# Synthesis and Herbicidal Activity of *N*-Alkyl-*N*-propargyl-*N'*-phenylureas and Related Compounds

William J. Pyne,* Steve S. Szabo, and Robert E. Holm[1]

A series of *N*-alkyl-*N*-propargyl-*N'*-phenylureas was synthesized and evaluated for herbicidal activity in greenhouse and compared to the standard urea herbicides *N,N*-dimethyl-*N'*-(4-chlorophenyl)urea (monuron) and *N,N*-dimethyl-*N'*-(3,4-chlorophenyl)urea (diuron). Eight of the most active compounds were tested in the field on several weed and crop species. The propargylureas show herbicidal activity in the greenhouse but were nonselective for the commercial crops tested. The propargylureas inhibited the Hill reaction with *N*-methyl-*N*-propargyl-*N'*-(3,4-dichlorophenyl)urea being as active as diuron.

*N,N*-Dimethyl-*N'*-(4-chlorophenyl)urea (monuron) and *N,N*-dimethyl-*N'*-(3,4-dichlorophenyl)urea (diuron) are highly active urea herbicides (Kearney and Kaufman, 1975). They enjoy limited use as selective herbicides on cotton and orchard crops. At higher rates, both materials are used as general weed killers. Crop tolerance in the urea series is highly dependent on the nature of the nonaromatic substituents on the *N*-nitrogen position. It has been increased by replacement of one or both of the *N,N*-dimethyl groups with *N*-methoxy substituent, as for linuron, and with a 2-methylcyclohexyl group, as for siduron.

In an effort to improve and further broaden crop tolerance in the urea series, a number of *N*-alkyl-*N*-propargyl-*N'*-(substituted phenyl)ureas were prepared and their herbicidal activity evaluated in the greenhouse. Eight *N*-methyl-*N*-propargyl-*N'*-phenylureas were further evaluated for crop tolerance in special field testing against soybean, corn, cotton, and wheat. A selected group of phenylureas were also tested in vitro as inhibitors of electron transport in isolated chloroplasts (Hill reaction).

## CHEMICAL METHODS

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

*N*-Methylpropargyl-, *N*-ethylpropargyl-, *N*-propylpropargyl-, and the isopropylpropargylamines were prepared in 31–65% yields from the reaction of the appropriate *N*-alkyl-2-chloroallylamine and sodium amide in liquid ammonia, using the general procedure of Peters and Hennion (1964):

$$CH_3NH_2 + ClCH_2C(Cl)=CH_2 \rightarrow CH_3NHCH_2C(Cl)=CH_2 \quad (1)$$

I

$$CH_3NHCH_2C(Cl)=CH_2 + NaNH_2 \rightarrow CH_3NHCH_2C\equiv CH \quad (2)$$

II

***N*-(2-Chloroallyl)methylamine (I).** Methylamine (40%, aqueous) (155 g, 2.0 M) was added to 111 g (1 M) of 2,3-dichloro-1-propene and the mixture heated at reflux (55–57 °C) for 2 h. The solution was cooled and 80 g (2 M) of sodium hydroxide pellets was added; the solution was stirred an additional 15 min. The organic layer was separated and dried over sodium hydroxide. The product distilled at 112–113 °C (760 mm), resulting in a 33.0 g (31%) yield. A higher boiling fraction which proved to be *N*-methylbis(2-chloroallyl)amine distilling at 71 °C (12 mm) also recovered.

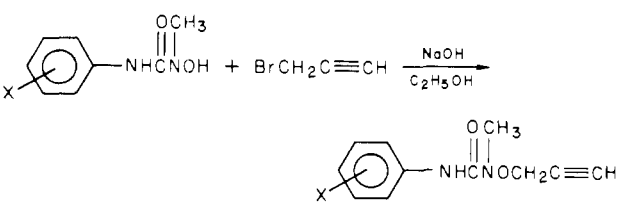
***N*-Methyl-*N*-propargylamine (II).** Liquid ammonia (500 mL) was charged into a 1-L three-necked flask, along with 25 g (0.64 M) of sodium amide. Into this solution was added, dropwise over a 30-min period, 25 g (0.24 M) of *N*-(2-chloroallyl)methylamine. This mixture was stirred for 4 h and the ammonia allowed to evaporate overnight. Fifty milliliters of dry xylene was added, followed by 50 mL of distilled water. The two-phase mixture was filtered, and the organic layer was separated and dried over potassium hydroxide. The organic layer was distilled to give 6.5 g (39% yield) of the amine as a colorless oil, bp 82–85 °C.

