

or toxicological symptoms and all the birds remained healthy throughout the study. Feed consumption was significantly reduced at the 300 g/ton level and the birds in this group ended the medication period gaining 60% as much weight as the control group. There were no discernible differences in the quality of the eggs or the egg shell.

Following the toxicology study, the feeding study described in the Experimental Section was carried out. In order to obtain some indication as to when a plateau in tissue level was reached, six eggs were randomly taken at weekly intervals and analyzed. The results from these analyses are shown in Table IV and, although there is a great variation between egg concentrations for each week, a plateau appears to have been reached by at least the fourth or fifth week. The variations in concentrations were great enough to warrant a study of the variations within the eggs of one hen. The results of these analyses are shown in Table V and indicate variations from 0.9 to 3.9 ppm for fenfluramine and 0.28 to 4.0 ppm for norfenfluramine. The source of these differences is not immediately apparent but may reflect daily variations in food consumption.

After the hens had been on the diet containing fenfluramine for 69 days, the diet was changed to one containing no fenfluramine. Beginning with the day the diet was changed and each day thereafter, three randomly selected hens were sacrificed. Eggs continued to be collected from the remaining hens and the rate of disappearance of fen-

fluramine was determined in these eggs. The results, shown in Table VI, indicate that at the sixth day after withdrawal of the drug no fenfluramine or its metabolite could be found.

Tissues and blood were taken for analysis when the birds were sacrificed and were analyzed at each interval until no further residue could be detected in the tissue. The results indicate that no detectable residue was present after the second day off of the medication. None could be detected in blood or muscle on the day of withdrawal of fenfluramine. (None could be detected in any of the tissues on the second day of withdrawal.) Residues persisted for 1 day longer in the kidney than in any of the other tissues including fat. The rate of disappearance would be expected to be slower from the eggs than from the tissues since these are formed several days prior to being laid.

LITERATURE CITED

- Beckett, A. H., Brookes, L. G., *J. Pharm. Pharmacol.* 16, 27T (1964).
 Bruce, R. B., Maynard, W. R., *J. Pharm. Sci.* 57, 1173 (1968).
 Duhault, J., Fenard, S., *Arch. Int. Pharmacodyn.* 158, 251 (1965).
 Franko, B. V., Honkomp, L. J., Ward, J. W., *J. Pharm. Pharmacol.* 17, 222 (1965).
 Gilbert, D. L., unpublished data, A. H. Robins Co., 1971.

Received for review August 16, 1972. Resubmitted July 31, 1974.
 Accepted August 26, 1974.

Synthesis and Herbicidal Activity of Fluorinated *N*-Phenylalkanesulfonamides

Robert D. Trepka,* Joseph K. Harrington, John W. McConville, Kelly T. McGurran, Arthur Mendel, David R. Pauly, Jerry E. Robertson, and John T. Waddington

Four general techniques have been developed for the preparation of a series of *N*-phenylalkanesulfonamides, fluorinated in the (alkanesulfonyl)-amino moiety. Herbicidal and plant growth regulatory activities were exhibited over a wide range of structure type. Preemergence herbicidal activity was greatest with halogen and sulfur aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. Crop selectivity with high herbicidal activity was apparent for 2-methylthio, 4-methylsulfanyl, 2,4-dichloro, and 2,4-dibromo aryl-sub-

stituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. Postemergence herbicidal activity paralleled preemergence activity but was generally less marked. High herbicidal activity in the 1,1,1-trifluoro-*N*-phenylmethanesulfonamides generally was accompanied by high acidity and lipophilicity. Computer correlations of herbicidal activity with structure indicated that lipophilic effects are more important for herbicidal activity with the 4-substituted than with the 3-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides.

Sulfonamides have found extensive medicinal applications since the discovery of Prontosil in 1932. Scores of sulfonamides have been synthesized and many found effective for the treatment of bacterial infections. These early drugs were essentially all benzenesulfonamides. Alkanesulfonamides have found little use in the medicinal area. Generally, alkanesulfonamides have been used as substituents to slightly modify the biological activity of compounds found active previously.

The first reported synthesis of *N*-phenylalkanesulfonamides, fluorinated in the (alkanesulfonyl)amino moiety (perfluoro-*N*-phenyloctanesulfonamide and 1,1,1-trifluoro-*N*-phenylmethanesulfonamide), was from these laboratories (Brice and Trott, 1956). More recently, 1-fluoro- and 1,1-difluoro-*N*-phenylmethanesulfonamides were reported

(Farrar, 1960). In 1970 we published preliminary reports of potent herbicidal (Trepka *et al.*, 1970) and antiinflammatory (Harrington *et al.*, 1970) activity for a number of these fluorinated *N*-phenylalkanesulfonamides. Biological activity is largely due to the presence of the fluorinated (alkanesulfonyl)amino group and we have found it to be highly dependent upon the degree of fluorination. However, activity can be modified by substitution in the aromatic portion of the structure. We now wish to describe the synthetic procedures used to prepare these compounds and to relate other details of their biological properties. Throughout this paper the term fluorinated *N*-phenylalkanesulfonamides refers to fluorination in the (alkanesulfonyl)-amino group.

RESULTS

Synthesis. Representative fluorinated *N*-phenylalkanesulfonamides and references to their methods of prepara-

Contribution No. 718 from the Central Research Laboratories, 3M Company, St. Paul, Minnesota 55101.

Table I. Aryl-Monosubstituted Fluorinated *N*-Phenylalkanesulfonamides (X-C₆H₄NHSO₂R_F)

