Synthesis of C-Nucleoside Analogues by 1,3-Dipolar Addition of a 1-Diazo-sugar to Acetylenes

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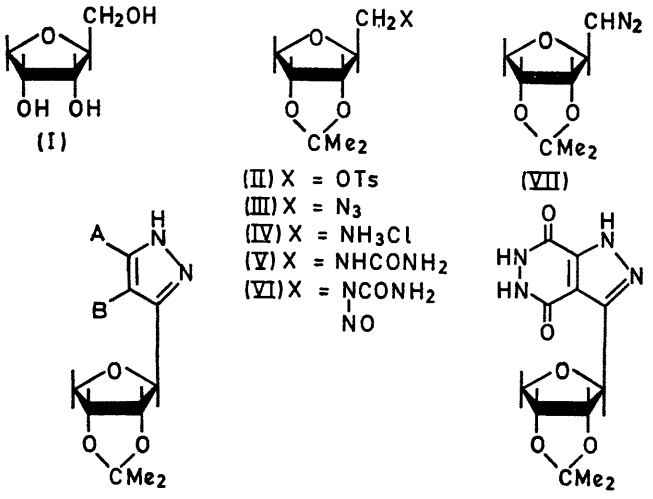
Summary The 1-diazo-sugar (VII), prepared by base treatment of 2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-1-nitrosoureido-DL-ribitol (VI), underwent 1,3-dipolar addition with dimethyl acetylenedicarboxylate in nearly quantitative yield, forming dimethyl 3-(2,3-*O*-isopropylidene-β-DL-erythrofuranosyl)pyrazole-4,5-dicarboxylate (VIII) and providing a pathway to *C*-nucleosides.

NUCLEOSIDE analogues, in which the sugar moiety is attached to a nitrogen heterocycle at a ring carbon rather than at nitrogen, are called *C*-nucleosides, and are of interest as analogues of the anti-tumour antibiotics formycin[1] and showdomycin[2,3] which contain D-ribofuranose as the sugar moiety. A general synthetic approach to *C*-nucleosides, previously lacking, is now made available by the synthesis, for the first time, of a 1-diazo-sugar[4] (VII), then applying it in a synthetic sequence devised by Sprinzl, Farkaš, and Šorm.[5] Thus, 1,3-dipolar addition of (VII) to acetylene-dicarboxylic ester[5,6] yielded nearly quantitatively a pyrazole-4,5-dicarboxylic ester (VIII) with a sugar attached at C-3.†

The 1-diazo-sugar was synthesized from 1-amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-DL-ribitol. Preparing the 1-diazo-sugar as the 2,5-anhydro-derivative was of prime importance, since upon incorporation of C-1 into the

† Satisfactory elemental analyses and i.r. and n.m.r. spectra have been obtained for the compounds described.

heterocycle the resultant sugar moiety was attached as a furanose, such that C-2 of the diazo-sugar became C-1′ in the nucleoside analogue. In these model studies, the sugar was used as the DL-racemate, taking advantage of its easy access from ribitol. The sequence should be generally applicable to other 1-amino-2,5-anhydro-1-deoxy-sugars containing a 5-hydroxymethyl group, and studies with this objective are in progress in our laboratories.



