1,2,3,4,6-Penta-azaindenes (8-Azapurines). Part V.[1] A Comparison of 1,2,3-Triazoles and Pyrimidines as Intermediates for the Preparation of 9-Substituted 8-Azapurines. Rearrangement of 6-Mercapto-8-azapurines and of 4-Aminotriazoles.†

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The relative usefulness of pyrimidine and 1,2,3-triazole intermediates for making 8-azapurines with or without an alkyl group in the 9-position was evaluated. 4-Amino-, 4-amino-3-benzyl-, and 4-amino-3-methyl-1,2,3-triazole-5-carboxamide, when condensed with formamide, gave 6-hydroxy-, 9-benzyl-6-hydroxy-, and 6-hydroxy-9-methyl-8-azapurine. Of these three reactions, the first was not so useful for preparing 6-substituted 8(9-*H*)-azapurines as were the corresponding 6-substituted 4,5-diaminopyrimidines. However, 9-benzyl-6-hydroxy-8-azapurine proved a convenient source of the 6-chloro-, amino-, methoxy-, mercapto-, methylthio-, and hydrazino-analogues; the last named was oxidised to 9-benzyl-8-azapurine. Likewise, 6-hydroxy-9-methyl-8-azapurine readily gave the 6-chloro- and mercapto-analogues, but 9-methyl-6-methylthio-8-azapurine (conveniently made from 5-amino-4-methylamino-6-methylthiopyrimidine and nitrous acid) was found to be a good source of 6-amino-(also 6-hydroxy- and hydrazino-)9-methyl-8-azapurine. The 6-hydrazino-analogue was oxidised to 9-methyl-8-azapurine.

An easily reversible rearrangement of 6-mercapto-8-azapurines to 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidines was discovered.

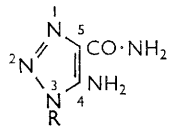
4-Methylamino-1,2,3-triazole-5-carboxamide was made by debenzylating the 3-benzyl derivative obtained by the action of dimethyl sulphate and alkali on 3-benzyl-4-diformylamino-1,2,3-triazole-5-carboxamide. The equilibrium between 3-methyl-(and 3-benzyl-)4-amino-1,2,3-triazole 5-carboxamide and 4-methyl (and benzyl)amino-1,2,3-triazole-5-carboxamide, was found to favour the former.

Ionisation constants and u.v. spectra are reported and discussed.

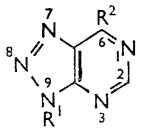
THE two previous parts of this series [1,2] showed that 7- and 8-alkyl-8-azapurines ‡ (none of which could be made by the traditional synthesis from pyrimidine intermediates) could readily be prepared from 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide § (Ia), a compound obtainable (80%) by condensing [3] cyanoacetamide with benzyl azide.

On the other hand, the preparation of 9-alkyl-8-azapurines, and also 8-azapurines without a substituent in the triazole ring (IIb), from 4,5-diaminopyrimidines (III) is well established. Hence it seemed desirable to evaluate the relative usefulness of pyrimidine and 1,2,3-triazole intermediates (of which the latter have so far been little used) for preparing these types of 8-azapurine. During these studies the (reversible) rearrangement of 6-mercapto-8-azapurines to thiadiazolopyrimidines was discovered. Further, the equilibrium between 3-alkyl-4-amino-1,2,3-triazole-5-carboxamides and the 4-alkylamino-isomers was found to favour the former.

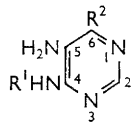
Once again the key intermediate was 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide (see above) which, when heated with formamide,[4] furnished 9-benzyl-6-hydroxy-8-azapurine (IIa; $R^2 = OH$) almost quantitatively. The normally placed carbonyl stretching band of this azapurine (1710 cm.$^{-1}$) contrasts with the corresponding band for 6-hydroxy-9-methyl-8-azapurine (1730 cm.$^{-1}$). 9-Benzyl-6-chloro-8-azapurine (IIa; $R^2 = Cl$) was obtained by the action of thionyl chloride (catalysed by



(I) a; R = CH_2Ph
b; R = H
c; R = Me



(II) a; R^1 = CH_2Ph
b; R^1 = H
c; R^1 = Me



(III) a; R^1 = CH_2Ph
b; R^1 = H
c; R^1 = Me

dimethylformamide [5]) or of phosphoryl chloride (catalysed by diethylaniline). Like other 6-chloro-8-azapurines [1,2] this product (obtained in only moderate yield because of the destructive action of the chlorinating agents) was readily hydrolysed by moisture but remained unaltered when stored over sodium hydroxide.

This chloro-compound was easily converted into 6-amino- (or 6-methoxy-)9-benzyl-8-azapurine when heated with ethanolic ammonia or methanolic sodium methoxide respectively. Similarly, reactions with thiourea furnished 9-benzyl-6-mercapto-8-azapurine, but it was more economical to make this compound by the consecutive actions of phosphorus pentasulphide and sodium hydroxide on 9-benzyl-6-hydroxy-8-azapurine.

† *Note added in proof:* Since the above work on 6-amino-(and 6-mercapto-) -9-benzyl-8-azapurine was completed, their synthesis from 9-benzyl-8-azapurinyl-6:1′-pyridinium chloride has been reported (H. Bredereck and W. Baumann, *Annalen*, 1967, **701**, 157).

‡ Although contrary to present I.U.P.A.C. nomenclature, ' 8-azapurine ' is permitted as a trivial name because of its widespread use in biochemical and biological literature.

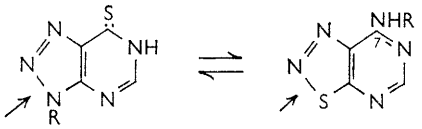
§ To avoid confusion, the amino-group in amino-1,2,3-triazoles is numbered 4 throughout this series (never 5). The position of ' indicated hydrogen ' (*e.g.* 3*H*) is always identical with that of the alkyl group and hence will not be specified further.

[1] Part IV, A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[2] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.
[3] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.
[4] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001.
[5] H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653; J. Žemlička and F. Šorm, *Coll. Czech. Chem. Comm.*, 1965, **30**, 2052.

This almost quantitative preparation followed a highly novel pathway. (A preliminary account has been published.[6]) Thus 9-benzyl-6-hydroxy-8-azapurine, boiled with phosphorus pentasulphide in pyridine, gave an equilibrium mixture of 9-benzyl-6-mercapto-8-azapurine (IV; R = CH_2Ph) and (mainly) 7-benzylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (V; R = CH_2Ph).

The latter substance, easily separated by its insolubility in alkali, lacked a thiocarbonyl stretching band [7] in the 1100—1200 cm.$^{-1}$ region. Its structure was confirmed by elemental analysis and by synthesis from benzylamine and 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]-pyrimidine [8] (obtained from nitrous acid and 5-amino-6-mercapto-4-methoxypyrimidine). When the benzylamino-compound was boiled with N-sodium hydroxide it rapidly gave the sodium salt of 9-benzyl-6-mercapto-8-azapurine. The free mercapto-compound, which showed a strong thiocarbonyl stretching band, was stable when stored at 25° but was isomerised to the thiadiazolopyrimidine (V; R = CH_2Ph) when heated in a solvent at 80°.

