2,4-Di-*O*-methyl and 3-*O*-Methyl Ethers of 1,6-Anhydro-β-L-idopyranose[1]

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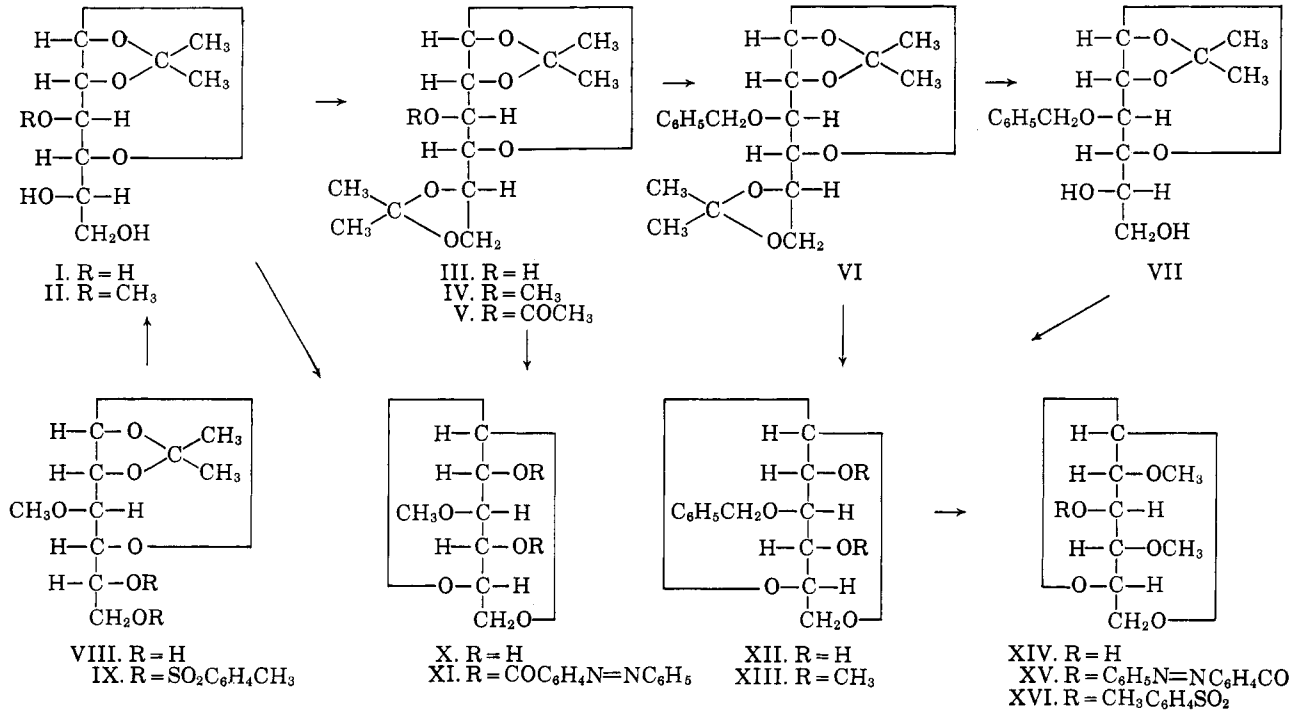
The syntheses of 1,6-anhydro-3-*O*-methyl-β-L-idopyranose and 1,6-anhydro-2,4-di-*O*-methyl-β-L-idopyranose are described.

The methylated derivatives described in this paper are two more members in the series of *O*-methyl-L-idose, of interest as reference substances in the elucidation of the structure of polymers containing L-iduronic acid.

Treatment of 1,2-*O*-isopropylidene-L-idofuranose (I)[3] with acetone gave a di-*O*-isopropylidene-L-idose, previously encountered in the D-series by Iwadare[4] and presumed to have the structure III. Methylation of this compound, followed by acid hydrolysis, gave 1,6-anhydro-3-*O*-methyl-β-L-idopyranose (X), the enantiomorph of which has been described by Reeves.[5] Proof that the methyl group was indeed at position 3 was obtained by synthesis of the same material from 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose[6] (VIII) by solvolysis, with resultant Walden inversion of the 5,6-di-*O*-*p*-tolylsulfonyl derivative IX. It is quite unlikely that there was any migration of the methyl group under the conditions used.

