v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part XVII.[1] Preparation of 1,6-Dihydro-8-azapurines by heating 4-Amino-5-aminomethyl-*N*-alkyl-1,2,3-triazoles † with Orthoesters or Amidines

By **Adrien Albert,***‡ Research School of Chemistry, Australian National University, Canberra, Australia 2600

Treatment of salts of 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (6a) with triethyl orthoformate and orthoacetate gave 9-benzyl- and 9-benzyl-2-methyl-1,6-dihydro-8-azapurine (1b and c), respectively. Small variations in the experimental conditions diverted these reactions to by-products, which illuminated the course of the normal reaction. These by-products were *NN'*-bis-(5-aminomethyl-3-benzyl-1,2,3-triazol-4-yl)formamidine (7) and 5-acetamidomethyl-3-benzyl-4-(α-ethoxyethylideneamino)-1,2,3-triazole (8a).

For straightforward production of 1,6-dihydro-8-azapurines, a new reaction is recommended in which amidines replace the orthoesters. With its aid, high yields were obtained of 9-benzyl-, 9-benzyl-2-methyl-, 7- and 8-methyl-, 2,7- and 2,8-dimethyl-, and 9-benzyl-2-trichloromethyl-1,6-dihydro-8-azapurine (1b—h). Ionization constants, and u.v., i.r., and ^{1}H n.m.r. spectra of this stable class of compounds are reported and discussed. All these dihydrocompounds were oxidised with manganese reagents to the corresponding 8-azapurines in high yields.

8-AZAPURINES, long used in the treatment of certain forms of cancer,[2] are now finding further areas of application, some as antiallergens that can inhibit the liberation of histamine [3] and others as strong deterrents of the release of anaphylaxis mediators in the human lung; the latter are undergoing clinical trial as antiasthmatics.[4] Little explored, and so far only indirectly accessible, are the reduced 8-azapurines, of which only four examples are known [1,6-dihydro-8-azapurine (1a),[5] and its 2-methyl-,[5] 2-mercapto-,[5] and 2-hydroxy-[6] derivatives], all made by reduction of the corresponding 8-azapurines.

A direct synthesis of 1,6-dihydro-8-azapurines was envisaged by cyclizing 1,2,3-triazole analogues of 2-aminobenzylamine (2), employing a reagent that could supply the final carbon atom. A precedent was available in the Gabriel–Colman synthesis [7] of 3,4-dihydroquinazoline (3), in which 2-aminobenzylamine was boiled with formic acid for 15 min. Later, two alternative reagents were developed: triethyl orthoformate under neutral conditions,[8] and *NN'*-diphenylformamidine, which splits off two molecules of aniline.[9]

The Gabriel–Colman reaction, which requires a high electron density in the ring-attached amino-group,

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

‡ *Present address:* Department of Pharmacological Sciences, State University of New York at Stony Brook, New York 11790, U.S.A.

[1] Part XVI, A. Albert, *J.C.S. Perkin I*, 1975, 345.

[2] G. Brulé, S. J. Eckhardt, T. C. Hall, and A. Winkler, 'Drug Therapy of Cancer,' World Health Organization, Geneva, 1973, pp. 46, 114, 132.

[3] C. J. Coulson, R. E. Ford, E. Lunt, S. Marshall, D. L. Pain, I. H. Rogers, and K. R. H. Wooldridge, *European J. Medicin. Chem.*, 1974, **9**, 313.

[4] B. Broughton, P. Chaplen, P. Knowles, E. Lunt, D. L. Pain, K. R. H. Wooldridge, R. Ford, S. Marshall, J. L. Walker, and D. R. Marshall, *Nature*, 1974, **251**, 650; B.P. 1,338,235/1973; Ger. Pat. 2,162,096.

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

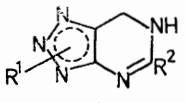
[6] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1972, 457.

[7] S. Gabriel and J. Colman, *Ber.*, 1904, **37**, 3643.

