PURINES AND PYRIMIDINES AND CONDENSED SYSTEMS BASED ON THEM.

2.* SYNTHESIS OF 1-METHYL-9-AMINOXANTHINE AND 9-AMINOTHEOPHYLLINE

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The previously unknown 9-aminotheophylline and 1-methyl-9-aminoxanthine were synthesized from 3-methyl-5-amino-6-hydrazinouracil. In the case of 1-methyl-9-aminoxanthine an x-ray diffraction study of an N-amino derivative of an NH heterocycle was made for the first time.

It was recently shown [1, 2] that 5,7-dimethylpyrimido [4,5-e]-1,2,4-triazine-6,8-dione (isofervenulin) – a structural isomer of the antibiotic fervenulin – is formed in good yield in the oxidation of 7-aminotheophylline with lead tetraacetate. In this connection it seemed of interest to synthesize the still unknown 9-amino-1-methylxanthine and 9-aminotheophylline, the oxidation of which may lead to the formation of the antibiotics reumycin and fervenulin. The difficulty in obtaining these amines consists in the fact that the direct amination of theophylline with electrophilic agents gives only 7-aminotheophylline [1-3], while, as we established, the amination of 1-methylxanthine proceeds primarily in the 3 position. In the present research we set out to synthesize 1-methyl-9-aminoxanthine and 9-aminotheophylline from suitable pyrimidine derivatives.

It is evident that 5-amino-6-hydrazinouracils should be the key compounds for obtaining the desired 9-aminoxanthines (see [4]). For their synthesis we started from 1-methyl- and 1,3-dimethylbarbituric acids (Ia,b), which were obtained by condensation of, respectively, methylurea and dimethylurea with malonic ester in the presence of sodium methoxide. This method for obtaining 1-methylbarbituric acid is considerably more convenient than previously described methods [5, 6]. In the method in [5], which is virtually nonreproducible, methylurea is condensed with malonic acid in the presence of acetic acid and acetic anhydride. The second method [6], which specified obtaining thiobarbituric acid and its subsequent methylation and hydrolysis, is extremely laborious and gives a low overall yield of Ia.

3-Methyl- and 1,3-dimethyl-6-chlorouracil (IIa,b) are formed in 70% and 93% yields, respectively, by brief heating of barbituric acids Ia,b with phosphorous oxychloride. Their nitration with a nitrating mixture at 3-4°C leads to the formation of 5-nitro derivatives IIIa,b in 85% and 97% yields, respectively. Compound IIb is nitrated in the same yield also by potassium nitrate in concentrated sulfuric acid. In a previously described method [7] for obtaining 3-methyl-5-nitro-6-hydrazinouracil (Va) a solution of nitro chloro derivative IIIa is added slowly to an equimolar amount of hydrazine hydrate in methanol. We were unable to reproduce this method. We found that the principal reaction product under these conditions is a substance which, judging from the results of elementary analysis and the spectra characteristics, is hydrazo derivative VII. Compound Va is obtained in almost quantitative yield by treatment of an alcohol solution of nitro chloro derivative IIIa with excess hydrazine hydrate. In this reaction the initial product is hydrazinium salt IVa, from which the free base is isolated by acidification. 1,3-Dimethyl-5-nitro-6-chlorouracil also gives the analogous hydrazinium salt IVb on treatment with hydrazine hydrate under the same conditions. The yield of the previously unknown nitro hydrazine Vb is also close to quantitative (see scheme).

The reduction of Va or hydrazinium salt IVa with sodium dithionite in ammonium hydroxide leads to the formation of the desired amino hydrazine VI in 80% yield. However, we were unable to obtain 1,3-dimethyl-5-amino-6-hydrazinouracil under these and other conditions (for

*See [1] for communication 1.

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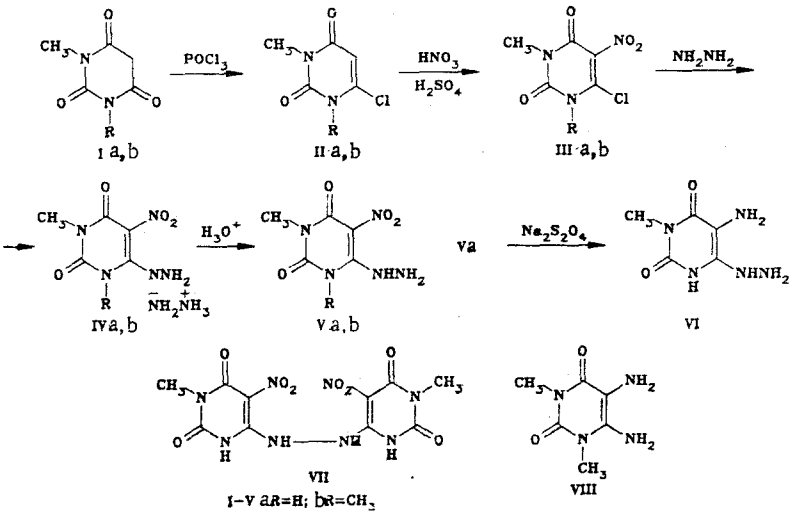
TABLE 1. Coordinates of the Atoms of 1-Methyl-9-aminoxanthine XIII ($\cdot 10^4$; $\cdot 10^3$ for H) and Their Amisotropic Temperature Factors (V_j for H) in the Form T = [exp $- 2\pi^2(h^2a^{*2}V_{11} + \ldots + 2hka^*\cdot b^*V_{12} + \ldots)$]

