THE PROAPORPHINE ALKALOIDS

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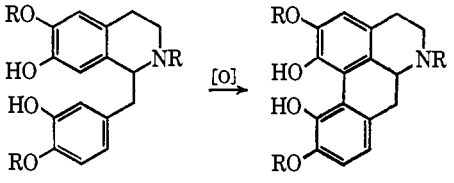
CONTENTS

I. INTRODUCTION

In 1957, Barton and Cohen published a now classical analysis of the biogenetic aspects of phenol oxidation in the formation of a wide variety of natural product structures (2). In considering logical mechanistic pathways for the formation of aporphine alkaloids from benzyltetrahydroisoquinolines, these authors noted that aporphines having certain substitution patterns (*e.g.*, I or II) could be formed in the plant by direct oxidative coupling. On the other hand, they realized that aporphines having other substitution patterns (*e.g.*, III or IV) could not be formed directly in this way, but that their formation could be rationalized within the general biogenetic scheme if dienones such as V were assumed to be intermediates in the process. Following known laboratory reactions, structure V should undergo an acid-catalyzed dienone–phenol rearrangement to III: after reduction to the corresponding dienol VI, the molecule should undergo an acid-catalyzed dienol–phenol rearrangement to IV.



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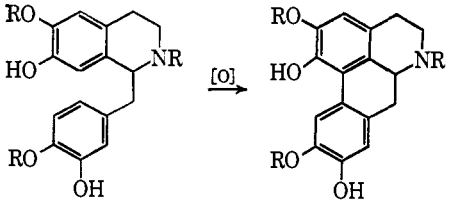

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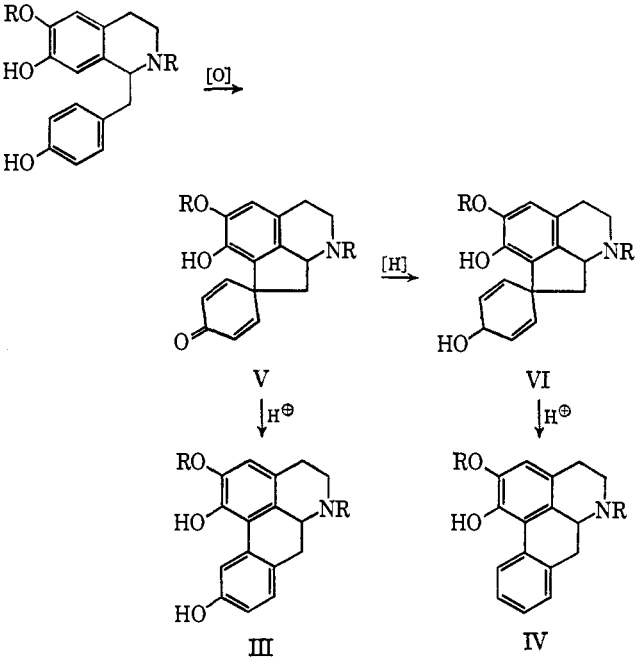
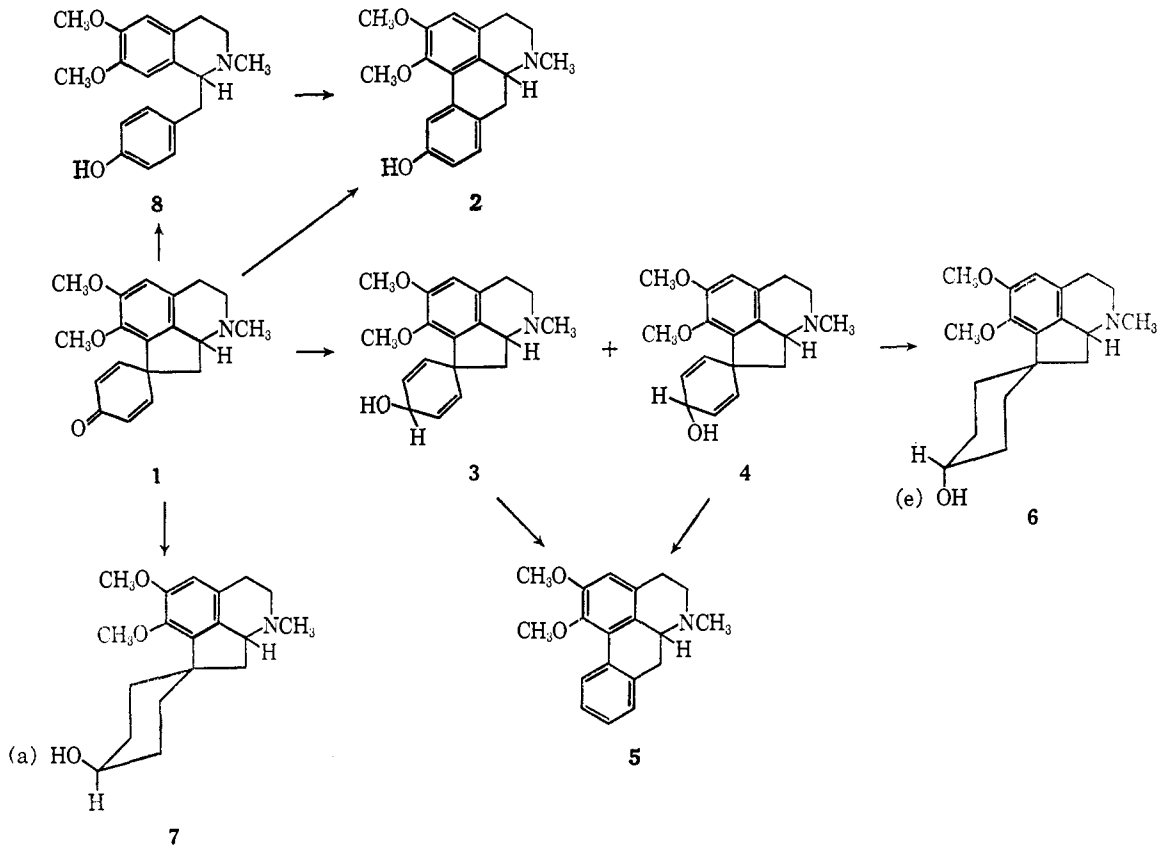


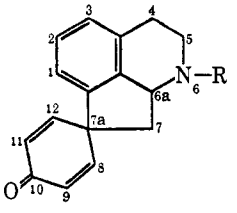
III IV

The hypothesis of Barton and Cohen received striking support in 1963 with the assignment of structures related to V to some naturally occurring alkaloids (15, 30). Dienone bases having the skeleton of V are now regarded as members of a new class of alkaloids designated as the *proaporphines* (19, 52). At the time of the writing of this review, seven proaporphine alkaloids have been reported from natural sources, as well as eight alkaloids having a partially reduced proaporphine system.

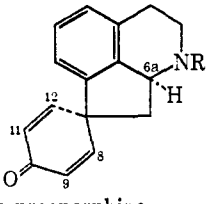
The numbering system indicated below will be used in this discussion. The absolute configuration of the proaporphines can correspond to either of the structures shown below, due to the asymmetry at C-6a.



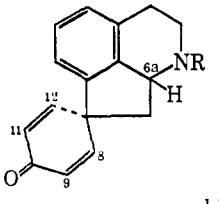
In addition, the spirodienone ring is not symmetrical with respect to the rest of the molecule; when neces-



sary, this asymmetry at C-7a will be indicated by assigning the lower numbers (C-8 and C-9) to the olefinic carbons which project from the plane of the paper when the structure is written so that the planar benzene ring is at the upper left-hand corner.



an L-proaporphine
((*S*) configuration at C-6a)



a D-proaporphine
((*R*) configuration at C-6a)

II. Chemistry and Stereochemistry of Proaporphines

In this section, the reactions, stereochemistry, and synthesis of the individual proaporphine alkaloids will be considered. Trivial derivatives (*e.g.*, salts, oximes, etc.) will not be included; these are referred to in Table I later in this review. Reduced proaporphine bases are discussed in a separate section.

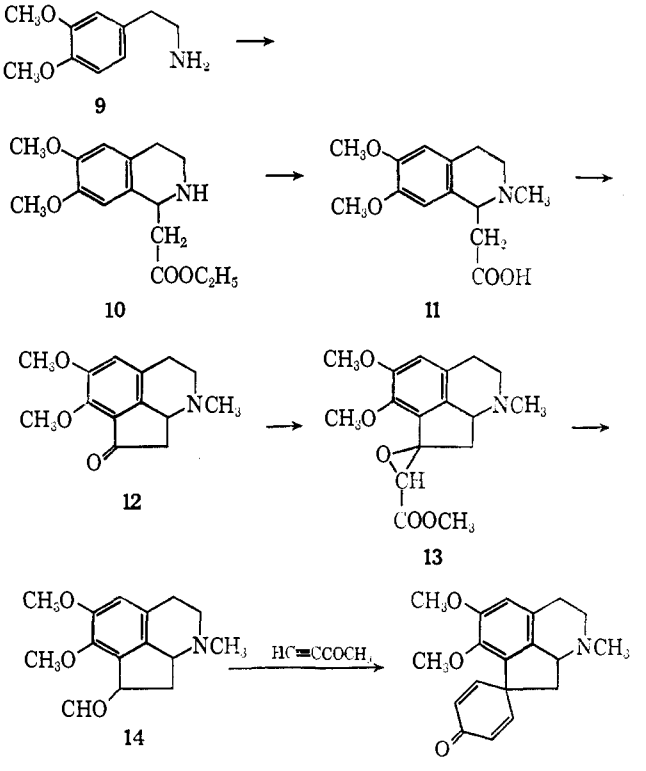
A. Pronuciferine

Pronuciferine (**1**) undergoes the dienone–phenol rearrangement when heated with aqueous sulfuric acid to give (−)-1,2-dimethoxy-10-hydroxyaporphine (**2**) (17). Reduction of pronuciferine with either lithium aluminum hydride or sodium borohydride affords a mixture of dienols **3** and **4**, which undergo the dienol–benzene rearrangement on treatment with mineral acid to give (−)-nuciferine (**5**) (15, 17). The dienol mixture can be separated chromatographically into an oily isomer (**3**) and a crystalline isomer (**4**). The crystalline isomer is assigned structure **4** since it is reduced catalytically to the cyclohexanol derivative **6**, which is different from the hexahydropronuciferine (**7**) obtained by the direct catalytic reduction of pronuciferine using platinum oxide in acetic acid. The stereochemistry of alcohol **7**, which is formed rapidly and almost stereospecifically, follows from the reasonable assumption that the carbonyl group of pronuciferine is reduced catalytically from the much less hindered lower side (17).

Sodium in liquid ammonia effects a reductive cleavage of pronuciferine to give D-(−)-armepavine (**8**). Since the absolute configuration of armepavine has been determined unambiguously (63), this transformation establishes conclusively the D (or *R*) configura-

tion for natural (+)-pronuciferine. Given the absolute configuration of pronuciferine, it follows that its levorotatory aporphine transformation products **2** and **5** must also have the D (or *R*) configuration as written (19, 20).[1]

A total synthesis of (±)-pronuciferine has been reported in which the two lower rings are constructed one at a time using classical methods. Thus, homoveratrylamine (**9**) was converted (*via* the Bischler–Napieralski synthesis) to the previously known ester **10**. N-Methylation of **10**, followed by hydrolysis, yielded acid **11**, which was cyclized by polyphosphoric acid to ketone **12**. The reaction of **12** with methyl chloroacetate and sodium amide afforded the glycidic ester **13**, which was hydrolyzed and decarboxylated to give the aldehyde **14**. The reaction of the latter aldehyde with methyl ethynyl ketone in the presence of a strong base (sodium hydride or potassium *t*-butoxide) yielded (±)-pronuciferine (14).



The methylation of synthetic (±)-glaziovine (*vide infra*) constitutes a second formal synthesis of (±)-pronuciferine.

