The Synthesis of 10-Hydroxy-2,3,9-trimethoxydibenzo[a,g]quinolizidine. A Contribution to the Structure of the Corydalmine Alkaloids[1]

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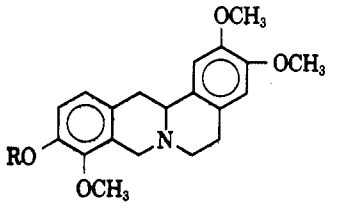
Starting with methyl 2,3-dihydroxybenzoate and proceeding *via* the preferential hydrogenolysis of methyl 2,3-dibenzyloxybenzoate, 3-hydroxy-2-methoxybenzoic acid and 3-benzyloxy-2-methoxybenzyl bromide have been prepared. By a modification of the method used by Bradsher and Dutta for the synthesis of palmatrubine, 3-benzyloxy-2-methoxybenzyl bromide was converted to 10-hydroxy-2,3,9-trimethoxybenz[*a*]acridizinium bromide and this was reduced to 10-hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine.

Among the alkaloids recently obtained by Imaseki and Taguchi[2] from the Chinese plant *Engosa* was a new dextrorotatory tetrahydroprotoberberine derivative to which they gave the name *corydalmine* and as-

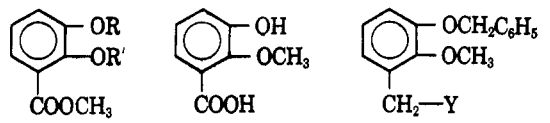


I, R = H
II, R = CH_3

signed the structure 10-hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine (I).

Since it has been shown that the aromatic cyclodehydration method makes possible the formation under very mild conditions[3-6] of dehydroberberinium salts which are easily reduced to tetrahydro derivatives, it seemed probable that a synthesis of I could be effected.

The 3-hydroxy-2-methoxybenzoic acid needed for the synthesis was unknown. The methyl ester III of 2,3-dihydroxybenzoic acid[7] could not be monobenzylated by the action of 1 equiv. of benzyl bromide.



III, R = R′ = H
IV, R = R′ = $CH_2C_6H_5$
V, R = $CH_2C_6H_5$; R′ = H
VI, R = $CH_2C_6H_5$; R′ = CH_3
VII, R = H; R′ = CH_3

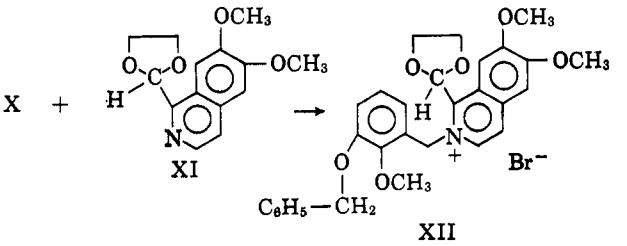
VIII

IX, Y = OH
X, Y = Br

Roughly half of the dihydroxy ester III was recovered unchanged and the product (35–45% yield) was the dibenzyloxy ester IV, insoluble in 2% sodium hydroxide solution. Through use of over 2 moles of benzyl bromide the yield of the dibenzyloxy derivative IV increased to 65%. Monodebenzylation of IV was carried out by catalytic hydrogenation,[8] stopping the reaction after the absorption of 1 mole. The phenolic compound V gave a green color with ferric chloride, suggesting that the benzyl group at the 2-position was the one removed. The benzyloxyhydroxy ester was next methylated with dimethyl sulfate and the product VI was debenzylated by hydrogenation over a palladium catalyst. Hydrolysis of the ester linkage followed by chromatography over silica gel afforded pure 3-hydroxy-2-methoxybenzoic acid (VIII). The acid did not give a color reaction with ferric chloride and was not identical with 2-hydroxy-3-methoxybenzoic acid.

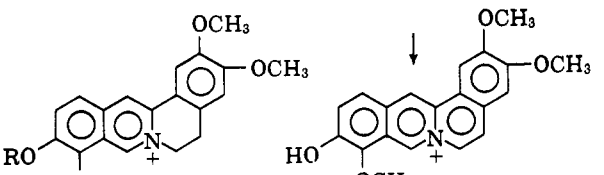
For the preparation of the desired benzyl bromide X, methyl 3-benzyloxy-2-methoxybenzoate was reduced with lithium aluminum hydride affording the benzyl alcohol IX which was converted to X by the action of phosphorus tribromide.

