v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part XV.[1] Degradation by Acid of Ring *N*-Alkylated Derivatives of 6-Amino-(and 1,6-Dihydro-6-imino-)8-azapurines to *N*-Alkylated 4-Amino-1,2,3-triazole-5-carboxamidines †

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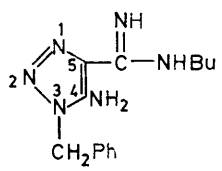
Degradation, in boiling dilute acid, is described for 6-amino-8-azapurines (3) (7-amino-*v*-triazolo[4,5-*d*]pyrimidines), alkylated on a ring-nitrogen atom and/or the exocyclic amino-group, to give the corresponding alkylated 4-amino-1,2,3-triazole-5-carboxamidines (4). Similar, but more rapid, degradation of the isomeric 1,6-dihydro-6-imino-1-methyl-8-azapurines (5) to the same class of product is reported. Yields are usually excellent. Preparations of new 8-azapurines are described. It is shown that earlier attempts to produce 1,2,3-triazole amidines had given the corresponding zwitterions.

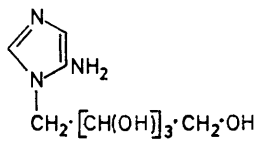
The action of acid on 6-alkylamino-8-azapurines, *e.g.* (8), becomes more complex when the triazole ring carries no *N*-substituent. Some rearrangement occurs to give a 6-amino-9-alkyl-8-azapurine, *e.g.* (10), which is degraded to an amidine, isomeric with the required product. The rearrangement can be effected quantitatively by heating the solid.

Ionization constants and u.v., i.r., and ^{1}H n.m.r. spectra are recorded and discussed.

ANTAGONISTS of intermediates in purine and pyrimidine biosynthesis, which necessarily inhibit the formation of new nucleic acids, are now widely used in the treatment of several forms of cancer, and have found a useful place among the still small class of antiviral drugs. 4-Amino-1,2,3-triazole-5-carboxamidines, *e.g.* (1), could be suitable antagonists of the early stages of purine biosynthesis and hence deserve investigation for a selective attack on cancer and viral diseases. The most likely sites for inhibition of purine biosynthesis by these compounds are the enzymes responsible for (i) the cyclodehydration of α-*N*-formylglycinamidine ribotide to 4-aminoimidazole 3-ribotide [2] (2), and (ii) the formylation of the amino-group in 5-amino-4-carbamoylimidazole 1-ribotide.[3] Such amidines are likely to be strong bases, existing as cations at pH 7, and hence are unlikely to penetrate the living cell unless made lipophilic by appropriate alkyl substitution.[4]



(1)



(2)

It will be shown here that 4-amino-(and 4-piperidino-) 1,2,3-triazole-5-carboxamidine, the only related com-

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

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

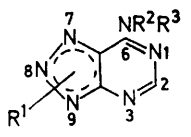
[2] B. Levenberg and J. M. Buchanan, *J. Amer. Chem. Soc.*, 1956, **78**, 504.

[3] J. M. Buchanan and M. P. Schulman, *J. Biol. Chem.*, 1953, **202**, 241; L. Warren and J. G. Flaks, *Fed. Proc.*, 1956, **15**, 379.

[4] A. Albert, ' Selective Toxicity,' 5th edn., Chapman and Hall, London, 1973, p. 294.

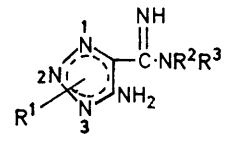
pounds in the literature,[5,6] are actually zwitterions (internal salts); but typical, highly basic amidines can be produced by prior *N*-alkylation of the triazole ring to suppress its natural acidity.

8-Methyl-6-methylamino-8-azapurine [7] (3a), boiled with N-hydrochloric acid for 4 h, gave the hydrochloride of 4-amino-2-methyl-1,2,3-triazole-5-*N*-methylcarboxamidine (4a) (92% yield). Other 6-alkylamino-8-azapurines (3b—d) similarly gave the amidines (4b—d), respectively. By analogy with the acidic hydrolysis of



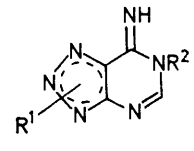
(3)

	R^1	R^2	R^3
a;	8-Me	Me	H
b;	8-Me	Bu^n	H
c;	7-Me	Me	Me
d;	7-Me	Bu^n	H
e;	9-$PhCH_2$	H	H
f;	9-$PhCH_2$	Bu^n	H
g;	7-Me	Me	H
h;	H	Bu^n	H
i;	H	H	H
j;	Me	H	H



(4)

	R^1	R^2	R^2
a;	2-Me	Me	H
b;	2-Me	Bu^n	H
c;	1-Me	Me	Me
d;	1-Me	Bu^n	H
e;	3-$PhCH_2$	H	H
f;	1-Me	Me	H
g;	3-$PhCH_2$	Me	H
h;	3-$PhCH_2$	Bu^n	H
i;	H	H	H
j;	H	Me	H
k;	H	Bu^n	H
l;	3-Me	H	H



(5)

