THE APORPHINE ALKALOIDS

MAURICE SHAMMA AND WILLIAM A. SLUSARCHYK

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania

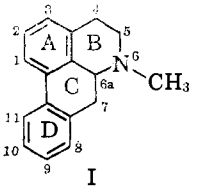
Received October 14, 1963

CONTENTS

I. INTRODUCTION

Several reviews on the aporphine alkaloids have appeared in the literature (17, 31, 36, 57, 85, 86, 99, 117) the most complete of which is that by Manske in 1954. Since that time a relatively large number of new aporphine alkaloids have been isolated, and many others synthesized. This review will emphasize the developments in the field since 1954.

All the aporphine alkaloids are based on the 4H-dibenzo[*de,g*]quinoline structure or its N-methyl derivative I commonly known as the aporphine nucleus. The numbering system is as indicated, so as to conform with the "Ring Index" (96).



I

The aporphine alkaloids can be divided into three groups depending upon the degree of methylation at the nitrogen atom. These groups are: (a) the aporphines as such, which contain an N-methyl function, (b) the noraporphines which possess a secondary nitrogen atom, and (c) the quaternary aporphine salts.

The liriodenine type alkaloids which probably originate in the plant by oxidation of aporphines are also included in this review.

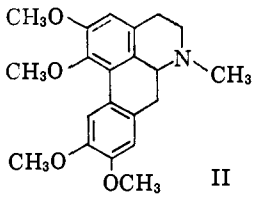
During the past eight or ten years the Japanese school in particular, headed by Tomita, has made substantial contributions to the isolation, characterization, and synthesis of several new aporphine alkaloids, including the quaternary aporphine salts. Hey and Lobo in England have carried out the first synthesis of a phenolic aporphine through protection of the phenolic function as a benzyl ether (59), and many of the subsequent syntheses of phenolic aporphines have used this same approach. Articles have appeared dealing with the nuclear magnetic resonance and ultraviolet spectra of aporphines, and also with their rotatory dispersion power. Lately, a study of the mass spectra of these compounds has also been carried out (95). An aporphine–benzylisoquinoline dimer, thalicarpine, has been characterized by Kupchan (84), and finally the first synthesis of an aporphine base through phenolic oxidative coupling has been reported by Franck, a transformation which emulates the biosynthetic process of nature (33). All of these topics will be discussed in the present review.

II. THE APORPHINE ALKALOIDS

In the following discussion of the individual aporphines, the plants listed as bearing alkaloids are in addition to those given in Manske's review of 1954 (85).

1. *Glaucine* (II)

$C_{21}H_{25}O_4N$
M.p. 120°
$[\alpha]_D$ +119° ($CHCl_3$)

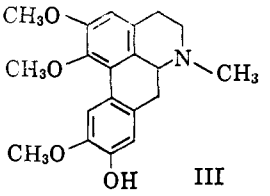


II

This widely occurring alkaloid has now been reported in *Glaucium flavum* (115), *Liriodendron tulipifera* (22, 128), *Magnolia kachirachirai* (160), *Neolitsea sericea* (92), and *Thalictrum minus* (165). In mammals, glaucine produces slight narcosis followed by convulsions, and is depressant to the heart and striated muscles (100).

2. *N-Methyllaurotetanine* (III)

$C_{20}H_{23}O_4N$
Amorphous base



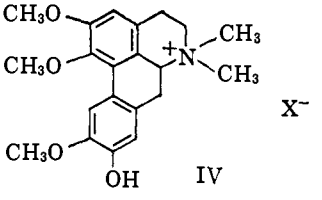
III

N-Methyllaurotetanine has been isolated by Ruegger from *Peumus boldus*. Although it is a stable base, only its salts could be crystallized (105). The hydrobromide salt has been shown to melt at 223–224°, $[\alpha]^{20}_D$ +72.8° (EtOH), while the methiodide salt melts at 187–188.5°.

The racemic form of N-methyllaurotetanine, m.p. 198°, has been prepared *via* a Clarke–Eschweiler N-methylation of synthetic laurotetanine (71, 72).

3. *Xanthoplanine* (IV)

$C_{21}H_{26}O_4N^+X^-$
Iodide hemihydrate
m.p. 148–149° dec.
$[\alpha]^{21}_D$ +71° (EtOH)



IV

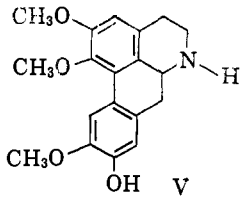
Xanthoplanine, a new quaternary aporphine, has been isolated together with magnoflorine from *Xanthoxylum planispium* (66). The alkaloid has one hydroxyl and three methoxyl groups. Reaction with methyl iodide and base gave O-methylxanthoplanine iodide, m.p. 225–227° dec., $[\alpha]^{26}_D$ +80° (EtOH), the infrared spectrum of which was identical with that of O,O-dimethyllaurifoline iodide.

The position of the free hydroxyl groups in xanthoplanine was settled by treatment of xanthoplanine chloride with ethyl iodide. The infrared spectrum of the resulting ethyl ether was found to be practically indistinguishable from that of O-ethyl-N-methyllaurotetanine methiodide. The hydroxyl function must therefore be at C-9, and xanthoplanine corresponds to the quaternary aporphine derived from N-methyllaurotetanine (65).

4. *Laurotetanine* (V)

The synthesis of racemic laurotetanine has recently been achieved by Kikkawa (71, 72).

$C_{19}H_{21}O_4N$
M.p. 125°
$[\alpha]^{25}D$ +98.5°



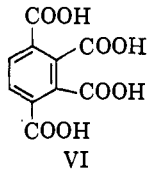
V

5. *Thalicmidine*

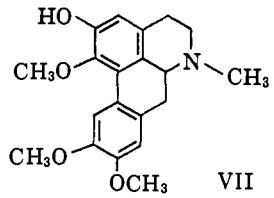
$C_{20}H_{23}O_4N$
M.p. 192–193°
$[\alpha]D$ −84° (EtOH)

Thalicmidine, a new aporphine alkaloid, has been found in *Thalictrum minus* together with thalicmine and other bases (164). The hydroiodide salt melts at 222–226° dec. in a sealed tube, and the methiodide at 217–217.5°. The free base has three methoxyls, one hydroxyl, and one N-methyl function, and it is weakly phenolic.

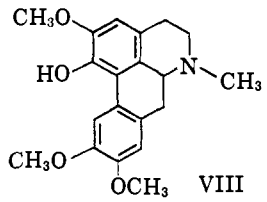
When refluxed with acetic anhydride and then with nitric acid, mellophanic acid (VI) was obtained, indicating that thalicmidine must be an aporphine alkaloid. Oxidation of thalicmidine with dilute acid permanganate at 40°, followed by treatment of the product with aniline, gave *m*-hemipinanilide. Hofmann degradation of O-methylthalicmidine methiodide yielded 3,4,6,7-tetramethoxy-1-vinylphenanthrene which proved to be identical with the same compound obtained from authentic glaucine. Although none of these findings settled the exact position of the phenolic function, structure VII was first advanced by Yunusov and Progressov for thalicmidine (165), and in 1960 the revised structure VIII was proposed (161).



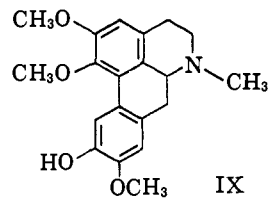
VI



VII



VIII

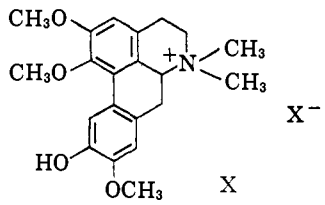


IX

It was later pointed out, however, that of the four possible O-desmethylglaucines three were known, namely N-methyllaurotetanine (III), glaucentrine (VIII), and O,N-dimethyllaurelliptine (VII). Since none of these compounds possessed a set of physical properties corresponding to those of thalicmidine, this base by a process of elimination should be 1,2,9-trimethoxy-10-hydroxyaporphine (IX) (21, 112). In 1963, Tomita did indeed report the isolation and characterization of the new quaternary aporphine cocsarmine (X), which is the quaternary salt from 1,2,9-trimethoxy-10-hydroxyaporphine, but the physical properties of cocsarmine iodide did not correspond to those of thalicmidine methiodide (130). A reconsideration of the experimental work on thalicmidine is necessary before the structure of this alkaloid can be settled.

6. *Cocsarmine* (X)

$C_{21}H_{26}O_4N^+X^-$
Iodide trihydrate m.p. 205–207° dec. with sintering at 185°
$[\alpha]^{22}D$ +27.9° (EtOH)



X

The new quaternary aporphine cocsarmine has been isolated from the roots of *Cocculus sarmentosus* along with trilobine, isotrilobine, and menisarine (130). The alkaloid possesses one hydroxyl and three methoxyl groups and forms a picrate salt, m.p. 226–227° dec.

O-Methylation of cocsarmine iodide gave O,O-dimethyllaurifoline iodide, a transformation which was confirmed by mixture melting point determination and infrared analysis. The O-ethyl derivative was found by paper chromatography and infrared spectra to be identical with an authentic sample of 1,2,9-trimethoxy-10-ethoxyaporphine methiodide. Cocsarmine, therefore, must be the (+)-N-methyl-1,2,9-trimethoxy-10-hydroxyaporphinium cation.

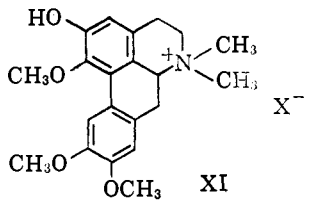
7. *Glaucentrine* (VIII)

$C_{20}H_{23}O_4N$
M.p. 148°

The presence of glaucentrine, which was originally found in three *Dicentra* species (85), has not been reported in any additional plants.

8. *Quaternary Aporphine from Fagara tinguassoiba* (XI)

$C_{21}H_{26}O_4N^+X^-$
Chloride m.p. 215–219° dec.
$[\alpha]^{25}D$ +30.2° (H_2O)



XI

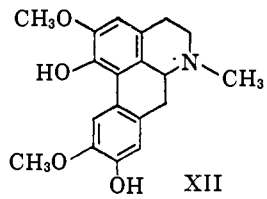
A quaternary alkaloid possessing one phenolic and three methoxyl groups has been isolated from the bark of *Fagara tinguassoiba* (103). The picrate melts at 146–151°, the hydroxide at 120° dec., and the iodide at 226–229° dec.

The ultraviolet spectrum of the chloride is nearly identical with that of glaucine. O-Methylation of the alkaloid iodide with diazomethane gave N-methylglaucinium iodide, thus proving that the oxygenated positions were at C-1, 2, 9, and 10.

The phenolic hydroxyl group in the alkaloid is not at position 1 since the product of O-ethylation of the quaternary iodide differed from O-ethyl-N-methylglaucentrinium iodide. The O-ethyl iodide salt was degraded ultimately to a compound which must be 3-ethoxy-4,6,7-trimethoxyphenanthrene-1-carboxylic acid, indicating the presence of the phenolic function at C-2. The free base corresponding to this alkaloid salt has not yet been found in nature.

9. *Isoboldine* (XII)

$C_{19}H_{21}O_4N$
M.p. 128°
$[\alpha]^{13}D$ +65.3° ($CHCl_3$)



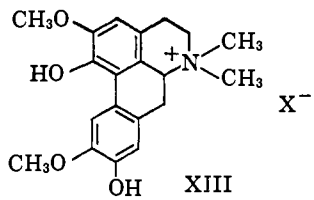
XII

Isoboldine, a new aporphine alkaloid, has been obtained from the trunk bark of *Nandina domestica* (20, 123).

Hofmann degradation of isoboldine diethyl ether yielded 3,6-dimethoxy-4,7-diethoxy-1-vinylphenanthrene. Subsequent oxidation and decarboxylation gave 2,5-diethoxy-3,6-dimethoxyphenanthrene. This result coupled with the fact that isoboldine methochloride is identical with laurifoline chloride established the structure of isoboldine.

10. *Laurifoline* (XIII)

$C_{20}H_{24}O_4N^+X^-$
Chloride m.p. 253° dec.
$[\alpha]^{24}D$ +26.3° (H_2O)



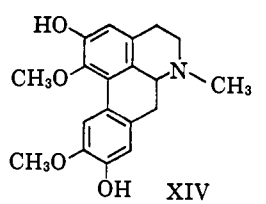
XIII

Laurifoline, the first quaternary aporphine to be isolated from nature, was obtained by Tomita and Kusuda together with coclaurine, trilobine, and coclanoline from *Cocculus laurifolius* (141). The chloride is readily soluble in water and hot alcohol, but is insoluble in less polar organic solvents. O,O-Dimethyllaurifoline iodide was degraded by the classical route to 2,3,5,6-tetramethoxyphenanthrene (142). The relative positions of the two methoxyl and the two hydroxyl groups in the alkaloid were settled by a total synthesis of the racemic chloride salt, m.p. 238° dec.

Laurifoline chloride has been found to possess blood pressure depressing activity due to its ganglion blocking action (138).

11. *Boldine* (XIV)

$C_{19}H_{21}O_4N$
M.p. 162–163°
$[\alpha]^{10}D$ +112° (EtOH)



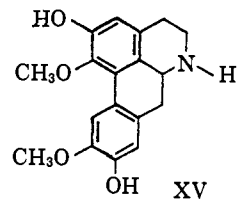
XIV

Boldine has been reisolated from *Peumus boldus* (105) where it is accompanied by isocorydine, norisocorydine, and N-methyllaurotetanine. It has also been found in *Neolitsea sericea* together with roemerine (92).

The physiological activity of boldine has been studied in detail since it is only slightly toxic, does not cause addiction, and its effects are not cumulative. It has no local anesthetic, analgesic, or antipyretic action. On the other hand, it showed diuretic activity, increased the secretions of the liver, salivary glands, mucous membrane, and also to a slighter extent the hydrochloric acid secretion in the stomach. Boldine also has a slight sedative and antiparasitic action, is cardiotonic, and decreases metabolism (79).

