SYNTHESIS OF 8-METHYLTHEOBROMINE FROM 3-METHYL-4-AMINOURACIL

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A new three-step method has been developed for the synthesis of 8-methyltheobromine from 3-methyl-4-aminouracil, based on its bromination, the conversion of 3-methyl-4-amino-5-bromouracil to 3-methyl-4-amino-5-dimethylaminouracil, and the reaction of the latter with acetic anhydride.

Methylated xanthine, substituted in position 8 through a carbon-carbon bond, is of interest as a potential starting point in the search for new drugs [1]. The starting material for the synthesis of theobromine compounds of this type can be 8-methyltheobromine (I) since the procedures developed earlier, with the participation of one of us, for converting it to 8-monochloromethyltheobromine [2] and theobromine-8-aldehyde [3], make it possible to obtain even more varied compounds. At the beginning of this century [4], 8-methyltheobromine had already been described as an intermediate in the synthesis of theobromine from uric acid, formed by the methylation of the 8-methylxanthine intermediate. Later a series of variations in the preparation of I were described, based on the same reaction, namely the methylation of 8-methylxanthine by different methylating agents under different conditions [5-8]. The main disadvantages of this procedure are the high stability of the uric acid starting material, the need for prolonged boiling (over 80 h) with acetic anhydride to convert it to 8-methylxanthine, as well as the relative low yields of I at the methylation step, which always leads to formation of mixtures of mono-, di-, and trimethyl derivatives of 8-methylxanthine. This list of disadvantages can be eliminated if, instead of 8-methylxanthine, 3,8-dimethylxanthine (II) is used as a starting material [4]. The latter is synthesized from 3-methyl-4-aminouracil (III) [9], but by this scheme the yield of I, when II is methylated in conditions suitable for the commercial synthesis of theobromine (IV) [10], cannot be considered acceptable. It barely reaches 60%, which corresponds to approximately 30%, based on starting III.

Approximately the same yield is obtained if III is converted to I by reaction of its 5-bromo derivative (V) [11, 12] with methylamine, acetylation of the 3-methyl-4-amino-5-methylaminouracil thus formed (VI) [12], and cyclization of the acetate (VII).

It should be noted, incidentally, that the melting point of the compound, which we obtained by aminolysis of bromide V (235-238°C), is 50° higher than that given in the literature [12] for 3-methyl-4-amino-5-methylaminouracil (VI) (183-185°). The empirical formula of the compound whose melting point is 235-238° ($C_6H_{10}N_4O_2 \cdot {}^1/_2H_2O$) and its properties also confirm the diamine structure VI proposed for it. Evidently the melting point for this compound, as given in the literature, should be considered erroneous. On heating with formamide [12] it forms IV, while on boiling for 5 h with acetic anhydride it is converted to a hitherto undescribed compound which, judging from its properties and analysis, appears to be 3-methyl-4-acetylamino-5-methylacetylaminouracil (VIII) [cf. 13, 14].

To increase the yield of I from III and to reduce the number of steps, we made use of the observations of H. Bredereck and coworkers [15], who discovered that when 1,3-dimethyl-4-amino-5-dimethylaminouracil reacts with acetic anhydride, methyl acetate is split off, and the imidazole ring is closed, forming 8-methylcaffeine. In an analogous reaction conducted with 3-methyl-4-amino-5-dimethylaminouracil (XI), which is formed in good yield by reaction of bromide V with dimethylamine, we obtained I in over 90% yield.

Intermediate IX was further characterized by methylation with dimethyl sulfate in an aqueous alkaline medium. The constants and properties of the resulting compound coincides with that published for 1,3-dimethyl-4-amino-5-dimethylaminouracil [15]:

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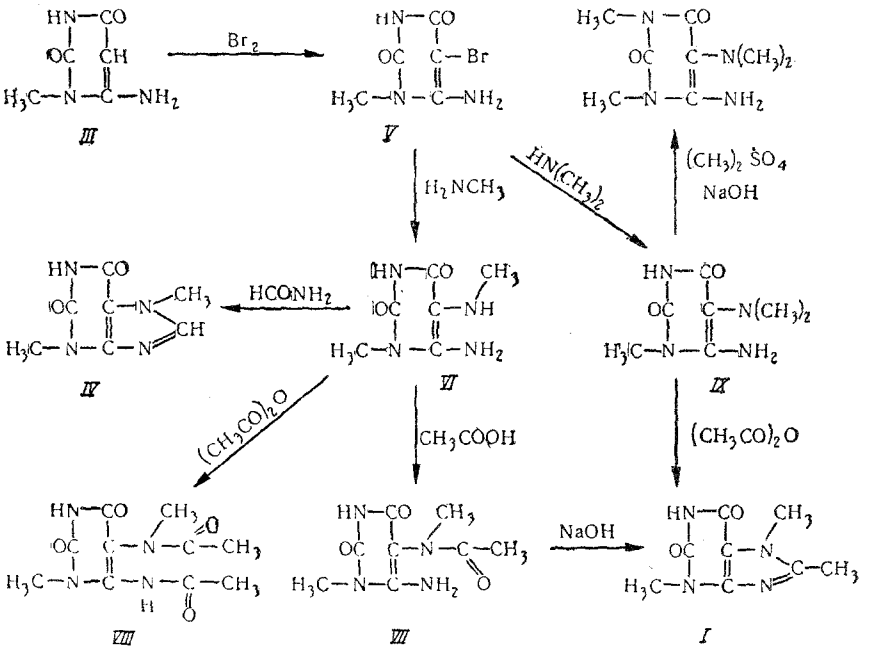