Analogously, the product obtained by benzylation of III, using the method of Croon and Lindberg,[7] was hydrolyzed, giving 1,6-anhydro-3-*O*-benzyl-β-L-idopyranose (XII), from which 1,6-anhydro-2,4-di-*O*-methyl-β-L-idopyranose (XIV) was readily obtained by complete methylation and reductive debenzylation.

The monomethyl ether X was characterized by a crystalline *p*-phenylazobenzoyl derivative XI, and the dimethyl ether XIV by the crystalline *p*-phenylazobenzoyl derivative XV and the *p*-tolylsulfonyl derivative XVI.



Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or dichloroethane, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent (ml.) was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen.

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The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

1,2:5,6-Di-*O*-isopropylidene-L-idofuranose (III).—To a solution of 960 mg. of 1,2-*O*-isopropylidene-β-L-idofuranose (I)[3] in 25 ml. of dry acetone was added *ca.* 1 g. of anhydrous copper sulfate, and the mixture was stored at room temperature for 1 week. The mixture was filtered, the residue washed with acetone, and the solution evaporated. The residue dissolved in chloroform was chromatographed on 60 g. of silica gel. Elution with ether gave 416 mg. of crystalline solid, which was recrystallized from a mixture of acetone and hexane to give 305 mg. (27%) of stout needles, m.p. 153–154°, $[\alpha]^{22}D$ −22° (in water, *c* 0.60); $[\alpha]^{23}D$ −25° (in acetone, *c* 0.55).[8]

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.33; H, 7.40.

Elution with acetone gave 687 mg. of material which was recrystallized from a mixture of acetone and hexane to give 599 mg. (63%) of unchanged starting material I, m.p. 114–115°.

3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-L-idofuranose (V).—A solution of 102 mg. of 1,2:5,6-di-*O*-isopropylidene-L-idofuranose (III) in 1 ml. of pyridine and 0.5 ml. of acetic anhydride was stored at room temperature for 60 hr. The solution was evaporated by codistillation with toluene, and the residue, dissolved in chloroform, was subjected to chromatography on silica gel. Elution with a mixture of chloroform and ethyl acetate, 4:1, afforded 104 mg. (88%) of crystalline material, which was recrystallized from a mixture of ether and pentane to give 82 mg. (69%) of the desired product, m.p. 77–78°, $[\alpha]^{15}D$ −12° (in chloroform, *c* 0.75).

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 55.62; H, 7.34. Found: C, 55.39; H, 7.32.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-idofuranose (IV).—A suspension of 218 mg. of III in 4 ml. of methyl iodide was heated under reflux, when most of it dissolved, and the compound was methylated with three additions of 270 mg. of silver oxide added over 45 hr. The mixture was filtered, the residue was washed with acetone, and the filtrate was evaporated to dryness. A solution of the residue in chloroform was chromatographed on silica gel. The major part (219 mg.) was eluted with chloroform and a mixture of chloroform and ether, 9:1, as a sirup. Part of this was distilled in a molecular still with a pressure of 0.1 cm. at a bath temperature of 100°, giving a sirup with $[\alpha]^{22}D$ −63° (in chloroform, *c* 2.09).

Anal. Calcd. for $C_{13}H_{22}O_6$: OCH_3, 11.32. Found: OCH_3, 11.05.

1,2-*O*-Isopropylidene-3-*O*-methyl-5,6-di-*O*-*p*-tolylsulfonyl-D-glucofuranose (IX). A solution of 1 g. of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (VIII)[6] and 3.27 g. (4 moles) of *p*-toluenesulfonyl chloride in 2 ml. of pyridine and 20 ml. of dry chloroform was stored overnight at room temperature. A few drops of water were added and the mixture shaken. The mixture was extracted with chloroform and the solution was washed with ice-cold *N* sulfuric acid, cold saturated sodium bicarbonate solution, and water. After evaporation of the solvent, the residue was dissolved in a mixture of benzene and hexane, 1:1, and chromatographed on silica gel. No definite crystalline fraction could be obtained, and, therefore, the total product was recombined, dried, and dissolved in 5 ml. of dry chloroform and 2 ml. of dry pyridine; 2.2 g. of toluene sulfonyl chloride was added, and the mixture stored at room temperature for 24 hr. The solvent was removed by evaporation, water was added to decompose the excess of *p*-toluenesulfonyl chloride, and the product was extracted with chloroform. The solution, after being washed with ice-cold *N* sulfuric acid, and cold saturated sodium bicarbonate solution, was dried and evaporated. The residue was dissolved in a mixture of hexane and benzene, 1:1, and chromatographed on silica gel. Elution with a mixture of benzene and ether, 24:1, gave 1.55 g. of crystalline fractions which were recrystallized from a mixture of methanol and water to give a total of 1.06 g. (46%) of needles, m.p. 90–93°, $[\alpha]^{22}D$ −20° (in chloroform, *c* 0.76).

