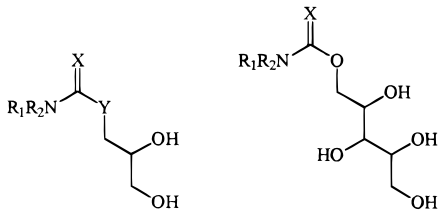
RAPID COMMUNICATIONS

Synthesis of Carbamic Esters Derivatives of Itols: Antifungal Activity against Various Crop Diseases

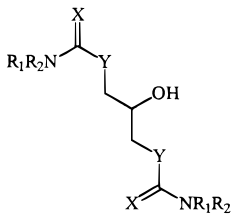
Keywords: *Fungicides; 1-carbamoyl-DL-glycerol; 1-carbamoyl-DL-xylitol; bis(1,3-carbamoyl)glycerol; in vitro activity*

Research has been conducted in our laboratories on new antifungal derivatives from natural products (Len et al., 1996) with the intention to prepare novel propesticides having greater residual effectiveness (Fahmy et al., 1981; Mallipudi et al., 1994) and higher plant systemic activity (Ziegler et al., 1975; Jojima et al., 1983). We have previously described the synthesis of mono(dithiocarbamic esters) such as 1-*S*-(*N*,*N*-diethyldithiocarbamoyl)-1-deoxy-DL-glycerol (**17**) and bis(dithiocarbamic esters) of glycerol such as bis[1,3-*S*-(*N*,*N*-diethyldithiocarbamoyl)]-1,3-dideoxyglycerol (**21**), bis[1,3-*S*-(morpho-4-yldithiocarbamoyl)]-1,3-dideoxyglycerol (**22**), and bis[1,3-*S*-(1-piperidyldithiocarbamoyl)]-1,3-dideoxyglycerol (**23**) and their *in vitro* and *in vivo* activities against different fungi (Len et al., 1996). Following a similar approach, we have now synthesized a series of novel carbamic esters having an itol hydrophilic moiety with one or two carbamoyl and thiocarbamoyl groups, respectively, such as 1-*O*-(*N*,*N*-diethylcarbamoyl)-DL-glycerol (**12**), 1-*O*-(*N*,*N*-diethylcarbamoyl)-DL-xylitol (**13**), 1-*O*-(*N*,*N*-diethylthiocarbamoyl)-DL-glycerol (**14**), 1-*O*-(*N*,*N*-diethylthiocarbamoyl)-DL-xylitol (**16**), bis[1,3-*O*-(*N*,*N*-diethylcarbamoyl)]glycerol (**18**), bis[1,3-*O*-(*N*,*N*-diethylthiocarbamoyl)]glycerol (**19**), and bis[1,3-*O*-(morpho-4-ylcarbamoyl)]glycerol (**20**) (Chart 1 and Scheme 1). This present work permitted us to compare (i) the importance of a multiple graft of carbamoyl groups on a low molecular weight itol; (ii) the part of the sulfur and oxygen atoms between dithiocarbamic, thiocarbamic, and carbamic esters as fungicides; and (iii) the activity between new carbamate propesticides and commercial Carbendazime (**I**) and Maneb (**II**).

Chart 1



12 : X = Y = O ; R_1 = R_2 = ethyl **13** : X = O ; R_1 = R_2 = ethyl
14 : X = S ; Y = S ; R_1R_2 = ethyl **16** : X = S ; R_1R_2 = ethyl
17 : X = Y = S ; R_1R_2 = ethyl



18 : X = Y = O ; R_1 = R_2 = ethyl
19 : X = S ; Y = O ; R_1 = R_2 = ethyl
20 : X = S ; Y = O ; NR_1R_2 = morpho-4-yl
21 : X = Y = S ; R_1 = R_2 = ethyl
22 : X = Y = S ; NR_1R_2 = morpho-4-yl
23 : X = Y = S ; NR_1R_2 = 1-piperidyl

MATERIALS AND METHODS

General. Technical grade Carbendazime (**I**), Maneb (**II**), *N*,*N*-diethylcarbamoyl chloride, 1-chloro-1-deoxyglycerol (**1**), and 2,3-*O*-isopropylidene-DL-glycerol (**2**) obtained from a commercial source (Aldrich) were used as starting material after purification by recrystallization from appropriate solvents or by distillation. Melting points were measured with an electrothermal melting point apparatus and are uncorrected. ^{1}H (at 300.13 MHz) and ^{13}C (at 75.47 MHz) NMR spectra were recorded on a Bruker AM 300 spectrometer. Deuteriochloroform (99.8% atom enriched, Aldrich) was used as NMR solvent throughout unless otherwise stated. ^{1}H and ^{13}C NMR chemical shifts are reported in δ values based on the internal reference tetramethylsilane. Column chromatography was carried out with a Matrex silica gel 60 Å (70−230 mesh, Merck).