Compounds **1–88** were isolated in 89–100% yields from the reaction of the appropriately substituted phenyl isocyanate and the desired propargylamine in dry benzene (see Table I). The procedure is given below for **7** and should be considered representative.

***N*-Ethyl-*N*-propargyl-*N'*-(4'-fluorophenyl)urea (7).** 4-Fluorophenyl isocyanate, 3.4 g (0.025 M), was reacted with 2.2 g of 94% *N*-ethyl-*N*-propargylamine in 50 mL of dry benzene. After the vigorous exothermic reaction had subsided, the mixture was heated on a steam bath for 30 min. The solution was cooled, and the product precipitated by the addition of petroleum ether. The solid was collected by vacuum filtration and air-dried. There was isolated 4.3 g (77%) of a solid which melted at 101–102 °C. The IR spectrum showed the NH band at 3.0 μm and the carbonyl band at 6.1 μm.

The structure of the novel *N*-alkyl-*N*-propargylphenylureas were confirmed by elemental, infrared, and NMR analyses.

Listed in Table II, the *N*-methyl-*N*-propargyloxy-*N'*-substituted phenylureas, **89–94**, were prepared in 44–60% yield by the reaction of *N*-hydroxy-*N'*-phenylureas with propargyl bromide in alcoholic sodium hydroxide:




A typical example is given for 89.

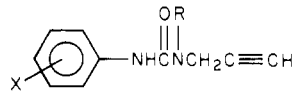
***N*-Methyl-*N*-propargyl-*N'*-phenylurea (89).** *N*-Hydroxy-*N*-methyl-*N'*-phenylurea [these compounds were prepared according to the method of French Patent

Diamond Shamrock Corporation, T. R. Evans Research Center, Painesville, Ohio 44077 (W.J.P., S.S.S.), and Boyce Thompson Institute for Plant Research, Inc., Yonkers, New York 10701.

[1]Present address: Mobil Chemical Co., Edison, NJ 08817.

0021-8561/79/1427-0537$01.00/0 

Table I. Structures, Chemical Properties, and Biological Activities of *N*-Alkyl-*N*-propargyl-*N*-substituted Phenylureas



