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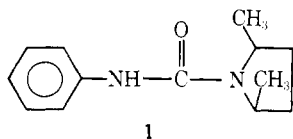
## Synthesis and Herbicidal Activity of Pyrrolidinecarboxanilides

William J. Pyne,\* Steve S. Szabo,<sup>1</sup> and Robert E. Holm

A series of pyrrolidinecarboxanilides and pyrrolidinethiocarboxanilides has been prepared and found to be herbicidally active. Substitution of methyl groups in the *cis* configuration at the 2 and 5 positions of the pyrrolidine ring of the carboxanilides increased the herbicidal activity, while methyl groups in the *trans* configuration reduced or eliminated the activity. In general, the thiocarboxanilides were less active than the

corresponding carboxanilides. Pyrrolidinecarboxanilides were very active inhibitors of the Hill reaction and the degree of inhibition correlated with the accumulation of nitrite in tissue. *cis*-2,5-Dimethyl-1-pyrrolidinecarboxanilide, one of the most herbicidally active compounds in the series, has undergone extensive field testing and is being developed as a selective corn herbicide.

Synthesis and biological evaluation of a series of pyrrolidine and alkylpyrrolidinecarboxanilides were initiated after several were found to have pre- and postemergence herbicidal activity. Synthesized compounds were evaluated in standard greenhouse herbicide tests and in special tests using isolated chloroplasts and excised leaf sections. From this work one compound, *cis*-2,5-dimethyl-1-pyrrolidinecarboxanilide (1), has been selected for further development and commercialization.



Compound 1, known by the trade name Rowtate, has been field tested for 2 years as a selective corn herbicide. In these tests, Rowtate has controlled broadleaf and certain grassy weeds in corn at 2-3 kg/ha, depending on soil type.

### MATERIALS AND METHODS

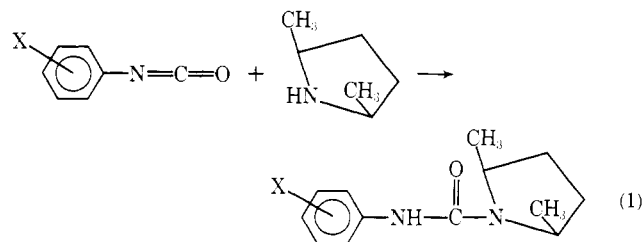
Phenyl isocyanates and thioisocyanates were purchased from commercial sources or were prepared by the reaction of phosgene and the appropriate aniline in ethyl acetate.

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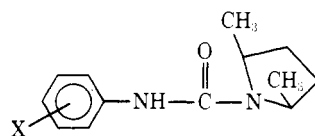
*cis*-2,5-Dimethylpyrrolidine was synthesized from the corresponding pyrrole using the procedures of Overberger *et al.* (1955) and Hill and Chan (1965). *trans*-2,5-Dimethylpyrrolidine was prepared by the method of Evans (1951).

Pyrrolidinecarboxanilides and thiocarboxanilides were synthesized by reaction of the appropriate phenyl isocyanate or thioisocyanate and the desired pyrrolidine in benzene (eq 1). The various pyrrolidinecarboxanilides are list-



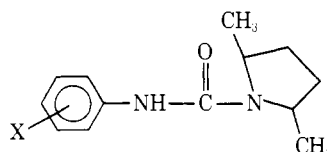
ed in Tables I-IV with yields, melting points, and pre-emergence and postemergence herbicidal activity ratings on broadleaf weeds and grasses.

Compounds 1 through 74 were prepared by the following method given for *cis*-2,5-dimethyl-1-pyrrolidinecarboxanilide (1). Phenyl isocyanate (11 g, 0.092 M) was allowed to react in 100 ml of anhydrous benzene with *cis*-2,5-dimethylpyrrolidine (9.1 g, 0.092 M). This mixture was heated to reflux for 3 hr, cooled, and filtered; the solvent was removed at reduced pressure. The residual solid was crystallized from a benzene-petroleum ether mixture to give 13 g (64% yield) of a solid melting at 119-120°.

