230. *The Synthesis of 2 : 3-Dimethyl L-Rhamnose ; The Action of Sodium Metaperiodate on 2 : 3- and 3 : 4-Dimethyl L-Rhamnoses.*

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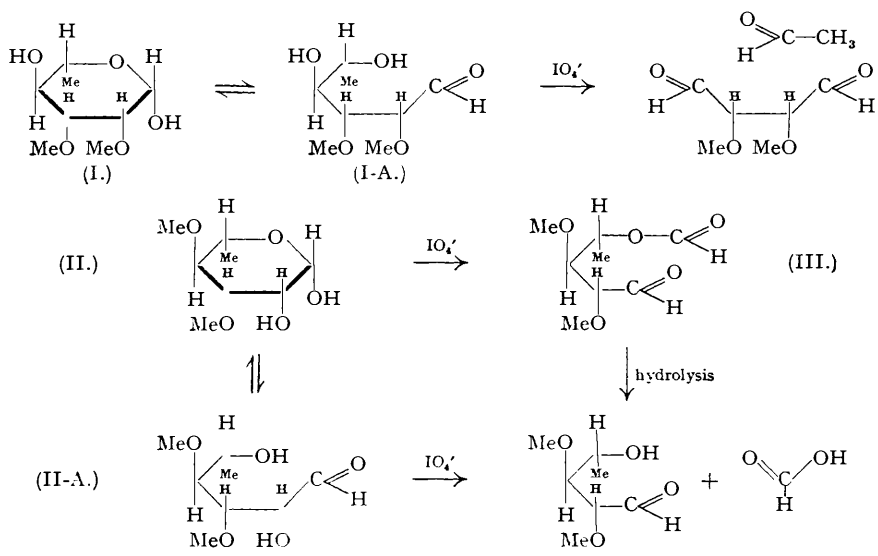
The synthesis is described of 2 : 3-dimethyl L-rhamnose *via* 4-benzoyl 2 : 3-*iso*propylidene α-methyl-L-rhamnoside. The oxidation of 2 : 3- and 3 : 4-dimethyl L-rhamnose with sodium metaperiodate has been shown to be anomalous.

During an investigation of the scission products of methylated *Sterculia setigera* gum (Hough and Jones, in the press) dimethyl L-rhamnose was encountered in admixture with 2 : 3 : 4 : 6-tetramethyl D-galactose and, since they could not be separated by distillation or partition, attention was given to the use of sodium periodate, a reagent diagnostic for α-glycol groups, for the determination of the dimethyl rhamnose. 2 : 4-Dimethyl rhamnose will not be oxidised by periodate, but 2 : 3-dimethyl rhamnose (I) should theoretically consume 1 mole of periodate and yield 1 mole of acetaldehyde per mole, and 3 : 4-dimethyl rhamnose (II) should consume 1 mole of periodate with the formation of 1 mole of formic acid per mole. This being so, a determination of the periodate uptake and the yields of acetaldehyde and formic acid should give the amounts of each of these dimethyl derivatives present in the mixture. An authentic specimen of 2 : 3-dimethyl rhamnose was not available and accordingly 2 : 3-dimethyl L-rhamnose was synthesised for model oxidation experiments by the following route. 2 : 3-*iso*-Propylidene α-methyl-L-rhamnoside (Levene and Muskat, *J. Biol. Chem.*, 1934, **105**, 431) was converted into 4-*benzoyl* 2 : 3-iso*propylidene α-methyl-L-rhamnoside*, m. p. 97—98°, which was



