825. *Synthesis of* 3 : 4- *and* 3 : 5-*Dimethyl Xylose.*

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3 : 5-Dimethyl D-xylose has been synthesised from 3 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl methyl-D-xyloside by methanolysis of the *iso*propylidene residue, followed by methylation and reductive fission of the toluene-*p*-sulphonyl group. Confirmation of a previous synthesis by Robertson and Speedie (*J.*, 1934, 825) of 3 : 4-dimethyl xylose has been obtained by substitution of position 2 by a benzoyl group, in place of the toluene-*p*-sulphonyl residue in the above synthesis, followed by a similar series of reactions. This led to a partial ring change from furanose to pyranose, and to the production of a mixture of dimethyl methylxylosides from which crystalline 3 : 4-dimethyl β-methylxyloside has been isolated.

Isolation of 3 : 4-dimethyl xylose from the hydrolysis products of a number of methylated polysaccharides has been reported (Mullan and Percival, *J.*, 1940, 1501; Nelson and Percival, *J.*, 1942, 58; James and Smith, *J.*, 1945, 739), and Robertson and Speedie (*J.*, 1934, 825) have recorded a synthesis based on the blocking of position 2 of the xylose molecule by a benzoyl group and the change of a furanose to a pyranose ring during methanolysis of a 3 : 5-*iso*propylidene residue. In view of the possibility of the migration of the

benzoyl group during methylation, the presumption of ring change, and the fact that there is still some doubt concerning the authenticity of the 3 : 4-dimethyl xylose derived from natural products we considered it advisable to repeat this synthesis and to attempt to characterise the product.

Robertson and Speedie prepared methyl 3 : 5-*iso*propylidene methyl-D-xyloside and blocked position 2 with a benzoyl group. Removal of the *iso*propylidene residue with 1% methanolic hydrogen chloride, followed by methylation, debenzoylation, and hydrolysis gave a syrupy dimethyl methylxyloside. Proof of the structure was based on the isolation of a syrupy dimethyl xylose phenylosazone and recovery of unchanged material after 3 days in cold methanolic hydrogen chloride, indicating that furanoside formation was prevented by the presence of a methoxyl residue on $C_{(4)}$. These authors also converted the dimethyl xylose into the 1 : 2-dibenzoate. Replacement of the benzoyl group at $C_{(1)}$ by bromine followed by methoxyl and removal of the benzoyl group from $C_{(2)}$ gave crystalline 3 : 4-dimethyl β-methyl-D-xyloside.

A synthesis essentially similar to this has now been carried out. By complete conversion of xylose into its methylfuranoside by the method of Levene, Raymond, and Dillon (*J. Biol. Chem.*, 1932, **95**, 699) and substitution of anhydrous copper sulphate for hydrogen chloride during the condensation with acetone, the yield of 3 : 5-*iso*propylidene methyl-xyloside was improved from 17·6 to 70%. In order to avoid the danger of acyl migration the toluene-*p*-sulphonyl residue was used to substitute position 2. This gave crystalline 3 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl methylxyloside (overall yield 41%). Removal of the *iso*propylidene residue by methanolysis followed by methylation and reductive fission of the toluene-*p*-sulphonyl residue gave a syrupy dimethyl methylxyloside. The presence of a furanose ring was indicated by the rate of hydrolysis to the free sugar, the reaction being complete in 0·5 hour with 0·1N-sulphuric acid at 100°. After separation from traces of xylose, monomethyl xylose, and 3 : 4-dimethyl xylose on a cellulose column, the product gave a single spot on a paper chromatogram corresponding to that given by an authentic specimen of 3 : 5-dimethyl xylose kindly supplied by Dr. R. G. Laidlaw. Oxidation of 3 : 5-dimethyl xylose, isolated from the column, with bromine water gave a syrupy lactone, the rate of hydrolysis of which was similar to that quoted by Haworth and Porter (*J.*, 1928, 617) for 3 : 5-dimethyl xylonolactone. Conversion of the 3 : 5-dimethyl xylose into trimethyl methylxyloside, followed by oxidation with nitric acid, esterification, and amide formation gave crystalline 2 : 3-dimethoxysuccindiamide, $[\alpha]_D$ +100° in water. Had Walden inversion occurred on removal of the toluenesulphonyl residue from $C_{(2)}$ the sugar would have been a dimethyl lyxose, which on methylation followed by oxidation would give rise to inactive dimethoxysuccinic acid.

