methylsilane as internal standard showed the two equivalent methyl groups at $\tau$ 8.05, the other methyl at $\tau$ 7.70, the malononitrile hydrogen at $\tau$ 4.94, the two equivalent aromatic hydrogens at $\tau$ 3.07, and the other four aromatic hydrogens as a weak, strong, strong, weak pattern centered at $\tau$ 2.65.

*Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.90; H, 6.03; N, 10.50.

**Acknowledgment.**—The advice and encouragement of Dr. R. E. Benson is greatly appreciated.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

# Thalictrum Alkaloids. III.[1] The Structure, Configuration, and Total Synthesis of Thalicarpine, a Novel Dimeric Aporphine–Benzylisoquinoline Alkaloid[2]

BY S. MORRIS KUPCHAN AND NAOKATA YOKOYAMA[3]

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Evidence is presented for assignment of structure and configuration (I) to thalicarpine. Elementary analysis of the alkaloid and the Hofmann degradation products IV and V supported a $C_{41}H_{48}O_8N_2$ molecular formula for thalicarpine. Sodium in liquid ammonia reduction of I afforded two nonphenolic bases (VI and VII) and a phenolic base (VIII). Base VI was characterized as the methiodide XVI and the Hofmann methine XIX. Positive identification as 3,6-dimethoxyaporphine was achieved by direct comparison with an authentic sample prepared from XIII. Phenol VIII was characterized as the hydriodide and the O-methyl methiodide (XXI). Hofmann degradation of XXI gave a methylmethine (XXIII). To locate the phenolic hydroxyl group, VIII was converted to the O-ethyl ethiodide (XX), which upon Hofmann degradation yielded the methine XXII. Methylation of XXII gave the methine methiodide XXIV, and Hofmann degradation gave the O-ethyl-des-N-methine (XXVI). Oxidation of XXVI with potassium permanganate gave 2-ethoxy-4,5-dimethoxybenzoic acid (XXV). Synthesis of thalicarpine was accomplished by modified Ullmann condensation of (−)-6-bromolaudanosine (XXVII) with isocorydine (XXVIII). Since practical total syntheses of laudanosine and of isocorydine had previously been accomplished, the condensation reaction constituted a total synthesis of thalicarpine. Furthermore, since the absolute configurations of (−)-laudanosine and of isocorydine had been elucidated earlier, the synthesis served also to establish the absolute configuration of thalicarpine.

Thalicarpine is a hypotensive alkaloid from *Thalictrum dasycarpum* Fisch. and Lall., and its isolation and preliminary characterization have recently been reported.[4] It is the purpose of this paper to present, in detail, the elucidation of structure and absolute configuration (I) and the total synthesis of thalicarpine. Thalicarpine represents a novel type of alkaloid; it appears to be the first recognized dimeric alkaloid which contains an aporphine moiety.

The molecular formula $C_{41}H_{48}O_8N_2$ was assigned for thalicarpine on the basis of elemental analysis and molecular weight determination by nonaqueous titration. Analysis showed the presence of seven O-methyl groups and two N-methyl groups. The n.m.r. spectrum in deuterated chloroform solution supports the formula, showing six N-methyl protons, twenty-one O-methyl protons, fourteen aliphatic protons, and seven aromatic protons. The infrared spectrum indicates the presence of aromatic rings and aromatic O-methyl groups, but absence of hydroxyl, carbonyl, and isolated double bonds.

A sequence of derivatives was prepared to seek confirmation of the empirical formula as well as to provide conversion products useful for structure elucidation.[4] Treatment of thalicarpine with methyl iodide afforded a product which resisted all attempts at crystallization. However, treatment of the amorphous methiodide II with alkali yielded a Hofmann methine (III) which was converted to a crystalline methiodide (IV). Analysis afforded results which support a $C_{45}H_{58}O_8N_2I_2$ formula for the Hofmann methine methiodide. A second Hofmann degradation yielded a des-N-methine (V), which afforded analytical results indicative of a $C_{39}H_{38}O_8$ empirical formula. The formulas of both methine derivatives support the $C_{41}H_{48}O_8N_2$ formula for thalicarpine.

It is well known that diphenyl ethers can be reductively cleaved into phenolic and nonphenolic products by the action of metallic sodium in liquid ammonia.[5] The latter reduction was carried out on thalicarpine to cleave the suspected diphenyl ether linkage and split the molecule into two smaller moieties. Two nonphenolic bases (VI and VII) and a phenolic base (VIII) were obtained from the reaction. The yield of VIII was the same regardless of the reaction conditions, but the ratio of the yields of VI and VII varied according to the conditions used for the reaction. The stronger the conditions used, the more compound VII was obtained. This fact suggested that VI and VII were initially formed in the reaction and that VI was further transformed into VII.

For the preliminary characterization of VI, several crystalline derivatives were prepared. The hydriodide of VI afforded analytical results in agreement with the empirical formula $C_{19}H_{21}O_2N\cdot HI$, with two O-methyl functions. Compound VI was also treated with methyl iodide in methanol to give the methiodide XVI, $C_{20}H_{24}O_2NI$, with two O-methyl groups. Hofmann degradation of XVI in strong aqueous alkaline solution yielded a crystalline methine (XIX), $C_{20}H_{23}O_2N$, with two O-methyl groups. The ultraviolet spectrum of XIX shows characteristic peaks for a phenanthrene derivative. The n.m.r. spectrum of XIX in carbon tetrachloride solution shows only one peak for O-methyl protons (the area corresponds to six protons),

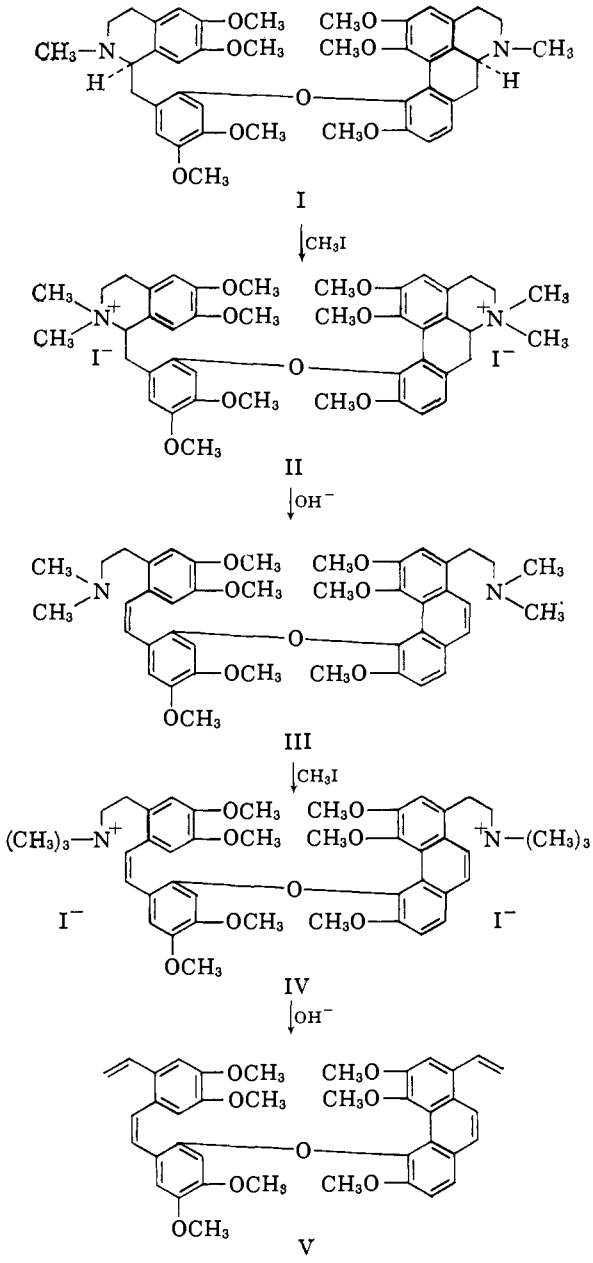
(1) Part II in the series: S. M. Kupchan and N. Yokoyama, *J. Am. Chem. Soc.*, **85**, 1361 (1963).