heated in acetic acid to remove the *iso*propylidene group. The resultant 4-benzoyl α-methyl-L-rhamnoside with silver oxide and methyl iodide gave the syrupy 2 : 3-dimethyl derivative along with a little monomethyl derivative formed by under-methylation. This mixture was produced deliberately so that the separation of 2- and 3-methyl L-rhamnose would be attempted (see below). Removal of the benzoyl group by potassium hydroxide and extraction of the alkaline solution (*A* ; see Experimental section) with chloroform gave mainly 2 : 3-dimethyl α-methyl-L-rhamnoside. Hydrolysis of this product followed by purification by partition chromatography on a column of cellulose using *n*-butanol–light petroleum as the mobile phase (Hough, Jones, and Wadman, *J.*, 1949, 2511) separated the monomethyl and traces of the trimethyl derivative from the syrupy 2 : 3-*dimethyl* L-*rhamnose* ([α] +42·5°), which gave one discrete spot only on the paper chromatogram. The benzoyl group, it might be argued, could have wandered during the methylation; however, we have come across no evidence in the literature which describes the migration of benzoyl groups during methylation with Purdie's reagents. In fact, 2 : 3 : 4-tribenzoyl methylglucoside passes into the 6-methyl derivative on methylation; no rearrangement occurs (Helferich and Günther, *Ber.*, 1931, **64**, 1276).

Acetyl groups are more prone to migration than are benzoyl groups, yet 3 : 4-diacetyl methyl-rhamnoside furnishes the 2-methyl derivative on methylation without rearrangement (Elderfield and McPhillamy, *J. Org. Chem.*, 1939, **4**, 150). When migration of acyl groups does occur, it is always away from the reducing grouping and not towards it. Had any migration occurred, 3 : 4- or 2 : 4-dimethyl L-rhamnose might have been produced. The product isolated is certainly not 3 : 4-dimethyl L-rhamnose, but it could have been 2 : 4-dimethyl L-rhamnose. The isolation in high yield of a crystalline anilide, identical with 2 : 3-dimethyl L-rhamnose anilide, prepared by Percival and Percival (*J.*, 1950, 690), places beyond doubt the identity of the sugar as the 2 : 3-isomer. This dimethyl sugar (R_G 0·83) moves rapidly on the paper chromatogram and is readily distinguished from 3 : 4-dimethyl rhamnose (R_G 0·90) by its slower rate of movement (Hirst, Hough, and Jones, *J.*, 1949, 928) and by the colours produced on spraying the paper chromatogram with a solution of aniline trichloroacetate in glacial acetic acid and then heating the paper; 2 : 3-dimethyl rhamnose gives a reddish-brown and 3 : 4-dimethyl rhamnose gives a green colour. 2 : 3-Dimethyl rhamnose gave a characteristic *anilide* (m. p. 135—136°). On treatment with sodium metaperiodate, 2 : 3-dimethyl L-rhamnose (I) was oxidised to a small extent, some 10% of the theoretical quantity of periodate being consumed, probably because the hydroxyl group on $C_{(4)}$ is masked by the relatively stable pyran ring, so that only the aldehydic form (I-A) (which possesses the necessary contiguous hydroxyl groups) will be oxidised. Bell (*J.*, 1948, 992) and Hirst and Jones (*J.*, 1949, 1659) have observed that other methyl sugars behave in an anomalous manner towards periodate. 3 : 4-Dimethyl L-rhamnose (II) (Bott, Haworth, and Hirst, *J.*, 1930, 1395; Levene and Kreider, *J. Biol. Chem.*, 1937, **120**, 602) consumes 70% of the theoretical amount of periodate and yet yields only 10% of the theoretical quantity of formic acid. This indicates the formation of 70% of a formyl ester (III) on oxidation, the free formic acid arising from either the oxidation of the aldehydic form (II-A) or the hydrolysis of the ester (III) (cf. Halsall, Hirst, and Jones, *J.*, 1947, 1430; Meyer and Rathgeb, *Helv. Chim. Acta*, 1949, **32**, 1102).

A similar synthesis of 2 : 3-dimethyl L-rhamnose has been achieved by Percival and Percival (*loc. cit.*), whose work was carried out simultaneously with ours but quite independently. Through the kindness of Dr. E. G. V. Percival we were able to compare his product with ours. Each dimethyl rhamnose moved at the same rate on the same paper chromatogram and they gave identical colours with the aniline trichloroacetate reagent. Schmidt, Plankenhorn, and Kübler (*Ber.*, 1942, **75**, *B*, 579) have also prepared 2 : 3-dimethyl L-rhamnose ($[\alpha]_D$ +47·6°), a syrup, by an alternative method *via* the 1 : 5-dibenzyl 2 : 3-*iso*propylidene compound.