	R^1	R^2
a;	8-Me	Me
b;	7-Me	Me
c;	9-$PhCH_2$	Me
d;	9-$PhCH_2$	Bu^n

6-methylthio-8-azapurines,[8] this reaction is assumed to involve rupture of the $N(1)^{\delta-}$–$C(2)^{\delta+}$ bond followed by irreversible deformylation of the resulting 4-formamidotriazole-5-carboxamidine. The required polarization of the 1,2-bond of the azapurine is helped by alkyl substituents in the 6-amino-group. When this group is primary, the desired reaction is slowed and the yield is lowered by side-reactions, particularly hydrolysis of the 6-amino-group. Thus 6-amino-9-benzyl-8-azapurine [9] (3e) required 12 h boiling to give the maximum yield (only 65%) of the amidine (4e); the principal by-product was 9-benzyl-8-azapurin-6-one.[9]

Of the new 8-azapurines required in the above reactions, 6-butylamino-8-methyl-8-azapurine (3b) was made by heating 5-cyano-4-dimethylaminomethyleneamino-2-methyl-1,2,3-triazole [7] with butylamine acetate, a procedure analogous to the preparation of the 6-methylamino-homologue (3a) in ref. 7; 6-butylamino-7-methyl-8-azapurine (3d) was made similarly. 7-Methyl-6-dimethylamino-8-azapurine (3c) was prepared by heating dimethylamine with 7-methyl-6-methylthio-8-azapurine.

In an alternative approach, 1,6-dihydro-6-imino-1,8-dimethyl-8-azapurine [10] (5a), boiled with N-hydrochloric acid for only 1 h, gave a 95% yield of the hydrochloride of the amidine (4a). That the imine (5a) reacted much faster than the isomeric amine (3a) is attributed to the relative closeness (to the bond to be broken) of the polarization-aiding methyl group. Similarly, the imines (5b—d) gave the amidines (4f—h), respectively. 9-Benzyl-1-butyl-1,6-dihydro-6-imino-8-azapurine (5d), required in this reaction, was prepared by a cold condensation of n-butylamine with 3-benzyl-4-ethoxymethyleneamino-1,2,3-triazole-5-carbonitrile; [10] it readily underwent a Dimroth rearrangement [11,12] in boiling ethanolic butylamine acetate to 9-benzyl-6-butylamino-8-azapurine (3f). The other imine intermediates (5b and c) were prepared as in ref. 10. Isolation of the amidines, whether from degradation of the amines (3) or the imines (5), was effected by adjusting the pH of the reaction mixture to 12 and (a) filtering off the amidine or (b), when it was too soluble in water, extracting it with a solvent (usually after evaporation to dryness).

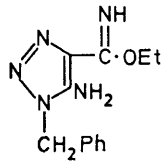
Alkaline degradation of the 8-azapurine imines (5), in cold N-sodium hydroxide, was complete in 30 min. The major products were, besides the required amidine (4), the corresponding 8-azapurine amines (3) formed by Dimroth rearrangement of the starting material (5) in about 20% yield. The 8-azapurine amines (3) resisted alkaline degradation under any conditions mild enough not to produce the triazole amides [8,13] corresponding to the amidines (4).

Attempts to synthesize the amidines (4) by standard procedures were unsuccessful. For example, 4-amino-3-benzyl-1,2,3-triazole-5-carbonitrile, heated with butylamine hydrochloride at 170° (conditions appropriate for the Bernthsen reaction), gave none of the expected amidine (4h). A Pinner reaction on the same nitrile, with ethanolic hydrogen chloride, produced the required formimidate, 4-amino-3-benzyl-5-ethoxy(imino)methyl-1,2,3-triazole (6), but this could not be induced to react with ammonia.

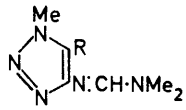
Properties.—These amidines are strong bases (pK_a

[5] M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Amer. Chem. Soc.*, 1960, **82**, 3189.
[6] Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, 1965, **30**, 2488.
[7] A. Albert, *J.C.S. Perkin I*, 1972, 461.
[8] A. Albert, *J. Chem. Soc.* (*C*), 1969, 2379.
[9] A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.
[10] A. Albert, *J.C.S. Perkin I*, 1973, 2659.
[11] D. J. Brown in ' Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience-Wiley, New York, 1968, vol 1, p. 209.
[12] D. D. Perrin and I. H. Pitman, *J. Chem. Soc.*, 1965, 7071.
[13] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.

9·3—10·4), but not as strong as benzamidine [14] (11·6) because of the demonstrated [15] greater electron-attracting



(6)



(7)

power of the triazole (than the benzene) ring. Formation of the cation is accompanied by a bathochromic shift in the u.v. absorption (Table 1) which indicates increased system bears no alkyl group [as with compound (4e)], melting is accompanied by evolution of ammonia and polymerization.

I.r. spectra of the amidines (Table 2) show N–H stretching in the 3200—3480 cm^{-1} region, also the expected [16] C=N stretching band between 1610 and 1660 cm^{-1}, as well as an N–H bending (Amidine II) band [16] between 1520 and 1610 cm^{-1}. The dimethylamino-compound (4c) characteristically [16b] shows a displacement of the C=N band to lower frequency; also a doublet due to Me_2N bending is seen at 1420 and 1410 cm^{-1}, and a band arising from asymmetric Me–N–Me stretching occurs at 1075 cm^{-1}.