B. STEPHARINE

Stepharine (**15**) undergoes the dienone–phenol rearrangement when heated with aqueous acid to give (−)-tuduranine (**16**) (20), and it reacts with acetic anhydride to give N-acetylstepharine (**17**), which is reductively cleaved by sodium in liquid ammonia to give (−)-N-acetylnorarmepavine (**18**) (19, 20). Naturally occurring (+)-stepharine has the D (or *R*) configuration, since it is methylated to (+)-pronuciferine (**1**) by formaldehyde and formic acid (19, 20).

The reductive methylation of stepharine by formaldehyde and hydrogen in the presence of palladium yields tetrahydropronuciferine (**19**); reduction of the dienone system of stepharine apparently takes place at least as rapidly as N-methylation (20).

C. CROTONOSINE

Crotonosine (**20**) undergoes the dienone–phenol rearrangement when heated with aqueous acid to give the aporphine base apocrotonosine (**21**) (27, 29). Rearrangement in methanolic acid yielded the 10-O-methyl derivative of **21** (**21b**) (27). In this as in similar proaporphine rearrangement the other possible isomer **21a** was not obtained. Methylation of apocrotonosine with methyl iodide and potassium carbonate yields a compound which is identical with O,N-dimethyltuduranine methiodide (**22**) (29).

Methylation of natural (+)-crotonosine with formaldehyde and formic acid yields (+)-N-methylcrotonosine (**23**); sodium borohydride reduction of **23** yields a dienol mixture (**24**) which undergoes the dienol–benzene rearrangement with acid to give (−)-1-methoxy-2-hydroxyaporphine (**25**), identical with a naturally occurring alkaloid from *Nelumbo nucifera* Gaertn (29, 31).

The orientation of the methoxyl and hydroxyl substituents in crotonosine was proven by nmr-controlled deuterium exchange experiments, which were in accord with the 1-methoxy-2-hydroxy arrangement but not with the isomeric 1-hydroxy-2-methoxy pattern. By using alkaline deuterium oxide to exchange any hydrogens *ortho* and *para* to phenolic groups, it was shown that apocrotonosine (**21**) contains three exchangeable aromatic hydrogens. Similarly, diacetyltetrahydrocrotonosine (**26**) shows the exchange of one aromatic hydrogen when treated similarly and then reacetylated; compound **26** can be prepared from crotonosine by acetylation, followed by catalytic reduction of the resulting O,N-diacetylcrotonosine (**27**) (29, 31).

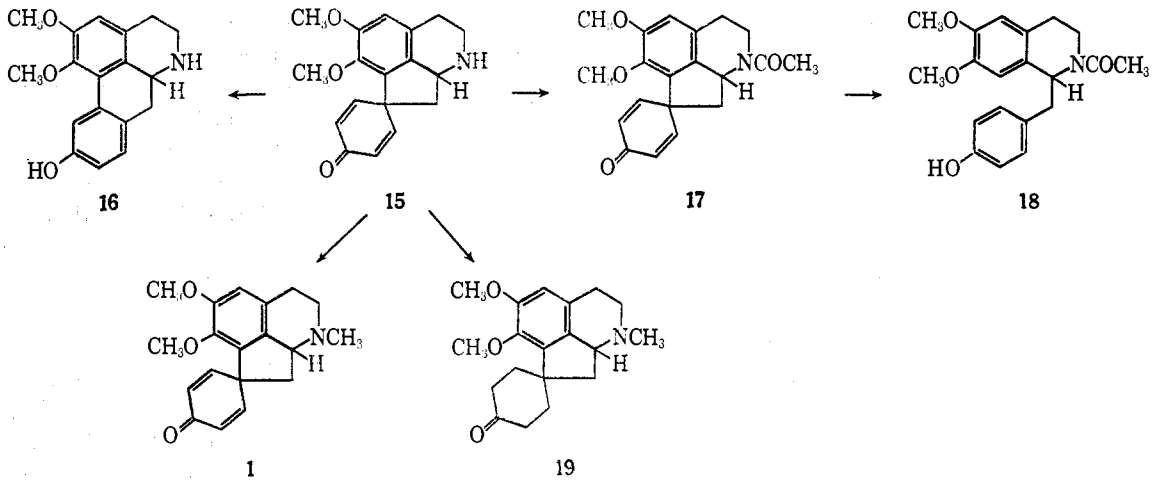
Crotonosine has been assigned the D (or *R*) configuration by correlation, *via* methiodide **22**, with D-(+)-pronuciferine (**1**) (29). This configuration is supported also by circular dichroism studies (58).

D. HOMOLINEARISINE

The naturally occurring base (−)-homolinearisine is L-(−)-N-methylcrotonosine (**28**), since it is identical in all respects except optical rotation with D-(+)-N-methylcrotonosine (**23**) (29, 31).

Reduction of homolinearisine with sodium borohydride affords a mixture of dienols (**29**) which undergo the dienol–benzene rearrangement when treated with acid to give (+)-1-methoxy-2-hydroxyaporphine (**30**);

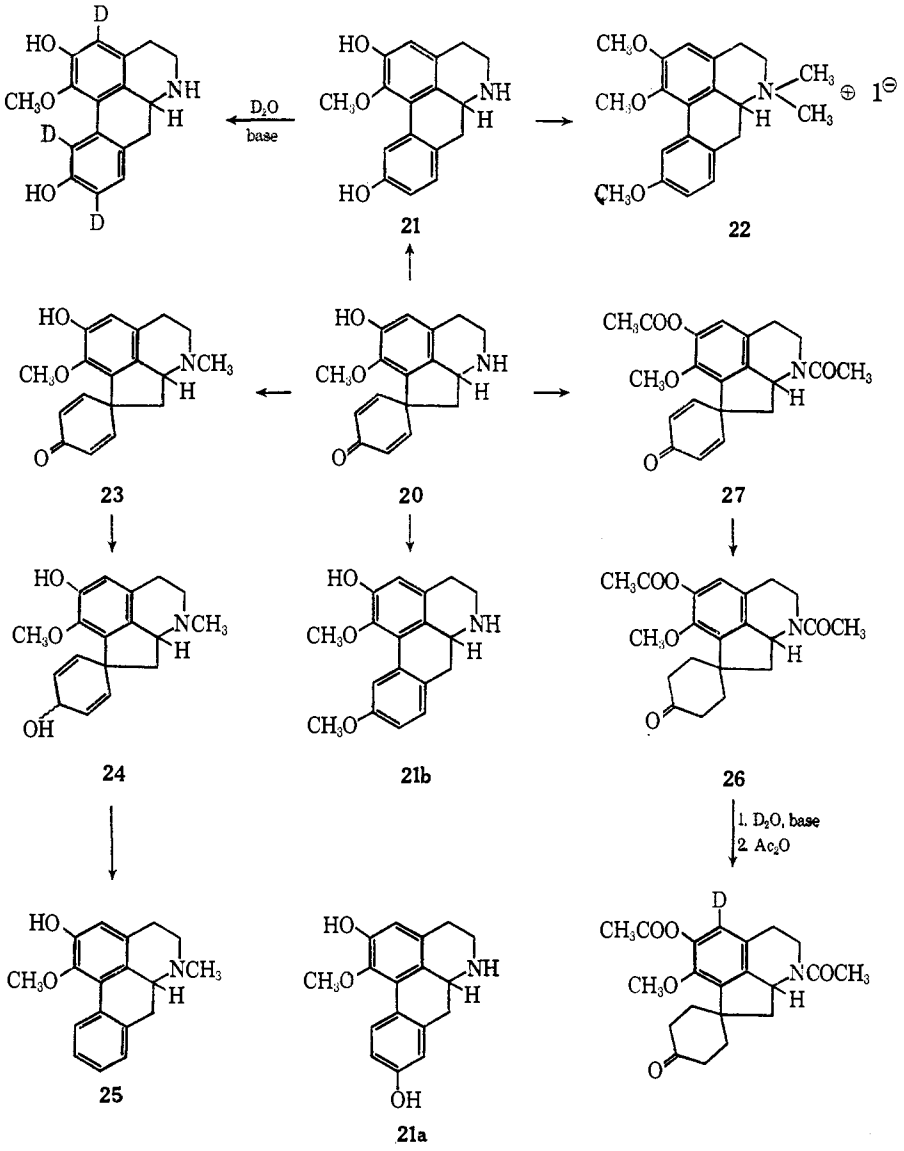
(1) The isolation of L-(−)-pronuciferine (*i.e.*, the *S* isomer) was reported very recently from *Papaver persicum* (47a); see Addendum.

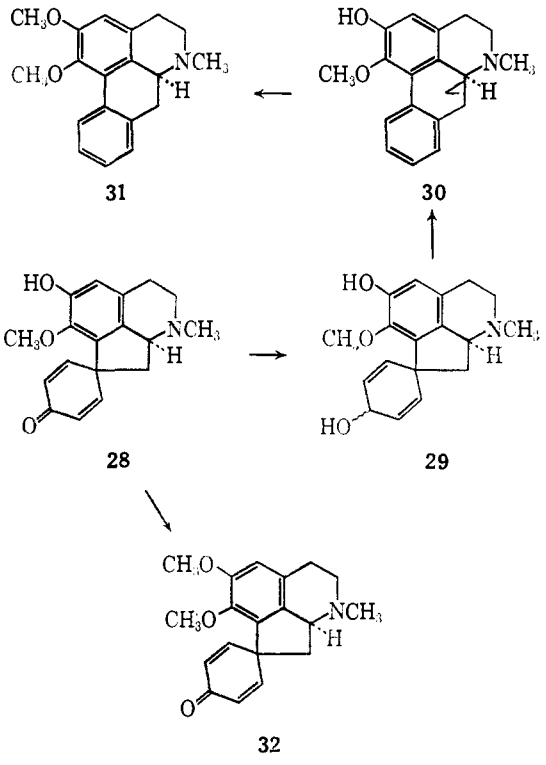


treatment of aporphine **30** with diazomethane yields (+)-nuciferine (**31**) (40).

Reaction of homolinearisine with diazomethane gives a pronuciferine: the product is presumably the otherwise unreported L-(−)-pronuciferine (**32**), but its rotation was not reported (40).

It should be pointed out that the name "homolinearisine" was assigned when the alkaloid appeared to have





the empirical composition $C_{19}H_{23}NO_3$, rather than $C_{18}H_{19}NO_3$ as determined subsequently (29).

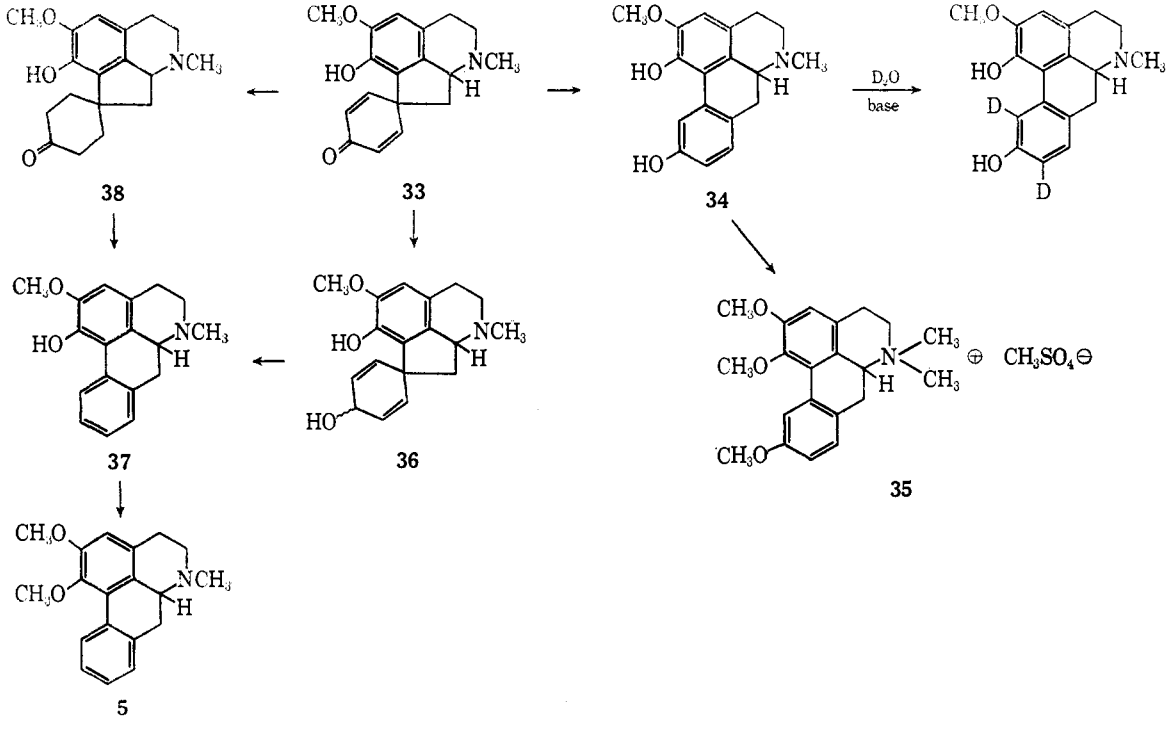
material prepared by the methylation of tuduranine (25).