Synthesis of 2,3:4,5-Di-*O*-isopropylidene-DL-xylitol (3). The synthesis of **3** was realized as described in the literature (Regnaut et al., 1993).

Synthesis of *N*,*N*-Diethyldithiocarbamic Acid Lithium Salt (4). The synthesis of **4** was realized as described previously (Len et al., 1996).

Synthesis of *N*,*N*-Diethylthiocarbamoyl Chloride (5). The synthesis of **5** was accomplished by adding dropwise diethylamine (6.4 g, 87.5 mmol) in hexane (10 mL) to a stirred solution of thiophosgene (5.0 g, 43.4 mmol) in hexane (40 mL) at 8 °C. At the end of the addition, the diethylammonium chloride was removed by filtration and the filtrate was concentrated under reduced pressure to yield 5.1 g (77%) of **5**. The structure was confirmed by spectral analyses.

Synthesis of Morpho-4-ylthiocarbamoyl Chloride (6). The above method applied to morpholine yielded the corresponding **6** in 78% yield. The structure was confirmed by spectral analyses.

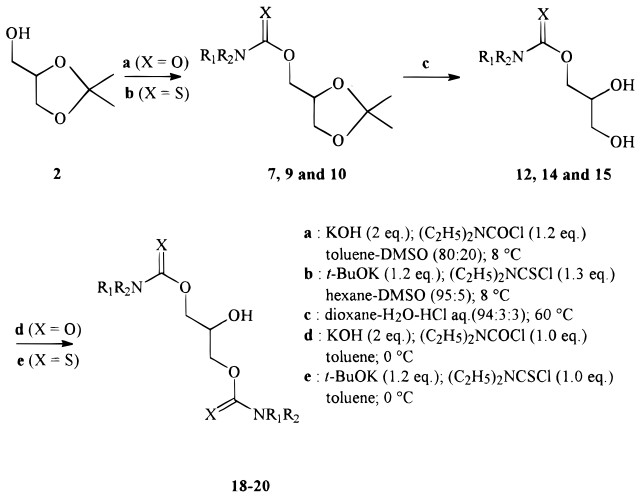
Synthesis of 1-*O*-(*N*,*N*-Diethylcarbamoyl)-2,3-*O*-isopropylidene-DL-glycerol (7). The synthesis of **7** was accomplished as shown in Scheme 1 by adding dropwise *N*,*N*-diethylcarbamoyl chloride (36.9 g, 0.27 mol) to a mixture of **2** (30.0 g, 0.23 mol) and finely powdered KOH (25.8 g, 0.46 mol) in toluene/dimethyl sulfoxide (DMSO) (80:20; 120 mL) at 0 °C. Upon completion of the addition, the reaction mixture was stirred at 8 °C for 1 h, whereupon ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel eluted with hexane/acetone (95:5) to give 44.6 g (85% yield) of **7** (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylcarbamoyl)-2,3:4,5-di-*O*-isopropylidene-DL-xylitol (8). The above method applied to **3** yielded **8** in 87% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylthiocarbamoyl)-2,3-*O*-isopropylidene-DL-glycerol (9). To a stirred solution of thiophosgene (33.9 g, 0.29 mol) in hexane (27 mL) at 8 °C was added diethylamine (43.2 g, 0.59 mol) dropwise in hexane (8 mL). At the end of the addition, the diethylammonium chloride was removed by filtration. The filtrate (35 mL) was added to a stirred mixture of **2** (30.0 g, 0.23 mol) and *t*-BuOK (31.0 g, 0.28 mol) in hexane/DMSO (90:10, 20 mL) below 8 °C.

