v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part 19.[1] Stability of *N*-Alkyl-8-azapurines. Degradation by Cold, Dilute Acid and Base to *N*-Alkyl-4-amino-1,2,3-triazole-5-carbaldehydes and -triazol-5-yl Ketones †

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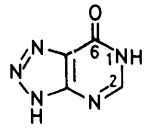
7-, 8-, and 9-Methyl and 8- and 9-benzyl derivatives of 8-azapurine (5) were hydrolysed by cold, aqueous N-hydrochloric acid to 1-, 2-, and 3-methyl and 2- and 3-benzyl (respectively) derivatives of 4-amino-1,2,3-triazole-5-carbaldehyde (6), mostly in high yield. Prior methylation in the 2-position prevented the hydrolysis. 6,9-Dimethyl-8-azapurine gave the analogous ketone (7a). Cold, aqueous N-sodium hydroxide behaved similarly expect that the presence of a 2-methyl group did not prevent reaction. From some of the alkaline hydrolyses, the same aldehydes (6) were isolated, as such or as their *N*-formyl or -acetyl derivatives which are intermediates, but in other cases self-condensation of the aldehyde occurred. Some of the 8-azapurines (5) were hydrolysed by simply boiling with water. 8-Azapurine disintegrated in acid but resisted alkali by forming an anion (Coulombic repulsion). These reactions, which have preparative value, were found by u.v. spectroscopy to show first-order behaviour. The half-lives of the starting materials were calculated. I.r. and n.m.r. spectra and ionization constants are discussed.

NOTHING has been recorded of the stability of 8-azapurines to acid or alkali at room temperature, although the following degradations at higher temperatures have been observed. With 2N-hydrochloric acid at 90 °C, 8-azapurin-6-one (1) gave 4-amino-1,2,3-triazole-5-carboxamide (2), whereas 2-amino-8-azapurin-6-one (the anticancer drug '8-azaguanine') decomposed to 2,4,5-triaminopyrimidin-6-one (the only known case of pyrimidine formation).[2] 6N-Sodium hydroxide at 180 °C converted 2-amino-8-azapurin-6-one into 4-amino-1,2,3-triazole,[3] and ammonia at 200 °C changed 8-azapurine-2,6-dione into the triazole amide (2).[4] A series of 6-methylamino-8-azapurines were rapidly converted by boiling N-hydrochloric acid into the corresponding 4-amino-1,2,3-triazole-5-carboxamidines (3),[5] and 6-amino-8-azapurine behaved similarly under severer conditions.[6] Several 6-methylthio-8-azapurines, when boiled for a few minutes with N-hydrochloric acid, gave high yields of 4-amino-5-(methylthio)carbonyl-1,2,3-triazoles (4).[7]

It has now been found that simple *N*-alkyl derivatives of 8-azapurines (5) are hydrolysed at room temperature, by dilute acid or base, to *N*-alkyl derivatives of 4-amino-1,2,3-triazole-5-carbaldehyde (6) and -triazol-5-yl methyl ketone (7). These results indicate what precautions are necessary in the preparation and storage of these azapurines. A structural feature that can protect them against gastric acidity, when used as drugs, will be described.

Solutions (4×10^{-4}M) of the following substances in N-hydrochloric acid and in N-sodium hydroxide were stirred for several days at 24 °C: 8-azapurine (5) [8] and its 7-methyl,[9] 8-methyl,[10] 9-methyl,[8] 8-benzyl,[11] 9-benzyl,[8,12] 9-benzyl-2-methyl,[12] 2,7-dimethyl,[12,13] 2,8-dimethyl,[12,13] and 6,9-dimethyl [8] derivatives. The reactions were followed by u.v. spectroscopy. Samples were removed and adjusted to the pH shown in Table 1 (for acid solutions only) by buffering [14] where necessary to isolate a single ionic species, allowing for covalent hydration of the cations.[8-10] The optical density (*A*) was measured at a wavelength (see Tables 1 and 2) chosen to represent the concentration of unchanged starting material with least possible interference from the products, whose spectra were taken from the



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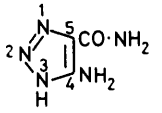

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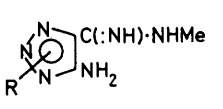

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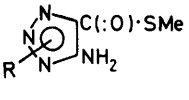

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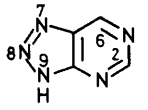

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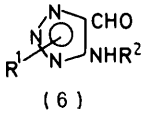
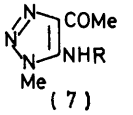


(6)

	R^1	R^2
a;	1-Me	H
b;	2-Me	H
c;	3-Me	H
d;	2-CH_2Ph	H
e;	3-CH_2Ph	H
f;	3-CH_2Ph	CHO
g;	3-CH_2Ph	COMe



(7)

a; R = H

b; R = CHO

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

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[1] Part 18, A. Albert and Clara J. Lin, *J.C.S. Perkin I*, 1977, 210.

