

dioxide, 7 predominated. Further, when 8 or 1 was hydrolyzed with 20% sodium hydroxide 7 was obtained in good yield.

The structure assigned to 8 was based on elemental analyses, mass spectrographic fragmentation, and nuclear magnetic resonance (nmr). Vonderwahl⁶ describes a similar stepwise hydrolytic cleavage of the N-ethyl analog of 1. However, in this instance use of 16.66% sodium hydroxide and a 5-hr reaction period was reported.

Experimental Section⁷

1,3,7,9-Tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8-octahydroprido[2,3-*d*:6,5-*d'*]dipyrimidine (1).—A mixture of 4.65 g (0.03 mole) of 6-amino-1,3-dimethyluracil (2) and 23.4 g (0.3 mole) of DMSO was heated under reflux for 48 hr. After cooling the precipitate was collected, washed with cold DMSO, and dried to give 3.25 g of pale yellow lustrous crystals, mp 310–314°. Recrystallization from toluene gave 2.8 g (61%) of 2 as white needles, mp 315–316°, lit. mp 319–320° and 308–310°.⁸ The infrared spectrum (KBr disk) showed the following characteristic absorption bands: 1725 (s), 1683 (s), 1620 (s), 793 (s), 749 (w), and 710 (w) cm⁻¹. The 60-Mc nmr spectrum (CDCl₃) showed peaks at τ 6.25 and 6.51 (N-CH₃) and 0.92 (CH).

Anal. Calcd for C₁₃H₁₃N₅O₄: C, 51.48; H, 4.32; N, 23.09. Found: C, 51.65; H, 4.35; N, 23.00.

During the course of the above reaction the system was flushed with air for a short time and formaldehyde was isolated from the exit gas as its 2,4-dinitrophenylhydrazone.

When DMSO-*d*₆ was used 1 labeled in the 5 position was formed. In the nmr spectrum the peak at τ 0.92 was absent.

Bis(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimid-5-yl)methane (3).—To a warm solution of 15.5 g (0.1 mole) of 2 in 200 ml of water, 150 ml of dioxane, 200 ml of 10% sodium hydroxide solution, and 75 ml of 37% aqueous formaldehyde solution were added. A dense white precipitate appeared immediately which was collected after stirring for 5 min. The yield of crude product was 13 g and, after recrystallization from dimethylformamide, 9.8 g (62%) of 3, mp 333–334° dec, was obtained. The infrared spectrum (Nujol mull) showed absorption bands at 3400 (w), 3120 (m), 1690 (infl) 1670 (s), 1620 (s), 1580 (s), 1150 (m), 1066 (m), 880 (w), 790 (m), 755 (m doublet), and 720 (w) cm⁻¹.

Anal. Calcd for C₁₃H₁₃N₅O₄: C, 48.44; H, 5.59; N, 26.09. Found: C, 48.33; H, 5.56; N, 25.98.

Isolation of 3 from the Reaction Mixture Leading to 1.—A mixture of 15.6 g (0.2 mole) of 2 and 15.6 g (0.2 mole) of DMSO was heated under reflux for 12 hr. After cooling the solid was collected and washed with cold DMSO leaving 2.1 g of a pale yellow solid which was shaken for several minutes with chloroform to remove 1. The insoluble material was boiled with 50 ml of water to remove unreacted 2. The insoluble material, mp 330–333°, was recrystallized from dimethylformamide to give 0.5 g of 3, mp 333–335° dec. The infrared spectrum was identical with that of 3 prepared as described above.

Bis(1,3-dimethyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimid-5-yl)methane (5).—To a boiling suspension of 2 g (0.0037 mole) of 3 in 60 ml of water 45 ml of concentrated hydrochloric acid was added in portions over 20 min. After refrigeration overnight, the white crystalline solid (0.8 g), mp 168–169°, was collected. Recrystallization from ethanol gave 0.6 g (50% of 5 as colorless plates, mp 168–169°. Compound 5 prepared by another method had lit.⁸ mp 167–168°.

Bis(6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimid-5-yl)methane (6).—Phosphorus oxychloride (51 g) was carefully added to a suspension of 7 g (0.022 mole) of 5 in 7 ml of water. After refluxing for 30 min the solvent was removed under reduced pressure and the viscous yellow residue was poured onto cracked ice. The yellow solid (5.7 g, mp 220–234°) was recrystallized from dimethylformamide to yield 4.3 g (53%) of white crystals,

(7) Nmr spectra were taken either on a Varian A-60 nmr spectrometer with tetramethylsilane as an internal standard or on a Varian HA-100 spectrometer. Infrared spectra were taken on a Perkin-Elmer 21 spectrometer. Melting points are uncorrected and were taken on a Thomas-Hoover Unimelt melting point apparatus. Microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(8) J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 2401 (1959).

mp 271–272°. The infrared spectrum (KBr disk) showed bands at 1725 (s), 1670 (s), 1620 (s), 1210 (m), and 750 (m) cm⁻¹. The 60-Mc nmr spectrum (CDCl₃) showed peaks at τ 6.25 (CH₂), 6.43 (NCH₃), and 6.72 (NCH₃).

