Purine N-Oxides. XX. Hydrolyses and Rearrangement of Purine 1-N-Oxides. Synthesis of 1-Hydroxyxanthine[1]

JAMES C. PARHAM, JENNIFER FISSEKIS, AND GEORGE BOSWORTH BROWN

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research, and Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

Received October 27, 1966

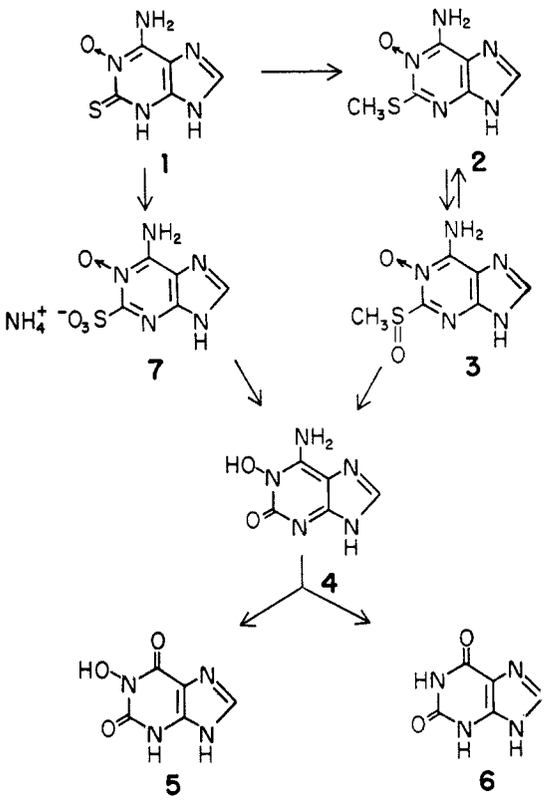
Hydrolysis of 1-hydroxyisoguanine in dilute acid yielded a mixture of 1-hydroxyxanthine and xanthine. The latter was formed by a competitive acid-catalyzed Dimroth-type rearrangement of the pyrimidine ring. Hydrolysis products of the open-ring intermediate were characterized. An improved preparation of 2-mercaptoadenine 1-N-oxide and an improved synthesis of 1-hydroxyisoguanine are reported.

The discovery of carcinogenic activity in N-hydroxy derivatives of guanine and xanthine[2] stimulated a specific interest in studying all possible N-hydroxy isomers of these purines for structure–activity relationships. The isomeric N-hydroxyxanthines appear most readily available. The carcinogenic N-hydroxyxanthine, presently regarded as 7-hydroxyxanthine, is available by hydrolysis of the oxidation product of guanine.[3] Since xanthine is inert to direct N oxidation, the isomeric N-hydroxyxanthines can only be prepared by other methods. A total synthesis of 3-hydroxyxanthine has been reported[4] and the preparation of 7-alkyl-1-hydroxyxanthines[5] and more recently of 1-hydroxyxanthine[6] has been recorded by Bauer, *et al.*, in conjunction with continuing studies of the Lossen rearrangement. However, that rearrangement afforded a low yield from rare starting materials and was not practical for preparation of the quantities needed for biological testing. Adenine 1-N-oxide is a convenient source of substituted purine 1-N-oxides, since its pyrimidine ring can be readily cleaved with loss of the 2 carbon and may then be reclosed to provide a number of derivatives.[7,8] We have investigated the use of various 2-substituted adenine 1-N-oxides as intermediates for the synthesis of 1-hydroxyxanthine (**5**) (Scheme I).

Attempts to obtain the corresponding 6-oxo-1-hydroxypurines by diazotization of 2-mercapto- (**1**), 2-methylmercapto- (**2**), and 2-methylsulfinyladenine 1-N-oxide (**3**), or 1-hydroxyisoguanine (**4**), and later of **7** were unsuccessful. Hydrolytic deamination in boiling mineral acid could not be accomplished with **1**, **2**, or **3**, but 1-hydroxyisoguanine did hydrolyze to impure 1-hydroxyxanthine (**5**).