TABLE 1

Ionization constants and u.v. spectra of 4-amino-1,2,3-triazole-5-carboxamidines

Amidine (4; R^3 = H)			Ionization in water (20°)				Spectroscopy [c] in water		
R^1	R^2	Species [a]	pK_a	Spread (±)	Concn. (M)	A.w.l.[b] (nm)	$\lambda_{max.}$/nm	log ε	pH
1-Me	Me	0					258	3·69	11·8
		+	9·26	0·04	10^{-3}	290	283	3·64	7·0
2-Me	Me	0					223, 266	3·80, 3·86	13·0
		+	10·39	0·03	10^{-4}	248	*227*, 278	*3·82*, 3·77	7·0
3-Bz	Me	0					229, 258	4·00, 3·91	12·2
		+	10·29	0·04	10^{-4}	285	*232*, 268	*3·84*, 3·96	7·0
3-H	H	−	12·23	0·04	10^{-4}	290	263	3·88	14
		Z					*234*, 276	*3·66*, 3·88	9·3
		+	6·38	0·05	10^{-4}	300	*227*, 272	*3·83*, 3·89	4·4
3-H	Me	−	12·41	0·05	10^{-4}	290	257	3·88	14
		Z					268	3·86	9·4
		+	6·35	0·05	10^{-4}	300	269	3·86	4·3

[a] Cation (+), anion (−), neutral (0), zwitterion (Z). [b] Analytical wave length. [c] Inflections in italics.

TABLE 2

I.r. spectra of 4-amino-1,2,3-triazole-5-carboxamidines (Nujol)

1,2,3-Triazole (4; R^3 = H)		
R^1	R^2	$\nu_{max.}$/cm^{-1}
1-Me	Me	3425s, 3330m, 3270m, 1655s, 1610m, 1425mw, and 1220mw
2-Me	Me	3365s, 3285m, 1610s, 1555s, 1425m, 1325m, 1225m, and 1185m (extra bands in hexachlorobutadiene mull: 2940w and 2810w). Hydrochloride: 3280m, 3190m, 3070m (NH^+ str.), 2800—2200br, 2100w, 1665s ($C{:}N^+$ str.), 1630s, 1580m, 1535m, 1305m, and 840m
3-$PhCH_2$	Me	3380br, m, 3280br, s, 1630br, s, 1525s, 1255m, and 745m
3-$PhCH_2$	H	3450m, 3330s, 3275m, 1635br, s, 1590m, 1270mw, 1260mw, and 745m
3-Me	H	Hydrochloride: 3280m, 3150br, s (NH^+ str.), 1670s ($C{:}N^+$ str.), 1640br, s, 1580br, s, 1335m, and 1020m
1-Me	Bu	3400s, 3330m, 3290m, 3210m, 1660br, s, 1615s, 1570m, 1515m, 1430m, 1210m, 1160m, and 780m
2-Me	Bu	3485m, 3365br, s, 1645br, s, 1595s, and 1005m
3-$PhCH_2$	Bu	3380s, 3280m, 1630br, s, 1520m, 1490m, 1270m, 1170m, and 800m
1-Me	Me [a]	3290s, 3140m, 1600br, s, 1565s, 1515m, 1420m, 1410m, 1310m, 1235m, 1075m, and 840m
3-H	H	3260br, s, 3070br, s (NH^+ str.), 2800—2200br, 1685s, 1580br, m, 1300mw, 1220m, and 1195m (extra bands in hexachlorobutadiene mull: 2940br, m and 2800br, m)
3-H	Me	3375m, 3300s, 3150br, s (NH^+ str.), 2800—2200br, 1600br, s, 1570br, s, 1275m, 1245m, 1075m, and 790m

[a] R^3 = Me.

conjugation of the cationic side-chain with the nucleus; this contrasts with the behaviour of the *N*-attached amidines, *e.g.* (7), described in ref. 7, which show a hypsochromic shift indicative of outward movement of the double bond in the side-chain during cation formation. The new amidines absorb carbon dioxide from the air but are otherwise stable in the solid state and, as follows from the methods of preparation and isolation, to hot dilute acid and cold very dilute alkali. In general they melt without decomposition, but when the amidine

The ^1H n.m.r. spectra (Table 3) of the amidines show a broad band about τ 3·5, removable by deuteriation, and attributed to NH in the amidine group; also another band (well-resolved because of hydrogen bonding) in the τ 4·2—5·2 region, characteristic [15] of a 4-amino-group in the 1,2,3-triazole series. Alkyl groups attached to a ring nitrogen atom display the same chemical shifts (Table 2) as in the correspondingly alkylated 4-amino-5-aminomethyl-1,2,3-triazoles,[15] whereas those attached to the amidine system give signals further upfield.

[14] A. Albert, J. A. Mills, and R. Royer, *J. Chem. Soc.*, 1947, 1452.

[15] A. Albert, *J.C.S. Perkin I*, 1973, 1634.

[16] (*a*) J. C. Grivas and A. Taurins, *Canad. J. Chem.*, 1961, **39**, 414; (*b*) J. Fabian, V. Delaroff, and M. Legrand, *Bull. Soc. chim. France*, 1956, 287.

