BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3245—3248 (1969)

Sugars Containing a Carbon-phosphorus Bond. I. Photochemical Addition of Diethyl Thiophosphonate to Unsaturated Sugars

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(Received April 26, 1969)

Sugars containing a carbon-phosphorus bond were synthesized by the photochemical addition of diethyl thiophosphonate to unsaturated sugars. By UV illumination from a high-pressure mercury lamp in the presence of diethyl thiophosphonate, D-glucal gave 1,5-anhydro-2-deoxy-2-(diethyl thiophosphonate)-D-glucit; 3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enose gave 1,2;5,6-di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-glucofuranose and 1,2;5,6-di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-galactofuranose (4:1 mol ratio); 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose gave 6-*O*-benzyl-5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-α-D-glucofuranose and 6-*O*-benzyl-5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-α-L-idofuranose (2:5 or 5:2 mol ratio), and 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose-4-ene gave 5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose.

Recently, a large number of sugars with sulfur and nitrogen atoms directly connected to the carbon chain have been synthesized and investigated not only with regard to their chemical properties, but also with regard to their biological activities. These sugars represent a potentially important area of sugar chemistry.[1] However, sugars with a phosphorus atom connected to the carbon chain are little-known. Exploration of the phosphorus sugars may be expected to provide information leading to another important new area of sugar chemistry.

In order to prepare the phosphorus sugars,[2] an investigation of the addition of diethyl thiophosphonate (DETP) to unsaturated sugars was undertaken. The results will be reported here. As the unsaturated sugars, D-glucal [1], 3-deoxy-1,2; 5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enose [2], 6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylohexofuran-5-enose [3], and 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose-4-ene [4] were used. The structures of the products were determined by studying the NMR spectra and by elementary analyses. The stereoselectivity of the radical addition will also be described.

Experimental

The infrared spectra were measured on a Hitachi-Perkin-Elmer 337 spectrophotometer. The nuclear magnetic resonance spectra were at 60 Mc 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[3] using various mixtures of ethyl acetate and petroleum ether, and phosphorus compounds were detected by spraying the plates with a cobalt chloride solution[4] and then heating them. The gas chromatograms were run on Yanagimoto GCG-3D gas chromatograph with a stainless column (2 mm × 2 m) packed with Apiezon Grease M[5] (20 wt % on Celite 545 of 40—60 mesh, using H_2 as the carrier gas (100 m*l*/min) at 200°C. The UV source was a 100-W Halos PIH-100 (high-pressure mercury lamp). Periodic sampling and examination by thin-layer chromatography permitted the determination of the most suitable irradiation times for the preparative runs.

Materials. The D-glucal [1] was prepared by the method of Roth and Pigman;[6] mp 57—59°C. The 3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enose [2] was prepared by the method of Schmidt;[7] mp 108—110°C. The 6-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-enose [3] was prepared by the

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[*1] This work was presented at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April 2, 1969.

[1] H. Paulsen and K. Todt, "Advances in Carbohydrate Chemistry," Vol. 23 ed. by M. L. Wolfrom and R. S. Tipson, Academic Press, New York and London (1968), p. 116.

[2] *Cf.* R. L. Whistler, C.-C. Wang, and S. Inokawa, *J. Org. Chem.*, **33**, 2495 (1968).

[3] Nakarai Chemicals Ltd., Kyoto.

[4] R. Donner and K. Lohs, *J. Chromatog.*, **17**, 349 (1965).

[5] Nishi Kogyo Co., Ltd., Tokyo.

[6] W. Roth and W. Pigman, "Methods in Carbohydrate Chemistry," Vol. II, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1963), p. 221.

[7] O. T. Schmidt, *ibid.*, p. 318.

method of Gramera and Whistler[8]; mp 113°C. The 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose-4-ene [4] was prepared by the method of Inokawa *et al.*;[9] bp 80°C/7 mmHg. The diethyl thiophosphonate [DETP] was prepared by the method of Krawiechi and Michalski;[10] bp 73—75°C/14 mmHg, λ_{max} 252 mμ, ε_{max} 162.

