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Note

Derivatives of phosphonate and vinyl phosphate analogs of D-ribose 5-phosphate

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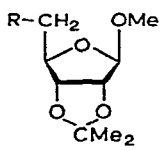
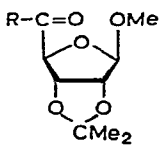
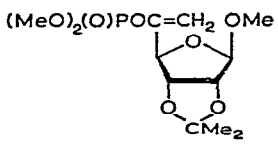
D-Ribose 5-phosphate is an essential metabolite for the biosynthesis of purine and pyrimidine nucleotides, nucleotide coenzymes, and nucleic acids. Phosphonate analogs in which the normal phosphate monoester system ($C–O–PO_3H_2$) of D-ribose 5-phosphate is replaced by $C–C–PO_3H_2$ are of biological interest because of the steric and electronic similarity between the two PO_3H_2 moieties. The only phosphonate analog of D-ribose 5-phosphate as yet reported contains an unsubstituted $CH_2CH_2PO_3H_2$ system; it was obtained as the diethyl ester of its 1,2,3-triacetate through reaction of a protected D-*ribo*-pentodialdo-1,4-furanose with tetraethyl methylenebis(phosphonate)[1]. Earlier work on synthetic sugar phosphonates produced 1,2,3-tri-*O*-acetyl-5-deoxy-5-*C*-(diethylphosphono)-D-ribofuranose[2] and 6-deoxy-6-*C*-phosphono-D-glucopyranose[3], in both of which the $CH_2OPO_3H_2$ group is replaced by the non-isosteric $CH_2PO_3H_2$ system. In this paper we describe the synthesis of an isosteric phosphonate analog of D-ribose 5-phosphate bearing a keto group α to the



1 R = OH
7 R = OTs
8 R = I
9 R = CN
10 R = CO_2H
11 R = CHO
12 R = $C(O)P(O)(OMe)_2$



2 R = OH
3 R = CHN_2
4 R = CH_2X
5 R = $CH_2P(O)(OMe)_2$



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phosphorus atom, and also work directed toward synthesis of a similar analog having a keto group β to the phosphorus atom; the latter synthesis led to a novel derivative of D-ribose 5-phosphate that contains a vinyl phosphate structure.

We investigated the possibility of obtaining the protected β-ketophosphonate analog **5** of D-ribose 5-phosphate by a Michaelis–Arbuzov reaction of the halomethyl ketones **4** (X = halogen) with trimethyl phosphite. The carboxylic acid **2** required for the synthesis of **4** could be obtained in good yield by treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[4,5] (**1**) with alkaline potassium permanganate. The acid **2** could be quantitatively converted, via its acid chloride, into the diazomethyl ketone **3**. Upon treatment with hydrochloric or hydrobromic acid, compound **3** produced the chloromethyl and bromomethyl ketones **4** in high yield. When treated at room temperature with sodium iodide in acetone these were converted into the corresponding iodomethyl ketone (**4**, X = I). The halomethyl ketones were too unstable to permit purification and full characterization, and their oximes were also unstable, and hence the halomethyl ketones were subjected immediately after preparation to reaction with trimethyl phosphite. It is to be noted that reaction of an α-haloketone with a trialkyl phosphite usually gives rise to a mixture of a dialkyl β-ketophosphonate (from the Michaelis–Arbuzov reaction) and a dialkyl vinyl phosphate (from the Perkow reaction). The Michaelis–Arbuzov reaction is favored by relatively high reaction-temperatures and by halogen groups in the order I > Br > Cl[6]. Treatment of the iodomethyl ketone **4** (X = I) with trimethyl phosphite in refluxing 1,4-dioxane gave a main product concluded to be the methyl ketone **4** (X = H); it was chromatographically identical with the product from platinum-catalyzed hydrogenation of the bromomethyl ketone (**4**, X = Br) and with that from treatment of the diazoketone **3** with hydriodic acid. Furthermore, its n.m.r. spectrum showed the usual signals arising from the protected ribofuranose moiety but showed an additional 3-proton singlet at δ 2.30. Similarly, it has been reported that iodoacetone becomes partially reduced to acetone (by an unknown route) during Michaelis–Arbuzov reaction of iodoacetone with triethyl phosphite[7]. At a lower temperature (60°) in tetrahydrofuran solution, the iodomethyl ketone **4** gave, in addition to the methyl ketone, small proportions of the vinyl phosphate **6** together with small proportions of a more polar, phosphorus-containing carbohydrate that was possibly the desired β-ketophosphonate **5**. At room temperature in ether, the bromomethyl and iodomethyl ketones produced **6** almost exclusively. At 60° in tetrahydrofuran, the bromomethyl ketone gave principally the vinyl phosphate **6** together with a small proportion of the more polar phosphono sugar, whereas the chloromethyl ketone in 1,4-dioxane at 100° gave a greater proportion of the more polar phosphono sugar than the vinyl phosphate **6**, but the yields of both were poor. The nature of the reaction conditions favoring formation of the relatively polar phosphono sugar show that this compound might be the β-ketoester **5**, but the low yields invariably obtained indicated that, in any event, this route was not feasible and so detailed characterization of the compound was not undertaken. The structure of **6** was assigned from its n.m.r. spectrum, in which the methylene groups resonated near δ 5.0 and showed a small geminal J value

