82. *The Condensation of α-Methylmannoside with Benzaldehyde.*

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THE interconversion of isomeric sugars by means of Walden inversion within the sugar molecule gives an added importance to the preparation of standard reference compounds in the mannose and galactose series, and the present research was undertaken with this aim in view. It also illustrates the marked effect produced by the *cis*-position of the hydroxyl groups on carbon atoms 2 and 3 on substitution reactions in the mannose molecule. Another striking example of this effect is afforded by mannose diacetone (Irvine and Skinner, J., 1926, 1089).

When α-methylglucoside is condensed with benzaldehyde, 4 : 6-benzylidene α-methylglucoside is produced and there is no indication of the formation of a dibenzylidene derivative (Irvine and Scott, J., 1913, **103**, 585). The reaction with α-methylgalactoside follows an analogous course and the only product which hitherto has been isolated is 4 : 6-benzylidene α-methylgalactoside (Lamb and Robertson, unpublished result). It would therefore appear that the *trans*-disposition of the hydroxyl groups on carbon atoms 2 and 3 in the above compounds is unfavourable to the entry of a second benzylidene residue in these positions. In the case of α-methylmannoside, however, the hydroxyl groups on carbon atoms 2 and 3 are in the *cis*-position and the smooth formation of 2 : 3—4 : 6-dibenzylidene derivatives is to be expected. This involves the formation of two new asymmetric centres in the molecule and it is therefore not surprising that the condensation of α-methylmannoside with benzaldehyde leads to the production of a complicated mixture.

The reaction was investigated by Van Ekenstein (*Rec. trav. chim.*, 1906, **25**, 153), who describes a dibenzylidene α-methylmannoside, m. p. 178°, and a monobenzylidene α-methylmannoside, m. p. 110°. In the present research two isomeric dibenzylidene α-methylmannosides have been isolated, of which one, m. p. 181—182°, is identical with that described by Van Ekenstein, and the *other*, m. p. 97—98°, is new. In addition a new *monobenzylidene α-methylmannoside*, m. p. 146—147°, has been obtained, but no trace of Van Ekenstein's monobenzylidene derivative, m. p. 110°, has been detected. It seems probable that the material he described was an impure specimen of the derivative melting at 146—147°, contaminated with traces of the low-melting dibenzylidene derivative, from which it is separable only with difficulty. A consideration of the optical data strengthens this view.

When benzylidene α-methylmannoside, m. p. 146—147°, is submitted to methylation, followed by hydrolysis, it gives rise to a dimethyl mannose, which, on careful treatment with phenylhydrazine, loses a methoxyl group with the production of 3-methyl glucosazone. The new sugar is therefore 2 : 3-*dimethyl mannose* and the parent benzylidene derivative is 4 : 6-*benzylidene α-methylmannoside*. Crystalline derivatives of 2 : 3-dimethyl mannose and 2 : 3-*dimethyl α-methylmannoside* are described.

EXPERIMENTAL.

α-Methylmannoside, m. p. 191°, was prepared from vegetable ivory meal by the method of Hudson (" Organic Syntheses," **7**, 64).

The Condensation of α-Methylmannoside with Benzaldehyde.—A typical experiment is described. Finely powdered α-methylmannoside (20 g.) was heated with freshly distilled benzaldehyde (100 c.c.) under *ca.* 330 mm. pressure in a current of carbon dioxide at 150—155°. When the sugar had dissolved (2—3 hours), the benzaldehyde was distilled as completely as possible at the same temperature by further diminution of the pressure. The residue, an almost colourless syrup, was poured while hot into absolute alcohol (200 c.c.), and a crystalline precipitate (A) was immediately obtained (8·1 g.). The alcoholic filtrate was evaporated to dryness in a current of carbon dioxide under diminished pressure, and the addition of ethyl acetate to the dry syrup gave a crystalline precipitate of unchanged α-methylmannoside (1·1 g.). The ethyl acetate mother-liquor was in turn evaporated to dryness under the same conditions and the residue was crystallised from light petroleum (b. p. 60—80°)–absolute alcohol. The crystalline separation (C) weighed 8·6 g. Further evaporation of the mother-liquor as described above and subsequent treatment of the residual syrup with ether gave a crystalline separation (D) (2·0 g.). The material (D), however, was not invariably isolated at this stage. In many experiments unchanged α-methylmannoside was obtained, owing to the hydrolysis of benzylidene residues through long contact with small amounts of benzoic acid. The yield of (A) may be increased from 8·1 g. to 20 g. by carrying out the condensation at 150°/230 mm., while the yield of (C) is reduced to mere traces.

