Tetrahedron Vol. 34, pp. 2821–2824
© Pergamon Press Ltd., 1978. Printed in Great Britain.
0040-4020/78/0915-2821/$02.00/0

GLYCOSYLATION OF ORGANIC PHOSPHORUS THIO- AND SELENOACIDS—II

THE REACTION OF ORGANIC PHOSPHORUS THIOSELENOACIDS WITH GLYCOSYL BROMIDES UNDER KINETICALLY AND THERMODYNAMICALLY CONTROLLED CONDITIONS

MARIA MICHALSKA
Department of Organic Chemistry, Pharmaceutical Faculty, Medical Academy, Narutowicza 120 A, 90-145 Lodz

and

IZABELA ORLICH-KRĘŻEL and JAN MICHALSKI
Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Boczna 5, 90-362 Lodz, Poland

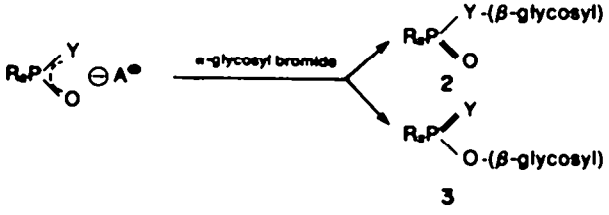
(*Received in UK 3 April 1978; Accepted for publication 10 April 1978*)

Abstract—Ambident anions derived from phosphorus thioselenoacids were glycosylated with 2,3,4,6 - tetra - O - acetyl - α - D - glucopyranosyl bromide, 2,3,4,6 - tetra - O - acetyl - α - D - galactopyranosyl bromide and 2,3,4 - tri - O - acetyl - α - D - xylopyranosyl bromide. The products were β-Se-glucosyl- and β-S-glucosylthioselenoates. The Se/S ratio of the glycosylated phosphorothioselenoates depends on the reaction conditions. At higher temperatures an equilibrium was observed. As a result of this equilibrium the Se/S ratio of the linkages formed in the glycosylated products was different from that observed under kinetic control. The structures of the glycosylated phosphorothioselenoates were confirmed by spectroscopy, independent synthesis and selective oxidation.

It has recently been shown[1,2] that ambident anions derived from phosphorus monothio- and monoselenoacids ($R_2P/Y/O^{\ominus}A^{\oplus}$) (Y = S, Se) 1 react with α-glycosyl bromides to give β-thiolo(selenolo) 2 and β-thiono(selenono) 3 isomers in various proportions depending on the type of counterion $A^{\oplus}$. Ammonium salts give mainly esters 2 whereas silver salts give mainly the isomeric esters 3.

The glycosylation reaction can be represented by the following scheme:

(1)



The present research is a continuation of our investigation of this type of reaction involving ambident anions derived from thioselenoacids of phosphorus[3,4] $R_2P(Se)S^{\ominus}A^{\oplus}$, 4. The reaction of 4 with alkylating reagents and other electrophiles is a particularly interesting subject, since the nucleophilic centre in 4 consists of a triad which contains two highly polarisable atoms, S and Se, attached to the P atom, showing a relatively small difference in electronegativity. Different electrophiles are likely to show very different degrees of ambidoselectivity in electrophilic attack on a system such as 4. The earlier work has established the validity of this conclusion for a variety of simple alkylating reagents such as alkyl halides, α-chloroethers and trialkyloxonium fluoroborates.[3] The ambidoselectivity of the attack was in full agreement with the HSAB reactivity rule. In this paper we wish to report the glycosylation of ambident thioselenoacids anions 4 with α-glycosyl halides under kinetically and thermodynamically controlled conditions.[a]

Table 1.

Compound	^{31}P NMR (ppm, H_3PO_4)	$J_{^{31}P-^{77}Se}$	Yield %
5a	−76	422	62
6a	−85	972	38
5b	−73	424	67
6b	−82	972	33
5c	−74	440	76
6c	−83	880	24
8a	−84	431	76
9a	−93	924	24

[a]The reaction of 4 with α-glycosyl halides was briefly reported in our preliminary communication.[5]

The starting thioselenoacids were prepared by addition of elemental selenium to the corresponding thiophosphites.[4]

$$(RO)_2P\text{–}Cl \xrightarrow[R_3N]{H_2S} (RO)_2P(S)H \xrightarrow[R_3N]{Se} (RO)_2P(Se)S^{\ominus}\overset{\oplus}{R_3}NH.$$

α-Glycosyl bromides were allowed to react with thioselenoates in boiling benzene. The course of the reaction was monitored by TLC and ^{31}P NMR. The glycosylation was complete in a few hours and in the case of more reactive reagents, such as α-xylopyranosyl bromide, in a few minutes.

