Synthesis, from 1,2,3-Triazole Intermediates, of 2-Amino-7-(also 8-)methyl-8-azapurin-6-ones (*N*-Methylated '8-Azaguanines') and Related 8-Azapurines

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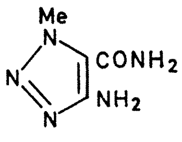
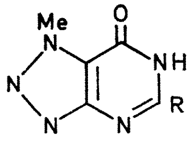
Summary 4-Amino-1-(also 2-)methyl-1,2,3-triazole-5-carboxamide, fused with thiourea, gave 2-mercapto-7-(also 8-)methyl-8-azapurin-6-one which, by successive *S*-methylation, oxidation, and demethylsulphonylamination, gave the corresponding *N*-methylated derivatives (named in the title) of the anti-cancer agent '8-azaguanine' (2-amino-8-azapurin-6-one).

'8-AZAGUANINE' strongly inhibits experimentally-induced cancer in mice and rats without harm to the host,[1] but it is less active in man. To provide depot-substances, from which 8-azaguanine would slowly be released by normal biochemical demethylation, a need has arisen for *N*-methylated derivatives of this compound. Because no general method existed for synthesizing 7- (or 8-)alkyl-8-azapurines further substituted in *both* 2- and 6- positions, the following sequence was devised. As the melting points of these azapurines are high, the thermometer was re-calibrated with caffeine (m.p. 237°), phenolphthalein (m.p. 263°), benzophenone (b.p. 304° at 760 mm.), and lead (f.p. 327·4°) (National Standards Laboratories specimens).

Fusion of 4-amino-1-methyl-1,2,3-triazole-5-carboxamide[2] (I) with thiourea at 176° gave 60% of 2-mercapto-7-methyl-8-azapurin-6-one (IIa), m.p. 311° from water, ν_{max} (paraffin mull) 3350w, 3050m, 1730s (C=O str.), 1605s, 1300m, 1190m (C=S str.), and 1140m cm^{-1}, $\tau[(CD_3)_2SO]$ 6·60 (1H, br, NH), 5·69 (3H, s, NCH_3), and −2·75 (1H, br, NH). This compound, dissolved in cold aqueous sodium hydroxide was rapidly converted by methyl iodide into 90% of 7-methyl-2-methylthio-8-azapurin-6-one (IIb), m.p. 305° (decomp.) from ethanol, $\tau[(CD_3)_2SO]$ 7·40 (3H, s, SCH_3), 5·63 (3H, s, NCH_3), and −3·05 (1H, br, NH). When stirred with potassium permanganate in cold dilute acetic acid, this methylthio-derivative gave 74% of 7-methyl-2-methylsulphonyl-8-azapurin-6-one (IIc), m.p. 231°



(I)



(II) a; R = SH
b; R = SMe
c; R = SO_2Me
d; R = OMe
e; R = NH_2

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† Approximate, derived from extrapolation of correction curve.

(eff.) from ethanol, $\tau[(CD_3)_2SO]$ 6·45 (3H, s, SCH_3), 5·55 (3H, s, NCH_3), and 2·28 (1H, br, NH).

This methylsulphonyl compound, with methanolic sodium methoxide, gave 80% of 2-methoxy-7-methyl-8-azapurin-6-one (IId), m.p. 227° from methanol, whereas with ethanolic ammonia at 160° it produced 85% of 2-amino-7-methyl-8-azapurin-6-one (IIe), m.p. >360° from water, ν_{max} 3350s (NH), 3200m (NH), 1705s (C=O str.), 1680s, 1630m, 1140m, and 880m cm^{-1}, $\tau(CF_3 \cdot CO_2H)$ 5·41 (3H, s, NCH_3) and 1·49 (2H,br, NH_2).

Similarly, fusion of 4-amino-2-methyl-1,2,3-triazole-5-carboxamide[3] with thiourea gave 58% of 2-mercapto-8-methyl-8-azapurin-6-one, m.p. 312° (eff.) from water, ν_{max} 3150m, 1705s, 1605s, 1300m, 1280m, 1165m, and 1150m cm^{-1}. Methylation gave 80% of 8-methyl-2-methylthio-8-azapurin-6-one, m.p. 285°, $\tau(CF_3 \cdot CO_2H)$ 7·00 (3H, SCH_3) and 5·47 (3H, NCH_3), which was oxidized (as above) to 78% of 8-methyl-2-methylsulphonyl-8-azapurin-6-one, m.p. 223° (eff.) from ethanol, $\tau[(CD_3)_2SO]$ 6·71 (3H, s, SCH_3) and 5·65 (3H, s NCH_3). Hydrolysis by aqueous potassium hydroxide (20 h at 25°) gave 8-methyl-8-azapurine-2,6-dione, m.p.† 352° (eff.) from water, identical with material prepared by fusing 4-amino-2-methyl-1,2,3-triazole-5-carboxamide with urea, and (in low yield) by the methylation[4] of 8-azapurine-2,6-dione. Heating the methylsulphonyl compound with ethanolic ammonia at 160° gave 90% of 2-amino-8-methyl-8-azapurin-6-one, m.p. >360° from water, ν_{max} 3380s (NH), 3210s (NH), 1710s (C=O str.), 1680s, 1630m, 1565s, 1320m, 1280m, and 900m cm^{-1}, $\tau(CF_3 \cdot CO_2H)$ 5·53 (3H, s NCH_3) and (2H, 1·6 br, NH_2).

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