S0021-8561(96)00737-6 CCC: $14.00

Scheme 1



After 1 h, ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel eluted with hexane/acetone (95:5) to give 48.3 g (86% yield) of **9** (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(Morpho-4-ylthiocarbamoyl)-2,3-*O*-isopropylidene-DL-glycerol (10). The above method applied to **2** and morpholine yielded **10** in 80% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylthiocarbamoyl)-2,3:4,5-di-*O*-isopropylidene-DL-xylitol (11). The above method applied to **3** and diethylamine yielded **11** in 83% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylcarbamoyl)-DL-glycerol (12). The synthesis of **12** was accomplished by adding dropwise **7** (7.0 g, 30.3 mmol) to a stirred solution of 0.6M HCl in H_2O/dioxane (12:88; 340 mL) at 60 °C for 30 min. After addition of sodium hydrogenocarbonate (pH 6), the mixture was stirred for 10 min and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluted with acetone to give 4.6 g (79% yield) of **12** (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylcarbamoyl)-DL-xylitol (13). The above method applied to **8** yielded **13** in 85% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylthiocarbamoyl)-DL-glycerol (14). The above method applied to **9** yielded the corresponding **14** in 95% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(Morpho-4-ylthiocarbamoyl)-DL-glycerol (15). The above method applied to **10** yielded the corresponding **15** in 95% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*O*-(*N*,*N*-Diethylthiocarbamoyl)-DL-xylitol (16). The above method applied to **11** yielded the corresponding **16** in 65% yield (physicochemical data are reported in Table 1).

Synthesis of 1-*S*-(*N*,*N*-Diethyldithiocarbamoyl)-DL-glycerol (17). The synthesis of **17** was accomplished by adding dropwise **4** (28.4 g, 0.14 mol) to a stirred solution of **1** (10.0 g, 90.6 mmol) in 300 mL of acetone. Upon completion of the addition, the reaction mixture was stirred at 56 °C for 30 min. The mixture was filtered and the solvent removed under reduced pressure to yield a viscous oil. This oily residue was purified by column chromatography on silica gel eluted with hexane/acetone (50:50) to give 17.2 g (85%) of **17** (physicochemical data are reported in Table 1).

Synthesis of Bis[1,3-*O*-(*N*,*N*-diethylcarbamoyl)]glycerol (18). The synthesis of **18** was accomplished as shown in Scheme 1 by adding a solution of *N*,*N*-diethylcarbamoyl chloride (3.6 g, 26.2 mmol) in toluene (17 mL) to a stirred mixture of **12** (5.0 g, 26.2 mol) and finely powdered of KOH (2.9 g, 52.4 mol) in toluene (83 mL) at 0 °C. Upon completion of the addition, the reaction mixture was stirred at 0 °C for 2 h, whereupon ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel eluted with hexane/acetone (85:15) to give 1.6 g (21% yield) of **18** (physicochemical data are reported in Table 1).

Synthesis of Bis[1,3-*O*-(*N*,*N*-diethylthiocarbamoyl)]-glycerol (19). The synthesis of **19** was accomplished as shown in Scheme 1 by adding **5** (3.7 g, 24.1 mmol) to a stirred mixture of **14** (5.0 g, 24.1 mmol) and finely powdered *t*-BuOK (3.2 g, 28.9 mol) in toluene (35 mL) at 0 °C. Upon completion of the addition, the reaction mixture was stirred at 0 °C for 2 h, whereupon ammonium chloride in aqueous solution was added and the mixture stirred for a further 10 min. The organic extract was dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel eluted with hexane/acetone (85:15) to give 2.0 g (26% yield) of **19** (physicochemical data are reported in Table 1).

Synthesis of Bis[1,3-*O*-(morpho-4-ylthiocarbamoyl)]-glycerol (20). The above method applied to **15** and **6** yielded **20** in 25% yield (physicochemical data are reported in Table 1).

Synthesis of Bis[1,3-*S*-(*N*,*N*-diethyldithiocarbamoyl)]-1,3-dideoxyglycerol (21), Bis[1,3-*S*-(morpho-4-yldithiocarbamoyl)]-1,3-dideoxyglycerol (22), and Bis[1,3-*S*-(1-piperidyldithiocarbamoyl)]-1,3-dideoxyglycerol (23). The syntheses of **21**−**23** were realized as described previously (Len et al., 1996).