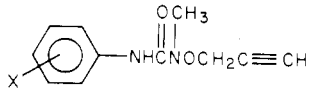

| | | | | | herbicidal activity[a,d] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | pre | | post | |
| no. | X | R | % yield | mp, °C | B | G | B | G |
| 1 | H | $CH_3$ | 92 | 101-102 | 4 | 0 | 5 | 3 |
| 2 | 2F | $CH_3$ | 91 | 99-100 | 4 | 1 | 5 | 1 |
| 3 | 2F | $C_2H_5$ | 81 | 54-55 | 4 | 2 | 4 | 2 |
| 4 | 3F | $CH_3$ | 79 | 90 | 4 | 0 | 6 | 5 |
| 5 | 3F | $C_2H_5$ | 77 | 101-102 | 5 | 3 | 6 | 6 |
| 6 | 4F | $CH_3$ | 79 | 90 | 4 | 0 | 6 | 5 |
| 7 | 4F | $C_2H_5$ | 77 | 101-102 | 5 | 3 | 6 | 5 |
| 8 | 4F | $C_3H_7$ | 77 | 79 | 0 | 0 | 1 | 1 |
| 9 | 3-Cl | H | 88 | 130-131 | 1 | 0 | 2 | 1 |
| 10 | 3-Cl | $CH_3$ | 89 | 93 | 4 | 0 | 4 | 3 |
| 11 | 4-Cl | H | 94 | 212 | 3 | 0 | 2 | 0 |
| 12 | 4-Cl | $CH_3$ | 66 | 107-108 | 5 | 4 | 8 | 6 |
| 13 | 4-Cl | $C_2H_5$ | 75 | 89-90 | 5 | 2 | 7 | 7 |
| 14 | 4-Cl | $C_3H_7$ | 78 | 95 | 3 | 0 | 3 | 0 |
| 15 | 4-Cl | $i$-$C_3H_7$ | 85 | 105 | 2 | 0 | 5 | 4 |
| 16 | 4-Cl | $C_6H_{12}$ | 98 | 105-107 | 0 | 0 | 0 | 0 |
| 17 | 4-Cl | $CH_2C{\equiv}CH$ | 88 | 55-57 | 0 | 0 | 2 | 2 |
| 18 | 3-Br | $CH_3$ | 73 | 96-97 | 4 | 0 | 5 | 3 |
| 19 | 4-Br | $CH_3$ | 95 | 94 | 2 | 1 | 8 | 6 |
| 20 | 4-Br | $C_2H_5$ | 93 | 103-104 | 4 | 2 | 7 | 6 |
| 21 | 4-I | $CH_3$ | 78 | 94-95 | 4 | 0 | 6 | 4 |
| 22 | 4-I | $C_2H_5$ | 48 | 116-117 | 4 | 0 | 6 | 5 |
| 23 | 3-$CH_3$ | H | 85 | 124-125 | 2 | 0 | 3 | 1 |
| 24 | 3-$CH_3$ | $CH_3$ | 78 | 99-100 | 2 | 3 | 4 | 4 |
| 25 | 4-$CH_3$ | $CH_3$ | 61 | 140-141 | 3 | 2 | 6 | 3 |
| 26 | 3-$C_2H_5$ | $CH_3$ | 82 | 75-76 | 5 | 2 | 7 | 5 |
| 27 | 4-$C_2H_5$ | $CH_3$ | 70 | 79-80 | 4 | 3 | 7 | 5 |
| 28 | 4-$i$-$C_3H_7$ | $CH_3$ | 76 | 110-112 | 2 | 0 | 7 | 7 |
| 29 | 4-$C_4H_9$ | $CH_3$ | 67 | 82 | 0 | 0 | 0 | 0 |
| 30 | 3-$OCH_3$ | $CH_3$ | 93 | 85 | 0 | 5 | 0 | 0 |
| 31 | 4-$OCH_3$ | H | 75 | 170-171 | 0 | 0 | 0 | 0 |
| 32 | 4-$OCH_3$ | $CH_3$ | 76 | 78 | 3 | 2 | 6 | 3 |
| 33 | 4-$OCF_3$ | $CH_3$ | 38 | 75-76 | 4 | 0 | 6 | 4 |
| 34 | 3-$OCF_2CF_2H$ | H | 84 | 87 | 3 | 0 | 5 | 5 |
