

Purine N-Oxides. XXXV. Alkylated Guanine 3-Oxides and 3-Hydroxyxanthines¹

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Peroxy acid oxidation of 1-, 7-, 8-, 9-mono-*N*-methylguanines and 1,7-di-*N*-methylguanine gave their 3-oxides. The corresponding methyl 3-hydroxyxanthines were obtained by acid hydrolysis of the guanine 3-oxides. The 1-methyl- and 1-benzyl-3-hydroxyxanthines were obtained by total syntheses. Two *O*-methyl derivatives were also prepared, 3-methoxyxanthine by total synthesis and 2-amino-6-methoxypurine 3-oxide by peroxy acid oxidation of the parent purine.

The 3-*N*-oxide derivatives of guanine and xanthine, both potent oncogens,^{2,3} react with acid anhydrides to yield the corresponding 8-hydroxypurine.⁴ An intermediate in this reaction, 3-acetoxypurine, reacts very rapidly with water or with nucleophiles to yield 8-substituted xanthines.⁵ Since 8-substituted xanthines are also among the products formed *in vivo* from 3-hydroxyxanthine,⁶ it is suggested that a metabolically formed analog of 3-acetoxypurine could be involved in the induction of cancer by these compounds.⁶

To facilitate studies of the course and mechanism of this unexpected reaction, and of the tautomeric structures of the various ions of the parent purine 3-oxides, several alkyl derivatives of these 3-*N*-oxides were required. We now report their syntheses and the evidence supporting the structures assigned.

The primary product of direct methylation of 3-hydroxyxanthine (**3a**)⁷ with Me₂SO₄ in DMF under mild conditions is 3-hydroxy-7,9-dimethylxanthine (**4**).⁴ At higher temperatures nucleophilic attack at C-8 occurs, the OH is lost from N-3, and 7,9-dimethyluric acid^{4,7} is the major product. Under a variety of other methylating conditions **3a** and guanine 3-oxide (**2a**) yield complex mixtures from which no monomethyl derivative has been isolated.

Several alkylguanine 3-oxide derivatives have been satisfactorily obtained by peroxyacid oxidations of the appropriate alkyl guanines. The 1-,⁹ 7-,¹⁰ and 8-methylguanines¹¹ and 1,7-dimethylguanine⁹ (**1b**, **1c**, **1e**, and **1d**) were oxidized to the corresponding 3-oxides, the first three in yields greater than 50%.

The oxidation of 9-methylguanine¹² (**5**) with CF₃COOH-30% H₂O₂ at room temperature was accompanied by excessive loss of ultraviolet-absorbing

material. Chromatographic analyses of the oxidation mixture indicated that 9-methylguanine 3-oxide (**6**), is oxidized further to nonultraviolet-absorbing material (Figure 1a). *N*-Oxidation of most purines is accompanied by some oxidation at the 4,5 double bond, particularly when one or more nitrogens are alkylated.¹³ Several conditions and reagents for improving the *N*-oxidation of 9-methylguanine were investigated (Figure 1). The use of 90% hydrogen peroxide with CF₃COOH increased the rate of reaction but did not improve the preparation of **6** (Figure 1b). However, lowering the temperature¹⁴ decreased ring oxidation and improved the ratio of starting material and its *N*-oxide (Figure 1c). At -15° the *N*-oxide was obtained in 44% yield.

Each methylguanine 3-oxide was hydrolyzed in hydrochloric acid to the corresponding 3-hydroxy-*N*-methylxanthine (Table IV). Proof of the position of the oxygen in the 7- and 9-methylguanine 3-oxides was provided by the methylation of each of the respective xanthine derivatives to the known 3-hydroxy-7,9-dimethylxanthine⁷ (**4**).

A total synthesis designed to lead to 3-hydroxy-1-methylxanthine by treatment of 6-amino-5-formamido-1-hydroxy-3-methyluracil (**8**, R = CH₃) with acetic anhydride¹⁵ resulted instead in 1-methyluric acid,⁷ because of subsequent acetylation of the 3-hydroxy moiety of **3e** and attack at C-8. The desired imidazole ring closure to 3-hydroxy-1-methylxanthine has now been accomplished in hexamethyldisilazane. The identity of this product with that from the hydrolysis of 1-methylguanine 3-oxide proves the position of *N*-oxidation of **1e**.

