Synthesis and Insecticidal Activity of New Procarbofurans

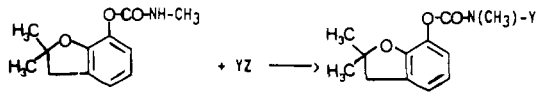
C. Vialaneix,† J. P. Senet,‡ Z. Mouloungui,*,† M. Delmas,† and A. Gaset†

Laboratoire de Chimie des Agroressources, Ecole Nationale Supérieure de Chimie, INP Toulouse, 118 Route de Narbonne, 31077 Toulouse Cédex, France, and Société Nationale des Poudres et Explosifs, Centre de Recherche du Bouchet, Le Bouchet, 91710 Vert-le-Petit, France

A series of *N*-methylcarbamates derived from carbofuran (2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate) was synthesized by using several different methods: (a) condensation of *N*-methylamine with 2,3-dihydro-2,2-dimethylbenzofuran-7-yloxycarbonyl chloride; (b) condensation of *N*-methylethanolamine with chlorosulfenylcarbofuran (2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-(chlorosulfenyl)-*N*-methylcarbamate); (c) hydroxymethylation of carbofuran in an aprotic organic solvent; (d) etherification after hydroxymethylation of carbofuran in 1,4-dioxan/alcohol. The insecticidal activity of these new procarbofurans was tested. Two derivatives, 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-(hydroxymethyl)-*N*-methylcarbamate (**6**) and 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-[*N*-(2-hydroxyethyl)-*N*-methylsulfamoyl]-*N*-methylcarbamate (**13**), were found to have marked insecticidal activity. The sulfenyl derivative had activity to comparable that of carbofuran.

INTRODUCTION

Carbofuran is an insecticide, acaricide, and nematicide with a wide spectrum of activity, although its mammalian toxicity (LD_{50} = 11 mg/kg; Metcalf et al., 1968)) restricts its usefulness considerably. Procarbofurans have been developed which are less toxic and, in some cases, more active than the parent carbofuran. Procarbofurans are derived from carbofuran, a derivative of *N*-methylcarbamate, by substituting the proton on the nitrogen atom with various groups.



The sulfenyl derivatives with a sulfur–nitrogen group are one of the most active and widely studied classes of procarbofurans. Carbosulfan or 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-[(dibutylamino)thio]-*N*-methylcarbamate, benfuracard of 2,3-dihydro-2,2-dimethylbenzofuran-7-yl *N*-[*N*-[2-ethoxycarbonyl)ethyl]-*N*-isopropylsulfenamoyl]-*N*-methyl-carbamate, and furathiocarb or 2,3-dihydro-2,2-dimethylbenzofuran-7-yl butyl *N*,*N*′-dimethyl-*N*,*N*′-thiobis(carbamato) are commercial insecticides with equivalent activity to but less mammalian toxicity than carbofuran (Fahmy and Fukuto, 1982; Fukuto, 1985). Derivatives with a methylene bridge NCH_2, which give potentially active procarbofurans, have also been reported (Jaëger et al., 1978; Lanyi et al., 1986), although this family has been relatively little studied.

In the present study, we describe the synthesis of new procarbofurans with a methylene or sulfur bridge by transformation of the N–N of carbofuran to N–CH_2 or N–S linkages by a variety of methods, of which some were developed in the laboratory. The insecticidal activity of these molecules was also evaluated.

EXPERIMENTAL PROCEDURES

Chemistry. *Analysis.* Analytical thin-layer chromatography was carried out on 60 F254 silica plates (5 × 7 cm, 0.2 mm, or 10 × 20 cm, 0.25 mm, Merck). Spots were visualized with a UV lamp at 284 nm. Preparative thin-layer chromatography used 60-Å silica gel (70–230-mesh, SDS).

The ^1H NMR spectra were recorded on a Bruker spectrometer at 300 MHz, and the chemical shifts (δ) were with respect to trimethylsilane (TMS) (s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet). Mass spectra after electron impact (70 eV) or chemical ionization (NH_3) were recorded on a Nermag R10-10C quadrupole mass spectrometer connected to output of the gas-phase chromatography column (CPSil 5, 25 m). Elemental analyses were performed on a Carlo Erba 1106 spectrometer. The NMR, MS, and microanalysis results are listed in Tables I and II.