(2) This investigation was supported in part by research grants from the National Institutes of Health (H-2952 and CY-4500).

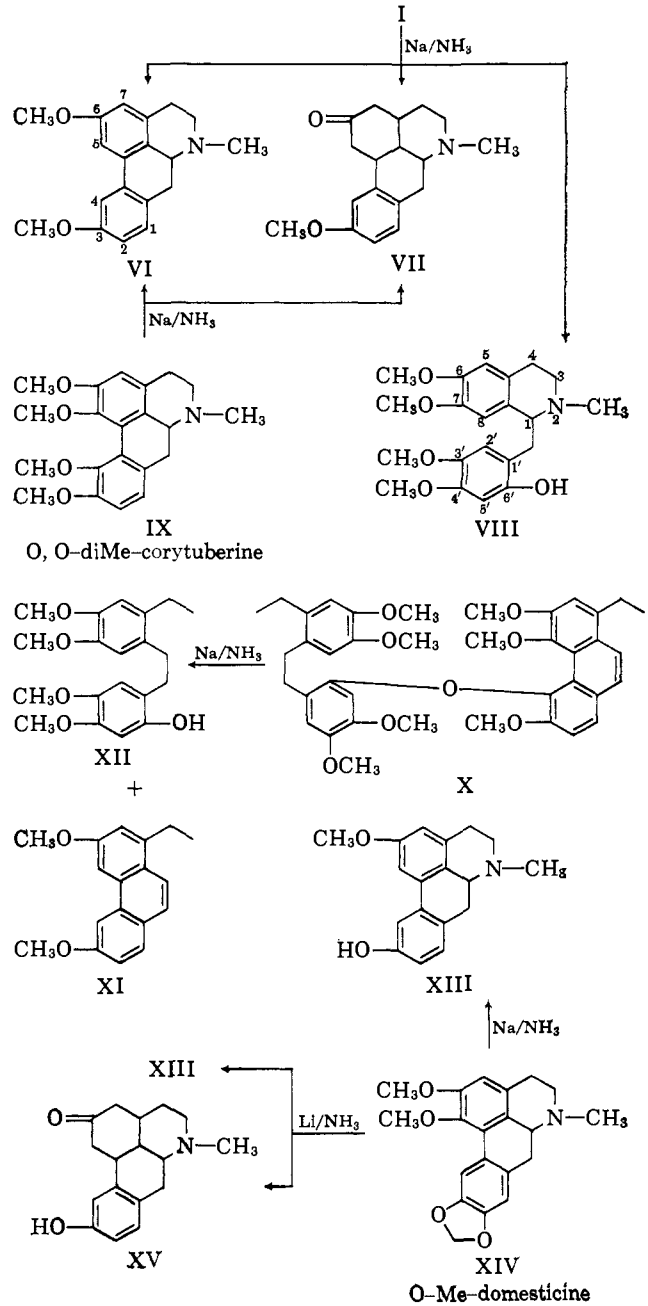
(3) Recipient of the 1962 Lunsford Richardson Pharmacy Award for a paper including part of this work.

(4) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci.*, **52**, 985 (1963).

(5) *Cf.* M. Tomita in "Progress in the Chemistry of Organic Natural Products," Vol. 9, L. Zechmeister, Ed., Springer Verlag, Vienna, 1952, p. 175; E. Fujita, *J. Pharm. Soc. Japan*, **72**, 213 (1952); F. G. Watt, *Chem. Rev.*, **46**, 331 (1949).




suggesting that two O-methyl groups are apart in the molecule and yet surrounded by similar environments. It is noteworthy that the mass spectrum of XIX shows three intense peaks, *m/e* 309 for $M^+$, *m/e* 251 for a phenanthrene moiety, and *m/e* 58 for dimethylaminomethylene ion.[6] It appears that each fragment can stabilize the electric charge very well; thus the cleavage of the carbon–carbon bond can apparently take place in either way to give both *m/e* 251 and *m/e* 58 peaks. The Hofmann methine XIX was again treated with methanolic methyl iodide to give the methine methiodide XVIII. Analysis of XVIII agreed with $C_{21}H_{26}O_2NI$, with two O-methyl groups. Second step Hofmann degradation on XVIII was carried out in strong aqueous alkali to yield the des-N-methine (XVII) and trimethylamine gas. Compound XVII afforded analytical results in agreement with the empirical formula $C_{18}H_{16}O_2$, with two O-methyl groups. Upon catalytic hydrogenation of compound XVII in glacial acetic acid, the dihydro-des-N-methine (XI), $C_{18}H_{18}O_2$, with two O-methyl groups, was obtained. The series of molecular formulas for VI, XVI, XIX, XVIII, XVII, and XI led to the hypothesis that the aporphine possessed structure VI. The compound was positively identified as 3,6-dimethoxyaporphine by direct comparison with an authentic sample prepared from 3-hydroxy-6-methoxyaporphine hydrochloride (XIII).[7]




It is interesting to note that the results of the reductive cleavage of thalicarpine are analogous to those of similar cleavage of O-methyldomesticine (XIV) and of O,O-dimethylcorytuberine (IX) (hydrogenolysis of methoxy groups in a biphenyl system and reduction of aromatic rings without addition of proton donors).[8,9] The ring-reduced product VII was characterized by analysis, mass spectrum, O-methyl group determination, and

(6) The authors thank Professor K. Biemann and Dr. B. C. Das, Massachusetts Institute of Technology, for the mass spectral data.