Atom	x	y	z	V_{11}/V_j for H*	V_{22}	V_{33}	V_{23}	V_{13}	V_{12}
$O_{(1)}$	4735(2)	4154(1)	2633(2)	0,039(1)	0,030(1)	0,046(1)	0,000(1)	0,003(1)	−0,009(1)
$O_{(2)}$	7836(2)	5446(1)	5(2)	0,025(1)	0,051(1)	0,034(1)	−0,0002(1)	0,004(1)	−0,003(1)
$N_{(1)}$	6264(2)	4816(1)	1285(2)	0,028(1)	0,030(1)	0,029(1)	−0,002(1)	0,001(1)	0,001(1)
$N_{(2)}$	4941(2)	5489(1)	3130(2)	0,023(1)	0,029(1)	0,034(1)	0,001(1)	0,004(1)	−0,003(1)
$N_{(3)}$	5478(2)	6898(1)	3605(2)	0,026(1)	0,030(1)	0,033(1)	0,001(1)	0,000(1)	0,000(1)
$N_{(4)}$	4610(2)	7160(1)	4785(3)	0,031(1)	0,034(1)	0,040(1)	−0,004(1)	0,003(1)	0,004(1)
$N_{(5)}$	7086(2)	6966(1)	1927(3)	0,030(1)	0,031(1)	0,035(1)	0,006(1)	−0,002(1)	−0,005(1)
$C_{(1)}$	6965(2)	5496(1)	959(3)	0,022(1)	0,037(1)	0,025(1)	0,003(1)	−0,004(1)	−0,001(1)
$C_{(2)}$	5279(2)	4781(1)	2368(3)	0,024(1)	0,030(1)	0,028(1)	0,002(1)	−0,002(1)	−0,001(1)
$C_{(3)}$	5606(2)	6160(1)	2877(3)	0,025(1)	0,026(1)	0,028(1)	0,003(1)	−0,004(1)	−0,001(1)
$C_{(4)}$	6575(2)	6200(1)	1841(3)	0,024(1)	0,031(1)	0,029(1)	0,005(1)	−0,003(1)	−0,005(1)
$C_{(5)}$	6397(2)	7356(1)	2981(3)	0,032(1)	0,027(1)	0,037(1)	0,004(1)	−0,004(1)	−0,004(1)
$C_{(6)}$	6681(3)	4042(2)	600(4)	0,041(1)	0,038(1)	0,047(1)	−0,010(1)	0,003(1)	0,003(1)
$H_{(N2)}$	428(3)	550(2)	380(4)	0,036(7)					
$H_{(N41)}$	391(3)	707(2)	421(4)	0,034(7)					
$H_{(N42)}$	460(3)	681(2)	573(4)	0,048(9)					
$H_{(5)}$	643(2)	790(2)	334(3)	0,037(7)					

*The hydrogen atoms of the $C_{(6)}$ methyl group are statically disordered; this is evidently due to rotation of the methyl group about the $N_{(1)}$–$C_{(6)}$ bond.



example, in the reduction of Vb with sodium dithionite in DMF in the presence of formic acid). We found that the reduction of Vb is accompanied by cleavage of the N–N bond of the hydrazino group, as a result of which diamine VIII is formed. In this connection we decided to introduce a second methyl group into the pyrimidine ring in later steps of the synthesis.

We were unable to subject amino hydrazine VI, as well as its mono- and diformyl derivatives, to cyclization to 1-methyl-9-aminoxanthine (these experiments will be published later). In this connection we tried another known approach [4], which consists in the cyclication of benzylidenehydrazines. When VI is heated with excess benzaldehyde or p-nitrobenzaldehyde in DMF or acetic acid, it is converted to dianils IXa,b in quantitative yields. It is interesting that dianils are also formed when equimolar ratios of the amino hydrazine and aldehyde are used. When IXa is refluxed in 99% formic acid, it undergoes hydrolysis of the benzylideneamino group and then formylation, as a result of which Xa is formed in 89% yield. Dianil IXb also undergoes a similar reaction with the formation of formyl hydrazone Xb. Only deformylation to give monoanil XI occurred in an attempt to cyclize Xa by heating in hydrochloric acid. We were able to accomplish the cyclization by heating a suspension of Xa or XI in a mixture of orthoformic ester and acetic anhydride (the use of this mixture to obtain purines often gives good results [8]). As a result of the reaction, 1-methyl-9-benzylideneaminoxanthine (XII) was obtained in 63% yield. Its alkaline hydrolysis leads to 1-methyl-9-aminoxanthine (XIII) in good yield. We were unable to carry out the hydrolytic transformation XII →

