same reaction work-up provided (+)-**lupine** (Ia): 170 mg, mp 57–58°, $[\alpha]^{26}D$ +1.43 ± 0.1° (*c* 14.1, ethanol).

**Registry No.**—VI, 493-10-7; IX, 7635-52-1; XI, 7688-06-4; X, 7695-29-6; Va, 7635-53-2; Vb, 7635-54-3; IIIa, 7635-55-4; IIIa picrate, 7635-56-5; IIIb, 7635-57-6; VIIa, 7635-58-7; VIIb, 7635-59-8; Ia, 7635-60-1; Ib, 3000-87-1; XV, 7635-62-3.

**Acknowledgments.**—We are pleased to acknowledge our thanks to the National Institute of Mental Health for their generous support of this work.

# Synthesis of (±)-Cryptowoline Iodide

F. BENINGTON[1] AND R. D. MORIN[1]

*Chemistry Department, Battelle Memorial Institute Columbus, Ohio, and the Department of Surgery, University of Alabama Medical Center, Birmingham, Alabama*

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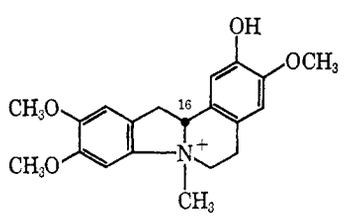
The synthesis of (±)-cryptowoline iodide by an unequivocal route confirms the previously assigned structure, 2-hydroxy-3-methoxy-8-methyl-11,12-methylenedioxy-6,7,15,16-tetrahydro[*b*,*g*]pyrrocolinium iodide.

Cryptowoline (XIII), one of the principal alkaloids of *Cryptocarya bowiei* (Hook) Druce, indigenous to southern Queensland, Australia, was isolated as its sparingly soluble iodide and characterized over a decade ago.[2] Both XIII and the related alkaloid cryptaustoline (Ia) were shown to be ethers of dehydrolaudanosoline, and a synthesis was reported of O-methylcryptaustoline[3] identical with the O-methylation product of Ia. Oxidation of *d*-laudanosine in the manner described by Robinson and Sugasawa[4] and by Schöpf and Thierfelder[5] was used to obtain the 2,3,11,12-tetramethoxy-8-methyl-6,7,15,16-tetrahydrodibenzo[*b*,*g*]-pyrrocolinium iodide (O-methylcryptaustoline iodide) which corresponds to natural cryptaustoline in having the correct configuration around $C_{16}$.




Ia

In the course of this study, we undertook the total synthesis of cryptowoline iodide[6] (XIII) from substituted aromatic intermediates which would lead ultimately to proper substituents in the A and D rings in XIII. The two key intermediates in this approach to XIII were 3-methoxy-4-benzyloxy-β-phenethylamine (II) and 6-bromohomopiperonylic acid (VI). In our initial attempts to obtain I, the β-nitrostyrene precursor of II, O-benzylvanillin,[7] was treated with nitromethane under the amine-catalyzed conditions described by Tomita and Watanabe.[8] In our hands, this condensation gave only polymeric compounds and none of the desired β-nitrostyrene (I). The same condensation reaction, when carried out in the presence of alcoholic potassium hydroxide, afforded I in good yield. Reduction of I with lithium aluminum hydride, in the usual manner, gave the desired 3-methoxy-4-benzyloxy-β-phenethylamine (II). Piperonyl alcohol (III) served as a starting material for the synthesis of 6-bromohomopiperonylic acid (VI).[9] Treatment of III with thionyl chloride gave crude 3,4-methylenedioxybenzyl chloride which was converted to homopiperonitrile in 90% yield by warming at 35–40° with potassium cyanide in dimethyl sulfoxide solution.[10] Esterification of IV followed by saponification gave the desired homo acid (V) which was, in turn, brominated smoothly to VI.

The acid chloride of VI was converted into N-(3-methoxy-4-benzyloxy-β-phenethyl)-6′-bromohomopiperonylamide (VII) by the action of excess 3-methoxy-4-benzyloxy-β-phenethylamine in ether solution. A Bischler–Napieralski cyclization of amide VII, effected by phosphoryl chloride in boiling toluene, gave 1-(6′-bromopiperonyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline (VIII) in 80% yield. Hydrogenation of a methanolic solution of VIII, containing slightly more than 1 equiv of concentrated hydrochloric acid, over a platinum oxide catalyst afforded (±)-1-(6′-piperonyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (IX).