Thus the five-membered rings can open at the arrow points of formulae (IV) and (V); heating leads to establishment of an equilibrium in which the isomer (V) preponderates, whereas alkali produces the stable anion of the other isomer (IV) (cf. ref. 9). No similar rearrangements could be effected for 6-amino-(and 6-hydroxy-)-9-benzyl-8-azapurine, which were unchanged after being heated at 220° for 20 min.



(IV) (V)

Rings open and close at arrow point

Methylation of 9-benzyl-6-mercapto-8-azapurine in alkali in the cold furnished the 6-methylthio-analogue which was easily converted, in excellent yield, into 9-benzyl-6-hydrazino-8-azapurine, also obtained from the 6-chloro-analogue (IIa; R^2 = Cl). The parent substance, 9-benzyl-8-azapurine, could not be obtained by catalytic hydrogenation of this chloro-compound, nor by desulphurisation of the 6-mercapto-analogue (IV); but it was obtained, in moderate yield, by oxidation of the hydrazino-compound (IIa; $R^2 = NH{\cdot}NH_2$) with silver oxide in 1-methylpropan-1-ol. A systematic study of the replacement of a hydrazino-group by hydrogen [10] had already indicated that mercuric and silver oxide were the best reagents for heterocycles containing several nitrogen atoms. Cumulative experience with azapurines (guided by parallel studies in the penta-azanaphthalene series [11]) has led to the conclusion that optimal yields require (*a*) 1·5 equiv. of silver oxide (not necessarily freshly prepared) and (*b*) the avoidance of water and primary alcohols (as solvents) because of the ease with which they add across a C:N double-bond in the products, and thus lead to further oxidation. Similar steric hindrance to the addition of secondary (and tertiary) alcohols across an activated double-bond has recently been demonstrated in the pteridine series.[12] Alternative use of pyridine or dimethylformamide as solvents caused much destruction. 9-Benzyl-8-azapurine, prepared thus, and separated by sublimation from a little 6-amino-9-benzyl-8-azapurine, was identical with a specimen made [13] by diazotizing 5-amino-4-benzylaminopyrimidine (IIIa; R^2 = H).

Because of the poor solubility of 9-benzyl-8-azapurines in water, more emphasis has been placed on the i.r. spectra (see Experimental section) than on ionisation constants and u.v. spectra; however, typical examples of these are included in the Table.

The choice between triazole and pyrimidine intermediates for preparing 9-benzyl-8-azapurines now seems to favour the former, for the following reasons. Benzyl azide, readily made [14] (90%) from benzyl chloride, can be converted in a few simple steps into a wide range of 8-azapurines, as indicated above. On the other hand, no 6-substituted 9-benzyl-8-azapurine has been prepared from a pyrimidine intermediate, only one suitable example of which is known, namely 5-amino-4-benzylamino-6-chloropyrimidine (IIIa; R^2 = Cl). This was made by condensing a formamidine salt with ethyl malonate [15] to give 4,6-dihydroxypyrimidine which was nitrated (in the 5-position) and then the two hydroxy-groups were replaced by chlorine.[16,17] This 4,6-dichloro-5-nitropyrimidine was hydrogenated to the 5-amino-analogue,[18] which reacted with benzylamine to give 5-amino-4-benzylamino-6-chloropyrimidine.[19] The sole use made of this substance was to furnish 5-amino-4-benzylaminopyrimidine (by dechlorination [19]), which was converted into 9-benzyl-8-azapurine.[13] In none of these stages did the yield fall below 70%, but the overall yield favoured the triazole approach.

The synthesis of 8-azapurines without a substituent on a ring nitrogen atom was next considered. Debenzylation of 9-benzyl-6-hydroxy-8-azapurine, exemplifying

[6] A. Albert and K. Tratt, *Angew. Chem. Internat. Edn.*, 1966, **5**, 587.
[7] E. Spinner, *J. Chem. Soc.*, 1960, 1237.
[8] E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 1964, **29**, 2121.
[9] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 1856.
[10] A. Albert and G. Catterall, *J. Chem. Soc.* (*C*), 1967, 1533.
[11] M. E. C. Biffin and D. J. Brown, *Tetrahedron Letters*, 1968, 2503.
[12] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117.
[13] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.
[14] T. Curtius and G. Ehrhart, *Ber.*, 1922, **55**, 1559.
[15] G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 1943, 388.
[16] W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 1951, 96.
[17] J. W. Daly and B. E. Christensen, *J. Org. Chem.*, 1956, **21**, 177.
[18] R. K. Robins, K. L. Dille, and B. E. Christensen, *J. Org. Chem.*, 1954, **19**, 930.
[19] D. J. Brown, P. W. Ford, and K. H. Tratt, *J. Chem. Soc.* (*C*), 1967, 1445.

one type of approach, occurred in 60% yield. For this purpose hydrogen (with palladium catalyst) proved a better reagent than sodium with ammonia. However, 6-hydroxy-8-azapurine was better prepared by debenzylation [3] of the triazole (Ia) (with sodium and ammonia) to 4-amino-1,2,3-triazole-5-carboxamide (Ib), which gave an excellent yield of the azapurine (IIb; R^2 = OH) when heated with formamide. The overall yield exceeded that of the published method in which thiourea was condensed with ethyl cyanoacetate to give 4-amino-6-hydroxy-2-mercaptopyrimidine,[20] which (after nitration and reduction) gave 4,5-diamino-6-hydroxy-2-mercaptopyrimidine: desulphurisation converted this into 4,5-diamino-6-hydroxypyrimidine [21] which (with nitrous acid) furnished 6-hydroxy-8-azapurine.[22] This substance has a sparingly soluble sodium salt with which commercial samples of '8-azahypoxanthine' are usually contaminated: it was found necessary to lower the pH of a hot aqueous suspension to 2·5 to liberate the required substance.

6-Hydroxy-8-azapurine was destroyed when chlorination was attempted by the two methods which succeeded for the 9-benzyl-derivative (see above). When heated with phosphorus pentasulphide in pyridine, 6-hydroxy-8-azapurine gave mainly 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (V; R = H) which was compared with an authentic sample by i.r. and u.v. spectroscopy and paper chromatography. This sample was prepared [8] by diazotizing 5-amino-4-mercapto-6-methoxypyrimidine to give 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine, which was then warmed with ammonia. Another sample was obtained by the action of nitrous acid on 4,5-diamino-6-mercaptopyrimidine (IIIb; R^2 = SH), a known reaction [23] the yield of which was improved. This aminothiadiazolopyrimidine was made also by isomerising 6-mercapto-8-azapurine at 160°.

The preparation of 6-mercapto-8-azapurine was first claimed [24] in 1953 from the action of phosphorus pentasulphide on 6-hydroxy-8-azapurine in boiling pyridine. The product (obtained in only 10% yield) agreed in melting behaviour and u.v. spectrum with the above thiadiazolopyrimidine (V; R = H). In the present work, very little 6-mercapto-8-azapurine could be isolated from this preparation, but the compound was readily obtained by isomerising the compound (V; R = H) with boiling aqueous sodium hydroxide. The two isomers are readily separable by use of the solubility of the latter (IV; R = H) in alkali, and the i.r. spectra are quite different. This mercapto-compound had the same properties as that prepared by the action of thiourea in boiling ethanol on 6-chloro-8-azapurine, made [25] by the action of nitrous acid on 4,5-diamino-6-chloropyrimidine. Moreover it had a characteristically strong thiocarbonyl stretching band (*cf.* the 9-benzyl-derivative, above).

