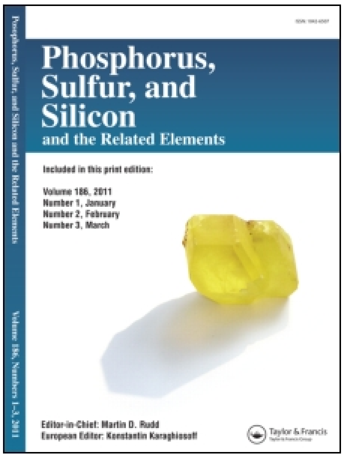

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF POLY(DITHIO-, THIO-AND CARBAMOYL (THIO)ESTER) DERIVATIVES OF D-GLUCOSE

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To cite this Article Len, Christophe , Postel, Denis , Meddah, Boumediene , Villa, Pierre and Ronco, Gino(2001) 'SYNTHESIS OF POLY(DITHIO-, THIO-AND CARBAMOYL (THIO)ESTER) DERIVATIVES OF D-GLUCOSE', Phosphorus, Sulfur, and Silicon and the Related Elements, 173: 1, 59 — 65

To link to this Article: DOI: 10.1080/10426500108045260

URL: http://dx.doi.org/10.1080/10426500108045260

Phosphorus, Sulfur and Silicon, 2001, Vol. 173, pp. 59-65
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SYNTHESIS OF POLY(DITHIO-, THIO- AND CARBAMOYL (THIO)ESTER) DERIVATIVES OF D-GLUCOSE

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(Received October 13, 2000; In final form November 29, 2000)

Regioselective carbamoylation of 3-*S*-(*N*,*N*-diethyldithiocarbamate) derivative of D-glucose gave the corresponding 6-*O*-(*N*,*N*-diethylcarbamate)-3-*S*-(*N*,*N*-diethyldithiocarbamate) as main product in yield of 43%. Transcarbamoylation was formed during the esterification in basic media and one of the by-product contained three different carbamic esters: *O*-carbamic, *S*-carbamic and *O*-thiocarbamic esters. The identification of each carbamate derivatives was realized by NMR analysis.

Keywords: carbamoyl ester; D-glucose; pesticide; fungicide

INTRODUCTION

Carbamate applications are known in medicinal[1] and agricultural areas.[2] Dithiocarbamic acid, *O*- and *S*-carbamoyl, *O*-thiocarbamoyl and dithiocarbamoyl esters are in current used as pesticides,[2] insecticides,[3] herbicides,[4] and fungicides.[5,6] Moreover literature reports indicate that carbamate and carbohydrate association enhance the polarity,[7] the phloem mobility, and increases plant systemic activity.[8] Research has been conducted in our laboratory to prepare new propesticides, and we previously demonstrated that compounds with two identical carbamoyl esters, such as bis(1,3-*S*-(*N*,*N*-diethyldithiocarbamoyl)-1,3-dideoxyglycerol (**1**), bis-3,6-*S*-(*N*,*N*-diethyldithio carbamoyl)-3,6-dideoxy-1,2-*O*-iso-

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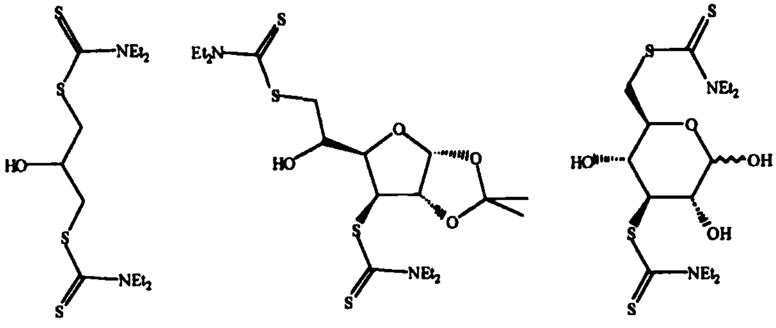
propylidene-α-D-glucofuranose (**2**) and bis-3,6-*S*-(*N*,*N*-diethyldithiocarbamoyl)-3,6-dideoxy-D-glucopyranose (**3**),[9,10] showed antifungal activities (Scheme 1) These encouraging results led us to explore the synthesis of new biscarbamic esters derivatives of monosaccharides including those with two different carbonyl groups. In this work, we describe the synthesis of 6-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethyldithiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**) having 6-*O*-carbamic and 3-*S*-dithiocarbamic esters and the identification of two by-products having differents carbamoyl groups.

