436. *Selective Esterification of Equatorial Hydroxyl Groups in the Synthesis of Some Methyl Ethers of* D-*Mannose.*

By G. O. Aspinall and G. Zweifel.

Methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A) and 1 : 6-anhydro-β-D-mannopyranose (B) (and its 4-methyl ether), compounds for which only one chair conformation is possible, undergo selective esterification at their equatorial hydroxyl groups. By employing these reactions, 3-*O*- and 3 : 4-di-*O*-methyl-D-mannose have been synthesised and a new synthesis of 2-*O*-methyl-D-mannose has been achieved.

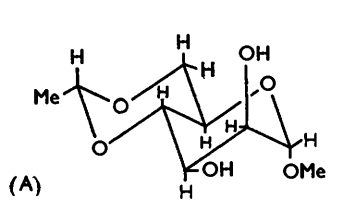
By conventional methods, syntheses of partially methylated derivatives of D-mannose [1] have been carried out in which the hydroxyl groups in the 4 and 6, 2 and 3, and the 6 positions have been blocked. In only two cases, namely, in the syntheses of 2-*O*- [2] and 3 : 4 : 6-tri-*O*- [3] methyl-D-mannose, has it been possible to differentiate between the hydroxyl groups at $C_{(2)}$ and $C_{(3)}$. It is, however, well established that in *cyclo*hexane systems [4] equatorial secondary hydroxyl groups are more readily esterified by derivatives of carboxylic acids than are axial hydroxyl groups. We have now shown that similar preferential reactivity obtains with some sugar derivatives, of whose most stable conformations there is little doubt. Starting with methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A) and 1 : 6-anhydro-β-D-mannopyranose (B) (and its 4-methyl ether), in which the D-mannopyranose rings are held in the C 1 and the 1 C conformation,[5] respectively, and by employing these selective reactions, 2- and 3-mono-*O*-, and 3 : 4-di-*O*-methyl-D-mannose have been synthesised.

Methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A) [6] reacts with 1 mol. of toluene-*p*-sulphonyl chloride to give the 3-toluene-*p*-sulphonate (I) in good yield; the 2-toluene-*p*-sulphonate (VIII) could not be detected. Methylation of the 3-toluene-*p*-sulphonate (I) followed by removal of the ester group with sodium amalgam gave methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside (III), hydrolysed to 2-*O*-methyl-α-D-mannose (IV). This sugar and its phenylhydrazone had similar physical constants to those reported by Pacsu and Trister.[2] The absence of a methoxyl group at $C_{(3)}$ was indicated as the derived syrupy mixture of methyl pyranosides consumed 1 mol. of periodate; the presence of methoxyl groups in positions other than 2 and 3 was precluded by the mode of synthesis.

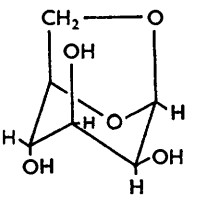
[1] For a review see Aspinall, *Adv. Carbohydrate Chem.*, 1953, **8**, 217.
[2] Pacsu and Trister, *J. Amer. Chem. Soc.*, 1941, **63**, 925.
[3] Bott, Haworth, and Hirst, *J.*, 1930, 1395.
[4] Barton, *J.*, 1953, 1027; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[5] Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 215.
[6] Honeyman and Morgan, *J.*, 1954, 744.

It is of interest to compare the selective tosylation of methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A) with that of methyl 4 : 6-*O*-benzylidene-α-D-glucoside.[7] The latter compound, in which the hydroxyl groups at $C_{(2)}$ and $C_{(3)}$ are both equatorial, reacts preferentially with toluene-*p*-sulphonyl chloride at position 2. Whatever explanation, steric or electronic, may be advanced for this selective reactivity, it is clear that the preferential reactivity of the equatorial 3-hydroxyl group in the D-mannose derivative can be explained on stereochemical grounds.

In the synthesis of 3-*O*-methyl-D-mannose (X), nitrate ester formation was used for the selective blocking of the 3-hydroxyl group. Selective esterification was not so marked in this case as it was necessary to use a large excess of nitrating reagent, but it was possible to modify the conditions used by Honeyman and Morgan [6] in the preparation of methyl 4 : 6-*O*-ethylidene-α-D-mannoside 2 : 3-dinitrate so that a reasonable quantity of the 3-nitrate (V) could be isolated; no 2-nitrate was detected. The structure of the 3-nitrate was proved by methylation followed by reductive removal of the nitrate ester to give methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside (III). Tosylation of the 3-nitrate



(A)



