266. *Deoxy-sugars. Part II. Synthesis of 2-Deoxy-D-ribose and 3-Deoxy-D-xylose from D-Arabinose.*

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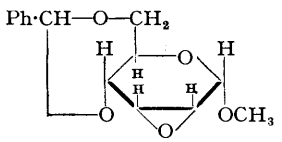
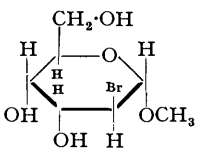
2 : 3-*Anhydro-β-methyl-D-riboside* has been obtained crystalline. Its anhydro-ring has been found to open readily with hydrobromic acid to yield mainly 3-*bromo β-methyl-D-xyloside* together with 2-bromo β-methyl-D-arabinoside. The latter has been converted into 2-deoxy-D-ribose, but the low overall yield of this compound makes the new synthesis of little practical value. New evidence on the structure of 3-deoxyxylose is presented.

2-Deoxy-D-ribose occurs as the sole identified sugar component of the deoxyribonucleic acid of cell nucleal material. It is thus a natural product of great biological importance and we are exploring various routes to its synthesis. The standard method from D-arabinal (Fischer, *Ber.*, 1914, **47**, 186; Meisenheimer and Jung, *Ber.*, 1927, **60**, 1462) as initial material does not give satisfactory yields, and the present method is concerned with the possible utilisation of 2 : 3-anhydro-sugars as the starting point. While the work was in progress, a closely similar route in the L-series was followed by Mukherjee and Todd (*J.*, 1947, 969), with essentially the same results as our own. Our approach was made possible by the work of Overend, Newth, and Wiggins (*J.*, 1947, 10), who showed that 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I) suffers ring scission with either hydrochloric or hydrobromic acid to form a mixture of the corresponding halogeno sugars. Thus, 2-bromo (or 2-chloro) α-methylaltroside (II) and 3-bromo(or 3-chloro) α-methylglucoside (III) were isolated. In this case the former predominated, and it was noted that there was a small increase in the proportion of the glucose isomer formed as compared with the amount obtained by ring scission with alkali of the same anhydro-ring compound.



(I.)



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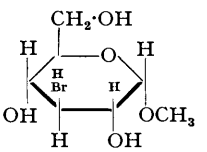


(III.)

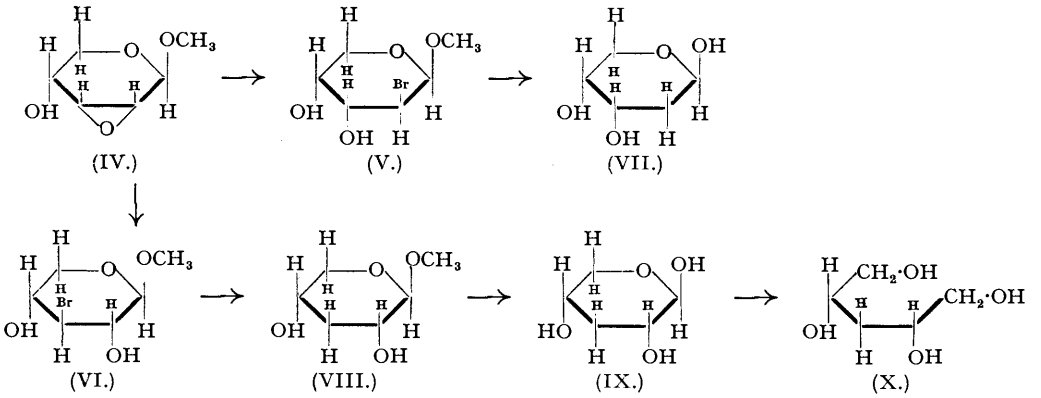
It was clear that 2 : 3-anhydromethylriboside should, by analogy with the anhydroalloside (I), undergo ring scission with hydrobromic acid to yield derivatives of 2-bromo arabinose and 3-bromo xylose. The relative amounts of these compounds, by analogy with the alloside case, should favour the production of the 2-bromo arabinose derivative. The preparation of crystalline 2 : 3-*anhydro-β-methyl-D-riboside* (IV) has now been achieved (cf. Honeyman, *J.*, 1946, 990), and its ring scission with hydrobromic acid accomplished, giving the expected two products, 2-bromo β-methyl-D-arabinoside (V) and 3-*bromo β-methyl-D-xyloside* (VI). The

relative amounts of those compounds, however, were such that it was the xylose derivative and not the arabinose derivative which was formed in predominating yield. A separation of the two products was achieved by reason of the fact that the xyloside crystallised with ease whereas the arabinoside remained liquid. Separation of these two substances was also secured by acetonisation of the mixture, whereby only the arabinoside formed an *iso*propylidene derivative, namely, 2-bromo 3 : 4-*iso*propylidene β-methyl-D-arabinoside, which remained as a liquid. An alternative and precise method of separation was by chromatographic adsorption of the mixture on an alumina column. The 2-bromo β-methylarabinoside was more readily eluted from the column than was the 3-bromo β-methylxyloside, and in this way the mixture (1·05 g.) of halogeno pentosides was resolved into the crystalline 3-bromo β-methylxyloside (0·85 g.) and the liquid 2-bromo β-methylarabinoside (0·09 g.).

