v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines).† Part X.[1,2] New Routes to *v*-Triazolo[4,5-*d*]pyrimidines *via* 4-Dimethylaminomethyleneamino-1,2,3-triazole-5-carbonitriles‡

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Treatment of various 4-amino-1,2,3-triazole-5-carboxamides with phosphoryl chloride in cold dimethylformamide gave the corresponding 4-dimethylaminomethyleneamino-5-carbonitriles, *e.g.* (1a). 2-Dimethylaminomethyleneaminobenzonitrile was similarly made from anthranilamide. An improved synthesis of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide is given. By-products from the reactions of this amide and its 2-methyl isomer with phosphoryl chloride and dimethylformamide were the 4-dimethylaminomethyleneamino-*N*-formyl amides (1b) and (2b), respectively. When melted, these cyclised to 1- and 2-methyl-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones (7- and 8-methyl-8-azapurin-6-ones), respectively; when subjected to mild alkaline hydrolysis they yielded 4-dimethylaminomethyleneaminotriazole-5-carboxamides, (1c) and (2c) respectively. The amide (1c) was also prepared from 4-amino-1-methyl-1,2,3-triazole-5-carboxamide, from 4-dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-carbonitrile, and from *S*-methyl 4-amino-1-methyl-1,2,3-triazole-5-thiocarboxylate (5). The *NN*-dimethylamide corresponding to (1c) was similarly prepared.

With boiling aqueous ammonium acetate, the 4-dimethylaminomethyleneamino-1- and 2-methyl-1,2,3-triazole-5-carbonitriles cyclised to 6-amino-7- and -8-methyl-8-azapurines. The 5-cyano-4-dimethylaminomethyleneamino-3-methyl isomer, a much weaker base, reacted only sluggishly. The 1- and 2-methyl isomers (1a) and (2a) were similarly cyclised by boiling aqueous methylamine acetate, and use of hot ethanolic sodium hydrogen sulphide gave 7- and 8-methyl-8-azapurine-6-thiones [*e.g.*, (6c)]. An improved synthesis of 1-methyl-*v*-triazolo-[4,5-*d*]pyrimidin-7(6H)-one (7-methyl-8-azapurin-6-one) (6a) from 4-amino-1-methyl-1,2,3-triazole-5-carboxamide is given.

Ionisation constants and u.v., i.r., and n.m.r. spectra are discussed.

8-AZAPURINES have previously been synthesised mainly by two routes: (*a*) ring-closure of 4,5-diaminopyrimidines with nitrous acid or an alkyl nitrite,[3,4] and (*b*) fusion of 4-amino-1,2,3-triazole-5-carboxamides with

† This series was previously entitled '1,2,3,4,6-Penta-azaindenes.'

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

[1] Part IX, A. Albert and W. Pendergast, preceding paper.

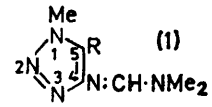
[2] Preliminary report, A. Albert, *Chem. Comm.*, 1970, 858.

[3] S. Gabriel and J. Colman, *Ber.*, 1901, **34**, 1249; R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290; P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 835.

[4] A. Albert, (*a*) *J. Chem. Soc.* (*B*), 1966, 427; (*b*) *J. Chem. Soc.* (*C*), 1969, 152.

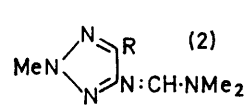
urea,[5] thiorea,[5] or formamide.[6,7] In a search for new routes, cyano-amidines of the 1,2,3-triazole series, *e.g.* (1a), were studied as promising intermediates because of (*a*) the ease of replacement of a tertiary (by a primary or secondary) amino-group in an amidine, and (*b*) the facility of addition across the triple bond of a cyano-group. 3-Benzyl-4-dimethylaminomethyleneamino-1,2,3-triazole-5-carbonitrile was recently prepared[8] by heating 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide with dimethylformamide and phosphoryl chloride. The yield has now been improved by conducting the reaction at room temperature, and the 1-, 2-, and 3-methyl analogues have been similarly prepared. (An improved preparation of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide is given.)

These cyano-amidines are stable to cold dilute acid and alkali and soluble in boiling water and benzene, and are characterised by a strong N=C stretching band at 1635—1640 cm^{-1}, and a ^1H n.m.r. signal (1H, s, N:CH) at τ 1·6—1·7. The low basic strength and large hypsochromic shift when the cation was formed (see Table), suggested that the cation was covalently hydrating,[9] but this hypothesis was disproved by the n.m.r. spectrum, which showed no upfield shift when the neutral species was added to aqueous acid. The unusual physical



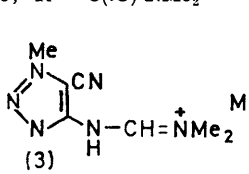
(1)

a; R = CN
b; R = C(:O)·NH·CHO
c; R = C(:O)·NH_2
d; R = C(:O)·SMe
e; R = C(:O)·NMe_2

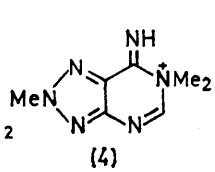


(2)

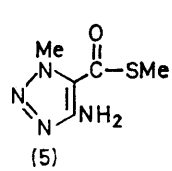
a; R = CN
b; R = C(:O)·NH·CHO
c; R = C(:O)·NH_2



(3)



(4)



(5)

properties were rationalised after an examination of dimethylaminomethyleneaminobenzene. The Table shows that this analogue has a pK_a of 8·71 (*cf.* 11·6 for benzamidine), and that of the 2-cyano-derivative (prepared from anthranilamide) is only 5·91. Given that the strength of an amidine is a measure of the ability of both nitrogen atoms to share the positive charge in the cation,[10] this ability must decrease in proportion as one nitrogen atom loses electron density (*a*) by participation in an aniline-like cross-resonance, and (*b*) from the inductive effect of a strong electron-attracting group (CN). Because 1,2,3-triazole is only weakly basic (pK_a 1·17),[7] it is certain that the ionisation under discussion occurs in the amidine side-chain of the 1- and 2-methyltriazoles (1a) and (2a). The 3-methyl isomer is a much weaker base, apparently because (as indicated by valency considerations) the negative charge (from the aniline-type resonance) can be accommodated in *two* positions of the ring (N-2 and C-5), but in only *one* position for each of its two isomers.

