The Preparation of Some Glucose Nitrates.

By D. O'Meara and D. M. Shepherd.

[Reprint Order No. 6675.]

The removal of the ethylidene group from methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2 : 3-dinitrate and 3-nitrate by acid hydrolysis is described. Methyl β-D-glucopyranoside 2 : 3-dinitrate prepared by this method had a higher melting point than, but in all other respects was identical with, specimens of the 2 : 3-dinitrate prepared by an earlier method. Methyl β-D-glucopyranoside 3-nitrate was obtained as a monohydrate. The two known forms of methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside were obtained and shown to consist of the anhydrous compound and the monohydrate respectively. The preparation of several new glucose nitrate derivatives is described.

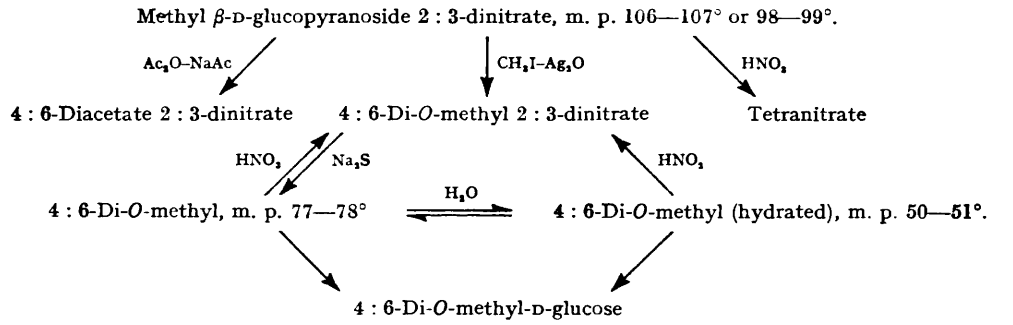
THREE methods have been described for the removal of ethylidene substituents from sugars : (*a*) acid hydrolysis (Ohle and Spencker, *Ber.*, 1928, **61**, 2387; Dewar and Fort, *J.*, 1944, 492); (*b*) acetolysis (Bell and Synge, *J.*, 1937, 1711); (*c*) nitration by fuming nitric acid in chloroform (Dewar and Fort, *J.*, 1944, 496). Method (*b*) suffers from the disadvantage that the ethylidene group is replaced by acetyl and acetoxyethyl substituents which must subsequently be removed by selective alkaline hydrolysis, while with method (*c*) two nitrate groups are introduced in place of the ethylidene group. Although method (*a*) removes the ethylidene group leaving two free hydroxyl groups, it has so far been found to be of limited applicability, since the presence of certain other substituents, particularly nitrate groups, renders the ethylidene group more resistant to hydrolysis (Bell and Synge, and Dewar and Fort, *locc. cit.*). Since we required considerable amounts of methyl β-D-glucopyranoside 2 : 3-dinitrate and 3-nitrate, which are normally prepared from the corresponding ethylidene derivatives in two stages by method (*b*) (Bell and Synge, *loc. cit.*), we re-investigated the direct acid hydrolysis of methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2 : 3-dinitrate and 3-nitrate.

The first stage, condensation of acetaldehyde with methyl β-D-glucopyranoside to give methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside (Helferich and Appel, *Ber.*, 1931, **64**, 1841; Dewar and Fort, *J.*, 1944, 492), has hitherto been accomplished by treating paraldehyde with the glucoside in the presence of concentrated sulphuric acid, but the yields are rather variable owing to a side reaction which gives methyl 4 : 6-*O*-ethylidene-2 : 3-*O*-oxidodiethylidene-β-D-glucopyranoside. The required derivative has been obtained uncontaminated and in good yield by using acetaldehyde dimethyl acetal instead of paraldehyde.

When methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2 : 3-dinitrate was refluxed with sulphuric acid in aqueous acetone, it was found that >0·1N-acid had no effect, while concentrations greater than 1·0N not only removed the ethylidene group but tended to split the methyl glucoside group as well. However, a crystalline compound was obtained in good yield when 0·67N-sulphuric acid was used. While the analysis and optical rotation of the product agreed with those of the expected methyl β-D-glucopyranoside 2 : 3-dinitrate, the melting point was 106—107° compared with 96—98° reported by Bell and Synge (*loc. cit.*). The 2 : 3-dinitrate prepared in this laboratory by Bell and Synge's method melted at 98—99° alone, and at 99—101° when mixed with our product. Attempts at interconversion of the two compounds were unsuccessful.

A detailed comparison of the reactions (see scheme) of our product and Bell and Synge's compound indicated that chemically the two substances were identical. Methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside exists in interconvertible anhydrous (m. p. 77—78°) and hydrated (m. p. 50—52°) forms. Bell and Synge (*loc. cit.*) obtained the latter, and Dennison and McGilvray (*J.*, 1951, 1616) the former. Reeves (*J. Amer. Chem. Soc.*, 1949, **71**, 215) obtained forms of m. p. 52—55° and 67—68°, but his substances possibly consisted of partially hydrated material. All our specimens were readily re-nitrated to the 2 : 3-dinitrate, and on acid hydrolysis yielded the same parent sugar as shown by paper chromatography.

Methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 3-nitrate was obtained from the 2 : 3-dinitrate by sodium iodide in pentan-2-one; the development of high pressures which occurs when acetone is used as solvent (Dewar and Fort, *loc. cit.*; Ansell and Honeyman, *J.*, 1952, 2778) was thus avoided.



The ethylidene group was removed from methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 3-nitrate by boiling 0·67N-sulphuric acid, the product being a monohydrate of methyl β-D-glucopyranoside 3-nitrate which gave a triacetate. This monohydrate was identical with the 3-nitrate described by Dewar and Fort (*loc. cit.*).

Methyl β-D-glucopyranoside 2-acetate 3 : 4 : 6-trinitrate was readily obtained by the nitration of methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2-acetate 3-nitrate with fuming nitric acid in chloroform : it is polymorphic, though the unstable form was obtained only in the first experiment.

The trinitrate was preferentially de-acetylated by dilute alkali, to give methyl β-D-glucopyranoside 3 : 4 : 6-trinitrate.

3-*O*-Methyl-D-glucose tetranitrate was prepared from 3-*O*-methyl-D-glucose by fuming nitric–sulphuric acid; the high specific rotation suggests that the product is the α-anomer.

Experimental

Light petroleum had b. p. 60—80°.

Methyl 4 : 6-O-*Ethylidene*-β-D-*glucopyranoside*.—Concentrated sulphuric acid (2·5 ml.) was added dropwise, with stirring, to a suspension of methyl β-D-glucopyranoside (58 g.) in acetaldehyde dimethyl acetal (250 ml.). After being shaken for 48 hr., the mixture was filtered, and the solid residue washed with light petroleum and recrystallized twice from ethanol, giving needles (38 g.), m. p. 188—189°, $[\alpha]_D^{20}$ −79·4° (*c*, 1·9 in H_2O). Helferich and Appel (*loc. cit.*) give m. p. 189—190°, $[\alpha]_D^{22}$ −79·1°. No m. p. depression was observed on admixture with material prepared by Helferich and Appel's method.

Methyl 4 : 6-O-*Ethylidene*-β-D-*glucopyranoside* 2 : 3-*Dinitrate* (cf. Honeyman and Morgan, *Chem. and Ind.*, 1953, 1035).—To a suspension of the ethylidene derivative (10 g.) in acetic anhydride (25 ml.) at 0° was added an ice-cold solution of fuming nitric acid (20 ml.) in acetic anhydride (50 ml.). After being stirred for 5 min. at 0°, the mixture was poured into ice-water. The solid which separated crystallized from ethanol as plates (11 g.), m. p. 88—89°, alone or mixed with methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2 : 3-dinitrate prepared as described by Bell and Synge (*loc. cit.*).

