

bamate Xc (3.58 g.) in 100 ml. of 1.5 *N* methanolic potassium hydroxide was refluxed for 2 hr. The solution was poured into water and worked up as usual. There was obtained 1.01 g. of crude imine (XII) as a semisolid. This material was dissolved in ether-hexane and 1 ml. of phenylisocyanate was added. The resulting white precipitate was filtered off, washed with hexane, and dried. The yield of product was 1.01 g., m.p. 157–160°. The material was identified by comparison of its infrared spectrum with that of the authentic material.

B. Isolation of Methyl (*trans*-1-Methoxy-2-tetralin)carbamate (XIV).—A solution of 6.18 g. of the isopropyl carbamate Xc in 200 ml. of 1.5 *N* methanolic potassium hydroxide was refluxed for

1.5 hr., then worked up as usual. There was obtained 2.353 g. of crude semisolid. The infrared spectrum of this material showed that it was mostly imine XII, contaminated with a small amount of a carbamate.

The crude product was dissolved in ether (50 ml.) and washed with 1 *N* sulfuric acid (40 ml.). After drying over magnesium sulfate, the solution was evaporated to dryness to yield 288 mg. (5.8%) of the product, m.p. 73–83°. Several recrystallizations from hexane gave pure methyl (*trans*-1-methoxy-2-tetralin)carbamate (XIV), m.p. 103–104°, identical by mixture melting point and infrared spectrum with a sample of the authentic material.

2-Deoxy-D-arabino-hexonic Acid 6-Phosphate and Methyl 2-Deoxy-β-D-arabino-hexopyranoside 4,6-(Monophenyl phosphate)

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Treatment of methyl 2-deoxy-β-D-arabino-hexopyranoside (I) with diphenyl phosphorochloridate under mild conditions yielded sirupy methyl 2-deoxy-β-D-arabino-hexopyranoside 6-(diphenyl phosphate) (II). Catalytic removal of the phenyl residues resulted in isolation of crystalline methyl 2-deoxy-β-D-arabino-hexopyranoside 6-[bis(cyclohexylammonium) phosphate] (IIb). Hydrolysis and oxidation with barium hypoiodite gave the crystalline bis(cyclohexylammonium) salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate (V). Treatment of a phosphorylation mixture with base produced the crystalline methyl 2-deoxy-β-D-arabino-hexopyranoside 4,6-(monophenyl phosphate) (III), obtained also from methyl 2-deoxy-β-D-arabino-hexopyranoside and phenyl phosphorodichloridate; III formed a crystalline hexylammonium salt. 3,4,5-Tri-*O*-benzoyl-2-deoxy-6-*O*-trityl-D-arabino-hexose diethyl dithioacetal is recorded.

Selective phosphorylations of primary hydroxyl groups in carbohydrates employing diphenyl phosphorochloridate have been noted in the literature. Maley and Lardy² synthesized 2-amino-2-deoxy-D-glucose 6-phosphate by selective phosphorylation of 2-amino-*N*-anisylidene-2-deoxy-D-glucose with diphenyl phosphorochloridate. Tener and Khorana³ phosphorylated benzyl β-D-ribofuranoside with diphenyl phosphorochloridate. Mild alkali hydrolyzed any secondary phosphate ester formed and they isolated benzyl β-D-ribofuranoside 6-(diphenyl phosphate). Ukita and Nagasawa⁴ reported the phosphorylation of an anomeric mixture of methyl 2-deoxy-D-erythro-pentofuranosides with diphenyl phosphorochloridate. The sirupy mixture isolated was identified as the 5-(diphenyl phosphate) ester and the 3,5-bis(diphenyl phosphate) diester. Remizov⁵ has reported the selective phosphorylation of methyl 2-deoxy-α-D-arabino-hexopyranoside with diphenyl phosphorochloridate at reduced temperature. Remizov was able to correlate the selective phosphorylation with a synthesis in which the primary hydroxyl group was protected as a trityl ether.

It was our desire to synthesize 2-deoxy-D-arabino-hexonic acid 6-phosphate for use as a possible metabolic blocking agent in the pentose phosphate pathway.⁶ 3-Deoxy-D-ribo-hexonic acid 6-phosphate has been reported by Dahlgard and Kaufmann.⁷ Several un-

successful reports of the chemical synthesis of 2-deoxy-D-arabino-hexose 6-phosphate⁸ had preceded Remizov's report. Enzymic syntheses of 2-deoxy-D-arabino-hexose 6-phosphate are known⁹; however, it did not appear that this route would provide the quantity of material needed.