Stock Cultures. The fungi *Alternaria brassicae*, *Pseudocercosporella herpotrichoides*, *Septoria nodorum*, and *Phytophtora cinnamomi* were used as test organisms. Cultures were obtained from the Institut National de la Recherche Agronomique (INRA, Paris, France) and the Service Régional de la Protection des Végétaux-Picardie (SRPV-Picardie, France) and maintained on potato dextrose agar (PDA) at 18 °C in a phytotron room. Fungal growth plugs were cut using a 4.5 cm cork borer and transferred from stock plates to fresh agar biweekly to maintain actively growing fungi.

Radial Fungal Growth Assays. Assays were conducted on PDA at 18 °C in continuous light in the phytotron room. Prior to the PDA being poured into plastic Petri plates (100 × 15 mm), both fungicide solutions and solvent were added to the molten PDA (50 °C) and mixed on a rotary shaker for 2 min. Agar was poured into five control and five test plates for each of the conditions used. Carbamic esters **12**−**16**, **18**−**23**, and commercial fungicides **I** (treatment of *Alternaria* and *Cercosporella* diseases) and **II** (treatment of *Septoria* and *Phytophtora* diseases) (*Index Phytosanitaire,* 1993) were tested against all four fungi at concentrations of 50, 20, and 2 ppm in DMSO. Small samples of *A. brassicae*, *P. herpotrichoides*, *S. nodorum*, and *P. cinnamomi* (30 mm diameter) were taken from the outer margin of fresh stock culture plates and transferred to the center of each medium. Measurements were taken three times daily over a period of 4−21 days, noting the distance from the edge of the fungal plug to the edge of the actively growing fungus. Measurements ceased when fungal growth reached the edge of the DMSO control plates.

RESULTS AND DISCUSSION

We have demonstrated that bis(dithiocarbamic esters) **21**−**23** were found to have *in vitro* antifungal activity against *A. brassicae* and *S. nodorum* and did not cause statistically significant growth inhibition of *P. herpotrichoides* (slow and fast fungus) and *P. cinnamomi*. We prepared **12**−**14** and **16**−**20** as shown in Scheme 1, using selective reactions, to compare the pesticidal activity of dithiocarbamoyl, carbamoyl, and thiocarbamoyl groups, respectively.

The growth inhibitory effect of **12**−**14** and **16**−**23** was tested on PDA plates using DMSO as solvent (Stratton, 1985; Len et al., 1996). The antifungal activities of **12**−**14** and **16**−**23** were compared to that of the commercial **I** and **II**. All inhibition data were normalized as percentage inhibition compared to the control plates

Table 1. Physicochemical Data for the Carbamates 7−17 and the Bis(carbamates) 18−20

