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Purine N-Oxides. VIII. N-Oxides of Azapurines[1]

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Comparisons have been made between the behavior of adenine 1-N-oxide and the behavior of the N-oxides of the azaadenines in which the 2- and/or 8-methylidyne groups are replaced by aza groups. 8-Azaadenine is oxidized by peroxyacetic acid to a 1-N-oxide. 2-Azaadenine is oxidized to two hydrolytically stable N-oxides. The structure of the 2-azaadenine N-oxide formed in larger amount is proved to be a 1-N-oxide by an alternative synthesis from 4-aminoimidazole-5-carboxamidoxime and nitrous acid. The structure of the other is unknown. The ribosyl derivative of 4-aminoimidazole-5-carboxamidoxime, obtained by the alkaline hydrolysis of adenosine 1-N-oxide, yields 2-azaadenosine 1-N-oxide with nitrous acid. 8-Azaadenine 1-N-oxide, like adenine 1-N-oxide, exhibits hydrolytic instability in the 6-membered ring and yields 4-aminotriazole-5-carboxamidoxime. This latter gives the corresponding carboxamide and carboxamidine upon hydrolysis and hydrogenation, respectively. Upon direct nitrosation this carboxamidoxime yields 2,8-diazaadenine 1-N-oxide. The oxime of the hydrolysis product of 6-methylpurine 1-N-oxide, 4-acetyl-5-aminoimidazole, gives 6-methyl-2-azapurine 1-N-oxide upon nitrosation.

Many of the aza derivatives of the purines (see Scheme 1), materials in which either the 2- or the 8-methylidyne (—CH=) groups are replaced by aza (—N=) moieties, show antimetabolite action in microbiological systems[2,3] and in *Tetrahymena geleii*.[4,5] In addition certain azapurines, notably 8-azaguanine, are incorporated into tobacco mosaic virus nucleic acid[6,7] and cause inhibition of the growth of certain forms of carcinoma and sarcoma of animals[8] and of lymphoid leukemia in mice.[9] Oxidation of these aza compounds to N-oxides might be expected to give compounds which, on administration to an animal, might be reduced slowly to the parent azapurine in a similar manner to the observed reduction of adenine 1-N-oxide[10] (I) by the rat, and might be expected to act as pools of azapurine antimetabolites.

8-Azaadenine[2] (II) (7-amino-3H-*v*-triazolo[4,5-d]pyrimidine) is found to give an N-oxide upon oxidation with mixtures of acetic acid and hydrogen peroxide. Because of the formation of by-products the yield of N-oxide isolated is only 56%. From the similarity of this N-oxide to adenine 1-N-oxide (6-aminopurine 1-N-oxide) in spectra and behavior upon hydrolysis, it is concluded that the major oxidation product of 8-azaadenine is the 1-N-oxide. Reduction of the 8-azaadenine 1-N-oxide (III) with hydrogen in the presence of Raney nickel results in 8-azaadenine. In an analogy to adenine 1-N-oxide[11] the 8-azaadenine 1-N-oxide is readily hydrolyzed by acid to give 4-amino-1,2,3-triazole-5-carboxamidoxime (IV). Further hydrolysis gives 4-amino-1,2,3-triazole-5-carboxamide (V),[12] confirming the 1-N-oxide structure of the main oxidation product of 8-azaadenine. V is an analog[6] of the purine precursor, 4-aminoimidazole-5-carboxamide. Hydrogenation of IV yields 4-amino-1,2,3-triazole 5-carboxamidine (VI). These triazole derivatives closely resemble the corresponding imidazole derivatives obtained from adenine 1-N-oxide, except they do not give colored diazo derivatives with diazotized sulfanilic acid (Pauly reagent). The unidentified oxidation products of 8-azaadenine exhibit no characteristic N-oxide absorption at 230 mμ.

