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Sugars Containing a Carbon-phosphorus Bond. II. Syntheses of Phosphinyl Sugars by the Michaelis-Arbuzov Reaction of Halogenated Sugars

Saburo Inokawa, Yoshimi Tsuchiya, Hiroshi Yoshida
and Tsuyoshi Ogata[*1]

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

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3,5-*O*-Benzylidene-6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose was prepared in an 80% yield by heating a solution of 3,5-*O*-benzylidene-6-deoxy-6-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) in an excess of triethyl phosphite (**5**). Similarly, 6-deoxy-6-diethoxyphosphinyl-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose was prepared in a 95% yield from 6-deoxy-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**), and (**5**); 5-deoxy-5-ethoxyphenylphosphinyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose was prepared in a 90% yield from 5-bromo-5-deoxy-1,2-*O*-isopropylidenne-3-*O*-methyl-α-D-xylofuranose and diethyl phenylphosphonite; 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-(*N*,*N*′-tetraethyldiaminophosphinyl)-α-D-glucofuranose was prepared in a 44% yield from **1** and ethyl *N*,*N*′-tetraethylphosphorodiamidite (**7**); 6-deoxy-1,2;3,4-di-*O*-isopropylidene-6-(*N*,*N*′-tetraethyldiaminophosphinyl)-α-D-galactose was prepared in a 70% yield from **2** and **7**.

In the previous investigation,1) sugars containing a carbon-phosphorus bond were synthesized by the photochemical addition of the phosphonates to the unsaturated sugars. This time, the Michaelis-Arbuzov reaction has been used in the preparation of the phosphorus sugars; the results will be reported here. As the halogenated sugars, 3,5-*O*-benzylidene-6-deoxy-6-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**), 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-α-D-galactose (**2**), 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (**3**), and 1-bromo-1-deoxy-2,3;4,5-*O*-isopropylidene-β-D-fructopyranose (**4**) were used, and as the phosphorus compounds, triethyl phosphite (**5**), diethyl phenylphosphonite (**6**), and ethyl *N*,*N*′-tetraethylphosphorodiamidite (**7**) were used. The structures of the products were determined by studying the NMR spectra and by elementary analyses.

Experimental

The infrared spectra were measured on a Hitachi-Perkin-Elmer 337 spectrophotometer. 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 chromatogram were run on a silica-layer G2); phosphorus compounds were detected by spraying the plates with a cobalt chloride solution3) and then by heating them. Periodic sampling and examination by thin-layer chromatography permitted the determination of the suitable reaction conditions for the preparation runs.

Materials. The 3,5-*O*-benzylidene-6-deoxy-6-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) was prepared by the method of Meyer and Reichstein;4) mp 142°C. The 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) was prepared by the method of Schmidt;5) mp 72°C. The 5-bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (**3**) was prepared by the method of Inokawa *et al.*;6) bp 67°C/0.2 mmHg. The 1-bromo-1-deoxy-2,3;4,5-*O*-isopropylidene-β-D-fructopyranose (**4**) was prepared in a 65% yield by heating 2.5 g of 2,3;4,5-di-*O*-isopropylidene-1-*O*-(*p*-toluenesulfonyl)-α-D-fructopyranose7) and 2.0 g of lithium bromide in 20 m*l* of dimethylformamide at 150°C for 55 hr; mp 49—50°C8) after sublimation. The triethyl phosphite (**5**)9) was used after distillation. The diethyl phenylphosphonite (**6**)10) and ethyl *N*,*N*′-tetra-

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1) K. Kumamoto, H. Yoshida, T. Ogata and S. Inokawa, This Bulletin, **42**, 3245 (1969).

2) Nakarai Chemicals, Ltd., Kyoto.

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

4) A. S. Meyer and K. Lohs, *Helv. Chim. Acta*, **29**, 139 (1946).

