[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Reactions of 1,3-Dimethyl-5,6-diaminouracil

BY F. F. BLICKE AND H. C. GODT, JR.[1,2]

RECEIVED JANUARY 11, 1954

1,3-Dimethyl-5,6-diaminouracil was condensed with nitrous acid, thionyl chloride, glyoxal, oxalic acid, diacetyl and benzil, respectively. It was also treated with dilute hydrochloric acid whereupon 1,1',3,3'-tetramethylhydurilic acid or 1,3,6,8-tetramethyl-2,4,7,9-tetraketodecahydrodipyrimido[4,5-b,4',5'-e]pyrazine or a mixture of both compounds was obtained.

During our synthesis of potential diuretics, we studied a number of reactions in which 1,3-dimethyl-5,6-diaminouracil (III), a key intermediate in the manufacture of theophylline, was condensed with nitrous acid, thionyl chloride, glyoxal, oxalic acid, diacetyl and benzil, respectively.

In order to obtain the required diamine III, N,N'-dimethylurea (I) and cyanoacetic acid were condensed in the presence of acetic anhydride to form N,N'-dimethyl-N-cyanoacetylurea which was converted by sodium hydroxide into 1,3-dimethyl-6-aminouracil; nitrous acid reacted with the uracil to form 1,3-dimethyl-5-nitroso-6-aminouracil monohydrate (II). Since we used the continuous process described by Campbell and Campbell,[3] only compound II was isolated; sodium hydrosulfite[4] transformed II into III. Traube[5] stated that the diamine III condensed with nitrous acid to form "1,3-dimethyl-4,5-aziminouracil"[6] and assigned formula IV to this compound; neither the yield nor the melting point was reported, and the compound was characterized only by solubility data and a nitrogen analysis. When we repeated Traube's experiment, we obtained a product which, presumably, was identical with the product obtained by him. However, our analytical data did not correspond exactly to that calculated for formula IV.[7] Acylation of IV with acetic anhydride and also with benzoyl chloride yielded the monoacyl derivatives (V). The complete analytical data obtained in the case of both acyl derivatives corresponded very closely to the calculated data. Although formula V indicates that these derivatives are 7-acyl compounds, the acyl group might be attached to the 8- or 9-nitrogen atom.

Interaction of the diamine III with thionyl chloride yielded a product to which we assigned formula VI.[8] It was assumed that the diamine had reacted with thionyl chloride in the same manner as *o*-phenylenediamine. In the latter instance, the structure of the heterocyclic produced, piazthiol, was established by physical chemical measurements.[9-11] Compounds which contain the ring system found in IV have been described recently by Schrage and Hitchings.[12]

The lumazine derivatives of type VII were obtained by condensation of the diamine with glyoxal, oxalic acid, diacetyl and benzil, respectively.

Interaction of the diamine with formaldehyde and hydrocyanic acid produced 1,3-dimethyl-5-cyanomethylamino-6-aminouracil (VIII). We believe that the cyanomethylamino group is attached to the 5- and not to the 6-position since acetylation of 5,6-diaminouracil is known to take place on the 5-amino group,[13] and condensation of 1-methyl-5,6-diaminouracil with phenyl isothiocyanate has been shown to yield the 5-phenylthioureido derivative.[14] When VIII was treated with potassium hydroxide dissolved in methanol, it was converted into 1,3-dimethyl-7-amino-5,6-dihydrolumazine (IX). When VIII was allowed to react with potassium hydroxide dissolved in methanol, and the reaction mixture was then treated with hydrogen peroxide, 1,3-dimethyl-7-aminolumazine (X) was produced.

It has been reported[15] that *o*-phenylenediamine reacted with malonic acid, in the presence of 4 *N* hydrochloric acid, to form *o*-phenylenemalonamide, a substance which contains a seven-membered ring. We attempted to effect a similar condensation with the use of the diamine III. Instead of the desired product, we obtained the known 1,1',3,3'-tetramethylhydurilic acid (XI).[16,17] Since the formation of XI was so surprising, a series of experiments was performed in the hope that more information might be obtained about this reaction. It was found that the maximum yield (54%) of XI was obtained by the use of two molecular equivalents of hydrogen chloride dissolved in 50 cc. of water. Under this condition, an additional product (m.p. 390°), also in maximum yield (31%), was obtained to which structure XII has been assigned. Depending on the amount of hydrochloric acid employed, either XI or XII could be obtained as the sole reaction product.

