CCCCI.—*Walden Inversion in the α-Glucoheptose Series. The Preparation of New Derivatives and the Determination of the Structure of Methyl-α-glucoheptoside.*

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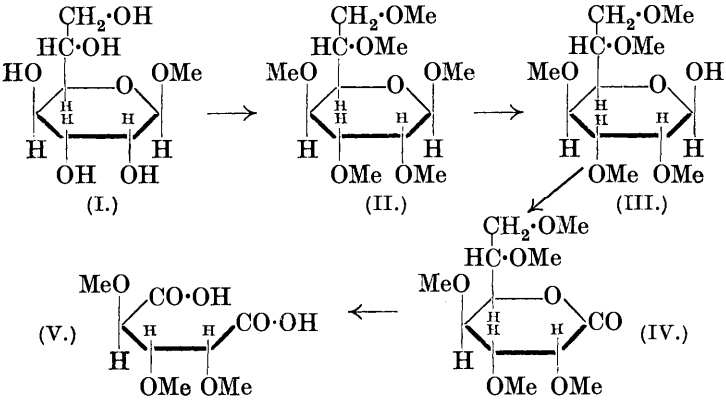
α-GLUCOHEPTOSE, in yields of 55—60% of the theoretical, is consistently obtained by a modification of the procedure involving the reduction of α-glucoheptonolactone. Following the direct method of preparation of the glycoside, the crystalline β-methyl-α-glucoheptoside (I) is the main product, and this by methylation gives in almost quantitative yield the *pentamethyl β-methyl-α-glucoheptoside* (II). From the latter, by hydrolysis, crystalline *β-pentamethyl α-glucoheptose* (III) was obtained having initially $[\alpha]_D^{18°}$ — 62·5° in

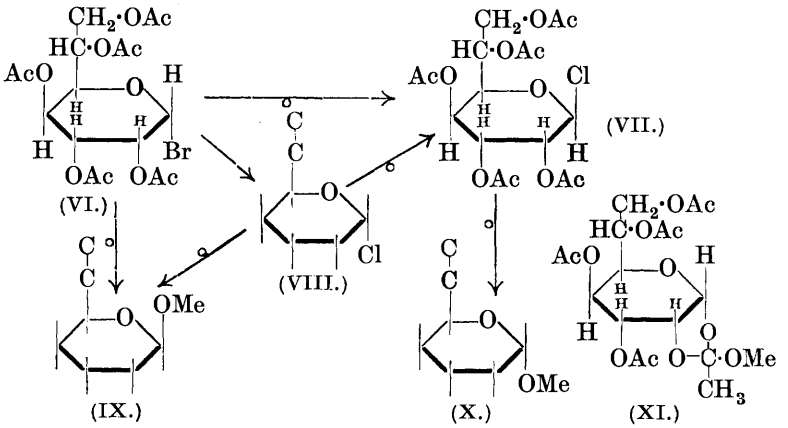
water. This passes readily by oxidation to the crystalline *penta-methyl α-glucoheptono-δ-lactone* (IV) and its rate of hydrolysis was studied polarimetrically, as was also the rate of formation of the lactone from the free *pentamethyl α-glucoheptonic acid.* The figures are comparable with those of other δ-lactones of the sugar series which have been studied. By degradative oxidation the lactone was converted into *l*-arabotrimethoxyglutaric acid (V), recognised as its crystalline methylamide, and this was accompanied by *i*-dimethoxysuccinic acid, which was again characterised as the methylamide derivative. For these reasons we ascribe the pyranose structure (I) to β-methyl-α-glucoheptoside.



A new method is described for the preparation of α-penta-acetyl α-glucoheptosidyl bromide (VI) (α-acetobromo-α-glucoheptose), 5 g. of the bromide being obtainable from 3 g. of the sugar. When this substance in contact with activated silver chloride was boiled for 10 minutes in dry ether it gave rise to *β-penta-acetyl α-glucoheptosidyl chloride* (VII) in almost quantitative yield. If the silver chloride had been kept for some weeks before use, this treatment yielded *α-penta-acetyl α-glucoheptosidyl chloride* (VIII), whilst this again was quantitatively converted into the β-isomeride (VII) by treatment with freshly prepared activated silver chloride.

