437. *Sugar Nitrates. Part III.* Mannose Derivatives.*

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Methyl 4 : 6-*O*-ethylidene-α-D-mannoside 2 : 3-dinitrate reacts with sodium methoxide, sodium iodide, and sodium nitrite in the same way as the corresponding D-glucose derivative; the ester group on $C_{(2)}$ is converted into the alcohol more readily than that on $C_{(3)}$.

The 2 : 3-ditoluene-*p*-sulphonate is more stable towards sodium methoxide than the D-glucose analogue, but the 3-toluene-*p*-sulphonate may be obtained by treatment of the ditoluene-*p*-sulphonate with this reagent.

As in the analogous glucose compound the nitrate group on $C_{(2)}$ of methyl 4 : 6-*O*-ethylidene-α-D-mannoside 2 : 3-dinitrate [1] is preferentially removed (yielding the alcohol) by reaction with sodium methoxide in cold methanol–chloroform, or by sodium iodide in acetone at 100°, or, best, by sodium nitrite in boiling aqueous ethanol. The action of sodium methoxide on the D-glucoside 2 : 3-dinitrate in which the nitrate groups are *trans* and equatorial in the preferred conformation yields the parent D-glucoside and the 2 : 3-anhydro-α-D-alloside. In the D-mannoside derivative the nitrate groups and their attached carbon atoms cannot become coplanar in any conformation. Newth [2] has pointed out, however, that coplanarity, favourable for an intramolecular S_N2 process resulting in epoxide formation, is possible for esters of methyl 4 : 6-*O*-benzylidene-α-D-glucoside. This accounts for the formation of an anhydro-compound from the D-glucose dinitrate and for the absence of such an epoxide during the present work on D-mannose.

Methyl 4 : 6-*O*-ethylidene-α-D-mannoside 2 : 3-ditoluene-*p*-sulphonate is converted by sodium methoxide into the 3-toluene-*p*-sulphonate rather more slowly than is the glucose derivative.

The products obtained are similarly substituted whether the starting compounds are glucose derivatives in which substituents on both $C_{(2)}$ and $C_{(3)}$ are equatorial or mannose where the one on $C_{(2)}$ is axial and the other equatorial. The enhanced reactivity of the group on $C_{(2)}$ does not, therefore, appear to arise from purely steric considerations such as greater accessibility. Electronic effects transmitted from the neighbouring methoxyl group or ring oxygen may be of importance.[3]

The characterization of the new compounds described has been achieved by establishing their identity with those obtained simultaneously but independently by Aspinall and Zweifel.[4]

EXPERIMENTAL

Chloroform solutions were dried over sodium sulphate before being evaporated under reduced pressure. The light petroleum used had b. p. 60—80°.

* Part II, *J.*, 1955, 3660.

[1] Honeyman and Morgan, *J.*, 1954, 744.
[2] Newth, *J.*, 1956, 441.
[3] Sugihara, *Adv. Carbohydrate Chem.*, 1953, **8**, 1.
[4] Aspinall and Zweifel, preceding paper.

Chromatographic separations were carried out with columns of activated alumina, Type H, 100/200S mesh, supplied by Messrs. Peter Spence and Sons Ltd.

Alkaline Hydrolysis of Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 2 : 3-*Dinitrate*.—After being kept for 6 weeks at 0° a solution of methyl 4 : 6-*O*-ethylidene-α-D-mannoside 2 : 3-dinitrate [1] (2 g.) in chloroform (24 ml.) and methanol (13 ml.) containing sodium (0·74 g.) was neutralized with glacial acetic acid. The residue obtained by evaporating the solution was dissolved in benzene, filtered, and chromatographed. Elution with benzene yielded *methyl* 4 : 6-O-*ethylidene*-α-D-*mannoside* 2-*nitrate* (6%), m. p. 125° after several recrystallizations from ether–light petroleum (Found : C, 41·0; H, 5·8. $C_9H_{15}O_8N$ requires C, 40·8; H, 5·7%). Further elution with chloroform removed methyl 4 : 6-*O*-ethylidene-α-D-mannoside 3-nitrate (29%), m. p. 165° (unaltered after admixture with Aspinall and Zweifel's preparation, m. p. 166°), $[\alpha]_D^{19}$ +51·3° (*c* 0·7 in $CHCl_3$), after recrystallization from ether–light petroleum (Found : C, 40·6; H, 5·7%). A final extraction of the column with methanol gave methyl 4 : 6-*O*-ethylidene-α-D-mannoside (20%), m. p. 115°, undepressed after admixture with authentic compound.