(1.9 Hz) and relatively small $J_{H,P}$ values (5.0 and 6.3 Hz), properties typical of methylene signals of simple vinyl phosphates[8–10]. These features readily distinguish a vinyl phosphate structure from an isomeric β-ketophosphonate structure in which, as exemplified by dimethyl 2-oxopropylphosphonate[11] and 2-oxopropylphosphonic acid[12], the methylene signal occurs near 3.0 p.p.m. and the $J_{H,P}$ value (~23 Hz) is much larger. In accord with the vinyl phosphate structure of **6**, this compound readily underwent hydrolysis in aqueous solution above pH 10 or below pH 4, with production of dimethyl phosphite and the methyl ketone **4** (X = H).

The hexofuranuronic acid **10** required for synthesis of the α-ketophosphonate **12** was obtained by two routes. In the first of these, the 5-*O*-tosyl derivative **7** of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside was converted in 84% yield into the β-anomer of the 5-deoxy-5-iodoribofuranoside **8** with sodium iodide in *N*,*N*-dimethylformamide, a procedure previously used to convert a mixture of the 5-*O*-mesyl derivatives of **1** and its α-anomer into the corresponding 5-iodo derivatives[13]. Treatment of **8** with sodium cyanide in *N*,*N*-dimethylformamide gave a 52% yield of 5-cyano-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside[14] (**9**); with dimethyl sulfoxide as solvent, the yield was 18%. Alkaline hydrolysis of **9** gave the crystalline acid **10** in 55–75% yield. To determine whether or not the alkaline treatment had induced epimerization at C-4, a milder route to the acid **10** was sought. The acid **10** was not obtained when the diazoketone **3** was subjected to the conditions of the Wolff rearrangement, a reaction that succeeds with other sugar diazoketones[15,16]. Likewise, **10** was not obtained by attempted formation of a Grignard reagent from **8** and its subsequent carbonylation. However, a successful alternative synthesis of **10** was found, based on a recent demonstration[17] that primary alkyl bromides can be converted in high yield and under mild conditions into the corresponding aldehydes through the use of sodium tetracarbonyl ferrate. The sulfonate **7** gave no identified product by this procedure, but the 5-iodo derivative **8** gave the 5-deoxy-D-*ribo*-hexodialdo-1,4-furanose **11** in 45% yield. Oxidation of **11** with silver oxide furnished a product indistinguishable from the carboxylic acid obtained by alkaline treatment of the cyano derivative **9**.