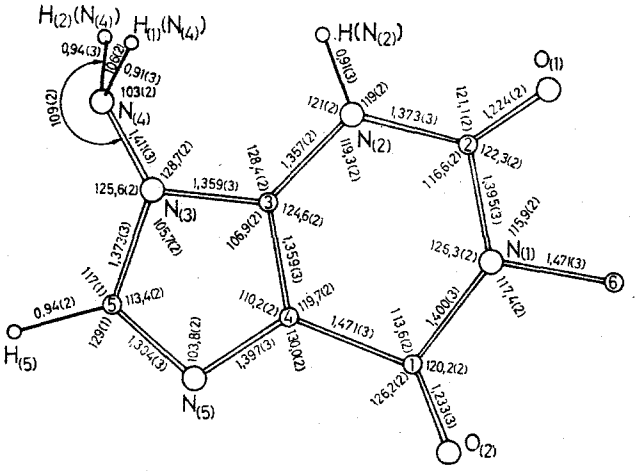
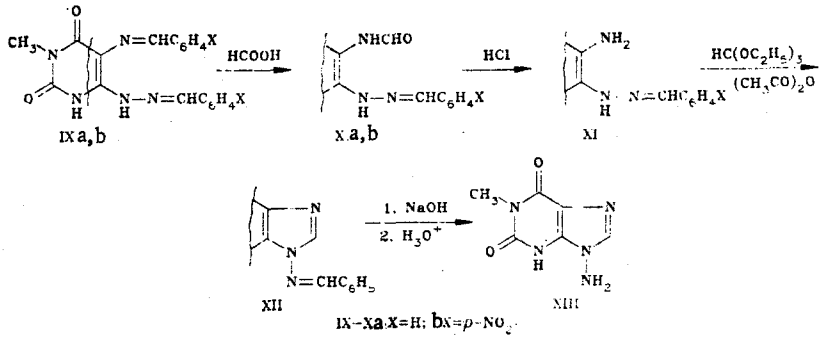


Fig. 1. Three-dimensional structure of 1-methyl-9-aminoxanthine (XIII).

XIII in an acidic medium, probably because of the insufficient solubility of the starting compound.



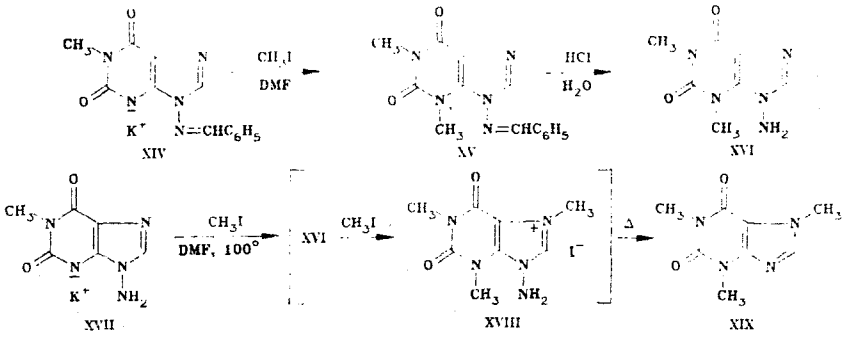
The molecular and crystal structures of XIII were determined by x-ray diffraction analysis. A three-dimensional model of the molecule with designation of the bond lengths and bond angles is shown in Fig. 1. The coordinates of the atoms and the anisotropic temperature factors are presented in Table 1. All of the nonhydrogen atoms in the molecule, as well as the $H_{(5)}$ and $H_{(N_2)}$ atoms, are virtually coplanar. The hydrogen atoms of the NH_2 group, which, as a consequence of the pyramidal character of the $N_{(4)}$ atom, deviate from the plane by −0.85 Å and 0.81 Å and are inclined appreciably toward the $N_{(2)}$–H group, constitute an exception.* The dihedral angle between the plane of the purine system and H–$N_{(4)}$–H plane is 87.3°, i.e., virtually no conjugation exists between the electron pair of the nitrogen atom in the NH_2 group and the π system of the imidazole ring. The length of the $N_{(3)}$–$N_{(4)}$ bond, which is 1.411(3) Å, is appreciably shortened as compared with hydrazine (1.48 Å) [9] and phenylhydrazine (1.46 Å) [10]. This shortening is evidently not associated with the development of a π component in this bond, since 1.411 Å is close to the sum of the covalent radii of sp^3- and sp^2-hybridized nitrogen atoms. It should be noted that this is the first information regarding the stereochemistry of an N-amino group in nitrogen heterocycles. In general, the lengths of the C–C and C–N ring bonds are typical for conjugated nitrogen-containing heterocycles [10]. One's attention is directed only to the increased double-bond character of the $C_{(3)}$–

*The hydrogen atoms of the $C_{(6)}$ methyl group could not be localized unambiguously; this is evidently due to the presence in the structure of several rotational "isomers" that differ with respect to rotation of the CH_3 group about the $N_{(1)}$–$C_{(6)}$ bond: in differential synthesis there are nine peaks of close value about the $C_{(6)}$ atom at distances of ~1.0 Å.

