less needles: mp 188–190° (lit.[8] mp 190–192°); ir (KBr) 2.80 (OH), 3.60 μ (NMe); nmr δ 8.09 (1 H, s, C_{11} H), 6.80 (1 H, s, C_8 H), 6.55 (1 H, s, C_3 H), 3.91 (6 H, s, 2 OCH_3), 3.90 (3 H, s, OCH_3), 2.55 (3 H, s, NCH_3); mass spectrum *m/e* 341 (M^+), 340 (M − 1, base peak), 326 (M − 15), 310 (M − 31); uv λ_{max}^{EtOH} 279 nm (log ε 4.04), 304 (4.04). The spectral properties and mixture melting point of **18** were identical with those of authentic (±)-thaliporphine.

Northaliporphine (17) from 12.—A suspension of the oxoaporphine **12** (40 mg) in tetrahydrofuran (10 ml) was added to a stirred suspension of zinc amalgam [prepared from 2% $HgCl_2$ (15 ml), zinc dust (1.5 g), and 2 *N* HCl (15 ml)].

The reaction was completed and worked up as for the reduction of **15** to give a reddish residue. Purification by preparative tlc [silica gel, $CHCl_3$–MeOH (5:1) eluent] afforded **17** (21 mg, 52%) as colorless needles, mp 212–214° (from $CHCl_3$–ether–hexane), identical by spectral properties and mixture melting point with the sample prepared by reduction of **15**.

Registry No.—**1**, 5630-11-5; **5**, 39945-32-9; **5** HCl, 39945-33-0; **7**, 39945-34-1; **8**, 5574-24-3; **10**, 58-74-2; **11**, 39945-36-3; **12**, 39945-37-4; **13**, 39945-38-5; **15**, 39945-39-6; **16**, 39945-40-9; **16** HCl, 39945-41-0; **16** picrate, 39945-42-1; **17**, 39945-43-2; $NaNO_2$, 7632-00-0; formaldehyde, 50-00-0; sodium borohydride, 16940-66-2; diazomethane, 334-88-3.

Acknowledgment.—We are grateful to Professor R. J. Spangler for a generous sample of (±)-thaliporphine and to Dr. C. A. Hetzel (Wyeth Laboratories) for determination of high-resolution mass spectra. We also thank the National Institutes of Health for a grant (CA 11445) in support of this work.

Purine *N*-Oxides. XLVII. Photochemistry of 1-Hydroxy- and 1-Methoxyhypoxanthines[1]

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The photochemistry of the cations, neutral species, and anions of 1-hydroxyhypoxanthine and 1-hydroxy-7-methylhypoxanthine is reported. Two types of reactions, rearrangement and reduction, occur upon uv excitation of these *N*-hydroxypurines. The influence of tautomeric structure and ionic state on the type and the extent of these two reactions is examined. 1-Methoxy-7-methylhypoxanthine, which undergoes photoreduction only, was used as a model for the un-ionized *N*-hydroxy species. It is deduced that deoxygenation is the primary reaction of the neutral *N*-hydroxy species, while rearrangement occurs from an excited state of the enolate anions of these 1-hydroxyhypoxanthines. Studies with triplet sensitizers in dioxane demonstrated that photoreduction of the neutral species of 1-hydroxy-7-methylhypoxanthine occurs through the triplet state, while in acetonitrile photoreduction of it takes place by a combination of triplet energy transfer and chemical sensitization. Photoreduction of 1-methoxy-7-methylhypoxanthine occurs from the excited singlet but it can also be accomplished by chemical sensitization with aromatic ketones. The enolate anions can also be photoreduced with aqueous acetone as sensitizer. Syntheses of the requisite 1-hydroxy-7-methyl- and 1-methoxy-7-methylhypoxanthines are described.

The photochemical sensitivity of purine *N*-oxides in solution has been reported[2–7] and products resulting from deoxygenation, rearrangement, and ring opening have been isolated. Study of a series of *N*-hydroxyxanthines showed that free radicals can be induced by ultraviolet irradiation of the dry solids.[8] These radicals are stable in the solid state, but are immediately reduced to the parent purines when dissolved in protic solvents. Irradiation of the same *N*-hydroxypurines in solution gave the deoxygenated derivatives as the primary photoproducts.[8] We have now studied the mechanism of photochemical reduction of *N*-hydroxypurines in solution, with consideration of the influence of the ionic and the tautomeric state on the photochemical behaviors of the irradiated compounds.

For initial study 1-hydroxyhypoxanthine[9] (**1**) and derivatives of it were selected. This system has the desired cyclic hydroxamic acid moiety, only one additional ionizable proton, and a minimal number of ionic species and tautomeric forms to be considered. In addition, the availability of 1-hydroxyinosine[9] (**12**) presented a route to the desired selectively methylated derivatives of **1**.

Results

Irradiations of 1-Hydroxyhypoxanthine (1).—The neutral species of **1** was studied at pH 3, which is more than 2 pH units from the first ionization p*K* of 5.65,[9] but above the protonation p*K* of 1.77 ± 0.05. Irradiation of **1** at pH 3 in the presence of O_2 resulted in rapid destruction of uv-absorbing components (expt 1–2, Table I); by 2 hr only 6% of the starting material could be accounted for, all as hypoxanthine (**8**). This loss could be greatly diminished by flushing with N_2 and all subsequent irradiations were done under N_2.

Irradiation of the neutral species of **1** under N_2 with a Corex filter (260-nm cutoff) for 30 min or more gave three isolable products (Scheme I): hypoxanthine (**8**) (40%), 2,6-dihydroxypurine (xanthine) (**10**) (9%), and 6,8-dihydroxypurine (**7**) (1%) (expt 8–10, Table I). Even under N_2 there was still a decrease in the total recovery of these products, based on uv absorption, as the photolysis proceeded (expt 5–10). The cation of **1**, irradiated in 3 *N* CF_3CO_2H (pH ~0) (expt 3–4), re-

(1) This investigation was supported in part by funds from the Atomic Energy Commission (Contract No. AT[11-1]-3521) and from the National Cancer Institute (Grant No. CA 08748).