5) O. Th. Schmidt, "Methods in Carbohydrate Chemistry," Vol I, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1962), p. 191.

6) S. Inokawa, H. Yoshida, C.-C. Wang and R. L. Whistler, This Bulletin, **41**, 1472 (1968).

7) S. B. Baker, *Can. J. Chem.*, **33**, 1460 (1955).

8) L. K. Dalton, *Aust. J. Chem.*, **19**, 445 (1966).

9) It was offered by Nippon Kagaku Kogyo, Ltd.

10) R. Schliebs, Ger. 1088955 (1959).

ethylphosphorodiamidite (**7**)[11] were prepared in the usual way.

3,5-*O*-Benzylidene-6-deoxy-6-diethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose (8). A solution of 2.0 g of **1** in 20 m*l* of **5** was heated at 150°C for 5 hr under a stream of nitrogen. The solution was then concentrated *in vacuo*; the residue was dissolved in ether, washed with water, dried over sodium sulfate, and concentrated *in vacuo* to give, in an 80% yield (1.6 g), a pale yellow oil (practically pure). An analytical sample was obtained by the use of a high vacuum at 125°C/10^{-2}—10^{-3} mmHg; $[\alpha]^{29}_{D}$ +17.4° (*c* 13.3, carbon tetrachloride).

Found: C, 55.0; H, 6.98%. Calcd for $C_{19}H_{29}O_8P$: C, 54.8; H, 7.02%. The PMR data (carbon tetrachloride) were as follows: 2.7 (five-proton multiplets, C_6H_5–), 4.1 (one-proton doublet, $J_{1,2}$=3.7 Hz, H_1), 4.4 (one-proton singlet, Ph–CH=), 5.4—6.3 [eight-proton multiplets, H_2, H_3, H_4, H_5, $(P\text{–}O\text{–}CH_2\text{–})_2$], 7.7 (two-proton quartet, $J_{6,P}$=18 Hz, $J_{5,6}$=8.0 Hz, $H_{6,6'}$), 8.6, 8.8 [six-proton singlets, overlapping with $(P\text{–}O\text{–}C\text{–}CH_3)_2$; $C(CH_3)_2$], and 8.8 [six-proton triplets, overlapping with $C(CH_3)_2$; $(P\text{–}O\text{–}C\text{–}CH_3)_2$].

6-Deoxy-6-diethoxyphosphinyl-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (9). A solution of 2.0 g of **2** in 20 m*l* of **5** was heated at 160° for 3 hr under a stream of nitrogen. The resulting solution was treated as has been described above to give, in a 95% yield (1.9 g), a pale yellow oil (practically pure). An analytical sample was obtained by high-vacuum distillation at 110°C/10^{-2}—10^{-3} mmHg; $[\alpha]^{19}_{D}$ −48.0° (*c* 10, carbon tetrachloride).

Found: C, 50.0; H, 7.81%. Calcd for $C_{16}O_8H_{29}P$: C, 50.2; H, 7.62%. The PMR data (chloroform-*d*) were as follows: 4.7 (one-proton doublet, $J_{1,2}$=4.0 Hz, H_1), 5.3—6.4 (eight-proton multiplets, H_2, H_3, H_4, H_5, $(P\text{–}O\text{–}CH_2\text{–})_2$], 7.8—8.3 (two-proton qualtet, $J_{6,P}$=18 Hz, $J_{5,6}$=6.8 Hz, $H_{6,6'}$), and 8.4—8.9 (twelve-proton multiplets, $C(CH_3)_2$, $(P\text{–}O\text{–}C\text{–}CH_3)_2$].

5-Deoxy-5-ethoxyphenylphosphinyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (10). A solution of 10 g of **3** in 30 m*l* of **6** was heated at 160°C for 5 hr. The resulting solution was treated as has been described above, and the oil thus obtained was distilled *in vacuo* to give, in a 90% yield, a colorless oil; bp 160—161°/0.1 mmHg, $[\alpha]^{25}_{D}$ −45.3° (*c* 10, chloroform).