$C_{(4)}$ bond [1.359(3) Å] common to the two rings, as well as the $C_{(5)}$–$N_{(5)}$ bond [1.304(3) Å].

In the crystals the protons of all of the N–H bonds participate in the formation of intermolecular hydrogen bonds; the XIII (x, y, z) and XIII (1 – x, 1 – y, 1 – z) molecules are joined together by $N_{(4)}$–$H_{(N12)}$...$O_{(1)}$ bonds into centrosymmetric dimers. The lengths of the H bonds in these dimers are 3.067(3) Å for O...N and 2.18(3) Å for O...H, and angle N–H...O is 157(1)°. In addition, the $H_{(N2)}$ and $H_{(N41)}$ atoms of the (x, y, z) molecule participate in the formation of hydrogen bonds with the $O_{(2)}$ and $N_{(5)}$ atoms of the (–1/2 + x, y, 1/2 – z) molecule, and the $O_{(2)}$ and $N_{(5)}$ atoms of the (x, y, z) molecule form hydrogen bonds with the $H_{(N2)}$ and $H_{(N41)}$ atoms of the (1/2 + x, y, 1/2 – z) molecule, which leads to the formation in the crystal of chains made up of H-bonded XIII molecules stretched out along the axis. The lengths of the $N_{(2)}$...$O_{(2)}$ and $H_{(N2)}$....$O_{(2)}$ bonds are, respectively, 2.779(3) Å and 1.87(1) Å, and angle $N_{(2)}$–H...$O_{(2)}$ is 177(2)°; the lengths of the $N_{(4)}$...$N_{(5)}$ and $H_{(N41)}$...$N_{(5)}$ bonds are, respectively, 3.152(3) Å and 2.24(3) Å, and angle $N_{(4)}$–H...$N_{(5)}$ is 180(3)°.

To obtain 9-aminotheophylline (XVI), the initially isolated (see the experimental section) crystalline 1-methyl-9-benzylideneaminoxanthine potassium salt (XIV) was methylated at 20°C with methyl iodide in DMF, and 9-benzylideneaminotheophylline (XV) was obtained in 88% yield. Its hydrolysis with dilute hydrochloric acid led to 9-aminotheophylline (XVI) in 93% yield. Compound XVI cannot be obtained by methylation of 1-methyl-9-aminoxanthine potassium salt (XVII). Virtually no reaction occurs at 20°C, and caffeine (XIX) is formed as the only product in 76% yield in the case of heating to 100°C in DMF. The initial product in this case is probably 9-aminotheophylline (XVI), which is then converted to quaternary salt XVIII. Salts of slightly basic heterocyclic compounds such as caffeine should undergo deamination in DMF, and this is observed in this reaction (see [11]). The fact that genuine 9-aminotheophylline is converted to caffeine in 71% yield when it is heated with methyl iodide in DMF constitutes evidence in favor of this explanation of the course of the reaction.



Data on the chemical properties of XIII and XVI, including their behavior with respect to oxidizing agents, will be published separately.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were obtained with Tesla BS-487 and Bruker-90 (90 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian-MAT spectrometer with direct introduction of the samples into the ion source under the following conditions: the accelerating voltage was 3.6 kV, the ionizing-electron energy was 70 eV, the cathode emission current was 1.5 mA, and the sample-vaporization temperature was 180-220°C.

X-Ray Diffraction Analysis of 1-Methyl-9-aminoxanthine (XIII). Rhombic crystals with the composition $C_6H_7N_5O_2$ were grown from water and had the following parameters: a = 11.235(3), b = 16.612(5), c = 7.827(2) Å, V = 1,460.8(7) Å^3, d_{calc} = 1.29 g/cm^3, Z = 8, and space group P_{bca}. The intensities of 1145 independent nonzero reflections with $F^2 \geq 3\sigma$ were measured with a Syntex P1 diffractometer by $\theta/2\theta$ scanning in copper emission up to $2\theta \leq 45°$. The model of the molecule was found by the direct method. The structure was refined by the method of least squares within the total-matrix anisotropic approximation (the hydrogen atoms, which were revealed by differential synthesis, were refined isotropically up to R = 0.041, R_W = 0.052).

1-Methylbarbituric Acid (Ia). A 32-g (0.2 mole) sample of malonic ester was added to a solution of sodium methoxide, obtained from 4.6 g (0.2 mole) of sodium in 80 ml of absolute methanol, and the mixture was refluxed for 10 min. A solution of N-methylurea obtained from 27.4 g (0.2 mole) of N-methylurea nitrate [12] by neutralization of equimolar amounts of sodium methoxide in 100 ml of absolute methanol was then added; a colorless precipitate formed from the solution after heating for 25 min. The reaction mixture was heated for 6 h on an oil bath at 110°C, after which it was cooled, and the precipitate was removed by filtration and dissolved in 30 ml of water. The aqueous solution was acidified to pH 1 with concentrated HCl and cooled to 0°C, and the resulting precipitate was removed by filtration and washed with 10 ml of alcohol and ether to give 18.7 g (66%) of colorless crystals with mp 132-133°C (from water) (mp 132°C [5]).