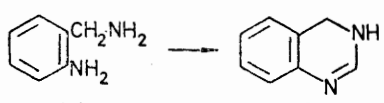
[8] R. v. Walther and R. Bamburg, *J. prakt. Chem.*, 1906, **73**, 209; R. N. Iyer, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res., India*, 1957, **16C**, 157.

[9] E. C. Wagner, *J. Org. Chem.*, 1940, **5**, 133.

becomes difficult to effect in π-deficient [10] ring systems. The first of the few known successes were the conversion of 2-amino-3-aminomethyl-4,6-dimethylpyridine (4) into 3,4-dihydro-5,7-dimethylpyrido[2,3-*d*]pyrimidine (5) by

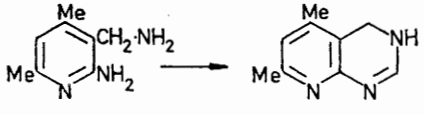


(1)

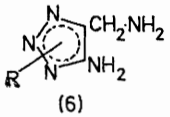


(2) (3)

	R^1	R^2
a;	H	H
b;	9-CH_2Ph	H
c;	9-CH_2Ph	Me
d;	7-Me	H
e;	7-Me	Me
f;	8-Me	H
g;	8-Me	Me
h;	9-CH_2Ph	CCl_3



(4) (5)



(6)

R

a; 3-CH_2Ph

b; 1-Me

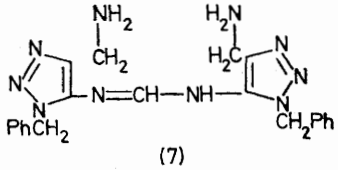
c; 2-Me

dehydrating the formate salt in a stream of distilling xylene,[11] and the cyclization of 2-amino-3-acetamidomethyl-4,6-dimethylpyridine, which required phosphoryl chloride.[11] Not even these forcing conditions sufficed to convert 2-amino-3-aminomethylpyrazine into 3,4-dihydropteridine, but heating with triethyl orthoformate was effective.[12] None of these methods proved satisfactory in the present work. Only a trace of 9-benzyl-1,6-dihydro-8-azapurine (1b) was obtained from 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (6a) [13] with triethyl orthoformate in boiling ethanol (increasing to 6% in boiling n-pentanol). Triethyl orthoacetate (in boiling ethanol) gave, more favourably, a 34% yield of the homologue (1c).[14]

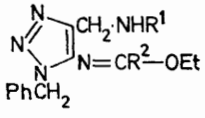
Later it was found that a dramatic increase in reactivity occurred when the triazole (6a) was replaced by one of its salts. Thus triethyl orthoformate and the hydrochloride of the triazole (6a) gave the required product in 76% yield. However the acetate furnished exclusively *NN'*-bis-(5-aminomethyl-3-benzyl-1,2,3-triazol-4-yl)-formamidine (7), identified by (*a*) the elemental analysis and those of the 1 : 1 salts given by monobasic acids, (*b*) the neutrality of the aqueous solution of the nitrate, (*c*) the u.v. spectrum of the neutral species [$\lambda_{max.}$ (MeOH) 253 nm (log ε 4.00); *cf.* 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (6a), $\lambda_{max.}$ 244 nm (log ε 3.70)], indicative of conjugation through the amidine group, (*d*) the n.m.r. spectrum, particularly the position of the 5-CH_2 signal (see Experimental section), and (*e*) quantitative hydrolysis, by boiling N-hydrochloric acid, to the starting material (6a).

Paradoxically, the hydrochloride of the triazole (6a) proved useless, but the acetate highly suitable, for condensation with triethyl orthoacetate to give 9-benzyl-1,6-dihydro-2-methyl-8-azapurine (1c) (65%). Use of the hydrochloride produced exclusively 5-acetamidomethyl-3-benzyl-4-(α-ethoxyethylideneamino)-1,2,3-triazole (8a), which showed no tendency to cyclize. A lower homologue (8b) was obtained from the triazole (6a) and triethyl orthoformate by heating with acetic anhydride. The structure of these imidic esters (8a and b) rests on (*a*) the elemental analysis, (*b*) the mass spectrum of the acetimidate (8a) [M^+ 315, with prominent loss of CH_3CO (43 m.u.) to give *m/e* 272, and other peaks at *m/e* 243, 182, 126, 109, and 91 ($PhCH_2$)], (*c*) the i.r. spectrum of the formimidate (8b), with characteristic bands for amide, imide, and ether groups (Table 2), and (*d*) the ^1H n.m.r. spectrum of the same compound (see Experimental section).