**Table I. Structures, Chemical Properties, and Biological Activities of the *cis*-2,5-Dimethyl-1-pyrrolidinecarboxanilides**

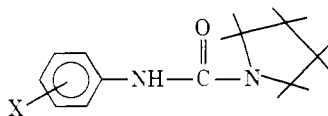
| No. | X  | Yield,<br>% | Mp, °C               | Rating no. <sup>a</sup> |       |              |       |
|-----|--|-------------|----------------------|-------------------------|-------|--------------|-------|
|     |  |             |                      | Preemergent             |       | Postemergent |       |
|     |  |             |                      | Broadleaf               | Grass | Broadleaf    | Grass |
| 1   | H  | 65          | 119–120              | 5                       | 0     | 7            | 5     |
| 2   | 2-F  | 100         | 125–127 <sup>b</sup> | 5                       | 1     | 7            | 4     |
| 3   | 3-F  | 80          | 117–118              | 5                       | 3     | 8            | 4     |
| 4   | 4-F  | 75          | 135                  | 5                       | 3     | 7            | 3     |
| 5   | 2-CF <sub>3</sub>                                    | 28          | 128–129              | 0                       | 0     | 0            | 0     |
| 6   | 3-CF <sub>3</sub>                                    | 85          | 129–130              | 3                       | 3     | 6            | 3     |
| 7   | 4-CF <sub>3</sub>                                    | 65          | 123–125              | 3                       | 0     | 5            | 2     |
| 8   | 3-Cl   | 81          | 118–119              | 1                       | 0     | 8            | 5     |
| 9   | 4-Cl   | 84          | 148–149              | 1                       | 0     | 7            | 5     |
| 10  | 3-Br   | 70          | 102–103              | 2                       | 2     | 5            | 2     |
| 11  | 4-Br   | 88          | 131–132              | 3                       | 0     | 7            | 3     |
| 12  | 3-I  | 83          | 103–105              | 2                       | 0     | 6            | 3     |
| 13  | 4-I  | 87          | 134–135              | 3                       | 0     | 8            | 0     |
| 14  | 4-CN   | 41          | 160–161              | 3                       | 0     | 6            | 2     |
| 15  | 3-NO <sub>2</sub>                                    | 84          | 130–131              | 0                       | 0     | 2            | 1     |
| 16  | 4-NO <sub>2</sub>                                    | 98          | 114–116              | 0                       | 0     | 2            | 0     |
| 17  | 3-CH <sub>3</sub>                                    | 76          | 73–75                | 1                       | 0     | 7            | 4     |
| 18  | 4-CH <sub>3</sub>                                    | 100         | 130–131              | 3                       | 0     | 4            | 2     |
| 19  | 4-CF <sub>3</sub> O                                  | 82          | 143–145              | 2                       | 0     | 4            | 2     |
| 20  | 2-CH <sub>3</sub> O                                  | 56          | 69                   | 0                       | 0     | 4            | 2     |
| 21  | 3-CH <sub>3</sub> O                                  | 61          | 106                  | 0                       | 0     | 5            | 2     |
| 22  | 4-CH <sub>3</sub> O                                  | 80          | 110–112              | 0                       | 0     | 5            | 1     |
| 23  | 3-CH <sub>3</sub> S                                  | 80          | 82                   | 2                       | 0     | 5            | 0     |
| 24  | 4-CH <sub>3</sub> S                                  | 84          | 108                  | 1                       | 0     | 4            | 0     |
| 25  | 3,4-Cl <sub>2</sub>                                  | 78          | 137–138              | 2                       | 0     | 8            | 2     |
| 26  | 2,5-Cl <sub>2</sub>                                  | 42          | 55                   | 0                       | 0     | 1            | 1     |
| 27  | 2,4-Br <sub>2</sub>                                  | 78          | 70–71                | 0                       | 0     | 0            | 0     |
| 28  | 2,5-Br <sub>2</sub>                                  | 74          | 62–63                | 0                       | 0     | 0            | 0     |
| 29  | 2,6-Br <sub>2</sub>                                  | 80          | 171–172              | 0                       | 0     | 0            | 0     |
| 30  | 2,4-F <sub>2</sub>                                   | 54          | 78–80                | 1                       | 0     | 3            | 5     |
| 31  | 2,5-F <sub>2</sub>                                   | 61          | 64–65                | 5                       | 1     | 8            | 2     |
| 32  | 3,4-F <sub>2</sub>                                   | 60          | 107–108              | 6                       | 0     | 7            | 6     |
| 33  | 3-Cl, 4-F  | 73          | 113–115              | 3                       | 0     | 5            | 3     |
| 34  | 3-CH <sub>3</sub> , 4-F                              | 96          | 99–100               | 4                       | 0     | 6            | 3     |
| 35  | 3-F, 4-CH <sub>3</sub>                               | 88          | 123–125              | 4                       | 0     | 6            | 2     |
| 36  | 3-CF <sub>3</sub> , 4-F                              | 76          | 115–116              | 2                       | 0     | 4            | 2     |
| 37  | 3,4-(CH <sub>3</sub> ) <sub>2</sub>                  | 81          | 112–113              | 0                       | 0     | 3            | 0     |
| 38  | 2-F, 4,5-Cl <sub>2</sub>                             | 71          | 103–104              | 2                       | 2     | 4            | 2     |
| 39  | 3-Cl, 4-Br   | 61          | 127–129              | 0                       | 0     | 4            | 3     |
| 40  | 3-CF <sub>3</sub> , 4-Br                             | 65          | 124–125              | 2                       | 0     | 4            | 0     |
| 41  | 3-CF <sub>3</sub> , 4-Cl                             | 63          | 110                  | 2                       | 0     | 5            | 0     |
| 42  | 4-(CH <sub>3</sub> ) <sub>3</sub> CNHCO <sub>2</sub> | 20          | 80                   | 2                       | 0     | 2            | 0     |
| 43  | 4-CH <sub>3</sub> C(CH <sub>3</sub> )H               | 63          | 115–117              | 0                       | 0     | 3            | 3     |
| 44  | 4-(CH <sub>3</sub> ) <sub>3</sub> C                  | 97          | 128                  | 0                       | 0     | 0            | 0     |
| 45  | 2,3,4,5-F <sub>4</sub>                               | 58          | 102–104              | 0                       | 0     | 0            | 0     |
| 46  | 2,3,5,6-F <sub>4</sub>                               | 24          | 163–166              | 0                       | 0     | 0            | 0     |
| 47  | 3-Cl, 4-CH <sub>3</sub> O                            | 87          | 115–116              | 0                       | 0     | 2            | 1     |

