v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part XIII.[1] Reaction of 8-Azapurines with Bifunctional Nucleophiles

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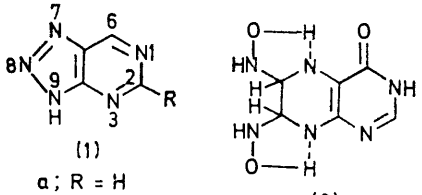
8-Azapurine and its 2-oxo- and 2-thioxo-derivatives were cleaved by 1,1-dimethylhydrazine to yield 4-dimethylhydrazonomethylamino- (7a), 4-ureido- (5a), and 4-thioureido- (5b) 1,2,3-triazole-5-carbaldehyde dimethylhydrazone,† respectively, and by hydrazine to give 4-amino- (9a), 4-ureido- (9b), and 4-thioureido- (9c) 1,2,3-triazole-5-carbaldehyde azine, respectively. 2-Amino-8-azapurine gave 4-hydrazonomethylamino-1,2,3-triazole-5-carbaldehyde hydrazone (7d).

With hydroxylamine, 8-azapurine and its 2-amino and 2-thioxo-derivatives yielded, respectively, 4-hydroxyiminomethylamino- (7b), 4-diaminomethyleneamino- (4a), and 4-thioureido- (5c) 1,2,3-triazole-5-carbaldehyde oxime, whereas the reaction with 8-azapurin-2(3*H*)-one stopped at the addition product 1,6-dihydro-6-hydroxyamino-8-azapurin-2(3*H*)-one (3a). Similarly 8-azapurine and methoxyamine yielded 5-methoxyiminomethyl-4-methoxyiminomethylamino-1,2,3-triazole (7c), whereas its 2-oxo-derivative gave 1,6-dihydro-6-methoxyamino-8-azapurin-2(3*H*)-one (3b).

^{1}H N.m.r. and u.v. spectra, and some pK_a values, are reported; their bearing upon the structures of the products and the reaction mechanisms is discussed.

THIS study continues our work on the reaction of 8-azapurines (1) with nucleophiles.[1,2] Recently interest has been shown in the cleavage of pteridines and pyrimido-[5,4-*e*]-*as*-triazines by bifunctional reagents, particularly hydrazine, methylhydrazines, hydroxylamine, and methoxyamine.[3-8] Clark *et al.*[6] suggested that the reactions involved preliminary addition of the reagents across a C=N bond [*e.g.* (2)], although no such adducts were isolated. This explanation was prompted by the addition reactions[9-14] given by pteridines and other highly π-deficient heterocycles. Thus we decided to investigate the effect of these bifunctional reagents on 8-azapurine and some 2-substituted derivatives (1a—d) for which we had already demonstrated additions at the 1,6-double bond.[2] The reactions were carried out at room temperature and in neutral or mildly alkaline aqueous solution.

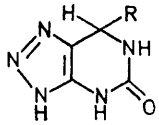
Four different modes of reaction were encountered. In the simplest of these (only two instances: the reactions of 8-azapurin-2(3*H*)-one with hydroxylamine and methoxyamine), the reagent added across the 1,6-double bond of azapurine to give the 6-substituted 1,6-dihydro-derivatives (3a and b). The u.v. spectra of these adducts resembled those of the 6-unsubstituted dihydro-compound[2] (3c) and the 1,6-hydrate (3d) (Table 1). ^{1}H N.m.r. spectroscopy revealed the expected[2,15] high-field signals for the C-6 protons of adducts (3a and b) at τ 4·70 and 4·60, respectively (Table 2), comparable with that of the structurally similar 1,6-methanol adduct of 8-azapurin-2(3*H*)-one[2] (τ 4·20), and in contrast to that of 8-azapurine (τ (0·32).[16a] The acidic and basic pK_a values of the hydroxylamine (3a) and the methoxyamine (3b) adducts are closely similar (see footnotes to Table 1), providing further evidence for the similarity of their structures. The basic pK_a values of both adducts are similar to that of the 1,6-dihydro-compound (3c). The fact that acidic pK_a values could be measured by the conventional spectroscopic method showed that these adducts were more stable than the corresponding hydrate (3d), which rapidly lost water on conversion into the anion.[16b]



(1)

a; R = H
b; R = NH_2
c; R = OH
d; R = SH

(2)