In the case of 2-azaadenine[3] (4-amino-7-imidazo-[4,5-d]-*v*-triazine) (VII) oxidation by a mixture of hydrogen peroxide and acetic acid at room temperature causes partial conversion to an oxide. If oxidation of 2-azaadenine is carried out at elevated temperature (60°), the reaction proceeds to complete loss of the starting material and the formation of two N-oxides in relative amounts of 3 to 1. The N-oxide formed at room temperature is the same as the major product of the oxidation at 60°.

The structure of these oxides of 2-azaadenine cannot be proved by the methods used for determining the structure of adenine 1-N-oxide and 8-azaadenine 1-N-oxide. Both of the 2-azaadenine oxides are resistant to hydrolysis with hot concentrated acid, and cannot be hydrogenated over nickel to 2-azaadenine. From their analyses both are monoxides. Both have spectra resembling that of adenine 1-N-oxide, with strong absorption in the 230–240 mμ region.[11] In the case of the 2-azaadenine N-oxide which most closely resembles adenine 1-N-oxide in spectrum (the oxide formed in the higher yield), the structure can be proved to be that of the 1-N-oxide by an alternate, unambiguous synthesis from 4-aminoimidazole-5-carboxamidoxime (VIII) and nitrous acid. This alternative synthesis gives 2-azaadenine 1-N-oxide (IX) in 80% yield. For the structure of the second 2-azaadenine N-oxide a 2- or 3-N-oxide structure (X) is favored, since Timmis[13] has demonstrated that purines oxidized on the imidazole moiety are acid labile.

A preferential ring closure of several carboxamidoxime derivatives upon treatment with nitrous

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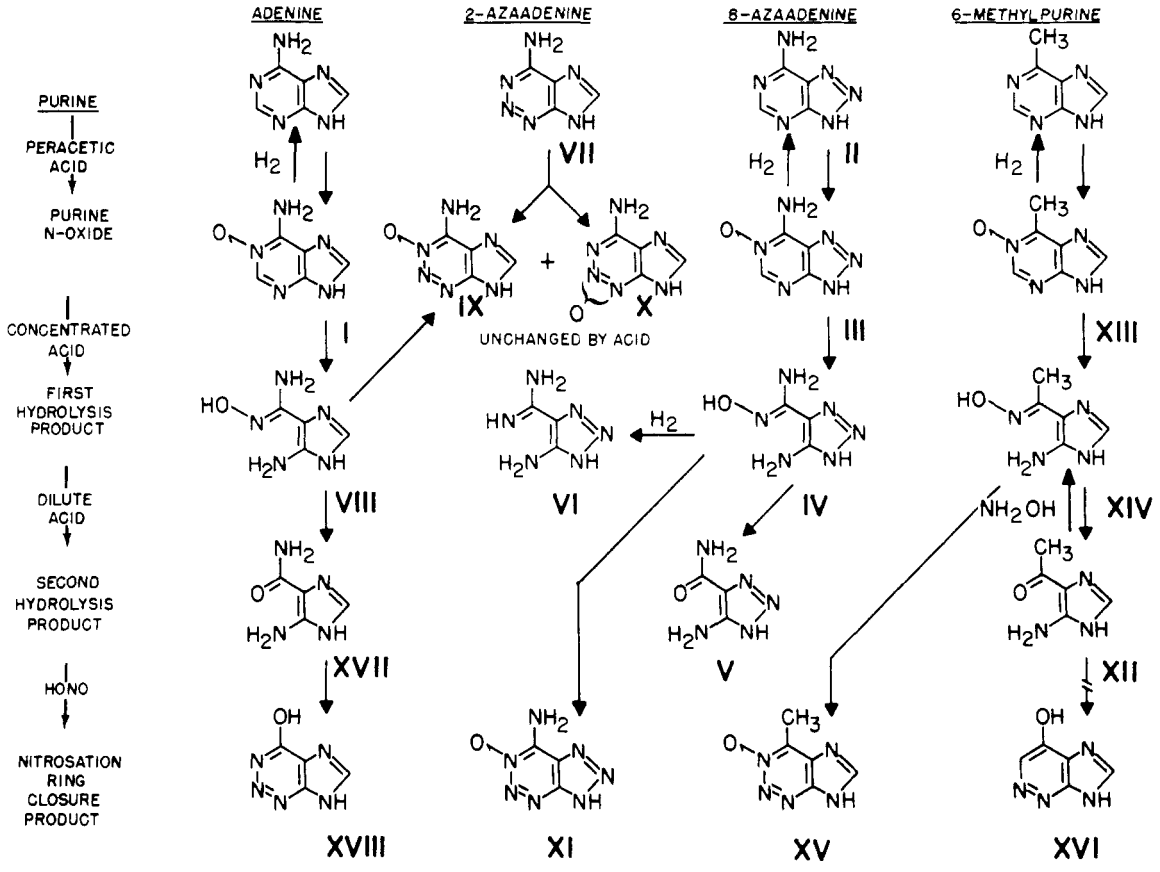