| 35 | 3-$OCF_2CF_2H$ | $CH_3$ | 85 | 87 | 2 | 0 | 7 | 6 |
| 36 | 3-$OCF_2CF_2H$ | $C_2H_5$ | 71 | 47-48 | 2 | 0 | 7 | 6 |
| 37 | 3-$OCF_2CF_2H$ | $C_3H_7$ | 76 | 46 | 4 | 0 | 6 | 6 |
| 38 | 3-$OCF_2CF_2H$ | $i$-$C_3H_7$ | 89 | 45-46 | 5 | 2 | 6 | 5 |
| 39 | 3-$OCF_2CF_2H$ | $CH_2C{\equiv}CH$ | 69 | 50-51 | 3 | 0 | 6 | 6 |
| 40 | 4-$OCF_2CF_2H$ | $CH_3$ | 59 | 77-78 | 0 | 0 | 3 | 0 |
| 41 | 3-$OCH{=}CCl_2$ | $CH_3$ | 99 | 107-108 | 4 | 0 | 6 | 0 |
| 42 | 4-$OCH{=}CCl_2$ | $CH_3$ | 83 | 123-124 | 5 | 3 | 8 | 6 |
| 43 | 4-$OCH_2C(Cl){=}CH_2$ | $CH_3$ | 99 | 85 | 3 | 2 | 5 | 2 |
| 44 | 4-$OC_6H_5$ | $CH_3$ | 99 | 121-122 | 0 | 0 | 0 | 0 |
| 45 | 4-$SCH_3$ | $CH_3$ | 62 | 98-99 | 0 | 0 | 3 | 1 |
| 46 | 3-$COCH_3$ | $CH_3$ | 97 | 84 | 3 | 2 | 6 | 4 |
| 47 | 3-$C(CH_3){=}NOCH_3$ | $CH_3$ | 74 | 127 | 3 | 2 | 4 | 0 |
| 48 | 4-$C(CH_3){=}NOCH_3$ | $CH_3$ | 84 | 95-96 | 2 | 0 | 0 | 0 |
| 49 | 4-CN | $CH_3$ | 61 | 140-141 | 0 | 0 | 4 | 0 |
| 50 | 2,5-$F_2$ | H | 93 | 144-145 | 4 | 3 | 6 | 5 |
| 51 | 2,5-$F_2$ | $CH_3$ | 88 | 76-78 | 6 | 4 | 7 | 4 |
| 52 | 2,5-$F_2$ | $C_2H_5$ | 65 | 46 | 5 | 2 | 7 | 4 |
| 53 | 2,5-$F_2$ | $i$-$C_3H_7$ | 90 | 73-74 | 4 | 1 | 5 | 8 |
| 54 | 2,5-$F_2$ | $CH_2C{\equiv}CH$ | 88 | 55-57 | 0 | 0 | 2 | 2 |
| 55 | 3,4-$F_2$ | H | 98 | 173-174 | 0 | 0 | 3 | 3 |
| 56 | 3,4-$F_2$ | $CH_3$ | 83 | 90-92 | 3 | 2 | 6 | 5 |
| 57 | 2-F, 3-Cl | H | 100 | 120-121 | 3 | 0 | 6 | 6 |
| 58 | 2-F, 3-Cl | $CH_3$ | 95 | 128 | 3 | 3 | 3 | 5 |
| 59 | 2-F, 4-Cl | $CH_3$ | 95 | 91-92 | 3 | 3 | 3 | 5 |
| 60 | 2-F, 5-Cl | H | 94 | 154-155 | 2 | 0 | 3 | 3 |
| 61 | 2-F, 5-Cl | $CH_3$ | 61 | 75-76 | 4 | 3 | 5 | 3 |
| 62[b] | 2-F, 5-Cl | $C_2H_5$ | 66 | oil | 2 | 2 | 4 | 4 |
| 63 | 2-F, 5-Cl | $i$-$C_3H_7$ | 82 | 75 | 2 | 0 | 2 | 0 |
| 64 | 2-F, 5-Cl | $CH_2C{\equiv}CH$ | 87 | 80-92 | 0 | 0 | 2 | 1 |
| 65 | 2-F, 5-$CF_3$ | $CH_3$ | 75 | 90-91 | 1 | 0 | 3 | 2 |
| 66 | 2-F, 5-$CH_3$ | $CH_3$ | 83 | 80 | 3 | 0 | 3 | 2 |
| 67 | 2,4-$Cl_2$ | $CH_3$ | 73 | 58-59 | 0 | 0 | 0 | 0 |
| 68 | 2,5-$Cl_2$ | $CH_3$ | 89 | 87 | 0 | 0 | 0 | 0 |

