Table I. Recoveries of Asulam in Spiked Wheat Products[a]

product	% recovery[b] 0.1 ppm	0.5 ppm	1.0 ppm	5.0 ppm	10.0 ppm
whole wheat cereal	81, 87	91, 83	90, 90	92, 91	94, 93
whole wheat flour	88, 89, 78	89, 88	–	–	–
refined white flour	81, 85	87, 87	–	–	–

[a] Dashes indicate that no sample analyses were carried out. [b] Determined at 280 nm.

coextractive peak which was not present at the other wavelengths. Table I lists recoveries obtained for asulam spiked at various levels in the wheat products. Good results were obtained as low as 0.1 ppm, the lowest spiking level attempted. The minimum detectable level was estimated to be about 0.02 ppm in the products studied. The cereal samples were slightly cleaner than the flour samples when monitored at 268 nm. All chromatograms were similar at 280 nm.

The hexane partition in the sample clean up was necessary to remove lipophilic coextractives such as oils which would be strongly retained by the column. Also if this was not done, at 0.1 ppm the residue would not dissolve completely in the mobile phase resulting in a cloudy solution. This could not be cleared either by centrifugation or by filtration through Millipore filters. It is probable that passage of the solution through a small reversed-phase precolumn or a disposable Sep-Pak cartridge would remove this material while permitting the clear solution containing the asulam to pass through. For our purposes the hexane partitioning performed well and was thus incorporated into the cleanup procedure.

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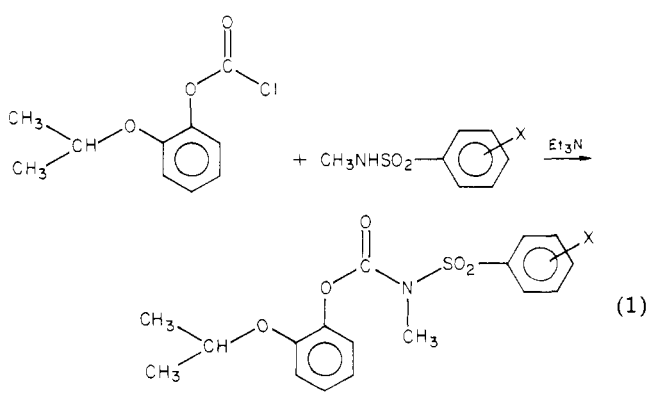
Insecticidal Properties of *N*-Sulfonyl Derivatives of Propoxur and Carbofuran

A series of substituted *N*-benzenesulfonyl derivatives of carbofuran and propoxur containing electron-withdrawing substituents on the benzene ring were synthesized and examined for toxicity to house flies and mosquito larvae. In general, the derivatives were noninsecticidal when tested alone, but some of the compounds were toxic to house flies when synergized with piperonyl butoxide. An explanation for the poor insecticidal activity and low mammalian toxicity of these derivatives is given.

Recent reports from this and other laboratories have described the favorable order of selectivity which is achieved when toxic methylcarbamate insecticides are derivatized by appropriate substitution of the hydrogen atom on the methylcarbamyl moiety. For example, replacement of the methylcarbamyl proton with acyl (Fraser et al., 1965), dialkoxyphosphinothioyl (Fahmy et al., 1970), alkyl- and arylsulfenyl (Black et al., 1973a), aminosulfenyl (Fukuto et al., 1975), and carbamylsulfenyl (Fahmy et al., 1974, 1978; Sousa et al., 1977) results in derivatives of generally low mammalian toxicity and high insecticidal activity. While a wide variety of sulfenyl derivatives of methylcarbamate insecticides have been examined for toxicological properties, little has been reported on the insecticidal activity of sulfur derivatives of higher oxidation state. In a previous report (Chiu et al., 1975), we described the poor insecticidal activity of a single arylsulfonyl derivative, the *N*-2-toluenesulfonyl derivative of carbofuran. The present study was conducted to determine whether derivatization with substituted benzenesulfonyl groups containing electron-withdrawing moieties would result in compounds with higher insecticidal activity.