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(3) G. B. Brown, G. Levin, and S. Murphy, *Biochemistry*, **3**, 880 (1964).

(4) G. Levin, R. B. Setlow, and G. B. Brown, *ibid.*, **3**, 883 (1964).

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(6) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *J. Med. Chem.*, **8**, 190 (1965).

(7) A. Giner-Sorolla, C. Gryte, M. L. Cox, and J. C. Parham, *J. Org. Chem.*, **36**, 1228 (1971).

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

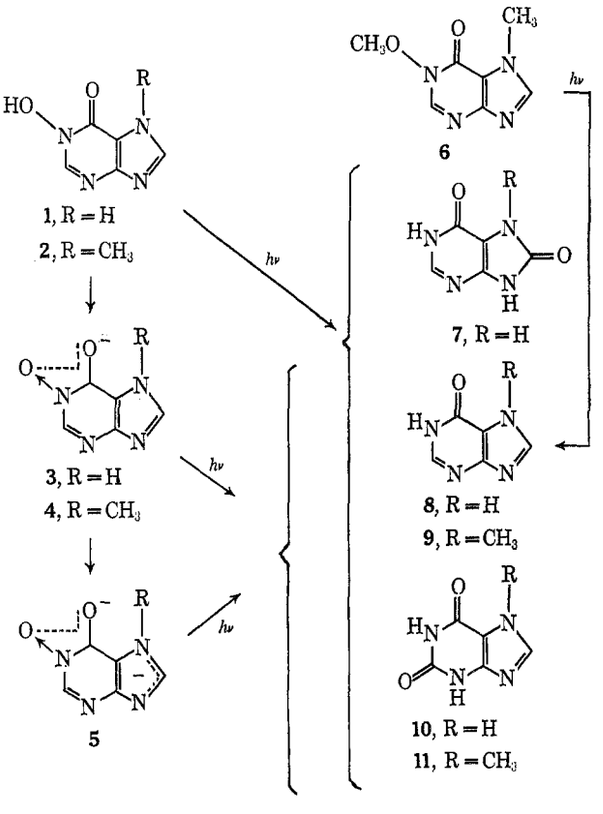
TABLE I

PHOTOLYSIS OF 1-HYDROXYHYPOXANTHINE (1) IN AQUEOUS SOLUTION[a]

Expt	pH	Time, min	Xanthine (10), %	Hypoxanthine (8), %	6,8-Dihydroxypurine (7), %	1, %	Recovery, %
1	3.0[b]	15	2	20	0	24	46
2	3.0[b]	120	0	6	0	0	6
3	0	30	<1	14	3	76	93[c]
4	0	120	<1	35	4	26	67[d]
5	3.0	5	4	16	0	77	97
6	3.0	10	6	24	<1	43	73
7	3.0	15	7	40	<1	16	63
8	3.0	30	9	38	1	2	50
9	3.0	60	9	42	1	0	51
10	3.0	120	9	40	1	0	50
11	8.5	30	17	7	0	6	30[e]
12	8.5	60	18	6	0	0	24[e]
13	13	30	24	9	0	24	57[e]
14	13	60	19	6	0	2	27[e]

[a] Corex filter. [b] Without N_2 flushing. [c] Trace of 8-trifluoromethylhypoxanthine. [d] 2% 8-trifluoromethylhypoxanthine. [e] Trace of a third, unidentified product.

SCHEME I

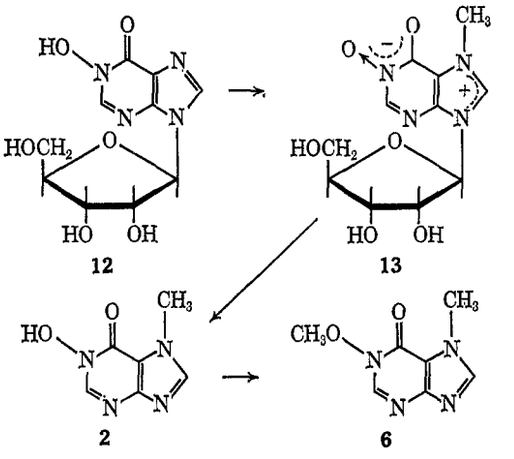


acted more slowly than the neutral species. Hypoxanthine was again the major product (35%), while the yield of 6,8-dihydroxypurine increased to 4%, and less than 1% of xanthine was found. In addition, 8-trifluoromethylhypoxanthine (2% after 120 min) was produced. It was identified from its uv spectral properties by comparison with an authentic sample.[10]

Irradiation of the monoanion **3** at pH 8.5 (pK_a = 5.65 and 10.10[9]) gave much less photoreduction to hypoxanthine (~6%), increased rearrangement to xanthine (17–18%), and no 6,8-dihydroxypurine (expt 11–12). A trace of a third product, not yet identified, was noted which showed uv absorption, λ_{max} (pH) 248, 286 (0), 276 nm (12). Irradiation of the dianion of **1** (**5**) in 28% NH_4OH, pH ~13, gave results similar to those from the monoanion **3** (expt 13–14).

Selectively Alkylated Derivatives of 1.—Methylation of **12**, an improved preparation of which is reported, can be achieved at N-7 by reaction of the neutral species with CH_3I in CH_3SOCH_3 (Scheme II).[11] Hydrolysis of

SCHEME II



1-hydroxy-7-methylinosine (**13**) yielded 1-hydroxy-7-methylhypoxanthine (**2**). Alkylation of the anion of **2** with CH_3I and K_2CO_3 in dimethylacetamide produced 1-methoxy-7-methylhypoxanthine (**6**). The uv spectra and nmr data confirm the assigned structures for **2** and **6**.