12. *Laurolitsine* (XV)

$C_{18}H_{19}O_4N$
Amorphous base m.p. 138–140°, with swelling at 115–118°
$[\alpha]^{11}D$ +102.5° (EtOH)



XV

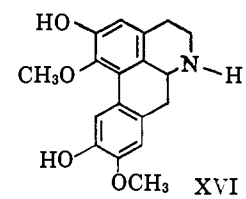
Laurolitsine has been isolated from the leaves of *Neolitsea sericea* (93) and the root, bark, and wood of *Litsea japonica* (78). It is an amorphous powder which can be characterized as the picrolonate, m.p. 239° dec., or the picrate salt, m.p. 212° dec. The alkaloid has two methoxyl and two hydroxyl groups, and in addition possesses a secondary aliphatic amine function as indicated by a positive Feigl test (92).

Treatment of laurolitsine with diazomethane gave an oil characterized as O,O-dimethyllaurolitsine. When this oil was heated with methyl iodide and sodium bicarbonate in a sealed tube, the corresponding N-methyl methiodide salt was obtained which was identical with glaucine methiodide.

In order to determine the exact positions of the two hydroxyl groups, laurolitsine was treated with diazoethane, and the product heated with methyl iodide. The resulting O,O-diethyl-N-methyllaurolitsine methiodide was subjected to Hofmann degradation, followed by oxidation and decarboxylation. The diethoxydimethoxyphenanthrene thus obtained proved to be identical with that derived from boldine by essentially the same degradative procedure. Finally, N-methylation of laurolitsine with formaldehyde and formic acid gave boldine. Laurolitsine corresponds, therefore, to norboldine (93).

13. *Laurelliptine* (XVI)

$C_{18}H_{19}O_4N$
M.p. 191°
$[\alpha]^{21}D$ +47° (EtOH)

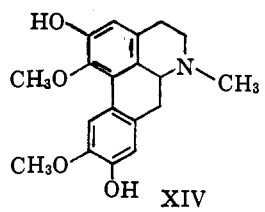


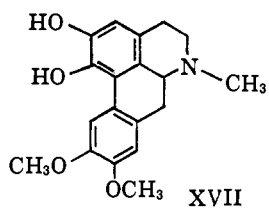
XVI

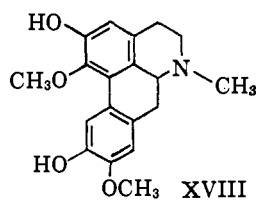
Laurelliptine, a new aporphine alkaloid, has been found in *Beilschmiedia elliptica* (21). It possesses two methoxyl and two hydroxyl groups, and upon treat-

ment with acetic anhydride yields O,O,N-triacetyllaurelliptine, m.p. 188–189°, $[\alpha]^{17}D$ +76° (EtOH). Methylation with diazomethane gives O,O-dimethyllaurelliptine, picrate m.p. 135–137°. When hydrogenated with Raney nickel in the presence of formaldehyde, N-methyllaurelliptine, m.p. 121–123°, $[\alpha]^{16}D$ +41° (EtOH), was obtained; consequently, laurelliptine is a dimethoxydiphenolic noraporphine.

Treatment of N-methyllaurelliptine with diazomethane afforded two products, O,O,N-trimethyllaurelliptine and O,N-dimethyllaurelliptine (VII), m.p. 189–191°, $[\alpha]^{17}D$ +43° (EtOH). The former was found by mixture melting point and infrared analysis to be identical with an authentic sample of glaucine. The latter when converted to its methiodide, m.p. 231–233°, $[\alpha]^{22}D$ +26° (H_2O), was identical through mixture melting point determination and optical rotation with the quaternary aporphine from *Fagara inguassoiba;* picrates of both bases, besides having identical infrared spectra, showed no depression on mixing, so that N-methyllaurelliptine must be either XIV, XVII, or XVIII.

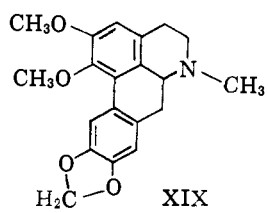

XIV


XVII


XVIII

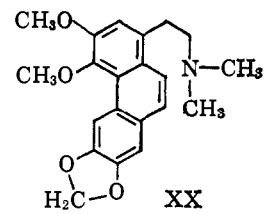
Structure XIV represents boldine, and XVII corresponds to the compound obtained from the hydrolysis of dicentrine with dilute sulfuric acid and phloroglucinol. Furthermore, laurelliptine gives a negative Quastel test for a 1,2-dihydroxyl group and has the same R_f value on plain and boric acid–sodium acetate-treated paper, eliminating the possibility of an *ortho* dihydroxyl group being present. N-Methyllaurelliptine, therefore, must have structure XVIII, and laurelliptine is 1,9-dimethoxy-2,10-dihydroxynoraporphine.

14. *Nantenine* (XIX)
$C_{20}H_{21}O_4N$
M.p. 138–139°
$[\alpha]^{18}D$ +101° ($CHCl_3$)


XIX

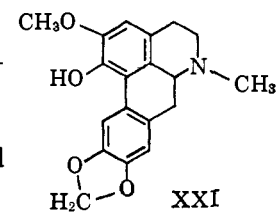
Nantenine (O-methyldomesticine) has been found in the seeds of *Nandina domestica* (140). When nantenine methiodide was submitted to a Hofmann degradation, nantenine methylmethine (XX), m.p. 127°, was produced. This optically inactive compound was found to be identical with the alkaloid thalicthuberine obtained from the roots of *Thalictrum thunbergii* (37).

The reduction of nantenine with sodium in liquid ammonia has been studied and found to give 2-methoxy-10-hydroxyaporphine (74). The structure of the product was proven by degradation and also by total synthesis of the O-methyl derivative, 2,10-dimethoxyaporphine (75).


XX

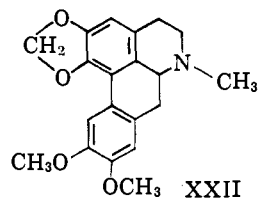
The pharmacology of nantenine has been studied in some detail (120).

15. *Domesticine* (XXI)
M.p. 115–116° (MeOH–H_2O)
84–85° (MeOH–C_6H_6)
152–153° dec. when dried at 60° over P_2O_5
$[\alpha]D$ +60.5°


XXI

Domesticine has again been isolated from *Nandina domestica* where it is accompanied by nantenine (140). When domesticine was reduced with sodium in liquid ammonia, 1,10-dihydroxy-2-methoxyaporphine was produced, hydrochloride salt m.p. 277° dec. Treatment of the free base of the hydrochloride with diazomethane yielded 1,2,10-trimethoxyaporphine, m.p. 122–124°, $[\alpha]^{25}D$ +150.6° (MeOH), whose structure was confirmed by synthesis of the racemic material, m.p. 140–141° (76). The physiological activity of domesticine has been discussed (122).

16. *Dicentrine* (XXII)
$C_{20}H_{21}O_4N$
M.p. 168–169°
$[\alpha]D$ +56° (EtOH)


XXII

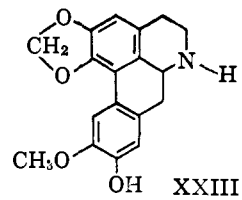
A total synthesis of racemic dicentrine *via* the classical Pschorr ring closure has been reported (55).

In frogs and mammals, small doses of dicentrine produce narcotic conditions, with larger doses causing convulsions (100).

17. *Actinodaphnine* (XXIII)

Racemic actinodaphnine methyl ether, m.p. 114–115°, has been prepared by Hey and Lobo, who in the same paper also reported the preparation of racemic 1,2,9,10-bismethylenedioxyaporphine, 1,2-methylene-

$C_{18}H_{17}O_4N$
M.p. 210–211°
$[\alpha]^{20}D$ +33° (EtOH)

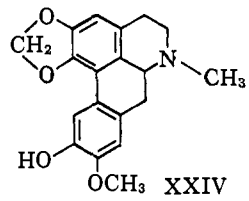


XXIII

dioxy-9-methoxy-10-hydroxyaporphine, and 1,2-methylenedioxy-10-hydroxy-11-methoxyaporphine. The last two compounds were the first members of the hydroxyaporphine series to be synthesized (59).

18. *Phanostenine* (XXIV)

$C_{19}H_{19}O_4N$
M.p. 210°
$[\alpha]^{20}D$ −36.7° ($CHCl_3$)

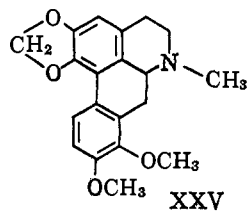


XXIV

The structure of phanostenine has been definitely proven by total synthesis of the racemic form (137). The isomeric base, 1,2-methylenedioxy-9-hydroxy-10-methoxyaporphine, was also synthesized and found to have infrared and ultraviolet absorption spectra different from those of natural phanostenine (136).

19. *Crebanine* (XXV)

$C_{20}H_{21}O_4N$
M.p. 126°
$[\alpha]^{20}D$ −57.5° ($CHCl_3$)

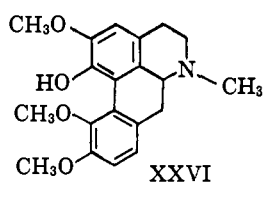


XXV

The structure of crebanine has now been confirmed by two independent syntheses proceeding *via* Pschorr ring closure (49, 132). The racemic tetramethoxy analog of crebanine, namely 1,2,8,9-tetramethoxyaporphine, has also been prepared (133).

20. *Corydine* (XXVI)

$C_{20}H_{23}O_4N$
M.p. between 103 and 149° depending on mode of recrystallization
$[\alpha]^{20-26}D$ +205° ($CHCl_3$)



XXVI

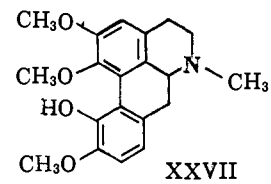
The presence of corydine has been shown in *Glaucium corniculatum* (114), *G. flavum* (115), and *G. vitellinum* (113). The alkaloid is best characterized by means of its hydrochloride salt, m.p. 255–256°. Two independent syntheses of corydine have now been reported (4, 60).

In animals, the alkaloid produces either narcosis or irritability, and the hydrochloride salt is known to destroy tumors incurred by intramuscular implantation of Sarcoma 37 in hybrid mice (97).

21. *Isocorydine* (XXVII)

Isocorydine is found in a variety of plants and has

$C_{20}H_{23}O_4N$
M.p. 186°
$[\alpha]^{24}D$ +202° (MeOH)



XXVII

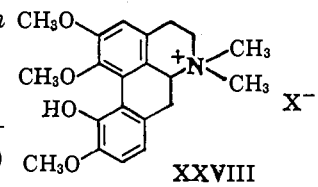
recently been reported in *Atherosperma moschatum* (14), *Corydalis govaniana* (28), *Dicranostigma franchetiatum* (116), *Glaucium corniculatum* (114), *G. flavum* (115), *G. vitellinum* (113), and *Peumus boldus* (105).

Two syntheses of the racemic alkaloid are now known (70, 80), after an initial attempt proved unsuccessful (60). In addition, racemic pseudocorydine (1,2,11-trimethoxy-10-hydroxyaporphine), m.p. 184–185° (*in vacuo*), has been synthesized (35).

The pharmacology of isocorydine is similar to bulbocapnine in that catalepsy often occurs in animals treated with the drug (101).

22. *N-Methylisocorydinium Cation* (XXVIII)

$C_{21}H_{26}O_4N^+X^-$
Chloride salt m.p. 217–221° (slow heating) or 235° (rapid heating)
$[\alpha]^{20}D$ +168.6° (H_2O)

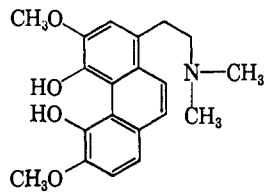


XXVIII

The N-methylisocorydinium (menisperine) cation has been found in *Bragantia wallichi* (69), *Cryptocarya angulata* and *C. triplinervis* (24), *Fagara coco* (23), *Legnephora moorei* (63), *Menispermum dauricum* (139), and *Xanthoxylum brachyacanthum* and *X. veneficum* (18). The iodide salt has been variously reported to melt at 219° (slow heating), or 231–232° (rapid heating), or 238–240°.

N-Methylisocorydinium iodide did not depress the melting point when admixed with the authentic methiodide salt of isocorydine, and the two samples gave identical infrared spectra. Additionally O-methyl-N-methylisocorydinium iodide showed no mixture melting point depression with O,O-dimethylcorytuberine methiodide (139).

A detailed degradation of N-methylisocorydinium iodide has also been reported (23), and the tetramethoxyiodide salt was eventually converted to 3,4,5,6-tetramethoxyphenanthrene. Direct oxidation of N-methylisocorydinium chloride with 5% potassium permanganate in aqueous potassium carbonate solution gave the methylimide of 4,5-dimethoxybenzene-1,2,3-tricarboxylic acid (23). Tomita and Takano have also shown that with ethanolamine at 160–170°, N-methylisocorydinium iodide undergoes Hofmann elimination accompanied by demethylation of the methoxyl group at position 1, so that the methine XXIX is formed (143).



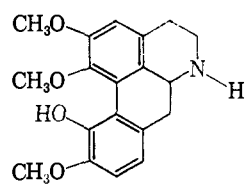
XXIX

A formal synthesis of racemic N-methylisocorydinium iodide was achieved by preparing the methiodide salt of synthetic isocorydine (70).

N-Methylisocorydinium chloride exhibits toxicological characteristics somewhat similar to those of other active tertiary aporphines. Respiratory failure results before heart failure (89), and in rabbits and toads direct and indirect contractibility and excitability of the skeletal muscles are diminished without any curarizing effect (90).