The replacement of the halogen in these compounds by the methoxyl group is readily effected in methyl-alcoholic solution by contact with dry silver oxide. Thus α-penta-acetyl α-glucoheptosidyl bromide (VI) gave the crystalline *penta-acetyl β-methyl-α-glucoheptoside* (skeleton formula IX) identical with the product which was obtained by the direct acetylation of β-methyl-α-glucoheptoside in the presence of pyridine. Similarly a quantitative yield of *penta-acetyl α-methyl-α-glucoheptoside* (skeleton formula X) was obtained by placing β-penta-acetyl α-glucoheptosidyl chloride in contact with

methyl alcohol and silver oxide. The same crystalline substance was also prepared in the following way. 3% Methyl-alcoholic



hydrogen chloride being used instead of the more usual 5% solution, α-glucoheptose was condensed at the boiling temperature with this reagent. Under these conditions it did not give exclusively β-methyl α-glucoheptoside, but yielded also a non-crystalline portion which on acetylation gave rise to penta-acetyl α-methyl-α-glucoheptoside.

When β-penta-acetyl α-glucoheptosidyl chloride was warmed with methyl alcohol and quinoline instead of silver oxide a *third crystalline variety of penta-acetyl methyl-α-glucoheptoside* was formed. This substance (XI) was comparable with the third or so-called "γ"-forms of tetra-acetyl β-methylmannoside and triacetyl β-methylrhamnoside (Haworth, Hirst, and Miller, J., 1929, 2469; Bott, Haworth, and Hirst, J., 1930, 1395; Haworth, Hirst, and Samuels, preceding paper). Four of the five acetyl residues were eliminated by cold alkali: the fifth acetyl group is associated with the methyl residue as an orthoacetic ester group at positions 1 and 2. The name which should be ascribed to this compound is *tetra-acetyl α-glucoheptose* 1 : 2-*orthomethylacetate* (XI) and a similar nomenclature should be adopted for the mannose and rhamnose analogues.

Experimental.

α-Glucoheptose (With Mr. R. W. Herbert).—The reduction of α-glucoheptonolactone (Fischer, *Annalen*, 1892, **270**, 64; Kiliani, *Ber.* 1886, **19**, 767) by Fischer's method (*loc. cit.*) or by Philippe's modification (*Ann. Chim. Phys.*, 1912, **26**, 289) gave variable, usually poor, yields of glucoheptose. When, however, the conditions were rigidly controlled as specified below, yields of 55—60% were consistently obtained. A solution of the lactone (10 g.) in

water (150 c.c.) was placed in a flask fitted with a stirrer and surrounded by a freezing mixture. 3% Sodium amalgam (150 g.) was added in portions of 10 g. By continuous addition of acid the mixture was kept very slightly acid to Congo-red. The solution was concentrated under diminished pressure at 45° until sodium sulphate began to crystallise, and the thin syrup was poured with stirring into warm 80% alcohol. After filtration more alcohol was added and the solution kept for several hours until the separation of sodium glucoheptonate was complete. The clear solution was evaporated to a thick syrup and set aside to crystallise. The α-glucoheptose, after recrystallisation from half its weight of hot water, had m. p. 193°, $[\alpha]_D^{20°}$ — 20° equilibrium value in water.