Carbofuran and 2,3-dihydro-2,2-dimethylbenzofuran-7-yl chloroformate were supplied by the Société National des Poudres et Explosifs (SNPE, Toulouse, France) and were recrystallized from toluene before use. Most of the solvents were purified. Chloroform, dichloromethane, toluene, ethyl acetate, dioxane, and hexane were distilled over $LiAlH_4$, $CaCl_2$, or K_2CO_3 and were kept on a 4-Å molecular sieve. The solutions in dioxane or ether were tested for the presence of peroxides (Perex Test, Merck No. 16206) before evaporation of solvent. A Perex kit (Merck No. 16207) was used to remove peroxides when present. The acid resin (Lewatit SPC 108, Bayer) was washed with deionized water, ethanol, and ether in succession and then dried in an oven at 60 °C before use.

Synthesis. 2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-(Carboxymethyl)-N-methylcarbamate (**1**). Sarcosine (8.9 g, 0.1 mol) was added to 11.3 g (0.05 mol) of 2,3-dihydro-2,2-dimethylbenzofuran-7-yl chloroformate in 200 mL of ethyl acetate. The mixture was maintained at 30 °C for 3 h. The sarcosine hydrochloride was filtered off and the solvent evaporated under vacuum. The residue was taken up in ethyl ether, giving 13 g of pure product as a white crystalline powder. Yield = 93%; mp 138 °C.

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-[(Methoxycarbonyl)methyl]-N-methylcarbamate (**2**). A solution of 14 fg (0.05 mol) of **1** in 300 mL of methanol with 10 g (43 mequiv of H^+) of sulfonic resin (Lewatit SPC 108 BG) was placed in a three-necked flask fitted with a Wean and Stark apparatus. The mixture was refluxed for 2 h. The resin was filtered off and the methanol evaporated under vacuum. The crude product was purified on a silica column

† Ecole Nationale Supérieure de Chimie.
‡ Société Nationale des Poudres et Explosifs.

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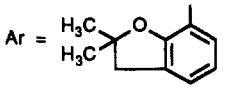
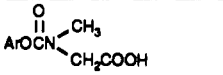
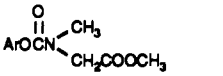
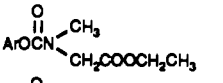
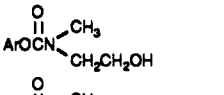
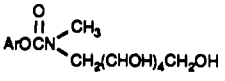
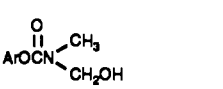
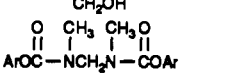
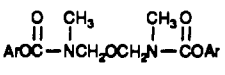
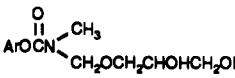
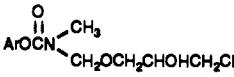
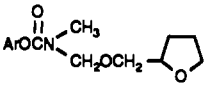
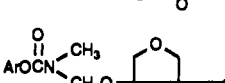
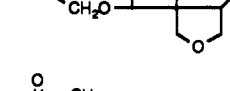
Table I. Microanalyses and MS of Procarbofurans 1–13 with

