The Synthesis of Caseadine Methyl Ether

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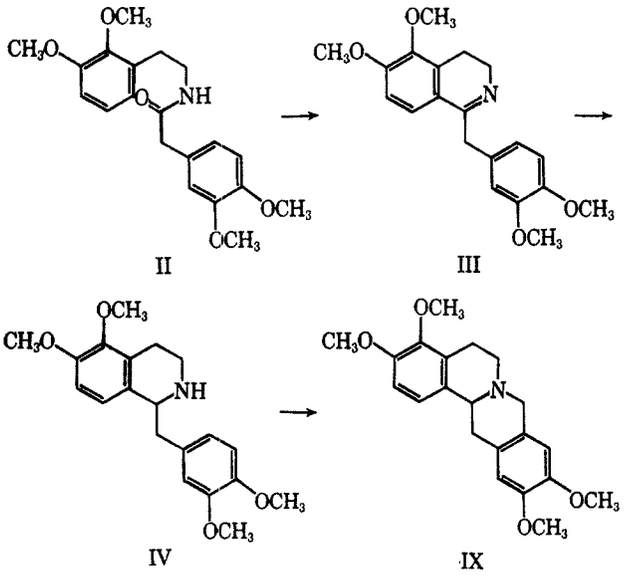
Syntheses are described for the isomeric racemic bases 3,4,10,11-tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (IX) and 1,2,10,11-tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine (X). The latter was shown to be the racemic form of the methyl ether of the novel tetrahydroprotoberberine base, (−)-caseadine, thus giving synthetic support to the caseadine structure Ia assigned by Chen, MacLean, and Manske on spectroscopic and biogenetic grounds.

The isolation of two minor phenolic alkaloids, originally designated F-33 and F-35, was reported from *Corydalis caseana A.* Gray in 1938.[1] A recent elegant study of these trace alkaloids, now named caseamine and caseadine, respectively, indicated that they are tetrahydroprotoberberines having the same novel substitution pattern. Spectroscopic considerations narrowed the structure of the more abundant monophenolic base caseadine to Ia or Ib. Of these two possibilities, structure Ia was regarded as the more likely on the basis of biogenetic analogy with other known alkaloids of the benzylisoquinoline family.[2] Since caseadine has been converted into a crystalline methyl ether, we undertook the synthesis of both of the possible methyl ether structures IX and X.

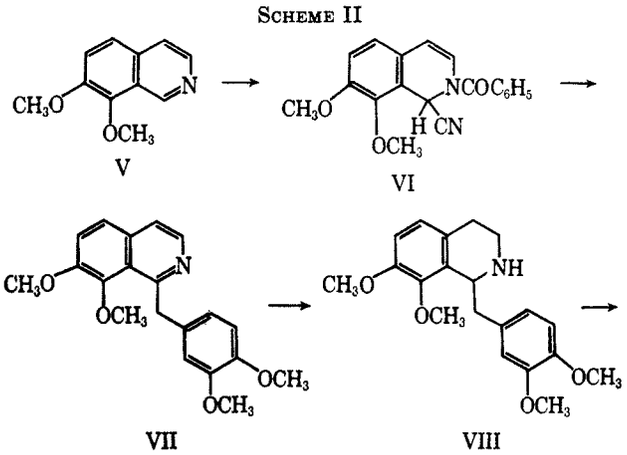
The starting material for the synthesis of the 3,4,10,-11-tetramethoxytetrahydroprotoberberine IX was the known dihydroisoquinoline III,[3] which we obtained by a much improved procedure (79% yield) involving polyphosphate ester cyclization of amide II (Scheme I). Sodium borohydride reduction of III afforded, in 61% yield, the crystalline 1-veratryl-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV), characterized as its hydrochloride. Condensation of the latter salt with formaldehyde according to the general procedure of Corrodi and Hardegger[4] gave a good yield of the desired tetrahydroprotoberberine IX, mp 158.5–160°. Infrared examination showed this base to be definitely different from caseadine methyl ether.

