4-Quinolineacetamide is reported to have a melting point of 211–213°.[10]

In another experiment 0.2 g of **9** was dissolved in 2 ml of concentrated sulfuric acid and treated as described above. In this case the basic solution deposited 0.12 g (52%) of 4-quinolylmalonamide (**10**). Continuous extraction of the filtrate gave 0.05 g of 4-quinolineacetamide.

4-Quinolylmalonamide (0.1 g) dissolved in 1 ml of concentrated sulfuric acid was heated for 1 hr on the steam bath, poured on crushed ice, and extracted with benzene. There was obtained 45% (0.05 g) of quinolineacetamide.

Cinchoninic acid.—To a mixture comprising 0.2 g of **9**, 2 ml of 95% ethanol and 2 ml of 30% hydrogen peroxide cooled in an ice bath, was added 4 drops of 6 *N* sodium hydroxide. After the mixture was heated at 50° for 5 hr, the resulting solution was neutralized with 5% sulfuric acid and then evaporated to dryness under reduced pressure depositing 0.3 g of a white solid. Extraction of the white solid with absolute ethanol gave 0.14 g (82%) of cinchoninic acid, which was recrystallized from ethyl acetate, mp 244–245°. (The infrared spectrum was identical with that of authentic sample of cinchoninic acid.)

Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.34; H, 4.37; N, 8.10.

1-Methyl-4-(α-carbamylmethylene)-1,4-dihydroquinoline (12).—A solution of 4.0 g of **6** dissolved in 20 ml of concentrated sulfuric acid was heated on the steam bath for 1 hr. The hot solution was poured on crushed ice and then made basic with 20% sodium hydroxide solution. The resulting red solution was continuously extracted with benzene for 2 days. The benzene layer was separated and the yellowish-green precipitate, which separated from the aqueous layer, was isolated by filtration and dissolved in the benzene extract. Evaporation of the benzene solution to a small volume caused precipitation of yellowish needles, 2.6 g (65%) which were recrystallized from a benzene–acetone mixture: mp 150° dec (the crystals darken on standing); ν_{max}^{KBr} (cm^{-1}) 3380, 3150, 1625, 1590, 1540, 1500; $\lambda_{max}^{CH_3OH}$ 413 mμ (ε 16,000), 435 mμ (ε 14,400).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.81; H, 6.13; N, 13.78.

1-Methyl-4-(α-carbethoxy-α-cyanomethylene)-1,4-dihydroquinoline (**16**)[9] when similarly treated formed a product with an identical infrared spectrum.

1-Methyl-1,2,3,4-tetrahydro-4-quinoline Acetamide (14).—A solution of 2.6 g of **12** in 150 ml of absolute ethanol was reduced using 10% palladium on charcoal as the catalyst and 40 psi of hydrogen. The initially dark yellow solution turned colorless. The catalyst was removed by filtration and the clear filtrate was evaporated to dryness depositing 1.6 g (60%) of white crystals, which were recrystallized from benzene: mp 139–140°; nmr bands, τ 8.0 (quadruplet) (C_3 protons), 7.6 (complex doublet) (CH_2CONH_2), 7.1 s (NCH_3), τ 6.8 (complex triplet) (NH and C_4 proton); ν_{max}^{KBr} 3380 and 3150 (NH_2), 2800 (C_3 protons), 2940 (NCH_3), 1650 ($CONH_2$ carbonyl), 1630, 1600, and 1500 cm^{-1} (aromatic C=C).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.83; H, 7.64; N, 13.61.

1-Methyl-4-(α,α-dicyanomethylene)-6-methoxy-1,4-dihydroquinoline (7).—To a mixture of 15 g (0.05 mole) of 1-methyl-6-methoxyquinolinium iodide, 3.3 g (0.05 mole) of malononitrile, and 100 ml of absolute ethanol, cooled in an ice bath, was added a solution of 2.3 g (0.10 g-atom) of sodium in 50 ml of absolute ethanol with vigorous stirring. This mixture was stirred for 3 hr in an ice bath and then stirred at room temperature overnight. A yellow precipitate formed and was isolated by filtration, yield 4.7 g (40%). It was crystallized from nitromethane, mp 319–320°.