Recently, DeGarmo[18] described a compound (m.p. 206–207°) to which a formula (XII') was assigned which is identical with that of XII except

---

[1] This paper represents part of a dissertation submitted by H. C. Godt, Jr., in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan.

[2] Monsanto Chemical Company Fellow.

[3] K. N. Campbell and B. K. Campbell, U. S. Patent 2,523,496; *C. A.*, **45**, 6657 (1951).

[4] G. P. Hager, J. C. Krantz, Jr., and J. B. Harmon (*J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 36 (1953)) stated that they used this reagent for this reaction but no details were mentioned.

[5] W. Traube, *Ber.*, **33**, 3035 (1900).

[6] This compound can be named 1,3-dimethyl-2,6-diketo-8-azapurine. According to Ring Index nomenclature it would be called 4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydro-1-v-triazolo[d]pyrimidine.

[7] The compound was prepared several times and each sample was analyzed.

[8] 1,3-Dimethyl-2,6-diketo-8-thiapurine or 4,6-dimethyl-5,7-diketohexahydropyrimido(4,5-c)(1,2,5)thiadiazole.

[9] V. Luzzati, *Compt. rend.*, **227**, 210 (1948).

[10] V. Luzzati, *Acta Cryst.*, **4**, 193 (1951).

[11] R. W. Hill and L. E. Sutton, *J. chim. phys.*, **46**, 244 (1949).

[12] A. Schrage and G. H. Hitchings, *J. Org. Chem.*, **16**, 207 (1951).

[13] H. Bredereck, I. Hennig and W. Pfleiderer, *Chem. Ber.*, **86**, 321 (1953).

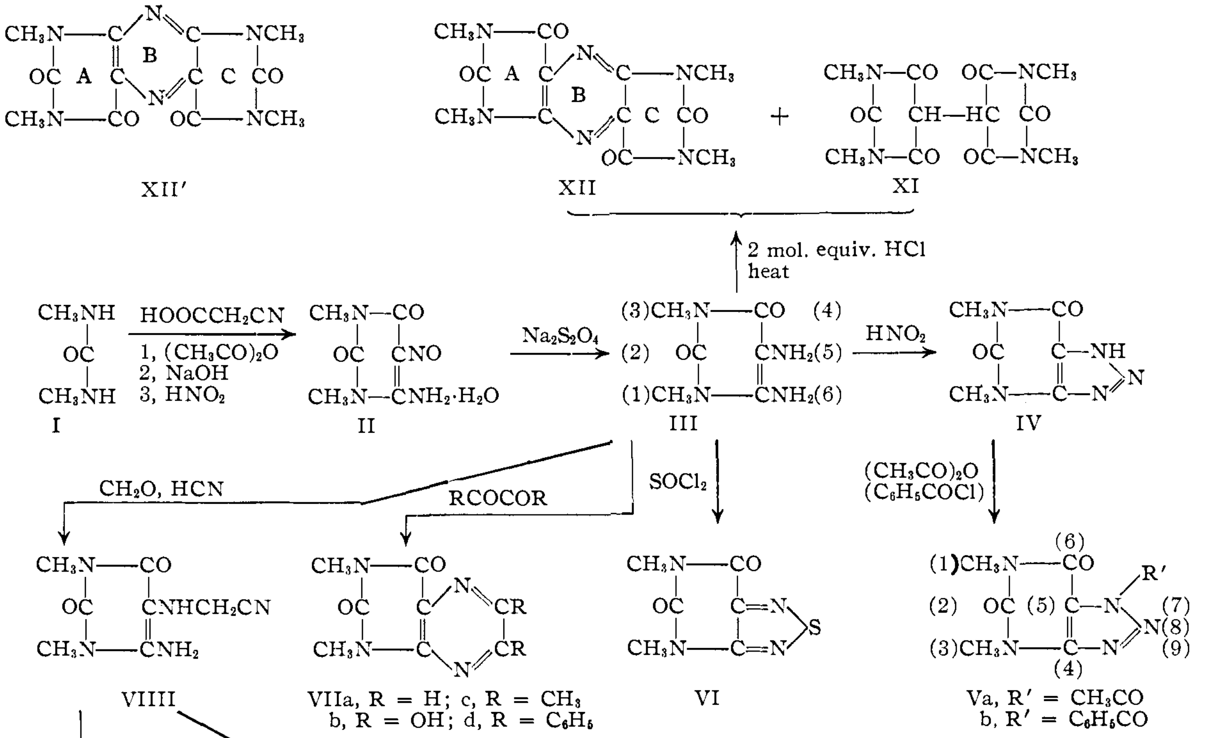
[14] W. Traube, *Ann.*, **432**, 266 (1923).