[2] Y. Hirata, K. Iwashita, and K. Teshima, *Nagoya Sangyo Kagaku*, 1957, No. 9, 83 (*Chem. Abs.*, 1957, **51**, 12074).

[3] S. Yamada, T. Mizoguchi, and A. Ayada, *Yakugaku Zasshi*, 1957, **77**, 441 (*Chem. Abs.*, 1957, **51** 12,107).

[4] L. L. Bennett and H. T. Baker, *J. Org. Chem.*, 1957, **22**, 707.

[5] A. Albert, *J.C.S. Perkin I*, 1974, 2030.

[6] Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, 1965, **30**, 2488.

[7] A. Albert, *J. Chem. Soc.* (*C*), 1969, 2379.

[8] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.

[9] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.

[10] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.

[11] A. Albert and D. Thacker, *J.C.S. Perkin I*, 1972, 468.

[12] A. Albert, *J.C.S. Perkin I*, 1976, 291.

[13] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1973, 2037.

[14] D. D. Perrin and B. Dempsey, 'Buffers for pH and Metal Ion Control,' Chapman and Hall, London, 1974.

literature [15] or else determined with specimens isolated from preliminary runs.

Because *o*-amino-aldehydes tend to polymerise,[16] the products of these azapurine hydrolyses were submitted to the same conditions of acid (or base) and time. They were found to be stable except for the 1-methyl (6a) and 2-benzyl (6d) derivatives, which polymerized in alkali

intermediates were isolated. The two *N*-benzyl analogues produced several unidentified by-products (on the evidence of t.l.c.). Only for the unsubstituted example (5) were these by-products judged to be polymeric, on the basis of their poor solubility, infusibility, and orange colour.[16]

Table 2 similarly reports the effects of cold N-sodium

TABLE 1

Effect of N-hydrochloric acid on 8-azapurines (24 °C)

		Analysis							
8-Azapurine	pK_a	pH	Species	λ/nm [a]	log ε	$t_{0.5}$/h	% Hydr.[b]	Product	Yield (%)
Unsubstituted	2.05 [c]	0.30	+	248	3.90	25.6	35	*d*	
7-Methyl	1.92 [e]	0.70	+	245	3.80	43.1	22	(6a)	85
8-Methyl	3.18 [f]	0.70	+	254	4.00	31.9	30	(6b)	96
9-Methyl	0.32 [e]	1.70	0	264	3.85	7.0	85	(6c)	74
8-Benzyl	3.31 [g]	0.70	+	256	4.09	17.3	53	(6d)	43
9-Benzyl	−0.05 [e]	1.70	0	263	3.85	25.5	35	(6e)	50
9-Benzyl-2-methyl		2.40	0	268	3.94	*h*			
2,7-Dimethyl		0.70	+	243	3.88	*h*			
2,8-Dimethyl		0.70	+	253	4.09	*h*			
6,9-Dimethyl	0.71 [e]	2.40	0	261	3.89	194.0	5	(7a)	90

[a] Analytical wavelength (usually a maximum). [b] Percentage hydrolysed in 19 h ($t_{0.5}$ for 9-benzyl-8-azapurine in N-NaOH). [c] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427. [d] Mainly polymers. [e] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344. [f] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076. [g] A. Albert and D. Thacker, *J.C.S. Perkin I*, 1972, 468 (values designated *e*, *f*, and *g* are p*K* values of equilibria in which the cations are largely covalently hydrated). [h] No reaction. [i] In 5 days at 40 °C.