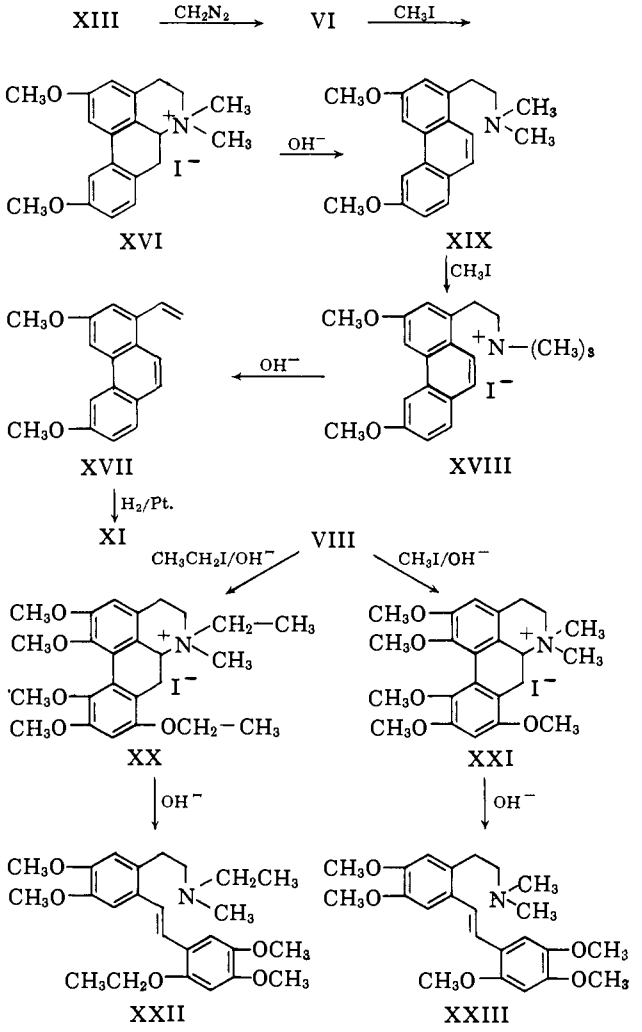
(7) The authors thank Professor M. Tomita, Kyoto University, for an authentic sample of 3-hydroxy-6-methoxyaporphine hydrochloride.

(8) T. Kitamura, *J. Pharm. Soc. Japan*, **80**, 1104 (1960).

(9) M. Tomita and K. Fukagawa, *ibid.*, **83**, 293 (1963).

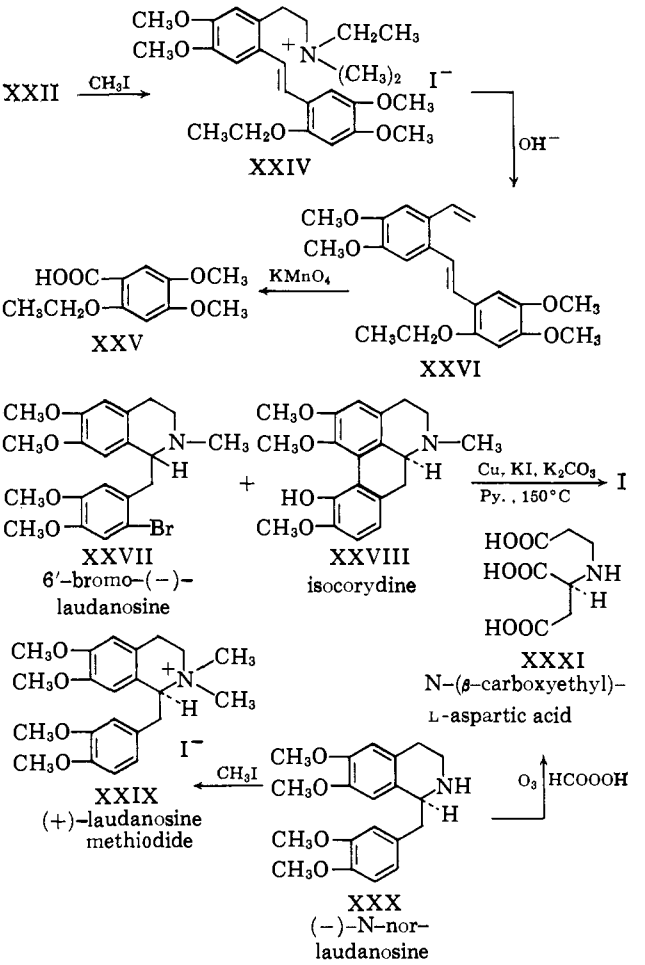
comparison of melting point and specific rotation of the base with reported values.[9]

Phenol VIII was characterized as the hydriodide, $C_{21}H_{27}O_5N \cdot HI \cdot H_2O$ and the O-methylmethiodide, $C_{23}H_{32}O_5NI$ (XXI). Hofmann degradation of XXI gave a methylmethine (XXIII), $C_{23}H_{31}O_5N$. The ultraviolet spectrum of VIII is similar to those of benzyltetrahydroisoquinoline alkaloids such as laudanosine or armepavine. An intense peak at *m/e* 206 in the mass spectrum strongly suggests the presence of a 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline moiety in the molecule.[10] Compound VIII was only difficultly soluble in strong aqueous alkali and could not be methylated easily with diazomethane. The infrared




spectrum of VIII in chloroform shows no absorption in the 2.7–3.2 $\mu$ region but has a broad peak in the 4 $\mu$ region. To confirm the phenolic nature of VIII, reductive cleavage of the des-N-methine (V) of thalicarpine was effected, after saturating the phenyl-substituted ethylene groups by catalytic reduction of V. Reductive cleavage of the hydrogenated des-N-methine X gave a neutral product (XI) and a phenol (XII). The neutral product was found to be identical with the dihydro-des-N-methine XI derived from VI. Phenol XII has not been obtained in crystalline form, but the infrared spectrum of XII in chloroform shows strong absorption at 2.95 $\mu$ (hydroxy) and the compound is readily soluble in a dilute aqueous sodium hydroxide solution.

The anomalous behavior of the phenolic hydroxyl group of VIII supported assignment of the group to the 2′-position, favorable for hydrogen bonding to the nitrogen atom. To prove the location of the hydroxyl group, VIII was converted to the O-ethylethiodide derivative XX, which upon Hofmann degradation yielded the methine XXII. Methylation of XXII gave the methine methiodide XXIV, and Hofmann degradation gave the O-ethyl-des-N-methine XXVI. Oxidation of XXVI with potassium permanganate in acetone afforded 2-ethoxy-4,5-dimethoxybenzoic acid (XXV), characterized by direct comparison with an authentic sample.[11]




The structural problems which remained at this stage were the locations of the two methoxyl groups in the benzylisoquinoline moiety, of the seventh methoxyl group (hydrogenolyzed during sodium–liquid ammonia reduction), and of the terminus of the diphenyl ether bridge in the aporphine moiety. Biogenetic considerations and careful study of the n.m.r. peaks for O-methyl and aromatic protons[12] narrowed the choice to a few alternative structures, among which structure I was regarded as most likely.