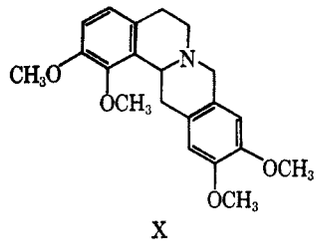
The isomeric 1,2,10,11-tetramethoxytetrahydroprotoberberine X was synthesized starting from 7,8-dimethoxyisoquinoline (V) (Scheme II).[5] Reaction of isoquinoline V with benzoyl chloride and potassium cyanide gave, in 43% yield, the corresponding Reissert compound VI, mp 158°. Using the general procedure of Kershaw and Uff,[6] reaction of VI with veratryl

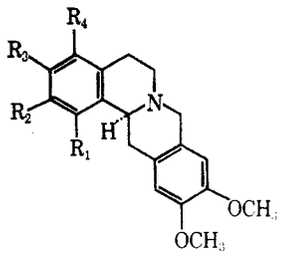
SCHEME I



SCHEME II







Ia, $R_1 = OH$; $R_2 = OCH_3$; $R_3 = R_4 = H$

b, $R_1 = R_2 = H$; $R_3 = OCH_3$; $R_4 = OH$

(1) R. H. F. Manske and M. R. Miller, *Can. J. Res., B*, **16**, 153 (1938).

(2) C.-Y. Chen, D. B. MacLean, and R. H. F. Manske, *Tetrahedron Lett.*, 349 (1968).

(3) A. Lindenmann, *Helv. Chim. Acta*, **32**, 69 (1949). The PCl_5 cyclization of II to the amorphous III in unspecified yield is reported in this paper; this product was not subjected to further transformations.

(4) H. Corrodi and E. Hardegger, *ibid.*, **39**, 889 (1956).

(5) W. J. Gensler, K. T. Shamsundar, and S. Marburg, *J. Org. Chem.*, **33**, 2864 (1968).

(6) J. R. Kershaw and B. C. Uff, *Chem. Commun.*, 331 (1966). In this communication concerning a new benzylisoquinoline synthesis, 1-anisyl-7,8-dimethoxyisoquinoline is mentioned as one of the compounds prepared. Implicitly, Reissert compound VI was the intermediate used in this case, although it was not specifically described in any way. We, therefore, report our synthesis of VI.

chloride and sodium hydride, followed by aqueous alkaline hydrolysis, gave, in 83% yield, 1-veratryl-7,8-dimethoxyisoquinoline (VII), mp 79–81°. Catalytic reduction of VII yielded the amorphous 1-veratryl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII), characterized as its crystalline N-acetyl derivative. Acid-catalyzed condensation of VIII with formaldehyde gave the desired tetrahydroprotoberberine X, mp 165°, the infrared spectrum of which in chloroform solution was identical with that of the methyl ether of natural (−)-caseadine. This result, considered with the earlier reported spectroscopic evidence, confirms the structure Ia for caseadine itself, as proposed by Chen, MacLean, and Manske.[2]

The facile resolution of several 1,2,3,4-tetrahydroisoquinolines by (2*R*:3*R*)-2′-nitrotartranilic acid was reported recently.[7] Although we were unable to effect a resolution of racemic caseadine methyl ester (X) using this acid, we found it to be an advantageous acid catalyst for the formaldehyde cyclization of VIII, since the salt of the acid with the resulting caseadine methyl ether crystallized directly in a state of purity from the reaction mixture.

Experimental Section[8]

Polyphosphate Ester.[9]—Phosphorus pentoxide (150 g) was added to a solution of 300 ml of anhydrous ether and 150 ml of alcohol-free chloroform. The reaction mixture was refluxed under dry nitrogen for 4 days and the resulting clear solution was decanted from a small amount of residue. The solution was concentrated to a colorless syrup in a rotary evaporator; residual traces of solvent were removed by heating the syrup for 36 hr at 40° *in vacuo*.

1-Veratryl-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV).—Amide II[3] (3.36 g, 9.35 mmol) was mixed with 24 g of polyphosphate ester and the mixture was heated on a hot plate at 80° for 12 hr. The reaction mixture was poured into 200 ml of water and the resulting clear solution was stirred at room temperature for 0.5 hr and was then extracted twice with 50-ml portions of ether. The aqueous layer was made basic with ammonium hydroxide and was extracted with four 100-ml portions of 1:1 benzene–ether. The organic extract was dried over magnesium sulfate and was evaporated to an oil *in vacuo*. The dihydroisoquinoline (III, yield 2.52 g, *ca.* 79%) could not be crystallized, but was used directly in the next step of the synthesis.