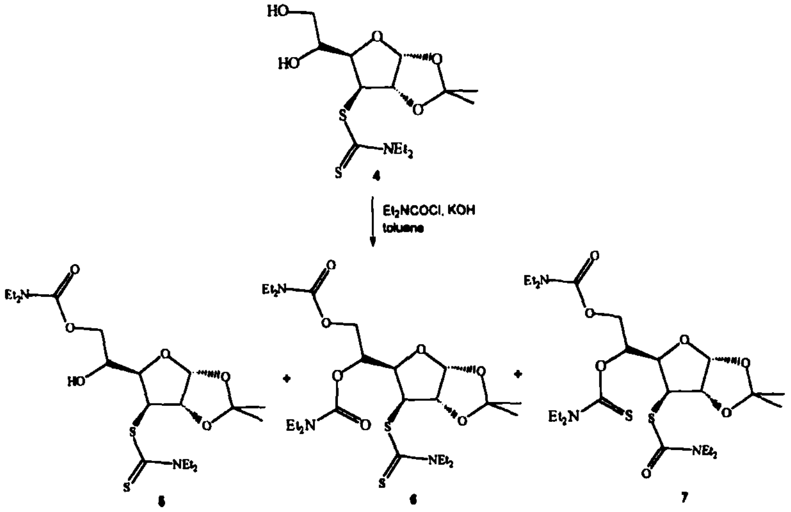


1 **2** **3**

SCHEME 1

RESULTS AND DISCUSSION

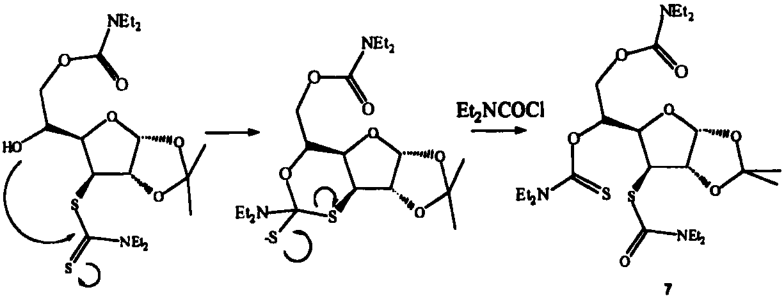
The carbamoyl esters reported in this paper were synthetized from 1,2–5,6-di-*O*-isopropylidene-α-D-glucofuranose in four steps *via* the 3-*S*-(*N*,*N*-diethyldithiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**).[10] Thus, as shown in Scheme 2, treatment of dithiocarbamate **4** with *N*,*N*-diethylcarbamoyl chloride (1.0 eq.) in dry toluene and in the presence of finely powdered KOH (2.0 eq.) gave 6-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethyldithiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) (43%). This regioselective *N*,*N*-diethylcarbamoylation at C-6 gave two tricarbamoylated by-products in small amounts. The first was 5,6-di-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethylthiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) which was the result of competitive carbamoylation. The second was 6-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethylcarbamoyl)-5-*O*-(*N*,*N*-diethylthiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α- D-glucofuranose (**7**) having three different carbamic esters: 6-*O*-carbamic, 3-*S*-carbamic and 5-*O*-thiocarbamic esters. The formation of **7** was the result of internal transthiocarbamoylation from C-3 to C-5 position followed by carbamoylation of the liberated C-3 alcoholate with *N*,*N*-diethylcarbamoyl chloride. The transesterification phenomenon during the carbamoylation in basic media was obtained by migration of the thioamide group from C-3 to C-5 position through a cyclic intermediate (Scheme 3).



SCHEME 2

NMR identification

The structure of biscarbamate **5**, tricarbamates **6** and **7** were supported by the ^{13}C and ^{1}H NMR data (TABLES Iand II). The chemical shift for the signals of the (thio)carbamoyl group were in character with the amide and thioamide functions. The carbonyl of the OCON group for compounds **5–7** had chemical shifts at 156.7–155.1 ppm in primary C-6 and 153.9 ppm in secondary C-5. The carbonyl of the SCON group and thiocarbonyl of the OCSN group for compound **7** had signals at 163.8 ppm and 185.4 ppm,