The material (A), m. p. 173—178°, crystallised from absolute alcohol, containing a little chloroform, in long fibrous needles, m. p. 181—182°. The pure substance is insoluble in hot water, soluble with difficulty in hot absolute alcohol, and easily soluble in chloroform. It is practically inactive ($\alpha = +0·03°$ in a 2-dcm. tube, $c = 1·645$), and is a dibenzylidene α-methylmannoside. Van Ekenstein (*loc. cit.*) records m. p. 178°, α_D — 5° in chloroform (Found : OMe, 8·7; C, 67·9; H, 6·0. Calc. for $C_{21}H_{22}O_6$: OMe, 8·4; C, 68·1; H, 5·95%).

Crystallisation of the material (C), m. p. 138—140°, from light petroleum (b. p. 60—80°)–absolute alcohol raised the m. p. to 142°, after which recrystallisation from hot water gave pure 4 : 6-*benzylidene α-methylmannoside*, m. p. 146—147°, in long, very slender needles, easily soluble in alcohol and chloroform; $[\alpha]_D + 71·7°$ in chloroform ($c = 1·185$) (Found : OMe, 10·1; C, 59·6; H, 6·2. $C_{14}H_{18}O_6$ requires OMe, 11·0; C, 59·6; H, 6·4%). Van Ekenstein (*loc. cit.*) records m. p. 110°, slightly lævo.

The material (D) crystallised from light petroleum (b. p. 60—80°)–absolute alcohol in beautiful clusters of stout prisms, m. p. 97—98°, $[\alpha]_D - 61·3°$ in chloroform ($c = 1·794$), which proved to be an isomeric *dibenzylidene α-methylmannoside* (Found : OMe, 7·95; C, 68·3; H, 6·1%).

The Partial Hydrolysis of Dibenzylidene α-Methylmannoside (A).—It was hoped that by carrying out the hydrolysis under very mild conditions it might be possible to effect the removal of one benzylidene residue with the consequent production of a monobenzylidene α-methylmannoside. The pure material, m. p. 181—182° (1·67 g.), was dissolved in a mixture of chloroform (30 c.c.) and ethyl alcohol (20 c.c.) containing 0·3% of dry hydrogen chloride. The reaction was carried out at room temperature and its course was observed polarimetrically ($l = 1$ dcm.) :

Time (mins.)	5	14	25	35	48	60	70	75
α	0·00°	+0·14°	+ 0·35°	+0·47°	+0·70°	+0·82°	+0·96°	+1·04°

After 80 minutes crystals of α-methylmannoside were deposited in the polarimeter tube and further observation was impossible. The reaction mixture was now shaken with dilute sodium carbonate solution and washed with water, and the chloroform solution was dried and evaporated to dryness. The residue crystallised immediately and no trace of any substance other than dibenzylidene α-methylmannoside, m. p. 181—182°, was detected. When the values of α_D are plotted against the time in minutes the resulting graph is practically a straight line. There is therefore little doubt that the two benzylidene residues are hydrolysed simultaneously and at practically the same rate.

The Methylation of 4 : 6-*Benzylidene α-Methylmannoside.*—Methylation was carried out with methyl iodide and silver oxide with the addition of acetone to effect complete solution of the material. Three successive treatments were necessary to effect maximum methylation. The final product, which was obtained in almost theoretical yield, distilled at 185—190°/0·47 mm. (bath temp.) as a clear colourless syrup which showed $n_D^{19°}$ 1·5172 and $[\alpha]_D$ + 62·7° in chloroform (c = 1·178). 4 : 6-*Benzylidene*-2 : 3-*dimethyl α-methylmannoside* could not be induced to crystallise (Found : OMe, 29·1; C, 62·0; H, 7·1. $C_{16}H_{22}O_6$ requires OMe, 30·0; C, 61·9; H, 7·1%).