Anal. Calcd for C₁₃H₁₄Cl₂N₄O₄: C, 43.21; H, 3.88; Cl, 19.66; N, 15.51. Found: C, 43.28; H, 3.82; Cl, 19.65; N, 15.40.

Compound 3 by Ammonolysis of 6.—To 224 ml of anhydrous ammonia was added 1 g of sodium. After the solution turned a permanent blue color, 0.5 g of powdered ferric nitrate was added followed by 12 g of sodium over 20 min. After addition of 3.0 g (0.0012 mole) of 6 the mixture was stirred for 2 hr. Excess ammonium chloride was added and the ammonia was evaporated. Trituration of the residue with a small volume of water gave 1.6 g of a brown solid which, after drying, was extracted with boiling dimethylformamide. On cooling the extract 0.5 g of crude 3, mp 306–320° separated. Recrystallization from dimethylformamide gave 0.3 g (11%) of 3, melting point and mixture melting point with 3 prepared as above 333–335°. The infrared spectra of 3 prepared by the two routes were identical.

Alkaline Cleavage of 1.—A mixture of 2.45 g (0.0082 mole) of 1, 25 ml of 10% sodium hydroxide, and 0.4 ml of ethanol was heated under reflux for 2.5 hr. After cooling 2.0 g of a white crystalline solid, mp 232–240°, separated. This was shaken with 200 ml of chloroform and the insoluble material (0.5 g, mp 276–278°) was recrystallized from ethanol to give 0.3 g of 7, mp 281–282°, lit.⁸ mp 272–273°. The infrared spectrum (Nujol mull) showed bands at 3350 (m), 3300 (m), 1590 (s), 1540 (s), 940 (m), and 790 (m) cm⁻¹.

The nmr spectrum taken at 60-Mc in hexadeuteriodimethyl sulfoxide at ambient temperature showed peaks at τ 1.16–1.46 (br multiplet) (2 NH), 2.07 (singlet) (C-4 H), 2.22–2.56 (br multiplet) (2 N-H), 7.12 (doublet) (2 NCH₃), and 7.30 (doublet) (2 NCH₃).

Anal. Calcd for C₁₁H₁₇N₅O₂: C, 52.59; H, 6.77; N, 27.88. Found: C, 52.53; H, 6.94; N, 27.70.

The chloroform filtrate after removal of 7 was evaporated to dryness to give 1.9 g of a white solid, mp 230–232°. Recrystallization from ethanol gave 1.5 g of 8 as fine white needles, mp 256–257°.

The nmr spectrum of 8 taken at 60 Mc in trifluoroacetic acid at ambient temperature showed peaks at τ 6.89 (singlet), 6.69 (singlet), 6.40 (singlet), 6.14 (singlet) (NCH₃), and at 1.13 (singlet) (C-5 proton). At 100 Mc in hexadeuteriodimethyl sulfoxide at 100° the spectrum showed peaks at τ 7.39 (doublet), 7.16 (doublet), 6.91 (singlet), 6.67 (singlet) (NCH₃), and at 1.75 (singlet) (C-5 proton). Integration was consistent with this interpretation. Further at 100 Mc a broad peak appeared at about τ 1.0 which is assigned to the NH function.

The mass spectrum⁹ confirmed the molecular weight. Three significant peaks appeared: parent peak, *m/e* 277, also the base peak (100%); *m/e* 247, P - 30, 85% of base peak; *m/e* 191, P - 86, 46% of base peak.

Anal. Calcd for C₁₂H₁₅N₅O₃: C, 51.98; H, 5.42; N, 25.27. Found: C, 51.93; H, 5.45; N, 24.94.

When the above reaction was done with 20% sodium hydroxide, 7 (78% yield) was the major product isolated.

Registry No.—1, 796-39-4; 2, 6642-31-5; 3, 10146-98-2; 5, 10182-02-2; 6, 10146-99-3; 7, 10147-00-9; 8, 10147-01-0; dimethyl sulfoxide, 67-68-5.

(9) This was done by Morgan Schaffer Corp., Montreal, Canada, with a Hitachi Perkin-Elmer RMU-6D instrument.

A Synthesis of Columbamine from Berberine

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Columbamine (I) is probably one of the most widely distributed alkaloids of the protoberberine group.

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Recently, we described the first efficient separation of columbamine and the related alkaloids berberine (II), palmatine (III), and jatrorrhizine (IV), as well as the characterization for the first time of pure columbamine (as the crystalline chloride and iodide) from natural sources.² Previous to this report, columbamine had been isolated in pure form only as its tetrahydro derivative.³ We wish now to report a procedure for the conversion of berberine (II) into columbamine (I). Since the total synthesis of berberine has already been carried out,³ this conversion constitutes a formal total synthesis of columbamine. Of greater importance, this synthesis should prove to be of considerable practical value to phytochemists who require authentic comparison samples of columbamine salts, particularly in view of the fact that berberine salts are articles of commerce.

