Syntheses of 6-Fluoropurine and 6-Fluoropurine-9-β-D-ribofuranoside

By J. KIBURIS and J. H. LISTER*

(*Chester Beatty Research Institute, Institute of Cancer Research, London* SW3)

ALTHOUGH various fluoropurines[1] and the related nucleoside[2] derivatives have been prepared as potential antitumour agents, previous attempts to synthesise either 6-fluoropurine (I; R = H) or the nucleoside form (I; R = β-D-ribofuranosyl) have not been successful.[3] Both derivatives have now been obtained by a route, found to be effective in forming fluoropyrimidines,[4] involving nucleophilic displacement of a trimethylammonium group by fluoride ion. Trimethylpurin-6-ylammonium chloride (II; R = H) and potassium hydrogen fluoride in EtOH–5% H_2O (60°, 3 hr.) gave, on extraction [hot ethyl acetate–ethanol (9 : 1)] and chromatography (silica gel), colourless 6-fluoropurine [27%, m.p. 125—126°, pK_a < 1·5 and 6·12, $\lambda_{max}^{(pH\,2)}$ 251 nm (ε 6580), $\lambda_{max}^{(pH\,11)}$ 260 (7430)].† The nucleoside analogue (I; R = β-D-ribofuranosyl) was obtained similarly from the trimethylpurin-6-yl derivative (I; R = β-D-ribofuranosyl), but, potassium fluoride in butanol was used (5 hr., 45°). 6-Fluoro-9-β-D-ribofuranosylpurine (26%) was obtained as colourless prisms [m.p. 140—141°, pK_a < 1·5 and 12·05, $\lambda_{max}^{(pH\,2)}$ 248 nm. (6610), $\lambda_{max}^{(pH\,14)}$ 254 (13,400), $[\alpha]_D^{25}$ −39°]†.

Attempts to improve the yields by carrying out the fluorination at a higher temperature (> 70°) led to Martius–Hofmann rearrangement of the quaternary purine, giving a 6-dimethylaminopurine.

6-Fluoropurine is unchanged in 1N-NaOH after 20 hr. In aqueous solution no hydrolysis was detected after 18 hr. at room temperature but hypoxanthine is formed after 7 hr. at 50° or 1 hr. at 100°. The least stability is shown in acid solution; total conversion into hypoxanthine results in 0·5N-HCl after 0·5 hr. at 25°. The different degree of reactivity of the fluorine atom in the two derivatives is illustrated by their conversion into the respective 6-aminopurines in methanolic ammonia, the nucleoside giving adenosine after 48 hr. at 0° whereas only a partial conversion into adenine occurs at room temperature after 5 hr.

We thank Dr. A. Knowles of this Institute for determining the pK_a values and u.v. spectral data. The work was supported by grants to the Chester Beatty Research Institute, Institute of Cancer Research from the British Empire Cancer Campaign for Research and the Medical Research Council.

(*Received, February 20th*, 1969; *Com.* 236.)

† The structures were confirmed by analysis and n.m.r. and i.r. spectra.

[1] J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, 1960, **82**, 463; E. O. Leonard, G. G. Skinner and W. Shive, *Arch. Biochem. Biophys.*, 1961, **92**, 33; H. Ballweg, *Annalen*, 1961, **649**, 114; A. G. Beaman and R. K. Robins, *J. Medicin. Chem.*, 1962, **5**, 1067; *J. Org. Chem.*, 1963, **28**, 2310; G. F. Gerster and R. K. Robins, *J. Org. Chem.*, 1966, **31**, 3258.

[2] J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, 1957, **79**, 4559; J. A. Montgomery, *J. Heterocyclic Chem.*, 1963, **4**, 463; G. F. Gerster, A. G. Beaman and R. K. Robins, *J. Medicin. Chem.*, 1963, **6**, 340; G. F. Gerster and R. K. Robins, *J. Amer. Chem. Soc.*, 1965, **87**, 3752; M. Ikehara and S. Yamada, *Chem. Comm.*, 1968, 1509.

[3] A. Bendich, A. Giner-Sorolla and J. J. Fox, "The Chemistry and Biology of Purines" eds. Wolstenholme and O'Connor, J. and A. Churchill Ltd., London 1957, p. 7; A. Giner-Sorolla, personal communication.

[4] J. P. Horwitz and A. G. Tomson, *J. Org. Chem.*, 1961, **26**, 3392.