6,7-Dimethoxy-1-(1,3-dioxolan-2-yl)isoquinoline (XI) was prepared from the corresponding aldehyde[5] and allowed to react with 2-methoxy-3-benzyloxybenzyl bromide (X). The resulting quaternary salt XII was cyclized and debenzylated by heating for



XI

XII



XIV, R = H
XV, R = CH_3

XIII

about 2 min. at 100° with 48% hydrobromic acid. The red 10-hydroxy-2,3,9-trimethoxybenz[*a*]acridizinium (XIII) bromide salt obtained was reduced over platinum oxide yielding 10-hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine (I) as colorless prisms, m.p. 187.5–188.5°. The compound behaved as a pure substance in thin layer chromatography and on sublimation. Methylation of I with diazomethane yielded *dl*-tetrahydropalmatine (II) which was shown to be identical with an authentic sample.

In the same investigation which led to the isolation of corydalmine, Imaseki and Taguchi[2] isolated an optically inactive compound which they named dehydrocorydalmine and assigned the structure of 10-hydroxy-

(1) This investigation was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

(2) I. Imaseki and H. Taguchi, *J. Pharm. Soc. Japan*, **82**, 1214 (1962).
(3) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).
(4) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).
(5) C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2331 (1961).
(6) C. K. Bradsher and N. L. Dutta, *ibid.*, **27**, 2213 (1962).
(7) W. H. Perkin, Jr., and V. M. Trikojus, *J. Chem. Soc.*, 2925 (1926).
(8) *Cf.* R. A. Baxter, G. R. Ramage, and J. A. Timson, *ibid.*, 530 (1949).

2,3,9-trimethoxy-5,6-dihydrobenz[a]acridizinium (XIV) iodide. They also methylated the compound to yield palmatine (XV). They likewise found that XIV could be reduced with zinc and acetic acid to yield a compound to which they assigned the structure of *dl*-10-hydroxy-2,3,9-trimethoxydibenzo[a,g]quinolizidine (I) ("*dl*-corydalmine") after comparison of the infrared spectrum with that of *d*-corydalmine and of known isomers in the tetrahydroprotoberberine series. The *dl*-corydalmine of Imaseki and Taguchi is reported to melt at 213–215° or over 20° higher than our preparation. Since we have not been able to obtain for comparison a sample of any of the corydalmine alkaloids, we are not able to say whether the difference in melting point can be attributed to polymorphism or whether it has implications with regard to the structure of dehydrocorydalmine.

Experimental

Unless otherwise indicated all analyses are by Dr. Ing. A. Schoeller, Kronach, Germany. Melting points were determined in capillaries with the Mel-Temp block and are corrected. The ultraviolet absorption spectrum was determined in 95% ethanol using the Cary Model 14 spectrophotometer. The petroleum ether used for crystallization had b.p. 30–60°.

Methyl 2,3-Dibenzyloxybenzoate (IV).—A mixture containing 3 g. of methyl 2,3-dihydroxybenzoate,[9] 75 ml. of acetone, 20 g. of anhydrous potassium carbonate, and 5.1 ml. of benzyl chloride was refluxed for 36 hr. The acetone was evaporated, the residue was steam distilled to remove excess benzyl chloride, and the aqueous suspension was extracted with ether. The ethereal layer was washed with 2% sodium hydroxide solution and then with water and finally dried over sodium sulfate. Evaporation of the ether afforded an oil which crystallized from petroleum ether as colorless needles, m.p. 62.5–63.5°, yield 4.1 g. (66%). This material gave no color with ferric chloride solution.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.78. Found: C, 75.82; H, 5.58.

Methyl 3-Benzyloxy-2-hydroxybenzoate (V).—A suspension of 0.1 g. of 10% palladium-on-charcoal catalyst in 50 ml. of ethanol was saturated with hydrogen and then 1.78 g. of methyl 2,3-dibenzyloxybenzoate was added. The mixture was hydrogenated at room temperature and at a pressure of 1 atm. until 1 molar equiv. of hydrogen had been absorbed. The filtered solution was concentrated under vacuum affording an oil which crystallized from petroleum ether as colorless needles, m.p. 69.5–70.5°, yield 1.1 g. (88%). This material gave a green color with ferric chloride solution.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.74; H, 5.44.

