Displacements on Furanoid Systems: Stepwise Introductions of Azide Functions into Methyl Pentofuranosides

By JEANINE CLEOPHAX, S. D. GERO,* and J. HILDESHEIM
(*Institut de Chimie des Substances Naturelles, C.N.R.S.,* 91-*Gif-sur-Yvette, France*)

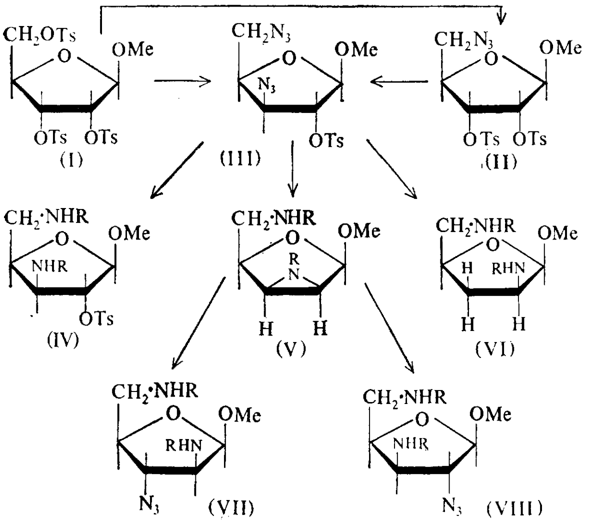
As part of a programme[1] directed towards the introduction of a variety of functional groups into tetrahydrofuranoid derivatives with the aim of preparing modified nucleosides with biological activity, we report the introduction of nitrogen-containing functional groups into methyl pentofuranosides. The introduction of one, two and three azido-functions into the tetrahydrofuranoid system has recently been accomplished.[1]

The direct displacement of secondary sulphonates located in a pyranoside ring has been used previously for the successful introduction of four nitrogen-containing functions.[2] Surprisingly few examples, however, of the preparation of multiple nitrogen-containing functions have thus far been reported in tetrahydrofuranoid derivatives.[3]

It is known,[4] that S_N2 displacement on a cyclopentyl ring is 10—100 times faster than on a cyclohexyl ring; therefore it seemed of considerable chemical and biological interest to investigate the direct displacement of the tetrahydrofuranoid sulphonates by azide ion.

Recently[6] it was shown that a monoazido-compound (II) could be readily obtained from methyl 2,3,5-tri-*O*-toluene-*p*-sulphonyl-β-D-ribofuranoside.[5] The monoazide (II) upon treatment with sodium azide in dimethylformamide for 2 hr. at 145° gave the diazido-compound (III) (46%), $[\alpha]_D$ $-56°$ (c, 0·65, $CHCl_3$), characterized as the crystalline di-*N*-benzoyl derivative (IV), m.p. 173·5—175°, $[\alpha]_D$ −79·2° (*c*, 0·65, $CHCl_3$). The identical diazido-compound (III) could also be obtained directly from the methyl 2,3,5-tri-*O*-toluene-*p*-sulphonyl-β-D-ribofuranoside (I) by treatment with sodium azide in dimethylformamide for 2·5 hr. at 145°. The structure of the diazide (III) was also supported by its n.m.r. spectrum; the signal at τ 5·13 ($J_{1,2}$ 2 c./sec.) is in accord with the *trans* relationship of the hydrogens on C-1 and C-2.

When the diazide (III) was treated with methanolic hydrazine hydrate and Raney nickel,[7] followed by direct benzoylation of the product, a compound, analyzed as methyl 2,5-dibenzamido-2,3,5-trideoxy-β-D-*threo*-pentofuranoside (VI), m.p. 161—163°, $[\alpha]_D$ −23·5° (*c*, 0·68, $CHCl_3$), and having a molecular ion peak in the mass spectrum at *m/e* 354, was obtained. It was concluded that the expected epimine (V) had been hydrogenolysed during the reaction, resulting in the formation of (VI) (*cf.* ref. 8). The C-1 hydrogen by virtue of spin coupling to the one adjacent hydrogen on C-2 (*cis*) gave a doublet centred at τ 5·02 ($J_{1,2}$ 4·5 c./sec.); this is consistent only with structure (VI).



R = COPh

The expected methyl 5-benzamido-2,3-benzoylepimino-2,3,5-trideoxy-β-D-lyxofuranoside (V) could be obtained in 61% yield from the diazido-compound (III) by treatment with lithium aluminium hydride, followed by direct benzoylation. The mass spectrum of (V) possessed the correct molecular ion peak at *m/e* 352 and the fragmentation pattern was in accord with the presence of an epimino-ring in the molecule. In addition when the epimine was treated under the same conditions (methanolic hydrazine hydrate and Raney nickel) used to produce the diaminotrideoxy-compound (VI) from (III), this same substance (VI) could be isolated. The formation of the latter suggests that hydrogenolysis of the epimine ring even if formed would occur under these reducing conditions.

The introduction of a third nitrogen-containing function into this series of compounds was accomplished by treatment of the epimine (V) with sodium azide in dimethylformamide. Two products were formed (separable by silica gel column chromatography) in the ratio 1·8 to 1·0, to which, on the basis of comparison of optical rotation with similar pairs of structures,[9] we tentatively assign the structures methyl 3-azido-2,5-dibenzamido-2,3,5-trideoxy-β-D-arabinofuranoside (VII), (54·7%) m.p. 158—160°, $[\alpha]_D$ −4° (*c*, 1·56 $CHCl_3$) and methyl 2-azido-3,5-dibenzamido-2,3,5-trideoxy-β-D-xylofuranoside (VIII), (29·3%) m.p. 193—195°, $[\alpha]_D$ −130° (*c*, 0·95, $CHCl_3$), respectively.

Satisfactory elemental analyses have been obtained for all the compounds described.

Professor E. Lederer is thanked for the constant encouragement with which he supported this work, which was aided by a grant from the Delegation Generale à la Recherche Scientifique et Technique aupres du Premier Ministre. We thank Dr. R. D. Guthrie for helpful discussions.

(*Received, December 6th,* 1967; *Com.* 1306.)

---

[1] J. Cleophax, J. Hildesheim, R. E. Williams, and S. D. Gero, *Bull. Soc. chim. France*, in the press.
[2] Y. Ali and A. C. Richardson, *Chem. Comm.*, 1967, 554.
[3] J. E. Christensen and L. Goodman, *J. Org. Chem.*, 1963, **28**, 2995.
[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, 1965, p. 204.
[5] J. Hildesheim, J. Cleophax, and S. D. Gero, *Tetrahedron Letters*, 1967, 1685.
[6] J. Hildesheim, J. Cleophax, S. D. Gero, and R. D. Guthrie, *Tetrahedron Letters*, 1967, 5013.
[7] R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1963, 5288.
[8] D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 1965, 2736.
[9] G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, 1964, **86**, 1427.