A solution of 0.445 g (1.30 mmol) of the dihydroisoquinoline (III)[3] in 10 ml of methanol was treated with 200 mg of sodium borohydride, added in small portions during 15 min. The reaction mixture was allowed to stand for 0.5 hr at room temperature and was then diluted with water to the cloud point. On standing overnight it deposited white needles of the tetrahydroisoquinoline (IV), 0.273 g (61%), mp 70–73°.

The product was analyzed in the form of its hydrochloride, which was recrystallized from ethanol. Thus, a solution of 3.00 g of IV in ethanol was treated with hydrogen chloride gas to give 2.58 g (78%) of the hydrochloride of IV: mp 237–238°; $\lambda_{max}^{H_2O}$ 230 mμ (log ε 4.22), 278 (3.62).

Anal. Calcd for $C_{20}H_{26}ClNO_4$: C, 63.26; H, 6.90; Cl, 9.33; N, 3.69. Found: C, 63.30; H, 7.01; Cl, 9.40; N, 3.55.

3,4,10,11-Tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo-[*a*,*g*]quinolizine (IX).—Aqueous formaldehyde solution (0.8 ml, 37%) was added dropwise during 0.25 hr with occasional stirring to a solution of 0.380 g (1.00 mmol) of the tetrahydroisoquinoline (IV) hydrochloride in 4.5 ml of water while the latter was heated on a steam bath. The reaction mixture was diluted with 1.0 ml of 6 *N* hydrochloric acid and was cooled in an ice bath to give 0.332 g (85%) of IX hydrochloride as white crystals, mp 232–234° dec, obtained in two crops. The analytical sample, mp 232–234° dec, was recrystallized from 0.05 *N* hydrochloric acid: $\lambda_{max}^{H_2O}$ 225 mμ sh (log ε 4.23), 282 (3.72).

Anal. Calcd for $C_{21}H_{26}ClNO_4$: C, 64.36; H, 6.69; Cl, 9.05; N, 3.57. Found: C, 64.08; H, 6.77; Cl, 9.05; N, 3.61.

Treatment of the hydrochloride salt of IX with base gave the free amine, mp 158.5–160°, which resembles caseadine methyl ether (X) in its R_f (0.87 on Merck tlc plates, silica gel F-254, developed with 1:10 absolute ethanol–chloroform), but which differed unmistakably from X in its nmr spectrum and its infrared spectrum.

1-Cyano-2-benzoyl-7,8-dimethoxy-1,2-dihydroisoquinoline (VI).[6]—A solution of 10 g (0.0052 mol) of the isoquinoline V[5] in 100 ml of methylene chloride was treated at 0° with excess benzoyl chloride (10 ml) in the presence of potassium cyanide (10 g, 0.154 mol) in 25 ml of water. The mixture was stirred for 1 additional hr at room temperature. The organic layer was washed several times with water and was dried. The solvent was removed and the residue was crystallized from alcohol to give VI, 8.56 g (43%), mp 158°.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.24; H, 5.17; N, 8.74.

1-Veratryl-7,8-dimethoxyisoquinoline (VII).—Sodium hydride (1.452 g) was added to a stirred mixture of 3.326 g (0.004 mol) of VI and 2.948 g (0.015 mol) of veratryl chloride[10] in 100 ml of dimethylformamide at 0° under nitrogen. The mixture was stirred for 3 hr more at ambient temperature, and then diluted with water and extracted with methylene chloride. The residue from the organic extract was refluxed with a mixture of 200 ml of 10% aqueous alkali and 100 ml of ethanol for 3 hr. The ethanol was removed in a rotary evaporator and the residue was extracted with ether. Reextraction of the ether extract with 2 *N* hydrochloric acid, followed by basification of the acid extract, furnished crude VII, mp 69–76° (2.936 g, 83%), which on recrystallization from dry ether gave the pure product: mp 79–81° (1.7 g); λ_{max}^{EtOH} 215 mμ (ε 3.71), 245 (3.68), 295 (2.85), 370 (2.71).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.54; H, 6.46; N, 4.30.