<sup>a</sup> Ratings range from 0 to 9 with 0 indicating no weed control at the highest rate tested (17.92 kg/ha) and 9 representing weed control at 0.07 kg/ha. Control of broadleaf weeds and grasses at each rating level had to be at least 50% for preemergent application and 80% for post-emergent application. See Materials and Methods for complete rating table. <sup>b</sup> Determined at 0.2 mm.

**Table II. Structures, Chemical Properties, and Biological Activities of the *trans*-2,5-Dimethyl-1-pyrrolidinecarboxanilides**

| No. | X                   | Yield,<br>% | Mp, °C  | Rating no. <sup>a</sup> |       |              |       |
|-----|---------------------|-------------|---------|-------------------------|-------|--------------|-------|
|     |                     |             |         | Preemergent             |       | Postemergent |       |
|     |                     |             |         | Broadleaf               | Grass | Broadleaf    | Grass |
| 48  | 2-F                 | 63          | 91-93   | 0                       | 0     | 0            | 0     |
| 49  | 3-F                 | 73          | 142-143 | 0                       | 0     | 0            | 0     |
| 50  | 4-F                 | 72          | 149-150 | 0                       | 0     | 0            | 0     |
| 51  | 3-CF <sub>3</sub>   | 80          | 115-117 | 0                       | 0     | 0            | 0     |
| 52  | 3-Cl                | 84          | 135-137 | 0                       | 0     | 0            | 0     |
| 53  | 4-Cl                | 100         | 151-152 | 0                       | 0     | 0            | 0     |
| 54  | 2,5-F <sub>2</sub>  | 48          | 105-107 | 0                       | 0     | 0            | 0     |
| 55  | H                   | 85          | 143     | 0                       | 0     | 0            | 0     |
| 56  | 3,4-Cl <sub>2</sub> | 83          | 147-148 | 0                       | 0     | 0            | 0     |

<sup>a</sup> Ratings range from 0 to 9 with 0 indicating no weed control at the highest rate tested (17.92 kg/ha) and 9 representing weed control at 0.07 kg/ha. Control of broadleaf weeds and grasses at each rating level had to be at least 50% for preemergent application and 80% for post-emergent application. See Materials and Methods for complete rating table.