compd	MW	mp (°C)	NMR data
7	231.29	syrup liquid	^{1}H δ 4.05 (d, 2H, H-1-1′); 3.97 (dd, 1H, $J_{2,3'}$ = 6.3 Hz, H-3); 3.68 (dd, 1H, $J_{3,3'}$ = 8.3 Hz, H-3′); 4.22 (m, 1H, $J_{2,3}$ = 6.4 Hz, H-2); 1.29 (s, 3H, CH_3); 1.03 (s, 3H, CH_3); 3.19 (q, 4H, NCH_2); 1.03 (t, 6H, $J_{CH2,CH3}$ = 7.1 Hz, CH_3); ^{13}C δ 64.9 (1C C1); 66.2 (1C C3); 74.0 (1C C2); 109.4 (1C Ciso); 26.5 (1C CH_3); 25.2 (1C CH_3); 155.4 (1C CO); 41.7 (1C NCH_2); 41.2 (1C NCH_2); 13.9 (1C CH_3); 13.4 (1C CH_3)
8	331.41	syrup liquid	^{1}H δ 4.15 (dd, 1H, $J_{1,2}$ = 5.3 Hz, H-1); 4.06 (m, 2H, $J_{1',2}$ = 4.1 Hz, $J_{1,1'}$ = 13.4 Hz, H-1′-2); 3.94 (dd, 1H, $J_{5,5'}$ = 8.1 Hz, H-5); 3.74 (dd, 1H, $J_{4,5'}$ = 6.7 Hz, H-5′); 3.77 (m, 1H, H-3); 4.02 (m, 1H, $J_{4,5}$ = 6.7 Hz, H-4); 1.30 (s, 9H, CH_3); 1.24 (s, 9H, CH_3); 3.16 (q, 4H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.00 (t, 6H, CH_3); ^{13}C δ 64.3 (1C C1); 65.5 (1C C5); 75.7 (1C C2); 77.4 (1C C3); 75.0 (1C C4); 109.7 (1C Ciso); 109.6 (1C Ciso); 27.0 (1C CH_3); 26.8 (1C CH_3); 26.0 (1C CH_3); 25.4 (1C CH_3); 155.3 (1C CO); 41.7 (1C NCH_2); 41.2 (1C NCH_2); 13.9 (1C CH_3); 13.3 (1C CH_3)
9	247.36	syrup liquid	^{1}H δ 4.05 (dd, 1H, $J_{1,2}$ = 4.5 Hz, H-1); 4.00 (dd, 1H, $J_{1,1'}$ = 11.5 Hz, $J_{1',2}$ = 5.3 Hz, H-1′); 3.69 (dd, 1H, $J_{2,3'}$ = 6.3 Hz, H-3); 3.39 (dd, 1H, $J_{3,3'}$ = 8.3 Hz, H-3′); 4.09 (m, 1H, $J_{2,3}$ = 6.5 Hz, H-2); 1.01 (s, 3H, CH_3); 0.94 (s, 3H, CH_3); 3.41(q, 2H, NCH_2); 3.12 (q, 2H, NCH_2); 0.83 (t, 3, $J_{CH2,CH3}$ = 7.2 Hz, CH_3); 0.80 (t, 3, $J_{CH2,CH3}$ = 7.2 Hz, CH_3); ^{13}C δ 70.9 (1C C1); 66.0 (1C C3); 73.6 (1C C2); 109.5 (1C Ciso); 26.9 (1C CH_3); 25.4 (1C CH_3); 186.8 (1C CS); 47.7 (1C NCH_2); 43.3 (1C NCH_2); 13.2 (1C CH_3); 11.7 (1C CH_3)
10	261.34	syrup liquid	^{1}H δ 4.55 (dd, 1H, $J_{1,1'}$ = 11.3 Hz, H-1); 4.46 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{1',2}$ = 5.5 Hz, H-1′); 4.03 (m, 1H, H-3); 3.73 (m 1H, H-3′); 4.38 (m, 1H, H-2); 1.39 (s 3H, CH_3); 1.32 (s 3H, CH_3); 4.03 (m, 2H, J = 7.3 Hz, NCH_2); 3.73 (m, 4H, J = 7.0 Hz, NCH_2−OCH_2); 3.62 (t, 2H, J = 7.0 Hz, OCH_2); ^{13}C δ 71.4 (1C C1); 66.0 (1C C3); 73.6 (1C C2); 109.7 (1C Ciso); 26.6 (1C CH_3); 25.1 (1C CH_3); 187.4 (1C CS); 66.2 (1C OCH_2); 66.0 (1C OCH_2); 49.7 (1C NCH_2); 45.8 (1C NCH_2)