Hydrochlorides, required for biological testing, were prepared by neutralization of the pure base with N-acid followed by evaporation of water at 40°; in two cases [compounds (4a and g)] they were obtainable by simple evaporation of the reaction mixture. All compounds which were recrystallized from the solvents shown in Table 4, were found to be highly soluble in cold water, and stable to drying in air at 80°. These amidine hydrochlorides did not react with acetone under conditions [17] that converted 2-aminobenzamidine to 1,2-dihydro-2,2-dimethylquinazoline. With boiling triethyl orthoformate, 4-amino-1-methyl-1,2,3-triazole-5-*N*-methylcarboxamidine hydrochloride gave a mixture of the 8-azapurine imine (5b) and the corresponding amine (3g).

TABLE 3

^{1}H N.m.r. spectra [34°; solvent $(CD_3)_2SO$] of 4-amino-1,2,3-triazole-5-carboxamidines

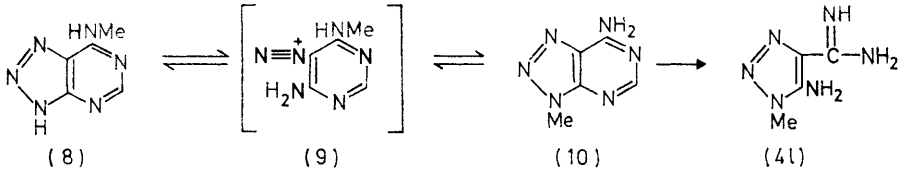
1,2,3-Triazole (4; R^3 = H)		τ Values [a]			
R^1	R^2	NH [b]	4-NH_2 [b]	R^1	R^2
1-Me	Me	3·7br	5·03 (2H)	6·00 (3H)	7·19 (3H)
2-Me	Me	3·85br, 6·62	4·25 (2H)	6·07 (3H)	7·17 (3H)
1-Me	Me [c]	3·0br	5·23 (2H)	6·17 (3H)	7·19 (6H)
3-$PhCH_2$	Me	4·0br		2·73 (5H), 4·62 (2H)	7·23 (3H)
3-H	Bu [d]				6·09 [e] (2H, t), 8·1 (4H, m), 8·61 (3H, t)

[a] Tetramethylsilane used as internal standard; all peaks are singlets except in the butyl compound. [b] Exchanged in D_2O. [c] R^3 = Me. [d] As formate in D_2O with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard. Extra peak at τ 1·47 (1H, HCO_2^-), *cf.* sodium formate (1·41) in same solvent. [e] Centres.

Zwitterions.—Three triazole amidines (4i—k) differ from those already discussed in possessing an acidic function that arises from the lack of an *N*-alkyl substituent in the triazole ring. It is shown here these three compounds are zwitterions. The simplest example, 4-amino-1,2,3-triazole-5-carboxamidine [5,6] (for which two improved preparations are given) is poorly soluble in cold water at pH 9, but soluble in N-sodium hydroxide and N-hydrochloric acid. It has two pK_a values, each of which differs markedly from the averaged value of the foregoing amidines; taken together these indicate the mutual enhancement of acidic and basic properties found in zwitterions, *e.g.* glycine.[18a] Thus the equilibrium between protonated and unprotonated amidine groups has the pK_a 12·23 for compound (4i) whereas it is 9·3—10·4 for the examples *N*-alkylated in the triazole ring (Table 1). Further, the value for the acidic ionization of the ring NH group is 6·38 in the zwitterion whereas it is 9·42 in the parent 1,2,3-triazole.[18b]

The u.v. spectra support the diagnosis that compound (4i) is an internal salt. Because the acidic ionization of the ring NH group in 1,2,3-triazole produces little spectral change,[19] and the normal amidines in the present series show marked bathochromic shifts on protonation, the large spectral shift in compound (4i), which occurs between pH 9·3 and 14, signifies the conversion of a zwitterion into an anion. Were this substance merely an amphion (*i.e.* not internally neutralized) the bathochromic shift should occur on passing from the neutral species to the cation, namely between pH 9·3 and 4·4. The strong, broad ammonium band [20] in the i.r. near 3100 cm^{-1} (Table 2) confirms the zwitterion structure, but the ammonium slope [20] between 2800 and 2100 cm^{-1} (most intense at the 2800 end) can be mimicked by hydrogen bonding, as in purine,[21] and hence lacks diagnostic value. Poor solubility defeated attempts to obtain n.m.r. data in a non-exchanging solvent.

Two homologues, the 4-amino-5-*N*-methyl-(and *N*-n-butyl-)carboxamidines (4j and k), were made by reductive debenzylation of the amidines (4g and h), respectively. Their physical properties, similar to those of compound (4i), indicate a similar zwitterionic nature. The butyl analogue (4h), being very hygroscopic, was best handled as the formate salt. Attempts to prepare these homologues by acidic hydrolysis of 6-methylamino -[10](and 6-butylamino-)8-azapurine gave only small yields because of an acid-catalysed rearrangement of the starting material to give 6-amino-9-methyl- [7](and 9-butyl-)8-azapurine respectively (see Scheme). The reaction was easily followed because the isomers of each pair had distinct R_F values.