SCHEME 1.

acid, to lead to an N-oxide of a heterocycle rather than to a hydroxylamino-heterocycle, appears to be quite general, and similar to a ring closure observed with a ketoxime.[14] For instance, 1-ribosyl 4-aminoimidazole-5-carboxamidoxime, obtained by hydrolysis of adenosine 1-N-oxide[15] with dilute alkali,[16] yields 2-azaadenosine 1-N-oxide with nitrous acid. Similarly, the product of the acid hydrolysis of 8-azaadenine 1-N-oxide, 4-amino-1,2,3-triazole-5-carboxamidoxime (IV), gives a product which is apparently 2,8-diazaadenine 1-N-oxide (XI). The latter closely resembles 2-azaadenine 1-N-oxide in its ultraviolet absorption spectrum, although satisfactory nitrogen analyses were difficult to obtain.

As a variation of the reaction of a carboxamidoxime with nitrous acid to give an aminopurine oxide, it should be possible[14] to prepare a 6-CH_3 substituted azapurine oxide from a compound containing an acetyloxime group ($CH_3C{=}NOH$) instead of a $NH_2C{=}NOH$ group. From 4-amino-5-acetylimidazole[17] (XII), the hydrolysis product of 6-methylpurine 1-N-oxide (XIII), it was possible to prepare the oxime XIV and then treat it with nitrous acid to give 6-methyl-2-azapurine 1-N-oxide (XV). The characteristic ultraviolet spectrum of purine N-oxides, with the high 230 mμ absorption at most *p*H's, is again found with this N-oxide.

Because of the similarity between 4-acetyl-5-aminoimidazole (XII) and 4-aminoimidazole-5-carboxamide (XVII), it would be expected that, by analogy with the conversion of XVII to 2-azahypoxanthine[3] (XVIII) 4-acetyl-5-aminoimidazole might give a pyridazine derivative (XVI) on nitrosation. This does not occur, however. An unusually stable diazonium chloride of XII can be isolated in an impure state. When heated, it loses nitrogen and gives a product which analysis indicates could be the 4-acetyl-5-chloroimidazole.

Experimental

All chromatographic analyses were performed, ascending, on Whatman No. 1 paper at 25° with solvents: A, 1% ammonium sulfate–isopropyl alcohol, 1:2 vol./vol., paper previously soaked in 1% ammonium sulfate and dried[18]; and B, 5% disodium phosphate–isoamyl alcohol, 3:2 vol./vol.[19] R_f-values are given in Table I. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer, and the extinction coefficients with a Beckman DU spectrophotometer.

