v-Triazolo[5,4-*d*]pyrimidines (8-Azapurines). Part 20.[1] 1-Alkyl Derivatives

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9-Benzyl-1-methyl-8-azapurin-6-one (2b) was made (*a*) by heating 4-amino-3-benzyl-1,2,3-triazole-5-(*N*-methylcarboxamide) (7a) with formamide, and (*b*), quantitatively, by methylating 9-benzyl-8-azapurin-6-one. It was debenzylated to 1-methyl-8-azapurin-6-one (2a), which was also prepared by condensing 4-amino-1,2,3-triazole-5-(*N*-methylcarboxamide) (7c) with formamide. The i.r. spectrum of compound (2a) indicates an unusually dipolar nature. 1-Butyl-8-azapurin-6-one and its 9-benzyl derivative were synthesized analogously. 1-Methyl-8-azapurine-6-thione (10), prepared from the 6-oxo-analogue (2a), resisted further changes. Attempted chlorination of the oxo-compound (2a), with thionyl chloride and dimethylformamide, produced what appears to be the pyrimidine (12).

4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole was mono- and bis-trifluoroacetylated, and the former product (13c) was *N*-methylated then deacylated to 4-amino-3-benzyl-5-methylaminomethyl-1,2,3-triazole (13f). The latter was condensed with formamidine to 9-benzyl-1,6-dihydro-1-methyl-8-azapurine (11b). 1-Methyl-8-azapurine (3) was made by nitrosating 5-amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (16). Compound (3) was found to be about 15% covalently hydrated at equilibrium in D_2O whereas the cation was completely hydrated (n.m.r. and u.v. evidence). The physical properties in which the neutral species differs most from its known isomers are m.p., volatility, and extractability from water, in all of which it behaves as a much more polarized substance.

ALTHOUGH many derivatives of 8-azapurine (1) methylated in the 7-, 8-, or 9-position are known, very few 1-alkylated analogues have been reported. Medical interest in 8-azapurines as anticancer drugs [2] and for the prevention of anaphylactic shock [3] prompted this exploration of the synthesis and properties of 1-alkyl derivatives such as (2a) and (3).

The known 1-alkyl derivatives are (a) 2-amino-1-methyl-8-azapurin-6-one (' 1-methyl-8-azaguanine ') (4), made [4] by the action of nitrous acid on 2,4,5-triamino-1-methylpyrimidin-6-one, and (b) a set of five 1,6-dihydro-6-imino-1-methyl-8-azapurines (5) (four of them have another *N*-methyl substituent in the triazole ring) [5] prepared by the action of methylamine on the corresponding 5-cyano-4-ethoxymethyleneamino-derivatives of 1,2,3-triazole. Unfortunately these imines proved unsuitable for the present project because they rapidly isomerized in cold alkali to 6-methylamino-8-azapurines (by a Dimroth rearrangement), and dilute acid brought about ring opening to triazole-5-carboxamidines.[5] However, the simplest example (5a) still held some promise because its basic strength (pK_a 3.25), more than a thousand times less [5] than that of the 9-methyl homologue (5b) (pK_a 6.84), indicated a different structure, namely the 6-amino derivative of structure (3), in resonance with the zwitterion (6). However, attempts to deaminate it by standard methods and by a new procedure (pentyl nitrite in tetrahydrofuran [6]) were fruitless, hence starting materials were sought among suitably substituted 4-amino-1,2,3-triazoles.†

An authentic specimen of 9-benzyl-1-methyl-8-azapurin-6-one (2b) was made by heating 4-amino-3-benzyl-1,2,3-triazole-5-(*N*-methylcarboxamide) (7a) with formamide. This triazole was obtained in two ways: (*a*) by the action of methylamine on 4-amino-3-benzyl-5-(methylthio)carbonyl-1,2,3-triazole (8a) by an improved method which avoids use [7] of a sealed tube, and (*b*) by heating benzyl azide with *N*-methylcyanoacetamide in methanolic sodium methoxide.[8] It was then found that the cold methylation of 9-benzyl-8-azapurin-6-one, readily prepared in two steps from benzyl azide and cyanoacetamide,[9] gave the 1-methyl derivative (2b) almost quantitatively and with no detectable amount of the 3-methyl isomer which was on hand from another project.

9-Benzyl-1-methyl-8-azapurin-6-one (2b) was rapidly

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

[1] Part 19, A. Albert and C. J. Lin, *J.C.S. Perkin I*, 1977, 1819.

[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; L. L. Bennett, M. H. Vail, P. W. Allan, and W. R. Laster, *Cancer Research*, 1973, **33**, 465.

[3] C. J. Coulson, R. E. Ford, S. Marshall, J. L. Walker, K. R. H. Wooldridge, K. Bowden, and T. J. Coombes, *Nature*, 1977, **265**, 545.

[4] C. W. Noell, L. B. Townsend, and R. K. Robins, *Synth. Proc. Nucleic Acid Chem.*, 1968, **1**, 44.

[5] A. Albert, *J.C.S. Perkin I*, 1973, 2659; 1974, 2030.

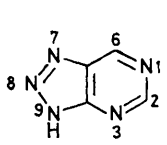
[6] J. Cadogan and G. Moliner, *J.C.S. Perkin I*, 1973, 541.