The course of the reaction leading to 1,6-dihydro-8-azapurines depends on the preference of orthoesters for reacting with aromatic, rather than aliphatic, primary amino-groups, because the extended conjugation, as in (8c), which the former course creates, stabilizes the intermediates.[15] Thus the by-products (7) and (8a) are viewed as being formed from intermediates that have been conserved by undergoing one further, inactivating, reaction. The beneficial effects of using a *salt* of the

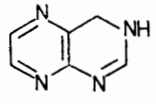


(7)



(8)

	R^1	R^2
a;	Ac	Me
b;	Ac	H
c;	H	H



(9)

starting material must derive from its being a source of hydrogen ions which provide the orthoester with a better leaving group ($Et\overset{+}{O}H$). The difference between the results of using salts of strong and of weak acids (taken in conjunction with electronic differences between the methylene and ethylidene groups) is seen as regulating the ionization of the aminomethyl group, and so (in a favourable combination) facilitating ring closure before a side-reaction can take place.

Further exploration of these condensations was halted when it was discovered that amidines could replace the orthoesters. This reaction gave better yields and was far

[10] A. Albert, 'Heterocyclic Chemistry,' London, Athlone Press, 1968, pp. 5, 56.
[11] P. J. Vanderhorst and C. S. Hamilton, *J. Amer. Chem. Soc.*, 1953, **75**, 656.
[12] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1970, 1540.
[13] A. Albert, *J.C.S. Perkin I*, 1973, 1634.
[14] Preliminary report, A. Albert, *Chem. Comm.*, 1970, 858.
[15] R. H. DeWolfe, 'Carboxylic Ortho Acid Derivatives,' New York, Academic Press, 1970.

less sensitive to electronic changes in the reactants. The best yields were obtained when the acetates of the amidines were condensed with the free triazoles (6). In this way, seven new 1,6-dihydro-8-azapurines were synthesized (1b—h).

Properties.—The 1,6-dihydro-8-azapurines are moderately weak bases but stronger than the corresponding 8-azapurines (even when the latter were in their covalently hydrated form; *cf.* 4.05 and 4.20 for hydrated

The ^{1}H n.m.r. spectra (Table 3) show a signal (2H) for the 6-methylene group near τ 5.3, as do two dihydro-8-azapurines (prepared by hydrogenating 8-azapurine and its 2-methyl derivative) which were assigned the 1,6-dihydro-structure on ^{1}H n.m.r. evidence.[5]

The 1,6-dihydro-8-azapurines with a free 2-position are reasonably stable to cold N-sodium hydroxide, but cold N-hydrochloric acid slowly hydrolyses them to the original 4-amino-5-aminomethyltriazoles (6) and formic

TABLE 1

Ionization constants and u.v. spectra

		Ionization in water (20°)				Spectroscopy [c] in water		
Compound	Species	pK_a	Spread (±)	Concn. (M)	A.w.l. [b] (nm)	$\lambda_{max.}$/nm	log ε	pH
1,6-Dihydro-8-azapurine								
7-Methyl	0					266	3.83	8.0
	+	5.71	0.04	0.0003	270	246 [d]	3.71	3.7
8-Methyl	0					281	3.96	8.0
	+	5.82	0.04	0.0001	290	267	3.82	3.7
9-Benzyl	0					*205*, 293	*4.10*, 3.85	7.0
	+	3.12	0.03	0.0001	300	*203*, 280	*4.13*, 3.65	1.0
8-Azapurine								
7-Methyl [e,f]	0	0.3 [g]				276	3.73	
8-Methyl [f,h]	0	0.3 [g]				270	4.00	
9-Benzyl [f,i]	0	−0.05				263	3.88	
9-Benzyl-2-methyl	0					267	3.88	E [j]
2,8-Dimethyl	0					273	3.90	E

[a] Neutral species (0), cation (+). [b] Analytical wavelength for spectrometric determination. [c] Inflections in italics. [d] Also a shoulder *ca.* 270 nm. [e] Ref. 15. [f] For comparison. [g] Approx. [h] Ref. 16. [i] Ref. 5. [j] In ethanol.