The acid chloride of **10** was formed by treatment of **10** with thionyl chloride and was found to react rapidly with trimethyl phosphite at room temperature to give the α-ketophosphonate **12** in good yield. The compound was unstable, even under anhydrous conditions. During the present work it was reported that dialkyl esters of α-ketophosphonates prepared from aldonyl chlorides are likewise unstable[18]. The structure of **12** was supported by its n.m.r. spectrum and by its i.r. spectrum, in which the carbonyl absorption occurred at low frequency (1695–1700 cm^{-1}), characteristic of dimethyl and diethyl esters of acylphosphonates derived from simple aliphatic acids[19–21]. The mass spectrum of **12** showed the molecular ion (*m/e* 324) at a relative intensity of 0.17%; cleavage of the P–C bond gave the dimethyl phosphitei on (*m/e* 110, 3%) together with a sugar ketene ion (*m/e* 214, 2%). The α-ketophosphonate **12** was readily hydrolyzed to the acid **10** and dimethyl phosphite. In aqueous 1,4-dioxane at 93°, the half-life of **12** was 3 h, which is the same (within experimental

error) as the value reported for hydrolysis under the same conditions of the P–C(O) bond of diethyl butyrylphosphonate[19].

EXPERIMENTAL

General. — Melting points (uncorrected) were determined by the capillary method. Elemental analyses were by Midwest Microlab, Ltd., Indianapolis, Ind. I.r. spectra were obtained with a Perkin–Elmer 137 spectrophotometer, u.v. spectra with a Cary Model 15 spectrophotometer, and n.m.r. spectra with Varian XL-100-15 and Jeolco MH-60 spectrometers. Chemical shifts are reported in p.p.m. from internal Me_4Si. Analytical t.l.c. was performed on Merck F-254 silica gel plates in (*A*) chloroform, (*B*) ethyl acetate, (*C*) 9:1 chloroform–methanol, (*D*) 19:1 chloroform–acetic acid, and (*E*) tetrahydrofuran. Column chromatography employed Merck silica gel (70–325 mesh). Carbohydrates were detected by means of the Molisch reagent, and phosphorus-containing compounds with Phospray (a molybdate spray from Supelco, Inc., Bellefonte, Pa.).

Methyl 2,3-O-isopropylidene-β-D-ribofuranosiduronic acid (**2**). — Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (Pfanstiehl Labs., Inc.) (20 g) was dissolved in water (250 ml) and cooled to 4°. Potassium permanganate (52 g) and sodium hydroxide (2.5 g) in water (1,200 ml) were added over a period of 14 h with vigorous stirring. When the consumption of permanganate was complete the mixture was filtered and the filtrate concentrated to ~300 ml under vacuum at 40°. The solution was extracted with chloroform (5 × 100 ml) to remove starting material (6.8 g), and then adjusted to pH 4.0 with 2.5M sulfuric acid and again extracted with chloroform (5 × 100 ml). The dried (magnesium sulfate) chloroform extract was evaporated to give a crystalline mass (8.1 g). The product was purified by sublimation at 100° and 1.0 torr to give long needles (7.8 g, 56%), m.p. 125–126°, of methyl 2,3-*O*-isopropylidene-β-D-ribofuranosiduronic acid; ν_{max} 3350, 3090, 1727, 1100, 1055, 956, and 873 cm^{-1}; n.m.r. ($CDCl_3$): δ 9.23 (s, 1, HO–CO–), 5.16 (d, 1, $J_{2,3}$ 6 Hz, H-3), 5.00 (s, 1, H-1), 4.62 (s, 1, H-4), 4.51 (d, 1, $J_{2,3}$ 6 Hz, H-2), 3.36 (s, 3, MeO), 1.47 and 1.31 (s, 3, Me_2C).

Anal. Calc. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.26; H, 6.33.