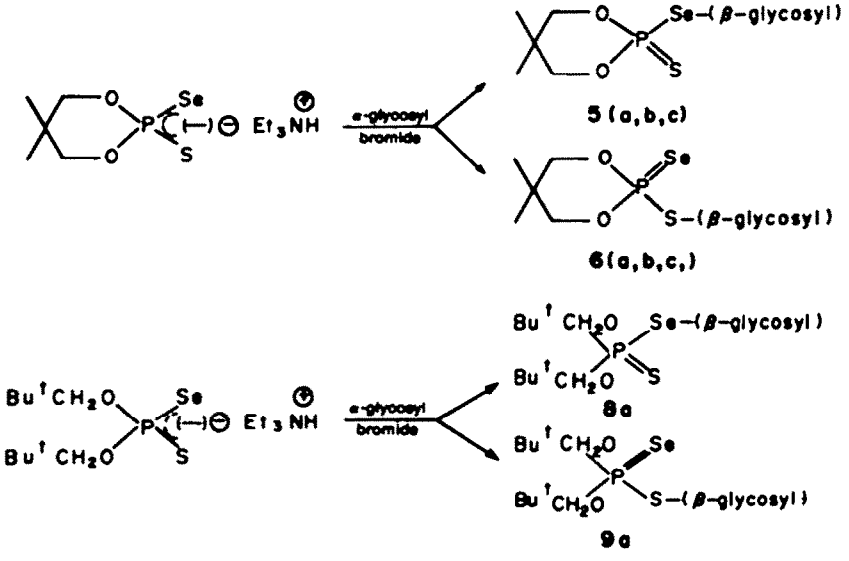
As expected, the glycosylation yields both S- and Se-glycosyl derivatives with the inversion of configuration at the glycosylic centre.

The yields were quantitative and according to ^{31}P NMR monitoring accuracy no phosphorus containing products other than **5**, **6**, **8** and **9** were formed. The attempted isolation of pure **5** and **6** failed because they could not be separated by crystallization from various solvents or by chromatography on silica gel columns and plates in various solvent systems. It is of interest that all the mixtures of products obtained after the evaporation of the reaction mixtures had sharp m.ps. In order to obtain pure **5a** and **6a** in the case of the β-glucosyl substituent two different methods were employed. For the preparation of pure **5a** the method of choice was the selective oxidation of the primary reaction mixture of **5a** and **6a** with *m*-chloroperbenzoic acid yielding **5a** and **10a** which were readily separated. The difference between the rates of oxidation of **5a** and **6a** at 0° in methylene chloride was sufficient for converting **6a** into **10a** without affecting **5a**. Elemental selenium precipitated immediately and after 10 min the oxidation process was complete.

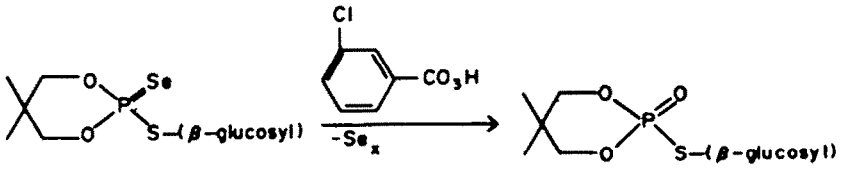
The relative ratio of **5a** to **10a** after the oxidation was almost identical with that of **5a** to **6a** prior to oxidation. The above mixture of products was separated by fractional crystallization. The structure of **10a** follows clearly from the results of our previous studies.[1] The selenono isomer **6a** was prepared from 1 - thiolo - 2,3,4,6 - tetra - O - acetyl - β - D - glucopyranose by condensation with the corresponding phosphoroselenochloridate.