For an analogous synthesis of 1-benzyl-3-hydroxyxanthine, 6-amino-1-benzoyloxyuracil (**9**, R = H)¹⁶ was benzylated to give 6-amino-3-benzyl-1-benzoyloxyuracil (**9**, R = C₆H₅CH₂), with some 6-amino-5-benzyl-1-benzoyloxyuracil as a by-product. Nitrosation of **9** (R = C₆H₅CH₂) followed by reduction and formylation yielded **8** (R = C₆H₅CH₂) which was silylated and ring closed to give 1-benzyl-3-hydroxyxanthine (**3f**) in low yield. Some 1-benzylxanthine, presumably formed by

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(6) G. Stöhrer and G. B. Brown, *Science*, **167**, 1622 (1970).

(7) Compounds **2a** and **3a**, originally designated as 7-*N*-oxides,⁸ were shown to be 3-*N*-oxides: U. Wölcke and G. B. Brown, *J. Org. Chem.*, **34**, 978 (1969).

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(10) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **85**, 193 (1963).

(11) W. Pfeiderer and M. Shanshal, *Justus Liebig's Ann. Chem.*, **726**, 201 (1969).

(12) H. C. Koppf and R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 2751 (1958).

(13) For example, xanthine is resistant to oxidation by peroxy acids but di- or trimethylxanthines are readily oxidized to methylparabanic acids, and tetramethyluric acid is oxidized to allocaffeine.⁸ The oxidation of 9-benzylguanine gave only 1-benzylparabanic acid. Even in the *N*-oxidation of guanine some loss of ultraviolet-absorbing material was noted; with ¹⁴C-labeled material a small amount of nonbasic material, which could be parabanic acid, has been detected. The lower yield of an *N*-oxide from 1,7-dimethylguanine can be attributed to the accompanying substantial ring oxidation.

(14) *N*-Oxidation of some sensitive purines by *m*-chloroperoxybenzoic acid proceeds optimally at 0 to -5°. I. Scheinfeld, unpublished data.

(15) A. D. McNaught and G. B. Brown, *J. Org. Chem.*, **32**, 3689 (1967).

(16) W. Klötzer, *Monatsh. Chem.*, **95**, 265 (1964).

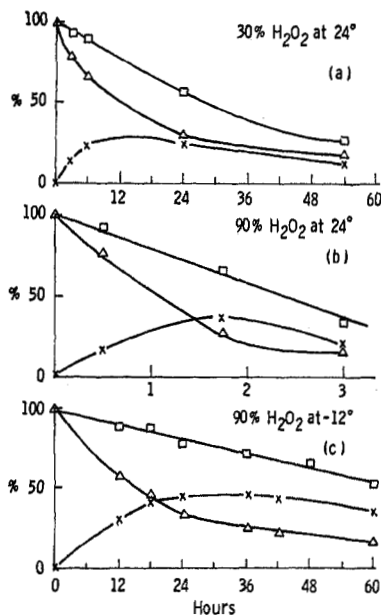
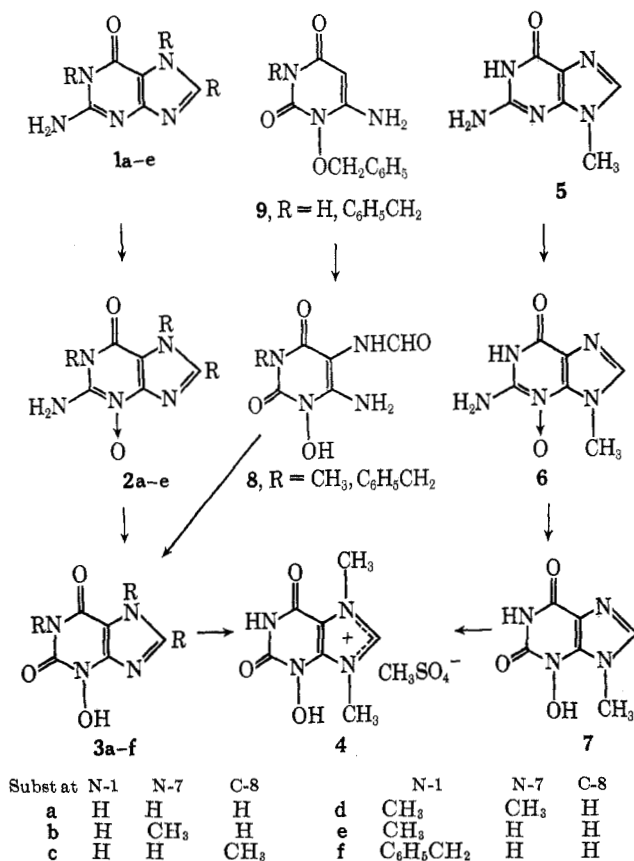


