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O,O-DIALKYLPHOSPHORO-THIOIC AND -DITHIOIC ACIDS AS FUNCTIONALISING REAGENTS OF MONOSACCHARIDES: SYNTHESIS OF 6-(DIALKOXYPHOSPHINYLTHIO)-α-D-GLUCOFURANOSES, AND A NEW ROUTE TO 5,6-EPISULPHIDES

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ABSTRACT

5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) reacts smoothly with *O,O*-dialkylphosphoro-thioic and -dithioic acids and with diarylphosphinothioic acids, to give 6-substituted phosphinylthio and phosphinothioylthio derivatives in high yields. The reaction of **1** with the anions of *O,O*-dialkylphosphoro-thioic and -dithioic acids yields, quantitatively, the 5,6-episulphide with inversion of the configuration at C-5. A mechanism for this reaction is proposed, which involves a pentacovalent phosphorus intermediate.

INTRODUCTION

Easily accessible organic thio- and seleno-acids of phosphorus of a general formula $(RO)_2P(X)YH$ (**2**, X = O, S; and Y = S, Se) are valuable reagents for functionalising monosaccharides. Their primary function is as thio- and seleno-phosphorylating reagents. Thus, thio- (or seleno-)phosphoryl groups have been introduced into the glycosidic position by reaction of pentosyl and hexosyl halides with the anions of thio- and seleno-acids of phosphorus[1–3], and by the addition of dithio acids to 1,2-unsaturated sugars, with simultaneous generation of the 2-deoxy function[4].

Removal of the phosphoryl residue by nucleophilic displacement at phosphorus, *e.g.*, by alkaline hydrolysis[5], would allow the synthesis of thio and seleno sugars having both anomeric configurations *via* thio- and seleno-phosphoric esters.

An alternative method of introducing thio- and seleno-phosphoryl groups into sugars is the reaction of sugar epoxides with the acids **2**. This route would enable the groups to be introduced into practically any position.

The synthesis of phosphoric acid esters starting from alkene oxides was first performed by Bailly[6] in 1916, and the application of this reaction in sugar chemistry by Todd and his co-workers led to the synthesis of model nucleotides[7]. The opening of epoxide rings with phosphates has been frequently applied in phosphorylation

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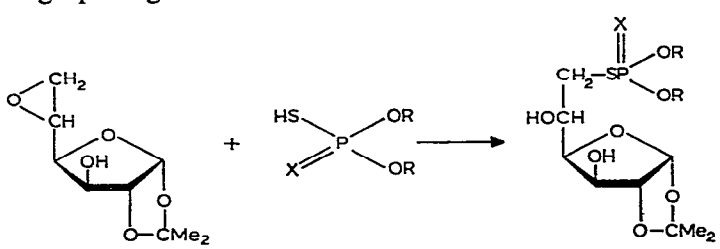
procedures[8]. The first report on the reaction of alkene oxides with dialkylphosphorothioic and -dithioic acids is due to Kabachnik and his co-workers[9].

We now report on the reaction of 5,6-epoxides with monothioic and dithioic acids **2** and with their ammonium salts.

RESULTS AND DISCUSSION

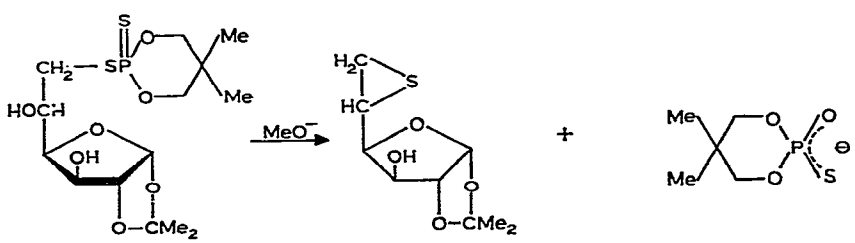
The reaction of 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose with O,O-dialkylphosphoro-thioic and -dithioic acids. 5,6-Anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) reacted smoothly with *O,O*-dialkylphosphoro-thioic and -dithioic acids (**2**), and with diarylphosphinothioic acids to give, regioselectively, 6-substituted phosphinylthio and phosphinothioylthio derivatives, **3a–f**, in high yields (see Table I). The structure of the products was established by i.r. and ^{1}H-n.m.r. data and confirmed for **3a** by independent synthesis based on nucleophilic displacement of TsO-6 in 1,2-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose by the appropriate monothioic acid anion. The rather drastic conditions of the latter reaction (in boiling butanone for several hours) gave a complex mixture of products from which **3a** was isolated in a low yield. This procedure is inferior to that involving the epoxide ring-opening.