All five amidines show a strong hypsochromic shift when converted into the cation, the exocyclic double-bond of which tends to become fixed in the non-conjugated positions, as in (3). The conjugation between side chain and nucleus in the neutral species is evident from comparison with the u.v. spectra of 4-amino-3-methyl-1,2,3-triazole,[11] of which the neutral species absorbs at only 238 nm (log ε 3·73) [the cation absorbs at 259 (3·63), signifying protonation on a ring nitrogen atom [11a]]. The possibility that the cations of the cyano-amidines are cyclised to 8-azapurinium salts, such as (4), was discounted by examination of the i.r. spectrum of the 2-methyltriazole (2a) in 2·5N-hydrochloric acid solution contained between calcium fluoride plates. Absorption at 2250 cm^{-1} showed the persistence of the cyano-group, and a strong band at 1715 cm^{-1} could best be assigned to an unconjugated iminium (:C=N^+:) group, as in (3).

By-products.—Each of the 1- and 2-methyl-amidines (1a) and (2a) was accompanied by 6—7% of a by-product less soluble in organic solvents; these will be referred to as (IA) and (IIA), respectively. Elemental analyses and mass spectra established the molecular formula of each as $C_8H_{12}N_6O_2$. The solid state i.r. spectra [see Figure for that of (IA); that of (IIA) was almost identical] proved misleading.

When heated, both by-products melted, evolved dimethylamine formate, and re-solidified to give, quantitatively, 7-methyl-8-azapurin-6-one[6] (6a) and the 8-methyl isomer,[7] respectively. Because oxazines[12] and benzoxazines[13] are known to undergo thermal rearrangement to pyrimidines and quinazolines, respectively, it was provisionally supposed[2] that the by-products were triazolo-oxazines. However neither this formulation, nor that of the ring-opened tautomer such as 4-*N*-(dimethylaminohydroxymethyl)formamido-1-methyl-1,2,3-triazole-5-carbonitrile,[2] agreed sufficiently well with the ^1H n.m.r. data. These were as follows for (IA): τ ($CDCl_3$) −1·7br (1H), 0·52 (1H, d, *J* 11 Hz), 1·36 (1H, s), 5·71 (3H, s, NMe), and 6·83 and 6·88 (each 3H, NMe_2). Deuteriation removed the peak at τ −1·7, and the doublet collapsed to a singlet at τ 0·57. The peak at τ 1·36 was assigned to the proton of an amidine group (N=C*H*–NMe_2), of which many examples were on hand. The doublet near τ 0·5 was assigned, on the

[5] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1972, 449.
[6] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.
[7] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[8] A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.
[9] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[10] I. T. Millar and H. D. Springall (revisers), 'Sidgwick's Organic Chemistry of Nitrogen,' Clarendon Press, Oxford, 1966, p. 247.
[11] A. Albert, *J. Chem. Soc.* (*C*), 1969, 2379.
[11a] A. Albert, 'Heterocyclic Chemistry,' 2nd edn., Athlone Press, London, 1968, p. 382.
[12] D. J. Brown, 'The Pyrimidines,' Wiley–Interscience, New York, vols. 1 (1962) and 2 (1970).
[13] R. C. Elderfield, W. H. Todd, and S. Gerber, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1957, vol. 6, p. 564.

Ionisation constants and u.v. spectra

Compound	Species [a]	Ionisation in water (20°): pK_a	Spread ±	Concn. (M)	A.w.l.[b] (nm)	Spectroscopy in water [c]: $\lambda_{max.}$/nm	log ε	pH
(1a)	0					281	4·17	7·0
	+	3·51	0·03	0·01	P	253	4·21	1·0
(2a)	0					266	4·26	7·0
	+	3·68	0·04	0·01	P	244	4·27	1·0
4-Dimethylaminomethylene-amino-3-methyl-1,2,3-triazole-5-carbonitrile [d]	0					267	4·14	7·0
	+	0·59	0·04	0·00004	280	235	4·07	−1·6
Dimethylaminomethylene-aminobenzene								
Unsubstituted [e]	0					266	4·20	10·5
	+	8·71	0·01	0·01	P	249	4·19	6·0
2-Cyano-[f]	0					229, 271, *305*	4·28, 4·11, *3·89*	8·0
	+	5·91	0·02	0·0001	310	221, 240, 283	4·48, 4·14, 3·60	3·0
(1b)	0					215, 288	4·11, 4·25	M [g]
(2b)	0					208, 278	4·08, 4·30	M
(1c)	0					229, 276, 319	4·36, 4·00, 4·12	E [g]
(2c)	0					226, 281	4·33, 4·22	E
(2c)	0					285	4·22	C [g]
6-Methylamino-8-azapurine								
7-Methyl-	0					210, 291	4·12, 4·02	7·0
	+	2·74	0·03	0·00006	294	*215*, *288*, 293, *303*	*3·86*, *4·14*, 4·14, *3·96*	1·0
8-Methyl- (7b)	0					214, 250, 299	4·21, 3·38, 4·11	7·0
	+	3·72	0·04	0·0001	265	209, 287, 296, *308*	4·18, 4·12, 4·09, *3·84*	1·0

[a] Neutral species (0), cation (+). [b] Analytical wavelength for spectrometric determinations, when not marked P (potentiometric determination). [c] Shoulders in italics. [d] Stable at pH 0 and 20° for 1 h, after which the u.v. spectrum of neutral species was regenerated when pH was raised to 7. [e] Slowly hydrolysed at pH 10·5, hence readings were taken within 6 min of addition of stock solution to the buffer. [f] Stable at pH 1 and pH 13 (20°). [g] In methanol (M), ethanol (E), or chloroform (C).