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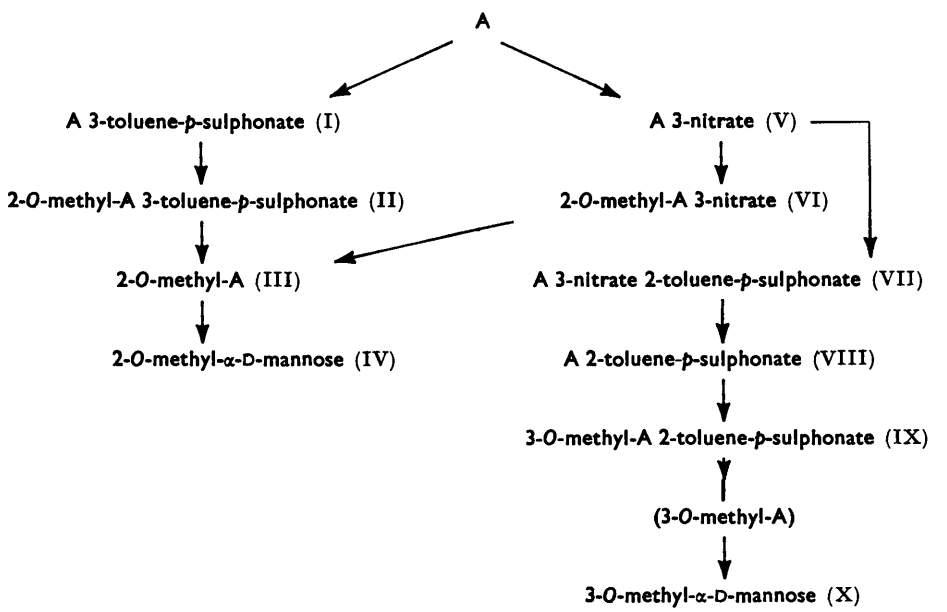


("A" denotes methyl 4 : 6-*O*-ethylidene-α-D-mannoside)

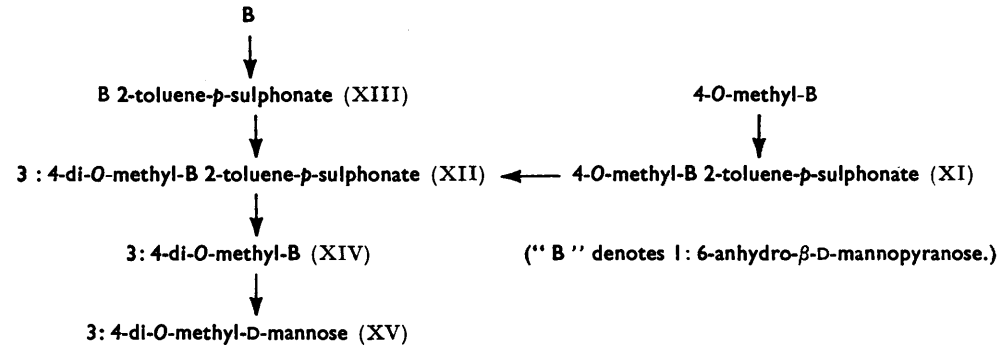
(V) followed by reductive denitration and methylation gave methyl 4 : 6-*O*-ethylidene-3-*O*-methyl-α-D-mannoside 2-toluene-*p*-sulphonate (IX). The axial toluene-*p*-sulphonate grouping in this compound was very resistant to reductive cleavage with lithium aluminium hydride (reaction was incomplete after 20 hr. in refluxing tetrahydrofuran), but the grouping was removed smoothly with sodium amalgam. Bollinger and Ulrich [8] have reported similar difficulties in the removal of the toluene-*p*-sulphonate group from

[7] Robertson and Griffith, *J.*, 1935, 1193; Bollinger and Prins, *Helv. Chim. Acta*, 1945, **28**, 465.
[8] Bollinger and Ulrich, *Helv. Chim. Acta*, 1952, **35**, 93.

methyl 4 : 6-*O*-benzylidene-3-*O*-methyl-α-D-altroside 2-toluene-*p*-sulphonate with lithium aluminium hydride; here also the ester grouping is axial. Hydrolysis of the syrupy product afforded crystalline 3-*O*-methyl-α-D-mannose (X). The structure of the sugar was confirmed by its conversion into 3-*O*-methyl-D-glucosazone and by the fact that the derived syrupy mixture of methyl pyranosides did not react with periodate.

Honeyman and Stening [9] have also prepared the 3-toluene-*p*-sulphonate (I) and the 3-nitrate (V) (but by different methods), and the 3-nitrate 2-methyl ether (VI) and the 3-nitrate 2-toluene-*p*-sulphonate (VII) of methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A). We are grateful to Dr. J. Honeyman for communicating to us the results of his investigations before publication and for supplying samples of these compounds for comparison.