Ar = 

compound no.	structure	empirical formula	MW	microanalysis[a] C	H	N	O	S	MS[b]
1		$C_{14}H_{17}NO_5$	279	c: 60.2 f: 60.1	6.1 6.1	5.0 5.1	28.7 28.7		297 (2.59); 280 (100); 164 (67.3)[c]
2		$C_{15}H_{19}NO_5$	293	c: 61.4 f: 61.4	6.5 6.5	4.8 4.7	27.3 27.4		293 (29.1); 164 (100)[d]
3		$C_{16}H_{21}NO_5$	307	c: 62.5 f: 62.4	6.8 6.9	4.6 4.6	26.1 26.1		307 (12.6); 192 (8.9); 144 (20.8); 116 (100)[d]
4		$C_{14}H_{19}NO_4$	265	f: 63.4 f: 63.4	7.1 7.1	5.2 5.2	24.2 24.2		265 (3.6); 164 (100)[d]
5		$C_{18}H_{27}NO_8$	385	c: 56.1 f: 56.1	7.0 7.2	3.6 3.6	33.3 33.1		403 (3.9); 386 (100); 239 (15.4); 222 (17.6); 182 (32.5); 164 (47.1)[c]
6		$C_{13}H_{17}NO_4$	251	c: 62.1 f: 62.1	6.8 6.5	5.6 5.6	25.5 25.8		251 (1.3); 164 (100); 221 (5.3); 149 (51.5)[d]
7		$C_{25}H_{30}N_2O_6$	454	c: 66.1 f: 65.8	6.6 6.6	6.2 6.0	21.1 21.6		472 (45.4); 455 (100); 234 (61.5); 222 (7.6)[c]
8		$C_{26}H_{32}N_2O_7$	484	c: 64.5 f: 64.3	6.6 6.8	5.8 5.8	23.1 23.1		484 (5.3); 234 (100); 177 (34.3); 164 (11.3)[d]
9		$C_{16}H_{33}NO_6$	325	c: 59.1 f: 59.2	7.1 7.1	4.3 4.2	29.5 29.5		325 (2.3); 234 (12.2); 164 (100); 149 (21.6)[d]
10		$C_{17}H_{25}NO_5$	323	c: 63.2 f: 63.2	7.7 7.6	4.3 4.5	24.8 24.7		323 (1.7); 234 (13.1); 164 (100); 149 (19.4)[d]
11		$C_{18}H_{25}NO_5$	335	c: 64.5 f: 64.0	7.4 7.7	4.2 4.6	23.9 23.7		353 (4.8); 336 (39.2); 251 (25.2); 164 (25.4); 222 (16.9); 164 (25.4)[c]
12		$C_{19}H_{25}NO_7$	379	c: 60.2 f: 60.2	6.6 6.5	3.7 3.6	29.5 29.7		379 (15.4); 322 (44.5); 234 (9.5); 176 (12.9); 164 (100); 149 (21.0)[d]
13		$C_{15}H_{22}N_2O_4S$	326	c: 55.2 t: 54.9	6.8 6.9	8.6 8.6	19.6 19.8	9.8 9.8	327 (2.8); 222 (88.4); 182 (100); 164 (63.7)[d]

[a] c, calculated; f, found. [b] m/z (%). [c] Chemical ionization (NH_3). [d] Electron impact.

eluted with chloroform/ethyl ether (2/1 v/v). Compound **2** was isolated as a yellowish oil in 73% yield.

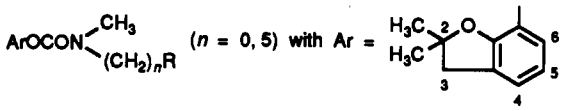
2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-[(Ethoxycarbonyl)methyl]-N-methylcarbamate (**3**). 2,3-Dihydro-2,2-dimethylbenzofuran-7-yl chloroformate 11.3 g, 0.05 mol) was added to a suspension of 1.53 g (0.1 mol) of sarcosine hydrochloride in 200 mL of ethyl acetate containing 10.1 g (0.1 mol) of triethylamine. The mixture was maintained at room temperature under agitation for 4 h. The precipitate was filtered off, and the solvent was evaporated under vacuum. The crude oily product was purified on a silica colum eluted with a mixture of ethyl ether/cyclohexane (2/1 v/v) to give **3** as a yellow oil (13.2 g). Yield = 86%; R_f = 0.26 (ethyl ether/hexane 3/1).

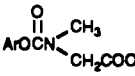
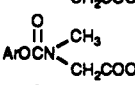
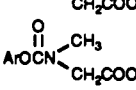
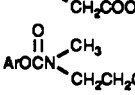
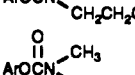
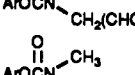
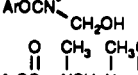
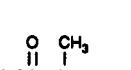
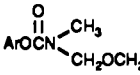
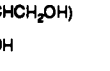
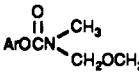
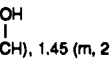
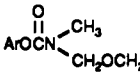
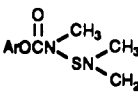
2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-(2-Hydroxyethyl)-N-methylcarbamate (**4**). This compound was prepared according to the method described for **1** with 7.5 g (0.1 mol) of *N*-methylethanolamine instead of sarcosine. *N*-Methylethanolamine hydrochloride was decanted from the organic phase as oily yellowish droplets. The organic phase was evaporated under vacuum. The crude product was purified on a silica column eluted with ethyl ether/cyclohexane (3/1 v/v). Compound **4** was obtained as a yellow oil (11.8 g). Yield = 89%; R_f = 0.13.