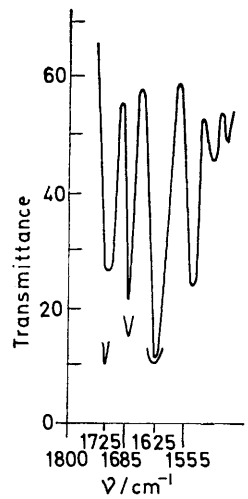
following evidence, to the proton of a formyl group coupled to the NH (τ −1·7) of a formamido-group.

No cyano-absorption could be demonstrated near 2200 cm^{-1} in the solid state i.r. spectrum; hence (IA) was re-examined in chloroform solution. This confirmed the lack of a cyano-group but disclosed two strong peaks (of comparable energy) at 1725 and 1685 cm^{-1}, assignable to the C=O stretching of two carbonyl groups (the former presumably a formyl group). The difference between these two spectra (Figure) is hard to explain, especially as *N*-formylbenzamide behaved normally, giving strong and equal C=O peaks at 1725 and 1695 cm^{-1} in Nujol, and similar peaks at 1749 and 1694 cm^{-1} in chloroform solution.

Both (IA) and (IIA) dissolved in cold 0·1N-sodium hydroxide (evidence of an acidic group) but the solutions soon deposited new substances of empirical formulae $C_7H_{12}N_6O$. This indicated that a formyl group had been lost under mild conditions [the new products will be referred to as (IB) and (IIB), respectively].

The mass spectrum of by-product (IA) showed the molecular ion (M^+ 224), with prominent loss of CO (28) (*m/e* 196; *m** 171·5), typical of diacylamines.[14] Other prominent peaks were at *m/e* 180, 164, 152, 135, 109, 83, 57, and 44; no loss of the N-1 methyl group as acetonitrile was observed.

All the foregoing evidence indicated that (IA) was 4-dimethylaminomethyleneamino-*N*-formyl-1-methyl-1,2,3-triazole-5-carboxamide (1b), and (IIA) was the 2-methyl isomer (2b). A review of the properties of diacylamines [15] refers to their fluorescence, a property shown by compounds (1b) and (2b) also. The isomeric *O*-formyl structures for these compounds were excluded by their stability in boiling methanol.



(a) (continuous curve): solid state i.r. spectrum of by-product (IA) in Nujol; (b) (shown as tips of the three principal peaks): i.r. spectrum of by-product (IA) in chloroform (1% solution in 0·5 cm cell)

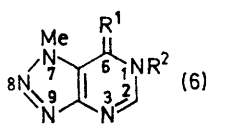
[14] C. Nolde, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, 1968, **24**, 1051.

[15] J. B. Polya and T. M. Spotswood, *Rec. Trav. chim.*, 1949, **68**, 573.

This interpretation was confirmed by examination of the degradation products (IB) and (IIB), which, when heated, melted with evolution of dimethylamine and then solidified to give (quantitatively) 7-methyl-8-azapurin-6-one (6a) [6] and its 8-methyl isomer,[7] respectively. The i.r. and n.m.r. spectra of (IB) and (IIB) were compatible with the structures (1c) and (2c), respectively.

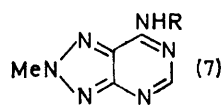
These assignments were confirmed by two syntheses of (IB). The cyano-amidine (1a) furnished (IB) by simple hydration in cold, alkaline hydrogen peroxide solution. *S*-Methyl 4-amino-1-methyl-1,2,3-triazole-5-thiocarboxylate (5) was converted into the corresponding amidine (1d) by phosphoryl chloride in dimethylformamide. Because *S*-methyl 1,2,3-triazole-5-thiocarboxylates have been shown [11] to yield the corresponding amides with aqueous ammonia at 25°, the amidine (1d) was treated similarly, and it gave (IB) in high yield. The corresponding dimethylamide (1e) was similarly made, to test the generality of this reaction. Finally, a high yield of by-product (IA) was obtained by the action of phosphoryl chloride in cold dimethylformamide on 4-amino-1-methyl-1,2,3-triazole-5-carboxamide by using less phosphoryl chloride than in the usual preparation of the cyano-amidine (1a), for which this by-product seems to be an intermediate.

The formylation of the amide (1c) to give the formamide (1b) did not take place in boiling formic acid (all starting material recovered) or in cold acetic formic anhydride (starting material decomposed). However when the amide (1c) was stirred with phosphoryl chloride in cold dimethylformamide, as in the preparation of the cyano-amidine (1a), the usual proportion of the by-product (1b) was obtained. The by-product, when treated similarly, remained unchanged. Thus the amide (1c) appeared to be the precursor of the formamide (1b), especially as the cyano-amidine (1a) gave none of the formamide (1b) under these conditions. Finally the amide (1c), when boiled with N-hydrochloric acid, a reagent known [2,8] to hydrolyse this type of amidine



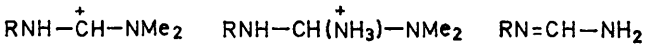
(6)

a; R^1 = O, R^2 = H
b; R^1 = NH, R^2 = Me
c; R^1 = S, R^2 = H



(7)

a; R = H
b; R = Me



(8) (9) (10)

group, furnished 4-amino-1-methyl-1,2,3-triazole-5-carboxamide, but in only moderate yield because the latter decomposes under these conditions.