The previous synthesis of 1-hydroxyisoguanine involved hydrolysis of the 2-methylsulfinyl group of **3**.[8] Attempts to hydrolyze **3** directly to 1-hydroxyxanthine in high concentrations of HCl were complicated by reversion of the sulfoxide (**3**) to the methylmercapto derivative (**2**). That anomalous reaction was previously observed in 12 *N* HCl,[8] but we now find

SCHEME I



that it occurs to a significant extent in HCl concentrations as low as 2 *N*. In more dilute acid the direct hydrolysis of **3** to **5** could be accomplished, but required prolonged heating and was accompanied by the appearance of xanthine and other products. The unexpected formation of substantial quantities of xanthine was initially presumed to be the result of thermal deoxygenation of 1-hydroxyxanthine. Such deoxygenation has been observed with other purine N-oxides, but usually under more drastic conditions.

To avoid the problem of the reversion of sulfoxide **3** to thio ether **2**, we examined other routes to 1-hydroxyisoguanine. The latter cannot be prepared by direct oxidation of isoguanine; attempts to cyclize 4-aminoimidazole-5-carboxamidoxime (**8**) to **4** with phosgene, urea, N,N-carbonyldiimidazole,[9] or other reagents were unsuccessful. Alkaline peroxidation of the 2-mercapto derivative (**1**) to adenine-2-sulfonic acid 1-N-oxide (**7**) provided an intermediate hydrolyzable to **4** even at room temperature. Chromatographic

(1) This investigation was supported in part by funds from the Atomic Energy Commission (Contract No. AT[30-1],910) and from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA-08748).

(2) G. B. Brown, K. Sugiura, and R. M. Cresswell, *Cancer Res.*, **25**, 986 (1965).

(3) T. J. Delia and G. B. Brown, *J. Org. Chem.*, **31**, 178 (1966).

(4) R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *ibid.*, **30**, 408 (1965).

(5) L. Bauer, C. N. V. Nambury, and D. Dhawan, *J. Heterocyclic Chem.*, **1**, 275 (1964).

(6) L. Bauer and D. Dhawan, *ibid.*, **2**, 220 (1965).

(7) M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **82**, 3189 (1960).

(8) R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, **28**, 2560 (1963).

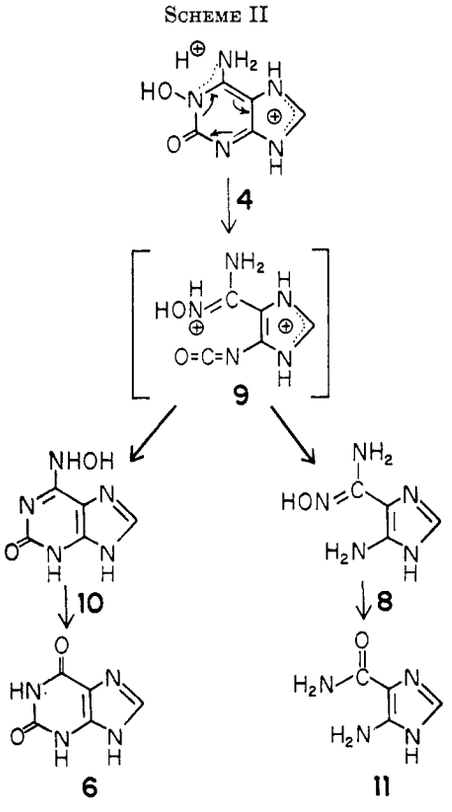
(9) W. B. Wright, *J. Heterocyclic Chem.*, **2**, 41 (1965). We wish to thank Dr. G. W. Anderson of the Lederle Laboratories for a generous gift of this reagent.

analysis of the hydrolysates of **7** in boiling 3 *N* HCl showed that the sulfonic acid was converted to **4** within 15 min and provided a convenient source of **4** *in situ*. This permitted the use of more concentrated acid and shorter reaction times for the further hydrolysis of **4**, and was the method of choice for the production of **5**.