(3)

a; R = NH·OH
b; R = NH·OMe
c; R = H
b; R = OH

The second mode of reaction was exemplified by condensations of (*a*) 2-amino-8-azapurine with hydroxylamine, (*b*) 8-azapurin-2(3*H*)-one with dimethylhydrazine, and (*c*) 8-azapurine-2(3*H*)-thione with dimethylhydrazine and hydroxylamine, all of which gave 1 : 1 adducts. N.m.r. spectroscopy, however, gave signals for the CH protons of these compounds between τ 1·6 and 2·6, incompatible with structures similar to (3a and b). The ring-opened structures (4a) and (5a—c), respectively,

† In this paper the amino-group of aminotriazoles is consistently numbered 4, to facilitate comparisons.

[1] Part XII, A. Albert and W. Pendergast, preceding paper.
[2] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1972, 457.
[3] A. Albert and C. F. Howell, *J. Chem. Soc.*, 1962, 1591.
[4] J. Clark and G. Neath, *J. Chem. Soc.* (*C*), 1966, 1112.
[5] J. Clark and G. Neath, *J. Chem. Soc.* (*C*), 1968, 919.
[6] J. Clark, G. Neath, and C. Smith, *J. Chem. Soc.* (*C*), 1969, 1297.
[7] J. Clark and C. Smith, *J. Chem. Soc.* (*C*), 1969, 2777.
[8] J. Clark and C. Smith, *J.C.S. Perkin I*, 1972, 247.
[9] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[10] A. Albert and F. Reich, *J. Chem. Soc.*, 1961, 127.
[11] W. L. F. Armarego, *J. Chem. Soc.*, 1965, 5360.
[12] A. Albert and J. J. McCormack, *J. Chem. Soc.*, 1965, 6930.
[13] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117.
[14] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1968, 63.
[15] T. J. Batterham, *J. Chem. Soc.* (*C*), 1966, 999; J. Clark, *ibid.*, 1967, 1543; J. Clark and W. Pendergast, *ibid.*, 1968, 1124.
[16] (*a*) J. W. Bunting and D. D. Perrin, *J. Chem. Soc.* (*B*), 1966, 433; (*b*) A. Albert, *ibid.*, p. 427.

were assigned to these compounds (typical n.m.r. absorptions for ArCH=N– groups lie in this range [17]), analogous to the ring-opened products [*e.g.* (6)] (CH at τ 1·5—2·2) obtained from the same azapurines with actions with dimethylhydrazine and methoxyamine had methyl groups of slightly differing chemical shift. Thus the products were assigned the structures (7a—c). If only one equivalent of the reagent was used these products, rather than the amidines (4b), were still obtained, but in lower yield.

TABLE 1

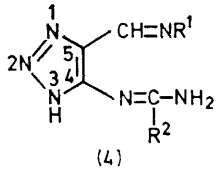
U.v. spectroscopy [a]

Compound	$\lambda_{max.}$/nm	log ε	Solvent [b]
1,6-Dihydro-8-azapurin-2(3*H*)-ones			
6-hydroxyamino (3a) [c]	209, 242	3·79, 3·84	2
6-methoxyamino (3b) [d]	210, 241	3·79, 3·88	2
Unsubstituted (3c) [e]	247	3·77	3
6-hydroxy (3d) Neutral species (for comparison) [f]	209, 241	3·73, 3·82	2·5
8-Azapurin-2(3*H*)-one (anion) [Anhydrous anion of (3d)] (for comparison) [f]	210, *276*, 311	4·17, *3·66*, 3·83	8·3
1,2,3-Triazole-5-carbaldehyde:			
oximes,			
4-hydroxyiminomethylamino (7b)	261, *290*	3·75, *3·44*	M
4-diaminomethyleneamino (4a)	218, 272	4·24, 3·86	M
4-thioureido (5c)	248, 268, *280*	4·19, 4·16, *4·13*	M
O-methyloxime,			
4-methoxyiminomethylamino (7c)	223, 262, *290*	4·19, 4·11, *3·91*	M
hydrazone,			
4-hydrazonomethylamino (7d)	276	4·06	M
dimethylhydrazones,			
4-dimethylhydrazonomethylamino (7a)	231, *243*, 292	4·01, *3·99*, 4·16	M
4-ureido (5a) [g] Cation	207, 236, 283	4·03, 3·73, 3·90	0·5
Neutral species	230, 292	3·92, 4·05	5
Anion	226, 289	3·78, 4·02	10
4-thioureido (5b)	260, *300*	4·38, *4·17*	M
azines,			
4-amino (9a)	249, 346	3·85, 4·37	4% Me_2SO–M
4-ureido (9b)	347	4·28	20% Me_2SO–M
4-thioureido (9c)	267, 364	4·69, 4·31	4% Me_2SO–M