Irradiation of Methyl Derivatives of 1.—The single pK_a of 1-hydroxy-7-methylhypoxanthine (**2**), 5.63 ± 0.02, is comparable to the first pK_a of **1**, and each is associated with increased absorption near 230 nm. Thus, both ionizations occur from the 1-hydroxyl group. The protonation pK of **2** is 1.6 ± 0.1. The neutral species of **2**, irradiated at pH 3 (expt 16–17, Table II), gave primarily deoxygenation to 7-methyl-

TABLE II

PHOTOLYSIS OF 1-HYDROXY-7-METHYLHYPOXANTHINE (2)

Expt	Solvent	pH	Time, min	7-Methylxanthine (11), %	7-Methylhypoxanthine (9), %	2, %	Recovery, %
15	H_2O[a]	0	30	2	13	63	78%[b]
16	H_2O[a]	3.0	15	9	14	39	62[c]
17	H_2O[a]	3.0	30	7	42	10	59[c]
18	H_2O[a]	9.0	15	6	3	66	>75[d]
19	H_2O[a]	9.0	30	10	5	17	>32[d]
20	CH_3OH[a]		15	0	27	54	81[c]
21	CH_3OH[a]		30	0	42	26	68[c]
22	EtOH[a]		15	0	42	32	74[c,d]
23	CH_3CN[a]		30	2	74	0	76[c]
24	Dioxane[a]		45	0	70	0	70
25	H_2O[e]	9.0	30	<1	<1	97	97
26	H_2O[e]	9.0	300	2	<1	68	70
27	H_2O[e,f]	9.0	30	<1	11	84	95
28	H_2O[e,f]	9.0	300	2	82	0	84

[a] Corex filter. [b] Product with properties similar to 6,8-dihydroxypurine, ~2%. [c] Small amount of product (<1%) thought to be 6,8-dihydroxy-7-methylpurine. [d] One additional unidentified product. [e] Pyrex filter. [f] 10% acetone as sensitizer.

(10) A. Giner-Sorolla and A. Bendich, *J. Amer. Chem. Soc.*, **80**, 5744 (1958).

(11) The anion of 1-hydroxyinosine (**12**) can be alkylated at the 1 position to produce 1-alkoxyinosines [private communications, A. A. Watson, this laboratory, and J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 1334 (1972), prior to publication]. These positions of alkylation of **12** parallel those observed for the anion and the neutral species of inosine.[12]

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

hypoxanthine (9), a small amount of 7-methylxanthine (11), and a trace of another material which resembled 6,8-dihydroxypurine, both in retention volume on a Dowex-50 [H+] column and in uv spectrum. It is presumably 6,8-dihydroxy-7-methylpurine (7, R = CH_3). Irradiation of the cation of 2 at pH 0 (expt 15) gave primarily deoxygenation, less 7-methylxanthine, and more product presumed to be 6,8-dihydroxy-7-methylpurine.

The anion of 2 (4), irradiated at pH 9.0, gave yields of deoxygenation (9) and rearrangement (11) products comparable to those obtained from monoanion 3 (expt 18–19). An unidentified product, similar to that obtained from 3 in trace amounts, was also obtained.[13]

1-Hydroxy-7-methylhypoxanthine (2) is sufficiently soluble to permit irradiation studies in nonaqueous media (expt 20–24, Table II). In methanol or ethanol solution, up to 40% or more of 2 was photoreduced to 9; traces of 6,8-dihydroxy-7-methylpurine (7, R = CH_3) were noted, but no rearrangement to 11 was obtained. In CH_3CN solution photolysis of 2 gave 9 (74%), 11 (2%), and a trace of 7 (R = CH_3). The irradiation of 2 in dioxane solution gave 9 (70%) and no other products.

1-Methoxy-7-methylhypoxanthine (6) was irradiated under N_2 through a Corex filter in several solvents (expt 29–32, Table III). Only photoreduction to 7-methylhypoxanthine (9) resulted, in a 50% or greater yield. Traces of two other products were detected in water.

TABLE III
PHOTOLYSIS OF 1-METHOXY-7-METHYLHYPOXANTHINE[a]

Expt	Time, min	Solvent	7-Methylhypoxanthine (9), %	6, %
29	15	H_2O	52[b]	0
30	10	CH_3OH	67	0
31	10	CH_3CN	60	0
32	20	Dioxane	52	0

[a] Corex filter. [b] Two additional minor peaks also noted.

Sensitizer Studies.—The solubility of 2 and 6 in acetonitrile and dioxane permitted studies with triplet sensitizers (Table IV).[16,17] A Pyrex filter (280-nm cutoff) eliminated the majority of the main absorption band at 256 nm, but not the small absorption that extends slightly beyond 280 nm. Direct irradiation of 2 or 6 for 30 min or more in each solvent, through Pyrex without a sensitizer, gave a low yield (1–6%) of the reduction product, 9, but no rearrangement to 7-methylxanthine (11) (expt 33 and 39, Table IV). This production of 9 was much lower than that obtained from irradiations through Corex (Tables II and III) and can be attributed to reaction following excitation of the small absorption beyond 280 nm. With sensitizers in each solvent, both 1-hydroxy- and 1-methoxy-7-methylhypoxanthine, 2 and 6, gave 9, and in most cases as the only photoproduct. In the presence of acetophenone, a small quantity of a second product was noted from 6.

Sensitized irradiation of anion 4 was limited, by solubility, to an aqueous medium. Irradiation of it at pH 9, through Pyrex in the presence of 10% acetone, gave a greater yield of photoreduction than did similar irradiation without acetone (expt 25–28, Table II).

Discussion

In most studies on the photochemistry of heterocyclic aromatic N-oxides,[18] little or no possibility existed for the presence of an alternative tautomeric species, as in the N-oxides of pyridine, quinoline, and isoquinoline. In purine N-oxides the presence of a carbonyl group in the same ring with the N-oxide favors existence of the neutral species as the N-hydroxy tautomer in preference to the hydroxy N-oxide form.[9,19] The enhanced formation of the N-hydroxy tautomer, in essence a cyclic hydroxamic acid, can occur when the two groups are either "ortho"[9] or "para"[19] to each other.