11	347.48	42−43	^{1}H δ 4.55 (dd, 1H, $J_{1,2}$ = 6.7 Hz, H-1); 4.45 (dd, 1H, $J_{1',2}$ = 7.9 Hz, $J_{1,1'}$ = 8.0 Hz, H-1′); 3.97 (dd, 1H, $J_{5,5'}$ = 11.9 Hz, H-5); 3.78 (dd, 1H, $J_{4,5'}$ = 5.4 Hz, H-5′); 4.16 (m, 1H, $J_{2,3}$ = 7.8 Hz, H-2); 3.80 (dd, 1H, $J_{3,4}$ = 5.9 Hz, H-3); 4.09 (m, 1H, $J_{4,5}$ = 3.3 Hz, H-4); 1.01 (s, 6H, CH_3); 0.94 (s, 6H, CH_3); 3.71 (q, 2H, $J_{CH2,CH3}$ = 6.9 Hz, NCH_2); 3.41 (q, 2H, $J_{CH2,CH3}$ = 6.9 Hz, NCH_2); 1.13 (t, 3H, CH_3); 1.09 (t, 3H, CH_3); ^{13}C δ 70.1 (1C C1); 65.6 (1C C5); 74.9 (1C C2); 77.1 (1C C3); 75.5 (1C C4); 109.8 (1C Ciso); 109.6 (1C Ciso); 27.1 (1C CH_3); 26.8 (1C CH_3); 26.1 (1C CH_3); 25.4 (1C CH_3); 186.7 (1C CS); 47.7 (1C NCH_2); 43.3 (1C NCH_2); 13.2 (1C CH_3); 11.7 (1C CH_3)
12	191.23	syrup liquid	^{1}H δ 3.98 (dd, 1H, $J_{1,1'}$ = 10.9 Hz, $J_{1,2}$ = 4.7 Hz, H-1); 3.87 (dd, 1H, $J_{1',2}$ = 5.9 Hz, H-1′); 3.35 (t, 2H, $J_{3,3'}$ = 5.7 Hz, H-3-3′); 3.62 (m, 1H, $J_{2,3}$ = 5.3 Hz, $J_{2,3'}$ = 5.6 Hz, H-2); 3.20 (q, 4H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.03 (t, 6H, CH_3); ^{13}C δ 66.0 (1C C1); 62.6 (1C C3); 73.0 (1C C2); 155.0 (1C CO); 40.9 (2C NCH_2); 13.4 (2C CH_3)
13	251.28	syrup liquid	^{1}H δ 4.01 (dd, 1H, $J_{1,1'}$ = 11.0 Hz, $J_{1,2}$ = 4.7 Hz, H-1); 3.95 (dd, 1H, $J_{1',2}$ = 6.6 Hz, H-1′); 3.45 (s, 2H, H-5-5′); 3.73 (m, 1H, H-2); 3.51 (m, 1H, H-3); 3.37 (m, 1H, H-4); 3.19 (q, 4H, $J_{CH2,CH3}$ = 7.0 Hz, NCH_2); 1.03 (t 6H, CH_3); ^{13}C δ 66.2 (1C C1); 62.4 (1C C5); 69.7 (1C C2); 71.8 (1C C3); 70.3 (1C C4); 155.0 (1C CO); 40.7 (2C NCH_2); 13.9 (1C CH_3); 13.3 (1C CH_3)
14	207.29	syrup liquid	^{1}H δ 4.56 (dd, 1H, $J_{1,1'}$ = 11.6 Hz, $J_{1,2}$ = 5.3 Hz, H-1); 4.49 (dd, 1H, $J_{1',2}$ = 5.7 Hz, H-1′); 3.64 (dd, 1H, $J_{3,3'}$ = 11.6 Hz, $J_{2,3}$ = 3.5 Hz, H-3); 3.54 (dd, 1H, $J_{2,3'}$ 5.6 Hz, H-3′); 3.94 (m, 1H, H-2); 3.75 (q 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 3.43 (q, 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.17 (t, 3H, CH_3); 1.12 (t, 3H, CH_3); ^{13}C δ 70.8 (1C C1); 63.1 (1C C3); 70.5 (1C C2); 187.1 (1C CS); 48.0 (1C NCH_2); 43.5 (1C NCH_2); 13.2 (1C CH_3), 11.8 (1C CH_3)
15	221.28	syrup liquid	^{1}H δ 4.39 (dd, 1H, $J_{1,1'}$ = 10.8 Hz, H-1); 4.23 (dd, 1H, $J_{1,2}$ = 3.9 Hz, $J_{1',2}$ = 6.2 Hz, H-1′); 3.37 (m, 2H, H-3-3′); 3.79 (m, 1H, H-2); 3.94 (m, 2H, NCH_2); 3.73 (m, 2H, NCH_2); 3.63 (t, 2H, OCH_2); 3.59 (t, 2H, OCH_2); ^{13}C δ 72.8 (1C C1); 62.5 (1C C3); 69.1 (1C C2); 187.1 (1C CS); 65.5 (1C OCH_2); 66.3 (1C OCH_2); 49.1 (1C NCH_2); 45.4 (1C NCH_2)
