*The Chemistry of Ribose and its Derivatives. Part IV.**
2 : 3-*Di-*O*-methyl-*D*-ribose.*

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The synthesis and characterisation of 2 : 3-di-*O*-methyl-D-ribose are described.

In Part II (Barker and Lock, *J.*, 1950, 23) methylated di-D-ribofuranose-1 : 5′-5 : 1′-dianhydride was shown to yield, on hydrolysis, 2 : 3-di-*O*-methyl-D-ribose. However, no crystalline derivatives were obtained and the structure of the sugar was assigned on the basis of evidence derived only from periodate oxidations. The behaviour of 2 : 3-di-*O*-methyl-D-ribose on paper chromatography and ionophoresis in presence of borate has

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* Part III, *J.*, 1954, 2151.

been described (Brown, Magrath, and Todd, *J.*, 1954, 1444), but the synthesis and characterisation of the sugar were not recorded. It was therefore desirable to confirm the structure of this sugar and this has now been undertaken as part of a study of all the methyl ethers of D-ribose.

Various compounds have been described in which the hydroxyl group at $C_{(5)}$ of ribose is blocked by the triphenylmethyl (trityl) group, and it was decided to attempt the synthesis of 2 : 3-di-*O*-methyl-D-ribose by use of a trityl derivative of the sugar. Tritylation of methyl D-ribofuranoside yielded amorphous methyl 5-*O*-trityl-D-ribofuranoside which was methylated with methyl iodide and silver oxide to syrupy methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-D-ribofuranoside. Removal of the trityl group by hydrogenolysis with a palladium–charcoal catalyst was slow and incomplete; however, some methyl 2 : 3-di-*O*-methyl-D-ribofuranoside was obtained. Detritylation with hydrogen chloride in chloroform was more convenient and yielded a mixture of 2 : 3-di-*O*-methyl-D-ribose and its methyl glycoside, which was converted into methyl 2 : 3-di-*O*-methyl-D-ribopyranoside by boiling methanolic hydrogen chloride. Hydrolysis of this material gave 2 : 3-di-*O*-methyl-D-ribose. Since trityl chloride is known to react preferentially with primary alcoholic groups (Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79), the structure of the dimethyl ribose obtained could be deduced with some degree of certainty from the method of synthesis. In order to confirm the correctness of the allocation of the methyl groups, the sugar was oxidised to a crystalline lactone, which was hydrolysed at a rate characteristic of γ-lactones. This indicates that the hydroxyl group at $C_{(4)}$ is unsubstituted. Furthermore, the methylated sugar yielded a crystalline phenylosazone with loss of one methoxyl group. This behaviour is characteristic of sugars bearing a methoxyl group at $C_{(2)}$. The only two structures possible for the sugar are, therefore, 2 : 3- and 2 : 5-di-*O*-methyl-D-ribose. In order to exclude the latter, the sugar was converted into a pyranose glycoside. Two distinct glycosides were obtained by treatment of the presumed 2 : 3-di-*O*-methyl-D-ribose with methanolic hydrogen chloride, respectively, at room temperature and at the boiling point. The former was hydrolysed by 0·2N-sulphuric acid at 95—100° at a rate characteristic of furanosides. The hydrolysis of the other glycoside was rapid in the initial stages, and slower in the later stages. This suggested that the material consisted of a pyranoside contaminated with some furanoside. Methylation of the mixed glycosides with methyl sulphate and sodium hydroxide, and hydrolysis of the product yielded a syrup which was shown by paper chromatography to consist of 2 : 3 : 4-tri-*O*-methyl-D-ribose together with a small quantity of 2 : 3 : 5-tri-*O*-methyl-D-ribose. The syrup partially crystallised when kept and the solid, after purification, was identical with authentic 2 : 3 : 4-tri-*O*-methyl-D-ribose. This trimethylribose must of necessity have been formed from a pyranose glycoside of the dimethylribose which is therefore 2 : 3-di-*O*-methyl-D-ribose.

