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1,2,3,4,6-Penta-azaindenes (8-Azapurines). Part IV.[1,2] A New Route to the 8-Methyl-8-azapurines through the 2-Methyl-1,2,3-triazoles

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4-Amino-1,2,3-triazole-5-carboxyamide was formylated to an anhydro-dimer (IV) of 4-formamido-1,2,3-triazole-5-carboxyamide. Methylation of the latter took place almost exclusively in the 2-position to give 4-formamido-2-methyl-1,2,3-triazole-5-carboxyamide (IIa) (some minor products of this methylation are also described). This formyl amide (IIa) was deformylated to the corresponding amine (IIb), and both substances were cyclised (by boiling formamide) to 6-hydroxy-8-methyl-8-azapurine (Ib). The latter was converted by the usual metathetical reactions into the 6-chloro-, 6-mercapto-, 6-methylthio-, 6-amino-, 6-methoxy-, and 6-hydrazino-derivatives of 8-methyl-8-azapurine. The last-named (VI; R = $NH{\cdot}NH_2$), when heated with silver oxide in propan-2-ol, gave the parent: 8-methyl-8-azapurine, the cation of which was shown to be covalently hydrated across the 1- and 6-positions. Many ionization constants and spectra of these triazoles and azapurines are reported for the first time.

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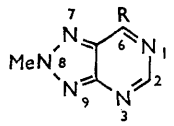
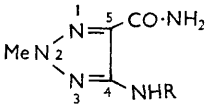
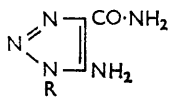
8-AZAPURINES * are of considerable interest in cancer research (see ref. 1), and occur in micro-organisms (*e.g.* pathocidin, 2-amino-6-hydroxy-8-azapurine, in *Streptomyces albus* [3]). Methods for the preparation of 7- and 8-alkyl derivatives of 8-azapurines have long been sought. Recently a convenient method was reported for preparing derivatives of 7-methyl-8-azapurine from a 1,2,3-triazole, and it has now been found that 8-methyl-8-azapurine (Ia), and many of its derivatives, can easily be made from a similar intermediate, 4-formamido-2-methyl-2*H*-1,2,3-triazole-5-carboxyamide (IIa).† Hitherto only eight 2-methyl-1,2,3-triazoles have been reported,[4] all obtained in small yields because of the simultaneous production of isomers or homologues.



(I) a; R = H
b; R = OH



(II) a; R = CHO
b; R = H
c; R = Me



(III) a; R = CH_2Ph
b; R = Me

The 1,2,3-*Triazole Intermediates.*—A convenient starting material was 4-amino-3-benzyl-1,2,3-triazole-5-carboxyamide (IIIa), prepared [5] in a single step from benzyl azide and cyanoacetamide, and readily debenzylated with sodium and ammonia [5] to 4-amino-1,2,3-triazole-5-carboxyamide. Methylation of the latter with methyl sulphate in aqueous alkali gave a 1 : 1 mixture of the 2-methyl (IIb) and 3-methyl (IIIb) derivatives. The complete absence of the 1-methyl derivative,[1] shown by paper chromatography, indicated that the 5-carboxyamide group strongly hindered methylation of the 1-position. This suggested that a small increase in size of the 4-substituent could generate enough steric hindrance to suppress methylation in the 3-position also.

Accordingly, 4-amino-1,2,3-triazole-5-carboxyamide was converted (by boiling with formic acid or by stirring with acetic formic anhydride at 25°) into the 4-formamido-analogue, isolated quantitatively as an anhydro-dimer (discussed further below), which was instantly converted into the monomeric anion by aqueous potassium hydroxide (the ^1H n.m.r. spectrum in sodium deuteroxide solution showed only a single peak, τ 1·05 (1H), indicative of C*H*O, whereas an amidine-type −CH= signal would be found between τ 2 and 3, and a paraffinic −C*H*(OH)− above τ 4). It seemed unlikely that this anion (or the other stable monomeric formyl compounds of Table 1) was acylated on a ring-nitrogen atom, because it was found [6] that 1-acetyl-1,2,3-triazole (obtained by acylating triazole) was instantly hydrolysed to triazole by dilute alkali, and the half-time of survival ($t_{\frac{1}{2}}$) in neutral aqueous solution was only 11 min. Moreover, the ring-nitrogen acyl group in a diacetyl derivative obtained by boiling 4-amino-1,2,3-triazole-5-carboxyamide with acetic anhydride was rapidly hydrolysed by water to 4-acetamido-1,2,3-triazole-5-carboxyamide.[7] Acidification of aqueous solutions of the monomeric anion of 4-formamido-1,2,3-triazole-5-carboxyamide caused instant reprecipitation of the anhydro-dimer. The latter was unchanged by boiling with water for 4 hr. However, boiling 2N-sodium carbonate completely hydrolysed it to the primary amine.

Methylation of the monoanion of 4-formamido-1,2,3-triazole-5-carboxyamide with methyl sulphate, in self-buffered aqueous alkali, gave 4-formamido-2-methyl-1,2,3-triazole-5-carboxyamide (75%). The mother liquors yielded unchanged starting material (recovered

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

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

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

[2] Preliminary report, A. Albert, *Chem. Comm.*, 1967, 684.

[3] K. Anzai and S. Suzuki, *J. Antibiotics* (*Japan*), 1961 (A), **14**, 253; K. Anzai, J. Nagatsu, and S. Suzuki, *ibid.*, p. 340; J. Nagatsu, K. Anzai, and S. Suzuki, *ibid.*, 1962 (A), **15**, 103 (*Chem. Abs.*, 1962, **56**, 8849, 10677).

[4] A. Tamburello and A. Milazzo, *Gazzetta*, 1908, **38**, I, 95; A. Peratoner and E. Azzarello, *ibid.*, p. 76; R. Hüttel and G. Welzel, *Annalen*, 1955, **593**, 207; M. Begtrup and C. Pedersen, *Acta Chem. Scand.*, 1965, **19**, 2022.

[5] J. R. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.

[6] R. Hüttel and J. Kratzer, *Chem. Ber.*, 1959, **92**, 2014.

[7] L. L. Bennett and H. T. Baker, *J. Org. Chem.*, 1957, **22**, 707.

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as anhydro-dimer; 10%), 2-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide (2%), and 3-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide (3%). None of the other substances listed in Table 1 was present, and hence the hypothesis that formylation of the 4-amino-group would favour alkylation in the 2-position was confirmed. The m.p.s of the three isomers are compared in Table 2.

TABLE 1

R_F Values (simultaneous paper chromatography)

Substances were dissolved in cold aqueous pyridine (the constant boiling mixture), except for the anhydro-dimer, which was dissolved in 0·1N-potassium hydroxide.