Sodium borohydride reduction of glaziovine affords a dienol mixture (**36**) which undergoes the dienol–benzene rearrangement on treatment with acid to give (−)-1-hydroxy-2-methoxyaporphine (**37**); diazomethane methylation of phenol **37** gives nuciferine (presumably (−)-nuciferine (**5**), although the rotation of the latter was not determined) (25). Catalytic reduction of glaziovine using platinum oxide in acetic acid affords tetrahydroglaziovine (**38**) (25).

The orientation of the methoxyl and hydroxyl substituents in glaziovine was proven as in the case of the isomeric alkaloid crotonosine, by deuterium exchange experiments using several glaziovine derivatives. Thus, tetrahydroglaziovine (**38**) exchanges no aromatic hydrogens in alkaline deuterium oxide, whereas apoglaziovine (**34**) exchanges two aromatic hydrogens (29, 31).

The absolute configuration of glaziovine is assumed to be D (or *R*), since it can be converted into the levorotatory aporphines **34** and **37** (25). Levorotatory aporphines probably all have the (*R*) configuration (21, 50).

A simple synthesis of (±)-glaziovine has been reported, making use of a biogenetically patterned intra-



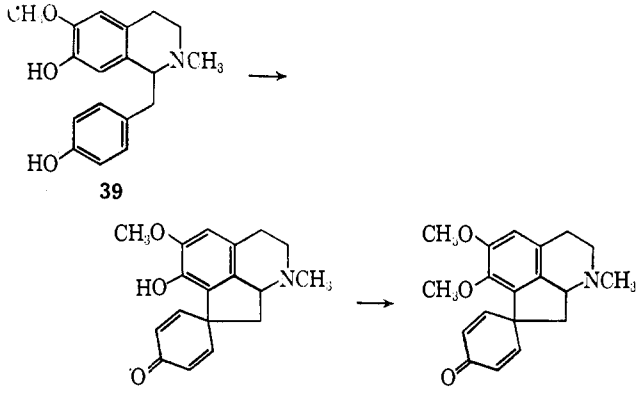
E. GLAZIOVINE

Glaziovine (**33**) is rearranged by aqueous acid to apoglaziovine or (−)-1,10-dihydroxy-2-methoxyaporphine (**34**); methylation of aporphine **34** affords 1,2,10-trimethoxyaporphine methosulfate (**35**), identical with

molecular oxidative coupling reaction. Thus, potassium ferricyanide oxidation of (±)-N-methylcoclaurine (**39**) affords (±)-glaziovine, albeit in only 1% yield.[2]

(2) A second independent synthesis of glaziovine by oxidative coupling was disclosed very recently (20a).

Diazomethane methylation of (±)-glaziovine gives (±)-pronuciferine (36b, 36c).



39

F. MECAMBRINE

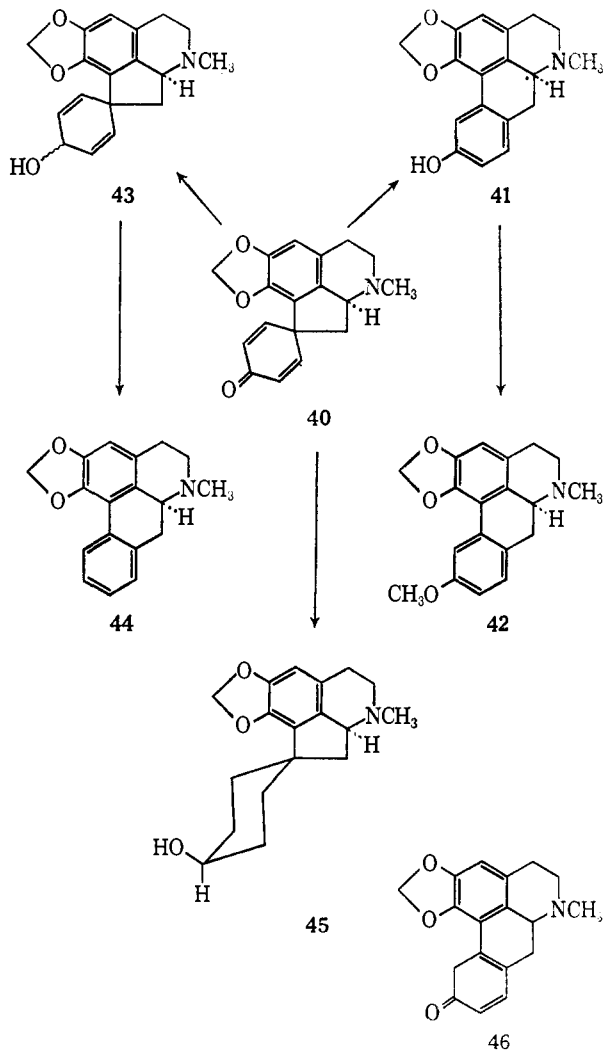
Acid-catalyzed rearrangement of mecambrine (**40**) yields the naturally occurring aporphine (+)-mecambroline (**41**); the structure of mecambroline follows from its methylation by diazomethane to give the known aporphine (+)-laureline (**42**) (18, 43, 55).

Reduction of mecambrine by either lithium aluminum hydride or sodium borohydride affords a dienol mixture (**43**), which undergoes the dienol–benzene rearrangement with acid to give the known (+)-roemerine (**44**) (18, 43, 56).

Catalytic reduction of mecambrine in the presence of platinum gives the alcohol hexahydromecambrine (18, 43). On the basis of analogy with the similarly prepared hexahydropronuciferine, hexahydromecambrine may be assigned structure **45** (see also litserisine, section III.F).

Natural (−)-mecambrine, which is convertible into (+)-aporphine bases, has been assigned the L (or *S*) configuration. This assignment is based upon analogy with the (*R*)-proaporphines stepharine (**15**) and pronuciferine (**1**), which are convertible into (−)-aporphine bases (56). The assignment of (*S*) configuration to mecambrine is supported by circular dichroism data (58).

The mecambrine literature is somewhat confused in that the alkaloid was independently isolated and studied under the name *fugapavine*, for which structure **46** was at first proposed; in this regard, isofugapavine is also synonomous with mecambroline (**41**) (18, 25, 43, 64, 65).



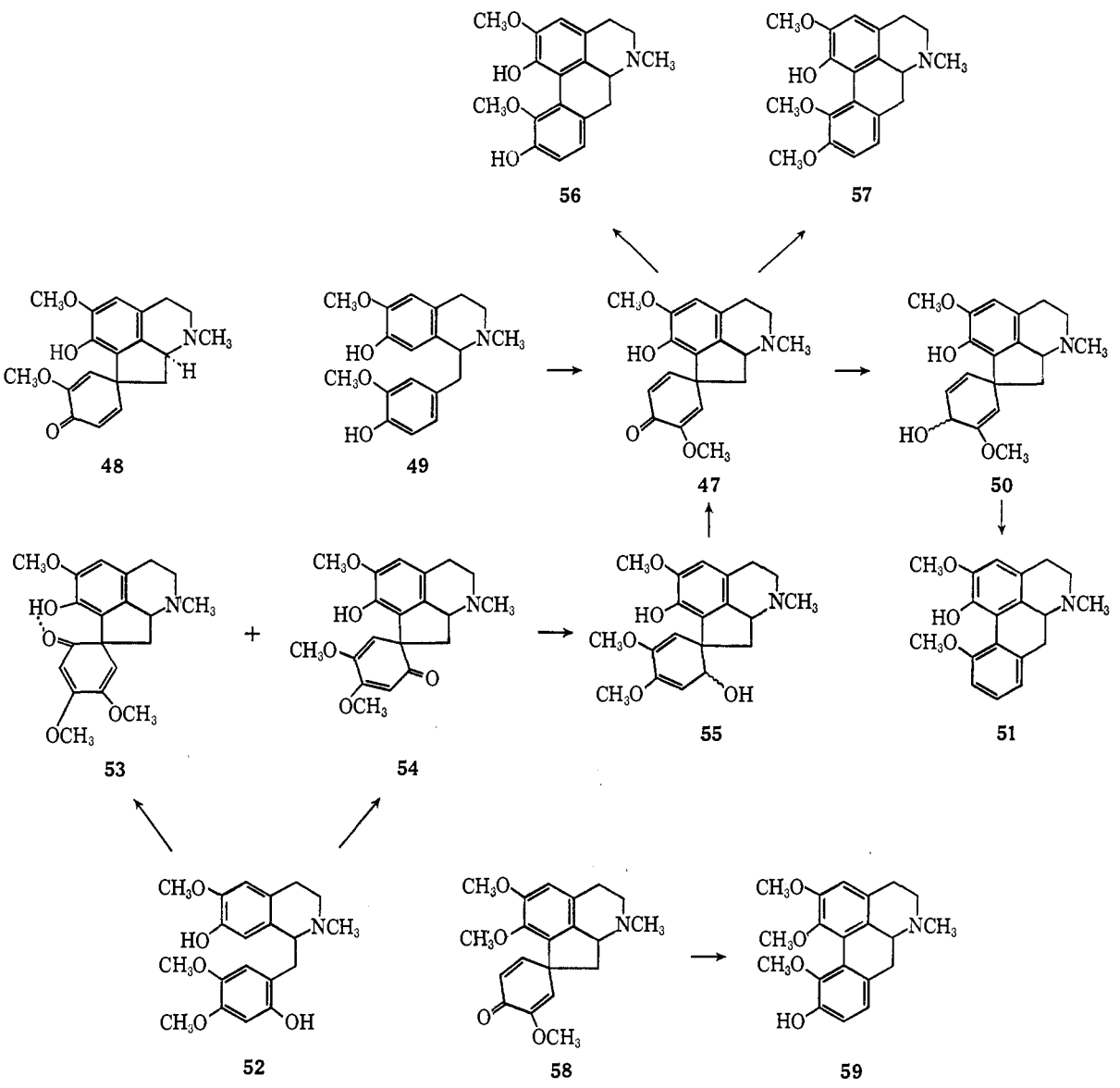
46

G. ORIENTALINONE

The alkaloid orientalinone is unusual in that (±)-orientalinone (**47**) was synthesized and its chemistry studied in some details before the isolation from natural sources of (−)-orientalinone (**48**). Little can be said concerning the natural base, except that it is said to give the same aporphine transformation products (identified only chromatographically) as (±)-orientalinone (8, 32). The absolute configuration of (−)-orientalinone has not been deduced in the literature; it may be assumed to have the L (or *S*) configuration (as in **48**), in view of its negative rotation (see also ref 10).