Since only a trace of 3 : 4-dimethyl xylose was formed during this synthesis the presence of the toluenesulphonyl residue on position 2 had clearly prevented ring change during the methanolysis and subsequent methylation. An explanation similar to that advanced by Percival and Percival (*J.*, 1938, 1585) to account for the stability of the glycosidic group in 2 : 4 : 6-trimethyl 3-toluene-*p*-sulphonyl methylgalactoside may be put forward. The close proximity of the toluenesulphonyl residue in the 2 position of the xylose derivatives to the glycosidic hydrogen atom, especially in the β-form, renders the ring completely stable either by mechanical shielding by the large aromatic residue or by formation of a bond between the glycosidic hydrogen atom and the strongly electronegative oxygen atoms of the sulphonyl residue.

Robertson and Speedie's synthesis (*loc. cit.*) was repeated therefore to ascertain the influence of the benzoyl group in the 2-position. The dimethyl methylxyloside prepared in this experiment partly crystallised and the crystals (A) (10·5% of the total yield) were shown to be 3 : 4-dimethyl methylxyloside, by a mixed melting point with an authentic specimen supplied by Dr. J. K. N. Jones. This is in agreement with Robertson and Speedie's results and showed that there had been at least a partial change in ring form from furanose to pyranose. The presence of a pyranose ring in the crystals (A) was proved by the rate of hydrolysis to the dimethyl sugar (see Experimental section). Identity as 3 : 4-dimethyl xylose was confirmed by oxidation with bromine water to crystalline 3 : 4-dimethyl xylonolactone (an authentic specimen was kindly supplied by Dr. J. K. N. Jones).

Complete methylation of the crystals (A) gave crystalline 2 : 3 : 4-trimethyl methylxyloside, and oxidation with nitric acid, esterification, and amide formation gave crystalline inactive *xylo*trimethoxyglutardiamide.

The syrup from which the crystals (A) had been removed was hydrolysed with sulphuric acid and the product separated on a cellulose column into 2 : 3 : 4-trimethyl xylose 22·5%, a mixture of dimethyl xyloses 41%, crystalline 2 : 4-dimethyl xylose 5%, and a mixture of monomethyl xylose and xylose 31·5%. Robertson and Speedie (*loc. cit.*) remarked on the presence of methyl benzoate after treatment with methyl-alcoholic hydrogen chloride and the presence of trimethyl methylxyloside after methylation. Separation of the mixture of dimethyl xyloses on the cellulose column was not successful but analysis by quantitative paper chromatography (Hirst, Hough, and Jones, *J.*, 1949, 928) showed 3 : 5- 26%, 3 : 4- 37%, and 2 : 4-dimethyl xylose 23%, and an unidentified portion 14%.

The mechanism of the reaction is difficult to explain since a number of transformations appear to take place simultaneously. That partial transformation from the furanose to the pyranose ring takes place when the benzoyl group occupies position 2 is shown by the isolation of 3 : 4-dimethyl xylose. The most likely explanation is that this occurs during the removal of the *iso*propylidene group through the influence of the methanolic hydrogen chloride. The reaction is complicated, however, by migration of some of the benzoyl substituent to the 3 position, as shown by the isolation of crystalline 2 : 4-dimethyl xylose. A further complication arises from loss of the benzoyl group and the isolation of considerable quantities of 2 : 3 : 4-trimethyl xylose.