23. *Norisocorydine* (XXX)

$C_{19}H_{21}O_4N$
HBr salt m.p. 203–205° dec.
$[\alpha]^{20}D$ +158.5° (EtOH) for free base

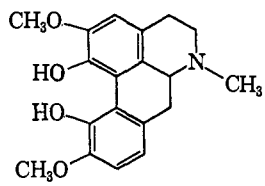


XXX

Norisocorydine, which is unstable as the free base, has been isolated from *Peumus boldus* (105). Treatment of norisocorydine with formaldehyde followed by catalytic hydrogenation gave isocorydine.

24. *Corytuberine* (XXXI)

$C_{19}H_{21}O_4N$
M.p. 240°
$[\alpha]^{20}D$ +282.5° (EtOH)



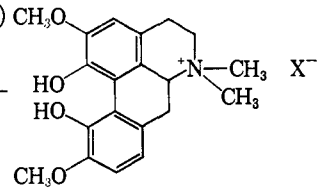
XXXI

Corytuberine has now been reported in *Glaucium vitellinum* (113), and the synthesis of the alkaloid has been carried out (135).

Corytuberine caused increased reflex irritation in the frog. It accelerated respiration, stimulated the secretion of tears and saliva, and slowed the pulse by vagus stimulation (100).

25. *Magnoflorine* (XXXII)

$C_{20}H_{24}O_4N^+X^-$
Iodide salt m.p. 248–249° dec.
$[\alpha]^{15}D$ +220.1° (MeOH)



XXXII

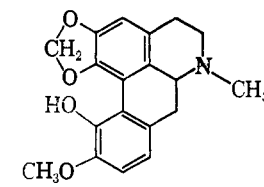
Magnoflorine was first isolated from *Magnolia grandiflora* (91), and later from an *Aquilegia species* (153), *Aristolochia debilis* (124), *Magnolia coco* and *M. kachirachirai* (160), *Michelia compressa* (155), *M. champaca* (159), *Thalictrum revolutum* (19), *and Xanthoxylum planispium* (66).

The iodide salt was shown to be identical with corytuberine methiodide (91); treatment of synthetic racemic corytuberine with methyl iodide gave racemic magnoflorine iodide, crystallizing with one and one-half moles of water, m.p. 243° dec. (135). Magnoflorine iodide has been shown to undergo smooth Hofmann elimination when heated with ethanolamine (143).

The quaternary alkaloid thalictrine has recently been reisolated from *Thalictrum foliolosum* and was found to be identical with magnoflorine (45).

26. *Bulbocapnine* (XXXIII)

$C_{19}H_{19}O_4N$
M.p. 202°
$[\alpha]D$ +237° ($CHCl_3$)



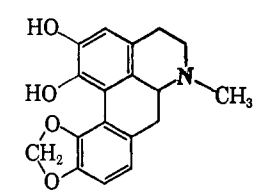
XXXIII

The synthesis of bulbocapnine has been achieved by Kikkawa, and the racemic compound was resolved *via* the tartrate salt (73). In addition, a detailed X-ray analysis of bulbocapnine methiodide has been carried out (*vide infra*) (5).

Animals treated with bulbocapnine develop catatonia (1), and several pharmacological studies have been carried out with the compound (103). The effect of added drugs on bulbocapnine catalepsy in the mouse has also been investigated. Of the 61 substances tested, those producing a sedative action on the central nervous system increased the duration of catalepsy, and conversely, excitatory compounds decreased catalepsy (118).

27. *Laurepukine* (XXXIV)

$C_{18}H_{17}O_4N$
M.p. 230–231°
$[\alpha]D$ −222° ($CHCl_3$)

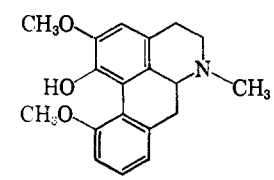


XXXIV

Although laurepukine has not yet been synthesized, the structural assignment has been reinforced by the fact that racemic 2,3-methylenedioxy-10,11-dimethoxyaporphine was prepared and found to have a different ultraviolet spectrum from that of O,O-dimethyllaurepukine (48).

28. *Isothebaine* (XXXV)

$C_{19}H_{21}O_3N$
M.p. 203–204°
$[\alpha]D$ +285.1° (EtOH)

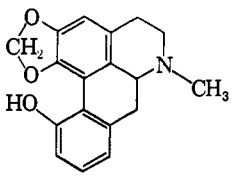


XXXV

It is in connection with the correct structural determination of isothebaine that Bentley evolved his interesting biogenetic generalization that all aporphine alkaloids found so far are substituted at positions 1 and 2 (12). The alkaloid gives only a pale fawn color when treated with diazotized sulfanilic acid in alkaline solution. This result was taken to indicate the absence of a free position *ortho* or *para* to hydroxyl available for coupling with diazonium salts. The cryptophenolic hydroxyl function was placed, therefore, at C-1, and the complete revised structure of the alkaloid then followed from this assignment.

No synthesis of isothebaine as such has been reported, although racemic 1,2,11-trimethoxyaporphine is known (50). The pharmacology of isothebaine has been investigated (77).

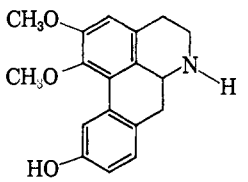
29. *Pukateine* (XXXVI)
$C_{18}H_{17}O_3N$
M.p. 200°
$[\alpha]^{15}D$ −220° (EtOH)



XXXVI

O-Methylpukateine has been prepared (8), but no synthesis of pukateine has been worked out. The alkaloid hydrochloride salt has been noted to have a convulsant action on the nerve cells of the spinal cord (6).

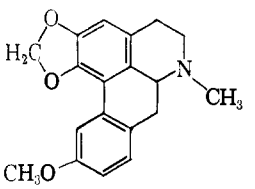
30. *Tuduranine* (XXXVII)
$C_{18}H_{19}O_3N$
M.p. 125 or 204° (47)
$[\alpha]^{20}D$ −127.5° (EtOH)



XXXVII

The structure of tuduranine is well established by degradation, but the alkaloid has not yet been synthesized in the laboratory.

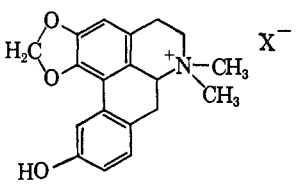
31. *Laureline* (XXXVIII)
$C_{19}H_{19}O_3N$
M.p. 97° (dry ether)
114° (hexane)
$[\alpha]D$ −98.5° (EtOH)



XXXVIII

Two syntheses of laureline have now been reported (30, 107).

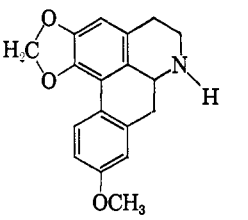
32. *Michepressine* (XXXIX)
$C_{19}H_{20}O_3N+X^-$
Iodide salt m.p. 235–236° dec.
$[\alpha]^{15}D$ −130.8° (MeOH)



XXXIX

Michepressine has been isolated by Ito from *Michelia compressa* (67). This new quaternary aporphine alkaloid has one phenolic hydroxyl and one methylenedioxy function, and on treatment with methyl iodide in basic solution yields O-methylmichepressine iodide, m.p. 220–222° dec., $[\alpha]^{14}D$ −116.9° (MeOH), which was found to be identical (infrared spectra and R_f values) with synthetic racemic laureline methiodide.

33. *Xylopine* (XL)
$C_{18}H_{17}O_3N$
M.p. 78–102° (acetone)
$[\alpha]^{25}D$ −23.4° (MeOH)

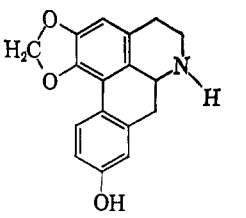


XL

Xylopine has been obtained by Schmutz from *Xylopia discreta*. The hydrochloride salt melts at 250°. The alkaloid gives a positive Gaebel test for a methylenedioxy function, and a negative ferric chloride test; and it has been shown to be identical with O-methylanolobine (109). In addition, the N-acetyl derivative, m.p. 213–214°, is identical with N-acetyl-O-methylanolobine. Clarke–Eschweiler N-methylation of xylopine yields (−)-isolaureline, m.p. 108–110°, $[\alpha]^{26}D$ −36.7° (EtOH), a base which has not been found in nature but has been prepared in the laboratory (30).

Schmutz has also pointed out that xylopine does not correspond in its physical properties to the alkaloid artabotrinine obtained from *Artabotrys suaveolens* (109).

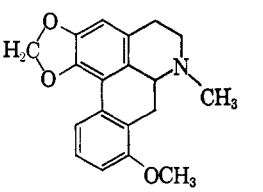
34. *Anolobine* (XLI)
$C_{17}H_{15}O_3N$
M.p. 262°
$[\alpha]^{27}D$ −22.5°
($CHCl_3$–MeOH)



XLI

Schmutz has shown that O-methylanolobine, obtained by treating anolobine with diazomethane, is identical with natural xylopine (109).

35. *Stephanine* (XLII)
$C_{19}H_{19}O_3N$
M.p. 155–157°
$[\alpha]D$ −92.5° ($CHCl_3$)



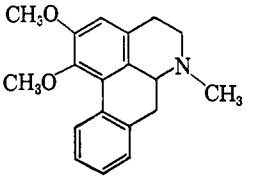
XLII

The isolation of stephanine from *Stephania japonica* has been reported. The methiodide salt melts at 211–215° (106).

Two syntheses of the alkaloid have been carried out, and the racemic methiodide salt was found to melt at 212–214° (58, 131). Racemic 1,2,8-trimethoxyaporphine has also been prepared (133).

36. *Nuciferine* (XLIII)

$C_{19}H_{21}O_2N$
M.p. 165.5°
$[\alpha]^{22}D$ −157.5° (EtOH) (3) or −215° (EtOH) (144)



XLIII

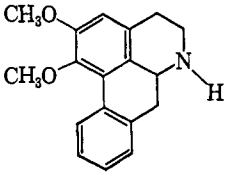
Nuciferine, a new aporphine alkaloid, has been found in the leaves of the Asiatic lotus, *Nelumbo nucifera* (3, 144), and also in the American lotus, *N. lutea* (82, 83). It has two methoxyls and one N-methyl group, and the hydrochloride salt has m.p. 241° (vac.).

The physical constants of nuciferine and its derivatives corresponded with those of the known (−)-1,2-dimethoxyaporphine derived from natural roemerine (162), while the racemic compound corresponding to nuciferine had been synthesized in the twenties by Gulland and Haworth (54).

From *Cryptocaria angulata* and *C. triplinervis* an optically inactive alkaloid corresponding to the N,N-dimethyl methine base of nuciferine has been isolated (24).

37. *Nornuciferine* (XLIV)

$C_{18}H_{19}O_2N$
M.p. 128–129°
$[\alpha]^{28}D$ −145° (EtOH)

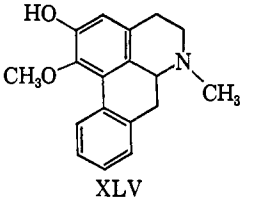


XLIV

Nornuciferine has very recently been isolated by Kupchan and co-workers from *Nelumbo lutea* (83). A synthesis of the racemate has already been reported in which, in the course of the work, the nitrogen atom was protected by benzylation. Treatment of the synthetic nornuciferine with formaldehyde and formic acid gave racemic nuciferine (152).

38. *1-Methoxy-2-hydroxyaporphine* (XLV)

$C_{18}H_{19}O_2N$
M.p. 195–196°
$[\alpha]^{22}D$ −265° ($CHCl_3$)



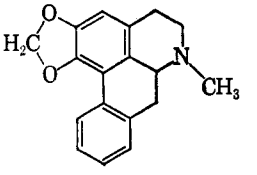
XLV

Tomita, *et al.*, have reported the isolation of 1-methoxy-2-hydroxyaporphine from *Nelumbo nucifera* (144–146). The alkaloid has one methoxyl group, one phenolic hydroxyl, and one N-methyl function. O-Methylation with diazomethane gave nuciferine. To determine the position of the hydroxyl group, the O-ethyl derivative was degraded by the classical procedure to 3-ethoxy-4-methoxyphenanthrene (145).

The alkaloid was originally named nornuciferine; however, since the prefix *nor* has now come to indicate a *des*-N-methyl relationship, the name nornuciferine is best given to the levorotatory base isolated by Kupchan and co-workers from *Nelumbo lutea* (83).

39. *Roemerine* (XLVI)

$C_{18}H_{17}O_2N$
M.p. 100–101°
$[\alpha]^{22}D$ −72.5° (EtOH)

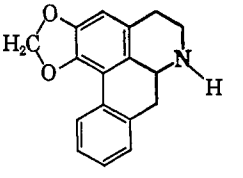


XLVI

Roemerine, whose hydroiodide salt melts at 245°, has been isolated from *Cryptocarya angulata* (24), and *Neolitsea sericea* (92), and also from *Nelumbo nucifera* (129, 144) where it is accompanied by nuciferine and 1-methoxy-2-hydroxyaporphine.

40. *Anonaine* (XLVII)

$C_{17}H_{15}O_2N$
M.p. 122–123°
$[\alpha]^{20}D$ −52° ($CHCl_3$)

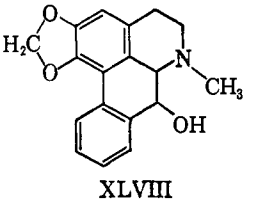


XLVII

Anonaine has recently been reisolated from *Anona reticulata* where it is found together with the alkaloid reticuline (46).

41. *Ushinsunine* (XLVIII)

$C_{18}H_{17}O_3N$
M.p. 180–181°
$[\alpha]^{18}D$ −117° ($CHCl_3$)



XLVIII

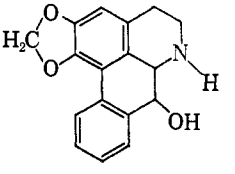
Ushinsunine (micheline-A), a novel aporphine base, has been found in *Michelia alba* (158), *M. champaca* (159), and *M. compressa* (127, 154, 155).