[a] Of neutral species except where otherwise indicated. Inflexions in italics. [b] M = Methanol. Me_2SO–M signifies a methanolic solution of dimethyl sulphoxide of the stated v/v concentration. Numerals refer to the pH of aqueous buffers. [c] Basic $pK_a = -1·43 \pm 0·05$; acidic $pK_a = 6·45 \pm 0·03$. [d] Basic $pK_a = 1·45 \pm 0·03$; acidic $pK_a = 6·48 \pm 0·05$. [e] Basic $pK_a = -1·36 \pm 0·05$; all values from ref. 2. [f] Values from ref. 16b. [g] Basic $pK_a = 2·49 \pm 0·02$; acidic $pK_a = 7·75 \pm 0·05$.

certain strongly activated methylene compounds.[1] U.v. spectroscopy provided additional evidence for ring-opening, as follows. Simple adduct formation in fully aromatic azapurines.[2,15b] as in other highly π-deficient heteroaromatic systems,[9] is known to cause a large hypsochromic shift (25—90 nm for azapurines) of the long wavelength absorption, reflecting the decrease in conjugation. However these new adducts have absorptions at much longer wavelength (270—300 nm) (Table 1). 2-Amino-8-azapurine did not react with dimethylhydrazine or methoxyamine.

8-Azapurine with a fourfold excess of dimethylhydrazine, hydroxylamine, or methoxyamine in each case gave a crystalline product which elemental analysis indicated contained two reagent units. This exemplified the third mode of reaction. N.m.r. spectroscopy showed two distinct low-field singlets in each case (Table 2) which demonstrated (*a*) that the pyrimidine ring had been cleaved, and (*b*) that the original azapurine 2-CH had been retained. Further, each product from re-

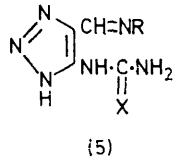


(4)

a; $R^1 = OH, R^2 = NH_2$

b; $R^1 = OH, OMe,$ or $NMe_2, R^2 = H$

c; $R^1 = R^2 = NH_2$

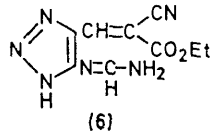


(5)

a; $R = NMe_2, X = O$

b; $R = NMe_2, X = S$

c; $R = OH, X = S$



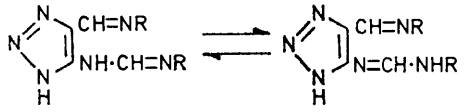
(6)

4-Hydroxyiminomethylamino-1,2,3-triazole-5-carbaldehyde oxime (7b) gave 4-amino-1,2,3-triazole-5-carbaldehyde oxime (8) when refluxed with aqueous acetic

[17] H. A. Szymanski and R. E. Yelin, ' N.m.r. Band Handbook,' I. F. I. Plenum, New York, p. 246.

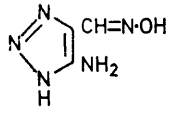
acid for 2 h. 2-Amino-8-azapurine reacted with two mol. equiv. of hydrazine to give the related product (7d), readily distinguished from another possible isomeric structure (4c) by the presence of signals for two non-exchangeable low-field protons in the n.m.r. spectrum (Table 2).