New Synthetic Method.—Two of the cyano-amidines (1a) and (2a), when boiled in water with an excess of ammonium acetate (initial pH 6·9), gave high yields of 6-amino-7- and 8-methyl-8-azapurine, *e.g.* (7a). When ammonium chloride or carbonate (initial pH 4·8 and 9·0, respectively) replaced the acetate, the yields were far lower, and the free base (sealed tube) gave only a trace of product. That an optimum pH exists between extremes (as in the combination of acetone with hydroxylamine) suggested the following mechanism. The amidine group, as in (2a), first forms a cation, the delocalised charge of which resides partly on the carbon atom as in (8). This, being an electrophilic reagent, attacks the neutral species of ammonia to give (9). The latter undergoes fission to dimethylamine and the primary amidine (10). The cyclisation of this substance to the amino-8-azapurine, *e.g.* (7a), should not be highly dependent on pH because either the carbonium ion of the (protonated) nitrile group, or the neutral nitrile is competent to add the neutral species or the anion (respectively) of the amidine side chain.

The ammonium acetate reaction is more convenient for preparing 6-amino-7- or 8-methyl-8-azapurine than existing methods.[6,7] However this reaction furnished only a 14% yield from the isomeric 4-dimethylaminomethyleneamino-3-methyl-1,2,3-triazole-5-carbonitrile because of the much lower basic strength (see Table). Lowering the pH progressively, to compensate for this, so reduced the concentration of free ammonia that hydrolysis to 4-amino-3-methyl-1,2,3-triazole-5-carbonitrile [11] (a slower reaction proceeding by a similar mechanism) took precedence at about pH 2·5.

The cyano-amidine (2a) reacted similarly with methylamine acetate to give 6-methylamino-8-methyl-8-azapurine (7b), which showed the expected coupling between NH and Me groups in the n.m.r. spectrum. No coupling was detectable in the product from the 1-methyl-amidine (1a), but this was undoubtedly the 6-methylamino-7-methyl derivative because it differed markedly in physical properties from 1,6-dihydro-6-imino-7-methyl-8-azapurine (6b) (m.p. 217°; available from concurrent work). It is likely that such imines are intermediates in the reaction with methylamine acetate, but that, at the temperature required for rapid amidine exchange (100°), the excess of reagent brought about a Dimroth rearrangement.[16] The cyano-amidines did not react with dimethylamine acetate in boiling methanol, a result that excludes the possibility that addition to the cyano-group precedes amidine exchange.

Finally, the cyano-amidines (1a) and (2a) reacted with ethanolic sodium hydrogen sulphide to give high yields of 7- and 8-methyl-8-azapurine-6-thione, respectively. The former thione (6c) has previously been prepared [6] only from 6-chloro-7-methyl-8-azapurine and thiourea. In the Experimental section it is shown how it can also be made from phosphorus pentasulphide and the 7-methyl-6-one (6a) (an improved synthesis of the latter is also given). 8-Methyl-8-azapurine-6-thione has been prepared from 8-methyl-8-azapurin-6-one and phosphorus pentasulphide,[7] but for both the thiones

[16] D. J. Brown, in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley–Interscience, New York, 1968, vol. 1, 209.

the present synthesis from cyano-amidines is the most advantageous because of the milder conditions.

Compound (1b) injected intraperitoneally into mice, depressed and stimulated portions of the central nervous system, progressively with increasing dose, until death occurred at 2·4 g per kg.

EXPERIMENTAL

Addition of vanadium pentoxide was necessary to effect the complete combustion of the aminotriazolopyrimidines in elemental analysis. U.v. spectra were measured with a Perkin-Elmer model 450 recording spectrometer, and the wavelengths and intensities of maxima were confirmed with an Optica CF4 manual instrument. I.r. spectra were taken (for mulls in Nujol or hexachlorobutadiene where marked N or H, respectively) with a Unicam SP 200 spectrophotometer and [for solutions in chloroform (C)] with a Perkin-Elmer model 21 instrument. N.m.r. spectra were determined with a Perkin-Elmer model R10 spectrometer operating at 33·3° and 60 MHz, with tetramethylsilane as internal standard for [$^2H_6$]DMSO (*i.e.* perdeuteriodimethyl sulphoxide) and $CDCl_3$, and sodium trimethylsilylpropanesulphonate for DCl. R_F Values refer to chromatography (ascending) on Whatman no. 1 paper (developer aqueous 3% NH_4Cl) viewed under light of 254 nm.

Chemical identity of two specimens was established by mixed m.p. (where practicable), paper chromatography as just described and in butanol–acetic acid, and i.r. spectra.