It has been repeatedly observed that the N-oxide group, regardless of its tautomeric form, decreases all ionization pK_a's relative to those of the parent purine.[19,20] Where the N-hydroxy tautomer predominates, the N-hydroxyl proton is usually the first to ionize. Its ionization is always accompanied by the appearance of an intense uv absorption band near 230 nm[9,19,21–23] that has been attributed to the formation of an enolate anion, as in 3, in which the resonance form of the N–O bond is equivalent to an N-oxide or nitrone group.[19] We have examined the effect of different pH's on the photochemistry of a simple N-hydroxypurine and correlated them with changes in ionic and tautomeric forms.

The first ionization of 1-hydroxyhypoxanthine (1) has been assigned to the proton of the 1-hydroxyl.[9] The neutral species of 1 shows a single absorption band at 250 nm similar to that of the neutral species of hypoxanthine (8) (λ_{max} 249 nm)[24] and 1-methylhypoxanthine (251 nm).[24] The neutral species of 1-hydroxy-7-methylhypoxanthine (2) also shows a single band at

(13) This product was well separated and followed 9 when eluted with 1 N HCl from a Dowex-50 [H+] column. A sample isolated from a Dowex-50 [H+] column and applied to a paper chromatogram had R_f 0.46 in CH_3CN–H_2O–(28%) NH_4OH (7:2:1, v/v) and gave a negative Pauly test.[14] It showed uv absorption, λ_{max} (pH 0) 248, 287 nm. In acid solution this product was slowly converted to 7-methylhypoxanthine (9), which was identified by paper and column (A-6) chromatography and its uv absorption properties.

On a Bio-Rex A-6[15] (formate) column eluted with 0.34 M ammonium formate buffer (pH 4.7), a third photolysis product was also eluted well after 11, 9, and 2. A paper chromatogram of the crude photolysis mixture developed in CH_3CN–H_2O–NH_4OH (7:2:1) showed one uv-absorbing spot at R_f 0.65 in addition to those of 11, 9, and 2, which were all near R_f 0.4. The component at R_f 0.65 gave a blue Pauly test on the chromatogram and had the same uv spectrum as the unknown product eluted from an A-6 (formate) column, λ_{max} (pH) 237 (0), 246 (6), 252 nm (11). This product was stable to acid hydrolysis, but was not stable to prolonged irradiation. In expt 5–10 (Table I) it gradually diminished after 30 min. The positions of elution on the two columns indicate that the unknowns are fairly basic and that the one that gave a positive Pauly test is an imidazole.

(14) H. Pauly, *Hoppe-Seyler's Z. Physiol. Chem.*, **42**, 508 (1904).

(15) M. Uziel, C. K. Koh, and W. E. Cohn, *Anal. Biochem.*, **25**, 77 (1968).

(16) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 298.

(17) (a) N. C. Yang, D. S. McClure, S. L. Muror, J. J. Houser, and R. Dusenberg, *J. Amer. Chem. Soc.*, **89**, 5466 (1967). (b) For examples see B. M. Monroe and C. C. Wamser, *Mol. Photochem.*, **2**, 213 (1970), and references therein.

(18) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

(19) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).

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

(21) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **32**, 1151 (1967).

(22) A. A. Watson and G. B. Brown, *ibid.*, **37**, 1867 (1972).

(23) G. Zvilichovsky and G. B. Brown, *ibid.*, **37**, 1871 (1972).

(24) G. B. Elion, *ibid.*, **27**, 2478 (1962).

TABLE IV

SENSITIZATION STUDIES[a]

Expt	Solvent Sensitizer[b]	1-Hydroxy-7-methylhypoxanthine (2) Time, min	9, %	2, %	Recovery, %	1-Methoxy-7-methylhypoxanthine (6) Time, min	9, %	6, %	Recovery, %
33	Acetonitrile	30	5	92	97	30	4	95	99
34	+ Acetophenone (73.6)[d]	30	65	0	65	30	75	0	>75[c]
35	+ *m*-CH_3O–acetophenone (72.4)[e]	30	53	47	100	30	6	92	98
36	+ Benzophenone (68.5)[d]	40	87	4	91	30	33	67	100
37	+ Benzophenone					120	63	12	75
38	+ Fluorene (67.6)[d]	30	8	92	100	30	9	91	100
39	Dioxane	30	6	92	98	30	1	99	100
		240	26	35	61				
40	+ Acetophenone	30	48	30	78	30	68	0	>68[c]
41	+ *m*-CH_3O–acetophenone	30	49	32	81	30	17	72	89
42	+ Benzophenone	30	9	88	97	30	4	96	100
43	+ Fluorene	30	3	80	83	30	4	96	100
44	Acetone (neat)	30	78	0	78	30	65	0	65

[a] Pyrex filter. [b] 0.2 *M* in sensitizer; values in parentheses are triplet energy levels in kcal/mol. [c] One additional unknown noted, λ_{max} (pH 0 and 11) 247 nm. [d] Reference 16. [e] Reference 17a.

256 nm, which is close to that of 7-methylhypoxanthine (255.5 nm)[24] and to that of 1-methoxy-7-methylhypoxanthine (256 nm), a derivative of **2** constrained in the *N*-alkoxy-6-oxo form. From these data it is deduced that the neutral species of both **1** and **2** exist as the *N*-hydroxy-6-oxo tautomer.