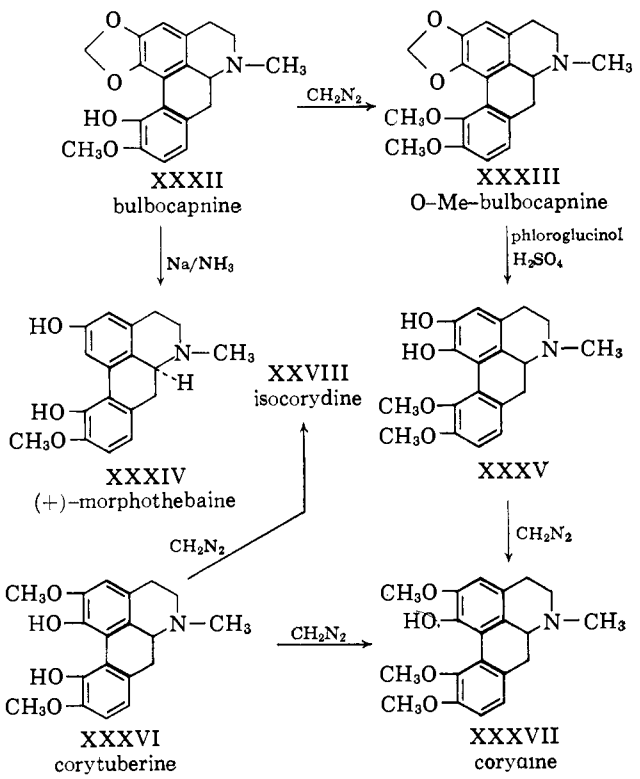
(10) *Cf.* M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2807 (1963).

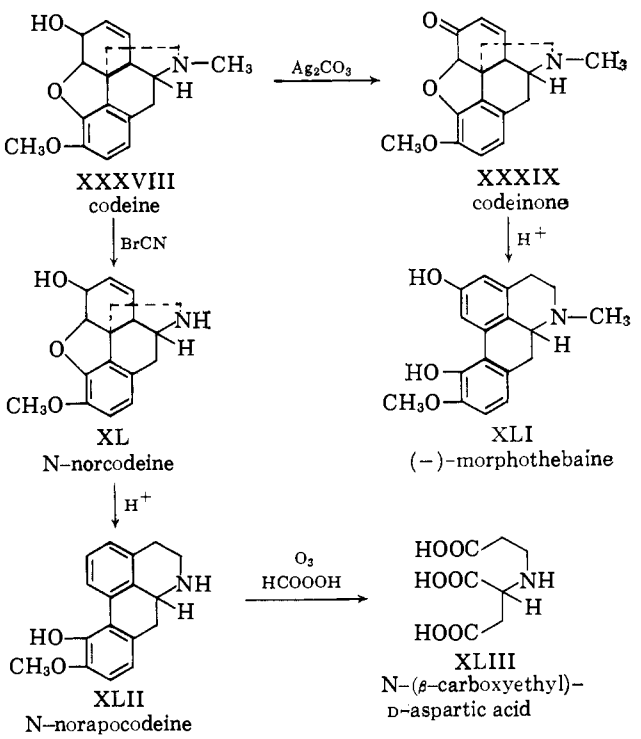
(11) J. B. D. Mackenzie and A. Robertson, *J. Chem. Soc.*, 497 (1949). We thank Professor W. B. Whalley, School of Pharmacy, University of London, for an authentic sample of 2-ethoxy-4,5-dimethoxybenzoic acid.

(12) *Cf.* L. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1896 (1961); S. Goodwin, *Proc. Chem. Soc.*, 306 (1958); A. R. Katritzky, R. A. Y. Jones, and S. S. Bhatnagar, *J. Chem. Soc.*, 1950 (1960).

Proof of the structure and absolute configuration (I) for thalicarpine was secured by synthesis of the natural product. (−)-6-Bromolaudanosine (XXVII) was prepared by the method of Tomita and Ito.[13] Compound XXVII was condensed with isocorydine[14] (XXVIII) under modified Ullman condensation conditions[15,16] which had been used successfully for the synthesis of tetrandrine. The identity of the synthetic product with thalicarpine was confirmed by mixture melting point, direct comparison of $R_f$ in several paper chromatographic systems, infrared spectra in solution, ultraviolet spectra, and specific rotation measurements. Since the total syntheses of (−)-laudanosine[17] and of isocorydine[18] had previously been accomplished, the condensation reaction constituted a formal total synthesis of thalicarpine.

The stereochemistry of (+)-laudanosine methiodide (XXIX) has been studied by Corrodi and Hardegger,[19] who established the absolute configuration at C-1. The configuration was determined by oxidative degradation of (−)-N-norlaudanosine (XXX) into N-(β-carboxyethyl)-L-aspartic acid (XXXI) by the action of ozone and performic acid. Isocorydine (XXVIII) has been interrelated with bulbocapnine (XXXII) by Späth and Berger.[20] Bulbocapnine was first converted into the O-methyl derivative XXXIII; demethylenation of XXXIII gave 3,4-dimethoxy-5,6-dihydroxyaporphine (XXXV). Partial methylation with diazomethane afforded corydine (XXXVII). Corydine and isocorydine are positional isomers related to corytuberine (XXXVI). Later, bulbocapnine was interrelated with (+)-morphothebaine (XXXIV) by Ayer and Taylor by cleaving the methylenedioxy group of bulbocapnine with metallic sodium in liquid ammonia.[19,21] The configuration of (+)-morphothebaine has been established by transformations from codeine (XXXVIII) through codeinone (XXXIX) to (−)-morphothebaine (XLI). Codeine has been related through N-norcodeine (XL) to N-norapocodeine (XLII). The absolute configuration of N-norapocodeine was established in the same manner as for (+)-laudanosine, by interrelation with N-(β-carboxyethyl)-D-aspartic acid (XLIII).[22] Consequently, the absolute configuration of isocorydine is established as indicated in XXVIII. Since the absolute configurations of both starting materials used in the synthesis of thalicarpine had been unequivocally assigned, the synthesis established not only the structure but also the absolute configuration of thalicarpine.




## Experimental

Melting points have been corrected for stem exposure. Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultraviolet absorption spectra were determined in methanol on a Cary Model 11 MS recording spectrophotometer. Infrared spectra were determined on a Model 5A Beckman infrared recording spectrophotometer. The n.m.r. spectra were determined on a Varian A-60 spectrometer. Microanalyses were carried out by Mr. J. Alicino, Metuchen, N. J. Paper chromatography was conducted by the descending technique on Whatman No. 4 paper pretreated with buffer at pH 3.5.