Since our synthesis was aimed originally at obtaining (−)-cryptowoline iodide, it was thought that the resolution of the tetrahydroisoquinoline base IX could be carried out to give the pair of enantimorphs, each of which would then be carried through intermediates IX–XIII; one of these isomers of IX would ultimately result in a correct configuration at $C_{16}$ in structure XIII corresponding to (−)-cryptowoline. Reaction of (±)-IX with sufficient O,O′-dibenzoyl-L-tartaric acid to form an acid salt of the base proved to be an excellent method for separating the required enantimorphs; the (+) base O,O′-dibenzoyl-L-tartrate was nearly insoluble in ethyl acetate whereas the corresponding salt of the (−) base was extremely soluble in this solvent. The pure (+) and (−) enantimorphs of IX were regenerated by treating the purified salts with alkali.

(1) Formerly of the Chemistry Department, Battelle Memorial Institute, Columbus, Ohio, and now at the University of Alabama Medical Center, Birmingham, Ala.

(2) J. Ewing, G. K. Hughes, E. Richie, and W. C. Taylor, *Australian J. Chem.*, **6**, 315 (1953).

(3) G. K. Hughes, E. Richie, and W. C. Taylor, *ibid.*, **7**, 317 (1954).

(4) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 743 (1932).

(5) C. Schöpf and K. Thierfelder, *Ann.*, **497**, 22 (1932).

(6) Following the ring-numbering system shown for Ia, this alkaloid is systematically named as 2-hydroxy-3-methoxy-11,12-methylenedioxy-6,7,15,16-tetrahydrodibenzo[*b*,*g*]pyrrocolinium iodide.

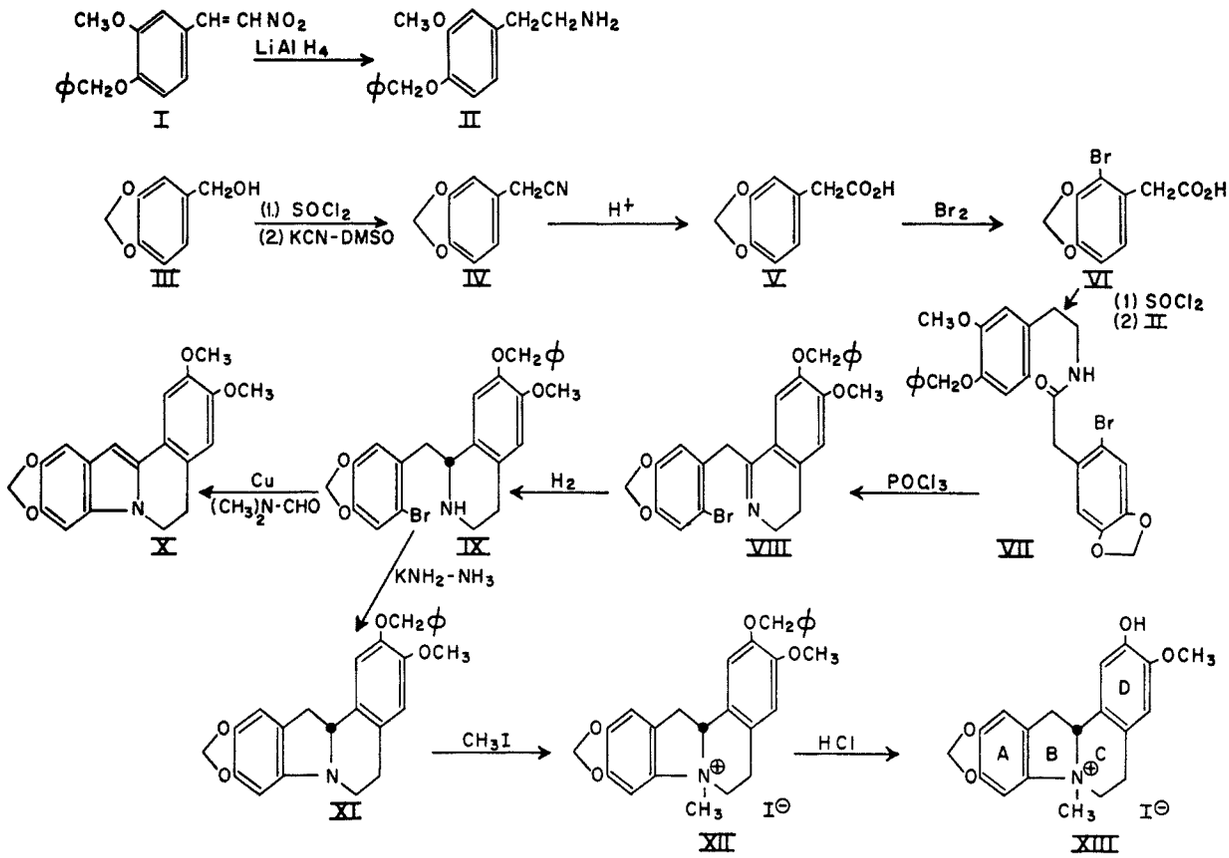
(7) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1895 (1927).