A study of the hydrolysis of **4** (or of **7**) in HCl concentrations ranging from 0.1 to 12 *N*, at room temperature, 50°, or 100°, showed that the time for complete disappearance of **4** could be shortened by increasing either the temperature or the acid concentration. Essentially the same mixture was always obtained, which consisted of 1-hydroxyxanthine, an almost equal amount of xanthine, and three other components. This suggested that the xanthine produced might not be arising by thermal deoxygenation, which was fully confirmed when a purified sample of 1-hydroxyxanthine failed to yield detectable quantities of xanthine when heated in 3 *N* HCl under the hydrolysis conditions.

Fractional crystallization or precipitation of xanthine from 1-hydroxyxanthine was not satisfactory, but column chromatography over cellulose or Dowex 50 (H^+) afforded an excellent separation of these two. The more acidic 1-hydroxyxanthine is eluted first from Dowex 50, well separated from xanthine and the other more basic hydrolysis products, and such a column was more satisfactory for preparative purposes. From a cellulose column the 1-hydroxyxanthine can be eluted last and this adsorbant was used to separate the minor components of the hydrolysate for identification. Two of these were aminoimidazole carboxamidoxime (**8**) (Scheme II) and the corresponding amide (**11**), which indicates that hydrolysis of the pyrimidine ring must compete with hydrolysis of the 6-amino substituent of **4**. Consideration of a mechanism for ring opening suggests that an acid-catalyzed rearrangement analogous to a Dimroth rearrangement[10] may well occur under these circumstances. Support for this conclusion comes from the recent demonstration[11] of a facile rearrangement of 1-ethoxy-9-ethyladenine to 6-ethoxyamino-9-ethylpurine under very mild conditions. In that case the formylaminoimidazole intermediate could be isolated and subsequently converted into the 6-ethoxyamino-9-ethylpurine.

SCHEME II



A corresponding intermediate in the hydrolysis of **4** might be the isocyanate (**9**), and Scheme II outlines a plausible mechanism for ring opening of the dication of **4**, and the two possible routes from the proposed isocyanate. Hydrolysis of the reactive isocyanate substituent would yield **8**, which is known to yield amide **11**.[12] Alternatively, a closure of **9** to 6-hydroxylamino-2-hydroxypurine (**10**) would in effect complete a Dimroth rearrangement of **4** to **10**. A similar isocyanate intermediate has been postulated by Ueda and Fox in a rearrangement of 3-methylcytosine.[13] It is known that 6-hydroxylaminopurine, in contrast to adenine, is readily hydrolyzed to hypoxanthine.[14] The expected rearrangement product from **9**, 6-hydroxylamino-2-hydroxypurine (**10**), has recently been synthesized by Giner-Sorolla.[15] Under the conditions used to hydrolyze 1-hydroxyisoguanine, **10** produced xanthine quantitatively with a half-time for the reaction of 9 min, while isoguanine (6-amino-2-hydroxypurine) showed a half-time of 144 min for the same reaction. Thus, **10** would hydrolyze almost immediately after the rearrangement and would not be detectable under the hydrolysis conditions. In contrast, 1-hydroxyxanthine yielded a detectable quantity of xanthine only after 3 days in boiling 6 *N* HCl. It is thus evident that the large quantity of xanthine produced during hydrolysis of **4** must result from hydrolysis of **10** and not from deoxygenation of **5**.

