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**Original Article**

# Synthesis and Biological Activity of New Aminosulfenyl Derivatives of the Methylcarbamate Insecticide, Carbofuran

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A number of new aminosulfenyl derivatives of carbofuran, linking different *N*-substituted amino acid esters and its analogs to the carbamyl nitrogen atom of carbofuran (2,3-dihydro-2, 2-dimethyl-7-benzofuranyl *N*-methylcarbamate) through a sulfur bridge, were synthesized, and their insecticidal activity and toxicity to mice were examined. Derivatization generally resulted in substantial improvement in mouse toxicity. All of the derivatized carbamates, with few exceptions, showed good insecticidal activity against houseflies, green rice leafhoppers and aphids in laboratory tests, though they were inferior to the parent methylcarbamate, carbofuran, on a weight basis. However, some derivatives were equally or more effective against these pests on a molar basis. Pot tests in greenhouse or field trials demonstrated that some of the derivatives were as effective as carbofuran even on a weight basis. Virtually all the derivatives tested were less effective inhibitors of acetylcholinesterase than carbofuran.

## INTRODUCTION

Among various classes of organic insecticides in use today, methylcarbamates rank at or near the top in acute mammalian toxicity. Fukuto[1,2] and Umetsu[3] have demonstrated that a toxic methylcarbamate insecticide can be converted into a derivative with less mammalian toxicity and other more favorable biological activities by appropriate substitution of the proton on the carbamyl nitrogen atom. During the past decade, a wide variety of derivatives of methylcarbamate insecticides with improved properties of selectivity have been developed. Sulfenyl,[4] aminosulfenyl[5,6] and sulfinyl[7] derivatives and thiodicarbamate[8,9] are among the derivatives studied. Of the aminosulfenyl derivatives, dialkylaminosulfenyl derivatives of carbofuran are reported to have reduced mammalian toxicity and excellent insecticidal activity.[5]

In a continuing study on aminosulfenyl derivatives of methylcarbamate insecticides, a number of new aminosulfenyl derivatives of carbofuran, linking different *N*-substituted amino acid esters and its analogs to the carbamyl nitrogen atom of carbofuran through a sulfur bridge, were synthesized and their toxicological properties were examined.

We report here the results on our investigations of new aminosulfenyl derivatives of carbofuran, linking iminodicarboxylic acid ester and its related compounds (type I derivative, whose structure being shown in Fig. 1), alkylaminocarboxylic acid ester and its related compounds (type II), phosphonomethylaminocarboxylic acid ester and its related compounds (type III), alkoxycarbonylaminocarboxylic acid ester (type IV), or acylaminocarboxylic acid ester (type V) to the carbamyl nitrogen atom of carbofuran through the sulfur bridge.

## MATERIALS AND METHODS

### 1. *Synthesis of Compounds*

#### 1.1 *General procedure*

The aminosulfenyl derivatives of carbofuran in Table 1 were obtained by the reaction between corresponding sulfenyl chlorides RR'N-S-Cl of *N*-substituted amino acid esters or its analogs (RR'NH) and carbofuran in the presence of base (Fig. 1). The aminosulfenyl chlorides were prepared either by Method A or Method B. In Method A, RR'N-S-Cl was obtained by the reaction between sulfur dichloride and RR'NH in the presence of base. In Method B, RR'NH was reacted with sulfur monochloride in the presence of base to give disulfide intermediates RR'N-S-S-NRR', which was then reacted with sulfuryl chloride to give RR'N-S-Cl.

All derivatives were identified by their $^1$H NMR spectra and elemental analyses. $^1$H NMR spectra were obtained with a Hitachi R-24B spectrometer.

As typical examples of the aminosulfenyl derivatives of carbofuran belonging to type I to V, the preparation of compound **2**, **24**, **36**, **38** and **40** are given.

#### 1.2 *2,3-Dihydro-2,2-dimethyl-7-benzofuranyl N-[N,N-bis(ethoxycarbonylmethyl)aminosulfenyl]-N-methylcarbamate* (***2***, *type I*)

Compound **2** was synthesized from carbofuran and [*N*,*N*-bis(ethoxycarbonylmethyl)]-aminosulfenyl chloride which was prepared by Method A. To a solution of 2.1 g (0.02 mol) of sulfur dichloride and 35 ml of carbon tetrachloride at 0°C was added dropwise 1.6 g (0.02 mol) of pyridine with stirring, and successively 3.8 g (0.02 mol) of ethyl iminodiacetate with stirring at 10–20°C. After stirring for 1 hr at 10–20°C, the solid substance formed was filtered off and the filtrate was concentrated under reduced pressure to give an oily product, [*N*,*N*-bis(ethoxycarbonylmethyl)]aminosulfenyl chloride.