Methyl 6-deoxy-6-diazo-2,3-O-isopropylidene-β-D-ribo-hexofuranosid-5-ulose (**3**). — The acid **2** (4.0 g) was placed in a 1000-ml flask fitted with a dropping funnel, magnetic stirrer, and a reflux condenser equipped with a guard tube. Thionyl chloride (10 ml, redistilled) was added and the mixture refluxed gently for 20 min, after which time the excess of thionyl chloride was removed *in vacuo* during 15 min. Dry ether (300 ml) and diazomethane (3 g) in dry ether (450 ml) were added in rapid succession. After 20 min, the solution was evaporated to a pale-yellow gum. The material was crystallized from ether–ligroin at 0° to give pale-yellow needles (4.0 g), m.p. 43.5–44.5°; R_F (system A), 0.52; ν_{max} 2100 (CHN_2), 1731 (C = O), 1649, 1215, 1105, 1055, 956, and 875 cm^{-1}; cyclohexane λ_{max} 249 nm (ε 8,500); n.m.r. ($CDCl_3$): 5.69 (s, 1, N_2CH–), 5.15 (d, 1, $J_{2,3}$ 6 Hz, H-3), 4.97 (s, 1, H-1), 4.52 (s, 1, H-4), 4.47 (d, 1, $J_{2,3}$ 6 Hz, H-2), 3.35 (s, 3, MeO), 1.45 and 1.30 (each s, 3, Me_2C).

Anal. Calc. for $C_{10}H_{14}N_2O_5$: C, 49.61; H, 5.78. Found (material dried at 20°, 0.1 mm): C, 49.10; H, 5.81.

*Methyl 6-deoxy-5-O-dimethylphosphoryl-2,3-O-isopropylidene-β-*D-ribo*-hex-5-enofuranoside* (**6**). — The diazoketone **4** (1.0 g) was dissolved in dry ether (100 ml) and treated with dry hydrogen bromide. After nitrogen evolution had ceased, t.l.c. (system A) showed that the u.v.-absorbing diazoketone was replaced by a non-absorbing spot (R_F 0.55) that gave a positive Molisch test and (after elution) positive tests for the presence of bromine. The solution was immediately evaporated to give the unstable bromomethyl ketone **4** (X = Br) as a gum. This was stored over potassium hydroxide for one h under vacuum, and then dissolved in dry ether and trimethyl phosphite (0.5 g) added. After refluxing for 45 min, no bromoketone could be detected by t.l.c. (system A). The major product (R_F 0.46) revealed by the Molisch spray contained phosphorus but no bromine, as did a minor component having R_F 0.30, although the latter reacted more slowly with the spray reagent for phosphorus. The ethereal solution was evaporated to dryness *in vacuo* and the residue was dissolved in chloroform (80 ml). This solution was poured through silica gel (20 g), which was washed with a further 20 ml of chloroform. The combined washings were evaporated to give **6** as a colorless gum that showed only one spot (R_F 0.46) on t.l.c. in system A; n.m.r.: (100 MHz, $CDCl_3$) δ 4.90 (d, 1, $J_{1,2}$ 0.7 Hz, H-1), 4.88 (dd, 1, $J_{2,3}$ 5.0 Hz, $J_{3,4}$ 0.8 Hz, H-3), 4.80 (ddd, 1, $J_{6a,6b}$ 1.9 Hz, $J_{4,6b}$ 1.0 Hz, $J_{6b,P}$ 5.0 Hz, H-6b), 4.71 (dd, 1, $J_{6a,6b}$ 1.9 Hz, $J_{6a,P}$ 6.3 Hz, H-6a), 4.47 (m, 1, H-4), 4.44 (dd, 1, $J_{2,3}$ 5.0 Hz, $J_{1,2}$ 0.7 Hz, H-2), 3.70 [d, 6, J_{POCH} 11.5 Hz, $PO(OMe)_2$], 3.26 (s, 3, OMe), 1.35, 1.17 (2s, 6, CMe_2). Proton H-6a is concluded to be *trans* (and H-6b *cis*) to the dimethylphosphate group because the *trans* coupling constant, $J_{Ha,P}$, of vinyl phosphates has been shown to be greater than the *cis* coupling constant[8]. The product decomposed too rapidly to permit elemental analyses.