The picrate of VII, mp 150–154°, was prepared and was recrystallized from ethanol.

Anal. Calcd for $C_{26}H_{24}N_4O_{11}$: C, 54.93; H, 4.25; N, 9.86. Found: C, 55.03; H, 4.45; N, 9.98.

1-Veratryl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII).—A solution of 0.600 g of VII in 60 ml of ethanol containing 2 drops of 6 *N* hydrochloric acid was shaken with hydrogen at 30 psi in the presence of 0.10 g of platinum oxide. After 7 hr, the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was basified and worked up in the usual manner to give 0.6 g of VIII as a gum which resisted crystallization. However, 0.099 g of an N-acetyl derivative, mp 91°, was obtained from 0.100 g of the crude product (VIII).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.44; H, 7.05; N, 3.71.

1,2,10,11-Tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo-[*a*,*g*]quinolizine (X).—The crude hydrochloride of VIII, obtained by reduction of 1.00 g of VII (see above), was dissolved in 10 ml of water on a steam bath and treated with 2 ml of 37% formaldehyde solution, added during 15 min. Heating was continued for 1 hr. The mixture was basified and extracted with methylene chloride as usual. The sticky solid (0.7 g) obtained by evaporation of the solvent was recrystallized from dry ether to give 0.2 g of X: mp 165°; λ_{max}^{EtOH} 215 mμ (log ε = 5.00), 235 (4.20), 288 (3.79).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.86; H, 7.12; N, 4.07.

In another run, a solution of 0.9 g of VIII in 10 ml of ethanol was treated with a solution of 0.5 g of (2*R*:3*R*)-2′-nitrotartranilic acid[7] in ethanol. The crude salt obtained by evaporation of the solvent was extracted with boiling water. The aqueous extract was treated with a few drops of formalin and heated on the steam

(7) T. A. Montzka, T. L. Pindell, and J. D. Matiskella, *J. Org. Chem.*, **33**, 3993 (1968).

(8) Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

(9) The procedure described here is based in part on the best features of three previous procedures: (a) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull. Jap.*, **12**, 773 (1964); (b) W. Pollmann and G. Schramm, *Biochem. Biophys. Acta*, **80**, 1 (1964); (c) G. Schramm, H. Grotsch, and W. Pollmann, *Angew. Chem. Intern. Ed. Engl.*, **1**, 1 (1962).

(10) K. Kindler and B. Gehlhaar, *Archiv. Pharm.*, **274**, 377 (1936).

bath for 2 hr. The yellow nitrotartranilate of X, 0.8 g, mp 165°, separated on cooling and was recrystallized from ethanol.

Anal. Calcd for $C_{31}H_{35}N_3O_{11}$: C, 59.52; H, 5.6; N, 6.72. Found: C, 59.07; H, 5.68; N, 6.47.

Treatment of the nitrotartranilate salt with base liberated the amine (X), identical in R_f, infrared spectrum ($CHCl_3$), and nmr spectrum ($CDCl_3$) with caseadine methyl ether prepared from natural (−)-caseadine.[2]

Registry No.—IV 20122-04-7; IV hydrochloride, 20122-05-8; VI, 20122-06-9; VII, 20122-48-9; VII picrate, 20122-49-0; VIII (N-acetyl derivative), 20122-07-0; IX, 20122-08-1; IX hydrochloride, 20122-09-2; X, 20122-10-5; X nitrotartranilate, 20122-11-6.

Acknowledgment.—We are grateful to Dr. D. B. MacLean and Dr. R. H. F. Manske for a small comparison sample of caseadine methyl ether, and for direct infrared and nmr comparisons of the synthetic and naturally derived bases. We also thank the Smith Kline and French Co., Philadelphia, for financial support of this investigation.