| No. | R _F | X | Procedure | Mp/bp (mm), °C | Yield, % | Av preemergence herbicide act. | |
|-----|--------------------------------|-----------------------------------|----------------|-------------------|-------------|-----------------------------------|-------------|
| | | | | | | Grasses | Broadleaves |
| 1 | CF ₃ | 2-F | B | 65.5-67.5 | 29.2 | 2+ | 3+ |
| 2 | CF ₃ | 3-F | B | 38-40 | 10.8 | <i>a</i> | 4+ |
| 3 | CF ₃ | 4-F | B | 60.5-62.5 | 36.6 | 4+ | 4+ |
| 4 | CF ₃ | 2-Cl | B | 75.5-76.5 | 17.4 | 1+ | 3+ |
| 5 | CF ₃ | 3-Cl | B | 76-77 | 23.7 | 1+ | 4+ |
| 6 | CF ₃ | 4-Cl | B | 50-51 | 48.3 | 4+ | 4+ |
| 7 | CF ₃ | 2-Br | B | 73.5-75.5 | 19.2 | 2+ | 4+ |
| 8 | CF ₃ | 3-Br | B | 79-80.5 | 54.6 | 1+ | 4+ |
| 9 | CF ₃ | 4-Br | B | 56.5-58 | 36.0 | 3+ | 4+ |
| 10 | CF ₃ | 2-I | B | 95 (0.075) | 31.4 | <i>b</i> | <i>b</i> |
| 11 | CF ₃ | 3-I | B | 79.5-81 | 16.5 | <i>a</i> | 4+ |
| 12 | CF ₃ | 4-I | B | 73-75 | 23.8 | 3+ | 4+ |
| 13 | CF ₃ | 3-CH ₃ | B | 64-65 | 30.0 | 1+ | 3+ |
| 14 | CF ₃ | 4-CH ₃ | B | 42-43 | 38.4 | 2+ | 4+ |
| 15 | CF ₃ | 4-C ₂ H ₅ | B | 33.5-35 | 15.7 | 3+ | 3+ |
| 16 | CF ₃ | 2-CF ₃ | B | 57 (0.13) | 10.4 | 1+ | 3+ |
| 17 | CF ₃ | 3-CF ₃ | B | 32-34 | 19.2 | <i>a</i> | 4+ |
| 18 | CF ₃ | 4-CF ₃ | B | 73.5-75 | 26.6 | 4+ | 4+ |
| 19 | CF ₃ | 2-CN | A | 104 (0.1) | 32.4 | <i>a</i> | <i>a</i> |
| 20 | CF ₃ | 4-CN | A | 147-149 | 24.5 | 3+ | 3+ |
| 21 | CF ₃ | 2-COCH ₃ | B | 53.5-56.5 | 70.3 | 3+ | 4+ |
| 22 | CF ₃ | 3-COCH ₃ | B | 101-102.5 | 17.3 | 2+ | 1+ |
| 23 | CF ₃ | 4-COCH ₃ | B | 142-143.5 | 57.2 | 2+ | 2+ |
| 24 | CF ₃ | 3-C ₆ H ₅ | B | 105-110 (0.1) | 37.8 | 1+ | 1+ |
| 25 | CF ₃ | 4-C ₆ H ₅ | B | 137-138 | 14.9 | 1+ | 2+ |
| 26 | CF ₃ | 2-NH ₂ | B ^c | 103-104 | 16.3 | <i>a</i> | <i>a</i> |
| 27 | CF ₃ | 3-NH ₂ | B ^c | 104-106 | 58.2 | 2+ | 2+ |
| 28 | CF ₃ | 4-NH ₂ | B ^c | 104-106 | 90.0 | 1+ | 1+ |
| 29 | CF ₃ | 2-NHCOCH ₃ | B ^d | 159-160 | 22.0 | 1+ | 1+ |
| 30 | CF ₃ | 3-NHCOCH ₃ | B | 159-161 | 7.6 | 2+ | ± |
| 31 | CF ₃ | 4-NHCOCH ₃ | B | 153-154 | 3.5 | 3+ | 1+ |
| 32 | CF ₃ | 2-NO ₂ | B | 68.5-69 | 26.3 | ± | ± |
| 33 | CF ₃ | 3-NO ₂ | B | 64-66 | 6.1 | 2+ | 3+ |
| 34 | CF ₃ | 4-NO ₂ | B | 150-151 (0.05) | 64.4 | 1+ | 2+ |
| 35 | CF ₃ | 2-OH | A ^e | 83-86 | 40.1 | 1+ | ± |
| 36 | CF ₃ | 3-OH | B | 98-100 | 16.3 | 1+ | 1+ |
| 37 | CF ₃ | 4-OH | B | 107-108 | 1.7 | <i>b</i> | <i>b</i> |
| 38 | CF ₃ | 2-OCH ₃ | A | 57-58 | 63.7 | 2+ | 3+ |
| 39 | CF ₃ | 3-OCH ₃ | B | 63-65 | 20.3 | ± | ± |
| 40 | CF ₃ | 4-OCH ₃ | B | 38-41 | 18.6 | 1+ | 2+ |
| 41 | CF ₃ | 3-SH | B | 108 (0.13) | 38.9 | 3+ | 3+ |
| 42 | CF ₃ | 4-SH | B | 140 (0.23) | 22.5 | 1+ | ± |
| 43 | CF ₃ | 2-SCH ₃ | B | 51.5-53.5 | 10.2 | 4+ | 4+ |
| 44 | CF ₃ | 3-SCH ₃ | B | 36-37.5 | 12.1 | 4+ | 4+ |
| 45 | CF ₃ | 4-SCH ₃ | B | 58-60 | 8.9 | 4+ | 3+ |
| 46 | CF ₃ | 2-SOCH ₃ | B ^f | 115.5-117.5 | 61.8 | 4+ | 2+ |
| 47 | CF ₃ | 3-SOCH ₃ | B ^f | 115-116 | 56.4 | 4+ | <i>a</i> |
| 48 | CF ₃ | 4-SOCH ₃ | B ^f | 142-143 | 94.0 | 4+ | 1+ |
| 49 | CF ₃ | 2-SO ₂ CH ₃ | B ^g | 91-91.5 | 31.4 | ± | 1+ |
| 50 | CF ₃ | 3-SO ₂ CH ₃ | B ^g | 99-100 | 87.0 | 4+ | 4+ |
| 51 | CF ₃ | 4-SO ₂ CH ₃ | B ^g | 166-166.5 | 86.1 | 4+ | 3+ |
| 52 | C ₂ F ₅ | 4-SCH ₃ | A | 114 (0.05) | 14.1 | 4+ | ± |
| 53 | C ₂ F ₅ | 4-SOCH ₃ | A ^h | 162-163.5 | 7.2 | 1+ | ± |
| 54 | C ₂ F ₅ | 4-SO ₂ CH ₃ | A ^g | 122-123 | 7.9 | 1+ | 1+ |
| 55 | C ₄ F ₉ | H | A | 63-65 | 4.0 | ± | ± |
| 56 | C ₄ F ₉ | 4-Cl | C | 76-78 | 2.4 | <i>a</i> | 3+ |
| 57 | C ₄ F ₉ | 3-CH ₃ | A | <i>i</i> | 26.1 | ± | 1+ |
| 58 | C ₄ F ₉ | 4-SCH ₃ | A | 89-90.5 | 41.2 | <i>b</i> | <i>b</i> |
| 59 | C ₈ F ₁₇ | 4-Cl | C | 113.5-115.5 | 3.8 | ± | ± |

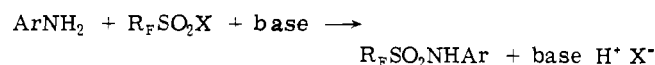
Table I (Continued)

| No. | R _F | X | Procedure | Mp/bp (mm), °C | Yield, % | Av preemergence herbicidal act. | |
|-----|---------------------------------|---------------------|----------------|-------------------|-------------|------------------------------------|-------------|
| | | | | | | Grasses | Broadleaves |
| 60 | C ₈ F ₁₇ | 4-CH ₃ | C | 93-95 | 5.3 | ± | ± |
| 61 | CF ₂ H | H | A | 55.5-57 | 41.6 | ± | 1+ |
| 62 | CF ₂ H | 3-Cl | A | 81-84 | 22.8 | b | b |
| 63 | CF ₂ H | 4-Cl | A | 89.5-91 | 20.1 | 1+ | 4+ |
| 64 | CF ₂ H | 3-Br | A | 84.5-86 | 43.7 | ± | 2+ |
| 65 | CF ₂ H | 2-CH ₃ | A | 56-59 | 8.1 | b | b |
| 66 | CF ₂ H | 2-CF ₃ | A | 90-100 (0.7) | 26.5 | b | b |
| 67 | CF ₂ H | 3-CF ₃ | A | 34.5-36 | 22.1 | ± | 3+ |
| 68 | CF ₂ H | 4-OCH ₃ | A | 48-50 | 7.9 | b | b |
| 69 | CF ₂ H | 4-SCH ₃ | A | 68.5-69.5 | 54.1 | 4+ | 1+ |
| 70 | CF ₂ H | 4-SOCH ₃ | A ^h | 115.5-118 | 44.4 | 4+ | 1+ |
| 71 | CH ₂ F | 4-Cl | A | 86.5-88 | 88.0 | ± | 1+ |
| 72 | CH ₂ CF ₃ | H | A | 77.5-80 | 78.0 | ± | ± |
| 73 | CH ₂ CF ₃ | 4-SCH ₃ | A | 107.5-108 | 38.7 | 1+ | 1+ |
| 74 | CH ₂ CF ₃ | 4-SOCH ₃ | A ^h | 149.5-150.5 | 38.0 | 1+ | ± |

^a Inactive at 10 lb/acre. ^b Inactive at 5 lb/acre. ^c Hydrogenation of nitro derivative with Pd/C in ethanol. ^d Hydrogenation of nitro derivative with Pd/C in acetic anhydride and acetic acid. ^e Hydrolysis of methoxy derivative with 57% HI in acetic acid. ^f Oxidation of sulfide with H₂O₂ in acetone. ^g Oxidation of sulfide with H₂O₂ in acetic acid. ^h Oxidation of sulfide with NaIO₄ in water. ⁱ Microdistillation.

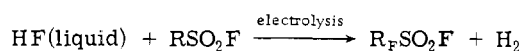
tion are listed in Tables I-IV. Satisfactory analytical ($\pm 0.4\%$ for C, H, N) and spectral data were obtained for all new compounds tabulated. The following general reaction schemes were used to prepare these sulfonamides where Ar is used to represent an aromatic or heterocyclic ring, while R_F signifies a perfluoro or partially fluorinated alkane group. Details of representative reactions are presented in the Experimental Section.