The yield of 6-mercapto-8-azapurine, obtained from 6-hydroxy-8-azapurine by the consecutive actions of phosphorus pentasulphide and sodium hydroxide, both of them destructive, was only 43%. This route cannot be recommended for the preparation of other 6-substituted 8-azapurines (IIb) along the lines used for the 9-benzyl derivatives (see above). The literature describes many preparations of 6-substituted-8-azapurines by the action of nitrous acid on appropriately substituted 4,5-diaminopyrimidines; [22,25,26] both 6-chloro- [25] and 6-methylthio-8-azapurine,[26] prepared in this way, have been used for preparing various 6-amino-derivatives. Hence the pyrimidine rather than the triazole approach seems preferable for all except the 6-hydroxy-derivative, the vulnerability of which to chlorinating and sulphurising reagents is attributed to the (unprotected) NH group in the triazole ring.

Preparation of the 9-methyl-8-azapurines (IIc) was then investigated. The most suitable triazole intermediate, 4-amino-3-methyl-1,2,3-triazole-5-carboxamide, was made [4,27] by the action of methyl azide on cyanoacetamide. It has been converted, in good yield, into 6-hydroxy-9-methyl-8-azapurine (IIc; R^2 = OH) by heating with formamide.[1] This route may not be acceptable for large scale production because of the toxic and explosive nature of methyl azide, and its low b.p. (20°). Hence the action was examined of formamide on the difficulty separable 1 : 1 mixture of 2-(and 3-)methyl-4-amino-1,2,3-triazole-5-carboxamides obtained by methylating [1] the readily available [3] 4-amino-1,2,3-triazole-5-carboxamide. An excellent yield of an approximately 1 : 1 mixture of 6-hydroxy-8-(and 9-)methyl-8-azapurines was obtained; the mixture was separated by use of the sparing solubility of the barium salt of the 9-methyl isomer. This approach is suitable if a use exists for the 8-methyl isomer, as in the present work.

The preparation of 6-hydroxy-9-methyl-8-azapurine from pyrimidine intermediates proved difficult at first. The obvious intermediate for conversion into this substance (with nitrous acid) is 5-amino-6-hydroxy-4-methylaminopyrimidine (IIIc; R^2 = OH). This has been prepared [28] from 4,6-dichloropyrimidine by a long route and in poor yield. Attempts to shorten this procedure by converting 4-chloro-6-hydroxypyrimidine into 6-hydroxy-4-methylaminopyrimidine failed. Also, boiling 6N-hydrochloric acid did not affect 5-amino-4-methylamino-6-methylthiopyrimidine [29] (IIIc; R^2 = SMe). However, the latter was readily cyclised (with nitrous acid) to 9-methyl-6-methylthio-8-azapurine (IIc; R^2 =

[20] A. G. Beaman, *J. Amer. Chem. Soc.*, 1954, **76**, 5633.
[21] A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.*, 1951, 474.
[22] R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290.
[23] M. Ishidate and H. Yuki, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 121.
[24] C. T. Bahner, B. Stump, and M. E. Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 6301.
[25] H. Ballweg, *Annalen*, 1962, **657**, 141.
[26] R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.*, 1960, **25**, 765.
[27] J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.*, 1958, 1651.
[28] D. J. Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[29] D. J. Brown, *J. Appl. Chem.*, 1957, **7**, 109.

SMe), which had already been obtained [30] in poor yield by the consecutive action of methyl iodide and nitrous acid on 5-amino-6-mercapto-4-methylaminopyrimidine without isolating the methylthiopyrimidine. When this azapurine (IIc; R^2 = SMe) was stirred with potassium permanganate and acetic acid, with the intention of oxidising it to the 6-methylsulphonyl analogue and hydrolysing the latter, both steps took place almost simultaneously and gave an excellent yield of 6-hydroxy-9-methyl-8-azapurine. For most purposes, this is the recommended method.

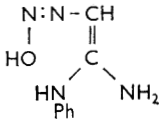
9-Methyl-6-methylthio-8-azapurine, when heated under reflux with aqueous ammonia, gave an exclent yield of 6-amino-9-methyl-8-azapurine [26] (IIc; R^2 = NH_2). (It was not attacked by boiling 2N-sodium carbonate, but boiling N-sodium hydroxide or N-hydrochloric acid caused complex changes.) Similarly, hydrazine hydrate in boiling methanol furnished 6-hydrazino-9-methyl-8-azapurine, which was oxidized by silver oxide in 1-methylpropan-1-ol to 9-methyl-8-azapurine, and this was identical with a specimen prepared [13] from 4-amino-5-methylaminopyrimidine and nitrous acid.

Although 6-hydroxy-9-methyl-8-azapurine was decomposed when heated with phosphoryl chloride (even under conditions that succeeded with the 9-benzyl analogue), it was readily converted into 6-chloro-9-methyl-8-azapurine (IIc; R^2 = Cl) by the Bosshard reagent.[5] The best yields were obtained when the dimethylformamide was added in portions, a departure from the published procedure.

Phosphorus pentasulphide in boiling pyridine converted 6-hydroxy-9-methyl-8-azapurine into an equilibrium mixture of 6-mercapto-9-methyl-8-azapurine (IV; R = Me) and 7-methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (V; R = Me). This reaction differed from that of the 9-benzyl analogue (IIa; R^2 = OH) in the much higher proportion of mercapto-compound present at equilibrium. A similar equilibrium mixture was obtained by diazotizing 5-amino-4-mercapto-6-methylaminopyrimidine (IIIc; R^2 = SH). The thiadiazolopyrimidine (V; R = Me) was rapidly isomerised by boiling N-sodium hydroxide to 6-mercapto-9-methyl-8-azapurine (although some destruction also took place). The latter was only partly isomerised to the thiadiazolopyrimidine at 80°: (in contrast with the *N*-benzyl analogue, see above) but completely at 160°. This agrees with a recent observation that, in some similar equilibria, high temperatures favour the sulphur-containing ring, and that electron-releasing substituents raise the minimal temperature for conversion.[9]

The 7-methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine obtained by these three methods was a feebly basic, non-acidic substance identical with an authentic specimen made by heating methylamine and 7-methoxy-[1,2,3]thiadiazolo[5,4-*d*]pyrimidine [8] (obtained by the action of nitrous acid on 5-amino-4-mercapto-6-methoxypyrimidine).

6-Mercapto-9-methyl-8-azapurine was also readily prepared, free from the isomer (V), by boiling 6-chloro-9-methyl-8-azapurine with thiourea in ethanol. It was stable when kept at 25°. For reasons of valency, equilibrium with thiadiazolopyrimidines cannot occur with 6-mercapto-8-azapurines substituted on N-8 or N-7; this has been confirmed experimentally (refs. 1 and 2, respectively). In the present work, neither 6-amino- (nor 6-hydroxy)-9-methyl-8-azapurine underwent any reaction when heated at 220°.