Methylation of β-Methyl-α-glucoheptoside.—α-Glucoheptose was boiled for 12 hours with 5% methyl-alcoholic hydrogen chloride: the product, which was isolated in the usual way, was mainly β-methyl-α-glucoheptoside, m. p. 169°, $[\alpha]_D$ — 75° in water (compare Fischer, *Ber.*, 1895, **28**, 1157). Some α-methyl-α-glucoheptoside was also formed and was identified as its crystalline penta-acetate (see below). A solution of β-methyl-α-glucoheptoside (3 g.) in water (10 c.c.) and acetone (60 c.c.) was methylated in the usual way with methyl sulphate (33 c.c.) and 30% aqueous sodium hydroxide (70 c.c.). The product (yield, almost quantitative) was distilled after one further methylation, giving *pentamethyl β-methyl-α-glucoheptoside* as a colourless mobile liquid, b. p. 140°/0·08 mm., $n_D^{17°}$ 1·4487, $[\alpha]_D^{21°}$ — 97° in water (*c*, 0·7), — 74° in chloroform (*c*, 1·1), — 58° in alcohol (*c*, 1·1), — 46° in ether (*c*, 1·0), — 42° in benzene (*c*, 1·2). The substance was non-reducing and was very soluble in all the ordinary solvents (Found: C, 53·0; H, 9·1; OMe, 61·2. $C_{13}H_{26}O_7$ requires C, 53·0; H, 8·9; OMe, 63·2%).

The hydrolysis of pentamethyl β-methyl-α-glucoheptoside (2·5 g.) by 5% aqueous hydrochloric acid (50 c.c.) at 100° was complete in about one hour. The acid was neutralised with barium carbonate, and the product extracted from the neutral solution by chloroform. On distillation *pentamethyl α-glucoheptose* (2·3 g.) was obtained as a mobile syrup, b. p. 157°/0·18 mm., which soon crystallised. Recrystallisation from a mixture of ether (1 vol.) and light petroleum (b. p. 60—80°; 4 vols.) gave large transparent monoclinic prisms of *β-pentamethyl α-glucoheptose* (1·6 g.), m. p. 84°, $[\alpha]_D^{18°}$ — 62·5°, initial value in water (*c*, 0·8); — 60° (40 mins. after dissolution); — 58° (100 mins.); — 52° (16 hrs.); — 49° (24 hrs.); — 44° (48 hrs.); — 42·5° (equilibrium value). This substance reduced Fehling's solution and was soluble in all the ordinary solvents except light petroleum (Found: C, 51·6; H, 8·8; OMe, 54·3. $C_{12}H_{24}O_7$ requires C, 51·4; H, 8·6; OMe, 55·3%).

Pentamethyl α-Glucoheptono-δ-lactone.—β-Pentamethyl α-glucoheptose (3·6 g.), dissolved in water (60 c.c.), was oxidised by bromine (7 c.c.) for 5 days at 35—40°. The product was isolated in the usual manner and crystallised when its solution was evaporated to dryness under diminished pressure. Recrystallisation from ethyl acetate–light petroleum gave *pentamethyl α-glucoheptono-δ-lactone* in small colourless prisms (3·2 g.), m. p. 83° (Found : C, 51·8; H, 8·2; OMe, 55·5. $C_{12}H_{22}O_7$ requires C, 51·8; H, 8·0; OMe, 55·7%).

The rate of hydrolysis of the lactone in aqueous solution was studied polarimetrically. $[\alpha]_D^{19°}$ + 40° (initial value in water; *c*, 1·1); 39° (12 mins. after dissolution); 38° (37 mins.); 37° (1 hr.); 36° (2 hrs.); 33° (4 hrs.); 30° (6 hrs.); 27·5° (8 hrs.); 24° (10 hrs.); 19° (15 hrs.); 13·5° (20 hrs.); 10° (30 hrs.); 9·4° (38 hrs., equilibrium value).

The rotation of the acid in aqueous solution was determined by the method previously described in papers from this laboratory. $[\alpha]_D^{17°}$ — 15° (initial value; *c*, 0·9, calc. as lactone); + 9° (equilibrium value after 24 hrs.). At equilibrium the proportions of acid and lactone were 56% and 44% respectively.