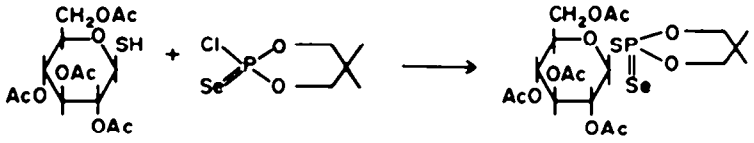
The above synthetic procedure in combination with ^{31}P NMR spectroscopy demonstrates the inversion of configuration in the course of glycosylation of **4**. This conclusion is consistent with our previous results on the glycosylation of dialkyl phosphorothioic and selenoic acids.[2]

The isomers **5a** and **6a** were characterised by ^{31}P NMR and IR spectra. The ^{31}P NMR spectra of **5a** and **6a** showed significant differences in ^{31}P–^{77}Se coupling constants. The selenolo compounds exhibited $J_{^{31}P-^{77}Se}$ in the 422–440 Hz region whereas the selenono isomers had a J value in the 880–972 Hz region. This is a new example of the usefulness of the $J_{^{31}P-^{77}Se}$ criterion in establishing structures of selenophosphorus compounds.[5,6] The



glycosyl: a 2,3,4,6-tetra-O-acetyl-o-glucopyranosyl-
b 2,3,4,6-tetra-O-acetyl-o-galactopyranosyl-
c 2,3,4-tri-O-acetyl-o-xylopyranosyl-





11
$\delta^{31}P = -52$ ppm
$J_{^{31}P-^{77}Se} = 1060$ Hz

6a; $\delta^{31}P = -85$ ppm

characteristic P=S absorption band in the IR spectra was noted at 670–680 cm^{-1}.

In order to investigate the possible isomerisation, pure 5a and 6a isomers were heated at 145°. After 5 min heating, thermodynamic equilibrium was reached; starting with either isomer, one obtained a 52:48 5a/6a ratio as observed by ^{31}P NMR spectroscopy.

This ratio is different from that observed in the glycosylation of the thioselenoate 7 which leads to the conclusion that the latter reaction is kinetically controlled. The equilibrium 5a ⇄ 6a is directly related to the known Pishchimukha isomerisation of thiono or selenonophosphates.[7]

The conservation of the β-configuration at the glycosylic C atom in our case and the ease of equilibration suggest a dissociation mechanism analogous to that discussed in the previous paper.[1]

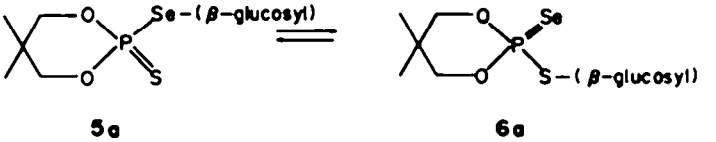
EXPERIMENTAL

M.ps (Kofler) are uncorrected. ^{31}P NMR spectra were recorded with a Jeol 60 MHz/FT operating at 24.3 MHz ($CHCl_3$ as solvent and 85% H_3PO_4 as external references). The chemical shifts are reported as δ values (±1 ppm). IR spectra were recorded with a Unicam SP-200 G (KBr tablets). Optical rotations were determined in $CHCl_3$ on a Perkin–Elmer 141 photopolarimeter. The elemental analyses were performed by Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies. TLC was carried out on Silica gel LS 5/90 (Lachema), detection was in parallel with iodine and ammonium molybdate spray.

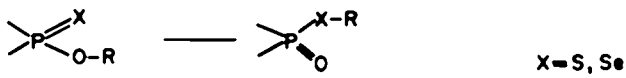
Glycosylation of triethylammonium hydrogen 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (7)[8] with α-acetobromoglucose. α-Acetobromoglucose (3 g; 7.2 mmole) and 7 (2.6 g; 7.2 mmole) were refluxed in benzene for 8 hr. Triethylamine hydrobromide (1.2 g; 96%) was filtered off, the filtrate washed with water and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, the syrupy residue refluxed in CCl_4–heptane to give 3.1 g (75%) of a crystalline product, (colourless needles) m.p. 144–46°. The product was shown to be a mixture of two components. (^{31}P NMR): δ = −85 ppm, $J_{^{31}P-^{77}Se} = 972$ Hz (–S–P(=Se)<); δ = −76 ppm, $J_{^{31}P-^{77}Se} = 442$ Hz (–Se–P(=S)<). The ^{31}P NMR signals were integrated as 38:62, respectively. (Found: C, 39.82; H, 5.34; P, 5.62. $C_{19}H_{29}O_{11}SSeP$ requires: C, 39.65; H, 5.04; P, 5.38%).