TABLE 2

Effect of N-sodium hydroxide on 8-azapurines (24 °C)

	Analysis					Yield
8-Azapurine	λ/nm [a]	log ε	$t_{0.5}$/h	% Hydr.[b]	Product	(%)
Unsubstituted	268	3.89	*b*			
7-Methyl	263	3.80	22.2	43	*c*	
8-Methyl	271	4.00	8.6	78	(6b)	90
9-Methyl	250	3.98	9.7	73	(6c)	92
8-Benzyl	274	3.98	7.1	88	*c*	
9-Benzyl	253	3.86	19.2	50	(6e) [e]	84
9-Benzyl-2-methyl	267	3.86	4.3	94	(6g)	65
2,7-Dimethyl	256	3.73		*d*	*c*	
	280	3.67				
2,8-Dimethyl	273	3.98	60.0	16	*c*	
6,9-Dimethyl	261	3.86	2.2	100	(7b)	80

[a] As in Table 1; analytical pH was always 13.3, and the species neutral except for unsbustituted example (pK_a 4.84, anionic). [b] Infinite (no reaction). [c] Mainly polymeric material. [d] Very little reaction. [e] For isolation of intermediate (6f) in shorter reaction, see Experimental section.

(only). Further, no Dimroth rearrangement [17] of 4-amino-3-methyl-(or -3-benzyl)-1,2,3-triazole-5-carbaldehyde to the 4-alkylamino-isomers [18] took place under our conditions.

A straight line of slope K obtained from the plot of A_0/A *versus* time indicated first-order kinetics. Half-lives for disappearance of the starting materials were calculated from the equation $t_{0.5} = \ln 2/K$.

Table 1 reports the effects of cold N-hydrochloric acid on the 8-azapurines under the headings $t_{0.5}$, percentage hydrolysed in unit time, nature of the product, and yield (the latter two under preparative conditions of duration $4 \times t_{0.5}$). The presence of a 2-methyl group greatly retarded, or even prevented, decomposition. The products of hydrolysis, the 4-amino-1,2,3-triazole-5-carbaldehydes (6) and the ketone (7a), were formed in high yields from the *N*-methyl-8-azapurines, and no hydroxide and shows that the alkaline reactions are generally the faster, and that a 2-methyl group seldom offers a substantial barrier to hydrolysis. Unsubstituted 8-azapurine which can form an anion, is protected from attack by coulombic repulsion.

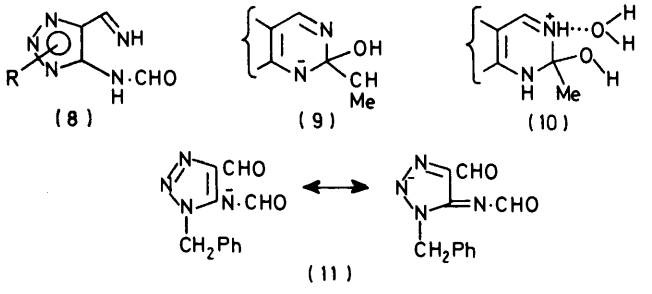
An intermediate, 4-formamido-3-benzyl-1,2,3-triazole-5-carbaldehyde (6f), was isolated from the incomplete alkaline hydrolysis of 9-benzyl-8-azapurine, whose 2-methyl derivative gave the corresponding 2-acetamido-triazole (6g) as its sole hydrolysis product. Interestingly too, 6,9-dimethyl-8-azapurine furnished high yields of 4-formamido-3-methyl-1,2,3-triazole-5-yl methyl ketone (7b) with alkali, whereas acid produced only the free primary amine (7a). Four examples in Table 2 yielded polymeric products.

In neutral boiling water, 7-methyl-8-azapurine was

[15] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1973, 1629.
[16] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*B*), 1966, 956; *J. Chem. Soc.* (*C*), 1968, 1944, 2289.
[17] D. J. Brown in ' Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience–Wiley, New York, 1968, vol. 1, p. 209.
[18] A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.

stable for 24 h, as were 8- and 9-benzyl-8-azapurine for 5 h, whereas 8- and 9-methyl-8-azapurine were completely transformed into the corresponding amino-aldehydes (6b) and (6c), respectively, in 24 h.