1,5-Anhydro-2-deoxy-2-(diethyl thiophosphonate)-D-glucit [5]. A solution of 5 g of [1] and 10 m*l* of DETP in 70 m*l* of dioxane in a reaction vessel was irradiated internally for 10 hr with a high-pressure mercury UV lamp (100 W) under a nitrogen atmosphere with stirring. The solution was then concentrated *in vacuo*; the residue was washed with petroleum ether and recrystallized from ethanol-petroleum ether to give, in a 90% yield (9.5 g), colorless needles of [5]; mp 93—95°C, $[\alpha]_D^{16}$ +23.4° (*c* 10, chloroform).

Found: C, 39.74; H, 7.04%. Calcd for $C_{10}H_{21}O_6PS$: C, 39.99; H, 7.06%.

The acetate; mp 93—95°C (from petroleum ether), $[\alpha]_D^{16}$ +62.5 (*c* 10, chloroform). The ^1H NMR data (carbon tetrachloride) were as follows: τ 4.50 (one-proton quartet, $J_{2,3}=9.0$ Hz, $J_{3,4}=9.0$ Hz, $J_{3,P}=15$ Hz, H_3), 5.06 (one-proton triplet, $J_{3,4}=9.0$ Hz, H_4), 5.4—6.7 [nine-proton multiplets, $H_{1,1',5,6'}$, $(P\text{-}O\text{-}CH_2\text{-})_2$], 6.35 (one-proton multiplet, $J_{1,2}=4.0$ Hz, $J_{1',2}=9.0$ Hz, $J_{2,P}=25$ Hz, H_2), 7.8—7.9 [nine-proton singlets, $(CH_3CO)_3$], and 8.7 [six-proton triplets, $(P\text{-}O\text{-}C\text{-}CH_3)_2$].

1,2;5,6-Di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-glucofuranose [6] and 1,2;5,6-di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-galactofuranose [7]. A mixture of 3 g of [2], 6 m*l* of DETP, and 6 m*l* of dioxane in a quartz tube was irradiated for 15 hr from a high-pressure mercury UV lamp (100 W) at a distance of about 3 cm under a nitrogen atmosphere. The mixture was then concentrated *in vacuo*; the residue was dissolved in ether, washed with water, dried over magnesium sulfate, and concentrated *in vacuo* to give an oil. The fractional vacuum distillation of the resulting oil gave, in a 42% yield (2.0 g), a pale yellow oil, a mixture of [6] and [7]; bp 175—177°C/2 mmHg.

Found: C, 48.74; H, 7.61%. Calcd for $C_{16}H_{29}O_7PS$: C, 48.46; H, 7.38%.

This mixture was separated into [6] and [7] by gas chromatography. The mol ratio of [6] and [7] in the mixture was 4 to 1. The product (retention time, 62 min) gave [6], $[\alpha]_D^{16}$ −4.6° (*c* 21, chloroform). The ^1H NMR data (carbon tetrachloride) were as follows: τ 4.4 (one-proton doublet, $J_{1,2}=4.0$ Hz, H_1), 5.2 (one-proton multiplet, $J_{3,4}=2.8$ Hz, $J_{4,5}=4.9$ Hz, $J_{4,P}=14.0$ Hz, H_4), 5.5—6.3 [eight-proton multiplets, $H_{2,5,6,6'}$, $(P\text{-}O\text{-}CH_2\text{-})_2$], 7.3 (one-proton multiplet, $J_{2,3}=7.0$ Hz, $J_{3,4}=2.8$ Hz, $J_{3,P}=16.0$ Hz, H_3), and 8.4—8.9 [eighteen-proton multiplets, $C(CH_3)_2$, $(P\text{-}O\text{-}C\text{-}CH_3)_2$]. The product (retention time, 78 min) gave [7]; $[\alpha]_D^{16}$ −9.3° (*c* 6, chloroform). The ^1H NMR data (carbon tetrachloride) were as follows: τ 4.3 (one-proton doublet, $J_{1,2}=4.0$ Hz, H_1), 5.1 (one-proton quartet, $J_{4,5}=3.5$ Hz, $J_{4,P}=9.0$ Hz, H_4), 5.4—6.4 [eight-proton multiplets, $H_{2,5,6,6'}$, $(P\text{-}O\text{-}CH_2\text{-})_2$], 7.3 (one-proton quartet, $J_{2,3}=5.0$ Hz, $J_{3,P}=16.0$ Hz, H_3], and 8.5—8.8 [eighteen-proton triplets, $C(CH_3)_2$, $(P\text{-}O\text{-}C\text{-}CH_3)_2$].