The report by Inglis, Schwarz, and MacLaren¹⁰ of the methoxy mercuration of tri-*O*-acetyl-D-glucal provided a ready route to methyl 2-deoxy-β-D-arabino-hexopyranoside (I). Phosphorylation of (I) with an equivalent amount of diphenyl phosphorochloridate using Remizov's method⁵ yielded 80% of the expected amount of material as a sirup which was converted to a crystalline bis(cyclohexylammonium) salt, $[\alpha]_D -30^\circ$. Using Remizov's value of $[\alpha]_D +42.8^\circ$ for the corresponding α-D-anomer and Hudson's isorotation rules, a value of $[\alpha]_D -29^\circ$ was calculated.

Removal of the glycosidic methyl group had been achieved by Remizov by heating the bis(cyclohexylammonium) salt on a boiling water bath with a slight excess of 0.5 *N* hydrobromic acid. Paper chromatography of the resulting product had demonstrated the presence of inorganic phosphate. We circumvented this by using a lower temperature (68°) for the hydrolysis of the β-D-anomer (II) by its own acidity. The oxidation used was a modification⁷ of the barium hypoiodite oxidation method of Goebel.¹¹ A crystalline bis(cyclohexylammonium) salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate was obtained and attempts to obtain the tris(cyclohexylammonium) salt were un-

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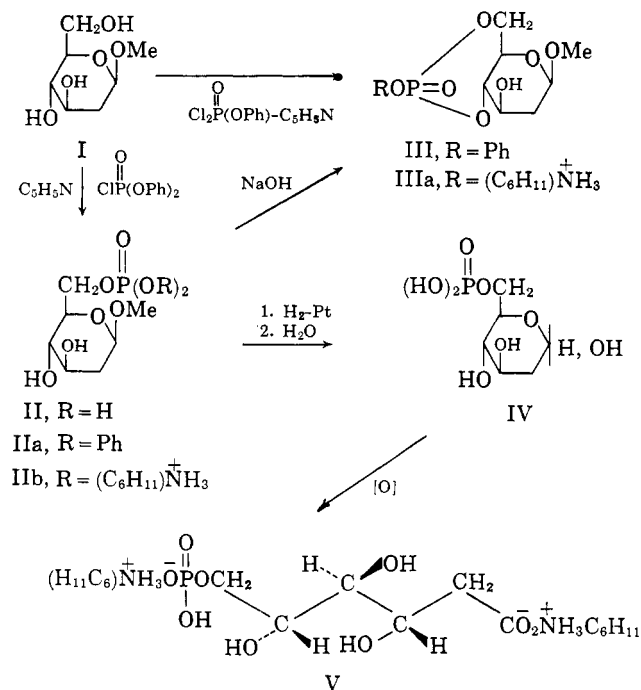
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cessful. Ballou and MacDonald¹² indicate that there is considerable variance in the stability of phosphate ester cyclohexylammonium salts.

Instead of alkali hydrolyzing any secondary phosphate esters present in the phosphorylation mixture and leaving the primary phosphate intact,³ alkali yielded the 4,6-cyclic phosphate (III) obtained also by direct phosphorylation with monophenyl phosphodichloridate. This synthetic step is similar to the synthesis of the 4,6-(monophenyl phosphate) esters of methyl α -D-glucopyranoside and phenyl β -D-glucopyranoside.¹³ The base cyclization of diphenyl phosphate esters is also known¹⁴ and is dependent on favorable spatial requirements.

We record herein the crystalline 3,4,5-tri-O-benzoyl-2-deoxy-6-O-trityl-D-arabino-hexose diethyl dithioacetate; Foster and associates⁸ have recorded the corresponding triacetate.

