741. *Potential Anti-purines. Part IV.* The Synthesis of 9-Dimethylaminopurines.*

By C. L. Leese and G. M. Timmis.

The synthesis of a series of 9-dimethylamino-8-methylpurines from 5-amino-1-dimethylamino-2-methylimidazole-4-carboxamide is described.

Anti-tumour activity[1,2] has been found in puromycin[3] [6-dimethylamino-9-(3-*p*-methoxy-L-phenylalanylamino-3′-deoxy-β-D-ribofuranosyl)purine] and in the aminonucleoside 9-(3-amino-3-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine;[3] puromycin has an anti-purine activity comparable with that of 6-mercaptopurine,[4] so has 2-mercapto-9-2′-pyridyl-8-azapurine.[5] These facts suggested that a basic centre in the 9-substituent, in conjunction with a dimethylamino- or mercapto-substituent in other positions might have a favourable influence on activity. Among purines not substituted in the 9-position 6-mercapto-[6] and 6-chloro-[7] purine are notable as anti-tumour and anti-purine agents.

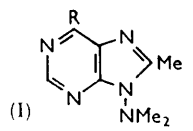
Examples of *N*-aminopurines had not been described until the recent synthesis of several 9-aminopurines by ring closure of substituted 5-amino-6-hydrazinopyrimidines.[8] The present communication describes the synthesis of some 9-dimethylamino-8-methylpurines (I) with a variety of substituents in the 6-position.

These compounds were prepared from 9-dimethylamino-8-methylhypoxanthine (I; R = OH) which was obtained by the combined formylation and ring closure of 5-amino-1-dimethylamino-2-methylimidazole-4-carboxamide[9] (II) in a mixture of acetic anhydride and ethyl orthoformate. Attempted ring closure with formamide led to decomposition.

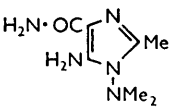
* Part III, *J.*, 1960, 327.

[1] Troy, Smith, Personeus, Moser, James, Sparks, Stevens, Halliday, McKenzie, and Oleson, *Antibiot. Ann.*, 1953—1954, p. 186.
[2] Oleson, Bennett, Halliday, and Williams, *Acta Un. Int. Cancr.*, 1955, **11**, 161.
[3] Fryth, Waller, Hutchings, and Williams, *J. Amer. Chem. Soc.*, 1958, **80**, 2736.
[4] Collier and Huskinson, "Chemistry and Biology of the Purines," Ciba Foundation Symposium, J. & A. Churchill Ltd., 1957, p. 146.
[5] Cf. Timmis, Cooke, and Spickett, ref. 4, p. 134.
[6] Farber, *Ann. New York Acad. Sci.*, 1954, **60**, 412.
[7] Murphy, Tan, Ellison, Karnofsky, and Burchenal, *Proc. Amer. Assoc. Cancer Res.*, 1955, **2**, 36.
[8] Montgomery and Temple, *J. Amer. Chem. Soc.*, 1960, **82**, 4592.
[9] Leese and Timmis, preceding paper.

Replacement of the hydroxyl group in the hypoxanthine (I; R = OH) was readily affected by using phosphoryl chloride without addition of tertiary base. The chloropurine (I; R = Cl) was converted into 9-dimethylamino-6-mercapto-8-methylpurine (I; R = SH)



(I)



(II)

by potassium hydrogen sulphide. Replacement of the chlorine atom in (I; R = Cl) by amino-residues was also smooth, yielding analogues of adenine, kinetin (6-furfurylaminopurine),[10] and puromycin (I; R = NH_2, NMe_2, NEt_2, and furfurylamine).

Experimental

Analyses are by Mr. P. R. W. Baker, Beckenham.

9-Dimethylamino-8-methylhypoxanthine.—5-Amino-1-dimethylamino-2-methylimidazole-4-carboxamide [9] (29·4 g.), acetic anhydride (58 ml.), and ethyl orthoformate (76 ml.) were heated on a steam-bath for 3 hr. The excess of acetic anhydride and orthoformic ester was removed *in vacuo* at 100° and the semi-solid product was dissolved in hot water. The solution was adjusted to pH 9 with dilute ammonia and on cooling afforded the *hypoxanthine* as white needles (16·1 g.), m. p. 335—336° (Found: C, 49·7; H, 5·7; N, 36·1. $C_8H_{11}N_5O$ requires C, 49·7; H, 5·7; N, 36·2%).