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

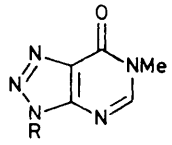
[8] May and Baker Ltd., Brit. Pat. 1,338, 235/1973, U.S. Pat. 3, 819,631/1974.

[9] (*a*) J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832; (*b*) A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001; (*c*) A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.

decomposed by boiling aqueous alkali to 3-benzyl-4-formamido-1,2,3-triazole-5-(*N*-methylcarboxamide) (7b) and the deformylated analogue (7a). 9-Benzyl-1-butyl-8-azapurin-6-one, a homologue of (2b), was made by heating formamide and 4-amino-3-benzyl-1,2,3-triazole-5-(*N*-butylcarboxamide), which was obtained

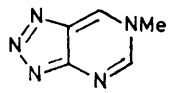


(1)



(2)

a; R = H
b; R = CH_2Ph



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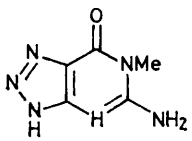

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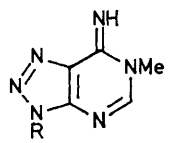
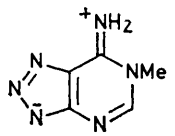


(5)

a; R = H
b; R = Me



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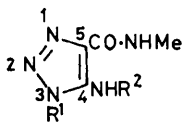
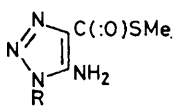


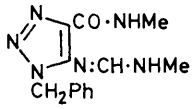
(7)

a; R^1 = CH_2Ph, R^2 = H
b; R^1 = CH_2Ph, R^2 = CHO
c; R^1 = R^2 = H



(8)

a; R = CH_2Ph
b; R = H



(9)

from butylamine and the (methylthio)carbonyl derivative (8a).

Although some cyclic tertiary amides can be deoxygenated, for example *N*-alkylacridones are reducible to *N*-alkylacridans by zinc and hydrochloric acid,[10] 9-benzyl-1-methyl-8-azapurin-6-one and its 1-butyl homologue were partly unchanged but mainly destroyed by this procedure, whereas zinc in boiling 90% acetic acid did not affect them. Lithium borohydride in cold tetrahydrofuran, and also sodium diethyldihydroaluminate, were destructive.

In attempted debenzylation of 9-benzyl-1-methyl-8-azapurin-6-one with sodium in liquefied methylamine (the purinone being insoluble in liquid ammonia), an unexpected product, of molecular weight 272, was formed in high yield. The ^1H n.m.r. spectrum (solvent dimethyl sulphoxide) showed a quartet at τ 1.15 (J 4.40 Hz) (singlet in deuterium oxide), assigned to N=CH coupled to CH–NH. A broad singlet at 1.90 (2 H), eliminated in D_2O, was assigned to two NH groups. A singlet at 2.70 (5 H) and another at 4.63 (2 H) were obviously derived from a non-eliminated benzyl group. A quartet at 7.22 (3 H) (J 4.40), and a doublet at 7.33 (3 H) (J 4.80), both signals changing to singlets in D_2O, were allocated to N=CH–NHMe and CONHMe respectively. This evidence combined with the i.r. spectrum and elemental analysis established the decomposition product as 3-benzyl-4-methylaminomethyleneamino-1,2,3-triazole-5-(*N*-methylcarboxamide) (9). This was confirmed by heating the product at 210 °C for 30 min, which converted it quantitatively into 9-benzyl-1-methyl-8-azapurin-6-one (2b). Several dimethylaminomethyleneamino-1,2,3-triazoles are known,[11] but this is the first monoalkyl analogue to be reported.

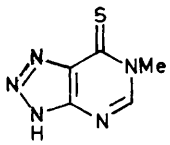
The elusive 1-methyl-8-azapurin-6-one (2a) was eventually made in two ways: (*a*) by condensing 4-amino-1,2,3-triazole-5-(*N*-methylcarboxamide) (7c) with formamide [the triazole was prepared [7] from the corresponding 5-(methylthio)carbonyltriazole (8b)]; (*b*) by hydrogenolytic debenzylation of 9-benzyl-1-methyl-8-azapurin-6-one (2b) over palladium. The latter reaction, reluctant under usual conditions, succeeded in hot butanol–acetic acid. The product was soluble in cold N-hydrochloric

[10] K. Lehmstedt and H. Hundertmark, *Ber.*, 1931, **64**, 2386.
[11] A. Albert, *J.C.S. Perkin I*, 1972, 461; A. Albert and H. Taguchi, *ibid.*, 1973, 2037.

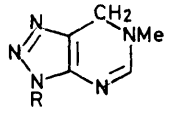
acid and N-sodium hydroxide, in both of which slow decomposition occurred, mainly to the methylcarboxamide (7c).

The i.r. spectrum of 1-methyl-8-azapurin-6-one is remarkably different from those of the 7-methyl,[12] 8-methyl,[13] and 9-methyl [13] isomers (all Nujol mulls) in having strong absorption in the 2 595 cm^{-1} area (particularly. evident in a hexachlorobutadiene mull), and 3 015s (NH), 1 685s (amide I), 1 560s (amide II), 1 345m, 1 315m, 1 245s (amide III), and 1 025m cm^{-1}.