Anal. Calcd. for $C_{24}H_{30}O_{10}S_2$: C, 53.14; H, 5.58; S, 11.80. Found: C, 53.18; H, 5.56; S, 11.94.

1,6-Anhydro-3-*O*-methyl-β-L-idopyranose (X). From IV.—A solution of 127 mg. of IV in 3 ml. of 1.3 *N* sulfuric acid was heated for 7 hr. at 100°. The acidic solution was extracted with chloroform overnight in a continuous extractor, with lead carbonate added to the chloroform solution. Evaporation of the filtered solution gave 76 mg. (93%), which was recrystallized from a mixture of acetone and ether to give 28 mg. (34%) of rectangular plates, m.p. 110–111°, $[\alpha]^{18}D$ +108° (in acetone, *c* 0.84).[9]

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87; OCH_3, 17.62. Found: C, 47.71; H, 6.88; OCH_3, 17.75.

From IX.—A mixture of 575 mg. of freshly fused potassium acetate, 574 mg. of IX, and 10 ml. of acetic anhydride was heated under reflux for 10 hr. The mixture was stored at room temperature overnight, then evaporated under reduced pressure. The mixture was shaken with 100 ml. of chloroform and 100 ml. of water. The chloroform solution was washed with water, dried over anhydrous potassium acetate, and evaporated. The residue was dissolved in benzene and chromatographed on 25 g. of silica gel. Elution with a mixture of benzene and ether, 9:1, gave 373 mg. of sirup which would not be induced to crystallize. The sirup was dried by evaporation with ethanol, dissolved in methanol, and stored overnight at room temperature with 1 ml. of 1.4 *N* barium methylate. Water was added and carbon dioxide passed into the solution. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in 20 ml. of ethanol and the solution was filtered and evaporated. The residue was dissolved in 5 ml. of acetone and the solution was filtered and evaporated. The remaining sirup was dissolved in ethylene dichloride and chromatographed on 10 g. of silica gel. The fractions eluted with a mixture of ether and ethyl acetate, 4:1, were combined and evaporated to give 146 mg. of sirup, probably 1,2-*O*-isopropylidene-3-*O*-methyl-L-idofuranose (II).

A solution of 32 mg. of this sirup in 1 ml. of *N* sulfuric acid was heated at 100° for 4 hr. The cooled solution was passed through a 5-ml. column of Dowex 1 in the acetate form and the column was washed with 25 ml. of a mixture of water and ethanol, 1:1. The solution was evaporated and the residue dissolved in ethylene dichloride and chromatographed on 1 g. of silica gel. Elution with ethyl acetate afforded 20 mg. of material, which was recrystallized to give 12 mg. (50%) of plates, m.p. 110–111°. This product showed no depression of the melting point in admixture with the product described earlier.

1,6-Anhydro-3-*O*-methyl-2,4-di-*O*-*p*-phenylazobenzoyl-β-L-idopyranose (XI).—A solution of 25 mg. of X and 140 mg. of *p*-phenylazobenzoyl chloride in 1 ml. of pyridine was heated in a sealed tube at 100° for 5 hr. After addition of 1 drop of water, the mixture was evaporated to dryness by codistillation with toluene. The residue was dissolved in a mixture of pentane and benzene, 1:2, and chromatographed on neutral alumina, Brockman activity III. The material eluted with a mixture of benzene and pentane, 2:1, was recrystallized from the same solvent to give 44 mg. (52%) of orange platelets, m.p. 198.5–199°, $[\alpha]^{22}D$ +74° (in chloroform, *c* 0.18).