	Solvent	
1,2,3-Triazole-5-carboxyamide	3% aq. NH_4Cl	Butanol–5N-acetic acid (7 : 3)
4-Amino-2-methyl (IIb)	0·75 V	0·60 V
4-Amino-3-methyl (IIIb)	0·70 D	0·55 D
4-Formamido-2-methyl (IIa)	0·80 B	0·55 B
4-Formamido-3-methyl	0·80 D	0·45 D
4-Methylamino-2-methyl (IIc).....	0·75 BM	0·75 VM
4-Methylamino-3-methyl	0·75 D	0·65 D
4-(*N*-Methylformamido)-2-methyl ...	0·90 DN	0·70 DI
4-(*N*-Methylformamido)-3-methyl ...	0·85 D	0·50 D
Anhydro-dimer (IV)	0·65 B	0·45 B

The dried paper was viewed in u.v. light of (mainly) 254 mμ.

Abbreviations: D dark (absorption) spot, V violet (B blue) fluorescent spot, M violet fluorescent spot in light of 360 mμ also, N as M but faint (spots not marked M or N did not fluoresce in 360 mμ light), I turned brown by iodine vapour.

TABLE 2

M.p.s of isomers

4-Aminotriazole-5-carboxyamide		6-Hydroxy-8-azapurine
1-Methyl.....174 [a]	⟶	7-Methyl.....262 [a,d]
2-Methyl.....193 [b]	⟶	8-Methyl.....261 [b,d]
3-Methyl.....243 [c]	⟶	9-Methyl.....305 [b]

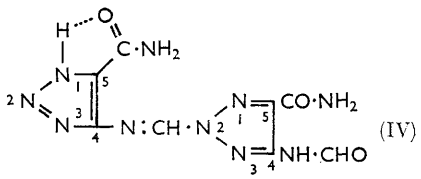
[a] Ref. 1. [b] New. [c] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001. [d] Mixed m.p. 202—223°.

To obtain an authentic specimen of 3-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide, methyl azide was condensed with cyanoacetamide to give 4-amino-3-methyl-1,2,3-triazole-5-carboxyamide,[8] m.p. 243°, which cold acetic formic anhydride changed into the 4-formamidoanalogue. This was converted to 3-methyl-4-methylamino-1,2,3-triazole-5-carboxyamide with methyl sulphate in an excess of aqueous alkali. The high pH required to produce an anion from the formamido-group caused the deformylation of the intermediate 3-methyl-4-(*N*-methylformamido)triazole-5-carboxyamide (which cannot form an anion and hence has no coulombic protection against attack by a hydroxide ion), but this hydrolysis was easily reversed by stirring the product with acetic formic anhydride.

An authentic specimen of 2-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide was obtained by stirring 2-methyl-4-formamidotriazole-5-carboxyamide (IIa) (see above) with methyl sulphate and stronger alkali than was used in its formation. This procedure gave a mixture of (*a*) 2-methyl-4-(*N*-methylformamido)- and (*b*) 2-methyl-4-methylamino-1,2,3-triazole-5-carboxyamide. This mixture was then completely hydrolysed with cold alkali to (b), which, after purification, was formylated to give (a) with cold acetic formic anhydride.

Identification of the first eight substances in Table 1 was helped by the large depressions of m.p. obtained on admixture of isomers, and the blood-red colours given by the primary amines when diazotized in dilute hydrochloric acid and added to an alkaline solution of 2-naphthol. All the formyl compounds in Table 1 were deformylated by N-potassium hydroxide in 24 hr. (or less) at 25°. Dimroth rearrangements are to be expected in the 1,2,3-triazole series. They take the following forms: (*a*) an alkyl group on the exocyclic amino-group could exchange with a hydrogen atom in the 3-position, or (*b*) an acyl or phenyl (but not a benzyl) group in the 3-position could exchange with a hydrogen atom on the exocyclic amino-group.[9] These possibilities were not available to any substance in this paper, and no rearrangement was observed.

4-Formamido-2-methyl-1,2,3-triazole-5-carboxyamide (IIa) was hydrolysed by cold N-potassium hydroxide to the 4-amino-analogue, which, in turn, gave 4-amino-2-methyl-1,2,3-triazole-5-carboxylic acid when boiled with the same reagent.



(IV)

The constitution of the anhydro-dimer of 4-formamido-1,2,3-triazole-5-carboxyamide will now be discussed. Elemental analysis gave the empirical formula $C_8H_8N_{10}O_3$ (*M* 292·22), corresponding to the loss of one molecule of water from two molecules of the monomer. The instant hydrolysis by cold alkali to the monomeric anion (see above) indicated that the carbon atom of one formamido-group was also attached to a ring-nitrogen atom, thus forming an analogue of the alkali-labile *N*-acylated 1,2,3-triazoles mentioned previously. The 2-position was indicated as the site of this link, because of the bright blue fluorescence of the dimer; this property is common in 2-substituted (and unknown in 1- and 3-substituted) 1,2,3-triazoles (see Table 1 for examples). No known triazole methylated on a ring-nitrogen atom (*e.g.* those in Table 1) is an anhydro-dimer, which suggests that a mobile hydrogen atom on a ring-nitrogen is necessary for such dimerization. Hence formula (IV) is proposed for the anhydro-dimer, the formation of which may be seen as analogous to the

[8] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001.

[9] D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley, New York, 1968, vol. 1; E. Lieber, C. N. R. Rao, and T. S. Chao, *J. Amer. Chem. Soc.*, 1957, **79**, 5962; E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 1957, **22**, 654.

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preparation of diphenylformamidine by heating formic acid with aniline under reflux.[10]

Instrumental methods were used in an attempt to confirm this structure [5-carbamoyl-2-(5-carbamoyl-1,2,3-triazol-4-yliminomethyl)-4-formamido-1,2,3-triazole (IV)]. However only two carbonyl stretching bands could be distinguished in the solid state i.r. spectrum. Feeble solubility in all appropriate solvents and destruction by trifluoroacetic acid permitted very little information to be had from ^{1}H n.m.r. However, by the use of a computer of average transients, broad peaks were obtained in dimethyl sulphoxide at τ 1·5, 2·1, 2·35, and 6·65. To find which of these came from non-exchangeable protons, a trace of deuterium oxide was added, but this precipitated the very small amount of dissolved compound. Dr. Q. N. Porter (University of Melbourne), who submitted the anhydro-dimer to mass spectrometry, reported that the peak of greatest mass was 155·0436 (cf. 155·0443 for the monomer, $C_4H_5N_5O_2$). The next most intense peak lay at 137 (cf. 137 for 6-hydroxy-8-azapurine). Presumably one molecule of the anhydro-dimer gave one of the monomer and one of the azapurine. When heated alone at 275°, the anhydro-dimer rapidly became brown without melting, and some 6-hydroxy-8-azapurine was formed; the latter was obtained quantitatively by heating the dimer in formamide at 220° for 20 min. However the dimer was unchanged when heated in tributylamine at 220°, or in diphenylmethane at 260°, for 20 min.