The synthesis of 3 : 4-di-*O*-methyl-D-mannose depended on the preferential reactivity of the 2-hydroxyl group in 1 : 6-anhydro-β-D-mannopyranose (B) and in its 4-methyl ether. Reeves [10] has shown by complex formation with cuprammonium that despite considerable non-bonded interactions (the axial 3-hydroxyl group lies in 1 : 3-relationship with the 1 : 6-anhydro-ring) both these compounds exist in the chair (1 C) rather than in the boat (3 B) conformation. Our observations agree with this result as both the anhydro-sugar (B) and its 4-methyl ether react with 1 mol. of toluene-*p*-sulphonyl chloride to give the equatorial 2-toluene-*p*-sulphonate (XIII and XI, respectively) in good yield. Both compounds (XIII and XI) yielded 1 : 6-anhydro-3 : 4-di-*O*-methyl-β-D-mannopyranose (XII) on complete methylation. It is noteworthy that under certain conditions the 4-methyl ether (XI) may be isolated during methylation of 1 : 6-anhydro-β-D-mannopyranose 2-toluene-*p*-sulphonate (XIII). An examination of models shows clearly that the 3-hydroxyl group is considerably more hindered than the axial 4-hydroxyl group which lies below the plane of the ring, and is in 1 : 3-relationship only with the axial hydrogen atom. It would be expected, therefore, that the 4- would be more reactive than the 3-hydroxyl group. Treatment of 1 : 6-anhydro-3 : 4-di-*O*-methyl-β-D-mannopyranose 2-toluene-*p*-sulphonate with sodium amalgam readily gave 1 : 6-anhydro-3 : 4-di-*O*-methyl-β-D-mannopyranose (XIV), hydrolysis of which afforded 3 : 4-di-*O*-methyl-D-mannose (XV). The sugar, isolated as the monohydrate, was identical with a sample previously isolated [11] and on oxidation yielded the known 3 : 4-di-*O*-methyl-D-mannonolactone.



These experiments show clearly that marked differences exist between the reactivities of equatorial and axial hydroxyl groups in methyl 4 : 6-*O*-ethylidene-α-D-mannoside (A) and 1 : 6-anhydro-4-*O*-methyl-β-D-mannopyranose so that the equatorial hydroxyl groups may be selectively esterfied. A similar result was found with 1 : 6-anhydro-β-D-mannopyranose (B), although in this case analogy with certain disubstituted *cyclo*hexane derivatives [12] would suggest that the equatorial 2-hydroxyl flanked by axial substituents should

[9] Honeyman and Stening, following paper.
[10] Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 2116.
[11] Aspinall, Hirst, and Warburton, *J.*, 1955, 651.
[12] Barton, *Chem. and Ind.*, 1953, 664.

be subject to greater steric compression and be less reactive than the 4-hydroxyl group. Without further knowledge of the chemistry of related compounds it is not yet possible to ascribe this result to electronic or steric factors. As far as we are aware the only example previously reported of this type of selective esterification in the carbohydrate group is the tosylation of the equatorial 3-hydroxyl group in 1 : 6-anhydro-2-*O*-benzoyl-β-D-altropyranose.[13] In this case, as with our examples, only one chair conformation is possible. It is probable that starting from stereochemically suitable compounds many partially substituted sugars, not readily accessible by other methods, may be synthesised by employing such preferential reactivity for the selective blocking of specific hydroxyl groups.

Experimental

Unless otherwise stated, chloroform solutions were dried (Na_2SO_4), evaporations were carried out under reduced pressure, and the light petroleum used had b. p. 60—80°. Chromatographic separations were carried out with columns of (*a*) activated alumina, Type H, 100/200 S mesh, supplied by Peter Spence and Sons, Ltd., and (*b*) as in (*a*) shaken with N-acetic acid, washed with water by decantation until free from acid, filtered, and dried at 260—280°. Paper partition chromatography was effected on Whatman No. 1 filter paper with (*a*) butan-1-ol–ethanol–water (4 : 1 : 5 v/v, upper layer) and (*b*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) as solvents.

Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside*.—Methyl α-D-mannoside (10 g.), paraldehyde (50 ml.), and concentrated sulphuric acid (0·08 ml.) were shaken at room temperature for 10 min. The solution was decanted into light petroleum (200 ml.)–saturated aqueous sodium carbonate (150 ml.). The residual methyl α-D-mannoside was treated four times with paraldehyde (25 ml.)–concentrated sulphuric acid (0·04 ml.) for periods of 10 min., and in each case the solution was decanted into the original light petroleum–sodium carbonate solution. Separation of the aqueous layer, after washing it with light petroleum (3 × 100 ml.), and evaporation yielded a white solid. Extraction of the solid with acetone and evaporation gave a syrup which crystallised from light petroleum–carbon tetrachloride (10 : 1). After three recrystallisations the mannoside (3·5 g.) had m. p. 112°, $[\alpha]_D^{17}$ +71° (*c*, 1·3 in $CHCl_3$). Honeyman and Morgan [6] give m. p. 117°, [α] +77° ($CHCl_3$).

Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 3-*Toluene*-p-*sulphonate* (I).—Toluene-*p*-sulphonyl chloride (2·6 g.) in pyridine (20 ml.) was added to methyl 4 : 6-*O*-ethylidene-α-D-mannoside (3 g.) in pyridine (20 ml.), and the solution was kept for 2 days at −5° and for 1 day at 0°. The solution was poured into aqueous sodium hydrogen carbonate; evaporation removed most of the pyridine. The mixture was extracted with chloroform and the chloroform extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. Concentration gave a syrup (4·5 g.) which was chromatographed from benzene on alumina (*a*). Elution with light petroleum–benzene gave a syrup (probably mainly the di-toluene-*p*-sulphonate) which would not crystallise. Elution with ether yielded *methyl* 4 : 6-O-*ethylidene*-α-D-*mannoside* 3-*toluene*-p-*sulphonate* (I) (3·1 g.), m. p. 129° (from ether–light petroleum) and mixed m. p. 125° (with a sample prepared by Honeyman and Stening,[9] m. p. 122—123°), $[\alpha]_D^{20}$ +25° (*c*, 0·6 in $CHCl_3$) (Found: C, 51·3; H, 5·9; S, 8·7. $C_{16}H_{22}O_8S$ requires C, 51·3; H, 5·9; S, 8·5%).

Methyl 4 : 6-O-*Ethylidene*-2-O-*methyl*-α-D-*mannoside* 3-*Toluene*-p-*sulphonate* (II).—The 3-toluene-*p*-sulphonate (I) (1 g.) was dissolved in boiling methyl iodide (5 ml.), and silver oxide (1·5 g.) was added during 5 hr.; heating was continued for a further 19 hr. The silver residues were filtered off and washed with chloroform. Evaporation of the filtrate afforded *methyl* 4 : 6-O-*ethylidene*-2-O-*methyl*-α-D-*mannoside* 3-*toluene*-p-*sulphonate* (II) (0·8 g.), m. p. 149—150° (from methanol), $[\alpha]_D^{18}$ +22° (*c*, 0·6 in $CHCl_3$) (Found: C, 51·9; H, 5·8; S, 7·9. $C_{17}H_{24}O_8S$ requires C, 52·5; H, 6·2; S, 8·0%).

Methyl 4 : 6-O-*Ethylidene*-2-O-*methyl*-α-D-*mannoside* (III).—Methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside 3-toluene-*p*-sulphonate (0·7 g.) was dissolved in methanol–water (9 : 1; 25 ml.), sodium amalgam (4%; 10 g.) was added, and the mixture was stirred at 45° for 4 hr. and at room temp. for 20 hr. After being decanted from mercury the solution was neutralised with carbon dioxide, inorganic salts were filtered off, and the filtrate was evaporated. The

[13] Newth, *J.*, 1956, 441.

residue was extracted with chloroform; evaporation gave a syrup which crystallised from ether–light petroleum to yield *methyl* 4 : 6-O-*ethylidene*-2-O-*methyl*-α-D-*mannoside* (III) (0·3 g.), m. p. 76—77°, $[\alpha]_D^{19}$ +42° (*c*, 0·6 in $CHCl_3$) (Found : C, 52·0; H, 7·6; OMe, 25·8. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7%; OMe, 26·3%).

2-O-*Methyl*-α-D-*mannose* (IV).—Methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside (1·6 g.) was heated with 0·5N-hydrochloric acid (25 ml.) at 100° for 6 hr. (constant rotation). The solution was neutralised with silver carbonate and filtered, hydrogen sulphide was passed through the filtrate, and the mixture concentrated. The residue was extracted with boiling ethanol from which the sugar slowly crystallised in a desiccator ($CaCl_2$). 2-*O*-Methyl-α-D-mannose (IV) (0·8 g.) (from ethanol) had m. p. 137°, $[\alpha]_D^{19}$ +15° ⟶ +5° (24 hr., constant) (*c*, 1·3 in H_2O), R_G 0·32 in solvent *a* (Found : C, 42·9; H, 7·2; OMe, 16·3. Calc. for $C_7H_{14}O_6$: C, 43·2; H, 7·2; OMe, 16·0%) {Pacsu and Trister [2] give m. p. 136—137°, $[\alpha]_D$ +7·0° ⟶ +4·5° (H_2O)}. The phenylhydrazone had m. p. 163—164° (Pacsu and Trister [2] record m. p. 163°) (Found : OMe, 11·3. Calc. for $C_{13}H_{20}O_5N_2$: OMe, 10·9%). The syrupy mixture of methyl pyranosides, prepared by refluxing the sugar with dry methanolic hydrogen chloride, consumed 1·01 mol. of periodate at 35° in 8 hr. (spectrophotometric determination [14] carried out by Mr. R. J. Ferrier).

Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 3-*Nitrate* (V).—Ice-cold fuming nitric acid (1·5 ml.) in acetic anhydride (3·5 ml.) was added to a suspension of methyl 4 : 6-*O*-ethylidene-α-D-mannoside (1·5 g.) in acetic anhydride (3·5 ml.) at 0°. After 5 min. at 0° the mixture was poured into ice-water (50 ml.) and the aqueous layer was decanted from the syrupy 2 : 3-dinitrate, neutralised with sodium carbonate, and extracted with chloroform (5 × 50 ml.). Concentration of the extract and two crystallisations of the residue from light petroleum–chloroform yielded *methyl* 4 : 6-O-*ethylidene*-α-D-*mannoside* 3-*nitrate* (V) (0·6 g.), m. p. 166° and mixed m. p. 165° (with a sample prepared by Honeyman and Stening,[9] m. p. 165°), $[\alpha]_D^{20}$ +57° (*c*, 0·9 in $CHCl_3$) (Found : C, 40·6; H, 5·7; N, 5·3. $C_9H_{15}O_8N$ requires C, 40·7; H, 5·7; N, 5·3%).

Methyl 4 : 6-O-*Ethylidene*-2-O-*methyl*-α-D-*mannoside* 3-*Nitrate* (VI).—Silver oxide (3 g.) was added portionwise during 5 hr. to a suspension of the 3-nitrate (V) (3 g.) in boiling methyl iodide (12 ml.), and the mixture was refluxed for a further 20 hr. The silver residues were washed with hot methanol. The combined washings and filtrate were concentrated to give a syrup which crystallised from light petroleum to yield *methyl* 4 : 6-O-*ethylidene*-2-O-*methyl*-α-D-*mannoside* 3-*nitrate* (VI) (2·6 g.), m. p. 100—101° and mixed m. p. 101° (with a sample prepared by Honeyman and Stening,[9] m. p. 101—102°), $[\alpha]_D^{21}$ +45° (*c*, 1·1 in $CHCl_3$) (Found : C, 43·6; H, 6·2; N, 4·6; OMe, 22·0. $C_{10}H_{17}O_8N$ requires C, 43·0; H, 6·1; N, 5·0; OMe, 22·0).

Denitration of Methyl 4 : 6-O-*Ethylidene*-2-O-*methyl*-α-D-*mannoside* 3-*Nitrate*.—A mixture of iron and zinc dust was added portionwise to methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside 3-nitrate (2·5 g.) in acetic acid (50 ml.) at 45°. When reaction started the solution was cooled and kept at room temperature for 15 min. (negative diphenylamine–sulphuric acid test). The filtrate and chloroform washings were combined and washed with water, and the chloroform layer was dried (K_2CO_3) and concentrated. The resulting syrup afforded methyl 4 : 6-*O*-ethylidene-2-*O*-methyl-α-D-mannoside (III) (1·9 g.) (from ether–light petroleum), m. p. and mixed m. p. 78—79°, $[\alpha]_D^{20}$ +42° (*c*, 1·2 in $CHCl_3$) (Found : C, 51·1; H, 7·4; OMe, 26·5. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7; OMe, 26·3%).

Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 3-*Nitrate* 2-*Toluene*-p-*sulphonate* (VII).—Toluene-*p*-sulphonyl chloride (5·5 g.) in pyridine (10 ml.) was added to a solution of the 3-nitrate (V) (5 g.) in pyridine (10 ml.) at 0°, and the solution kept for 5 days at room temperature. Water was added and, after standing overnight, the solution was extracted with chloroform. The extract was washed with dilute sulphuric acid, and concentrated to a syrup which yielded *methyl* 4 : 6-O-*ethylidene*-α-D-*mannoside* 3-*nitrate* 2-*toluene*-p-*sulphonate* (VII) (5·7 g.) (from methanol), m. p. 123—124° and mixed m. p. 121—123° (with a sample prepared by Honeyman and Stening,[9] m. p. 121—122°), $[\alpha]_D^{19}$ −12° (*c*, 0·8 in $CHCl_3$) (Found : C, 45·9; H, 4·7; N, 3·1. $C_{16}H_{21}O_{10}NS$ requires C, 45·8; H, 5·0; N, 2·8%).