16	267.34	65−68	^{1}H δ 4.36 (dd, 1H, $J_{1,1'}$ = 11.0 Hz, $J_{1,2}$ = 4.2 Hz, H-1); 4.28 (dd, 1H, $J_{1',2}$ = 6.6 Hz, H-1′); 3.37 (s, 2H, H-5-5′); 3.84 (m, 1H, H-2); 3.50 (m, 1H, H-3); 3.47 (m, 1H, H-4); 3.72 (q, 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 3.50 (q, 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.13 (t, 3H, CH_3); 1.10 (t, 3H, CH_3); ^{13}C δ 72.4 (1C C1); 62.5 (1C C5); 69.5 (1C C2); 71.7 (1C C3); 70.5 (1C C4); 186.3 (1C CS); 46.8 (1C NCH_2); 42.8 (1C NCH_2); 13.1 (1C CH_3), 11.6 (1C CH_3)
17	223.36	syrup liquid	^{1}H δ 3.46 (dd, 1H, $J_{1,1'}$ = 9.6 Hz, $J_{1,2}$ = 5.3 Hz, H-1); 3.38 (1H, $J_{1',2}$ = 2.5 Hz, H-1′); 3.34 (1H, $J_{3,3'}$ = 13.2 Hz, H-3); 3.17 (dd, 1H, $J_{2,3'}$ = 7.8 Hz, H-3′); 3.66 (m, 1H, H-2); 3.94 (q, 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 3.74 (q, 2H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.19 (t, 3H, CH_3); 1.17 (t, 3H, CH_3); ^{13}C δ 40.8 (1C C1); 69.8 (1C C3); 64.9 (1C C2); 194.5 (1C CS); 48.9 (1C NCH_2); 46.3 (1C NCH_2); 12.2 (1C CH_3); 11.3 (1C CH_3)
18	290.36	syrup liquid	^{1}H δ 3.99 (d, 4H, H-1-1′−3-3′); 3.90 (m, 1H, H-2); 3.11 (2q, 8H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 0.95 (t, 12H, $J_{CH2,CH3}$ = 7.1 Hz, CH_3); ^{13}C δ 66.1 (2C C1−3); 68.7 (1C C2); 155.9 (2C CO); 41.7 (2C NCH_2); 41.2 (2C NCH_2); 13.8 (2C CH_3); 13.2 (2C CH_3)
19	322.49	syrup liquid	^{1}H δ 4.48 (dd, 2H, $J_{1,1'}$, $J_{3,3'}$ = 11.3 Hz, H-1−3); 4.43 (dd, 2H, $J_{1,2}$, $J_{2,3}$ = 4.6 Hz, H-1′−3′); 4.14 (m, 1H, $J_{1',2}$, $J_{2,3'}$ = 5.5 Hz, H-2); 3.67 (q, 4H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 3.37 (q 4H, $J_{CH2,CH3}$ = 7.1 Hz, NCH_2); 1.09 (t, 6H, CH_3); 1.07 (t 6H, CH_3); ^{13}C δ 70.3 (2C C1−3); 67.7 (1C C2); 186.0 (2C CS); 46.9 (2C NCH_2); 42.5 (2C NCH_2); 12.3 (2C CH_3); 10.8 (2C CH_3)
20	350.46	syrup liquid	^{1}H δ 3.68 (dd, 2H, $J_{1,1'}$, $J_{3,3'}$ = 11.6 Hz, H-1−3); 3.61 (dd, 2H, $J_{1,2}$, $J_{2,3}$ = 4.6 Hz, H-1′−3′); 4.28 (m, 1H, $J_{1',2}$, $J_{2,3'}$ = 5.8 Hz, H-2); 4.07 (4H, NCH_2); 3.76 (8H, NCH_2−CH_2); 3.55 (4H, CH_2); ^{13}C δ 71.4 (2C C1−3); 68.8 (1C C2); 187.5 (2C CS); 49.9 (2C NCH_2); 46.0 (2C NCH_2); 63.3 (2C OCH_2); 65.9 (2C OCH_2)