N,N'-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yloxycarbonyl), Methyl-1-amino-1-deoxyglucitol (**5**). This compound was prepared according to the method described for **1** with 19.5 g (0.1 mol) of *N*-methylglucamine instead of sarcosine. The precipitate of *N*-methylglucamine hydrochloride was filtered off, and the solvent was evaporated under vacuum. The residue was taken up in ethyl ether to give 18.8 g of **5**. Yield = 97%; mp 69 °C (ethyl acetate); R_f = 0.08 (ethyl ether/hexane 3/1).

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-(Hydroxymethyl)-N-methylcarbamate (**6**). A mixture of 11 g (0.5 mol) of carbofuran, 3 g (0.1 mol) of paraformaldehyde, and 3 g (12.5 mequiv of H^+) of Lewatit SPC 108 BG resin in 100 mL of 1,4-dioxane hydrated with 0.36 mL (0.02 mol) of water was stirred at 60 °C for 2 h. After filtering, the dioxane was evaporated under vacuum. The crude product was purified on a silica column eluted with a mixture of ethyl ether/hexane/chloroform (3/1/1 v/v);

Table II. ^{1}H NMR of Procarbofurans 1–11 and 13 in $CDCl_3$



compound no.		 δ	 δ	R δ
1		3.06 3.18	4.14 4.22	8.30 (s, 1 H, COOH)
2		3.04 3.16	4.10 4.16	3.76 (s, 3 H, OCH_3)
3		3.06 3.17	4.19 4.26	1.30 (t, 3 H; CH_2CH_3), 4.23 (q, 2 H, CH_2CH_3, $J_{CH_3CH_3}$ = 7.1 Hz)
4		3.03 3.14	3.48 (t) 3.58 (d)	3.80 (m,[b] 2H, CH_2OH, $J_{CH_2CH_2}$ = 5.1 Hz)
5		3.06 3.20	3.50 (d) 3.66 (d) J_{CH_2CH} = 6.4 Hz	3.6–3.9 (m, 6 H, $(CHOH)_4CH_2O$)
6		3.09 3.19	4.87 4.95	3–5 (br, OH)
7		3.01 (1)[d] 3.13 (1) 3.17 (1) 3.24 (1)	5.07 (1) 5.17 (2) 5.27 (1)	
8		3.10 (1)	4.94 (1) 4.99 (1) 3.20 (1) 5.09 (1)	5.03 (1)
9		3.01 3.12	4.82 4.93	3.54–3.84 (m, 5H, 
10		3.03 3.13	4.82 4.92	 3.3–3.7 (m, 4 H, CH_2CH), 1.45 (m, 2 H, CH_2CH_3), 0.92 (t, 3 H, CH_3, $J_{CH_2CH_3}$ = 7.5 Hz)
11		3.04 3.14	4.89 4.92	3.8 (m, 2 H, CH_2), 4.1 (m, 1 H, H_2'), 3.6 (m, 2 H, H_5'), 1.8 (m, 4 H, $H_3'H_4'$)
13		3.46		3.10 (s, 3 H, $SNCH_3$), 3.36 (t, 2 H, $SNCH_2$), 3.81 (t, 2 H, CH_2O, $J_{CH_2CH_2}$ = 5.5 Hz)

[a] Chemical shifts of the benzofuranol moiety Ar: 1.48 (s, 6 H, $C(CH_3)_2$); 3.02 (s, 2 H, H_1 and H_2); 6.77 (dd, 1 H, H_4, $J_{H_5H_4}$ = $J_{H_4H_6}$ = 7.8 Hz); 6.93 (d, 1 H, H_3, $J_{H_3H_4}$ = 7.8 Hz, $J_{H_3H_5}$ = 1 Hz); 6.96 (d, 1 H, H_5), J_{H_5H} = 7.8 Hz, $J_{H_5H_3}$ = 1 Hz). [b] m egal two triplets 0.03 ppm apart. [c] NMR spectra recordered in D_2O + TMS. [d] The figures in parentheses indicate relative intensity of the pics. [e] Same shape of spectra of Ar except for proton chemical shifts H_3 and H_5: δ_{H_3} = 6.88 ppm; δ_{H_5} = 6.97 ppm.