Glycosylation of triethylammonium hydrogen 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (7) with α-acetobromogalactose. α-Acetobromogalactose (2 g; 4.8 mmole) and 7 (1.65 g; 4.8 mmole) were refluxed in benzene for 8 hr. Triethylammonium hydrobromide (0.8 g; 96%) was filtered off, the filtrate washed twice with water, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, the residual syrup refluxed in CCl_4–heptane to give 2.2 g (80%) of a crystalline mixture of isomers, (colourless needles) m.p. 165–7°. The ^{31}P NMR spectrum showed two signals: δ = −82 ppm, $J_{^{31}P-^{77}Se} = 972$ Hz (–S–P(=Se)<); δ = −73 ppm, $J_{^{31}P-^{77}Se} = 424$ Hz (–Se–P(=S)<), integrated as 33:67, respectively. (Found: C, 39.60; H, 5.19; P, 5.67. $C_{19}H_{29}O_{11}SSeP$ requires: C, 39.65; H, 5.04; P, 5.38%).

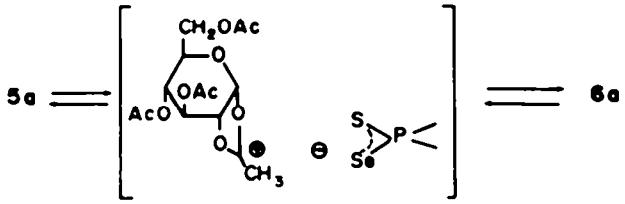
Glycosylation of triethylammonium hydrogen 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane (7) with α-acetobromoxylose. α-Acetobromoxylose (2 g; 5.9 mmole) and 7 (2 g; 5.9 mmole) were heated in boiling benzene for 2 min. Triethylammonium hydrobromide (0.9 g; 89%) was filtered off, the filtrate washed with water, dried over $MgSO_4$ and benzene evaporated under vacuum. The syrupy residue was refluxed in CCl_4–light



5a 6a



X=S, Se



petroleum (b.p. 60–80°) to give 2.5 g (87%) of a crystalline mixture of isomers (colourless needles) m.p. 134–36°. ^{31}P NMR: $\delta = -83$ ppm, $J^{31}_{P-^{77}Se} = 880$ Hz (–S–P(=Se)<); $\delta = -74$ ppm, $J^{31}_{P-^{77}Se} = 440$ Hz (–Se–P(=S)<); the signals were integrated as 24:76, respectively. (Found: C, 38.21; H, 4.97; P, 6.15. $C_{16}H_{23}O_9SSeP$ requires: C, 38.17; H, 4.95; P, 6.12%).

Triethylammonium O,O - di - neopentylphosphoroselenothioate. To the benzene soln containing O,O - di - neopentylthiophosphite[9] (2.38 g; 0.01 mmole) black Se powder (1 g; 0.01 mmole) was added portionwise under continuous stirring at ambient temp. Mixing was continued for 15 hr, traces of unreacted Se were filtered off, the solvent evaporated under vacuum. The solid residue was purified by crystallization (light petroleum) giving 3.2 g (78%) of colourless plates, m.p. 101–2°; ^{31}P NMR: $\delta = -97$ ppm; $J^{31}_{P-^{77}Se} = 724$ Hz. (Found: C, 45.86; H, 7.41; P, 9.99. $C_{16}H_{38}O_2NPSSe$ requires: C, 45.48; H, 7.40; P, 10.20%).