In a search for other examples of anhydro-dimers, 4-amino-1,2,3-triazole [5] was converted to 4-formamido-1,2,3-triazole, but this was not dehydrated when heated at 110°. Next, 4-amino-1,2,3-triazole-5-carboxyamide [5] was converted, in turn, into the corresponding carboxylic acid and the methyl ester. The latter, when heated with formic acid, gave a product with an elemental analysis as expected for 4-formamido-5-methoxycarbonyl-1,2,3-triazole, and which had the correct molecular weight for the monomer (mass spectrometry). Nevertheless the main u.v. absorption peak (log ε 4·05) was at 252 mμ (expected *ca.* 220), and ^{1}H n.m.r. showed no peak near τ 1·5 (expected for C*H*O) nor near 4·5 [expected for N–C*H*(OH)–N], in either dimethyl sulphoxide or 0·3M-sodium deuteroxide [however, for a solution in the latter the expected methyl peak (3H) appeared at τ 6·63].

The 8-Azapurines.—Hitherto only three 8-azapurines methylated in the 8-position were known,[11] namely 2,6-dihydroxy-8-methyl-8-azapurine (obtained, as one of several isomers, by methylating 2,6-dihydroxy-8-azapurine), and its 3- and 1,3-methylated derivatives made by further methylation. In the present work, several other 8-methyl-8-azapurines were made from 6-hydroxy-8-methyl-8-azapurine (Ib), which was obtained almost quantitatively by heating 4-formamido-2-methyl-1,2,3-triazole-5-carboxyamide in formamide (heating without solvent at 240° gave only 55%, and boiling with 2N-sodium carbonate only 25% yield because of partial loss of the formyl group). The same azapurine was obtained by heating the less accessible 4-amino-2-methyl-1,2,3-triazole-5-carboxyamide with formamide.

6-Hydroxy-9-methyl-8-azapurine, required for comparison, was similarly made from 4-amino-3-methyl-1,2,3-triazole-5-carboxyamide [8] and also from the formyl derivative of the latter. It had been shown [1] that the i.r. spectrum of 6-hydroxy-7-methyl-8-azapurine was unusual: steric hindrance by the 7-methyl group prevented the carbonyl stretching band at 1715 cm.$^{-1}$, as measured for a solution in chloroform, from undergoing the usual shift (indicative of intermolecular hydrogen bonding) when examined in the solid state (potassium bromide disc). It is now found that the 8-methyl isomer is free from this anomaly because the band at 1728 cm.$^{-1}$ in chloroform shifts to 1714 in the solid state (*cf.* 6-hydroxy-8-azapurine: band in solution at 1721 cm.$^{-1}$ moves to 1691 in potassium bromide). However the 9-methyl isomer shows a different and unexplained anomaly: the band at 1720 cm.$^{-1}$ in chloroform moves to 1730 in the solid state.

6-Mercapto-8-methyl-8-azapurine, made by heating the 6-hydroxy-analogue with phosphorus pentasulphide, was converted by methyl iodide into 8-methyl-6-methylthio-8-azapurine, and this gave 6-amino- and 6-hydrazino-8-methyl-8-azapurine when heated with the appropriate amine. The excellent yields in these replacements of the methylthio-group, which took place under mild conditions, greatly exceeded those obtainable from *N*-methylated 6-methylthiopurines,[12a,b] and are attributed to the extra electron-attracting power of the 8-nitrogen atom. However, 8-methyl-6-methylthio-8-azapurine gave only a moderate yield of the 6-methoxy-analogue with methanolic sodium methoxide, which agrees with general experience that a methoxy-group is not so nucleophilic as a methylthio-group.[12c]

6-Methoxy-8-methyl-8-azapurine was prepared similarly, but in higher yield, from 6-chloro-8-methyl-8-azapurine. The latter could be obtained (but not reproducibly) in 75% yield by the action of phosphoryl chloride on the 6-hydroxy-analogue. The erratic feature could not be removed by varying the nature of the phosphorus halide or the catalyst (diethylaniline). Hence recourse was had to thionyl chloride which, as Swiss workers [13a] first showed, can be greatly activated by dimethylformamide; this combination has proved effective for replacing an α-hydroxy-group by chlorine in the pyrimidine series.[13b] In the present case it gave lower but more reproducible yields (30—50%) than the phosphoryl halides.

8-Methyl-8-azapurine, the parent of this series, was readily obtained by heating the 6-hydrazino-derivative under reflux with silver oxide in propan-2-ol (only poor

[10] W. Weith, *Ber*, 1876, **9**, 454.
[11] G. Nübel and W. Pfleiderer, *Chem. Ber.*, 1965, **98**, 1060.
[12] (*a*) D. J. Brown, P. W. Ford, and K. H. Tratt, *J. Chem. Soc.* (*C*), 1967, 1445; (*b*) J. H. Lister, 'The Purines,' Wiley-Interscience, New York, 1968; (*c*) D. J. Brown and R. V. Foster, *Austral. J. Chem.*, 1966, **19**, 2321.
[13] (*a*) H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653; (*b*) J. Žemlička and F. Šorm, *Coll. Czech. Chem. Comm.*, 1965, **30**, 2052.

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yields were given in water, methanol, or ethanol, apparently because these solvents combined with the parent and the products were further oxidised). The parent substance was identical with the substance of m.p. 125—128° obtained by Pfleiderer in the methylation of 8-azapurine (unpublished, see ref. 1), and hence all three of his monomethyl-8-azapurines are now identified.

8-Methyl-8-azapurine [like 8-azapurine and 7- (but not 9-) methyl-8-azapurine] underwent covalent hydration as the cation. This was first indicated by the u.v. spectra (Table 3): the single peak (at 270 mμ) due to the neutral species corresponded to that at 263 mμ due to the parent [14] and that at 264 due to the 9-methyl isomer. But, whereas the absorption peak of the latter isomer, the cation of which does not become hydrated,[14] moved by only 1 mμ in acid solution, the peak of 8-methyl-8-azapurine was displaced by 16 mμ (cf. 15 mμ in the case of the parent) to shorter wavelength, which suggests the loss of a double bond. The equilibrium pK of 8-methyl-8-azapurine is 3·18 whereas that of the 9-methyl isomer is only 0·32; this difference shows that a more basic cation participates in the former value, another indication of hydration.[15a] Rapid reaction technique,[16] used to measure the equilibrium between the stably hydrated cation and the unstably hydrated neutral species, gave pK_a 4·20 (±0·04) at 20° (analytical wavelength 275 mμ). From this, the ratio of hydrated to anhydrous *neutral species* (at equilibrium) was calculated to be 0·1 from the equation given in ref. 1. This is high for a neutral species in this series, although not quite so high as that of pteridine.[15b] Values of $t_{\frac{1}{2}}$ for the reversible hydration–dehydration were 1·15 sec. at pH 3·75 and 32·6 sec. at pH 6·17 (20°); the reaction showed acid catalysis and the expected first-order kinetics. The ratio of hydrated to anhydrous *cations* at equilibrium was *ca.* 700, calculated from an approximation in ref. 1.