The latter substance on catalytic hydrogenation over Raney nickel in the presence of calcium hydroxide gave a liquid which on mild hydrolysis with acetic acid produced 2-deoxy-D-ribose (VII), isolated as the *anilide* identical with that obtained by Deriaz, Stacey, Teece, and Wiggins (forthcoming publication). This compound gives a positive diphenylamine reaction (Dische, *Mikrochemie*, 1930, **8**, 4) identical with that given by authentic 2-deoxy-D-ribose.

This constitutes a new synthesis of 2-deoxyribose, although the relatively low yield obtained deprives the method of any preparative significance.

The designation of the crystalline bromo methylpentoside as 3-bromo β-methylxyloside (cf. Mukherjee and Todd, *loc. cit.*, for the same compound in the L-series) is shown by the



following facts : (*a*) The compound did not react with lead tetra-acetate under Hockett and McClenahan's conditions (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). (*b*) Catalytic hydrogenation of the crystalline bromo methylpentoside gave a deoxymethylpentoside which failed to give Dische's test for 2-deoxypentoses. This test as developed by Deriaz, Stacey, Teece, and Wiggins (preceding paper) indicates the presence of 2-deoxypentoses only. (*c*) The deoxymethylpentoside on hydrolysis, followed by hydrogenation, afforded a crystalline deoxypentitol identified by formation of its tetrabenzoate. Both the deoxypentitol and the tetrabenzoate were optically inactive in polarized light of a range of wave-lengths in the visible spectrum. A deoxypentitol with the deoxy-group at C_3, namely, 3-deoxyxylitol, is the only deoxypentitol which shows no dissymmetry.

Hence, the bromo methylpentose is 3-bromo β-methyl-D-xyloside (VI), the hydrogenation product is 3-deoxy-β-methyl-D-xyloside (VIII), and the hydrolysis product is 3-*deoxy-D-xylose* (IX). 3-*Deoxy-D-xylitol* (X) was obtained by hydrogenation of 3-deoxy-D-xylose, and its benzoyl derivative undoubtedly was 1 : 2 : 4 : 5-*tetrabenzoyl* 3-*deoxyxylitol*. The 3-deoxy-D-xylose gave a crystalline *p*-nitrophenylhydrazone having the same melting point as that recorded by Mukherjee and Todd (*loc. cit.*) for the enantiomorph.

Experimental.

2-*Toluene*-p-*sulphonyl* β-*Methyl-D-arabinoside*.—The 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabinoside described by Jones, Kent, and Stacey (*J.*, 1947, 1341) (2·4 g.) was heated at 100° for 3 hours with N-acetic acid (23 c.c.). The solution was then evaporated to dryness in a vacuum over potassium hydroxide. 2-*Toluene*-p-*sulphonyl* β-*methyl-D-arabinoside*, crystallised and recrystallised from chloroform, had m. p. 53—55°, $[\alpha]_D^{19°}$ −177·4° in methanol (*c*, 3·4), $[\alpha]_D$ −111·1° in $CHCl_3$ (*c*, 0·2); yield 1·9 g. (Found : C, 48·8; H, 5·7. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7%). Honeyman (*loc. cit.*) described the enantiomorph as having m. p. 48—49°, $[\alpha]_D$ +110·9° in chloroform.

2 : 3-*Anhydro*-β-*methyl*-D-*riboside*.—To the foregoing compound (2·8 g.), dissolved in dry chloroform (10 c.c.) at 0°, was added a solution of sodium (0·2 g.) in dry methyl alcohol. After being kept for 12 hours at room temperature, the solution was diluted with chloroform (50 c.c.) and shaken with water (100 c.c.). The aqueous solution was neutralised with dilute sulphuric acid (litmus) and evaporated to dryness. The residue was extracted repeatedly with hot ethyl acetate, and the extract evaporated to dryness. The product distilled at 110° (bath temp.)/0·05 mm., and completely crystallised on cooling. The *anhydro*-compound, recrystallised from ether–ligroin, had m. p. 46°; yield 0·75 g., $[\alpha]_D^{22°}$ −35·8° in chloroform (*c*, 0·6) (Found: C, 49·0; H, 6·80; OMe, 21·3. $C_6H_{10}O_4$ requires C, 49·4; H, 6·85; OMe, 21·4%).