In the fourth mode of reaction, 8-azapurine and its 2-oxo- and 2-thioxo-derivatives reacted with hydrazine

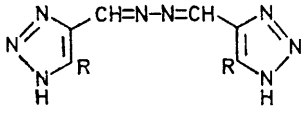


(7)

a; R = NMe_2
b; R = OH
c; R = OMe
d; R = NH_2



(8)

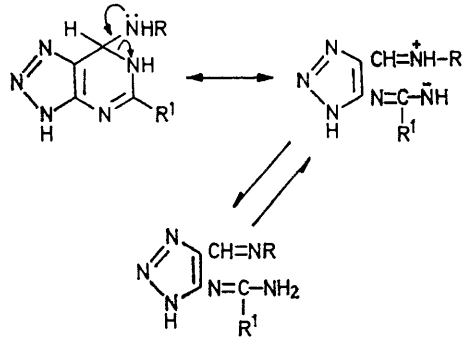


(9)

a; R = NH_2
b; R = NH·CO·NH_2
c; R = NH·CS·NH_2

to yield 4-amino- (9a), 4-ureido- (9b), and 4-thioureido- (9c) 1,2,3-triazole-5-carbaldehyde azine, respectively. Structures were assigned on the basis of elemental analysis and the n.m.r. spectra; low-field protons in the latter (Table 2) indicated ring-opening, and u.v. spectroscopy showed long-wavelength absorptions (346—364 nm) indicative of extended conjugation.

Discussion.—8-Azapurine and its 2-substituted derivatives showed no tendency to react with ammonia or with primary amines of basic strengths similar to those of the bifunctional reagents. The bifunctional nucleophiles are more reactive than simple amines because of the unshared pair of electrons on the electronegative atom



SCHEME 1

adjacent to the nucleophilic centre. The extra nucleophilicity with which this property endows the bifunctional reagents is known as the ' α-effect '.[18]

[18] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.

Thus 8-azapurin-2(3*H*)-one forms stable 1,6-adducts (3) with hydroxylamine and methoxyamine, additional stability being conferred by urea-type resonance [9] in the pyrimidine ring. When this special stabilisation is absent, or when the α-effect is more powerful (as with hydrazines) cleavage of the pyrimidine ring occurs. We suggest that, after a 1,6-adduct is formed, the lone pair of electrons on the nitrogen atom adjacent to the ring participates in a rapid ring-opening reaction as indicated in Scheme 1.

TABLE 2

^{1}H N.m.r. spectroscopy [a]

Compound	τ [b]	Assignment
1,6-Dihydro-8-azapurin-2(3*H*)-ones		
6-hydroxyamino (3a)	4·70	H-6
6-methoxyamino (3b)	4·60	H-6
6-methoxy (for comparison)	4·20	H-6
	6·77 (3) [c]	OCH_3
1,2,3-Triazole-5-carbaldehyde:		
oximes,		
4-hydroxyiminomethylamino (7b)	1·64 [d]	5-Oxime
	2·37 [d]	4-Substituent
4-diaminomethyleneamino (4b) [f]	2·45	5-Oxime
4-amino (8)	1·80	5-Oxime
4-thioureido (5c)	1·62	5-Oxime
O-methyloxime,		
4-methoxyiminomethylamino (7c)	1·44 [d]	5-Oxime
	2·68 [d]	4-Substituent
	6·00 (3) [e]	OCH_3
	6·12 (3) [e]	OCH_3
hydrazone,		
4-hydrazonomethylamino (7d)	2·08	5-Hydrazone
	3·00	4-Substituent
dimethylhydrazones,		
4-dimethylhydrazonomethylamino (7a)	2·27 [d]	5-Hydrazone
	2·41 [d]	4-Substituent
	7·06 (6) [e]	NMe_2
	7·57 (6) [e]	NMe_2
4-ureido (5a)	2·60	5-Hydrazone
	7·04	NMe_2
4-thioureido (5b)	2·59	5-Hydrazone
	7·06	NMe_2
1,2,3-Triazole-5-carbaldehyde:		
azines,		
4-amino (9a)	1·20 (2)	Azine CH
4-ureido (9b)	0·90 (2)	Azine CH
4-thioureido (9c)	0·90 (2)	Azine CH

[a] Spectra were obtained in [$^2H_6$]dimethyl sulphoxide with tetramethylsilane as internal standard, except for the azines (9b and c) which were in N-NaOD and N-Na_2CO_3 in D_2O, respectively, with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard. [b] Only those signals which were not removed by addition of D_2O are reported. [c] Where the signal represents more than one proton, this figure is given in parentheses. [d,e] Assignments for these pairs of protons may be interchangeable. [f] Unstable in $(CD_3)_2SO$; equilibrium spectrum (rapidly attained on dissolution) showed signals for this triazole, 2-amino-8-azapurine (τ 0·8), and 4-amino-1,2,3-triazole (8) (τ 1·80) (40, 20, and 40 mol %, respectively). The presence of the decomposition products was confirmed by comparison with authentic materials on paper chromatography in butanol–5N-acetic acid (7 : 3), and in 3% ammonium chloride solution.