TABLE 2

I.r. spectra (Nujol)

	$\nu_{max.}$/cm^{-1}
9-Benzyl-2-trichloromethyl-8-azapurine	1 585s, 1 210m, 1 060m, 880m, 855m, 800m, and 775s (Cl—C str.)
1,6-Dihydro-8-azapurines	
7-Methyl	3 240s (NH str.), 1 610m, 1 580s (C:N str.), 1 400m, 1 345s (CN str.), and 760m [a]
2,7-Dimethyl	3 230, 1 610, 1 585, 1 550, 1 395, 1 385, and 1 180 (all m)
8-Methyl	3 250s, 3 120m (NH), 1 595s, 1 510m, 1 405m, and 1 300m
2,8-Dimethyl	3 230m, 3 130m, 1 610m, 1 575br s, 1 530s, 1 410m, 1 340m, 1 295s (C—N str.), and 695m
9-Benzyl	3 350s (NH str.), 1 615ms, 1 580s, 1 540m, 1 295m, 1 275ms (C—N str.), 1 105m, and 735s

[a] Extra peaks in hexachlorobutadiene: 3 020m, 2 950m, 2 890m, and 2 840m.

7- and 8-methyl-8-azapurine respectively).[16,17] Their u.v. spectra are displaced relative to those of the parent 8-azapurines, some to longer (but one to shorter) wavelengths. The most relevant comparison (because no spectrum of a simple 1,6-dihydropurine is known) is with 3,4-dihydropteridine (9) ($\lambda_{max.}$ 335 nm; [12] *cf.* pteridine, 308 nm [18]). This shift is not found in 3,4-dihydroquinazoline (3) ($\lambda_{max.}$ 291 nm; *cf.* quinazoline, 305 nm).[19] Clearly the direction of u.v. shift caused by hydrogenation of a fused pyrimidine ring is variable.

The 1,6-dihydro-8-azapurines melt at higher temperatures than their parent substances, just as do the 3,4-dihydro-derivatives of quinazoline and pteridine. Their i.r. spectra are characterized by N–H stretching bands around 3 200 cm^{-1}, and the C–N stretching band near 1 300 cm^{-1} is often stronger than in the dehydrogenated analogues.

[16] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.
[17] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[18] D. D. Perrin, *J. Chem. Soc.*, 1962, 645.

acid. Unlike the 1,6-dihydropurines,[20] the dihydro-8-azapurines are stable to aerial oxidation. Oxidation of the dihydro-8-azapurines (1b—h) with aqueous potassium permanganate, or a suspension of manganese dioxide in benzene, produced the corresponding 8-azapurines in high yield.

EXPERIMENTAL

^{1}H N.m.r. spectra were obtained with a Varian HA 100 (100 MHz) instrument, and i.r. spectra with a Perkin-Elmer 257 grating spectrometer. Specimens said to be identical were compared by (i) mixed m.p. determination where applicable, (ii) i.r. spectroscopy, and (iii) comparative chromatography on Whatman no. 1 paper developed in (*a*) aqueous 3% NH_4Cl, and (*b*) butanol–5N-acetic acid (7 : 3). ' Pyridine trihydrate ' (the azeotrope, b.p. 92°) was the solvent used to apply the samples to the paper. Elemental

[19] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 2689.
[20] J. H. Lister, 'The Purines,' New York, Wiley–Interscience, 1971, p. 433.

analyses were performed by the Australian National University Analytical Services Unit. Unless otherwise specified, material for analysis was dried at 80 °C in air. The ortho-esters were fractionally distilled before use.