Methyl 3-Benzyloxy-2-methoxybenzoate (VI).—A mixture containing 1 g. of methyl-3-benzyloxy-2-hydroxybenzoate (V), 10 g. of anhydrous potassium carbonate, and 0.6 ml. of dimethyl sulfate in 50 ml. of acetone was refluxed for 24 hr. The acetone was evaporated, and the residue was treated with water and extracted with ether. The ethereal layer was dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oil distilled at 168–170° (1 mm.) and gave no color with ferric chloride solution; the yield was 1 g. (99%).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.41; H, 5.92. Found: C, 70.22; H, 5.78.

Methyl 3-Hydroxy-2-methoxybenzoate (VII).—A suspension of 0.07 g. of palladium on charcoal in 25 ml. of ethanol was saturated with hydrogen and 0.7 g. of methyl 3-benzyloxy-2-methoxybenzoate (VI) was added. Hydrogenation was continued until about 1 molar equiv. of hydrogen had been absorbed. On concentration of the solution an oil was obtained, b.p. 125–126° (1 mm.), yield 0.45 g. (97%).

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.34; H, 5.86.

3-Hydroxy-2-methoxybenzoic Acid (VIII).—A solution of 0.2 g. of methyl 3-hydroxy-2-methoxybenzoate in 10 ml. of 5% ethanolic sodium hydroxide solution was refluxed on the steam bath for 1 hr. After evaporation of the ethanol the residue was treated with 20 ml. of water. The solution was acidified and extracted with ether. The ethereal layer gave an acid which was chromatographed on silica gel using methanol as an eluent. The acid, which did not give a color reaction with ferric chloride solution, crystallized from benzene as colorless plates, m.p. 150–151°, yield 0.14 g. (80%). Despite the similarity in melting point to the isomeric 2-hydroxy-3-methoxybenzoic acid (lit.[10] m.p. 151–152°), the two compounds were not identical and the mixture melting point was depressed to 125°. Indication of the relative position of the hydroxyl and carboxyl groups is afforded not only by the ferric chloride color test (positive for 2-hydroxy-3-methoxybenzoic acid), but also by the infrared absorption in the carbonyl region: 2-hydroxy-3-methoxybenzoic acid, 1663 cm.$^{-1}$ (intramolecular hydrogen bonding); 3-hydroxy-2-methoxybenzoic acid (VIII), 1705 cm.$^{-1}$.

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.79. Found: C, 57.47; H, 5.07.

3-Benzyloxy-2-methoxybenzyl Alcohol (IX).—A solution of 2.5 g. of methyl 3-benzyloxy-2-methoxybenzoate (VI) in 50 ml. of dry ether was added dropwise over a 45-min. period to a stirred suspension of 0.76 g. of lithium aluminum hydride in 50 ml. of dry ether, and the mixture was refluxed for 2 hr. The flask was cooled in ice and 20 ml. of water was added cautiously, followed by 20 ml. of 10% sulfuric acid. The ether layer was separated, washed with sodium bicarbonate solution and water, and dried over magnesium sulfate. Concentration of the solution followed by distillation afforded an oil, b.p. 175° (1 mm.), which crystallized from petroleum ether as colorless needles, m.p. 56.5°, yield 1.7 g. (77%).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.78; H, 6.60. Found: C, 74.08; H, 6.27.

3-Benzyloxy-2-methoxybenzyl Bromide (X).—To a solution containing 1.22 g. of the benzyl alcohol IX in 10 ml. of dry ether at 0° an ethereal solution containing 0.5 ml. of phosphorus tribromide was added. The mixture was stirred at 0° for 10 min. and at room temperature for 1 hr. The mixture was poured into ice–water and extracted with ether. The ether solution was washed with water, bicarbonate solution, and again with water. The dried (magnesium sulfate) solution was concentrated and the residue crystallized from petroleum ether as colorless plates, m.p. 54.5–55.5°, yield 1.3 g. (86%).

Anal. Calcd. for $C_{15}H_{15}BrO_2$: C, 58.66; H, 4.92. Found: C, 59.00; H, 4.78.