The photochemical reactivity of the neutral species of **1** and **2** was studied and in both cases the major product (~40%), from the direct irradiation in aqueous solution through a Corex filter, was the deoxygenated purine **8** or **9** (Tables I and II). The xanthine derivatives **10** and **11** were also produced from the irradiations of **1** and **2**, but in yields of only 9–10%. These two types of reactions, deoxygenation and rearrangement, are analogous to those observed earlier for the direct irradiation of adenine and adenosine 1-oxides,[2-5] both of which are thought to exist primarily in the *N*-oxide form.[20] The predominance of the deoxygenation path for the neutral species of **1** and **2** contrasts with the ratio of reduction to rearrangement observed for adenine *N*-oxide, from which almost equal amounts of reduction and rearrangement products were obtained.[3,5]

A third product from the irradiation of **1** at pH's 0 and 3 was identified as 6,8-dihydroxypurine (**7**), and a similar product, presumed to be the 7-methyl derivative of **7**, was also obtained from **2**; in each instance it represented 4% or less of the starting material. This production of an 8-hydroxypurine is reminiscent of the photochemical hydroxylation of naphthalene that is induced by irradiation of it with pyridine *N*-oxide in CH_2Cl solution,[25] and of the photochemical epoxidation of olefins in the presence of *N*-oxides.[26]

In 1-methoxy-7-methylhypoxanthine (**6**), the absence of any ionizable or tautomerizable proton unequivocally defines the tautomeric form. Thus, **6** should provide a model for the photochemical products that would be expected from the 1-hydroxy-6-oxo tautomer in the total absence of other species. In aqueous solution **6** was rapidly reduced photochemically to one product, 7-methylhypoxanthine (**9**), in 52% yield (expt 29, Table III). This yield correlates well with the ~40% of **8** or **9** produced from the neutral species of **1** and **2**.

The ionization of the *N*-hydroxyl proton of **1** or **2** to the anionic species, **3** or **4**, modifies the predominant form of the N–O bond from *N*-hydroxy to an enolate *N*-oxide, and this is accompanied by an alteration in the ratio of the photochemical products. Irradiation of the monoanion **3** (expt 11–12) produced a greater extent of rearrangement to **10** (17–18%) than that obtained from the neutral species **1**. In turn, the yield of the deoxygenated purine **8** from **3** was reduced to about 6%. Further ionization of the imidazole hydrogen of **3** to the dianion **5** had no influence on the course of photochemical reactions (expt 13–14).

Irradiation of the anion of the 7-methyl derivative, **4** (expt 18–19, Table II), resulted in a similar decrease in the reduction to **9**, relative to that (expt 16–17) of its neutral species, **2**. However, the yields of the rearrangement product, **11**, from either **2** or its anion **4** were virtually unchanged, in contrast to the effect of ionization of **1** to **3** that was accompanied by an increase in photoisomerization to xanthine from 9 to 17% (expt 8–9 and 11–12).

From the results of the irradiations of **1**, **2**, and **6**, it may be deduced that (a) the primary photochemical reaction of the *N*-hydroxy tautomer is deoxygenation and that (b) rearrangement proceeds *via* the enolate anion. Several results require consideration in relation to these deductions. These include the observation of some rearrangement from the neutral species **1** and **2** at pH 3, some deoxygenation from the anions **3**, **4**, and **5**, and the less than quantitative recoveries even from **6**.

The photolysis products, hypoxanthine (**8**), xanthine (**10**), and 6,8-dihydroxypurine (**7**), are stable under the irradiation conditions; continued irradiation after the disappearance of **1** did not reduce the recoveries of **7**, **8**, and **10** and overall recoveries remained near 50%. A time study irradiation of **1** at pH 3 (expt 5–10) showed that the decrease in the total recovery of material was associated with direct destruction of the chromophore, which suggests that **1** undergoes additional reactions.

Upon irradiations of the enolate anions **3** or **4**, there was a smaller overall recovery, ~25% (expt 11–12 and 18–19). Only a trace of one uv-absorbing product

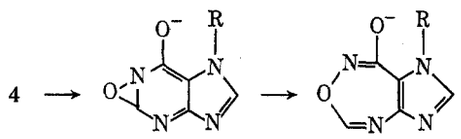
(25) D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970).

(26) T. Tsuchiya, H. Arai, and H. Igeta, *ibid.*, 2747 (1969).

other than those in Table I was detected from the irradiation of **3**, but larger amounts of a similar product were noted from the irradiation of **4**.

Since the N–O group in these enolate anions may be considered as a nitrone or *N*-oxide, it is reasonable to assume that the photochemical rearrangement to xanthine proceeds *via* an oxazirane intermediate (**14**) (Scheme III). Oxaziranes have been proposed as inter-

SCHEME III



14 **15**

mediates in the N to C rearrangement of oxygen both for nitrones and for aromatic *N*-oxides.[18] They have been shown to yield not only the expected rearrangement product,[18,27] but also oxadiazepines, which result from isomerization of the oxazirane intermediates, and hydrolysis products of the oxadiazepines.

If an oxazirane intermediate is assumed, then the lower recoveries from the irradiations of **3** and **4** and the additional products from **4** could well be derived from secondary reactions, including photochemical, of the oxazirane **14** and the imidazolo oxadiazepine **15**. Chromatograms of the photolysis mixtures showed the presence of a product that gave a positive Pauly test for imidazoles.[13] This supports the proposal that **14** or, more likely, **15** undergoes ring opening to an imidazole. The alkaline pH's necessary for anions **3** and **4** should facilitate decomposition of such intermediates. The comparison of the photochemistry of the enolate anions, **3**, **4**, and **5**, to that of heterocyclic *N*-oxides can also be extended to the photoreduction noted for these anions, since photochemical deoxygenation is frequently observed for *N*-oxides of aromatic amines.[18]

Some photorearrangement of oxygen to the adjacent carbon occurred from **1** and **2** even at pH 3, where less than 1% of the corresponding anionic species **3** or **4** should be present. For the rearrangement to proceed through the enolate anions at pH 3, either the quantum efficiency of the rearrangement reaction must be considerably higher than that of the reduction reaction, or the pK_a of the excited singlet of **1** and **2** must be lower than that of the ground state. The amount of starting material photochemically modified in a given time was similar for the neutral species and for the monoanions (Tables I and II), which would argue against a significantly higher quantum efficiency for the rearrangement reaction than for photoreduction.