Experimental

Methyl 2-Deoxy- β -D-arabino-hexopyranoside 6-[Bis(cyclohexylammonium) phosphate] (IIb).—The phosphorylation was carried out essentially according to the procedure of Remizov⁶ for the anomer. Freshly prepared diphenylphosphochloridate¹⁵ (2.6 g., 1 mmole) in 16 ml. of dry benzene was added, with stirring, to a solution of 1.8 g. (1 mmole) of methyl 2-deoxy- β -D-arabino-hexopyranoside (I) in 15 ml. of pyridine at -20° . The addition required 90 min. and precautions were taken to exclude moisture. The solution was stirred an additional hour at 10° and was then maintained at 10° overnight. After then standing at room temperature for 4 hr. the solvents were removed under reduced pressure, and the resultant sirup was dissolved in 200 ml. of chloroform and the solution was washed twice with 5% sulfuric acid (saturated with sodium sulfate), water, aqueous sodium bicarbonate, and again with water. The dried chloroform solution was concentrated to a sirup, yielding 3.2 g. (80%).

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Examination of this sirup by thin layer chromatography on silica gel G (Stahl) with diethyl ether-ethyl acetate (1:1, v.v.) showed one main zone, R_f 0.25–0.3, after spraying with 1% potassium permanganate in 10% sodium hydroxide.

This sirup (1.5 g.) was dissolved in 25 ml. of anhydrous methanol and refluxed for 5 min. with a small amount of acid-washed carbon. The carbon was filtered and washed with a small portion of methanol, and Adams catalyst (0.2–0.3 g.) was added. The mixture was shaken with hydrogen (30 lb./in.²) for 12 to 16 hr. after which the catalyst was removed and fresh catalyst was added. This was shaken with hydrogen for 4 to 6 hr. and the catalyst was removed. The methanol solution was treated with cyclohexylamine (pH 8–9), and ethyl acetate was added until just before the product began to separate in gelatinous form. The solution was placed in the refrigerator and a product appeared after the wall of the flask was scratched with a glass rod. After several recrystallizations from methanol-ethyl acetate, 0.7 g. of material (IIb) was obtained: m.p. 183–184° dec. (softening above 175°); $[\alpha]^{22D} -30^\circ$ (c 2, water); X-ray powder diffraction data,¹⁶ 13.29 vs (1), 6.75 w, 5.68 m, 5.04 s (2), 4.60 s (3), 4.29 s, 4.15 w, 3.71 vw, 3.63 vw, 3.34 w, 3.12 vw, 3.03 w, 2.97 vw, and 2.83 vw.

Anal. Calcd. for $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_9\text{P}$: C, 50.00; H, 8.99; N, 6.14; P, 6.80. Found: C, 49.81; H, 9.28; N, 6.30; P, 6.55.

In some experiments, especially when the rate of addition of the phosphorylating reagent was more rapid, a second spot, R_f 0.7–0.8, appeared in smaller amount (about 1:9 by visual estimation). This was presumed to be the 4,6-diphosphate derivative but was not further investigated.

2-Deoxy-D-arabino-hexonic Acid 6-Phosphate.—An amount of 1.0 g. (2.2 mmoles) of methyl 2-deoxy- β -D-arabino-hexopyranoside 6-[bis(cyclohexylammonium) phosphate] (IIb) was dissolved in 8 ml. of water and treated with 15 g. of Dowex 50-X8 (H^+).¹⁷ Removal of the resin and subsequent washing of it made a total volume of about 25 ml. After hydrolysis at 68° for 12 hr. (interval paper chromatograms¹⁸ of the hydrolysate indicated complete hydrolysis in 8 hr.; inorganic phosphate was absent throughout), a solution of 0.56 g. (2.2 mmoles) of iodine and 1.2 g. of barium iodide in 4 ml. of water was added. Saturated barium hydroxide was added dropwise with stirring until the solution attained pH 8 and remained at that value; stirring was then continued for an additional 15 min. After filtration with carbon and washing, the total volume of the solution was 60 ml. Ethanol (90 ml.) was added and the product was collected by centrifugation. The supernatant was tested for additional product by adding more ethanol. The total product was redissolved in water and reprecipitated with ethanol. A last washing with absolute ethanol was followed by drying under reduced pressure and at room temperature for 1 hr. Washing with absolute ether yielded 0.8 g. (80%) of the barium salt of 2-deoxy-D-arabino-hexonic acid 6-phosphate. The infrared spectrum (potassium bromide pellet) of this compound demonstrated strong peaks at 1550 and 1400 cm^{-1} . This salt was converted to the free acid by dissolving it in 50 ml. of water, cooling, and adding 10 g. of Dowex 50-X8 (H^+). The resin was filtered and washed with a small amount of water and the filtrate (slightly red in color) was treated with cyclohexylamine to pH 6.5. Concentration under reduced pressure and drying by azeotropic distillation under reduced pressure with absolute ethanol yielded a solid. This solid was dissolved in absolute ethanol and filtered with carbon; after warming, acetone was added to opalescence. Scratching the flask wall and cooling yielded clusters of fine, short needles. Recrystallization from the above solvent system gave pure material (V): m.p. 145–146° dec. (dependent on rate of heating); $[\alpha]^{25D} +6^\circ$ (c 1, 95% ethanol); X-ray powder diffraction data,¹⁶ 14.2 s (2), 9.69 m, 7.05 vw, 6.05 w, 5.48 w, 4.70 m, 4.60 vs (1), 4.37 s (3), 4.00 w, and 3.86 w.