**Table III. Structures, Chemical Properties, and Biological Activities of the Pyrrolidinecarboxanilides**

| No. | X                   | Yield,<br>% | Mp, °C  | Rating no. <sup>a</sup> |       |              |       |
|-----|---------------------|-------------|---------|-------------------------|-------|--------------|-------|
|     |                     |             |         | Preemergent             |       | Postemergent |       |
|     |                     |             |         | Broadleaf               | Grass | Broadleaf    | Grass |
| 69  | H                   | 91          | 180-181 | 2                       | 2     | 5            | 2     |
| 70  | 3-Cl                | 91          | 143-144 | 1                       | 0     | 3            | 2     |
| 71  | 4-Cl                | 100         | 167-168 | 3                       | 0     | 3            | 1     |
| 72  | 3,4-Cl <sub>2</sub> | 78          | 179-180 | 1                       | 0     | 4            | 2     |
| 73  | 3-CF <sub>3</sub>   | 67          | 160-161 | 3                       | 0     | 3            | 0     |
| 74  | 2,5-F <sub>2</sub>  | 68          | 69-70   | 1                       | 0     | 3            | 1     |

<sup>a</sup> Ratings range from 0 to 9 with 0 indicating no weed control at the highest rate tested (17.92 kg/ha) and 9 representing weed control at 0.07 kg/ha. Control of broadleaf weeds and grasses at each rating level had to be at least 50% for preemergent application and 80% for post-emergent application. See Materials and Methods for complete rating table.

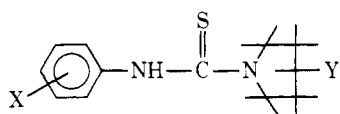
Compounds 75 through 82 were synthesized by the following general procedure outlined for *cis*-2,5-dimethyl-1-pyrrolidinethiocarboxanilide (77). *cis*-2,5-Dimethylpyrrolidine (9.9 g, 0.1 M) was allowed to react in 100 ml of anhydrous benzene with phenyl isothiocyanate (13.5 g, 0.1 M). After the slightly exothermic reaction subsided, the reaction mixture was heated at reflux for 3 hr and cooled, and the solvent removed at reduced pressure. The residual solid was crystallized from a pentane-benzene mixture to give 14 g (60% yield) of a solid melting at 104-105°.

Structures of novel carboxanilides were verified by quantitative elemental analysis of carbon, hydrogen, and nitrogen (accuracy within ±0.3%), by infrared spectroscopy, and by nmr analysis.

Test formulations were prepared by mixing 20 ml of an acetone solution containing 0.083 g of the test compound with 20 ml of water containing 0.01 g of Triton X-155 surfactant ("Triton" is a registered trademark). The resultant formulations contained 2080 ppm of test compound in 50% by volume of acetone and 0.025% by weight of surfactant. Appropriate lower concentrations were obtained by diluting the stock formulation with 50% aqueous acetone containing 0.025% surfactant.

The pre- and postemergence tests were run in 23 cm × 23 cm × 5 cm aluminum pans containing 3.8 cm of composted soil. Seeds of buckwheat (*Fagopyrum esculentum* Moench), turnip (*Brassica rapa* L.), zinnia (*Zinnia elegans* Jacq.), browntop millet (*Panicum ramosum* L.), pe-

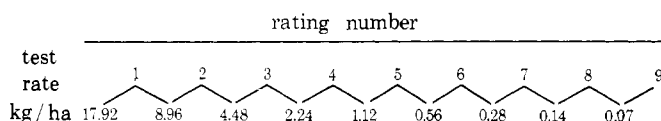
**Table IV. Structures, Chemical Properties, and Biological Activities of the Pyrrolidinethiocarboxanilides**



| No. | Yield,<br>% | Mp, °C  | X                 | Y                                   | Geometrical<br>isomer | Rating no. <sup>a</sup> |       |                 |       |
|-----|-------------|---------|-------------------|-------------------------------------|-----------------------|-------------------------|-------|-----------------|-------|
|     |             |         |                   |                                     |                       | Preemergent             |       | Postemergent    |       |
|     |             |         |                   |                                     |                       | Broadleaf Grass         | Grass | Broadleaf Grass | Grass |
| 75  | 93          | 149-150 | H                 | H                                   |                       | 2                       | 2     | 2               | 2     |
| 76  | 80          | 120-121 | 3-CF <sub>3</sub> | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Cis                   | 0                       | 0     | 6               | 0     |
| 77  | 60          | 104-105 | H                 | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Cis                   | 2                       | 0     | 5               | 0     |
| 78  | 94          | 104-105 | 3-F               | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Cis                   | 3                       | 0     | 3               | 3     |
| 79  | 98          | 123-125 | 3-F               | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Trans                 | 0                       | 0     | 0               | 0     |
| 80  | 90          | 109-110 | 2-F               | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Trans                 | 0                       | 0     | 0               | 0     |
| 81  | 83          | 141-143 | 3-CF <sub>3</sub> | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Trans                 | 0                       | 0     | 0               | 0     |
| 82  | 68          | 78-79   | 2-F               | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | Cis                   | 2                       | 0     | 2               | 0     |