1-Methyl-8-azapurine-6-thione (10) was readily prepared by the action of phosphorus pentasulphide in boiling pyridine on 1-methyl-8-azapurin-6-one (2a). All attempts to desulphurize it to compound (3) or (11a), with Raney nickel, failed: mild conditions left it unchanged whereas a more vigorous attack completely

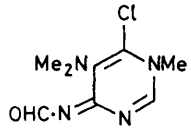


(10)

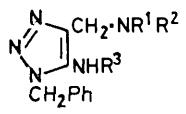


(11)

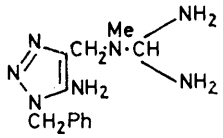
a; R = H
b; R = CH_2Ph



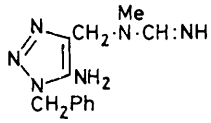
(12)



(13)

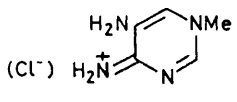


(14)

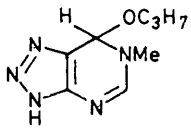


(15)

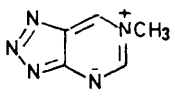
a; $R^1 = R^2 = R^3 = H$
b; $R^1 = CHO$, $R^2 = R^3 = H$
c; $R^1 = CO{\cdot}CF_3$, $R^2 = R^3 = H$
d; $R^1 = R^3 = CO{\cdot}CF_3$, $R^2 = H$
e; $R^1 = Me$, $R^2 = CO{\cdot}CF_3$, $R^3 = H$
f; $R^1 = Me$, $R^2 = R^3 = H$



(16)



(17)



(18)

two well defined peaks at 1 945 and 1 815 cm^{-1} which, although weak, are prominent because of the lack of general absorption in this region. It is interesting that two related compounds, 9-benzyl-1-methyl- and -1-butyl-8-azapurin-6-one, show absorption near 1 950 cm^{-1}, but not the other anomalies (re-examination of the parent, 9-benzyl-8-azapurin-6-one, revealed a faint peak at 1 945 cm^{-1} overlooked in the original report).[9c] This extra absorption in the spectrum of 1-methyl-8-azapurin-6-one is taken as evidence of a strongly dipolar nature. The related 1-methylpurine-6-one has strong absorption in the 2 800—2 500 cm^{-1} area.[14] In other ways, the spectrum of 1-methyl-8-azapurin-6-one closely resembles those of its isomers, having bands at 3 150m,

destroyed it. Equally unsuccessful were the use of hydrogen peroxide,[15] nitrous acid,[15] iodine,[16] and aluminium amalgam. 1-Methyl-8-azapurine-6-thione (10) was destroyed by iodomethane in cold aqueous sodium hydroxide, a procedure that converted the 7-, 8-, and 9-isomers into the corresponding 6-methylthio-compounds; [9c,12,13] the use of iodomethane with potassium carbonate in cold dimethylformamide also failed.

Conversion of 1-methyl-8-azapurin-6-one into 6-chloro-1-methyl-8-azapurine using triphenylphosphine in carbon tetrachloride [17] proved unsuccessful, as did the use of thionyl chloride, catalysed by dimethylformamide,[18] in boiling chloroform. The latter procedure had proved useful [13] for preparing 6-chloro-8-methyl-8-azapurine, of which the 1-methyl isomer may have

[12] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.
[13] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[14] J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, 1965, **30**, 3235.
[15] W. Traube and F. Winter, *Arch. Pharm.*, 1906, **244**, 11; W. Traube, *Annalen*, 1904, **331**, 64.
[16] I. L. Doerr, I. Wempen, D. A. Clark, and J. J. Fox, *J. Org. Chem.*, 1961, **26**, 3401.
[17] J. B. Lee and T. J. Nolan, *Canad. J. Chem.*, 1966, **44**, 1331.
[18] H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653.

been formed here but underwent further attack. Most surprisingly, the product seems to be 6-chloro-4-formylimino-1-methyl-5-dimethylamino-1,6-dihydropyrimidine (12), on the basis of the elemental analysis (with its unexpectedly high C : N ratio), molecular weight, and ^{1}H n.m.r. and i.r. spectra. With one exception,[19] the reported decompositions of 8-azapurines have produced 1,2,3-triazoles (summarized in ref. 1), but 2-amino-8-azapurin-6-one gave 2,4,5-triaminopyrimidin-6-one with hot, dilute acid. In the present example, the reagents, or their product (chloromethylenedimethylammonium chloride [20]), may attack at N-9; this is followed by elimination of a molecule of nitrogen from N-7 and N-8 and converted attack of Me_2N on the 5-position of the pyrimidine ring. Further work is planned to test the constitution (12).