Found: C, 57.7; H, 7.05%. Calcd for $C_{17}H_{25}O_6P$: C, 57.3; H, 7.07%. The PMR data (carbon tetrachloride) were as follows: 2.0—2.7 (five-proton multiplets, C_6H_5–), 4.3 (one-proton doublet, $J_{1,2}$=3.4 Hz, H_1), 5.5—6.5 (five-proton multiplets, H_2, H_3, H_4, $P\text{–}O\text{–}CH_2\text{–}$), 6.8 (three-proton doublet, $\text{–}OCH_3$), 7.4—8.0 (two-proton multiplets, $H_{5,5'}$), 8.6, 8.8 [six-proton singlets, overlapping with $P\text{–}O\text{–}C\text{–}CH_3$; $C(CH_3)_2$], and 8.8 (three-proton triplets, overlapping with $C(CH_3)_2$, $P\text{–}O\text{–}C\text{–}CH_3$).

3,5-*O*-Benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-(*N*,*N*′-tetraethyldiaminophosphinyl)-α-D-glucofuranose (11). A solution of 1 g of **1** in 10 m*l* of **7** was heated at 140°C for 24 hr under a stream of nitrogen, and the solution was then concentrated *in vacuo*; the residue was dissolved in chloroform, washed with an aqueous sodium carbonate solution and water, dried over sodium sulfate, and concentrated *in vacuo*; the residue was extracted with petroleum ether under reflux, and the extract was evaporated *in vacuo* to give, in a 44% yield (0.5 g), a brown oil. High-vacuum distillation gave a pale yellow oil, pure enough for a NMR measurement but not enough for an elementary analysis; bp 120—130°C/10^{-2}—10^{-3} mmHg, $[\alpha]^{15}_{D}$ −55.5° (*c* 0.9, chloroform). The PMR data (chloroform-*d*) were as follows: 2.4—2.8 (five-proton multiplets, C_6H_5–), 4.0 (one-proton doublet, $J_{1,2}$=3.8 Hz, H_1), 4.4 (one-proton singlet, Ph–CH=), 5.3—5.6 (four-proton multiplets, H_2, H_3, H_4, H_5), 6.7—7.3 [eight-proton multiplets, $[N\text{–}(CH_2\text{–})_2]_2$], 7.5—8.0 (two-proton multiplets, $H_{6,6'}$), 8.5, 8.7 [six-proton singlets, overlapping with $[N\text{–}(C\text{–}CH_3)_2]_2$; $C(CH_3)_2$], and 8.9 [twelve-proton triplets, overlapping with $C(CH_3)_2$; $[N\text{–}(C\text{–}CH_3)_2]_2$].

6-Deoxy-1,2;3,4-di-*O*-isopropylidene-6-(*N*,*N*′-tetraethyldiaminophosphinyl)-α-D-galactopyranose (12). A solution of 1 g of **2** in 10 m*l* of **7** was heated at 150—160°C for 5 hr under a stream of nitrogen. The resulting solution was treated as has been described above to give, in a 70% yield (0.7 g), a brown oil. High-vacuum distillation gave a pale yellow oil, pure enough for a NMR measurement but not enough for an elementary analysis; bp 90—100°C/10^{-2}—10^{-3} mmHg, $[\alpha]^{15}_{D}$ +18.5° (*c* 1.2, chloroform). The PMR data were as follows: 4.6 (one-proton doublet, $J_{1,2}$=4.4 Hz, H_1), 5.4—6.0 (four-proton multiplets, H_2, H_3, H_4, H_5), 6.7—7.3 [eight-proton multiplets, $[N\text{-}(CH_2\text{–})_2]_2$], 7.7—8.3 (two-proton multiplets, $H_{6,6'}$), and 8.4—9.1 [eighteen-proton multiplets, $C(CH)_{32}$, $[N\text{–}(C\text{–}CH_3)_2]_2$].