The alkaloid has one methylenedioxy function, one N-methyl function, and interestingly enough one alcoholic function which can be easily acetylated (155). This alcoholic function was placed at C-7 to explain both the loss of water from the molecule to yield an optically inactive compound, m.p. 88–89°, on treatment with phosphorus oxychloride, and the facile O-acetylation of the alkaloid itself (156).

Ushinsunine under Clemmensen conditions gave dehydroxyushinsunine, $C_{18}H_{17}O_2N$, m.p. 87–88°, which was found to be identical with racemic roemerine. The methylenedioxy function can therefore be placed at position 1,2 (156). Furthermore, oxidation of ushinsunine with manganese dioxide in chloroform was found to give liriodenine whose structure had already been elucidated (*vide infra*). Ushinsunine is, therefore, 7-hydroxyroemerine (156).

The nuclear magnetic resonance spectrum of ushinsunine showed a spin–spin coupling constant of only 2.5 c.p.s. for the C-6a and C-7 hydrogens indicating that the two protons are in a *cis* relationship to one another (157). Ushinsunine is the first aporphine found to possess an alcohol group at C-7 and can therefore be considered an intermediate in the oxidation of classical aporphine alkaloids to aromatic bases of the liriodenine type. A separate degradative scheme and proof of structure for ushinsunine paralleling that discussed above has also been offered (154).

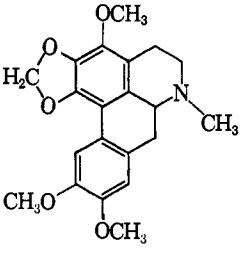
42. *Norushinsunine* (XLIX)
$C_{17}H_{15}O_3N$
M.p. 205–207°
$[\alpha]^{15}D$ −105.2° ($CHCl_3$)



XLIX

Norushinsunine (michelalbine, normicheline-A) has been isolated from *Michelia alba* together with ushinsunine and liriodenine (158). On analysis it showed no methoxyl or N-methyl groups, but had a methylenedioxy function, a secondary nitrogen, and an aliphatic alcohol group. Methylation with formaldehyde and formic acid gave ushinsunine thus proving the structure of this new aporphine alkaloid.

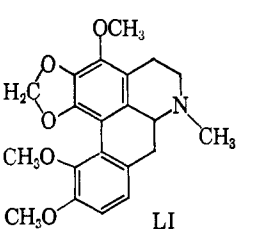
43. *Ocoteine* (thalicmine) (L)
$C_{21}H_{23}O_5N$
M.p. 140°
$[\alpha]^{25}D$ +33.3° ($CHCl_3$)
+37.6 (EtOH)



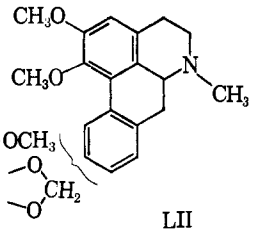
L

The aporphine alkaloids thalicmine, isolated by Yunusov and Progressov from *Thalictrum minus* (164), and ocoteine, found by Iacobucci in *Ocotea puberula* (64), were until recently considered to be different and isomeric. Vernengo, however, has made a direct comparison of thalicmine with ocoteine and has found them to be identical (149), in spite of the fact that thalicmine was originally reported to have $[\alpha]D$ +255.3° (EtOH) (164).

Considering first the so-called thalicmine, the hydrochloride salt melts at 268–270°, the hydroiodide at 223–224° dec., and the methiodide at 236–237° in a sealed tube. Treatment of thalicmine with acetyl chloride gave the optically inactive N-acetyl derivative which on zinc dust distillation yielded phenanthrene. Hofmann degradation of the methiodide salt of the alkaloid eventually led to a compound, m.p. 185–186°, which was claimed to be 2,5,6-trimethoxy-3,4-methylenedioxy-1-vinylphenanthrene, so that structure LI was proposed for the aporphine (165).



LI



LII

A synthesis of racemic LI was subsequently carried out, but a sample of the authentic alkaloid was not available for comparison (51). The preparation of a number of racemic aporphines structurally related to LI have also been reported, including 1,2-methylenedioxy-9,10,11-trimethoxyaporphine (62), 1,2-methylenedioxy-8,9,10-trimethoxyaporphine, and 1,2,8,9,10-pentamethoxyaporphine (61).

Turning now to ocoteine, hydrochloride m.p. 265°, the degradation of the alkaloid to a trimethoxymethylenedioxyphenanthrene, m.p. 197°, by classical methods, as well as the oxidation by potassium permanganate to *m*-hemipinic acid methylimide have been reported by the Argentinean school (150). On the basis of these findings partial structure LII was suggested for ocoteine (150).

Recently, however, Vernengo has proposed the alternate structure L for ocoteine (thalicmine) on the grounds of ultraviolet and nuclear magnetic resonance spectroscopy and optical rotation (149). The nuclear magnetic resonance spectrum of ocoteine shows that either C-1 or C-11 is unsubstituted, since one of the aromatic protons shows up downfield at 2.43 τ and only a C-1 or C-11 proton could absorb in that range. This conclusion is also supported by the low specific rotation of ocoteine, for it has been pointed out that 1,11-disubstituted aporphines exhibit substantial specific rotations of about ±200° (111). Furthermore, the ultraviolet spectrum of ocoteine, λ_{max} 283 mμ (log ϵ 4.25) and 300 mμ (log ϵ 4.25) also indicates that either C-1 or C-11 must be unsubstituted. Again considering the nuclear magnetic resonance spectrum of ocoteine, none of the three methoxyl groups present (6.01, 6.07, and 6.13 τ) are in position 1, since a methoxyl at 1 would absorb at relatively high field (6.37–6.45 τ). Additionally, the optical rotatory dispersion curve of ocoteine was found to be almost identical with that of (+)-dicentrine which has methoxyl substituents at C-9 and C-10.

Based on the above observations, and given that all naturally occurring aporphines have been substituted at C-1 and C-2, structure L was offered for ocoteine as already mentioned (149), although on this basis the formation of 4,5-dimethoxy-N-methylphthalimide upon oxidation of the alkaloid is rather difficult to explain.

44. *Fugapavine*

$C_{18}H_{17}O_3N$
M.p. 178.5–179.5°
$[\alpha]_D$ −116° ($CHCl_3$)

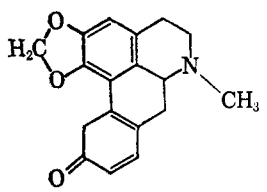
It has been reported that the base fugapavine, obtained from *Papaver fugax* by Yunusov and co-workers might possibly be of the aporphine type (88, 163).

Fugapavine possesses a tertiary N-methyl function and a methylenedioxy group. The infrared and ultraviolet spectra are claimed to indicate the presence of a conjugated carbonyl and an isoquinoline nucleus. The alkaloid gives a semicarbazone, m.p. 237°, and on hydrogenation over Adams catalyst yields a hexahydro compound, m.p. 267–269°, $[\alpha]_D$ −38.2°.

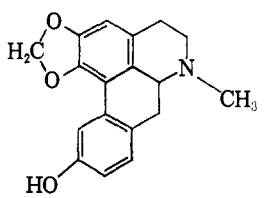
On treatment with acid and heat, fugapavine is transformed into the isomeric phenolic compound isofupagavine, m.p. 238–240°, $[\alpha]_D$ +88.8° (MeOH). With acetic anhydride, isofugapavine gives an optically inactive compound which was oxidized with nitric acid to mellophanic acid.

Furthermore, when isofugapavine was treated with diazomethane, O-methylisofugapavine, apparently identical with (+)-laureline, was produced, m.p. 114°, $[\alpha]_D$ +90.1° (MeOH), hydrochloride m.p. 282° dec., nitrate m.p. 239–240°, and methiodide m.p. 220–222°. Neutral permanganate oxidation of O-methylisofugapavine gave 4-methoxyphthalic acid.

On the basis of the above results, the unlikely structure LIII was assigned to fugapavine, so that, isofugapavine became LIV. It is clear that the chemistry of



LIII



LIV

fugapavine requires additional attention.

45. *Vitricine*

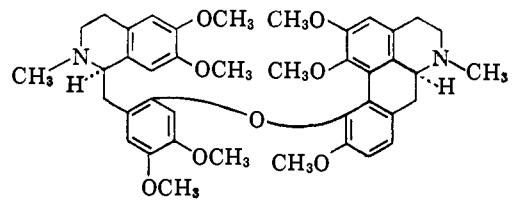
$C_{17}H_{15}O_3N$
M.p. 237° dec.
$[\alpha]_D$ +108° ($CHCl_3$)

Vitricine is an alkaloid recently isolated by Doepke (27) from *Vitex trifolia*. The picrate melts at 228° dec., the perchlorate at 178° dec., the styphnate at 243° dec., and the picrolonate at 211° dec. It is not yet certain that the alkaloid is an aporphine. Vitricine has no O-methyl or N-methyl groups, but does possess one hydroxyl and one methylenedioxy function. The ultraviolet spectrum has not been published, but is said to resemble that of an aporphine alkaloid.

III. A DIMERIC APORPHINE ALKALOID: THALICARPINE

Thalicarpine (LV)

$C_{41}H_{48}O_8N_2$
M.p. 160–161°
$[\alpha]^{25}_D$ +89° ($CHCl_3$)

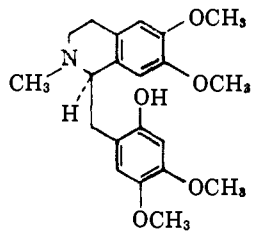


LV

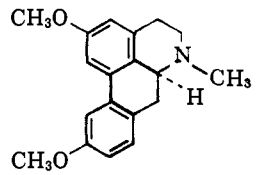
The genus *Thalictrum* has been found to be rich in alkaloids. In an elegant piece of research work, Kupchan and co-workers isolated from *Thalictrum dasycarpum* a new hypotensive alkaloid, thalicarpine, and characterized it as the first example of a dimeric alkaloid involving an aporphine moiety (81, 84).

The ultraviolet spectrum of thalicarpine in methanol exhibited λ_{max} 282 mμ (ε 17,000) and 302 mμ (ε 13,000). The nuclear magnetic resonance spectrum showed peaks for two N-methyl and seven methoxyl functions. Hofmann degradation gave a methine analyzed as the dimethiodide salt, $C_{45}H_{58}O_8N_2I_2 \cdot H_2O$, m.p. 275–276°. A second Hofmann yielded the *des*-N-methine, $C_{39}H_{38}O_8$, m.p. 170–172°.

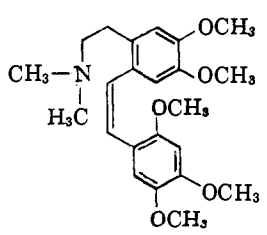
Thalicarpine was treated with sodium in liquid ammonia to give two amorphous products, namely (−)-6′-hydroxylaudanosine (LVI) and (+)-2,10-dimethoxyaporphine (LVII). (−)-6′-Hydroxylaudanosine was characterized as the hydriodide salt, m.p. 184–186°, $[\alpha]^{26}_D$ −71° (MeOH), and the O-methylmethiodide, m.p. 223–224°, $[\alpha]^{23}_D$ +109° ($CHCl_3$). Hofmann degradation of the O-methyl methiodide



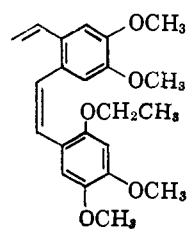
LVI



LVII



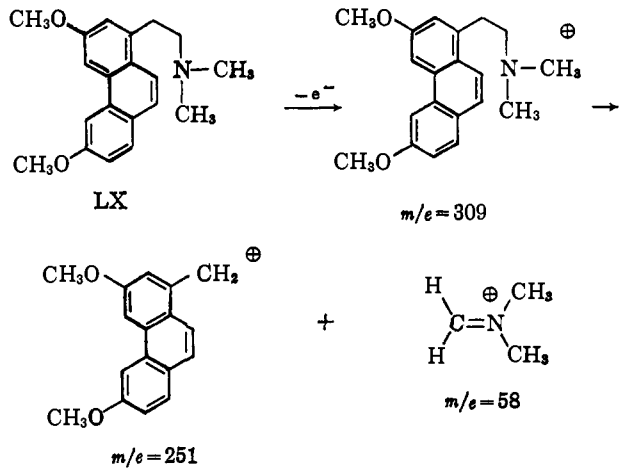
LVIII



LIX

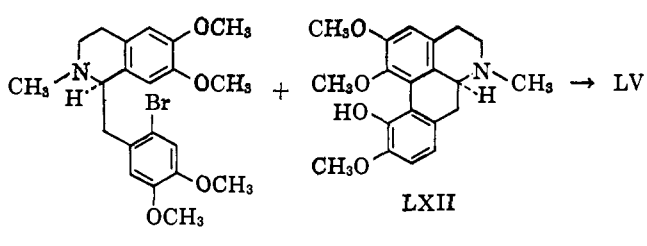
gave an optically inactive methyl methine (LVIII) having mass spectral peaks at *m/e* 401 (parent peak), and *m/e* 58 ($H_2C{=}\overset{+}{N}\langle^{CH_3}_{CH_3}$ ion). The position of the hydroxyl group in LVI was established by degrading the O-ethyl derivative under Hofmann conditions to the *des*-N-methine LIX. Treatment of LIX with potassium permanganate gave 2-ethoxy-4,5-dimethoxybenzoic acid, thereby indicating the relative position of the hydroxyl group in the benzylisoquinoline fragment.

The structure of the second fragment, 2,10-dimethoxyaporphine, was determined by converting the compound to the methiodide salt, m.p. 164–165°, $[\alpha]^{25}D$ +66° (MeOH), which was then treated with base. The Hofmann methine LX obtained gave mass spectral peaks *m/e* 309, 251, and 58.



The position of the two methoxyl groups was settled when the hydriodide of LVII, m.p. 238–240°, was found by direct comparison to be identical with an authentic sample of 2,10-dimethoxyaporphine hydriodide.