The position of hydroxylation was indicated to be C-4 by gentle oxidation, with acidified hydrogen peroxide, to give 6-hydroxy-8-methyl-8-azapurine.

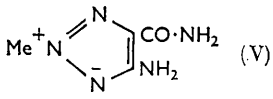
The ^{1}H n.m.r. spectra were consistent with this interpretation. In deuterium oxide, the neutral species showed a methyl band at τ 5·4 and also two peaks at 0·31 and 0·82 (1H each) corresponding to two aromatic-type protons in the 6- and 2-positions respectively; the former is the more deshielded as in the cases of purine and pteridine.[17] These signals were as expected for the anhydrous neutral molecule (cf. 8-azapurine in ref. 16). The presence of a small proportion of the hydrated form was demonstrated by use of a computer of average transients to enhance the n.m.r. signals [extra peaks at τ 2·56 and 3·57 (1H each)].

The cation, in deuterium chloride–deuterium oxide, gave signals at τ 5·81 (3H) and 1·56 and 3·35 (1H each), of which the last two corresponded to a proton on an ethylenic and one on a saturated carbon atom, respectively. Hence the cation was entirely in the hydrated state, like that of 8-azapurine.[16] It was not possible to demonstrate the presence of the anhydrous cation in trifluoroacetic acid (as in refs. 1 and 16) because of decomposition (effervescence).

8-Methyl-8-azapurine was volatile in steam and unchanged when set aside for 20 hr. (25°) in aqueous solutions in the pH range 0—12. The R_F values of 7-, 8-, and 9-methyl-8-azapurine in butanol–5N-acetic acid (7 : 3) were 0·70, 0·80, and 0·85 respectively (paper chromatography). The dark absorption spots from these compounds were visible in u.v. light (254 mμ), which rapidly decomposed the 8-isomer (only), the spot of which then became visible (white fluorescence) in light of 365 mμ also.

U.v. Spectra and Ionization Constants.—1,2,3-Triazole has a single absorption peak at 210 mμ (ethanol; log ε 3·64), and the spectrum of the cation is practically identical.[18] The 4-amino-derivative absorbs [5] at 239 mμ (log ε 3·69), and its cation at 245 mμ (3·50). Both the amino- and the carbamoyl group are highly bathochromic in this series.[5] The triazole spectra recorded in Table 3 fulfil these expectations of bathochromy; *N*-formylation evidently moves the absorption peak to a much lower wavelength. The similarity of the absorptions of the neutral species of 2- and 3-methyl isomers in this series (and also of the 1-methyl isomers in ref. 1) indicates that there is not so much contrast in the disposition of bonds as a comparison of formulae (II) and (III) may suggest. Thus the 2-methyl isomers may have structure (V) as a significant component of their resonance hybrid. However the 2-methyl isomers showed a hypsochromic instead of the normal bathochromic shift when converted into cations, and this suggested a change in site of protonation. The characteristic fluorescence of the 2-methyl isomers was mentioned above.

The spectra of the 8-methyl-8-azapurines differed little from those of the 7-methyl isomers (see ref. 1) and of the single available 9-methyl isomer (Table 3). Thus, substitution in the 8-position cannot be diagnosed from u.v. spectroscopic evidence. Fluorescence (under 254 mμ light), although seemingly confined to the 8-methyl series, was not shown by all its derivatives.



(V)

1,2,3-Triazole is both a very weak base (pK_a 1·17), and an acid (pK_a 9·42) of about the same strength as phenol; [19] the 1-methyl derivative has pK_a 1·25, the 2-methyl derivative has much feebler basic properties,

[14] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.
[15] (*a*) A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; (*b*) D. D. Perrin, *ibid.*, p. 43 (reviews).
[16] J. W. Bunting and D. D. Perrin, *J. Chem. Soc.* (*B*), 1966, 433.
[17] S. Matsuura and T. Goto, *J. Chem. Soc.*, 1965, 623.
[18] D. Dal Monte, A. Mangini, R. Passerini, and C. Zavli, *Gazzetta*, 1958, **88**, 977.
[19] A. Albert in ' Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, p. 1.

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TABLE 3

Ionization constants and u.v. spectra

		Ionization in water (20°)				Spectroscopy in water [c]		
	Species [a]	pK_a	Spread (±)	Concn. (M)	A.w.l.[b] (mμ)	$\lambda_{max.}$ (mμ)	log ε	pH
1,2,3-Triazole								
4-Amino-5-carbamoyl [d]	0					225, 260	3·87, 3·85	
	−	7·79				223, 265	3·67, 3·90	
	+	−0·23				221, 280	3·91, 3·41	
4-Amino-5-carbamoyl-2-methyl	0					*217*, 273	*3·81*, 3·80	7·0
	+	0·10	0·02	10^{-4}	274	224 [e]	3·94	−2·2
4-Amino-5-carboxy	0					226, 261	3·85, 3·86	2·0
	−	4·27	0·03	0·01	P	217, 256	3·75, 3·75	7·0
	− −	9·43	0·03	0·01	P			
4-Amino-5-methoxycarbonyl	0					226, 261	3·87, 3·90	6·0
4-Amino-5-carboxy-2-methyl	0					276	3·78	1·8
	+	−0·28	0·05	10^{-4}	276	227	3·88	−2·4
	−	3·76	0·05	10^{-4}	290	266	3·80	7·0
4-Amino-5-carbamoyl-3-methyl	0 [f]					227, 260	3·99, 3·92	7·0
4-Formamido	0					224	3·96	6·0
	−	8·20	0·02	10^{-4}	260	232	3·94	11·0
5-Carbamoyl-4-formamido-2-methyl	0					237	4·16	E [i]
5-Carbamoyl-4-formamido-3-methyl	0					224 [g]	3·98	7·0
5-Carbamoyl-2-methyl-4-methylamino	0					225, 291	3·87, 3·75	7·0
5-Carbamoyl-3-methyl-4-methylamino	0					240, 268	3·94, 3·78	7·0
8-Methyl-8-azapurine								
(Unsubstituted)	0					270	4·06	7·0
	+ [h]	3·18	0·03	10^{-4}	270	254	4·00	1·0
6-Chloro	0					270	4·02	E [i]
6-Hydroxy	0					267	3·96	5·0
	−	8·81	0·01	0·003	P	286	3·98	11·0
	+	−0·6 [j]				265 [e]	4·05	−3·3
6-Amino	0					291	4·03	7·0
	+	3·54	0·01	10^{-4}	300	281	4·06	1·0
6-Mercapto	0					232, 342	4·12, 4·25	5·0
	−	7·64	0·02	10^{-4}	244	232, 262, 348	4·19, 3·54, 4·18	10·0
6-Methylthio	0					264	4·01	7·0
6-Methoxy	0					264	4·01	7·0
6-Hydrazino	0					216, 299	4·17, 4·03	7·0
	+	4·15	0·03	10^{-5}	310	217, 285	4·05, 4·06	1·0
9-Methyl-8-azapurine								
6-Hydroxy	0					254	3·98	5·0
	−	8·06	0·01	0·003	P	273	4·02	11·0
	+	−3 [j]						

