Synthesis of 7-Glycosylpurines

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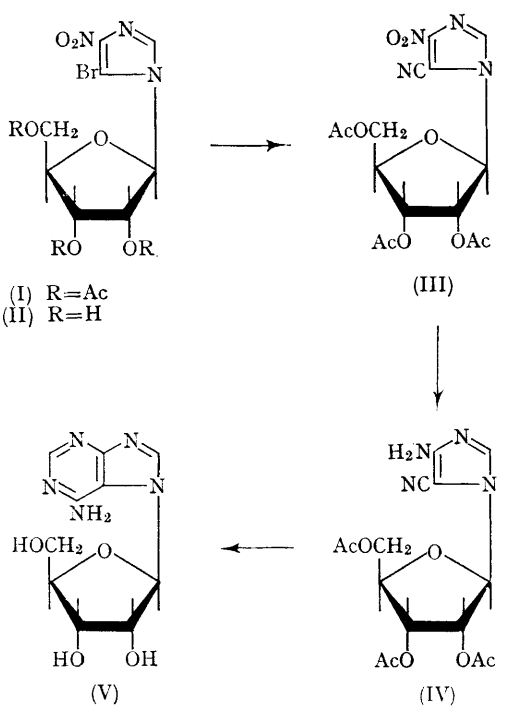
A NUMBER of 7-D-ribofuranosylpurines[1] have been isolated from pseudo-vitamin B_{12}; however, the laboratory syntheses of these compounds have been retarded by the inability[2] to develop a simple method for directing the carbohydrate moiety to N-7 rather than N-9 in the glycosidation of purines. The only major exceptions being 7-glycosyltheophyllines[3,4] which possess a methyl group at N-1 and N-3. Other 7-glycosylpurines have recently been prepared[5,6] by utilizing the directive influence,[7,8] probably steric, exerted by 3-substituted purines but this approach possesses some serious inherent disadvantages.[6,8] The recent finding[9] that a number of reported 7-glycosylpurines were in actuality 3-glycosylpurines would imply that N-3 must be blocked to ensure glycosidation at N-7 of preformed purines. The preceding difficulties strongly suggested that an alternate synthetic route originating from precursors other than preformed purines might be more rewarding. The pyrimidine approach, *via* ring closure of appropriate 4-amino-5-glycosylaminopyrimidines, has already been found[10] to be unsuccessful.

We now report a new synthetic route for the preparation of 7-glycosylpurines in general and the first glycosidation of an imidazole[11] *via* the fusion procedure.[12] A mixture of 4(5)-bromo-5(4)nitroimidazole and tetra-*O*-acetyl-β-D-ribofuranose were heated at 180° with a catalytic amount of chloroacetic acid to produce a 59% yield of (I), m.p. 93—95°, $[\alpha]_D^{25}$ + 1·71° (*c*, 2; EtOH). This was the only crystalline compound isolated from the fusion reaction, and the site of glycosidation was assigned by comparison of ultraviolet absorption[13] with model compounds. Deacetylation of (I) with methanolic ammonia afforded (II), m.p. 180—182°, $[\alpha]_D^{24}$ −8·54 (*c*, 1·0; H_2O). When (I) was treated with potassium iodide and potassium cyanide in anhydrous dimethyl sulphoxide at room temperature there occurred a ready displacement of the bromo-group to afford an 82% yield of (III), m.p. 99—100°, $[\alpha]_D^{24}$ + 11·2 (*c*, 1·0; $CHCl_3$), i.r. (KBr) 2250 cm.$^{-1}$ (C≡N). This provided additional evidence for the site of glycosidation since bromine is readily displaced by cyanide only when the *N*-substituent resides adjacent to the bromo-group.[11] When (III) was treated with Raney nickel in anhydrous ethanol at 50 p.s.i. for three hours at room temperature there was obtained a light yellow crystalline foam, m.p. 58—60°. This product was established as (IV) by p.m.r. spectra (absorption peak at δ 7·6, NH_2), ultraviolet absorption comparison with 4-amino-5-cyano-1-methylimidazole[14] and i.r. spectra (KBr) 2225 cm.$^{-1}$ (C≡N). A 1 : 1 mixture of ethyl orthoformate and acetic anhydride containing (IV) was heated at reflux for 4 hr. to produce a viscous syrup which was assumed to be the 4-ethoxymethylene derivative of (IV). Treatment of this light yellow syrup with methanolic ammonia produced a 73% yield of 7-β-D-ribofuranosyladenine (V). The ultraviolet absorption



spectra, R_f-values, and optical rotation observed for (V) were found to be in accord with those previously reported[6] and established the site of glycosidation and anomeric configuration of all compounds reported in this Communication. All compounds showed appropriate elemental analyses and were found to be homogeneous by thin-layer

chromatography. This preparation of (V) illustrates the inherent potential of utilizing appropriately substituted imidazole nucleosides which are now readily available as intermediates in the direct synthesis of the naturally occurring 7-glycosylpurines.

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