Anal. Calcd. for $C_{33}H_{28}N_4O_7$: C, 66.88; H, 4.76; N, 9.46; OCH_3, 5.24. Found: C, 66.70; H, 4.80; N, 9.37; OCH_3, 5.48.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (VI).—A solution of 100 mg. of III in 1 ml. of benzyl bromide and 3 ml. of dimethylformamide was stirred with 1 g. of silver oxide for 24 hr. at room temperature. The mixture was filtered and the residue washed with 3 ml. of dimethylformamide. Then 20 ml. of chloroform and 50 ml. of 1% aqueous potassium cyanide were added to the solution, and the mixture shaken and extracted with chloroform. The dried chloroform solution was evaporated and the residue, dissolved in a mixture of benzene and hexane, 1:1, was chromatographed on silica gel. Two incompletely separated peaks of sirupy material (680 mg.) were eluted with benzene and mixtures of benzene and ether, 4:1 and 2:1. One of the fractions of the latter part of the second peak was dissolved in ether. The solution was filtered through a sintered fritted glass and evaporated, giving a sirup with $[\alpha]^{25}D$ −74° (in chloroform, *c* 0.40).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.12; H, 7.53.

3-*O*-Benzyl-1,2-*O*-isopropylidene-L-idofuranose (VII).—A mixture of 463 mg. of III and *ca.* 0.5 g. of sodium in 25 ml. of ether was refluxed overnight with exclusion of moisture. The translucent suspension was decanted from the excess sodium, 2 ml. of benzyl bromide was added, and the solution concentrated to half the volume and then refluxed for 5 hr. The mixture was diluted with chloroform and the solution was washed with water, dried, and evaporated. Hexane was added and 110 mg. (24%) of III was obtained by crystallization. The mother liquor was evaporated and the residue dissolved in benzene and chromatographed on silica gel. Elution with ether gave 243 mg. of crystals, which

(8) Iwadare[4] reported m.p. 151–152.5, $[\alpha]^{5}D$ +36° (in acetone) for the D-substance.

(9) Reeves[5] reported m.p. 104–106°, $[\alpha]D$ −107° (in acetone, *c* 0.99).

were recrystallized from ether to give 179 mg. (32%) of fine needles, m.p. 89–90°, $[\alpha]^{15}D$ −48° (in chloroform, *c* 0.59).

The product corresponded to VII and had resulted from hydrolysis, due to the acid developed by the decomposition of benzyl chloride.

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.65; H, 6.86.

Further elution with acetone gave 124 mg. (27%) of III.

1,6-Anhydro-3-*O*-benzyl-β-L-idopyranose (XII). From VI.—A solution of 282 mg. of partially purified VI in 10 ml. of 2 *N* sulfuric acid and 2 ml. of ethanol was heated for 7 hr. at 150° in a sealed tube. The mixture was partially evaporated and then extracted continuously overnight with chloroform, with lead carbonate added to the organic solvent. After filtration and drying, the solution was evaporated, and the residual product, dissolved in benzene, was chromatographed on silica gel. A mixture of ether and ethyl acetate, 2:1, eluted 48 mg. of crystalline material. It was recrystallized from a mixture of acetone and pentane to give 34 mg. (40%) of platelets, m.p. 157–157.5°, $[\alpha]^{20}D$ +42° (in chloroform, *c* 0.80).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.73; H, 6.27.

From VII.—A solution of 50 mg. of VII in 0.5 ml. of ethanol and 1 ml. of *N* sulfuric acid was heated at 100° for 3 hr. The solution was evaporated to one-half and extracted continuously overnight with chloroform, with lead carbonate added to the organic solvent. The solution was evaporated after filtration. The crystalline residue was recrystallized from a mixture of acetone and pentane, giving 23 mg. (57%) of material identical to the product described previously.

1,6-Anhydro-3-*O*-benzyl-2,4-di-*O*-methyl-β-L-idopyranose (XIII).—A solution of 118 mg. of XII in 11 ml. of methyl iodide and 1 ml. of acetone was heated under reflux and stirred with 1.6 g. of silver oxide added in four portions over 3 days. The mixture was filtered, the residue washed with chloroform, and the solution evaporated. The residual product was dissolved in a mixture of hexane and benzene, 9:1, and chromatographed on silica gel. The major fraction (121 mg., 92%) of sirup was eluted with a mixture of benzene and ether, 4:1, $[\alpha]^{30}D$ +58° (in chloroform, *c* 2.0).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; OCH_3, 22.15. Found: C, 64.15; H, 7.08; OCH_3, 22.45.

1,6-Anhydro-2,4-di-*O*-methyl-β-L-idopyranose (XIV).—A solution of 115 mg. of XIII in 50 ml. of methanol was stirred with 100 mg. of 2% palladized charcoal under a slight pressure of hydrogen for 8 hr., when the uptake of hydrogen ceased. The solution was filtered and evaporated, and the residual product crystallized from ether, giving 59 mg. (76%) of rectangular prisms, m.p. 82–83°, $[\alpha]^{25}D$ +91° (in chloroform, *c* 1.10).