The 2 : 3-di-*O*-methyl-D-ribose obtained from di-D-ribose-1 : 5′-1′ : 5-dianhydride (Barker and Lock, *loc. cit.*) consumed one mol. of sodium metaperiodate and gave no formic acid. However, although the amount of oxidant used was that expected on the basis of oxidation in the open-chain form, the theoretical quantity of formaldehyde could not be recovered. In view of the fact that certain sugars are now known to be oxidised by sodium metaperiodate in a lactol form (Barker and Smith, *Chem. and Ind.*, 1952, 1035), 2 : 3-di-*O*-methyl-D-ribose was investigated further. The sugar consumed one mol. of sodium metaperiodate with the production of a negligible quantity of titratable acid, and approximately one mol. of formaldehyde was isolated as its dimedone complex. The low yield of formaldehyde obtained in the previous experiments was apparently due to the fact that the oxidation was of necessity carried out on a small scale resulting in incomplete precipitation of the dimedone complex. It is concluded that the sugar from the ribose anhydride was correctly identified and that 2 : 3-di-*O*-methyl-D-ribose behaves as an aldehydo-sugar towards periodate.

EXPERIMENTAL

M.p.s were determined on a Kofler block.

Methyl 5-O-*Trityl-αβ-*D*-ribofuranoside.*—Methyl αβ-D-ribofuranoside (Barker, *J.*, 1948, 2035) (5·4 g.) and triphenylchloromethane (9·9 g.) in dry pyridine (100 c.c.) were shaken until dissolved, and after 7 days at 15° poured into water (1·5 l.). The precipitated gum was dissolved in chloroform, washed three times with ice-cold 5% aqueous sodium hydrogen sulphate, once with water, and once with sodium hydrogen carbonate solution, and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded the *product* as a fluffed glass (12·1 g.) (Found : OMe, 7·4; $OCPh_3$, 63·1. $C_{25}H_{26}O_5$ requires OMe, 7·6; $OCPh_3$, 63·9%).

Methyl 2 : 3-*Di*-O-*methyl*-5-O-*trityl*-αβ-D-*ribofuranoside*.—Methyl 5-*O*-trityl-αβ-D-ribofuranoside (11·9 g.) in methyl iodide (35 c.c.) was boiled under reflux with vigorous stirring, and silver oxide (32 g.) was added in four portions at intervals of 15 min. The mixture was refluxed for 1 hr. longer, and then filtered, and the treatment was repeated a further three times. After the final filtration, the solvent was removed under reduced pressure yielding a syrupy *glycoside* (11·4 g., 90%) which was purified by molecular distillation (Found : OMe, 21·5. $C_{27}H_{30}O_5$ requires OMe, 21·4%).

Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—A solution of methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-αβ-D-ribofuranoside (11·2 g.) in chloroform (250 c.c.) was saturated with hydrogen chloride at 0°, and kept at this temperature for 2 hr. Chloroform and hydrogen chloride were removed under reduced pressure, and the residue triturated with water. Triphenylmethanol (6·8 g.) was filtered off, and the filtrate was titrated to pH 7 with N-sodium hydroxide, evaporated to dryness, and extracted with methanol. The syrup (3·9 g.) obtained after removal of solvent was boiled with 2% methanolic hydrogen chloride (75 c.c.) for 7 hr. Chloride ions were removed by grinding with silver oxide and filtration through charcoal, and the filtrate was evaporated. The *product* (3·3 g.) had b. p. 130° (bath temp.)/0·01 mm., n_D^{19} 1·4557 (Found : C, 50·5; H, 8·7. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3%).

2 : 3-*Di*-O-*methyl*-D-*ribose*.—Methyl 2 : 3-di-*O*-methyl-αβ-D-ribopyranoside (0·51 g.) in 0·2N-sulphuric acid (5 c.c.) was heated at 95—100° to constant rotation, passed through Amberlite IR-4B(OH), evaporated, and distilled in the molecular still to give 2 : 3-*di*-O-*methyl*-D-*ribose* as a viscous syrup, $[\alpha]_D^{17}$ −16·6° (*c*, 6·48 in H_2O), n_D^{16} 1·4750 (Found : C, 47·2; H, 7·8; OMe, 32·2. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9; OMe, 34·8%). It yielded a *toluene*-p-*sulphonylhydrazone*, m. p. 139—140° (Found : C, 48·8; H, 6·7; N, 8·4; OMe, 18·4. $C_{14}H_{22}O_6N_2S$ requires C, 48·5; H, 6·4; N, 8·1; OMe, 17·9%).