using only DMSO. The five compounds **12**−**14, 16**, and **17** having only one graft of carbamoyl group on glycerol and xylitol had slight growth inhibition against the five fungi tested at 50, 20, and 2 ppm. The six carbamic esters **18**−**23** were found to lack significant antifungal activity against *P. herpotrichoides* (slow fungus). On the other hand, the biological results against *P. herpotrichoides* (fast fungus) showed that **20** was more antifungal than the commercial carbamate **I** at 50 ppm (inhibition percent: day 4, 45 *vs* 38; day 7, 41 *vs* 23; day 14, 19 *vs* 20; day 21, 5 *vs* 0), and all of the bis(carbamic esters) **18**, **19**, and **21**−**23** had medium

Table 2. Percent Growth Inhibition of *A. brassicae* Caused by the Bis(carbamates) 18−23 and Carbendazime (I)

		days			
compd	concn (ppm)	4	7	14	21
18	50	13	11	9	5
	20	23	26	4	2
	2	5	4	2	0
19	50	62	56	53	31
	20	46	21	16	0
	2	37	24	13	0
20	50	41	24	20	0
	20	20	3	7	0
	2	29	9	9	0
21	50	58	58	54	37
	20	58	45	32	8
	2	35	6	4	0
22	50	49	29	28	5
	20	53	55	37	16
	2	35	16	15	0
23	50	49	42	34	8
	20	51	29	23	0
	2	25	13	6	0
I	50	38	23	23	0

Table 3. Percent Growth Inhibition of *S. nodorum* Caused by the Bis(carbamates) 18−23 and Maneb (II)

		days			
compd	concn (ppm)	4	7	14	21
18	50	0	0	0	10
	20	0	0	0	2
	2	0	0	0	0
19	50	39	41	34	20
	20	28	26	21	2
	2	6	0	0	0
20	50	39	48	56	49
	20	28	26	40	38
	2	17	18	34	28
21	50	55	57	67	62
	20	55	58	66	62
	2	50	58	58	53
22	50	50	59	62	61
	20	50	56	64	60
	2	50	63	64	58
23	50	27	42	42	29
	20	29	35	43	25
	2	29	32	50	45
II	50	36	29	23	5

pesticidal activity against *P. herpotrichoides* (fast fungus) (growth inhibition <26%). All of the bis(carbamic esters) **18**−**23** had lower activity than commercial dithiocarbamate **II** against *P. cinnamomi* (growth inhibition <30%). We also examined the effect of **18**−**23** compared to that of **I** for *A. brassicae* (Table 2) and **II** for *S. nodorum* (Table 3). The results noted in Table 2 showed that **18**−**23** had good pesticidal activity at different concentration ranges. It appeared that **19** (at 20 and 50 ppm), **20** (at 50 ppm), and **21**−**23** (at 20 and 50 ppm) were more antifungal than **I** at 50 ppm. The results described in Table 3 showed that the bis(thiocarbamic esters) **19** and **20** and the bis(dithiocarbamic esters) **21**−**23** had good antifungal activity against *S. nodorum* at the three concentrations tested (excepted for **19** at 2 ppm) and the glycerol derivatives **18** having two *N,N*-diethylcarbamoyl groups had no activity. It was remarkable that the bis(thiocarbamic esters) **19** and **20** at 50 ppm and the bis(dithiocarbamic esters) **21**−**23** at the three concentrations tested were more antifungal than the commercial dithiocarbamate **II** at 50 ppm.

Compounds **12**−**14** and **16**, having the identical carbamoyl group on xylitol and glycerol moieties, had different hydrophilic/lipophilic balances. This parameter did not cause a biological effect since **12**−**14** and **16** were shown to have similar slight antifungal activities. The compounds having one carbamoyl group such as **12**−**14**, **16**, and **17** had lower antifungal activities than the bis(carbamic esters) **18**−**23** and confirmed that the synthesis of new compounds having two carbamates led to an enhanced activity. The part of the amine moiety was not really significant because compounds **20**−**23** having, respectively, diethylamine, morpholine, and piperidine moieties showed equal activity against the five fungi tested. It was remarkable that the bis(thiocarbamic esters) **19** and **20** and the bis(dithiocarbamic esters) **21**−**23** were usually the most antifungally active members of the carbamate series and the bis(*N,N*-diethylcarbamate) **18** generally showed a poor biological activity. This study therefore confirmed that thiocarbamoyl and dithiocarbamoyl groups were more active than the carbamoyl group.

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