Glycosylation of triethylammonium O,O - di - neopentylphosphoroselenothioate with α - acetobromoglucose. α-Acetobromoglucose (0.82 g; 2 mmole) and triethylammonium O,O - di - neopentylphosphoroselenothioate (0.84 g; 2 mmole) were refluxed in benzene for 5 hr. Triethylammonium hydrobromide (0.3 g 86%) was filtered off, the filtrate washed with water and dried over $MgSO_4$. Benzene was evaporated under vacuum and the semi-crystalline residue crystallized twice from light petroleum (b.p. 60–80°) to give 1.1 g (84%) of a crystalline mixture of isomers as colourless prisms, m.p. 120–22°. The ^{31}P NMR spectrum showed two signals, $\delta = -93$ ppm, $J^{31}_{P-^{77}Se} = 924$ Hz (–S–P(=Se)<); $\delta = -84$ ppm, $J^{31}_{P-^{77}Se} = 431$ Hz (–Se–P(=S)<). (Found: C, 44.51; H, 6.42; P, 5.00

$C_{36}H_{41}O_{11}SSeP$ requires: C, 44.51; H, 6.31; P, 4.79%).

The synthesis of 2 - chloro - 2 - seleno - 5,5 - dimethyl - 1,3,2 - dioxaphosphorinane (according to Zemlyanskii's method[10]). 2 - Chloro - 5,5 - dimethyl - 1,3,2 - dioxaphosphorinane[11] (8.4 g; 0.05 mmole) and black Se powder (3.8 g; 0.05 mmole) were refluxed in toluene for 8 hr. A minute amount of unreacted Se was filtered off and the solvent evaporated under vacuum. The solidified residue was crystallized (benzene–light petroleum) to give 11 g (90% yield) of colourless needles m.p. 72–74°; δ ^{31}P = −52 ppm; $J^{31}_{P-^{77}Se} = 1060$ Hz. (Found: C, 24.00; H, 4.15; P, 12.30. $C_5H_{10}O_2PSeCl$ requires: C, 24.29; H, 4.04; P, 12.55%).

2 - S - (2,3,4,6 - Tetra - O - acetyl - β - D - glucopyranosyl) - 2 - Se - 5,5 - dimethyl - 1,3,2 - dioxaphosphorinane. 2-Chloro-2-seleno - 5,5 - dimethyl - 1,3,2 - dioxaphosphorinane (1 g; 4.04 mmole), 1 - thio - 2,3,4,6 - tetra - O - acetyl - β - D - glucopyranose (1.4 g; 4.04 mmole) and triethylamine (0.4 g; 4.04 mmole) were dissolved in benzene (50 ml) and stirred at room temp for 12 hr. The resulting mixture was washed twice with water and dried over $MgSO_4$. Benzene was evaporated under vacuum, the semi-crystalline residue crystallized (CCl_4–Et_2O–light petroleum) to give 1.6 g (67%) of colourless needles, m.p. 146–147°; $[\alpha]_D^{20} = +2.4°$ ($c = 1.3$, $CHCl_3$); ^{31}P NMR: $\delta = -85$ ppm; $J^{31}_{P-^{77}Se} = 972$ Hz. (Found: C, 39.48; H, 5.12; P, 5.70; S, 5.87. $C_{19}H_{29}O_{11}SSeP$ requires: C, 39.65; H, 5.04; P, 5.38; S, 5.65%).

General oxidation procedure

The crystalline mixture of selenono- and thiono isomers obtained in glycosylation reactions was dissolved in CH_2Cl_2 and cooled to 0°. The stoichiometric amount of *m*-chloroperbenzoic acid calculated for the selenono isomer was suspended in CH_2Cl_2, cooled to 0° and added in one portion to the soln of isomers. An immediate separation of elemental Se was observed. After 10 min the mixture was washed with a sat. Na_2CO_3aq, and the organic layer dried over $MgSO_4$. CH_2Cl_2 was evaporated under vacuum and the crude syrupy product analysed by means of ^{31}P NMR. The unoxidized thiono isomer was separated from the oxidation product of the selenono component by fractional crystallization, and characterized by physical and spectroscopic methods.