Oxidation of Pentamethyl α-Glucoheptono-δ-lactone.—The lactone (2·8 g.) was heated at 90° for 6 hours with concentrated nitric acid (*d* 1·42; 12·5 c.c.). The solution was evaporated to a syrup under diminished pressure, water was added and removed by distillation, the latter procedure being repeated until the whole of the nitric acid had been removed. The syrupy oxidation product was boiled for 7 hours with 4% methyl-alcoholic hydrogen chloride (150 c.c.). The acid was neutralised with silver carbonate, the solvent removed, and the syrup so obtained was distilled, giving (a) 1 g., b. p. 130—132°/0·02 mm., $n_D^{15°}$ 1·4404, $[\alpha]_D^{20°}$ + 28° in methyl alcohol (*c*, 1·04) (Found : OMe, 58·9%), (b) 1 g., b. p. about 150°/0·02 mm., n_D^{15} 1·4450, $[\alpha]_D^{20°}$ + 20° in methyl alcohol (*c*, 0·8) (Found : OMe, 59·2; CO_2Me, 46·0. Calc. for methyl trimethoxyglutarate : OMe, 62·0; CO_2Me, 47·2%).

Fraction (a) crystallised partly on nucleation with a crystal of methyl *i*-dimethoxysuccinate (yield, 0·3 g.); m. p., alone or when mixed with an authentic sample, 68°. When treated with methyl-alcoholic methylamine, the syrupy portion of (a) gave *i*-dimethoxysuccinomethylamide, m. p. 208°. A mixed m. p. determination with an authentic specimen showed no depression.

Fraction (b) when digested at 15° with methyl-alcoholic methylamine gave in 50% yield the methylamide of *l*-arabotrimethoxyglutaric acid, m. p., alone or in admixture with a genuine specimen, 171°. $[\alpha]_D^{19°}$ + 60° in water (*c*, 0·9).

Preparation of α-Acetobromo-α-glucoheptose.—α-Acetobromo-

α-glucoheptose, m. p. 110°, was prepared from β-hexa-acetyl α-glucoheptose (Fischer, *loc. cit.*) by Glaser and Zuckermann's method (*Z. physiol. Chem.*, 1927, **166**, 103) or directly from α-glucoheptose by the following modification of Levene and Raymond's method (*J. Biol. Chem.*, 1931, **90**, 247).

The sugar (3 g.) was dissolved in acetic anhydride (75 c.c.) containing anhydrous sodium acetate (0·5 g.) by heating at 100° for 30 minutes. The solution was cooled, a little acetic acid being added to dissolve some crystalline material which separated, and hydrogen bromide was passed in until the solution was saturated. This was then kept for 2 hours at room temperature, toluene (300 c.c.) added, and the solvents rapidly removed by evaporation under diminished pressure at 35°. More toluene was added and evaporated until all the acetic anhydride had been removed. The syrupy product was dissolved in ether, the solution filtered, and the solvent removed. The acetobromo-compound (α-penta-acetyl α-glucoheptosidyl bromide) then crystallised readily; it was recrystallised from ether–light petroleum (yield, 5 g.). Material prepared by this method was more stable but less reactive than that obtained by Glaser and Zuckermann's method.

The rotation of the acetobromo-derivative was determined in chloroform, $[\alpha]_D^{20°}$ + 156° (*c*, 0·9), and in acetone, $[\alpha]_D^{20°}$ + 109° (*c*, 0·6).

β-*Acetochloro-α-glucoheptose.*—Activated silver chloride (1 g.) (Schlubach and Gilbert, *Ber.*, 1930, **63**, 2295; 1926, **59**, 844) was added to a solution of α-acetobromo-α-glucoheptose (0·8 g.) in boiling dry ether (20 c.c.). The mixture was boiled for 10 minutes and after filtration the solution was concentrated to 3 c.c. and placed in the refrigerator. Large prismatic crystals of *β-penta-acetyl α-glucoheptosidyl chloride* (β-acetochloro-α-glucoheptose) soon separated and after recrystallisation from ether–light petroleum had m. p. 125°, $[\alpha]_D^{20°}$ + 11° in chloroform (*c*, 0·96). The yield was almost quantitative when the operations were conducted with small amounts of material (not more than 0·8 g.) and with rigid exclusion of light (Found: C, 46·3; H, 5·4; Cl, 8·0. $C_{17}H_{23}O_{11}Cl$ requires C, 46·5; H, 5·3; Cl, 8·1%).