Hydrolysis. To a solution of the dinitrate (12 g.) in acetone (96 ml.) were added water (48 ml.) and concentrated sulphuric acid (2·4 ml.). The solution was refluxed for 7 hr., cooled, and passed down a column of the anion-exchange resin Amberlite IR-4B (OH). When the neutral filtrate was distilled to remove all the acetone, a small amount of oil was precipitated. Alcohol was then added to redissolve the oil and the distillation continued until crystals separated. After cooling and filtration, these crystals (2·5 g.) were identified by mixed m. p. as unchanged ethylidene derivative. The filtrate was then evaporated to dryness and the residual syrup dissolved in chloroform. When dried and distilled, the chloroform extract yielded a syrup which crystallized on addition of light petroleum. Recrystallization of the product from chloroform–light petroleum gave needles (4·5 g.), m. p. 106—107°, $[\alpha]_D^{22}$ −20·8° (*c*, 1·8 in $CHCl_3$ containing 5% of acetone) (Found : C, 30·1; H, 4·6; N, 9·9; OMe, 11·3. Calc. for $C_7H_{12}O_{10}N_2$: C, 29·6; H, 4·2; N, 9·9; OMe, 10·9%). Bell and Synge (*loc. cit.*) record m. p. 96—98°, $[\alpha]_D^{20}$ −20·5°. A mixture of the above product with methyl β-D-glucopyranoside 2 : 3-dinitrate, m. p. 98—99°, prepared in this laboratory by Bell and Synge's method, had m. p. 99—101°.

Nitration of Methyl β-D-*Glucopyranoside Dinitrate, m. p.* 106—107°.—The dinitrate, on nitration by Honeyman and Morgan's method (*loc. cit.*), gave methyl β-D-glucopyranoside tetranitrate, m. p. and mixed m. p. 115—116°.

Acetylation of Methyl β-D-*Glucopyranoside Dinitrate, m. p.* 106—107°.—The dinitrate (2 g.) was heated for 2 hr. at 100° with acetic anhydride (10 ml.) and sodium acetate (1·6 g.). The product, after isolation in the usual way, crystallized from ethanol as stout needles (1 g.), m. p. 139—140°, $[\alpha]_D^{20}$ −4·7° (*c*, 3·8 in $CHCl_3$) (Found : C, 36·1; H, 4·6; N, 7·1. Calc. for $C_{11}H_{16}O_{12}N_2$: C, 35·9; H, 4·4; N, 7·6%), and gave no m. p. depression with methyl 4 : 6-di-*O*-acetyl-β-D-glucopyranoside 2 : 3-dinitrate prepared from methyl β-D-glucopyranoside 2 : 3-dinitrate, m. p. 98—99°, by the same method.

Methylation of Methyl β-D-*Glucopyranoside Dinitrate, m. p.* 106—107°.—The dinitrate (6·7 g.) was refluxed with methyl iodide (27 ml.) and silver oxide (27 g.) for 4 hr., some dry chloroform being added to assist dissolution. After isolation by the usual procedure the syrup crystallized and, when recrystallized from alcohol, had m. p. 52—53°, $[\alpha]_D^{22}$ −11·5° (*c*, 1·1 in $CHCl_3$) (Found : C, 34·6; H, 5·5; N, 9·8; OMe, 28·6. Calc. for $C_9H_{16}O_{10}N_2$: C, 34·6; H, 5·1; N, 9·0; OMe, 29·8%), and gave no m. p. depression with methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside 2 : 3-dinitrate prepared by methylation of methyl β-D-glucopyranoside 2 : 3-dinitrate under identical conditions.