4.5 g of solid product was isolated. Yield = 36%; mp 78 °C (cyclohexane); R_f = 0.31 (ethyl ether/chloroform 1/2).

N,N'-Methylenebis(carbofuran) (7). This compound was formed during the preparation of compound 6. It was isolated as a coproduct in the form of a white powder during the chromatographic purification of 6. Yield = 27%; mp 125 °C (cyclohexane); R_f = 0.81 (ethyl ether/chloroform 1/2).

Bis(N-methylenecarbofuran) Oxide (8). This compound was formed during the preparation of compound 6. It was isolated in the form of a white powder as a coproduct during the chromatographic purification of 6. Yield = 19%; mp 130 °C (cyclohexane); *Rf* = 0.70 (ethyl ether/chloforom 1/2).

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-(2,3-Dihydroxypropoxy)methyl-N-methylcarbamate (9). This compound was prepared according to the method described for 6 with 16.4 g (0.2 mol) of glycerol instead of water. The product was isolated in the form of a yellowish oil (5.2 g) after purification on a silica column eluted with a mixture of ethyl ether/ethyl acetate (1/1 v/v). Yield = 32%; R_f = 0.26 (ethyl ether/ethyl acetate 1/1).

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-[(2-Hydroxybutoxy)methyl]-N-methylcarbamate (10). This compound was prepared according to the method described for 6 with 18 g (0.2 mol) of butane-1,2-diol instead of water. The product was isolated in the form of a yellowish oil (5.8 g) after purification on a silica column eluted with a mixture of ethyl ether/hexane (1/1 v/v). Yield = 36%; R_f = 0.37 (ethyl ether/hexane 3/1).

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-[(Tetrahydro-2-furylmethoxy)]methyl-N-methylcarbamate (11). This compound was prepared according to the method described for 6 with 20.6 g (0.2 mol) of tetrahydrofurfuryl alcohol instead of water. The product was isolated in the form of a yellowish oil (8.5 g) after purification on a silica

Table III. Insecticidal Activity of Procarbofurans via Systemic Route

compound no.	structure	log P	dose, ppm	S. littoralis tobacco 48 h	E. kuehniella, Petri dish 24 h	E. kuehniella, Petri dish 48 h	A. fabee bean 48 h	M. domestica, Petri dish 30 min	M. domestica, Petri dish 2 h	M. domestica, Petri dish 24 h	T. confusum, Petri dish 2 h	T. confusum, Petri dish 24 h	T. confusum, Petri dish 48 h	C. granaria, Petri dish 2 h	C. granaria, Petri dish 24 h	C. granaria, Petri dish 48 h
6	CF[a]CH_2OH	0.41	1000	97												
			250	67												
			62.5	23												
			25		100	100	30									
			6.4		50	90	0									
			1.6		17	50	0	0	40	70	0	23	78	0	100	100
			0.4					0	0	0	0	0	22	0	75	100
			0.1					0	0	0	0	0	0	0	0	0
13	CF[a]S—N(CH3)(CH2CH2OH)	2.2	1000	100												
			250	77												
			62.5	13												
			25				100									
			6.4				78									
			1.6		100	100	12	73	100	100	56		100	100	100	100
			0.4		80	90		13	100	100	10		100	100	100	100
			0.1		37	50		0	100	100	0		88	82	100	100
	carbofuran	1.5	1000	100												
			250	90												
			62.5	37												
			25				100									
			6.4				83									
			1.6		100	100	7	63	100	100	43		100	100	100	100
			0.4		100	100		0	100	100	27		100	100	100	100
			0.1		83	90		0	90	100	0		98	85	100	100

[a] CF = ArOCON(CH3).

colum eluted with a mixture of ethyl ether/hexane (3/1 v/v). Yield = 51%; R_f = 0.50.

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-(O-Isosorbidylmethyl)-N-methylcarbamate (12). This compound was prepared according to the method described for 6 with 30.4 g (0.2 mol) of isosorbide instead of water. The product was isolated in the form of a yellowish oil (7.9 g) after purification on a silica column eluted with a mixture of ethyl ether/ethyl acetate (3/1 v/v). Yield = 42%; R_f = 0.39.