The chloromethyl ketone **4** (R_F 0.48 in system A) was prepared by the procedure already described for the corresponding bromomethyl ketone. Both ketones were very unstable under acidic or basic conditions; for example, upon brief t.l.c. analysis they showed traces of contaminants having R_F 0.25–0.27 and 0.69–0.71 and these became more pronounced when contact time with the silica gel was increased. Treatment of the ketones in methanolic solution for 2 h at room temperature with hydroxylamine hydrochloride in 2.5M aqueous sodium acetate gave predominantly acid- and base-unstable products having R_F 0.18 (system A), which contained nitrogen and halogen. The iodo ketone **4** (X = I) (R_F 0.58 in system A) was obtained by treatment of the chloro or bromo ketone with 3 molecular equivalents of sodium iodide in acetone for 2 h at room temperature, and was isolated by dilution of the reaction mixture with water and extraction of **4** (X = I) into chloroform. The preparation contained lesser amounts of the methyl ketone **4** (X = H) having R_F 0.69, which was also produced by hydrogenation of **4** (X = Cl or Br) with Adams' catalyst in aqueous methanol containing M sodium acetate.

*Methyl 5-deoxy-5-iodo-2,3-O-isopropylidene-β-*D-ribo*furanoside* (**8**). — A solution of dry methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-ribofuranoside

(Pfanstiehl Labs., Inc.) (10.75 g, 0.030 mole) and dry sodium iodide (4.49 g, 0.039 mole) in 90 ml of dry *N,N*-dimethylformamide was stirred for 25 min under reflux at 165–170° under nitrogen in the dark. The cooled, orange solution was evaporated to a sludge at 30° (0.1–0.3 torr) and the solid was removed by filtration and washed with ether. After evaporation of the filtrate and addition of 300 ml of water, the crude iodo sugar was extracted into ether (7 × 50 ml). The solution was filtered through anhydrous magnesium sulfate and Norit A. Evaporation yielded a pale-yellow oil (8.42 g, 90%) that exhibited one major spot, R_F 0.74 (compound **8**), and two minor spots (R_F 0.32 and 0.15) on t.l.c. with chloroform. The crude product (7 g) was applied in 10 ml of acetone to a silica gel column (200 g, 2 × 52 cm) and eluted with 3 liters of 1:1 benzene–ligroin (b.p. 30–60°) to give pure compound **8** (6.54 g, 93% recovery); ν_{max} 2907, 1449, 1372, 1105, 877 cm^{-1}; n.m.r. ($CDCl_3$): δ 5.00 (s, 1, H-1), 4.72 (d, 1, $J_{2,3}$ 5.5 Hz, H-2), 4.56 (d, 1, $J_{2,3}$ 5.5 Hz, H-3), 4.40 (m, 1, H-4), 3.32 (s, 3, OMe), 3.17 (m, 2, H-5), 1.45, 1.30 (2s, 6, CMe_2).