6-*O*-Benzyl-5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-α-D-glucofuranose [8] and 6-*O*-benzyl-5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-α-L-idofuranose [9]. A mixture of 1.8 g of [3], 2 m*l* of DETP, and 4 m*l* of dioxane in a quartz tube was irradiated for 5 hr from a high-pressure mercury UV lamp (100 W) at a distance of about 3 cm under a nitrogen atmosphere. The solution was then concentrated *in vacuo*; the residue was dissolved in ether, washed with water, dried over magnesium sulfate, and concentrated *in vacuo* to give an oil. The high-vacuum distillation of the resulting oil gave, in a 55% yield (1.6 g), a pale yellow oil, a mixture of [8] and [9], bp 120—125°C/10^{-3}—10^{-4} mmHg, in company with small amounts of impurities. The mixture was separated into [8] and [9] by thin-layer chromatography using a solvent of ethyl acetate and petroleum ether (1 : 1 v/v). The mol ratio of [8] and [9] in the mixture was 2 to 5 or 5 to 2. The product of R_f 0.6 showed $[\alpha]_D^{16}$ +32° (*c* 17, chloroform). The ^1H NMR data (carbon tetrachloride) were as follows: τ 2.7 (five-proton singlet, C_6H_5), 4.2 (one-proton doublet, $J_{1,2}=4.0$ Hz, H_1), 5.5 (two-proton singlet, CH_2Ph), 5.5—6.5 [nine-proton multiplets, $H_{2,3,4,6,6'}$, $(P\text{-}O\text{-}CH_2\text{-})_2$], 6.8 (one-proton singlet, OH), 7.6 (one-proton multiplet, H_5), and 8.5—9.0 [twelve-proton multiplets, $C(CH_3)_2$, $(P\text{-}O\text{-}C\text{-}CH_3)_2$]. The product of R_f 0.5 showed $[\alpha]_D^{16}$ −13° (*c* 17, chloroform). The ^1H NMR data (carbon tetrachloride) were as follows: τ 2.8 (five-proton singlet, C_6H_5), 4.3 (one-proton doublet, $J_{1,2}=4.0$ Hz, H_1), 5.6 (two-proton singlet, CH_2Ph), 5.6—6.5 [nine-proton multiplets, $H_{2,3,4,6,6'}$, $(P\text{-}O\text{-}CH_2\text{-})_2$], 6.7 (one-proton singlet, OH), 7.5 (one-proton multiplet, H_5), and 8.5—8.8 [twelve-proton multiplets, $C(CH_3)_2$, $(P\text{-}O\text{-}C\text{-}CH_3)_2$].

5-Deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose [10]. A mixture of 2.5 g of [4], 5 m*l* of DETP, and 5 m*l* of dioxane in a quartz tube was irradiated for 40 hr from a high-pressure mercury UV lamp (100 W) at a distance of about 3 cm under a nitrogen atmosphere. The mixture was then concentrated *in vacuo*; the residue was dissolved in ether, washed with water, dried over magnesium sulfate, and concentrated *in vacuo* to give an oil. The vacuum distillation of the resulting oil gave, in a 95% yield, a colorless oil; bp 149°C/2 mmHg, $[\alpha]_D^{20}$ −23.2° (*c* 10, carbon tetrachloride).