2,3-Dihydro-2,2-dimethylbenzofuran-7-yl N-[(N-(2-Hydroxyethyl)-N-methylsulfenamoyl]-N-methylcarbamate (13). A solution of 2.21 g (0.01 mol) of carbofuran in 20 mL of dichloromethane was added dropwise to a solution of 0.64 mL (0.01 mol) of sulfur dichloride in 20 mL of dichloromethane cooled to between −5 and 0 °C. A solution of 1.6 mL (0.02 mol) of pyridine in 10 mL of dichloromethane was then added. The reaction mixture was stirred for 6 h in the cold and then for 10 h at room temperature. Crystals of pyridine hydrochloride were filtered off, and the reaction mixture was cooled to −5 °C. *N*-Methylethanolamine was then added dropwise. After stirring for 6 h in the cold, the oily phase was removed and the dichloromethane evaporated. The crude product was purified on a silica column eluted with a mixture of ethyl ether/cyclohexane (4/1 v/v) to give 13 as a thick yellow oil (7.9 g). Yield = 20%; R_f = 0.39.

Biology. The insecticidal activity of the carbofurans synthesized was tested by SIPCAM laboratories (Milan, Italy) in collaboration with SNPE (Le Bouchet, France). Each compound was tested on contact and after systemic adminsitration to the following species: *Spodoptera littoralis, Ephestia kuehniella, Aphis fabae, Musca domestica, Tribolium confusum*, and *Calandra granaria*. The results for the active compounds 6 and 13 are listed in Tables III and IV. For these two compounds, the partition coefficient representing the lipophilicity of the molecule, expressed as log *P*, was measured according to the procedure of Fujita et al. (1964). The results are listed in Table III.

RESULTS AND DISCUSSION

The procarbofurans 1 and 3–5 were synthesized by the reaction between 2,3-dihydro-2,2-dimethylbenzofuran-7-yl chloroformate and a functional *N*-methylamine. The high reactivity of the chloroformate toward double stoichiometric quantities of the amines affords the carbamates in excellent yield under simple reaction conditions at room temperature in ethyl acetate (Scheme I). This solvent was found to be particularly convenient as the insoluble amine hydrochloride could be readily removed by filtration (Ronwin, 1953).

The selectivity of the reaction is illustrated by the condensation with sarcosine, leading to the carbamate 1 with a free acid group which was subsequently esterified by methanol in the presence of the cationic resin (Lewatit SPC 108 BG) as catalyst according to a method developed in the laboratory (Masson et al., 1985). The methyl ester 2 was obtained in good yield (Scheme II). The modified carbamates 6–8 were produced during the hydroxymethylation reaction. This involves carbamate and paraformaldehyde in slightly hydrated 1,4-dioxane in the presence of a cation-exchange resin at 60 °C. At this temperature, paraformaldehyde depolymerizes rather than sublimes (Scheme III). These compounds are readily separated by chromatography on a silica column. By use of this method, the hydroxymethyl derivative 6 was transformed in situ into the ethers 9–12 by replacing water with the corresponding alcohol (Vialaneix, 1989) (Scheme IV).

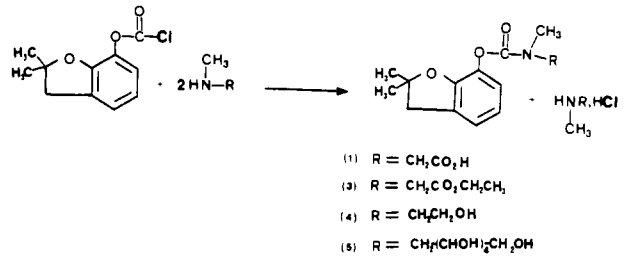
The sulfenamoylcarbamate 13 was derived from carbofuran via the intermediate chlorosulfenylcarbofuran formed in the presence of pyridine (Brown et al., 1977). In the second stage, crude *N*-chlorosulfenylcarbofuran was reacted with a twice stoichiometic amount of *N*-methylethanolamine to give compound 13. In contrast to other descriptions of this reaction (Goto et al., 1982), we found that the reaction occurred in the absence of pyridine or triethylamine as catalyst. The sulfenyl derivative 13 is not readily separated on a silica column from the mixture of *N*-chlorodisulfocarbofuran (CFSSCl), bis(*N*,*N*-sulfo-