α-*Acetochloro-α-glucoheptose.*—This substance, *α-penta-acetyl α-glucoheptosidyl chloride*, was obtained in quantitative yield when α-acetobromo-α-glucoheptose was treated in the above manner with activated silver chloride which had been kept for some weeks and which had possibly become "de-activated"; m. p. 97°, $[\alpha]_D^{20°}$ + 95° in chloroform (*c*, 1·1) (Found: C, 46·8; H, 5·4; Cl, 8·1. $C_{17}H_{23}O_{11}Cl$ requires C, 46·5; H, 5·3; Cl, 8·1%).

On treatment with freshly prepared activated silver chloride

α-acetochloro-α-glucoheptose was converted quantitatively into the above β-isomeride, m. p. 125°, $[\alpha]_D^{20°}$ + 11° in chloroform. These transformations carried out by means of silver chloride are somewhat capricious and their course cannot always be predicted with certainty. The reactions appear to depend on a catalyst which is usually present in freshly prepared substances of this type but is often absent from rigorously purified, highly stable material.

Penta-acetyl β-Methyl-α-glucoheptoside.—Dry silver oxide (1 g.) was added to a solution of acetobromo-α-glucoheptose (1·5 g.) in methyl alcohol (15 c.c.). The mixture was shaken for 3 hours, filtered, and the solvent removed by distillation under diminished pressure. The crystalline product was recrystallised from hot water, giving long prisms of *penta-acetyl β-methyl-α-glucoheptoside*, m. p. 150°. This substance was soluble in hot water and in the usual organic solvents with the exception of light petroleum. $[\alpha]_D^{21°}$ — 28° in acetone (*c*, 0·5), $[\alpha]_D^{20°}$ — 16° in chloroform (*c*, 0·8) (Found : C, 49·8; H, 6·3; OMe, 7·4; CH_3·CO, 50·6. $C_{18}H_{26}O_{12}$ requires C, 49·8; H, 6·0; OMe, 7·1; CH_3·CO, 49·5%).

The same penta-acetate, m. p. 150° alone or in admixture with the material just described, was obtained when β-methyl-α-glucoheptoside (0·4 g.) was acetylated in pyridine (8 c.c.) by acetic anhydride (10 c.c.). After remaining for 2 days at 15°, the mixture was diluted with an equal volume of chloroform and poured into water (200 c.c.). The chloroform layer was washed with aqueous sodium bicarbonate and water and evaporated to dryness under diminished pressure. The solid residue was recrystallised from hot water. In this and in the preceding case the yield was quantitative.

Penta-acetyl β-methyl-α-glucoheptoside on treatment with methyl-alcoholic ammonia gave quantitatively β-methyl-α-glucoheptoside, m. p. 170°, $[\alpha]_D^{20°}$ — 75° in water.

Penta-acetyl α-Methyl-α-glucoheptoside.—As shown above, α-glucoheptose and boiling 5% methyl-alcoholic hydrogen chloride give almost exclusively β-methyl-α-glucoheptoside. The equilibrium mixture formed by the action of boiling 3% methyl-alcoholic hydrogen chloride contains a smaller proportion of the β-derivative (5 g. from 8 g. of sugar). The non-crystalline portion (3 g.) was dissolved in pyridine and allowed to react with acetic anhydride (24 c.c.) for 3 days at room temperature. An equal volume of chloroform was added, and the solution poured slowly into ice-water. The chloroform layer was washed with aqueous sodium bicarbonate and with water, dried over magnesium sulphate and evaporated under diminished pressure to a thin syrup (A), which partly crystallised. The solid material was separated by filtration and crystallised

several times from aqueous alcohol, giving *penta-acetyl α-methyl-α-glucoheptoside* (1·5 g.) as short prisms, m. p. 169°, $[\alpha]_D^{19°}$ + 91° in chloroform (*c*, 1·2) (Found: C, 49·6; H, 6·2; OMe, 7·0; CH_3·CO, 49·4. $C_{18}H_{26}O_{12}$ requires C, 49·8; H, 6·0; OMe, 7·1; CH_3·CO, 49·5%).