[a] Neutral species (0), cation (+), anion (−), dianion (− −). [b] Analytical wavelength for spectrometric determinations; P signifies that potentiometry was used instead. [c] Inflections in italics. [d] For comparison, see ref. 1. [e] Spectrum measured quickly because cation decomposes in strong acid. [f] A basic pK_a (about −1) could not be measured because of sensitivity of cation to acid; for constants of the 1-methyl isomer, see ref. 1. [g] Mid-point of a plateau. [h] The pK_a is an equilibrium value (anhydrous and hydrated species, see text); the spectrum is that of the *hydrated* cation exclusively. [i] In ethanol. [j] Approximate value; is decomposed by acid.

and neither is acidic. The pK_a of 4-amino-1,2,3-triazole is unknown, but the many derivatives (Table 3) that have both this group and an electron-attracting substituent, have only feeble basic properties. This low basic strength cannot be due entirely to the presence of a 2-methyl group, because 4-amino-5-carbamoyl-1-methyl-1,2,3-triazole (ref. 1) has a pK_a of only 0·69.

The acidic strength of 1,2,3-triazole is increased in the 4-amino-5-carbamoyl-derivative (Table 3), and a stronger acidic centre is seen in the 4-amino-5-carboxy-derivative (−CO_2H, 4·27), which exerts a coulombic depression on the ionization of the nuclear NH group. (The presence of a 2-methyl group removes the possibility of imino-group ionization.) The ionization constants of 8-methyl-8-azapurine have been discussed above; those of the 6-substituted derivatives do not differ greatly from the isomeric 6-substituted-7-methyl-8-azapurines discussed in ref. 1.

EXPERIMENTAL

Yields refer to material sufficiently pure to give only one spot in chromatography (on Whatman no. 1 paper) in both systems described in Table 1. Microanalyses were carried out by Dr. J. E. Fildes and her staff; all specimens were dried in air at 110° unless otherwise indicated.

Ionization constants were determined by D. T. Light and A. Juodvalkis under the supervision of Dr. D. D. Perrin. Optical spectra were measured by I. Pavelić under supervision of Dr. E. Spinner. The i.r. spectra were measured and interpreted by Dr. Spinner (KBr discs except where otherwise specified). The n.m.r. spectra were obtained by S. Brown, supervised by Dr. T. J. Batterham, with a Perkin-Elmer model R10 instrument, operating at 33·5° and 60 Mc./sec., with sodium trimethylsilylpropane sulphonate (τ 10) as internal standard.

Methylation of 4-Amino-1,2,3-triazole-5-carboxyamide.—This reaction, carried out as for the 4-formamido-analogue (below), gave (60%) a mixture (1 : 1) of 4-amino-2-(and

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3-)methyl-2-(and 3-)*H*-1,2,3-triazole-5-carboxyamide, of which the former is described below, and the latter in ref. 8. The components, identified by paper chromatography, proved difficult to separate because of cocrystallization from many solvents.

Formylation of 4-Amino-1,2,3-triazole-5-carboxyamide.—(*a*) The amide [5] (12 g.) and formic acid (72 ml.) were heated at 97° for 30 min. The excess of reagent was distilled off *in vacuo* and the residue was heated under reflux in ethanol (120 ml.) for 30 min. The suspension was filtered hot and the residue, dried at 110°, gave the *anhydro-dimer* (IV) (98%). This became very brown at 275° without melting and was insoluble in dilute mineral acids and most organic solvents. The solution in N-sodium hydroxide soon deposited the sodium salt, but solutions in N-potassium hydroxide or N-ammonia did not crystallize, although that in N-methanolic potassium methoxide quickly did so (these solubilities suggested the best conditions for methylation, see below). For analysis, the anhydro-dimer was recrystallized from much water, in which it could be boiled for 4 hr. without change (Found: C, 32·6; H, 3·3; N, 47·9. $C_8H_8N_{10}O_3$ requires C, 32·9; H, 2·8; N, 47·9%), $\nu_{max.}$ 3390m, 3250s,br, 1680s and 1670s (two C=O stretching bands), 1605s (amide scissoring), 1365m, 1215m, 1000m, and 665m (no nitrile band at 2210) cm.$^{-1}$.

(*b*) 4-Amino-1,2,3-triazole-5-carboxyamide (1 g.) and acetic formic anhydride [20] (8 ml.) were magnetically stirred at 25° for 20 hr. The excess of reagent was removed *in vacuo* at 45°. The residue, washed with benzene and dried at 25°, gave the anhydro-dimer (IV) (95%) identical with the product of (*a*).

Methylation of the Anhydro-dimer of 4-Formamido-1,2,3-triazole-5-carboxyamide.—The anhydro-dimer (IV) (11·68 g., 0·04 mole) was magnetically stirred with N-potassium hydroxide (72 ml.) in a bath at 20°. To the thin suspension, dimethyl sulphate (11·0 g., 1·1 equiv.) was added during 45 min. while the pH was held at 9·5 by adding 10N-potassium hydroxide. The thick suspension was stirred for 1 hr. longer at 24°, then refrigerated for 3 hr. The pH was readjusted to 9·5 and the precipitate was filtered off; it was immediately ground with ice–water (24 ml.) to remove methyl potassium sulphate. The pH of the suspension was adjusted to 9·5 (if necessary) with 2N-potassium carbonate and the product was filtered. The combined filtrates were set aside. The cake, washed with ethanol and dried at 25° then at 110°, gave *4-formamido-2-methyl-1,2,3-triazole-5-carboxyamide* (75%) which, recrystallized from 135 parts of alcohol, had m.p. 217° (Found: C, 35·6; H, 4·3; N, 41·4. $C_5H_7N_5O_2$ requires C, 35·5; H, 4·2; N, 41·4%), $\nu_{max.}$ 3270s, 1710s (CO stretch in formamido-group), 1676vs (conjugated C=O stretch), 1575s, 1340m, and 1245m cm.$^{-1}$, τ (0·3N-NaOD) 1·52 (1H, C*H*O) and 6·02 (3H, Me), τ [dimethyl sulphoxide (DMSO)] 2·2—2·4 (2H, N*H*·C*H*O).