The method developed for the synthesis of I from III has obvious advantages over the other variants shown above.* All reactions proceed in high yields and the yield of I, starting from III, is about 70%.

EXPERIMENTAL

3-Methyl-4-amino-5-bromouracil(V) [11, 12]

A suspension of 141 g (1 mole) of finely ground 3-methyl-4-aminouracil (III) in 840 ml of methyl or ethyl alcohol was cooled with ice water and stirred vigorously. With the temperature at 10-20°, 160 g (1 mole) of bromine was added over the course of 20-30 min. Mixing was continued for another hour. The mixture was then filtered, washed free of hydrobromic acid with water, and then rinsed with alcohol and dried† at 75-80°. The bromide V weighed 211 g. Its m.p. was 260-265° (literature value [11] 278-280°).

3-Methyl-4-amino-5-dimethylaminouracil (IX)

A mixture of 211 g of bromide V and 660 g of 33%, or 800 g of 25% aqueous dimethylamine, was heated with agitation to 50-55° (about 1 h). After the solids have dissolved, stirring was continued for another 2 h at 55-60°. After standing for 12 h at 20°, the mixture was filtered, and the residue washed with water and dried.

The yield was 117 g and the m.p. 238-240°. An additional 24 g of IX (m.p. 220-235°) was isolated by evaporation of the filtrate to a volume of 150-170 ml. The total yield of IX was 141 g. An analytical sample crystallized from water (1 : 15) melts at 240-241°. Found %: C 44.90; H 6.40; N 30.29; $C_7H_{12}N_4O_2$. Calculated %: C 45.65; H 6.52; N 30.42.

After 0.85 g (0.0046 mole) of IX was dissolved in 4.6 ml of a normal solution of NaOH (0.0046 mole) and heated to 50°, a solution of 0.582 g (0.0046 mole) of dimethyl sulfate in 5 ml of methanol was added. The solution was concentrated over the course of 20 min, forming a precipitate which after recrystallization from alcohol yielded 0.7 g of a solid, m.p. 193-194° (1,3-dimethyl-4-amino-5-dimethylaminouracil [15] melts at 194°).

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*Compound I can be obtained also from theobromine by first forming theobromine-8-acetic acid [16] and then decarboxylating it. Such a route is not considered in detail in this paper, since it is unlikely to have any practical value.

†The yields in this reaction are so constant that, in the subsequent step, the reaction product can be used while still moist.

3-Methyl-4-amino-5-(N-methyl-N-acetyl)-aminouracil (VII)

Boiling 1 g (0.0059 mole) of amine VI in 10 ml of acetic acid for 4 h and filtering and washing the precipitate with water yielded 0.63 g, m.p. 280-285°. After crystallization from aqueous alcohol (1 : 1) the m.p. was 288-290°. Found %: C 44.90; H 5.84; N 26.42. $C_8H_{12}N_4O_3$. Calculated %: C 45.20; H 5.65; N 26.40.

Diacetyl Derivative of 3-Methyl-4-amino-5-methylaminouracil (VIII)

Boiling 1 g (0.0059 mole) of amine VI in 10 ml of acetic anhydride for 5 h and filtering and washing the precipitate with water yielded 1.1 g, m.p. 303-305°. After recrystallization from water, the m.p. was 309-311°. Found %: C 47.34; H 5.66. $C_{10}H_{14}N_4O_4$. Calculated %: C 47.24; H 5.51.

8-Methyltheobromine (I) [4]

a) From 3-Methyl-4-amino-5-dimethylaminouracil (IX). Boiling 141 g of IX with 420 ml of acetic anhydride for 2 h results in dissolution of solids followed by precipitation. The excess acetic anhydride is boiled off under vacuum, and the residue crystallized from water, using charcoal. The yield was 139 g (92%), m.p. 304-305° (literature value [4] 302-303°).

b) From 3-Methyl-4-amino-5-(N-methyl-N-acetyl)aminouracil (VII). Boiling 0.4 g of VII in 4 ml of normal NaOH solution for 3 h and acidifying to pH 6.0 and filtering yielded 0.33 g, m.p. 304-305°. A mixture with I melted at 304-305°.

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