Direct measurement of excited state pK_a's was not possible because of the weak fluorescence of **1** and **2**, but these were calculated[28] from uv absorption data to be 2.73 and 1.26 for the first ionizations of **1** and **2**. These pK_a's for the excited singlets of **1** and **2** are, thus, sufficiently lower than those of the ground states to explain the extent of rearrangement observed at pH 3. They also permit an explanation of the differing amounts of rearrangement observed from the neutral species of **1** and **2**, in comparison to that observed from their respective monoanions, **3** and **4**. The yield of xanthine from **3** was twice that from **1** (expt 11–12 and 8–9), while the yield of 7-methylxanthine (**11**) was the same for both **2** and **4** (expt 16–19). From the calculated pK_a^* of 2.7 for the excited singlet of **1**, a medium at pH 3 would allow this singlet to be only about half dissociated and an increase in pH will permit further ionization. This, in turn, will lead to a larger amount of rearrangement from the excited state of anion **3**. By comparison, from the calculated pK_a^* of 1.2 for the excited singlet of **2**, a medium at pH 3 would permit almost complete ionization, and an increase in pH should cause no change in the yield of product from **4**.

At pH 0, well below the pK_a's of the excited singlets of **1** and **2**, photoreduction was not affected, but the amount of rearrangement to **10** or **11** was significantly decreased. The greater yield of **11** (2%) than **10** (<1%) is also in agreement with the calculated values for the excited state pK_a's, since **1** ($pK_a^* = 2.7$) should be essentially un-ionized at pH 0, while a medium of pH 0 should permit **2** ($pK_a^* = 1.2$) to ionize slightly (~6%). These interpretations of the results in terms of the pK's of the excited states are in accord with the proposal that rearrangement occurs *via* the enolate anion. It also follows that the recoveries of only 50% from **1** and **2** at pH 3 may, in part, be attributed to greater production of the labile imidazolo oxadiazepine **15**, as suggested above for the anions **3** and **4**.

However, when neither tautomerism nor ionization was possible and no rearrangement was observed, as in the case of **6** (Table III), recoveries still did not exceed 70%. This indicates that reactions which destroy the purine ring system occur even from the 1-methoxy compound, and that similar reactions should be expected for the 1-hydroxy derivatives. In agreement with this, there was still some loss of uv-absorbing components at pH 0, where reactions from the *N*-hydroxy species are favored and those from the enolate anions should be minimal. Oxidation of the 4–5 double bond is common in purines,[29,30] and the isolation of 6,8-dihydroxypurine demonstrates that reaction can occur at the imidazole ring. In fact, the amount of 8 substitution increased under conditions that favored reaction from the *N*-hydroxy species.[31] Loss of the purine chromophore may occur from reactions of the oxygen lost from N-1, which might react either as a hydroxyl radical or as singlet oxygen.

Irradiation studies of **2** in organic solvents (expt 20–24) showed that photoreduction predominated under these conditions. The absence of photorearrangement in nonaqueous solvents, except the more polar CH_3CN (expt 23), suggests that the less polar organic solvents do not support ionization of **2**. Therefore, a decreased proportion of the reaction products originate from the anion **4**, and the photolysis of **2** approaches that for the *N*-hydroxy species alone and more closely resembles the irradiation of the nonionizable **6**.

Sensitizer Studies.—The photoreduction of **2** and **6**

(27) J. Streith, C. Leibovici, and P. Martz, *Bull. Soc. Chim. Fr.*, 4152 (1971).

(28) H. H. Jaffe, D. L. Beveridge, and H. L. Jones, *J. Amer. Chem. Soc.*, **86**, 2932 (1964). pK^*'s were calculated from the expression $pK^* - pK = (\nu_B - \nu_{BH^+})Nhc/2.303\,RT$ using 300°K for T and for ν_B and ν_{BH^+} 259 and 250 nm for **1**[9] and 271 and 256 nm for **2**.

(29) P. H. Stahl, *Biochemistry*, **8**, 733 (1969).

(30) N. J. M. Birdsall, T.-C. Lee, T. J. Delia, and J. C. Parham, *J. Org. Chem.*, **36**, 2635 (1971).

(31) See expt 3–10 (Table I) and expt 15–17 (Table II), footnotes *b* and *c*.

was promoted by acetophenone in CH_3CN (expt 34, Table IV). In dioxane it promoted reduction of **6**, but was less effective with **2** (expt 40). Benzophenone gave less consistent results as a sensitizer. In CH_3CN it promoted photoreduction of **2** but was less efficient with **6** (expt 36); in dioxane it was not an active sensitizer for either **2** or **6** (expt 42).

To determine whether the photoreduction could be proceeding through chemical sensitization, that is, by reduction by ketyl radicals rather than by triplet energy transfer, *m*-methoxyacetophenone was also studied (expt 35 and 41). *m*-Methoxyacetophenone is a high energy sensitizer (E_T 72.4 kcal) with a lower $\pi-\pi^*$ than $n-\pi^*$ triplet energy level.[17a] Thus, it is a poor hydrogen abstractor and has a low efficiency as a chemical sensitizer.[17b] In CH_3CN it did not sensitize the photoreduction of **6** (expt 35) and in dioxane it was only marginally effective for **6** (expt 41), even though the triplet energy is above 72 kcal/mol.[17] These results indicate that for 1-methoxy-7-methylhypoxanthine chemical sensitization plays a predominant role in photoreduction sensitized by ketones. Since *m*-methoxyacetophenone fails to sensitize the photoreduction of **6** by triplet energy transfer, the loss of the methoxy group from **6** must occur from the excited singlet.

In contrast, the *m*-methoxyacetophenone-sensitized photoreduction of 1-hydroxy-7-methylhypoxanthine (**2**) in CH_3CN must take place by a combination of chemical sensitization and triplet-energy transfer. While half the starting material was photoreduced in 30 min in the presence of *m*-methoxyacetophenone (expt 35), much more was photoreduced with acetophenone or benzophenone (expt 34 and 36). In dioxane the similarity of the results with acetophenone and *m*-methoxyacetophenone (expt 40 and 41) demonstrates that deoxygenation from **2**, and therefore probably also from **1**, occurs from the triplet state and that sensitization takes place only through a triplet energy transfer mechanism in this solvent. Fluorene did not sensitize the photoreduction of **2** or **6** in either solvent (expt 38 and 43). Acetone promoted the photoreduction of both **2** and **6**, presumably by mechanisms similar to those for acetophenone (expt 44).