By-products of the Methylation of the Anhydro-dimer.—The pH of the combined aqueous filtrates from the above formylation were adjusted to 6·5 with formic acid and the solution was refrigerated overnight. The precipitate (anhydro-dimer; 10% recovery) was filtered off and the filtrate was concentrated to 30 ml. at 40°. This solution was continuously extracted with ethyl acetate which, when finally taken to dryness, gave a solid (1·25 g.) which was extracted with benzene in a Soxhlet thimble. The benzene-insoluble material was 4-formamido-2-methyl-1,2,3-triazole-5-carboxyamide (0·6 g.; included in above yield). Evaporation of the benzene gave *3-methyl-4(N-methylformamido)-1,2,3-triazole-5-carboxyamide* (3%), obtained as crystals (from 30 parts of ethanol) m.p. 169° (Found: C, 39·2; H, 5·35; N, 38·0. $C_6H_9N_5O_2$ requires C, 39·3; H, 4·95; N, 38·2%), $\nu_{max.}$ 3350s and 3160s (NH stretch), 1700—1675s,br (unresolved C=O stretch), 1595s (NH_2 bend), 1490s, 1305m, 1125m, and 785m cm.$^{-1}$. The aqueous layer from the ethyl acetate extraction was taken to dryness at 40°. The large monoclinic prisms of potassium methyl sulphate [21] were heated under reflux with ethanol (25 ml.) which, concentrated to 5 ml., deposited *2-methyl-4-(N-methylformamido)1,2,3-triazole-5-carboxyamide* (2%), which gave crystals (from ethanol), m.p. 167°, greatly depressed by admixture with the above isomer (Found: C, 39·4; H, 5·0; N, 38·2%), $\nu_{max.}$ 3430m, 3330m, 1685s (C=O stretch of formyl-group), 1665vs (conjugated C=O stretch), 1600m, 1540m, 1340m, 1225m, 1115m, and 815m cm.$^{-1}$.

2-Methyl-4-(N-methylformamido)-1,2,3-triazole-5-carboxyamide.—Dimethyl sulphate (0·2 g.) was added in one portion at 24° to a stirred mixture of 4-formamido-2-methyltriazole-5-carboxyamide (0·34 g., 0·002 mole) and 0·33N-sodium hydroxide (6·6 ml.). Extra N-sodium hydroxide (1 ml.) was added during the next 12 min. The mixture was stirred for 12 min. more, the pH was adjusted to 7 with phosphoric acid, and the product was refrigerated overnight. Next day, the precipitate (unchanged starting material) was filtered off, and the filtrate was concentrated at 40° to 1 ml. The solid deposited by the cooled solution was Soxhlet-extracted with benzene; the extract, taken to dryness, was a mixture of *2-methyl-4-methylamino-1,2,3-triazole-5-carboxyamide* (IIc) and its formyl derivative. This mixture was hydrolysed to the former compound [crystals, m.p. 193° (from cold benzene)] overnight by N-sodium hydroxide (2 equiv.) (Found: C, 38·5; H, 5·8; N, 45·1. $C_5H_9N_5O$ requires C, 38·7; H, 5·85; N, 45·1%). The methylamino-compound (0·8 g.) and acetic formic anhydride (10 ml.) were stirred magnetically at 24° for 12 hr. The excess of reagent was removed at 45°, to give 2-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide [crystals (from ethanol) m.p. 167°), identical with a substance isolated in the methylation of the anhydro-dimer (see above).

Hydrolysis of 4-Formamido-2-methyl-1,2,3-triazole-5-carboxyamide.—This amide (1·02 g.) was set aside in N-sodium hydroxide (8 ml., 1·3 equiv.) at 24° for 20 hr., then refrigerated overnight. The crystals were filtered off, washed with a little ethanol, then recrystallized from 50 parts of ethanol to give *4-amino-2-methyl-1,2,3-triazole-5-carboxyamide* (IIb) (90%), m.p. 193° (greatly depressed by the two isomers in Table 2). It is much more soluble than the formyl derivative in cold water (Found: C, 34·2; H, 5·4; N, 49·8. $C_4H_7N_5O$ requires C, 34·0; H, 5·0; N, 49·6%). The amino-group could readily be diazotized and coupled. 4-Amino-2-methyltriazole-5-carboxyamide (1 g.) was heated with N-sodium hydroxide (1·5 equiv.) on a steam-bath for 4 hr. The pH was adjusted to 2 with 5N-sulphuric acid and the solution was refrigerated. The crystals of *4-amino-2-methyl-1,2,3-triazole-5-carboxylic acid* (92%) had m.p. 175° (from 5 parts of ethanol) and b.p. *ca.* 250° with only partial decarboxylation. The compound is soluble in about 2 parts of boiling water (Found: C, 33·9; H, 4·3; N, 39·45. $C_4H_6N_4O_2$ requires C, 33·8; H, 4·3; N, 39·4%).

[20] A. Béhal, *Compt. rend.*, 1899, **128**, 1460.
[21] J. Schabus, *Jahresbericht über die Fortschritte der Chemie*, 1854, p. 552.

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3-Methyltriazoles.— 4-Amino-3-methyl-1,2,3-triazole-5-carboxyamide,[8] (1·14 g.) and acetic formic anhydride (7 ml.) were stirred magnetically for 40 hr. at 24°. The excess of reagent was removed at 40°. The *4-formamido-3-methyl-1,2,3-triazole-5-carboxyamide* (97%) gave crystals, m.p. 221° (with effervescence) (from 230 parts of alcohol) (Found: C, 35·25; H, 4·4; N, 41·2. $C_5H_7N_5O_2$ requires C, 35·5; H, 4·2; N, 41·4%), $\nu_{max.}$ 3350s and 3180s (NH stretch), 1700vs and 1670vs (C=O stretch), 1610s and 1580s (NH bend), 1490m, 1425m, 1380m, 1300s, and 770m cm.$^{-1}$. To this formamido-derivative (0·34 g., 0·002 mole) in N-sodium hydroxide (6 ml.) at 20° was added dimethyl sulphate (0·52 g.) during 6 min. The mixture was stirred for 30 min. longer, then extracted with chloroform (2 × 40 ml.). When dried (Na_2SO_4) and evaporated, the extract yielded *3-methyl-4-methylamino-1,2,3-triazole-5-carboxyamide* (65%), which gave crystals, m.p. 151° (from 70 parts of toluene) (Found: C, 38·8; H, 5·8; N, 45·0. $C_5H_9N_5O$ requires C, 38·7; H, 5·85; N, 45·1%). The same methylamino-compound was obtained from 3-methyl-4-(*N*-methylformamido)-1,2,3-triazole-5-carboxyamide (see above) in N-potassium hydroxide (2 equiv.) in 2 days at 24°. Crystals of the product were deposited.