Methyl 4 : 6-*Di*-O-*methyl*-β-D-*glucopyranoside*.—Methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside 2 : 3-dinitrate was denitrated as described by Bell and Synge (*loc. cit.*). Recrystallization of the product from ether gave long colourless needles, m. p. 77—78°, $[\alpha]_D^{18}$ −33·7° (*c*, 0·41 in $CHCl_3$) (Found : C, 48·9; H, 8·3; OMe, 40·8. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·1; OMe, 41·8%).

When this compound, m. p. 77—78°, was left for 48 hr. in air, the m. p. fell to 50—52°. This *hydrate* had $[\alpha]_D^{18}$ −30·5° (*c*, 0·43 in $CHCl_3$) (Found : C, 45·6; H, 8·4; OMe, 38·1; loss in a vacuum over $CaCl_2$, 7·4. $C_9H_{18}O_6,H_2O$ requires C, 45·0; H, 8·3; OMe, 38·8; H_2O, 7·5%).

On nitration the hydrate, like the anhydrous compound, was converted into methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside 2 : 3-dinitrate, m. p. and mixed m. p. 52—53°.

Hydrolysis and Proof of Identity of Methyl 4 : 6-*Di*-O-*methyl*-β-D-*glucopyranoside from Various*

Sources.—Samples (50 mg.) of the hydrated and unhydrated forms of methyl 4 : 6-di-*O*-methyl-β-D-glucopyranoside derived from both the high- and the low-melting form of methyl β-D-glucopyranoside 2 : 3-dinitrate by the reactions shown in the scheme (p. 4233), were hydrolyzed at 90—95° in centrifuge tubes with N-hydrochloric acid (2 ml.) for 1 hr. Water (5 ml.) was added to each tube and the excess of acid neutralized with silver carbonate. After centrifuging, the supernatant liquids, suitably diluted, were subjected to paper chromatography. When sprayed with aniline oxalate the chromatograms showed one spot from each sample, having R_F in butanol–acetic acid–water (4 : 1 : 5 by vol.) 0·53, and in phenol–water (4 : 1 by wt.) 0·82.

Methyl 4 : 6-O-*Ethylidene*-β-D-*glucopyranoside* 3-*Nitrate.*—Methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2 : 3-dinitrate (10 g.), sodium iodide (20 g.), and pentan-2-one (70 ml.) were heated for 6 hr. on a boiling-water bath. The 3-nitrate, isolated as described by Dewar and Fort (*loc. cit.*), formed needles (4·1 g.), m. p. 147—148°, $[\alpha]_D^{19}$ −30·6° (*c*, 1·69 in $CHCl_3$).

Hydrolysis. To a solution of this nitrate (6·2 g.) in acetone (50 ml.) were added water (25 ml.) and concentrated sulphuric acid (1·25 ml.). After 3 hours' refluxing the solution was neutralized with Amberlite IR-4B(OH), and the acetone removed by vacuum-distillation. Crystals separated from the aqueous residue which was then cooled and filtered. The crystals (1·8 g.) were unchanged ethylidene derivative (mixed m. p.). Evaporation of the filtrate gave a syrup which crystallized and, when recrystallized once from water and once from alcohol–ether–light petroleum, yielded prisms of a *hydrate*, m. p. 102—104° (soften at 95°), $[\alpha]_D^{19}$ −16·1° (*c*, 0·53 in EtOH) (Found, for material dried over $CaCl_2$: C, 33·2; H, 5·8; N, 5·7. $C_7H_{13}O_8N,H_2O$ requires C, 32·8; H, 5·8; N, 5·5%). The compound gave no m. p. depression with methyl β-D-glucopyranoside 3-nitrate prepared by Dewar and Fort (*loc. cit.*). When dried in a vacuum over P_2O_5 at 40°, the monohydrate slowly lost water (loss, 6·8. $C_7H_{13}O_8N,H_2O$ requires 7·0%) to give the anhydrous *compound* (Found : C, 35·1 ; H, 6·0. $C_7H_{13}O_8N$ requires C, 35·1 ; H, 5·4%).