Preparation of 8-Azaadenine 1-N-Oxide (III).—8-Azaadenine (1 g.) was dissolved in boiling acetic acid (70 ml.). The solution was cooled, diluted with 30% hydrogen peroxide (4 ml.) and stirred at room temperature (25–30°). The slurry that first formed went into solution after 2 days, and after 5 days the solution had again turned into a slurry. The solid material (0.65 g., 56.4%) was collected and re-

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TABLE I

Substance	Decomp. point, °C.	Rf A[a]	Rf B[a]	Other	Spectral data: Maxima, mμ at	pH
2-Azaadenine	>350	0.57	0.38	...	259, sh. 278–290	6.5[b]
2-Azaadenine 1-N-oxide	>350	.43	.49	...	232, 273, 328	8.0
					232, 272, 335	6.0
					230, 270, 335	2.0
2-Azaadenine 2(or 3)-N-oxide	>350	.45	.38	...	222, 235, 287, 316	11.0
					240, 280	6.5
					239, 280	2.0
8-Azaadenine	>310	.68	.30	...	275	11.0
					209, 275	7.0[c]
					270	3.0
8-Azaadenine 1-N-oxide	Over a range	.55	.50	...	234, 302	12.5[d]
					231, 272	6.2
					235, 262	3.8
4-Amino-1,2,3-triazole-5-carboxamidoxime	HCl, 172	.59[f]	.62	0.43[e]	211, 237, 260	1.3
					264	13.0
					262	4.0
4-Amino-1,2,3-triazole-5-carboxamidine	295	.25	.65	.47[e]	217, 268	1.0
					261	13.0
					274	5.0
					270	2.0
4-Amino-1,2,3-triazole-5-carboxamide	To 228	[f]	.74	.49[e]	266	12.0
					224, 261	7.0
					223, 261	2.0
2,8-Diazaadenine 1-N-oxide	206	.60	.48	...	221, 370 (sh. 280–285, 240–245)	12.5
					225, 241, 276, 348	5.0
					218, 245, 277, 362	2.0
6-Methyl-2-azapurine 1-N-oxide	230	.58	.58	...	244, 283, 330	12.0
					240, 278, 330	6.0
					239, 279, 330	2.0
2-Azaadenosine 1-N-oxide	165–170 melts	.49	.74	...	260, 370	12.0
	195–200 decomp.				223, 246, 352, 270 (sh.)	10.4
					224, 245, 272, 350	7.0
					224, 246, 272, 347	2.0

[a] For solvents A and B see Experimental. [b] Ref. 3, a_M 7.2 × 10³. [c] Ref. 2. [d] a_M 14.6 and 6.9 × 10³ at *p*H 12.5, a_M 27.2 and 6.1 × 10³ at *p*H 6.2, a_M 20.8 and 6.1 × 10³ at *p*H 3.8; a_M 14.9, 7.7 and 8.7 × 10³ at *p*H 1.3. [e] Isopropyl alcohol–HCl (G. R. Wyatt, *Biochem. J.*, **48**, 584 (1951)). [f] Variable.

crystallized from hot water. The material obtained from the slurry was virtually pure 8-azaadenine 1-N-oxide. After recrystallization from water, the oxide was obtained as fine buff-colored crystals which decomposed over a wide range starting at 120° and which, after drying at 90° for 3 hours over phosphorus pentoxide, was analyzed.

Anal. Calcd. for $C_4H_4N_6O$: C, 31.58; H, 2.64; N, 55.25. Found: C, 31.53; H, 3.04; N, 54.74.

The mother liquors from the filtration of the 8-azaadenine 1-N-oxide precipitate were found to contain a further component, R_f in solvent A of 0.67 and R_f in solvent B of 0.62. This does not possess the high absorption at 230 mμ which is characteristic of purine and azapurine 1-N-oxides.

Hydrogenation of 8-Azaadenine 1-N-Oxide.—8-Azaadenine 1-N-oxide (9.9 mg.) was dissolved in water (9 ml.) and hydrogenated at 40° for 2 hours in the presence of Raney nickel (12 mg.). During this time 2.0 ml. of hydrogen was taken up, about 25% in excess of one molar proportion of hydrogen. Aliquots of the solution after hydrogenation were chromatographed on paper in solvents A and B. In both systems the major product had an R_f identical with 8-azaadenine and after elution from the paper had a spectrum identical with 8-azaadenine. The small amount of by-product showing on the chromatogram is thought to be a further hydrogenation product of 8-azaadenine.