Table IV. Insecticidal Activity of Procarbofurans via Systemic Route

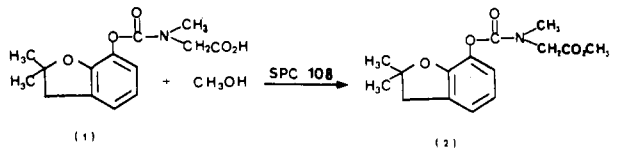
compound no.	structure	soil: dose, kg/ha	soil: *Spodoptera* L. tobacco 10 day	soil: *Spodoptera* L. tobacco 18 day	soil: *A. fabae* bean 10 day	soil: *A. fabae* bean 18 day	seed: dose, ppm	seed: *A. fabae* bean 10 day	seed: *A. fabae* bean 15 day	seed: *A. fabae* bean 21 day
6	CF[a]CH_2OH	8	43	70						
		2	0	0						
		0.5	0	0	44	53	1280	0		17
		0.125			0	0	320	0		0
					0	0	80	0		0
13	CF[a]S–N(CH_3)(CH_2CH_2OH)	8	100	100						
		2	83	53	100	100	1280		100	
		0.5	10	17	100	100	320		100	
		0.125			84	31	80		81	
	carbofuran	8	100	100	100	100	1280		100	
		2	83	100	100	100	320		100	
		0.5	37	60	74	71	80		54	
		0.125								

[a] CF = ArOCON(CH_3).

Scheme I

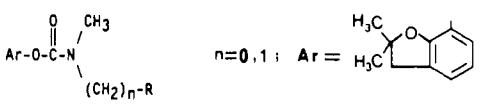


Scheme II



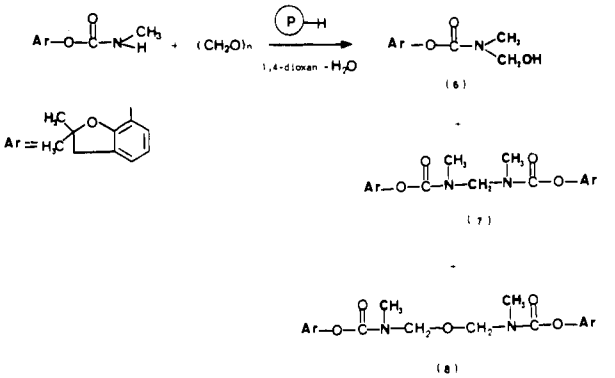
carbofuran) (CFSCF), and the disulfo analogue (CFSSN-$(CH_3)CH_2CH_2OH$) formed during the reaction. These compounds appear to decompose in contact with silica. When the duration of contact by flash chromatography was reduced, enough material could be obtained for MS and ^1H NMR analyses and the biological tests. The masses observed on MS (Table I) correspond to molecular ions M^+ or quasimolecular ions $[M + 1]^+$ or $[M + 18]^+$ characteristic of EIMS (70 eV) or CIMS (ammonia). A peak corresponding to the 2,3-dihydro-2,2-dimethylbenzofuran-7-ol fragment (m/z 164) was usually observed.

The ^1H NMR spectra (Table II) of the precarbofurans **1–6** and **9–11** were quite similar with a splitting of the N–CH_3 and N–CH_2 signals. The appearance of this double pair of singlets was attributed to the presence of cis/trans isomers.



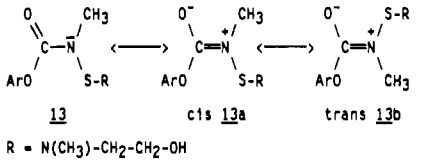
The partial double bond character was attributed to the limiting forms of the amide part of the carbamate (Keith and Alford, 1970; Lee and Norton, 1990). This leads to a magnetic and geometric inequality of the substituent on the nitrogen atom. From the peak heights, the cis/trans isomers were in a 50/50 ratio. By analogy with *N*-methyl-*N*-alkylformamide (Stewart and Siddell, 1970) and from the anisotropy of the amide, the protons on the *N*-methyl group resonating at higher field have the methyl group cis to the oxygen (Scheme V). The N–CH_3 protons in the cis

Scheme III

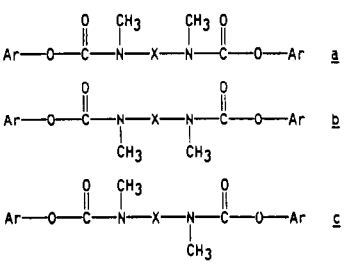


isomer thus produce signals upfield (δ between 3.01 and 3.09) from those of the N–CH_3 protons in the trans isomer (δ between 3.12 and 3.20 ppm).