The product (5.1 g, 0.02 mol) thus obtained, 4.4 g (0.02 mol) of carbofuran and 4.7 g (0.06 mol) of pyridine were dissolved in 35 ml of dichloromethane and stirred for 35 hr at 30–35°C. The reaction mixture was successively washed with water, 5% sulfuric acid and water. The dichloromethane phase was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure to give 8.2 g of oily product, compound **2** (purity: 91.2%, yield: 85%). The product was purified by silica gel column chromatography using *n*-hexane–ethyl acetate (4 : 1) as an eluting solvent to give a light yellow oily product. $^1$H NMR (in $CDCl_3$) $\delta$ ppm: 6.6–7.2 (3 H, m, aromatic protons), 4.28 (4 H, s, $NC\underline{H}_2$), 4.20 (4 H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 3.42 (3 H, s, $NC\underline{H}_3$), 3.02 (2 H, s, Ph-$C\underline{H}_2$), 1.48 (6 H, s, *gem*-di-$C\underline{H}_3$), 1.24 (6 H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$). Anal. Calcd. for $C_{20}H_{28}N_2O_7S$: C, 54.53; H, 6.41. Found: C, 54.49; H, 6.47.

#### 1.3 *2,3-Dihydro-2,2-dimethyl-7-benzofuranyl N-[N-[2-(ethoxycarbonyl)ethyl]-N-isopropylaminosulfenyl]-N-methylcarbamate* (***24***, *type II*)

Compound **24** was synthesized from carbo-

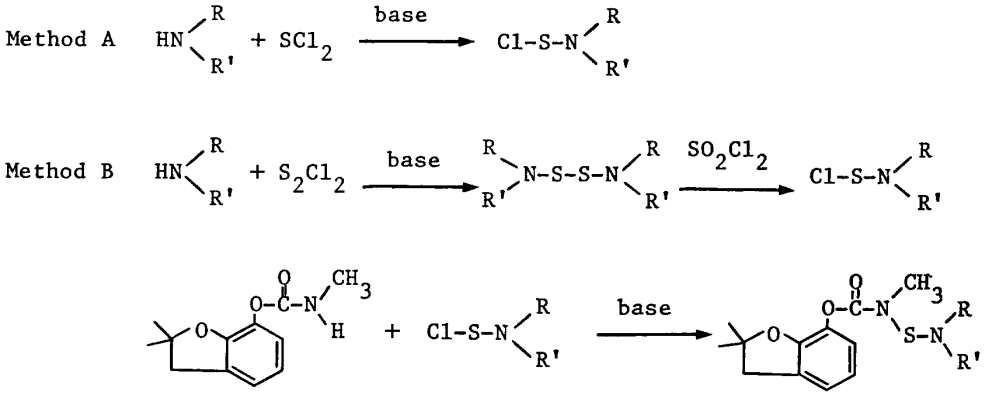



Fig. 1 Scheme for the synthesis of aminosulfenyl derivatives of carbofuran.

Type I: R, R'=$-(CH_2)_nCOOR_1$ (or $-(CH_2)_nCN$), II: R=$-(CH_2)_nCOOR_1$ (or $-(CH_2)_nCN$), R'=alkyl, aryl, III: R=$-CH_2P(OR_1)_2$, R'=$-CH_2COOR_2$ (or $-CH_2CN$), IV: R=$-(CH_2)_nCOOR_1$ (or $-(CH_2)_nCN$), R'=$-COOR_2$, V: R=$-(CH_2)_nCOOR_1$, R'=$-COR_2$.

furan and *N*-[2-(ethoxycarbonyl)ethyl]-*N*-isopropylaminosulfenyl chloride which was prepared by Method B. To a solution of 3.2 g (0.02 mol) of ethyl *N*-isopropylaminopropionate, 2.2 g (0.02 mol) of triethylamine and 50 ml of 1,2-dichloroethane at 0°C was added dropwise 1.4 g (0.01 mol) of sulfur monochloride with stirring. After stirring for 2 hr at 0–10°C, the mixture was washed with water. The 1,2-dichloroethane phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give an oily product, bis[*N*-[2-(ethoxycarbonyl) ethyl]-*N*-isopropylamino]disulfide. The product was dissolved in 30 ml of 1,2-dichloroethane and cooled to 0°C. To the solution was added dropwise 1.4 g (0.01 mol) of sulfuryl chloride. After stirring for 1 hr at 0–10°C, the solvent was removed under reduced pressure to give an oil, *N*-[2-(ethoxycarbonyl) ethyl] -*N*- isopropylaminosulfenyl chloride.