Figure 1.—The oxidation of 9-methylguanine (Δ) to 9-methylguanine 3-oxide (\times). Total recovery of ultraviolet absorption is indicated by \square .



deoxygenation under the cyclization conditions, was also obtained. By a similar sequence of reactions, 3-methoxyxanthine was synthesized from 6-amino-1-methoxyuracil. The latter was obtained from methoxyurea by a procedure similar to that of Klötzer.¹⁶

Peroxy acid oxidation of 2-amino-6-methoxypurine gave the 3-oxide derivative. Acid hydrolysis to 3-hydroxyxanthine (**3a**) demonstrated the position of oxidation.

The nmr spectra of the alkylated 3-hydroxyxanthines (Table I) are in complete agreement with the assigned

TABLE I
CHEMICAL SHIFTS (τ)^a

	Protons			
	1	3	7(9)	8
3b	-0.96	-1.20	6.15 ^b	2.08
3c	-0.95	-2.7 ^b	-2.7 ^c	7.62
3d	6.76	-1.10	6.08 ^b	1.95
3e	6.72 ^b	-1.6 ^c	-1.6 ^c	1.93
3f	4.92, ^d 2.73 ^e	-2.0 ^c	-2.0 ^c	1.96
7	-1.20 ^c	-1.20 ^c	6.20 ^b	2.43
2d	6.60 ^b		6.08 ^b	2.00

^a In DMSO-*d*₆, relative to TMS. ^b Methyl group. ^c Coalesced. ^d CH₂ of benzyl group. ^e C₆H₅ of benzyl group.

structures, and correlated quite closely with the nmr spectra of the parent xanthines.¹⁷ In general, the peak of the 3-hydroxy function coalesces with that of another exchangeable proton to give a single broad absorption integrating for two protons at a position between the expected positions of the two peaks. The nmr spectrum (Table I) of 1,7-dimethylguanine 3-oxide (**2d**) and the ultraviolet spectra¹⁸ of it and **3d** support the assignment of the 3-*N*-oxide structures. The ultraviolet absorption spectra of these alkyl derivatives and their contribution toward the understanding of the tautomeric structures of the parent molecules are reported in the accompanying paper.¹³

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., or by Galbraith Laboratories, Inc., Knoxville, Tenn. Compounds were dried *in vacuo* over P₂O₅ at room temperature, unless otherwise stated. Melting points, obtained on a Mel-Temp apparatus, are uncorrected. Paper chromatograms (Table II) were developed, ascending, on What-

TABLE II
PAPER CHROMATOGRAPHY^a

	$-R_f$ values $\times 10^2$				$-R_f$ values $\times 10^2$		
	A	B	C		A	B	C
2b	26	25	68	3e	66	42	71
3b	59	10	68	3f	98	98	
2c	24	15	63	2d	39	56	78
3c	39	16	63	3d	62	56	79
6	24	23	70	2e	28	32	72
7	30	41	64	3-OCH ₃ ^b	71	62	84
				6-OCH ₃ ^c	74	43	62

^a Solvent systems: (A) CH₃CN-H₂O (3:1 v/v), (B) CH₃CN-H₂O-28% NH₄OH (7:2:1 v/v), (C) 3% NH₄Cl. ^b 3-Methoxyxanthine. ^c 2-Amino-6-methoxypurine 3-oxide.

man No. 1 paper and viewed under ultraviolet light. The nmr spectra were determined with a Varian A-60 spectrometer in DMSO-*d*₆. An ISCO ultraviolet analyzer was used to monitor column eluates.

General Procedure for the Peroxide Oxidation of Methylguanines.—A stirred solution of the methylguanine was oxidized with 30% H₂O₂ under the conditions indicated in Table III. The reaction mixture was poured slowly into Et₂O; the solids were collected, triturated with water, except for **1d** and **1e**, and recrystallized as specified. All gave blue-purple ferric chloride tests.

Hydrolysis of the Methylguanine 3-Oxides.—The methylguanine 3-oxides were hydrolyzed in a boiling water bath under the conditions specified in Table IV. When the solutions were cooled, the 7-, 8-, and 9-methyl derivatives crystallized. Addition of EtOH precipitated further quantities. With the 1-methyl-

(17) N. J. M. Birdsall, unpublished data.