Continuous extraction of the alkaline solution (*A*; see above) with chloroform afforded a mixture of 2- and 3-monomethyl L-rhamnosides, which could not be separated by partition chromatography on cellulose. An estimate of the amount of periodate consumed by the mixture and of the acetaldehyde produced showed that they were incompletely oxidised.

Experimental.

4-Benzoyl 2 : 3-iso*Propylidene* α-*Methyl*-L-*rhamnoside*.—Benzoyl chloride (2·2 ml.) was added with shaking to a solution of 2 : 3-*iso*propylidene α-methyl-L-rhamnoside (2·2 g.) (Levene and Muskat, *loc. cit.*) in dry pyridine (5 ml.), and the mixture was set aside at room temperature overnight. The whole was dissolved in chloroform (50 ml.) and then washed with successive portions of water, dilute hydrochloric acid, dilute sodium hydroxide solution, and twice more with water. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to a pale yellow syrup which, on cooling, crystallised. The *rhamnoside* recrystallised from light petroleum (b. p. 60—80°) in the form of white needles (3·4 g.), m. p. 97—98°, $[\alpha]_D^{23}$ −2° (*c*, 2·14 in methanol) (Found : C, 63·5; H, 6·9. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·8%).

4-Benzoyl α-*Methyl*-L-*rhamnoside*.—4-Benzoyl 2 : 3-*iso*propylidene α-methyl-L-rhamnoside (3·3 g.) was dissolved in glacial acetic acid (20 ml.) and heated on a boiling water-bath. Water (100 ml.) was added in small portions during 1 hour. After 1½ hours the solution was evaporated at 40° under reduced pressure to a syrup (2·5 g.) which partly crystallised.

4-Benzoyl 2 : 3-*Dimethyl* α-*Methyl*-L-*rhamnoside*.—4-Benzoyl α-methyl-L-rhamnoside (2·5 g.) was methylated with Purdie's reagents and the product (2·3 g.) isolated in the usual manner (Found : OMe, 25·6. Calc. for $C_{16}H_{22}O_6$: OMe, 30·0%).

2 : 3-*Dimethyl* α-*Methyl*-L-*rhamnoside*.—The dimethyl compound (2·3 g.) was hydrolysed in potassium hydroxide solution (10%; 50 ml.) for 1 hour on a boiling water-bath. The solution (*A*) was then extracted with chloroform (4 × 50 ml.), and the combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to a syrup (0·835 g.). The product was distilled in a high vacuum, yielding a colourless syrup, $[\alpha]_D$ −14° (*c*, 1·94), n_D^{21} 1·4565 (Found : OMe, 38·6. Calc. for $C_9H_{18}O_5$: OMe, 45·1%).

2 : 3-*Dimethyl* L-*Rhamnose*.—The methylrhamnoside (0·485 g.) was hydrolysed in 0·5N-sulphuric acid (25 ml.) on the boiling water-bath, and the reaction followed polarimetrically : $[\alpha]_D$ −14° (*c*, 1·94;