1 **2** **3**

The yields of **3a–f**, determined spectroscopically, are quantitative in most cases. The yields of the isolated pure adducts and the reaction conditions are given in Table I.

The data in Table I show that phosphorodithioic acids react more rapidly with **1** than do the monothioic acids. Reaction conditions more drastic than those noted in Table I lead to the formation of the 5,6-episulphide **7** and to the appropriate desulphurated acid. The transformation of, for example, **3b** into **7** can also be effected in quantitative yield with sodium methoxide.



3b **7a**

TABLE I

PRODUCTS OF REACTION OF **1** WITH PHOSPHORO-THIOIC AND -DITHIOIC ACIDS (**2**)

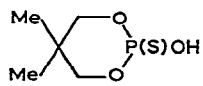
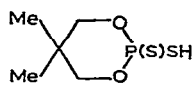
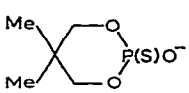
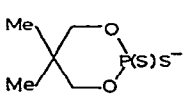
Phosphoro-thioic and -dithioic acid		*Reaction conditions (in benzene)*	*Epoxide adducts*			
				Yield (%)	*^{31}P (p.p.m.)*	*M.p. (degrees)*
2a		20°, 24 h	**3a**	78	−7.5	134–135
2b		20°, 24 h	**3b**	85	+89.5	130–131
2c	$(EtO)_2P(S)OH$	80°, 7 h	**3c**	54	−0.2	oil
2d	$(EtO)_2P(S)SH$	20°, 21 h	**3d**	88	+94	oil
2e	$Ph_2P(S)CH$	80°, 6 h	**3e**	61	+36	142–143
2f	$(Me_3CCH_2O)_2P(S)SH$	15°, 30 h	**3f**	63	+95	oil

TABLE II

REACTION OF ALKYLAMMONIUM SALTS (**4**) WITH **1**

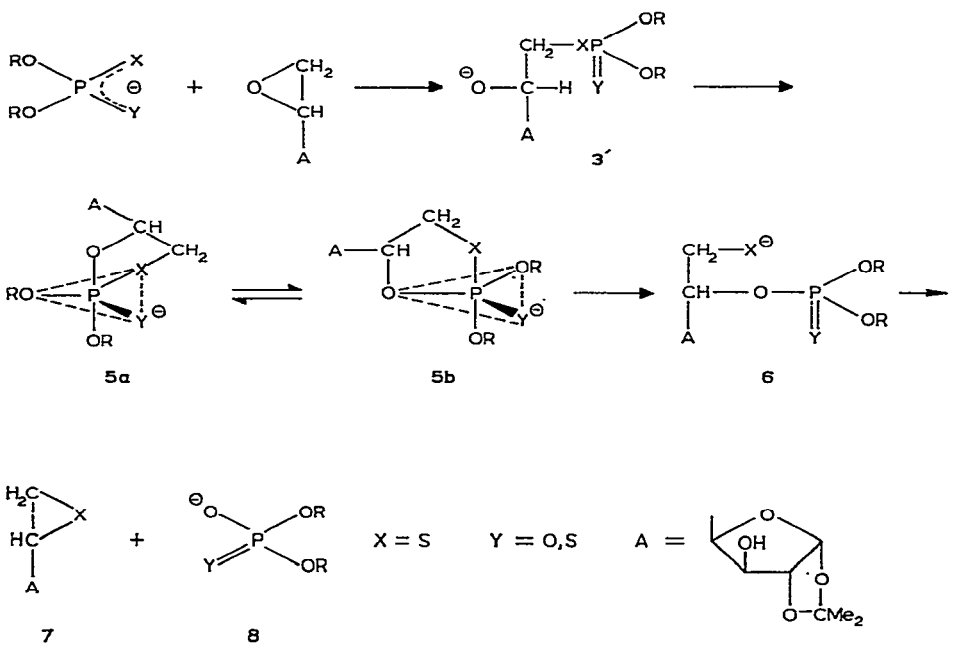
Alkylammonium salts of **2**		*Reaction conditions (in benzene)*	*Yield of* **7** (%)
4a	$(EtO)_2P(S)O^-$	80°, 5 h	65[a]
4b	$(EtO)_2P(S)S^-$	80°, 5 h	92
4c		80°, 7 h	73
4d		80°, 3 h	92
4e	$(MeO)_2P(S)O^-$	20°, 30 days	80
4f	$Ph_2P(S)O^-$	80°, 6 h	70