The Partial Hydrolysis of 4 : 6-*Benzylidene*-2 : 3-*dimethyl α-Methylmannoside.*—A typical example is described. The material (10·9 g.) was dissolved in a mixture of acetone (160 c.c.), water (70 c.c.), and *N*-hydrochloric acid (10 c.c.) and the solution was boiled until the rotation became constant. The reaction mixture was neutralised with barium carbonate and filtered, and the acetone was evaporated under diminished pressure. The aqueous residue was extracted twice with chloroform to remove benzaldehyde and traces of unchanged material; it was then evaporated to dryness in the presence of a little barium carbonate. The dry residue was extracted with chloroform, and the extract yielded a syrup (6·9 g. or 88·4% of the theoretical yield) which was distilled. 2 : 3-*Dimethyl α-methylmannoside* is a colourless syrup, $n_D^{18°}$ 1·4729, and $[\alpha]_D$ + 43·5° in chloroform (c = 2·387) (Found : OMe, 41·2. $C_9H_{18}O_6$ requires OMe, 41·9%).

6-*Triphenylmethyl*-2 : 3-*dimethyl α-Methylmannoside.*—2 : 3-Dimethyl α-methylmannoside (1·9 g.) and triphenylchloromethane (2·38 g.) were dissolved in pyridine (17 c.c.) and heated on a boiling water-bath for 2 hours. Benzene was added to the cooled solution and the mixture was extracted with dilute hydrochloric acid. The benzene solution was dried over anhydrous sodium carbonate, filtered, and evaporated. The *product* (3·35 g. or 84·4%) crystallised spontaneously. Recrystallised from rectified spirit, it formed lustrous plates, m. p. 172—173° (Found : OMe, 19·4. $C_{28}H_{32}O_6$ requires OMe, 20·05%).

4 : 6-*Dibenzoyl*-2 : 3-*dimethyl α-Methylmannoside.*—2 : 3-Dimethyl α-methylmannoside was dissolved in dry pyridine and a 20% excess of benzoyl chloride was gradually added. After 24 hours the reaction mixture was diluted with benzene and extracted in turn with dilute hydrochloric acid, dilute sodium hydroxide solution, and water. The dried benzene solution was evaporated and yielded a syrup which crystallised on treatment with ether. The yield was 50%. Pure 4 : 6-*dibenzoyl*-2 : 3-*dimethyl α-methylmannoside* separated from ether in stout prisms, m. p. 121°, $[\alpha]_D$ + 52·9° in chloroform (c = 1·643) (Found : OMe, 21·4; $C_6H_5\cdot CO$, 50·2; C, 64·1; H, 5·9. $C_{23}H_{26}O_8$ requires OMe, 21·6; $C_6H_5\cdot CO$, 48·8; C, 64·2; H, 6·05%).

The Hydrolysis of 2 : 3-*Dimethyl α-Methylmannoside.*—A solution of 2 : 3-dimethyl α-methylmannoside (14·6 g.) in 8% hydrochloric acid (230 c.c.) was boiled until the rotation became constant. The solution was then neutralised with barium carbonate and evaporated to dryness under diminished pressure. The dry residue was extracted with boiling chloroform and yielded a syrup (11·0 g. or 80·4%). 2 : 3-Dimethyl mannose could not be crystallised. The sugar showed $[\alpha]_D$ + 6·0° in methyl alcohol (c = 2·968), + 10·6° in ethyl alcohol (c = 1·88), − 4·3° in chloroform (c = 2·329), − 15·8° in water (c = 2·772), and − 34·4° in *n*-propyl alcohol (c = 1·798) (Found : OMe, 28·8. $C_8H_{16}O_6$ requires OMe, 29·8%).

The Action of Phenylhydrazine on 2 : 3-*Dimethyl Mannose.*—The action of phenylhydrazine under normal conditions for the formation of osazones led to extensive decomposition. When the sugar (1 g.) in 50% acetic acid was carefully mixed with an excess of phenylhydrazine (3·8 g.) in 50% acetic acid and the mixture was warmed at 60° for an hour, a crystalline precipitate (0·25 g.), m. p. 165—170°, was obtained, and one recrystallisation from aqueous alcohol raised the m. p. to 168—172°. When mixed with 3-methyl glucosazone (m. p. 170—172°) the mixture melted at 169—172°.

The Oxime of 2 : 3-*Dimethyl Mannose.*—The sugar (1 g.) was dissolved in alcohol containing the theoretical amount of hydroxylamine. After 2 days the solution was evaporated to dryness and a syrup was obtained which slowly crystallised. The syrupy material was drained on tile and 0·5 g. of hard crystals, m. p. 107°, was obtained. Recrystallised from ether, the *oxime* separated in microscopic needles, m. p. 112—114° (Found : N, 6·3. $C_8H_{17}O_6N$ requires N, 6·3%).

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