Procedure A. Fluorinated Alkanesulfonyl Halide as Reactant Where X Is F or Cl. The base in this reaction

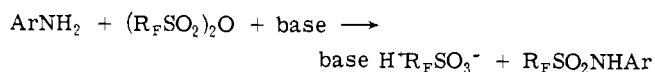


may be organic or inorganic but the former was generally utilized. A relatively volatile tertiary amine such as triethylamine was preferred due to its unreactivity and ease of removal. An excess of the arylamine reactant was often used as the acid receptor. When a volatile perfluoroalkanesulfonyl halide was utilized, a pressure reactor was generally necessary for successful reactions.

This reaction sequence is the most versatile of the available synthetic techniques due to the availability of the perfluoroalkanesulfonyl halides. Perfluoroalkanesulfonyl fluorides are readily prepared by means of the electrochemical fluorination of the corresponding alkanesulfonyl fluorides as described in detail by Brice and Trott (1956).



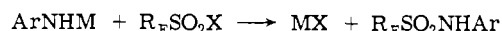
Procedure B. Fluorinated Alkanesulfonic Acid Anhydride as Reactant. Procedure B was preferred when the



arylamine was weakly basic since the perfluoroalkanesulfonic anhydrides are exceedingly reactive. The higher boiling points of the anhydrides also allow most reactions to proceed at atmospheric pressure. Preparation of perfluoroalkanesulfonic acid anhydrides has also been described (Brice and Trott, 1956).

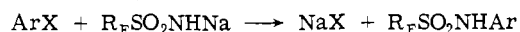
Procedure C. Fluorinated Alkanesulfonyl Halide as

Reactant with Preformed Aromatic Amine Salt Where M Is Na or K and X Is F, Cl, or CF₃SO₂O. This reaction was



generally utilized whenever the arylamine was especially weakly basic or rendered unreactive due to steric effects.

Procedure D. Fluorinated Alkanesulfonamide as Reactant Where X Is Cl, Br, or I. Procedure D was generally limited to aromatic halides which are suitably activated, e.g., 2,6-dinitrochlorobenzenes.



Herbicidal Testing. Screening results are included in Tables I-IV. Weed species, planted in four rows of replicated 6-in. plastic pots, were: giant foxtail, *Setaria faberii*; barnyardgrass, *Echinochloa crus-galli*; crabgrass, *Digitaria ischaemum*; quackgrass, *Agropyron repens*; pigweed, *Amaranthus retroflexus*; purslane, *Portulaca oleracea*; wild mustard, *Brassica kaber*; and annual morning glory, *Ipomoea purpurea*. Aliquots of test chemical in aqueous acetone were spray applied to the weed species before emergence to give the proper treatment levels.

Soil was a sandy loam (68% sand, 20% silt, 9% clay, 2-2.8% organic matter) and tests were run in an artificially illuminated greenhouse. Data were taken 2 weeks after treatment and rated as follows: \pm , inactive at 20 lb/acre; 1+, $\geq 50\%$ kill at 20 lb/acre; 2+, $\geq 50\%$ kill at 10 lb/acre; 3+, $\geq 50\%$ kill at 5 lb/acre; 4+, $\geq 50\%$ kill at 2.5 lb/acre. In some cases, initial testing was at the 10- and 5-lb levels and if inactive, no further testing was undertaken. These cases are shown in Tables I-IV as footnotes *a* and *b* respectively.

DISCUSSION

Preemergence Herbicidal Activity. When applied as preemergence treatments, most of the fluorinated *N*-phenylalkanesulfonamides were more active on grassy weeds than on broadleaved weeds. Three groups of 1,1,1-trifluoro-*N*-phenylalkanesulfonamides from Tables I-IV exhibited outstanding preemergence herbicidal activity. These were monohalogenated (1-12, 16-18), 2,4-dihalogenated (81, 83, 87, and 98) and various sulfur (43-51) aryl-

Table II. Aryl-Disubstituted Fluorinated *N*-Phenylalkanesulfonamides (X,Y-C₆H₃NHSO₂R_F)

| No. | R _F | X | Y | Procedure | Mp/bp (mm), °C | Yield, % | Av preemergence herbicidal act. | |
|-----|-----------------|-----------------------------------|-----------------------------------|-------------------|-------------------|-------------|------------------------------------|-------------|
| | | | | | | | Grasses | Broadleaves |
| 75 | CF ₃ | 2-Cl | 3-Cl | B | 83-87 | 34.6 | <i>a</i> | 4+ |
| 76 | CF ₃ | 2-Cl | 3-CH ₃ | B | 84-86 | 12.5 | 1+ | 1+ |
| 77 | CF ₃ | 2-CH ₃ | 3-CH ₃ | B | 121-122 | 21.7 | 2+ | <i>a</i> |
| 78 | CF ₃ | 2-CH ₃ | 3-NO ₂ | B | 75-77 | 5.1 | <i>b</i> | <i>b</i> |
| 79 | CF ₃ | 2-OCH ₃ | 3-Cl | B | 100 (1.7) | 69.7 | <i>b</i> | <i>b</i> |
| 80 | CF ₃ | 2-SCH ₃ | 3-Cl | B | 30.5-31.5 | 3.5 | 3+ | <i>b</i> |
| 81 | CF ₃ | 2-F | 4-F | B | 64.0-65.5 | 51.1 | 4+ | 4+ |
| 82 | CF ₃ | 2-F | 4-CH ₃ | B | 53-56 | 17.5 | <i>b</i> | <i>b</i> |
| 83 | CF ₃ | 2-Cl | 4-Cl | B | 89.5-90.5 | 3.4 | 4+ | 4+ |
| 84 | CF ₃ | 2-Cl | 4-CH ₃ | B | 83.5-85 | 27.2 | 2+ | <i>a</i> |
| 85 | CF ₃ | 2-Cl | 4-NH ₂ | B ^{c, d} | 174 dec | 55.6 | <i>a</i> | <i>a</i> |
| 86 | CF ₃ | 2-Cl | 4-NO ₂ | B | 87-88 | 14.5 | ± | 1+ |
| 87 | CF ₃ | 2-Br | 4-Br | B | 106-107 | 13.1 | 4+ | 4+ |
| 88 | CF ₃ | 2-Br | 4-CH ₃ | B | 76-78.5 | 47.4 | 3+ | <i>b</i> |
| 89 | CF ₃ | 2-Br | 4-NH ₂ | A ^c | 130-132 | 61.3 | <i>b</i> | <i>b</i> |
| 90 | CF ₃ | 2-Br | 4-NO ₂ | A | 75-76 | 2.1 | <i>b</i> | <i>b</i> |
| 91 | CF ₃ | 2-CH ₃ | 4-F | B | 42.5-44 | 13.6 | 3+ | 4+ |
| 92 | CF ₃ | 2-CH ₃ | 4-Cl | B | 89-90 | 21.9 | 1+ | 4+ |
| 93 | CF ₃ | 2-CH ₃ | 4-CH ₃ | B | 91-92 | 32.6 | 2+ | 3+ |
| 94 | CF ₃ | 2-CH ₃ | 4-NH ₂ | A ^e | 125-126 | 6.0 | <i>a</i> | <i>a</i> |
| 95 | CF ₃ | 2-CH ₃ | 4-NO ₂ | A | 104.5-106 | 3.5 | 4+ | 4+ |
| 96 | CF ₃ | 2-CF ₃ | 4-F | B | 43-45(0.2) | 15.7 | 4+ | 3+ |
| 97 | CF ₃ | 2-CF ₃ | 4-Cl | B | 66.5-67.5 | 15.6 | 3+ | 2+ |
| 98 | CF ₃ | 2-CF ₃ | 4-Br | A | 80-82 | 16.8 | 4+ | 4+ |
| 99 | CF ₃ | 2-CF ₃ | 4-NH ₂ | A ^e | 122.5-124 | 23.1 | <i>b</i> | <i>b</i> |
| 100 | CF ₃ | 2-CF ₃ | 4-NO ₂ | A | 65-66.5 | 9.5 | 3+ | 4+ |
| 101 | CF ₃ | 2-NH ₂ | 4-CH ₃ | A ^e | 115-116 | 78.8 | <i>b</i> | <i>b</i> |
| 102 | CF ₃ | 2-NO ₂ | 4-CH ₃ | A | 53-55 | 84.2 | <i>b</i> | <i>b</i> |
| 103 | CF ₃ | 2-NO ₂ | 4-CF ₃ | A | 105 (3.5) | 48.8 | 2+ | 2+ |
| 104 | CF ₃ | 2-NO ₂ | 4-NO ₂ | A | 107-108 | 59.5 | ± | 2+ |
| 105 | CF ₃ | 2-OCH ₃ | 4-NH ₂ | A ^e | 123-124 | 23.3 | <i>b</i> | <i>b</i> |
| 106 | CF ₃ | 2-OCH ₃ | 4-OCH ₃ | B | 60.8-61.5 | 17.5 | 1+ | 1+ |
| 107 | CF ₃ | 2-SCH ₃ | 4-SCH ₃ | B | 87-88 | 25.8 | 2+ | 2+ |
| 108 | CF ₃ | 2-SO ₂ CH ₃ | 4-SO ₂ CH ₃ | B ^f | 190-191 | 53.8 | ± | ± |
| 109 | CF ₃ | 2-F | 5-F | B | 79-80 | 14.3 | 3+ | 4+ |
| 110 | CF ₃ | 2-F | 5-CH ₃ | B | 93-95.5 | 49.6 | <i>b</i> | <i>b</i> |
| 111 | CF ₃ | 2-F | 5-CF ₃ | B | 52-54 | 2.8 | <i>b</i> | <i>b</i> |
| 112 | CF ₃ | 2-F | 5-NHCOCH ₃ | A | 168.5-169.5 | 21.7 | <i>b</i> | <i>b</i> |
| 113 | CF ₃ | 2-Cl | 5-Cl | B | 71-73 | 29.2 | 1+ | 4+ |
| 114 | CF ₃ | 2-Cl | 5-CH ₃ | B | 86.5-88 | 14.8 | <i>a</i> | 3+ |
| 115 | CF ₃ | 2-Cl | 5-CF ₃ | C | 51-54 | 8.5 | 1+ | 1+ |
| 116 | CF ₃ | 2-Cl | 5-NH ₂ | A ^c | 88.5-90.5 | 54.0 | 2+ | 2+ |
| 117 | CF ₃ | 2-Cl | 5-NHCOCH ₃ | A ^{c, g} | 186-188 | 71.3 | 2+ | <i>a</i> |
| 118 | CF ₃ | 2-Cl | 5-NO ₂ | A | 97-98.5 | 7.1 | 3+ | 2+ |
| 119 | CF ₃ | 2-Br | 5-Br | B | 73.5-76 | 2.6 | <i>b</i> | 3+ |
| 120 | CF ₃ | 2-Br | 5-CF ₃ | B | 64-66.5 | 6.3 | <i>b</i> | <i>b</i> |
| 121 | CF ₃ | 2-CH ₃ | 5-F | B | 73.5-75.5 | 29.5 | <i>b</i> | <i>b</i> |
| 122 | CF ₃ | 2-CH ₃ | 5-CH ₃ | B | 88-89 | 41.2 | 2+ | 2+ |
| 123 | CF ₃ | 2-CH ₃ | 5-NO ₂ | A | 102.5-104 | 47.1 | 1+ | 1+ |
| 124 | CF ₃ | 2-NO ₂ | 5-Cl | A | 64-66 | 6.7 | <i>b</i> | <i>b</i> |
| 125 | CF ₃ | 2-OCH ₃ | 5-Cl | B | 85.5-88 | 35.9 | 3+ | <i>b</i> |
| 126 | CF ₃ | 2-OCH ₃ | 5-CH ₃ | B | 98-99.5 | 52.8 | <i>b</i> | <i>b</i> |
| 127 | CF ₃ | 2-OCH ₃ | 5-NH ₂ | A ^e | 168-170 | 6.6 | 3+ | <i>b</i> |
| 128 | CF ₃ | 2-OCH ₃ | 5-NHCOCH ₃ | A ^{e, g} | 198.5-199 | 4.8 | <i>b</i> | <i>b</i> |
| 129 | CF ₃ | 2-OCH ₃ | 5-NO ₂ | A | 109-110.5 | 8.8 | <i>a</i> | <i>a</i> |
| 130 | CF ₃ | 2-OCH ₃ | 5-OCH ₃ | B | 63-65 | 21.0 | ± | 1+ |
| 131 | CF ₃ | 3-F | 4-CH ₃ | B | 56-58 | 29.7 | 2+ | 2+ |
| 132 | CF ₃ | 3-Cl | 4-F | A | 70.5-72 | 67.9 | 3+ | 4+ |