*Methyl 5-cyano-5-deoxy-2,3-*O*-isopropylidene-β-*D*-ribofuranoside* (**9**). — At a bath temperature of 50–51°, a solution of dry methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (2.80 g, 9.93 mmole) in 30 ml of dry, distilled *N,N*-dimethylformamide was added dropwise with stirring to a suspension of dry, pulverized sodium cyanide (2.45 g, 50.0 mmole) in 45 ml of dry *N,N*-dimethylformamide under nitrogen. The mixture was stirred for 4 h at 50° and then kept for 15 h at 25°. The brown-black mixture was filtered through Celite, evaporated at 30° and 0.2 torr to 25 ml. Water (80 ml) was added and the product was extracted into ether (7 × 50 ml), which was dried and evaporated to yield a yellowish oil (2.75 g). This was dissolved in 5 ml of acetone and applied to a column (3.0 × 110 cm) of silica gel. Elution with 3 liters of chloroform gave, firstly, unreacted **8** (0.153 g) followed by chromatographically pure **9** (0.934 g, 52%) which solidified to a waxy mass, m.p. 47–50° (reported[14] 50–52°); R_F (chloroform) 0.41; ν_{max} (neat) 2899, 2237 (CN), 1453, 1374 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.92 (s, 1, H-1), 4.65 (d, 1, $J_{2,3}$ 6.0 Hz, H-2), 4.45 (d, 1, $J_{2,3}$ 6.0 Hz, H-3), 4.24 (m, 1, H-4), 3.30 (s, 3, OMe), 2.63 (m, 2, H-5), 1.42, 1.26 (2s, 6, CMe_2).

*Methyl 5-deoxy-2,3-*O*-isopropylidene-β-*D*-ribo-hexofuranosiduronic acid* (**10**). — To methyl 5-cyano-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (0.103 g, 0.48 mmole) in 3.5 ml of water and 2 ml of methanol was added 1 ml of 45% aqueous potassium hydroxide. The yellow mixture was refluxed for 25 min under nitrogen. T.l.c. (system D) showed that no starting material (R_F 0.74) was left. The solution was diluted with 5 ml of water and extracted with two 10 ml portions of chloroform. The aqueous layer was adjusted to pH 5 at 0° with AG 50W-X8 (H^+) (200–400 mesh) cation-exchange resin, and filtered. The filtrate was concentrated *in vacuo* and extracted with three 10-ml portions of chloroform and two 10-ml portions of ethyl acetate. Evaporation of the combined extracts gave essentially homogeneous **10** (0.062 g, 55%). Recrystallization from ethanol–ligroin (30–60°) gave fine needles, m.p. 154–155°; t.l.c.: system B, R_F 0.10; system D, R_F 0.11; tetrahydrofuran, R_F 0.54; ν_{max} 3030 (OH), 2899, 1724 (C=O), 1449, 1408 cm^{-1}; n.m.r. [$(CD_3)_2CO$]:

δ 5.13 (s, 1, H-1), 4.59 (d, 1, $J_{2,3}$ 6.5 Hz, H-2), 4.32 (d, 1, $J_{2,3}$ 6.5 Hz, H-3), 3.60 (m, 1, H-4), 3.22 (s, 3, OMe), 3.11 (CO_2OH exchanging with H_2O in the solvent), 2.60 (m, 2, H-5), 1.32, 1.23 (2s, 6, CMe_2).

Anal. Calc. for $C_{10}H_{16}O_6 \cdot 0.25\ H_2O$: C, 50.7; H, 7.0. Found (for material dried at 25°): C, 50.6; H, 6.5.