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.74; H, 4.70; N, 17.71.

1-Methyl-4-(α-carboethoxy-α-cyanomethylene)-6-methoxy-1,4-dihydroquinoline (16).—To a mixture of 15 g (0.05 mole) of 1-methyl-6-methoxyquinolinium iodide, 5.65 g (0.05 mole) of ethyl cyanoacetate, and 100 ml of absolute ethanol, cooled in an ice bath, was added a solution of 1.2 g (0.05 g-atom) of sodium in 50 ml of absolute ethanol with vigorous stirring. The mixture was stirred at room temperature overnight. The yellow precipitate which formed was isolated by filtration and washed with acetone leaving 7.5 g of the starting quaternary salt. From the acetone solution 0.35 g (5%) of yellow needles were isolated and recrystallized from acetone, mp 219°.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.80; H, 5.72; N, 9.75.

1-Methyl-4-(α-carbamylmethylene)-6-methoxy-1,4-dihydroquinoline (17).—A solution of 2.0 g of **7** dissolved in 20 ml of concentrated sulfuric acid was heated for 1 hr on a steam bath. The hot solution was poured on crushed ice and then made basic with 20% sodium hydroxide. The resulting red solution was continuously extracted with benzene for 2 days. The benzene layer was separated and the yellowish precipitate, which separated from the aqueous layer, was isolated by filtration and dissolved in the benzene extract. Evaporation of the benzene solution to a small volume caused separation of yellow needles, 1.0 g (50%), which were recrystallized from a benzene–methanol mixture, mp 170° dec. The crystals darkened on standing.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.20; N, 12.07.

The same substance (**17**) was obtained in 90% yield by treating a small quantity of 1-methyl-4-(α-carbethoxy-2-cyanomethylene)-6-methoxy-1,4-dihydroquinoline (**16**) with concentrated sulfuric acid for 1 hr at steam-bath temperature. The product was isolated as described above.

1-Methyl-6-methoxy-1,2,3,4-tetrahydro-4-quinolineacetamide (18).—A solution of 0.25 g of **17** in 150 ml of absolute ethanol was reduced using 200 mg of 10% palladium on charcoal and 40 psi of hydrogen until the initially colored solution turned colorless. The mixture was filtered to remove the catalyst and the clear filtrate was evaporated to dryness depositing 0.1 g (40%) of white crystals which were recrystallized from benzene, mp 101°.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.65; H, 7.75; N, 11.96. Found: C, 67.04; H, 7.96; N, 11.80.

Registry No.—**5**, 10147-02-1; **7**, 10182-03-3; **9**, 10147-03-2; **10**, 10147-04-3; **11**, 10147-05-4; **12**, 10182-04-4; **14**, 10147-06-5; **16**, 10147-07-6; **17**, 10147-08-7; **18**, 10147-09-8.

Acknowledgment.—The authors wish to thank Professor D. L. Coffen for his helpful discussion of spectral data.

(10) F. Zymalkowski and W. Schauer, *Arch. Chem.*, **290**, 218 (1957).

Synthesis of 1,3,7,9-Tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-*d*:6,5-*d'*]-dipyrimidine from 6-Amino-1,3-dimethyluracil and Dimethyl Sulfoxide[1]

ROBERT C. ELDERFIELD AND MALCOLM WHARMBY

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48104

Received September 29, 1966

Since dimethyl sulfoxide (DMSO) has become readily available considerable attention has been devoted to the diverse reactions which this compound displays. Under certain conditions it can serve as a source of formaldehyde. Nace and Monagle[2] noted the formation of formaldehyde during the reaction of DMSO with primary halides. Later Traynelis and Hergenrother[3] made a detailed study of products of the thermal decomposition of DMSO. On refluxing for 3 days it decomposes into methanethiol and formaldehyde as primary products. Other products isolated (dimethylthioformal, dimethyl disulfide, dimethyl sulfide, and dimethylsulfone) were accounted for as the result of

(1) This work was supported by Research Grant CA-02961 from the National Cancer Institute of the National Institutes of Health.

