Note

Selective oxidation of a diol with methyl sulfoxide–acetic anhydride

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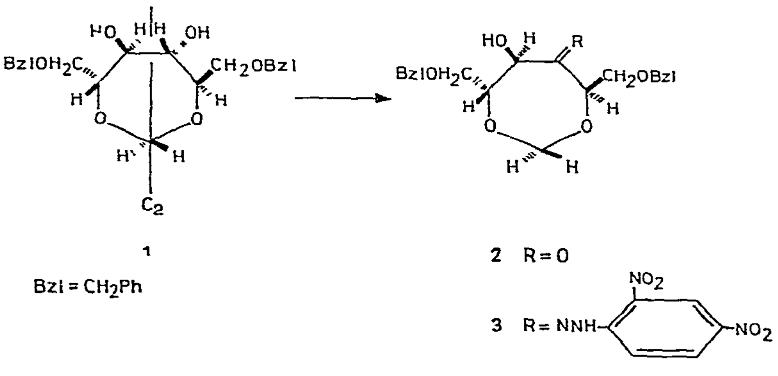
The utility of methyl sulfoxide–acetic anhydride as a convenient reagent for converting "isolated" secondary alcohols into ketones[1] has been well established in the carbohydrate field[2]. In the case of primary alcohol groups in carbohydrate molecules, the yields of aldehydes with this reagent have been substantially less than with other oxidation mixtures containing methyl sulfoxide. Frequently, the oxidations with methyl sulfoxide–acetic anhydride have been accompanied by the formation of acetates and (methylthio)methyl ethers. The present report describes the results obtained on treatment of the *vic*-diol **1** with methyl sulfoxide–acetic anhydride.

1,6-Di-*O*-benzyl-2,5-*O*-methylene-D-mannitol (**1**) was readily prepared from D-mannitol, as described by Gigg and Gigg[3], by way of 1,6-di-*O*-benzoyl-3,4-*O*-benzylidene-2,5-*O*-methylene-D-mannitol[4]. The diol **1** was treated with a 3:2 (*v/v*) mixture of methyl sulfoxide–acetic anhydride for 5.5 h at room temperature, and the reaction mixture was poured into ice–water; the monoketone **2**, 1,6-di-*O*-benzyl-2,5-*O*-methylene-D-*arabino*-hex-3-ulose, was deposited in crystalline form. Processing of



1

Bzl = CH$_2$Ph

2 R = O

3 R = NNH–

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the filtrate in the usual manner (see Experimental section) gave more of compound **2**; the total yield of crystalline **2** isolated was 68% Compound **2** was readily converted into crystalline 1,6-di-*O*-benzyl-2,5-*O*-methylene-D-*arabino*-hex-3-ulose 2,4-dinitrophenylhydrazone (**3**) on treatment with 2,4-dinitrophenylhydrazine in aqueous alcohol containing sulfuric acid

By virtue of its C_2 axis of symmetry, 1,6-di-*O*-benzyl-2,5-*O*-methylene-D-mannitol (**1**) possesses two equivalent hydroxyl groups, and hence only one α-hydroxy ketone would be expected However, it has been reported[5] that epimerization of vicinal, axial substituents may accompany methyl sulfoxide–acetic anhydride oxidations In the present work the possibility of epimerization was examined in the following manner The ketone isolated from the methyl sulfoxide–acetic anhydride oxidation of **1** was treated with sodium borohydride, and the reduced product was hydrogenated over palladium-on-charcoal to remove the benzyl groups *O*-Demethylenation was accomplished by an acid-catalyzed hydrolysis, and the resultant product was treated with acetic anhydride–pyridine; a gas–liquid chromatographic examination revealed the presence of only D-mannitol and D-altritol (D-talitol) hexaacetates, a result which establishes that no epimerization occurred with the oxidation procedure, and hence that the α-hydroxy ketone has the structure 1,6-di-*O*-benzyl-2,5-*O*-methylene-D-*arabino*-hex-3-ulose (**2**) The observed lack of epimerization is chemical evidence for the suggestion[6 7] that the 1,3-dioxepane rings in derivatives of 2,5-*O*-methylene-D-mannitol exist preponderantly in conformations which have all of the substituents equatorial