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_9\text{P}$: C, 47.16; H, 8.52; N, 6.11. Found: C, 47.14; H, 8.53; N, 6.12.

Attempts were made to convert the above bis(cyclohexylammonium) phosphate to the corresponding tris(cyclohexylammonium) phosphate with an excess of cyclohexylamine. The resulting product had a higher melting point, but analysis of the compound failed to yield correct values.

(16) Interplanar spacing, Å, Cu $K\alpha$ radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few lines are numbered (1, strongest).

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Methyl 2-Deoxy- β -D-arabino-hexopyranoside 4,6-(Monophenyl phosphate) (III).—A mixture of 1 g. of sirupy methyl 2-deoxy- β -D-arabino-hexopyranoside 6-(diphenyl phosphate) (IIa) and (presumably) methyl 2-deoxy- β -D-arabino-hexopyranoside 4,6-bis(diphenyl phosphate) (9:1 by visual estimation) was dissolved in 100 ml. of chloroform. The chloroform was shaken for 10 min. at room temperature with 50 ml. of 10% sodium hydroxide solution. The chloroform solution was then washed with 50-ml. portions of saturated aqueous sodium sulfate until the washings were neutral (three times). The dried chloroform solution was concentrated under reduced pressure. Solid material recovered amounted to 0.26 g., which, when examined by thin layer chromatography (silica gel G and diethyl ether-ethyl acetate as above), indicated three zones (R_f 0.25, 0.49, and 0.95). The zones of R_f 0.25 and 0.49 were of nearly equal intensity while the zone with R_f 0.95 was much less intense. The starting material showed only a trace of material with R_f 0.49. An authentic sample of methyl 2-deoxy- β -D-arabino-hexopyranoside 4,6-(monophenyl phosphate) (III, see following) was also run: R_f 0.49. Crystallization was effected from ether-acetone-petroleum ether, yielding 0.078 g., m.p. 168–174°.

Methyl 2-deoxy- β -D-arabino-hexopyranoside (1 g., 5.6 mmoles) was dissolved in 20 ml. of dry pyridine. Benzene (10 ml.) was added and the solution was cooled to -10° in an ice-salt bath. Monophenyl phosphorodichloridate¹⁵ (1.19 g., 6.6 mmoles) was added over a 45-min. period with care being taken to exclude extraneous moisture. After stirring an additional 45 min., the mixture was maintained at -10° overnight followed by several hours at 25° . Concentration under reduced pressure yielded a material which was dissolved in 150 ml. of ethylene dichloride. The ethylene dichloride solution was washed twice with 5% sulfuric acid, aqueous sodium bicarbonate, and with water, dried, and concentrated under reduced pressure to a solid. Crystallization from acetone-diethyl ether-petroleum ether gave fine needles, 0.425 g. (25%). Recrystallization, effected in the same manner, gave material: m.p. 182–183° dec.; $[\alpha]^{25}_D -58^\circ$ (c 1, chloroform); X-ray powder diffraction data,¹⁶ 8.32 w, 8.13 w, 7.76 w, 7.38 vw, 6.78 m (2), 5.42 w, 5.26 w, 4.60 w, 4.43 m (3), 4.25 s (1), 4.05 w, 3.88 vw, 3.78 w, 3.58 w, and 3.40 w.