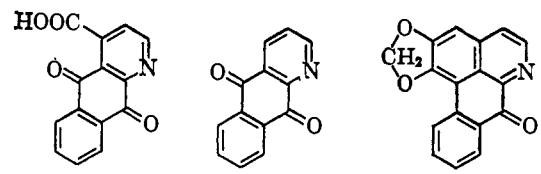
Finally, the synthesis of thalicarpine was affected by a modified Ullmann condensation of (−)-6′-bromolaudanosine (LXI) with (+)-isocorydine (LXII). The absolute configurations of LXI and LXII are known, so that the absolute configuration of thalicarpine is now established.



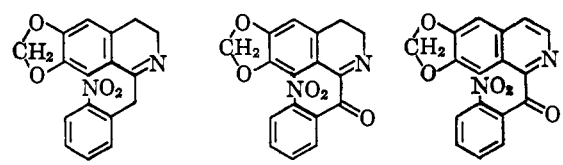
IV. Liriodenine Type Alkaloids

Liriodenine (oxoushinsunine) is the first example of an optically inactive alkaloid containing a carbonyl function and probably derived by oxidation of an aporphine in the plant. Initially isolated from the heartwood of the yellow poplar, *Liriodendron tulipifera*, liriodenine is yellow, analyzes for $C_{17}H_9O_3N$, melts at 282°, and yields an oxime, m.p. 271° (16, 126). More recently it has been found in *Magnolia coco* (160), *Michelia alba* (158), *M. compressa* (155), and *M. champaca* (159).

Oxidation of liriodenine with chromic acid in aqueous sulfuric acid yielded carboxylic acid LXIII which decarboxylated upon heating to the known azaanthraquinone LXIV (16, 121). Since the alkaloid was highly aromatic, showed only one sharp carboxyl peak in the infrared near 6.1 μ, and had a methylenedioxy group, but no NH or OH absorption, structure LXV was proposed by Taylor (121).

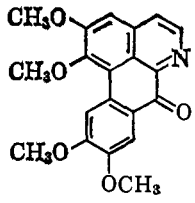


This structural assignment for liriodenine received full confirmation through a facile and refined synthesis carried out by Taylor (121). The known 1-(2′-nitrobenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (LXVI) was oxidized with chromic acid in acetic acid to the nitrobenzoyl derivative LXVII which upon treatment with hot alcoholic alkali furnished the desired 1-(2′-nitrobenzoyl)-6,7-methylenedioxyisoquinoline (LXVIII).



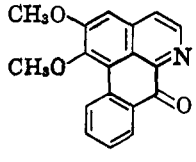
Reduction of LXVIII with Raney nickel, followed by diazotization and heating to effect Pschorr cyclization, gave liriodenine (LXV). Yang, at a later date, reported the conversion of the aporphine ushinsunine (XLVIII) to liriodenine by oxidation with chromic acid in pyridine (155). A separate investigation of the chemistry of liriodenine has also been presented (154).

In addition to liriodenine, a second optically inactive yellow alkaloid, as yet unnamed, was isolated from *L. tulipifera* (16). This base analyzed for $C_{20}H_{17}O_5N$ and exhibited m.p. 235–236°. That this accompanying alkaloid is a tetramethoxy analog of liriodenine was shown through the synthesis of 1,2,9,10-tetramethoxydibenz[*de,g*]quinolin-7-one (LXIX) which proved to be identical with the unnamed alkaloid (22).

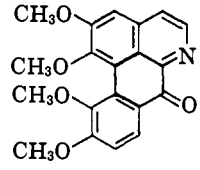


LXIX

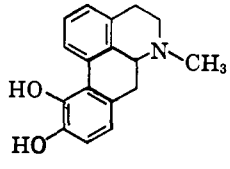
It has been hypothesized that the liriodenine type alkaloids are derived oxidatively from co-occurring aporphines (22). The fact that glaucine is found in *L. tulipifera* lends strong support to this reasoning. Further indirect evidence is seen in the chromic acid in pyridine oxidation of three aporphines which are not oxygenated at C-7. From each of the compounds studied the corresponding liriodenine type base was obtained (147). Thus nuciferine gave LXX, m.p. 208–210° dec., glaucine gave LXIX, m.p. 225–227°, and O,O-dimethylcorytuberine gave LXXI, m.p. 225–227° dec.



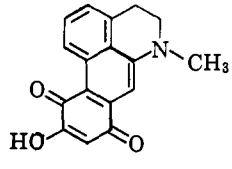
LXX



LXXI



LXXII



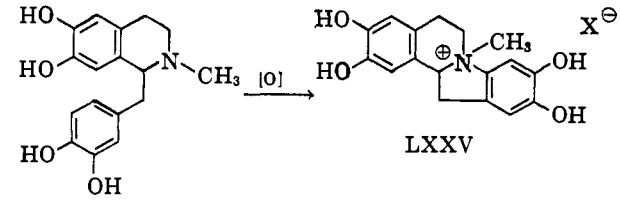
LXXIII

On the other hand, the oxidation of the diphenolic apomorphine (LXXII) has been studied and found to take a different course (53). When apomorphine in basic aqueous solution was subjected to air oxidation, a blue powder was obtained which analyzed for $C_{17}H_{13}O_3N$, m.p. 238° dec., and exhibited infrared peaks at 3.07 and 6.08 μ. The quinonoid structure LXXIII was assigned to this compound.

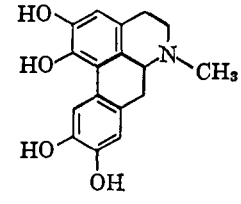
V. Biosynthesis

Aporphines are probably formed in nature by intramolecular phenolic condensation. Two early attempts to achieve such an oxidation *in vitro* with N-methyllaudanosoline (LXXIV) were carried out independently and almost simultaneously in two laboratories, and the results were practically identical, the product being LXXV instead of the expected aporphines LXXVI or LXXVII (104, 110).

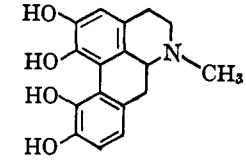
In 1962, however, Franck, Blaschke, and Schlingloff (33, 34) did indeed report the synthesis of an aporphine salt by oxidative coupling. Thus oxidation of N-



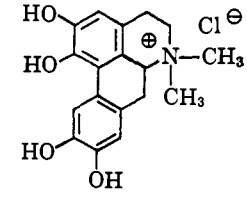
LXXIV LXXV



LXXVI



LXXVII



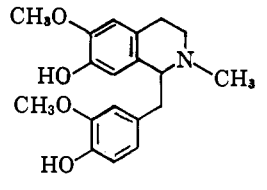
LXXVIII

methyllaudanosoline methiodide in aqueous ferric chloride solution gave a 60% yield of crystalline LXXVIII, m.p. 215–220°. In a subsequent note, Franck pointed out that secondary, tertiary, or N-acyl bases of type LXXIV tend to undergo dehydrogenation and aromatization to isoquinoline derivatives instead of coupling, and that quaternary salts are more capable of undergoing the desired condensation in good yields (32).

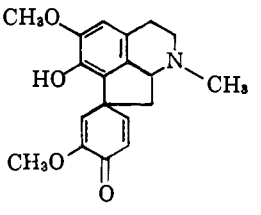
Both Barton and Battersby have recently discussed the ingenious possibility of an allylic elimination during aporphine biosynthesis (9). In connection with isothebaine and stephanine, which have unusual oxygenation patterns, the normally oxygenated 1-benzyltetrahydroisoquinoline LXXIX could cyclize to the dienone LXXX by oxidative coupling. If LXXX then underwent reduction to the dienol LXXXI (R = H), allylic elimination could occur, probably as the phosphate ester LXXXI (R = phosphate), accompanied by rearrangement of the carbon skeleton to give either isothebaine (XXXV) or a product LXXXII close to stephanine. The formation of anonaine, roemerine, and nuciferine can also be explained by a somewhat similar mechanism.

It is worth noting that all of the aporphine alkaloids so far isolated from nature are optically active, and that antipodal pairs for any one alkaloid seem to be rare up to the present. In the early thirties the isolation of (−)-corydine, (−)-isocorydine, and (−)-glaucine was reported (40–43), whereas these alkaloids have been reported elsewhere as the dextrorotatory isomers. These three cases need further substantiation,

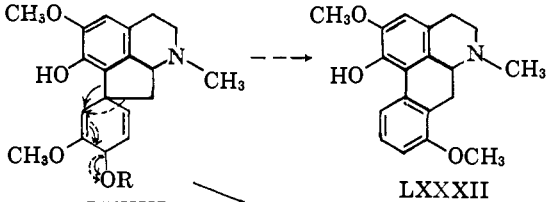
however, especially in view of some of the other claims made in the same series of papers. The fact that enantiomeric aporphines are very seldom found in nature is an interesting phenomenon, since there are many examples in which such pairs do occur for other type alkaloids derived from the benzylisoquinoline nucleus.



LXXIX



LXXX



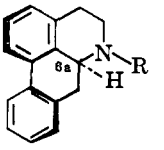
LXXXI XXXV LXXXII

A tentative effort has been made to relate the ring D substituents of aporphines with their rotations and absolute configurations (112). Thus, if only the ring D substituents are considered, it is generally found that certain functional groups at particular positions in ring D can be associated with a particular sign of rotation. For instance the 9-hydroxy-10-methoxy combination, as in boldine, laurolitsine, laurotetanine, N-methyllaurotetanine, xanthoplanine, actinodaphnine, isoboldine, and laurifoline, is associated with a positive sign of rotation. Alternatively, an unsubstituted ring D as in nuciferine, nornuciferine, 1-methoxy-2-hydroxyaporphine, roemerine, anonaine, ushinsunine, and norushinsunine, is associated with *levo* rotation. Most of the aporphines isolated since this generalization was made conform to the rule. Recently, however, two aporphines, namely cocsarmine (X) and laurelliptine (XVI) were found to diverge from the trend. It can be said at present, therefore, that a certain relationship can be observed between the nature and position of the ring D substituents on the one hand, and the specific rotation and absolute configuration on the other, but that some exceptions will be found.

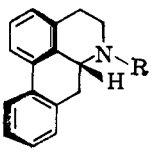
VI. Stereochemistry and Absolute Configuration

The aporphine alkaloids are not planar, but can exist in either of two stereochemical arrangements, LXXXIII or LXXXIV (44, 111).

The absolute configuration of aporphines was initially considered by Faltis and Adler who converted the benzylisoquinoline base (−)-laudanosine of known

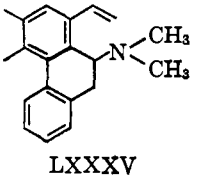


LXXXIII

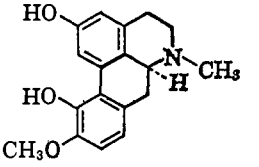


LXXXIV

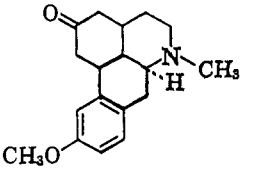
absolute configuration to (−)-glaucine by diazo coupling (29). Bentley and Cardwell then noted that since (+)-glaucine and (−)-morphothebaine are enantiomeric at C-6a, and the absolute configuration of the latter compound is known, (+)-glaucine must be as in LXXXIII (11). Furthermore, because of the actual chemical interrelationships between (+)-glaucine on the one hand and (+)-dicentrine, (+)-laurotetanine, (+)-actinodaphnine, and (+)-boldine on the other, Bentley and Cardwell generalized that all aporphines that are appreciably dextrorotatory in ethanol or chloroform also belong to the series that can be presently represented by expression LXXXIII. They also pointed out that aporphine alkaloids on Hofmann degradation give isomethines LXXXV of opposite sign of rotation to the parent base. Dextrorotatory aporphines, whether substituted at C-9, C-10, or C-11, all give levorotatory isomethine bases, while levorotatory aporphines (such as (−)-roemerine) yield dextrorotatory isomethine derivatives and therefore belong to absolute configuration LXXXIV (11).



LXXXV



LXXXVI



LXXXVII

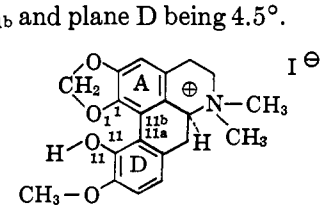
The absolute configuration of (+)-bulbocapnine is known with certainty because Ayer and Taylor have converted the alkaloid by treatment with sodium in liquid ammonia to (+)-morphothebaine (LXXXVI), which is the antipode of (−)-morphothebaine of known absolute configuration (7, 25, 68).

The use of alkali metal in liquid ammonia reduction for settling the stereochemistry of aporphine alkaloids has recently been extended by Tomita and Fukagawa (125). Thus conversion of (+)-magnoflorine iodide to (+)-O,O-dimethylcorytuberine was followed by reductive cleavage with alkali metal in liquid ammonia to yield (+)-2,10-dimethoxyaporphine (LVII) and (+)-2-oxo-10-methoxy-1,2,3,3a,11b,11c-hexahydroaporphine (LXXXVII). The same two products

were also obtained from (+)-nantenine. Furthermore, (+)-laurifoline iodide was converted by O-methylation and lithium aluminum hydride reduction to (+)-glaucine, which was then submitted to reductive cleavage to yield again LVII and LXXXVII. It follows, therefore, that all the aporphines in question possess the same absolute configuration LXXXIII.