(8) M. Tomita and H. Watanabe, *J. Pharm. Soc. Japan*, **68**, 783 (1938).

(9) A. Girardet, *Helv. Chim. Acta*, **14**, 514 (1931).

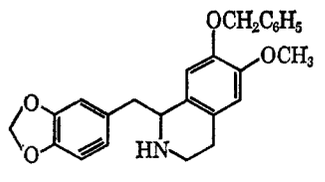
(10) L. Friedman and H. Schecter, *J. Org. Chem.*, **25**, 877 (1960).

SCHEME I



In a first attempt to prepare XI, racemic IX was subjected to the action of copper powder in boiling dimethylformamide.[11] Although cyclization occurred *via* elimination of hydrogen bromide, further oxidation took place to give 2-benzyloxy-3-methoxy-11,12-methoxylenedioxy-6,7-dihydrodibenzo[*b*,*g*]pyrrocoline (X) as the sole reaction product. This cyclic product gave an intense blue color reaction with Ehrlich's reagent which is characteristic of substituted indoles.

Cyclization of (±)-IX was carried out in accordance with the general procedure described by Bunnett and Hrutford[12] and by Konig and Huisgen[13] which is reported to involve the formation of a "benzyne" intermediate of the form shown as IXa. Thus, the aromatic halogen in the potential A ring is eliminated by the action of potassium amide in liquid ammonia solution *via* a nucleophillic displacement reaction to give racemic O-benzylnorcryptowoline (XI). Application of the potassium amide–liquid ammonia reaction to either the (+) or (−) enantiomorph of IX resulted in crystalline products with a wide melting range which could not be altered by repeated chromatography over alumina. This suggests that a base-catalyzed ($KNH_2$) racemization of IX occurred.



IXa

Clearly, this method of cyclization could not be applied to the preparation of enantiomorphic forms of XI. In still a further attempt to obtain a pair of optical isomers to carry through the proposed synthesis, (±)-XI was treated with O,O′-dibenzoyl-L-tartaric acid in the hope of resolving this base. However, no appreciable salt formation occurred, and the unresolved base was recovered along with a minor quantity of X; the latter compound was probably formed as a result of air oxidation of the somewhat acid solution of XI. Accordingly, it was decided to complete the outlined synthesis of XIII with racemic intermediates.

A comparison of the infrared spectra of IX with its cyclization product, O-benzylnorcryptowoline (XI), showed that the 3315-$cm^{-1}$ band (cyclic NH stretching) in IX is absent in XI whereas the spectrum of the latter exhibits a moderately sharp band at 2780 $cm^{-1}$; this band is characteristic of certain bridgehead nitrogen compounds such as quinolizidines.

Conversion of O-benzylnorcryptowoline (XI) to the corresponding quaternary iodide (XII) was accomplished in 98% yield by reaction with methyl iodide in dry benzene at room temperature. The infrared spectrum of the resulting (±)-O-benzylcryptowoline (XII) showed only a general diminution in the sharpness of the corresponding bands of the precursor in the 2700–2800-$cm^{-1}$ region (see Scheme I).