The first synthesis of (±)-orientalinone (**47**) was carried out by intramolecular oxidative coupling of (±)-orientaline (**49**), using potassium ferricyanide as the oxidizing agent; the crude dienone fraction (4% yield) contains orientalinone among other products. Reduction of (±)-orientalinone with sodium borohydride gives a dienol mixture (**50**) which undergoes the dienol–benzene rearrangement under acid conditions to yield (±)-isothebaine (**51**) in good yield (9). By resolving the starting benzylisoquinoline, syntheses of (+)-isothebaine and (−)-orientalinone have also been achieved (10).

The second synthesis of (±)-orientalinone involves a more complex series of steps which, however, was claimed to lead to an assignment of configuration to the unsymmetrical spirodienone ring. Thus, ferricyanide oxidation of the diphenolic base **52** yields a mixture of two 2,4-dienones (**53** and **54**); the hydrogen-bonded structure **53** was assigned to that isomer which was adsorbed more weakly on alumina. Whereas the isomer



53 was said to be resistant to borohydride reduction, isomer 54 was reduced to a dienol mixture (55) which was converted to (±)-orientalinone under mild aqueous acid conditions. Since orientalinone is obtained starting with the nonhydrogen-bonded 2,4-dienone (54), it must have the relative orientation of the dienone ring as shown in structure 47 (34, 35). Carrying this reasoning one step further, the complete stereochemistry of natural (−)-orientalinone may be as shown in structure 48.[3]

The dienone–phenol rearrangement of (±)-orientalinone gives different products depending upon the solvent used. Thus, rearrangement of (±)-orientalinone with a few drops of concentrated hydrochloric acid in acetic acid gives the normal product, (±)-isocorytuberine (56); on the other hand, the same rearrangement in dry methanol containing hydrogen chloride yields (±)-corydine (57) (34, 35).

The synthesis of (±)-O-methylorientalinone (58) from the 2,4-dienone mixture (53 and 54) and its acid rearrangement to (±)-pseudocorydine (59) has also been reported (51).

III. Chemistry of Reduced Proaporphines

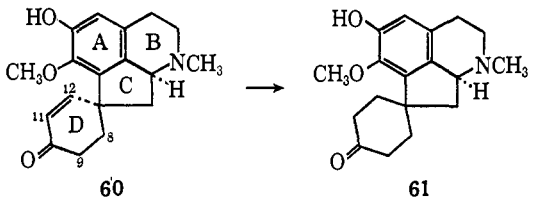
This section discusses the chemistry of the reduced proaporphines. It will be noted that, in all these examples of reduced proaporphines isolated from natural sources, establishment of structures has been achieved by correlating derivatives of these alkaloids with derivatives of proaporphines with confirmed structures.

A. LINEARISINE

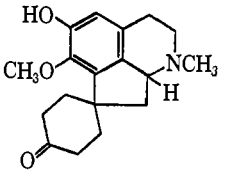
The proaporphine-type skeleton and aromatic substitution pattern of linearisine (60) was established by

(3) Reviewers' Note—It is claimed (ref 35) that Dreiding models of isomers 53 and 54 show that hydrogen bonding between carbonyl and hydroxyl groups is possible in 53 but not in 54. According to our personal observations, however, no such differences between 53 and 54 could be detected, Dreiding models suggesting no appreciable hydrogen bonding in either isomer. If this is, indeed, the case, there is no longer any validity for the assignment of configuration to C-7a of orientalinone.

comparing the dihydro product **61** with the epimeric N-methyltetrahydrocrotonosine (**62**) (29, 31).



60 **61**

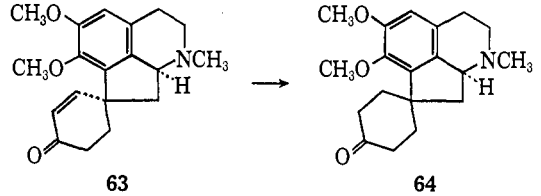


62

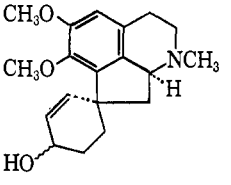
The configuration of the 7a-spiro-carbon was established as 7aR by CD studies (58) which placed the olefin in ring D at the C-11, C-12 rather than C-8, C-9 position.

B. AMURONINE

Amuronine (**63**) (22) was shown to be identical with (±)-dihydropronuciferine (13), and dihydroamuronine hydrobromide was identical with (±)-tetrahydropronuciferine hydrobromide (22). Reduction gave the dihydro derivative (**64**).



63 **64**



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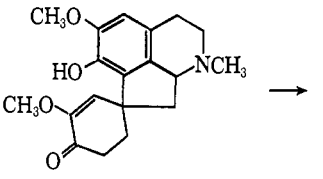
The configuration of the 6a and 7a centers were proposed on the basis of CD studies (58), and these assignments were confirmed by a direct comparison of amuronine methiodide and O-methyllinearisine methiodide (59).

C. AMUROLINE

Amuroline (**65**) which occurs in *Papaver nudicaule* (22) with amuroline (**63**) was transformed into amuronine by manganese dioxide oxidation. Reduction of amuronine with $NaBH_4$ produced epiamuroline (22).

D. DIHYDROORIENTALINONE

Dihydroorientalinone was established as structure **66** by transforming this alkaloid and orientalinone (**48**) by $NaBH_4$ reduction to an identical mixture of epimeric alconols (**67**) (8). The apparently specific reduction of the unsubstituted double bond of **48** is worthy of note.



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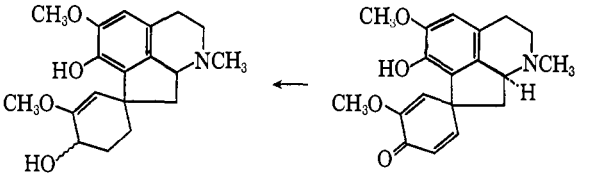


67 **48**

E. BASE E ACETATE

This minor alkaloid (**68**) was isolated from alkaloid residues after acetylation (**27**); it almost certainly occurs naturally as the unacetylated base **68a**.

Catalytic reduction of base E acetate resulted in the loss of the alcoholic acetate with concomitant reduction of the double bond. This indicated the presence of an allylic system and yielded the compound **69**. Hydrolysis of the remaining acetate followed by methylation with methyl iodide gave compound **70**. This was identical with the compound obtained by olefinic reduction, Wolff–Kishner reduction, and, finally, methyl iodide methylation of crotonosine (**20**) (26). The decision as to the orientation of the aromatic substituents was made on the basis of nmr evidence and the dissimilarity of the compounds **71**, prepared from crotonosine, and **72**, prepared from base E acetate. The configuration of the alcoholic acetate has still to be determined.

F. LITSERISINE

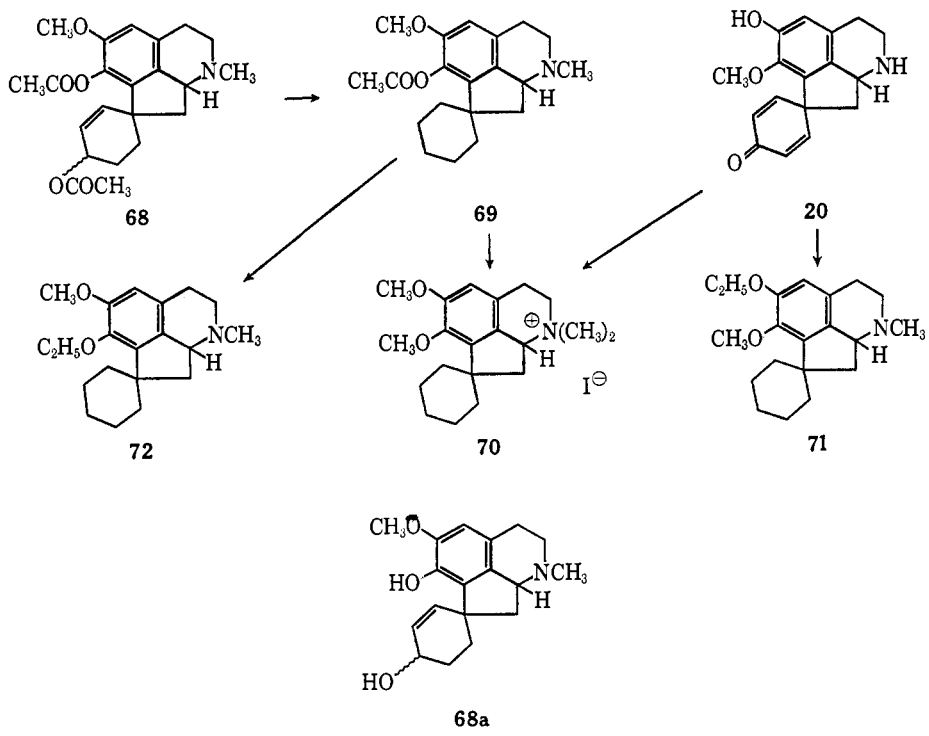
Litserisine (**73**) could be oxidized to the isoquinoline (**74**), and after N-methylation also oxidized to yield N-methyllitserisinone **75** (45).

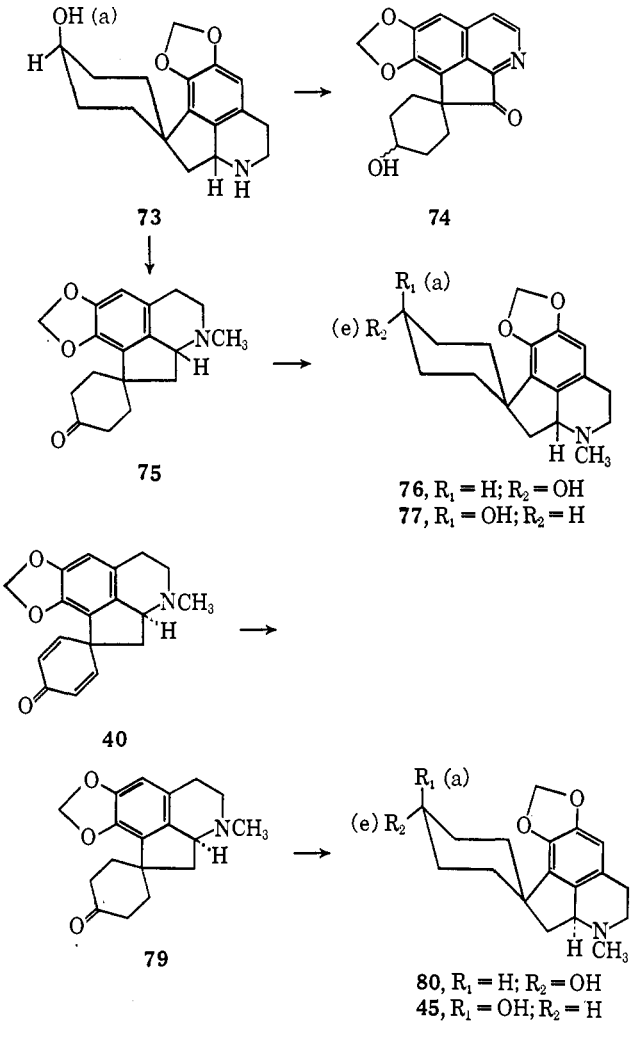
$NaBH_4$ reduction of N-methyllitserisinone (**75**) gave the two hexahydro derivatives, **76** and **77**, the latter being identical with N-methyllitserisine.

By using an analogous argument to that used by Bernauer (17) (see the discussion on pronuciferine), a comparison of products **80** and **45** obtained from mecambrine (**40**) proved that hexahydromecambrine (**45**) was the enantiomer of N-methyllitserisine (**77**) and so fully describes the configuration and conformation of litserisine (**73**) (46).