Optical rotatory dispersion has also been used to study the absolute configuration of the aporphines (26, 148). In analogy with (+)-bulbocapnine, the alkaloids (+)-corydine, (+)-isocorydine, (+)-norisocorydine hydrobromide, and (+)-magnoflorine iodide, all exhibited rotation curves that were continuously positive and tended toward a positive Cotton effect, so that all of these 1,2,10,11-tetrasubstituted bases can be represented by the absolute configuration LXXXIII (26). In a similar fashion and taking (+)-glaucine instead of (+)-bulbocapnine as the prime exemplar, (+)-boldine, (+)-N-methyllaurotetanine hydrobromide, (+)-laurifoline chloride, (+)-dicentrine, (+)-domesticine, and (+)-nantenine all gave rotatory dispersion curves that were of positive sign in the visible region, but exhibited a negative Cotton effect. Hence all of these 1,2,9,10-tetrasubstituted alkaloids must also belong to configuration LXXXIII. (−)-Anolobine and (−)-xylopine share with the group of 1,2,9,10-substituted aporphines the 282-mμ peak in the ultraviolet, but exhibit rotatory dispersion curves that are opposite to that of that group, so that these two levorotatory alkaloids must exist in the enantiomeric form LXXXIV. Optical rotatory dispersion, therefore, bears out so far the Bentley assumption that a positive D line rotation is associated with absolute configuration LXXXIII. It is, however, safer and preferable to use rotatory dispersion measurements than simple specific rotations, especially when the latter values are small in magnitude.

A full three-dimensional X-ray analysis of bulbocapnine methiodide has yielded some interesting data (5). The absolute configuration of this salt is indeed as in LXXXIII. The angle of twist of the biphenyl system is 29.9°. The distance between O_1 and O_{11} is 2.74 Å. which is just under the sum of the van der Waals radii of two oxygens (2.80 Å.). C_{11a} is in the plane of ring A, but C_{11b} is 0.15 Å. above plane D, the angle between bond C_{11a}–C_{11b} and plane D being 4.5°.



O_1 lies 0.17 Å. above plane A, while O_{11} is 0.20 .Å below plane D. The angle between bond C_1–O_1 and plane A is 6.4°, and that between C_{11}–O_{11} and plane D is 6.6°. The angles O_1–C_1–C_{11b}, C_1–C_{11b}–C_{11a}, C_{11b}–C_{11a}–C_{11}, and C_{11a}–C_{11}–O_{11} are all significantly larger than 120°.

All these data indicate that the biphenyl system in bulbocapnine methiodide is appreciably strained.

VII. Nuclear Magnetic Resonance Spectra

A number of studies on the nuclear magnetic resonance spectra of aporphine alkaloids have appeared (15, 28, 44, 56, 69, 149, 157), and this physical tool can yield valuable information leading to the structural elucidation of aporphines. When chloroform or deuteriochloroform is used as solvent and tetramethylsilane as an internal standard, the following chemical shifts in parts per million on the τ scale (TMS = 10) have been observed:

Methoxyl Groups

The chemical shifts of methoxyl groups at C-1 appear at higher fields (6.37–6.58 τ) than those at C-2, C-9, or C-10 (6.11–6.28 τ). Methoxyl groups at C-11 have intermediate chemicals shifts (6.28–6.35 τ) (15).

Methylenedioxy Groups

With good resolution the methylenedioxy function when at C-1 and C-2 gives rise to two doublets corresponding to a small difference in chemical shifts between the two nonequivalent protons due to the twisted biphenyl system. The two doublets are usually centered near 3.98 and 4.13 τ (44, 157).

Aromatic Hydrogens

The aromatic hydrogen at C-11 is found downfield between 1.95 and 2.43 τ (44, 149), while the hydrogens at C-3, C-8, and C-9 are located relatively upfield between 3 and 3.62 τ and cannot be easily differentiated from one another (44,149).

The actual spectra of bulbocapnine, dicentrine (13), roemerine, and ushinsunine (157) have been published.

VIII. Mass Spectra

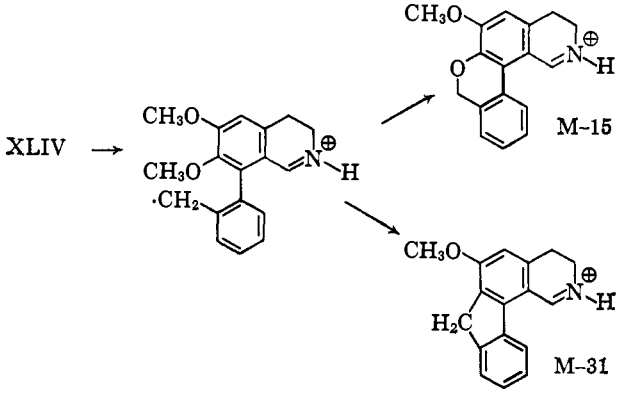
The mass spectra have been measured for several aporphine alkaloids, including nornuciferine, stephanine, crebanine, bulbocapnine, nantenine, boldine, isocorydine (95), and thalicarpine (84). A typical example, nornuciferine (XLIV) (mol. wt., 281), gives an intense M − 1 base peak formed by loss of a hydrogen atom from the molecular ion as in the yohimbine and ajmalicine series. In addition, peaks occur at *m/e* 266 and 250 (M − 15 and M − 31, respectively), probably from the loss of methyl or methoxyl from one of the methoxyl substituents. Presumably, the resulting ions are stabilized at first by fission of the benzylic bond, and then by formation of a new ring.

TABLE I

ULTRAVIOLET ABSORPTIONS OF APORPHINES[a]

Positions of substituents	Aporphines	λ_{max}, mμ (log ε)			Ref.
1,2,9,10	Glaucine	302 (4.16)	280–282 (4.18)	218 (4.58)	22
	Boldine	303 (4.2)	284 (4.2)	220 (4.6)	105
	Quaternary aporphine from *Fagara tinguassoiba* (chloride)	307 (4.21)	281 (4.12)	228 (4.60)	103
	Phanostenine	309 (4.19)	281 (4.14)	221 (4.48)	137
	Nantenine	310 (4.1)	284 (4.0)		92
	Cocsarmine iodide	308 (4.22)	282 (4.11)		130
1,2,10,11	Bulbocapnine	308 (3.6)	270 (3.9)		50
	Isocorydine	302 (3.8)	268 (4.2)	220 (4.6)	105
	N-Methylisocorydinium chloride	300 (3.76)	268 (4.16)	220 (4.59)	69
	Pseudocorydine	302 (3.66)	272 (4.04)		35
1,2,11	Pukateine HCl	303 (4.0)	268 (4.1)	220 (4.4)	108
	1,2,11-Trimethoxyaporphine	300 (3.9)	270 (4.1)	230 (4.1)	50
1,2,8,9,10	1,2-Methylenedioxy-8,9,10-trimethoxyaporphine	304 (3.92)	280 (4.22)		61
	1,2,8,9,10-Pentamethoxyaporphine	290–310 (sh)	280 (4.23)		61
1,2,9,10,11	1,2-Methylenedioxy-9,10,11-trimethoxyaporphine	320 (sh)	282 (1.9)		62
1,2,3,10,11	1,2-Methylenedioxy-3,10,11-trimethoxyaporphine HI		280 (4.24)		51
1,2,8,9	Crebanine		280 (4.29)		49
	1,2,8,9-Tetramethoxyaporphine		282 (4.35)		133
1,2,10	Michepressine iodide	316 (3.60)	273 (4.14)		67
	1,2,10-Trimethoxyaporphine	304 (3.87)	276 (4.40)	267 (4.14)	76
1,2,9	Xylopine		281 (4.45)	217 (4.49)	109
1,2,8	Stephanine		272 (4.28)		133
	1,2,8-Trimethoxyaporphine		271 (4.26)		133
1,2	Nornuciferine HCl	310 (3.36)	270 (4.25)	231 (4.35)	152
	Nuciferine	310 (3.32)	272 (4.19)	230 (4.26)	83
	Roemerine HCl	315 (3.59)	272 (4.27)	235 (4.19)	92
	Ushinsunine	321 (3.51)	274 (4.21)		155
	Norushinsunine	328 (3.49)	275 (4.23)		158
2,10	2,10-Dimethoxyaporphine HCl	320 (3.86)	273 (4.14)		74
	2-Methoxy-10-hydroxyaporphine HCl	320 (3.86)	274 (4.12)		74
1,10,11	Isothebaine methyl ether	302 (3.92)	273 (4.1)		12
2,10,11	Morphothebaine	300 (3.87)	273 (4.2)		10
10,11	Apomorphine		272 (4.18)		10
	Apomorphine dimethyl ether		272 (4.2)		119
2,3,10,11	2,3-Methylenedioxy-10,11-dimethoxyaporphine HI	305 (3.93)	285 (3.93)		48
No substituents	Aporphine HCl		282 sh (4.19)	270 (4.27)	151
	Noraporphine HCl			271 (4.26)	94

[a] Some of these values are estimated from charts.

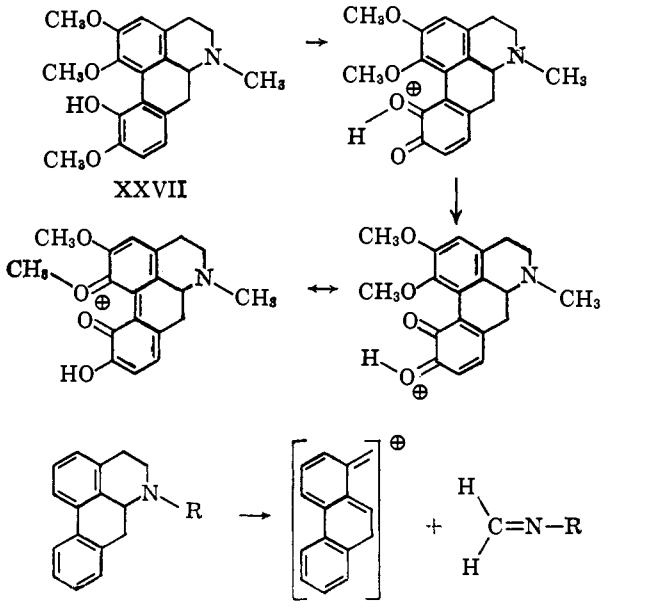


The spectra of bulbocapnine (XXXIII), boldine (XIV), and isocorydine (XXVII) exhibit a very strong M − 15 peak in contrast to stephanine (XLII) and crebanine (XXV). This is probably due to the four oxygen substituents in the first three compounds which could stabilize a positive charge by distributing it among the oxygen atoms.

The ion M − 29 is found to occur in all aporphines having an N–H grouping, while the M − 43 ion appears in those having an N-methyl function. Such fragments are caused by loss of the methylenimine moiety $H_2C{=}NR$ where R = H or CH_3.

Finally, an interesting phenomenon is seen in the occurrence of peaks *m/e* 152 and 165 in all of the aporphines studied. This finding is hard to explain since the compounds studied varied in their oxygenation patterns; however, the peaks in question may be of

diagnostic use in the examination of spectra of unknown alkaloids.



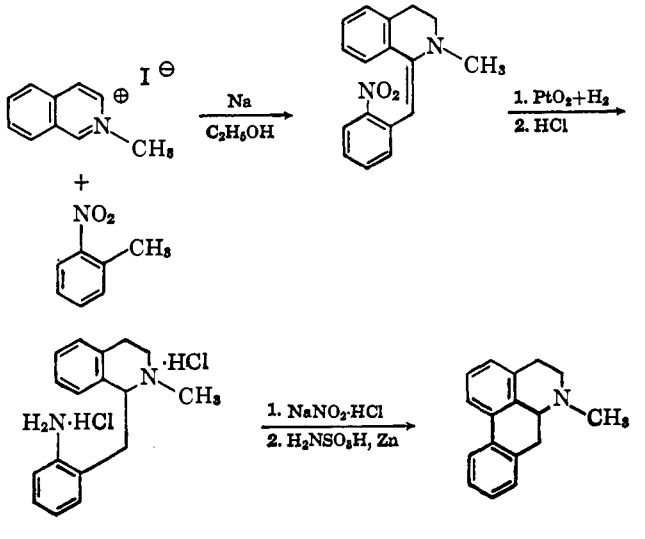
XXVII

IX. Ultraviolet Spectra

Some of the ultraviolet data on the aporphine alkaloids has been discussed (111). However, since that time, additional measurements have been made on a number of new aporphines. Table I lists much of the information available at present. Two points need to be made here, namely that it is the position rather than the nature of the substituents that primarily affects the wave length of the maximum absorption, and that consequently ultraviolet spectroscopy can be a useful tool in the structural elucidation of new aporphines.

X. Aporphines for Physiological Testing

The following discussion will concern itself with aporphines which have been synthesized for pharmacological study and are not found in nature.

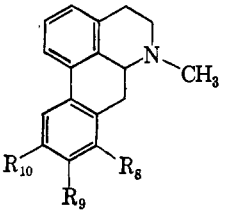


Eleven new aporphines bearing substituents at C-8, C-9, or C-10 have been prepared (151) by a modification of the classical synthesis of aporphines worked out by Gadamer, Oberlin, and Schoeler (39). Such a synthesis, that of aporphine itself, is illustrated below. It is noteworthy that Pschorr ring closure proceeded in approximately 50% yield for most of the compounds studied.

Extensive testing on mice of the pharmacology of the eleven aporphines shown in Table II was carried out. Almost all of the compounds screened produced depression of the central nervous system, but none were found to have clinical usefulness as therapeutic agents.

Table II

Synthetic Aporphines



Compounds	R_8	R_9	R_{10}
a	H	H	H
b	Cl	H	H
c	H	Cl	H
d	H	H	Cl
e	CH_3	H	H
f	H	H	CH_3
g	H	OCH_3	H
h	H	H	OCH_3
i	H	OC_2H_5	H
j	H	H	F
k	H	H	CF_3

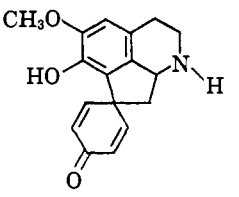
In the course of the above work, the gas–liquid chromatography of several natural and synthetic aporphine alkaloids was also carried out in an attempt to correlate retention times and determine if molecular weights and structural features of constituents in crude alkaloidal mixtures might be predicted (2). This chromatographic study was unsuccessful in its primary goals, but gas chromatography is still useful for analyzing crude alkaloidal mixtures when a direct comparison can be made with pure components.

The N-aminoaporphinium salts of apomorphine and boldine have been prepared, but did not show any interesting physiological activity (52).