Mechanism.—The first product of these hydrolyses is likely to be an imine (8), somewhat analogous to (*a*) the similar intermediate isolated in the hydrolysis [7] of 6-methylthio-8-azapurines to the thioesters (4), and (*b*) the amidines (3) formed by hydrolysing 6-methylamino-8-azapurines.[5] Further hydrolysis should give the acid-labile 4-acylamino-5-carbaldehydes, two of which (6f and g) and the analogous ketone (7b) were actually isolated from alkaline decompositions. The retarding effect of a 2-methyl group on nucleophilic acidic hydrolysis is both electronic and steric. Whereas alkaline hydrolysis presumably begins with the simple adduct (9), acidic hydrolysis must start with protonation of the most basic nitrogen atom (N-1), which is followed by covalent addition of water across the 2,3-double bond to furnish the spatially unfavourable adduct (10). These hydrolyses have preparative value. Amino-triazole ketones (7) were previously unknown, and as aminotriazole aldehydes (6) have always resisted



(8) (9) (10)

(11)

acylation,[13] the acylation products (6f and g) are entirely novel.

Physical Constants.—The formamidotriazoles (6f) and (7b) are acids of strength intermediate between benzoic acid and phenol. The considerable acidity of 3-benzyl-4-formamido-1,2,3-triazole-5-carbaldehyde (pK_a 7.4) is attributed to the acid-strengthening resonance (11) in which the negative charge is shared between N-2 and the exocyclic nitrogen atom.

The i.r. spectrum of 4-amino-3-methyl-1,2,3-triazol-5-yl methyl ketone (7a) shows strong carbonyl stretching absorption at 1 638 cm^{-1}, characteristic of the sequence $C(NH_2)$:C·CO when internally hydrogen bonded.[19] Of the two strong carbonyl bands in the spectrum of the formyl derivative (7b) (at 1 668 and 1 710 cm^{-1}), the former is assigned to the ketonic group which is now less hydrogen-bonded, and the latter to the formamido-group which assumes similar high values when *ortho* to other electron-attracting groups such as carbamoyl [10] and cyano.[20]

The n.m.r. spectra of the three new aldehydes give signals for the formyl group in the expected region [15] near to τ 0; the two new formamido-derivatives have signals near τ 1.5, as is usual for 4-formamidotriazoles.[10,11] The three new benzyl compounds display methylene signals near τ 4.4, as is diagnostic of benzyl groups attached to a ring nitrogen atom [11,18] in this series. The ketonic and the acetyl methyl groups also gave rational signals.

Conclusion.—Simple *N*-alkyl derivatives of 8-azapurine are less stable to cold dilute acid and alkali, even in some cases to boiling water, than had been supposed; preparative yields could be improved by attention to these factors. The retarding effect on acidic hydrolysis of a 2-methyl group may prove useful in preventing decomposition in the stomach of 8-azapurines, which are beginning to be more widely used as drugs.[12]

EXPERIMENTAL

^1H N.m.r. spectra were obtained with a Varian HFT-80 instrument at 80 MHz and 33 °C, and i.r. spectra (for Nujol mulls) with a Perkin-Elmer 727 B spectrometer calibrated with polystyrene at 1 603 cm^{-1}. U.v. spectra were measured with a Beckman DB-GT grating spectrophotometer. Specimens said to be identical were compared by (i) mixed m.p. determination, (ii) i.r. spectrometry, and (iii) comparative chromatography on Whatman no. 1 paper developed in (*a*) aqueous 3% ammonium chloride, and also (*b*) butanol–5N-acetic acid (7 : 3). Elemental analyses were performed by Galbraith Laboratories, Inc., Tennessee. Ionization constants were determined as in ref. 21.

Known amino-aldehydes were extracted and purified as in ref. 15.

3-Benzyl-4-formamido-1,2,3-triazole-5-carbaldehyde (6f).—9-Benzyl-8-azapurine (0.22 g, 0.001 mol) was stirred with N-sodium hydroxide (2 ml) for 24 h at 24 °C. The mixture was filtered and the insoluble material, recrystallized from a little benzene, gave 4-amino-3-benzyl-1,2,3-triazole-5-carbaldehyde (20%), m.p. 168° (lit.,[15] 169°). Evaporation of the benzene filtrate furnished starting material (37%), m.p. 114—115°. The aqueous filtrate, acidified to pH 2.5 with 5N-sulphuric acid, gave *3-benzyl-4-formamido-1,2,3-triazole-5-carbaldehyde* (36%), m.p. 114° (from 15 parts of benzene or 30 parts of water) (Found: C, 57.8; H, 4.5; N, 24.7. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.4; N, 24.3%), τ [$(CD_3)_2SO$] −0.05 (1 H, C·CHO), 1.47 (1 H, N·CHO), 2.66 (5 H, Ph), and 4.39 (2 H, CH_2) (all singlets), pK_a 7.38 ± 0.03 (0.001M; λ 300 nm).

