BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 1431—1432 (1971)

The Novel Synthesis of Halodeoxy Sugars

Saburo INOKAWA, Kuniaki SEO,* Hiroshi YOSHIDA, and Tsuyoshi OGATA

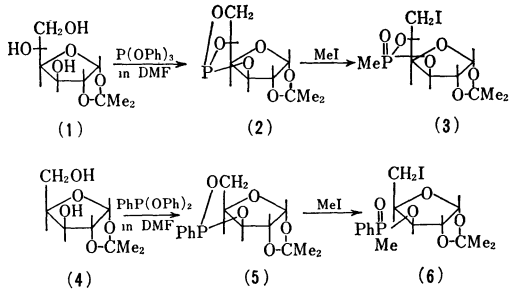
Department of Synthetic Chemistry, Faculty of Engineering, Shizuoka University, Johoku, Hamamatsu

**Department of Applied Chemistry, College of Technology, Ooka, Numazu*

(Received December 3, 1970)

The halodeoxy sugars are important synthetic intermediates,[1] but their preparation is often an involved process. This paper will describe a facile method for the formation of halodeoxy sugars by the reaction of cyclic phosphite or phosphonite derivatives of sugars with methyl iodide. The usefulness of this reaction is demonstrated by the conversion of 1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) into 6-deoxy-6-iodo-1,2-*O*-isopropylidene-3,5-*O*-(methylphosphonate)-α-D-glucofuranose (**3**) *via* the intermediate 1,2-*O*-isopropylidene-3,5,6-*O*-(phosphite)-α-D-glucofuranose (**2**). No evidence for the presence of another iodo isomer was obtained. To explore the scope of this facile reaction, 5-deoxy-5-iodo-3-*O*-(methylphenylphosphinate)-α-D-xylofuranose (**6**) was prepared *via* the 1,2-*O*-isopropylidene-3,5-(phenylphosphonite)-α-D-xylofuranose (**5**) from 1,2-*O*-isopropylidene-α-D-xylofuranose (**4**). The structures of the products were determined by studying the NMR spectra and by elementary analyses.

1) For reviews of halodeoxy sugars see: a) S. Hanessian, *Advan. Carbohyd. Chem.*, **21**, 142 (1966); b) J.E.G. Barnett, *ibid.*, **22**, 177 (1967).



Experimental

The nuclear magnetic resonance spectra were taken at 60 MHz on a Hitachi-Perkin-Elmer R-20 spectrometer, using tetramethylsilane as the internal reference. The thin-layer chromatograms were run on a silica-layer G;[2] phosphorus compounds were detected by spraying the plates with a cobalt chloride solution[3] and by then heating them. Periodic sampling and examination by thin-layer chromatography (tlc) permitted the determination of the most suitable reaction conditions for the preparation runs.

Materials. The 1,2-*O*-isopropylidene-α-D-glucofuranose (**1**)[4] and 1,2-*O*-isopropylidene-α-D-xylofuranose (**4**)[5] were prepared in the usual way. The triphenyl phosphite was used after the vacuum distillation of a commercial substance. The diphenyl phenylphosphonite[6] (bp 174—176°C/2 mmHg) was prepared by the reaction of an excess of phenol and phenylphosphonous dichloride.[7]

1,2-O-Isopropylidene-3,5,6-O-(phosphite)-α-D-glucofuranose (2). A solution of 5.0 g of **1** and 8.0 g of triphenyl phosphite in 30 m*l* of dimethylformamide (DMF) with 0.1 g of sodium ethoxide was allowed to stand at room temperature for 15 hr. The solution was then concentrated *in vacuo*; the residue was sublimated twice *in vacuo* at 120°C/2 mmHg to give, in an 80% yield (4.5 g), colorless needles; mp 155°C; $[\alpha]_D^{25}$ −24.3° (*c* 10, DMF); tlc upper (petroleum ether - ethyl acetate 4:1).

Found: C, 43.2; H, 5.25%. Calcd for $C_9H_{13}O_6P$: C, 43.6; H, 5.28%.

The PMR data (chloroform-*d*) were as follows: τ 3.88 (one-proton doublet, $J_{1,2}$=4.0 Hz, H_1), 5.47 (one-proton doublet, $J_{2,3}\fallingdotseq 0$ Hz, H_2), 5.6—6.2 (four-proton multiplets, $H_{3,4,5,6}$), and 8.54, 8.71 [six-proton singlets, $C(CH_3)_2$].

6-Deoxy-6-iodo-1,2-O-isopropylidene-3,5-O-(methylphosphonate) α-D-glucofuranose (3). A solution of 2 g of **2** in 15 m*l* of methyl iodide, with a small amount of copper powder, was heated at 100°C for 20 hr in a sealed tube. The solution was then filtered and concentrated *in vacuo*; the residue was dissolved in chloroform, washed with a sodium carbonate aqueous solution and water, dried over sodium sulfate, and concentrated *in vacuo* to give, in an 80% yield (2.5 g), colorless needles; mp 176—177°C (from methanol); $[\alpha]_D^{25}$ +15.2° (*c* 10, chloroform); tlc medium (petroleum ether - ethyl acetate, 4:1).