Salts of 4-*Amino*-5-*aminomethyl*-3-*benzyl*-1,2,3-*triazole* (6a).—These were made by neutralization and evaporation of aqueous solutions, and drying the products at 110 °C in air. The *hydrochloride*, recrystallized from 3 parts of water, decomposed at 208° (Found: Cl, 15.0. $C_{10}H_{13}N_5$,HCl requires Cl, 15.0%). The *acetate*, recrystallized from 5 parts of ethanol, had m.p. 152° (Found: C, 55.0; H, 6.5; N, 26.8. $C_{12}H_{17}N_5O_2$ requires C, 54.7; H, 6.5; N, 26.6%).

light petroleum (b.p. 60—80°; 10 ml) was added. The resulting suspension was chilled. The solid hydrochloride was filtered off and dissolved in water (5 ml). Adjustment of the pH to 8 produced crystals of the dihydro-8-azapurine, m.p. 141°.

9-*Benzyl*-1,6-*dihydro*-2-*methyl*-8-*azapurine* (3-*Benzyl*-6,7-*dihydro*-5-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*) (1c).—(a) *Preferred method.* This synthesis was effected as for the lower homologue, but by using acetamidinium acetate.[21]

(b) The acetate of the triazole (6a) (0.26 g, 0.001 mol), triethyl orthoacetate (2 ml), and ethanol (2 ml) were heated under reflux for 2 h. Volatile material was distilled off at

TABLE 3

^{1}H N.m.r. spectra [*ca.* 34°; solvent $(CD_3)_2SO$]

Compound	τ Values [a]
1,6-Dihydro-8-azapurine	
9-Benzyl	1.8 [b]br (1 H, NH), 2.45 (5 H, Ph), 2.62 [c] (centre) (1 H, d, *J* 5 Hz), 4.50 (2 H, PhCH_2), 5.10 (2 H, 6-CH_2)
9-Benzyl-2-methyl	2.1 [b]br (1 H, NH), 2.68 (5 H, Ph), 4.62 (2 H, PhCH_2), 5.24 (2 H, 6-CH_2), 8.04 (3 H, Me)
7-Methyl	2.6 [b]br (NH), 3.08 (1 H, s, 2-H), 5.23 (2 H, CH_2), 6.20 (3 H, Me)
2,7-Dimethyl	2.67 [b]sl br (NH), 5.27 (2 H, CH_2), 6.21 (3 H, 7-Me), 8.16 (3 H, 2-Me)
8-Methyl	2.4 [b]br (NH), 2.96 (1 H, s, 2-H), 5.35 (2 H, CH_2), 6.08 (3 H, Me)
2,8-Dimethyl	2.53 [b]sl br (NH), 5.39 (2 H, CH_2), 6.09 (3 H, 8-Me), 8.13 (3 H, 2-Me)
8-Azapurine	
Unsubstituted [d]	0.32 (1 H, H-6), 0.80 (1 H, H-2)
9-Benzyl	0.19 (1 H, H-6), 0.70 (1 H, H-2), 2.64 (5 H, Ph), 4.02 (2 H, CH_2)
9-Benzyl-2-methyl	0.34 (1 H, H-6), 2.66 (5 H, Ph), 4.09 (2 H, CH_2), 7.19 (3 H, Me)
9-Benzyl-2-trichloromethyl	−0.52 (1 H, H-6), 2.36 (5 H, Ph), 3.82 (2 H, CH_2)

[a] Tetramethylsilane as internal standard. [b] Vanishes when D_2O is added. [c] Becomes singlet when D_2O is added (H-2 coupled to NH). [d] For comparison [J. W. Bunting and D. D. Perrin, *J. Chem. Soc.* (*B*), 1966, 433].

TABLE 4

Preparation of 1,6-dihydro-8-azapurines (1) from 4-amino-5-aminomethyl-1,2,3-triazoles (6) and amidines (in boiling butanol)