A. The (62:38) mixture of thiono and selenono isomers (5a + 6a; 1.5 g) reacted with 0.2 g of 85% *m*-chloroperbenzoic acid. The syrupy product showed two signals (^{31}P NMR): $\delta = -76$ ppm, $J^{31}_{P-^{77}Se} = 422$ Hz (–Se–P(=S)<); $\delta = -13.5$ ppm (–S–P(=O)<). After 2 crystallizations from MeOH 0.7 g (70%) of the unchanged thiono isomer was isolated as colourless needles, m.p. 140–41°; $[\alpha]_D^{20} = +11.6°$ ($c = 1.7$, $CHCl_3$); IR: $\gamma_{(P=S)} = 686$ cm^{-1}. (Found: C, 39.30; H, 5.16; P, 5.70. $C_{19}H_{29}O_{11}SSeP$ requires: C, 39.65; H, 5.04; P, 5.38%).

B. The (67:33) thiono and selenono isomers (5b + 6b; 1.0 g) reacted with 0.13 g of 85% *m*-chloroperbenzoic acid. ^{31}P NMR spectrum of the semi-crystalline product showed 2 signals: $\delta = -75$ ppm, $J^{31}_{P-^{77}Se} = 424$ Hz (–Se–P(=S)<); $\delta = -16.0$ ppm (–S–P(=O)<). Two crystallizations from MeOH gave 0.4 g (59%) of the unchanged thiono isomer as colourless needles, m.p. 166–68°; $[\alpha]_D^{20} = +3.2°$ ($c = 1.4$, $CHCl_3$); IR: $\gamma_{(P=S)} = 676$ cm^{-1}. (Found: C, 39.39; H, 5.22 P, 5.70. $C_{19}H_{29}O_{11}SSeP$ requires: C, 39.65; H, 5.04; P, 5.38%).

C. The (76:24) mixture of thiono and selenono isomers (5c + 6c; 1.6 g) reacted with 0.15 g of 85% *m*-chloroperbenzoic acid. ^{31}P NMR spectrum of the semi-crystalline product showed 2 signals: $\delta = -74$ ppm, $J^{31}_{P-^{77}Se} = 440$ Hz (–Se–P(=S)<); $\delta = -16.5$ ppm (–S–P(=O)<). Two crystallizations from MeOH gave 0.6 g (50%) of the thiono isomer as colourless needles, m.p. 136–38°; $[\alpha]_D^{20} = +3.6°$ ($c = 1.4$, $CHCl_3$); IR: $\gamma_{(P=S)} = 680$ cm^{-1}. (Found: C, 38.50; H, 5.06; P, 6.20. $C_{16}H_{29}O_9SSeP$ requires: C, 38.17; H, 4.95; P, 6.12%).

D. The (76:24) mixture of thiono and selenono isomers (8a + 9a; 1.5 g) reacted with 0.1 g of 85% *m*-chloroperbenzoic acid. The ^{31}P NMR of the crude product showed 2 signals: $\delta = -84$ ppm, $J^{31}_{P-^{77}Se} = 431$ Hz (–Se–P(=S)<); $\delta = -21$ ppm (–S–P(=O)<). Attempts to separate the thionoglycosylic ester from the oxidized product failed.

REFERENCES

[1]Part I. M. Michalska, J. Michalski and I. Ortlich, *Tetrahedron* 34, 617 (1978).

[2]M. Michalska, J. Michalski and I. Ortlich, *Bull. de l'Acad. Polon. des Sciences, Ser. des Sci. Chim.* 22, 1053 (1974).

[3]J. Michalski and Z. Tulimowski, *Ibid.* 4, 217 (1966).

[4]C. Krawiecki, J. Michalski and Z. Tulimowski, *Chem. Ind.* 34, (1965).

[5]W. J. Stec, A. Okruszek, B. Uznański and J. Michalski, *Phosphorus* 2, 97 (1972).

[6]Ch. Glidwell and E. J. Leslie, *J. C. S. Dalton* 527 (1977).

[7]A. Martowska and T. Nowicki, *Chem. Ber.* 111, 56 (1978).

[8]J. Michalski and Z. Tulimowski, unpublished results.

[9]A. Łopusiński, Ph.D. Thesis.

[10]N. I. Zemlyanskii, N. M. Chernaya, V. V. Turkevich and V. J. Krasnoshchek, *Zh. Obshch. Khim.* 36, 1240 (1966).

[11]R. S. Edmundson, *Chem. Ind.* 1220 (1965).