Experimental

3 : 5-iso*Propylidene Methyl*-D-*xyloside*.—Xylose (22 g.) was kept at room temperature with methanolic hydrogen chloride (500 c.c.; 0·5%) until the reducing power had dropped to 5% of the initial value (5 hours) (see Levene, Raymond, and Dillon, *loc. cit.*). Neutralisation with silver carbonate, filtration, and evaporation gave a slightly reducing syrup which after extraction with ethyl acetate and removal of the latter gave a non-reducing syrup (19·2 g.). This was converted into the 3 : 5-*iso*propylidene derivative by Percival and Percival's method (*J.*, 1950, 690). The product was a colourless syrup (B) (22·5 g.) which distilled at 110°/0·1 mm. (21·3 g.), and had n_D^{15} 1·4640, $[\alpha]_D^{15}$ −26° (*c*, 0·6 in water) (Found : $COMe_2$, 30·1. Calc. for $C_9H_{16}O_5$: $COMe_2$, 28·4%).

3 : 5-*Dimethyl* 2-*Toluene*-p-*sulphonyl Methyl*-D-*xyloside*.—To the syrup (B) (21·3 g.) in dry pyridine (60 c.c.) was added powdered toluene-*p*-sulphonyl chloride (29 g.). After 2 days at 15° the mixture was poured on ice, giving a crystalline solid (29·1 g.). Recrystallisation from methanol gave 3 : 5-iso*propylidene* 2-*toluene*-p-*sulphonyl methyl*-D-*xyloside* (19·1 g.), m. p. 120°, $[\alpha]_D^{15}$ −45° (*c*, 0·1 in methanol) (Found : C, 54·4; H, 6·0; S, 9·0. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·2; S, 8·95%). Treatment of this substance (19·10 g.) with methanolic hydrogen chloride (100 c.c.; 1%) at 70° for 1 hour gave 2-*toluene*-p-*sulphonyl methylxylofuranoside* as a yellow syrup (16·9 g.), n_D^{15} 1·5269, $[\alpha]_D^{15}$ +41° (*c*, 1·2 in methanol). This substance (16·5 g.) was then methylated 3 times with methyl iodide and silver oxide, giving a pale yellow syrup (17·9 g.), n_D^{15} 1·5025. Solution in light petroleum (b. p. 60—80°) (100 c.c.) and extraction with water (4 × 10 c.c.) removed any fully methylated xyloside. After drying (Na_2SO_4), the light petroleum was evaporated, leaving 3 : 5-*dimethyl* 2-*toluene*-p-*sulphonyl methyl*-D-*xyloside* as a colourless oil (C) (15·5 g.), n_D^{18} 1·5061 (Found : OMe, 26·45. $C_{15}H_{22}O_7S$ requires OMe, 26·9%).

3 : 5-*Dimethyl Methylxyloside*.—The substance (C) (15·4 g.) in methanol (300 c.c.)–water (80 c.c.) was reduced with sodium amalgam (150 g.; 4%) with stirring at 35° during 16 hours. After filtration and repeated extraction with chloroform the chloroform extracts were neutralised with carbon dioxide, dried (Na_2SO_4), and evaporated under diminished pressure. Extraction of the residue with ethyl acetate and removal of the solvent gave a syrup which on distillation gave : Fraction 1 (4·3 g.), b. p. 105—115°/0·01 mm., n_D 1·4500 (Found : OMe, 49·3. Calc. for $C_8H_{16}O_5$: OMe, 48·4%), shown to consist of 3 : 5-dimethyl xylose very slightly contaminated with xylose, monomethyl xylose, and 3 : 4-dimethyl xylose; fraction 2 (2·3 g.), b. p. 115—130°/0·01 mm., n_D 1·4553 (Found : OMe, 26·2%), which was purified by extraction with ethyl acetate from aqueous solution. Redistillation at 105—115°/0·1 mm. gave a colourless syrup (1·1 g.), n_D^{15} 1·4512 (Found : OMe, 47·9%).