Notes Added in Proof

(1) The first alkaloids belonging to what may be called the proaporphine series have been isolated and characterized. They all contain a cyclohexadienone system and rearrange to aporphines on treatment with acid.

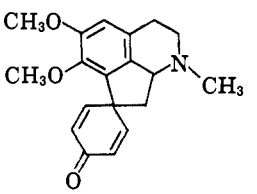
(a) Crotonosine (LXXXVIII), $C_{17}H_{17}O_3N$, found in *Croton linearis* (56). The alkaloid has $[\alpha]^{28}D$ +180°



LXXXVIII

(MeOH) and when recrystallized from 2-propanol softens at 197° dec., but does not melt below 300°. The ultraviolet spectrum shows λ_{max} 226, 235, 282, and 290 mμ (log ε 4.30, 4.33, 3.37, and 3.41). When refluxed with 3 *N* hydrochloric acid in methanol, crotonosine underwent rearrangement to an aporphine. Subsequent treatment of the aporphine with diazomethane followed by acetylation with acetic anhydride gave N-acetyl-O-methyltuduranine. A thorough examination of the nuclear magnetic resonance data strongly supports the structure finally given to crotonosine (Haynes, L. J., Stuart, K. L., Barton, D. H. R., and Kirby, G. W., *Proc. Chem. Soc.*, 280 (1963)).

(b) Pronuciferine (LXXXIX), $C_{19}H_{21}O_3N$, m.p.



LXXXIX

127–129°, $[\alpha]^{25}D$ +99° ($CHCl_3$) or +105.8° (EtOH), λ_{max} 230 and 282 mμ (log ε 4.46 and 3.46), found in *Nelumbo nucifera*. Reduction of pronuciferine with sodium borohydride followed by treatment with acid gave nuciferine (Bernauer, K., *Helv. Chim. Acta*, **46,** 1783 (1963)). Pronuciferine (Base A) has also been found to accompany crotonosine in *Croton linearis* (56).

Yunusov's fugapavine (88, 163) is very probably identical with mecambrine isolated from *Meconopsis cambrica*, and furthermore isofugapavine (LIV) may correspond to the alkaloid mecambroline also found in *M. cambrica*. Mecambrine analyzes for $C_{18}H_{17}O_3N$, melts at 178°, and has $[\alpha]^{20}D$ −94° ($CHCl_3$). The ultraviolet spectrum of this base exhibits λ_{max} 231 and 294 mμ (log ε 4.5 and 3.7). When treated with hot acid, mecambrine rearranges to mecambroline, m.p. 252–253°, $[\alpha]^{23}D$ +76° ($CHCl_3$) (Slavik, J., *Collection Czech. Chem. Commun.*, **25**, 1663 (1960), and Slavik, J., and Slavikova, L., *Collection Czech. Chem. Commun.*, **28,** 1720 (1963)).

The occurrence of the proaporphine alkaloids in nature is an excellent indication of the essential correctness of the superior speculations of Barton and Battersby regarding the biosynthesis of some of the aporphine alkaloids (9).

(2) From *Papaver dubium* Slavik has obtained mecambrine and (+)-roemerine. The isolation of the latter alkaloid is the first fully authenticated case of an aporphine alkaloid existing in an antipodal form in nature (Slavik, J., *Collection Czech. Chem. Commun.*, **28,** 1738 (1963)). A compound which could possibly be (+)-roemerine has also been isolated from *Papaver fugax* (163).

(3) The new aporphine alkaloid launobine has been isolated from the bark and woods of *Laurus nobilis*. It analyzes for $C_{18}H_{17}O_4N$; m.p. 214–215° dec.; and $[\alpha]^{21}D$ +192.7° ($CHCl_3$). Clarke–Eschweiler N-methylation gave (+)-bulbocapnine, so that launobine corresponds to norbulbocapnine (Tomita, M., Kozuka, M., Nakagawa, E., and Mitsunori, Y., *J. Pharm. Soc. Japan*, **83,** 763 (1963)).

XI. REFERENCES

(1) Alema, G., and Sergio, C., *Boll. Soc. Ital. Biol. Sper.*, **33,** 274 (1957); *Chem. Abstr.*, **54,** 5934 (1960).

(2) Arndt, R. R., Baarshers, W. A., Douglas, B., Shoop, E. C., and Weisbach, J. A., *Chem. Ind.* (London), 1163 (1963).

(3) Arthur, H. R., and Cheung, H. T., *J. Chem. Soc.*, 2306 (1959).

(4) Arumugam, N., Govindachari, T. R., Nagarajan, K., and Ramadas, R. U., *Chem. Ber.*, 91, 40 (1958).

(5) Ashida, T., Pepinsky, R., and Okaya, Y., talk delivered at International Union of Crystallography Congress, Rome, Italy, September 9–18, 1963; *Z. Krist.*, paper to be published.

(6) Aston, B. C., *J. Chem. Soc.*, **97,** 1381 (1910).

(7) Ayer, W. A., and Taylor, W. I., *J. Chem. Soc.*, 472 (1956).

(8) Barger, G., and Schlittler, E., *Helv. Chim. Acta*, **15,** 381 (1932).

(9) Barton, D. H. R., *Proc. Chem. Soc.*, 293 (1963); Battersby, A. R., *Proc. Chem. Soc.*, 189 (1963).

(10) Bentley, K. W., "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, p. 310.

(11) Bentley, K. W., and Cardwell, H. M. E., *J. Chem. Soc.*, 3252 (1955).

(12) Bentley, K. W., and Dyke, S. F., *Experientia*, 12, 205 (1956).

(13) Bhacca, N. S., Johnson, L. F., and Shoolery, J. N., "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(14) Bick, I. R. C., Clezy, P. S., and Crow, W. D., *Australian J. Chem.*, 9, 111 (1956).

(15) Bick, I. R. C., Harley-Mason, J., Sheppard, N., and Vernengo, M. J., *J. Chem. Soc.*, 1896 (1961).

(16) Buchanan, M. A., and Dickey, E. E., *J. Org. Chem.*, **25,** 1389 (1960).

(17) Burnes, D. M., "The Chemistry of Heterocyclic Compounds," Vol. 2, Interscience Publishers, New York, N. Y., 1951, p. 228.

(18) Cannon, J. R., Hughes, G. K., Ritchie, E., and Taylor, W. C., *Australian J. Chem.*, 6, 86 (1953).

(19) Cava, M., Reed, T., and Beal, J., private communication to reviewers.

(20) Chikamatsu, H., and Tomita, M., *J. Chem. Soc. Japan*, **82,** 1708 (1961); English summary, *J. Chem. Soc. Japan*, **82,** A110 (1961); *Chem. Abstr.*, **59,** 7571 (1963).

(21) Clezy, P. S., Nichol, A. W., and Gellert, E., *Experientia*, 19, 1 (1963).

(22) Cohen, J., Von Langenthal, W., and Taylor, W. I., *J. Org. Chem.*, **26**, 4143 (1961).
(23) Comin, J., and Deulofeu, V., *J. Org. Chem.*, 19, 1774 (1954).
(24) Cooke, R. G., and Haynes, H. F., *Australian J. Chem.*, **7**, 99 (1954).
(25) Corrodi, H., and Hardegger, E., *Helv. Chim. Acta*, **39**, 889 (1956).
(26) Djerassi, D., Mislow, K., and Shamma, M., *Experientia*, **18**, 53 (1962).
(27) Doepke, W., *Naturwissenschaften*, **49**, 375 (1962); *Chem. Abstr.*, **57**, 13814 (1962).
(28) Edwards, O. E., and Handa, K. L., *Can. J. Chem.*, **39**, 1801 (1961).
(29) Faltis, F., and Adler, E., *Arch. Pharm.*, **284**, 281 (1951).
(30) Faltis, F., Wagner, G., and Adler, E., *Chem. Ber.*, **77**, 686 (1944).
(31) Fieser, L. F., and Fieser, M., "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 29.
(32) Franck, B., *Angew. Chem. Intern. Ed. Engl.*, 1, 559 (1962).
(33) Franck, B., Blaschke, G., and Schlingloff, G., *Tetrahedron Letters*, **No. 10**, 439 (1962).
(34) Franck, B., and Schlingloff, G., *Ann. Chem.*, **659**, 123 (1963).
(35) Frydman, B., Bendisch, R., Comin, J., and Deulofeu, V., *J. Org. Chem.*, **25**, 100 (1960).
(36) Fujita, E., *Japan. J. Pharm. Chem.*, **31**, 25 (1959); *Chem. Abstr.*, **53**, 22745 (1959).
(37) Fujita, E., and Tomimatsu, T., *J. Pharm. Soc. Japan*, **79**, 1252 (1959); *Chem. Abstr.*, **54**, 4643 (1960).
(38) Gadamer, J., and Kuntze, F., *Arch. Pharm.*, **249**, 598 (1911).
(39) Gadamer, J., Oberlin, M., and Schoeler, A., *Arch. Pharm.*, **263**, 81 (1925).
(40) Go, J., *J. Pharm. Soc. Japan*, **49**, 801 (1929); *Chem. Abstr.*, **24**, 620 (1930).
(41) Go, J., *J. Pharm. Soc. Japan*, **49**, 814 (1929); *Chem. Abstr.*, **24**, 620 (1930).
(42) Go, J., *J. Pharm. Soc. Japan*, **49**, 821 (1929); *Chem. Abstr.*, **24**, 620 (1930).
(43) Go, J., *J. Pharm. Soc. Japan*, **50**, 933 (1930); *Chem. Abstr.*, **25**, 518 (1931).
(44) Goodwin, S., Shoolery, J. N., and Johnson, L. F., *Proc. Chem. Soc.* (London), 306 (1958).
(45) Gopinath, K. W., Govindachari, T. R., Rajappa, S., and Ramadas, C. V., *J. Sci. Ind. Res.* (India), **18B**, 444 (1959); *Chem. Abstr.*, **54**, 14287 (1960).
(46) Gopinath, K. W., Govindachari, T. R., Pai, B. R., and Viswanathan, N., *Chem. Ber.*, **92**, 776 (1959).
(47) Goto, K., and Yamamoto, I., *Proc. Japan Acad.*, **29**, 513 (1953); *Chem. Abstr.*, **49**, 8317 (1955).
(48) Govindachari, T. R., Nagarajan, K., Rajadurai, S., and Ramadas, R. U., *Chem. Ber.*, **91**, 36 (1958).
(49) Govindachari, T. R., Nagarajan, K., and Ramadas, C. V., *J. Chem. Soc.*, 983 (1958).
(50) Govindachari, T. R., and Pai, B. R., *J. Org. Chem.*, **18**, 1352 (1953).
(51) Govindachari, T. R., Rajadurai, S., Ramadas, C. V., and Viswanathan, N., *Chem. Ber.*, **93**, 360 (1960).
(52) Grace, W. R., and Co., British Patent 885,960; *Chem. Abstr.*, **59**, 2885 (1963).
(53) Gries, H., *Monatsh. Chem.*, **93**, 941 (1962).
(54) Gulland, J. M., and Haworth, R. D., *J. Chem. Soc.*, 590 (1928).
(55) Haginiwa, J., and Murakoshi, I., *J. Pharm. Soc. Japan*, **75**, 462 (1955); *Chem. Abstr.*, **50**, 2619 (1956).
(56) Haynes, L. J., and Stuart, K. L., *J. Chem. Soc.*, 1784, 1789 (1963).
(57) Henry, T. A., "The Plant Alkaloids," P. Blakiston's Son and Co., Philadelphia, Pa., 1939, p. 281.
(58) Hey, D. H., and Husain, A., *J. Chem. Soc.*, 1876 (1958).
(59) Hey, D. H., and Lobo, L. C., *J. Chem. Soc.*, 2246 (1954).
(60) Hey, D. H., and Palluel, A. L., *J. Chem. Soc.*, 2926 (1957).
(61) Hirai, K., *J. Pharm. Soc. Japan*, **80**, 608 (1960); *Chem. Abstr.*, **54**, 22696 (1960).
(62) Hirai, K., and Harada, K., *J. Pharm. Soc. Japan*, **80**, 1429 (1960); *Chem. Abstr.*, **55**, 5527 (1961).
(63) Hughes, G. K., Kaiser, F. P., Matheson, N., and Ritchie, E., *Australian J. Chem.*, **6**, 90 (1953).
(64) Iacobucci, G. A., *Ciencia Invest.* (Buenos Aires), **7**, 48 (1951); *Chem. Abstr.*, **45**, 7129 (1951).
(65) Ishii, H., *J. Pharm. Soc. Japan*, **81**, 243 (1961); *Chem. Abstr.*, **55**, 14495 (1961).
(66) Ishii, H., and Harada, H., *J. Pharm. Soc. Japan*, **81**, 238 (1961); *Chem. Abstr.*, **55**, 14495 (1961).
(67) Ito, K., *J. Pharm. Soc. Japan*, **81**, 703 (1961); *Chem. Abstr.*, **55**, 23571 (1961).
(68) Kalvoda, J., Buchschacher, P., and Jeger, O., *Helv. Chim. Acta*, **38**, 1847 (1955).
(69) Katritzky, A. R., Jones, R. A. Y., and Bhatnagar, S. S., *J. Chem. Soc.*, 1950 (1960).
(70) Kikkawa, I., *J. Pharm. Soc. Japan*, **78**, 1006 (1958); *Chem. Abstr.*, **53**, 3260 (1959).
(71) Kikkawa, I., *J. Pharm. Soc. Japan*, **79**, 83 (1959); *Chem. Abstr.*, **53**, 10269 (1959).
(72) Kikkawa, I., *J. Pharm. Soc. Japan*, **79**, 425 (1959); *Chem. Abstr.*, **53**, 17163 (1959).
(73) Kikkawa, I., *J. Pharm. Soc. Japan*, **79**, 1244 (1959); *Chem. Abstr.*, **54**, 4649 (1960).
(74) Kitamura, T., *J. Pharm. Soc. Japan*, **80**, 219 (1960); *Chem. Abstr.*, **54**, 13162 (1960).
(75) Kitamura, T., *J. Pharm. Soc. Japan*, **80**, 613 (1960); *Chem. Abstr.*, **54**, 21161 (1960).
(76) Kitamura, T., *J. Pharm. Soc. Japan*, **80**, 1104 (1960); *Chem. Abstr.*, **55**, 595 (1961).
(77) Konson, B. L., and Saksonov, P. P., *Farmakol. i Toksikol.*, 9, 14 (1946); *Chem. Abstr.*, **41**, 5634 (1947).
(78) Kozuka, M., *J. Pharm. Soc. Japan*, **82**, 1567 (1962).
(79) Kretmair, H., *Pharmazie*, **7**, 507 (1952); *Chem. Abstr.*, **47**, 11558 (1953).
(80) Kuck, A. M., and Frydman, B., *J. Org. Chem.*, **26**, 5253 (1961).
(81) Kupchan, S. M., Chakravarti, K. K., and Yokoyama, N., *J. Pharm. Sci.*, in press.
(82) Kupchan, S. M., Dasgupta, B., Fujita, E., and King, M. L., *J. Pharm. Sci.*, **51**, 599 (1962).
(83) Kupchan, S. M., Dasgupta, B., Fujita, E., and King, M. L., *Tetrahedron*, 19, 227 (1963).
(84) Kupchan, S. M., and Yokoyama, N., *J. Am. Chem. Soc.*, **85**, 1361 (1963).
(85) Manske, R. H. F., "The Alkaloids," Vol. 4, Academic Press, New York, N. Y., 1954, p. 119.
(86) Manske, R. H. F., "The Alkaloids," Vol. 7, Academic Press, New York, N. Y., 1960, p. 426.
(87) Manske, R. H. F., Charlesworth, E. H., and Ashford, W. R., *J. Am. Chem. Soc.*, **73**, 3751 (1951).
(88) Mnatsakanyan, V. A., and Yunusov, S. Y., *Dokl. Akad. Nauk Uz. SSR*, 36 (1961); *Chem. Abstr.*, **58**, 1503 (1963).
(89) Moisset de Espanés, E., *Rev. Soc. Arg. Biol.*, **31**, 241 (1955); *Chem. Abstr.*, **50**, 11513 (1956).
(90) Moisset de Espanés, E., *Rev. Soc. Arg. Biol.*, **32**, 108 (1956); *Chem. Abstr.*, **51**, 5992 (1957).