(8) (9) (10) (4l)

SCHEME

This reaction [(8) ⇌ (10)], which is the retrogression * of a Dimroth-like [11] rearrangement, recalls the isomerization [22] of 2-amino-6-ethylamino- to 2,6-diamino-9-ethyl- 8-azapurine in boiling pyridine. However

* By convention,[11] a Dimroth ' rearrangement ' is the movement of a group from a ring to an exocyclic nitrogen atom, whereas a ' retrogression ' is the rarer reverse process.

[17] H. C. Carrington, *J. Chem. Soc.*, 1955, 2527.

[18] (*a*) A. Albert and E. P. Serjeant, ' The Determination of Ionization Constants,' 2nd edn., Chapman and Hall, London, 1971, ch. 7; (*b*) A. Albert in ' Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, **1**, 1.

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

[20] K. Nakanishi, ' Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1962, p. 39.

[21] J. H. Lister, ' Purines,' Wiley-Interscience, London, 1971, p. 505.

[22] C. Temple, B. H. Smith, and J. A. Montgomery, *J.C.S. Chem. Comm.*, 1972, 52.

there seems to be no precedent for acidic catalysis of a Dimroth retrogression. The present example probably begins after protonation of N-1 (usually the most basic nitrogen atom in an 8-azapurine) the positive charge of which should be shared with N-9 by a 4-aminopyridinium-type resonance.[23] It is proposed that combined electron depletion of N-8 and N-9 leads to breaking of the 8,9-bond to give the presumed intermediate (9). The rearrangement [(8) ⟶ (10)] did not occur in boiling water or pyridine but was favoured (72% conversion at equilibrium) by heating at 150° in dimethylformamide; dry heat at 290° produced complete rearrangement in 5 min and hence provides the most convenient known synthesis of 6-amino-9-methyl-8-azapurine (10). It follows that the apparent m.p. of 6-methylamino-8-azapurine is really that of the latter compound (10): both substances melt at 306—307° (with some decomposition) on steadily heating from room temperature.

The action of boiling N-hydrochloric acid on the amine (8) also produced a third compound, 4-amino-3-methyl-1,2,3-triazole-5-carboxamidine (4l) (see Scheme), which was more conveniently made by the action of acid on a pure specimen of the amine (10).

The 6-n-butylamino-8-azapurine (3h), mentioned in the foregoing, was prepared by the action of sodium in ammonia on the 9-benzyl derivative (3f), and better by heating 6-methylthio-8-azapurine with butylamine.

EXPERIMENTAL

U.v. spectra were first obtained with a Perkin-Elmer 450 recording spectrometer; peaks were then measured more accurately with a Cary 16 spectrometer used manually. I.r. spectra were taken (for mulls) with a Perkin-Elmer 257 grating instrument. N.m.r. spectra were determined at 34° with a Varian HA100 (100 MHz) 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 [developers (*a*) aqueous 3% NH_4Cl, and (*b*) butanol–5N-acetic acid (7 : 3)]. Material for analysis was dried, unless otherwise specified, at 80° and 0·01 mmHg.

8-*Azapurines*

6-*n*-*Butylamino*-8-*methyl*-8-*azapurine* (7-*Butylamino*-2-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*) (3b).—2-Methyl-4-dimethylaminomethyleneamino-1,2,3-triazole-5-carbonitrile [7] (0·18 g, 0·001 mol) and aqueous 2M-butylamine acetate (5 ml, 10 equiv.) were heated under reflux for 1 h. The solid deposited on chilling, collected and recrystallized from water (46 parts), gave 6-*butylamino*-8-*methyl*-8-*azapurine* (75% yield in 2 crops), m.p. 127° (Found: C, 52·5; H, 6·8; N, 41·1. $C_9H_{14}N_6$ requires C, 52·4; H, 6·8; N, 40·8%), τ [$(CD_3)_2SO$] 1·35br (exchangeable, NH), 1·67 (1H, 2-H), 5·57 (3H, 8-Me), 7·48 (2H, t, 1-H_2 of Bu), 8·3—8·8 (4H, complex m, 2- and 3-H_2 of Bu), and 9·07 (3H, Me of Bu). 1-Methyl-4-dimethylaminomethyleneamino-1,2,3-triazole-5-carbonitrile [7] similarly gave 6-*butylamino*-7-*methyl*-8-*azapurine* (75%), m.p. 167° (from 48 parts of water in 2 crops) (Found: C, 52·8; H, 6·6; N, 40·8%).

[23] A. Albert, ' Heterocyclic Chemistry,' Athlone Press, London, 1968, p. 84.

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

9-*Benzyl*-1-*n*-*butyl*-1,6-*dihydro*-6-*imino*-8-*azapurine* (3-*Benzyl*-6-*butyl*-6,7-*dihydro*-7-*imino*-v-*triazolo*[4,5-d]*pyrimidine*) (5d).—Butylamine (1·17 g, 2 equiv.) in ethanol (16 ml) was added to a stirred solution of 3-benzyl-4-ethoxymethyleneamino-1,2,3-triazole-5-carbonitrile [10] (2·04 g, 0·008 mol) in ethanol (80 ml) (prepared at 30° and cooled to 4°). After 15 min further stirring at 4°, the suspension was set aside overnight at 22°, then filtered. The crystals of 9-*benzyl*-1-*butyl*-1,6-*dihydro*-6-*imino*-8-*azapurine* (93% in 2 crops) had m.p. 139°, unchanged by recrystallization from 8 parts of ethanol (Found: C, 63·8; H, 6·4; N, 30·0. $C_{15}H_{18}N_6$ requires C, 63·8; H, 6·4; N, 29·8%), $\nu_{max.}$ (Nujol) 3225s (NH), 1660s (C:N), 1270m, 1175m, and 1125m cm^{-1}.