*Methyl 5-deoxy-6-dimethoxyphosphinyl-2,3-*O*-isopropylidene-β-*D*-ribo-hexofuranosid-6-ulose* (**12**). — To the carboxylic acid **10** (0.23 g) was added freshly distilled thionyl chloride (10 ml) dropwise under nitrogen. The yellowish solution was heated under reflux in a bath for 30 min at 80°, whereupon it became red. T.l.c. of an aliquot treated with an excess of methanol showed that no **10** remained and that only one Molisch-reactive component (R_F 0.95 in solvent B), presumably the methyl ester of **10**, was present. The thionyl chloride was removed *in vacuo*, and dry trimethyl phosphite (20 ml) was added during 30 min at 0° in a nitrogen atmosphere. The resulting solution was kept for 3 h at 25° under nitrogen, whereupon t.l.c. in solvent B showed that virtually all the acid chloride of **10** had reacted to give a Molisch-reactive product (R_F 0.6) together with a trace component (R_F 0.9). The trimethyl phosphite was evaporated off at 28° and 0.01 torr, and the residue was extracted with light petroleum (15 ml) to remove more trimethyl phosphite. The petroleum-insoluble fraction was subjected to preparative-layer chromatography at 5° on silica gel in solvent B. Compound **12** (R_F ~0.5) so obtained was rechromatographed at 5° in solvent A in order to remove a minor product (R_F 0.2). Compound **12** (120 mg) was obtained as a colorless glass that was homogeneous upon chromatography in solvents A (R_F 0.6), B (R_F 0.1), and (19:1) dichloromethane–methanol (R_F 0.5), except that traces of **10** were always observed. The amount of **10** increased when development of the chromatograms was delayed after application of the sample, showing that some, if not all of the **10**, is formed by contact of **12** with the silica gel. I.r.: ν_{max} 1692 (C=O), 1202 (P=O), 1053 (P–O–C) cm^{-1}; n.m.r.: ($CDCl_3$, 100 MHz) δ 4.85 (s, 1, H-1), 4.20 (m, 1, H-2), 4.01 (m, 1, H-3), 3.86 (m, 1, H-4), 3.71 [d, 6, J_{POCH} 11.0 Hz, $PO(OMe)_2$], 3.40 (s, 3, OMe), 2.71 (m, 2, H-5), 1.53, 1.35 (2s, 6, CMe_2). Satisfactory elemental analyses could not be obtained because of the instability of this compound.

To determine the rate of hydrolysis of **12**, a 0.2% solution of **12** in 7:3 1,4-dioxane–water was maintained under reflux and analyzed after 0.5, 1.0, 2.0, 3.0, and 19.0 h by t.l.c. in (19:1) chloroform–methanol with visualization of the components with the Molisch spray-reagent. The only components observed were unchanged **12** (R_F 0.30) and the acid **10** (R_F 0.05). Hydrolysis was 45–55% complete after 3 h and 90–95% complete after 19 h.

*Methyl 5-deoxy-2,3-*O*-isopropylidene-β-*D*-ribo-hexodialdo-1,4-furanoside* (**11**). — Sodium tetracarbonyl ferrate[17] was prepared by the addition of iron pentacarbonyl (185 µl, 1.38 mmole) to 1% sodium amalgam (27.09 g) in 12 ml of freshly distilled tetrahydrofuran under nitrogen. The mixture was stirred for 1 h at 25°, the amalgam was removed by suction, and a solution of triphenylphosphine (0.32 g, 1.20 mmole) in 2 ml of dry tetrahydrofuran was added, followed by dropwise addition of dry

methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (0.31 g, 1.0 mmole) in 2 ml of tetrahydrofuran. The mixture was stirred for 3 h at 25° and then treated with glacial acetic acid (3 ml). The mixture was stirred for 5 min, and then poured into 100 ml of ice–water. Extraction with 2 × 100 ml of cyclohexane removed triphenylphosphine and soluble iron complexes. Benzene (4 × 50 ml) was then evaporated *in vacuo* from the aqueous layer at 30°, and 30 ml of water added to the residue, which was then extracted with 3 × 75 ml of chloroform. The chloroform solution was concentrated to low volume and applied to three 20 × 20 cm × 2 mm silica gel plates, which were developed with chloroform. The band having R_F 0.15–0.25, which reacted positively to the *p*-anisidine spray test for aldehydes, was eluted with chloroform to yield compound **11** (0.096 g, 44% yield), which was homogeneous by t.l.c. in systems A (R_F 0.22) and C (R_F 0.77); ν_{max} 2890, 1730 (C=O), 1451, and 1374 cm^{-1}. N.m.r. data could not be obtained because of difficulty in removing traces of finely divided iron.