[a]Determined by ^{31}P-n.m.r. spectroscopy.

The reaction of 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose with O,O-dialkylphosphoro-thioic and -dithioic acid anions. The epoxide–episulphide transformation by means of *O,O*-dialkylphosphoro-thioic and -dithioic acid salts was first described in the patent literature[10] and subsequently investigated by several authors[11]. The mechanism proposed for this transformation involves a pentacovalent phosphorus intermediate[12].

Our investigations have demonstrated that **1** reacts smoothly with alkylammonium salts of phosphoro-thioic and -dithioic acids under very mild conditions, giving the 5,6-episulphide in quantitative yields. These reactions could be monitored by ^{31}P-n.m.r. spectroscopy. The signal corresponding to the dialkylphosphoro-thioic and -dithioic acid anions **4a–f** disappeared and that of its desulphurated analogue appeared. The alkylammonium salts of phosphorodithioic acids reacted faster than did the phosphoromonothioic analogues.

The most likely mechanism for the epoxide–episulphide transformation is depicted in Scheme 1. The adduct **3′** is formed first and then reacts further to give the pentacovalent intermediate **5a**, ligand reorganisation of which affords **5b**. Rearrangement of **5b** affords **6**, and internal nucleophilic displacement at C-5 then yields the desulphurated anion **8** and the episulphide **7**. This sequence of reactions should occur with retention of configuration at phosphorus and inversion of configuration at C-5 of the hexofuranose. The inversion of configuration at C-5 in **1** to give **7** was proved by comparison of the physical and spectral properties of **7** with the authentic *β*-L-*ido*-episulphide[13].



Scheme 1. Mechanism for the epoxide – episulphide transformation.

Hexofuranose 5,6-episulphides are important, potential sources of deoxy sugars[14], unsaturated sugars[15], and 5-thio sugars[16]. The simplicity of the preparative procedure described herein, the high yields and purity of the episulphides obtained, and the facile isolation procedure make the easily accessible anions of dialkylphosphoro-thioic and -dithioic acids valuable reagents for the synthesis of carbohydrate episulphides.

EXPERIMENTAL

General methods. — Melting points (Kofler) are uncorrected. ^{31}P-N.m.r. spectra were recorded for solutions in $CHCl_3$ (external 85% H_3PO_4) with a Jeol 60-MHz F.t. instrument. I.r. spectra were recorded for KBr discs with a Unicam SP-200 G spectrometer. Optical rotations were determined on solutions in $CHCl_3$ with a Polamat polarimeter. Analyses were performed at the Microanalytical Laboratories of the Centre of Molecular and Macromolecular Studies (Lodz) and the Institute of Organic Chemistry of the Polish Academy of Sciences (Warsaw).

T.l.c. was performed on silica gel (Stahl) with benzene–acetone–chloroform (3:1:1). Reactions were monitored by t.l.c. and detection with ammonium molybdate and iodine vapour. In reactions where episulphide was formed, monitoring was effected by ^{31}P-n.m.r. spectroscopy. The signs of the ^{31}P chemical-shifts are given according to the new convention. Acids **2a–f** and their salts **4a–f** were prepared by methods given in refs. 1–4.