2,5-Anhydro-DL-ribitol (I) was obtained[7] from ribitol, and was converted *via* the 3,4-*O*-isopropylidene 1-*O*-tosylate (II), m.p. 94—95·5°, to the 1-azide (III), somewhat modifying procedures described for the D-isomers.[8] To avoid formation of secondary amine, the azide was reduced with sodium borohydride in boiling isopropyl alcohol. The primary amine[8] was isolated as the hydrochloride (IV), m.p. 235—237°, and was converted with potassium cyanate in aqueous solution into the urea (V), m.p. 167—168·5°. Nitrosation was best accomplished in aqueous 40% acetic acid solution with sodium nitrite. After 3 days at 3°, the yellow nitrosourea (VI) was extracted with chloroform and crystallized from ether–pentane (1 : 1), m.p. 122—123° (44% yield), λ_{max} (EtOH) 233 nm (ϵ 4450). Upon treatment with a mixture of ether and aqueous 40% potassium hydroxide, the nitrosourea showed good solubility in the base layer, and the 1-diazo-sugar (VII) was gradually generated and extracted into ether. Several extracts were obtained at 15 min. intervals, combined, and dried over potassium hydroxide. Presence of (VII) was verified by treatment of a portion with *p*-nitrobenzoic acid; the resultant 1-*O*-*p*-nitrobenzoate was identical with an authentic sample obtained from 2,5-anhydro-3,4-*O*-isopropylidene-DL-ribitol. Then, ethereal 2,5-anhydro-1-deoxy-1-diazo-3,4-*O*-isopropylidene-DL-ribitol (VII), without further isolation, was added to dimethyl acetylenedicarboxylate in ether solution (10% excess, relative to VI used). Ether was removed under reduced pressure and the residual oil crystallized from benzene–cyclohexane (5 : 1) to afford dimethyl 3-(2,3-*O*-isopropylidene-β-DL-erythrofuranosyl)-pyrazole-4,5-dicarboxylate (VIII), m.p. 94—96° (91% yield) λ_{max} (pH 1) 228 nm (ϵ 6930), λ_{max} (pH 7) 227 nm (ϵ 6580), λ_{max} (pH 13) 253 nm (ϵ 10,100); n.m.r. data (60 MHz, $CDCl_3$, internal tetramethylsilane): τ 4·51 d [1′-H, J(1′,2′) 1·2 Hz], 6·05 s, and 6·11 s (2× CO_2CH_3). Appearance of the doublet for 1′-H downfield from the other sugar proton signals but upfield from 1′-H of normal *N*-furanosyl nucleosides was diagnostic for a *C*-nucleoside.[1-3] The low coupling constant was as expected from the β-configuration, and lack of coupling with a heterocyclic ring proton confirmed that the product was a 1*H*-pyrazole, as expected from previous adducts of acetylenes and diazo-compounds.[5,6] Selective ammonolysis of the 5-ester of (VIII) with methanolic ammonia at 25° for 24 hr. was assumed, as in ref. 5, by analogy with dimethyl pyrazole-4,5-dicarboxylate,[9] and yielded methyl 5-carbamyl-3-(2,3-*O*-isopropylidene-β-DL-erythrofuranosyl)pyrazole-4-carboxylate (IX), m.p. 160—162° (67% yield, from isopropyl alcohol), λ_{max} (pH 1) 225 nm (sh), λ_{max} (pH 7) 225 nm (sh), λ_{max} (pH 13) 255 nm (10,000); n.m.r. data: τ — 3·92 broad (N-1–H), —3·18 and —0·84 (5-$CONH_2$), 4·39 s (1′-H), and 6·02 s (CO_2CH_3). The possibility of elaboration to a 1*H*-pyrazolo[4,3-*d*]pyrimidine, as a purine analogue, through a 4-amino-pyrazole-5-carboxamide to be derived[5] from (IX), was demonstrated by hydrazinolysis of the amide ester (IX) at 25° to yield the 5-amide-4-hydrazide (X), m.p. 220—225° with gas evolution, followed by re-solidification at 235—240° and melting with decomposition above 265° (25% yield, from chloroform–methanol), λ_{max} (pH 1) 232 nm (sh), λ_{max} (pH 13) nm (8050); n.m.r. data: τ 4·58 s (1′-H). Hydrazine and (IX) at 100° afforded the cyclic hydrazide as another *C*-nucleoside, whose base is isomeric with xanthine, 3-(2,3-*O*-isopropylidene-β-DL-erythrofuranosyl)-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (XI), m.p. 303—306° dec., λ_{max} (pH 1) 261 nm (ϵ 5410), λ_{max} (pH 7) 274 (ϵ 6470), λ_{max} (pH 13) 275 (ϵ 7750). An identical sample was obtained in 81% yield directly from the 4,5-diester with hydrazine at 100°.

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