A SYNTHESIS OF 5-*O*-METHYL D-GLUCOSE AND OF 2-*O*-METHYL D-GLYCERONAMIDE[1]

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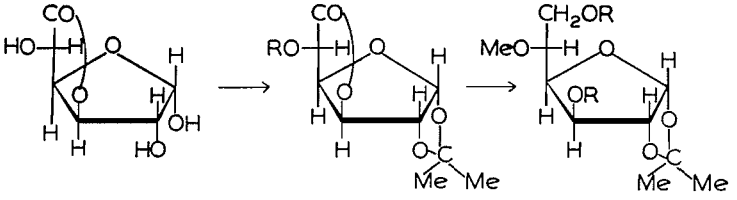
ABSTRACT

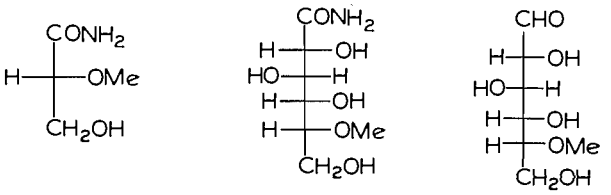
A preparation of 5-*O*-methyl D-glucose from 1,2-*O*-*iso*propylidene D-glucurone is described. Oxidation of the D-glucose derivative with periodate gave 2-*O*-methyl D-glycerose from which 2-*O*-methyl D-glyceronamide was prepared.

INTRODUCTION

The reference compound 2-*O*-methyl D-glyceronamide (VIII) was required. Its preparation from a suitably substituted derivative of D-glucose was considered to be feasible and, accordingly, the preparation of 5-*O*-methyl D-glucose (VI) was undertaken. This compound had been prepared earlier (3) from D-glucose. The ready availability of D-glucurone made this substance a more attractive starting material. D-Glucurone (I) condenses with acetone to give the well-characterized 1,2-*O*-*iso*propylidene derivative (II) which possesses a free hydroxyl group on C-5. Previous workers (2) had indicated that this material could not be methylated with Purdies' reagents without decomposition. It was observed that when water was rigorously excluded and if the reaction was carried out in the presence of anhydrous calcium sulphate methylation proceeded in the normal manner. The resultant 5-*O*-methyl



I II, R=H III, R=Me IV, R=H V, R=CO.CH$_3$



VIII VII VI

derivative (III) on reduction with lithium aluminum hydride in ether gave 1,2-*O*-*iso*propylidene 5-*O*-methyl D-glucose (IV) which was characterized as its crystalline 3,6-di-*O*-acetyl derivative (V). Hydrolysis of this material gave 5-*O*-methyl D-glucose (VI), a sirup which on oxidation with bromine water yielded 5-*O*-methyl D-gluconic acid, characterized as the crystalline amide (VII). Oxidation of this product with periodic acid resulted in the formation of 2-*O*-methyl D-glycerose. Attempts to isolate this material by

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extraction with either chloroform or ether were unsuccessful. Accordingly the aldehyde was oxidized *in situ* with bromine and the resultant glyceronic acid derivative converted first to the ester and then to the required amide (VIII). The racemic amide was prepared previously by Baker (1), and has a lower melting point, 71°C. compared with 87°C. The analytical values for methoxyl are likely to be unreliable as reported by Baker (1).

EXPERIMENTAL

The following solvents (v/v) were used to separate sugars on paper chromatograms: (A) ethyl acetate: acetic acid: formic acid: water—18: 3: 1: 4; (B) butan-2-ol: pyridine: water—10: 3: 3. Solvents were removed by evaporation at 40°C. or less and optical rotations were determined at 20 ± 2°C. and in water unless otherwise stated.

1,2-O-iso-Propylidene 5-O-Methyl D-*Glucurone*

1,2-*O-iso*-Propylidene D-glucurone (7 gm.) (II) was converted to the 5-*O*-methyl ether by methylating it with Purdies' reagents in the presence of drierite. The product, which was isolated in the usual manner, was a sirup which was purified by distillation, b.p. 140–145°C. at 0.01 mm. (bath temp.), $n_D^{29°}$ 1.4690, yield, 4.7 gm.; $[\alpha]_D$ 48° (*c*, 0.9). The lactone gave with alcoholic ammonia an amide, m.p. 174°C., $[\alpha]_D$ −29° (*c*, 2.5). Anal.: Calc. for $C_{10}H_{17}O_6N$: C, 48.7; H, 6.9; N, 5.7; OMe, 12.6. Found: C, 48.7; H, 6.7; N, 5.7; OMe, 14.5.

The lactone derivative on hydrolysis with dilute formic acid yielded 5-*O*-methyl D-glucurone which moved at 1.35 times the speed of rhamnose in solvent (A).