Oxidation of 2-Azaadenine (VII).—A suspension of 2-azaadenine (680 mg.) in a mixture of acetic acid (50 ml.) and 30% hydrogen peroxide (10 ml.) was stirred at 60–65° for a total of 20 hours. Three hours after the start of this oxidation chromatographic analysis of the mixture showed it to contain mainly starting material, but also two oxides. During the oxidation most material remained undissolved. It was found, however, that the material in suspension after 17 hours was solely a mixture of two oxides. The suspension was filtered hot and the solid obtained (630 mg., 84%) was washed with acetic acid. Dissolution of this light yellow solid in 6% ammonium hydroxide (14 ml.) at 65° followed by adjustment of the *p*H of the solution to 8 by the slow addition of 60% aqueous acetic acid gave a precipitate of 2-azaadenine 2(or 3)-N-oxide (X) (113.5 mg., 15%), decomposition point above 350°. This oxide after filtering from the solution and washing with a little acetic acid was found to be chromatographically pure. Adding 60% acetic acid dropwise to the filtrate until it had a *p*H of 6.5 caused precipitation of pure 2-azaadenine 1-N-oxide (IX) (393 mg., 52%). This oxide darkens slightly on heating to 115–120° but does not decompose completely until over 350°. The latter oxide was shown to be identical, in spectra and R_f in solvents A and B, to the product of the reaction of 4-aminoimidazole-5-carboxamidoxime with nitrous acid. Before analysis both 2-azaadenine N-oxides were dried at 57° in vacuum over phosphorus pentoxide for 3 hours.

Anal. Calcd. for $C_4H_4N_6O$: C, 31.57; H, 2.64; N, 55.25. Found: 1-N-Oxide: C, 31.73; H, 2.85; N, 55.02. 2(or 3)-N-Oxide: C, 31.74; H, 2.76; N, 54.96.

Alternative Synthesis of 2-Azaadenine 1-N-Oxide (IX).—Adenine 1-N-oxide (2 g.) was dissolved in 3 *N* hydrochloric acid (40 ml.) and the solution was boiled for 10 minutes to effect hydrolysis to 4-aminoimidazole-5-carboxamidoxime. The carboxamidoxime dihydrochloride was isolated in a virtually pure state by evaporating the hydrolysate at room temperature *in vacuo*. The 4-aminoimidazole-5-carboxamidoxime dihydrochloride was dissolved in water (100 ml.) and the stirred solution was treated at 0° with a solution of sodium nitrite (900 mg.) in water (50 ml.) at the rate of 2 ml./min. The color of the solution changed

during the addition of the nitrite from green to brown to purple. The precipitate started to form half way through the nitrite addition. The suspension was allowed to warm to room temperature, and the purple solid (1.60 g. after drying, 80%) was collected by filtration. The product was found by chromatography to be virtually pure 2-azaadenine 1-N-oxide. Solution of this solid in a mixture of hot water (300 ml.) and 6% ammonium hydroxide (5 ml.), treatment with Norite, filtering, and treatment of the hot solution with acetic acid (1 ml.), followed by cooling, gave a light yellow solid (1.40 g., 70%). This solid was identical in R_f, spectra, and decomposition point to the 2-azaadenine 1-N-oxide prepared by the oxidation of 2-azaadenine with hydrogen peroxide–acetic acid.