EXPERIMENTAL SECTION

The *N*-arylsulfonyl derivatives of propoxur (2-isopropoxyphenyl methylcarbamate) and carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate) were prepared by reacting the appropriate aryl chloroformate and ring-substituted methylbenzenesulfonamide according to eq 1 for a propoxur derivative. A typical procedure is



(1)

given as follows. To a chilled solution of 2.5 g of *p*-bromo-*N*-methylbenzenesulfonamide and 2.15 g of 2-isopropoxyphenyl chloroformate was added 1.75 g of triethylamine dropwise with stirring. After being stirred at room temperature for 2 h, the mixture was washed in turn with water, 5% hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and the solution was dried over anhydrous sodium sulfate. Removal of the solvent gave

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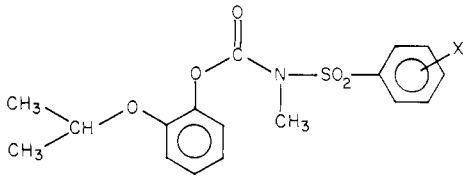
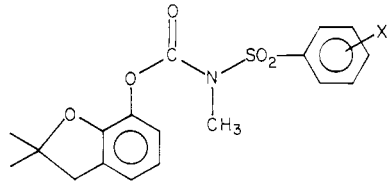
Table I. Physical and Insecticidal Properties of Substituted Benzenesulfonyl Derivatives of Propoxur and Carbofuran



no.	X	mp, °C	C, H anal., % calcd	C, H anal., % found	house fly LD_{50}, μg/g alone	house fly LD_{50}, μg/g 1:5 PB	Culex fatigans LC_{50}, ppm
1	4-Cl	100-101	53.19, 4.73	53.84, 5.06	>500	>50	>10
2	4-Br	95-96	47.67, 4.24	47.70, 4.11	>500	>50	>10
3	2-NO_2	141-141.5	51.77, 4.60	51.93, 4.90	>500	50	6.8
4	3-NO_2	117-118	51.77, 4.60	51.95, 4.97	>500	>50	>10
5	4-NO_2	130.5-131	51.77, 4.60	51.30, 4.77	>500	>50	7.5
6	2,5-di-Cl	82-83.5	48.81, 4.10	49.44, 4.72	>500	>50	4.2
7	2,4-di-NO_2	91-92	46.47, 3.90	47.09, 4.39	>500	16	0.17



8	4-Cl	127-128	54.61, 4.58	54.67, 4.87	>500	>50	>10
9	4-Br	122-122.5	49.10, 4.12	49.14, 4.24	>500	>50	>10
10	2-NO_2	106-106.5	53.20, 4.46	53.32, 4.41	>500	20	0.26
11	3-NO_2	124-125	53.20, 4.46	53.23, 4.65	>500	>50	4.0
12	4-NO_2	173-174	53.20, 4.46	53.36, 4.45	>500	>50	0.14
13	2,5-di-Cl	169.5-170.5	50.24, 3.98	50.27, 4.29	>500	>50	>10
14	2,4-di-NO_2	161-162	47.89, 3.80	47.89, 4.29	>500	9	0.11

a solid which was recrystallized from a 3:1 mixture of hexane–dichloromethane, resulting in colorless crystals, mp 95–96 °C. Elemental analyses for all final products are given in Table I.

The substituted methylbenzenesulfonamides were prepared in the usual manner by the reaction between methylamine and substituted benzenesulfonyl chloride.