1,3-Dimethylbarbituric Acid (Ib). This compound was similarly obtained in 71% yield from N,N'-dimethylurea and malonic ester. The colorless crystals had mp 122-123°C, in agreement with the data in [13].

3-Methyl-6-chlorouracil (IIa). A 12-ml (0.67 mole) sample of water was added carefully dropwise to a suspension of 36 g (0.25 mole) of acid Ia in 290 ml (3.15 mole) of $POCl_3$, and the mixture was heated cautiously to the boiling point and refluxed for 30-40 min. The excess $POCl_3$ was removed from the resulting yellow solution by distillation under reduced pressure (10 mm), and the yellow viscous residue was poured over 250 g of ice. The resulting precipitate was removed by filtration and washed with water, alcohol, and ether to give 28 g (70%) of colorless crystals with mp 267-268°C (from a large volume of water), in agreement with the data in [14].

1,3-Dimethyl-6-chlorouracil (IIb). A 2,5-ml (0.14 mole) sample of water was added dropwise to a suspension of 7.8 g (0.05 mole) of 1,3-dimethylbarbituric acid in 60 ml (0.66 mole) of $POCl_3$, and the mixture was refluxed until a clear solution formed (30-40 min). The excess $POCl_3$ was removed by distillation under reduced pressure. (Avoid overheating! It is best to heat on a boiling-water bath.) The yellow viscous residue was poured over 50 g of ice (the residue on the walls of the flask was also triturated with ice), and the resulting viscous oil was extracted with chloroform (150 ml). The chloroform extract was dried with calcium chloride, the chloroform was removed by distillation, and the residue was dried in a vacuum desiccator over $CaCl_2$. The yield of the slightly yellowish crystalline mass was 8.1 g (93%). Recrystallization from hexane gave colorless crystals with mp 112-113°C, in agreement with the data in [15]. IR spectrum (in $CHCl_3$): 1670, 1715 cm^{-1} (C=O).

3-Methyl-5-nitro-6-chlorouracil (IIIa). A 27-g (0.17 mole) sample of uracil IIa was dissolved in 80 ml of concentrated H_2SO_4 with addition of chlorouracil IIa at such a rate that the temperature did not rise above 10°C (~30 min). A 7.57-ml (0.18 mole) sample of HNO_3 (density 1.52) was added dropwise at 15°C to the resulting solution. After 15 min, the cooling bath was removed, and the mixture was stirred at 20°C for 1 h. It was then poured over 150 g of ice, and the resulting light-yellow precipitate was separated and washed with water to give 20.8 g (77%) of light-yellow crystals with mp 195-197°C (from water), in agreement with th data in [6].

1,3-Dimethyl-5-nitro-6-chlorouracil (IIIb). A) A 2,6-ml (0.063 mole) sample of HNO_3 (density 1.54) was added dropwise to a suspension of 6.98 g (0.04 mole) of 1,3-dimethyl-6-chlorouracil in 25 ml of concentrated H_2SO_4 at such a rate that the temperature of the mixture did not rise above 7°C, after which the mixture was stirred at this temperature for 1 h and at 20°C for 30 min. It was then poured over 100 g of ice, and the aqueous mixture was extracted with chloroform (three 50-ml portions). The extract was dried with Na_2SO_4, and the chloroform was evaporated. The residual yellow oil began to crystallize when it was triturated with petroleum ether. The yield was 8.5 g (97%). The light-yellow crystals had mp 65-68°C (from alcohol with benzene), in agreement with the data in [16].

B) A 0.3-g (3 mmole) sample of finely ground KNO_3 was sprinkled in portions into a solution of 0.5 g (2.9 mmole) of 1,3-dimethyl-6-chlorouracil in 2 ml of concentrated H_2SO_4 while maintaining the temperature of the mixture at 7°C. The mixture was stirred at 7°C for 15 min and at 20°C for 30 min. Compound IIIb was isolated as described in method A. The yield was 0.62 g (98%).. IR spectrum (in $CHCl_3$): 1700, 1740 cm^{-1} (C=O).

3-Methyl-5-nitro-6-hydrazinouracil (Va). A solution of 4 g (0,02 mole) of chloronitrouracil IIIa in 10 ml of alcohol was added rapidly with vigorous stirring to 25 ml of a 30% solution of hydrazine, during which the mixture heated up markedly, and a yellow precipitate formed immediately. The mixture was stirred at 20°C for 15 min and refluxed for 5 min, after

which it was cooled, and the precipitate was removed by filtration and washed with water, alcohol, and ether. The yield of the 3-methyl-5-nitro-6-hydrazinouracil hydrazinium salt was 4.3 g (86%). The pale-yellow needles had mp 184°C (from water). Found, %: C 23.6, H 5.1, N 39.2. $C_5H_{11}N_7O_4 \cdot H_2O$. Calculated, %: C 23.9, H 5.2, N 39.0. The hydrazinium salt was treated with 10% acetic acid until the mixture had pH 3-4 and Va precipitated. The pale-yellow needles had mp 213-214°C (from a large volume of water). Found, %: C 29.9, H 3.6, N 35.1. $C_5H_7N_5O_4$. Calculated, %: C 29.9, H 3.5, N 34.8.

