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The Benzoylation of Some Glycosides with a Mixture of Benzoic Acid, Triphenylphosphine, and Diethyl Azodicarboxylate

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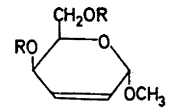
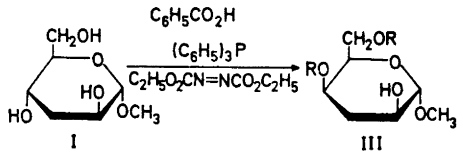
Mitsunobu and Eguchi have described the substitution of alchohols using nucleophiles such as benzoic acid, dibenzyl hydrogen phosphate, and phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate.[1,2] The reactions lead to products with inverted configuration and are of potential interest in carbohydrate chemistry for the synthesis of phosphorylated sugars, amino sugars, and for the inversion of the configuration at specific positions *via* benzoylation. A preliminary report by Jones and co-workers on the synthesis of some amino sugars using phthalimide,[3] following the procedures outlined by Mitsunobu and Eguchi [1,2] prompts us to report our experiences in attempted inversion reactions using benzoic acid as the nucleophile.

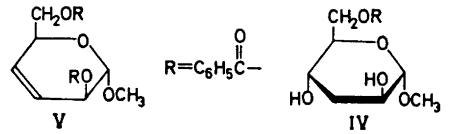
In connection with the synthesis of disaccharide derivatives containing 3,6-dideoxyhexopyranosyl moieties [4–6] it would be of interest to be able to effect the simultaneous inversion of two hydroxyl groups at the 2- and 4-positions in 3-deoxy-D-*arabino*-hexosides. This would give access to 3,6-dideoxy-D-*xylo*-hexosides from the previously synthesized D-*arabino* stereoisomers.[4] As a model for this conversion, methyl 3-deoxy-α-D-*arabino*-hexopyranoside (I) [4,7] was treated with benzoic acid,



II



I III



V IV

triphenylphosphine, and diethyl azodicarboxylate. The reaction mixture was fractionated on silica gel to give methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (II, 23 %) in crystalline form and with physical constants in agreement with literature values,[8] methyl 4,6-di-*O*-benzoyl-3-deoxy-α-D-*lyxo*-hexopyranoside (III, 47 %) and methyl 6-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexopyranoside (IV, 12 %). The dibenzoate III was identified as follows. The NMR indicated the presence of two benzoyl groups. Acetylation afforded a monoacetate (NMR) and debenzoylation of III afforded syrupy methyl 3-deoxy-α-D-*lyxo*-hexopyranoside $[\alpha]_D$ +84° (methanol) (lit.[9] $[\alpha]_D$ +98°). Hydrolysis, conversion into the corresponding 3-deoxy-D-hexitol acetate and examination by GLC-MS showed that the derivative had the MS expected, but retention

time different to the corresponding *arabino*-, *ribo*-, and *xylo*-stereoisomers. These findings, together with the known inversion at chiral carbinol carbons in the reaction [1,2] show that the dibenzoate is III. The monobenzoate IV upon debenzoylation gave crystalline starting material (I). The assignment of the benzoate group to position 6 is based upon the expected higher reactivity at primary carbon and upon the fact that IV had the same configuration as I.

In the reaction of I with the above reagents, facile nucleophilic attack with inversion at the 4- and 6-positions therefore takes place. No inversion at C-2 was observed, presumably due to hindrance from the anomeric position. The olefin II presumably is produced from III substituted in the 2-position by a phosphonium ion intermediate, which undergoes elimination more rapidly than bimolecular nucleophilic substitution.

The sensitivity of the reaction to steric interference from neighbouring groups is indicated from the following. Methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside was treated as described for I above. The only product isolated, in 77 % yield, was methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranoside with physical properties corresponding to those described in the literature.[10] On the other hand, similar treatment of methyl 3-deoxy-α-D-*ribo*-hexopyranoside produced an olefinic sugar in 41 % yield, tentatively suggested from NMR evidence to be a 3,4-dideoxy-hex-3-enopyranoside.

The steric requirements of the reaction thus are similar to those observed by Jones and co-workers for phthalimide as nucleophile.[3] Substitution at the 6-position is much more readily effected than ring substitution. The latter process is subject to interference from vicinal groups. Provided the geometry is *trans*-1,2-diaxial, an intermediate phosphonium ion may well give rise to elimination instead of substitution.

Experimental. General methods were the same as those described in a previous paper.[6] NMR spectra on the various compounds were in accordance with the presumed structures.