On the other hand, for compound **13**, a single signal was observed for the N–CH_3 protons. The electrostatic repulsion between the negatively charged oxygen and the sulfur atom in the limiting form **13b** favors the cis isomer **13a** over the trans isomer **13b**.

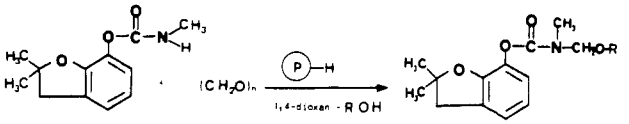


For compounds **7** and **8**, the N–CH_3 and N–CH_2 protons gave rise to multiplets due to the presence of three main forms derived from the different orientations of these groups with respect to the carbonyl groups:

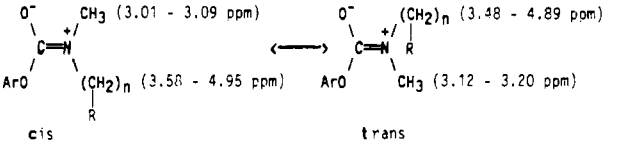


Whatever the nature of X, the two forms a and b are symmetrical, giving rise to two signals each from the CH_3 and the CH_2 protons. In the third form, c, this symmetry

Scheme IV



Scheme V



is absent, which in compound 7 (X = CH_2) gives rise to two further signals for the CH_3 protons and one signal for the CH_2 protons. In compound 8 (X = CH_2OCH_2), the two methyl signals were identical with those of the symmetric form. From the peak intensities, the asymmetric form c appeared to be twice as abundant as the a and b forms.

Tables III and IV show the results of the tests of insecticidal activity for the active compounds 6 and 13. In the series of procarbofurans with a methylene bridge, only *N*-(hydroxymethyl)carbofuran 6 had significant, albeit inadequate, insecticidal activity via the systemic route. The presence of an oxygen α to the *N*-methylene group in these new procarbofurans appears to confer insecticidal activity, although activity was lost when the hydroxyl terminal was etherified (cf. compounds 9–12). The insecticidal activity of compound 6 probably stems from the recognized instability of these *N*-hydroxymethyl derivatives which give a delayed release of the active starting compound (Johansen and Bundegaard, 1979). It has been shown that the *N*-CH_2OHCF derivatives are metabolites of benfuracarb (Tanaka et al., 1985). This may account for the comparable activity of 6 with respect to benfuracarb, especially toward *S. littoralis*, *E. kuehniella*, *T. confusum*, and *C. granaria*.

The sulfenyl derivative synthesized 13 had activity similar to that of the proinsecticidal methylcarbamates containing a sulfur bridge. At all doses on all species tested, either by contact or by the systemic route, it had activity similar to that of carbofuran. This derivative retains the biological activity of the parent compound which is liberated in the insect after enzymatic cleavage of the N–S bond (Umetsu et al., 1980).

The insecticidal activities of 6 and 13 appear to be more related to their instability in the insect than to their lipophilicity. It is of interest that compound 13 contains the *N*-methylethanolamine moiety which is a precursor of choline in vivo. This structural resemblance probably favors enzymatic recognition since the target of carbofuran and procarbofurans is acetylcholinesterase (Yu et al., 1972). Furthermore, the cis configuration of the molecule should, in principle, enhance the biological activity.

ACKNOWLEDGMENT

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Registry No. 1, 133797-86-1; 2, 133797-87-2; 3, 133797-88-3; 4, 133797-89-4; 5, 133797-90-7; 6, 133797-91-8; 7, 133797-92-9; 8, 133797-93-0; 9, 133797-94-1; 10, 133797-95-2; 11, 133815-70-0; 12, 133868-43-6; 13, 133797-96-3; sarcosine, 107-97-1; 2,3-dihydro-2,2-dimethylbenzofuran-7-yl chloroformate, 4790-86-7; *N*-methylethanolamine, 109-83-1; *N*-methylglucamine, 6284-40-8; carbofuran, 1563-66-2.