1,3-Dimethyl-5-nitro-6-hydrazinouracil (Vb). A solution of 2.2 g (0.01 mole) of 1,3-dimethyl-5-nitro-6-chlorouracil in 15 ml of alcohol (dissolved by heating) was added with stirring to 12 ml of a 30% alcohol solution of hydrazine hydrate, during which a dark-cherry red clear solution, from which a copious yellow precipitate formed, developed. The carrying out of the experiment and the isolation of the product in the form of hydrazinium salt IVb were similar to the procedures in the preceding experiment. The hydrazinium salt was dried in a vacuum desiccator over $CaCl_2$. The yield was 2.4 g (98%). PMR spectrum (in D_6-DMSO): 3.05 (3H, s, N–CH_3); 3.17 (3H, s, N–CH_3); and 6.17 ppm (7H, broad m, $\tilde{N}NH_2$, $NH_2N^+H_3$). Found, %: C 29.3, H 5.4, N 40.0. $C_7H_{13}N_7O_4$. Calculated, %: C 29.2, H 5.3, N 39.7. A 2.4-g sample of salt IVb was triturated with 10 ml of 10% acetic acid, and the almost colorless precipitate was removed by filtration and washed with 20 ml of ice water and alcohol. The yield of Vb was 2.1 g (6%). The yellowish crystals had mp 128-130°C (dec., from alcohol). IR spectrum: 1685, 1735 (C=O); 3345 cm^{-1} (N–H).

3-Methyl-5-amino-6-hydrazinouracil (VI). An 8.4-g (0.04 mole) sample of sodium dithionite was added in portions to a suspension of 2.5 g (0.01 mole) of hydrazinium salt IVa in 14 ml of 10% NH_4OH, during which heating up of the reaction mixture occurred in the course of 20 min. After all of the sodium dithionite had been added, the mixture was heated to the boiling point and refluxed for 5 min. It was then cooled on an ice bath, and the resulting precipitate was separated and washed with water, alcohol, and ether. The yield was 1.5 g (88%). The colorless needles (from water) decomposed without melting at 170-270°C. Found, %: C 35.4, H 5.6, N 41.2. $C_5H_9N_5O_2$. Calculated, %: C 35.0, H 5.3, N 40.9.

6,6'-Hydrazo(3-methyl-5-nitrouracil) (VII). A solution of 0.5 g (2.5 mmole) of IIIa in 2 ml of methanol was added dropwise at 0°C with vigorous stirring to a solution of 0.1 ml (3.0 mmole) of hydrazine hydrate in 10 ml of methanol, during which a pale-yellow precipitate formed immediately. The mixture was stirred at 0°C for 1 h, and the precipitate was removed by filtration. The yield was 0.5 g (51%). The pale-yellow prisms had mp 169-170°C (dec., from water). IR spectrum: 1590, 1675, 1740 (C=O); 3160 (N–H); 3510, 3580 cm^{-1} (H_2O). Found, %: C 30.7, H 3.2, N 28.6. $C_{10}H_{10}N_8O_8 \cdot H_2O$. Calculated, %: C 30.9, H 3.1, N 28.9.

1,3-Dimethyl-5,6-diaminouracil (VIII). A 4.0-g (22.0 mmole) sample of sodium dithionite was added in portions at 50°C to a solution of 1.1 g (5.0 mmole) of 1,3-dimethyl-5-nitro-6-hydrazinouracil in 10 ml of 12% NH_4OH, after which the mixture was cautiously heated up to the boiling point (vigorous frothing of the mixture!) and refluxed for 10 min. It was then cooled, and the precipitated crystals were removed by filtration and washed with 5 ml of cold water. The yield was 0.5 g (60%). The light-gray crystals had mp 183-184°C (from water) (mp 209°C [17]). IR spectrum: 1620-1700 (C=O); 3200, 3378 (N–H); 3535 cm^{-1} (H_2O). Found, %: C 37.2, H 6.3, N 30.1. M^+ 170. $C_6H_{10}N_4O_2 \cdot H_2O$. Calculated, %: C 38.2, H 6.3, N 29.8.

3-Methyl-5-benzylideneamino-6-benzylidenehydrazinouracil (IXa). A 6.2-ml (0.06 mole) sample of benzaldehyde was added to a solution of 5.0 g (0.03 mole) of o-aminohydrazinouracil VI in 50 ml of DMF, and the mixture was refluxed for 5 min. It was then diluted to twice its original volume with water, and the pale-yellow precipitate was removed by filtration and washed with water and alcohol. The yield was 10.0 g (96%). The compound was purified by recrystallization from aqueous DMF. The pinkish-orange needles turned yellow at 200-205°C, melted at 240-245°C, resolidified, and melted with decolorization at 270°C. Found, %: C 65.9, H 5.0, N 20.3. $C_{19}H_{17}N_5O_2$. Calculated, %: 65.7, H 4.9, N 20.2.