3-O-*Methyl*-D-*ribose Phenylosazone*.—2 : 3-Di-*O*-methyl-D-ribose (72 mg.), phenylhydrazine (175 mg.), acetic acid (170 mg.), and water (5 c.c.) were heated at 80° for 5 hr. and evaporated to dryness *in vacuo*, and the residue, in the minimum of ether, chromatographed on a column (diameter 2·8 cm.) of alumina [Spence, grade H (80 g.), deactivated by shaking in ether with water (12 c.c.) and acetic acid (0·4 c.c.)]. The yellow phenylosazone band was collected, the solvent evaporated, and the residue taken up in boiling methanol (2 c.c.) and precipitated by addition of water till just turbid and cooled, giving amorphous yellow flocks (22 mg.), m. p. 135—140° (Found: C, 62·1; H, 6·7; N, 14·6; OMe, 8·2. $C_{18}H_{22}O_3N_4$ requires C, 63·1; H, 6·5; N, 16·4; OMe, 9·1%).

Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribofuranoside*.—(*a*) Methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-αβ-D-ribofuranoside (11·4 g.) was hydrogenated at approximately atmospheric pressure in presence of a palladium–charcoal catalyst (0·7 g.; 12% Pd). When uptake of hydrogen became slow, the mixture was shaken with air for 10 min., and shaking with hydrogen was then resumed. This procedure was repeated six times. The grey solid, containing the catalyst, was removed by filtration. Extraction of the solid with hot benzene and removal of the solvent gave bistriphenylmethyl peroxide, m. p. 188° (decomp.) (Found : C, 87·4; H, 5·9. Calc. for $C_{38}H_{30}O_2$: C, 88·0; H, 5·8%). The filtrate from the catalyst was concentrated to dryness. Crystals of triphenylmethane which appeared during the distillation were collected and after crystallisation from methanol had m. p. 90°. The residue was taken up in a mixture of benzene (50 c.c.) and water (50 c.c.), and the aqueous layer after evaporation under reduced pressure yielded *methyl* 2 : 3-*di*-O-*methyl*-αβ-D-*ribofuranoside* as a mobile syrup (1·3 g.), b. p. 110° (bath temp.)/0·01 mm., n_D^{22} 1·4554 (Found : OMe, 46·0. $C_8H_{16}O_5$ requires OMe, 48·4%).

(*b*) A solution of 2 : 3-di-*O*-methyl-D-ribose (0·378 g.) in 1% methanolic hydrogen chloride (30 c.c.) was kept at 25° for 50 min. The solution was neutralised with silver oxide, filtered through " Norit," and evaporated to a syrup. This was used immediately for the following experiments since it is very hygroscopic and slowly underwent slight hydrolysis.

Hydrolysis of Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribofuranside and Methyl* 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—Each riboside was hydrolysed at 95—100°, and the reactions followed polarimetrically. The furanoside (378 mg.) in 0·2N-sulphuric acid (3 c.c.) had α_D (1 dm.) +1·29° (initial), −0·73° (10 min.), −1·26° (20 min.), −1·43° (30 min.), −1·56° (40 min.), −1·61° (50 min.), −1·62° (60 min.). The pyranoside (512 mg.) in 0·2N-sulphuric acid (5 c.c.) had α_D

(1 dm.) −2·12° (initial), −2·55° (10 min.), −2·61° (20 min.), −2·63° (30 min.), −2·61° (40 min.), −2·56° (50 min.), −2·44° (70 min.), −2·25° (98 min.), −1·74° (208 min.), −1·25° (368 min.), −1·02° (538 min.), −0·81° (778 min.).