**Sodium–Liquid Ammonia Reduction of Thalicarpine (I).**—A 3-necked, 1-l. flask equipped with a mechanical stirrer, a dropping funnel with a nitrogen gas inlet, and a nitrogen gas outlet was placed in an acetone–Dry Ice bath (bath temperature −65 to −70°). Dried ammonia gas was induced into the flask through the nitrogen gas inlet to a volume of 500 ml. of liquid ammonia. A small amount of metallic sodium was put in the flask to color the solution blue. Thalicarpine (2.05 g.) was dissolved in 75 ml. of dried toluene and filtered (toluene-insoluble part, 0.05 g.) into the dropping funnel. The reaction was carried out under a nitrogen gaseous atmosphere by adding small portions of the

(13) M. Tomita and K. Ito, *J. Pharm. Soc. Japan*, **78**, 103 (1958).
(14) The authors thank Dr. R. H. F. Manske, Dominion Rubber Co., Ltd., Guelph, Ontario, for a generous gift of isocorydine.
(15) Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 144 (1961).
(16) M. Tomita, K. Fujitani, T. Fujitani, and T. Kishimoto, *J. Pharm. Soc. Japan*, **82**, 1148 (1962).
(17) A. Pictet and M. Finkelstein, *Ber.*, **42**, 1979 (1909).
(18) I. Kikkawa, *J. Pharm. Soc. Japan*, **78**, 1006 (1958).
(19) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).
(20) E. Späth and F. Berger, *Ber.*, **64**, 2038 (1931).
(21) W. A. Ayer and W. I. Taylor, *J. Chem. Soc.*, 472 (1956).
(22) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **38**, 2038 (1955).

toluene solution and metallic sodium to the reaction vessel alternately so that the blue color of the reaction mixture was maintained. The bath temperature was kept constant by occasional addition of Dry Ice to the bath. The reaction was stopped 15 min. after all the toluene solution had been added to the reaction mixture; the mixture maintained its blue color. About 0.6 g. of metallic sodium had been consumed in the reaction. The reaction mixture was allowed to stand overnight in a hood to evaporate the solvent. The residue was treated with 5% hydrochloric acid (50 ml.) and ether (50 ml.). The ether layer was washed with water. The washing was combined with the acidic layer and made alkaline with concentrated ammonium hydroxide and extracted with ether (150 ml.). The ethereal extract was then extracted with a mixture of potassium hydroxide (40 g.), water (30 ml.), and methanol (100 ml.). The ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to yield 0.88 g. of yellow oil (the nonphenolic reaction product). The alkaline extract was combined with the water washing and brought to dryness under reduced pressure. The residue was carefully acidified with concentrated hydrochloric acid. The acidic solution was washed with ether (20 ml.), basified with concentrated ammonium hydroxide, and extracted with ether (200 ml.). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave 1.01 g. of dark yellow oil (the phenolic reaction product).

**The Nonphenolic Sodium–Liquid Ammonia Reduction Product.**—The fraction was purified by column chromatography (Woelm neutral alumina, 20 g.). The ethereal elute gave 0.49 g. of yellow oil on evaporation (fraction A). The chloroform eluate yielded 0.29 g. of brown residue (fraction B).

(A) **The Preparation of Crystalline Derivatives of VI.** (i) **Hydriodide.**—The basic oil (0.12 g.) was dissolved in a small volume of dilute hydrochloric acid. Saturated potassium iodide aqueous solution was added to the acidic solution to complete precipitation. The precipitate was collected on a sintered glass filter and dried in a vacuum desiccator. The dried precipitate was crystallized from methanol to yield needles (0.11 g., HI salt of VI), m.p. 238–240°; $\lambda_{max}$ 268 mμ (ε 10,800), 273 (10,900), 299 (4,700), 311 (5,200), 319 (5,300).

*Anal.* Calcd. for $C_{19}H_{21}O_2N \cdot HI$: C, 53.91; H, 5.24; N, 3.31. Found: C, 53.48; H, 5.20; N, 2.72.

(ii) **Methiodide (XVI).**—The basic oil (0.49 g.) was dissolved in the mixture of methanol (10 ml.) and methyl iodide (5 ml.). The solution was kept at boiling temperature for 3 hr. and then brought to dryness to leave a semicrystalline solid, which was readily crystallized from acetone–methanol to yield 0.58 g. of prisms, m.p. 164–166°, $[\alpha]^{25}D$ +66° (*c* 1.22, methanol); $\lambda_{max}$ 268 mμ (ε 10,800), 273 (10,900), 300 (4,600), 311 (5,000), 319 (5,200).

*Anal.* Calcd. for $C_{20}H_{24}O_2NI$: C, 54.92; H, 5.53; N, 3.20; I, 29.02; 2($OCH_3$), 14.19. Found: C, 55.14; H, 5.48; N, 3.06; I, 28.68; ($OCH_3$), 14.08.

(iii) **Hofmann Methine (XIX).**—The methiodide XVI (0.91 g.) was dissolved in 10 ml. of methanol. Potassium hydroxide (5 g.) was added to the solution in small portions. The mixture was heated for 3 hr. on a steam bath and brought to dryness under reduced pressure. The residue was treated with water (20 ml.) and ether (20 ml.). The aqueous layer was washed with another portion of ether. The combined ether solutions were washed with water, dried over hydrous sodium sulfate, and evaporated to dryness to leave a residue which gave prisms from ether (0.63 g.), m.p. 102–103°, $[\alpha]^{28}D$ ±0° (*c* 1.22, chloroform); $\lambda_{max}$ 236 mμ (ε 37,400), 251 (43,200), 259 (44,000), 277 (15,700), 286 (16,700), 298 (10,500), 309 (13,000), 330 (sh., 2,400), 348 (1,400), 364 (1,500); n.m.r. spectrum ($CDCl_3$): τ 8.80 (6H, N-methyl), 6.15 (6H, O-methyl); mass spectral peaks: *m/e* 309 ($M^+$), 251, 58.

*Anal.* Calcd. for $C_{20}H_{23}O_2N$: C, 77.64; H, 7.49; N, 4.53; 2($OCH_3$), 20.06. Found: C, 76.64; H, 6.97; N, 4.23; ($OCH_3$), 19.20.

(iv) **Hofmann Methine Methiodide (XVIII).**—The methine base XIX (0.09 g.) was dissolved in the mixture of methanol (2 ml.) and methyl iodide (2 ml.). The solution was kept boiling for 3 hr. on a steam bath. Evaporation to dryness left a semicrystalline solid which afforded needles upon crystallization from methanol (0.06 g.); m.p. 240–241°, $[\alpha]^{23}D$ ±0° (*c* 0.75, methanol); $\lambda_{max}$ 236 mμ (ε 39,400), 251 (47,200), 259 (51,400), 278 (14,400), 288 (18,600), 300 (11,000), 311 (13,200), 333 (800), 349 (1,400), 366 (1,600).

*Anal.* Calcd. for $C_{21}H_{26}O_2NI$: C, 55.88; H, 5.81; N, 3.10; I, 28.12; 2($OCH_3$), 13.75. Found: C, 55.72; H, 5.95; N, 3.02; I, 28.29; ($OCH_3$), 12.80.

(v) **Des-N-methine (XVI).**—The Hofmann methine methiodide XVIII (0.3 g.) was dissolved in 30 ml. of methanol. Sodium hydroxide (15 g.) was added to the solution in small portions. Immediate evolution of trimethylamine gas was observed. The reaction mixture was heated on a steam bath for 4 hr. Evaporation to dryness under reduced pressure yielded a residue which was triturated with water (20 ml.) and ether (40 ml.). The ethereal extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a residue which was crystallized from ether to give needles (0.15 g.), m.p. 86–87°, $[\alpha]^{26}D$ ±0° (*c* 0.82, chloroform); $\lambda_{max}$ 224 mμ (ε 37,500), 259 (41,000), 289 (20,000), 312 (15,500), 349 (2,200), 365 (2,300).

*Anal.* Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10; 2($OCH_3$), 23.48. Found: C, 82.43; H, 6.32; ($OCH_3$), 23.77.