(VI)

Dimroth Rearrangements.—It has long been known that 4-amino-3-phenyl-1,2,3-triazole (when boiled with water, or pyridine, or simply melted) is readily converted, *via* the intermediate (VI), into an equilibrium mixture of the starting material with 4-phenylamino-1,2,3-triazole, with the latter preponderating.[31] Further work (much of it from Lieber's group [32]) is summarised in Brown's review [33] as follows. Electron-attracting groups and large, rigid groups tend to migrate to the exocyclic (and alkyl groups to the cyclic) nitrogen atom. In view of the leading part which two *N*-alkyltriazole intermediates (Ia and c) played in the present work, it was thought essential to check their stability. When they were heated alone or in solvents at 240° no evidence of change was observed. On the grounds that the N-3 anion of the exocyclically alkylated isomer could be sufficiently out of equilibrium to swing the isomerisation in that direction, 4-amino-3-methyl-(and 3-benzyl-)-1,2,3-triazole-5-carboxamides were heated for 4 hr. in an excess of 3N-ethanolic ammonia at 180° (sealed tubes), but the starting materials were recovered unchanged. As a final check, 4-methylamino-1,2,3-triazole-5-carboxamide was prepared as follows.

4-Amino-3-benzyl-1,2,3-triazole-5-carboxamide [3] and cold acetic formic anhydride gave a quantitative yield of 3-benzyl-4-diformylamino-1,2,3-triazole-5-carboxamide, whereas heating under reflux with formic acid gave a mixture of this diformyl derivative and unchanged starting material. The monoformyl derivative was obtained by boiling the diformyl compound with methanol. The n.m.r. signal for the aldehyde group in the diformyl derivative was shifted considerably upfield and halved in intensity by this procedure. However, the diformyl compound proved to be equally suitable for the next step (methylation) because it was quickly hydrolysed by cold N-sodium hydroxide to the monoformyl compound, a reasonably strong acid, the anion of which ($-N^-\cdot CHO$) gave coulombic protection against

[30] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.
[31] O. Dimroth, *Annalen*, 1909, **364**, 183; 1910, **377**, 127.
[32] E. Lieber, C. N. Ramachandra-Row, and T. S. Chao, *J. Amer. Chem. Soc.*, 1957, **79**, 5962; E. Lieber, T. S. Chao, and C. N. Ramachandra-Row, *J. Org. Chem.*, 1957, **22**, 654.
[33] D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley, New York, vol. 1, 1968.

further attack by the hydroxide anion. The addition of methyl sulphate produced an excellent yield of 3-benzyl-4-methylamino-1,2,3-triazole-5-carboxamide (the formyl group was instantly lost when methylation suppressed ionisation).

Debenzylation with sodium and ammonia gave 4-methylamino-1,2,3-triazole-5-carboxamide, distinguishable from its isomer (Ic) by the ready ionization of a ring NH group (see Table). It was completely converted into this isomer when heated under reflux in cyclohexanol (160°) for 1 hr., but only about half converted after 2 hr. in ethanol under reflux. Thus the prediction that equilibration would move an alkyl group from the exocyclic (to the relevant cyclic) nitrogen atom, and not *vice versa*, was upheld.

Physical Properties.—Many ionisation constants and u.v. spectra are assembled in the Table. Attention is drawn to the first acidic constants of 6-hydroxy- and 6-mercapto-8-azapurine, which are as strong as aliphatic carboxylic acids. Alkylation of N-3 is seen to block this ionisation, but strengthen that of the hydroxy- and mercapto-groups, which suffer coulombic depression in the non-alkylated compounds. The amino-8-azapurines are weak bases and, in general, the constants for the 9-methyl-8-azapurines differ little from those of their 8-methyl [1] and 7-methyl [2] isomers. However 9-methyl-6-methylthio-8-azapurine has a spectrum (neutral species) quite unlike that of its 8-methyl isomer, although that of the 7-methyl isomer is now seen to have features related to the spectra of both the 9- and the 8-isomer.

Ionisation constants and u.v. spectra

		Ionisation in water (20°)				Spectroscopy in water [c]		
			Spread	Concn.	A.w.l. [b]			
	Species [a]	pK_a	(±)	M	mμ	$\lambda_{max.}$ (mμ)	log ε	pH
8-Azapurines								
9-Benzyl-6-hydroxy-	0					255	4·03	5·0
	—	7·98	0·05	10^{-5}	285	275	4·06	11·0
9-Benzyl-6-mercapto-	0					232,[d] 332	3·97, 4·27	M [e]
	—					231, 335	4·12, 4·24	13·0
9-Benzyl-6-methoxy-	0					252	4·05	E [e]
6-Hydroxy [f] (ref. 2)	0					253	3·94	
	—	5·16 [g]				259	3·96	
	2—	10·78				370	4·01	
6-Mercapto-	0					*226*, 330	*3·99*, 4·25	2·0
	—	4·13 [g]	0·03	0·025	P	*226*, 328	*2·98*, 4·34	7·0
	2—	9·44 [h]	0·03	10^{-4}	339	221, 323 [i]	4·17, 4·18	12·0
6-Amino [f] (ref. 2)	0					273	4·01	
	+	2·70				263	4·03	
9-Methyl [f] (ref. 13)	0					264	3·88	
	+	0·32				263	3·73	
6-Hydroxy-9-methyl [f] (ref. 1)	0					254	3·98	
	—	8·06				273	4·02	
6-Mercapto-9-methyl-	0					229, 327	3·97, 4·30	5·0
	—	7·21	0·04	10^{-4}	350	229, 269, 333	4·12, 3·30, 4·19	10·0
6-Amino-9-methyl-	0					277	4·01	7·0
	+	2·80	0·03	10^{-4}	280	264	4·03	0·2
6-Hydrazino-9-methyl-	0					211, 285	4·16, 4·08	7·0
	+	3·39	0·03	10^{-4}	295	268	4·10	1·0
9-Methyl-6-methylthio-	0					223, 296	4·00, 4·18	E [e]
1,2,3-Triazoles								
4-Amino-5-carbamoyl-3-methyl [f] (ref. 1) [j]	0					227, 260	3·99, 3·92	7·0
5-Carbamoyl-4-methylamino	0					232, 275	3·93, 3·86	5·0
	—	7·96 [k]	0·04	0·003	P	277	3·85	11·0
3-Benzyl-5-carbamoyl-4-methylamino [j]	0					244, 265	3·99, 3·92	E [e]

[a] Neutral species (0), cation (+), anion (−), dianion (2−). [b] Analytical wavelength for spectrometric determinations (P potentiometric) as in A. Albert and E. P. Serjeant, Ionisation Constants, Methuen, London, 1962. [c] Inflections in italics. [d] Broad. [e] M, methanol; E, ethanol. [f] For comparison. [g] Ionisation of the ring NH group. [h] Ionisation of the SH group. [i] Peaks at 226 and 328 mμ (pH 1), and at 224 and 325 mμ (pH 11) were given by H. Ballweg, *Annalen*, 1962, **657**, 141 without any extinction value. [j] A non-acidic compound. [k] Cf. 7·79 for non-methylated analogue (ref. 2).