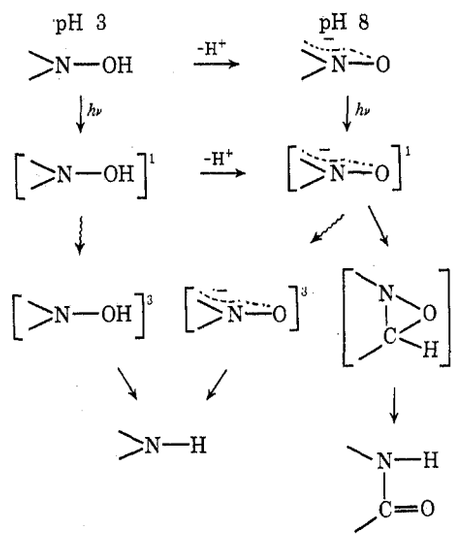
In a triplet quenching experiment irradiation of 1-hydroxy-7-methylhypoxanthine (**2**) for 30 min in CH_3CN (Corex) in the presence of piperylene (1.0 *M*) gave 7-methylxanthine (1.4%), 7-methylhypoxanthine (47%), and unreacted **2** (15%). Under similar conditions but in the absence of piperylene (expt 23, Table II), no starting material remained and the yield of 7-methylhypoxanthine was notably higher (74%). These results complement those in Table IV and are compatible with a triplet intermediate for photoreduction.

The differing results obtained with the triplet sensitizers in CH_3CN and in dioxane (Table IV) indicate some influence of the solvent, of a type not previously noted in chemical sensitizations. In CH_3CN both acetophenone and benzophenone reduced **2** and **6**, while dioxane did not permit chemical sensitization by benzophenone for either. Dioxane eliminated such sensitization by acetophenone for **2**, but did not prevent the reduction of **6** by acetophenone. This suggests that acetonitrile, usually considered to be an unreactive solvent for photochemistry, may have sufficiently labile hydrogens to support chemical sensitization while dioxane does not.[32]

Ten per cent of acetone at pH 9 was used for the sensitization of the monoanion **4** (expt 25–28, Table II). Since the Pyrex filter did not completely eliminate absorption by **4**, some rearrangement as well as photoreduction was detected without a sensitizer. The much greater extent of photoreduction in the presence of acetone suggests that deoxygenation proceeds from the triplet state of **4**, although the possibility of chemical sensitization, in whole or in part, cannot be excluded. These results imply that rearrangement may occur from the excited singlet of the enolate anions, paralleling the conclusions of a recent study of pyridine *N*-oxide which proposed that photoisomerization occurs from the singlet state while photoreduction is a triplet process.[35]

The results and proposals discussed are summarized in Scheme IV. Excitation of the neutral *N*-hydroxy

SCHEME IV



species at pH 3 or below would produce the excited singlet >NOH[1]. Intersystem crossing would yield the *N*-hydroxy triplet >NOH[3], which leads ultimately to the photoreduced purine. Alternatively, ionization of the >NOH[1] singlet, which is more acidic than the ground state, would produce the excited singlet of the

(32) The influence of solvent polarity should be considered as a possible contributor to the differing results obtained in dioxane and in CH_3CN. Excited-state energy inversion can result from a difference in solvent polarity.[33,34] As the polarity of the medium is increased, the $\pi-\pi^*$ state drops in energy and the $n-\pi^*$ state rises. Both acetophenone and benzophenone have $n-\pi^*$ lowest excited triplets. In CH_3CN, the $\pi-\pi^*$ state of these ketones should be lower and the $n-\pi^*$ state higher than in dioxane. It is evident that in CH_3CN $^3\pi-\pi^*$ is not lowered below $^3n-\pi^*$ for either ketone, since their ability to act as sensitizers is opposite to that of *m*-methoxyacetophenone which is known to have $^3n-\pi^* > {}^3\pi-\pi^*$.[17] In dioxane the lower polarity would increase the difference in energy between these states, making $\pi-\pi^* \gg n-\pi^*$. Thus, the results in Table IV do not agree with those expected from an inversion of energy levels owing to a different solvent polarity. This supports the proposal of chemical sensitization.

In the case of benzophenone it is possible that solvent polarity may play some role. This would require that $^3n-\pi^*$ energy in CH_3CN is just sufficient for triplet energy transfer, but that in dioxane its energy level is below the requisite levels for transfer to **2** or **6**.

(33) L. A. Singer, *Tetrahedron Lett.*, 923 (1969).

(34) A. A. Lamola, *J. Chem. Phys.*, **47**, 4810 (1967).

(35) F. Bellamy, L. G. R. Barragan, and J. Streith, *J. Chem. Soc. D*, 456 (1971).

enolate anion $=NO^{-1}$. This excited anion may also be obtained by direct excitation of the ionized ground state. The excited anion singlet may photoisomerize to xanthine or decay to the triplet anion $=NO^{-3}$, which, in turn, also yields the photoreduction product.

Experimental Section

General Procedure for Direct Irradiation.—Samples were irradiated in 1.4×10^{-4} *M* solutions of the solvents specified. CF_3CO_2H (3 *M*), 10^{-3} *M* HCl, and dilute NH_4OH were used for pH 0, 3, and 8.5, respectively. Nitrogen was bubbled through the solutions for 2 hr prior to irradiation, and they were irradiated in an immersion type apparatus equipped with a 450-W Hanovia high-pressure mercury lamp, with the use of either a Corex or a Pyrex filter. The disappearance of starting material was followed by changes in the uv absorption or by paper chromatography of aliquots withdrawn at various intervals during the irradiations. When the reactions were complete, the solutions were concentrated under vacuum to a small volume, and the products were separated and isolated by chromatography over a BioRad AG-50, X8 [H^+], 200–400 mesh column (9 × 400 mm). The products were eluted with 1 *N* HCl from the column in the sequence **10** (or **11**), **1** (or **2**), **8** (or **9**), **6**, unknowns (from anions). Yields of the reaction products were calculated from their respective ϵ_{max} values.[9,24,36] For 8-trifluoromethylhypoxanthine[10] λ_{max} (ϵ_{max}) at pH 0 is 253.5 nm (11,100). The results, expressed as per cent yields based on starting material, are in Tables I–IV. Values were reproducible within ±5%.