6,7-Dimethoxy-1-(1,3-dioxolan-2-yl)isoquinoline (XI).—A solution containing 2.4 g. of 6,7-dimethoxyisoquinoline-1-carboxaldehyde,[5] 2.76 g. of ethylene glycol, 0.9 g. of *p*-toluenesulfonic acid, and 15 ml. of benzene was refluxed for 48 hr. using a modified Dean–Stark water separator. The mixture was poured into sodium carbonate solution and the benzene layer was separated. The water layer was extracted several more times with benzene and the combined benzene solutions were washed once with water and dried over magnesium sulfate. The solution was concentrated and the residue was crystallized from benzene–hexane as pale yellow plates, m.p. 168–169°, yield 2.2 g. (73%).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.39; H, 5.79; N, 5.36. Found: C, 64.68; H, 6.08; N, 5.68.

2-(3-Benzyloxy-2-methoxybenzyl)-6,7-dimethoxy-1-(1,3-dioxolan-2-yl)isoquinolinium Bromide (XII).—A mixture containing 0.52 g. of the acetal XI and 0.61 g. of 3-benzyloxy-2-methoxybenzyl bromide (X) in 1 ml. of tetramethylene sulfone was left at room temperature for 8 days. The quaternary salt was precipitated by addition of ethyl acetate and was crystallized from methanol–ethyl acetate as pale yellow prisms, m.p. 173.5–174.5°, yield 1.0 g. (90%).

Anal. Calcd. for $C_{29}H_{30}BrNO_6 \cdot 0.5H_2O$: C, 60.31; H, 5.41; N, 2.42. Found: C, 60.69; H, 5.57; N, 2.25.

10-Hydroxy-2,3,9-trimethoxybenz[a]acridizinium Bromide (XIII).—The quaternary salt XII (0.2 g.) was cyclized by heating it with 48% hydrobromic acid on the steam bath until red crystals began to separate from solution (about 2 min.). The acid was removed under vacuum (aspirator) and the residue was crystallized from methanol as red needles, decomposing at >260° but not melting below 400° in sealed tube; the yield was 0.24 g. (83%).

Anal. Calcd. for $C_{20}H_{18}BrNO_4$: C, 57.70; H, 4.35; N, 3.37; OCH_3, 22.36. Found: C, 57.40; H, 4.30; N, 3.44; OCH_3, 21.83.

(9) Bayer and Co., German Patent 281,214; *Chem. Zentr.*, **I**, 180 (1915).

(10) J. M. Shackelford, *J. Org. Chem.*, **26**, 4908 (1961).

The **perchlorate** crystallized from methanol as orange needles, m.p. 291–292° dec. (sealed tube).

Anal. Calcd. for $C_{20}H_{18}ClNO_8$: C, 54.00; H, 4.30; N, 3.15; OCH_3, 22.36. Found: C, 53.75; H, 4.64; N, 3.33; OCH_3, 21.83.

10-Hydroxy-2,3,9-trimethoxydibenzo[*a*,*g*]quinolizidine (I).—A suspension of 0.2 g. of 10-hydroxy-2,3,9-trimethoxybenz[*a*]acridizinium bromide (XIII) in 100 ml. of ethanol was hydrogenated in the presence of platinum oxide (0.03 g.) for 72 hr. The colorless solution was filtered and concentrated under reduced pressure. The residue was treated with a dilute solution of ammonium hydroxide and extracted with chloroform. The residue obtained by evaporation of the chloroform was crystallized from methanol in colorless prisms, m.p. 187.5–188.5°.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.58; H, 6.51; N, 4.15.

This compound (I) gave evidence of complete homogeneity when chromatographed on alumina plates with benzene–methanol, ether–methanol, and methanol. The melting point was unchanged by vacuum sublimation.

2,3,9,10-Tetramethoxydibenzo[*a*,*g*]quinolizidine (II, Tetrahydropalmatine).—A solution of 10-hydroxy-2,3,9-trimethoxybenz[*a*,*g*]quinolizidine (0.2 g.) in 10 ml. of dry methanol was mixed with an excess of diazomethane in dry ether (100 ml.) and the mixture was allowed to remain at refrigerator temperature for 7 days and then was allowed to evaporate at room temperature. The residue crystallized from methanol as colorless needles, m.p. 148° (lit.[11] m.p. 147°), and was shown to be identical with an authentic sample (no mixture melting point depression).

(11) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, Jr., *J. Chem. Soc.*, 548 (1927).

