obtained. Recrystallization from methanol gave 120 mg. of crystalline alkaloid.

B. **Olivacine.**—A larger batch of ground root (4.7 kg.) was extracted with benzene and 55 g. of alkaloidal residue obtained. Repeated extraction with 5% tartaric acid solution, followed by dissolving the insoluble portion in glacial acetic acid and water gave upon standing in the cold a yellow precipitate. Recrystallization from ethanol gave 1.6 g. of olivacine tartrate. For analysis, the material was recrystallized repeatedly from ethanol, m.p. 209–211° dec.

Anal. Calcd. for $C_{21}H_{20}O_6N_2$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.45; H, 5.17; N, 7.19.

The base was liberated from the tartrate and recrystallized two times from methanol; prisms, m.p. 317–325° dec.

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.16; H, 5.85; N, 11.30.

Base Methiodide.—A solution of the base (180 mg.) in warm acetone (100 ml.) was treated with excess (10 ml.) of freshly distilled methyl iodide. After standing for 6 hours, the crystals of methiodide were collected and recrystallized from boiling methanol (120 mg.), m.p. <270°.

Anal. Calcd. for $C_{18}H_{17}N_2I$: C, 55.68; H, 4.41; N, 7.22; I, 32.69. Found: C, 55.76; H, 4.63; N, 6.90; I, 32.27.

Sodium Borohydride Reduction of Base Methiodide.—To 150 mg. of methiode in ethanol was added a solution of 250 mg. of $NaBH_4$ in 8 ml. of water. The yellow solution was allowed to stand overnight at room temperature. After this time, the solution became colorless. After the usual workup, 140 mg. of the reduced base was obtained. Recrystallization from acetone yielded 110 mg. of crystalline material, m.p. 218–221° dec. The ultraviolet spectrum of olivacine is characterized by the following bands: λ_{max}^{EtOH} 222, 236 mμ (log a_M 4.39, 4.30), 266, 275, 285, 292 mμ (log a_M 4.50, 4.66, 4.84, 4.81), 312, 327, 342 mμ (log a_M 3.58, 3.70, 3.50), 375, 392 mμ (log a_M 354, 3.51).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.75; H, 7.41; N, 10.35.

T. oppositifolia.—Chromatography of 3.5 g. of alkaloids obtained from the benzene extract of the root (1.2 kg.) yielded 300 mg. of crystalline ibogamine, 70 mg. of coronaridine and, finally, 75 mg. of voacangine. Following elution with benzene–chloroform (1:1), 100 mg. of voacamine was obtained.

T. australis.—From the Skelly B extract prepared from 3.5 kg. of stems, there was obtained 2.0 g. of alkaloids. The chromatography of this material gave 1.7 g. of crystalline voacangine followed by 100 mg. of voacamine. Chromatography of the alkaloids prepared from the benzene extract yielded by elution with benzene 180 mg. of voacangine followed by 450 mg. of crystalline voacamine (benzene–chloroform mixture, 2:1).

T. undulata.—The alkaloids (1.83 g.) from the stems (1.3 kg.) gave no crystalline materials on repeated chromatography.

Ibogamine from Coronaridine.—A solution of 30 mg. of coronaridine in 8 ml. of 60% ethanol containing 0.5 g. of KOH was refluxed for 6 hours. Evaporation of the ethanol *in vacuo* and addition of 5 *N* hydrochloric acid (10 cc.) at 0° gave a clear solution of coronaridic acid. The acid solution was warmed on a steam-bath for 30 minutes, made basic with ammonia and extracted with ether. Crystallization of the residue from methanol yielded 21 mg. of material, m.p. 160–162°, identified as ibogamine (Id).