Found: C, 45.86; H, 7.51%. Calcd for $C_{14}H_{25}O_8PS$: C, 45.88; H, 7.36%. The ^1H NMR data (carbon tetrachloride) were as follows: τ 4.3 (one-proton quartet, $J_{1,2}=4.0$ Hz, H_1), 5.6 (one-proton doublet, partially overlapping with H_4; H_2), 4.5—6.2 [five-proton multiplets, partially overlapping with H_3; H_4, $(P\text{-}O\text{-}CH_2\text{-})_2$], 8.2 (one-proton doublet, partially overlapping with $(P\text{-}O\text{-}CH_2\text{-})_2$; $J_{3,4}=1.6$ Hz, H_3), 7.6 (two-proton quartet, $J_{4,P}=16$ Hz, H_4), 8.5, 8.8 [six-proton singlets, overlapping with $(P\text{-}O\text{-}C\text{-}CH_3)$; $C(CH_3)_2$], and 8.7 [six-proton triplets, overlapping with $C(CH_3)_2$; $(P\text{-}O\text{-}C\text{-}CH_3)_2$].

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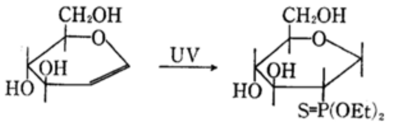
8) R. E. Gramera and R. L. Whistler, *J. Org. Chem.*, **29**, 878 (1965).

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

10) Cz. Krawiechi and V. Michalski, *Chem. & Ind.*, **1957**, 1323.

Results and Discussion

According to Pudovik and Konovalova,[11] the radical addition of diethyl thiophosphonate (DETP) to olefins affords a carbon-phosphorus bond. Also, Lehmann has made it clear that the radical addition to an enolic sugar derivative occurs at the β-position[12] to a hydroxyl group. When [1] is exposed to UV radiation in the presence of DETP, a reaction takes place, with the formation of one major product, as is indicated by thin-layer chromatography. The concentration on the solution gave, in a good yield, a solid residue. After recrystallization from ether-petroleum ether, this product was identified as 1,5-anhydro-2-deoxy-2-(diethyl thiophosphonate)-D-glucit [5]. The structure of this product was established by elementary analysis and by a study of the NMR spectrum of its acetate. The coupling constants,[13] $J_{1,2}=4.0$ Hz, $J_{1',2}=9.0$ Hz, and $J_{2,3}=9.0$ Hz, show that a diethyl thiophosphonate group is in an equatorial conformation.

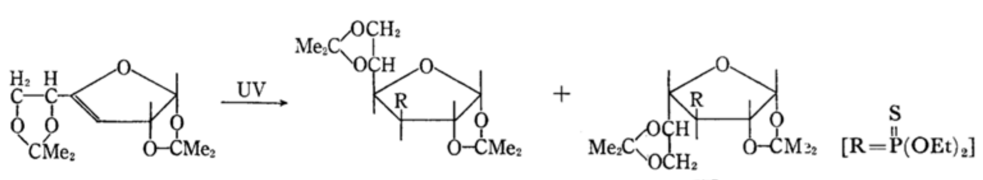


[1] [5]

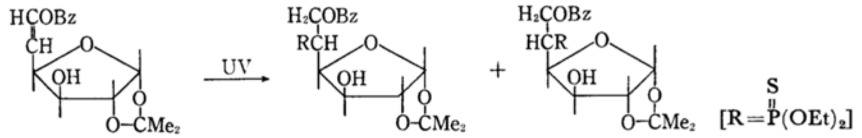
The compound [2] was exposed to UV radiation in the presence of DETP: the solution was then concentrated *in vacuo* to give, in a good yield, an oil, a mixture of two major products. After purification by vacuum distillation and separation by gas chromatography, they were identified as 1,2; 5,6-di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-glucofuranose [6] and 1,2; 5,6-di-*O*-isopropylidene-3-deoxy-3-(diethyl thiophosphonate)-α-D-galactofuranose [7]. The structures of these two products were established by elementary analyses and by studies of the NMR specta. It was generally accepted[14] that the *endo*-side of [2] was sterically strongly hindered by the 1,2-*O*-isopropylidene group. Therefore, the diethyl thiophosphonate group should be on the *exo*-side at the C-3 position. The fact that, in these NMR spectra, the coupling constant,[15] $J_{3,4}$, is 2.8 Hz for [6] and practically zero for [7] shows that [6] has the configuration of 1,2-*O*-isopropylidene-α-D-glucofuranose, while [7] has that of 1,2-*O*-isopropylidene-α-D-galactose. The mol ratio of [6] and [7] in the product was 4 to 1.