initial); 0° (1 hour); +15° (2 hours); +23° (3 hours); +32° (4 hours; constant). The solution was neutralised with Amberlite resin IR-4B and the solution evaporated to a syrup (0·36 g.). On the paper chromatogram the product was observed to contain largely dimethyl rhamnose (R_G 0·83) with traces of trimethyl rhamnose (R_G 1·03) and monomethyl rhamnoses (R_G 0·45 and 0·47; spots overlapped). A solution (2·5%) of aniline trichloroacetate in glacial acetic acid was used for the detection of the methyl rhamnoses on the paper. When heated, 2 : 3-dimethyl rhamnose and the monomethyl rhamnose spots became reddish-brown, whereas those of 2 : 3 : 4-trimethyl and 3 : 4-dimethyl rhamnose became green. The syrupy mixture (0·25 g.) was separated on a column of cellulose using a mixture of *n*-butanol (3 parts) and light petroleum (b. p. 100—120°) (7 parts) as the mobile phase (cf. Hough, Jones, and Wadman, *loc. cit.*). After separation, 2 : 3-dimethyl L-rhamnose was obtained, on removal of the solvent by distillation under reduced pressure, as a syrup (0·1 g.), $[\alpha]_D$ +42·5° (*c*, 0·82), R_G 0·83 (Found: OMe, 31·6. $C_8H_{16}O_5$ requires OMe, 32·3%). A portion (6·32 mg.) was treated with sodium metaperiodate (0·2M.; 1 ml. added from an Agla micrometer syringe) at room temperature for 3 hours. An estimate of the periodate consumed by the addition of an excess of 0·142N-sodium arsenite (5 ml.) and back-titration with 0·0169N-iodine (16·7 ml.) revealed that only about 10% of the 2 : 3-dimethyl rhamnose was oxidised. A control determination was carried out on 1 ml. of periodate (0·2M.) and 5 ml. of arsenite (0·142N.); it required 17·15 ml. of 0·0169N-iodine. Another portion (50 mg.) was converted into the crystalline anilide by the method of Percival and Percival (*loc. cit.*). The product was washed with a little ether to remove excess of aniline. The slightly impure *anilide* was recrystallised from ether–light petroleum and then had m. p. 135—136° (yield, 89%) (Found: OMe, 23·0. $C_{14}H_{21}O_4N$ requires OMe, 23·2%), not depressed on admixture with an authentic specimen supplied by Drs. E. E. and E. G. V. Percival.

2- *and* 3-*Monomethyl* L-*Rhamnoses*.—The alkaline solution (*A*) above was extracted continuously for 8 hours with chloroform. The extract was dried ($MgSO_4$) and evaporated to a syrup (0·27 g.), n_D^{20} 1·4700, $[\alpha]_D^{20}$ +31° (*c*, 1·2) (Found: OMe, 28·7. Calc. for $C_8H_{16}O_5$: OMe, 32·3%). The product (0·25 g.), in 0·5N-sulphuric acid (25 ml.), was heated on the boiling water-bath: $[\alpha]_D$ +31° (initial value) ⟶ +40° (5 hours; constant). The solution was neutralised with Amberlite resin IR-4B and evaporated to a syrup (0·14 g.) which was examined on the paper chromatogram. It consisted mainly of monomethyl rhamnoses (R_G 0·45 and 0·42; spots overlapped) with a trace of 2 : 3-dimethyl rhamnose. The product was purified by partition chromatography on a column of cellulose, using *n*-butanol half-saturated with water as the mobile phase. The monomethyl rhamnoses were not separated one from another but they were separated from the 2 : 3-dimethyl rhamnose to yield a syrup (0·06 g.) (Found: OMe, 15·5. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). Oxidation of a portion (13·3 mg.) with sodium metaperiodate (0·2M.; 2 ml.) showed that 1 mole of the monomethyl L-rhamnoses consumed 1 mole of periodate, which is half of the theoretical quantity. Oxidation of another portion (13·3 mg.) with sodium metaperiodate for 3 hours and determination of the acetaldehyde produced by the method of Nicolet and Shinn (*J. Amer. Chem. Soc.*, 1941, **63**, 1456) gave 6·4% of acetaldehyde, proving that the oxidation under these conditions was incomplete.

Periodate Oxidation of 3 : 4-*Dimethyl* L-*Rhamnose*.—3 : 4-Dimethyl L-rhamnose (25·6 mg.) was treated with sodium metaperiodate (0·2M.; 1 ml.) for 3 hours at room temperature. An estimate of periodate consumed (0·0193 ml. of N-sodium periodate), by the method described above, showed that 0·7 mole of periodate was consumed per mole of dimethyl rhamnose. Oxidation of another portion (11·97 mg.) with sodium metaperiodate (0·2M.; 1 ml.) and determination of the formic acid liberated after 3 hours by the addition of ethylene glycol (2 ml.) to destroy the excess of periodate followed by titration with 0·01N-sodium hydroxide (0·57 ml.) gave about 0·1 mole of formic acid per mole of dimethyl sugar. Further acidity developed on storage.

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