6-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinanylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3a**). — A solution of **1** (1 g) and **2a** (0.9 g) in benzene (40 ml) was stirred at room temperature for 24 h. The organic layer was washed twice with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The syrupy product was crystallised from CCl_4, to give **3a** (1.5 g, 78.8%) as colourless needles, m.p. 134–135°, $[\alpha]_D^{20}$ +0.8° (*c* 0.4); ν_{max}^{KBr} 1260 (P=O) and 3320 cm^{-1} (HO).

Anal. Calc. for $C_{14}H_{25}O_8PS$: C, 43.75; H, 6.5. Found: C, 43.97; H, 6.6.

A solution of 1,2-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (1.87 g) and **4c** (1.41 g) in butanone was heated under reflux for 25 h, and then washed with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The syrupy product was crystallised from CCl_4, to give **3a** (0.2 g, 10.5%) as colourless needles, m.p. 134–135°.

6-(5,5-Dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3b**). — Solutions of **2b** (0.9 g) in benzene (10 ml) and **1** (1 g) in benzene (30 ml) at 0–5° were mixed, and then stirred at room temperature for 24 h. The crystalline, colourless product which precipitated was **3b** (1.7 g, 85%), m.p. 130–131°, $[\alpha]_D^{20}$ +0.25° (*c* 2); ν_{max}^{KBr} 680 (P=S) and 3310 cm^{-1} (HO).

Anal. Calc. for $C_{14}H_{25}O_7PS_2$: C, 42.0; H, 6.3; P, 7.7; S, 16.0. Found: C, 41.85; H, 6.3; P, 8.2; S, 16.0.

6-(Diethoxyphosphinylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3c**). — A solution of **1** (1 g) and **2c** (0.85 g) in benzene (40 ml) was heated under reflux for 7 h,

and then washed twice with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. Elution of the product from Kieselgel (0.2–0.5 mm) with chloroform–methanol (50:1) gave **3c** as a colourless oil (1 g, 54%), $[\alpha]_D^{20}$ +0.7° (*c* 2.25).

Anal. Calc. for $C_{13}H_{25}O_8PS$: C, 41.56; H, 6.81; P, 8.39. Found: C, 41.93; H, 6.76; P, 8.49.

6-(Diethoxyphosphinothioylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3d**).— Solutions of **1** (1 g) in benzene (30 ml) and **2d** (0.9 g) in benzene (10 ml) were mixed at 0–5°, and then stirred for 20 h at room temperature, washed twice with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The product was a colourless oil (1.7 g, 88%), $[\alpha]_D^{20}$ +0.22° (*c* 1.1); ν_{max}^{KBr} 670 (P=S) and 3400 cm^{-1} (HO).

Anal. Calc. for $C_{13}H_{25}O_7PS_2$: C, 40.20; H, 6.49. Found: C, 40.53; H, 6.88.

6-(Diphenylphosphinylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3e**). — A solution of **1** (1 g) and **2e** (1.17 g) in benzene (40 ml) was heated under reflux for 6 h and then washed twice with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The syrupy residue was crystallised from chloroform–light petroleum, to give **3e** (1.3 g, 61%) as colourless needles, m.p. 142–143°, $[\alpha]_D^{20}$ +8° (*c* 1.5); ν_{max}^{KBr} 1200 (P=O) and 3320 cm^{-1} (HO).

Anal. Calc. for $C_{21}H_{25}O_6PS$: C, 57.79; H, 5.73; P, 7.11. Found: C, 57.38; H, 6.07; P, 7.26.

6-(Dineopentyloxyphosphinothioylthio)-1,2-O-isopropylidene-α-D-glucofuranose (**3f**). — Solutions of **1** (1 g) in benzene (30 ml) and **2f** (1.35 g) in benzene (10 ml) were mixed at 0–5°, and stored for 30 h at room temperature, and then washed twice with aqueous 5% $KHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*, to give **3f** (1.5 g, 63%) as a colourless oil, $[\alpha]_D^{19}$ +0.8° (*c* 2); ν_{max}^{KBr} 670 (P=S) and 3650 cm^{-1} (OH).