Ring Scission of 2 : 3-*Anhydro*-β-*methyl*-D-*riboside with Hydrobromic Acid*.—2 : 3-Anhydro-β-methyl-D-riboside (1·2 g.) was dissolved in acetone (160 c.c.) to which had been added 3·78N-hydrobromic acid (5·8 c.c.). The mixture was heated under reflux for 5 hours and then neutralised with lead carbonate. The solution was evaporated to a small bulk, diluted with water (100 c.c.), and extracted with ether in order to remove coloured impurities. The aqueous solution was evaporated to dryness, and the residue extracted with hot ethyl acetate. The product consisted of a mixture of 2-bromo β-methyl-D-arabinoside and 3-bromo β-methyl-D-xyloside.

Separation of products. (*A*) The foregoing product partly crystallised and some 3-*bromo* β-*methylxyloside* (0·9 g.) separated; m. p. 101—102°, $[\alpha]_D^{18°}$ −16·4° in methyl alcohol (*c*, 0·4) (Found: C, 31·5; H, 4·80; Br, 34·9. $C_6H_{11}O_4Br$ requires C, 31·7; H, 4·83; Br, 35·2%). This substance showed no reaction when treated with lead tetra-acetate under Hockett and McClenahan's conditions (*loc. cit.*). The residual syrup was dissolved in dry acetone (100 c.c.) containing concentrated sulphuric acid (0·3 c.c.). After being shaken for 12 hours, the solution was neutralized with anhydrous sodium carbonate, filtered, and evaporated to dryness. The product contained 3-bromo β-methyl-D-xyloside and 2-bromo 3 : 4-*iso*propylidene β-methyl-D-arabinoside. The former compound crystallised and was removed by treatment with ethyl acetate–ligroin, and the residual liquid was mainly the latter compound; $n_D^{17°}$ 1·4517, $[\alpha]_D^{17°}$ −47·1° in methanol (*c*, 0·3) (Found: OMe, 12·0. Calc. for $C_9H_{15}O_4Br$: OMe, 11·6%). Attempts to purify this substance by distillation under high vacuum were unsuccessful owing to extensive decomposition (even in the presence of barium carbonate).

(*B*) The halogeno pentoside mixture (1·05 g.) obtained by the ring scission of another sample of 2 : 3-anhydro-β-methylriboside was dissolved in ethanol–benzene (1 : 1; 100 c.c.) and adsorbed on an alumina column, which was immediately eluted with benzene (150 c.c.). The eluate was collected in 15-c.c. portions. From the first two fractions syrupy 2-bromo β-methyl-D-arabinoside (0·09 g.) was obtained. Evaporation of the remaining fractions furnished only crystalline 3-bromo β-methyl-D-xyloside (0·85 g.). By further elution of the column with ethyl acetate–benzene (1 : 1) and 75% ethyl acetate in benzene, only traces of the 3-bromo xyloside were isolated.

Formation of 2-*Deoxy*-β-*methyl*-D-*riboside* (*Arabinoside*) *from* 2-*Bromo* β-*Methyl*-D-*arabinoside*.—2-Bromo β-methyl-D-arabinoside (0·17 g.) was dissolved in methanol (30 c.c.) to which calcium hydroxide (0·1 g.) and Raney nickel (1 g.) were added. The mixture was shaken with hydrogen at room temperature. After 4 hours, the solution was saturated with carbon dioxide, filtered, and evaporated to dryness. Extraction of the residue with ethyl acetate and evaporation of the solvent gave a halogen-free syrup, which was 2-deoxy-β-methyl-D-riboside. This distilled at 112° (bath temp.)/0·02 mm.; yield 0·08 g., $n_D^{24°}$ 1·4665 (Found: OMe, 20·43. Calc. for $C_6H_{12}O_4$: OMe, 20·94%).

2-*Deoxy*-D-*ribose Anilide*.—2-Deoxy-β-methyl-D-riboside (0·075 g.) was heated with 0·01N-acetic acid (10 c.c.) for 2 hours. The solution was then strongly reducing to Fehling's solution. The hydrolysate was evaporated to dryness at room temperature over potassium hydroxide and phosphoric oxide in a vacuum desiccator. The syrupy 2-deoxy-D-ribose so obtained was heated under reflux with dry ethanolic aniline (2 c.c., 2·5%) for 3 hours. On evaporation of the solvent, a solid separated which, recrystallised from ethanol (0·04 g.), had m. p. 165—166° alone or in admixture with authentic 2-*deoxy*-D-*ribose anilide* as obtained by Deriaz, Stacey, Teece, and Wiggins (unpublished work) (Found: C, 62·92; H, 7·16. $C_{11}H_{15}O_3N$ requires C, 63·17; H, 7·18%).