Anal. Calcd. for $C_{13}H_{17}O_7P$: C, 49.36; H, 5.38; P, 9.81. Found: C, 49.66; H, 5.43; P, 9.81.

Methyl 2-Deoxy- β -D-arabino-hexopyranoside 4,6-(Cyclohexylammonium phosphate) (IIIa).—Methyl 2-deoxy- β -D-arabino-hexopyranoside 4,6-(monophenyl phosphate) [(III), 0.5 g.] was refluxed for 10 min. in anhydrous methanol with about 0.5 g. of acid-washed carbon. The solution was suction-filtered and washed with another 10 ml. of methanol. Adams catalyst (0.1 g.) was added and the mixture was shaken with hydrogen (15 lb./in.²) for 16 hr. The catalyst was removed and cyclohexylamine was added to the solution pH 8–9. Concentration under reduced pressure gave a material which was crystallized from ethanol-ether, yielding 0.33 g. Recrystallization (ethanol-ether) gave pure material: m.p. 197–198° dec., $[\alpha]^{25}_D -60.5^\circ$ (c 2, ethanol).

Anal. Calcd. for $C_{13}H_{26}NO_7P$: C, 46.01; H, 7.67; N, 4.13. Found: C, 46.12; H, 7.65; N, 4.02.

3,4,5-Tri-O-benzoyl-2-deoxy-6-O-trityl-D-arabino-hexose Diethyl Dithioacetal.—2-Deoxy-D-arabino-hexose diethyl dithioacetal¹⁹ (2 g.) was dissolved in dry pyridine and to this was added 2.1 g. of trityl chloride. After standing at room temperature for 40 hr., the solution was cooled to 0° and 4 g. of benzoyl chloride was added dropwise. The solution was then allowed to stand at room temperature for 2 days whereupon it was poured into 200 ml. of iced water. The separated gum was extracted with ethylene chloride and the extract was washed with aqueous sodium bicarbonate and water. Residual pyridine in the sirup obtained on solvent removal from the dried (decolorizing carbon) solution was removed by codistillation, under reduced pressure, with toluene. Crystallization was effected from ethanol, yielding 3.8 g., m.p. 123–124.5°. On allowing the product to stand at room temperature for some time, another melting point was taken. A slight softening was noted at 123° but the material then melted at 145 – 146° . In other preparations, only the higher melting form was obtained: $[\alpha]^{25}_D +35.5^\circ$ (c 2, chloroform).

Anal. Calcd. for $C_{50}H_{48}O_7S_2$: C, 72.81; H, 5.83; S, 7.76. Found: C, 72.76; H, 5.81; S, 7.91.

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Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides.

IX. The Migration of Benzoyl Groups in the Ammonolysis of 1,2,3,4,6-Penta-O-benzoyl-D-galactoses¹

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By ammonolysis of 1,2,3,4,6-penta-O-benzoyl-D-galactoses, having labeled benzoyl groups at different carbon atoms, the following contributions of each benzoyl group to the formation of 1,1-bis(benzamido)-1-deoxy-D-galactitol have been found: C-2, 0.13; C-3, 0.62; C-4, 1.02; C-6, 0.18 moles per mole. Compared with the penta-O-benzoyl-D-glucoses, the most interesting variation is the increase of the contribution of the benzoyl group at C-4, from 0.82 in the D-glucose series to total migration in the D-galactoses, that takes place at the expense of the contribution of the benzoyls in C-3 and C-6.

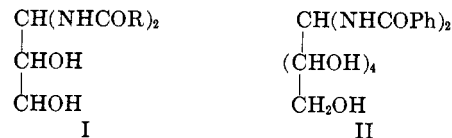
Ammonolysis, in methanolic solution, of acetylated and benzoylated pentoses,² L-rhamnose,³ and hexoses⁴ produces in various yields 1,1-bis(acylamido)-1-deoxyalditols (I, R = CH₃ or Ph). These products derive formally from the condensation of two molecules of acetamide or benzamide with the aldehyde group of one molecule of the sugar.

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The migration of the O-acyl groups from the different carbon atoms of monosaccharides to C-1, with the final production of the bisacylamido compounds (I), is an intramolecular reaction.⁵ The formation of the acyclic 1,1-bis(acylamido)-1-deoxyalditols from the cyclic pyranose derivatives of the monosaccharides re-

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