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TABLE III
N-OXIDATION OF METHYLGUANINES

Starting material	Product (guanine 3-oxide)	CF ₃ CO ₂ H, ml	H ₂ O ₂ , ml	Time, hr	Temp, °C	Temp, %	Analysis, % for C ₈ H ₇ N ₅ O ₂ ·H ₂ O				
							Calcd	C	H	N	
1b (10.0 g)	7-Methyl	80	40	8	24	70 ^a	Found	36.18	4.55	35.16	
1c (11.0 g)	8-Methyl	110	55	11	24	63 ^b	Found	36.45	4.75	35.69	
5 (10.0 g)	9-Methyl	100	40 ^c	72	-15	44 ^a	Found	36.24	4.35	34.78	
1e (480 mg)	1-Methyl	5.0	2.0	72		4	Found	36.28	4.52	34.75	
								C ₇ H ₆ N ₅ O ₂ ·H ₂ O			
								Calcd	39.43	5.20	32.84
1d (360 mg)	1,7-Dimethyl	3.0	1.5	7	24	23 ^{d,f}	Found	39.69	4.74	32.82	

^a Recrystallized from water. ^b Reprecipitated from 1 N NaOH with AcOH. ^c 90% H₂O₂. ^d Purified over a silica gel column (12 × 2 cm) by elution with MeOH. ^e 1e was eluted first, followed by the product, 2e, which is unstable to heat (melting point greater than 400°, gradual decomposition). Evaporation of the MeOH yielded analytically pure material. ^f 1d (55%) was eluted first, followed by 2d, which was recrystallized from MeOH and EtOAc (mp 207–210° dec).

TABLE IV
HYDROLYSIS OF METHYLGUANINE 3-OXIDES TO 3-HYDROXY-N-METHYLXANTHINES

Starting material	Product (3-hydroxyxanthine)	HCl, N (ml)	Time, hr	Yield, %	Analyses, % for C ₈ H ₈ N ₄ O ₂				
					Calcd	C	H	N	
2b (8.5 g)	7-Methyl	6 (125)	18	56 ^a	Found	39.57	3.32	30.77	
2c (8.3 g)	8-Methyl	4 (45)	24	63 ^b	Found	39.37	3.53	30.61	
6 (3.0 g)	9-Methyl	4 (15)	16	58 ^c	Found	39.88	3.46	31.02	
2e (100 mg)	1-Methyl	4 (5)	16	55 ^a	...	Found	39.63	3.36	30.66
						C ₈ H ₈ N ₄ O ₂			
						Calcd	42.86	4.11	28.56
2d (85 mg)	1,7-Dimethyl	2 (75)	20	76 ^{a,e}	Found	42.65	4.09	28.32	

^a Recrystallized from water. ^b Reprecipitated from 1 N NaOH with AcOH. ^c The crystals were analytically pure. ^d Identical with the sample prepared by total synthesis. ^e Mp 239–241° (dried at 110°).

and 1,7-dimethyl derivatives, the solutions were evaporated to dryness and the solids were recrystallized. All gave blue-purple ferric chloride tests.

Kinetics of the Oxidation of 9-Methylguanine.—9-Methylguanine (100 mg) was dissolved in CF₃CO₂H (1.00 ml) and the H₂O₂ (0.40 ml) was added to the solution at the specified temperature (±2°). Aliquots (50 μl) taken at various times were diluted to 0.5 ml with water, applied to a BioRad AG-50 (H⁺), 200–400 mesh, column (7 × 1 cm), and eluted with 1.5 N hydrochloric acid with continuous monitoring of the ultraviolet absorption of the eluate. The 9-methylguanine, ϵ_{261}^{\max} 12,000 at pH 0,⁹ and 9-methylguanine 3-oxide, ϵ_{249}^{\max} 9400¹⁸ at pH 0, were eluted in that order and the values plotted in Figure 1 were calculated from the optical densities and the measured volumes.

Oxidation of 9-Benzylguanine.—A mixture of 9-benzylguanine (1.0 g), CF₃CO₂H (10 ml), and 30% H₂O₂ (5 ml) was stirred for 5 hr. Pd/C was added and the stirring continued overnight. The solution was filtered and concentrated to an oily residue, soluble in organic solvents, which was thrice recrystallized from water to yield needles of benzylparabanic acid, mp 168–169°. The ultraviolet spectra showed a low 260-nm absorption in acid and neutral solution and only end absorption in alkali.