<sup>a</sup> Ratings range from 0 to 9 with 0 indicating no weed control at the highest rate tested (17.92 kg/ha) and 9 representing weed control at 0.07 kg/ha. Control of broadleaf weeds and grasses at each rating level had to be at least 50% for preemergent application and 80% for post-emergent application. See Materials and Methods for complete rating table.

rennial ryegrass (*Lolium perenne* L.), and sorghum (*Sorghum vulgare* Pers.) were planted about 1 cm deep in one-half of the tray. The trays were transferred to the greenhouse where the test species were allowed to grow until one true leaf was present on the slowest growing species (zinnia). This required 7-14 days depending on the time of the year. The other one-half of the tray was planted with the same six species and the tray was sprayed with 40 ml of the stock solution so that the soil surface and plants were uniformly covered. Application rates varied from 17.92 to 0.07 kg/ha. The tests were evaluated 2 weeks after treatment and assigned ratings, as listed in Tables I-IV, according to the following scheme



The criterion for passing the preemergent test was 50% control of all broadleaf weeds or grasses. Eighty per cent control of all broadleaf weeds or grasses was required for passage of the postemergence test. When the minimum concentration of a compound necessary to achieve the above level of control fell within a range, the compound received the rating shown for that range. A compound with borderline activity received the higher rating. Thus, a compound that gave 50% preemergence control of broadleaf weeds at 4.48 kg/ha and less than 50% control at 2.24 kg/ha would receive a 3 rating. Therefore, an increase of 1 rating number corresponds to a twofold increase in activity in any given test.

Field evaluations were run in plots which had been cleared of all annual weeds and sown with the following crop and weed plants: crops—corn (*Zea mays* L.) and alfalfa (*Medicago sativa* L.); broadleaf weeds—redroot pigweed (*Amaranthus retroflexus* L.), prickly sida (*Sida spinosa* L.), wild mustard (*Brassica kaber* (D.C.) L. C. Wheeler), velvetleaf (*Abutilon theophrasti* Medic), and purslane (*Portulaca oleracea* L.); grasses and sedge—crowfoot grass (*Dactyloctenium aegyptium* (L.) Richter) and annual sedge (*Cyperus compressus* L.). On the day before sowing, the field was treated with aqueous suspensions prepared from 50% wetttable powders of the various

test compounds and commercial herbicide standards. Herbicide test compounds and standards were incorporated by raking in two directions at 90° angles to one another. Test compounds were applied at rates of 4.48, 2.24, 1.12, and 0.56 kg/ha. Eight weeks after treatment, the degree of damage to the test plants was assessed on a scale of 0-10, 0 denoting a completely normal plant and 10 denoting complete destruction. The degrees of damage to the crops, broadleaf weeds, grasses, and sedge described above are shown in Table V.

The nitrite accumulation assay used wheat leaves from 2-week-old seedlings grown in greenhouse potting soil. Leaves were cut into 5-mm sections and floated on distilled water until used. The incubation medium consisted of 0.1 M KH<sub>2</sub>PO<sub>4</sub> (pH 7.5), 0.05 M KNO<sub>3</sub>, 2.5% 1-propanol, and 25 µg/ml of chloramphenicol. Test chemical solutions were prepared in 1-propanol at concentrations of 5000, 500, 50, and 5 ppm. The incubation medium (4.9 ml) was placed in 50-ml beakers and 0.1 ml of the 1-propanol solution was added to give final chemical concentrations of 100, 10, 1, and 0.1 ppm. Controls were run with 0.1 ml of 1-propanol alone added. The final 1-propanol concentration was 4.5% in the leaf incubation medium. The wheat leaves were blotted to remove excess moisture and 200 mg of leaf tissue was weighed and added to each beaker. The beakers were placed in a water bath shaker (30°) under a bank of fluorescent and incandescent lights (50,000-lx intensity). Nitrite accumulation was linear for 2 hr. After 1 hr of incubation, 2 ml of 1 part of 1% sulfanilamide in 25% HCl and 1 part of 0.02% N-(1-naphthyl)ethylenediamine dihydrochloride was added. The red color indicating the presence of NO<sub>2</sub><sup>-</sup> was allowed to develop for 20 min before an aliquot was read for absorbance at 540 nm. A standard curve was run with KNO<sub>2</sub>. Nitrite accumulation was proportional to the herbicide concentration, and data are expressed as micromolar nitrite formed per gram fresh wt per hour at 100 ppm of chemical.