7

SCHEME 3

respectively. The thiocarbonyl of the SCSN group for compounds **4–6** had chemical shift, at 191.9–192.7 ppm. In comparison with that of the initial compound **4**, the 6-*O*-carbamate-3-*S*-dithiocarbamate **5** showed a downfield shift for the resonances of H-5 (ca. + 0.2 ppm), H-6 (ca. + 0.6 ppm), H-6′ (ca. + 0.5 ppm), and C-6 (ca. + 2.9 ppm), along with an upfield shift for the resonance of C-4 (ca. – 0.9 ppm), and C-5 (ca. – 0.8 ppm). The 5,6-di-*O*-carbamate-3-*S*-dithiocarbamate **6** showed a downfield shift for the resonances of H-4 (ca. + 0.3 ppm), H-5 (ca. + 1.3 ppm), H-6 (ca. + 0.6 ppm), H-6′ (ca. + 0.4 ppm), and C-5 (ca. + 1.5 ppm), along with an upfield shift for the resonance of H-3 (ca. – 0.2 ppm), C-3 (ca. – 0.9 ppm), and C-4 (ca. – 3.0 ppm). The 6-*O*-carbamate-3-*S*-carbamate-5-*O*-thiocarbamate **7** showed a downfield shift for the resonances of H-4 (ca. + 0.3 ppm), H-5 (ca + 1.9 ppm), H-6 (ca. + 0.8 ppm), H-6′ (ca. + 0.5 ppm), and C-5 (ca. + 5.7 ppm), along with an upfield shift for the resonances of H-2 (ca. – 0.2 ppm), H-3 (ca. – 0.5 ppm), C-3 (ca. - 7.7 ppm), C-4 (ca. – 2.8 ppm), and C-6 (ca. – 0.8 ppm).

The chemical shift for the signals of the diethyl group were in character with the amide and thioamide functions. In the case of *O*-diethylcarbamoyl ester, the ^{1}H and ^{13}C NMR data were 3.15–3.06 ppm 0.99–0.87 ppm and 41.7–41.3 ppm 13.9–13.2 ppm, respectively. In the case of the *S*-diethyltcarbamoyl ester, the ^{1}H and ^{13}C NMR data were 3.11 ppm 0.93–0.90 ppm and 42.1 ppm 13.0 ppm, respectively. In the case of the *O*-diethylthiocarbamoyl ester, the ^{1}H and ^{13}C NMR data were 3.61–3.14 ppm 0.98–0.95 ppm and 47.6–43.1 ppm 13.0–11.6 ppm, respectively. In the case of the S-diethyldithiocarbamoyl ester, the ^{1}H and ^{13}C NMR data were 3.92–3.60 ppm 1.16–1.13 ppm and 50.2–46.9 ppm 12.5–11.3 ppm, respectively.

TABLE I ^{13}C NMR chemical shifts (δ in ppm, in $CDCl_3$) for Compounds 4–7

Compd Chemical shifts (δ)							
C-2	C-3	C-4	C-5	C-6	$C(CH_3)_2$	$C(CH_3)_2$	Others
85.9	58.5	78.8	70.3	64.1	112.2	26.4; 26.2	192.7 (CS), 50.2, 47.4 (2C, NCH_2), 12 5, 11.4 (2C, CH_3)
86.4	58.1	77.9	69.5	67.0	112.1	26.5; 26.3	192.6 (CS), 156.7 (CO), 49.8, 47.1 (2C, $CSNCH_2$), 41.5 (2C, $CONCH_2$), 13. 13.4 (2C, $CONCH_2CH_3$), 12.5, 11.4 (2C, $CSNCH_2CH_3$)
86.6	57.6	75.8	71.8	63.9	112.1	26.5; 26.2	191.9 (CS), 155.1 (C-6-OCO), 153.9 (C-5-OCO), 49.5, 46.9 (2C, $CSNCH_2$), 41.3 (4C, $CONCH_2$), 13.9, 13.2 (4C, $CONCH_2CH_3$), 12.3, 11.3 (2C, CSNCH
86.9	50.8	76.0	76.0	63.3	111.7	26.5; 26.1	185.4 (OCS), 163.8 (SCO), 155.1 (OCO), 47.6, 43.1 (2C, $CSNCH_2$), 42.1 (2C $SCONCH_2$), 41.3 (2C, $OCONCH_2$), 13.2 (2C, $OCONCH_2CH_3$), 13.0 (2C, $SCONCH_2CH_3$), 13.0, 11.6 (2C, $OCSNCH_2CH_3$)