Methyl 4 : 6-O-*Ethylidene*-α-D-*mannoside* 2-*Toluene*-p-*sulphonate* (VIII).—A mixture of iron and zinc dust was added portionwise to a solution of the 3-nitrate 2-toluene-*p*-sulphonate (VII) (5·5 g.) in acetic acid (110 ml.) and after 15 min. (negative diphenylamine–sulphuric acid

[14] Aspinall and Ferrier, unpublished results.

test) the solid was filtered off and washed with chloroform. The combined filtrate and washings were washed with water, and the chloroform layer was dried (K_2CO_3) and evaporated to a syrup which afforded *methyl* 4 : 6-O-*ethylidene*-α-D-*mannoside* 2-*toluene*-p-*sulphonate* (VIII) (4·2 g.) (from methanol), m. p. 165—166°, $[\alpha]_D^{17}$ +10° (*c*, 1·5 in $CHCl_3$) (Found: C, 50·8; H, 5·9; S, 8·0. $C_{16}H_{22}O_8S$ requires C, 51·3; H, 5·9; S, 8·5%).

Methyl 4 : 6-O-*Ethylidene*-3-O-*methyl*-α-D-*mannoside* 2-*Toluene*-p-*sulphonate* (IX).—Silver oxide (4 × 3 g.) was added to a suspension of the 2-toluene-*p*-sulphonate (VIII) (4 g.) in boiling methyl iodide (15 ml.) during 24 hr., and heating was continued for a further 16 hr. The silver residues were filtered off and washed with chloroform; evaporation gave a syrup which yielded *methyl* 4 : 6-O-*ethylidene*-3-O-*methyl*-α-D-*mannoside* 2-*toluene*-p-*sulphonate* (IX) (3·9 g.) (from light petroleum), m. p. 131°, $[\alpha]_D^{21}$ −16° (*c*, 0·8 in $CHCl_3$) (Found: C, 52·4; H, 6·4; OMe, 8·1. $C_{17}H_{24}O_8S$ requires C, 52·5; H, 6·2; OMe, 8·0%).

3-O-*Methyl*-α-D-*mannose* (X).—Sodium amalgam (4%; 20 g.) was added to methyl 4 : 6-*O*-ethylidene-3-*O*-methyl-α-D-mannoside 2-toluene-*p*-sulphonate (1·7 g.) in methanol–water (9 : 1; 35 ml.), and the mixture was stirred at 45° for 4 hr. and at room temperature for 20 hr. After the solution had been decanted from mercury it was neutralised with carbon dioxide, inorganic salts were filtered off, and the filtrate was evaporated. The residue was extracted with chloroform, and concentration yielded a syrup (0·8 g.; presumably methyl 4 : 6-*O*-ethylidene-3-*O*-methyl-α-D-mannoside). This was heated with 0·5N-hydrochloric acid (15 ml.) at 100° for 5·5 hr. (constant rotation), and the solution was neutralised with silver carbonate. The filtrate was treated with Amberlite resin IR-120(H) and concentrated to a syrup which crystallised from methanol to give 3-O-*methyl*-α-D-*mannose* (X) (0·35 g.), m. p. 133—134° (from ethanol–ether), $[\alpha]_D^{19}$ +14° ⟶ +3° (±1°) (24 hr., constant) (*c*, 0·6 in H_2O) (Found: C, 43·2; H, 6·5; OMe, 16·1. $C_7H_{14}O_6$ requires C, 43·2; H, 7·2; OMe, 16·0%). A mixture with 2-*O*-methyl-α-D-mannose had m. p. 110—125°. The sugar had a similar R_G 0·30 in solvent *a* to the 2-methyl ether, but travelled more slowly ($R_{mannose}$ 1·9) than the 2-methyl ether ($R_{mannose}$ 2·1) in solvent *b*. When heated with phenylhydrazine acetate the sugar (X) gave 3-*O*-methyl-D-glucosazone, m. p. 165—166° which gave an *X*-ray powder photograph identical with that given by an authentic sample. The derived syrupy mixture of methyl pyranosides (prepared by refluxing the sugar with dry methanolic hydrogen chloride) consumed 0·0 mol. of sodium metaperiodate solution during 8 hr. at 35°.

Preparation of 1 : 6-*Anhydro*-4-O-*methyl*-β-D-*mannopyranose*.—Finely ground ivory nuts (400 g.) were pyrolysed as described by Knauf, Hann, and Hudson.[15] The dark distillate was neutralised with barium carbonate and treated with charcoal–Celite. Evaporation yielded a thick syrup which was dissolved in acetone (500 ml.) and shaken with concentrated sulphuric acid (3 ml.) for 48 hr. After neutralisation with cupric carbonate the filtrate was concentrated to a syrup which crystallised on addition of propan-2-ol, and after recrystallisation from the same solvent gave 1 : 6-anhydro-2 : 3-*O*-*iso*propylidene-β-D-mannopyranose (20 g.), m. p. 161—162°, $[\alpha]_D^{19}$ −57° (*c*, 1·2 in H_2O).