The product (2.4 g, 0.011 mol) thus obtained and 2.2 g (0.01 mol) of carbofuran were dissolved in 30 ml of 1,2-dichloroethane and cooled to 0°C. To the mixture was added dropwise 3.0 g (0.03 mol) of triethylamine with stirring. After stirring for 3 hr at 0–10°C, the reaction mixture was successively washed with water, 5% sulfuric acid and water. The 1,2-dichloroethane phase was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure to give 4.0 g of oily product, compound **24** (purity: 94.3%, yield: 92%). The product was purified by silica gel column chromatography using *n*-hexane–ethyl acetate (6 : 1) as an eluting solvent to give a colorless oily product. $^1$H NMR (in $CDCl_3$) $\delta$ ppm: 6.6–7.2 (3 H, m, aromatic protons), 4.12 (2 H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 3.4–3.9 (1 H, m, $C\underline{H}(CH_3)_2$), 3.45 (2 H, t, $J$= 6 Hz, $NC\underline{H}_2CH_2$), 3.42 (3 H, s, $NCH_3$), 3.04 (2 H, s, Ph-$C\underline{H}_2$), 2.78 (2 H, t, $J$=6 Hz, $C(O)C\underline{H}_2CH_2$), 1.50 (6 H, s, *gem*-di-$C\underline{H}_3$), 1.23 (6 H, d, $J$=7 Hz, $CH(C\underline{H}_3)_2$), 1.21 (3 H, t, $J$= 7 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd. for $C_{20}H_{30}N_2O_5S$: C, 58.52; H, 7.37. Found: C, 58.43; H, 7.29.

*1.4 2, 3-Dihydro-2, 2-dimethyl-7-benzofuranyl N-(N-diethylphosphonomethyl-N-cyanomethylaminosulfenyl)-N-methylcarbamate (**36**, type III)*

Compound **36**, a light yellow oil, was prepared by the method described in section *1.2* in 81% yield. $^1$H NMR (in $CDCl_3$) $\delta$ ppm: 6.6–7.2 (3 H, m, aromatic protons), 4.42 (2 H, s, $C\underline{H}_2CN$), 3.6–4.5 (4 H, m, $OC\underline{H}_2CH_3$), 3.83 (2 H, d, $J$=10 Hz, $C\underline{H}_2P$), 3.48 (3 H, s, $NC\underline{H}_3$), 3.00 (2 H, s, Ph-$C\underline{H}_2$), 1.45 (6 H, s, *gem*-di-$C\underline{H}_3$), 1.30 (6 H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd. for $C_{19}H_{28}N_3O_6PS$: C, 49.88; H, 6.17. Found: C, 50.03; H, 6.11.

*1.5 2, 3-Dihydro-2, 2-dimethyl-7-benzofuranyl N-(N-ethoxycarbonyl-N-ethoxycarbonylmethylaminosulfenyl)-N-methylcarbamate (**38**, type IV)*

Compound **38**, a light yellow oil, was prepared by the method described in section *1.2* in 85% yield. $^1$H NMR (in $CDCl_3$) $\delta$ ppm: 6.5–7.0 (3 H, m, aromatic protons), 4.41 (2 H, s, $C\underline{H}_2CO$), 4.15 (2 H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.05 (2 H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 3.41 (3 H, s, $NC\underline{H}_3$), 2.94 (2 H, s, Ph-$C\underline{H}_2$), 1.44 (6 H, s, *gem*-di-$C\underline{H}_3$), 1.29 (3 H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 1.17 (3 H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$). Anal. Calcd. for $C_{19}H_{26}N_2O_7S$: C, 53.51; H, 6.14. Found: C, 53.46; H, 6.31.

*1.6 2, 3-Dihydro-2, 2-dimethyl-7-benzofuranyl N-(N-propionyl-N-ethoxycarbonylmethylaminosulfenyl)-N-methylcarbamate (**40**, type V)*

Compound **40**, light yellow crystals, was prepared by the method described in section *1.2* in 70% yield. Melting point: 108–109°C. $^1$H NMR (in $CDCl_3$) $\delta$ ppm: 6.6–7.1 (3 H, m, aromatic protons), 4.50 (2 H, s, $C\underline{H}_2C(O)$), 4.15 (2 H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 3.48 (3 H, s, $NC\underline{H}_3$), 3.02 (2 H, s, Ph-$C\underline{H}_2$), 2.7–3.3 (2 H, m, $C(O)C\underline{H}_2CH_3$), 1.49 (6 H, s, *gem*-di-$C\underline{H}_3$), 1.23 (3 H, t, $J$=7 Hz, $OCH_2C\underline{H}_3$), 1.14 (3 H, t, $J$= 8 Hz, $C(O)CH_2C\underline{H}_3$). Anal. Calcd. for $C_{19}H_{26}N_2O_6S$: C, 55.59; H, 6.38. Found: C, 55.35; H, 6.41.

*2. Mouse Toxicity*

Mouse toxicity was determined orally on ICR male mice using corn oil as a carrier according to the usual procedure.[10] Animals weighing between 25 and 28 g were given 1 ml of the test compound suspensions per 100 g of body weight. Based on the 14-day accumulative mortality, the $LD_{50}$ values were calculated using the Probit method.

*3. Insecticidal Activity*

Housefly toxicity was determined on a susceptible (Takatsuki) strain of female houseflies (4- to 5-day old), *Musca domestica*, according to the usual procedure.[11] One microliter of acetone solution of each compound was topically applied by means of a Arnold Hand Microapplicator onto the thorax of ten houseflies. The treated flies were held at 25°C and their mortality was estimated after 24 hr. Data are means of three replications.