Preparation of 2-Azaadenosine 1-N-Oxide.—Adenosine 1-N-oxide (5 g.) was boiled for 9 minutes with 3 *N* sodium hydroxide (75 ml.), cooled, made acid with glacial acetic acid and treated with sodium nitrite (1.5 g.). The dark red solution so formed was diluted with water (500 ml.), taken to *p*H 7 with 2 *N* sodium hydroxide solution and passed through a column of 275 ml. of Dowex 50 (H^+ form). During absorption and subsequent elution from this column, it was kept at 0°. Part of the 2-azaadenosine 1-N-oxide was absorbed on the column together with the sodium ion, but a substantial proportion came through with the effluent. This effluent was evaporated under vacuum at room temperature to give a red solid which upon recrystallization from hot 90% ethanol (60 ml.) gave an orange solid (235 mg.). The crystallization of the 2-azaadenosine 1-N-oxide took place over a period of 10 days, even after seeding. The column was washed with water (1000 ml.), 2 *N* aqueous acetic acid (2000 ml.) and the eluates combined and evaporated at room temperature to a red solid. After recrystallization from 90% ethanol this gave 400 mg. of 2-azaadenosine 1-N-oxide, dec. 195–200° (total yield 635 mg., 13%).

Anal. Calcd. for $C_9H_{12}N_6O_5$: C, 38.02; H, 4.25; N, 29.56. Found: C, 38.07; H, 4.25; N, 29.43.

Hydrolysis of 2-azaadenosine 1-N-oxide (20 mg.) with boiling 2 *N* HCl (15 ml.) gave a product, after evaporation of the HCl, identical in R_f in solvents A and B and in spectrum with 2-azaadenine 1-N-oxide.

Prolonged hydrogenation of the oxide over Raney nickel at 35° gave an unidentified product.

Preparation of 4-Amino-1,2,3-triazole-5-carboxamidoxime (IV).—8-Azaadenine 1-N-oxide (280 mg.) was suspended in concentrated (36%) HCl (2 ml.). After 5 minutes at room temperature the oxide had hydrolyzed and gone into solution. The mixture was evaporated at room temperature under vacuum to a yellow-green solid. This solid was treated with hot methanol (3 ml.). The insoluble portion (66 mg.) was collected, and the soluble fraction evaporated to half volume and treated with a small amount of ether. The insoluble portion and the fraction crystallizing from the methanol–ether were both virtually pure 4-amino-1,2,3-triazole-5-carboxamidoxime hydrochloride. A fraction crystallizing from the methanol later was less pure. A total of 260 mg. (81%) of carboxamidoxime was obtained, and the residue (28 mg.) from the mother liquors also was mainly carboxamidoxime. 4-Amino-1,2,3-triazole-5-carboxamidoxime hydrochloride crystallizes from methanol in light orange-yellow crystals, decomp. point 174°.

Anal. Calcd. for $C_3H_7N_6OCl$: C, 20.18; H, 3.95; N, 47.06. Found: C, 20.73; H, 3.94; N, 47.46.

The carboxamidoxime gives a dark brown color with ferric chloride solution.

Preparation of 4-Amino-1,2,3-triazole-5-carboxamidine (VI).—4-Amino-1,2,3-triazole-5-carboxamidoxime hydrochloride (236 mg.) was dissolved in 10% aqueous potassium carbonate solution (10 ml.) and hydrogenated at 40°, over Raney nickel (30 mg.) at atmospheric pressure. After 6 hours, uptake of hydrogen substantially ceased at 29.5 ml. (30.0 ml. theoretical). Chromatographic analysis showed the solution to contain only one substance, so the yield is indicated to be essentially quantitative. When the solution was filtered, evaporated to 2 ml., and allowed to crystallize at 5°, 4-amino-1,2,3-triazole-5-carboxamidine (70 mg., 41%) precipitated from the solution. Recrystallization of this from 75% aqueous ethanol gave white crystals which decomposed over a range, with most rapid decomposition and browning of crystals at about 295°.

Anal. Calcd. for $C_3H_6N_6$: C, 28.57; H, 4.80; N, 66.64. Found: C, 28.82; H, 4.83; N, 66.65.

Preparation of 4-Amino-1,2,3-triazole-5-carboxamide (V).—4-Amino-1,2,3-triazole-5-carboxamidoxime monohydrochloride (255 mg.) was dissolved in water (80 ml.) and heated under pressure at 150° for 8 hours. After cooling, a red precipitate (20 mg.) in the solution was collected and discarded. The filtrate was evaporated to a volume of 3 ml. and set aside to crystallize. A light yellow solid (71 mg., 39%) slowly separated. The 4-amino-1,2,3-triazole-5-carboxamide was recrystallized from acetic acid and then from water to give yellow needles, m.p. 225° dec.