The Hill reaction assay was performed using chloroplasts isolated from spinach leaves according to the procedure published previously (Holm and Stallard, 1974).

**RESULTS AND DISCUSSION**

The pyrrolidinecarboxanilides (Table III), the first members of this series to be prepared, were found to be

Table V. Preemergence Herbicide Field Tests<sup>a</sup>

| Compd                                | Weed control <sup>b</sup> |      |      |      |                        |      |      |      | Crop injury <sup>b</sup> |      |      |      |                |      |      |      |
|--------------------------------------|---------------------------|------|------|------|------------------------|------|------|------|--------------------------|------|------|------|----------------|------|------|------|
|                                      | Broadleaf, kg/ha          |      |      |      | Grass and sedge, kg/ha |      |      |      | Corn, kg/ha              |      |      |      | Alfalfa, kg/ha |      |      |      |
|                                      | 4.48                      | 2.24 | 1.12 | 0.56 | 4.48                   | 2.24 | 1.12 | 0.56 | 4.48                     | 2.24 | 1.12 | 0.56 | 4.48           | 2.24 | 1.12 | 0.56 |
| 25                                   | 10                        | 10   | 9    | 8    | 10                     | 10   | 9    | 7    | 0                        | 0    | 0    | 0    | 6              | 6    | 3.8  | 2    |
| 1                                    | 10                        | 10   | 9.7  | 9.5  | 10                     | 10   | 9    | 8.7  | 0                        | 0    | 0    | 0    | 1              | 0.5  | 0    | 0    |
| 14                                   | 10                        | 10   | 10   | 9    | 10                     | 10   | 10   | 7    | 0                        | 0    | 0    | 0    | 3.6            | 3    | 0.6  | 0    |
| 4                                    | 10                        | 10   | 9.7  | 9.5  | 10                     | 10   | 9    | 8.7  | 0                        | 0    | 0    | 0    | 0.7            | 0    | 0    | 0    |
| 6                                    | 10                        | 10   | 10   | 10   | 10                     | 10   | 10   | 10   | 0                        | 0    | 0    | 0    | 3.8            | 3.8  | 2    | 1.8  |
| 11                                   | 10                        | 7    | 8    | 7.5  | 10                     | 8    | 7    | 5    | 0                        | 0    | 0    | 0    | 2.3            | 0.8  | 0    | 0    |
| Standards                            |                           |      |      |      |                        |      |      |      |                          |      |      |      |                |      |      |      |
| Fluometuron <sup>c</sup><br>(80% WP) | 10                        | 9    | 8    | 8    | 10                     | 10   | 10   | 10   | 10                       | 10   | 10   | 10   | 10             | 10   | 10   | 10   |
| Linuron <sup>d</sup><br>(50% WP)     | 10                        | 10   | 10   | 10   | 10                     | 10   | 10   | 8.5  | 8                        | 8    | 8    | 8    | 10             | 10   | 10   | 10   |
| Diuron <sup>e</sup><br>(80% WP)      | 10                        | 10   | 10   | 9.5  | 10                     | 10   | 8    | 7    | 10                       | 10   | 10   | 9    | 10             | 10   | 10   | 10   |

<sup>a</sup> Corn, alfalfa, broadleaf weed (redroot pigweed, prickly sida, wild mustard, velvetleaf, and purslane), crowfoot grass, and annual sedge seeds were sown a day after aqueous suspensions of the herbicides were applied and incorporated by raking. Crop injury and weed control were recorded after 8 weeks. <sup>b</sup> Average weed control and crop injury of three replications (Pre-Plant Incorporated) using scale of 0–10 where 0 is a completely normal plant and 10 is complete destruction. <sup>c</sup> 3-(3'-Trifluoromethylphenyl)-1,1-dimethylurea as 80% WP (wetable powder). <sup>d</sup> 3-(3',4'-Dichlorophenyl)-1-methoxy-1-methylurea as 50% WP (wetable powder). <sup>e</sup> 3-(3',4'-Dichlorophenyl)-1,1-dimethylurea as 80% WP (wetable powder).

herbicidally active, particularly against broadleaf weed species. Substitution of methyl groups at the 2 and 5 positions of the pyrrolidinyl ring markedly altered herbicidal activity. In the *cis* configuration (Table I) the methyl groups increased activity, whereas in the *trans* configuration (Table II) the effect was to reduce or eliminate herbicidal activity. A similar *cis-trans* effect was noted with the 2,5-dimethylpyrrolidinethiocarboxanilides (Table IV), although the entire group of thio derivatives was less active than their corresponding oxygen analogs. The origin of this stereospecific response is as yet unexplained.