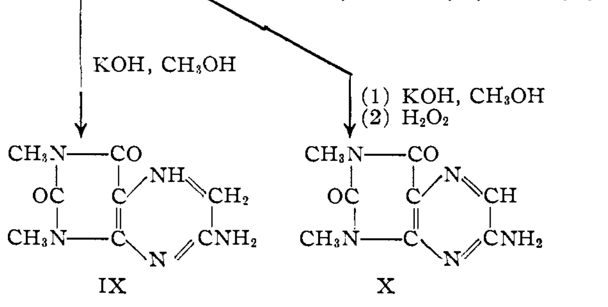
[15] R. L. Shriner and P. G. Boehrmans, THIS JOURNAL, **66**, 1810 (1944).

[16] H. Biltz and T. Hamburger, *Ber.*, **49**, 655 (1916).

[17] H. Biltz and M. Heyn, *ibid.*, **52**, 1298 (1919).

[18] O. DeGarmo, U. S. Patent 2,561,324; *C. A.*, **46**, 1595 (1952).





that ring A is attached to ring B in an inverted position.

Timmis[19] allowed 1,3-dimethyl-5-nitroso-6-aminouracil (II) to react with 1,3-dimethylbarbituric acid and obtained a substance (m.p. 403°) to which he assigned structure XII′.

While this investigation was in progress, Bredereck, *et al.*,[20] described the condensation of the monohydrochloride of the diamine III with dimethylalloxan in aqueous solution; they obtained a product (m.p. 390°) which they stated might possess either of the structures XII or XII′. They also treated the diamine, as well as its monoacetyl derivative, with 2 *N* sulfuric acid and obtained a mixture of 1,1′,3,3′-tetramethylhydrilic acid and another product, XII or XII′.

Experimental

1,3-Dimethyl-5-nitroso-6-aminouracil Monohydrate (II).—N,N′-Dimethylurea (I, 88.1 g.), 85 g. of cyanoacetic acid and 125 cc. of acetic anhydride were heated, with the exclusion of moisture, at 60° for 3 hours. The excess anhydride and the acetic acid formed during the reaction were removed under reduced pressure. A 5% sodium hydroxide solution (500 cc.) was added[21] slowly to the cooled, stirred residue whereupon the 1,3-dimethyl-6-aminouracil precipitated. A solution of 83 g. of sodium nitrite in 500 cc. of water was added to the cooled, stirred mixture and it was acidified by the dropwise addition of 120 cc. of acetic acid over a period of 1 hour. The stirring was continued for an additional 2 hours at room temperature. The mixture was thoroughly cooled, the red-violet precipitate was filtered and washed with water, 95% ethanol and finally with ether; yield 162 g. (80%), m.p. 233° dec.[22]

1,3-Dimethyl-5,6-diaminouracil (III) and Hydrochloride.—Compound II (80.8 g.) was stirred and 400 cc. of concd. ammonia water was added. The yellow-orange ammonium salt was warmed on a steam-bath, stirred and a solution of 220 g. of sodium hydrosulfite in 1 liter of water was added during a 20-minute period. The salt dissolved and the solution underwent a series of color changes. The solution was stirred and heated for 15 minutes, filtered while hot and the filtrate was cooled. The precipitate was suitable for use without purification; m.p. 209° dec.,[23] yield 80–85%.

In order to obtain the hydrochloride, a solution of 5.1 g. of the base in 125 cc. of hot absolute ethanol was treated with hydrogen chloride. The hydrochloride, which precipitated from the cooled solution, was recrystallized from absolute methanol; m.p. 310° dec., yield 5.5 g. (89%).

Anal. Calcd. for $C_6H_{11}O_2N_4Cl$: N, 27.12; Cl, 17.16. Found: N, 26.90; Cl, 17.28.

1,3-Dimethyl-2,6-diketo-8-azapurine (IV).—Compound III (5.1 g.) was dissolved in a mixture of 2.6 g. of concd. hydrochloric acid and 50 cc. of water. To the cooled, stirred solution there was added, dropwise, 2.1 g. of sodium nitrite dissolved in 20 cc. of water whereupon a red precipitate formed. The mixture was stirred for 2 hours at room temperature, the precipitate was filtered, washed with water and ethanol and recrystallized from water; m.p. 252–253°,[24] yield 4.4 g. (81%).