3-Benzyl-4-dimethylaminomethyleneamino-1,2,3-triazole-5-carbonitrile.—To 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide [8] (0·22 g, 0·001 mol), in dimethylformamide (1 ml) at 20°, phosphoryl chloride (0·17 ml, 0·002 mol) was slowly added. The solution was set aside at 25° for 50 h. Ice (2 g) was added, then 14N-ammonia (*ca.* 0·6 ml) until pH 8 was reached. Chilling and filtration furnished 92% of the amidine, m.p. 118°, identical with material obtained previously.[8]

4-Dimethylaminomethyleneamino-3-methyl-1,2,3-triazole-5-carbonitrile.— 4-Amino-3-methyl-1,2,3-triazole-5-carboxamide [11,17] (1·4 g, 0·01 mol) was stirred at 25° with dimethylformamide (5 ml) while phosphoryl chloride (1·7 ml, 0·02 mol) was added dropwise. The viscous solution was stirred at 25° for 2 h more. Ice (8 g) was added. When it had melted and the mixture was homogeneous, the container was placed in a bath maintained at 10° while aqueous 14N-ammonia (*ca.* 4 ml) was added (to pH 2·5). The precipitate, filtered off after 15 min and recrystallised from 40 parts of water (or 12 parts of benzene) gave the *cyano-amidine* (85%), m.p. 131° [Found (material dried in air at 95°): C, 47·1; H, 5·7; N, 47·25. $C_7H_{10}N_6$ requires C, 47·2; H, 5·7; N, 47·2%], $\nu_{max.}$ (N) 2260w (C≡N str.), 1640s (C=N str.), 1570s, 1445m, 1410m, and 1130m cm^{-1}, τ ([$^2H_6$]DMSO) 1·69 (1H, s, :CH), 6·21 (3H, s, 3-CH_3), and 6·83 and 6·92 (in all 6H, NMe_2).

2-Methyl Isomer (2a).—4-Amino-2-methyl-1,2,3-triazole-5-carboxamide [7] (1·4 g) was treated similarly, except that the pH was adjusted to 5·5 with 14N-ammonia (*ca.* 6 ml), and the mixture was filtered after 15 min. The precipitate, dried at 20°, was heated under reflux with benzene (10 parts) for 15 min. The suspension was cooled, set aside at 20—25° for 1 h, and filtered. The filtrate, taken to dryness, gave *4-dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-5-carbonitrile* (85%), m.p. 92° (from 40 parts of water, or 80 of cyclohexane), and soluble in 5 parts of benzene or 22 of ethanol, at 25° [Found (for material dried in air at 85°): C, 46·9; H, 5·8; N, 47·0%], $\nu_{max.}$ (N) 2220w (C≡N), 1635s (C=N), 1535s, 1445m,br, 1405m, and 1105m cm^{-1}, τ([$^2H_6$]-DMSO) 1·73 (1H, s, :CH), 5·89 (3H, s, 2-CH_3), and 6·88 and 6·98 (6H, NMe_2), spectrum unchanged by addition of D_2O, τ (0·1N-DCl) 1·27, 5·70, 6·45, and 6·58.

4-Dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-carbonitrile (1a).—4-Amino-1-methyl-1,2,3-triazole-5-carboxamide (see later) (1·4 g) was treated like the foregoing isomer, but the quantity of ice was restricted to 4 g because of the high solubility of this isomer in water. The product, filtered off after 15 min at pH 5·5, was heated under reflux with benzene (4 parts) for 15 min; the mixture was set aside at 20—25° for 3 h, and filtered. The filtrate, taken to dryness, gave the *cyano-amidine* (1a), m.p. 93—95°. Recrystallisation from a variety of solvents did not improve this product. However, the m.p. was raised to 99° by chromatography in benzene solution on a short column of alumina, or by grinding in a mortar with 2 parts of 2N-ammonia for exactly 2 min [to remove the formamide (1b) before it could be hydrolysed], filtering, pressing, and recrystallization from 2 parts of water (or 100 of cyclohexane) * (yield 60%) [Found (material dried at 80°): C, 47·1; H, 5·9; N, 47·6%], $\nu_{max.}$ (N) 2210w (C≡N), 1630s (C=N), 1550s, 1415m, and 1110m cm^{-1}, τ ($CDCl_3$) 1·57 (1H, s, :CH), 5·89 (3H, s, 1-CH_3), 6·93 (6H, s, NMe_2) (0·1N-DCl) 1·23, 5·61, 6·47, and 6·61 (6H, NMe_2). When 8N-potassium hydroxide replaced the 14N-ammonia in this preparation the yield was unchanged. No improvement was effected by increasing the amount of phosphoryl chloride to 0·025 mol.

4-Amino-1-methyl-1,2,3-triazole-5-carboxamide.— The following is an improvement over the method given in ref. 6. 4-Amino-3-benzyl-5-carbamoyl-1-methyl-1,2,3-triazolium toluene-*p*-sulphonate [6] (11·5 g) was hydrogenated in a mixture of ethanol (200 ml) and aqueous 2N-ammonia (100 ml) over freshly reduced 10% palladium–carbon (2 g) at 75° and 4—20 atm pressure for 3 h. Kieselguhr (0·2 g) was added and the mixture was filtered at 70°. The residue was briefly boiled with ethanol (40 ml). The combined filtrates were taken to dryness. The residue was boiled with nitromethane (15 parts) for 15 min and filtered hot. The filtrate, set aside at −5°, deposited 4-amino-1-methyl-1,2,3-triazole-5-carboxamide (82%), m.p. 174°, identical with material previously obtained. It was soluble in 28 parts of boiling ethanol and 10 parts of cold water.

Dimethylaminomethyleneaminobenzene Hydrochloride.— This was made according to ref. 18.

2-Dimethylaminomethyleneaminobenzonitrile.— 2-Aminobenzamide [19] (1·36 g, 0·01 mol) was stirred at 25° with dimethylformamide (10 ml) while phosphoryl chloride (1·7 ml, 0·02 mol) was slowly added. The solution, which soon began to deposit crystals, was stirred for 2 h longer. Acetone (40 ml) was added, and the homogenised suspension was stored overnight at −5°. Next day the salts were filtered off, washed with acetone, air-dried, and dissolved in cold water (10 ml). The solution, immersed in ice, was stirred while 8N-potassium hydroxide (*ca.* 2·5 ml) was added

* Purification was conveniently monitored by paper chromatography: R_F 0·85 (dark), 0·60 (streaks, violet fluorescence), and 0·65 (dark) for compounds (1a), (1b), and (1c), respectively.