The $LD_{50}$ value of the compounds against a resistant (Nakagawara) strain of female green rice leafhoppers (3- to 4-day old), *Nephotettix cincticeps*, was determined by the same method as mentioned for housefly toxicity determination. In this case, a sample volume was 0.5 $\mu$l per insect.

The insecticidal activity against female green peach aphids (3- to 4-day old), *Myzus persicae*, was evaluated as follows. Duplicated ten green peach aphids were released onto 1-month-old cabbage (4 to 5 leaf stage), followed by spraying of 10 ppm emulsion of each compound. Mortality was determined 24 hr after the release of the insects.

The insecticidal activity against susceptible (Miyagi) and resistant (Nakagawara) strains of female green rice leafhoppers (3- to 4-day old) in intact rice plants was determined as follows. Ten milliliters of emulsions (300 ppm) of each compound were sprayed on eight 12-day-old rice seedlings (about 10 cm high, 2.5 leaf stage) in 12 cm ($\phi$) pots where ten insects had been released. Entire plants and pots were covered with a net in a greenhouse. Mortality was determined 24 hr after the release of the insects. Data are means of three replications.

Field trials against oriental corn borers, *Ostrinia furnacalis*, and pink borers, *Chilo partellus*, were conducted as follows. Five percent granular formulations of each compound were applied into seed furrows in Japan in 1981 and the number of larvae of corn borers and pink borers in a stem of corn plants were counted 46 days after treatment.

*4. Antiacetylcholinesterase Activity*

The *in vitro* inhibition of acetylcholinesterase in housefly heads was determined at 37°C by the reported procedure, using acetylthiocholine as a substrate.[12]

The heads of female flies (4- to 5-day old) of an insecticide-susceptible (Takatsuki) strain, were homogenized in 0.1 M phosphate buffer at pH 7.5 (4.0 heads/ml). The homogenate was centrifuged at 30,000×$g$ for 10 min to obtain the supernatant as an enzyme source. The enzyme solution (0.9 ml) and 0.1 ml of an inhibitor in various concentrations in acetone were incubated at 37°C for 30 min, to which were added 1.0 ml of acetylthiocholine ($2.8\times10^{-3}$ M), 1.0 ml of 5,5'-dithiobis(2-nitrobenzoic acid) ($2.5\times10^{-4}$ M) and 4.0 ml of 0.1 M phosphate buffer of pH 7.5. The mixture was incubated at 30°C for 10 min, to measure enzyme activity from the absorbance at 412 nm with a Shimadzu model UV-240 spectrophotometer.

## RESULTS

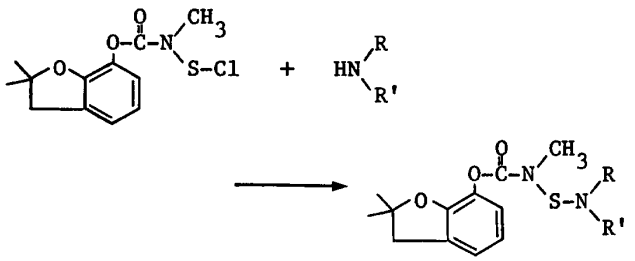
*1. Synthesis*

Fukuto *et al.*[4,13] described that the reaction between methylcarbamate and *N*,*N*-dialkylaminosulfenyl chloride, which was prepared from dialkylamine and sulfur dichloride, gave the corresponding *N*-(*N*,*N*-dialkylaminosulfenyl)-*N*-methylcarbamate in good yield. In the present study, this reaction was applied to prepare the four types of aminosulfenyl derivatives of carbofuran (types I, III, IV and V). The *N*-substituted amino acid ester or its analog reacted readily with sulfur dichloride to give aminosulfenyl chloride RR'N-S-Cl (Method A), which, in turn, reacted smoothly with carbofuran to give the corresponding final products in good yield. The total yield based on carbofuran was over 70% for all products. All the products, except compound **40**, were obtained as oil.

The aminosulfenyl derivatives of carbofuran linking alkylaminocarboxylic acid ester (type II) were also prepared from carbofuran and sulfenyl chloride of alkylaminocarboxylic acid ester (RR'N-S-Cl). In this case, however, the aminosulfenyl chloride was synthesized by a two-step reaction (Method B) through a disulfide intermediate, RR'N-S-S-NRR', which had been prepared by the reaction between sulfur monochloride and alkylaminocarboxylic acid ester. The preparation of RR'N-S-Cl from disulfide, RR'N-S-S-NRR' was achieved by

using sulfuryl chloride in good yield. The use of chlorine gas instead of sulfuryl chloride was also effective to obtain RR'N-S-Cl. In general, the final products were obtained in good yield of over 75%. All the products except compounds **15** and **16**, were obtained as oil. Melting points of **15** and **16** were 92–93 and 54–55 °C, respectively. The sulfenyl chloride of alkylaminocarboxylic acid ester could also be prepared by the reaction between sulfur dichloride and alkylaminocarboxylic acid ester. The results, however, indicated that the aminosulfenyl chloride was obtained in higher purity and yield by the two-step reaction using sulfur monochloride than sulfur dichloride.