Product	Starting triazole	Other ponent [a]	Reflux Time (h)	Recrystallization Solvent	Recrystallization Parts	M.p. (°C)	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(1b)	(6a)	F	4	Benzene [b]	60	142	85	61.95	5.1	33.1	$C_{11}H_{11}N_5$	61.95	5.2	32.85
(1c)	(6a)	A	4	Ethanol	9	196	86	63.2	5.5	31.1	$C_{12}H_{13}N_5$	63.4	5.8	30.8
(1d)	(6b)	F	2 [c]	Nitromethane	120	250 [d]	95	43.8	5.2	51.0	$C_5H_7N_5$	43.8	5.1	51.1
(1e)	(6b)	A	2	Ethanol	33	269	70	47.7	6.1	46.4	$C_6H_9N_5$	47.7	6.0	46.3
(1f)	(6c)	F	1	Benzene	470	180	65	43.5	5.1	51.65	$C_5H_7N_5$			
(1g)	(6c)	A	1	Ethanol	23	244—248	88	47.3	6.15	46.7	$C_6H_9N_5$			
(1h)	(6a)	TC	4	Benzene [e]	15	153 [d]	60	(See text)						

[a] F, formamidine; A, acetamidine; TC trichloroacetamidine (all as acetates). [b] Water (15 parts) also suitable, but operation must be done quickly to prevent hydrolysis. [c] Chilled after 1 h, first crop filtered off; process repeated. [d] Decomposes. [e] Two crops taken.

1,6-*Dihydro*-8-*azapurines* (6,7-*Dihydro*-v-*triazolo*[4,5-d]-*pyrimidines*) (1b—h).—The preparation of these compounds is summarized in Table 4. This information is extended by the following typical preparations and modifications to suit particular cases.

9-*Benzyl*-1,6-*dihydro*-8-*azapurine* (3-*Benzyl*-6,7-*dihydro*-v-*triazolo*[4,5,d]*pyrimidine*) (1b).—(a) *Preferred method.* 4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole (6a) [13] (2.03 g, 0.01 mol), formamidinium acetate (Fluka; 3.1 g, 0.03 mol), and sieve-dried butanol (20 ml) were heated under reflux for 4 h. The solvent was removed at 90 °C and 25 mmHg. The residue, stirred with warm water (20 ml), then chilled, deposited the pure *dihydro*-8-*azapurine*, m.p. 142°.

(b) *Use of orthoester.* The hydrochloride of the triazole (1b) (1.20 g, 0.005 mol), triethyl orthoformate (10 ml), and ethanol (10 ml) were heated under reflux in a 100 °C bath for 1 h. After removal of the ethanol at 50 °C *in vacuo*, 100 °C and 25 mmHg and the residue, ground under water, furnished crystals of the title substance, m.p. 195°, strongly depressed by admixture with a possible product, 5-acetamidomethyl-4-amino-3-benzyl-1,2,3-triazole [13] (m.p. 199°).

The Methyl-substituted 1,6-*Dihydro*-8-*azapurines* (1d—g).—These were prepared from the appropriate triazoles (6b—c) [13] and amidines by the method used for the 9-benzyl analogues, but modified as in Table 4. 1,6-Dihydro-8-methyl-8-azapurine (1f), highly soluble in cold water, and hygroscopic, was dried at 110 °C and 25 mmHg.

9-*Benzyl*-1,6-*dihydro*-2-*trichloromethyl*-8-*azapurine* (3-*Benzyl*-6,7-*dihydro*-5-*trichloromethyl*-v-*triazolo*[4,5-d]*pyrimidine*) (1h).—The triazole (6a) (1.015 g, 0.005 mol), trichloroacetamidine [22] (2.50 g, 0.015 mol), anhydrous acetic

[21] E. C. Taylor and W. A. Ehrhart, *J. Amer. Chem. Soc.*, 1960, **82**, 3138.

[22] A. Albert and B. Paal, *Chem. and Ind.*, 1974, 874.

acid (0.9) g), and butanol (10 ml) were heated under reflux for 4 h. Volatile material was removed at 90° and 25 mmHg. The residue was triturated with 0.5 N-potassium carbonate (6 ml). After decantation of the aqueous layer, the plastic mass was covered with 0.5 N-potassium carbonate (5 ml) and shaken out with chloroform (2 × 25 ml). The united extracts were dried (K_2CO_3) and the solvent was distilled off. The residue, recrystallized from benzene (7 ml), gave a 60% yield of the *azapurine*, the crystals of which retained solvent; m.p. 153° (decomp) [Found (for material dried at 24 °C and 0.01 mmHg): C, 48.5; H, 3.4; N, 18.8. $C_{12}H_{10}Cl_3N_5,0.5C_6H_6$ requires C, 48.75; H, 3.5; N, 18.9%].