[17] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001.
[18] H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, 1959, **92**, 837.
[19] H. Kolbe, *J. prakt. Chem.*, 1884, **30**, 467.

slowly (to pH 9·0). The suspension was refrigerated overnight and filtered to give the *nitrile* (88%), m.p. 38·5° (from dilute methanol) [Found (material dried at 25° and 0·1 mmHg): C, 69·05; H, 6·5; N, 24·7. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%], τ ([$^2H_6$]DMSO) 1·90 (1H, s, HC:N), 2·2—2·5 and 2·6—2·9 (4H, multiplets, ring protons), 6·9 (6H, s, Me_2), no exchange with D_2O, τ (DCl) 1·14, 1·8—2·3, and 6·49 and 6·58 (2 × 3H, Me_2).

4-*Dimethylaminomethyleneamino*-N(5)-*formyl*-1-*methyl*-1,2,3-*triazole*-5-*carboxamide* (1b) [*By-product* (IA)].—The benzene-insoluble fraction from the preparation of the cyano-amidine (1a) was ground with cold water (4 ml) and filtered. The solid, dried at 20° and recrystallised from 70 parts of methanol or 20 of benzene, gave 6% of the *formamide*, m.p. 187° (introduced at 160°) [Found (material dried at 85° in air): C, 43·1; H, 5·3; N, 37·6. $C_8H_{12}N_6O_2$ requires C, 42·85; H, 5·4; N, 37·5%], $\nu_{max.}$ (N) 1720m, 1680ms, 1625s, 1560m, and 1190m, $\nu_{max.}$ (C) 3120w,sh, 2930m,br (NH), 1725s (C=O), 1685s (C=O), 1625s,br (N=C), 1555m, 1505m, 1370s, 1180m, 1130m, and 1105m cm^{-1}; for τ values see Discussion section.

4-*Dimethylaminomethyleneamino*-N(5)-*formyl*-2-*methyl*-1,2,3-*triazole*-5-*carboxamide* (2b) [*By-product* (IIA)].—The benzene-insoluble residue obtained when preparing the cyano-amidine (2a) was triturated with water (5 ml), filtered off, dried at 20°, and recrystallised from methanol (300 parts) to give the *formamide* (7%), m.p. 217° [Found (material dried at 80° in air): C, 42·8; H, 5·4; N, 37·8%], $\nu_{max.}$ (N) 1730m, 1680ms, 1635s, 1545m, 1525m, and 1190m cm^{-1}, $\nu_{max.}$ (H) additional bands at 3420w, 3010m, 2950m, and 1355m cm^{-1}, τ ($CDCl_3$) −1·4 (1H, s, NH), 0·54 (1H, d, CHO, *J* 10 Hz), 1·64 (1H, s, N=CH), 5·79 (3H, s, NMe), and 6·76 (6H, s, NMe_2) (the −1·4 peak disappeared and the doublet collapsed to a singlet when D_2O was added), τ (0·1N-DCl) 0·69, 1·19, 5·71, and 6·44 and 6·58 (6H in all, NMe_2).

N-*Formylbenzamide*.—This was prepared by the method of Einhorn *et al.*[20] (oxidation of *N*-hydroxymethylbenzamide); $\nu_{max.}$ (CCl_4) 1742s, 1730s, 1700s, 1688s, 1458s, 1359m, and 1160m,br cm^{-1}.

4-*Dimethylaminomethyleneamino*-1-*methyl*-1,2,3-*triazole*-5-*carboxamide* (1c) [*By-product* (IB)].—(*a*) The formamide (1b) (0·22 g, 0·001 mol) was stirred with 0·5N-sodium hydroxide (4 ml) for 1 h. The precipitate, filtered off and crystallised from 9 parts of water, gave the *carboxamide*, m.p. 168°, soluble also in boiling methanol and benzene [Found (material dried in air at 110°): C, 42·6; H, 6·1; N, 42·9. $C_7H_{12}N_6O$ requires C, 42·85; H, 6·2; N, 42·8%], $\nu_{max.}$ (N) 3350, 3170m (NH_2), 1670s (C=O), 1650s, 1610s, 1555m, and 1345m, $\nu_{max.}$ (H) 2590w, 1435m, 1405m, and 1380m cm^{-1} (in addition to the foregoing), τ ($CDCl_3$) 1·31 (1H, s, N=CH), 3·9br (*ca.* 2H, NH_2), 5·64 (3H, s, NMe), and 6·81 and 6·88 (in all 6H, NMe_2) (the 3·9 signal was removed by D_2O), τ (0·1N-DCl) 1·43, 5·77, 6·55, and 6·68.

(*b*) To the cyano-amidine (1a) (0·18 g, 0·001 mol), dissolved in 25 parts of cold water, were added 10M- (100 vol) hydrogen peroxide (1·0 ml, 5 equiv.) and 10N-sodium hydroxide (0·05 ml). After 12 h at 25° the amide (1c) was filtered off and recrystallised from water; yield 87%, m.p. 167°.

(*c*) Phosphoryl chloride (0·85 ml, 0·01 mol) was added dropwise to a suspension of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide (1·4 g, 0·01 mol) in dimethylformamide (5 ml) at 25°. Stirring was continued for 2 h. Ice (4 g) was added, and as soon as the mixture was homogeneous the flask was placed in a bath maintained at 10° while 14N-ammonia (*ca.* 2·5 ml) was added (to pH 5·5). After 15 min more at 10°, the suspension was filtered. The solid, dried at 20°, was boiled with 4 volumes of benzene; the mixture was cooled and filtered [filtrate gave 15% of the cyano-amidine (1a)]. The solid was rubbed with water (9 ml) and filtered off (saline filtrate discarded). The residue was rubbed with 0·5N-sodium hydroxide (5 ml) to hydrolyse a little of the formamide [(1b) detected by paper chromatography], filtered off, and recrystallised from water (9 parts) to give the amide (1c) (54%), m.p. 167°.