Catalytic hydrogenolysis of the 4-benzyl group in IX failed to bring about ether cleavage to give (±)-cryptowoline iodide. The final compound was, however, obtained by selective acid scission of the benzyl

(11) P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. J. Saggiomo, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1138 (1961).

(12) J. F. Bunnett and B. F. Hrutford, *J. Am. Chem. Soc.*, **83**, 1691 (1961).

(13) H. Konig and R. Huisgen, *Chem. Ber.*, **92**, 429 (1959).

ether. A comparison of the infrared spectra of natural (−)-cryptowoline iodide with synthetic (±)-XIII showed no significant differences excepting for a few weak absorptions which could be attributed to minor impurities probably present in the natural alkaloid sample.

## Experimental Section[14]

3-Methoxy-4-benzyloxy-β-phenethylamine (II) was obtained in 80% yield by the reduction of 3-methoxy-4-benzyloxy-β-nitrostyrene with lithium aluminum hydride[15] (HCl salt, mp 175–176°, lit. 176–178°), and also more conveniently by catalytic hydrogenation of 3-methoxy-4-benzyloxyphenylacetonitrile over Raney nickel in methanol solution in the presence of ammonia as described for hydrogenation of phenylacetonitrile.[16] The yield of amine boiling at 188–190° (2 mm), mp 66–68° (lit.[17] 67–69°) was 75%. The intermediate **3-methoxy-4-benzyloxyphenylacetonitrile** was obtained in 70% yield by treatment of 3-methoxy-4-benzyloxybenzyl chloride with sodium cyanide in dimethyl sulfoxide,[10] mp 69–70° after recrystallization from ethanol.

*Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 5.5; N, 5.5. Found: C, 76.3; H, 5.7; N, 5.4.

**N-(4′Benzyloxy-3′-methoxy-β-phenylethyl)-6-bromohomopiperonylamide (VII).**—A mixture of 19 g (0.073 mole) of 6-bromohomopiperonylic acid,[9] 15 ml of dry benzene, and 19 ml of thionyl chloride was heated under reflux for 2 hr when hydrogen chloride evolution had ceased. The benzene and excess thionyl chloride were removed by evaporation under reduced pressure, using two portions of fresh benzene to remove the last traces of thionyl chloride. The residual acid chloride was dissolved in 50 ml of anhydrous ether and added gradually to a stirred solution of 38 g (0.148 mole) of 3-methoxy-4-benzyloxy-β-phenethylamine in 800 ml of absolute ether. The solid mixture of product and amine hydrochloride which precipitated was collected by suction filtration, washed with ether, and stirred with 250 ml of warm (50°) water for 15 min to dissolve amine salt. The insoluble product was filtered off, washed with water, and air dried to yield 34 g (93%), mp 140–141°. After recrystallization from benzene–ethanol, a sample melted at 142.5–143°.

*Anal.* Calcd for $C_{25}H_{24}BrNO_5$: C, 60.3; H, 4.8. Found: C, 60.3; H, 4.8.

**1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline (VIII).**—A mixture of 29.8 g of VII, 120 ml of toluene, and 53 ml of phosphorus oxychloride was heated under reflux for 1.5 hr when a clear, brown solution was obtained. Upon cooling a pale yellow, dense solid crystallized. This material was dissolved in a hot mixture of methanol–water, and the clear solution was made distinctly alkaline with 10% aqueous sodium hydroxide and cooled to precipitate the product in the form of the free base to yield 25.0 g (82%), mp 165–166°. A sample recrystallized from benzene had the same melting point.

*Anal.* Calcd for $C_{25}H_{22}BrNO_4$: C, 62.5; H, 4.6. Found: C, 62.4; H, 4.6.