Anal. Calc. for $C_{19}H_{37}O_7PS_2$: C, 48.29; H, 7.89. Found: C, 48.30; H, 7.99.

5,6-Dideoxy-5,6-epithio-1,2-O-isopropylidene-β-L-idofuranose (**7**). — Solutions of equimolar amounts of **1** and **4(a–f)** in dry benzene were heated under reflux or left at room temperature, as appropriate. When the reactions were complete, each solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give **7**, m.p. 167–168°, $[\alpha]_D^{20}$ −18° (*c* 2); lit.[13] m.p. 169–170°, $[\alpha]_D$ − 18.1°. The reaction times, temperatures, and yields of **7** are given in Table II. The yields of the isolated **7** were nearly equal to those determined by ^{31}P-n.m.r. spectroscopy.

To a solution (5 ml) of methanolic sodium methoxide (from 0.27 g of sodium) was added **3b** (0.2 g). The mixture was left at 0–5° for 30 min and then at room temperature for 30 min, neutralised with 0.05M H_2SO_4 (120 ml), and extracted with $CHCl_3$ (2 × 30 ml). The combined extracts were dried ($MgSO_4$) and concentrated, and the solid residue (0.1 g) was recrystallised from benzene to give colourless needles of **7**, m.p. 162–163°.

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REFERENCES

1 M. MICHALSKA, J. MICHALSKI, AND I. ORLICH, *Tetrahedron*, 34 (1978) 617–622.
2 M. MICHALSKA, I. ORLICH-KREZEL, AND J. MICHALSKI, *Tetrahedron*, 34 (1978) 2821–2824.
3 M. MICHALSKA, I. ORLICH-KREZEL, AND J. MICHALSKI, *Pol. J. Chem.*, 53 (1979) 253–264.
4 J. BOROWIECKA AND M. MICHALSKA, *Carbohydr. Res.*, 68 (1979) c8–c10.
5 F. GRIMMER, W. DEDEK, AND E. LEIBNITZ, *Z. Naturforsch., Teil B*, 23 (1968) 10–17.
6 O. BAILLY, *Ann. Chim.*, 6 (1916) 96–154.
7 W. E. HARVEY, J. MICHALSKI, AND A. R. TODD, *J. Chem. Soc.*, (1951) 2271–2278.
8 P. SZABÓ AND L. SZABÓ, *J. Chem. Soc.*, (1964) 5139–5143; J. STVERTECZKY, P. SZABÓ, AND L. SZABÓ, *J. Chem. Soc., Perkin Trans. 1*, (1973) 872–874.
9 M. I. KABACHNIK, T. A. MASTRYUKOVA, AND W. N. ODNOROŁOVA, *Zh. Obshch. Khim.*, 25 (1955) 2274–2277.
10 Ger. Pat. 1,082,915 (1960); *Chem. Abstr.*, 55 (1961) 25983b.
11 O. N. NURETDINOVA, *Zh. Obshch. Khim.*, 39 (1969) 2141–2142; O. N. NURETDINOVA AND B. A. ARBUZOV, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1970) 145–147; (1971) 353–358; (1975) 962–963.
12 N. K. HAMER, *Chem. Commun.*, (1968) 1399; D. C. GAY AND N. K. HAMER, *J. Chem. Soc., B*, (1970) 1123–1127.
13 L. D. HALL, L. HOUGH, AND R. A. PRITCHARD, *J. Chem. Soc.*, (1961) 1537–1545.
14 E. J. HEDGLEY, O. MÉRÉSZ, AND W. G. OVEREND, *J. Chem. Soc., C*, (1967) 888–894.
15 V. CALO, L. LOPEZ, A. MINCUZZI, AND G. PESCE, *Synthesis*, (1976) 200–201; J. E. CHRISTENSEN AND L. GOODMAN, *J. Am. Chem. Soc.*, 83 (1961) 3827–3834.
16 R. M. ROWELL AND R. L. WHISTLER, *J. Org. Chem.*, 31 (1966) 1514–1516; CHUNG WAI CHIU AND R. L. WHISTLER, *ibid.*, 38 (1973) 832–834.