The level of herbicidal activity of the *cis*-2,5-dimethylpyrrolidinecarboxanilides also was influenced by the substitution on the phenyl ring as shown in Table I. Postemergence broadleaf weed activity was increased slightly relative to the unsubstituted carboxanilide (1) by the introduction of a halogen at the 3 or 4 position of the phenyl ring (compounds 3, 8, 13, 25, and 31). Electron-donating alkyl substituents had little effect on activity when compared to 1. A methyl group in the 3 or 4 position of the phenyl moiety as found in 17 or 18 was much more activating than an isopropyl or *tert*-butyl group in the para position of the phenyl ring (compounds 43 and 44). Compounds with electron-withdrawing groups such as a cyano or nitro group were less active than the unsubstituted 1. Compound 14, having a cyano group in the para position of the phenyl ring, was much more active as a herbicide than the corresponding nitro compound 16. Substitution other than a hydrogen or fluorine in the ortho position of the phenyl ring likewise decreased the herbicidal activity or, in most cases, completely eliminated it (compounds 20, 26, 27, 28, and 29). Field test results (Table V) showed that a number of *cis*-2,5-dimethylpyrrolidinecarboxanilides were selective as corn herbicides. Only the unsubstituted 1 and the para fluoro isomer 4 of the six compounds field tested were selective on alfalfa.

*cis*-2,5-Dimethyl-1-pyrrolidinecarboxanilides have been shown to inhibit photochemical activity (Hill reaction) of isolated spinach chloroplasts (Holm and Stallard, 1974). *trans*-2,5-Dimethyl-1-pyrrolidinecarboxanilides were completely inactive.

Klepper (1974) has recently suggested that many herbicides may kill plants through accumulation of nitrite in the tissue. Nitrite reductase is located in the chloroplast (Beever and Hageman, 1969) and receives the electrons for reduction of nitrite to ammonia from the chloroplast photosystems. Thus, compounds which interfere with electron transport in the chloroplast might cause build-up of nitrite in the tissue. A series of the pyrrolidinecarboxanilides was tested in an assay using wheat leaves to determine their effect on nitrite accumulation. Diuron and compound 25 caused 50-fold increases in nitrite accumulation while the other chemicals tested had lesser effects (Table VI). A good correlation existed between the relative effectiveness of compounds in this series in promoting

Table VI. Comparison of Pyrrolidinecarboxanilides in the Hill Reaction and in the Nitrite Test

| Compd  | Hill reaction                  |  | Nitrite assay        |  |
|--------|--------------------------------|--|----------------------|--|
|        | $I_{50}$<br>concn <sup>a</sup> | Rel<br>effective-<br>ness <sup>b</sup> | Nitrite <sup>c</sup> | Rel<br>effective-<br>ness <sup>d</sup> |
| Diuron | $1.51 \times 10^{-7}$          | 100                                    | 14.25                | 100                                    |
| 25     | $1.50 \times 10^{-7}$          | 100                                    | 14.40                | 100                                    |
| 6      | $0.81 \times 10^{-6}$          | 19                                     | 2.15                 | 15                                     |
| 8      | $1.19 \times 10^{-6}$          | 15                                     | 1.65                 | 12                                     |
| 9      | $1.19 \times 10^{-6}$          | 15                                     | 1.70                 | 12                                     |
| 3      | $1.48 \times 10^{-6}$          | 12                                     | 1.90                 | 13                                     |
| 31     | $2.0 \times 10^{-6}$           | 9                                      | 1.65                 | 12                                     |
| 1      | $3.62 \times 10^{-6}$          | 4                                      | 1.65                 | 12                                     |
| 17     | $4.96 \times 10^{-6}$          | 3                                      | 1.05                 | 7                                      |
| 4      | $8.90 \times 10^{-6}$          | 2                                      | 1.00                 | 6                                      |
| 2      | $8.90 \times 10^{-6}$          | 2                                      | 0.75                 | 5                                      |

<sup>a</sup> Molar concentration necessary to obtain 50% inhibition. <sup>b</sup> Based on Diuron = 100. <sup>c</sup>  $\mu$ M nitrite/g fresh weight per hr at 100 ppm of chemical. Control nitrite subtracted. <sup>d</sup> Based on Diuron = 100.

nitrite accumulation and their relative effectiveness in inhibiting the Hill reaction. This suggests that the nitrite test may be useful in determining the effect of a chemical on chloroplast electron transport. An advantage of this test is the time saved in excising tissue compared with isolating chloroplasts as required for the Hill reaction assay.