Anal. Calcd for C₁₀H₈N₂O₃: N, 13.72. Found: N, 14.02.

Methylation of 3-Hydroxy-7- (or -9-) methylxanthine.—3-Hydroxy-7- (or -9-) methylxanthine (100 mg) was stirred in DMF (2 ml) containing Me₂SO₄ (0.4 ml) at 45° for 3 days. Unreacted starting material was separated, the solvents were evaporated at 50° *in vacuo*, and *i*-PrOH (3 ml) was added. When cooled overnight the solution yielded crystals. These had uv and ir spectra and chromatographic mobility identical with authentic 3-hydroxy-7,9-dimethylxanthine methosulfate (4).

3-Hydroxy-1-methylxanthine (3e).—6-Amino-5-formamido-1-hydroxy-3-methyluracil¹⁶ (200 mg) and hexamethyldisilazane (2 ml) were heated in an oil bath at 130° for 4 hr. After heating, the excess hexamethyldisilazane was evaporated *in vacuo*, and the residue was boiled with EtOH (10 ml) for 15 min. Cooling the solution yielded 3-hydroxy-1-methylxanthine (150 mg, 83%) as a brown precipitate which was recrystallized from water as colorless needles, mp 270°.

Anal. Calcd for C₈H₈N₄O₃ (182.14): C, 39.57; H, 3.32; N, 30.77. Found: C, 39.58; H, 3.40; N, 30.75.

6-Amino-3-benzyl-1-benzoyloxyuracil (9, R = C₆H₅CH₂).—6-Amino-1-benzoyloxyuracil¹⁶ (10.5 g), sodium carbonate (4.8 g), and benzyl chloride (11.7 g) were dissolved in 60% EtOH (200 ml) and the solution was heated under reflux for 4 hr. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate to give 6-amino-3-benzyl-1-benzoyloxyuracil (11.8 g, 73%). Recrystallization from ethyl acetate-hexane (1:3) gave colorless needles: mp 174–175°; nmr (DMSO-*d*₆) τ 4.91 (2, 3-benzyl CH₂), 4.81 (2, 1-*O*-benzyl CH₂), 5.00 (1, 5-H), 2.61 [12, two C₆H₅ (10) and 6-NH₂ (2)].

Anal. Calcd for C₁₈H₁₇N₃O₃ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 67.02; H, 5.31; N, 13.13.

6-Amino-5-benzyl-1-benzoyloxyuracil.—The mother liquors from the recrystallization of 6-amino-3-benzyl-1-benzoyloxyuracil were evaporated to dryness, and the residue (~4.0 g) was chromatographed over a silica gel column with chloroform as the eluent. The first ultraviolet-absorbing fraction collected from the column was evaporated and recrystallized from EtOH to yield the 5-benzyluracil (1.0 g, 7%), mp 216°. The structure was assigned²¹ from the fact that it could not be nitrosated, and from its nmr spectrum: τ 6.47 (2) and 2.86 (5) (5-benzyl), 4.89 (2) and 2.59 (5) (1-*O*-benzyl), 3.30 (2, 6-NH₂), -0.9 (1, 1-NH).

Anal. Calcd for C₁₈H₁₇N₃O₃ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.77; H, 5.16; N, 12.99.

6-Amino-3-benzyl-1-benzoyloxy-5-nitrosouracil.—Crude 6-amino-3-benzyl-1-benzoyloxyuracil (11.8 g) and NaNO₂ (3.5 g) were dissolved in 60% EtOH (150 ml), and 1 N hydrochloric acid (50 ml) was added at 0 to -5° with stirring. After stirring at room temperature for 12 hr, the pink precipitate was collected and recrystallized from EtOH, 5.0 g, 37%, mp 190°.

Anal. Calcd for C₁₈H₁₆N₄O₄ (352.35): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.62; N, 15.78.

1-Benzyl-3-hydroxyxanthine.—The nitrosouracil (5.0 g) was hydrogenated at atmospheric pressure in formic acid (120 ml) with 10% Pd/C (1.0 g) for 30 hr at room temperature. The

(21) Alkylation of 6-aminouracils is, in part, similar to that of the alkylation of barbituric acids. A similar 5-alkylation has been observed in the benzylation of 6-methylaminouracil to 5,5-dibenzyl-6-methylaminouracil: N. J. M. Birdsall and U. Wölcke, unpublished data.