Methyl β-D-*Glucopyranoside* 2 : 4 : 6-*Triacetate* 3-*Nitrate.*—Methyl β-D-glucopyranoside 3-nitrate (2·2 g.) was heated for 2 hr. at 100° with acetic anhydride (11 ml.) and sodium acetate (1·8 g.). After isolation in the usual way the *triacetate* 3-*nitrate* crystallized from ethanol as needles, m. p. 61—62°, $[\alpha]_D^{20}$ −20° (*c*, 1·35 in $CHCl_3$) (Found : C, 42·8; H, 5·2; N, 3·9. $C_{13}H_{19}O_{11}N$ requires C, 42·7; H, 5·2; N, 3·9%).

Methyl β-D-*Glucopyranoside* 2-*Acetate* 3 : 4 : 6-*Trinitrate.*—Methyl 4 : 6-*O*-ethylidene-β-D-glucopyranoside 2-acetate 3-nitrate (4 g.) (Dewar and Fort, *loc. cit.*) was nitrated with fuming nitric acid in chloroform, the product being isolated in the usual way. The acetate *trinitrate* crystallized from ethanol as needles, m. p. 57—58°, $[\alpha]_D^{19}$ −7·5° (*c*, 0·75 in $CHCl_3$) (Found : C, 29·2; H, 3·7; N, 10·8. $C_9H_{13}O_{13}N_3$ requires C, 29·1; H, 3·5; N, 11·3%).

In all later preparations the product had m. p. 66—67°, $[\alpha]_D^{20}$ −8·4° (*c*, 2·486 in $CHCl_3$) (Found : C, 29·8; H, 3·6; N, 11·5%). A mixture of the two forms had m. p. 66—67°.

Methyl β-D-*Glucopyranoside* 3 : 4 : 6-*Trinitrate.*—The above product (2·2 g.) was dissolved in chloroform (25 ml.) and anhydrous methanol (25 ml.) containing sodium (0·03 g.). After 2 hr. glacial acetic acid (0·08 ml.) was added, and the solvents were distilled off, leaving a syrup from which a solid (0·5 g.) separated on addition of a little chloroform. *Methyl* β-D-*glucopyranoside* 3 : 4 : 6-*trinitrate* crystallized from chloroform as needles, m. p. 117—118°, $[\alpha]_D^{19}$ +14° (*c*, 3·1 in $CHCl_3$) (Found : C, 25·2; H, 3·5; N, 11·4. $C_7H_{11}O_{12}N_3$ requires C, 25·5; H, 3·3; N, 12·7%).

3-O-*Methyl*-D-*glucose Tetranitrate.*—3-*O*-Methyl-D-glucose (9 g.) (Levene and Meyer, *J. Biol. Chem.*, 1922, **54**, 805) was dissolved in fuming nitric acid (90 ml.) at 0°; and concentrated sulphuric acid (180 ml.) also at 0° was added during 20 min. with stirring and ice-cooling. After 1 hr. chloroform (150 ml.) was added, and the mass stirred vigorously. The chloroform layer was separated and the product isolated in the usual way as a syrup which soon solidified. 3-O-*Methyl*-D-*glucose tetranitrate* crystallized from methanol as prisms, m. p. 99—100°, $[\alpha]_D^{23}$ +140·3° (*c*, 2·1 in MeOH) (Found : C, 22·6; H, 2·7; N, 15·1. $C_7H_{10}O_{14}N_4$ requires C, 22·5; H, 2·7; N, 15·0%).

We are grateful to Dr. E. S. Steele for providing samples for mixed melting points. One of us (D. O'M.) is indebted to the Wellcome Research Foundation for a grant.

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS,
QUEEN'S COLLEGE, DUNDEE. [*Received, August 8th,* 1955.]