A further example of the facile opening of the pyrimidine ring of **4** is its reaction with acetic anhydride. It is converted within 15 min to at least two products, one of which was identified by chromatography as 5-methyl-3-[5′-(4′-acetamido)imidazolyl]-1,-2,4-oxadiazole, a compound previously obtained from acetic anhydride and adenine 1-N-oxide.[16]

The ionization constants and spectral data are given in Table I. The p*K* at 6.41 of 1-hydroxyisoguanine corresponds to the first proton removal and is accompanied by the appearance of strong absorption at 230 mμ. This behavior is observed in purine oxides with proton loss either from the cation of N-oxides[12] or from the neutral molecule or monoanion of predominantly N-hydroxy derivatives. 1-Hydroxyhypoxanthine, which exists primarily as the 1-hydroxy-6-keto tautomer,[17] shows the same marked increase in optical density at 228 mμ with the first proton removal at p*K* = 5.65.[17] The similarity in spectral behavior sug-

(10) D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.*, 164 (1966), and previous papers.

(11) T. Fujii, T. Itaya, C. C. Wu, and S. Yamada [*Chem. Ind.*, 1967 (1966)] whom we thank for prior private communication.

(12) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).

(13) T. Ueda and J. J. Fox, *J. Org. Chem.*, **29**, 1762, 1770 (1964).

(14) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **80**, 3932 (1958).

(15) A. Giner-Sorolla, S. O'Bryant, J. H. Burchenal, and A. Bendich, *Biochemistry*, **5**, 3057 (1966).

(16) M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **82**, 1148 (1960).

(17) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **31**, 966 (1966).

TABLE I

IONIZATION CONSTANTS AND SPECTRAL DATA

Compd	pH (charge)	λ_{max}, mμ	ε × 10^{-3}	pK_a values
1-Hydroxyiso-guanine[a]	1.7 (+1)	283	9.9	
				3.64 ± 0.04
	5.0 (0)[b]	243–244[c]	5.3	
		288	7.6	
				6.41 ± 0.03
	9.0 (−1)	228	22.3	
		251[c]	5.2	
		295	7.2	
				11.48 ± 0.06
	13.1 (−2)	225	21.0	
		260	4.8	
		300	8.1	
1-Hydroxy-xanthine	−1 (+1)	261	8.5	
				0.85 ± 0.03
	3.0 (0)	267	9.5	
				6.54 ± 0.04
	8.5 (−1)[b]	242	6.8	
		276	7.5	
				9.94 ± 0.06
	11.2 (−2)[b]	225	20.	
		283	7.1	
				12.4 ± 0.3
	14 (−3)[b]	226	25.	
		287	8.0	
Ammonium adenine-2-sulfonate 1-N-oxide	1.1	262	10.	
	12.4	240	43.	
		273–274	10.7	
		300[c]	2.4	

[a] Slight spectral changes indicate two additional pK values at approximately +1 and −1. [b] Pure ionic species not available. [c] Shoulder.

gests that the neutral species of 1-hydroxyisoguanine also exists mainly as the N-hydroxy tautomer (**4**) rather than the N-oxide tautomer. Similarly, the 1-hydroxyxanthine shows increased optical density at 226 mμ associated with the second proton removal at pK = 9.94 which suggests that it, too, is primarily the 1-hydroxy tautomer. This is in agreement with the presence of two carbonyl absorption bands in the infrared spectrum.[6]

The initial assay results, by procedures described,[2] indicate that 1-hydroxyxanthine is decidedly carcinogenic in Wistar rats.

Experimental Section

Analyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Mich., or Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points are corrected. Chromatograms were developed (ascending) on Whatman No. 1 paper and viewed under ultraviolet light of primarily 254 mμ. The solvent systems were (A) 3% ammonium chloride, (B) 5% disodium hydrogen phosphate–isoamyl alcohol (3:2), (C) isopropyl alcohol–water–58% ammonium hydroxide (7:2:1), (D) *t*-butyl alcohol–methyl ethyl ketone–88% formic acid–water (40:30:15:15, v/v), and (E) *n*-propyl alcohol–water (3:1, v/v) (Table II). The pK values were determined spectrophotometrically by methods described,[18] with 0.01 M buffers[19] at 22°. (See Table I.)