EXPERIMENTAL

Yields refer to material sufficiently pure to give only one spot in chromatography on Whatman No. 1 paper developed with solvent A (3% aqueous ammonium chloride) or (B) (butanol–5N-acetic acid, 7 : 3) and viewed in 254 mμ light. Material was applied to the paper in aqueous pyridine (the constant-boiling mixture). All specimens for microanalysis (by Dr. J. E. Fildes and her staff) were dried in air at 110° unless otherwise specified. Ionisation constants were determined by Mr. D. T. Light and Miss M. D. Basell under the supervision of Dr. D. D. Perrin. Optical spectra were measured by Mr. I. Pavelić under supervision by Dr. E. Spinner (i.r. spectra for KBr discs; u.v. spectral maxima confirmed with a manual instrument). N.m.r. spectra were obtained by Mr. S. Brown, supervised by Dr. T. J. Batterham, with a Perkin-Elmer model R10 instrument, operating at 33·5° and 60 Mc/sec., with tetramethylsilane as internal standard.

9-Benzyl-6-hydroxy-8-azapurine (IIa; R^2 = OH).—In a capacious wide-mouthed flask, 3-benzyl-4-amino-1,2,3-triazole-5-carboxamide [3] (4 g.) and formamide (20 ml.) were heated at 220° (bath) for 45 min., cooled to 100°, and diluted with water (20 ml.). The mixture was chilled overnight and filtered. The solid was rubbed with water (20 ml.), filtered off, and dried at 110° to give 9-benzyl-6-hydroxy-8-azapurine (95%), m.p. 249° (slight decomp.; lit.,[4] 246°); when recrystallised from 200 parts of ethanol, then 770 parts of water it had $\nu_{max.}$ 3100 + 3050m, 1710s, and 1590, 1557, 1275, and 735 (all m) cm.$^{-1}$.

9-Benzyl-6-chloro-8-azapurine (IIa; R^2 = Cl).—(*a*) 9-Benzyl-6-hydroxy-8-azapurine (1 g.) and phosphoryl chloride (30 ml.) were heated under reflux for 1 hr. The excess of reagent was removed at 60° *in vacuo*, and the hot, fluid residue was agitated with light petroleum (b.p. 60—80°; 15 ml.). The mixture was cooled and the liquid poured from the crystals which were dried at 25 mm./25°. They were then stirred with ice at 0°; sodium hydrogen carbonate was added until the pH became 6. The solid was filtered off, dried at 25°, then recrystallised from light petroleum (b.p. 60—80°; 40 ml.). A small second crop was obtained by re-extraction of the insoluble portion, and concentration of the pooled mother liquors; recrystallisation gave needles (51%) of *9-benzyl-6-chloro-8-azapurine*, m.p. 92° (Found: C, 53·5; H, 3·2; N, 28·4. $C_{11}H_8ClN_5$ requires C, 53·75; H, 3·3; N, 28·5%). It gave a red colour with cold pyridine.

(*b*) To a boiling suspension of 9-benzyl-6-hydroxy-8-azapurine (0·23 g.) in chloroform (5 ml.) were added thionyl chloride (1·2 g,; 10 equiv.) then dimethylformamide (0·1 ml.; 1·4 equiv.). The mixture was heated under reflux until clear (about 40 min.) and then for 30 min. more. The volatile components were removed *in vacuo* at 30°. The tacky residue, cooled to 0°, was rubbed with ice (*ca.* 1 g.). The solid was filtered off and dried to give 9-benzyl-6-chloro-8-azapurine (50%), m.p. 92° (from light petroleum).

9-Benzyl-6-methoxy-8-azapurine.—To the 6-chloro-analogue (IIa; R^2 = Cl) (0·49 g.; 0·002 mole) suspended in methanol (5 ml.) was added a solution of sodium methoxide [from sodium (0·046 g.; 1 equiv.) and methanol (2 ml.)]. The suspension was heated under reflux for 20 min. and filtered hot from sodium chloride. The refrigerated filtrate deposited crystals (72%) of *9-benzyl-6-methoxy-8-azapurine* which, after one recrystallisation from light petroleum (b.p. 60—80°) had m.p. 109° (Found, for material dried at 40° and 0·01 mm.; C, 59·7; H, 4·45; N, 29·15. $C_{12}H_{11}N_5O$ requires C, 59·7; H, 4·6; N, 29·0%), $\nu_{max.}$ 1600sh + 1580, and 1495, 1365, 1330, 1245, and 725 (all m) cm.$^{-1}$.

6-Amino-9-benzyl-8-azapurine.— 9-Benzyl-6-chloro-8-azapurine (0·5 g.; 0·002 mole) and 3·5N-ethanolic ammonia (25 ml.) were stirred for 2 hr. at 25°, then heated under reflux for 1 hr. The suspension was chilled and filtered. The solid was boiled with water (5 ml.) to remove ammonium chloride and gave *6-amino-9-benzyl-8-azapurine* (80%), m.p. 248° (from 250 parts of ethanol), insoluble in 0·1N-acid or alkali, but soluble in cold N-hydrochloric acid (Found: C, 58·4; H, 4·4; N, 37·4. $C_{11}H_{10}N_6$ requires C, 58·4; H, 4·5; N, 37·15%), $\nu_{max.}$ 3280, 3060, 1705, 1575, 1325, and 730 (all m) cm.$^{-1}$.

9-Benzyl-6-mercapto-8-azapurine (IIIb).— (*a*) 9-Benzyl-6-chloro-8-azapurine (0·3 g.), thiourea (0·3 g.), and methanol (10 ml.) were boiled for 15 min., and the mixture was then taken to dryness. The residue was dissolved in cold 0·5N-sodium hydroxide and filtered. The pH of the filtrate was adjusted to 4 with acetic acid. The precipitate gave *9-benzyl-6-mercapto-8-azapurine* (90%) as colourless needles (yellow when free from solvent), m.p. 150° (from 70 parts of methanol) (Found: C, 54·3; H, 3·5; N, 28·7. $C_{11}H_9N_5S$ requires C, 54·3; H, 3·7; N, 28·8%).

(*b*) 7-Benzylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (see below; 1 g.) and N-sodium hydroxide (10 ml., 2·5 equiv.) were boiled for 30 min., and cooled to below 5° while the pH was adjusted to 2 with 5N-sulphuric acid. The deposited crystals (90%), m.p. 150°, were identical with the product of (*a*) (mixed m.p. and i.r. spectra); $\nu_{max.}$ 3140m, 3030s, 2970m, 2900m, 1590s, 1560s, 1535m, 1345s, 1195s (C:S stretch) 730s, 700m, and 550m cm.$^{-1}$.

(*c*) (The preferred method.) Phosphorus pentasulphide [purified (Fluka); 10 g.] was added to a solution of 9-benzyl-6-hydroxy-8-azapurine (5 g.) in boiling anhydrous pyridine (100 ml.). The mixture was heated under reflux for 2 hr., cooled, diluted with water (75 ml.), then taken to dryness on a rotary evaporator at 55°. Water (25 ml.) was added to the residue and the pH was adjusted to 3—5; after refrigeration the mixture was filtered (to remove pyridine salts) and the cake (an equilibrium product containing much of the thiadiazolopyrimidine described above) was heated under reflux with N-sodium hydroxide (50 ml.) for 30 min. and cooled; while the vessel was immersed in ice the pH was adjusted to 3—5. Filtration next day gave 9-benzyl-6-mercapto-8-azapurine (90%), m.p. 147—148°, identical with the product of (*a*).