TABLE II ^1H NMR chemical shifts (δ in ppm, in $CDCl_3$) for Compounds 4–7

Compd Chemical shifts (δ)							
H-2	H-3	H-4	H-5	H-6	H-6′	$C(CH_3)_2$	Others
.67	4.74	4.30	3.67	3.79	3.57	1.44; 1 23	3.92, 3.78, 3.73 (4H, NCH_2), 1.20, 1.17 (6H, CH_3)
.65	4.67	4.33	3.88	4.36	4.07	1.40; 1.19	3.86, 3.60 (4H, $CSNCH_2$), 3.15 (4H, $CONCH_2$), 1.16, 1.13 (6H, $CSNCH_2CH_3$), 0.99 (6H, $CONCH_2CH_3$)
.57	4.55	4.61	4.94	4.42	4.01	1.38; 1.16	3.81, 3.55 (4H, $CSNCH_2$), 3.09 (8H, $CONCH_2$), 1.08, 0.94 (6H, $CSNCH_2CH_3$), 0. 0.87 (12H, $CONCH_2CH_3$)
.49	4.24	4.63	5.61	4.56	4.03	1.31; 1.11	3.61–3.14 (4H, $OCSNCH_2$), 3.11 (4H, $SCONCH_2$), 3.06 (4H, $OCONCH_2$), 0.98, 0.95 (6H, $OCSNCH_2CH_3$), 0.93- 0.90 (12H, $CONCH_2CH_3$)

Antifungal activity

Antifungal properties of the carbamic esters **4–7** were studied against *Alternaria brassicae, Septoria nodorum, Pseudocercosporella herpatrichoides*, and *Phytophtora cinnamomi*using a solid medium (Czapek Yeast Agar, glycine, aga)[11] and a Fayret liquid medium (glucose, ammonium nitrate).[12] The four carbamates **4–7** exhibited slight growth inhibition against the five fungi tested at 50, 20, and 2 ppm compared to that of the commercial Carbendazime® and Maneb®.

EXPERIMENTAL

Melting points were determined on an electrothermal automatic apparatus and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or MeOH, were measured with a digital polarimeter JASCO model DIP-370, using a sodium lamp at 25 °C. NMR spectra were recorded with a Bruker WB-300 instrument for solutions in $CDCl_3$ (internal Me_4Si). Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France). Reactions were monitored by either HPLC (Waters 721), using the reverse phase columns RP-18 (Merck). Analytical TLC was performed on Merck aluminium backed silica gel (Silica Gel F254). Column chromatography was performed on silica gel (60 mesh, Matrex) by gradient elution with hexane-diethyl ether.

3-S-(N,N-Diethyldithiocarbamoyl)-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (4)

Compound **4** was synthesized in accordance with previous work.[9]

6-O-(N,N-Diethylcarbamoyl)-3-S-(N, N-diethyldithiocarbamoyl)-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (5)

A solution of N,N-diethylcarbamoyl chloride (0.8 g, 5.7 mmol) in dry toluene (4 mL) was added dropwise to a stirred solution of **4** (2.0 g, 5.7 mmol) and KOH (0.6 g, 11.4 mmol) in dry toluene (20 mL) at 0 °C. Stirring was continued at 0 °C until HPLC monitoring indicated that maximum conversion was achieved (3 h), whereupon a saturated aqueous solution of ammonium chloride was added. The mixture was stirred for a further 10 min. The organic extract was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column eluted with hexane-diethyl ether (85:15) to give 0.3 g of 6-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethylcarbamoyl)-5-*O*-(*N*,*N*-diethylthiocarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α- D-glucofuranose (**7**) (92% estimated by ^1H and ^{13}C NMR integration). Further elution provided 0.4 g of 5,6-di-*O*-(*N*,*N*-diethylcarbamoyl)-3-*S*-(*N*,*N*-diethylcarbamoyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) (96% estimated by ^1H and ^{13}C NMR integration). Further elution provided 1.1 g of compound **5** (43%); $[\alpha]_D^{22}$ +29° (*c* 1.5, $CHCl_3$); Anal. Calcd for $C_{19}H_{34}O_6S_2N_2$(450.62): C, 50.64; H, 7.61; N, 6.22; S, 14.23. Found: C, 50.58; H, 7.63; N, 6.19; S, 14.02.

Further elution provided 0.6 g of initial starting material **4**.

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