2-Mercaptoadenine 1-N-Oxide (1).—To maintain reasonable yields in the preparation of **1**,[8] reagents must be dry and care should be taken to expose the reaction mixture to as little light and moisture as possible. Pyridine (1100 ml, dried over KOH) was distilled into a dry, 3-l. flask, and 42.8 g (0.2 mole) of 4-aminoimidazole-5-carboxamidoxime dihydrochloride (**8**), 840 ml of absolute methanol, and 420 ml of carbon disulfide were added. The flask was sealed and the reaction was stirred magnetically (and thereby heated slightly) in the absence of light for 1 week. After 1 week 26.5 g of precipitate (**1**) was collected and the vessel was resealed and its contents were stirred for another week to produce an additional 4.3 g (total yield 30.8 g, 79%). The product darkened rapidly on exposure to light but was chromatographically pure and satisfactory for the preparation of **7**.

TABLE II

Compd	R_f values in solvent A	B	C	D	E
2-Mercaptoadenine 1-N-oxide (**1**)	0.30[a]	0.46	0.46	0.29	0.29
Ammonium adenine-2-sulfonate 1-N-oxide (**7**)	0.58	0.65	0.16	0.07	0.19
1-Hydroxyisoguanine (**4**)	0.29[a]	0.48	0.14	0.27	0.06
1-Hydroxyxanthine (**5**)	0.56	0.55	0.05	0.27	0.18
Xanthine (**6**)	0.39	0.47	0.33	0.27	
4-Aminoimidazole-5-carboxamidoxime (**8**)	0.70	0.57[b]	0.43	0.62	0.52
4-Aminoimidazole-5-carboxamide (**11**)	0.65	0.57[b]	0.55	0.42	0.44
5-Methyl-3-[5′-(4′-acetamido)imidazolyl]-1,2,4-oxadiazole	0.72	0.42	0.73	0.80	0.75

[a] Reference 8. [b] Reference 14.

Ammonium Adenine-2-sulfonate 1-N-Oxide (7).—To a chilled solution of 18.3 g (0.1 mole) of 2-mercaptoadenine 1-N-oxide in 600 ml of concentrated (58%) ammonium hydroxide, 100 ml (*ca.* 1 mole) of 30% hydrogen peroxide was added dropwise with stirring over a period of 15 min. After the addition of peroxide, the ice bath was removed and the solution was stirred at room temperature for 6 hr. The ammonia was then removed under vacuum and the solution was reduced in volume until precipitation began. The solution was then acidified with glacial acetic acid and the precipitate was collected and washed with ethanol and ether. One volume of ethanol was added to the filtrate and the solution was chilled overnight to produce an additional 10 to 15% of product (total yield 18.6 g, 75%). It could be recrystallized by the addition of ethanol to a hot ammoniacal solution, but some decomposition inevitably accompanied attempts to recrystallize large batches. The crude product could be used for the hydrolysis.

An analytical sample was obtained from water–ethanol as tiny, colorless needles, and was dried for 2 hr at 100°, mp 296–300° (decomposition and gas evolution, with previous darkening above 267°).

Anal. Calcd for $C_5H_6N_6O_4S$: C, 24.19; H, 3.25; N, 33.85; S, 12.91. Found: C, 24.33; H, 3.54; N, 33.79; S, 13.24.

