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PURINE N-OXIDES XXIV. THE PREPARATION OF 8-SUBSTITUTED XANTHINES AND GUANINES BY A NUCLEOPHILIC DISPLACEMENT OF A 3-SUBSTITUENT

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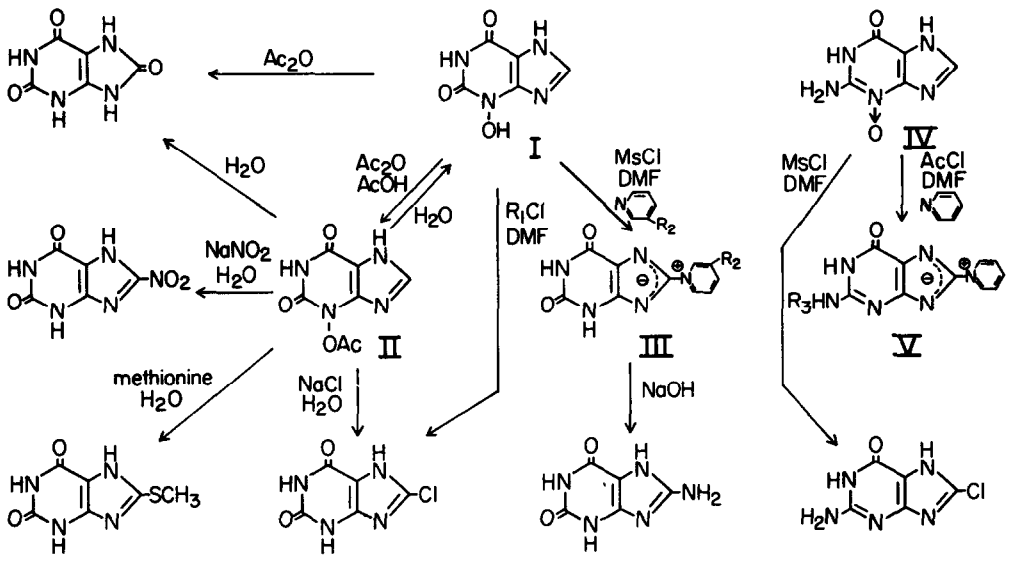
In a recent publication (2) on the rearrangement of purine 3-N-oxides to 8-hydroxypurines in acid anhydrides, a postulated intermediate was the O-acyl derivative of the N-oxide. Such an intermediate, 3-acetoxyxanthine (II), [$\lambda_{max}^{pH\ 5}$ 267 mμ (ϵ 14,000)], has now been prepared by the treatment of 3-hydroxyxanthine (I) (3), with acetic acid/acetic anhydride at room temperature for 6 days. The structure of II is supported by the facts: (a) II gives uric acid in refluxing acetic anhydride in the time required for I to form uric acid under the same conditions. (b) The IR spectrum, (KBr) $\nu C{=}O$ 1820 cm^{-1}, supports an $O\text{-}COCH_3$ rather than a $N\text{-}COCH_3$ structure (4). (c) The NMR spectrum is in agreement with the structure II. (d) I forms an immediate purple color with ferric chloride, but II develops this color slowly.

In water at room temperature II reacts (half-life of 50 min.) to give uric acid and I. In the presence of methionine, sodium nitrite, and sodium chloride, 8-methylmercaptoxanthine (5), 8-nitroxanthine (6), and 8-chloroxanthine (7), respectively, are produced [Table I]. In these reactions II is always partially hydrolyzed to I.

The reaction of 3-hydroxyxanthine (I) with various acid chlorides in DMF leads directly to 8-chloroxanthine [Table I], presumably <u>via</u> the 3-acyloxy (or sulfonyloxy)-xanthine, which is not hydrolyzed in the dipolar aprotic solvent. When pyridine is added to a stirred suspension of I and mesyl chloride in DMF at 0°, a bright yellow compound, 8-(N-pyridinium)xanthine (IIIa) [$\lambda_{max}^{pH\ 2}$ 372, 266; 242, $\lambda_{max}^{pH\ 10}$ 414, 275, 250] is formed. In the NMR spectra (CF_3CO_2H) the pyridine protons of IIIa and of N-methylpyridinium methosulphate show identical patterns. In addition, IIIa is hydrolyzed by 2 <u>N</u> NaOH at 75° to 8-aminoxanthine (8). With nicotinic acid and nicotinamide instead of pyridine, 8-(N-3-carboxypyridinium)xanthine IIIb and 8-(N-3-carbamoyl-pyridinium)xanthine IIIc are formed.