Results and Discussion

The Michaelis-Arbuzov reaction is one of the most important reactions making a phosphorus-carbon bond, but the application of this reaction to carbohydrate chemistry has been made in only a few reports.[12] When a solution of the halogenated sugars, **1**, **2**, **3**, or **4** in an excess of **5** was heated at 150—160°C for several hr under a stream of nitrogen, **1**, **2**, and **3** gave the corresponding phosphonyl sugars, **8**, **9**, and **10**, in a good yield.

In the case of **4**, however, the reaction did not proceed practically.[13] The reason for this seems to be the steric effect of two isopropylidene groups and the electron-withdrawing effect from the anomeric acetal group, which would hinder the cleavage of the C-Br bond. For the same reason, the formation of **4** from the corresponding tosyl compounds with lithium bromide in dimethylformamide was very slow, as has been shown in the Experimental part. The reaction of **3** with **8** was also carried out with ease to give **10** in a good yield. The structures of **8**, **9**, and **10** were established by elementary analyses and by studies of the NMR

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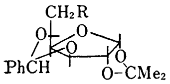
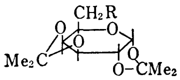
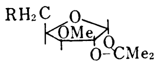
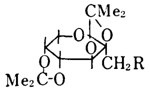
[11] A. Michaelis, *Ann. Chem.*, **326**, 160 (1903).

[12] R. L. Whistler and C.-C. Wang, *J. Org. Chem.*, **33**, 4455 (1968); A. Holy, *Tetrahedron Lett.*, **1967**, 881.

[13] H. Muller and T. Reichstein, *Helv. Chim. Acta*, **21**, 263 (1938); J. M. Williams, "Rodd's Chemistry of Carbon Compounds," Vol. I-F, ed. by S. Coffey, Elsevier Publishing Co., Amsterdam, London, New York (1967), p. 403.

TABLE 1. THE FORMATATION OF SUGARS CONTAINING A CARBON-PHOSPHORUS BOND BY THE MICHAELIS-ARUBUZOV REACTION

Sugar moieties	Halogenated sugars	Phosphorus compounds	Products	Yields (%)	$[\alpha]_D$ (temp.)
	[1] (R=I)	$(EtO)_3P$ [5]	[8] (R=$\overset{O}{\overset{\|}{P}}(OEt)_2$)	80	+17.4° (29°C) (*c* 13.3, CCl_4)
	[1] (R=I)	$EtOP(NEt_2)_2$ [7]	[11] (R=$\overset{O}{\overset{\|}{P}}(NEt_2)_2$)	44	+18.5° (15°C) (*c* 1.2, $CHCl_3$)
	[2] (R=I)	[5]	[9] (R=$\overset{O}{\overset{\|}{P}}(OEt)_2$)	95	−48.0° (19°C) (*c* 10, CCl_4)
	[2] (R=I)	[7]	[12] (R=$\overset{O}{\overset{\|}{P}}(NEt_2)_2$)	70	−55.5° (15°C) (*c* 0.9, $CHCl_3$)
	[3] (R=Br)	$PhP(OEt)_2$ [6]	[10] (R=$\overset{O}{\overset{\|}{P}}Ph(OEt)$)	90	−45.3° (25°C) (*c* 10, $CHCl_3$)
	[4] (R=Br)	[5]	no reaction		

spectra. The resonance of $H_{6,6'}$ in **8** and **9** was shifted to a higher field and showed a characteristic multiplet-shape upon P–H coupling. It was the same concerning the resonance of $H_{5,5'}$ in **10**. When a solution of **1**, or **2** in an excess of **7** was heated at 140—160°C for several 1 hr under a stream of nitrogen, the solution became brown, but **11** or **12** was afforded in a moderate yield. The structures were established by studies of the NMR spectra. The results described above are summarized in Table 1.

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