6-Chloro-9-dimethylamino-8-methylpurine.—The foregoing hypoxanthine (20 g.) and phosphoryl chloride (250 ml.) were refluxed for 2 hr. Phosphoryl chloride was distilled off, finally *in vacuo*, yielding crystals that were triturated with water, neutralised with solid sodium carbonate, and extracted with ether (4 × 200 ml.). The ether extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield the *chloropurine*. Recrystallisation from light petroleum (b. p. 60—80°) gave white prisms (20·5 g.), m. p. 133—134° (Found: C, 45·6; H, 4·5; N, 33·3; Cl, 16·6. $C_8H_{10}ClN_5$ requires C, 45·4; H, 4·8; N, 33·1; Cl, 16·7%). The above chloro-compound (0·5 g.), when boiled with 2N-sodium hydroxide (5 ml.), dissolved during 15 min. On neutralisation with dilute acetic acid the solution deposited 9-dimethylamino-8-methylhypoxanthine (0·3 g.), m. p. 334°.

9-Dimethylamino-8-methyladenine.—6-Chloro-9-dimethylamino-8-methylpurine (5 g.) and methanol (50 ml.), saturated at 0° with ammonia, were heated at 100° for 6 hr. in an autoclave. Removal of the solvent *in vacuo* and recrystallisation of the residue from benzene gave the *adenine derivative* as needles (4·5 g.), m. p. 239—240° (Found: C, 50·2; H, 6·5; N, 43·8. $C_8H_{12}N_6$ requires C, 50·0; H, 6·3; N, 43·7%).

9-Dimethylamino-6-mercapto-8-methylpurine.—6-Chloro-9-dimethylamino-8-methylpurine (5 g.) was heated in ethanol (20 ml.) and aqueous N-potassium hydrogen sulphide (24 ml.) for 3 hr. with a stream of hydrogen sulphide passing through the mixture. The solution was concentrated *in vacuo*, and the residue triturated with water (30 ml.) and filtered off. Recrystallisation from dioxan afforded *9-dimethylamino-6-mercapto-8-methylpurine* (4·3 g.), m. p. 277—278° (decomp.) (Found: C, 45·9; H, 5·4; N, 33·4; S, 15·3. $C_8H_{11}N_5S$ requires C, 45·9; H, 5·3; N, 33·5; S, 15·3%).

6,9-Bisdimethylamino-8-methylpurine.—6-Chloro-9-dimethylamino-8-methylpurine (3·3 g.) and 33% w/w ethanolic dimethylamine (50 ml.) were heated for 5 hr. at 100°. After removal of the excess of amine *in vacuo* the semi-crystalline residue was extracted with hot benzene (3 × 30 ml.). Evaporation of the combined benzene extracts yielded pale yellow crystals (3·0 g.), m. p. 62—63°, distillation of which *in vacuo* afforded *6,9-bisdimethylamino-8-methylpurine* (2·5 g.), b. p. 120°/0·5 mm., m. p. 62·3° (Found: C, 54·7; H, 7·6; N, 38·5. $C_{10}H_{16}N_6$ requires C, 54·5; H, 7·3; N, 38·2%).

6-Diethylamino-9-dimethylamino-8-methylpurine.—6-Chloro-9-dimethylamino-8-methylpurine (5 g.) and diethylamine (20 ml.) were refluxed together for 1 hr. The excess of diethylamine was removed *in vacuo* and the residue recrystallised from aqueous methanol. The *purine*

[10] Miller, Skoog, Okumura, Von Saltya, and Stroug, *J. Amer. Chem. Soc.*, 1955, **77**, 2662.

was obtained as needles (5·1 g.), m. p. 85—86° (Found: C, 58·2; H, 7·9; N, 34·0. $C_{12}H_{20}N_6$ requires C, 58·0; H, 8·1; N, 33·9%).

9-*Diethylamino*-6-*furfurylamino*-8-*methylpurine*.—6-Chloro-9-dimethylamino-8-methylpurine (5 g.), furfurylamine (5 g.), and ethanol (10 ml.) were refluxed for 1 hr. The residual gum, after removal of the excess of amine and solvent *in vacuo* was triturated with water. After 2 days at 0° the crystals were collected and recrystallised from light petroleum (b. p. 60—80°), yielding 9-*dimethylamino*-6-*furfurylamino*-8-*methylpurine* as prisms (4·8 g.), m. p. 94—95° (Found: C, 57·5; H, 5·9; N, 31·1. $C_{13}H_{16}N_6O$ requires C, 57·3; H, 5·9; N, 30·9%).

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