1,2-O-iso-Propylidene 5-O-Toluene-p-sulphonyl D-*Glucurone*

1,2-*O-iso*-Propylidene D-glucurone (1 gm.) was dissolved in pyridine (10 ml.) and toluene-*p*-sulphonyl chloride (1 gm.) was added. The solution became warm and, after the initial reaction was over, was allowed to stand at room temperature for a day. The reaction mixture was poured on to ice when the crystalline 5-*O*-toluene-*p*-sulphonyl derivative separated. It was collected on the filter, washed well with water, and recrystallized from methanol or aqueous acetone, m.p. 189°–194°C. not changed on further recrystallization, $[\alpha]_D$ 84° (*c*, 0.44 in acetone.) Anal.: Calc. for $C_{16}H_{18}O_8S$: C, 52.0; H, 4.9; S, 8.7. Found: C, 52.0; H, 4.8; S, 8.5. The product dissolved in aqueous alkali with the formation of an intense yellow color.

1,2-O-iso-Propylidene 5-O-Methyl D-*Glucose* (*IV*)

1,2-*O-iso*-Propylidene 5-*O*-methyl D-glucurone (4.4 gm.) was reduced by adding its solution in ether (25 ml.) to a solution of lithium aluminum hydride (4 gm.) in ether (25 ml.). The glucose derivative was isolated from the neutralized and filtered solution by extracting it continuously with chloroform. The sirupy product was purified by distillation, b.p. 160°C. (bath temp.) at 0.1 mm., $[\alpha]_D$ −8° (*c*, 1.0), yield, 4.1 gm. Anal.: Calc. for $C_{10}H_{14}O_6$: C, 52.2; H, 6.1; OMe, 13.5. Found: C, 52.2; H, 6.25; OMe, 13.7. Acetylation of the product with pyridine and acetic anhydride yielded the known crystalline 3,6-di-*O*-acetyl derivative (4.0 gm.) (V), m.p. 87°C. after recrystallization from

ligroin (b.p. 60–80°C.). Anal.: Calc. for $C_{14}H_{22}O_8$; C, 52.9; H, 7.0; OMe, 9.8. Found: C, 52.5; H, 7.0; OMe, 9.9. Pure 1,2-*O*-*iso*propylidene 5-*O*-methyl D-glucose was recovered from the diacetate after it had been deacetylated with *N* sodium hydroxide solution.

5-O-Methyl D-*Glucose* (*VI*)

1,2-*O*-*iso*-Propylidene 5-*O*-methyl D-glucose (2.0 gm.) was hydrolyzed with 0.1 *N* sulphuric acid (20 ml.) at 100°C., $[\alpha]_D$ $-8° \rightarrow -3°$ (constant value, 1 hr.). The sirupy product (1.77 gm.) was isolated after removal of the sulphuric acid as barium sulphate. Its rate of movement relative to that of rhamnose was 1.1 (in solvent A) and 1.2 (in solvent B). It was converted, without purification, to 5-*O*-methyl D-gluconic acid by oxidizing it with bromine water in the usual manner. Excess of bromine was removed by aeration when chromatographic examination of the solution (solvent B) showed that reducing sugar was absent. Hydrobromic acid was removed with silver carbonate and the solution filtered. The acid, isolated by the usual procedure, was converted to the lactone, which crystallized. This product was difficult to purify. The crude material, which had m.p. 130°C., was converted to the amide (VII) by saturating its solution in methanol with ammonia. The amide was recrystallized either from water or from methanol, m.p. 150°C., and had $[\alpha]_D$ 25° (*c*, 0.14) and therefore obeys Hudson's amide rule. Its rate of movement was identical with that of glucose in solvent (B). Anal.: Calc. for $C_7H_{15}O_6N$: C, 40.0; H, 7.2; N, 6.7; OMe, 14.9. Found: C, 40.2; H, 7.4; N, 6.2; OMe, 15.0.

Oxidation of 5-O-Methyl D-*Gluconamide with Periodate*

The amide (VII) (0.7 gm.) was dissolved in water (10 ml.) and oxidized with paraperiodic acid (0.7 gm.) at 24°C. during 24 hr. In a trial experiment attempts to isolate 2-*O*-methyl D-glycerose were unsuccessful. Accordingly bromine was added to the reaction mixture and the oxidation was allowed to proceed for 48 hr. Excess of bromine was then removed by aeration and the solution was neutralized with barium carbonate and filtered. The filtrate was shaken with silver carbonate, filtered, and silver ions removed from solution as silver sulphide. The filtered solution was then concentrated to a sirup which was boiled with methanolic hydrogen chloride for six hours in order to esterify the glyceronic acid derivative. The 2-*O*-methyl D-glyceronamide (VIII) was prepared from the resultant ester in the usual manner. Yield, 60 mgm. of white crystals, m.p. 86–87°C., $[\alpha]$ 71°±4° (*c*, 0.7 in methanol). Anal.: Calc. for $C_4H_9O_3N$: C, 40.3; H, 7.56; N, 11.8; OMe, 26.1. Found: C, 40.2; H, 7.6; N, 11.9; OMe, 26.7.

ACKNOWLEDGMENT

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