All the aminosulfenyl derivatives of carbofuran (type I–V) could be prepared by the reaction (see the equation below) between *N*-substituted amino acid esters (or its analogs) and sulfenyl chloride which had been prepared from sulfur dichloride and carbofuran. The final products obtained by this method, however, contained a number of impurities such as biscarbofuran sulfide and its polysulfide analogs.[14] Therefore, overall yield *via* this route was relatively poor.

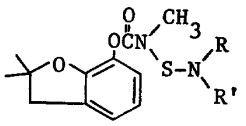


The formation of an aminosulfenyl derivative of carbofuran was easily confirmed by comparison of its $^1$H NMR spectrum with that of carbofuran. The *N*-methyl protons of the derivative showed a singlet and downfield shift ($\delta$ 3.20–3.50) as compared to a doublet and upfield absorption ($\delta$ 2.87) of the *N*-methyl protons of carbofuran.

## 2. *Insecticidal Activity*

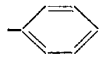
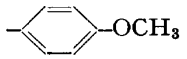
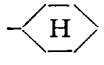
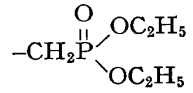
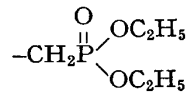
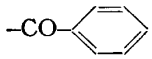
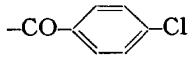
Data on the insecticidal activity of five different types of new aminosulfenyl derivatives of carbofuran (type I–V) to the houseflies, green rice leafhoppers and green peach aphids are given in Table 1.

Table 1 Toxicological properties of aminosulfenyl derivatives (type I–V) linking different *N*-substituted amino acid esters and its analogs through a sulfur bridge.



| No. | R | R′ | Topical $LD_{50}$ (μg/g) Housefly | Topical $LD_{50}$ (μg/g) Green rice leafhopper (R) | 24 hr mortality of aphid (%) | Mouse oral $LD_{50}$ (mg/kg) |
|---|---|---|---|---|---|---|
| Type I | | | | | | |
| **1** | $-CH_2COOCH_3$ | $-CH_2COOCH_3$ | 40 | 43 | 90 | 46 |
| **2** | $-CH_2COOC_2H_5$ | $-CH_2COOC_2H_5$ | 58 | 56 | 85 | 118 |
| **3** | $-CH_2COOCH(CH_3)_2$ | $-CH_2COOCH(CH_3)_2$ | 33 | 243 | 10 | — |
| **4** | $-CH_2COOC_2H_5$ | $-(CH_2)_2COOC_2H_5$ | 31 | 90 | 100 | >100 |
| **5** | $-CH_2COOC_2H_5$ | $-\underset{C_2H_5}{\overset{\vert}{C}}HCOOC_2H_5$ | 93 | 74 | 95 | >100 |
| **6** | $-CH_2COOC_2H_5$ | $-(CH_2)_3COOC_2H_5$ | 46 | 66 | 95 | — |
| **7** | $-CH_2COOC_2H_5$ | $-(CH_2)_2CN$ | 24 | 60 | 90 | — |
| **8** | $-(CH_2)_2COOC_2H_5$ | $-(CH_2)_2COOC_2H_5$ | 50 | 225 | 45 | — |
| **9** | $-(CH_2)_2CN$ | $-(CH_2)_2CN$ | — | 297 | 40 | >50 |
| Type II | | | | | | |
| **10** | $-CH_2COOC_2H_5$ | $-CH_3$ | 15 | 20 | 100 | 50 |
| **11** | $-CH_2COOC_2H_5$ | $-CH(CH_3)_2$ | 33 | 41 | 100 | 110 |
| **12** | $-CH_2COOC_2H_5$ | $-(CH_2)_3CH_3$ | 16 | 37 | 100 | 100 |
| **13** | $-CH_2COOC_2H_5$ |  | — | 76 | 85 | >100 |
| **14** | $-CH_2COOC_2H_5$ |  | 22 | 141 | 75 | >100 |

Table 1 (continued)