Anal. Calcd. for $C_6H_7O_2N_5$: C, 39.78; H, 3.90; N, 38.66. Found: C, 40.79; H, 4.00; N, 39.40.

---

[19] G. M. Timmis, U. S. Patent 2,581,889; *C. A.*, **46**, 7594 (1952).

[20] H. Bredereck, I. Hennig, W. Pfleiderer and O. Deschler, *Chem. Ber.*, **86**, 845 (1953).

[21] The addition of alkali represents a modification of the published process (ref. 3); it was required since we were unable to remove completely the acetic anhydride and the acetic acid by distillation.

[22] We are unable to find a melting point for this compound in the literature.

[23] Reference 5, m.p. 209°.

[24] Reference 5; neither the melting point nor the yield was reported.

7(8 or 9)-Acetyl-1,3-dimethyl-2,6-diketo-8-azapurine (Va).—A mixture of 3.6 g. of IV and 30 g. of acetic anhydride was refluxed for 1 hour. The liquid material was removed under reduced pressure and the residue, which solidified when cooled, was recrystallized from butyl acetate; m.p. 109–111°, yield 3.8 g. (84%).

Anal. Calcd. for $C_8H_9O_3N_5$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.19; H, 3.86; N, 31.62.

7(8 or 9)-Benzoyl-1,3-dimethyl-2,6-diketo-8-azapurine (Vb).—A mixture of 3.6 g. of IV and 40 cc. of benzoyl chloride was refluxed for 1 hour. The solution was cooled for some time and the precipitate was recrystallized from methyl ethyl ketone; m.p. 197–198°, yield 5.3 g. (93%).

Anal. Calcd. for $C_{13}H_{11}O_3N_5$: C, 54.73; H, 3.89; N, 24.55. Found: C, 54.90; H, 3.76; N, 24.58.

1,3-Dimethyl-2,6-diketo-8-thiapurine (VI).—A mixture of 5.9 g. of III, 10 g. of thionyl chloride and 150 cc. of benzene was refluxed until hydrogen chloride was no longer evolved (about 15 hours). The filtered solution was evaporated to dryness and the residue was recrystallized from 50% ethanol; m.p. 149–151°, yield 5.0 g. (73%).

Anal. Calcd. for $C_6H_6O_2N_4S$: C, 36.36; H, 3.05; N, 28.27; S, 16.18. Found: C, 36.11; H, 3.00; N, 28.13; S, 16.24.

1,3-Dimethyllumazine (VIIa).—Compound III (5.9 g.), 9.7 g. of a 30% aqueous solution of glyoxal, 10.4 g. of sodium bisulfite, 10.0 g. of concd. ammonia water and 200 cc. of water were heated at 90° for 20 minutes. The product precipitated from the cooled solution in the form of brown crystals; m.p. 197–199° after recrystallization from water with the use of charcoal, yield 2.0 g. (30%).

Anal. Calcd. for $C_8H_8O_2N_4$: C, 50.00; H, 4.19; N, 29.16. Found: C, 50.22; H, 4.38; N, 28.98.

1,3-Dimethyl-6,7-dihydroxylumazine (VIIb).—Oxalic acid (35 g.) and 5.1 g. of III were triturated and then heated gradually in a distillation flask during 1 hour until the temperature reached 240°; the pressure was maintained at 300 mm. The cold mixture was dissolved in a hot solution of 6.4 g. of sodium hydroxide in 180 cc. of water. After decolorization with charcoal, the solution was filtered into 100 cc. of boiling 2 *N* hydrochloric acid. The yellow-brown product crystallized from the cooled solution in the form of a monohydrate. The water of hydration was removed at 110° under 1 mm. pressure; m.p. above 360°, yield 3.9 g. (58%).

Anal. Calcd. for $C_8H_8O_4N_4$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.98; H, 3.70; N, 24.81.

1,3,6,7-Tetramethyllumazine (VIIc).—Compound III (5.1 g.) and 50 cc. of water were heated to 90° and 3.0 g. of diacetyl was added, dropwise. The mixture was heated for 1 hour at 90° and then cooled for 2 days. The precipitate was recrystallized from absolute ethanol; m.p. 158–159°,[25] yield 4.2 g. (64%).

1,3-Dimethyl-6,7-diphenyllumazine (VIId).—A mixture of 5.1 g. of III, 6.3 g. of benzil, 600 cc. of 50% ethanol and 30 cc. of concd. ammonia water was heated at 90° for 1 hour. The mixture was cooled and the precipitate recrystallized from ethyl acetate; m.p. 226–227°, yield 8.2 g. (80%).

