Synthesis of 8-Fluoroadenosine

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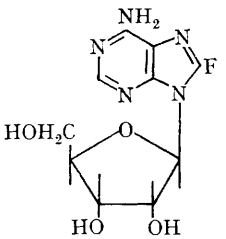
MANY 8-substituted purine nucleosides have been synthesized,[1,2] some of which revealed static activity against cancer cells.[3] Position 8 of the purine nucleoside can be assumed to be analogous to position 5 of the pyrimidine nucleoside, since neither position is involved in the Watson–Crick base-pairing site.[4] Since 5-fluorouridine and 5-fluoro-2′-deoxyuridine are known to be active against cancer cells[5] and viral systems,[6] we attempted to synthesize 8-fluoroadenosine.



Application of the Sheeman reaction to purine nucleosides has been reported and the 2-fluoroinosine derivative[7] and 2-fluoroadenosine[8] have been successively synthesized. We have, therefore, appliedthe selective Sheeman reaction to 8-aminoadenosine[2] to obtain 8-fluoroadenosine, but the only product isolated was 8-fluorohypoxanthine because of the extreme lability of the nucleosidic linkage in the product.

To avoid cleavage of the nucleosidic linkage, 2′,3′,5′-tri-*O*-acetyl-8-azidoadenosine (78%) was synthesized from 8-azidoadenosine[2] with acetic anhydride. The triacetate, thus obtained, was hydrogenated with palladium–charcoal as catalyst to give 2′,3′,5′-tri-*O*-acetyl-8-aminoadenosine [glass (69%), t.l.c. (chloroform–ethanol, 35 : 5) R_F 0·40, λ_{max}^{pH1} 270, λ_{max}^{pH7} 272, λ_{max}^{pH12} 273 mμ]. Triacetyl-8-aminoadenosine (4·12 g., 10 mmole) was dissolved in fluoroboric acid (42%, 60 ml.) at −20° and sodium nitrite (1·38 g., 20 mmole) dissolved in 10 ml. of water was added slowly at −20° with stirring. After 30 min., ethanol (30 ml.; precooled to −20°) was added and the mixture was neutralized with concentrated ammonia to pH 7·0. The salt was filtered off and the product was extracted with chloroform (3 × 100 ml.). The chloroform was evaporated off and the residue was chromatographed on a column of silica gel. Elution with chloroform gave a fraction having R_F 0·28 t.l.c. chloroform–ethanol, 37 : 3). Evaporation of the solvent and crystallization of the residue from benzene gave pale yellow needles [m.p. 170—171°, λ_{max}^{pH1} 263·5 (ε 17,200), λ_{max}^{pH7} 263 (14,600), λ_{max}^{pH13} 263 mμ (15,300), n.m.r. δ 1·94 (s, 3H, 5′-acetyl), 2·10 (d, 6H, 2′ and 3′-acetyl), 4·28 (m, 2H, 4′ and 5′-H), 5·77 (m, 1H, 3′-H), 6·09 (m, 2H, 1′ and 2′-H), 7·48 (s, 2H, 6-NH_2) and 8·18 (s, 1H, 2-H)]. In some cases, small amounts of the 6,8-difluoro-derivative was obtained as by a product.

Triacetyl-8-fluoroadenosine was finally deacetylated by the treatment with methanolic ammonia at room temperature for 10 hr. The aqueous solution obtained after the evaporation of the ammonia, was passed through a cellulose column and the effluents lyophilized to give a glass (82%). Recrystallisation from ethanol gave a crystalline product, m.p. 190–191°, [λ_{max}^{pH1} 261·5, λ_{max}^{pH7} 263, λ_{max}^{pH13} 264 mμ, paper chromatography : R_F 0·77 (isopropyl alcohol–ammonia–water, 7 : 1 : 2), R_F 0·51 (n-butanol–water, 86 : 14), R_F 0·50 (water adjusted to pH 10 with ammonia), t.l.c. R_F 0·75 (chloroform–ethanol, 1 : 1)]. From the u.v. absorption properties, paper chromatography and t.l.c. data, we concluded that the product was 8-fluoroadenosine.

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* Performed in [$^2H_6$]dimethyl sulphoxide at 60 Mc. % sec. with tetramethylsilane as internal standard.

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