The Synthesis of Unsaturated Adenine Nucleosides Related to Angustmycin A

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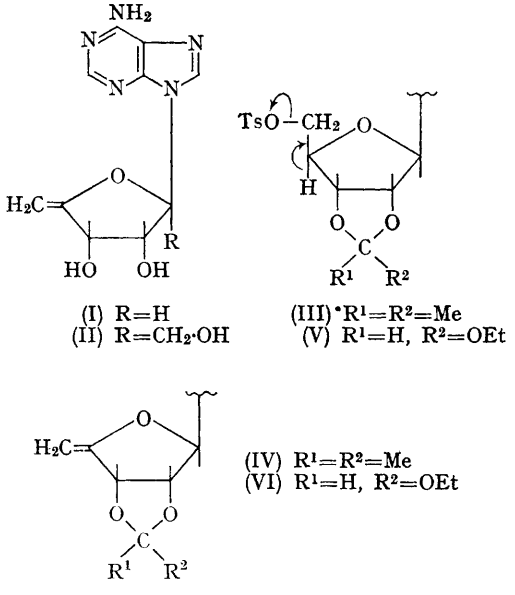
WE have prepared 6-amino-9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine (4′,5′-didehydro-5′-deoxyadenosine) (I), the first synthetic purine nucleoside with an exocyclic methylene group and a structural homologue of the antibiotic angustmycin A (decoyinine) (II).[1]

Recently, Hough and Otter[2] reported the preparation of 3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidine-β-L-*threo*-pent-4-enofuranose and other furanoid vinyl ethers by treatment of the corresponding primary halogen derivatives with silver fluoride in pyridine.[3] Verheyden and Moffatt[4] have successfully extended this procedure to 2′,3′-di-*O*-acetyl-5′-iodo-5′-deoxyuridine. In a different approach to the problem, we have employed the mild base-catalyzed *E*2 elimination of the toluene-*p*-sulphonate group which proved successful in our earlier syntheses of the 2′,3′-unsaturated furanosyl adenine nucleoside derivatives.[5] Thus, treatment of 5′-*O*-toluene-*p*-sulphonyl-2′,3′-*O*-isopropylidineadenosine (III)[6] with an excess of potassium t-butoxide in t-butyl alcohol at room temperature for 0·5 hr. gave 6-amino-9-(2,3-*O*-isopropylidine-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine (IV) which crystallized from ethanol in 26% yield, m.p. 182—183°, λ_{max}(MeOH) 258 mμ (ε 15,600).

Attempts to deblock (IV) to yield (I) *via* mild acid hydrolysis gave only adenine. Treatment of 2′,3′-*O*-ethoxymethylidineadenosine[7] with toluene-*p*-sulphonyl chloride in pyridine at −20° gave (V) in 70% yield as crystals from methanol, strong infrared band at 1170 cm.$^{-1}$ (OTs). Similar treatment of (V) with potassium t-butoxide gave a 31% yield of 6-amino-9-(2,3-*O*-ethoxymethylidine-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-purine (VI), m.p. 155°, after purification on an alumina column and crystallization from ethanol. The 60 Mc./sec. ^{1}H n.m.r. spectrum of (VI) showed an AB splitting pattern (with secondary splitting) corresponding to the 5′-methylene group with multiplets centred at δ 4·44 and δ 4·58 and two

multiplets centred at δ 5·42 and δ 5·61 corresponding to the 3′- and 2′-protons respectively. The anomeric proton peak appeared as a narrowly split (1·2 c./sec.) peak at δ 6·37. The peaks corresponding to the 4′- and 5′-protons in the starting material were absent.



(I) R=H
(II) R=CH_2·OH

(III) R^1=R^2=Me
(V) R^1=H, R^2=OEt

(IV) R^1=R^2=Me
(VI) R^1=H, R^2=OEt

Compound (VI) was treated first with 20% aqueous acetic acid in dioxan at 50°, the solvents removed, and the residue treated with methanolic ammonia. The resulting 6-amino-9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine (I) was obtained in 32% yield after crystallization first from methanol and then from acetone as needles, m.p. 195—196° decomp., λ_{max} (MeOH) 258 mμ (ε 14,700). The ^{1}H n.m.r. spectrum of (I) shows a poorly defined multiplet of four, centred at δ 4·48, corresponding to the 5′-methylene protons. This peak is clearly separated from the multiplet of four for the 3′- and 2′-protons centred at δ 4·97. Compound (I) has been found[8] to possess higher potency than angustmycin A *per se* against *Streptococcus faecalis*, which has been employed for detailed studies of the mechanism of action of angustmycin A (decoyinine).[9]

The presence of the exocyclic methylene group was further confirmed by catalytic hydrogenation of (VI) in ethanol over 5% palladium on charcoal. The product, presumably 6-amino-9-(2,3-*O*-ethoxymethylidine-5-deoxy-α-L-*lyxo*-pentofuranosyl)-purine,[10] crystallized from ethanol. The ^{1}H n.m.r. spectrum of these needles exhibited a doublet centred at δ 1·39 corresponding to the 5′-methyl protons and overlapping the methyl triplet (δ 1·28, J = 7 c./sec.) from the EtO·CH group, a singlet at δ 6·12 (1′-proton), a doublet centred at 5·69 (2′-H), a multiplet of four centred at δ 5·08 (3′-H), and a complex multiplet centred at δ 4·62 (4′-H). The dihydro-structure of the hydrogenated derivative of (VI) was thus confirmed.

It is noteworthy that *E*2 elimination under these conditions competes successfully with cyclonucleoside formation in the case of the blocked 5′-*O*-toluene-*p*-sulphonate derivatives (III) and (V). The attempted preparation of (I) directly from 5′-*O*-toluene-*p*-sulphonyladenosine[6] with t-butoxide gave a mixture of products which exhibited at least six spots observed by thin-layer chromatography.

Correct elemental analyses were obtained for all new compounds reported and chromatographic homogeneity was observed by thin-layer chromatography. The application of this general base-catalyzed elimination reaction to the synthesis of angustmycin A (II) and other unsaturated nucleosides is in progress.

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