4-Acetamido-3-benzyl-1,2,3-triazole-5-carbaldehyde (6g).—9-Benzyl-2-methyl-8-azapurine (0.1 g) was stirred with N-sodium hydroxide (50 ml) for 17 h at 24 °C. The solution was cooled in ice, and neutralized with 10N-hydrochloric acid. The mixture was evaporated to dryness and the residue dried ($CaCl_2$), then extracted with chloroform (2 × 50 ml). The residue from the evaporated extracts was recrystallized from cyclohexane (800 parts) to give *4-acetamido-3-benzyl-1,2,3-triazole-5-carbaldehyde* (65%), m.p. 134° (Found: C, 59.2; H, 5.0; N, 23.1. $C_{12}H_{12}N_4O_2$ requires C, 59.0; H, 4.95; N, 22.9%), τ ($CDCl_3$) −0.14 (1 H, s, CHO), 1.35br (NH). 2.5—3.0 (5 H, m, Ph), 4.17 (2 H, s, CH_2), and 7.80 (3 H, s, CH_3).

4-Amino-2-benzyl-1,2,3-triazole-5-carbaldehyde (6d).—8-Benzyl-8-azapurine (0.1 g) and N-hydrochloric acid (100 ml)

[19] K. Nakanishi, 'Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1962.

[20] A. Albert, work in progress.

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

were stirred for 28 h at 24 °C. The suspension was cooled in ice, neutralized with 10N-sodium hydroxide, and extracted with chloroform (2 × 50 ml). The residue, left after evaporating the extracts was sublimed at 80 °C and 0.01 mmHg or recrystallized from cyclohexane (150 parts) to yield *4-amino-2-benzyl-1,2,3-triazole-5-carbaldehyde* (43%), m.p. 116° (Found: C, 59.4; H, 5.1; N, 27.7. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 5.0; N, 27.7%), τ ($CDCl_3$) −0.10 (1 H, s, CHO), 2.65 (5 H, m, Ph), 4.50 (2 H, s, CH_2), and 4.95—5.20 (2 H, NH_2).

The Amino-ketones.—6,9-Dimethyl-8-azapurine (0.05 g, 0.000 34 mol) and N-sodium hydroxide (10 ml) were stirred at 24 °C for 4 h. The solution was neutralized with 5N-sulphuric acid then evaporated to dryness. The desiccator-dried residue was extracted with chloroform (2 × 20 ml). The residue from the evaporated extracts was sublimed at 90 °C and 0.01 mmHg, and the sublimate recrystallized from dichloromethane (20 parts), yielding *4-formamido-3-methyl-1,2,3-triazol-5-yl methyl ketone* (7b), m.p. 146° (Found: C, 42.7; H, 4.85; N, 33.1. $C_6H_8N_4O_2$ requires C, 42.9; H, 4.8; N, 33.3%), $\nu_{max.}$ 3 330m (NH str.), 1 710s, 1 668br,s, and 1 580br,m cm^{-1}, τ [$(CD_3)_2SO$] 1.66 (1 H, s, CHO), 6.10 (3 H, s, NMe), and 7.44 (3 H, s, COMe), pK_a 8.16 ± 0.03 (0.005M; potentiometric).

6,9-Dimethyl-8-azapurine (0.05 g) and N-hydrochloric acid (20 ml) were stirred for 5 days at 40 °C; the mixture was neutralized with 10N-sodium hydroxide and evaporated. The desiccator-dried residue was extracted with boiling benzene (5 ml). The crystals that separated on cooling were recrystallized from dichloromethane (24 parts) to furnish *4-amino-3-methyl-1,2,3-triazol-5-yl methyl ketone* (90%), m.p. 156.5° (Found: C, 42.8; H, 5.8; N, 39.8. $C_5H_8N_4O$ requires C, 42.85; H, 5.75; N, 40.0%), $\nu_{max.}$ 3 440m, 3 320m (NH_2 str.), 1 638s, 1 525m, and 1 318m cm^{-1}.

Both ketones give a positive iodoform test.

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