414. *The Chemistry of Ribose and its Derivatives. Part I. Methyl-D-ribofuranoside and the Characterisation of Trimethyl D-Ribofuranose.*

By G. R. Barker.

Methyl-D-ribofuranoside has been prepared and its structure confirmed by (*a*) oxidation with sodium metaperiodate and (*b*) methylation and characterisation of trimethyl D-ribofuranose, which yielded the following crystalline compounds: 2 : 3 : 5-*trimethyl* D-*ribose anilide*, 3 : 5-*dimethyl* D-*ribose phenylosazone*, 2 : 3 : 5-*trimethyl* D-*ribonolactone*, and 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide*. The natural occurrence of ethyl-D-riboside is discussed.

In connection with work on ribonucleic acids, the carbohydrate radicals of which have been shown to be of the furanose configuration (Lythgoe and Todd, *J.*, 1944, 592, and references therein), it became necessary to explore methods by which furanose derivatives of ribose could readily be obtained and characterised. Of the various routes which have been used for the synthesis of such compounds the most favourable appears to be that of Levene and Stiller (*J. Biol. Chem.*, 1933, **102**, 187) who prepared 5-methyl D-ribofuranose and 2 : 3 : 5-trimethyl D-ribofuranose from 2 : 3-*iso*propylidene D-ribofuranose. However, even this method of approach is susceptible of application only to a limited range of compounds. The present paper describes the preparation of *methyl-D-ribofuranoside*, a more generally suitable starting material for syntheses in this field.

Levene and Tipson (*ibid.*, 1931, **92**, 109) found that D-ribose in methyl alcohol containing 1% of hydrogen chloride exhibited a maximum positive rotation after 14 minutes, and Levene, Raymond, and Dillon (*ibid.*, 1932, **95**, 699) observed that, under these conditions after one hour, the mixture of glycosides produced contained a small quantity of pyranoside in addition to the furnanoside. In neither of these two series of experiments, however, was an attempt recorded to isolate any product of the condensation. In the present investigations, D-ribose was condensed with methyl alcohol in presence of 1% of hydrogen chloride and the reducing power of the solution was measured by Somogyi's method (*ibid.*, 1926, **70**, 599) at various intervals of time. After 50 minutes the solution was non-reducing, and the product of the condensation was isolated and distilled under reduced pressure. The furanoside nature of the distillate was suggested by its rapid hydrolysis by dilute mineral acid at 100° and was confirmed by oxidation of the syrup with sodium metaperiodate which produced no formic acid, showing

the presence in the molecule of only two adjacent hydroxyl groups. The identity and homogeneity of the glycoside was established beyond doubt by subjecting it to the following reactions.

Repeated methylation with methyl sulphate yielded 2 : 3 : 5-trimethyl methyl-D-ribofuranoside from which trimethyl D-ribofuranose was obtained by hydrolysis with dilute aqueous mineral acid. The properties of these two syrupy compounds approximated closely to those reported for them by Levene and Stiller (*loc. cit.*) and it was now found possible to characterise the trimethyl D-ribofuranose as its crystalline *anilide* and also to prepare from it 3 : 5-*dimethyl* D-*ribose phenylosazone*. Proof of the structure of the trimethyl D-ribofuranose was obtained by oxidation to crystalline 2 : 3 : 5-*trimethyl* D-*ribonolactone* which gave crystalline 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide*. Measurement of the rate of hydrolysis of the lactone in aqueous solution indicated that it was a furanolactone, and hence the trimethyl ribose and the methylriboside must also have possessed the furanose configuration. The crystalline lactone had a higher negative rotation than the compound previously claimed to be 2 : 3 : 5-trimethyl D-ribonolactone (Levene and Tipson, *J. Biol. Chem.*, 1931—32, **94**, 809; Levene and Stiller, *loc. cit.*) but which was neither crystallised nor characterised.

The very rapid formation of the ribofuranoside is of interest in connection with the natural occurrence of the sugar. The only well-authenticated natural derivatives of this sugar are the glycosides of nitrogenous bases concerned in the ribonucleic acids and allied compounds. However, the presence in certain animal tissues of an ethylriboside has been reported (Winter, *Biochem. J.*, 1927, **21**, 467). Winter considered that the ethylriboside may have arisen during the process of extraction from the tissues, but dismissed this possibility on account of the failure of arabinose to yield a glycoside under the conditions employed in the isolation of the alkylriboside. This analogy, however, is not justified since, under similar treatment to that described for ribose in the experimental section, condensation of arabinose takes place much more slowly (Montgomery and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 992). The question of the natural occurrence of an ethylriboside, therefore, would need further consideration before it could be regarded as fully established.

Experimental.

Methyl-D-ribofuranoside.—D-Ribose (30 g.), prepared from guanosine following the method of Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) and dried in a vacuum over phosphoric oxide at 50°, was dissolved in absolute methyl alcohol (750 c.c.) containing 1% of hydrogen chloride. Samples (0·2 c.c.) were withdrawn and, after neutralisation, analysed by Somogyi's method (*loc. cit.*). After 15 and 30 minutes 82·1% and 94·5%, respectively, of the reducing power of the solution had been lost, and after 50 minutes the solution was non-reducing. It was immediately ground in a mortar with excess of silver oxide, and after standing for 2·5 hours, the silver salts were removed by filtration through charcoal. Distillation below 30° of the solvent gave *methyl-D-ribofuranoside*, as a very hygroscopic syrup, b. p. 150° (bath temp.)/0·01 mm., $n_D^{15°}$ 1·4880, a_D^{15} + 13·1° (in methyl alcohol; *c*, 1·903) (Found : C, 43·6; H, 7·3; OMe, 18·3. $C_6H_{12}O_5$ requires C, 43·9; H, 7·3; OMe, 18·9%). This substance consumed 1·02 mols. of sodium metaperiodate, no formic acid being detected by titration of an aliquot with N/100-sodium hydroxide.