Methyl 3-deoxy-α-D-*arabino*-hexopyranoside [7] (I, 900 mg), triphenylphosphine (4.014 g) and benzoic acid (1.881 g) were dissolved in tetrahydrofuran (10 ml). A solution of diethyl azodicarboxylate (2.688 g) in tetrahydrofuran (4 ml) was added with stirring at room temperature. The reaction was followed by TLC (toluene-ethyl acetate 4:1). No further reaction took place after 1 h. The solvent was removed and the residue taken up in ether. Undissolved material was filtered off and the filtrate was fractionated on silica gel (toluene-ethyl acetate 4:1). The following products (in the order of decreasing R_F value) were obtained: *Methyl 4,6-di-O-benzoyl-2,3-dideoxy*-α-D-threo-*hex-2-eno-pyranoside* (II, 425 mg) m.p. 101–102°, $[\alpha]_D$ −191° (*c*, 0.2, chloroform) (lit.[8] m.p. 101.5–102°, $[\alpha]_D$ −197°). *Methyl 4,6-di-O-benzoyl-3-deoxy*-α-D-lyxo-*hexopyranside* (III, 891 mg). Debenzoylation of part of the material (77 mg) with barium oxide in methanol afforded syrupy methyl 3-deoxy-α-D-*lyxo*-hexopyranoside (31 mg) $[\alpha]_D$ + 84° (*c*, 0.2, methanol) (lit.[9] $[\alpha]_D$ + 98°). The hexoside was converted into the corresponding 3-deoxyhexitol pentaacetate which was examined by GLC-MS. The MS corresponded to those given by the pentaacetates of 3-deoxy-D-*arabino*-, D-*ribo*- and D-*xylo*-hexitols, the GLC retention time, however, differed. Retention times on an XE-60, 3 % on Gas-Chrom Q, relative to 1,5-di-*O*-acetyl-2, 3, 4, 6-tetra-*O*-methyl-D-glucitol were 6.06, 7.08, 6.28, and 7.12 for the *arabino*-, *lyxo*, *ribo*-, and *xylo*-isomers, respectively. *Methyl 3-deoxy-6-O-benzoyl*-α-D-arabino-*hexopyranoside* (IV, 170 mg) upon debenzoylation with barium oxide in methanol afforded starting material (I).

Methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside (76 mg) was treated with benzoic acid (69 mg), triphenylphosphine (147 mg), and diethyl azodicarboxylate (99 mg) in tetrahydrofuran (1 ml) as described above. The reaction was followed by TLC (diethyl ether-light petroleum (40–60°) 3:1). No further reaction was observed after 30 min. Work-up as described above and fractionation on silica gel (diethyl ether-light petroleum (40–60°) 3:1) afforded *methyl 2,3-di-O-acetyl-6-O-benzoyl*-α-D-*glucopyranoside* $[\alpha]_D$ + 97° (*c*, 0.2, chloroform) (lit.[10] $[\alpha]_D$ + 102°). Debenzoylation of an aliquot followed by acetylation with excess acetic anhydride in pyridine afforded methyl 2,3,4, 6-tetra-*O*-acetyl-α-D-glucopyranoside indistinguishable from reference material (TLC, GLC, NMR).

Methyl 3-deoxy-α-D-*ribo*-hexopyranoside (47 mg) was treated with 2.5 molar equivalents of each of benzoic acid, triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran overnight and worked up as described above. The major product (40 mg) $[\alpha]_D$ + 44° (*c*, 0.1, chloroform) was obtained chromatographically pure by TLC (diethyl ether-petroleum ether (40–60°) 3:1). NMR (deuteriochloroform): δ 3.55 (3H), singlet, methoxyl protons;

δ 4.6 (3H), multiplets, H-5, H-6, H-6'; δ 5.00 (1H), $J < 1$ Hz, H-1; δ 5.25 (1H), multiplet, H-2; δ 6.12 (2H), multiplets, H-3 and H-4; δ 7.3 – 7.6 and 8.0 – 8.2 (10H) aromatic protons. These tentative NMR assignments are based on shift considerations (aromatic protons, H3- and H-4 olefinic protons, low-field signal for H-2 on benzoxylated carbon) and upon the observation of the lanthanide induced shifts[11] caused by the successive addition of tris(dipivaloylmethanato) europium, which *inter alia* caused substantial down-field shift changes of the presumed H-2, H-6, and H-6' signals. The latter two signals became clearly differentiated. The down-field shift change of H-6 and H-6' clearly revealed H-5 as a multiplet at higher field; its coupling pattern showed coupling to three protons, excluding the possibility of the compound being a 4,5-hexenopyranoside. The small coupling constant of H-1 precludes the presence of a 2,3-hexenopyranoside, which for an α-D-glycoside would have $J_{1,2} = 2 - 3.5$ Hz[12] as displayed by III. The small coupling constant for H-2 and the above considerations indicate instead, the presence of a 3,4-hexenopyranoside, tentatively identified as methyl 2,6-di-*O*-benzoyl-3,4-dideoxy-α-D-*threo*-hex-3-enopyranoside V.

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The Reaction between Bis(2-bromoethyl)selenide and Potassium Selenocyanate

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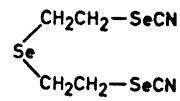
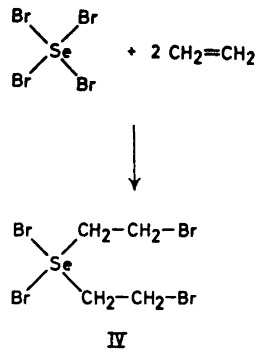
Aliphatic selenocyanates are most conveniently synthesized by reacting the corresponding alkyl halide with potassium selenocyanate in acetone or ethanol.[1] The reaction between bis(2-bromoethyl) selenide (I) and potassium selenocyanate, however, did not give the expected bis-(2-selenocyanatoethyl) selenide (II). The main product consisted of diselenocyanatoethane (III). Elemental selenium was also isolated from the reaction mixture.



II

Bis(2-bromoethyl) selenide (I) has been subjected to some decomposition reactions and has been found to be a rather unstable compound. In several cases one of the decomposition products has been ethylene.[2] In order to investigate whether ethylene is produced also in this case, the gas evolved during the reaction was allowed to pass through a solution of selenium tetra-



IV

Scheme 1.