In azine formation, which occurs on reaction of hydrazine with 8-azapurine, or its 2-oxo or 2-thioxo-derivative, initial ring-opening probably follows a similar

TABLE 3

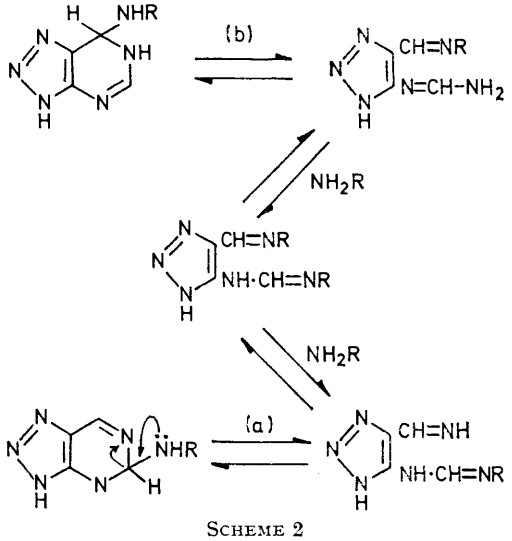
Reaction of 8-azapurines (*v*-triazolo[4,5-*d*]pyrimidines) with bifunctional nucleophiles

8-Azapurine	Reagent	Product	Yield (%)	M.p. (°C)	Analyses: Found (%) C	H	N	Formula	Required (%) C	H	N
		1,6-Dihydro-8-azapurin-2(3*H*)-ones									
2-Oxo	NH_2·OH	6-hydroxyamino (3a)	85	decomp. >200 [a]	28·2	3·8	49·4	$C_4H_6N_6O_2$	28·2	3·6	49·4
2-Oxo	NH_2·OMe	6-methoxyamino (3b)	62	188	32·8	4·8	45·4	$C_5H_8N_6O_2$	32·6	4·4	45·6
		1,2,3-Triazole-5-carbaldehyde:									
	NH_2·OH	oximes,									
Unsubstituted		4-hydroxyiminomethylamino (7b)	77	190 [b]	28·5	3·8	49·0	$C_4H_6N_6O_2$	28·2	3·6	49·4
2-Amino		4-diaminomethyleneamino (4b)	80	decomp. >250	28·0	4·5	57·3	$C_4H_7N_7O,0·25H_2O$	28·1	4·4	57·4
2-Thioxo		4-thioureido (5c) [c]	55	decomp. >200	25·7	3·4	44·7	$C_4H_6N_6OS$	25·8	3·3	45·1
	NH_2·NH_2	hydrazone,									
2-Amino		4-hydrazonomethylamino (7d)	90	decomp. >250	25·4	5·5	60·0	$C_4H_8N_8,H_2O$	25·8	5·4	60·2
	NH_2·NMe_2	dimethylhydrazones,									
Unsubstituted		4-dimethylhydrazonomethylamino (7a) [d]	81	151	42·6	7·2	50·2	$C_8H_{16}N_8$	42·8	7·2	50·0
2-Oxo		4-ureido (5a) [d]	63	209	36·5	5·8	49·6	$C_6H_{11}N_7O$	36·5	5·6	49·7
2-Thioxo		4-thioureido (5b) [d]	77	194	33·5	5·3	45·7	$C_6H_{11}N_7S$	33·8	5·2	46·0
	NH_2·OMe	*O*-methyloxime,									
Unsubstituted		4-methoxyiminomethylamino (7c) [d]	87	155	36·3	5·1	42·8	$C_6H_{10}N_6O_2$	36·4	5·1	42·4
	NH_2·NH_2	azines,									
Unsubstituted		4-amino (9a)	73	decomp. >200	32·7	3·9	63·5	$C_6H_8N_{10}$	32·7	3·7	63·6
2-Oxo		4-ureido (9b)	88	decomp. >300	31·1	3·5	54·7	$C_8H_{10}N_{12}O_2$	31·4	3·3	54·9
2-Thioxo		4-thioureido (9c)	72	decomp. >220	27·7	3·3	48·7	$C_8H_{10}N_{12}S_2,0·5H_2O$	27·7	3·2	48·4

[a] The product decomposed gradually above the stated temperature. [b] Decomposed explosively. [c] Crystallised from water (*ca.* 12 parts). [d] Crystallised from methanol.

course to that in Scheme 1, but the availability of a free NH_2 group allows reaction with a second azapurine molecule. The greater stability and extremely low water-solubility of these compounds must provide considerable driving force for the reactions.