INDIANAPOLIS 6, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

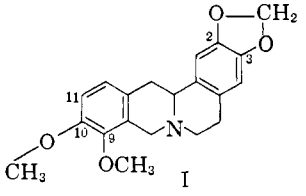
Aromatic Cyclodehydration. XLIII.[1,2] Synthesis of Tetrahydroberberine and Some Dehydroberberine Analogs

BY C. K. BRADSHER AND N. L. DUTTA

RECEIVED JULY 13, 1959

6,7-Methylenedioxyisoquinoline-1-aldehyde (IV) and its oxime V have been synthesized, and used to prepare dehydroberberine (VI) and some of its analogs (VII–IX). The catalytic reduction of dehydroberberine gave the known tetrahydroberberine (I).

Berberine is perhaps the most important member of a group or alkaloids which bear the generic name. Although Perkin[3,4] and his associates effected an



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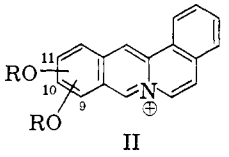
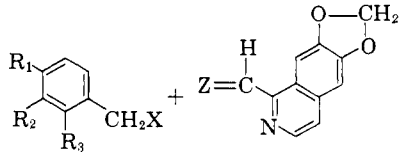


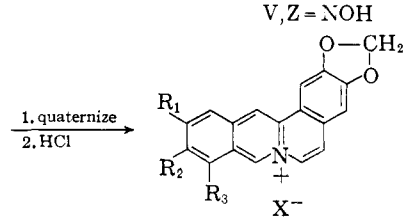
II

elegant and unequivocal synthesis of tetrahydroberberine (I), there has remained a need for a simple synthetic method suitable for the convenient preparation of tetrahydroberberine and its analogs.

In earlier work[5] it was shown that benzo[a]acridizinium derivatives (II) having alkoxyl substituents in one terminal ring (9- and 10-positions) could be prepared by cyclization of quaternary salts obtained by the reaction of suitable alkoxybenzyl halides with isoquinoline-1-aldehyde. It seemed very likely that if 6,7-methylenedioxyiso-



III IV, Z = O V, Z = NOH



VI, R_1 = H; R_2 = R_3 = OCH_3
VII, R_1 = R_2 = OCH_3; R_3 = H
VIII, R_1–R_2 = O–CH_2–O; R_3 = H
IX, R_1 = R_3 = H; R_2 = OCH_3

(1) For the preceding communications of this series, see C. K. Bradsher and K. B. Moser, *J. Org. Chem.*, **24**, 592 (1959).

(2) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(3) (a) W. H. Perkin, J. N. Rây and R. Robinson, *J. Chem. Soc.*, **127**, 740 (1925); (b) R. D. Haworth, W. H. Perkin and H. S. Pink, *ibid.*, **127**, 1709 (1925); (c) R. D. Haworth, J. B. Koepfli and W. H. Perkin, *ibid.*, 548 (1927).

(4) *Cf.* I. K. Jezo and D. Rybár, *Chem. Zvesti*, **8**, 14 (1954); *C. A.*, **50**, 373 (1956).

(5) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

quinoline-1-aldehyde (IV) could be prepared, the way would be opened for the synthesis of the previously unknown dehydroberberinium salts VI as well as tetrahydroberberine (I). It was found that the known[6] 1-methyl-6,7-methylenedioxyisoquinoline, conveniently prepared by the Bischler–Napieralski cyclization[7] of homopiperonylacetamide, followed by dehydrogenation,[6] can be oxidized to the aldehyde IV in 37% yield by the action of selenium dioxide.[8] The new aldehyde IV is much less soluble in organic solvents than isoquinoline-1-aldehyde, and it was found that quaternization could best be achieved when the methylenedioxyisoquinoline-1-aldehyde was heated at 100° with the alkoxybenzyl halide in acetonitrile. When the benzyl halide was 2,3-dimethoxybenzyl chloride (III, R_1 = H; R_2 = R_3 = OCH_3) and the crude quaternary salt was cyclized by heating it in concentrated hydrochloric acid, the over-all yield of dehydroberberinium chloride (VI, X = Cl) was 30%.