**(±)-1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (IX).**—A hot solution of 9.6 g (0.02 mole) of VIII in 250 ml of methanol containing 2 ml of hydrochloric acid was placed in a prewarmed Parr hydrogenation bottle. The free space over the solution was swept out with nitrogen, 0.5 g of Adams catalyst was added, and the mixture was shaken with hydrogen (50 psi). Absorption was rapid, and as soon as 1 mole of hydrogen was absorbed (about 1 min) the shaker was stopped, and the catalyst was removed by filtration. The filtrate was made distinctly alkaline with 10% aqueous sodium hydroxide, and on cooling and dilution with water the crude product precipitated. The dry, crude product was recrystallized from methanol–benzene by adding just sufficient benzene to a boiling methanol suspension of the solid to achieve solution. After filtration and being allowed to cool, the product crystallized as small prisms: mp 142–143°, 6.2 g (64%).

*Anal.* Calcd for $C_{25}H_{24}BrNO_4$: C, 62.2; H, 5.0. Found: C, 62.3; H, 4.9.

**Resolution of (±)-1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline.**—To a hot solution of 9.0 g (18.7 mmoles) of (±)-IX in 225 ml of ethyl acetate was added a hot solution of 6.7 g (18.7 mmoles) of O,O′-dibenzoyl-L-tartaric acid[18] in 90 ml of ethyl acetate. After a few moments crystallization began, and after allowing to cool to room temperature, the solid was collected yielding 8.0 g, mp 177–178°. This salt was completely pure from the initial crystallization, and the optically active base was recovered by treating a warm aqueous ethanol solution with dilute, aqueous sodium hydroxide to precipitate the base, which was filtered off, dried, and recrystallized from methanol–benzene to recover 3.9 g (86%) of (+)-base: mp 158–159°; $[\alpha]^{25}D$ +69.5° (*c* 2, chloroform). The other isomer was recovered from the original ethyl acetate filtrate by evaporation, treatment of an aqueous alcohol solution of the residue whith dilute aqueous sodium hydroxide, collecting the precipitate, and recrystallization from methanol–benzene to yield the (−) base: 3.7 g (83%) mp 158–159°; $[\alpha]^{25}D$ −69.7° (*c* 2, chloroform).

**(±)-2-Benzyloxy-3-methoxy-11,12-methylenedioxy-6,7,15,16-tetrahydrodibenzo[*b*,*g*]pyrrocoline (XI).**—A solution of potassium amide in anhydrous liquid ammonia was prepared from 2 g of clean potassium, 150 ml of liquid ammonia, and a trace of ferric nitrate. To this solution was added 4.8 g (10 mmoles) of (±)-IX, and the resulting mixture was stirred at refluxing liquid ammonia temperature (Dry Ice condenser, protected from atmospheric moisture) for 4 hr. The condenser was removed to allow the ammonia to evaporate. The dark residue was treated with 50 ml of water, and the mixture was then extracted with chloroform. The chloroform extract was washed with water and dried (anhydrous magnesium sulfate), and chloroform was removed by evaporation under reduced pressure. The dark, gummy residue was dissolved in 150 ml of benzene, and this solution was chromatographed through a column of alumina (2 × 22 cm) eluting with about 800 ml of benzene or until no additional material was removed from the column. The benzene eluate was evaporated to dryness under reduced pressure, and the white solid residue was recrystallized from ethyl acetate to yield 0.91 g (23%) of XI, mp 180–181°.

*Anal.* Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.7; N, 3.5. Found: C, 74.6; H, 5.8; N, 3.4.

Concentration of the mother liquid yielded a second crop of crystals, mp 157–158°, which was identified as 2-benzyloxy-3-methoxy-11,12-methylenedioxy-6,7-dihydrodibenzo[*b*,*g*]pyrrocoline (X) on the basis of analytical and nmr spectral data and formation of a blue color with Ehrlich's reagent indicating the presence of an indole nucleus.

*Anal.* Calcd for $C_{25}H_{21}NO_4$: C, 75.1; H, 5.3. Found: C, 75.0; H, 5.4.

This compound was also formed in very low yield when IX was treated with copper powder and dimethylformamide at reflux for 16 hr.

Attempts to cyclize either (+)-IX or (−)-IX with potassium amide in liquid ammonia resulted in the formation of products which were partially racemized, and it was not possible to isolate the (+) or (−) isomers of XI in pure form.