7-Benzylamino[1,2,3]thiadiazolo[5,4-d]pyrimidine.—(*a*) 7-Methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine [8] (0·5 g.), benzylamine (0·4 g.), and ethanol (12 ml.) were heated under reflux for 1 hr. The colourless crystals (75%) of the *thiadiazolopyrimidine*, obtained after cooling and recrystallization from ethanol, had m.p. 140° and were insoluble in boiling 0·1N-hydrochloric acid [Found: C, 54·0; H, 3·6; N, 28·4; S, 13·3%; *M* (in camphor), 248. $C_{11}H_9N_5S$ requires C, 54·3; H, 3·7; N, 28·8; S, 13·2%; *M*, 243], $\lambda_{max.}$ (ethanol) 248, 268, and 325 mμ (log ε 4·02, 4·73, and 3·86).

(*b*) 9-Benzyl-6-hydroxy-8-azapurine (0·5 g.), purified phosphorus pentasulphide (1 g.), and pyridine (20 ml.) were boiled for 2 hr. The mixture, diluted with water (250 ml.) and then concentrated under vacuum to remove pyridine, was made slightly alkaline and chilled. The precipitated thiadiazolopyrimidine (70%) had m.p. 140° (from ethanol) and did not depress the m.p. of the product of (*a*); $\nu_{max.}$ 3310, 1615, 1530, 1330, and 1305 cm.$^{-1}$ (all s).

(*c*) 9-Benzyl-6-mercapto-8-azapurine (0·2 g.) was heated under reflux with ethanol (10 ml.) for 3 hr. The solvent was evaporated off and the residue, ground under cold 0·5N-sodium hydroxide, gave the same thiadiazolopyrimidine (80%).

9-Benzyl-6-methylthio-8-azapurine.—To the 6-mercapto-analogue (IIIb) (1·22 g., 0·005 mole) in N-sodium hydroxide (6 ml.) magnetically stirred at 25° was added methyl iodide (0·85 g., 1·2 equiv.). The suspension was filtered after 15 min. to give *9-benzyl-6-methylthio-8-azapurine* (91%), m.p. 139° (from 30 parts of methanol) (Found: C, 56·05; H, 4·4; N, 27·15. $C_{12}H_{11}N_5S$ requires C, 56·0; H, 4·3; N, 27·2%), $\nu_{max.}$ 1583s, 1555, 1420, 1303, 1207, 1060, and 865 (all m), and 726s cm.$^{-1}$.

9-Benzyl-6-hydrazino-8-azapurine.— (*a*) The 6-chloro-analogue (0·83 g.), finely powdered, was added slowly to

ethanol (20 ml.) under reflux containing an excess of hydrazine hydrate (1·4 ml.). The suspension was heated under reflux for a further 20 min., mixed with hot water (20 ml.), and refrigerated. The precipitate gave 9-*benzyl*-6-*hydrazino*-8-*azapurine* (80%), m.p. 202° with effervescence (from 1 : 1 toluene–butanol), insoluble in either boiling benzene or boiling ethanol but readily soluble in a mixture of these. It gave a yellow precipitate with *p*-nitrobenzaldehyde in boiling ethanol (Found: C, 54·8; H, 4·8; N, 40·7. $C_{11}H_{11}N_7$ requires C, 54·8; H, 4·6; N, 40·6%).

(*b*) (The preferred method.) 9-Benzyl-6-methylthio-8-azapurine (0·86 g.) was suspended in boiling methanol (10 ml.), then removed from the source of heat. Hydrazine hydrate (2·5 ml., 15 equiv.) was added in one portion, and the whole was magnetically stirred while slowly cooling, then chilled. The solid, filtered off and washed with methanol, was pure 9-benzyl-6-hydrazino-8-azapurine (95%), m.p. 202°.

9-*Benzyl*-8-*azapurine*.— 9-Benzyl-6-hydrazino-8-azapurine (1·45 g., 0·006 mole) and a well triturated suspension of silver oxide (2·10 g., 1·5 equiv.) in 1-methylpropan-1-ol (90 ml.) were heated under reflux for 1 hr., Kieselguhr (0·5 g.) was added, and the boiling solution was filtered. The filtrate was taken to dryness on a rotary evaporator and the product, sublimed at 100°/0·01 mm., gave 9-benzyl-8-azapurine (55%), m.p. 115—116°, identical with an authentic specimen.[13] The residue, crystallised from ethanol gave 6-amino-9-benzyl-8-azapurine (10%), identical with material described above.

6-*Hydroxy*-8-*azapurine*.— 4-Amino-1,2,3-triazole-5-carboxamide [3] (1·54 g., 0·01 mole) and formamide (6 ml.) were heated at 220—225° (bath) for 45 min. Acetone (6 ml.) was added to the cooled mixture. The crystals were filtered off, stirred with acetone (6 ml.), and collected. Recrystallisation from 27 parts of water (solution acidified to pH 2·5 to decompose ammonium salt) gave 6-hydroxy-8-azapurine (90%), m.p. 306° (sharp, decomp.) (lit.,[23] 308°), which was found to be identical with authentic material (paper chromatography and i.r. spectra).

7-*Amino*[1,2,3]*thiadiazolo*[5,4-d]*pyrimidine*.—(*a*) 6-Hydroxy-8-azapurine (1 g.) and dried pyridine (12 ml.) were brought to the boil, phosphorus pentasulphide (purified, 2·5 g.) was added, and the suspension was heated under reflux at 130° (bath) for 1 hr. The mixture was cooled and diluted with water (9 ml.), and the volatile components were removed *in vacuo* at 55°. The residue was stirred with water (12 ml.), then acidified (to pH 2·5) with 5N-sulphuric acid. The solid, filtered off and ground under N-sodium hydroxide (3 ml., rejected), was recrystallised from 1000 parts of water, then sublimed at 180°/0·01 mm. to give the thiadiazolopyrimidine (62%),[23] decomp. *ca.* 270°, insoluble in N-sodium hydroxide, but very soluble in hot N-hydrochloric acid, $\lambda_{max.}$ (ethanol) 244 and 313 mμ (log ε 3·80 and 3·67), $\nu_{max.}$ 2900, 1685, 1580, 1530, and 1305 cm.$^{-1}$.

(*b*) A solution of 4,5-diamino-6-mercaptopyrimidine [34] (0·6 g.) in hot 0·5N-hydrochloric acid (50 ml.) was stirred and maintained at 20° while sodium nitrite (0·6 g.) in water (10 ml.) was added during 10 min. The mixture was stirred for 2 hr. more, neutralised, cooled, and filtered. The solid, recrystallised from water, gave the thiadiazolopyrimidine (70%) obtained in (*a*).

(*c*) Powdered 6-mercapto-8-azapurine (0·5 g.) was heated at 165° for 2 hr., cooled, and ground under N-sodium hydroxide (6 ml.). The suspension was filtered to give insoluble thiadiazolopyrimidine (63%). Boiling with water produced only 10% of the thiadiazolopyrimidine in 5 hr.

6-*Mercapto*-8-*azapurine*.— 7-Amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (0·3 g.) and N-sodium hydroxide (5 ml.) were boiled for 20 min. The clear solution was cooled, adjusted to pH 2·0 with 5N-sulphuric acid, and refrigerated overnight. The pale yellow solid was collected and recrystallized as quickly as possible from 100 parts of water to give 6-mercapto-8-azapurine (70%) [25] as pale yellow crystals completely soluble in cold 0·1N-sodium hydroxide; they begin to turn brown at 250° but are not melted at 300°; $\nu_{max.}$ 3185s, 3040m, 3000m, 2890m, 2840m, 1590s, 1565s, 1535m, and 1180s (C:S stretch) cm.$^{-1}$ (Found, for material dried at 40° and 0·01 mm.: C, 31·6; H, 2·0; N, 45·9. Calc. for $C_4H_3N_5S$: C, 31·4; H, 2·0; N, 45·7%).