A different approach to 1-methyl-8-azapurines with no oxygen atom in the 6-position was then made through derivatives of 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (13a). The latter can be cleanly monoformylated on the 5-aminomethyl group without affecting the less basic 4-amino group.[21] Unfortunately, the 5-formamido proton in the product (13b) proved insufficiently activated for replacement by a methyl group. In a search for the more reactive 5-trifluoroacetamido analogue (13c), the initial difficulty in finding conditions to favour *mono*acylation were overcome by the use of trifluoroacetic anhydride in cold trifluoroacetic acid. [The deliberate preparation of the diacyl derivative (13d) is also described in the Experimental section.] The insolubility of the monoacyl compound in cold N-hydrochloric acid confirmed the position of acylation, and the solubility in cold N-sodium hydroxide bore witness to the mobility of the neighbouring proton.

The trifluoroacetamido compound (13c) gave a good yield of 4-amino-3-benzyl-5-(*N*-methyltrifluoroacetamidomethyl)-1,2,3-triazole (13e) with iodomethane, and this product was cleanly deacylated to 4-amino-3-benzyl-5-methylaminomethyl-1,2,3-triazole (13f) (purified as the phosphate) by brief heating in aqueous sodium hydroxide.

In an application of the new general method [22] for synthesizing 1,6-dihydro-8-azapurines, the methylaminomethyltriazole (13f) was condensed with formamidinium acetate to give an excellent yield of 9-benzyl-1,6-dihydro-1-methyl-8-azapurine (11b). The retention of the *N*-methyl group gives the first indication that this reaction proceeds through a tetrahedral intermediate (14) which, by acquiring a proton and ejecting an ammonium ion, produces the final intermediate (15).

The new dihydro-8-azapurine (11b) was stable to aerial oxidation. Unfortunately, it resisted debenzylation, both by sodium in ammonia and by hydrogenation over palladium. When conditions were forced, as with hydrogenation in boiling butanol, the molecule was fragmented. In an attempt to obtain the compound (11b) by another route, 9-benzyl-1,6-dihydro-8-azapurine [22] was stirred with iodomethane and potassium carbonate in dimethylformamide. Even when less than one molecular proportion of iodomethane was used, the sole product was a dimethyl derivative, 9-benzyl-1,6-dihydro-*x*,*y*-dimethyl-8-azapurinium iodide (pending the results of *X*-ray crystallography, *x* and *y* are tentatively assigned as 1 and 3).

1-Methyl-8-azapurine (3) proved more accessible from pyrimidine intermediates than from triazoles. 5-Amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride (16), obtained by methylating 4,5-diaminopyrimidine,[23] reacted with propyl nitrite in propanol to give the hydrochloride of 1,6-dihydro-1-methyl-6-propoxy-8-azapurine (17), which is the propanol adduct of the cation of the goal (3), and has a main u.v. absorption peak displaced from that of 1-methyl-8-azapurines, as expected, to a shorter wavelength near to that of the corresponding peak of the (hydrated) cation of the parent (3).

Silver carbonate converted this adduct into 1-methyl-8-azapurine which differed little from its 7-methyl,[12] 8-methyl,[13] and 9-methyl,[12,24] isomers in pK_a and u.v. or n.m.r. spectrum. The n.m.r. spectrum (in D_2O) showed weak, highfield signals which denote equilibrium with about 15% of the covalent hydrate as in 8-methyl-8-azapurine.[13] The cation has a u.v. spectrum displaced to much shorter wavelengths, showing that it is entirely hydrated, as are the cations of the 7- and 8-methyl isomers. Nevertheless 1-methyl-8-azapurine has a much more polar character than its isomers, as indicated by the higher m.p. (235°; *cf.* 167, 153, and 88° for the 7-, 8-, and 9-methyl isomers respectively), and by its inability to be sublimed (even at 200 °C and 0.03 mmHg), or extracted from water by dichloromethane, whereas the three known isomers are easily sublimed and extractable.[25] Moreover, it is much less stable than the three isomers. The polar characteristics are attributed to a high proportion of the charged canonical form (18) in the resonance hybrid. Comparison with 1-methylpurine [26] (*vis-à-vis* the latter's 7- and 9-methyl isomers [27]) shows few parallels. There is a similar increase in m.p. for the 1-methylpurine isomer, but a u.v. spectral shift of about 10 nm to longer wavelengths, in both neutral species and cation, signifies a change in conjugation but no covalent hydration. No marked differences in solubility are evident from the literature. 1-Ethylpurine is significantly (about 2.6 pK units) more basic

[19] Y. Hirata, K. Iwashita, and K. Teshima, *Nagoya Sangyo Kagaku*, 1957, No. 9, 83 (*Chem. Abs.*, 1957 1957, **51**, 12074).
[20] H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1659.
[21] A. Albert, *J.C.S. Perkin I*, 1973, 1634.
[22] A. Albert, *J.C.S. Perkin I*, 1976, 291.
[23] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1962, 3172.
[24] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.
[25] A. Albert, W. Pfleiderer, and D. Thacker, *J. Chem. Soc.* (*C*), 1969, 1084.
[26] L. B. Townsend and R. K. Robins, *J. Org. Chem.*, 1962, **27**, 990.
[27] A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073; Fischer, E., *Ber.*, 1898, **31**, 2550; A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.

than the 7- and 9-ethyl isomers.[28] Calculation of charge distribution (CNDO method)[29] indicated that the pyrimidine ring is positively charged in 1-methylpurine, but negative in the 7- and 9-methyl isomers.