Attempts to resolve the base, (±)-XI, into its optically active isomers with O,O′-dibenzoyl-L-tartaric acid were unsuccessful. When a warm ethyl acetate solution containing equimolar quantities of (±)-XI and the optically active acid was allowed to cool, most of the base crystallized unchanged, apparently because salt formation did not occur. From the mother liquor, a small amount of X, mp 157–158°, was obtained indicating that some oxidation of XI had occurred.

**(±)-2-Benzyloxy-3-methoxy-8-methyl-11,12-methylenedioxy-6,7,15,16-tetrahydrodibenzo[*b*,*g*]pyrrocolinium Iodide (XII).**—To a solution of 0.98 g of (±)-XI in 50 ml of benzene was added 5 ml of methyl iodide. After standing at room temperature for 2 days, the product had crystallized completely to yield 1.3 g (98%), mp 211–212° dec.

(14) Melting points were taken in open capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. All infrared spectra were recorded from KBr pellets using a Perkin-Elmer 221 spectrophotometer.

(15) J. M. Bobbitt and T. Chou, *J. Org. Chem.*, **24**, 1106 (1959).

(16) J. C. Robinson, Jr., and H. R. Snyder, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 720.

(17) S. Kobayashi, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **6**, 149 (1927); *Chem. Abstr.*, **22**, 1345 (1928).

(18) O,O′-Dibenzoyl-L-tartaric acid is available from Frinton Laboratories, Vineland, N. J.

*Anal.* Calcd for $C_{26}H_{26}INO_4$: C, 57.5; H, 4.8. Found: C, 57.3; H, 4.6.

(±)-**Cryptowoline Iodide (XIII).**—A solution of 1.3 g of XII in 100 ml of methanol was shaken with hydrogen (50 psi) at 25° for 3 hr in the presence of 0.2 g of 10% palladium on charcoal. After removal of the catalyst by filtration and evaporation of the solvent, 1.25 g (95%) of the starting material was recovered unchanged. Therefore, to effect debenzylation of XII, a 200-mg sample dissolved in a mixture of 5 ml of methanol and 3 ml of hydrochloric acid was heated on a steam bath for 10 min and then evaporated to dryness under reduced pressure at 45°. The residue crystallized when triturated with methanol to yield 100 mg (60%) of XIII, mp 150–151° dec.

*Anal.* Calcd for $C_{19}H_{20}INO_4$: C, 50.4; H, 4.4. Found: C, 50.3; H, 4.4.

**Registry No.**—XIII, 7695-55-8; 3-methoxy-4-benzyloxyphenylacetonitrile, 1700-29-4; VII, 7687-04-9; VII, 7686-98-8; IX, 7686-99-9; (+)-1-(2′-bromo-4′,5′-methylenedioxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline, 7690-89-3; (−) base, 7687-00-5; XI, 7687-01-6; X, 7687-02-7; XII, 7687-03-8.

**Acknowledgment.**—This research was supported by a Battelle Memorial Institute grant. We are indebted to R. J. Jakobsen and T. F. Page for the measurement of infrared spectra. We also wish to thank Dr. E. Richie for a reference sample of natural (−)-cryptowoline iodide.