The liquid portion of (A) when evaporated to dryness under diminished pressure gave a crystalline mass, m. p. about 140° (indef.), $[\alpha]_D$ + 31° in chloroform (*c*, 1·0). This appeared to contain both the α- and the β-variety of penta-acetyl methyl-α-glucoheptoside, but complete separation of the components could not be effected.

Penta-acetyl α-methyl-α-glucoheptoside was obtained in quantitative yield when β-acetochloro-α-glucoheptose (1 g.), dissolved in dry methyl alcohol (10 c.c.), was shaken with silver oxide (0·5 g.) for 2 hours at 15°. After filtration of the liquid and concentration to a thin syrup, light petroleum was added until a faint permanent turbidity appeared. Penta-acetyl α-methyl-α-glucoheptoside soon crystallised; after recrystallisation from aqueous alcohol it had m. p. 169°, alone or when mixed with a sample prepared by the method given above. $[\alpha]_D^{20°}$ + 91° in chloroform.

A Third Form of Penta-acetyl Methyl-α-glucoheptoside.—β-Acetochloro-α-glucoheptose (0·7 g.) was heated for 5 hours at 40° with methyl alcohol (10 c.c.) containing quinoline (1 c.c.). The solution was kept over-night at room temperature, diluted with chloroform (3 vols.), and shaken several times with dilute aqueous hydrochloric acid until all the quinoline had been removed. After being shaken successively with aqueous sodium bicarbonate and with water, the chloroform layer was evaporated at 30° under diminished pressure to a stiff syrup, which was dissolved in ether. On the addition of light petroleum a jelly separated which crystallised on trituration and after draining on porous tile had m. p. 112°. This substance tended to separate as a jelly from aqueous alcohol. It was obtained in long needles (0·6 g.) by crystallisation from ether–light petroleum (b. p. 40—60°); m. p. 112°, $[\alpha]_D^{17°}$ + 43° in chloroform (*c*, 0·6). The analytical figures for carbon, hydrogen, and methoxyl corresponded exactly to those required by "*γ*"-*penta-acetyl methyl-α-glucoheptoside* (Found: C, 49·5; H, 6·0; OMe, 7·4. $C_{18}H_{26}O_{12}$ requires C, 49·8; H, 6·0; OMe, 7·1%).

Four of the five acetyl groups were removed in less than 2 hours when the substance, in acetone solution, was hydrolysed by *N*/10-aqueous sodium hydroxide at room temperature (Found: CH_3·CO, 41·0. Calc. for 5 acetyl groups, 49·5; calc. for 4 acetyl groups, 39·7%). Prolonged treatment (6 hours) under similar conditions failed to hydrolyse the fifth group.

"*γ*"-Penta-acetyl methyl-α-glucoheptoside differed completely

in appearance from both α- and β-methyl-α-glucoheptoside penta-acetates. It was proved in the following way that the "γ"-form could not be a mixture of the α- and the β-isomeride. Mixtures were made of α-methyl-α-glucoheptoside penta-acetate (m. p. 169°) and its β-isomeride (m. p. 150°). Each mixture melted over a range of several degrees, and none began to melt below 135°. One of the mixtures (B), containing approximately 55% of the α-isomeride and 45% of the β-isomeride, had a rotation exactly equal to that of the "γ"-form ($[\alpha]_D^{20°}$ + 43° in chloroform). The mixture (B) melted over the range 141—150°, whereas the "γ"-form melted sharply at 112°. A mixture of (B) with the "γ"-form had m. p. 80—130°. A mixture of the α- and the "γ"-form melted over the range 110—155°, and a mixture of the β- and the "γ"-form over the range 105—130°.

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