A solution of the substance (0·1903 g.) in N/100-hydrochloric acid (10 c.c.) was heated at 100°, and samples were withdrawn, neutralised with dilute aqueous sodium hydroxide, and analysed by Somogyi's method (*loc. cit.*). After 5 minutes 41·3% of the glycoside had been hydrolysed; after 20 minutes, hydrolysis was complete.

Trimethyl Methyl-D-ribofuranoside.—Methyl-D-ribofuranoside (18 g.) was dissolved in aqueous sodium hydroxide (240 c.c.; 40%) and methylated twice with methyl sulphate (124·5 g.) at 60° during 5 hours. The reaction mixture was heated at 100° for 10 minutes, and after cooling to 0°, sodium sulphate was removed by filtration and the filtrate was extracted four times with chloroform. The combined extracts were dried ($MgSO_4$) and distillation of the solvent yielded trimethyl methyl-D-ribofuranoside, b. p. 133° (bath temp.)/15 mm., $n_D^{15°}$ 1·4350, $a_D^{18°}$ + 59·1° (in methyl alcohol; *c*, 4·784) (Found : C, 52·3; H, 8·3; OMe, 59·7. Calc. for $C_9H_{18}O_5$: C, 52·4; H, 8·73; OMe, 60·2%).

2 : 3 : 5-*Trimethyl* D-*Ribose*.—A solution of trimethyl methyl-D-ribofuranoside (2 g.) in N/25-hydrochloric acid (25 c.c.) was boiled under reflux for 1 hour and cooled, and chloride ions were removed by addition of silver carbonate and filtration. Concentration of the solution under reduced pressure yielded syrupy 2 : 3 : 5-trimethyl D-ribose, b. p. 97° (bath temp.)/0·01 mm., $n_D^{20°}$ 1·4523, $a_D^{24°}$ + 41·4° (in methyl alcohol; *c*, 1·112) (Found : C, 50·2; H, 8·4; OMe, 49·8. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·34; OMe, 48·4%).

2 : 3 : 5-*Trimethyl* D-*Ribose Anilide*.—2 : 3 : 5-Trimethyl D-ribose (0·13 g.) was heated with aniline (0·99 mol.) in absolute alcohol (5 c.c.) for 4 hours. Removal of the solvent in a vacuum desiccator gave the *anilide*, which crystallised on trituration with ether–light petroleum and separated from light petroleum containing a little ether in large rectangular plates and prisms, m. p. 56·5° (Found : C, 63·4; H, 7·8; N, 5·1; OMe, 35·2. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2; OMe, 35·0%).

3 : 5-*Dimethyl* D-*Ribose Phenylosazone*.—2 : 3 : 5-Trimethyl D-ribose (0·1 g.) was heated at 100° with phenylhydrazine (4 mols.) in dilute acetic acid (5 c.c.) for 4·5 hours. After being cooled to 0°, the crystals were collected and crystallised twice from aqueous alcohol. The *phenylosazone* separated in small yellow needles, m. p. 161° (Found : C, 63·6; H, 7·5; N, 15·3; OMe, 16·3. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 6·7; N, 15·7; OMe, 17·3%).

2 : 3 : 5-*Trimethyl* D-*Ribonolactone*.—Trimethyl methyl-D-ribofuranoside (2 g.) was heated at 100° with N/25-hydrobromic acid (25 c.c.) for 1 hour and then allowed to react with bromine (2·5 g.) at 30° for 4 days. The solution, which was then non-reducing, was freed from bromine by aeration, from bromide ions by addition of silver carbonate and filtration, and from silver ions by passage of hydrogen sulphide followed by filtration. Concentration of the filtrate under reduced pressure gave 2 : 3 : 5-*trimethyl* D-*ribonolactone*, b. p. 120° (bath temp.)/0·01 mm., $n_D^{26^\circ}$ 1·4508, which on cooling to 0°, crystallised in needles, m. p. 18·5—19° (Found : C, 50·2; H, 7·9; OMe, 47·7. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 49·0%). The material showed the following rotations in water (*c*, 4·702) : $a_D^{23^\circ}$ −20·2° (initial), −18·1° (46 hours), −14·5° (93 hours), −10·6° (141 hours). Levene and Tipson (*loc. cit.*) give $a_D^{27^\circ}$ −18·9° (in water, initial value) for syrupy 2 : 3 : 5-trimethyl D-ribonolactone.

2 : 3 : 5-*Trimethyl* D-*Ribonophenylhydrazide*.—2 : 3 : 5-Trimethyl D-ribonolactone (0·05 g.) was heated at 100° with phenylhydrazine (1 mol.) in absolute ethyl alcohol (2 c.c.) for 4 hours. The solvent was allowed to evaporate and the residual 2 : 3 : 5-*trimethyl* D-*ribonophenylhydrazide* then crystallised on being rubbed with dry ether. It separated from ethyl acetate–light petroleum in needles, m. p. 108·5—109·5° (Found : C, 55·8; H, 7·6; N, 9·1. $C_{14}H_{22}O_5N_2$ requires C, 56·4; H, 7·4; N, 9·4%).

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