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## Insecticidal Activity of $\alpha,\alpha,\alpha$ -Trifluoroacetophenone Oxime Carbamates and Thiophosphates

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Approximately 20 *N*-methylcarbamates and the corresponding monothiophosphates of substituted 2,2,2-trifluoroacetophenone oximes have been synthesized and their insecticidal activity examined. This activity has been compared to their corresponding anticholinesterase values. The carbamate exhibiting the highest anticholinesterase activity contained an ortho methoxy substituent.

The toxicity to house flies by topical application was less than expected, but the activity was raised to the expected level by synergism with piperonyl butoxide. A comparison between the substituted 2,2,2-trifluoroacetophenone oxime carbamates and the corresponding ring-substituted phenylcarbamates shows the former to be about 20–30 times more toxic to house flies.

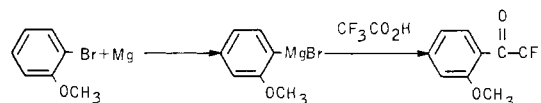
For many years phenol carbamates and phosphates have been known to impart insecticidal activity. Of more recent origin, the oxime carbamates and phosphates have aroused the interest of pesticide chemists. Such examples as Tranid, Temik, and Lannate have well established the insecticidal activity of this class of compounds. We now wish to report the results of our investigations into the biological activity of the oxime carbamates and thiophosphates of  $\alpha,\alpha,\alpha$ -trifluoroacetophenones.

#### SYNTHESIS

None of the chemicals whose biological activity is discussed herein have appeared previously in the literature. The intermediate ketones for this study (except for the meta nitro-substituted ketone) were synthesized by reacting the appropriately substituted halogen compound with magnesium to form the Grignard, which was then treated with trifluoroacetic acid. This was found to be the best method of several that were available. The nitro ketone was prepared by the direct nitration with mixed acid of  $\alpha,\alpha,\alpha$ -trifluoroacetophenone. Oximation of the ketones was carried out in anhydrous methanol with an excess of hydroxylamine. It was found that longer than usual reflux times were necessary for better yields. Several of the meta-substituted ketones did not give the expected oximes under these conditions. However, by vacuum distillation of the intermediate that was formed, we were able to isolate sufficient amounts of the oxime to complete our study of these chemicals. The identification and chemistry of these intermediates will be the subject of a future publication.

The oxime carbamates were prepared by reaction with methyl isocyanate, while the corresponding thiophosphates were synthesized by forming the sodium salt of the oxime, and then reacting this with diethylthiophosphoryl chloride. Table I lists the new oxime derivatives synthesized during this study, along with their analytical data. The following examples illustrate the synthetic procedures used.

**Ketone.** To a 5-l. flask fitted with a stirrer, reflux condenser, thermometer, and addition tube was charged 39 g (1.6 mol) of magnesium. This was flushed with a nitrogen stream and then 100 ml of ether and 1 ml of ethyl bro-



mid were added. *o*-Bromoanisole (300 g; 1.6 mol) was dissolved in 1300 ml of anhydrous ether and added slowly to the magnesium. Addition time was 5 hr. The temperature during addition was maintained between 25 and 30°. The reaction mixture develops the characteristic dark brown color. The reaction was stirred for 2 hr after the addition was complete.

To the above was slowly added 61 g (0.54 mol) of trifluoroacetic acid in 200 ml of anhydrous ether. The addition took 2.5 hr with rapid stirring at a temperature of 35°. The mixture was then refluxed for 2 hr after the addition was completed.

The reaction was then cooled to 0° and 200 ml of H<sub>2</sub>O was slowly added keeping the temperature between 0 and 10°. This was followed by 200 ml of concentrated HCl in 300 ml of H<sub>2</sub>O. The organic layer was separated and washed with two 500-ml portions of 10% Na<sub>2</sub>CO<sub>3</sub> followed by two 500-ml portions of H<sub>2</sub>O. The ether layer was dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was con-

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