Triazole By-products.—(a) *The amidine* (7). 4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazolium acetate (0.46 g, 0.0018 mol) and triethyl orthoformate (3.6 ml) were heated under reflux at 100 °C (bath temp.) for 1 h. The suspension, mixed with light petroleum (b.p. 60—80°; 3.6 ml) then refrigerated, deposited *NN′-bis-(5-aminomethyl-3-benzyl-1,2,3-triazol-4-yl)formamidinium acetate* (90%), m.p. 162° (from 20 parts of methanol) (Found: C, 58.45; H, 6.0; N, 30.2. $C_{21}H_{24}N_{10},C_2H_4O_2$ requires C, 58.0; H, 5.9; N, 29.4%), $\lambda_{max.}$ (MeOH) 251 nm (log ε 4.03). Addition of potassium nitrate to a hot aqueous solution precipitated the *nitrate*, m.p. 200° (decomp.) (from 210 parts of methanol) (Found: N, 32.5. $C_{21}H_{24}N_{10},HNO_3$ requires N, 32.8%). The *free base*, from the acetate and cold N-sodium hydroxide, had m.p. 147° (from 12 parts of methanol), was soluble (0.0005M) in cold water and insoluble in boiling benzene, and gave a large depression of m.p. with the normal product, 9-benzyl-1,6-dihydro-8-azapurine (m.p. 142°) [Found (material dried at 24 °C and 0.01 mmHg): C, 60.5; H, 5.8; N, 33.75. $C_{21}H_{24}N_{10}$ requires C, 60.5; H, 5.8; N, 33.6%], τ [$(CD_3)_2SO$] 2.46 (1 H, :CH), 2.72 (10 H, 2 × Ph), 4.5br (exchangeable, NH), 4.68 (4 H, 2 × CH_2Ph), and 5.81 (4H, 2 × 5-CH_2) (the corresponding signal is shifted only to 5.71 in the acetate, further confirming the 4,4′-amidine link).

(b) *The acetamidomethyl compounds.* The triazole (6a) (0.6 g.; 0.003 mol), triethyl orthoformate (2 ml), and acetic anhydride (2 ml) were heated under reflux at 100° (bath) for 1 h. The solution was taken to dryness at 100 °C and 25 mmHg. The residual solid, recrystallized from benzene–cyclohexane (1 : 2), gave *5-acetamidomethyl-3-benzyl-4-ethoxymethyleneamino-1,2,3-triazole* (8b) (80%), m.p. 122° (Found: C, 59.8; H, 6.5; N, 23.0. $C_{15}H_{19}N_5O_2$ requires C, 59.8; H, 6.4; N, 23.2%), $\nu_{max.}$ (Nujol) 3 300m, 3 310m (NH), 1 665s (CO), 1 635s (CH:N), 1 285m, 1 235s (:COC), and 1 190m cm^{-1}, τ[$(CD_3)_2SO$] 1.66 (CH:N), 2.67 (5 H, Ph), 4.61 (CH_2Ph), 5.7 [centre of m formed from q (CH_2 of Et) and d ($NHCH_2$); D_2O changed m to an apparent s (4 H, 5.71)], 8.19 (3 H, Me of Ac), and 8.72 (3 H, Me of Et).

The hydrochloride of the triazole (6a) (0.24 g., 0.001 mol), triethyl orthoacetate (2 ml), and ethanol (2 ml) were heated at 100 °C under reflux for 15 min. The solution was taken to dryness at 90 °C and 25 mmHg. 2N-Potassium carbonate (3 ml) was added to the cold residue, and the mixture was shaken out with chloroform (2 × 10 ml). The extract was dried (K_2CO_3), and the solvent distilled off, leaving *5-acetamidomethyl-3-benzyl-4-(α-ethoxyethylideneamino)-1,2,3-triazole* (8a) (50%), m.p. 99.5° [from 1 500 parts of light petroleum (b.p. 60—80°)] [Found (for material dried at 80 °C and 0.01 mmHg): C, 61.2; H, 6.9; N, 22.3. $C_{16}H_{21}N_5O_2$ requires C, 60.9; H, 6.7; N, 22.2%].