(*d*) *S*-Methyl 4-dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-thiocarboxylate (0·7 g) (see later) in ethanolic 8N-ammonia (25 ml) was set aside for 18 h at 25°. Removal of the volatile components at 40° left the carboxamide (1c) (99%), m.p. 166°.

4-*Dimethylaminomethyleneamino*-2-*methyl*-1,2,3-*triazole*-5-*carboxamide* (2c) [*By-product* (IIB)].—The formamide (2b), treated with 0·5N-sodium hydroxide as was the 1-methyl isomer (1b) gave the *carboxamide* (1c) (86%), m.p. 193° (when inserted at 185°) [Found (material dried at 85° in air): C, 42·5; H, 6·3; N, 42·6%], $\nu_{max.}$ (N) 3370s, 3250m,br, 1675s (C=O), 1640s,br, 1600s, 1525s, 1405m, 1365m, 1330m, and 1110m cm^{-1}, τ ($CDCl_3$) 1·67 (1H, s, N:CH), 3·5br (exchangeable), 5·90 (3H, s, NMe), and 6·88 and 6·96 (in all 6H, NMe_2), τ (0·1N-DCl) 1·22, 5·76, 6·50, and 6·64.

v-*Triazolo*[4,5-d]*pyrimidin*-7(6H)-*ones* (8-*Azapurin*-6-*ones*) *from Fusion Reactions*.—The amidine (1c) (0·5 g), heated (dry) in a bath at 180° for 10 min, gave (quantitatively) 1-methyl-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (7-methyl-8-azapurin-6-one), m.p. 264° (lit.,[6] 262°). The carboxy-formamide (1b) was converted quantitatively into the same 8-azapurine, and the isomeric amide (2c) and formamide (2b) were converted quantitatively into the 8-methyl-8-azapurin-6-one, m.p. 261° (lit.,[7] 261°) by heating for 10 min at a bath temperature 12—15° above the m.p.

S-*Methyl* 4-*Amino*-1-*methyl*-1,2,3-*triazole*-5-*thiocarboxylate* (5) (*Improved Method*).—1-Methyl-7-methylthio-*v*-triazolo-[4,5-*d*]pyrimidine (7-methyl-6-methylthio-8-azapurine) [6] (1·1 g, 0·006 mol) and 2N-hydrochloric acid (6·25 ml) were heated under reflux for 10 min, and chilled overnight. The solid, recrystallised from 12 parts of water, gave the triazole (80%), m.p. 132°, identical with material obtained earlier.[11]

S-*Methyl* 4-*Dimethylaminomethyleneamino*-1-*methyl*-1,2,3-*triazole*-5-*thiocarboxylate* (1d).—The ester (5) (1·04 g, 0·006 mol) was stirred with dimethylformamide (3 ml) while phosphoryl chloride (1·02 ml, 0·012 mol) was slowly added. The solution was set aside at 20° for 10 min, heated at 85° for 30 min, and cooled to 20°. Ice (9 g) was added, then powdered potassium hydrogen carbonate (*ca.* 5·4 g) to give pH 7·5. The suspension was refrigerated and filtered. The solid, recrystallised from the minimum of water, gave the *ester* (1d) (80%), m.p. 99° [Found (material dried at 25° and 25 mmHg): C, 42·0; H, 5·95; N, 30·5; S, 14·1. $C_8H_{13}N_5OS$ requires C, 42·3; H, 5·8; N, 30·8; S, 14·1%], $\nu_{max.}$ (N) 1615s,br (C=O), 1555s, 1175m, 1120m, 915s (:C−S str.) (no band above 1700) cm^{-1}, τ ([$^2H_6$]DMSO) 1·40 (1H, s, N:CH), 5·81 (3H, s, 1-Me), 6·84 and 6·89 (in all 6H, NMe_2), and 7·68 (3H, s, SMe); signals unchanged by addition of D_2O.

4-*Dimethylaminomethyleneamino*-1,N(5),N(5)-*trimethyl*-1,2,3-*triazole*-5-*carboxamide* (1e).—The thiol ester (1d) (0·23

[20] A. Einhorn, E. Bischkopff, and B. Szelinski, *Annalen*, 1905, **343**, 223.

g, 0·001 mol) and ethanolic 33% w/w dimethylamine (5 ml, 20 equiv.) were set aside at 25° for 24 h. The solvent was removed *in vacuo*. The viscous residue was extracted with boiling cyclohexane (3 × 4 ml) and the product was recrystallised from the same solvent (40 parts) to give the *dimethylamide* (70%), m.p. 73°, very soluble in cold water [Found (material dried at 23° and 0·01 mmHg): C, 48·4; H, 7·5; N, 37·0. $C_9H_{16}N_6O$ requires C, 48·2; H, 7·2; N, 37·5%], $\nu_{max.}$ (N) 1635s,br, 1565m, 1515m, 1410m, 1125m, and 1095m (no band above 1700) cm^{-1}, τ ([$^2H_6$]DMSO), 1·52 (1H, s, N:CH), 5·97 (3H, s, Me), and 6·9 (12H, 2 × NMe_2).