A solution similar to the above was badly coloured after 10 minutes' boiling. The products isolated were methyl 4 : 6-*O*-ethylidene-α-D-mannoside (15%) and its 3-nitrate (4%).

Alkaline Hydrolysis of Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 2 : 3-*Ditoluene*-p-*sulphonate*.—A solution of this 2 : 3-ditoluene-*p*-sulphonate [1] (1·5 g.) in chloroform (18 ml.) and methanol (5·6 ml.) containing sodium (0·33 g.) was kept at 0° for 6 weeks. Neutralization with glacial acetic acid followed by evaporation gave a solid residue which was chromatographed in benzene. Elution with benzene gave unchanged starting compound (41%); further elution with chloroform yielded a solid which, after recrystallization from ether–light petroleum, was methyl 4 : 6-*O*-ethylidene-α-D-mannoside 3-toluene-*p*-sulphonate (24%), m. p. 122—123° raised to 125° by admixture with Aspinall and Zweifel's compound of m. p. 129° (Found : C, 51·3; H, 5·8. Calc. for $C_{16}H_{22}O_8S$: C, 51·3; H, 5·9%).

Preparation of Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 3-*Nitrate and its* 2-*Toluene*-p-*sulphonate*.—(1) The 2 : 3-dinitrate (3 g.) and sodium iodide (6 g.) in acetone (25 ml.) were kept at 100° in a sealed tube for a day. The chloroform extract of the evaporated solution was washed with aqueous sodium thiosulphate and then chromatographed. Elution with chloroform removed methyl 4 : 6-*O*-ethylidene-α-D-mannoside 3-nitrate (34%), m. p. 165—166° after recrystallization. Further extraction of the column with methanol gave methyl 4 : 6-*O*-ethylidene-α-D-mannoside (23%).

Under these conditions the corresponding 2 : 3-ditoluene-*p*-sulphonate was recovered unchanged (90%).

(2) A solution of the 2 : 3-dinitrate (2·8 g.) and sodium nitrite (1·8 g.) in ethanol (20 ml.) and water (5 ml.) was boiled under reflux for 20 hr. before the solvents were evaporated. The chloroform extract of the residue was evaporated to a syrup which was dissolved in benzene and chromatographed. Elution with benzene yielded starting compound (16%); further elution with chloroform afforded the 3-nitrate (58%).

The 3-nitrate (0·48 g.), toluene-*p*-sulphonyl chloride (0·5 g.), and pyridine (4 ml.) were mixed at 0° and after 4 days at room temperature poured into water. Recrystallization of the resulting solid from ethanol–light petroleum led to methyl 4 : 6-*O*-ethylidene-α-D-mannoside 3-nitrate 2-toluene-*p*-sulphonate (83%), m. p. 121—122° (undepressed after admixture with Aspinall and Zweifel's compound, m. p. 123—124°), $[\alpha]_D^{21}$ −17·0° (*c* 0·2 in $CHCl_3$) (Found : C, 46·0; H, 5·2. Calc. for $C_{16}H_{21}O_{10}NS$: C, 45·8; H, 5·0%).

Preparation of Methyl 2-O-*Methyl*-α-D-*mannoside* 3-*Nitrate*.—Silver oxide (3 g.) was added during 5 hr. to methyl iodide (20 ml.) boiling under reflux and containing methyl 4 : 6-*O*-ethylidene-α-D-mannoside 3-nitrate (1 g.). After being boiled for 19 hr. more the mixture was filtered and evaporated. The white solid obtained by extraction of the residue with chloroform was, after recrystallization from light petroleum, methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside 3-nitrate (70%), m. p. 101—102° (unchanged on admixture with Aspinall and Zweifel's compound, m. p. 100—101°), $[\alpha]_D^{21}$ +43·8° (*c* 0·9 in $CHCl_3$) (Found : C, 43·2; H, 6·0. Calc. for $C_{10}H_{17}O_8N$: C, 43·0; H, 6·1%).

A suspension of this compound (0·85 g.) in acetone (10 ml.) and water (5 ml.) containing sulphuric acid (0·55 ml.) was boiled under reflux for 13 hr. After neutralization with barium hydroxide the mixture was evaporated and the residue extracted with chloroform. Evaporation left a syrup which was chromatographed in benzene solution. Elution with benzene and

with chloroform removed impurities and elution with methanol gave ***methyl*** 2-O-***methyl***-α-D-***mannoside*** 3-***nitrate*** (51%), m. p. 98°, $[\alpha]_D^{19}$ +43·9° (*c* 1·0 in $CHCl_3$) (Found : C, 38·0; H, 6·0. $C_8H_{15}O_8N$ requires C, 38·0; H, 6·0%).

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