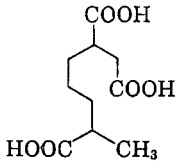
### A. CHAKSINE

The kernels of the seeds of *Cassius absus* L., known in India and Pakistan as "chaksu," contain an alkaloid

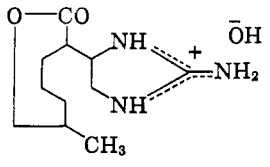
chaksine, which has been isolated by several investigators (55, 76, 88, 152). The free base has not, however, been obtained in a pure condition, but several crystalline salts have been prepared. Analysis of these pointed to a molecular formula $C_{11}H_{21}N_2O_3$ for chaksine (2, 55, 80, 82, 156), the chemistry of which has been reviewed (139, 158).

Chaksine is an optically active quaternary ammonium hydroxide, which forms anhydronium salts. It does not yield nitrogen when treated with nitrous acid, so that it is not a primary amine (80); benzoylation studies suggested that two secondary amino groups were present (57). The behavior of the base toward phosphorus halides indicated that no hydroxyl groups were present (57). No N- or O-methyl groups could be detected (2, 180), and the iodoform reaction with chaksine was negative. A Kuhn–Roth estimation showed the presence of one C-methyl group (180).

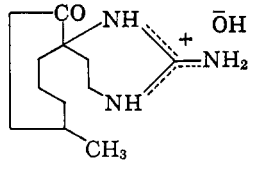
Several pyrogenetic reactions have been carried out on chaksine and its salts. Zinc dust or soda lime distillation yielded ammonia as sole basic product. Fusion with potash gave a number of small fragments, including hydrogen cyanide, formaldehyde, oxalic acid, acetic acid, and adipic acid (2, 57, 82). Pyrolysis of chaksine iodide at 310–320° with copper or silver filings afforded, after hydrolysis, *p*-isopropylbenzoic acid (154, 155) and phthalic acid (154). Pyrolysis of the sulfate with baryta gave an oil showing pyrrole color reactions (55). A closer study of the potash fusion of chaksine enabled the isolation of two nitrogen-free acids, which were separated by fractional distillation of their methyl esters. Hydrolysis of the fractions led to 2-methylpimelic acid and chaksinic acid, $C_{10}H_{16}O_6$, an optically inactive tricarboxylic acid which formed an anhydride readily, but gave an unexpectedly negative result in a Kuhn–Roth estimation (156, 159). The constitution of chaksinic acid, that of 3-carboxy-7-methylsuberic acid (CXLIV), was settled by synthesis (159).



CXLIV



CXLV



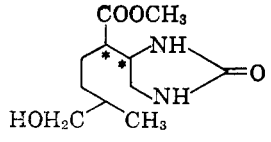
CXLVI

The lactonic character of chaksine has not been proved rigorously, but has been inferred from the failure to detect other oxygenated functional groups in the molecule and from the presence of a carbonyl band in the infrared spectrum of chaksine iodide. No report of the hydrolysis and relactonization of chaksine has been noted, and it is inferred that the lactone ring is not five- or six-membered, but is larger (180). Alkaline hydrolysis of chaksine yielded a ureidohydroxy acid $C_{11}H_{20}N_2O_4$, the ester of which shows a carbonyl band and a band at 1710 cm.$^{-1}$ in its infrared spectrum, ascribed to a five-membered cyclic urea (180).

Of several structures proposed for chaksine (55, 56, 157, 180), the most attractive seem to be CXLV (180) and CXLVI (157); the latter, however, would not yield a five-membered cyclic urea on hydrolysis. The formation of 2-methylpimelic acid on potash fusion is explained, on the basis of structure CXLV, by a reverse Mannich reaction followed by oxidation of the primary alcohol group (180), while phthalic acid must result from extensive molecular rearrangement.

When chaksine is heated with aqueous alkali, ammonia (two molecules) and carbon dioxide (one molecule) are liberated. This behavior supports the formulation of chaksine as a urea or guanidine derivative. Further, treatment of the alkaloid with nitric and sulfuric acids affords nitrochaksine sulfate, a reaction which may be compared with the nitration of guanidine under similar conditions (55, 80, 160). Some additional reactions of chaksine have also been described (79).

A reinvestigation of the alkaline hydrolysis of chaksine revealed that two ureidohydroxy acids were formed; the infrared spectra of the acids and of their methyl esters were almost indistinguishable. The nuclear magnetic resonance spectra of the two methyl esters have been measured; they, too, are virtually identical, except for the signals ascribed to protons linked to nitrogen. One ester has a singlet signal, and the other two singlets; the spectra have been satisfactorily interpreted on the basis of structure CXLVII for the esters, which must be stereoisomers differing in configuration at one or both of the asterisked asymmetric carbon atoms. This analysis establishes CXLV as the structure of chaksine (39).



CXLVII

Chaksine appears to be the first recorded example of a monoterpene alkaloid and is also unusual in being derived from guanidine.

### B. ISOCHAKSINE

The alkaloid isochaksine, isomeric with chaksine, has also been isolated from *C. absus* L. (152, 153). It is formed from chaksine by treatment with base, but isochaksine is present in the seeds as such and is not

an artefact. Isochaksine forms a series of crystalline salts and may differ from chaksine in the stereochemistry at the asymmetric carbon atom neighboring the carbonyl group.

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