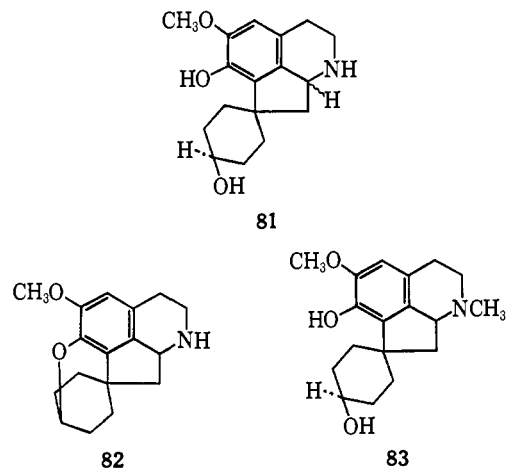
G. OREOLINE

Structure **81** has been assigned to this alkaloid. Structural proof was based on a direct comparison of





the N,O-dimethyl methiodide derivative with (±)-hexahydropronuciferine methiodide and on the elimination of water on acid treatment of oreoline to yield



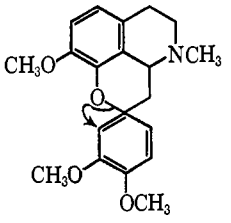
most probably the epoxy compound **82**. The interesting epoxy structure **82** was supported by mass spectral evidence (mol wt 271) and the nonphenolic character of the compound, acetylation of which yielded only a monoacetyl derivative, namely the N-acetyl derivative. Dreiding models also illustrate the feasibility and lack of strain in such a system (41).

H. N-METHYLOREOLINE

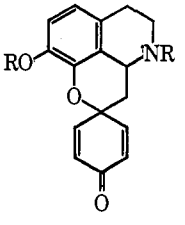
This phenolic alkaloid (**83**) was correlated to oreoline by N-methylation of the latter compound and was also shown to yield hexahydropronuciferine on O-methylation (41).

IV. Possible New Alkaloid Types Related to the Proaporphines

Cularine (**84**) is the best known representative of a small group of alkaloids which differ from the aporphines in that the two aromatic rings are linked *via* an ether bridge rather than directly. The intermediacy of 1,4-dienones of the type **85** in the biogenesis of cularine and related alkaloids seems reasonable. Recently,

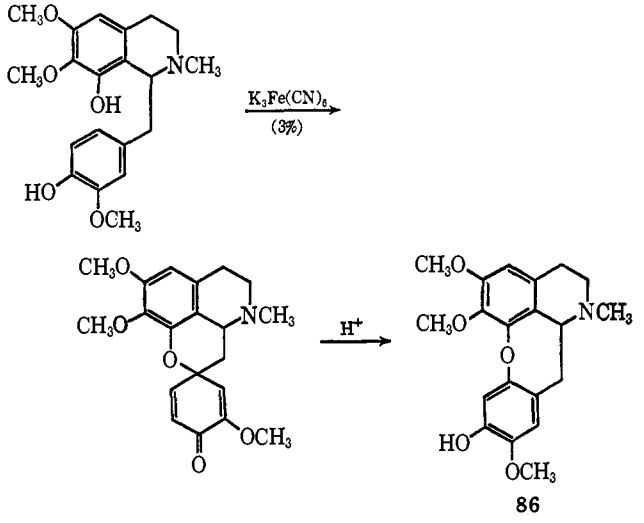


84



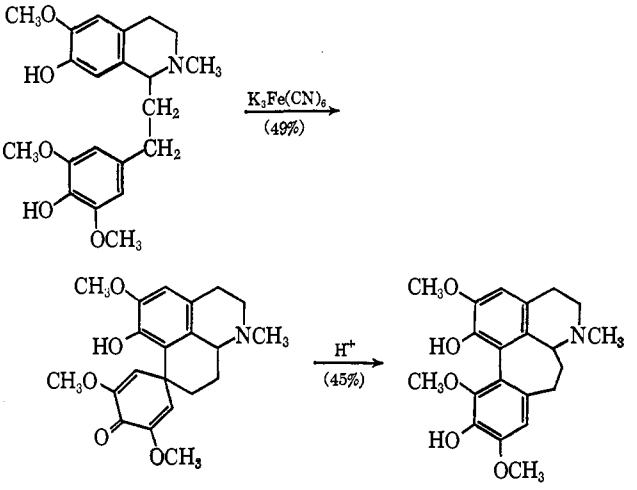
85

a biogenetically patterned synthesis of a cularine-type base (**86**, not a natural alkaloid) was reported in which a derivative of **85** was isolated in low yield (3%) as an intermediate (36). The synthesis is outlined below.

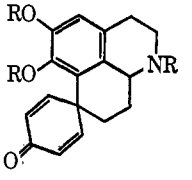


86

The recent announcement of the discovery of a new class of alkaloids, the homoaporphines (typified by multifloramine (**87**), was coupled with the description of the synthesis of several of these bases using as the key step the oxidative coupling of a diphenol to a compound having the homoproaporphine skeleton (**88**) (7). The synthesis of multifloramine (**87**) is outlined below; the remarkably high yield (49%) in the formation of the dienone intermediate is worthy of note.



87



88

It may be predicted with reasonable certainty that new types of alkaloids derived from the 1,4-dienone systems **85** and **88** will soon be isolated from natural sources (see Addendum).

V. Spectroscopy

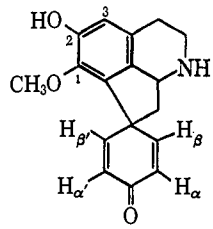
The use of physical tools, namely uv, ir, nmr, and mass spectroscopy can be of great value in the identification and structural elucidation of compounds of this new group of alkaloids. The discussion in this section will be confined to the spectral characteristics of the proaporphines (see Table I for data on the reduced proaporphines).

The uv spectra of these compounds are consistent with that expected from the summation curves of homoveratrylamine and 4-methyl-4-allyl-cyclohex-2,5-dien-1-one, and they usually show three absorption bands: λ_{max}^{EtOH} ~215 mμ (log ε 4.40), ~230 (4.4), and ~285 (3.50), the latter sometimes appearing as a split peak. Circular dichroism studies have been used in assigning the 6a configuration to these compounds (58).

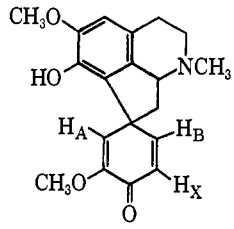
The ir spectra of proaporphines have been determined in KBr, Nujol, and chloroform, and, although one usually notes small band shifts in the different media, most proaporphines show characteristic cyclohexadienone absorption bands at ~1665, 1622, and 1605 cm^{-1}. In the case of substituted cyclohexadienones (*e.g.*, orientalinone), no significant changes are noted in this region of the ir spectrum.

The absorption bands (~3200 cm^{-1}) indicating the presence of a secondary amine can be clearly seen in the appropriate compounds; in some bases (*e.g.*, crotonosine) containing a phenolic hydroxyl group, strong intermolecular hydrogen bonding involving this group can be observed.

The nmr spectra of these compounds are not only characteristic of the 1,4-dienone structural type, but they also yield information on the location of the aromatic substituents. Part of the spectrum of crotonosine **20** (in DMSO) is reproduced in Figure 1 to illustrate the location and coupling of the cyclohexadienone ring pro-



20



47

tons and also the location of the C-3 proton. The olefinic pattern is greatly simplified in the case of orientalinone (**47**) showing the H_A proton at τ 4.08 (J_{AB} = 2.5 cps) as a doublet, H_X also as a doublet at τ 3.67 (J_{BX} = 10 cps), and H_B appearing as a quartet centered at τ 3.21, being coupled by H_X and transannularly by H_A.

The position of the methoxyl group or groups in the nmr gives information of their location on the aromatic ring. The shielding by the cyclohexadienone ring on a methoxyl group at C-1 causes a shift from the normal τ 6.18 position (*e.g.*, at C-2) to $\sim\tau$ 6.42 (29). Nmr control has also been very helpful in deuterium labeling experiments used in establishing the substitution pattern of crotonosine and glaziovine (29). By using suitable models, a comparison of the nmr spectra of phenolic proaporphines and their O-acetyl derivatives has also been successfully used in assisting with the assignment of the aromatic substitution pattern (26).

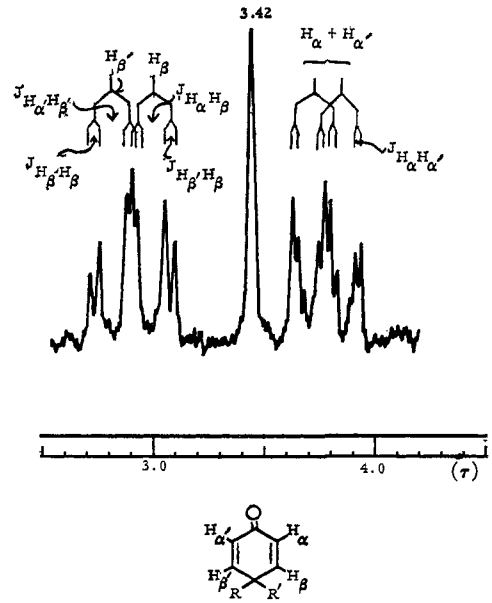
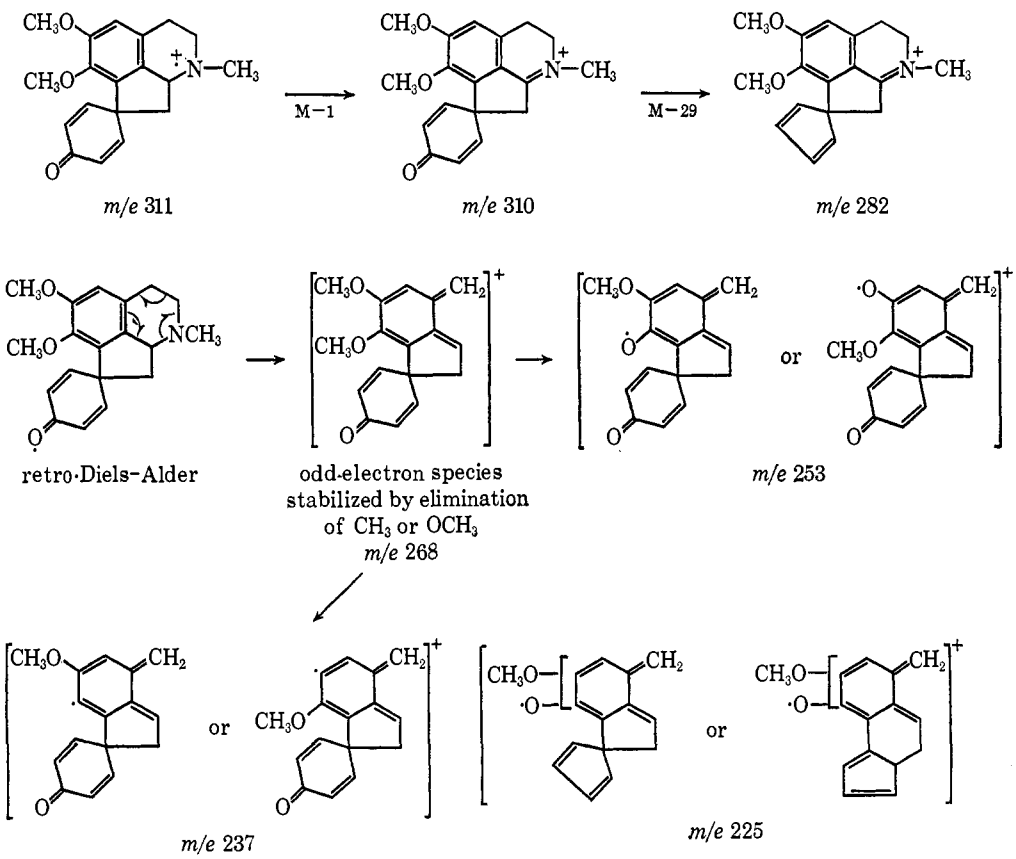


Figure 1.—Partial nmr spectrum of crotonosine.

This method depends on the deshielding effect of an acetoxyl group on the *ortho* proton at C-3.