The reactions of 8-azapurine with dimethylhydrazine, hydroxylamine, and methoxyamine, and of 2-amino-8-azapurine with hydrazine, differ in that two reagent residues are present in the products (7a—d). These may arise either *via* an attack of the reagent at the 2-position and subsequent imine exchange [Scheme 2(a)] or by attack at the 6-position, as in Scheme 1, followed by amidine exchange [Scheme 2(b)]. We suggest that the latter is the more likely mechanism in view of the known preference for attack at the 6-position by water,[16b] alcohols, and active methylene compounds.[2] The ease of exchange of the terminal group of amidines has been demonstrated in 4-dimethylaminomethyleneamino-5-cyano-8-azapurines; with ammonia these readily gave the corresponding 4-aminomethyleneamino-derivatives, which spontaneously cyclised to 6-amino-8-azapurines.[19]



SCHEME 2

EXPERIMENTAL

Samples for microanalysis were dried at 100° and 0·05 mmHg unless otherwise stated. ^{1}H N.m.r. spectra were determined with a Perkin-Elmer R10 instrument operating at 33·3° and 60 MHz. U.v. spectra were measured on Perkin-Elmer 450 and Unicam SP 800 recording spectrophotometers, and the wavelengths and intensities of maxima were confirmed with a Unicam SP 500 or an Optical CF 4 manual instrument. Ionisation constants were determined

[19] A. Albert, *J.C.S. Perkin I*, 1972, 461.

by methods previously described.[20] Azapurines were rigorously purified prior to the reactions, because purification by crystallisation of the products was not always possible. Similarly, unstable products could not be dried for prolonged periods at elevated temperatures.

Condensations with Hydroxylamine and Methoxyamine.—The hydrochloride of the reagent (0·002 mol) was added to a solution of the azapurine (0·0005 mol) and potassium carbonate (0·2 g) in water (*ca.* 1 ml). The solution was set aside overnight and any precipitated solid purified by washing with cold water or by crystallisation from water or methanol (see Table 3) to give the *triazole* or *dihydro-8-azapurine*. It was necessary in some cases to adjust the pH of the solution to *ca.* 4 with acetic acid to obtain the product.

Condensations with Hydrazine and Dimethylhydrazine.—A solution of the azapurine (0·0005 mol) in the hydrazine (0·02 mol) and water (*ca.* 1 ml) was set aside overnight and adjusted to pH 6, if necessary, to give the *azine* or *hydrazone* which was purified as above (see Table 3).

4-Amino-5-hydroxyiminomethyl-1,2,3-triazole (8).—4-Hydroxyiminomethylamino-5-hydroxyiminomethyl-1,2,3-triazole (7b) (0·085 g, 0·0005 mol) was heated under reflux with M-acetic acid (1 ml) for 2 h, then the solution was evaporated to dryness under reduced pressure. The residue, sublimed at 125° and 0·01 mmHg then crystallised from *ca.* 10 parts of water, gave the *triazole* (52%), needles, m.p. 155° (effervescence) [Found (for material dried at 60° and 0·01 mmHg): C, 24·6; H, 4·8; N, 48·3. $C_3H_5N_5O,H_2O$ requires C, 24·8; H, 4·9; N, 48·3%].

We thank Drs. D. J. Brown and H. Mizuno for discussions. Microanalyses were performed by Dr. J. E. Fildes and her staff; ionisation constants were determined by Mr. I. Hawkins (under the supervision of Dr. D. D. Perrin), u.v. spectra by Mr. D. T. Light (under Dr. E. Spinner), and n.m.r. spectra by Mr. S. E. Brown (under Dr. T. J. Batterham), all of whom we thank.

[2/1253 *Received*, 2*nd June*, 1972]

[20] A. Albert and E. P. Serjeant, 'The Determination of Ionisation Constants,' Chapman and Hall, London, 1971.