Table II (Continued)

| No. | R _F | X | Y | Procedure | Mp/bp (mm), °C | Yield, % | Av preemergence herbicidal act. | |
|-----|-----------------------------------|-----------------------|------------------------------------|-------------------|-------------------|-------------|------------------------------------|-------------|
| | | | | | | | Grasses | Broadleaves |
| 133 | CF ₃ | 3-Cl | 4-Cl | B | 135-145 (1.0) | 58.2 | 3+ | 4+ |
| 134 | CF ₃ | 3-Cl | 4-CH ₃ | B | 57-60 | 26.1 | b | b |
| 135 | CF ₃ | 3-Cl | 4-N(CH ₃) ₂ | B | 85-86 | 28.1 | 3+ | 3+ |
| 136 | CF ₃ | 3-CH ₃ | 4-F | B | 85 (0.15) | 66.6 | 3+ | 4+ |
| 137 | CF ₃ | 3-CH ₃ | 4-Cl | B | 63-64 | 61.8 | b | b |
| 138 | CF ₃ | 3-CH ₃ | 4-CH ₃ | B | 61-62 | 18.0 | b | b |
| 139 | CF ₃ | 3-CF ₃ | 4-F | B | 114 (0.6) | 54.7 | 3+ | 4+ |
| 140 | CF ₃ | 3-CF ₃ | 4-Cl | B | 89-90.5 | 37.5 | 1+ | 3+ |
| 141 | CF ₃ | 3-CF ₃ | 4-Br | B | 64.5-66.5 | 17.3 | b | b |
| 142 | CF ₃ | 3-NH ₂ | 4-Cl | A ^c | 84.5-86 | 50.0 | b | b |
| 143 | CF ₃ | 3-NH ₂ | 4-CH ₃ | A ^c | 73-74 | 76.0 | 2+ | a |
| 144 | CF ₃ | 3-NHCOCH ₃ | 4-Cl | A ^{c, f} | 186.5-188 | 50.9 | 4+ | a |
| 145 | CF ₃ | 3-NHCOCH ₃ | 4-CH ₃ | A ^{c, f} | 140.5-142 | 37.1 | 4+ | 2+ |
| 146 | CF ₃ | 3-NHCOCH ₃ | 4-CF ₃ | A ^{c, f} | 193-194.5 | 57.1 | b | b |
| 147 | CF ₃ | 3-NO ₂ | 4-F | B | 70.5-73.5 | 22.9 | ± | 3+ |
| 148 | CF ₃ | 3-NO ₂ | 4-Cl | A | 71.5-72.5 | 66.4 | 2+ | 4+ |
| 149 | CF ₃ | 3-NO ₂ | 4-CH ₃ | A | 75-76.5 | 5.1 | a | a |
| 150 | CF ₃ | 3-Cl | 5-Cl | B | 76.5-79 | 10.2 | 2+ | 3+ |
| 151 | CF ₃ | 3-CH ₃ | 5-CH ₃ | B | 76-77 | 17.4 | b | b |
| 152 | CF ₃ | 3-CF ₃ | 5-CF ₃ | B | 89-91 (0.5) | 25.4 | ± | 1+ |
| 153 | CF ₃ | 2-Cl | 6-Cl | B | 141-142.5 | 9.1 | ± | 3+ |
| 154 | CF ₃ | 2-CH ₃ | 6-NO ₂ | A | 133-135 | 1.4 | b | b |
| 155 | C ₂ F ₅ | 2-F | 4-F | A | 33-35 | 26.2 | 4+ | 4+ |
| 156 | CF(CF ₃) ₂ | 2-F | 4-F | A | 67.5-68.5 | 2.6 | 4+ | 2+ |
| 157 | C ₄ F ₉ | 2-F | 4-F | A | 39.5-40.5 | 6.3 | ± | 4+ |
| 158 | CF ₂ H | 2-F | 4-F | A | 83.5-84.5 | 52.9 | 2+ | 4+ |
| 159 | CF ₂ H | 2-Cl | 5-Cl | A | 93.5-94.5 | 3.9 | b | b |
| 160 | CF ₂ H | 2-CH ₃ | 5-CH ₃ | A | 104.5-105.5 | 33.8 | b | b |
| 161 | CFH ₂ | 2-F | 4-F | A | 80.0-80.5 | 73.3 | ± | 1+ |



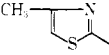

^a Inactive at 10 lb/acre. ^b Inactive at 5 lb/acre. ^c Hydrogenation of nitro derivative with Raney nickel in ethanol. ^d Isolated as oxalic acid salt. ^e Hydrogenation of nitro derivative with Pd/C in ethanol. ^f Oxidation of sulfide with H₂O₂ in acetic acid. ^g Acetyl chloride with amino derivative in benzene and triethylamine.