Characterisation of 3 : 5-*Dimethyl Xylose*.—The 3 : 5-dimethyl methylxyloside (138 mg.), $[\alpha]_D^{15}$ + 102° (*c*, 1·39 in water), was hydrolysed at 100° with 0·1N-sulphuric acid (11 c.c.) until

the rotation ($[\alpha]_D^{15}$ +17·5°) was constant (0·5 hour). After neutralisation of the solution with barium carbonate and evaporation to dryness 3 : 5-dimethyl xylose was obtained as a colourless syrup. This was separated from traces of 3 : 4-dimethyl xylose, monomethyl xylose, and xylose on a column of powdered cellulose (Chanda, Hirst, and Percival, *J.*, 1951, 1240). The solvent employed for elution was purified light petroleum (b. p. 100—120°)–*n*-butanol (6 : 4) saturated with water. A colourless syrup was obtained, having n_D 1·4583, $[\alpha]_D$ +23° (*c*, 1·3 in water), +10° (*c*, 1·3 in chloroform). Laidlaw (*J.*, 1952, 2942) reports +25° (*c*, 1·13 in water), +11° (*c*, 0·84 in chloroform). Attempts to prepare a crystalline anilide were unsuccessful, with the exception of once when a minute quantity of crystals, m. p. 126—127°, was obtained. The sugar (0·8 g.) was oxidised to the lactone (0·7 g.), b. p. 110—125°/0·08 mm., $[\alpha]_D$ +75° (4 minutes), +82° (24 minutes), +72° (24 hours), +67° (7 days), +56° (11 days), +27° (33 days, constant) (*c*, 1·34 in water) (cf. Laidlaw, *loc. cit.*; Haworth and Porter, *loc. cit.*; Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 331).

3 : 5-Dimethyl methylxyloside (0·8 g.) was methylated 3 times with methyl iodide and silver oxide, and a colourless syrup (2 : 3 : 5-trimethyl methylxylose) (0·8 g.) was isolated. This had n_D^{15} 1·4431, $[\alpha]_D^{15}$ +114° (*c*, 0·1 in methanol), +134° (*c*, 0·33 in water) (Found: OMe, 60·6. Calc. for $C_9H_{18}O_6$: OMe, 60·3%). This syrup (0·7 g.) in nitric acid (10 c.c.; *d* 1·4) was heated at 50° until the evolution of brown fumes had ceased (2 hours). The solution was then kept at 95° for 6 hours. The acid was removed by continuous addition and removal of water under diminished pressure. The syrup (0·420 g.) so obtained was esterified by methanolic hydrogen chloride (10 c.c.; 2%) for 6 hours at 65°. After neutralisation and evaporation of the solvent distillation gave a syrupy ester (0·25 g.), b. p. 120—130°/0·1 mm., n_D^{15} 1·4370, $[\alpha]_D^{15}$ +52° (*c*, 0·1 in methanol). Treatment of this ester for 2 days at 0° with methanol (10 c.c.) saturated with ammonia gave crystals of 2 : 3-dimethoxysuccindiamide (18 mg.), m. p. 270° (decomp.), unchanged on admixture with an authentic specimen, $[\alpha]_D$ +100° (*c*, 0·31 in water) (Found: OMe, 35·5; N, 16·2. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·2, N, 15·9%).

2-*Benzoyl* 3 : 4-*Dimethyl Methylxyloside.*—3 : 5-*iso*Propylidene methylxyloside (6·4 g.) was treated with benzoyl chloride by Robertson and Speedie's method (*loc. cit.*). The product was a syrup (8·8 g., 94·5%) which partly crystallised at 0°. The crystals (2-benzoyl 3 : 5-*iso*propylidene methylxyloside) (1·2 g.) had m. p. 86°, $[\alpha]_D^{15}$ +114° (*c*, 0·1 in chloroform) (Found: C, 62·3; H, 6·5; $COMe_2$, 18·65. Calc. for $C_{16}H_{19}O_6$: C, 62·5; H, 6·2; $COMe_2$, 18·8%). A mixture of syrup and crystals (7·6 g.) when treated with methanolic hydrogen chloride as described for the 2-toluenesulphonyl derivative gave a syrup (6·6 g.), n_D 1·5217, $[\alpha]_D^{15}$ +31° (*c*, 1·3 in chloroform) (Found: OMe, 16·15. Calc. for $C_{13}H_{16}O_6$: OMe, 11·6%), which after 3 methylations with silver oxide and methyl iodide gave a pale yellow syrup (6·4 g.). Solution of the latter in benzene and extraction with water (4 × 25 c.c.) partly removed trimethyl methylxyloside. The purified material (5·2 g., 71%) was debenzoylated by Zemplén's method (*Ber.*, 1929, **62**, 1613), giving a colourless syrup (D) (2·3 g., 68%) which partly crystallised. The crystals (needles; 0·25 g.) were separated and after recrystallisation from light petroleum (b. p. 60—80°) had m. p. 88—89°, not depressed by an authentic specimen of 3 : 4-dimethyl methylxyloside supplied by Dr. J. K. N. Jones (Found: C, 49·9; H, 8·3; OMe, 48·5. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·4; OMe, 48·45%), $[\alpha]_D^{18}$ −33° (*c*, 2·48 in chloroform), −58° (*c*, 0·47 in water). Robertson and Speedie recorded m. p. 89—90°, $[\alpha]_D$ −82·5° (*c*, 2·0 in chloroform), for 3 : 4-dimethyl β-methylxyloside.