EXPERIMENTAL

Determinations of physical constants and establishment of chemical identity were made essentially as in Part 19.[1] The mass spectra were obtained with a Hewlett–Packard 5983 A instrument. Most of the elemental analyses were performed by Galbraith Laboratories, Tennessee, and the others by the Australian National University's Analytical Service, in Canberra.

9-Benzyl-1-methyl-8-azapurin-6-one (2b) (*3-Benzyl-3,6-dihydro-6-methyl-v-triazolo*[4,5-d]*pyrimidin-7-one*).—(*a*) 4-Amino-3-benzyl-1,2,3-triazole-5-(*N*-methylcarboxamide) (see following) (2.3 g, 0.01 mol) and formamide (20 ml) were heated at 190 °C (bath temp.) in an open vessel for 1 h. The volatile materials were removed at 150 °C and 25 mmHg. The solid residue was rubbed with water (10 ml), filtered off, dried, and recrystallized from 60 parts of benzene–ethanol (1 : 1), yielding 62% of *9-benzyl-1-methyl-8-azapurin-6-one*, m.p. 221.5°. It also crystallized well from 13 parts of 2-methoxyethanol but was poorly soluble in boiling ethanol or water (Found: C, 59.9; H, 4.5; N, 29.2. $C_{12}H_{11}N_5O$ requires C, 59.7; H, 4.6; N, 29.0%), τ [$(CD_3)_2SO$] 1.47 (1 H, H-2), 2.70 (5 H, Ph), 4.27 (2 H, CH_2), and 6.53 (3 H, CH_3), $\nu_{max.}$ 1 950w, 1 700br s (C : O str), 1 555m, 1 325m, 1 270m, and 1 200m cm^{-1}.

(b) *Preferred method.* 9-Benzyl-8-azapurin-6-one [9] (2.27 g, 0.01 mol), dimethylformamide (28 ml), potassium carbonate (flame-dried and finely powdered; 2.8 g, 4 equiv.), and iodomethane (4.3 g, 3 equiv.) were stirred at 24 °C for 24 h. Volatile materials were removed at 110 °C and 25 mmHg. Water (20 ml) was added to the residue and 9-benzyl-1-methyl-8-azapurin-6-one, m.p. 221°, was filtered off in 94% yield after washing with ethanol and drying at 110 °C (identical with authentic material).

4-Amino-3-benzyl-1,2,3-triazole-5-(N-methylcarboxamide)-(7a).— 4-Amino-3-benzyl-5-[(methylthio)carbonyl]-1,2,3-triazole (8a) (1.0 g, 0.004 mol), in fine powder, was stirred with ethanolic 35% methylamine (20 ml; Fluka) for 45 h. The solution was taken to dryness at 50 °C, giving 94% of this amide, m.p. 155° (lit.,[7] 155°), from 8 parts of ethanol.

Hydrolysis of 9-Benzyl-1-methyl-8-azapurin-6-one.—This azapurinone (0.241 g, 0.001 mol) and N-potassium hydroxide (2.5 ml) were heated under reflux for 5 min; the mixture was then refrigerated and filtered. The precipitate was pure 4-amino-3-benzyl-1,2,3-triazole-5-(*N*-methylcarboxamide) (7a) (50%), m.p. 155° (see foregoing). The filtrate, adjusted to pH 2.5 with sulphuric acid gave a white precipitate of *3-benzyl-4-formamido-1,2,3-triazole-5-(N-methylcarboxamide)* (7b), m.p. 138°, from 19 parts of water and 8 parts of 95% ethanol (40% yield) (Found: C, 55.6; H, 5.1; N, 27.0. $C_{12}H_{13}N_5O_2$ requires C, 55.6; 5.05; N, 27.0%), *M* 231 [other prominent signals at *m/e* 200, 199, 173, 171, 145, and 91 (benzyl)] [this spectrum is identical with that for the deformylated analogue (7a)].

4-Amino-3-benzyl-1,2,3-triazole-5-(N-butylcarboxamide).— 4-Amino-3-benzyl-5-[(methylthio)carbonyl]-1,2,3-triazole (8a) [7] (0.62 g, 0.0025 mol) and butylamine (5 ml, 20 equiv.) were refluxed for 2 h. Excess of amine was removed (oil-bath at 100 °C and 25 mmHg). The residue, recrystallized from a little ethanol (2 crops) gave the *butylcarboxamide* almost quantitatively, m.p. 150° (Found: C, 61.2; H, 6.8; N, 25.7. $C_{14}H_{19}N_5O$ requires C, 61.5; H, 7.0; N, 25.6%), $\nu_{max.}$ 3 350, 3 290, 3 230, 3 180 (all m, NH str.), 1 645s, 1 630s (amide I band, free and assoc.), and 1 540s cm^{-1} (amide II), insoluble in cold N-NaOH and -KOH (test confirmation that no Dimroth rearrangement of benzyl group has occurred).