General Procedure for Sensitized Irradiation.—A solution 1.4×10^{-4} *M* in sample and 0.2 *M* in sensitizer in either *p*-dioxane or CH_3CN was flushed with N_2 for 2 hr in an immersion apparatus and was irradiated with a high-pressure mercury lamp through a Pyrex filter. The solvent was evaporated under vacuum; the solid residue was washed with 200 ml of ether. The flask was rinsed again with a small amount of ether, then with 100 ml of water. The combined ethereal extractions were washed with 100 ml of water. The aqueous layers were combined and evaporated to a small volume under vacuum, and the products were separated and quantitated as described previously.

Materials.—Spectroquality *p*-dioxane and CH_3CN (Matheson Coleman and Bell) and analytical grade acetone and anhydrous methanol (Mallinckrodt) were used as received. Benzophenone, *m*-methoxyacetophenone (Aldrich), and acetophenone and fluorene (J. T. Baker) were used without purification. Melting points are uncorrected. Paper and tlc chromatograms were developed, ascending, with Whatman No. 1 paper or Chromagram silica gel sheet with fluorescent indicator (Eastman). Nmr spectra were measured with a Varian A-60 spectrometer and fluorescence spectra with a Ferrand spectrofluorometer. An ISCO uv analyzer was used to monitor column eluates. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. pK_a's were determined at 27 ± 1° by methods described[37] titrimetrically in 0.001 *M* solutions or spectrophotometrically in 0.01 *M* buffers.[38]

1-Hydroxyhypoxanthine.—This was prepared as described.[9,39]

1-Hydroxyinosine (12).—A solution of adenosine 1-oxide[40] (28.3 g, 0.1 mol) and $NaNO_2$ (69 g, 1.0 mol) dissolved in 1 l. of 29% (v/v) acetic acid was allowed to stand at room temperature for 24 hr. It was then extracted with ether and the aqueous layer was evaporated to dryness under vacuum. The residue was extracted three times with 300-ml aliquots of hot CH_3OH. The extracts were combined and the CH_3OH was evaporated under reduced pressure. Pure 1-hydroxyinosine[9,41] was isolated from the residue by chramatography over Dowex-50, X8, 200–400 mesh [H^+] by elution with H_2O, yield 15.5 g (54%). It was identical in all respects with an authentic sample.[9]

1-Hydroxy-7-methylhypoxanthine (2).—A suspension of 1-hydroxyinosine (7.0 g, 25 mmol) in 40 ml of DMSO was stirred with excess CH_3I (10 ml) at 25° for 5 hr. As reaction proceeded, unreacted **2** gradually dissolved. The solution was then diluted with 300 ml of acetone and filtered through Celite, and the reddish filtrate was diluted with 300 ml of MeOH saturated with NH_3 and adjusted to an apparent pH of 8–9 by bubbling with NH_3. The white precipitate was collected and hydrolyzed with 50 ml of 1 *N* HCl on a steam bath for 30 min. 1-Hydroxy-7-methylhypoxanthine was isolated by chromatography over Dowex-50 [H^+], eluting with water: yield 1.7 g (41%); mp >290° dec; nmr (DMSO-d_6) δ 4.05 (s, 3, NCH_3), 8.18 (s, 1), 8.40 (s, 1).

A sample for analysis was obtained by dissolving a sample in aqueous NH_4OH, treating it with charcoal, filtering, and then acidifying with HOAc and chilling. Colorless crystals were collected and dried at 80° under vacuum over P_2O_5.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.09; H, 3.60; N, 33.66.

pH	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)	Apparent pK_a
0	+	251 (8.4)	
			1.6 ± 0.1
3.6	0	256 (7.9)	
			5.63[a] ± 0.02
9	−	230.5 (35.3), 272 (6.4)	

[a] Titrimetrically.

1-Methoxy-7-methylhypoxanthine (6).—To a solution of 333 mg (2.0 mmol) of 1-hydroxy-7-methylhypoxanthine and 276 mg (2.0 mmol) of finely powdered anhydrous K_2CO_3 in 50 ml of *N*,*N*-dimethylacetamide was added an excess, over 300 mg, of CH_3I, and the mixture was stirred overnight. Tlc ($CHCl_3$–CH_3OH, 9:1 v/v) showed the disappearance of starting material, R_f 0.0, and the appearance of a new spot with R_f 0.8. The yellow mixture was filtered and the filtrate was treated with charcoal and evaporated to dryness under vacuum. The 1-methoxy-7-methylhypoxanthine was chromatographed over a silica gel column, 100–200 mesh, with $CHCl_3$–CH_3OH, (9:1) v/v, yield 240 mg (66%), mp 190–191°. The column eluate was monitored (ISCO) until all **6** had been eluted. The analytical sample was obtained after recrystallization from MeOH and it was dried at 80° over P_2O_5 under vacuum: nmr (D_2O) δ 4.02 (s, 3, NCH_3), 4.12 (s, 3, OCH_3), 8.13 (s, 1), and 8.50 (s, 1); λ_{max} (pH 9) 213 nm (ε 24,900), 256 (7500); (pH 0) 250 (8200).

Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.09. Found: C, 46.69; H, 4.46; N, 31.15.

Registry No.—**1**, 5193-34-0; **2**, 40387-36-8; **6**, 40387-37-9; **12**, 5383-06-2; adenosine 1-oxide, 146-92-9; CH_3I, 74-88-4.

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(37) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

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