SCHEME I



Two major mass spectrometric studies have been made of the proaporphine alkaloids (1, 60). In all compounds and their derivatives (except O-ethylcrotonosine) the molecular peak was the base peak (1). Scheme I succinctly summarizes the major fragmenta-

TABLE I

PHYSICAL PROPERTIES[a]

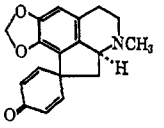
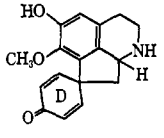
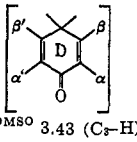
Compound	Derivatives and mp, °C	Optical rotation, deg	Uv, mμ (log ε)	Ir, cm^{-1}	Nmr[c] at 60 Mc/sec	Plant source
Mecambrine (fugapavine), $C_{18}H_{17}NO_3$ 	178–179	$[\alpha]D$ −94 ($CHCl_3$)[57] $[\alpha]D$ −116 ($CHCl_3$)[54]	$\lambda_{max}^{CH_3OH}$ 231 (4.5); 294 (3.70)[57]	ν_{max} 1675[43] ν_{max}^{KBr} 1667 $\nu_{max}^{CHCl_3}$ 1673, 1650, 1630[55]		*Meconopsis cambrica* (L) Vig[42,57] *Papaver fugax* Poir[42,62] *P. caucasicum* Marsch-Bieb.[38] *P. armeniacum* (L) DC[38] *P. triniaefolium* Boiss[38,39] *P. persicum* Lind L.[38,39] *P. polychaetum* Schott et Kotschy[38,39] *P. dubium* L.[53] *P. dubium sp. albiflorum* (Boiss) Dost[54] *P. oveophilum*[56]
	Hydrochloride, 269–270 dec Picrate, 165 Semicarbazone, 237 Oxime, >285 2,4-DNP, >285 dec					
	Hexahydromecambrine, 267–269	$[\alpha]D$ −38.2[43]				
	Tetrahydromecambrine, 144–146[45]		λ_{max}^{EtOH} 240 sh (3.64), 290 (3.58)	$\nu_{max}^{CHCl_3}$ 1715		
	Hexahydromecambrine-A, 186 *Hexahydromecambrine-B, 256	$[\alpha]D$ −47 (CH_3OH)[46] $[\alpha]D$ −44[46]				
Crotonosine, $C_{17}H_{17}NO_3$ 	197 dec, >300[27]	$[\alpha]^{28}n$ +180 (CH_3OH)	λ_{max}^{EtOH} 226 (4.30), 235 (4.33), 282 (3.37), 290 (3.47)[27]	ν_{max}^{Nujol} 3220, 2600, 1664, 1622, 858[27]	 τ^{DMSO} 3.43 (C_8–H), $\beta\beta'$ 2.96 ($J_{\beta\beta'}$ = 2.5 cps) (8 lines) ($J_{\alpha'\beta'}$ = 10 cps), $\alpha\alpha'$ 3.80 ($J_{\alpha\alpha'}$ = 1.5 cps) (8 lines)	*Croton linearis* Jacq.[27] *C. discolor* Wild.[29]
	Methiodide, >250 dec			ν_{max}^{Nujol} 3333, 1667		
	N,O-Diacetyl deriv, 203–205[27]			ν_{max}^{Nujol} 1775, 1670, 1640, 1628, 1258	τ^{CDCl_3} 7.82 ($NCOCH_3$), 6.42 (OCH_3), 7.71 ($OCOCH_3$), 3.07 (C_8–H), 4.80 (C_{6a}–H), $\beta\beta'$ 2.95 ($J_{\beta\beta'}$ = 2.5 cps), $\alpha\alpha'$ 3.75 ($J_{\alpha\alpha'}$ = 1.6 cps)	
	N,O-Diacetyltetrahydrocrotonosine, 106–108[29]			$\nu_{max}^{CHCl_3}$ 1760, 1715, 1630	[τ^{CDCl_3} 7.80 ($NCOCH_3$), 6.18 (OCH_3), 7.55 ($OCOCH_3$), 3.25 (C-3), 5.1 (C-6a)][29]	
	N-Methyltetrahydrocrotonosine, 225–228 dec	$[\alpha]^{20}D$ +59 (CH_3OH)[29]		ν_{max}^{Nujol} 1700		
	N-Acetylcrotonosine, 205[29]			ν_{max}^{Nujol} 3150, 1652, 1625		
	N-Acetyl-O-ethyl deriv, 170–174[29]					
	(+)-N,O-Dimethyldesoxyhexahydrocrotonosine CH_3I, 231–235	$[\alpha]^{25}D$ +2.3 (CH_3OH)[23]				

TABLE I (*Continued*)

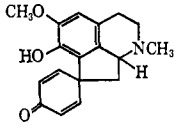
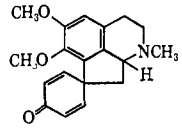
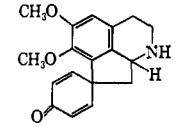
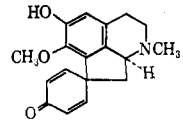
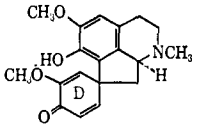
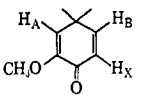
Compound	Derivatives and mp, °C	Optical rotation, deg	Uv, mμ (log ε)	Ir, cm^{-1}	Nmr[c] at 60 Mc/sec	Plant source
Glaziovine, $C_{18}H_{19}NO_3$ 	235–237 dec[25]	$[\alpha]_D$ +7 ($CHCl_3$)	λ_{max}^{EtOH} 288 (3.57) $\lambda_{max}^{EtOH+KOH}$ 308 (3.74)	$\nu_{max}^{CHCl_3}$ 1657, 1619[25]	τ^{CDCl_3} 7.6 (NCH_3), 6.15 (OCH_3), 4.0 (OH), 3.35 (C_8–H), $\beta\beta'$ 3.40 → 3.75 $\alpha\alpha'$ 2.7 → 3.3[25]	*Ocotea glaziovii* Mez.[25] *Papaver caucasicum* Marsch-Bieb.[40b]
	Picrate, 199–203 Tetrahydroglaziovine, 112–116			$\nu_{max}^{CHCl_3}$ 3520, 1699	7.65 (NCH_3), 6.25 (OCH_3), 4.7–5.5 (OH), 3.5 (C_8–H)[25]	
	Methiodide, 251–253[25] Methochloride hydrate, 226–229					
Pronuciferine (base A), $C_{19}H_{21}NO_3$ 	127–129[15]	$[\alpha]^{25}D$ +99 ($CHCl_3$)[17] $[\alpha]^{25}D$ +105.8 (EtOH)[27]	λ_{max}^{EtOH} 230 (4.41), 282 (3.49)	ν_{max}^{KBr} 1656, 1634, 1613[15] $\nu_{max}^{CHCl_3}$ 1656, 1618[15]	τ^{CDCl_3} 3.42 (C_8–H), 3.9 → 3.5 and 3.3 → 2.9 (dienone), 7.59 (NCH_3), 6.43 (OCH_3), 6.22 (OCH_3)[17]	*Nelumbo nucifera* Gaertn.[15,16,60] *Croton linearis* Jacq.[27] *Stephania glabra* Miers[19] *Papaver caucasicum* Marsch-Bieb.[38,47b]
						P. triniaefolium Boiss[38,39] *P. polychaetum* Schott et Korschy[38,39]
			λ_{max}^{EtOH} 227 (4.40), 230 (4.41), 280 (3.55), 285 (3.35)[27]	ν_{max}^{Nujol} 1658, 1618; 1605, 1486[27]		*P. fugax* Poir[39] *P. persium* Lind,[39b]
	Oxime HCl, >210, dec[17] Oxalate, 170–172 Methiodide, 244–245 dec					
	Hydrochloride, >190 dec Hydriodide, 225–227 dec Hydrobromide, 224–227 dec	$[\alpha]^{20}D$ +101.1	λ_{max}^{EtOH} 229 (4.40), 278 (3.42)			
	Dihydropronuciferine-I, 142–144		λ_{max}^{EtOH} 287 (3.37)	ν_{max}^{KBr} 3155 $\nu_{max}^{CHCl_3}$ 3597		
	Hexahydropronuciferine-I HCl, 253–254 Hexahydropronuciferine-II HCl, 205–208		λ_{max}^{EtOH} 225 (3.95), 280 (3.29)			
Stepharine, $C_{18}H_{19}NO_3$ 	179–181[19]	$[\alpha]^{26}D$ +143 ($CHCl_3$)	λ_{max}^{EtOH} 213 (4.62), 231 (4.44), 284 (3.48)[49]	ν_{max} 1665[62]	τ^{CDCl_3} 8.00 (N–H) exchangeable in D_2O, 6.18 and 6.39 ($2OCH_3$)[62]	*Stephani glabra* Miers[19] *S. rotunda* Loureiro[60,62] *Pericampylus* formosanus[61]
	180–183[62]	$[\alpha]^{25}D$ +158[62] ($CHCl_3$)				
	N-Acetyl deriv,[19] 234–235, 220–221[62]	$[\alpha]^{24}D$ −80[19] ($CHCl_3$)		ν_{max} 1660, 1630[62]	τ^{CDCl_3} 7.80 ($NCOCH_3$), 6.13 and 6.35 ($2OCH_3$)[62]	
L-(−)-N-Methylcrotonosine, $C_{18}H_{19}NO_3$ 	218–220 dec	$[\alpha]^{16}D$ −116.5 (CH_3OH)	λ_{max}^{EtOH} 228 (4.29), 282 (3.18), 288 (3.18)[27]	ν_{max}^{Nujol} 1664, 1625[27]	τ^{DMSO} 6.48 (OCH_3), 3.37 (C_8–H), 2.85 ($\beta\beta'$-H_S) (J = 2.5 cps), 3.76 ($\alpha\alpha'$-H_S) ($J\alpha\beta = J\alpha'\beta'$ = 10 cps)[29]	*Croton linearis* Jacq.[27] *Papaver caucasicum* Marsch.-Bieb.[40]

TABLE I (*Continued*)

Compound	Derivatives and mp, °C	Optical rotation, deg	Uv, mμ (log ε)	Ir, cm^{-1}	Nmr[c] at 60 Mc/sec	Plant source
Orientalinone, $C_{19}H_{21}NO_4$ 	230–232 dec[22]	$[\alpha]^{20}D$ −76[22] ± 10 ($CHCl_3$)	$\lambda_{max}^{CH_3OH}$ 231 (4.30), 242 (4.14), 284 (3.77)[22]	ν_{max}^{KBr} 1610, 1640, 1667[22] $\nu_{max}^{CHCl_3}$ 1605, 1630, 1665[9]	3.46 C_3–H  4.08 and 3.57, H_A; J_{AB} = 2.5 cps, H_X; J_{BX} = 10 cps 3.21, H_B coupled to H_A and H_X; J_{AX} = ~0	*Papaver orientale*[8] *P. bracteatum* Lindl[22] [(+)-Orientalinone?][22,37]