2 : 3-*Di*-O-*methyl*-D-*ribonolactone*.—Methyl 2 : 3-di-*O*-methyl-αβ-D-ribopyranoside (0·862 g.) was hydrolysed in N-sulphuric acid (5 c.c. at 95—100° for 7 hr.), and the cooled solution was passed through Amberlite IR-4B(OH) to remove sulphuric acid. The eluate was evaporated to 20 c.c., mixed with bromine (1 c.c.), and kept in a stoppered flask at room temperature for 4 days. Excess of bromine was removed by aeration, bromide ions were removed by grinding with silver oxide, and silver ions were removed from the filtrate with hydrogen sulphide. The filtrate after removal of silver sulphide was evaporated to a syrup which crystallised (0·758 g.). This was sublimed in a high vacuum (yield 0·670 g.). The *lactone* was then recrystallised by dissolving it in warm ethyl acetate (6 parts), adding ether (6 parts), and cooling. It was obtained as flat prisms, m. p. 77·5°, $[\alpha]_D^{19}$ −31·5° (initial value), −29·6° (38 min.), −24·4° (95 min.), −19·3° (180 min.), −16·0° (278 min.), −14·3° (381 min.) (*c*, 17·39 in H_2O) (Found : C, 47·6; H, 6·9; OMe, 35·5. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 35·6%). By dissolving the lactone in the equivalent amount of N-sodium hydroxide, warming the solution to 80° for 20 min., cooling it, and adding the exact equivalent of N-hydrochloric acid, a solution of 2 : 3-di-*O*-methyl-D-ribonic acid was obtained, having $[\alpha]_D^{20}$ +36·1° (initial value; *c*, 5·80 in 0·5N-sodium chloride).

Periodate Oxidation of 2 : 3-*Di*-O-*methyl*-D-*ribose*.—A solution of 2 : 3-di-*O*-methyl-D-ribose (170·3 mg.) in 0·294M-sodium metaperiodate (5·0 c.c.) was kept at room temperature. Excess of periodate was determined by Barneby's method (*J. Amer. Chem. Soc.*, 1916, **38**, 330), formaldehyde by Reeves's method (*ibid.*, 1941, **63**, 1476), and free acid by titrating samples with 0·01N-sodium hydroxide to the end-point of screened methyl red, after reduction of the excess of periodate with ethylene glycol. After 6·5 hr. 1·01 mol. of periodate had been consumed, 0·95 mol. of formaldehyde was recovered and 0·08 equivalent of acid was titrated.

Methylation of Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—The compound (1·0 g.) in 40% aqueous sodium hydroxide (15 c.c.) was stirred in an atmosphere of nitrogen at 60°, and methyl sulphate (6·9 c.c.) was added continuously during 5 hr. Stirring was continued for 2 hr., then at 100° for 20 min. The mixture was filtered, diluted to 50 c.c., and extracted with chloroform. The extract was neutralised and dried ($MgSO_4$), and on evaporation yielded a syrup (0·88 g.), b. p. 100° (bath temp.)/15 mm., n_D^{20} 1·4451 (Found : OMe, 59·0. Calc. for $C_9H_{18}O_4$: OMe, 60·2%). The riboside (0·25 g.) was hydrolysed in N-hydrochloric acid at 95—100° to constant rotation (3 hr.), and the solution neutralised with silver carbonate, filtered through "Norit," and evaporated to a syrup (0·08 g.). Paper chromatography in *n*-butanol–water showed two spots : a stronger one, R_F 0·62, corresponding to authentic 2 : 3 : 4-tri-*O*-methyl D-ribose, and a weaker one, R_F 0·65, corresponding to authentic 2 : 3 : 5-tri-*O*-methyl-D-ribose. Repeated recrystallisation of the partly crystalline syrup from ether–light petroleum (b. p. 30—40°) gave 2 : 3 : 4-tri-*O*-methyl-D-ribopyranose (13 mg.), m. p. 88·5—91° (Found : C, 49·9; H, 8·4. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·3%). It yielded an *anilide* as needles [from light petroleum (b. p. 40—60°)], m. p. 57·5—58·5° (Found : C, 64·2; H, 8·9; N, 6·0. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2%).

3 : 4-*Di*-O-*methyl*-D-*ribose Phenylosazone*.—2 : 3 : 4-Tri-*O*-methyl-D-ribose (94 mg.), phenylhydrazine (253 mg.), acetic acid (260 mg.), and water (4 c.c.), were heated at 95—100° for 2 hr., and the mixture evaporated to dryness, and chromatographed as described above. After being rechromatographed twice, the *phenylosazone* was obtained from methanol–water as yellow amorphous flocks, m. p. 141° after softening at 135—140° and crystallising as needles at 140° (Found : C, 63·0; H, 7·0; N, 16·7; OMe, 15·0. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 7·0; N, 15·7; OMe, 17·5%).

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