Of relevance to the selective oxidation of the diol **1** in the present work are some results obtained in an earlier study[8], namely, that the aliphatic α-hydroxy ketones, 3-hydroxy-2-butanone and 2-hydroxycyclohexanone, give only low yields of diketones with methyl sulfoxide–acetic anhydride, although aromatic α-hydroxy ketones are smoothly oxidized in good yield to the diketones, under the same conditions, Bloomfield *et al* [9], however, have reported the oxidation of a four-membered, cyclic acyloin with methyl sulfoxide–acetic anhydride in 75% yield In the carbohydrate field, Wolfrom and Wang[10] have shown that oxidation of 6-*O*-tritylamylose with methyl sulfoxide–acetic anhydride occurs predominantly at C-2, an analogous conclusion has been reported by Bredereck[11] with 6-*O*-tritylcellulose However, when methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was oxidized with the same reagent for 16 h, t l c indicated the presence of seven components[10]*

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*The formation of several components was also observed[6] when *dl*-cyclohexane-*trans*-1,2-diol or *dl*-cyclopentane-*trans*-1,2-diol was treated with methyl sulfoxide–acetic anhydride for 24 and 45 h, respectively. In the former case, five impure fractions were isolated, by column chromatography on silica gel and distillation On the basis of their n m r and mass spectra they were tentatively formulated as being predominantly the mono- and diacetate, mono- and di(methylthio)methyl ether, and monoacetate–mono(methylthio)methyl ether derivatives It is interesting that treatment of the *vic*-diol, 3,4-dihydro-3,4-dihydroxy-9,10-dimethyl-1,2-benzanthracene, with methyl sulfoxide–acetic anhydride gave the diketone, 9,10-dimethyl-1,2-benzanthra-3,4-quinone, in 47% yield[12]

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at $23\pm3°$. I.r. spectra were measured on a Beckman-IR5A spectrophotometer. N.m.r. spectra were recorded at 60 MHz, with tetramethylsilane as the internal standard. T.l.c. was performed with Silica Gel G as the adsorbent; the developed plates were air-dried, sprayed with 5% ethanolic sulfuric acid, and heated at about 150°. G.l.c. was performed on an F and M Model 402 gas chromatograph by using 3% ECNSS-M on acid-washed DMCS-treated Chromosorb W (100–120 mesh) as the stationary phase at an operating temperature of 180°.

*1,6-Di-*O*-benzyl-2,5-*O*-methylene-*D-arabino*-hex-3-ulose* (**2**). — 1,6-Di-*O*-benzyl-2,5-*O*-methylene-D-mannitol[3] (**1**, 1.1 g) in methyl sulfoxide (9 ml) and acetic anhydride (6 ml) was kept for 5.5 h at room temperature. The solution was poured, with vigorous stirring, into ice–water (50 ml); crystals (0.6 g) were deposited, which were removed by filtration. The filtrate was extracted with two 30-ml portions of chloroform, and the chloroform extracts were dried (magnesium sulfate) and evaporated to dryness. When the residual syrup was diluted with ethanol (5 ml) and water (5 ml), more crystals (0.15 g) were deposited. The combined, crystalline material (0.75 g, 68%) was recrystallized twice from ethanol–water to yield compound **2** as lustrous white flakes, m.p. 91.5–93.0°, $[\alpha]_D$ −12.1° (*c* 1.74, chloroform), R_F 0.56 [t.l.c., 19:1 (*v/v*) chloroform–methanol], λ_{max}^{film} 2.9 (OH), 5.83 μm (C=O); n.m.r. data (chloroform-*d*): τ 2.61–2.74 (10-proton multiplet, aromatic protons), 4.95 (2-proton AB quartet, $J_{A,B}$ 13.2 Hz, $\Delta\nu = 3.3$ Hz, benzyl-methylene), 5.43 (2-proton singlet, benzyl-methylene); n.m.r. data (benzene-d_6): τ 2.67–2.94 (10-proton multiplet, aromatic protons), 5.23 (2-proton AB quartet, $J_{A,B}$ 6.3 Hz, $\Delta\nu$ <2Hz, $-OCH_2O-$), 5.61, 5.73 (2-proton singlets, benzyl-methylenes).