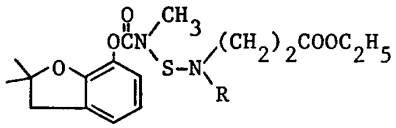
| | | | | | | |
|---|---|---|---|---|---|---|
| **15** | $-CH_2COOC_2H_5$ |  | 12 | 68 | 100 | >50 |
| **16** | $-CH_2COOC_2H_5$ |  | 45 | 133 | 90 | >100 |
| **17** | $-CH_2CN$ | $-CH(CH_3)_2$ | 16 | 19 | 100 | 55 |
| **18** | $-CH_2CN$ | $-(CH_2)_3CH_3$ | 9 | 21 | 100 | 62 |
| **19** | $-(CH_2)_2CN$ | $-CH(CH_3)_2$ | — | 35 | 95 | 50 |
| **20** | $-(CH_2)_2CN$ | $-(CH_2)_3CH_3$ | 17 | 28 | 95 | 82 |
| **21** | $-(CH_2)_2CN$ | $-CH_2CH(CH_3)_2$ | 37 | 70 | 100 | 50–100 |
| **22** | $-(CH_2)_2CN$ | $-(CH_2)_5CH_3$ | — | 90 | 95 | 50–100 |
| **23** | $-(CH_2)_2COOC_2H_5$ | $-(CH_2)_2CH_3$ | 18 | 40 | 100 | 96 |
| **24** | $-(CH_2)_2COOC_2H_5$ | $-CH(CH_3)_2$ | 9 | 22 | 95 | 106 |
| **25** | $-(CH_2)_2COO(CH_2)_3CH_3$ | $-CH(CH_3)_2$ | 11 | 89 | 100 | 50–100 |
| **26** | $-(CH_2)_2COOCH_3$ | $-(CH_2)_3CH_3$ | 17 | 42 | 90 | >100 |
| **27** | $-(CH_2)_2COOC_2H_5$ | $-(CH_2)_3CH_3$ | 13 | 34 | 100 | 118 |
| **28** | $-(CH_2)_2COO(CH_2)_3CH_3$ | $-(CH_2)_3CH_3$ | 17 | 38 | 75 | >100 |
| **29** | $-(CH_2)_2COOC_2H_5$ | $-CH_2CH(CH_3)_2$ | 32 | 64 | 100 | 186 |
| **30** | $-(CH_2)_2COOC_2H_5$ | $-CH(CH_3)C_2H_5$ | 22 | 52 | 100 | >100 |
| **31** | $-(CH_2)_2COOC_2H_5$ | $-C(CH_3)_3$ | 15 | 27 | 100 | — |
| **32** | $-(CH_2)_2COOC_2H_5$ | $-(CH_2)_2CH(CH_3)_2$ | 16 | 41 | 100 | 100 |
| **33** | $-(CH_2)_2COOC_2H_5$ | $-(CH_2)_5CH_3$ | 33 | 38 | 100 | 50–100 |
| **34** | $-(CH_2)_2COOC_2H_5$ |  | 32 | 71 | 100 | >100 |
| Type III | | | | | | |
| **35** | $-CH_2COOC_2H_5$ |  | — | 609 | 10 | — |
| **36** | $-CH_2CN$ |  | — | 835 | 0 | — |
| Type IV | | | | | | |
| **37** | $-CH_2COOC_2H_5$ | $-COOCH_3$ | 15 | 56 | 70 | >50 |
| **38** | $-CH_2COOC_2H_5$ | $-COOC_2H_5$ | 16 | 43 | 40 | >50 |
| **39** | $-(CH_2)_2COOC_2H_5$ | $-COOC_2H_5$ | 18 | 67 | 60 | 50–100 |
| Type V | | | | | | |
| **40** | $-CH_2COOC_2H_5$ | $-COC_2H_5$ | 14 | 22 | 50 | — |
| **41** | $-CH_2COOC_2H_5$ | $-COCH_2Cl$ | 29 | 99 | 50 | >50 |
| **42** | $-CH_2COOC_2H_5$ |  | 33 | 219 | 50 | — |
| **43** | $-CH_2COOC_2H_5$ |  | — | 696 | 40 | >100 |
| | Carbofuran | | 6.7 | 11.5 | 100 | 5.6 |

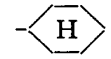
In general, the aminosulfenyl derivatives of carbofuran, except type III, showed good insecticidal activity by topical application against houseflies, green rice leafhoppers and green peach aphids with a few exceptions, although all of the derivatives were inferior to the parent methylcarbamate, carbofuran, on a weight basis. On a molar basis, compounds **15**, **18**, **24** and **25** appeared more effective against houseflies than carbofuran. Compounds **10**, **18**, **24** (all belong to type II) and **40** (type V) were almost equally effective against green rice leafhoppers on a molar basis. Most of the derivatives showed good insecticidal activity against green peach aphids. Compounds of type III did not show insecticidal activity against green rice leafhoppers and green peach aphids.

Because of excellent insecticidal activity of **24** (type II) against green rice leafhoppers by

topical application, the effectiveness of **24** and its analogs, *N*-[2-(ethoxycarbonyl)ethyl]-*N*-alkylaminosulfenyl derivatives against susceptible and resistant strains of green rice leafhoppers were also examined when they were treated to the foliage of intact rice plants in pots. As shown in Table 2, compounds **23**, **24**, **27** and **29** among the six derivatives tested were highly effective against both susceptible and resistant strains of this pest. It should be noted that compounds **23** and **29**, which exhibited relatively poor insecticidal activity by topical application, appeared more effective against this pest when applied to intact plants where insects had been released. The results indicate that these derivatives are systemic insecticides with contact and/or stomach action.