When the project was near completion, the newly discovered advantages which arise from the use of picolinic aldoxime (rather than the free aldehyde) in the acridizinium ion synthesis[9] suggested that the oxime of 6,7-methylenedioxyisoquinoline-1-aldehyde be tried in the present synthesis. Using the oxime, the over-all yield for quaternization (in dimethylformamide) and cyclization was 67%. The ultraviolet and visible absorption spectra of dehydroberberinium chloride resembled those of the benzo[a]acridizinium salts previously prepared.[5] Catalytic reduction of the new salt (VI, X = Cl) afforded tetrahydroberberine identical with that obtained by the catalytic reduction of berberinium chloride.

Since interest in the berberine isomer, with methoxyl groups at positions 10 and 11 (pseudoberberine), dates back to probably the earliest report[10a] (since discredited)[10b,c] of the synthesis of tetrahydroberberine, it appeared worthwhile to attempt the first synthesis of dehydropseudoberberine (VII). Since veratryl bromide (III, R_1 = R_2 = OCH_3, R_3 = H) is very prone to self-condensation[11] it seemed well to study its behavior with the readily available picolinic aldehyde. It was found that one can effect the quaternization and cyclization reactions to afford the new 8,9-dimethoxyacridizinium chloride (X) in an over-all yield of 80%. The new dimethoxyacridizinium derivative X was identified by reduction to the known[12] 8,9-dimethoxybenzo[b]quinolizidine (XI).

The quaternization of 6,7-methylenedioxyisoquinoline-1-aldehyde (IV) by the action of veratryl bromide, followed by cyclization of the crude salt in hydrochloric acid, afforded a mixture of 2,3,6,7-tetramethoxy-9,10-dihydroanthracene (produced by self-condensation of the veratryl derivatives)[11] and a salt which had the properties expected for dehydropseudoberberine chloride (VII). Two additional benzo[a]acridizinium compounds were synthesized for comparison. For the first of these, the 2,3,10,11-bis-methylenedioxybenzo[a]acridizinium salt, the yield obtained starting with 6,7-methylenedioxyisoquinoline-1-aldehyde was quite satisfactory, by either the aldehyde or oxime method (66%). In the case of the second, dehydro-des-(9)-methoxyberberinium chloride (IX), the oxime route was definitely superior (63%) to the aldehyde route (30%).

The methods described in this communication not only permit the facile synthesis of the hitherto unknown dehydroberberinium salts, but provide a route to the tetrahydroberberines and berberines as well. Work is near completion on the synthesis of a number of compounds related to palmatine.

Experimental[13]

1-Methyl-6,7-methylenedioxyisoquinoline.—The required homopiperonylamine was prepared by lithium aluminum hydride reduction of piperonylidenenitromethane[14] essentially as described earlier[15,16] except that the use of tetrahydrofuran as a solvent eliminated the need for a Soxhlet extractor[15] with no sacrifice in yield[16] (85%). 1-Methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline prepared by cyclization of crude N-homopiperonylacetamide[16] was dehydrogenated by heating 20 g. for 1.5 hours with 6 g. of 10% palladium-on-charcoal catalyst at 150°, m.p. 160° (lit.[6] 159–160°), yield 16 g. (81%). Purification of the isoquinoline was best effected by passing it through a column of alumina and eluting it with benzene.

6,7-Methylenedioxyisoquinoline-1-carboxaldehyde (IV).—A solution of 6,7-methylenedioxy-1-methylisoquinoline (5 g.) in purified dioxane (50 ml.) was added dropwise in the course of 30 minutes to a hot, stirred, solution of freshly prepared and sublimed selenium dioxide (3.5 g.) in dioxane (50 ml.) and water (3 ml.). In the course of a few minutes a red precipitate slowly appeared and the whole mixture was heated on the steam-bath with continued agitation for 5 hours. At the end of this period, the precipitated selenium was filtered from the hot solution and the bulk of the dioxane was removed under diminished pressure. The residual material was collected, diluted with water, made alkaline with sodium hydroxide solution, and exhaustively extracted with ether. The dark colored ethereal solution was dried (sodium sulfate) and decolorized[17] (Norite). The almost colorless solution was concentrated and the residue crystallized from alcohol. The expected aldehyde was obtained as colorless needles, yield 1.1 g. By concentration of the mother liquor, 2 g. of the unreacted methylisoquinoline was obtained, m.p. 156–159°. On the basis of starting material consumed, the yield was 37%.