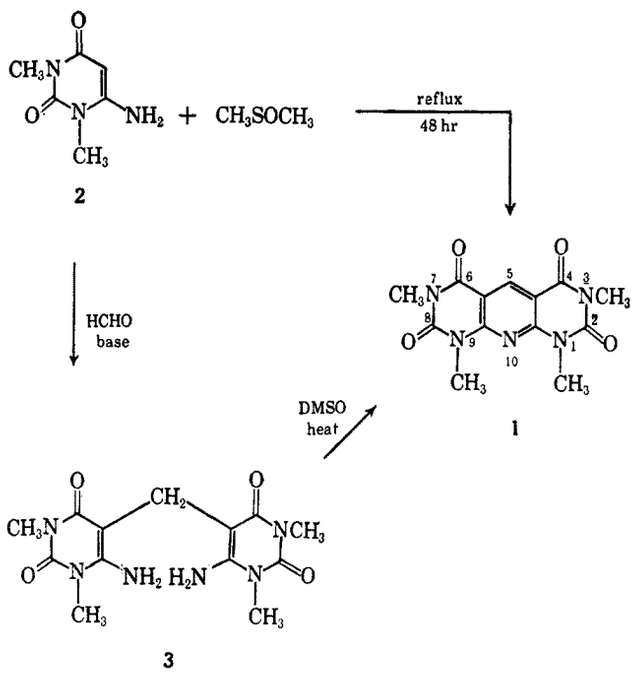
(2) H. R. Nace and J. R. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(3) V. J. Traynelis and W. L. Hergenrother, *ibid.*, **29**, 221 (1964).

secondary reactions. When acetamide or benzamide was refluxed with DMSO the methylene bisamides were formed in 55–66% yields by reaction of the liberated formaldehyde with the amides.

We now wish to report the formation of 1,3,7,9-tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine (**1**) in good yield when 6-amino-1,3-dimethyluracil (**2**) is refluxed in DMSO.

SCHEME I

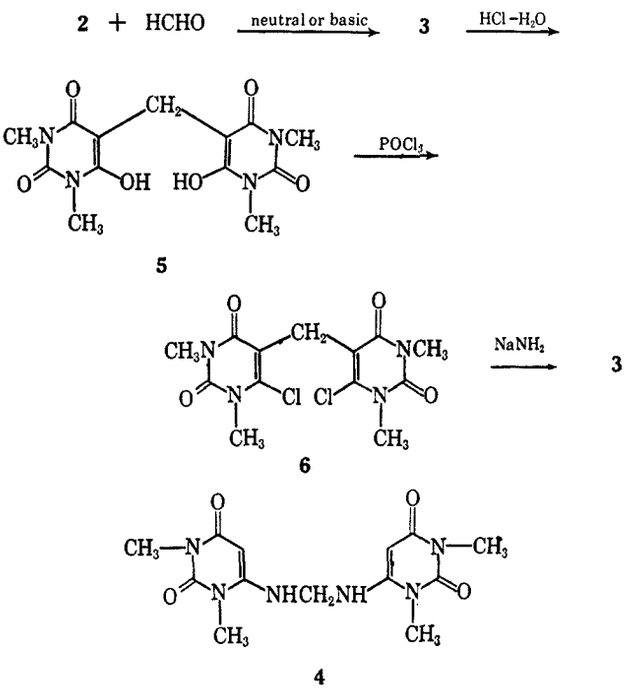


The formation of **2** presents several points of interest. The source of C-5 in **2** is readily accounted for on the assumption that **2** undergoes the expected condensation with formaldehyde arising from decomposition of the DMSO with formation of an intermediate (**3**). However, loss of ammonia from **3** and aromatization to the pyridine **1** in DMSO represents, as far as we are aware, a new reaction accomplished by DMSO. The aromatization possibly is not too unexpected in view of the strong oxidizing properties of DMSO which have been noted previously. It is not excluded that the formation of **1** may be a purely thermal process at the boiling point of DMSO since Bredereck, Effenberger, and Sauter[4] have reported the preparation of **1** by fusion of **2** with formamide.