# A Practical Synthesis of Protostephanine

B. PECHERER AND A. BROSSI

*Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110*

*Received November 21, 1966*

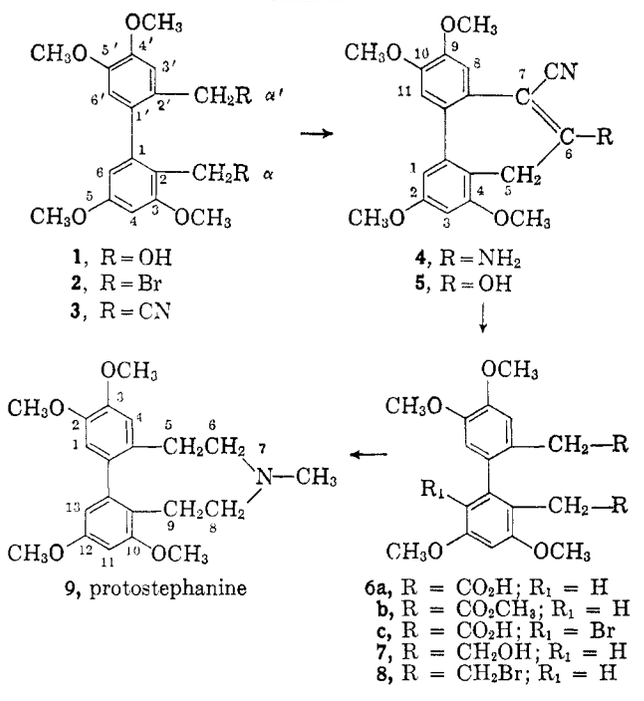
A synthesis of the alkaloid protostephanine, 6,7,8,9-tetrahydro-2,3,10,12-tetramethoxy-7-methyl-5H-dibenz[*d*,*f*]azonine, is described. The readily available 3,4′,5,5′-tetramethoxy-2,2′-biphenyldimethanol is converted into its homologous dibromide which is treated with methylamine to yield protostephanine identical with the natural material. The yield obtained in the ring-closure stage (34%) indicates that the formation of dibenz[*d*,*f*]azonines in this manner occurs more readily than might have been anticipated.

The structure determination of the alkaloid protostephanine, isolated from *Stephania japonica*, Miers, was reported in a series of papers by Kondo, Takeda, *et al.*,[1] to be 6,7,8,9-tetrahydro-2,3,10,12-tetramethoxy-7-methyl-5H-dibenz[*d*,*f*]azonine (**9**). Recently Takeda[2] gave added support for this formula by nmr spectra and a synthesis. However, the synthesis produced insufficient material for a satisfactory comparison with the natural product.[3]

In this paper a practical synthesis of protostephanine is described which starts from the readily available diol (**1**).[4] This approach resembles that of Takeda; however, it differs in many important details and proceeds as shown in Scheme I.

Diol **1** was first converted to diacetonitrile **3** *via* dibromide **2**. Attempts to hydrolyze **3** to the corresponding diacetic acid (**6a**) with acidic or basic reagents were unsuccessful. The following sequence gave **6a** in high yield. Treatment of diacetonitrile **3** in ethanol with a catalytic amount of sodium ethoxide gave a cyclic aminonitrile, probably **4**.[5] Acid hydrolysis of **4** yielded the hydroxynitrile (**5**). Treatment of the latter compound with methanolic sodium hydroxide caused simultaneous saponification of the cyano group and ring cleavage yielding the desired diacetic acid (**6a**) in an over-all yield of 84% based on the original diacetonitrile.

SCHEME I




The detailed structures of compounds **4** and **5** are of interest. In the solid state, compound **4** exists entirely as the aminonitrile as indicated by the infrared spectrum. There was no evidence for the presence of corresponding tautomer **4a** (Chart I). However, the product obtained by acid hydrolysis of **4** seems to be a mixture of hydroxynitrile **5** and ketonitrile **5a** (Chart I), since the infrared spectrum shows a hydroxyl band at 3585, and carbonyl band at 1730 $cm^{-1}$ and two cyano bands. One of these at 2250 $cm^{-1}$ corresponds to the unconjugated ketonitrile while the other at 2200 $cm^{-1}$ is attributed to a conjugated cyano group.

(1) For a summary and review of the early work, *cf.* H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie Verlag, Berlin, 1961, p 402, and the references given in our previous paper: B. Pecherer and A. Brossi, *Helv. Chim. Acta*, **49**, 2261 (1966).

(2) K. Takeda, *Itsuu Kenkyusho Nempo*, **13**, 45 (1963); *Chem. Abstr.*, **60**, 5570*f* (1964).

(3) The comparison of the synthetic and natural materials depended on the similarity of the $R_f$ value on paper strip chromatography and a micro melting point determination. While the $R_f$ values for both materials were identical, the melting point of the synthetic material was 65–68° whereas the natural alkaloid melts at 70–75°. These are data for the methanol complex of the alkaloid, but our experience has shown that the melting points do not constitute a reliable criterion in this series.

(4) Diol **1** is compound IX of the previous paper.[1]

(5) The present data, however, do not exclude structure **4c** (Chart I) which would originate by an alternate mode of ring closure. In this latter case the cyano group would occupy position 5.