9-*Benzyl*-6-*n*-*butylamino*-8-*azapurine* (3-*Benzyl*-7-*butylamino*-v-*triazolo*[4,5-d]*pyrimidine*) (3f).—Aqueous 2N-butylamine acetate (5 ml, 4 equiv.) was added to the foregoing imine (1·41 g, 0·005 mol) dissolved in boiling ethanol (15 ml). The mixture, heated under reflux for 90 min, chilled overnight, and filtered, yielded 9-*benzyl*-6-*butylamino*-8-*azapurine* (90%), m.p. 138·5° (from 10 parts of ethanol) (Found: C, 63·8; H, 6·4; N, 29·7. $C_{15}H_{18}N_6$ requires C, 63·8; H, 6·4; N, 29·8%), $\nu_{max.}$ (Nujol) 3275m, 3205w (NH), 1640s (C:N), 1590m, and 1320s cm^{-1}.

6-*Dimethylamino*-7-*methyl*-8-*azapurine* (7-*Dimethylamino*-1-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*) (3c).—7-Methyl-6-methylthio-8-azapurine [24] (2 g, 0·011 mol) and dimethylamine (33% w/w in ethanol; 11 ml) were heated in a sealed tube at 95—100° for 4 h. Volatile material was removed at 65° and 25 mmHg. The residue, recrystallized from 3 parts of water then sublimed at 125° and 0·01 mmHg, yielded 6-*dimethylamino*-7-*methyl*-8-*azapurine* (80%), m.p. 136° (Found: C, 47·3; H, 5·5; N, 46·8. $C_7H_{10}N_6$ requires C, 47·2; H, 5·7; N, 47·2%), τ [$(CD_3)_2SO$] 1·61 (1H, H-2), 5·55 (3H, 7-Me), and 6·70 (6H, s, NMe_2).

6-*n*-*Butylamino*-8-*azapurine* (7-*Butylamino*-v-*triazolo*-[4,5-d]*pyrimidine*) (3h).—(a) *Preferred method.* 6-Methylthio-8-azapurine [25] (0·84 g, 0·005 mol), ethanol (5 ml), and butylamine (5 ml, 10 equiv.) were heated in a sealed tube at 120° for 5 h. Volatile material was removed at 80° and 25 mmHg, water (5 ml) was added to the residue, and the pH was adjusted to 3·7 with formic acid. The solid was filtered off and rubbed in a mortar with N-hydrochloric acid (25 ml), and the suspension was filtered. The filtrate, readjusted to pH 3·7 (with sodium formate and 10N-sodium hydroxide), gave 6-*butylamino*-8-*azapurine* (70%), m.p. 203° (from 20 parts of ethanol; 2 crops), soluble in about 1000 parts of boiling water (Found: C, 50·2; H, 6·3; N, 43·7. $C_8H_{12}N_6$ requires C, 50·0; H, 6·3; N, 43·7%), $\nu_{max.}$ (Nujol) 3260m, 3200m (NH), 2800—2020vbr (H-bonding), 1630s, 1610s, 1340s (C–NH str.), 1220m, and 915 cm^{-1}.

(b) Sodium (0·5 g, 3 equiv.) was added to 9-benzyl-6-butylamino-8-azapurine (3f) (1·0 g, 0·0036 mol) suspended in liquid ammonia (100 ml). After evaporation of the ammonia, water (5 ml) was added and the suspension acidified to pH 4·5 with citric acid. The precipitate, collected and recrystallized from ethanol, gave material (70%), m.p. 203°, identical with the foregoing.

6-*Amino*-9-*methyl*-8-*azapurine* (7-*Amino*-3-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*) (10) *by Retrogression.*—6-Methylamino-8-azapurine [10] (0·15 g, 0·001 mol) and dimethylformamide (2 ml) were heated under reflux for 14 h. The solvent was removed at 25 mmHg and (eventually) 100°.

[25] R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.*, 1960, **25**, 765.

The residue, rubbed with N-sodium hydroxide (2 ml) and filtered off, gave 72% of 6-amino-9-methyl-8-azapurine, m.p. 307°, identical with an authentic [7,25] specimen. For superior conversion by dry heat, see Discussion section.

1,2,3-*Triazoles*

The preparation of most examples of 4-amino-1,2,3-triazole-5-carboxamidines by the action of acid on 6-amino-(and 1,6-dihydro-6-imino-)8-azapurines is set forth in Table 4, together with properties of the products. The preparation of some other 1,2,3-triazoles follows.