9-Benzyl-1-butyl-8-azapurin-6-one.—The foregoing amide (0.274 g, 0.001 mol) and formamide (2 ml) were heated at 225 °C (bath) for 1 h in an open vessel. Addition of water (4 ml), chilling, and filtering produced *9-benzyl-1-butyl-8-azapurin-6-one* (90%), m.p. 99°, from 65 parts of 33% ethanol (Found, for material dried at 80° in air: C, 63.4; H, 5.9; N, 25.0. $C_{15}H_{17}N_5O$ requires C, 63.6; H, 6.05; N, 24.7%), $\nu_{max.}$ 1 960w, 1 695s (C:O), 1 560m, 1 350m, 1 270m, 1 185m, and 800 m cm^{-1}, τ [$(CD_3)_2SO$] 1.38 (1 H, H-2), 2.66 (5 H, Ph), 4.26 (2 H, CH_2), and 5.97 (2 H, t), 8.5 (4 H, m), and 9.06 (3 H, t) (all centres, Bu), $\lambda_{max.}$ (EtOH) 259 nm (log ε 3.90).

3-Benzyl-4-methylaminomethyleneamino-1,2,3-triazole-5-(N-methylcarboxamide) (9) (with A. M. Trotter).—9-Benzyl-1-methyl-8-azapurin-6-one (0.24 g, 0.001 mol) was stirred with liquefied methylamine (10 ml) while sodium (0.046 g) was added. Evaporation of the methylamine, and recrystallization of the residue from 17 parts of ethanol, gave the *carboxamide* (75%), m.p. 186° (Found: C, 57.2; H, 5.9; N, 30.7. $C_{13}H_{16}N_6O$ requires C, 57.3; H, 5.9; N, 30.9%), $\nu_{max.}$ 3 225m (NH), 1 635br, s (CO), 1 540br, s, 1 410m, 1 260m, and 1 200m cm^{-1}, M^+ 272 [other prominent signals at *m/e* 243, 212, 186, 171, 91 (benzyl), and 69]; ^1H n.m.r. data in main text; insoluble in cold N-sodium hydroxide and N-formic acid; soluble in N-hydrochloric acid.

1-Methyl-8-azapurin-6-one (2a) (*3,6-Dihydro-6-methyl-v-triazolo*[4,5-d]*pyrimidin-7-one*).—(a) *By debenzylation* (with A. M. Trotter). 9-Benzyl-1-methyl-8-azapurin-6-one (0.482 g, 0.002 mol), dissolved in butanol (20 ml) and acetic acid (2 ml), was hydrogenated over pre-reduced palladium–carbon (10%; 0.08 g) at 117 °C and atmospheric pressure for 1.5 h. Without prior filtration, the suspension was dried at 90 °C and 25 mmHg. The residue, well cooled, was stirred with 0.25N-sodium hydroxide (12 ml) and kieselguhr (0.1 g), and rapidly filtered. The filtrate, adjusted to pH 5.5 with acetic acid, and concentrated at 35 °C (to 4 ml), was cooled, and acidified to pH 3.5 (with 5N-H_2SO_4). Refrigeration yielded *1-methyl-8-azapurin-6-one* (72%), m.p. 253° (with slight effervescence), from 6 parts of water or 65 parts of 90% ethanol (Found: C, 39.8; H, 3.4; N, 46.2. $C_5H_5N_5O$ requires C, 39.75; H. 3.3; N, 46.3%), τ [$(CD_3)_2SO$] 1.59 (1 H, H-2) and 6.49 (3 H, Me).

(b) *By ring closure of a triazole.* 4-Amino-1,2,3-triazole-5-(*N*-methylcarboxamide) (7c) [7] (3.53 g, 0.025 mol) and formamide (50 ml) were heated in an open vessel at 195 °C (bath) for 45 min. Excess of reagent was removed at 160 °C and 25 mmHg, and the residue, recrystallized from a little water, gave 1-methyl-8-azapurin-6-one (2a) (78%), m.p. 253°.

1-Methyl-8-azapurine-6-thione (10).—Phosphorus pentasulphide (0.22 g) was added to a hot solution of 1-methyl-8-azapurin-6-one (0.15 g, 0.001 mol) in dried pyridine (2 ml) and the whole was heated under reflux for 4 h. Water

[28] R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, 1961, **26**, 3446.
[29] Z. Neiman, *Experientia*, 1975, **31**, 996.

(1.5 ml) was added, and the volatile materials were removed *in vacuo* at 50 °C. Water (1.5 ml) was again added and the pH adjusted, when necessary, to 2.5—4.5. Chilling and filtration gave 1-*methyl* 8-*azapurine*-6-*thione* (83%), m.p. about 240° (blackens) when introduced at 230° (from 140 parts of boiling water or 75 parts of 90% ethanol); soluble in cold N-sodium hydroxide (Found: C, 35.9; H, 3.1; N, 41.6. $C_5H_5N_5S$ requires C, 35.9; H, 3.0; N, 41.9%). It was not even partly isomerized to a thiadiazolopyrimidine (the Christmas rearrangement, given by analogues [9c]) when heated under reflux with butanol for 1 h.