 Table III. Aryl Tri-, Tetra-, and Penta-Substituted Fluorinated N-Phenylmethanesulfonamides (X_nC₆H_{5-n}NHSO₂R_F)

| No. | R _F | Substituent position | | | | | Pro- cedure | Mp/bp (mm), °C | Yield, % | Av preemergence herbicidal act. | |
|-----|-------------------|----------------------|----|------------------|-----------------|-----------------|----------------|-------------------|-------------|------------------------------------|------------------|
| | | 2 | 3 | 4 | 5 | 6 | | | | Grasses | Broad- leaves |
| 162 | CF ₃ | F | | F | F | | A | 57.5-58.5 | 13.9 | b | 3+ |
| 163 | CF ₃ | Cl | | Cl | Cl | | A | 106-107 | 9.0 | 2+ | 4+ |
| 164 | CF ₃ | OCH ₃ | | OCH ₃ | Cl | | B | 109.5-110 | 3.1 | ± | 4+ |
| 165 | CF ₃ | Cl | | NH ₂ | Cl | | B ^c | 153-154 | 35.3 | 1+ | 1+ |
| 166 | CF ₃ | CH ₃ | | NO ₂ | CH ₃ | | A | 101-102 | 3.2 | b | b |
| 167 | CF ₃ | Cl | | Cl | | F | B ^d | 63.5-64.5 | 3.6 | 3+ | 3+ |
| 168 | CF ₃ | Cl | | Cl | | Cl | C | 106-107.5 | 7.3 | 1+ | 3+ |
| 169 | CF ₃ | Cl | | NO ₂ | | Cl | B | 157-159.5 | 5.7 | ± | ± |
| 170 | CF ₃ | NO ₂ | | CF ₃ | | NO ₂ | D | 106-107 | 26.4 | a | a |
| 171 | CF ₃ | | Cl | Cl | Cl | | B | 110.5-111.5 | 10.2 | 1+ | 1+ |
| 172 | CF ₃ | | Cl | NH ₂ | Cl | | B | 120-121.5 | 17.1 | 1+ | ± |
| 173 | CF ₃ | F | F | F | F | | A | 64-67 | 28.0 | b | 3+ |
| 174 | CF ₃ | F | F | F | F | F | B | 93-95 | 15.7 | 3+ | 2+ |
| 175 | CF ₃ | F | F | F | F | F | A | 68-69 | 24.4 | ± | 1+ |
| 176 | CF ₂ H | CH ₃ | | Br | CH ₃ | | A ^e | 118.5-119.5 | 82.8 | b | b |

^a Inactive at 10 lb/acre. ^b Inactive at 5 lb/acre. ^c Hydrogenation of nitro derivative with Pd/C in ethanol. ^d Cl₂ in acetic acid-AlCl₃ with 2-substituted sulfonamide. ^e Br₂ in ethanol-water on 2,5-disubstituted sulfonamide.

Table IV. Fluorinated *N*-Heterocyclic Methanesulfonamides (R-NHSO₂R_F)

| No. | R _F | R | Procedure | Mp, °C | Yield, % | Av preemergence herbicidal act. | |
|-----|-------------------|---|-----------|-------------|-------------|------------------------------------|------------------|
| | | | | | | Grasses | Broad- leaves |
| 177 | CF ₃ |  | A | 202.5–203.5 | 83.5 | 4+ | 4+ |
| 178 | CF ₃ |  | B | 253.5–255.5 | 9.8 | ± | ± |
| 179 | CH ₂ F |  | A | 171–174 | 5.1 | <i>a</i> | <i>a</i> |
| 180 | CF ₃ |  | B | 222–223 | 8.8 | 4+ | 2+ |

^a Inactive at 5 lb/acre.Table V. Preemergence Herbicidal Effect of Aryl-Substituted 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides on Cotton, Soybeans, and Corn

| No. | Substituent | Cotton | Soybeans | Corn |
|-----|-----------------------------------|----------|----------|------|
| 3 | 4-F | 5+ | <i>a</i> | 3+ |
| 6 | 4-Cl | 2+ | 3+ | 3+ |
| 12 | 4-I | <i>a</i> | <i>a</i> | 3+ |
| 43 | 2-SCH ₃ | <i>a</i> | <i>a</i> | 4+ |
| 44 | 3-SCH ₃ | 3+ | 5+ | 5+ |
| 45 | 4-SCH ₃ | 4+ | <i>a</i> | 3+ |
| 47 | 3-SOCH ₃ | <i>a</i> | 4+ | 4+ |
| 48 | 4-SOCH ₃ | <i>a</i> | <i>a</i> | 3+ |
| 50 | 3-SO ₂ CH ₃ | 4+ | 4+ | 4+ |
| 51 | 4-SO ₂ CH ₃ | 2+ | <i>a</i> | 3+ |
| 81 | 2,4-diF | 3+ | 2+ | 4+ |
| 83 | 2,4-diCl | 3+ | <i>a</i> | 4+ |
| 87 | 2,4-diBr | <i>a</i> | 2+ | 2+ |

^a Inactive at 10 lb/acre.

substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. Some of the most active 1,1,1-trifluoro-*N*-phenylmethanesulfonamides were tested in greater detail for herbicidal activity and for crop selectivity with the results shown in Table V. The previous rating system was used except that 5+ refers to ≥50% kill at 1.25 lb/acre.

In general, crop tolerance was related to weed control, *i.e.*, broadleaf crops were tolerant to 1,1,1-trifluoro-*N*-phenylmethanesulfonamides which were weak on broad-leaved weeds and grassy crops were tolerant to those compounds which did not control grassy weeds. However, distinct and important crop selectivities were apparent for certain compounds such as 2-CH₃S (43), 4-CH₃SO₂ (51), 2,4-diF (81), 2,4-diCl (83), and 2,4-diBr (87) aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. On the basis of broad spectrum herbicidal activity and crop tolerances, *N*-(2,4-dichlorophenyl)-1,1,1-trifluoromethanesulfonamide (83) and *N*-(2,4-difluorophenyl)-1,1,1-trifluoromethanesulfonamide (81) (coded MBR 3356 and MBR 3957, respectively) were extensively field tested as pre-emergence herbicides. Excellent results were obtained under conditions of heavy soils and moderate rainfall. Large seeded legumes such as soybeans and peanuts were the most tolerant crops evaluated. However, crop injury and low herbicidal activity sometimes occurred under conditions of light soils and/or high amounts of rainfall. It was

concluded that under these conditions, MBR 3356 and MBR 3957 were subject to vertical movement in the soil by water away from the soil surface (where weed seed germination occurred) to lower levels (where crop seed germination occurred).

Postemergence Herbicidal Activity. When applied topically to foliage of target weed species, most of the aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides were more active on broadleaved weeds than on grassy weeds. A solution of 500–2000 ppm of the sulfonamide in water was applied to run off. Few compounds of this series were sufficiently active in the 500-ppm level to justify further study as postemergence herbicides. However, the effect of various surfactants on postemergence activity of many of these compounds has not been fully explored and may justify further investigation.

Plant Growth Regulatory Effects. Numerous and interesting growth regulating effects were observed with the fluorinated *N*-phenylalkanesulfonamides. Treatments of various plant species were carried out as topical, post-emergence applications, usually to runoff with concentrations ranging from 500 to 2000 ppm. The following effects on pinto beans were noted for many of the compounds in the series: dwarfing, dark coloration, thickening of primary leaves, proliferation of subsequent terminal growth, and dark veination of new leaflets which were generally reduced in size. Sulfonamides 31 and 47 exhibited excellent control of terminal bud growth in tobacco at 500 ppm after the plant had been decapitated to induce axillary bud formation. Usually, however, a basal bud became dominant and grew rapidly to a point that it equalled the growth of the untreated check.