4-Amino-1-methyl-1,2,3-triazole-5-NN-dimethylcarboxamidine (4c).—7-Methyl-6-dimethylamino-8-azapurine (see foregoing) (0·178 g, 0·001 mol) and N-hydrochloric acid (2 ml) were heated under reflux for 45 min (a critical time); the mixture was quickly chilled and adjusted to pH 12 with 10N-sodium hydroxide. The solution was taken to dryness at 40° and 25 mmHg. The powdered residue was boiled for 15 min with benzene (17 ml) and filtered hot. The reground residue was treated similarly. The combined filtrates, on concentration, deposited 60% of this *dimethylcarboxamidine*, m.p. 155° (from 140 parts of benzene) (Found: C, 42·5; H, 7·0; N, 50·3. $C_6H_{12}N_6$ requires C, 42·8; H, 7·2; N, 50·0%).

4-Amino-1,2,3-triazole-5-carboxamidine (4i).—(*a*) 6-Amino-8-azapurine [26] (0·68 g, 0·005 mol) and N-hydrochloric acid (10 ml) were heated under reflux for 2 h. The solution was taken to dryness at 40° and 25 mmHg. The residue and kieselguhr (0·05 g) were stirred with water (8 ml) and the suspension was filtered. The pH of the filtrate was adjusted to 9 with 2N-potassium carbonate. Refrigeration caused deposition of the title compound (in the zwitterionic form) in 72% yield, chromatographically homogeneous. It was recrystallized from 27 parts of water because the solubility in boiling 75% ethanol, as previously used,[5] was found to be only 1 in 210 (Found: C, 28·8; H, 4·9; N, 66·8. Calc. for $C_3H_6N_6$: C, 28·6; H, 4·8; N, 66·6%). The main by-product identified was 8-azapurin-6-one.[26]

(*b*) (For isolation of pure hydrochloride). 6-Amino-8-azapurine (0·136 g), 2N-hydrochloric acid (1 ml, 2 equiv.), and dioxan (5 ml) were heated under reflux for 4 h. Volatile material was removed at 40° and 25 mmHg, leaving an almost quantitative yield of the hydrochloride [6] of the title compound, m.p. 266° (effervesces), colourless, and chromatographically pure.

4-Amino-1,2,3-triazole-5-N-methylcarboxamidine (4j).—(*a*) 4-Amino-3-benzyl-1,2,3-triazole-5-*N*-methylcarboxamidine (4 g) (0·27 g, 0·001 mol) in ethanol (16 ml) was added to 8N-ammonia (in ethanol) (3 ml) and pre-reduced palladized carbon (10%; 0·1 g) and hydrogenated at 1 atm for 3 h at 70°. The suspension was filtered, and the filtrate taken to dryness at 40°. The residue, recrystallized from water (20 parts) while the pH was maintained at 9 with K_2CO_3 gave *4-amino-1,2,3-triazole-5-N-methylcarboxamidine* (70%), m.p. 229° (effervesces) (analysis in Table 4).

(*b*) 6-Methylamino-8-azapurine [10] (0·15 g, 0·001 mol) and N-hydrochloric acid (2 ml) were heated under reflux for 2 h. The cooled solution was adjusted to pH 3·7 with 10N-sodium hydroxide. The precipitate was collected, rubbed with N-sodium hydroxide (1 ml), and filtered. The alkali-insoluble portion (0·008 g) was identified as 6-amino-9-methyl-8-azapurine.[7,25] The alkaline solution, acidified to pH 4·7 with acetic acid, deposited 17% of starting material. The filtrate, set aside earlier at pH 3·7, was adjusted to pH 9 with 2N-potassium carbonate, and deposited 27% of 4-amino-1,2,3-triazole-5-*N*-methylcarboxamidine, m.p. 229°. Paper chromatography showed that 4-amino-3-methyltriazole-5-carboxamidine (see later) was abundantly present in the pooled filtrates.

4-Amino-1,2,3-triazole-5-N-butylcarboxamidine (4k).—

TABLE 4

Preparation of 4-amino-1,2,3-triazole-5-carboxamidines from 8-azapurines with boiling N-hydrochloric acid (2 equiv.)

Product (4; R^3 = H)								Found (%)				Required (%)		
R^1	R^2	Starting material	Reflux time (h)	Isolation method *	Recrystallization solvent	(parts)	M.p. (°C)	Yield (%)	C	H	N	Formula	C	H	N
2-Me	Me	(5a)	1	A,B	Benzene	(2·5)	90	95	39·2	6·5	54·9	$C_5H_{10}N_6$	39·0	6·5	54·5
2-Me	Me	(3a)	4	A,B	Benzene	(2·5)	90	92							
1-Me	Me	(5b)	1	C	Benzene	(150)	130	75	38·9	6·8	54·9	$C_5H_{10}N_6$	39·0	6·5	54·5
1-Me	Bu	(3b)	3	C	Benzene	(15) [c]	105	95	49·0	8·4	43·0	$C_8H_{16}N_6$	49·0	8·2	42·8
2-Me	Bu	(3d)	2	D	Cyclohexane	(26)	66	85	48·9	8·5	42·9	$C_8H_{16}N_6$	49·0	8·2	42·8
3-$PhCH_2$	Me	(5c)	2	A,D	Benzene	(12)	137	98	57·0	6·0	36·7	$C_{11}H_{14}N_6$	57·4	6·1	36·5
3-$PhCH_2$	Bu	(5d)	1	D	Cyclohexane	(80)	93	94	61·9	7·5	30·1	$C_{14}H_{20}N_6$	61·7	7·4	30·9
3-$PhCH_2$	H	(3e)	12	D	Benzene–ethanol (9 : 1)	(60)	156 [b]	65	55·8	5·8	39·1	$C_{10}H_{12}N_6$	55·5	5·6	38·9
3-H	Me	*a*		E	Water	(20)	229 [b]	70	34·2	5·6	60·3	$C_4H_8N_6$	34·3	5·7	60·0
3H	H	(3i)	2	E	Water	(27)	— [d]	90	28·9	4·9	66·8	$C_3H_6N_6$	28·6	4·8	66·6 [f]