Chlorination of 1-*Methyl*-8-*azapurin*-6-*one* (2a).—Thionyl chloride (3.8 ml, 0.05 mol), dimethylformamide (1.0 ml, 0.014 mol), and 1-methyl-8-azapurin-6-one (1.51 g, 0.01 mol), suspended in chloroform (40 ml), were heated under reflux for 4 h (the mixture became clear after 20 min and began to deposit material 10 min later. The suspension was left at —10 °C overnight, and filtered. The solid, dissolved in water (1 ml), was adjusted to pH 10 with ammonia and shaken out with chloroform (2 × 15 ml). The lower layers were bulked, dried (K_2CO_3), and evaporated *in vacuo*. The residue, recrystallized from 10 parts of benzene–cyclohexane (1 : 1), gave presumed 6-*chloro*-4-*formylimino*-1-*methyl*-5-*dimethylamino*-1,6-*dihydropyrimidine* (12) (41%), m.p. 125.5°. Sodium carbonate could replace the ammonia without much loss of yield (Found: C, 45.0; H, 5.3; Cl, 16.7; N, 26.3. $C_8H_{11}ClN_4O$ requires C, 44.8; H, 5.2; Cl, 16.5; N, 26.1%); M^+ 214 (^{35}Cl) and 216 (^{37}Cl) (other prominent peaks at *m/e* 199, 186, 179, 172, 170, 163, 138, 57, and 42), τ(D_2O) 2.01 (1 H, CHO), 219 (1 H, H-2), 6.49 (3 H, 1-Me), and 6.98 (6 H, NMe_2), $\nu_{max.}$ (Nujol) 1 650br,s (CO str), 1 585br,s, 1 410m, 1 330m, 1 100m, 955s, and 780m cm^{-1} (Cl–C str.)

4-*Amino*-3-*benzyl*-5-*trifluoroacetamidomethyl*-1,2,3-*triazole* (13c).—4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole (13a) [19] (2.30 g, 0.01 mol) was dissolved in trifluoroacetic acid (15 ml) with cooling to 24 °C. Trifluoroacetic anhydride (2.4 g; 15% excess) was added, and the solution set aside at 24 °C for 8 h. The volatile portion was removed *in vacuo* at 35 °C, and the residue recrystallized twice from 25% ethanol (45 ml, then 80 ml) giving the title *compound* (67%), m.p. 188° (Found: C, 48.3; H, 4.0; F, 19.0. N, 23.2. $C_{12}H_{12}F_3N_5O$ requires C, 48.15; H, 4.0; F, 19.0; N, 23.4%). It can also be recrystallized from 300 parts of water or 190 parts of benzene.

3-*Benzyl*-4-*trifluoroacetamido*-5-*trifluoroacetamidomethyl*-1,2,3-*triazole* (13d).—4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole (0.203 g, 0.001 mol) was rubbed with trifluoroacetic anhydride (1.6 g) until dissolved, then the solution was set aside at 24 °C for 24 h. The thick paste was taken to dryness at 40 °C giving the *product* (85%), m.p. 149° from 4.5 parts of benzene (Found: C, 42.6; H, 2.8; F, 28.9; N, 17.4. $C_{14}H_{11}F_6N_5O_2$ requires C, 42.5; H, 2.8; F, 28.8; N, 17.7%).

4-*Amino*-3-*benzyl*-5-(N-*methyltrifluoroacetamidomethyl*)-1,2,3-*triazole* (13e).—4-Amino-3-benzyl-5-trifluoroacetamidomethyl-1,2,3-triazole (0.30 g, 0.001 mol) dissolved in dimethylformamide (2 ml) at 24 °C, flame-dried potassium carbonate (0.21 g, 3 equiv.), and iodomethane (0.28 g, 2 equiv.) were stirred for 1.5 h. The volatile portion was then removed at 110 °C and 25 mmHg. Water (4 ml) was added to the well-cooled residue. The precipitate, filtered off at once and washed with much water and a little 25% ethanol, gave the N-*methyl derivative* (74%), m.p. 142.5° (from about 4 parts of methanol) (Found: C, 49.9; H, 4.5; N, 22.4. $C_{13}H_{14}F_3N_5O$ requires C, 49.8; H, 4.5; N, 22.4%).

4-*Amino*-3-*benzyl*-5-*methylaminomethyl*-1,2,3-*triazole* (13f).—The trifluoroacetamido-derivative (13e) (0.42 g, 0.001 34 mol) and N-sodium hydroxide (2.1 ml, 1.5 equiv.) were boiled for 30 s; the mixture was then quickly cooled and shaken out with chloroform (2 × 7 ml). The chloroform layer was dried (K_2CO_3) and taken to dryness, *in vacuo*, at eventually 55 °C. N-Phosphoric acid was added until the pH fell to 8. The addition of acetone (7.5 ml) initiated precipitation (completed at —10 °C overnight) of *bis*-(4-*amino*-3-*benzyl*-5-*methylaminomethyl*-1,2,3-*triazolium*) *hydrogen phosphate* (84%), m.p. 180° from 150 parts of ethanol [Found: C, 49.5; H, 6.3; N, 26.4. $(C_{11}H_{15}N_5)_2$,H_3PO_4 requires C, 49.6; H, 6.25; N, 26.3%]. The base was liberated by shaking the phosphate (1.25 g) with 2N-sodium hydroxide (2.5 ml) and chloroform (3 × 15 ml); 97% recovery; m.p. 93° (from benzene). The quantitative extraction shows that no Dimroth rearrangement to the acidic 4-benzylamino isomer had taken place during boiling with alkali.