Oxidations of 1,6-Dihydro-8-azapurines.—(a) *In aqueous pyridine.* 0.1M-Potassium permanganate (16.5 ml, 1 equiv.) was added dropwise to a stirred solution of 9-benzyl-1,6-dihydro-8-azapurine (0.53 g, 0.0025 mol), in pyridine trihydrate (see preamble) (11 ml) at 15 °C. After 15 min further stirring, N-acetic acid (1.65 ml) and kieselguhr (0.25 g) were added, and the suspension was filtered. The insoluble part was dried at 20 °C and 25 mmHg, powdered, and boiled with ethanol (5 ml). The conbined filtrates were taken to dryness at 50 °C. Water (7 ml) was added to the residue, and the pH was adjusted to 3, liberating 9-benzyl-8-azapurine (80%), m.p. 117° (from 4 parts of ethanol), identical with authentic material.[5,23] It was not attacked by either N-sodium carbonate or N-hydrochloric acid at 20 °C. Similar conditions produced 9-benzyl-2-methyl-8-azapurine (90%) from the dihydro-analogue (1c); m.p. 64° [from 20 parts of light petroleum (b.p. 60—80°)], identical with authentic material [24] [Found (material dried at 22 °C and 25 mmHg): C, 63.8; H, 4.9; N, 31.2. Calc. for $C_{12}H_{11}N_5$: C, 64.0; H, 4.9; N, 31.1%].

(b) *In water.* 0.1M-Potassium permanganate (6.6 ml, 1 equiv.) was added dropwise to a stirred solution of 1,6-dihydro-7-methyl-8-azapurine (1d) (0.137 g, 0.001 mol) in 50 parts of cold water. Kieselguhr (0.1) and N-phosphoric acid (0.66 ml, 1 equiv.) were then added and stirring was continued for 5 min longer. After filtration, the insoluble part was pasted in a mortar with ethanol (2.5 ml), and the suspension briefly refluxed then filtered at the boil. The combined aqueous and ethanolic filtrates were taken to dryness and extracted with boiling ethanol (4 and 2 ml). Concentration of the extracts yielded 7-methyl-8-azapurine (81%), m.p. 167° (from 16 parts of ethanol), identical with authentic material.[16] 8-Methyl-8-azapurine was similarly prepared from the dihydro-analogue (1f), in 75% yield; m.p. 133° after sublimation at 120 °C and 0.01 mmHg, identical with an authentic sample.[17] 2,7- and 2,8-Dimethyl-8-azapurine, similarly prepared (74% after sublimation) were identical with authentic material.[24]

(c) *In benzene.* The benzene adduct of 9-benzyl-1,6-dihydro-2-trichloromethyl-8-azapurine (0.740 g, 0.002 mol), dissolved in benzene (100 ml), was stirred at 24 °C with active (precipitated) manganese dioxide (4 g) overnight. The suspension was filtered. The filtrate, taken to dryness, produced *9-benzyl-2-trichloromethyl-8-azapurine* (*3-benzyl-5-trichloromethyl-v-triazolo*[4,5-d]*pyrimidine*) (87%), m.p. 94° [from 2 parts of methanol or 45 parts of light petroleum (b.p. 60—80°)] (Found: C, 44.1; H, 2.6; Cl, 31.9; N, 21.1. $C_{12}H_8Cl_3N_5$ requires C, 43.85; H, 2.5; Cl, 32.4; N, 21.3%). A solution in ethanolic 3N-ammonia was unchanged after 20 h at 24 °C.

I thank Drs. D. D. Perrin and R. Bramley and their staffs for the ionization constants and ^1H n.m.r. spectra respectively; also Mr. B. Paal and Miss L. Hagan for experimental help.

[5/1443 *Received* 22*nd July*, 1975]

[23] A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.
[24] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1973, 2037.