The conversion of berberine into columbamine was carried out using a simple two-step process. In the first step, commercial berberine (II) was demethylated by sulfuric acid in the presence of phloroglucinol.⁴ In the second step, the resulting demethyleneberberine (V) was subjected to partial methylation by dimethyl sulfate in the presence of sodium bicarbonate, and the methylation products were separated as the chlorides by chromatography on acid alumina as described previously for the natural Columbo root alkaloids.²

The critical factor in the successful partial methylation of V to columbamine is control of the basicity of the reaction medium. Both jatrorrhizine (IV) and demethyleneberberine (V) give a red coloration in sodium bicarbonate solution, a reaction which is not shown by columbamine (I); in the case of jatrorrhizine, the red color has been attributed to the anion, one canonical form of which is a quinonoid structure (VI).² It is apparent that columbamine (I), which cannot form an anion stabilized by a quinonoid contributor, should be a weaker acid than either IV or V. This prediction was confirmed experimentally by pK_a determinations: the pK_a of columbamine (8.54) is appreciably higher than that of either jatrorrhizine (7.09) or demethyleneberberine (7.29); as expected, the latter compound is methylated, albeit very slowly,

in an aqueous sodium bicarbonate solution at 40°. After 8 hr, methylation takes place to the extent of about 30%, the methylation products consisting of columbamine, jatrorrhizine, and palmatine in a ratio of about 8:3:1; the yield of columbamine from V in this reaction, which probably could be run to advantage for a longer reaction period, is 19%.

Experimental Section

pK_a Measurements.—The chlorides of I, IV, and V were dissolved in distilled water, acidified with standard hydrochloric acid, and back titrated with standard aqueous hydroxide. Changes in pH were followed using a Model G Beckman pH meter. End points were determined by plotting dpH/dV against volume of base added.

Controlled Methylation of Demethyleneberberine.—Demethyleneberberine iodide (0.2 g)⁴ was converted into the corresponding chloride by passing its solution in 1:1 acetone-water through a column (1 × 8 cm) of Amberlite IR-A 410 resin (chloride form), which was washed in 1:1 acetone-water prior to use.

A mixture of demethyleneberberine chloride (0.1597 g), water (50 ml), dimethyl sulfate (1 ml), and saturated aqueous sodium bicarbonate (5 ml) was stirred at 40° for 8 hr; additional dimethyl sulfate and sodium bicarbonate were added as required during this time in order to assure an excess of these reagents during the reaction. The reaction solution was concentrated, the alkaloids were precipitated as the iodides, and the iodides were converted to the chlorides using Amberlite IR-A 410 resin. The mixed chlorides were chromatographically resolved using Woelm acid alumina as described previously for the naturally occurring compounds.² Unreacted demethyleneberberine was not recovered, owing to the tenacity with which it is adsorbed on alumina.

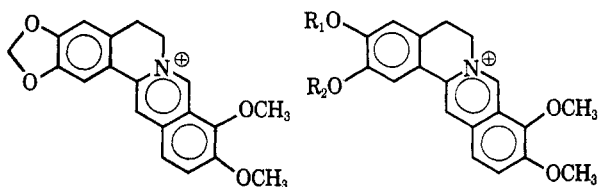
The following yields of alkaloids were obtained, the total representing about a 30% conversion of demethyleneberberine methylated products. All products were identified by melting point and by infrared spectra comparison with pure alkaloids of natural origin. (See Table I.)

TABLE I

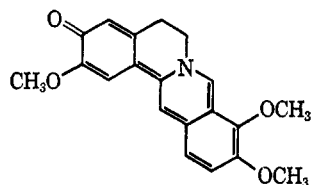
Column eluent	Product (as chloride)	Yield, mg
4% methanol in chloroform	Palmatine	4.0
5.5–8% methanol in chloroform	Columbamine	31.3
12–15% methanol in chloroform	Jatrorrhizine	11.8

Registry No.—I, 1355-76-6; II, 2086-83-1.

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I, $R_1 = CH_3$; $R_2 = H$
 III, $R_1 = R_2 = CH_3$
 IV, $R_1 = H$; $R_2 = CH_3$
 V, $R_1 = R_2 = H$



VI

Reaction of Diimide N-Oxide Derivatives and Grignard Reagents. Evidence for Radical Intermediates¹

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During the studies on the synthesis of azoxy compounds from the reaction of Grignard reagents and

(2) M. P. Cava, T. A. Reed, and J. L. Beal, *Lloydia*, **28**, 73 (1965).
 (3) R. H. F. Manske and W. R. Ashford, "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1954, Chapter 29.

(4) E. Späth and H. Quietensky, *Ber.*, **58**, 2267 (1925).

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