9-*Benzyl*-1,6-*dihydro*-1-*methyl*-8-*azapurine* (11b) (3-*Benzyl*-6,7-*dihydro*-6-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*.—4-Amino-3-benzyl-5-methylaminomethyl-1,2,3-triazolium phosphate (0.266 g, equiv. to 0.001 mol of base), formamidinium acetate (0.21 g, 2 equiv.), and sieve-dried butanol (3 ml) were heated under reflux for 2 h. More formamidinium acetate (0.21 g) was added and refluxing was continued for 2 h longer. The volatile portion was removed at 90 °C and 25 mmHg, and the residue quickly boiled with water (1.5 ml) and refrigerated (the pH at this stage must be maintained above 4 to avoid loss as a soluble salt). Filtration gave 9-*benzyl*-1,6-*dihydro*-1-*methyl*-8-*azapurine* (80%), m.p. 106°, from 23 parts of water. It was very soluble in cold benzene, but only slightly in boiling cyclohexane (Found: C, 63.2; H, 5.6; N, 30.5. $C_{12}H_{13}N_5$ requires C, 63.4; H, 5.8; N, 30.8%), M^+ 227 (other prominent peaks at *m/e* 198, 157, 108, and 91), τ [$(CD_3)_2SO$] 2.76 (5 H, Ph), 2.85 (1 H, H-2), 4.69 (2 H, $PhCH_2$), 5.34 (2 H, 6-H_2), and 7.08 (3 H, Me).

Methylation of 9-*Benzyl*-1,6-*dihydro*-8-*azapurine*.—Iodomethane (0.42 g, 3 equiv.) and flame-dried potassium carbonate (0.21 g, 3 equiv.) were added to a solution of 9-benzyl-1,6-dihydro-8-azapurine [22] (0.213 g, 0.001 mol) in dried dimethylformamide (2 ml). The suspension was stirred at 24 °C for 48 h, then filtered. The solid was washed with a little ethanol, then suspended in water (1 ml) and filtered off, yielding 9-benzyl-1,6-dihydro-*x*,*y*-dimethyl-8-azapurinium iodide (50%), m.p. 206° (effervesces), from 50 parts of ethanol or 8 parts of water; insoluble in acetone or ethyl acetate (Found: C, 42.3; H, 4.4; N, 19.0. Calc. for $C_{13}H_{16}IN_5$: C, 42.6; H, 4.4; N, 19.0%), τ [$(CD_3)_2SO$] 2.46 (1 H, H-2), 2.66 (5 H, Ph), 4.47 (2 H, $PhCH_2$), 5.12 (2 H, 6-H_2), and 5.98 and 6.95 (each 3 H, 2 × Me).

1-*Methyl*-8-*azapurine* (6-*Methyl*-v-*triazolo*[4,5-d]*pyrimidine*) (with D. Thacker) (3).—5-Amino-1,4-dihydro-4-imino-1-methylpyrimidine hydrochloride [23] (16) (0.161 g, 0.001 mol), propyl nitrite (1.6 ml), and propanol (16 ml) were stirred at 24 °C for 4 h. The solution was concentrated *in vacuo* and diluted with light petroleum (b.p. 40—60 °C). The deposited solid, recrystallized from propanol–light petroleum, gave 1,6-*dihydro*-1-*methyl*-6-*propoxy*-8-*azapurine* (17) *hydrochloride* (6,7-*dihydro*-6-*methyl*-7-*propoxy*-v-*triazolo*[4,5-d]*pyrimidine hydrochloride*) (60%), m.p. 137° (foams) (Found: C, 41.0; H, 6.0; Cl, 15.55; N, 30.5.

$C_8N_{14}ClN_5O$ requires C, 41.45; H, 6.1; Cl, 15.3; N, 30.2%), pK_a 3.24 ± 0.03 (0.000 4M, in water at 20 °C; analyt. λ 250 nm), $\lambda_{max.}$ 261 nm (log ε 3.94) (in propanol).

This hydrochloride (0.2 g), silver carbonate (0.28 g), and methanol (3 ml) were stirred overnight. The mixture was then filtered, the filtrate was taken to dryness, and the residue was repeatedly recrystallized from methanol–ether and dried at 140 °C and 0.01 mmHg to give 1-*methyl*-8-*azapurine* (40%), m.p. about 235° (decomp.) (Found: C, 44.6; H, 4.1; N, 51.3. $C_5H_5N_5$ requires C, 44.45; H, 3.7; N, 51.8%), τ(D_2O) (*a*) peaks integrating to 85%, 0.21, 0.88, and 5.57 (*cf.* 0.31, 0.82, and 5.40 for 8-methyl-8-azapurine [13]), (*b*) peaks integrating to 15%, 2.39 and 3.64 (*cf.* 2.56 and 3.57 for 8-methyl-8-azapurine [13]); τ(D_2O–DCl) 1.50, 3.39, and 6.43, $\lambda_{max.}$ 215 nm (log ε 4.31) and 270 nm (3.80) (neutral species in H_2O at pH 7.0) or 253 nm (log ε 3.96) (hydrated cation at pH 1.0).

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