Data for Reduced Proaporphines

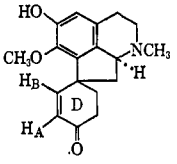
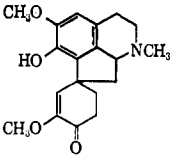
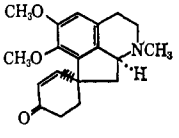
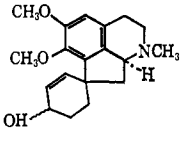
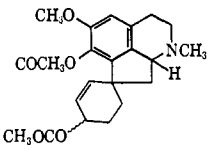
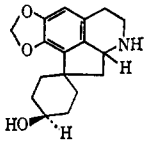
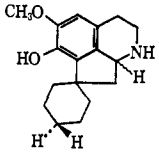
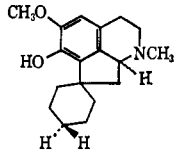
Linearisine, $C_{18}H_{21}NO_5$ 	219–222[27]	$[\alpha]^{28}D$ +116 (CH_3OH)	λ_{max}^{EtOH} 228 (4.30), 282 (3.19), 288 (3.22)[27]	ν_{max}^{Nujol} 1664, 1608, 1600, 1500, 865, 685	τ^{CDCl_3} 7.58 (NCH_3), 6.30 (OCH_3), 3.58 (C_3–H), 3.16 ($\alpha\beta$-unsaturated), 3.92 (ring D) (J_{AB} = 10 cps)[29]	*Croton linearis* Jacq.[27]
	Hydrochloride, <300 dec[27]			ν_{max}^{Nujol} 2632–2353, 1681[27]		
	Dihydrolinearisine (dec. started ~210, mp 225–227)	$[\alpha]^{20}D$ −60.6 (CH_3OH)		ν_{max}^{Nujol} 1700		
	O-Methylinearisine CH_3I, 240–242 dec	$[\alpha]^{150}D$ +81.5[59] (CH_3OH)				
Dihydroorientalinone, $C_{19}H_{23}NO_4$ 	Tetrahydroorientalinone	$[\alpha]D$ +50 ($CHCl_3$)[8]		ν_{max} 1680, 1625	τ 6.22, 6.46 ($2OCH_3$), 7.65 (NCH_3), 3.52 (C_3–H), 4.36 (olefinic H)[8]	*Papaver orientale*[8]
Amuronine, $C_{19}H_{23}NO_3$ 	120 and 131–132[22]	$[\alpha]^{22}D$ +124 ($CHCl_3$)	λ_{max}^{EtOH} 225 (4.41), 285 (3.30)	ν_{max}^{KBr} 1680	τ^{CDCl_3} 3.40 (C_3–H), 3.95 and 3.22 (α- and β-Hs), 6.19 and 6.28 ($2OCH_3$), 7.63 (NCH_3), 6.50–8.38 (complex)[22]	*Papaver nudicaule var. amurense*[22] *P. alpinum* L.[22]
	Methiodide, 235–237[22]					
	Dihydroamuronine, 125–126	$[\alpha]^{22}D$ −40 ($CHCl_3$)	τ_{max}^{EtOH} 285 (3.33), 316 (2.96)	ν_{max}^{KBr} 1713	τ^{CDCl_3} 3.42 (C_3–H), 6.21 ($2OCH_3$), 7.62 (NCH_3)	
	Methiodide of dihydroamuronine, 242–244	$[\alpha]^{21}D$ −23 (EtOH)				
	Hydrobromide, 269–270[22]					
Amuroline, $C_{19}H_{23}NO_3$ 	169–170[22]	$[\alpha]^{21}D$ +106 ($CHCl_3$)	$\lambda_{max}^{CH_3OH}$ 285 (3.37)	$\nu_{max}^{CHCl_3}$ 3605		*Papaver nudicaule var. amurense*[22]
	Acetyl deriv, 153–154[22]					

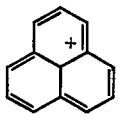
TABLE I (*Continued*)

Compound	Derivatives and mp, °C	Optical rotation, deg	Uv, mμ (log ε)	Ir, cm^{-1}	Nmr[c] at 60 Mc/sec	Plant source
Base E acetate, $C_{22}H_{27}NO_5$ 	190–193[28]	$[\alpha]^{26}D$ −18 (CH_3OH)	λ_{max}^{EtOH} 285 (3.44), sh 278 (3.41)[26]	ν_{max}^{Nujol} 1770, 1724, 1265, 1250, 1622, 1660	τ^{CHCl_3} 3.40 (C_3–H), 4.18–4.22 (olefinic H), 4.74 (H on C bearing $OCOCH_3$), 6.23 (OCH_3), 7.66 (NCH_3), 7.79 (phenolic $OCOCH_3$), 7.95 ($OCOCH_3$), 6.60–8.60 (complex)[26]	*C. linearis* Jacq.[23,27]
	Hydrogenation product,[26] 164–166			ν_{max}^{Nujol} 1750, 1260		
Litserisine, $C_{17}H_{21}NO_3$ 	156[44]	$[\alpha]^{22}D$ +67 (EtOH)	λ_{max}^{EtOH} 240 sh (3.57), 291 (3.54)[44]		τ^{CDCl_3} 3.57 s (C_3–H), 4.17 q ($-OCH_2O$), 6.02 m, 6.14 m[45]	*Neolitsea sericea* (Blume) *koidz* (Lauraceae)[44,48]
	Hydrobromide, 278[44]					
	N,O-Diacetate, 154		λ_{max}^{EtOH} 240 sh (3.61), 288 (3.55)	ν_{max}^{Nujol} 1757, 1629	τ^{CDCl_3} 3.56 (C_3–H), 4.16 ($-OCH_2O$), (q, J = 12 cps), 6.10 >CHOH (m), 7.65 (NCH_3)[46]	
	Acetyl-N-methyl-litserisine,[46] 152			$\nu_{max}^{CHCl_3}$ 1730	τ^{CDCl_3} 3.54 (C_3–H), 4.12 ($-OCH_2O-$), 4.98 ($-CHOCOCH_3$) (m), 7.63 (NCH_3), 7.91 $-COCH_3$[46]	
Oreoline, $C_{17}H_{23}NO_3$ 	234–236[41]					*Papaver oreophilum* Rupr.[41,48]
	Methiodide,[41] 259–261	$[\alpha]^{20}D$ −87 (EtOH)	$\lambda_{max}^{CH_3OH}$ 285 (3.58)[41]			
N-Methyloreoline, $C_{18}H_{25}NO_3$ 	192–193[41]		$\lambda_{max}^{CH_3OH}$ 285 (3.48)			*Papaver oreophilum* Rupr.[41,48]

[a] An asterisk denotes identical compounds. References treated as superscript numbers. [b] See Addendum. [c] d = doublet, m = multiplet, q = quartet, s = singlet.

tion pattern of the proaporphines. Pronuciferine is used as a typical example.

The spectra of all these compounds show a small peak due to loss of methyl and hydroxyl; in the spectra of N-acetyl compounds (*e.g.*, N-acetylstepharine, N,O-diacetylcrotonosine) the retro Diels–Alder fragmentation is often overshadowed by a process involving the transfer of an H atom as outlined in Scheme II (1).



89

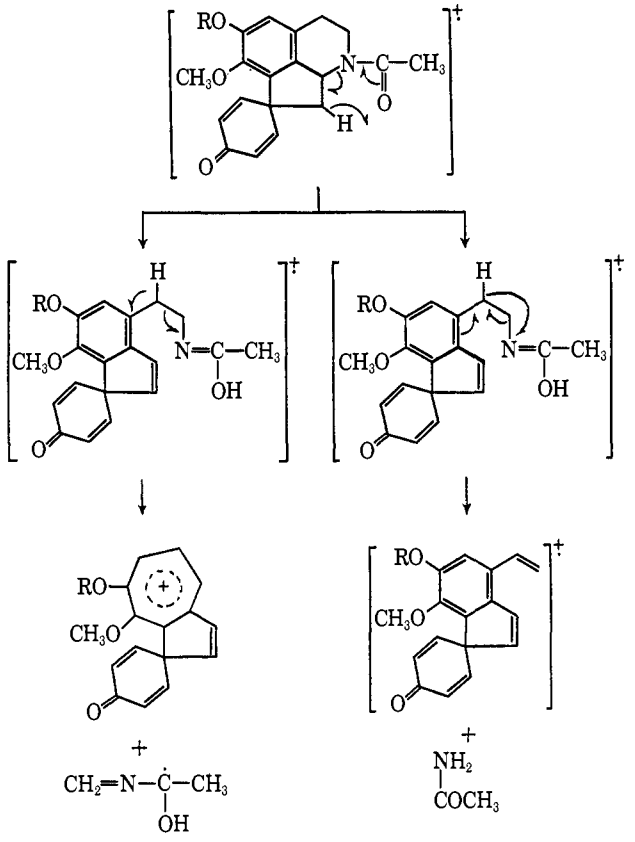
All of the spectra of the proaporphines contain a fragment at *m/e* 165.069 ($C_{13}H_9$), probably due to the perinaphthenyl cation **89** (1).

VI. BIOSYNTHESIS

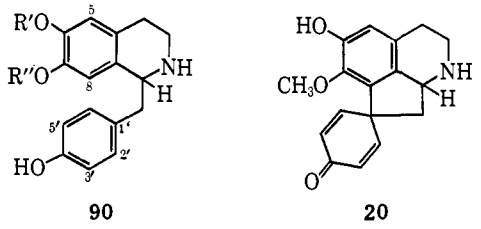
The role of oxidative cyclizations of 1-benzylisoquinolines in the production of aporphine alkaloids has now been placed beyond doubt by *in vivo* and *in vitro* studies.

The use of radioisotopically labeled compounds greatly facilitated the *in vivo* studies, and Haynes, *et al.* (28), showed that (+)-[8,3′,5′-$^3H_3$]-coclaurine (**90**, R′ = CH_3; R″ = H) and (±)-[5,8,3′,5-$^3H_4$]-nor-

SCHEME II



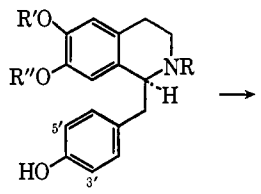
coclaurine fed as the hydrochloride were efficiently incorporated into crotonosine (**20**) in the *Croton linearis* plant. As was expected, the enantiomer of **90**, (−)-[8,3′,5′-$^3H_3$]-coclaurine (**90**, R′ = CH_3; R″ = H), and (±)-[5,5′,3′-$^3H_3$]-isococlaurine (**90**, R′ = H; R″ = CH_3) were not precursors for crotonosine.



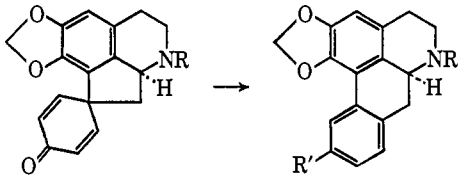
90 **20**

By using (±)-[O-methyl-^{14}C,8,3′,5′-$^3H_3$]-coclaurine (**90**, R′ = CH_3; R″ = H), it was shown that a mechanism involving demethylation (and dilution) and remethylation was in operation in the biosynthesis of crotonosine from coclaurine (4).

Similar studies (3) supported the biogenetic theory (**91** → **92** → **93**) (2) for the formation of roemerine (**93**, R = CH_3; R′ = H) and anonaine [antipode of **93**, R = R′ = H]. Labeled coclaurine, norcoclaurine, and N-methylcoclaurine fed to *Papaver dubium* were incorporated into roemerine by a stereospecific sequence and, as predicted, isococlaurine, which lacks the free hydroxyl group required for phenol coupling, was not incorporated. The presumed dienone intermediates (**92**) were not isolated.



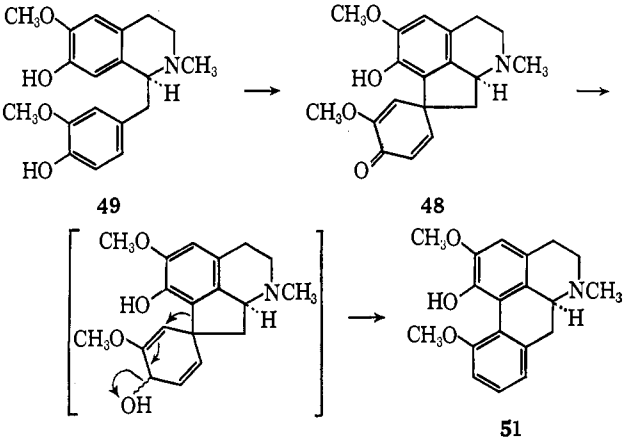
91



92 **93**

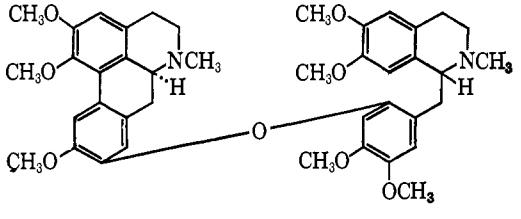
Coclaurine and norcoclaurine were good precursors for (−)-anonaine in *Anona reticulata*, while coclaurine was incorporated into mecambrine (**92**, R = CH_3) in *Meconopsis cambrica*. An unexpected finding in these experiments by Barton, *et al.* (3), was the significant dilution of the labeled methylenedioxy group which was previously shown to be formed by cyclization of an O-methoxyphenol in other alkaloids, but without dilution (5, 12).