(19) W. Pfeiderer, *Justus Liebig's Ann. Chem.*, **647**, 167 (1961).

(20) H. Biltz and E. Topp, *Ber.*, **46**, 1387 (1913).

catalyst was removed and the formic acid was evaporated. Recrystallization of the residue from EtOH gave 6-amino-3-benzyl-5-formamido-1-hydroxyuracil (**8**, R = C₆H₅CH₂), 3.4 g, 87%, mp 220° dec. The 5-formamido derivative (3.3 g) and hexamethyldisilazane (25 ml) were heated under reflux for 4 hr. The solution was evaporated nearly to dryness, and the residue was boiled with EtOH (200 ml) for 5 min. The insoluble residue, also insoluble in hot water and but slightly soluble in DMSO, was discarded. The EtOH filtrate was concentrated to 15 ml, applied to a Dowex 50 (H⁺) (45 × 240 mm) column, and eluted with 2 l. of 70% EtOH with continuous monitoring of the ultraviolet absorption. 1-Benzyl-3-hydroxyxanthine (**3f**, 210 mg, 7%) was eluted after an unidentified fraction, and was followed by 1-benzylxanthine (130 mg, 5%) and two more unidentified fractions. No additional material was eluted with 1 *N* hydrochloric acid. **3f**'s uv spectrum showed $\lambda_{\max}^{\text{EtOH}}$ 275 nm (ϵ 8000).

Anal. Calcd for 1-benzyl-3-hydroxyxanthine, C₁₂H₁₀N₄O₃ (258.24): C, 55.81; H, 3.90; N, 21.70. Found: C, 55.97; H, 4.09; N, 21.50.

Anal. Calcd for 1-benzylxanthine, C₁₂H₁₀N₄O₂ (242.24): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.69; H, 4.07; N, 22.89.

6-Amino-1-methoxyuracil.—To sodium ethoxide (0.258 mol), prepared from 5.95 g of sodium and 100 ml of EtOH, were added ethyl cyanoacetate (30 ml) and a solution of methoxyurea²² (0.258 mol, 23.2 g) in 100 ml of EtOH. After the mixture was refluxed for 5.5 hr, the EtOH was removed *in vacuo* and the residue dissolved in 200 ml of water. Neutralization to pH 6 with acetic acid gave crude 6-amino-1-methoxyuracil. Recrystallization from 300 ml of 50% EtOH with treatment with charcoal yielded 14.9 g of pure 6-amino-1-methoxyuracil. Concentration of the mother liquor gave an additional 2.3 g, total yield 17.2 g, 43%: mp 248–249° dec; uv λ_{\max} 267 nm, at pH 2 and 10; *R*_f 0.84 in 3% NH₄Cl and 0.71 in CH₃CN–H₂O (3:1). The nmr spectrum corroborated the structure: τ 6.13 (3, 3-OCH₃), 5.48 (1, 5-H), 2.80 (2, NH₂), –0.30 (1, N–H).

Anal. Calcd for C₅H₇N₃O₃: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.16; H, 4.55; N, 26.76.

6-Amino-1-methoxy-5-nitrosouracil.—To 8.35 g (50 mmol) of 6-amino-1-methoxyuracil in 60 ml of 1 *N* hydrochloric acid, was added 3.45 g (50 mmol) of sodium nitrite slowly with stirring at 10°; the stirring was continued for 2 hr. Violet crystals were collected and washed with water, EtOH, and ether. The 10.0 g of the 5-nitrosouracil represented a quantitative yield. It was recrystallized from EtOH–water, mp 194 dec.

Anal. Calcd for C₅H₆N₄O₄: C, 32.27; H, 3.25; N, 30.10. Found: C, 32.15; H, 3.40; N, 30.30.

6-Amino-5-formamido-1-methoxyuracil.—The 5-nitrosouracil (7.98 g, 43 mmol) was reduced in 200 ml of 98% formic acid containing slightly over 1 equiv of hydrochloric acid, 44 ml of 2 *N* hydrochloric acid, by slowly adding 8.0 g of zinc powder with continued stirring. The solution became colorless in about 30 min; the unreacted zinc powder was separated, and the filtrate was evaporated nearly to dryness *in vacuo*. The oily residue in 100 ml of water was adjusted to pH 3 with sodium formate. The 6-amino-5-formamido-1-methoxyuracil precipitated, and 5.90 g, 78%, was collected. Recrystallization from 50% EtOH gave colorless crystals, mp 215° dec, uv λ_{\max} 268 nm at pH 5 and 10.