Preemergence applications of many of these compounds resulted in several interesting growth regulation effects. Monocots in particular were observed to emerge and stop growth with approximately 2–4 mm of growth protruding above the soil line. Dark coloration and twisting of the coleoptile were typical characteristics observed with rates of application ranging from 20 lb/acre to 1.25 lb/acre. While this effect sometimes gave the impression of useful growth regulating activity, the coleoptile usually became necrotic leading to death of the plant.

Acute Toxicity. Acute mammalian toxicity values were obtained by standard techniques. Principal toxic effects were dyspnea, ptosis, depressed motor activity, ataxia, prostration, and death in an extended position with immediate rigor mortis. Table VI summarizes acute toxicity for some of the more herbicidally significant 1,1,1-trifluoro-*N*-phenylmethanesulfonamides.

Structure-Activity Relationships. Variation in the (Fluoroalkanesulfonyl)amino Moiety. Acidity, lipophili-

Table VI. Acute Mammalian Toxicity for Aryl-Substituted 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

| No. | Species | Sex | Route | LD ₅₀ , mg/kg |
|-----|---------|-------|--------|--------------------------|
| 81 | Mouse | M | P.O. | 87 ± 5 |
| 83 | Mouse | M | P.O. | 89 ± 7 |
| 6 | Mouse | M | P.O. | 59 ± 8 |
| 81 | Rabbit | M + F | Dermal | ~50 |
| 83 | Rabbit | M + F | Dermal | 50-100 |

city, and steric properties of the fluorinated *N*-phenylalkanesulfonamides can be altered by changing either the aromatic substituent X or the fluorinated alkane group R_F (Trepka *et al.*, 1974) (X_nC₆H_{5-n}NHSO₂R_F). These properties are highly dependent upon fluorine content. The pK_a of three series of fluorinated *N*-phenylmethanesulfonamides was found to be linearly related to the number of fluorine atoms in the methane group. Each additional fluorine atom increased the acidity by 1.46 pK_a units with a pK_a of 4.45 (in water at 25°) for the unsubstituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamide. Lipophilicity as measured by the partition coefficient *P* also increased with an increase in the number of fluorine atoms in the methane group, but a second-order equation was needed to relate log *P* to the number of fluorine atoms. *N*-Phenylmethanesulfonamide and 1,1,1-trifluoro-*N*-phenylmethanesulfonamide have log *P* values of 0.95 and 3.05, respectively.

Herbicidal activity as a function of fluorine content in the (alkanesulfonyl)amino group is illustrated in Table VII. The 1,1,1-trifluoro-*N*-phenylmethanesulfonamides 6, 81, and 183 exhibited the greatest herbicidal activity and also possessed higher lipophilicity and acidity than the partially fluorinated members of their respective series (Trepka *et al.*, 1974).

Variation in Aromatic Substitution. With variation of acidity and lipophilicity by change of substituent on the aromatic ring, the effects upon herbicidal activity are much more subtle and no correlations are immediately evident. However, a computer correlation with 15 1,1,1-trifluoro-*N*-phenylmethanesulfonamides (Yapel, 1972) brought forth some distinct trends. Yapel's study utilized the well-known Hansch treatment (Fujita *et al.*, 1964; Hansch and Fujita, 1964; Hansch, 1966, 1967a,b, 1968) which correlates biological activity with a partitioning parameter π and the Hammett substituent σ . The Hansch equation is usually given as

$$\log (1/C) = A\pi^2 + B\pi + \rho\sigma + D \quad (1)$$

where *C* is a measure of herbicidal activity (usually LD₅₀ or LD₉₀) and $\pi = (\log P_X - P_H)$ where *P*_H is the partition coefficient for the parent compound and *P*_X that of a derivative. Parameters *A*, *B*, ρ , and *D* are calculated by stepwise regression analysis. Two grasses (foxtail and cheatgrass) and a broadleaf weed (wild mustard) were utilized in the cited study.

The 3-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides required a different form of eq 1 than did the 4-substituted members depending upon the specific weed type. In addition the absence or presence of a surfactant had a significant effect upon herbicidal activity. This surfactant effect was dependent upon the sulfonamide and weed type. Presumably, the surfactant effect was a result of enhanced penetration into the plant in some cases. In spite of these complications, several general conclusions were reached (Yapel, 1972). (1) Herbicidal activity was more dependent upon partitioning effects (π) for the 4-substituted than for the 3-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides, especially in the absence of

Table VII. Herbicidal Activity as a Function of the Degree of Fluorination

| No. | Structure | Av preemergence herbicidal act. | |
|-----|--|---------------------------------|--------------|
| | | Grasses | Broad-leaves |
| 181 | C ₆ H ₅ NHSO ₂ CH ₃ ^a | ± | ± |
| 182 | C ₆ H ₅ NHSO ₂ CH ₂ F ^a | ± | ± |
| 61 | C ₆ H ₅ NHSO ₂ CHF ₂ | ± | 1+ |
| 183 | C ₆ H ₅ NHSO ₂ CF ₃ ^b | 2+ | 4+ |
| 55 | C ₆ H ₅ NHSO ₂ C ₁ F ₃ | ± | ± |
| 184 | 4-ClC ₆ H ₄ NHSO ₂ CH ₃ ^a | ± | ± |
| 71 | 4-ClC ₆ H ₄ NHSO ₂ CH ₂ F | = | 1+ |
| 63 | 4-ClC ₆ H ₄ NHSO ₂ CHF ₂ | 1+ | 4+ |
| 6 | 4-ClC ₆ H ₄ NHSO ₂ CF ₃ | 4+ | 4- |
| 56 | 4-ClC ₆ H ₄ NHSO ₂ C ₁ F ₃ | c | 3+ |
| 59 | 4-ClC ₆ H ₄ NHSO ₂ C ₈ F ₁₇ | ± | ± |
| 161 | 2,4-diFC ₆ H ₃ NHSO ₂ CH ₂ F | ± | 1+ |
| 158 | 2,4-diFC ₆ H ₃ NHSO ₂ CHF ₂ | 2+ | 4+ |
| 81 | 2,4-diFC ₆ H ₃ NHSO ₂ CF ₃ | 4+ | 4+ |
| 157 | 2,4-diFC ₆ H ₃ NHSO ₂ C ₁ F ₃ | ± | 4+ |

^a Trepka *et al.*, 1974. ^b Brice and Trott, 1956. ^c Inactive at 10 lb/acre.

surfactant. (2) Large, positive Hammett σ values of the aromatic substituent, with resultant greater acidity of the sulfonamide, usually resulted in increased herbicidal activity with other factors being constant.

EXPERIMENTAL SECTION

General. Fluoromethanesulfonyl chloride and 1,1-difluoromethanesulfonyl chloride were prepared according to Farrar. The 2,2,2-trifluoroethanesulfonyl fluoride was prepared by chlorination of the corresponding mercaptan in water at 0°. Perfluoroalkanesulfonyl fluorides and anhydrides were obtained from the 3M Co., Chemical Division. All melting points are uncorrected.

Procedure A. Fluoroalkanesulfonyl Halide as Reactant. 1,1,1-Trifluoro-*N*-(4-methyl-2-nitrophenyl)methanesulfonamide (102). A mixture of trifluoromethanesulfonyl fluoride (200 g, 1.32 mol), 2-nitro-4-methylaniline (201 g, 1.32 mol), and triethylamine (334 g, 3.3 mol) was heated with shaking at 100° for 48 hr in a sealed stainless steel pressure reactor. The dark brown reaction mixture was made basic with 10% aqueous NaOH and steam distilled to remove triethylamine and unreacted 2-nitro-4-methylaniline. The distillation residue was decolorized with activated charcoal and acidified with aqueous HCl, and the crystalline product filtered. The crystals were air dried and recrystallized from hexane-benzene to afford 316 g (84.2%) of 102, mp 53-55°. *Anal.* Calcd for C₈H₇F₃N₂O₄S; C, 33.8; H, 2.5; N, 9.9. Found: C, 33.9; H, 2.5; N, 9.8.