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.7; H, 6.5. Found: C, 67.4; H, 6.4.

In other experiments, after treatment of compound **1** with methyl sulfoxide–acetic anhydride for 5.5 h, the reagents were removed by lyophilization. T.l.c. examination [19:1(*v/v*) chloroform–methanol] of the residue revealed the presence of the 3-ketone **2** and two other components having R_F values 0.67 and 0.76. Although compound **2** could again be isolated by crystallization from ethanol–water, the yields were lower (~50%) than that obtained from the original procedure.

*1,6-Di-*O*-benzyl-2,5-*O*-methylene-*D-arabino*-hex-3-ulose 2,4-dinitrophenylhydrazone* (**3**). — A solution of the 3-ketone **2** (0.2 g) in 95% ethanol (5 ml) was treated with a solution (8 ml) of 2,4-dinitrophenylhydrazine [prepared by dissolving 2,4-dinitrophenylhydrazine (7 g) in a mixture of ethanol (145 ml), water (20 ml) and concentrated sulfuric acid (20 ml)]; a precipitate was formed, almost immediately. The mixture was kept for 0.5 h at 0°, and the 2,4-dinitrophenylhydrazone was removed by filtration (162 mg, 55%). Recrystallization from ethanol–water gave pure **3**, m.p. 142.5–143.5°, $[\alpha]_D$ +202.5° (*c* 1.46, chloroform); n.m.r. data (chloroform-*d*): τ 1.88 (1-proton quartet, J_{meta} 2 8 Hz, J_{ortho} 9 6 Hz, hydrazone-aryl H-5), 2 38 (1-proton doublet, J_{ortho} 9 6 Hz, hydrazone-aryl H-6), 2 73–2 83 (11 protons, benzyl-aryl protons and hydrazone-aryl H-3), 5 46 (4-proton singlet, benzyl-methylenes)

Anal Calc for $C_{27}H_{28}N_4O_9$ C, 58 7, H, 5 1, N, 10 1 Found C, 58 4, H, 5 2, N, 9 9

Proof of absence of inversion of configuration on oxidation of compound **1** — A solution of the crystalline oxidized product (0 5 g) in ethanol (30 ml) was added dropwise to a stirred solution of sodium borohydride in 50% aqueous ethanol (50 ml) at room temperature After 12 h, the reaction mixture was treated with Amberlite IR-120 resin (H^+) The resin was removed, and the solution was concentrated to dryness under diminished pressure, boric acid was removed by repeated evaporation of methanol from the product The syrupy residue gave one spot by t l c in 19 1 (*v/v*) chloroform–methanol A solution of this material (0 43 g) in ethanol (100 ml) containing 10% palladium-on-charcoal catalyst (2 g) was subjected to a hydrogen pressure of 40 lb in $^{-2}$ gauge for 16 h at room temperature The suspension was filtered free of catalyst, and the filtrate was concentrated to dryness, only one spot was revealed by t l c in ethyl acetate A solution of the syrup in ethanol (30 ml) containing M sulfuric acid (2 ml) was kept for 30 h at room temperature, and then passed through a column of Duolite A-4 resin (OH^-) The solution was concentrated, and the syrupy residue was dried over phosphorus pentaoxide in a vacuum desiccator and then treated with acetic anhydride (3 ml) and pyridine (5 ml) for 12 h The reagents were removed by evaporation, and the residue was repeatedly dissolved in toluene and reconcentrated The product was examined by g l c and compared with authentic samples of D-mannitol, D-altritol, and D-iditol hexaacetates, only the presence of an approximately 1 1 mixture of D-mannitol and D-altritol hexaacetates was indicated

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