Anal. Calcd. for $C_{20}H_{16}O_2N_4$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.88; H, 4.74; N, 16.32.

1,3-Dimethyl-5-cyanomethylamino-6-aminouracil (VIII).—A suspension of 34 g. of III in 100 cc. of methanol was stirred and maintained below 30° while 20 cc. of concd. hydrochloric acid was added, dropwise. A solution of 10.8 g. of sodium cyanide in 50 cc. of water was added, dropwise, to the stirred solution while the temperature was held below 30°. The mixture was adjusted to a *p*H of 6.5 and then warmed to 40–45°. A 37% aqueous solution of formaldehyde (17 g.) was then added. The diamine dissolved and the product then precipitated. The mixture was stirred for 1 hour and the temperature held at 45°. After the mixture had been cooled for several hours, the precipitate was recrystallized from 50% ethanol; yield 30 g. (72%), m.p. 236–238°.

Anal. Calcd. for $C_8H_{11}O_2N_5$: C, 45.93; H, 5.30; N, 33.47. Found: C, 45.90; H, 5.35; N, 33.33.

1,3-Dimethyl-7-amino-5,6-dihydrolumazine (IX).—Compound VIII (10.5 g.) was suspended in 100 cc. of absolute methanol, a solution of 3.1 g. of potassium hydroxide in 100 cc. of the same solvent was added and the mixture was stirred for 24 hours in a nitrogen atmosphere. The yellow precipitate was washed with water and recrystallized from 50% aqueous pyridine; m.p. 325° dec., yield 7.6 g. (72%).

Anal. Calcd. for $C_8H_{11}O_2N_5$: C, 45.93; H, 5.30; N, 33.47. Found: C, 46.49; H, 5.36; N, 33.50.

1,3-Dimethyl-7-aminolumazine (X).—Compound VIII (9.4 g.) was suspended in a solution of 1.4 g. of potassium hydroxide in 150 cc. of absolute methanol and the mixture was stirred in a nitrogen atmosphere for 30 hours. Ferrous chloride (0.1 g.) was added and the temperature of the mixture was maintained at 30° while 15.7 g. of 10% hydrogen peroxide solution was added, dropwise. The mixture was stirred for an additional hour and then treated with 0.1 g. of sodium bisulfite to destroy any remaining hydrogen peroxide. The precipitate was washed with water and recrystallized from 50% aqueous pyridine; m.p. above 360°, yield 5.3 g. (57%).

Anal. Calcd. for $C_8H_9O_2N_5$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.63; H, 4.29; N, 33.84.

1,1′,3,3′-Tetramethylhydurilic Acid (XI) and 1,3,6,8-Tetramethyl-2,4,7,9-tetraketodecahydrodipyrimido[4,5-b,4′,5′-e]pyrazine (XII).—A mixture of 5.1 g. of III and 50 cc. of water which contained 5.2 cc. of concd. hydrochloric acid (2 mol. equiv.) was refluxed for 12 hours. The mixture was cooled for 12 hours and the precipitate (4.0 g.) was treated with 50 cc. of a 5% solution of sodium bicarbonate. The residue (XII) was recrystallized from dimethylformamide; m.p. 390°, yield 1.4 g. (31%).

Anal. Calcd. for $C_{12}H_{12}O_4N_6$: C, 47.36; H, 3.98; N, 27.63. Found: C, 47.67; H, 3.77; N, 27.63.

When the sodium bicarbonate extract was acidified with dil. hydrochloric acid, XI precipitated; m.p. 260–262°,[26] yield 2.5 g. (54%).

Anal. Calcd. for $C_{12}H_{14}O_6N_4$: C, 46.45; H, 4.55; N, 18.06; neut. equiv., 155.1. Found: C, 46.62; H, 4.70; N, 18.05; neut. equiv., 154.7.

The diammonium salt melted at 272° dec.[27]

When only 1 molecular equivalent of hydrochloric acid was employed, only XII was obtained. When 4 molecular equivalents of the acid was used, XI was the only reaction product.

ANN ARBOR, MICHIGAN

---

[25] F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908), gave m.p. 159.5°.

[26] E. Fischer and L. Reese, *Ann.*, **221**, 336 (1883), gave m.p. 260°; ref. 17, m.p. 260–262°.

[27] H. Biltz, *Ann.*, **504**, 186 (1914), reported m.p. 272° dec.