A sample was purified for analysis by chromatography on alumina and crystallization from alcohol, m.p. 187.5°.

Anal. Calcd. for $C_{11}H_7O_3N$: C, 65.76; H, 3.51; N, 6.96. Found[18]: C, 65.55; H, 3.40; N, 7.07.

The oxime V of the aldehyde IV was prepared in the usual way, and crystallized from ethanol as colorless needles, m.p. 256–257°.

(6) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(7) B. B. Dey and T. R. Govindachari, *Proc. Natl. Inst. Sci. India*, **6**, 195 (1940); *C. A.*, **36**, 5178 (1942).

(8) For details of a similar oxidation see R. S. Barrows and H. G. Lindwall, THIS JOURNAL, **64**, 2430 (1942).

(9) These observations will be described in a forthcoming publication.

(10) (a) A. Pictet and A. Gams, *Ber.*, **44**, 2480 (1911); (b) R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.*, **125**, 1686 (1924); (c) T. G. H. Jones and R. Robinson, *ibid.*, **111**, 903 (1917).

(11) P. Carré and D. Libermann, *Compt. rend.*, **199**, 791 (1934), has shown that even veratryl chloride easily undergoes self-condensation to yield 2,3,6,7-tetramethoxy-9,10-dihydroanthracene.

(12) N. Sugimoto, *J. Pharm. Soc., Japan*, **76**, 1047 (1956.)

(13) Except as noted all melting points were determined on the Fisher–Johns block and are uncorrected. Infrared absorption spectra were determined by the potassium bromide plate method using the Perkin–Elmer model 137 Infracord spectrophotometer. All ultraviolet spectra were measured in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. silica cells. Except as noted all analyses were by Drs. Weiler and Strauss, Oxford, England.

(14) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

(15) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(16) W. J. Gensler and C. M. Samour, THIS JOURNAL, **73**, 5555 (1951).

(17) Omission of this step results in a significant decrease in the yield of aldehyde.

(18) Analysis by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_{11}H_8O_3N_2$: N, 12.96. Found[18]: N, 12.75.

9,10-Dimethoxy-2,3-methylenedioxybenzo[a]acridizinium Chloride (Dehydroberberinium Chloride, VI). (a) By the Aldehyde Method.—One gram of the aldehyde IV was refluxed for 3 hours under a nitrogen atmosphere with 1.2 g. of 2,3-dimethoxybenzyl bromide[19,20] in 20 ml. of acetonitrile, after which the solvent was removed under vacuum, and the light yellow solid residue washed with ether. Concentrated hydrochloric acid (30 ml.) was used to dissolve the residue, and the red solution was heated on the steam-bath for one hour. Orange needles separated, and were collected from the cooled mixture. The product was crystallized from ethanol as orange needles, m.p. 215° dec., yield 0.65 g. (30%). No improvement in yield was effected by changes in the solvent used for quaternization, or in the refluxing time.

(b) By the Oxime Method.—The oxime (V, 0.5 g.) was dissolved in 7 ml. of dimethylformamide by heating on a steam-bath, and 0.65 g. of 2,3-dimethoxybenzyl bromide was added to the hot solution. After one hour on the steam-bath and 48 hours at room temperature, ether and ethyl acetate were added to the yellow solution to precipitate the quaternary salt. The yellow precipitate was collected, washed twice with ether, and dried under vacuum. The crude salt was dissolved in 15 ml. of concentrated hydrochloric acid and heated on the steam-bath. After 7–8 minutes orange crystals appeared in the solution, but heating was continued for an additional 10 minutes. The product was collected from the cooled reaction mixture and crystallized from ethanol as orange needles, m.p. 215° dec., yield 0.65 g. (67%). The analytical sample melted at the same temperature; λ_{max} 246, 278, 310, 348 and 460 mμ; λ_{min} 257, 290.5, 332 and 405 mμ.