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42; OCH_3, 32.63. Found: C, 50.64; H, 7.37; OCH_3, 33.29.

1,6-Anhydro-2,4-di-*O*-methyl-3-*O*-*p*-phenylazobenzoyl-β-L-idopyranose (XV).—A solution of 15 mg. of XIV and 40 mg. of *p*-phenylazobenzoyl chloride in 0.5 ml. of pyridine was stored at 50° for 1 hr. then overnight at room temperature. A mixture of water and pyridine was added, and after 10 min. the mixture was extracted with chloroform. The chloroform solution was washed with ice-cold *N* sulfuric acid, with cold saturated sodium bicarbonate solution, and then with water, and dried over sodium sulfate. It was then passed through a column of neutral alumina, Brockman activity III. The material eluted with dry chloroform was recrystallized from a mixture of benzene and hexane to give 15 mg. (48%) of long orange needles, m.p. 172–173.5°, $[\alpha]^{15}D$ +27° (in chloroform, *c* 0.26).

Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03; OCH_3, 15.58. Found: C, 63.38; H, 5.55; N, 6.95; OCH_3, 15.85.

1,6-Anhydro-2,4-di-*O*-methyl-3-*O*-*p*-tolylsulfonyl-β-L-idopyranose (XVI).—A solution of 30 mg. of XIV in 0.2 ml. of dry pyridine was cooled and a solution of 100 mg. of *p*-toluenesulfonyl chloride in 0.05 ml. of dry pyridine and 0.1 ml. of ethylene dichloride was added. The solution was stored at room temperature for 1 week. Water was added to decompose the acid chloride, and the mixture was poured onto ice. It was extracted with chloroform, and the chloroform solution was washed with ice-cold *N* sulfuric acid, then with water, dried over sodium sulfate, and evaporated. The residue, dissolved in benzene, was chromatographed on silica gel. The crystalline fractions, eluted with mixtures of benzene and ether, 4:1 and 2:1, and with pure ether, were combined and recrystallized from ether and pentane to give 40 mg. (74%) of needles, m.p. 106–106.5°, $[\alpha]^{25}D$ +58° (in chloroform, *c* 1.01).

Anal. Calcd. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.86; OCH_3, 18.02. Found: C, 52.37; H, 5.85; OCH_3, 18.24.

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Monophosphate Esters of D-Erythronic Acid

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The syntheses of D-erythronic acid 2-phosphate and 4-phosphate are described. The synthesis of erythronic acid 3-phosphate from 2-*O*-benzoyl erythronolactone was unsuccessful. Some properties of the phosphate esters and the synthetic intermediates are reported.

In a continuing study of the chemical and biochemical properties of a number of phosphate esters of mono- and polyhydroxy acids,[1] it was of interest to prepare the monophosphates of D-erythronic acid. The starting material for the synthesis was 2,4-*O*-ethylidene-D-erythrose (I).[2]

In the preparation of the 2-phosphate the following sequence of reactions was used.

I → 2,4-*O*-ethylidene-D-erythrose dimethyl acetal → 3-*O*-benzyl-2,4-*O*-ethylidene-D-erythrose dimethyl acetal (II) → 3-*O*-benzyl-D-erythrose (III) → 3-*O*-benzyl-D-erythronolactone (IV). This material, IV, was phosphorylated using diphenyl phosphorochloridate, which after hydrogenolysis of the benzyl and phenyl groups, gave D-erythronolactone 2-phosphate (V) which was isolated as the cyclohexylammonium salt.

In attempts to prepare D-erythronic acid 3-phosphate (VII), IV was converted to 2-*O*-benzoyl-3-*O*-benzyl-D-erythronolactone which on hydrogenolysis gave 2-*O*-benzoyl-D-erythronolactone (VI). Attempts to phosphorylate this compound, using either diphenyl phosphorochloridate or the more reactive (less hindered) phosphorus oxychloride, gave extremely poor yields of phosphorylated products. Moreover, the properties of the products were not compatible with the expected properties of the desired 3-phosphate ester. Examination of space filling models offers no apparent reason for the low reactivity of the 2-*O*-benzoyl ester (VI) as compared to the 3-*O*-benzyl ether (IV).

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