The predictions about the role of orientaline (**49**) in the formation of isothebaine (**51**) *via* the proaporphine orientalinone (**48**) (6) were verified by the appropriate feeding experiments in *Papaver orientale* plants (8, 11).



49 **48** **51**

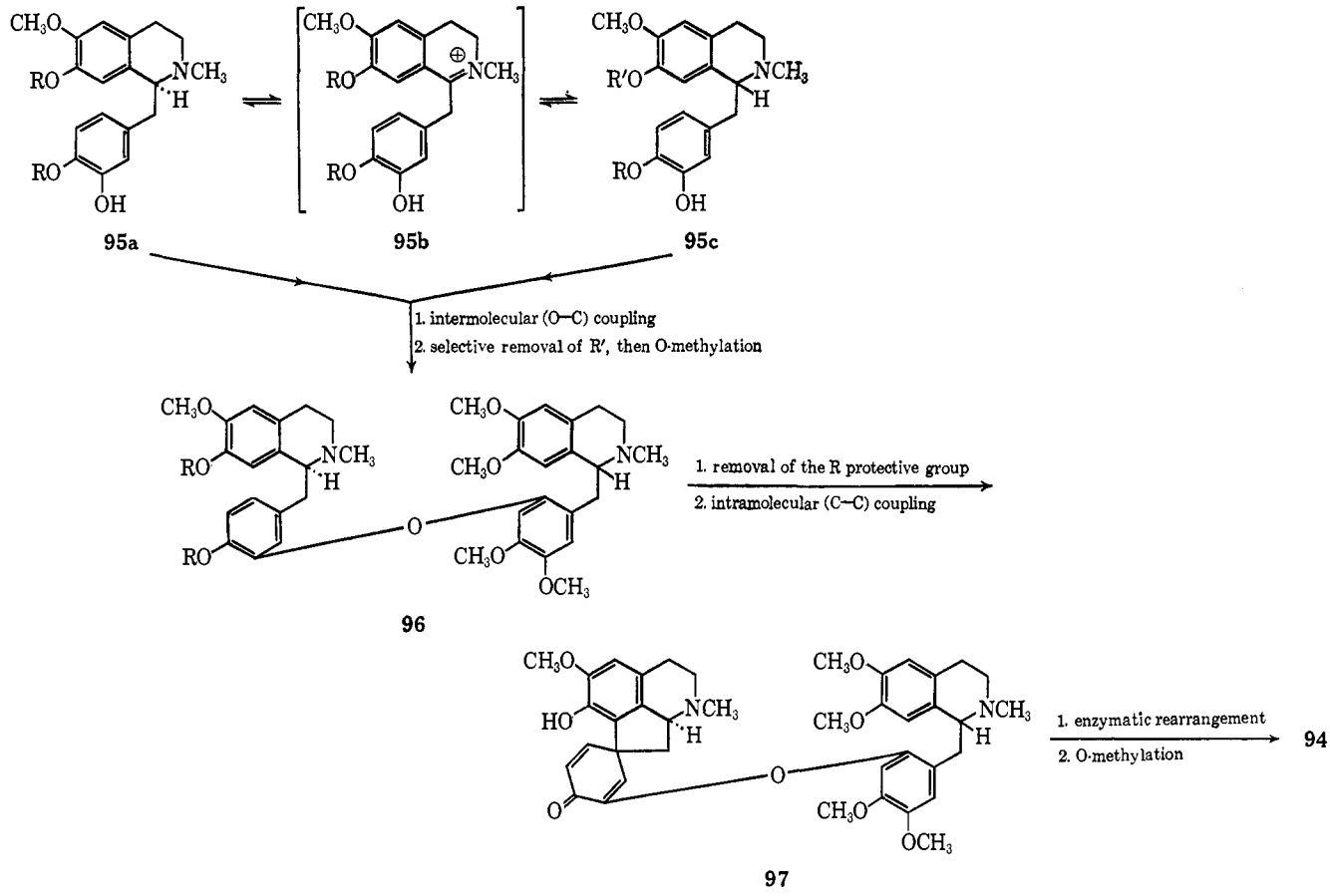
In this, as in the previously described experiments, the absence of randomization of specific radioisotopic labels was proven by appropriate degradative studies, and, although these experiments clearly indicate the biosynthetic pathway for some simple aporphines, further work is required to establish the biogenetic pathway for such dimeric aporphine structures as thalicarpine (**94**).



94

SCHEME III

[R = R′ = protective sugar moiety]



The scheme **95** → **96** → **97** → **94**, involving proaporphine-type intermediates, has recently been suggested to account for the formation of these compounds (33); see Scheme III.

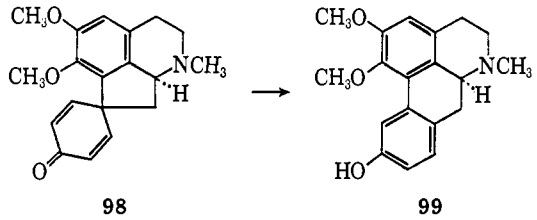
VII. PHARMACOLOGY

Only one report has been made of the pharmacological activity of some members of this group of alkaloids. Gaskin and Feng (24) recently described preliminary findings on the pharmacology of crotonosine, pronuciferine, and their respective methiodides. A full account of this work has now appeared (23). The pharmacological behavior of these compounds can be summarized as being due to their cholinesterase-inhibiting, neuromuscular-blocking, and local anesthetic activities (23). Of particular interest is the fact that both crotonosine and pronuciferine are potent local anesthetics compared with procaine and lignocaine (23).

VIII. ADDENDUM

A few very recent but significant publications came to the attention of the reviewers after the completion of this manuscript. The important points pertaining to proaporphine chemistry are summarized briefly below.

(1) (*S*)-(−)-Pronuciferine (**98**) has been described for the first time (47a). It occurs in both *Papaver persicum* and *P. caucasicum* Marsch.-Bieb.; the previous report (47) that *P. caucasicum* contains (+)-pronuciferine is in error. The following constants are recorded for (−)-pronuciferine: mp 242–244°; $[\alpha]^{20}D$ −109 ± 3° (*c* 0.29, ethanol); $\lambda_{max}^{CH_3OH}$ 230, 280 mμ (log ε 4.40, 3.53); ν_{max}^{KBr} 1665 cm^{-1}. Acid rearrangement of **98** gives (+)-nuciferoline (**99**), which also occurs naturally in *P. caucasicum* (47a).



(2) (+)-Stepharine (**15**) has been isolated from *Laurelia novae-zelandiae* Acunn (17a).

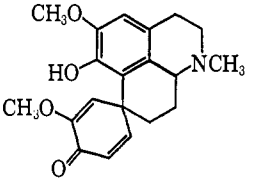
(3) The first naturally occurring homoproaporphine alkaloids have been reported. Thus, kreysiginone (**100**) and dihydrokreysiginone (**101**) have been isolated from *Kreysigia multiflora* (12a). Data bearing upon

the stereochemistry of **100** and **101** have not yet been divulged. The following constants have been given.

Kreysiginone (12a): mp 155°, then mp 194° dec; M^+ 341; τ 4.05 (d, H_A, J = 3 cps), 3.72 (d, H_X, J = 10 cps), 3.17 (dd, H_B, J = 3 and 10 cps), 3.48 (s, 1H), 6.24 (s, 3H), 6.46 (s, 3H), 7.55 (s, 3H); $\nu_{max}^{CHCl_3}$ 3550, 1614, 1633, 1659 cm^{-1}; λ_{max}^{EtOH} 214, 243, 287 mμ (log ϵ 4.54, 4.15, 3.78).

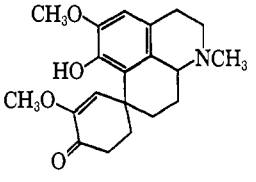
Dihydrokreysiginone (12a): mp 217–222° dec; M^+ 343; τ 4.26 (s, 1H), 3.46 (s, 1H), 6.16 (s, 3H), 6.46 (s, 3H), 7.43 (s, 3H); $\nu_{max}^{CHCl_3}$ 3500, 1678, 1635, 1610 cm^{-1}; λ_{max}^{EtOH} 220, 269 mμ.

(4) Intramolecular oxidative coupling has been employed in the synthesis of the following racemic homoproaporphines: kreysiginone (**100**) (12a, 35b), epikreysiginone (**102**) (12a, 35b), and the dienone **103** (35b). Compounds **102** and **103** are not yet known from natural sources.

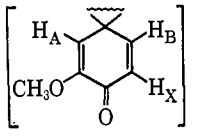


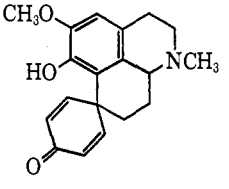
100

102, 6a epimer of **100**



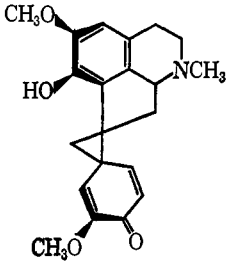
101



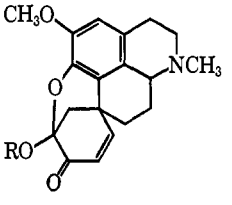


103

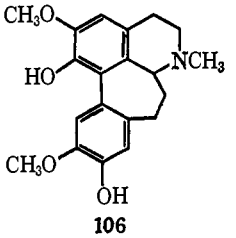
Kametani and coworkers (36a) have recently indicated that (±)-kreysiginone (**100**) can best be represented by structure **100b**, in which the dienone ring is not at right angles to the benzene ring. When treated with concentrated hydrochloric acid in glacial acetic acid at 20° under nitrogen for 48 hr, kreysiginone yields compounds **104, 105,** and **106**. Compound **104** can be converted to **105** by acid hydrolysis at room temperature.



100b



104, R = CH_3
105, R = H

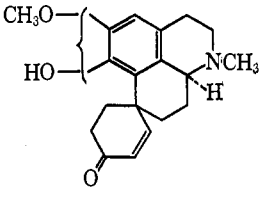


106

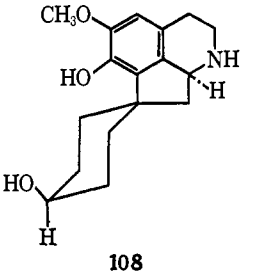
(5) The full paper on the biosynthesis of mecambrine, roemerine, and anonaine has now appeared (3a). Tritium-labeled mecambrine (**92**, R = CH_3; ^3H in α positions of the dienone ring) was well incorporated into roemerine (**93**, R = CH_3; R′ = H) (2.34%) in *P. dubium* and into mecambroline (**93**, R = CH_3; R′ = OH) (2.76%) in *M. cambrine*, indicating that formation of the methylenedioxy group occurs at the dienone stage.

(6) From nmr studies, the hydroxyl group at C-10 in amuroline (**65**) has been assigned the α position based upon the assumption that the preferred conformation of ring D is a half-chair (35a).

(7) Bulbocodine, mp 220–222°, $[\alpha]^{22}D$ +111° ($CHCl_3$), $C_{19}H_{23}NO_3$, has been isolated from *Bulbocodium vernum L.* and on the basis of uv, ir, mass spectral, and CD data has been assigned structure **107** recently (49a).



107



108

Oridine from *Papaver oreophilum* has now been characterized as the reduced proaporphine **108**, in which the ring D hydroxyl group is axial (49b). Oreoline (**81**), which was also isolated from this plant (41), must either be identical with oridine or differ only in configuration at C-6a.

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