Found: C, 30.8: H, 4.17%. Calcd for $C_{10}H_{16}O_6PI$: C, 30.8; H, 4.13%.

The PMR data (chloroform-*d*) were as follows: τ 4.00 (one-proton doublet, $J_{1,2}$=4.0 Hz, H_1), 5.09 (one-proton multiplet, H_3), 5.33 (one-proton doublet, $J_{2,3}\fallingdotseq 0$ Hz, H_2), 5.5—5.9 (two-proton multiplets, $H_{4,5}$), 6.45 (two-proton doublet, $J_{5,6}$=7.0 Hz, H_6), 8.40 (three-proton doublet, $J_{P,CH}$=18.0 Hz, P-CH_3), and 8.49, 8.66 [six-proton singlets, $C(CH_3)_2$].

5-Deoxy-5-iodo-3-O-(methylphenylphosphinate)-α-D-xylofuranose (6). A solution of 7 g of **4** and 12 g of diphenyl phenylphosphonite in 40 m*l* of DMF with 0.1 g of sodium ethoxide was allowed to stand at room temperature for 20 hr. The solution was then concentrated *in vacuo*, and the resulting oil was fractionally distilled *in vacuo* to give 4.0 g of crude **5** contaminated with small amounts of phenol and diphenyl phenylphosphonite at 160—162°C/2mmHg; tlc medium (petroleum ether-ethyl acetate, 9:1). The crude **5** obtained above, without further purification, was dissolved in 15 m*l* of methyl iodide; then solution was heated with a small amount of copper powder at 100°C for 4 hr in a sealed tube. The solution was then filtered and concentrated *in vacuo*. Fractional high-vacuum distillation gave, in a 20% yield (3.1 g) based on **4**, a thick colorless sirup at 120°C/10^{-2}—10^{-3} mmHg; $[\alpha]_D^{20}$=−23° (*c* 3.04, carbon tetrachloride); tlc upper (petroleum ether - ethyl acetate, 1:4).

Found: C, 41.3; H, 4.65%. Calcd for $C_{15}H_{20}O_5PI$: C, 41.1; H, 4.60%.

The PMR data (carbon tetrachloride) were as follows: τ 2.0—2.8 (five-proton multiplets, C_6H_5), 4.25 (one-proton doublet, $J_{1,2}$=4.0 Hz, H_1), 5.20 (one-proton d. doublet, $J_{2,3}\fallingdotseq 0$ Hz, $J_{3,4}$=2.0 Hz. $J_{P,CH}$=9.0 Hz, H_3), 5.42 (one-proton doublet, H_2), 5.65 (one-proton broad doublet, H_4), 6.81 (two-proton doublet, $J_{4,5}$=7.0 Hz, H_5), 8.26 (three-proton doublet, $J_{P,CH}$=14.5 Hz, P-CH_3), and 8.60, 8.83 [six-proton singlets, $C(CH_3)_2$].

Results and Discussion

When a solution of **1** and triphenyl phosphite (1:1.2 molar ratio) in DMF was allowed to stand in the presence of sodium ethoxide at room temperature, **1** was transformed almost quantitatively into the product, **2**, as the tlc showed one major spot. When the solution was evaporated *in vacuo*, the sublimation of the resulting residue gave colorless needles in an 80% yield. The structure of **2** was established by elementary analysis and by studying the NMR spectrum.

The treatment of **2** with methyl iodide in a sealed tube at 100°C afforded **3** as colorless needles (from methanol) in an 80% yield. The structure of **3** was established by elementary analysis and by a study of the NMR spectrum. The appearance of the two-proton doublet at τ 6.45, shifted from 5.6—6.2 in the NMR spectrum of **1**, shows that **3** is a 6-deoxy-6-iodo compound, while the appearance of the three-proton doublet with a large coupling constant (J=18.0 Hz) at τ 8.40 shows that a CH_3 group is bonded to the phosphorus atom.

Similarly, the compound **6** was prepared by the reaction of **4** and diphenyl phenylphosphonite, followed by treatment with methyl iodide, in a poor yield (20%). Although the tlc showed that the reaction was rather clear, the poor yield seems to be due to difficulty in separation by fractional distillation.

This reaction may be effected to provide convenient and widely-usable route to halodeoxy sugars.

2) Nakarai Chemicals, Ltd., Kyoto.

3) R. Donner and K. Lohs, *J. Chromatogr.*, **17**, 349 (1965).

4) O. Th. Schmidt, "Methods in Carbohydrate Chemistry," Vol. II, ed by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1963), p. 318.

5) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

6) A. E. Arbusov, G. Kamai, and L. V. Nesterov, *Chem. Abstr.*, **51**, 5720 (1957).

7) B. Buchner and L. B. Lockhart, Jr., "Organic Syntheses," Coll. Vol. IV, p. 784 (1963).