3-Methyl-5-(p-nitrobenzylideneamino)-6-(p-nitrobenzylidenehydrazino)uracil (IXb). A 0.34-g (2 mmole) sample of VI and 0.6 g (4 mmole) of p-nitrobenzaldehyde were mixed at 20°C in 5 ml of acetic acid, during which a red precipitate formed immediately. The precipitate was removed by filtration after 20 min and washed with alcohol and ether. The yield was 0.85 g (98%). The bright-red fibrous crystals melted above 330°C (from DMF). Found, %: 51.6, H 3.4, N 21.9. $C_{19}H_{15}N_7O_6$. Calculated, %: C 52.2, H 3.4, N 22.4.

3-Methyl-5-formylamino-6-benzylidenehydrazinouracil (Xa). A solution of 8.5 g (0.02 mole) of IXa in 50 ml of 99.7% formic acid was refluxed for 2 h, after which it was poured into

100 ml of water. The aqueous mixture was cooled, and the pale-yellow precipitate was removed by filtration and washed with water and alcohol. The yield was 6.2 g (89%). The colorless crystals had mp 280°C (dec., from aqueous DMF). Found, %: C 54.5, H 4.5, N 24.1. $C_{13}H_{13}N_5O_3$ Calculated, %: C 54.3, H 4.5, N 24.4.

3-Methyl-5-formylamino-(p-nitrobenzylidenehydrazino)uracil (Xb). This compound was similarly obtained in 90% yield. The pale-yellow needles melted above 320°C (from DMF). Found, %: 47.3, H 3.9, N 25.4. $C_{13}H_{12}N_6O_5$. Calculated, %: C 47.0, H 3.6, N 25.3.

3-Methyl-5-amino-6-benzylidenehydrazinouracil (XI). A 0.25-g (0.87 mmole) sample of Xa was added to 5 ml of concentrated HCl, and the mixture was refluxed for 5 min, during which the solid material initially dissolved, after which a precipitate formed. The mixture was cooled, and the precipitate was removed by filtration and washed with water. The precipitate (the hydrochloride of amino derivative XI) was treated with concentrated NH_4OH, after which the ammonia was evaporated at 20°C, and the residue was separated and washed with water (if the ammonia was not evaporated, the substance dissolved in it). The yellowish-green crystals had mp 208-209°C (from butanol). Found, %: C 55.7, H 5.3, N 27.1. $C_{12}H_{13}N_5O_2$. Calculated, %: C 55.6, H 5.0, N 26.0.

1-Methyl-9-benzylideneaminoxanthine (XII). A) A suspension of 0.47 g (1.8 mmole) of 5-aminouracil XI in 8 ml of a mixture of orthoformic ester and acetic anhydride (1:1) was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol and ether. The yield was 0.3 g (63%). The colorless crystals melted above 330°C (from aqueous DMF). IR spectrum: 1675, 1715 (C=O); 3110 cm^{-1} (C–H_a). PMR spectrum (d_6-DMSO): 3.22 (3H, s, N–CH_3); 7.6 (3H, m, m- and p-H of C_6H_5); 8.01 (2H, m, o-H of C_6H_5); 8.47 (1H, s, 8-H); 9.09 (1H, s, N=CH–); and 12.46 ppm (1H, s, N–H, vanished after deuteration). Found, %: C 57.9, H 4.2, N 26.4. M^+ 269. $C_{13}H_{11}N_5O_2$. Calculated, %: C 58.0, H 4.1, N 26.0.

B) A suspension of 15.0 g (0.05 mole) of Xa in 300 ml of orthoformic ester and acetic anhydride (1:1) was refluxed with stirring for 5 h, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol. The yield was 11.2 g (83%). The pale-yellow prisms melted above 330°C (from DMF). With respect to its physicochemical characteristics, the product was identical to the sample obtained by method A.

1-Methyl-9-aminoxanthine (XIII). A solution of 1.0 g (3.7 mmole) of xanthine XII in 15 ml of 4% KOH solution was refluxed for 3 h, during which the course of the reaction was followed from the amount of benzaldehyde that was removed by distillation. The mixture was cooled, and the solution was acidified with concentrated HCl to pH 5-6. The resulting precipitate was separated and washed with cold water, alcohol, and ether. The yield was 0.5 g (74%). The colorless needles had mp 304-305°C (from water). IR spectrum: 1650, 1670 (C=O); 3115 (C–H_a); 3230, 3345 cm^{-1} (N–H). PMR spectrum (d_6-DMSO): 3.08 (3H, s, N–CH_3); 5.95 (2H, m, NH_2, vanished after deuteration); and 7.55 ppm (1H, s, 8-H). Mass spectrum, m/z (%): M^+ 181 (100), 166 (9.3), 153 (7.3), 124 (72.6), 109 (8.2), and 96 (7.6). Found: C 39.6; H 3.9; N 38.5%. $C_6H_7N_5O_2$. Calculated: C 39.8; H 3.9; N 38.7%.