Methylation acording to the method of Knauf *et al.*[15] gave a product which was dissolved in benzene and chromatographed on alumina (*b*). Elution with ether–light petroleum (b. p. 40—60°) afforded a syrup which crystallised from the same solvent to give 1 : 6-anhydro-4-*O*-methyl-2 : 3-*O*-*iso*propylidene-β-D-mannopyranose (16 g.), m. p. 52—53°, $[\alpha]_D^{19}$ −33° (*c*, 0·7 in $CHCl_3$).

Hydrolysis of the *iso*propylidene compound gave syrupy 1 : 6-anhydro-4-*O*-methyl-β-D-mannopyranose (Found: OMe, 18·0. Calc. for $C_7H_{12}O_5$: OMe, 17·6%).

1 : 6-*Anhydro*-4-O-*methyl*-β-D-*mannopyranose* 2-*Toluene*-p-*sulphonate* (XI).—Toluene-*p*-sulphonyl chloride (4·6 g.) in pyridine (25 ml.) was added to 1 : 6-anhydro-4-*O*-methyl-β-D-mannopyranose (4 g.) in pyridine (25 ml.) at 0°. The mixture was kept for 48 hr. at −5° and then for 24 hr. at 0°. The solution was poured into sodium hydrogen carbonate solution, the mixture evaporated to remove most of the pyridine, the residue extracted with chloroform, and the extract washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. Concentration gave a syrup which when crystallised from acetone–ether had m. p. 84—86°. This crystalline substance (5·1 g.) was dissolved in benzene and chromatographed on alumina (*b*). Elution with benzene–ether afforded 1 : 6-*anhydro*-4-O-(*ethyl*-β-D-*mannopyranose* 2-*toluene*-p-*sulphonate* (XI), m. p. 85—87°, $[\alpha]_D^{20}$ −42° (*c*, 1·0 in $CHCl_3$) (Found: C, 51·0; H, 5·4; S, 9·4; OMe, 9·0. $C_{14}H_{18}O_7S$ requires C, 50·9; H, 5·5; S, 9·7; OMe, 9·4%); elution with

[15] Knauf, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1447.

ether and acetone–ether yielded further small quantities of the same compound but no other substance could be detected.

1 : 6-*Anhydro*-3 : 4-*di*-O-*methyl*-β-D-*mannopyranose* 2-*Toluene*-p-*sulphonate* (XII).—The 2-toluene-*p*-sulphonate (XI) (4 g.) was dissolved in acetone (8 ml.), and methyl iodide (8 ml.) and anhydrous calcium sulphate (5 g.) were added. Silver oxide (3 × 5 g.) was added during 3 hr. to the boiling solution and heating was continued for a further 13 hr. The solid was filtered off and extracted with hot acetone; evaporation gave a syrup which crystallised from acetone–ether. This product (3·5 g.; m. p. 96—100°) was dissolved in benzene and chromatographed on alumina (*b*). Elution with benzene–light petroleum gave a syrup which crystallised from ether to yield 1 : 6-*anhydro*-3 : 4-*di*-O-*methyl*-β-D-*mannopyranose* 2-*toluene*-p-*sulphonate* (XII) (1·8 g.), m. p. 88—89°, $[\alpha]_D^{19}$ −35° (*c*, 1·0 in $CHCl_3$) (Found: C, 52·4; H, 5·5; S, 9·2; OMe, 18·1. $C_{15}H_{20}O_7S$ requires C, 52·3; H, 5·9; S, 9·3; OMe, 18·0%). Elution with ether and acetone–ether gave unchanged starting material (XI) (1·7 g.), m. p. and mixed m. p. 85—87° (from ether); this material was suspended in boiling methyl iodide (5 ml.) and silver oxide (7 g.) was added during 12 hr. The product was worked up in the usual way and chromatographed on alumina (*b*) to give more of the dimethyl ether (XII) (1·4 g.), m. p. and mixed m. p. 87—89°.