(vi) **Dihydro-des-N-methine (XI).**—To a solution of des-N-methine XVII (0.2 g.) in 20 ml. of glacial acetic acid was added platinum oxide (0.05 g.). The mixture was submitted to catalytic hydrogenation at room temperature under atmospheric pressure. The reaction was stopped after 24 hr., and the reaction mixture was filtered. The catalyst was washed with a small volume of ethyl acetate. The filtrate was combined with the washing and evaporated to dryness under reduced pressure to leave an oily residue. The residue was purified by chromatography on an alumina column (Woelm neutral alumina, 5 g.). The 2% ether Skellysolve B eluate on concentration of solvent gave needles (0.16 g.), m.p. 57–58°, $[\alpha]^{28}D$ ±0° (*c* 0.67, chloroform); $\lambda_{max}$ 238 mμ (ε 32,000), 251 (42,000), 259 (46,000), 278 (sh., 15,000), 286 (18,000), 297 (10,500), 308 (13,000), 331 (900), 347 (1,500), 363 (1,700).

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.61. Found: C, 80.61; H, 6.77.

(B) **Preparation of the Comparison Sample of VI.**—3-Hydroxy-6-methoxyaporphine hydrochloride (0.02 g.) was converted into free base by shaking with dilute ammonium hydroxide and ether to obtain 0.015 g. of an oily residue. The residue was dissolved in methanol (1 ml.) and mixed with freshly prepared diazomethane ethereal solution (2 ml.). A fresh charge of diazomethane was added 3 hr. later after concentrating the reaction mixture. After a total of 6 hr. the reaction mixture was brought to dryness. The dried residue was treated with ether and 1.5% hydrochloric acid. The acidic layer was made alkaline with concentrated ammonium hydroxide and extracted with ether. The ethereal extract was washed with 5% aqueous potassium hydroxide solution and with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a yellow oil (0.011 g.), $[\alpha]^{23}D$ +114° (*c* 1.10, chloroform); $\lambda_{max}$ 266 mμ (ε 10,300), 273 (10,400), 298 (4,900), 312 (5,600), 320 (5,600). The product obtained, 3,6-dimethoxyaporphine, was found to be identical with the sample of IX derived from thalicarpine by direct comparison of infrared and ultraviolet spectra specific rotations, paper chromatographic behavior, infrared spectra of the respective hydriodide salts in Nujol mulls, and mixture melting point of the hydriodide salts.

(C) **Isolation of VII from Fraction B.**—The dried residue was crystallized from ether to give needles (VII, 0.21 g.), m.p. 172–173°, $[\alpha]^{25}D$ +110° (*c* 1.35, methanol), $[\alpha]^{23}D$ +94° (*c* 1.60, chloroform); $\lambda_{max}$ 281 mμ (ε 2,600), 289 (2,400); $\lambda_{max}^{CHCl_3}$ 5.85 μ (carbonyl); mass spectral peak, *m/e* 285 ($M^+$).

*Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12; N, 4.91; $OCH_3$, 10.87. Found: C, 75.89; H, 8.17; N, 4.91; $OCH_3$, 11.04.

**The Phenolic Sodium–Liquid Ammonia Reduction Product (VIII).**—The crude material (1.01 g.) was dissolved in 5 ml. of 5% hydrochloric acid. The acidic solution was filtered to remove a small amount of acid-insoluble material. About 0.6 g. of potassium iodide was dissolved in the minimum amount of water and added to the acidic solution, whereupon a precipitate formed. Precipitation was completed by allowing the mixture to stand overnight. The precipitate was collected on a sintered-glass filter, dried under reduced pressure, and crystallized from acetone to yield fine prisms (1.08 g.), m.p. 184–186°, $[\alpha]^{26}D$ −76° (*c* 0.67, methanol), $\lambda_{max}$ 289 mμ (ε 5,800).

*Anal.* Calcd. for $C_{21}H_{27}O_5N \cdot HI \cdot H_2O$: C, 48.75; H, 5.45; N, 2.71. Found: C, 48.92; H, 5.68; N, 2.95.

The free base regenerated from the crystalline hydriodide could not be obtained crystalline; $[\alpha]^{26}D$ −103° (*c* 1.93, chloroform), $\lambda_{max}$ 289 mμ (ε 7,800).

**6'-Methoxylaudanosine Methiodide (XXI).**—The phenolic cleaved product VIII (0.2 g.) derived from thalicarpine was dissolved in a mixture of methanol (10 ml.), methyl iodide (3 ml.), and sodium hydroxide (0.5 g.). The reaction mixture was refluxed for 36 hr. A fresh charge of methyl iodide (3 ml.) and sodium hydroxide (0.5 g.) was added every 6 hr. After the reaction was stopped, the mixture was brought to dryness under reduced pressure. The dried residue was dissolved in water (10 ml.) and extracted with chloroform (30 ml.). The chloroform extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a brown semisolid residue (0.32 g.) which was purified by passing a chloroform solution through a small alumina column (Woelm neutral alumina, 1.5 g.). The eluate was brought to dryness to yield a yellow semisolid residue which was crystallized from acetone to give prisms (0.21 g.), m.p. 223–224°, $[\alpha]^{23}D$ +109° (*c* 1.40, methanol), $\lambda_{max}$ 289 mμ (ε 7,500).

*Anal.* Calcd. for $C_{23}H_{32}O_3NI$: C, 52.18; H, 6.09; N, 2.65; 5($OCH_3$), 29.31. Found: C, 51.96; H, 6.05; N, 2.89; $OCH_3$, 31.24.

**6'-Methoxylaudanosine Methylmethine (XXIII).**—The methiodide XXI (0.2 g.) was dissolved in 10 ml. of methanol. Potassium hydroxide (5 g.) was added to the methanolic solution in portions. The reaction mixture was heated on a steam bath for 6 hr. and brought to dryness under reduced pressure. The dried residue was triturated with water (7 ml.), and extracted with ether (30 ml.). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to yield a semicrystalline solid which was recrystallized from ether to give needles (0.11 g.), m.p. 125–127°, $[\alpha]^{28}D$ ±0° (*c* 1.82, chloroform); $\lambda_{max}$ 282 mμ (ε 19,200), 343 (30,500); n.m.r. spectrum ($CDCl_3$), 7.78 (6H, N-methyl), 6.22 (15H, O-methyl), 3.55, and 3.40 τ (2H, *trans*-stilbene); mass spectral peaks, *m/e* 401 ($M^+$) and 58.

*Anal.* Calcd. for $C_{28}H_{31}O_5N$: C, 68.80; H, 7.78; N, 3.49; 5($OCH_3$), 38.64. Found: C, 68.50; H, 7.68; N, 3.65; $OCH_3$, 36.50.