Anal. Calcd. for $C_3H_5N_5O$: C, 28.35; H, 3.96; N, 55.10. Found: C, 28.59; H, 4.18; N, 55.25.

On a chromatogram the carboxamide differed from the carboxamidoxime in having a fluorescence in ultraviolet light.

Preparation of 2,8-Diazaadenine 1-N-Oxide (XI).—8-Azaadenine 1-N-oxide (400 mg.) was added to 2 *N* HCl (25 ml.) and the suspension was heated to 75–80° for 20 minutes. The resulting yellow-green solution of 4-amino-1,2,3-triazole-5-carboxamidoxime hydrochloride was cooled to 5° and treated with a solution of sodium nitrite (200 mg.) in water (5 ml.). The light yellow solid which separated from the solution during the first 3 hours was found to be nearly pure 2,8-diazaadenine 1-N-oxide. After filtering this solid (120 mg.) from the solution, the mother liquor was allowed to stand overnight in a refrigerator. A second crop of chromatographically-pure 2,8-diazaadenine 1-N-oxide (120 mg., total yield 60%) separated. This was collected, washed with water (3 ml.) and dried in a desiccator at room temperature. This was analyzed directly, since recrystallization is complicated by the instability of the compound.

Anal. Calcd. for $C_3H_3N_7O$: C, 23.53; H, 1.97; N, 64.05. Found: C, 22.46; H, 2.22; N, 62.34.

On the same sample nitrogen determinations varied between 57.63 and 62.34. This sample decomposed explosively on heating to 206°. On other samples of the oxide decomposition points of up to approximately 300° were recorded depending on the rate of heating and the purity. If the pure oxide is dried at elevated temperatures (50–100°) it slowly loses nitrogen.

ADDENDUM IN PROOF.—A homogeneous sample of a by-product encountered in the preparation of 2,8-diazaadenine 1-N-oxide, particularly at other than low temperatures, has now been obtained. At 25–30°, in 1 *N* HCl solution, the 4-amino-1,2,3-triazole-5-carboxamidoxime reacted with $NaNO_2$ in 2–3 minutes to give a yellow, chromatographically pure precipitate. This product explodes on heating to 230° and microanalytical evidence suggests that it is the 4-hydroxy derivative of 1,2,3-triazole-5-carboxamidoxime hydrochloride.

Anal. Calcd. for $C_3H_6N_5O_2Cl$: N, 39.00; Cl, 19.18. Found: N, 38.68; Cl, 19.41.

Preparation of 6-Methyl-2-azapurine 1-N-Oxide (XV).—Hydroxylamine hydrochloride (306 mg.) was added to a solution of 4-acetyl-5-amino-imidazole hydrochloride (370 mg.) in methanol (50 ml.). The resulting solution was refluxed for 94 hours and was evaporated *in vacuo* to a green solid. *n*-Butyl nitrite (3 ml. in 7 ml. of acetic acid) was added slowly to a solution of this green solid in a mixture of acetic acid (75 ml.) and water (10 ml.). During the early stages of the addition the color of the solution changed to dark red which faded slowly. The mixture was kept at 5° overnight, then evaporated *in vacuo* to dryness. A small quantity of ethanol was added to the orange gum formed from the evaporation which caused the gum to solidify. The ethanol was evaporated and the pale orange powder was taken up in hot methanol (40 ml.). Upon cooling, 65 mg. 20% of substantially pure 6-methyl-2-azapurine 1-N-oxide precipitated. Further recrystallization from water gave a light yellow sample (20 mg.) of the oxide with a decomposition point of 230°.

Anal. Calcd. for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.35. Found: C, 39.77; H, 3.50; N, 46.52.