# A New Route to 8-Methyl-8-azapurines[1] (2-Methyl-2*H*-1,2,3,4,6-penta-azaindenes)

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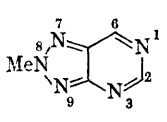
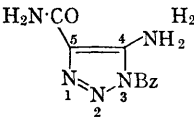
THE 8-azapurines are highly active against experimental tumours in mammals, but few *N*-alkyl derivatives have been available for testing because of difficulties in synthesis (usually attempted from pyrimidine intermediates). A new route to 7-methyl-8-azapurines from 1,2,3-triazole intermediates has recently been described;[2] it is now reported that derivatives of 8-methyl-8-azapurine (I) can be produced from similar intermediates. Hitherto only three derivatives of (I) were known,[3] namely 2,6-dihydroxy-8-methyl-8-azapurine (obtained as one of several isomers by the methylation of 2,6-dihydroxy-8-azapurine) and its 3- and 1,3-methyl derivatives obtained by further methylation.

The new direct approach to 8-methyl-8-azapurines begins with 4-amino-3-benzyl-3*H*-1,2,3-triazole-5-carboxyamide (II), prepared[4] in a single step from cyanoacetamide and benzyl azide. This triazole was debenzylated[4] with sodium and ammonia; and methylation of the product with methyl sulphate and alkali gave a 1 : 1 mixture of the 2-methyl (IIIa) and 3-methyl derivatives. The complete absence of the 1-methyl derivative[2] was shown by paper chromatography; this finding suggested that a small increase in the complexity of the 4-substituent could provide enough steric hindrance to suppress methylation in the 3-position also. Accordingly, 4-amino-1,2,3-triazole-5-carboxyamide was converted by acetic–formic anhydride into the 4-formamido-analogue, isolated quantitatively as the anhydro-dimer (decomp. 275°). This became monomeric in aqueous potassium hydroxide (the $^1$H n.m.r. spectrum in NaOD–$D_2O$ showed only a single peak, $\tau$ 1·05, attributed to the C*H*O proton). Methylation, as above, gave a high yield of 4-formamido-2-methyl-2*H*-1,2,3-triazole-5-carboxyamide (IIIb), m.p. 217°, with no other product (apart from unchanged starting material). This amide, in cold 1N-sodium hydroxide, was hydrolysed to 4-amino-2-methyl-2*H*-1,2,3-triazole-5-carboxyamide (IIIa), m.p. 193° (90% yield), which differed greatly in m.p. and in i.r. spectra from the known 1-methyl[2] and 3-methyl[5]

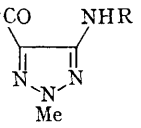
isomers. Hitherto only eight 2-methyl-2*H*-1,2,3-triazoles have been reported,[6] all obtained in small yields because of the simultaneous production of isomers or homologues.



(I)



(II)



(III) a; R=H
b; R=CHO

Both amides (IIIa and b), heated at 215° in formamide, yielded 6-hydroxy-8-methyl-8-azapurine, m.p. 261° (90%), which gave a large depression of m.p. with the 7- and the 9-methyl isomers. Heating the azapurine with phosphoryl chloride produced 6-chloro-8-methyl-8-azapurine, m.p. 125° (75%). The chlorine atom in this compound is highly labile and this facilitated preparation of the parent substance (m.p. 134°), also many 6-substituted derivatives.

(*Received, May* 31*st*, 1967; *Com.* 542.)

[1] Although contrary to present IUPAC nomenclature, "8-azapurine" is permitted as a trivial name because of its widespread use in the biological literature.

[2] A. Albert and K. Tratt, *Chem. Comm.*, 1966, 243.
[3] G. Nübel and W. Pfleiderer, *Chem. Ber.*, 1965, **98**, 1060.
[4] J. R. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.
[5] A. Dornow and J. Helberg, *Chem. Ber.*, 1960, **93**, 2001.
[6] 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.