Table 2 Mortality of green rice leafhopper 24 hr after release of aminosulfenyl derivatives of carbofuran onto rice plants in pots.



| No. | R | 24 hr mortality (%) S-strain | R-strain |
|---|---|---|---|
| **23** | $-(CH_2)_2CH_3$ | 90 | 83 |
| **24** | $-CH(CH_3)_2$ | 87 | 90 |
| **27** | $-(CH_2)_3CH_3$ | 83 | 87 |
| **29** | $-CH_2CH(CH_3)_2$ | 93 | 83 |
| **33** | $-(CH_2)_5CH_3$ | 67 | 27 |
| **34** |  | 40 | 27 |
| | Carbofuran | 93 | 90 |

In order to know more about the insecticidal properties of the aminosulfenyl derivatives, 5% granules of four *N*-[2-(ethoxycarbonyl)ethyl]-*N*-alkylaminosulfenyl derivatives (type II) were prepared and subjected to a field trial. The field trial was conducted in Japan in 1981 against oriental corn borers and pink borers on corn plants. As shown in Table 3, 5% granules of the four derivatives (**24**, **27**, **29**, **31**) applied into seed furrows exhibited outstanding activity against these pests, indicating its excellent systemic activity following the soil application. Efficacy data 46 days after application indicate the excellent residual effectiveness of the derivatives, compound **24** in particular.

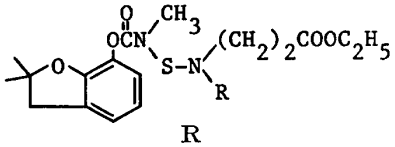
### 3. *Mouse Toxicity*

Toxicological data presented in Table 1 show that, compared to the original methylcarbamate, carbofuran (oral $LD_{50}$: 5.6 mg/kg), the aminosulfenyl derivatives (type I–V) were at least 8-fold less toxic against white mice. Although a large number of aminosulfenyl derivatives were prepared, no obvious correlation was observed between substituent and mouse toxicity.

### 4. *Antiacetylcholinesterase Activity*

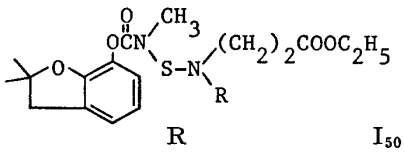
The 50% inhibition-concentration ($I_{50}$) for acetylcholinesterase in a housefly head preparation was determined with several *N*-[2-(ethoxycarbonyl)ethyl]-*N*-alkylaminosulfenyl derivative. As shown in Table 4, all of the derivative tested were a less effective anti-

Table 3 Control of oriental corn borer and pink borer on corn plants by formulated aminosulfenyl derivatives of carbofuran in Japan in 1981.



| No. | R | Dose (kg a.i./ha) | % control Oriental corn borer | Pink borer |
|---|---|---|---|---|
| **24** | $-CH(CH_3)_2$ | 1.5 | 67 | 84 |
| **27** | $-(CH_2)_3CH_3$ | 1.5 | 28 | 84 |
| **29** | $-CH_2CH(CH_3)_2$ | 1.5 | 49 | 82 |
| **31** | $-C(CH_3)_3$ | 1.5 | 45 | 80 |
| | Diazinon | 3.0 | 58 | 65 |
| | Carbofuran | 1.5 | 60 | 84 |

Table 4 Antiacetylcholinesterase activity of aminosulfenyl derivatives of carbofuran.



| No. | R | $I_{50}$ (M) |
|---|---|---|
| **23** | $-(CH_2)_2CH_3$ | $1.1\times10^{-4}$ |
| **24** | $-CH(CH_3)_2$ | $5.8\times10^{-5}$ |
| **27** | $-(CH_2)_3CH_3$ | $7.8\times10^{-4}$ |
| **29** | $-CH_2CH(CH_3)_2$ | $>1.0\times10^{-4}$ [a] |
| **33** | $-(CH_2)_5CH_3$ | $>1.0\times10^{-4}$ [a] |
| | Carbofuran | $1.7\times10^{-7}$ |

[a] Maximum solubility in the reaction mixture.

acetylcholinesterase than the parent *N*-methylcarbamate, carbofuran, the difference in activity being at least 341-fold (compound **24**).

## DISCUSSION

By analogy with the rational proposed for the selective toxicity of various derivatives of methylcarbamate esters,[1-8] it seems likely that aminosulfenylation of carbofuran linking *N*-substituted amino acid esters and its analogs to the carbamyl nitrogen atom of carbofuran can provide additional opportunities to obtain new promising carbamate insecticides with improved mammalian safety. Of the compounds synthesized, the derivative linking *N*-isopropyl *β*-alanine ethyl ester (**24**, benfuracarb) has been commercialized in many countries both as soil and foliar insecticides.[15,16] Compound **24** has outstanding insecticidal activity against a number of economically important insects and improved mammalian safety.