R_1 = Ms, Ts, Ac, SO_3H $\quad$ R_2 = H (IIIa), CO_2H (IIIb), $CONH_2$ (IIIc) $\quad$ R_3 = Ac (Va), H (Vb)

The reaction has been extended to guanine 3-oxide (IV) (3). With mesyl chloride in DMF, IV gives 8-chloroguanine [UV $\lambda_{max}^{pH\ 0}$ 270, 250 sh; $\lambda_{max}^{pH\ 11}$ 277, 260 sh]. Its NMR spectrum (CF_3CO_2H) shows no peak for a C-8 proton, and the UV spectrum is similar to that of 8-bromoguanine [$\lambda_{max}^{pH\ 11}$ 278, 260 sh] (9). Addition of pyridine to a solution of IV and acetyl chloride in DMF forms N^2-acetyl-8-(N-pyridinium)guanine (Va) [UV $\lambda_{max}^{pH\ 0}$ 347, 275, 243; $\lambda_{max}^{pH\ 5}$ 370, 270 sh, 248; $\lambda_{max}^{pH\ 11}$ 394, 250; NMR (DMSO-d_6) CH_3CONH- 7.85 τ, cf. CH_3CONH- 7.85 τ for N^2-acetyl-8-methylguanine]. The pyridine protons of Va show the same pattern as those of IIIa in their NMR spectra. Acid hydrolysis of Va gives 8-(N-pyridinium)guanine [UV $\lambda_{max}^{pH\ 0}$ 347, 233; $\lambda_{max}^{pH\ 5}$ 386, 267.5, 244, 214; $\lambda_{max}^{pH\ 11}$ 420, 250.5].

We suggest that the N-O bond of the neutral molecule or of the monoanion of the 3-N-acyloxy-(or sulfonyloxy-)purine is cleaved heterolytically, and that a nucleophile attacks at the 8-position. A similar mechanism was proposed (2) for the rearrangement of 2-substituted purine 3-N-oxides in acid anhydrides.

TABLE I

Acid Chloride	Solvent	Nucleophile	Temp.	Time hr.	Product	Yield (%)
			3-ACETOXYXANTHINE			
None	H_2O	H_2O	23	24	Uric acid	12
					3-Hydroxyxanthine	70
''	H_2O	NO_2^-	23	24	8-Nitroxanthine	50
					Xanthine	20
					3-Hydroxyxanthine	9
''	H_2O	Cl^-	23	24	8-Chloroxanthine	42
					3-Hydroxyxanthine	27
					Xanthine	< 10
''	H_2O	Methionine	23	24	8-Methylmercaptoxanthine,	40
					3-Hydroxyxanthine	54
			3-HYDROXYXANTHINE			
AcCl	DMF	Cl^-	100	1	8-Chloroxanthine	40
TsCl	DMF	Cl^-	23	18	''	35
$ClSO_3H$	DMF	Cl^-	23	2	''	50
MsCl	DMF	Cl^-	23	1	''	65
MsCl	DMF	Pyridine	0	1	8-(N-Pyridinium)xanthine	65
MsCl	DMF	Nicotinic acid	0	1	8-(N-3-Carboxypyridinium)xanthine	20
MsCl	DMF	Nicotinamide	0	1	8-(N-3-Carbamoylpyridinium)xanthine	25
			GUANINE 3-OXIDE			
MsCl	DMF	Cl^-	23	1	8-Chloroguanine	75
AcCl	DMF	Pyridine	23	20	N^2-Acetoxy-8-(N-pyridinium)guanine	30

This unique reaction of I and IV is a method for the production of 8-substituted xanthines and guanines which would be difficult to synthesize by other means.

The reaction of 3-acetoxyxanthine in aqueous solution with methionine is reminiscent of that of N-acetoxy-2-acetamidofluorene (10) and of N-benzoyloxy-N-methyl-4-aminoazobenzene (11) with methionine. The latter N-acyloxy compounds are more proximate oncogens than the corresponding N-OH derivatives (12). The 3-acyloxy- or related derivatives of the oncogenic 3-hydroxyxanthine and guanine 3-oxide should be considered as possible proximate oncogens.

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