1 : 6-*Anhydro*-β-D-*mannopyranose* 2-*Toluene*-p-*sulphonate* (XIII).—1 : 6-Anhydro-β-D-mannopyranose (prepared by the hydrolysis of 1 : 6-anhydro-2 : 3-*O*-*iso*propylidene-β-D-mannopyranose) (3 g.) was dissolved in pyridine (20 ml.) at 0° and a solution of toluene-*p*-sulphonyl chloride (2·5 g.) in pyridine (20 ml.) at 0° was added. The mixture was kept at −5° for 48 hr. and then at 0° for 24 hr. Water (2 ml.) was added and the mixture was poured into water (50 ml.) containing sodium hydrogen carbonate (3 g.). The aqueous layer was decanted from the small quantity of syrup which separated and the solution was concentrated (more syrup separated during the evaporation). The residue was extracted with acetone and the extract concentrated; addition of water gave 1 : 6-*anhydro*-β-D-*mannopyranose* 2-*toluene*-p-*sulphonate* (XIII) (2·9 g.), m. p. 146—147° (after recrystallisation from acetone–ether), $[\alpha]_D^{19}$ −74° (*c*, 0·5 in $COMe_2$) (Found: C, 49·3; H, 5·2. $C_{13}H_{16}O_7S$ requires C, 49·4; H, 5·1%).

Methylation of 1 : 6-*Anhydro*-β-D-*mannopyranose* 2-*Toluene*-p-*sulphonate*.—1 : 6-Anhydro-β-D-mannopyranose 2-toluene-*p*-sulphonate (2·5 g.) was dissolved in acetone (5 ml.), and methyl iodide (8 ml.) and anhydrous calcium sulphate (4 g.) were added. Silver oxide (5 × 3 g.) was added during 5 hr. to the boiling solution and heating was continued for a further 7 hr. After being worked up in the usual way the syrup was dissolved in benzene and chromatographed on alumina (*b*). Elution with benzene–light petroleum and crystallisation from ether gave the 3 : 4-dimethyl ether (XII) (1·1 g.), m. p. and mixed m. p. 87—88°. Elution with benzene–ether and crystallisation from ether gave the 4-methyl ether (XI) (1·0 g.), m. p. and mixed m. p. 85—87°. Remethylation of the 4-methyl ether (XI) with methyl iodide and silver oxide followed by chromatography on alumina (*b*) afforded the 3 : 4-dimethyl ether (XII) (0·8 g.), m. p. and mixed m. p. 86—87°.

1 : 6-*Anhydro*-3 : 4-*di*-O-*methyl*-β-D-*mannopyranose* (XIV).—1 : 6-Anhydro-3 : 4-di-*O*-methyl-β-D-mannopyranose 2-toluene-*p*-sulphonate (1·8 g.) was dissolved in methanol–water (9 : 1; 35 ml.), and sodium amalgam (4%; 35 g.) was added. The mixture was stirred at 40° for 4 hr. and at room temperature overnight. The solution and methanol washings were decanted from the mercury and neutralised with carbon dioxide; inorganic salts were filtered off and the filtrate was concentrated. The residue was extracted with chloroform, and the extract evaporated to a syrup which was crystallised from acetone–ether and then from light petroleum–ether. 1 : 6-*Anhydro*-3 : 4-*di*-O-*methyl*-β-D-*mannopyranose* (XIV) (0·85 g.) had m. p. 63—65°, $[\alpha]_D^{20}$ −90° (*c*, 0·6 in $CHCl_3$) (Found: C, 50·7; H, 7·2; OMe, 31·8. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 32·6%).

3 : 4-*Di*-O-*methyl*-D-*mannose* (XV).—1 : 6-Anhydro-3 : 4-di-*O*-methyl-β-D-mannopyranose (0·8 g.) was heated with N-hydrochloric acid (30 ml.) at 100° for 110 min. (constant rotation), and the solution was neutralised with silver carbonate and filtered. Hydrogen sulphide was passed through the solution, the mixture was taken to dryness, and the residue extracted with methanol yielding a solution from which 3 : 4-di-*O*-methyl-α-D-mannose monohydrate, m. p. 109—111°, crystallised. The sugar slowly changed to a more stable crystalline form, m. p. 78—80°. After recrystallisation from acetone–ether the sugar had m. p. 78—80° and mixed m. p. 78—81° (with an authentic sample, m. p. 80—82°), $[\alpha]_D^{19}$ +18° (4 min.) ⟶ +6° (24 hr., constant) (Found: C, 42·2; H, 8·0; OMe, 27·2. Calc. for $C_8H_{16}O_7$: C, 42·5; H, 8·0; OMe,

27·2%). The sugar had R_g 0·67 in solvent *a*, and on oxidation with bromine gave 3 : 4-di-*O*-methyl-D-mannonolactone, m. p. 159—160° and mixed m. p. 159—161° (with an authentic sample, m. p. 161—162°), $[\alpha]_D^{19}$ +178° (20 min.) ⟶ +132° (68 hr., constant) (*c*, 0·56 in H_2O).

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