Anal. Calcd for C₆H₈N₄O₄·H₂O: C, 33.03; H, 4.62; N, 25.68. Found: C, 33.00; H, 4.70; N, 25.85.

3-Methoxyxanthine.—Hexamethyldisilazane (13 ml) was added to a stirred mixture of 4.0 g of 6-amino-5-formamido-1-methoxy-

uracil and 6 ml of formic acid. The mixture was heated under reflux for 3.5 hr and then evaporated nearly to dryness *in vacuo* at 60°. The oily residue was treated with EtOH, and the insoluble fraction was extracted three times with 30 ml of boiling water. The extract was concentrated and chromatographed over a 4 × 14 cm Dowex-50 [H⁺] column. Elution with water yielded 2.80 g of starting material, followed by 150 mg, 13.5% based upon unrecovered starting material, of 3-methoxyxanthine. Further elution of the column with 1 *N* hydrochloric acid gave 350 mg of xanthine. Recrystallization of 3-methoxyxanthine from water gave long, fine needles. The compound started to decompose at 127°. Its instability in base is reported in the accompanying paper.¹⁸ The nmr spectrum corroborated the structure: τ 6.04 (3, OCH₃), 1.91 (1, 8-H), –1.40 (1, NH).

2-Amino-6-methoxypurine 3-Oxide.—A solution of 660 mg (4 mmol) 2-amino-6-methoxypurine,²³ 8 ml of CF₃CO₂H, and 4 ml of 30% H₂O₂ was allowed to stand at 22° for 6 days. The addition, with stirring, of Et₂O precipitated the product and, after chilling the reaction mixture, the ether layer was decanted and discarded. The product was collected and recrystallized from *i*-PrOH to yield colorless granules, 680 mg. The absence of NH₂ absorption in the nmr spectrum and the presence of a signal at τ 1.53, corresponding to one exchangeable proton, suggested that this was a trifluoroacetyl derivative of the desired product and also indicated the product contained 1 mol of 2-propanol, which was consistent with elemental analyses.

The product was dissolved in 10 ml of dilute NH₄OH and heated at 80° for 15 min. The solution was neutralized to pH 5 with HOAc and chilled. The 2-amino-6-methoxypurine 3-oxide crystallized as colorless prisms, yield 160 mg (20%). The analytical sample was dried *in vacuo* at 80° over P₂O₅ for 2 hr, mp 231–232° dec (with gas evolution).

Anal. Calcd for C₆H₇N₅O₂·H₂O: C, 36.18; H, 4.55; N, 35.16. Found: C, 36.16; H, 4.57; N, 35.20.

A sample of 2-amino-6-methoxypurine 3-oxide was dissolved in 20 ml of 2 *N* hydrochloric acid and the solution was refluxed 18 hr. The solvent was removed *in vacuo* to yield 3-hydroxyxanthine (**3a**)⁷ and not 1-hydroxyxanthine.²⁴ It was identical with an authentic sample as shown by paper chromatography and ultraviolet spectra at three pH's.¹⁸

Registry No.—**2b**, 30477-04-4; **2c**, 22888-26-2; **2d**, 30345-29-0; **2e**, 30345-23-4; **3b**, 30409-21-3; **3c**, 22888-28-4; **3d**, 30345-26-7; **3e**, 14002-16-5; **3f**, 30409-24-6; **5**, 5502-78-3; **6**, 30345-36-9; **7**, 30345-24-5; **8** (R = C₆H₅CH₂), 30345-83-6; **9** (R = C₆H₅CH₂), 30345-84-7; benzylparabanic acid, 30345-85-8; 6-amino-5-benzyl-1-benzylxyuracil, 30345-86-9; 6-amino-3-benzyl-1-benzylxy-5-nitrosouracil, 30345-87-0; 6-amino-1-methoxyuracil, 30345-88-1; 6-amino-1-methoxy-5-nitrosouracil, 30345-89-2; 6-amino-5-formamido-1-methoxyuracil, 30345-90-5; 3-methoxyxanthine, 30345-91-6; 2-amino-6-methoxypurine 3-oxide, 30345-92-7.

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