Hydrochlorides		Solvent	M.p. (°C)	Cl (Found %)	Formula	Cl (Required %)
2-Me	Me	Ethanol	265	18·3	$C_5H_{11}ClN_6$	18·6
1-Me	Bu	Ethanol	201	15·3	$C_8H_{17}ClN_6$	15·2
2-Me	Bu	Ethanol	138 [e]	15·1	$C_8H_{17}ClN_6$	15·2
3-$PhCH_2$	Me	Ethanol–benzene (1 : 2)	173 [e]	13·2	$C_{11}H_{15}ClN_6$	13·3
3-$PhCH_2$	Bu	Water	184	11·5	$C_{14}H_{21}ClN_6$	11·5
3-$PhCH_2$	H	Ethanol	264	14·1	$C_{10}H_{13}ClN_6$	14·0

[a] For comparison, made by debenzylation. [b] With effervescence. [c] Two crops taken. [d] No definite m.p. [e] M.p. sensitive to trace of moisture. [f] Calculated (*i.e.* not a new compound).

* A. The hydrochloride was first isolated by evaporation at 40° and 25 mmHg; the next stage is indicated. B. The aqueous solution (pH 12) was shaken twice with two volumes of chloroform. C. The aqueous solution (pH 12) was evaporated to dryness at 40° and 25 mmHg, and the residue extracted with boiling benzene. D. The aqueous suspension (at pH 12) was filtered. E. The pH of the aqueous solution was adjusted to 9 with 2N-K_2CO_3, and the product filtered off.

[26] R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290.

(*a*) 4-Amino-3-benzyl-1,2,3-triazole-5-*N*-butylcarboxamidine (4h) (0·27 g, 0·001 mol) was hydrogenated like the methyl homologue. The catalyst was filtered off and the filtrate evaporated at 40° and 25 mmHg. Formic acid (0·055 g, 1·2 equiv.) was added to the hygroscopic residue dissolved in ethanol (1 ml). The solution was aside at −10°, and the *formate* salt of 4-*amino*-1,2,3-*triazole*-5-N-*butylcarboxamidine* (85%) was deposited; m.p. 160°, unchanged by recrystallization from 19 parts of ethanol (Found: C, 41·9; H, 7·4; N, 36·6. $C_7H_{14}N_6,CH_2O$ requires C, 42·1; H, 7·1; N, 36·8%).

(*b*) 6-Butylamino-8-azapurine (3h) was boiled with N-hydrochloric acid. Work-up similar to that for the reaction with 6-methylamino-8-azapurine gave 23% of the above formate, m.p. 159°, 22% of starting material, and 17% of the retrogression product 6-*amino*-9-*butyl*-8-*azapurine*, m.p. 184° (from 500 parts of water) (Found: C, 49·8; H, 6·3; N, 43·2. $C_8H_{12}N_6$ requires C, 50·0; H, 6·3; N, 43·7%).

4-*Amino*-3-*methyl*-1,2,3-*triazole*-5-*carboxamidine* (4l).—6-Amino-9-methyl-8-azapurine (3j) (0·15 g, 0·001 mol) and N-hydrochloric acid (2 ml), heated under reflux for 3 h and then refrigerated, deposited 4-*amino*-3-*methyl*-1,2,3-*triazole*-5-*carboxamidine hydrochloride* (30%); a small further crop was obtained by adding acetone (2 vol.) to the mother liquor. Recrystallized from a little water, it effervesced and blackened suddenly at 295° (Found: C, 27·5; H, 5·5; N, 47·2. $C_4H_9ClN_6$ requires C, 27·2; H, 5·1; N, 47·6%).

4-*Amino*-3-*benzyl*-5-*ethoxy*(*imino*)*methyl*-1,2,3-*triazole* (*Ethyl* 4-*Amino*-3-*benzyl*-1,2,3-*triazole*-5-*formimidate*) (6).—A solution of 4-amino-3-benzyl-1,2,3-triazole-5-carbonitrile[27] (0·40 g, 0·002 mol) in dried ethanol (75 ml) was saturated at −15° with dried hydrogen chloride. The solution, concentrated *in vacuo* to 30 ml and mixed with light petroleum (75 ml; b.p. 60—80°), gave crystals (90%) of the hygroscopic *hydrochloride* of the title compound, m.p. 235° (effervesces). For analysis, it was recrystallized from cold ethanol overlayered with ether (Found: C, 51·1; H, 5·6; N, 24·7. $C_{12}H_{16}ClN_5O$ requires C, 51·2; H, 5·7; N, 24·9%).

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[27] A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.