Ring-closure of Anhydro-dimer (IV).—Formamide (2·4 ml.) and the dimer (0·58 g.) were heated at 220° in an open vessel for 20 min., cooled, and diluted with acetone. The deposited solid, crystallized from a little water gave 6-hydroxy-8-azapurine (90%), identical with an authentic specimen prepared from 4,5-diamino-6-hydroxypyrimidine and nitrous acid.[22]

4-Formamido-1,2,3-triazole.— 4-Amino-1,2,3-triazole hydrochloride[5] (0·14 g.) and formic acid (1·4 ml.) were heated for 1 hr. under reflux and the excess of acid was removed at 40°. The residue, crystallized from a little water and dried at 110°, gave *4-formamido-1,2,3-triazole* (75%), m.p. 174° (Found: C, 32·4; H, 3·7; N, 50·1. $C_3H_4N_4O$ requires C, 32·1; H, 3·6; N, 50·0%), τ (DMSO) 1·74, (1H, C*H*O) and 2·08 [1H, C(5)H], rapidly destroyed by 0·3N-sodium deuteroxide.

4-Amino-5-methoxycarbonyl-1,2,3-triazole.— 4-Amino-1,2,3-triazole-5-carboxyamide (2·56 g., 0·02 mole) and 10N-sodium hydroxide (8 ml.) were heated at 98° in a polypropylene flask for 8 hr. The pH was adjusted to 6·7 with acetic acid. The precipitated monosodium salt was collected and dissolved in hot water (12 ml.). The pH was lowered to 1·5 with 5N-sulphuric acid. The *4-amino-1,2,3-triazole-5-carboxylic acid* (85%) was filtered off and (from a little water) had m.p. 153° (with effervescence; m.p. varies with rate of heating) (Found: C, 27·9; H, 3·35; N, 43·45. $C_3H_4N_4O_2$ requires C, 28·1; H, 3·15; N, 43·7%). This acid (1·66 g., 0·013 mole) was added to a chilled mixture of methanol (6·5 ml.) and sulphuric acid (*d* 1·84; 2 ml.). The solution was set aside at 25° for 48 hr., then slowly added to ice–water (20 g.). The pH was raised to 6 with sodium hydrogen carbonate (4·4 g.), and the solution continuously extracted with ethyl acetate. The residue after evaporation of the solvent furnished *4-amino-5-methoxycarbonyl-1,2,3-triazole* (25%) m.p. 199° (with effervescence) (from methanol) (Found: C, 33·6; H, 4·5; N, 39·35. $C_4H_6N_4O_2$ requires C, 33·8; H, 4·3; N, 39·4%).

Formylation of 4-Amino-5-methoxycarbonyl-1,2,3-triazole.—This ester (0·35 g.) and formic acid (2·1 ml.) were heated at 98° under reflux for 1 hr. The excess of reagent was removed *in vacuo* and the product (0·4 g.) was heated at 110° for 1 hr., then crystallized from methanol and re-dried at 110° (Found: C, 35·35; H, 3·3; N, 33·3. $C_5H_6N_4O_3$ requires C, 35·3; H, 3·55; N, 32·9%), $\nu_{max.}$ 3290s, 3230m, 1740s, 1685s, 1610s, 1395m, 1245m, 1140m, and 1005m cm.$^{-1}$. When set aside at 32° in N-sodium hydroxide, it was quantitatively converted into 4-amino-1,2,3-triazole-5-carboxylic acid in 20 hr.

6-Hydroxy-8-methyl-8-azapurine (Ib).—(*a*) 4-Formamido-2-methyl-1,2,3-triazole-5-carboxyamide (IIa) (8·5 g., 0·05 mole) was boiled in an open vessel with formamide (34 ml.) at 220° (bath) for 45 min. The mixture was cooled and stirred vigorously with acetone (34 ml.). The refrigerated mixture was filtered, and the cake was stirred again with acetone. The solid was filtered off and dried at 110° to give *6-hydroxy-8-methyl-8-azapurine* (94%), m.p. 261° (from 60 parts of ethanol) (depressed greatly by the isomers in Table 2) (Found: C, 39·7; H, 3·2; N, 45·8. $C_5H_5N_5O$ requires C, 39·7; H, 3·3; N, 46·3%), $\nu_{max.}$ 3190m, 1714 (C=O stretch), 1600s, 1530m, 1300m, and 1280m cm.$^{-1}$.

(*b*) 4-Amino-2-methyl-1,2,3-triazole-5-carboxyamide (0·34 g.) and formamide (1·4 ml.), similarly treated, gave the same azapurine (85%), m.p. 261°.

6-Hydroxy-9-methyl-8-azapurine.—(*a*) 4-Amino-3-methyl-1,2,3-triazole-5-carboxyamide[8] (0·56 g.) and formamide (2·2 ml.), similarly treated, gave *6-hydroxy-9-methyl-8-azapurine* (78%), m.p. 305° (from 260 parts of ethanol), soluble in 30 parts of boiling water (Found: C, 39·5; H, 3·4; N, 46·1. $C_5H_5N_5O$ requires C, 39·7; H, 3·3; N, 46·3%), $\nu_{max.}$ 3080m, 2890m, 1730s (C=O stretch), 1706w, 1565s, and 1285s cm.$^{-1}$.

(*b*) 4-Formamido-3-methyl-1,2,3-triazole-5-carboxyamide (see above) (1·0 g.), similarly treated, gave the same azapurine (86%).