Separation of 1-Hydroxyxanthine (5) and By-products over Cellulose.—Twenty grams (0.08 mole) of ammonium adenine-2-sulfonate 1-N-oxide in 1.5 l. of 3 N HCl was refluxed for 8 hr. The solvent was removed under vacuum and the residue was twice dissolved in 100 ml of water and taken to dryness. The yellow solid was dissolved in *ca.* 200 ml of hot water by the addition of concentrated (58%) ammonium hydroxide and the hot ammoniacal solution was filtered, treated with charcoal, and refiltered. A portion of the hot solution was adsorbed to 30 g of powdered cellulose (Whatman CF11) until the cellulose was saturated. This was dried over silica gel under vacuum overnight, then subsequent portions of the hot, ammoniacal solution were adsorbed to the cellulose and dried in similar fashion. The cellulose was finally dried overnight with P_2O_5 under vacuum, slurried in acetone, and packed on the top of a 50 × 10 cm cellulose column, which had been packed in isopropyl alcohol. The column was eluted with solvent C and 8-ml fractions were collected. Every tenth fraction was chromatographed in solvent C and those of similar content were combined and reduced to dryness. Table III summarizes the combined fractions and their content.

Fractions 0–65.—The two components proved identical in R_f and color development with the Pauley reagent[20] when chro-

(18) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

(19) D. D. Perrin, *Australian J. Chem.*, **16**, 572 (1963).

(20) H. Pauly, *Z. Physiol. Chem.*, **42**, 508 (1904).

TABLE III

Tube no.	R_1 values[a] and identification		Wt, g
0–65	0.53/0.43	11/8	0.2
66–120	0.40/0.26	Adenine N-oxide /6	2.2
121–250	0.26	6	2.1
251–320	0.26/0.12	6/4	0.2
321–455	0.12/0.06	4/5	0.4
456–900[b]	0.06	5	3.5

[a] R_f in solvent C. [b] After tube 780, 15-ml fractions were collected.

matographed with authentic samples of **8** and **11**. The 4-aminoimidazole-5-carboxamide (**11**) was isolated by dissolving the residue from the combined fractions in acetone, bubbling in HCl, discarding a purple inorganic precipitate which appeared, reducing the solution in volume, and adding ether to precipitate **11** as the hydrochloride. The infrared and ultraviolet spectra, chromatographic properties, and color development (blue) with the Pauly reagent were identical with an authentic sample.

Fractions 66–120.—The components were identical with xanthine and adenine 1-N-oxide in ultraviolet spectra of samples eluted from thin layer plates at several pH values and in chromatographic behavior in five solvents. The latter compound is not likely to be present as a small contamination in the starting material, but might be the result of reductive desulfonation, a phenomenon analogous to that observed in the pyrimidine series with sulfinic acids.[21]

Fractions 456–900.—The crude yellow sample (3.48 g) of 1-hydroxyxanthine was recrystallized from water (charcoal) twice to produce 1.9 g (14%) of chromatographically pure **5**. This sample was chromatographically and spectrally identical with the main component of a sample kindly provided by Dr. L. Bauer.[6] An analytical sample, obtained by two additional recrystallizations from water, was a colorless, microcrystalline powder, mp >400°, darkening above 360° (lit.[6] mp 480°).

Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.46; N, 33.33. Found: C, 35.36; H, 2.64; N, 33.08.

The analytical sample was dried at 140° for 2 hr and from the observed weight loss (found, 17.8%; calcd, 17.6%) the product was a dihydrate. It gives an orange-to-red ferric chloride test, depending upon the concentration.

Preparative Chromatography of 5 on Dowex 50.—A solution of 4 g of **7** in 400 ml of 3 *N* HCl was refluxed 7 hr and evaporated to drynesss, and the residue was redissolved in 150 ml of water with the addition of concentrated NH_4OH to pH 9. This was loaded on to a 4.4 × 20 cm column of Dowex 50 W-X8 (H^+), 200–400 mesh, wrapped with a heating tape, and warmed to about 40°. This column was eluted with 0.1 *N* HCl at 7 ml/min, and the ultraviolet absorption was monitored. After 2200 ml of forerun the 1-hydroxyxanthine was eluted in the next 1200 ml; it partially crystallized when this fraction cooled. Xanthine, which is well separated with this concentration of HCl, and the other materials were then stripped with 4 *N* HCl.