1,1-Difluoro-*N*-(2,4-difluorophenyl)methanesulfonamide (158). To a stirred solution of 2,4-difluoroaniline (20 g, 0.155 mol) and *N,N*-dimethylaniline (18.8 g, 0.155 mol) in dichloromethane (75 ml) under nitrogen, difluoromethanesulfonyl chloride (23.4 g, 0.155 mol) in dichloromethane (120 ml) was added dropwise at room temperature. After refluxing for 20 hr, the dark green solution was washed twice with 100 ml of 5% aqueous HCl and then extracted twice with 150-ml portions of 5% aqueous NaOH. Basic extracts were combined, acidified with aqueous HCl, and cooled and crystals filtered. The crystalline product was sublimed under vacuum to yield 20 g (52.9%) of 158, mp 83.5-84.5°. *Anal.* Calcd for C₇H₅F₄NO₂S; C, 34.6; H, 2.1. Found: C, 34.8; H, 2.1.

1,1,1-Trifluoro-*N*-2-thiazolylmethanesulfonamide (177). A mixture of 2-aminothiazole (200 g, 2 mol), triethyl-

amine (222 g, 2.2 mol), *N,N*-dimethylformamide (800 ml), and trifluoromethanesulfonyl fluoride (304 g, 2 mol) was heated with shaking at 50° for 24 hr in a sealed stainless steel pressure reactor. The resulting dark brown mixture was poured with stirring into about 10 l. of water. The buff solid was filtered and dissolved in 10% aqueous NaOH. After the dark brown liquid was cooled and acidified with aqueous HCl the buff solid was filtered and dried to yield 387 g (83.5%) of 177, mp 202.5–203.5°. *Anal.* Calcd for C₄H₃F₃N₂O₂S₂: C, 20.7; H, 1.3. Found: C, 20.9; H, 1.5.

Procedure B. Trifluoromethanesulfonic Acid Anhydride as Reactant. *1,1,1-Trifluoro-N-(2,4-difluorophenyl)methanesulfonamide* (81). To a stirred solution of 2,4-difluoroaniline (9.67 g, 0.075 mol), triethylamine (7.62 g, 0.075 mol), and chloroform (200 ml) at 0–5°, trifluoromethanesulfonic acid anhydride (21.25 g, 0.075 mol) was added dropwise over a period of 1 hr. The reaction mixture was then refluxed for 1 hr, cooled, and poured into 200 ml of water. The water layer was extracted twice with 100-ml portions of chloroform. Chloroform extracts were combined, dried, and evaporated. The residue from the chloroform extracts was redissolved in excess 10% NaOH, extracted with chloroform, filtered, and acidified with HCl. The crystals were filtered, sublimed at 65° (1 mm), and then recrystallized from hexane to yield 10.0 g (51.1%) of 81, mp 64.0–65.5°. *Anal.* Calcd for C₇H₄F₅NO₂S: C, 32.2; H, 1.5. Found: C, 32.4; H, 1.8.

N-2-Benzothiazolyl-1,1,1-trifluoromethanesulfonamide (178). To a stirred solution of 2-aminobenzothiazole (37.5 g, 0.25 mol), triethylamine (25.3 g, 0.25 mol) and chloroform (250 ml), trifluoromethanesulfonic acid anhydride (70.5 g, 0.25 mol) was added dropwise at room temperature. The reaction mixture was stirred with excess 10% NaOH and the basic layer washed with dichloromethane and acidified with HCl. The yellow crystals were filtered and recrystallized from ethanol–water to yield 6.9 g (9.8%) of 178, mp 253.5–255.5°. *Anal.* Calcd for C₈H₅F₃N₂O₂S₂: C, 34.0; H, 1.8. Found: C, 34.3; H, 2.1.

Procedure C. *N-(2,4,6-Trichlorophenyl)-1,1,1-trifluoromethanesulfonamide* (168). Sodium naphthalene was prepared by treatment of naphthalene (12.8 g, 0.1 mol) in dry tetrahydrofuran (200 ml) with sodium (2.3 g, 0.1 mol) under nitrogen. To this stirred solution under nitrogen, 2,4,6-trichloroaniline (19.6 g, 0.1 mol) was added dropwise. The brown solution was transferred under nitrogen to a stainless steel autoclave and trifluoromethanesulfonyl fluoride (15.2 g, 0.1 mol) was added. After the reaction mixture was heated at 50° with shaking for 20 hr, the tetrahydrofuran was evaporated and the residue dissolved in dichloromethane and extracted with excess aqueous KOH. The basic solution was acidified with HCl to yield an oily solid which was triturated with cold petroleum ether. The resulting solid was sublimed under vacuum to yield 2.4 g (7.3%) of 168, mp 106–107.5°. *Anal.* Calcd for C₇H₃Cl₃F₃NO₂S: C, 25.6; H, 0.9; N, 4.3. Found: C, 25.5; H, 1.1; N, 4.3.

N-(4-Chlorophenyl)perfluorooctanesulfonamide (59). Sodium naphthalene (0.1 mol) was prepared as in the previous example. To the stirred solution of sodium naphthalene under nitrogen was added perfluorooctanesulfonyl fluoride (50.2 g, 0.1 mol) over a period of 1 hr with ice bath cooling to keep the temperature below 50°. The reaction mixture was stirred for 1 hr at room temperature, solvent evaporated and the gummy residue dissolved in excess 10% NaOH. The basic solution was washed with chloroform, made acidic with HCl, and a yellow oil separated. Upon trituration with diethyl ether, the oil solidified. Recrystallization from ethanol–water afforded 2.3 g (3.8%) of 59, mp 113.5–115.5°. *Anal.* Calcd for C₁₄H₅ClF₁₇NO₂S: C, 27.6; H, 0.8; F, 53.0. Found: C, 27.6; H, 1.1; F, 52.9.

Procedure D. *1,1,1-Trifluoro-N-(4-trifluoromethyl-2,6-*

dinitrophenyl)methanesulfonamide (170). The sodium salt of trifluoromethanesulfonamide was prepared by treatment of trifluoromethanesulfonamide in ethanol with sodium ethoxide at room temperature and subsequent evaporation of the solvent. A solution of 4-chloro-3,5-dinitrobenzotrifluoride (27.1 g, 0.1 mol) and the sodium salt of trifluoromethanesulfonamide (34.2 g, 0.2 mol) in 1,2-dimethoxyethane (100 ml) was refluxed under nitrogen for 92 hr. After cooling, sodium chloride was removed by filtration and the solvent evaporated. The resulting light red residue was dissolved in excess 10% NaOH, washed with chloroform, and made acidic with HCl. The crystalline product was filtered, sublimed at 100° (1 mm), and recrystallized from hexane–benzene to afford 10.1 g (26.4%) of 170, mp 106–107°. *Anal.* Calcd for C₈H₃F₆N₃O₆S: C, 25.1; H, 0.8; N, 11.0. Found: C, 25.1; H, 0.8; N, 10.6.

General Reduction Procedure. *N-(4-Amino-2-bromophenyl)-1,1,1-trifluoromethanesulfonamide* (89). Raney nickel (2 g) was added under nitrogen to a solution of *N*-(2-bromo-4-nitrophenyl)-1,1,1-trifluoromethanesulfonamide (90) (45.0 g, 0.13 mol) in absolute ethanol (400 ml) and the mixture shaken on a Parr hydrogenator until hydrogen uptake ceased. Catalyst was removed by filtration, solvent was evaporated, and the resulting crystals were recrystallized from ethanol–water to afford 25.2 g (61.3%) of pure 89, mp 130–132°. *Anal.* Calcd for C₇H₆BrF₃N₂O₂S: C, 26.3; H, 1.9; N, 8.8. Found: C, 26.2; H, 1.9; N, 8.8.

General Oxidation Procedure. *1,1,1-Trifluoro-N-(4-methylsulfonylphenyl)methanesulfonamide* (51). Hydrogen peroxide (0.15 mol, 30% in water) was added dropwise to a solution of 1,1,1-trifluoro-*N*-(4-methylthiophenyl)methanesulfonamide (45) (14.0 g, 0.52 mol) in glacial acetic acid (20 ml) at –5°. The reaction mixture was then refluxed for 4 hr and poured into ice water and crystals were removed by filtration. One recrystallization from methanol gave 13.5 g (86.1%) of 51, mp 166.0–166.5°. *Anal.* Calcd for C₈H₈F₃NO₄S₂: C, 31.7; H, 2.7. Found: C, 31.4; H, 2.8.