Methylation of 4-*Amino*-1,2,3-*triazole*-5-*carboxamide*.—To the amide [3] (1·16 g., 0·008 mole), dissolved in a solution of sodium methoxide [1·1 equiv., from sodium (0·20 g.) and methanol (20 ml.)] at 20°, was added methyl sulphate (1·1 g., 1·1 equiv.) during 30 min. with vigorous stirring. The suspension was set aside at 20° for 2 hr., then taken to dryness *in vacuo*. The product was stirred with water (3 ml.), refrigerated, and filtered, to give an approx. 1 : 1 mixture (75%) of 4-amino-2-(and 3-)methyl-1,2,3-triazole-5-carboxamides [R_F values 0·75 (violet) and 0·70 (dark) in solvent (A)].

6-*Hydroxy*-9-*methyl*-8-*azapurine*.—(*a*) The above mixture of methylated triazole amides (2·37 g.) and formamide (9·5 ml.) was heated at 225° for 45 min., cooled, diluted with acetone (10 ml.), refrigerated overnight, and filtered. The solid, washed well with acetone and dried at 110°, gave a 1 : 1 mixture (85%) of 6-hydroxy-8-(and 9-)methyl-8-azapurines. To this solid, dissolved in cold N-sodium hydroxide (17 ml.) and well stirred, was added a warm solution of barium chloride dihydrate (3·42 g.) in water (13 ml.). The mixture was stirred for 2 hr. at 25° and refrigerated overnight and the suspension was filtered. The solid, dissolved in boiling water (35 ml.) and acidified (to pH 6·0) with acetic acid, yielded 6-hydroxy-9-methyl-8-azapurine (0·66 g.), m.p. 302°, identical with material prepared [1] from pure 4-amino-3-methyl-1,2,3-triazole-5-carboxamide and formamide. The filtrate from the barium salt was acidified (to pH 6·0) with acetic acid and taken to dryness *in vacuo*. The residue, further dried at 110°, then Soxhlet-extracted with ethanol, gave 6-hydroxy-8-methyl-8-azapurine (0·94 g.), m.p. 258°, identical with material prepared [1] from pure 4-amino-2-methyl-1,2,3-triazole-5-carboxamide.

(*b*) To 9-methyl-6-methylthio-8-azapurine (1·98 g., 0·11 mole) dissolved in acetic acid (14 ml.) was slowly added at 23° with stirring, a solution of potassium permanganate (2·75 g., 1·2 equiv.) in water (44 ml.). Sodium sulphite (about 2·6 g.) was added until the suspension was decolorised, and the bulk was reduced to about one third *in vacuo* at 60°. The mixture was chilled overnight and the solid was filtered off and recrystallised from the minimum of water to give 6-hydroxy-9-methyl-8-azapurine (80%), m.p. 301°, identical with authentic material.[1]

9-*Methyl*-6-*methylthio*-8-*azapurine*.— To 5-amino-4-methylamino-6-methylthiopyrimidine monohydrate [29] (1·86 g., 0·01 mole) dissolved in N-sulphuric acid (15 ml.) was slowly added, with stirring at 2°, sodium nitrite (0·76 g., 1·1 equiv.) in water (2·5 ml.). The mixture was stirred at room temperature for 3 hr. more, then the pH was adjusted to 3·5 with sodium citrate. The mixture was chilled for

[34] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.

3 hr. and filtered to give 9-methyl-6-methylthio-8-azapurine (85%), m.p. 118° (sharp) (from 35 parts of water), not raised by recrystallisation from other solvents or sublimation and hence represents a different crystal form from that in the literature [26] (m.p. 122—124°) (Found, for material dried at 95°/0·01 mm.: C, 39·5; H, 3·9; N, 38·7. Calc. for $C_6H_7N_5S$: C, 39·8; H, 3·9; N, 38·65%). Boiling N-sodium hydroxide or hydrochloric acid quickly caused complex decomposition.

6-*Hydrazino*-9-*methyl*-8-*azapurine*.— 9-Methyl-6-methylthio-8-azapurine (0·72 g., 0·004 mole) was dissolved in boiling methanol (7 ml.) and removed from the source of heat. Hydrazine hydrate (3 ml., 15 equiv.) was then added all at once. The mixture was stirred while cooling slowly, then chilled for 3 hr. and filtered. The solid, washed with methanol, gave yellow 6-*hydrazino*-9-*methyl*-8-*azapurine* (90%), m.p. 215° (Found, for material recrystallised from 340 parts of ethanol and dried at 80°/0·01 mm.: C, 36·2; H, 4·4; N, 59·2. $C_5H_7N_7$ requires C, 36·4; H, 4·3; N, 59·4%).

9-*Methyl*-8-*azapurine*.—This hydrazino-compound (0·33 g.; 0·002 mole) was heated under reflux for 1 hr. with a fine suspension of silver oxide (0·7 g., 1·5 equiv.) in 1-methylpropan-1-ol (30 ml.). Kieselguhr (0·1 g.) was added, and the suspension was filtered at the boil. The cake was washed with a little boiling solvent and discarded. When cooled to 20°, the filtrate deposited 6-amino-9-methyl-8-azapurine [26] (0·05 g.). The supernatant, taken to dryness *in vacuo* at 50°, gave 9-methyl-8-azapurine (60%),[13] m.p. 87° (after sublimation at 60°/0·01 mm.).

6-*Chloro*-9-*methyl*-8-*azapurine*.—To 6-hydroxy-9-methyl-8-azapurine (0·45 g., 0·003 mole), suspended in chloroform (9 ml.) were added, in turn, thionyl chloride (1·14 ml., 0·015 mole) and dimethylformamide (0·2 ml.; 0·0026 mole). The suspension was heated under reflux for 1 hr., and more dimethylformamide (0·1 ml.) was added. After 100 min. total boiling, the mixture became clear, and was boiled for 30 min. longer. The volatile components were removed *in vacuo* at 30°. The residue, well cooled in ice–water, was stirred with ice (*ca.* 2 g.), and the mixture was set aside for 30 min. in ice, then filtered. The solid, dried at 20°, dissolved in boiling benzene (2 ml.) and filtered from a little sediment, gave (on evaporation of the solvent) 6-*chloro*-9-*methyl*-8-*azapurine* (71%), m.p. 104° [from light petroleum (b.p. 60—80°)]. It was readily hydrolysed to the 6-hydroxy-analogue, but could be stored unchanged over sodium hydroxide. It gave an intense orange colour with pyridine. Neutralisation and extraction with chloroform of the aqueous filtrate obtained in this preparation yielded no more product (Found, for material dried at 20°/25 mm.: C, 35·5; H, 2·5; Cl, 21·15; N, 41·1. $C_5H_4ClN_5$ requires C, 35·4; H, 2·4; Cl, 20·9; N, 41·3%).