Anal. Calcd. for $C_{20}H_{16}ClNO_4 \cdot 3H_2O$: C, 56.66; H, 5.19; N, 3.31. Found: C, 56.26; H, 4.89; N, 3.34.

The perchlorate formed well-defined reddish needles from methanol, m.p. >500° (darkens above 400°).

Anal. Calcd. for $C_{20}H_{16}ClNO_8$: C, 55.43; H, 3.69; N, 3.23. Found: C, 55.22; H, 3.76; N, 3.00.

2,3-Methylenedioxy-9,10-dimethoxydibenzo[a,g]quinolizidine (Tetrahydroberberine).—A solution containing 0.5 g. of dehydroberberinium chloride in 200 ml. of methanol was hydrogenated at atmospheric pressure in the presence of 60 mg. of platinum oxide catalyst until the solution became colorless. The catalyst was removed by filtration and the filtrate concentrated under vacuum, yielding the reduction product as an almost colorless solid. The solid, which developed color on storage, was dissolved in a small amount of water and ammonia was added to precipitate the free base. The base was collected and recrystallized from ethanol as colorless needles, m.p. 170–171° (lit.[10b] 170–171°). The base gave no depression of melting point when mixed with an authentic sample prepared by catalytic reduction[10b] of berberine and infrared spectra of the two preparations were identical.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.79; H, 6.19; N, 4.13. Found: C, 70.85; H, 6.09; N, 4.37.

8,9-Dimethoxyacridizinium Chloride (X).—The quaternization of picolinic aldehyde (0.5 g.) by 3,4-dimethoxybenzyl bromide could be carried out at room temperature in a period of 24 hours if a few drops of dimethylformamide was added, but in the absence of the dimethylformamide a period of 60–72 hours was required for quaternization. The glassy red mass was washed with ether and cyclized in concentrated hydrochloric acid at 100° in two hours. The product which crystallized from the acid was found to have both bromide and chloride anions; therefore an aqueous solution was passed through an anion exchange resin (Amberlite IRA 410) loaded with chloride ion, and finally recrystallized from alcohol. The product was obtained as yellow needles, m.p. 211–213° dec., yield 1.2 g. (80%); λ_{max} 250, 303, 380 and 398 mμ; λ_{min} 228, 257, 390.

Anal. Calcd. for $C_{15}H_{14}ClNO_2 \cdot 3H_2O$: C, 54.71; H, 6.07; N, 4.25. Found: C, 55.15; H, 5.83; N, 4.23.

The perchlorate was obtained as light green needles from excess methanol, m.p. 230–232°.

Anal. Calcd. for $C_{15}H_{14}ClNO_6$: C, 51.72; H, 4.31; N, 4.02. Found: C, 51.55; H, 4.45; N, 4.15.

The picrate was obtained as yellow plates from methanol, m.p. 260–262°.

Anal. Calcd. for $C_{21}H_{16}N_4O_9$: C, 53.84; H, 3.41; N, 11.96. Found: C, 53.70; H, 3.35; N, 11.75.

8,9-Dimethoxybenzo[b]quinolizidine (XI).—The dimethoxyacridizinium chloride (X, 0.5 g.) was hydrogenated in methanol (25 ml.) in the presence of platinum oxide (50 mg.). Worked up in the usual way the free base was obtained from dilute ethanol as colorless prisms, m.p. 108–108.5° (lit.[12] 108–109°).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.50; H, 8.34; N, 5.67.

10,11-Dimethoxy-2,3-methylenedioxybenz[a]acridizinium Chloride (Dehydropseudoberberinium Chloride).—The quaternization of 6,7-methylenedioxyisoquinoline-1-carboxaldehyde (0.5 g.) with 3,4-dimethoxybenzyl bromide was carried out in acetonitrile (20 ml.) at 100°. The resulting salt was washed with ether and then cyclized with concentrated hydrochloric acid by heating at 100° for 20 minutes. The crude product consisted of almost equal parts of two compounds. Separation of the substances was effected by crystallization from methanol, the more insoluble compound being identified as **2,3,6,7-tetramethoxy-9,10-dihydroanthracene**, m.p. 228–230° (lit.[21] 227°).