Some Approaches to the Total Synthesis of Lycorine

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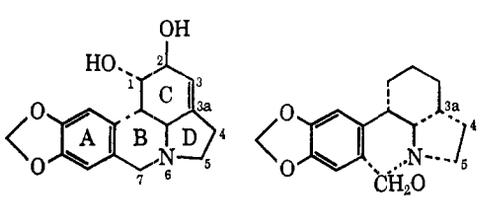
The problem of the synthesis of the lycorine family of *Amaryllidaceae* alkaloids is analyzed and two separate kinds of synthetic routes are examined experimentally. The first route, based on a Diels–Alder formation of ring C, leads to a product containing the lycorine skeleton with a nonaromatic ring C reasonably functionalized to complete the synthesis. The second approach, involving several variations on a roughly biosynthetic analogy, was frustrated on each occasion by reactions, usually internal conjugate additions, which took an undesirable course.

Lycorine (**1**) is the principal member of a family of *Amaryllidaceae* alkaloids[2] which have not been synthesized to date and which present an interesting synthetic challenge. In the present work we present an analysis of the synthetic problem and experimental work directed to several of the routes developed from this analysis, over a number of years.

The problem chiefly centers around ring C, which bears all four asymmetric centers and is in the same oxidation state as an aromatic ring, to which it readily reverts by double dehydration, destroying all asymmetric centers. The glycol is *trans* diaxial, hence in an unstable configuration on the rigid, *trans* decalin ring system. This situation argues for *trans* hydroxylation of a $\Delta^{1,2}$ double bond, while a $\Delta^{3,3a}$ double bond, presumably more susceptible to oxidation, must be retained in lycorine.



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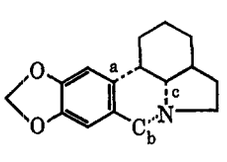

3

Starting material for the synthesis will presumably be piperonal (3,4-methylenedioxybenzaldehyde), which is readily available. Hence a second C–C bond must be formed to the aromatic ring. The piperonal aldehyde carbon can either be used as the carbon at the B/C-ring junction or as the aromatic link to the nitrogen atom. Two dissections of the skeleton into reasonable "synthons"[3] are shown in **2** and **3**, using piperonal in these two possible ways. The first dissection, **2**, is built on a Diels–Alder creation of ring C so as to assure *trans*-ring-fusion stereochemistry; the requisite diene can be four or six carbons and ring B would finally be cyclized using formaldehyde. The second dissection, **3**, is that which is utilized in biosynthesis of the *Amaryllidaceae* alkaloids,[4] oxidative coupling of phenols creating bond "a", followed by conjugate addition of nitrogen for bond "c"; this conjugate addition destroys the aromaticity of ring C which arises biosynthetically from tyrosine. We considered the Pschorr cyclization on a diazonium site to substitute for the biosynthetic oxidative coupling in linking rings A and C (bond "a").

The Diels–Alder Approach.[5]—The dienophile implicit in dissection **2** is 3,4-methylenedioxy-ω-nitrostyrene, bearing the correct skeleton and *trans* geometry and easily prepared from piperonal and nitromethane.[6] Unfortunately, this is a weakly activated dienophile, so that, while it reacted acceptably with butadiene to form **4a**, only polymers (and unchanged nitrostyrene) resulted from dienes with more than four carbons, like hexatriene or vinylacrylic acid. With vinylfuran, the nitrostyrene was consumed, but the reaction yielded a host of products (with saturated $-NO_2$ in the ir spectra) inseparable by chromatography. The expected product, **5**, should yield a bromo ketone

(1) Abstracted in part from the doctoral dissertation of D. R. D., UCLA, 1961.

(2) (a) W. C. Wildman, "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 289; (b) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960, "Akademie–Verlag, Berlin, 1961.

(3) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(4) (a) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, 1957, p 117; (b) A. R. Battersby, *Quart. Rev.*, **15**, 278 (1961); (c) D. A. Archer, S. W. Breuer, R. Binks, A. R. Battersby, and W. C. Wildman, *Chem. Comm.*, 168 (1963).

(5) A similar Diels–Alder construction was later used to synthesize the lycoranes by R. K. Hill, J. A. Joule, and L. J. Loeffler, *J. Amer. Chem. Soc.*, **84**, 4951 (1962).

(6) L. Bouveault and A. Wahl, *Compt. Rend.*, **135**, 42 (1902). We used a modification of the procedure of D. E. Worrall, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941.