7-*Methylamino*[1,2,3]*thiadiazolo*[5,4-d]*pyrimidine*.—(*a*) To 5-amino-4-mercapto-6-methylaminopyrimidine (0·57 g., 0·0037 mole) suspended (as the sulphate) in N-sulphuric acid (30 ml.) and stirred at 1° was added an excess (15%) of sodium nitrite (0·3 g.) in water (1 ml.) during 15 min. The suspension was stirred for 1 hr. below 5° and for 4 hr. at 22°. The pH was raised to 2·5 with sodium hydroxide. The solid was filtered off and stirred with N-sodium hydroxide (7 ml.). The suspension yielded (i) a filtrate which, on acidification (to pH 2·5), deposited pure 6-mercapto-9-methyl-8-azapurine (see below) (25%), and (ii) solid 7-methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine [8] (55%), m.p. 216° (from 120 parts of ethanol), unchanged by sublimation at 125°/0·01 mm. It was almost insoluble in boiling water but readily soluble in cold N-hydrochloric acid (Found: $\lambda_{max.}$ 219, 246, 267sh, 274sh, and 325 mμ (log ε 4·13, 3·97, 3·63, 3·60, and 3·83).

(*b*) Purified phosphorus pentasulphide (1·35 g.) was added to a solution of 6-hydroxy-9-methyl-8-azapurine (0·45 g., 0·003 mole) in boiling pyridine (12 ml.). The mixture was heated under reflux for 30 min., cooled, and diluted with water (9 ml.). The volatile components were removed *in vacuo* at 55°. The residue was stirred with water (6 ml.), acidified (to pH 2·5) with 5N-sulphuric acid and filtered. The solid was ground with N-sodium hydroxide (3 ml.) and filtered at once. The filtrate, acidified (to pH 2·5) gave 6-mercapto-9-methyl-8-azapurine (30%), and the precipitate was the above thiadiazolopyrimidine (40%), m.p. 215° (from ethanol).

(*c*) 6-Mercapto-9-methyl-8-azapurine (0·4 g.), heated under reflux with cyclohexanol (5 ml.) for 5 hr., gave the above thiadiazolopyrimidine, m.p. 210°, almost quantitatively when the solvent was removed *in vacuo* at 110°. Heating for 5 hr. in boiling ethanol gave only 25% conversion, whereas heating at 160° in the absence of solvent caused much destruction.

6-*Mercapto*-9-*methyl*-8-*azapurine*.—(*a*) In method (*b*) for making the thiadiazolopyrimidine the precipitate, instead of being ground with N-sodium hydroxide, was heated under reflux with this reagent (5·5 ml.) for 30 min. The resultant solution, cooled in ice–water, and acidified with 5N-sulphuric acid (to pH 2·5), deposited 6-*mercapto*-9-*methyl*-8-*azapurine* (55%), which formed golden spangles (from 90 parts of water) which melted indefinitely about 200°; it fluoresced yellow on paper chromatography whereas the isomeric thiadiazolopyrimidine fluoresced violet (Found, for material dried at 20°/0·01 mm.: C, 35·7; H, 2·8; N, 42·3. $C_5H_5N_5S$ requires C, 35·9; H, 3·0; N, 41·9%).

(*b*) The isomeric thiadiazolopyrimidine (0·64 g.) and N-sodium hydroxide (6 ml.) were heated under reflux until the former dissolved, then for 5 min. more. Acidification, as in (*a*), gave 6-mercapto-9-methyl-8-azapurine (75%) identical with the above specimen.

(*c*) (Recommended preparation.) 6-Chloro-9-methyl-8-azapurine (0·3 g.), thiourea (0·3 g.), and ethanol (4·5 g.) were heated under reflux for 30 min., then the mixture was taken to dryness. The product, recrystallised from water, gave 6-mercapto-9-methyl-8-azapurine (92%), identical with the above.

Formylation of 3-*benzyl*-4-*diformylaminotriazole*-5-*carboxamide*.—This amide [3] (1·08 g.; 0·005 mole) and freshly distilled acetic formic anhydride (7 ml.) were stirred at 23° for 24 hr. The volatile components were removed *in vacuo* at 50°. The residue, stirred with a little ethanol and then filtered off, yielded 3-*benzyl*-4-*diformylaminotriazole*-5-*carboxamide* (95%), m.p. 153°, unchanged by recrystallization from 55 parts of ethanol (Found, for material dried at 60°/0·01 mm.: C, 52·8; H, 4·1; N, 25·6. $C_{12}H_{11}N_5O_3$ requires C, 52·7; H, 4·1; N, 25·6%) τ([$^3H_6$]acetone + D_2O) 0·68 (2H, CHO), 2·63 (5H, Ph), and 4·49 (2H, CH_2). This substance (1 g.), when heated under reflux with methanol (10 ml.) until dissolved (50 min.) and for 40 min. longer, then taken to dryness, yielded 3-*benzyl*-4-*formamidotriazole*-5-*carboxamide* (95%), m.p. 150° (from toluene). It was very soluble in cold aqueous N-sodium carbonate (but not in water), whereas the diformyl analogue was insoluble in cold *N*-sodium hydroxide (Found, for material dried at 80°/0·01 mm.: C, 54·0; H,

4·6; N, 28·4. $C_{11}H_{11}N_5O_2$ requires C, 53·9; H, 4·5; N, 28·6%), τ([$^3H_6$]acetone + D_2O) 1·53 (1H, CHO), 2·63 (5H, Ph), and 4·34 (2H, CH_2), R_F in solvent (A) 0·05 less than that of the diformyl analogue [no difference in solvent (B)].

3-*Benzyl*-4-*methylamino*-1,2,3-*triazole*-5-*carboxamide*.—Dimethyl sulphate (1·4 g.) was added during 20 min. to the above diformyl compound (1·47 g.) in N-sodium hydroxide (22 ml.) with rapid stirring and the temperature maintained at 20°. The suspension, stirred for 30 min. more, then refrigerated for 7 hr. and filtered, produced 3-*benzyl*-4-*methylamino*-1,2,3-*triazole*-5-*carboxamide* (85%), m.p. 158·5° (from 15 parts of ethanol) (Found: C, 57·45; H, 6·05; N, 30·5. $C_{11}H_{13}N_5O$ requires C, 57·1; H, 5·7; N, 30·3%), n.m.r. spectrum ([$^3H_6$]acetone + D_2O) showed nothing downfield from the 2·65 (5H, Ph) and 4·38 (2H, CH_2) signals.

4-*Methylamino*-1,2,3-*triazole*-5-*carboxamide*.—The above benzyl derivative (0·62 g.) was debenzylated with sodium and liquid ammonia.[3] Ice (*ca.* 4 g.) was added to the resulting sodium salt, and the pH of the solution was adjusted to 6 with 8M-phosphoric acid. The suspension, taken to dryness *in vacuo* to remove toluene, then rubbed with a little water to remove salts, gave alkali-soluble 4-*methylamino*-1,2,3-*triazole*-5-*carboxamide* (85%), softening at 160° and melting at 241° to form 4-amino-3-methyl-1,2,3-triazole-5-carboxamide (lit.,[1] 243°) R_F 0·1 less than that of the methylamino-isomer in solvent (B) (Found, for material recrystallised from methanol and dried at 20°/0·01 mm.: C, 33·9; H, 5·1; N, 49·1. $C_4H_7N_5O$ requires C, 34·0; H, 5·0; N, 49·6%).

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