3-*Deoxy*-β-*methyl*-D-*xyloside*.—3-Deoxy-β-methyl-D-xyloside (0·9 g.) was hydrogenated at room temperature by shaking a methyl-alcoholic solution of it with hydrogen under 1 atm. in the presence of Raney nickel (2 g.) and potassium hydroxide (0·1 g.). The mixture was then saturated with carbon dioxide, filtered (charcoal), and evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl acetate and the extract evaporated to a syrup (0·68 g.). This 3-*deoxy*-β-*methyl*-D-*xyloside* distilled at 110—112° (bath temp.)/0·01 mm., and had $n_D^{26°}$ 1·4566, $[\alpha]_D^{19°}$ −13·3° in water (*c*, 3·0) (Found: C, 48·3; H, 8·3; OMe, 20·2. $C_6H_{12}O_4$ requires C, 48·6; H, 8·1; OMe, 20·9%).

2 : 4-*Bis*-3′ : 5′-*dinitrobenzoyl* 3-*Deoxy*-β-*methyl*-D-*xyloside* (as VIII).—3-Deoxy β-methyl-D-xyloside (0·1 g.) was dissolved in dry pyridine (10 c.c.) at 0°, 3 : 5-dinitrobenzoyl chloride (0·1 g.) added, and the mixture kept for 12 hours. Thereafter the solution was poured into water and the *ester* so obtained was recrystallised from ethanol; m. p. 157—158°; yield 0·05 g. (Found: C, 44·6; H, 2·9. $C_{20}H_{16}O_{12}N_4$ requires C, 44·8; H, 2·99%).

3-*Deoxy*-D-*xylose*.—3-Deoxy-β-methyl-D-xyloside (0·6 g.) was hydrolysed by being heated at 100° with 0·05N-hydrochloric acid (20 c.c.) for 4 hours. (During this time the $[\alpha]_D$ changed from −9·3° to −2·8°.) The resulting solution was neutralised with silver carbonate, filtered (charcoal), and evaporated to dryness at 40° under reduced pressure. The product (0·57 g.) reduced Fehling's solution and had $n_D^{16°}$ 1·4610, $[\alpha]_D^{24°}$ −6·3° (*c*, 1·3) in water. Mukherjee and Todd describe the enantiomorph as having $[\alpha]_D$ +8·7°.

3-*Deoxy*-D-*xylose* p-*Nitrophenylhydrazone*.—3-Deoxy-D-xylose (0·04 g.) was dissolved in glacial acetic acid (1·5 c.c.). *p*-Nitrophenylhydrazine (0·085 g.) was added, and the mixture heated for 45 minutes at 100°. A red solid separated which recrystallised from ethyl alcohol; m. p. 253—255°, yield 0·06 g. Mukherjee and Todd (*loc. cit.*) described the enantiomorph as having m. p. 254—256°.

3-*Deoxyxylitol*.—3-Deoxy-D-xylose (0·4 g.) was dissolved in water (250 c.c.), and Raney nickel (1·5 g.) added to the solution. The mixture was hydrogenated at 100° for 10 hours at 30 atm. The catalyst was removed by filtration (charcoal), and the solution evaporated to dryness. A colourless non-reducing

syrup (0·38 g.), $n_D^{22°}$ 1·4730, was obtained. This 3-*deoxyxylitol* crystallised on keeping, and on recrystallisation from ether–ligroin had m. p. 68—69°. The optical rotation of this compound was zero (*c*, 4·1 in ethanol) when measured in sodium light, the 5461 line of the mercury spectrum, or the red line in the cadmium spectrum (Found: C, 43·8; H, 8·90. $C_5H_{12}O_4$ requires C, 44·1; H, 8·82%).

Tetrabenzoyl 3-*Deoxyxylitol.*—3-Deoxyxylitol (0·11 g.) was dissolved in dry pyridine (4·5 c.c.) at 0°, benzoyl chloride (0·45 g.) was added, and the mixture kept for 12 hours at room temperature. When the solution was poured into ice-water (60 c.c.), the solid *tetrabenzoyl* derivative separated; this, recrystallised from ethanol, had m. p. 104—105°, $[\alpha]_D$ ±0° (for the above three lines) (Found: C, 70·9; H, 5·0. $C_{33}H_{28}O_8$ requires C, 71·5; H, 5·07%).

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[*Received, November 11th*, 1948.]