GENERAL CONCLUSIONS

Numerous studies have been reported of plant growth regulating activities of benzoic and phenoxyacetic acids. Exact comparison of the fluorinated *N*-phenylalkanesulfonamides with these acids is difficult since a rigorous study of the plant growth regulating activity of the sulfonamide series has not been accomplished. However, some approximate comparisons can be made. Generally 3-Cl (Muir and Hansch, 1951), 4-Cl (Muir and Hansch, 1951; Zimmerman *et al.*, 1952), and 2,4-diCl (Veldstra, 1952) substituted benzoic acids are inactive or weakly active while the corresponding substituted phenoxyacetic acids (Leaper and Bishop, 1951; Wain and Wightman, 1953) and 1,1,1-trifluoro-*N*-phenylmethanesulfonamides are highly active. Conversely, 2,6-diCl-substituted benzoic acid (Zimmerman *et al.*, 1952; Veldstra, 1952) and 1,1,1-trifluoro-*N*-(2,6-dichlorophenyl)methanesulfonamide are active while the corresponding phenoxyacetic acid is inactive (Leaper and Bishop, 1951; Wain and Wightman, 1953). Numerous other comparisons of this type indicate that the fluorinated *N*-phenylalkanesulfonamides are a unique series of herbicides and plant growth regulators. This conclusion was also reached by Yapel in his correlations of preemergence herbicidal activity with the partition parameter π and the Hammett substituent σ (Yapel, 1972).

Further research in this series of fluorinated *N*-phenylalkanesulfonamides has recently resulted in the discovery of a new plant growth regulator, Sustar, and a new herbicide, Destun. Short papers on these compounds have been presented (Fridinger *et al.*, 1973, 1974) and full papers are in preparation. Because of the unique biological and chemical properties of these fluorinated *N*-phenylalkane-

sulfonamides, active investigation is continuing in these laboratories.

ACKNOWLEDGMENT

The authors are indebted to P. B. Olson and coworkers for elemental analyses and R. R. Hamilton and coworkers for toxicity measurements. We especially wish to thank T. S. Reid for overall direction of this work.

LITERATURE CITED

- Brice, T.J., Trott, P.W., U.S. Patent 2,732,398 (1956).
 Farrar, W.V., *J. Chem. Soc.*, 3058 (1960).
 Fridinger, T.L., Pauly, D.R., Moore, G.G.I., 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, Abstract PEST-83.
 Fridinger, T.L., Pauly, D.R., Trepka, R.D., Moore, G.G.I., 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1973, Abstract PEST-63.
 Fujita, T., Iwasa, J., Hansch, C., *J. Amer. Chem. Soc.* 86, 5175 (1964).

- Hansch, C., *Annu. Rep. Med. Chem.* 34, 347 (1966).
 Hansch, C., *Annu. Rep. Med. Chem.* 35, 348 (1967a).
 Hansch, C., *Proc. Int. Pharmacol. Meet.*, 3rd 7, 141 (1967b).
 Hansch, C., *Farmaco, Ed. Sci.* 23, 293 (1968).
 Hansch, C., Fujita, T., *J. Amer. Chem. Soc.* 86, 1616 (1964).
 Harrington, J.K., Robertson, J.E., Kvam, D.C., Hamilton, R.R., McGurran, K.T., Trancik, R.J., Swingle, K.F., Moore, G.G.I., Gerster, J.F., *J. Med. Chem.* 13, 137 (1970).
 Leaper, J.M.F., Bishop, J.R., *Botan. Gaz.* 112, 250 (1951).
 Muir, R.M., Hansch, C., *Plant Physiol.* 26, 369 (1951).
 Trepka, R.D., Harrington, J.K., Belisle, J.W., *J. Org. Chem.* 39, 1094 (1974).
 Trepka, R.D., Harrington, J.K., Robertson, J.E., Waddington, J.T., *J. Agr. Food Chem.* 18, 1176 (1970).
 Veldstra, H., *Recl. Trav. Chim. Pays-Bas* 71, 15 (1952).
 Wain, R.L., Wightman, F., *Ann. Appl. Biol.* 40, 244 (1953).
 Yapel, A.F., Jr., *Advan. Chem. Ser. No.* 114 (1972).
 Zimmerman, P.W., Hitchcock, A.E., Prill, E.A., *Contrib. Boyce Thompson Inst.* 16, 419 (1952).

Received for review April 30, 1974. Accepted August 2, 1974.

Behavior and Fate of Two Phenylpyridazinone Herbicides in Cotton, Corn, and Soybean

R. Harry Strang¹ and R. Larry Rogers*

The absorption, translocation, and metabolism of [¹⁴C]SAN 6706 [4-chloro-5-(dimethylamino)-2-(α,α,α -trifluoro-*m*-tolyl)-3(2*H*)-pyridazinone] and [¹⁴C]SAN 9789 (norflurazone) [4-chloro-5-(methylamino)-2-(α,α,α -trifluoro-*m*-tolyl)-3(2*H*)-pyridazinone] by cotton (*Gossypium hirsutum* L. "Coker 203"), corn (*Zea mays* L. "WF 9"), and soybean [*Glycine max* (L.) Merr. "Lee"] were investigated. Differences in absorption and translocation appeared to be major factors determining the tolerance of plants to SAN 6706 and SAN 9789. Autoradiographic and combustion analyses indicated that most of the radioactivity

absorbed by cotton (tolerant) was retained in the roots while significantly more radioactivity was translocated into the shoots of soybean (susceptible) and corn (very susceptible). Tolerant cotton mediated only limited breakdown of the herbicides while the susceptible species rapidly degraded them by the process of N-demethylation. The rapid degradation of SAN 6706 by corn and soybean did not represent a detoxification mechanism since the primary degradation product formed (*i.e.*, SAN 9789) was more phytotoxic than SAN 6706.

SAN 6706 [4-chloro-5-(dimethylamino)-2-(α,α,α -trifluoro-*m*-tolyl)-3(2*H*)-pyridazinone] and SAN 9789 [4-chloro-5-(methylamino)-2-(α,α,α -trifluoro-*m*-tolyl)-3(2*H*)-pyridazinone] are experimental herbicides which show promise for the selective preemergence control of many broadleaf and grassy weeds, including nutsedge (*Cyperus sp.*), in cotton fields.

The limited information available on the absorption and translocation of SAN 6706 and SAN 9789 indicated that the herbicides are absorbed by the roots of both susceptible and resistant species (Hilton *et al.*, 1969; Strang and Rogers, 1972, 1973). Hilton *et al.* (1969) reported that SAN 6706 was resistant to metabolic detoxication in plants. Strang and Rogers (1972, 1973) reported that SAN 6706 and SAN 9789 were readily degraded by several plant species. Soil degradation of SAN 6706 and SAN 9789 has since been reported (Rahn and Zimdahl, 1973; Rogers, 1972).

This present investigation was divided into three major parts. A study was made of the absorption, translocation,

and metabolism of SAN 6706 by the three plant species. A similar study was conducted with SAN 9789. Finally, the absorption and translocation of SAN 6706 was compared to that of SAN 9789 within each plant species. The latter study was initiated to determine whether differences in the movement of the two herbicides in the test species that were observed in the earlier experiments were statistically significant. To avoid excessive duplication of data, only the absorption and translocation results from the latter experiment were presented. These studies were conducted to determine if differential absorption, translocation, and/or metabolism could explain differences in the tolerance of cotton (resistant), corn (very susceptible), and soybean (susceptible) to SAN 6706 and SAN 9789. Such information should contribute to the intelligent utilization of these herbicides in the field.

MATERIALS AND METHODS

Cotton (*Gossypium hirsutum* L. "Coker 203"), corn (*Zea mays* L. "WF 9"), and soybean [*Glycine max* (L.) Merr. "Lee"] seed were germinated in flats of vermiculite, which were watered as required with half-strength Hoagland and Arnon's No. 2 nutrient solution (Hoagland and Arnon, 1950). Seven ten-day-old seedlings were transferred to half-strength nutrient solution for a 3-day equilibration period. Uniform plants were selected and transferred to

Plant Pathology Department, Louisiana State University, Baton Rouge, Louisiana 70803.

¹Present address: Vero Beach Labs, Vero Beach, Florida 32960.