Structure of Tomatillidine

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Tomatillidine (I) subjected to Wolff–Kishner reduction gave deoxotomatillidine (VII), which afforded dihydrodeoxotomatillidine (VIII) by catalytic hydrogenation. VIII was converted into O,N-diacetyl-Δ^{22}-dihydrodeoxotomatillidine (X) by treatment with acetic anhydride, then into 3β-acetoxy-26-acetylaminocholestan-22-one (XII), by acid hydrolysis. The latter (XII) yielded 3β-acetoxybisnorallocholanic acid (XIV) by chromic acid oxidation. Selenium dehydrogenation of deoxotomatillidine (VII) afforded a 2,5-disubstituted pyridine derivative which aided in the elucidation of the structure of the basic moiety of the molecule. Mass spectral patterns of hexahydrotomatillidine (III), tetrahydrodeoxotomatillidine (XV), deoxotomatillidine (VII), tomatillidine (I), its O-acetyl derivative (Ia), and dihydrotomatillidine (II) and spectral data (ultraviolet, infrared, and n.m.r.) of O,N-diacetyltomatillidine (VI) showed the location of the carbonyl group.

Solasodine and two new alkaloids, tomatillidine (I)[2] and dihydrotomatillidine (II), have been isolated from *Solanum tomatillo* (Philippi) of Chilean botanical origin. When the crude extract of leaves from old plants of *S. tomatillo* (Philippi) collected in March–April (beginning of fall in the southern hemisphere) was chromatographed, a small amount (0.02%) of crude tomatillidine followed by the major component solasodine in yields of 1.3%, was obtained. Further purification of the crude fraction of tomatillidine by gradient elution chromatography and fractional recrystallization afforded dihydrotomatillidine (*ca.* 15–20%, based on crude tomatillidine). From leaves of young plants collected in December (beginning of summer), the yields of dihydrotomatillidine were much higher (*ca.* 80%, based on crude tomatillidine), although the total alkaloidal content was somewhat lower.

From consideration of its empirical formula, $C_{27}H_{41}NO_2$, and the fact that it accompanied solasodine,[3] a well-known steroidal alkaloid, it was suspected that tomatillidine (I) was steroidal in nature. Of the two oxygen functions in tomatillidine, one was shown to be alcoholic by its conversion to O-acetyltomatillidine (Ia) in the usual manner (acetic anhydride–pyridine). Alkaline hydrolysis of Ia readily regenerated the parent compound. A double bond, whose presence was revealed in the n.m.r. spectrum of tomatillidine (olefinic proton, 5.35 p.p.m.), was found to be located in the proximity of the alcoholic function by Oppenauer oxidation which converted I into an α,β-unsaturated oxo derivative V, $\lambda_{max}^{C_2H_5OH}$ 240 mμ (log ϵ 4.24). The same compound V was also obtained by isomerizing the product IV of the Kiliani[4] oxidation of tomatillidine with methanolic alkali.[5] The ketonic nature of the second oxygen atom in tomatillidine was indicated by its characteristic low ultraviolet absorption at about 285 mμ and verified by the formation of a semicarbazone.[6a] The rotatory dispersion curve of tomatillidine displayed a positive Cotton effect but the shift of the peak from the normal[6b] toward the shorter wave length pointed to the presence of an external disturbing factor in its environment. The failure of tomatillidine to form the N-acetyl derivative under normal acetylating conditions, along with the infrared absorption band in tomatillidine at 6.18 μ of medium intensity, indicated that the nitrogen atom in all probability was present as a part of a C=N group.

In order to explore the compound more fully without the ketonic function, tomatillidine was submitted to Wolff–Kishner reduction (Huang-Minlon modification).[7] The resulting deoxotomatillidine (VII, mol. wt. 397, mass spectrum) possessed an infrared absorption band at 6.04 μ ascribable to a >C=N– moiety

(1) (a) Appointment supported by International Cooperation Administration under the visiting research scientist program administered by the National Academy of Sciences of the United States of America. Guest investigator at Stanford University, 1962–1963, and at the National Institutes of Health, 1963–1964. (b) To whom inquiries should be made at College of Pharmacy, University of Arizona, Tucson, Ariz. (c) National Institute of Arthritis and Metabolic Diseases.

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(3) L. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray, and R. N. Seelye, *J. Chem. Soc.*, 3013 (1950).

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(7) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).