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.63; H, 6.62.

Concentration of the mother liquor afforded the expected **dehydropseudoberberinium chloride** as buff colored micro needles, m.p. 242–245° dec., λ_{max} 235, 278, 302, 312, 326 and 422 mμ; λ_{min} 262, 290, 306, 320, 376 mμ.

Anal. Calcd. for $C_{20}H_{16}ClNO_4 \cdot 3/2H_2O$: C, 60.60; H, 4.80; N, 3.53. Found: C, 60.52; H, 4.92; N, 3.70.

The perchlorate was obtained as yellow micro needles from dimethylformamide and methanol, m.p. 340–342° dec.

Anal. Calcd. for $C_{20}H_{16}ClNO_8 \cdot 1/2H_2O$: C, 54.30; H, 3.84. Found: C, 54.32; H, 3.78.

10,11-2,3-Bis-methylenedioxybenz[a]acridizinium Chloride (VIII).—Quaternization of 6,7-methylenedioxyisoquinoline-1-carboxaldehyde (IV, 0.5 g.) by 3,4-methylenedioxybenzyl bromide[22] was carried out in the usual way and the crude salt cyclized at 100° in hydrochloric acid. After 15 minutes cyclization, 0.6 g. (66%) of yellow crystals, m.p. 292–296°, was obtained. The yield was no better when the oxime V was used in place of the aldehyde IV. The analytical sample was obtained by recrystallization from ethanol as yellow needles, m.p. 294–296°; λ_{max} 282, 306, 317, 332 and 417 mμ; λ_{min} 254, 292, 312, 326 and 368 mμ.

Anal. Calcd. for $C_{19}H_{12}ClNO_4 \cdot 2H_2O$: C, 58.8; H, 4.11; N, 3.6. Found: C, 59.1; H, 4.05; N, 3.5.

The perchlorate crystallized from dimethylformamide–methanol as yellow needles, which turned black above 300°, but did not melt below 400°.

Anal. Calcd. for $C_{19}H_{12}ClNO_8$: C, 54.6; H, 2.87; N, 3.3. Found: C, 54.5; H, 2.78; N, 3.3.

10-Methoxy-2,3-methylenedioxybenz[a]acridizinium Chloride (Des-(9)-methoxydehydroberberinium Chloride, IX).—The quaternization of the isoquinoline aldehyde oxime (V, 1 g.) with *m*-methoxybenzyl bromide[23] (1.1 g.) was carried out in dimethylformamide at steam-bath temperature. The salt was precipitated with ether and ethyl acetate and cyclized in hydrochloric acid at 100°. The product crystallized from ethanol as yellow needles, m.p. 302–305° dec., yield 1.1 g. (63%). The observed ultraviolet absorption spectrum was λ_{max} 240, 280, 320, 342 and 437 mμ; λ_{min} 226, 253, 330 nd 388 mμ.

Anal. Calcd. for $C_{19}H_{10}ClNO_4 \cdot 3/2H_2O$: C, 62.29; H, 4.64; N, 3.82. Found: C, 62.15; H, 4.55; N, 3.92.

The perchlorate was obtained as yellow needles, m.p. 330–331° (dec., sealed tube).

Anal. Calcd. for $C_{19}H_{14}NClO_7$: C, 56.57; H, 3.47; N, 3.47. Found: C, 56.38; H, 3.68; N, 3.72.

DURHAM, N. C.

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(21) G. M. Robinson, *J. Chem. Soc.*, **107**, 267 (1915).

(22) G. M. Robinson and R. Robinson, *ibid.*, **105**, 1463 (1914).

(23) E. Späth, *Monatsh.*, **34**, 1965 (1913).