Oxidation of compound **11** *to* **10**. — Silver nitrate (17.0 mg, 0.12 mmole) dissolved in 50 μl of water was added to a solution of sodium hydroxide (10.0 mg, 0.25 mmole) in 100 μl of water[22]. The 6-aldehyde **11** (10.0 mg, 0.05 mmole) in 100 μl of methanol was added at 0°. After 10 min, the mixture (pH ~9) was centrifuged, the centrifugate was washed twice with 1.5 ml of water, and the supernatant was acidified with hydrochloric acid to pH 2.5. The solution was evaporated to dryness *in vacuo*. Purification of the residue by preparative t.l.c. in solvent C gave the 5-deoxy-D-*ribo*-hexofuranuronic acid (**10**) (7.0 mg, 60% yield). The i.r. spectrum was superposable on that of **10** from **9**. The R_F values of the two compounds were the same in solvents B, C, D, and E. The product formed colorless needles, from ethanol–ligroin, having m.p. 151–153°, alone or in admixture with **10** obtained from **9**.

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REFERENCES

1 J. A. Montgomery and K. Hewson, *Chem. Commun.*, (1969) 15.
2 J. R. Parikh, M. E. Wolff and A. Burger, *J. Amer. Chem. Soc.*, 79 (1957) 2778.
3 B. S. Griffin and A. Burger, *J. Amer. Chem. Soc.*, 78 (1956) 2336.
4 P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, 104 (1934) 299.
5 N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, 3 (1966) 485.
6 A. N. Pudovik and V. P. Avery'anova, *Zh. Obshch. Khim.*, 26 (1956) 1426; *Chem. Abstr.*, 50 (1956) 14512.
7 H. I. Jacobson, M. J. Griffin, S. Preis, and E. V. Jensen, *J. Amer. Chem. Soc.*, 79 (1957) 2608.

8 W. BRUGEL, TH. ANKEL, AND F. KRUCKEBERG, *Z. Elektrochem.*, 64 (1960) 1121.
9 E. M. GAYDOU, *Can. J. Chem.*, 51 (1973) 3412.
10 M. COHN, J. E. PEARSON, E. L. O'CONNELL, AND I. A. ROSE, *J. Amer. Chem. Soc.*, 92 (1970) 4095.
11 P. A. GRIECO AND C. S. POGONOWSKI, *J. Amer. Chem. Soc.*, 95 (1973) 3071.
12 R. KLUGER AND P. WASSERSTEIN, *J. Amer. Chem. Soc.*, 95 (1973) 1071.
13 H. M. KISSMAN AND B. R. BAKER, *J. Amer. Chem. Soc.*, 79 (1957) 5534.
14 J. A. MONTGOMERY AND K. HEWSON, *J. Org. Chem.*, 29 (1964) 3436.
15 M. L. WOLFROM, S. W. WAISBROT, AND R. L. BROWN, *J. Amer. Chem. Soc.*, 64 (1942) 1701.
16 I. DIJONG AND W. VON DER HEYDT, *Ann.*, 735 (1970) 138.
17 M. P. COOKE, *J. Amer. Chem. Soc.*, 92 (1970) 6080.
18 YU. A. ZHDANOV AND L. A. UZLOVA, *Zh. Obshch. Khim.*, 40 (1970) 2138; *Chem. Abstr.*, 74 (1971) 42579.
19 B. ACKERMAN, T. A. JORDAN, C. R. EDDY, AND D. SWERN, *J. Amer. Chem. Soc.*, 78 (1956) 4444.
20 Y. OGATA AND H. TOMIOKA, *J. Org. Chem.*, 35 (1970) 596.
21 K. D. BERLIN, D. M. HELLWEGE, AND M. NAGABHUSHANAM, *J. Org. Chem.*, 30 (1965) 1265.
22 E. CAMPAIGNE AND W. M. LESUER, *Org. Syntheses*, 4 (1963) 919.