The reaction between the 2,4-dinitrobenzenesulfonyl derivative of carbofuran (14) and *p*-thiocresol was examined as follows. To an ethanol–dichloromethane solution containing 46 mg (0.102 mmol) of **14** was added 23 mg (0.185 mmol) of *p*-thiocresol dissolved in ethanol and an equivalent amount of potassium hydroxide. A yellow precipitate formed which was removed by filtration and washed with ethanol and hexane. This material did not melt at 170 °C and was soluble in water, and its NMR spectrum showed the presence of carbofuran. The filtrate was diluted with water and extracted with benzene. Removal of the benzene gave 56.7 mg of a yellow solid which was recrystallized from ethanol, mp 103–103.5 °C, identical with that of *p*-tolyl 2,4-dinitrophenyl sulfide (Shriner et al., 1964). NMR spectrum was consistent with this structure.

For the reaction between 14 and triethylamine, a mixture of 0.45 g (1 mmol) of 14 and 0.362 (3.6 mmol) of Et_3N in 10 ml of dichloromethane was allowed to stand for several days during which period the solution turned dark red. After the mixture was washed with water, TLC analysis showed the presence of carbofuran phenol and another major product whose NMR spectrum and elemental analysis showed the compound to be 2,3-dihydro-2,2-dimethyl-7-benzofuranyl 2,4-dinitrophenyl ether, mp 145–145.5 °C. Anal. Calcd. for $C_{16}H_{14}O_6N_2$: C 58.18; H 4.27. Found: C 58.36; H 3.89. The ^1H NMR spectrum showed the following signals ($CDCl_3$, Me_4Si): δ 1.44 (6 H, s, gemdi-CH_3), 3.13 (2 H, s, benzylic CH_2), 7.1 (4 H, m, aromatic protons), 8.4 (1 H, 2 d, dinitrobenzene proton), and 8.95 (1 H, d, dinitrobenzene proton).

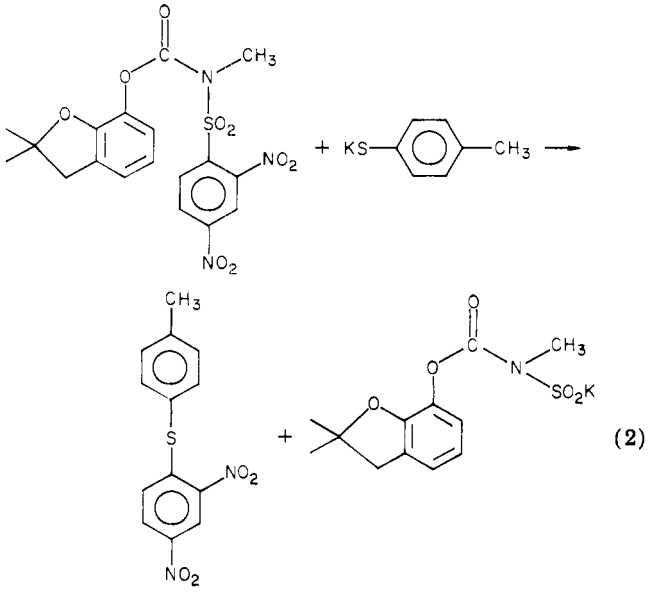
RESULTS AND DISCUSSION

Compared to the *N*-arylsulfenyl derivatives of carbofuran and propoxur, the substituted benzenesufonyl derivatives were relatively ineffective against house flies and mosquito larvae (Black et al., 1973a). In fact, none of the sulfonyl derivatives were effective against house flies at 500 μg/g, and cotreatment with five parts of piperonyl butoxide was required before any sign of intoxication was evident.