7-*Amino*-v-*triazolo*[4,5-d]*pyrimidines* (6-*Amino*-8-*azapurines*).— 4-Dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-5-carbonitrile (0·18 g, 0·001 mol), ammonium acetate (0·3 g, 0·004 mol), and water (3 ml), when heated under reflux for 30 min, refrigerated, and filtered, yielded the 2-methyltriazolopyrimidine (6-amino-8-methyl-8-azapurine) (7a) (80%), m.p. 266° (lit.,[7] 264°), $\nu_{max.}$ (N) 3390, 3140 (NH_2), 1670, 1610, 1570, and 1255 (all m) cm^{-1}. (When ammonium chloride was substituted for the acetate, the yield fell to 7%.) The isomeric 1-methyl cyano-amidine (1a), similarly treated with ammonium acetate, gave 6-amino-7-methyl-8-azapurine (87%),[6] $\nu_{max.}$ (N) 3350, 3120, 1665, 1645, 1605, 1570, and 1220 (all m) cm^{-1}. The 4-dimethylaminomethyleneamino-3-methyl-5-carbonitrile (0·18 g), ammonium acetate (0·3 g), and water (5 ml) were heated under reflux for 3 h. The solution, refrigerated overnight, gave a precipitate which was dried and extracted with boiling benzene (2 ml). The residue was the 6-amino-9-methyl-8-azapurine,[4,21] $\nu_{max.}$ (N) 3270, 3090, 1690, 1615, 1585, and 1230 (all m) cm^{-1}. These last two triazolopyrimidines decompose before melting. The initial pH in this reaction was 6·9; at pH 9·0, all the starting material was recovered; at pH 4·4, the yield was 7%; at pH 2·4 ($NH_4H_2PO_4$), the only product was 4-amino-3-methyl-1,2,3-triazole-5-carbonitrile [11] (50%), m.p. 229—230°.

7-*Methylamino*-v-*triazolo*[4,5-d]*pyrimidines* (6-*Methylamino*-8-*azapurines*).—The cyanoamidine (2a) (0·18 g, 0·001 mol), methylamine acetate (0·45 g, 0·005 mol), and methanol (3 ml) were refluxed for 30 min, then taken to dryness. The residue, triturated with water (1 ml), gave the 2-*methyl*-7-*methylaminotriazolopyrimidine* (8-*methyl*-6-*methylamino*-8-*azapurine*) (88%) (from 40 parts of water), m.p. 255° [Found (material dried at 110° and 0·1 mmHg): C, 43·6; H, 4·85; N, 50·8. $C_6H_8N_6$ requires C, 43·9; H, 4·9; N, 51·2%], τ ([$^2H_6$]DMSO), 1·1br (1H, NH), 1·36 (1H, s, H-5), 5·44 (3H, s, 2-Me), and 6·91 (3H, d, NH*Me*, *J* 6 Hz) (addition of D_2O removed the signal at 1·1 and the doublet collapsed to a singlet). The isomeric 1-methyl-cyano-amidine (1a) (0·18 g), methylamine acetate (0·45 g), and water (2 ml), heated under reflux for 30 min, cooled, and filtered, gave the 1-*methyl isomer* (7-*methyl*-6-*methylamino*-8-*azapurine*) (81%), m.p. 302° (from 80 parts of water) [Found (material dried at 110° in air): C, 43·8; H, 5·2; N, 51·05%], τ (DMSO), 1·38 (1H, s, H-5), 2·0br (1H, NH, exchangeable with D_2O), 5·42 (3H, s, 1-Me), and 6·56 (3H, s, NH*Me*). These reactions did not take place when free methylamine (in ethanol at 70°) was substituted for the acetate.

1-*Methyl*-v-*triazolo*[4,5-d]*pyrimidine*-7(6H)-*thione* (7-*Methyl*-8-*azapurine*-6-*thione*) (6c).—(*a*) The cyano-amidine (1a) (0·18 g) and ethanolic 1·5N-sodium hydrogen sulphide (5 ml) were heated under reflux for 10 h. The volatile materials were removed under vacuum. The residual sodium salt was dissolved in hot water (2 ml) and acidified to pH 5. The precipitate, recrystallised from water (60 ml), gave the thione (6c) (84%), m.p. 302° (efferv.), identical with an authentic specimen.[6]

(*b*) To 1-methyl-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (see later) (2·4 g, 0·016 mol), dissolved in boiling dried pyridine (20 ml), was added redistilled phosphorus pentasulphide (Fluka; 7·2 g). The suspension was heated under reflux for 30 min and cooled. Water (15 ml) was added and the solvents were removed at 40—60° and 25 mmHg. The residue was homogenised with water (36 ml) and the mixture was chilled and filtered. The solid, recrystallised from water (300 parts), gave the thione (78%), m.p. 302° (efferv.).

1-*Methyl*-v-*triazolo*[4,5-d]*pyrimidin*-7(6H)-*one* (7-*Methyl*-8-*azapurin*-6-*one*) (6a) (*Improved Preparation*).—4-Amino-1-methyl-1,2,3-triazole-5-carboxamide [6] (2 g) and formamide (4 ml) were heated at 220° (bath temp.) for 45 min; the mixture was cooled, homogenised with acetone (8 ml), and chilled overnight. The solid was filtered off, boiled with ethanol (50 ml), cooled, filtered off, and dried at 110° to give the cyclic amide (6a) (87%), m.p. 264°, identical with authentic material.[6]

2-*Methyl*-v-*triazolo*[4,5-d]*pyrimidine*-7(6H)-*thione* (8-*Methyl*-8-*azapurine*-6-*thione*).—The cyano-amidine (2a) (0·18 g) and ethanolic 1·5N-sodium hydrogen sulphide were heated under reflux for 11 h. The ethanol was distilled off *in vacuo* and the residue, dissolved in water (2 ml) and acidified to pH 6, gave the thione (90%), m.p. 326° (efferv.) (from 300 parts of water), identical with authentic material.[7]

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