(91) Nakano, T., *Chem. Pharm. Bull.* (Tokyo), **2**, 329 (1954); *Chem. Abstr.*, **50**, 7117 (1956).
(92) Nakasato, T., and Nomura, S., *J. Pharm. Soc. Japan*, **79**, 1267 (1959); *Chem. Abstr.*, **54**, 4646 (1960).
(93) Nakasato, T., and Nomura, S., *Chem. Pharm. Bull.* (Tokyo), **7**, 780 (1959).
(94) Ochiai, E., and Kuniyoshi, I., *Chem. Pharm. Bull.* (Tokyo), **5**, 292 (1957).
(95) Ohashi, M., Wilson, J. M., Budzikiewicz, H., Shamma, M., Slusarchyk, W. A., and Djerassi, C., *J. Am. Chem. Soc.*, **85**, 2807 (1963).
(96) Patterson, A. M., Capell, L. T., and Walker, D. F., "The Ring Index," Serial No. 5171, The American Chemical Society, Washington, D. C., 1960, p. 704.
(97) Peters, V., Hartwell, J. L., Dalton, A. J., and Shear, M. J., *Cancer Res.*, **6**, 490 (1946); *Chem. Abstr.*, **42**, 5540 (1948).
(98) Pictet, A., and Finkelstein, M., *Chem. Ber.*, **42**, 1979 (1909).
(99) Pinder, A. R., "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Vol. 4^c, Elsevier Publishing Co., Amsterdam, London, New York, Princeton, 1960, p. 1941.
(100) Reynolds, A. K., and Randall, L. O., "Morphine and Related Drugs," University of Toronto Press, Toronto, 1957, p. 223.
(101) Reynolds, A. K., and Randall, L. O., "Morphine and Related Drugs," University of Toronto Press, Toronto, 1957, p. 224.
(102) Reynolds, A. K., and Randall, L. O., "Morphine and Related Drugs," University of Toronto Press, Toronto, 1957, p. 225.
(103) Riggs, N. V., Antonaccio, L., and Marion, L., *Can. J. Chem.*, **39**, 1330 (1961).
(104) Robinson, R., and Sugasawa, S., *J. Chem. Soc.*, 789 (1932).
(105) Ruegger, A., *Helv. Chim. Acta*, **42**, 754 (1959).
(106) Satomi, M., *Ann. Rept. Itsuu Lab.* (Japan), 31 (1955); *Chem. Abstr.*, **50**, 10112 (1956).
(107) Schlittler, E., *Helv. Chim. Acta*, **15**, 394 (1932).
(108) Schlittler, E., and Lindenmann, A., *Helv. Chim. Acta*, **32**, 1880 (1949).
(109) Schmutz, J., *Helv. Chim. Acta*, **42**, 335 (1959).
(110) Schopf, C., and Thierfelder, K., *Ann. Chem.*, **497**, 22 (1932).
(111) Shamma, M., *Experientia*, **16**, 484 (1960).
(112) Shamma, M., *Experientia*, **18**, 64 (1962).
(113) Slavik, J., *Collection Czech. Chem. Commun.*, **24**, 3999 (1959); *Chem. Abstr.*, **54**, 7071 (1960).
(114) Slavik, J., and Slavikova, L., *Chem. Listy*, **50**, 969 (1956); *Chem. Abstr.*, **50**, 16800 (1956).
(115) Slavik, J., and Slavikova, L., *Collection Czech Chem. Commun.*, **24**, 3141 (1959); *Chem. Abstr.*, **54**, 2390 (1960).
(116) Slavikova, L., and Slavik, J., *Chem. Listy*, **51**, 1923 (1957); *Chem. Abstr.*, **52**, 2344 (1958).
(117) Stanek, J., "Alkaloidy," Ceskoslovenske Nakladatelstvi Akademie Ved, Prague, 1957, p. 192.
(118) Stern, P., and Mitrovic-Kociec, D., *Arch. Intern. Pharmacodyn.*, 116, 489 (1958); *Chem. Abstr.*, **53**, 9451 (1959).
(119) Sugasawa, S., and Tachikawa, R., *Tetrahedron*, **4**, 205 (1958).
(120) Takase, T., and Ohashi, H., *J. Pharm. Soc. Japan*, **541**, 210 (1927); *Chem. Abstr.*, **21**, 2336 (1927).
(121) Taylor, W. I., *Tetrahedron*, **14**, 42 (1961).
(122) Tobitani, T., *J. Okayama Med. Soc.*, **51**, 1447 (1938); *Chem. Abstr.*, **37**, 1186 (1943).
(123) Tomita, M., and Fujie, M., *J. Pharm. Soc. Japan*, **82**, 1457 (1962).
(124) Tomita, M., and Fukagawa, K., *J. Pharm. Soc. Japan*, **82**, 1673 (1962).
(125) Tomita, M., and Fukagawa, K., *J. Pharm. Soc. Japan*, **83**, 293 (1963); *Chem. Abstr.*, **59**, 5211 (1963).
(126) Tomita, M., and Furukawa, J., *J. Pharm. Soc. Japan*, **82**, 616 (1962).
(127) Tomita, M., and Furukawa, J., *J. Pharm. Soc. Japan*, **82**, 925 (1962); *Chem. Abstr.*, **58**, 7992 (1963).
(128) Tomita, M., and Furukawa, J., *J. Pharm. Soc. Japan*, **82**, 1199 (1962).
(129) Tomita, M., and Furukawa, H., *J. Pharm. Soc. Japan*, **82**, 1458 (1962).
(130) Tomita, M., and Furukawa, H., *J. Pharm. Soc. Japan*, **83**, 190 (1963).
(131) Tomita, M., and Hirai, K., *J. Pharm. Soc. Japan*, **77**, 290 (1957); *Chem. Abstr.*, **51**, 11362 (1957).
(132) Tomita, M., and Hirai, K., *J. Pharm. Soc. Japan*, **78**, 733 (1958); *Chem. Abstr.*, **52**, 20222 (1958).
(133) Tomita, M., and Hirai, K., *J. Pharm. Soc. Japan*, **79**, 723 (1959); *Chem. Abstr.*, **53**, 22041 (1959).
(134) Tomita, M., and Kikkawa, I., *Chem. Pharm. Bull.* (Tokyo), **4**, 230 (1956); *Chem. Abstr.*, **51**, 8116 (1957).
(135) Tomita, M., and Kikkawa, I., *J. Pharm. Soc. Japan*, **77**, 195 (1957); *Chem. Abstr.*, **51**, 9648 (1957).
(136) Tomita, M., and Kikkawa, I., *J. Pharm. Soc. Japan*, **77**, 1011 (1957); *Chem. Abstr.*, **52**, 3833 (1958).
(137) Tomita, M., and Kikkawa, I., *J. Pharm. Soc. Japan*, **77**, 1015 (1957); *Chem. Abstr.*, **52**, 3834 (1958).
(138) Tomita, M., Kikkawa, I., and Ogiu, K., Japanese Patent 7976 (1958); *Chem. Abstr.*, **54**, 4651 (1960).
(139) Tomita, M., and Kikuchi, T., *Chem. Pharm. Bull.* (Tokyo), **3**, 100 (1955); *Chem. Abstr.*, **50**, 4459 (1956).
(140) Tomita, M., and Kitamura, T., *J. Pharm. Soc. Japan*, **79**, 1092 (1959); *Chem. Abstr.*, **53**, 22740 (1959).
(141) Tomita, M., and Kusuda, F., *Chem. Pharm. Bull.* (Tokyo), 1, 1 (1953); *Chem. Abstr.*, **48**, 12131 (1954).
(142) Tomita, M., and Kusuda, F., *Chem. Pharm. Bull.* (Tokyo), 1, 5 (1953); *Chem. Abstr.*, **48**, 12132 (1954).
(143) Tomita, M., and Takano, Y., *J. Pharm. Soc. Japan*, **80**, 1645 (1960); *Chem. Abstr.*, **55**, 7452 (1961).
(144) Tomita, M., Watanabe, Y., and Furukawa, H., *J. Pharm. Soc. Japan*, **81**, 469 (1961); *Chem. Abstr.*, **55**, 18015 (1961).
(145) Tomita, M., Watanabe, Y., and Furukawa, H., *J. Pharm. Soc. Japan*, **81**, 942 (1961); *Chem. Abstr.*, **55**, 27393 (1961).
(146) Tomita, M., Watanabe, Y., and Furukawa, H., *J. Pharm. Soc. Japan*, **81**, 1644 (1961); *Chem. Abstr.*, **57**, 8625 (1962).
(147) Tomita, M., Yang, T.-H., Furukawa, H., and Yang, H.-M., *J. Pharm. Soc. Japan*, **82**, 1574 (1962); *Chem. Abstr.*, **58**, 14012 (1963).
(148) Vernengo, M. J., *Experientia*, **17**, 420 (1961).
(149) Vernengo, M. J., *Experientia*, **19**, 294 (1963).
(150) Vernengo, M. J., Cerezo, A. S., Iacobucci, G. A., and Deulofeu, V., *Ann. Chem.*, **610**, 173 (1957).
(151) Weisbach, J. A., Burns, C., Macko, E., and Douglas, B., *J. Med. Chem.*, **6**, 91 (1963).
(152) Weisbach, J. A., and Douglas, B., *J. Org. Chem.*, **27**, 3738 (1962).
(153) Winek, C., Beal, J., and Cava, M., private communication to reviewers.
(154) Yang, S.-S., Huang, W.-Y., Lin, L.-C., and Yeh, P.-Y., *Chemistry* (Taipei), 144 (1961); *Chem. Abstr.*, **56**, 1489 (1962).
(155) Yang, T.-H., *J. Pharm. Soc. Japan*, **82**, 794 (1962); *Chem. Abstr.*, **58**, 7991 (1963).

(156) Yang, T.-H., *J. Pharm. Soc. Japan*, **82**, 798 (1962); *Chem. Abstr.*, **58**, 7991 (1963).
(157) Yang, T.-H., *J. Pharm. Soc. Japan*, **82**, 804 (1962); *Chem. Abstr.*, **58**, 7991 (1963).
(158) Yang, T.-H., *J. Pharm. Soc. Japan*, **82**, 811 (1962); *Chem. Abstr.*, **58**, 7991 (1963).
(159) Yang, T -H., and Hsiao, C.-Y., *J. Pharm. Soc. Japan*, **83**, 216 (1963).
(160) Yang, T.-H., Lu, S.-T., and H., C.-Y., *J. Pharm. Soc. Japan*, **82**, 816 (1962); *Chem. Abstr.*, **58**, 7991 (1963).
(161) Yunusov, S., and Ismailov, Z. F., *J. Gen. Chem. USSR*, **30**, 1710 (1960); *Zh. Obshch. Khim.*, **30**, 1721 (1960); *Chem. Abstr.*, **55**, 3631 (1961).
(162) Yunusov, S., Konowalowa, R., and Orekhov, A., *Bull. soc. chim. France*, **7**, 70 (1940); and *J. Gen. Chem. USSR*, **9**, 1868 (1939).
(163) Yunusov, S. Y., Mnatsakanyan, V. A., and Akramov, S. T., *Dokl. Akad. Nauk Uz. SSR*, 43 (1961); *Chem. Abstr.*, **57**, 9900 (1962).
(164) Yunusov, S., and Progressov, N. N., *Zh. Obshch. Khim.*, **20**, 1151 (1950); *Chem. Abstr.*, **45**, 1608 (1951).
(165) Yunusov, S., and Progressov, N. N., *Zh. Obshch. Khim.*, **22**, 1047 (1952); *Chem. Abstr.*, **47**, 8084 (1953).