Earlier studies on the metabolism and the mode of action of derivatized methylcarbamate esters have shown that their lower mammalian toxicity is attributable to preferential metabolic detoxication of the derivative to nontoxic phenols.[1] It is reasonable that this also explains the mammalian safety of new aminosulfenyl derivatives of carbofuran linking *N*-substituted amino acid esters and its analogs. This was actually confirmed by the rat metabolism study of **24**.[16]

The poor correlation between *in vitro* antiacetylcholinesterase activity and toxicity to insects suggests that metabolic processes *in vivo* are responsible for the observed insecticidal activity. The housefly metabolism study of **24**[17] demonstrates that the appreciable amount of carbofuran is accumulated internally in houseflies, indicating its role as a toxic agent.

Progress of the research has provided us with new findings concerning insecticidal properties of the derivatized carbamate. The indoor test indicates that several of the aminosulfenyl derivatives of carbofuran are more active to some insects such as houseflies than carbofuran on a molar basis. It is likely that the increase in activity is due to factors such as penetration, transportation and protection from premature detoxication. Pot tests in greenhouse and field trials demonstrate that the aminosulfenyl derivatives are particularly effective when their granular or liquid formulations are applied to soil. The field trial of 5% granules of **24** indicate that **24** is, in some cases, more effective than carbofuran even on a weight basis.[15] Detailed work on the properties of action of the aminosulfenyl derivative is now in progress.

## ACKNOWLEDGMENTS

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## REFERENCES

1) T. R. Fukuto: *J. Pesticide Sci.* **2**, 541 (1977)
2) T. R. Fukuto: Proc. 5th Int. Congr. Pestic. Chem. Human Welfare and the Environment, Vol. 1, Synthesis and Structure-Activity Relationships, p. 203, 1983
3) N. Umetsu: *J. Pesticide Sci.* **9**, 169 (1984)
4) A. L. Black, Y. C. Chiu, M. A. H. Fahmy & T. R. Fukuto: *J. Agric. Food Chem.* **21**, 747 (1973)
5) T. R. Fukuto, A. L. Black, Y. C. Chiu & M. A. H. Fahmy: *Environ. Qual. Saf. Suppl.* **III**, 394 (1975)
6) E. G. Maitlen & N. A. Sladen: Proc. 1979 Br. Crop Prot. Conf. Pests and Diseases, p. 557, 1979
7) M. A. H. Fahmy & T. R. Fukuto: *J. Agric. Food Chem.* **29**, 567 (1981)
8) M. A. H. Fahmy & T. R. Fukuto: *J. Agric. Food Chem.* **22**, 59 (1974)
9) M. A. H. Fahmy, N. M. Mallipudi & T. R. Fukuto: *J. Agric. Food Chem.* **26**, 550 (1978)
10) R. M. Hollingworth, T. R. Fukuto & R. L. Metcalf: *J. Agric. Food Chem.* **15**, 235 (1967)

11) R. L. Metcalf & R. B. March: *J. Econ. Entomol.* **42**, 721 (1949)
12) S. Kimura, K. Toeda, T. Miyamoto & I. Yamamoto: *J. Pesticide Sci.* **9**, 137 (1984)
13) A. L. Black & T. R. Fukuto: U.S. US 4006231 (1977)
14) N. Umetsu & T. R. Fukuto: *J. Pesticide Sci.* **7**, 117 (1982)
15) T. Goto, A. K. Tanaka, N. Yasudomi, N. Osaki, S. Iida & N. Umetsu: Proc. 10th Int. Congr. Plant Prot. 1983, Plant Protection for Human Welfare, p. 360, 1983
16) N. Umetsu: *J. Pesticide Sci.* **11**, 493 (1986)
17) M. Usui & N. Umetsu: *J. Pesticide Sci.* **11**, 401 (1986)

## 要　　約

## メチルカルバマート殺虫剤カルボフランの新規アミノスルフェニル誘導体の合成と生物活性

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メチルカルバマート系殺虫剤，カルボフランのアミノスルフェニル誘導体について検討を行なった．カルボフランのカルバミル窒素に硫黄を介してアミノ酸あるいはその類縁体を結合させた一連の化合物を合成し，それらの毒性ならびに各種害虫に対する殺虫活性を測定した．マウス急性経口毒性については，いずれの誘導体もカルボフランより著しく軽減された．一方，イエバエ，ツマグロヨコバイおよびアブラムシを用いた室内の一次スクリーニングにおいては少数の例外を除いて高い活性を示した．親化合物のカルボフランと活性を比較した場合，重量比較では劣るものの分子量を考慮すると同等あるいはそれ以上の活性を示す化合物も見いだされた．これらの優れた活性を示したいくつかの化合物を温室内のポット試験や圃場試験に供すると重量比較でもカルボフランと同等の活性を示した．一連の誘導体のアセチルコリンエステラーゼ阻害活性はカルボフランに比較するといずれも微弱であった．