9-Benzylideneaminotheophylline (XV). A 0.15-ml (2.4 mmole) sample of methyl iodide was added to a suspension of 0.62 g (2.0 mmole) of 1-methyl-9-benzylideneaminoxanthine potassium salts (XIV) (obtained by mixing equimolar amounts of xanthine XII and KOH in water with subsequent precipitation with alcohol) in 4 ml of absolute DMF, and the mixture was stirred at 20°C for 4 h. The precipitate was removed by filtration and washed with alcohol and ether. The yield was 0.5 g (88%). The colorless needles had mp 274-275°C (dec., from DMF). IR spectrum: 1660, 1695 (C=O); 3122 cm^{-1} (C–H_a). PMR spectrum (CF_3COOH): 3.10 (3H, s, N_1–CH_3); 3.60 (3H, s, N_3–CH_3); 7.1 (3H, m, m- and p-H of C_6H_5); 7.5 (2H, m, o-H of C_6H_5); 8.5 (1H, s, 8-H), and 8.95 ppm (1H, s, N=CH–). Found, %: C 59.7, H 4.8, N 24.6. $C_{14}H_{13}N_5O_2$. Calculated, %: C 59.9, H 4.6, N 24.7.

9-Aminotheophylline (XVI). A suspension of 5.9 g (0.02 mole) of benzylideneamino derivative XV in 110 ml of 10% HCl was refluxed with removal of benzaldehyde by distillation until the latter had been removed completely (~2 h). The resulting clear solution was cooled and neutralized with 22% NH_4OH, and the resulting precipitate was separated and washed with water, alcohol, and ether. The yield was 3.8 g (93%). The colorless needles had mp 309-311°C (dec., from water). IR spectrum: 1635 (N–H); 1650, 1685 (C=O); 3097 (C–H_a); 3323 cm^{-1} (N–H). Found, %: C 43.2, H 4.7, N 35.7. $C_7H_9N_5O_2$. Calculated, %: C 43.1, H 4.6, N 35.9.

1-Methyl-9-aminoxanthine Potassium Salt (XVII). A 1.0-g (5.5 mmole) sample of xanthine

XIII was added to a solution of 0.35 g (6.3 mmole) of KOH in 10 ml of water, and the mixture was heated for 2 min. It was then cooled, 100 ml of alcohol was added, and the precipitate was removed by filtration and washed with alcohol. The yield was 0.95 g (79%).

Alkylation of Potassium Salt XVII with Methyl Iodide. A) At 20°C. A suspension of 0.45 g (2.0 mmole) of salt XVII and 0.15 ml (2.4 mmole) of methyl iodide in 4 ml of absolute DMF was stirred at 20°C for 3 h, after which the precipitate was removed by filtration and washed with alcohol and ether. The mass of the precipitate was 0.1 g. The precipitate was dissolved in 1 ml of water (pH 7), the solution was acidified to pH 5-6 with acetic acid, and the resulting precipitate was removed by filtration and washed with water and alcohol. The yield of XIII was 0.05 g (14%). The colorless needles had mp 304-305°C (dec., from water). No melting-point depression was observed for a mixture of this product with a genuine sample of XIII.

The organic filtrate was evaporated to dryness, and the brown residue was triturated with acetone. The mixture was filtered to give 0.2 g (63%) of the starting 1-methyl-9-aminoxanthine with mp 302-304°C (dec., from water).

B) At 100°C. A solution of 0.45 g (2.0 mmole) of potassium salt XIX and 0.3 ml (4.8 mmole) of methyl iodide in 5 ml of absolute DMF was stirred at 100°C for 3 h (during which the solution darkened markedly), after which the solvent was removed by distillation to dryness under reduced pressure, and the residue was dissolved in 15 ml of chloroform and purified by chromatography with a column packed with Al_2O_3 by elution with chloroform. The first fraction was collected to give 0.32 g (76%) of 1,3,7-trimethylxanthine. The colorless needles had mp 232-233°C (from ethyl acetate). No melting-point depression was observed for a mixture of this product with a genuine sample of caffeine.

Alkylation of 9-aminotheophylline with Methyl Iodide. A solution of 0.2 g (1.0 mmole) of 9-aminotheophylline and 0.2 ml (3.0 mmole) of methyl iodide in 2 ml of DMF (the reaction did not occur in alcohol or propanol because of the low solubility of the starting amine) was stirred at 100°C for 1 h, after which it was cooled, and the precipitate that formed from the dark solution was separated and washed with alcohol. The yield of caffeine was 0.15 g (71%). The colorless needles had mp 232-233°C (from ethyl acetate). With respect to its physicochemical constants, the product was identical to the preceding samples.

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