Previous studies from this laboratory have demonstrated that sulfenylated derivatives of toxic methylcarbamate insecticides are effective against insects and safe to mammals because the sulfenylated derivative is converted to the methylcarbamate in insects and into nontoxic degradation products in mammals (Black et al., 1973b). Owing to the poor insecticidal activity of the substituted benzenesulfonyl derivatives of carbofuran and propoxur listed in Table I, it appears that the parent methylcarbamates are not readily generated from the sulfonyl derivatives in insects. If it is assumed that the parent methylcarbamate is responsible for intoxication, then the synergized house fly toxicity of compounds 7 and 14 suggests that generation of the methylcarbamate takes place to a greater extent when two strongly electron-withdrawing nitro groups are attached to the benzenesulfonyl ring. In these cases, the two nitro groups probably promote hydrolytic cleavage of the nitrogen–sulfur bond, resulting in some formation of the parent methylcarbamate in vivo, at least to the extent that intoxication of house flies is observed when a synergist is present.

Qualitative examination of 14 showed that it is not easily converted to carbofuran and is transformed into a variety of products in the presence of different reagents. Compound 14 was stable in acetone–water solution and returned virtually all of the starting material after standing

for 70 h at room temperature. However, when 14 was allowed to stand in a dichloromethane–ethanol mixture containing potassium *p*-thiocresylate, the major product identified was *p*-tolyl 2,4-dinitrophenyl sulfide and an unidentified water-soluble salt containing the carbofuran moiety. The reaction probably occurs as in eq 2. This



(2)

is in contrast to the reaction between the highly insecticidal *N*-toluenesulfenyl carbofuran and an arylthiolate anion where the major product isolated was carbofuran (Chiu et al., 1975).

When 14 was allowed to stand in the presence of excess triethylamine in dichloromethane solvent, the products which were isolated and identified were carbofuran phenol and 2,3-dihydro-2,2-dimethyl-7-benzofuranyl 2,4-dinitrophenyl ether. Thus, in neither case, i.e., in the presence of thiolate anion or triethylamine, was the toxic methylcarbamate carbofuran generated from 14. These findings are consistent with the poor insecticidal activity of the sulfonyl derivatives listed in the table.

Compounds 8 and 14 were examined for their toxicity to the white mouse. Neither compound produced any symptoms of intoxication in mice treated at 400 mg/kg. As a reference point, the LD_{50} value of carbofuran to mice is 2 mg/kg (Black et al., 1973a). Therefore, substituted benzenesulfonyl derivatives of toxic methylcarbamates are toxic neither to insects nor mammals.

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Anticholinesterase Effects of Carbamate Insecticide Thiofanox and Its Metabolites in Rats

The anticholinesterase activity of the carbamate insecticide thiofanox (P), 3,3-dimethyl-1-(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime, and its three metabolites 3,3-dimethyl-1-(methylsulfinyl)-2-butanone *O*-[(methylamino)carbonyl]oxime (P_1), 3,3-dimethyl-1-(methylsulfonyl)-2-butanone *O*-[(methylamino)carbonyl]oxime (P_2), and 3,3-dimethyl-1-(methylsulfonyl)-2-butanone *O*-[(hydroxymethylamino)carbonyl]oxime (P_2OH) was investigated in the rat. The relative order of potency was $P_2 > P_1 > P > P_2OH$ for both the plasma ChE and RBC ChE. Time-dependent studies with P showed that maximum observed inhibition of cholinesterase (ChE) activity of plasma and red blood cells (RBC) of the rat was attained at 30 min after the peroral administration of 1 mg/kg P in aqueous solution. The maximum depression of brain ChE activity was observed 1–2 h postdose. In all three tissues, complete recovery of ChE activity was attained at 24 h after administration.

Thiofanox (P), 3,3,dimethyl-1-(methylthio)-2-butanone *O*-[(methylamino)carbonyl]oxime, is a potent systemic and contact insecticide developed by Diamond Shamrock Corp. Metabolic studies in soils (Duane, 1974) and plants (Whitten and Bull, 1974) showed rapid oxidation of P to its metabolities 3,3-dimethyl-1-(methylsulfinyl)-2-butanone *O*-[(methylamino)carbonyl]oxime (P_1) and 3,3-dimethyl-1-(methylsulfonyl)-2-butanone *O*-[(methylamino)-

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