The compound [3] was exposed to UV radiation in the presence of DETP; the solution was then concentrated *in vacuo* to give an oil containing two major products, as indicated by thin-layer chromatography. After purification by high-vacuum distillation and separation by thin-layer chromatography, these products were identified as 6-*O*-benzyl-5-deoxy-5-(diethyl thiophosphonate)-1, 2-*O*-isopropylidene-α-D-glucofuranose [8]*2 and 6-*O*-benzyl-5-deoxy-5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-α-L-idofuranose [9].*2 The structure of these products were established by a study of the NMR spectra. The NMR spectra of these two products are very similar and shown that the number of hydrogen atoms at the carbon-bearing phosphorus is one. The optical rotations differed by +32° and −13° respectively. However, from the present results, it seems to be difficult to identify either of the two products as [8] or [9]. The mol ratio of the two products was 5 to 2.

The compound [4] was exposed to UV radiation in the presence of DETP; the solution was then concentrated *in vacuo* to give, in an almost quantitative yield, an oil containing one product, as indicated by thin-layer chromatography. After vacuum distillation, this product was identified as 5-deoxy-



[2] [6] [7]



[3] [8] or [9] [9] or [8]

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[11] A. N. Pudovik and I. V. Konovalova, *Zh. Obshch. Khim.*, **30**, 2348 (1960).

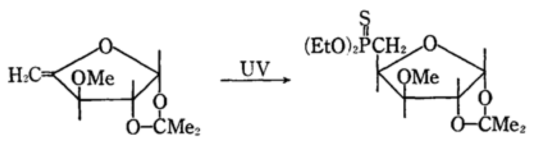
[12] J. Lehmann, *Carbohydrate Res.*, **2**, 486 (1966).

[13] J. Lehmann, *ibid.*, **2**, 499 (1966).

[14] H. Paulsen, *ibid.*, **2**, 80 (1966); L. Lehmann, *ibid.*, **2**, 1 (1966), and so on.

[15] R. J. Abraham, L. D. Hall, L. Hough and K. A. McLauchlan, *J. Chem. Soc.*, **1962**, 3699.

*2 The product still contained a small amount of impurities.



[4] [10]

5-(diethyl thiophosphonate)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose [10]. The structure of this product was established by elementary analysis and by a study of the NMR spectrum. The coupling constant, $J_{3,4}=1.6$ Hz, in the NMR spectrum and the finding that the photochemical addition of benzyl mercaptan to [4] gave only one product, 5-benzylthio-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose,9) show that [10] has the configuration of xylofuranose.

The results described above are summarized in Table 1.

The authors express their sincere thanks to Professor R. L. Whistler of Purdue University for his continued interest in this work and to Professor S. Kunichika of Kyoto University for carrying out elementary analyses. They are also grateful to Hashimoto Kaseikogyo, Ltd. for supplying them silver fluoride.

TABLE 1. THE FORMATION OF SUGARS CONTAINING A CARBON-PHOSPHORUS BOND BY THE PHOTOCHEMICAL ADDITION OF DIETHYL THIOPHOSPHONATE TO UNSATURATED SUGARS

Unsaturated sugars	Products	Mol ratios of products	Mp or bp	$[\alpha]_D^{16}$ ($CHCl_3$)
[1]	[5]	—	mp 114°C	+23.4° (*c* 10)
[2]	[6]	4	bp 175—177°C/2 mmHg	− 4.6° (*c* 21)
	[7]	1		− 9.3° (*c* 6)
[3]	[8]	2 or 5	bp 120—125°C/10^{-3}—10^{-4} mmHg	+32° (*c* 17)
	[9]	5 2		−13° (*c* 17)
[4]	[10]	—	bp 149°C/2 mmHg	−23.2° (*c* 10)*

* $[\alpha]_D^{20}$ (CCl_4)