Confirmation of the role of **3** as the intermediate in the formation of **1** was obtained by preparation of **3** by condensation of **2** with formaldehyde. When **3**, prepared in this manner, was heated in DMSO **1** was obtained in 65% yield. Further, when the reaction of **2** in refluxing DMSO was interrupted in the early stages significant amounts of compound **3** could be isolated.

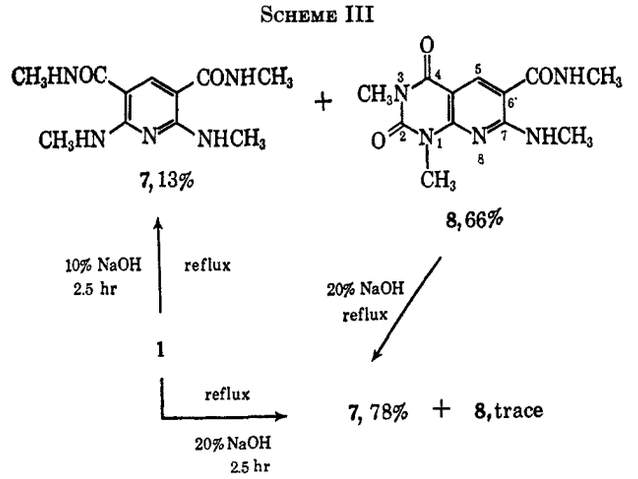
Prior to the present work, Fel'dman[5] had reported that condensation of **2** with formaldehyde under neutral conditions yielded the N-methylene compound (**4**). Inasmuch as the structure of the product of this condensation is vital for the interpretation of the course of the reaction of **2** with DMSO, we have reinvestigated the reaction of **2** with formaldehyde and find that under both neutral and basic conditions a single product (**3**), mp 333–335°, is formed. This is apparently the same compound reported by Fel'dman who gives mp 333–334°. The structure of **3** was confirmed by acid hydrolysis to the barbituric acid derivative **5**, conversion of **5** to the chloro derivative **6**, and ammonolysis of **6** to **3**.

SCHEME II



Vonderwahl[6] describes the preparation of **2** by condensation of **1** with dimethylformamide in the presence of chlorosulfonic or sulfuric acid. He also reports cleavage of **1** with 10% sodium hydroxide to 2,6-bismethylaminopyridine-3,5-bis-N-methylcarboxamide (**7**) (Scheme III). This cleavage was repeated with **1** prepared both from DMSO and from formamide[4] and the results were not in agreement with those reported by Vonderwahl. With 10% sodium hydroxide the major product was 1,3-dimethyl-7-methylamino-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-(N-methylcarboxamide) (**8**). With 20% sodium hy-

SCHEME III



(4) H. Bredereck, F. Effenberger, and R. Sauter, *Chem. Ber.*, **95**, 2049 (1962).

(5) M. Y. Fel'dman, *Biokhimiya*, **26**, 822 (1961).

(6) R. Vonderwahl, U. S. Patent 3,035,061 (May 15, 1962).

droxide, **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). Vonderwahl[6] 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 Section[7]

1,3,7,9-Tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8-octahydropyrido[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°[4] and 308–310°.[5] 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 ($CDCl_3$) showed peaks at τ 6.25 and 6.51 ($N-CH_3$) and 0.92 (CH).

Anal. Calcd for $C_{13}H_{13}N_5O_4$: 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 $C_{13}H_{18}N_6O_4$: 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, 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 ($CDCl_3$) showed peaks at τ 6.25 (CH_2), 6.43 (NCH_3), and 6.72 (NCH_3).

Anal. Calcd for $C_{13}H_{14}Cl_2N_4O_4$: 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.[6] 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 NCH_3), and 7.30 (doublet) (2 NCH_3).

Anal. Calcd for $C_{11}H_{17}N_5O_2$: 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) (NCH_3), 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) (NCH_3), 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 spectrum[9] 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 $C_{12}H_{15}N_5O_3$: 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.

(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).

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

A Synthesis of Columbamine from Berberine

M. P. CAVA[1] AND T. A. REED

Evans Chemical Laboratory, The Ohio State University, Columbus, Ohio

Received December 2, 1966

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

(1) Department of Chemistry, Wayne State University, Detroit, Mich. 48202