**Catalytic Reduction of Thalicarpine-des-N-methine (V).**—The des-N-methine V (0.2 g.), and platinum oxide (0.05 g.) were suspended in 20 ml. of glacial acetic acid. The mixture was submitted to catalytic hydrogenation under atmospheric pressure at room temperature with magnetic stirring. The reaction was stopped after 24 hr. and the mixture was filtered. The catalyst was washed with a small amount of ethyl acetate. The filtrate was combined with the washing and evaporated to dryness under reduced pressure to yield a yellow oil (0.175 g.). The reaction product was purified on a Woelm neutral alumina column (5 g.). The benzene eluate gave a colorless oil on evaporation which could not be obtained crystalline. No absorption due to ethylenic hydrogen was seen in the infrared spectrum of the oil in chloroform solution; $\lambda_{max}$ 231 mμ (ε 48,000), 261 (34,400), 283 (28,300), 310 (sh., 9,800), 345 (870), 362 (650).

**Sodium–Liquid Ammonia Reduction of the Hydrogenated Des-N-methine (X).**—The reaction was carried out in the same manner as for thalicarpine. Hexahydro-des-N-methine (X, 0.7 g.) yielded a phenolic residue (0.31 g.) and a nonphenolic residue (0.26 g.). The latter was crystallized after purification on a Woelm neutral alumina column (10 g.), eluting with 2% ether–Skellysolve B. The crystalline compound was found to be identical with 8-ethyl-3,6-dimethoxyphenanthrene (XI) by direct intercomparison of infrared and ultraviolet spectra. The phenolic reaction product could not be obtained crystalline after purification on an alumina column. Elution with chloroform gave colorless oil (XI); $\lambda_{max}^{CHCl_3}$ 2.95 μ (hydroxyl), $\lambda_{max}$ 282 mμ (ε 11,000).

**Degradation of the Phenolic Reaction Product (VIII). (i) O-Ethyl Ether Ethiodide (XX).**—The free base regenerated from crystalline hydriodide (0.38 g.) was dissolved in a mixture of absolute ethanol (20 ml.), ethyl iodide (10 ml.), and potassium hydroxide (2 g.). The reaction mixture was refluxed for 24 hr. on a steam bath and brought to dryness under reduced pressure. The dried residue was dissolved in water (20 ml.) and extracted with chloroform (90 ml.). The chloroform extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave 1.06 g. of brown oil. The reaction product was purified on a small alumina column (Woelm neutral alumina, 5.5 g.). Attempts at crystallization of the eluate were unsuccessful.

(ii) **Hofmann Methine (XXII).**—The purified O-ethyl ether ethiodide XX (1.05 g.) was dissolved in 40% alcoholic potassium hydroxide solution (10 ml.). The solution was heated on a steam bath for 3 hr. The mixture was then brought to dryness under reduced pressure. The dried residue was triturated with water (30 ml.) and extracted with ether (90 ml.). The ethereal extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a semicrystalline solid which was crystallized from ether to give needles (0.63 g.), m.p. 88–89°, $[\alpha]^{27}D$ ±0° (*c* 1.24, chloroform); $\lambda_{max}$ 290 mμ (ε 12,000), 336 (12,600).

*Anal.* Calcd. for $C_{25}H_{35}O_5N$: C, 69.90; H, 8.21; N, 3.26; 4($OCH_3$) and ($OCH_2CH_3$), 36.13. Found: C, 68.26; H, 8.04; N, 3.33; ($OCH_3$) and ($OCH_2CH_3$), 34.09.

(iii) **The Methine Methiodide (XXIV).**—The methine XXII (0.60 g.) was dissolved in a mixture of methanol (10 ml.) and methyl iodide (2 ml.). The reaction mixture was refluxed for 3 hr. and brought to dryness under reduced pressure to leave a residue which was crystallized from acetone to yield prisms (0.46 g.), m.p. 201–202°, $[\alpha]^{25}D$ ±0° (*c* 1.06, methanol); $\lambda_{max}$ 291 mμ (ε 11,000), 336 (11,200).

*Anal.* Calcd. for $C_{26}H_{38}O_5NI$: C, 54.64; H, 6.70; N, 2.45; 4($OCH_3$) and ($OCH_2CH_3$), 27.15. Found: C, 53.18; H, 6.70; N, 2.57; ($OCH_3$) and ($OCH_2CH_3$), 25.04.

(iv) **Des-N-methine (XXVI).**—The methine methiodide XXIV (0.35 g.) was dissolved in 50% methanolic potassium hydroxide solution (10 ml.). The solution was heated on a steam bath for 4 hr. and then brought to dryness to leave a residue which was triturated with water (30 ml.) and extracted with ether (90 ml.). The ethereal extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to deposite rhombs (0.16 g.), m.p. 129–130°; $\lambda_{max}$ 230 mμ (ε 22,900), 261 (22,800), 310 (sh., 18,700), 345 (30,100).

*Anal.* Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; 4($OCH_3$) and ($OCH_2CH_3$), 41.86. Found: C, 71.17; H, 7.15; ($OCH_3$) and ($OCH_2CH_3$), 39.33.

(v) **Oxidation of the Des-N-methine.**—The des-N-methine XXVI (0.19 g.) was dissolved in 20 ml. of acetone. A saturated potassium permanganate–acetone solution was added to the solution slowly and dropwise under magnetic stirring at the boiling point of the solvent. The reaction was continued overnight in the presence of slight excess of potassium permanganate; 24 hr. later, the excess of permanganate ion was decomposed by adding 1% oxalic acid–acetone solution dropwise. The reaction mixture was evaporated to dryness, triturated with 5% sodium bicarbonate aqueous solution (30 ml.), and filtered. The filtrate was washed with ether (30 ml.), made acidic by adding concentrated hydrochloric acid, and extracted with ether (90 ml.). The ether extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to deposit plates (0.07 g.), m.p. 144–146°; $\lambda_{max}$ 225 mμ (ε 22,600), 258 (9,400), 305 (5,600). The melting point was not depresssed upon admixture with an authentic sample of 2-ethoxy-4,5-dimethoxybenzoic acid (XXV). The infrared (Nujol mull) and ultraviolet spectra were identical with those of the authentic sample.

*Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24; 2($OCH_3$) and ($OCH_2CH_3$), 41.16. Found: C, 58.33; H, 6.19; ($OCH_3$) and ($OCH_2CH_3$), 41.33.

**Synthesis of Thalicarpine. (−)-6'-Bromolaudanosine (XXVII)** was prepared by Tomita's method[13]; m.p. 139–141°, $[\alpha]^{23}D$ −47° (*c* 1.05, chloroform).