Characterisation of 3 : 4-*Dimethyl Xylose.*—Crystalline 3 : 4-dimethyl methylxyloside (47 mg.), $[\alpha]_D^{15}$ −58° (*c*, 0·47 in water), was hydrolysed with 0·1N-sulphuric acid at 100° for 6·5 hours, by which time the rotation had changed to $[\alpha]_D^{15}$ +22°. After a further 40 minutes' heating with N-sulphuric acid the rotation was $[\alpha]_D^{15}$ +35° (constant). After neutralisation and evaporation of the solvent 3 : 4-dimethyl xylose was obtained as a colourless syrup (35 mg.). This was oxidised by bromine water in the usual way. The product which distilled at 125—135°/0·03 mm. solidified on cooling and was obtained on recrystallisation from light petroleum (b. p. 60—80°) as large needles, m. p. 68°, unchanged on admixture with an authentic sample of 3 : 4-dimethyl xylonolactone.

Crystalline 3 : 4-dimethyl methylxyloside (250 mg.) when twice treated with methyl iodide and silver oxide gave crystalline 2 : 3 : 4-trimethyl methylxyloside which after purification by sublimation (yield 106 mg.) had m. p. 44—45°, $[\alpha]_D^{15}$ −46° (*c*, 1·0 in chloroform). This substance (106 mg.) was oxidised with nitric acid as described previously. Esterification of the product with methanolic hydrogen chloride followed by amide formation with methanolic ammonia gave crystalline *xylo*trimethoxyglutardiamide, m. p. 197°, alone or on admixture with an authentic specimen, $[\alpha]_D$ 0° (*c*, 0·5 in water).

Examination of the Syrup (D).—Hydrolysis of the syrup (D), after removal of the crystalline 3 : 4-dimethyl methylxyloside, with N-sulphuric acid at 100° until the rotation was constant ($[\alpha]_D$ +36°), and examination of the product on a paper chromatogram revealed the presence of trimethyl xylose (R_G 0·94), 3 : 5- (R_G 0·52), 3 : 4- (R_G 0·42), and 2 : 4-dimethyl xylose (R_G 0·39), an unidentified sugar (R_G 0·30), and some monomethyl xylose and xylose. This mixture (1·06 g.) was separated on a column of powdered cellulose (Chanda, Hirst, and Percival, *loc. cit.*). The solvent employed for elution was purified light petroleum (b. p. 100—120°)–*n*-butanol (1 : 1) saturated with water. Fraction 1 (0·260 g.) was trimethyl xylose, n_D 1·4560. Fraction 2 (0·423 g.) was a mixture of 3 : 5-, 3 : 4-, and 2 : 4-dimethyl xylose. Fraction 3 (0·052 g.) was crystalline 2 : 4-dimethyl xylose, m. p. 110°. Fraction 4 (0·32 g.) was a mixture of monomethyl xylose and xylose. Quantitative determination of the dimethyl sugars in fraction 2 by the method of Hirst, Hough, and Jones (*loc. cit.*) with benzene–amyl alcohol–ethanol–water (1·7 : 1 : 1 : 0·25) as the eluting solvent indicated the presence of 3 : 5-dimethyl xylose 26%, 3 : 4-dimethyl xylose 37%, 2 : 4-dimethyl xylose 23%, and an unidentified sugar (R_G 0·30) 14·5%.

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