8-Methyl-6-methylthio-8-azapurine.— To 6-hydroxy-8-methyl-8-azapurine (0·8 g.), dissolved in pyridine (12 ml.) by heating to 115° then cooling to 90°, was added purified phosphorus pentasulphide (Fluka; 2·4 g.) during 1 min., and the whole was boiled under reflux for 30 min. then cooled. Water (9 ml.) was added, and the solvents were removed *in vacuo* at 40°. The residue was stirred with water (12 ml.) and chilled. Filtration yielded *6-mercapto-8-methyl-8-azapurine* (82%) as bright yellow crystals m.p. 321° (with effervescence) (from 300 parts of boiling water). Heating for 15 min. (or 1 hr.) gave a lower yield, 78% (or 73%) (Found: C, 35·6; H, 3·1; N, 42·15. $C_5H_5N_5S$ requires C, 35·9; H, 3·0; N, 41·9%). A specimen was unchanged at 155° for 20 min.; these conditions isomerise 9-alkyl-6-mercapto-8-azapurines.[23] 8-Methyl-6-mercapto-8-azapurine (1 g.) in cold N-sodium hydroxide (7·2 ml.) was magnetically stirred with methyl iodide (1 g.) for 15 min. at 24° and filtered at once. The solid, washed and recrystallized from 110 parts of water, gave *8-methyl-6-methylthio-8-azapurine* (86%), m.p. 147° (Found: C, 39·5; H, 3·6; N, 38·95. $C_6H_7N_5S$ requires C, 39·75; H, 3·9; N, 38·65%).

6-Hydrazino-8-methyl-8-azapurine.— 8-Methyl-6-methylthio-8-azapurine (0·6 g.) was dissolved in the minimum of boiling methanol (10 ml.) and removed from the source of heat. Hydrazine hydrate (2·5 ml., 15 equiv.) was added all at once, and the mixture was stirred while it was slowly cooled. It was finally chilled well and filtered. The solid, washed with methanol and dried at 20°, gave *6-hydrazino-*

[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] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 1856.

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8-*methyl*-8-*azapurine* (93%). Crystallized from 210 parts of methanol it melts sharply at 198° (if inserted at 170°) but resolidifies and begins to melt again at 210°. It is soluble in cold 0·1N-hydrochloric acid and sodium hydroxide, but not in N-sodium carbonate; it is insoluble in boiling chloroform (Found, for material dried at 24°/20 mm.: C, 36·3; H, 4·4; N, 59·95. $C_5H_7N_7$ requires C, 36·4; H, 4·3; N, 59·4%).

6-*Amino*-8-*methyl*-8-*azapurine*.— 8-Methyl-6-methylthio-8-azapurine (0·17 g.) and 3·5N-ethanolic ammonia (4 ml.) were heated at 150° for 6 hr. Removal of the volatile components left 6-*amino*-8-*methyl*-8-*azapurine* (92%), m.p. 264° (from 50 parts of water) (Found: C, 39·8; H, 4·2; N, 56·25. $C_5H_6N_6$ requires C, 40·0; H, 4·0; N, 56·0%).

6-*Methoxy*-8-*methyl*-8-*azapurine*.—(*a*) 6-Methylthio-8-methyl-8-azapurine (0·14 g.), dissolved in boiling methanol (4 ml.), was added to methanolic sodium methoxide (2 ml.; 1 equiv.) and the whole was heated under reflux for 1 hr. The methanol was removed *in vacuo* at 25° and the residue was dissolved in benzene (2·5 ml.) at 20° and filtered. The benzene was removed *in vacuo*. Ice (*ca.* 0·5 g.) was added to the residue, and the resultant suspension was brought to pH 4·5 with acetic acid. The 6-*methoxy*-8-*methyl*-8-*azapurine* (50%) was filtered off; m.p. 142·5° (from 200 parts of cyclohexane) (Found: C, 43·5; H, 4·35; N, 42·85. $C_6H_7N_5O$ requires C, 43·6; H, 4·3; N, 42·4%).

(*b*) A suspension of 6-chloro-8-methyl-8-azapurine (0·6 g.) in methanol (15 ml.) was heated under reflux for 10 min. with sodium (0·09 g., 1 equiv.) in methanol (7·5 ml.). The residue left after evaporation of the methanol was extracted with boiling benzene (20 ml.). The evaporated extract gave 6-methoxy-8-methyl-8-azapurine (75%), m.p. 142°.

6-*Chloro*-8-*methyl*-8-*azapurine*.—(*a*) 6-Hydroxy-8-methyl-8-azapurine (0·5 g.) and phosphoryl chloride (15 ml.) were brought to the boil. Diethylaniline (0·25 ml.) was added and the whole was heated under vigorous reflux for 15 min. The excess of reagent was recovered by evaporation under reduced pressure. The residue, stirred with ice (*ca.* 1 g.), liberated crystals of 6-*chloro*-8-*methyl*-8-*azapurine*, which were dried at 25° (no more could be obtained by adding sodium hydrogen carbonate to the filtrate and extracting with chloroform), m.p. 125° [from 350 parts of light petroleum (b.p. 60—80°)], rapidly hydrolysed to the 6-hydroxy-analogue in moist air (Found, for material dried at 25°/25 mm.: C, 35·5; H, 2·5; N, 41·5. $C_5H_4ClN_5$ requires: C, 35·4; H, 2·4; N, 41·3%).

(*b*) Redistilled thionyl chloride (0·38 ml., 0·005 mole) and dimethylformamide (0·1 ml., 0·0014 mole) were added to a suspension of 6-hydroxy-8-methyl-8-azapurine (0·15 g., 0·001 mole) in dichloromethane (5 ml.). The mixture was heated under reflux until all had dissolved, then for 30 min. more. The solvent was removed under reduced pressure and the residue, when stirred with ice (*ca.* 0·5 g.), liberated crystals of 6-chloro-8-methyl-8-azapurine, m.p. 124°.

8-*Methyl*-8-*azapurine*.— 6-Hydrazino-8-methyl-8-azapurine (0·8 g.), propan-2-ol (80 ml.), and silver oxide (3·4 g., 3 equiv.) were stirred at 25° for 15 min., then heated under reflux for 1 hr. Kieselguhr (0·1 g.) was added, and the suspension was filtered. The solvent was removed under reduced pressure. The residue, sublimed at 110°/0·01 mm., gave 8-*methyl*-8-*azapurine* (53%), m.p. 133·5° (from a little benzene). It is odourless, very soluble in water and chloroform but poorly soluble in boiling light petroleum (Found: C, 44·5; H, 3·8; N, 51·6. $C_5H_5N_5$ requires C, 44·4; H, 3·7; N, 51·8%). The major component of the unsublimed residue was 6-amino-8-methyl-8-azapurine.

Oxidation of 8-*Methyl*-8-*azapurine*.—The azapurine (0·135 g., 0·001 mole), dissolved in 5N-sulphuric acid (0·1 ml., 0·5 equiv.) and water (1 ml.), was set aside with hydrogen peroxide (30% w/v; 0·12 ml., 1 equiv.) for 2 days at 30°. The precipitate (from 60 parts of ethanol) gave 6-hydroxy-8-methyl-8-azapurine (50%), identical with the above specimen.

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