**Condensation of Isocorydine (XXVIII) with (−)-6'-Bromolaudanosine (XXVII).**—A mixture of (−)-6'-bromolaudanosine (0.48 g.), isocorydine (0.34 g.), copper powder (0.135 g.), potassium iodide (0.045 g.), and anhydrous potassium carbonate (0.45 g.) was suspended in 2 ml. of dry pyridine. The reaction mixture was heated in an oil bath (bath temperature 149.5–150.5°) for 36 hr. with an air condenser. The reaction mixture was brought to dryness under reduced pressure. The dried residue was extracted with benzene repeatedly (ten 50-ml. portions). The benzene extract was filtered and evaporated to leave a solid residue which was crystallized from ether to give crystalline starting materials ((−)-6'-bromolaudanosine and isocorydine, 0.23 g.). The mother liquor was brought to dryness to yield 0.18 g. of semisolid residue. The residue was fractionated by paper chromatography (six sheets of paper of 8.5 in. width).[23] The

(23) The method involved the use of paper pretreated with buffer at pH 3.5 and the detection of alkaloidal spots with a chloroform solution of bromophenol blue. The solvent system was the upper layer of a mixture of 1-butanol–*n*-butyl acetate–pyridine–water (30:15:10:50 vol.) prepared by shaking well and allowing to stand at room temperature for 24 hr.

alkaloidal zone on the chromatogram with the same $R_f$ value as that of thalicarpine was cut from the chromatogram and extracted in a Soxhlet extractor with methanol. The methanolic extract was brought to dryness to leave a resinous residue. The residue was dissolved in 1.5% hydrochloric acid (10 ml.), washed with ether (10 ml.), made alkaline with concentrated ammonium hydroxide, and extracted with ether (30 ml.). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to yield a yellow oil (0.033 g.), which was crystallized from ethyl acetate to give pale yellow needles (0.013 g.), m.p. 151–153°, $[\alpha]^{21}D$ +131° (*c* 1.30, methanol). The melting point was not depressed on admixture with an authentic sample of thalicarpine. The paper chromatographic behavior, infrared spectrum in chloroform solution, and ultraviolet spectrum were identical with those of the authentic thalicarpine.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

# Steroidal Cyclic Ketals. XXV.[1] The Preparation of Steroidal $\Delta^4$-3-Ethyleneketals

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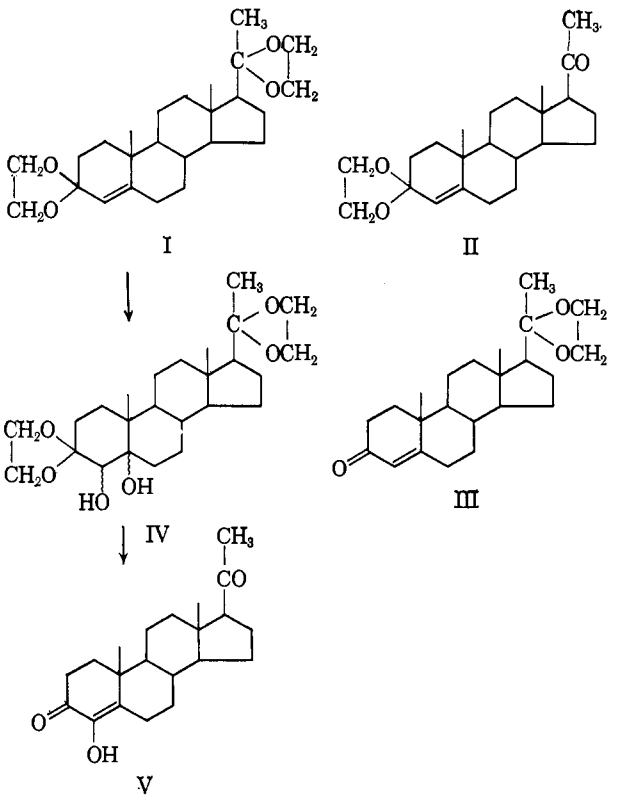
Steroidal $\Delta^4$-3-ethyleneketals have been prepared by substitution of oxalic or preferably adipic acid for *p*-toluenesulfonic acid in the Salmi method for the preparation of steroidal $\Delta^5$-3-ethyleneketals. A possible mechanism is discussed.

When progesterone was ketalized by a modified Salmi[2] procedure, *i.e.*, oxalic acid in place of *p*-toluenesulfonic acid as catalyst, three products were obtained: a 3,20-bisethyleneketal I, a 3-ethyleneketal II, and 20-ethylenedioxypregn-4-en-3-one (III).[3] The unknown compounds I and II did not show absorption in the ultraviolet and exhibited a sharp, weak band in the infrared at 1668 cm.$^{-1}$ which is not shown by $\Delta^5$-3-ethyleneketals. That these compounds I and II were $\Delta^4$-3-ethyleneketals was established when oxidation of the bisethyleneketal I with osmium tetroxide in pyridine[4] gave a dihydroxybisethyleneketal IV from which the known[5] 4-hydroxypregn-4-ene-3,20-dione (V) was obtained by treatment with formic acid. This showed that the dihydroxy bisethyleneketal IV was 3,20-bisethylenedioxypregnane-4ξ,5ξ-diol and that the double bond in the bisethyleneketal I was in the 4,5-position. Thus, compounds I and, consequently, II were assigned the unique structures of 3,20-bisethylenedioxypregn-4-ene (I) and 3-ethylenedioxy-4-en-20-one (II), respectively.

When a solution of the $\Delta^4$-bisethyleneketal I in wet benzene (benzene saturated with water) was shaken with anhydrous magnesium sulfate, the 3-ethyleneketal was removed[6] quantitatively to give 20-ethylenedioxypregn-4-en-3-one (III). The 3-ethyleneketal of 3,20-bisethylenedioxypregn-5-ene (VI)[7] was unaffected by this treatment although the 20-ethyleneketal was removed to a greater or lesser extent according to the time of the reaction to give 3-ethylenedioxypregn-5-en-20-one (VII).[8]

The modified ketalization reaction was applied to several steroids (see Table I). With oxalic acid as catalyst, $\Delta^4$-3-ketones gave either the $\Delta^4$-3-ethyleneketal or a mixture of the $\Delta^4$- and $\Delta^5$-3-ethyleneketals. When oxalic acid was replaced by the weaker adipic acid as catalyst, only the $\Delta^4$-3-ethyleneketal was obtained. In the case of saturated 3-ketosteroids, 5α- and 5β-dihydrocortisone acetate gave good yields of the 3-ethyleneketals but, surprisingly, cholestanone and coprostanone failed to react.

The $\Delta^4$-3-ethyleneketals are stable to base but are extremely sensitive to acid. In contrast to $\Delta^5$-3-ethyleneketals, they are hydrolyzed almost quantitatively in benzene by magnesium sulfate. This enabled the proportions of $\Delta^4$- and $\Delta^5$-3-ethyleneketals in a crude reaction mixture to be determined by comparison of the ultraviolet absorption before and after such treatment of a sample. The $\Delta^4$-3-ethyleneketals ex-




(1) This work has been described in part in a preliminary communication: J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 309 (1962).

(2) E. Salmi, *Ber.*, **71**, 1803 (1938); E. Salmi and V. Rannikko, *ibid.*, **72**, 600 (1939).

(3) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

(4) J. S. Baran, *ibid.*, **25**, 257 (1960).

(5) R. H. Bible, Jr., C. Placek, and R. D. Muir, *ibid.*, **22**, 607 (1957).

(6) D. N. Robertson, *ibid.*, **25**, 931 (1960), noted that magnesium sulfate is sufficiently acidic to hydrolyze dihydropyran adducts of tertiary alcohols containing an ethynyl group to the alcohol in a few hours.

(7) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *ibid.*, **17**, 1369 (1952).

(8) F. Sondheimer, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 192 (1955).