Concentration of the 1-hydroxyxanthine fraction and recrystallization from hot, dilute ammonia, with charcoal treatment, yielded 900 mg of chromatographically homogeneous product.

On this column the colored products, which were distributed on the cellulose column, broke through with the first bed volume or were retained on the top of the resin bed.

Hydrogenation of 5.—In agreement with previous observations,[6] 1-hydroxyxanthine was not reduced by catalytic hydrogenation. We observed no reduction to xanthine after 24 hr in 1 *N* NaOH with Raney nickel under 1 atm of hydrogen.

Other Hydrolyses of 7.—The sulfonic acid (**7**) was not affected by trifluoroacetic acid, but in concentrated sulfuric acid at room temperature it was converted to **4** with the evolution of SO_3. No further hydrolysis of **4** occurred under these conditions. Boiling 88% formic acid rapidly converted **7** to **4**, thence preferentially to **6**, **8**, and **11**, but not to 1-hydroxyxanthine.

Hydrolysis of 6-Hydroxylamino-2-hydroxypurine (10).—A solution of **10** dissolved in 3 *N* HCl was refluxed and the hydrolysis was followed spectrophotometrically until no further spectral change was observed. The solvent was removed and the single product proved to be spectrally and chromatographically identical with xanthine. Isosbestic points were observed in the hydrolysis curves at 243 and 268 mμ. The half-time for the reaction (9 min) was determined from a plot of OD change at 285 mμ *vs.* time. It is corrected for the lag time of *ca.* 5 min required for the solution to come to boiling and the reaction rate to reach a constant value.

Hydrolysis of Isoguanine.—A solution of isoguanine in 3 *N* HCl was refluxed and the hydrolysis monitored by ultraviolet spectral change. Isosbestic points were observed in the spectra at 232 and 270 mμ. The reaction product was chromatographically and spectrally identical with xanthine.[22] The reaction half-time (2.4 hr) was determined as described above from the spectral change at 283 mμ.

1-Hydroxyisoguanine (4).—A solution of 2.5 g (0.01 mole) of **7** dissolved in 200 ml 3 *N* HCl was stirred at room temperature for 40 hr. Attempts to decrease the reaction time by heating, even on a steam bath, resulted in the production of xanthine and 1-hydroxyxanthine. The solvent was removed under reduced pressure and the residue was treated with water and reduced to dryness twice. The product was dissolved in about 50 ml of dilute ammonia, boiled, and cooled. The precipitate was collected and the filtrate was acidified with 1 drop of acetic acid. The additional precipitate was collected and the combined samples were washed with ethanol and ether (crude yield 1.66 g). Reprecipitation with charcoal treatment afforded 1.4 g (84%) of a pale yellow powder identical in ultraviolet spectrum and chromatographic behavior with an authentic sample.[8]

Registry No.—**1**, 7593-43-3; **7**, 7593-44-4; **5**, 7593-45-5; **4**, 7593-46-6; **6**, 69-89-6; **8**, 7593-47-7; **11**, 932-15-0; 5-methyl-3[5′-(4′-acetamido)imidazolyl]-1,2,4-oxadiazole, 7593-49-9.

Acknowledgment.—We wish to acknowledge the capable assistance of Mr. John Schwarz and to thank Dr. Alfredo Giner-Sorolla for a sample of 6-hydroxylamino-2-hydroxypurine, Dr. Kanematsu Sugiura for cooperation in the carcinogenesis assay, and Dr. L. Bauer for a sample of his product.

(21) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

(22) Reported yields of xanthine by hydrolysis of isoguanine in concentrated solutions have varied from moderate [J. R. Spies, *J. Am. Chem. Soc.*, **61**, 350 (1939)] to poor [A. Bendich, J. F. Tinker, and G. B. Brown, *ibid.*, **70**, 3109 (1948)].