Table I. (*Continued*)

| no. | X | R | % yield | mp, °C | herbicidal activity[a,d] pre B | pre G | post B | post G |
|---|---|---|---|---|---|---|---|---|
| 69 | 3,4-$Cl_2$ | H | 89 | 179-180 | 4 | 0 | 6 | 4 |
| 70 | 3,4-$Cl_2$ | $CH_3$ | 87 | 85 | 5 | 0 | 8 | 6 |
| 71 | 3,4-$Cl_2$ | $C_2H_5$ | 74 | 74-75 | 8 | 2 | 8 | 8 |
| 72 | 3,4-$Cl_2$ | $C_3H_7$ | 76 | 74-75 | 3 | 0 | 4 | 4 |
| 73[c] | 3,4-$Cl_2$ | *i*-$C_3H_7$ | 77 | 83-84 | 5 | 0 | 8 | 7 |
| 74 | 3,4-$Cl_2$ | $CH_2C{\equiv}CH$ | 94 | 84-85 | 3 | 0 | 6 | 6 |
| 75 | 3,5-$Cl_2$ | $CH_3$ | 97 | 141-142 | 0 | 0 | 0 | 0 |
| 76 | 3,5-$Cl_2$ | *i*-$C_3H_7$ | 59 | 92-93 | 0 | 0 | 0 | 0 |
| 77 | 3-Cl, 4-F | $CH_3$ | 80 | 65-66 | 7 | 4 | 8 | 7 |
| 78 | 3-Cl, 4-Br | $CH_3$ | 84 | 93-94 | 3 | 2 | 8 | 7 |
| 79 | 3-Cl, 4-$CH_3$ | $CH_3$ | 57 | 82 | 2 | 2 | 6 | 6 |
| 80 | 3-Cl, 4-$OCH_3$ | $CH_3$ | 61 | 130 | 4 | 1 | 8 | 8 |
| 81 | 3-Cl, 4-$C(CH_3)_3$ | $CH_3$ | 96 | 120-121 | 3 | 0 | 6 | 6 |
| 82 | 2-$CH_3$, 5-Cl | $CH_3$ | 78 | 93 | 0 | 0 | 0 | 0 |
| 83 | 2,6-(*i*-$C_3H_7$)$_2$ | $CH_3$ | 90 | 218-220 | 0 | 0 | 0 | 0 |
| 84 | 3,4-$(CH_3)_2$ | $CH_3$ | 89 | 110-111 | 2 | 0 | 4 | 2 |
| 85 | 3-$CH_3$, 4-$OCF_2CF_2H$ | $CH_3$ | 82 | 103-104 | 0 | 3 | 7 | 5 |
| 86 | 3,4-$O_2CH_2$ | H | 91 | 190 | 0 | 0 | 0 | 0 |
| 87 | 2-F, 4,5-$Cl_2$ | $CH_3$ | 50 | 80-81 | 4 | 0 | 6 | 4 |
| 88 | 3,4,5-$Cl_3$ | $CH_3$ | 61 | 101-102 | 4 | 0 | 5 | 6 |

[a] 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 preemergence application and 80% for postemergence application. See Biological Methods for complete rating table. [b] Yellow oil. [c] U.S. Patent 2 867 520, Beaver and Hamm (1959). [d] B, broadleaf; G, grasses.

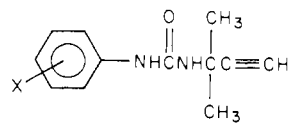
Table II. Structure, Chemical Properties, and Biological Activity of *N*-Methyl-*N*-propargyloxy-*N*-phenylureas



| no. | X | % yield | mp, °C | herbicidal activity[a] pre B | pre G | post B | post G |
|---|---|---|---|---|---|---|---|
| 89 | H | 44 | 154-155 | 0 | 0 | 0 | 0 |
| 90 | 3-Cl | 70 | 36-38 | 2 | 1 | 5 | 5 |
| 91 | 4-Cl | 20 | 66-67 | 5 | 1 | 5 | 4 |
| 92 | 3-$CH_3$ | 24 | 58-59 | 2 | 0 | 3 | 0 |
| 93 | 3,4-$Cl_2$ | 62 | 87-88 | 3 | 2 | 6 | 8 |
| 94 | 2,4-$F_2$ | 85 | 37-38 | 5 | 2 | 5 | 5 |

[a] 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 preemergence application and 80% for postemergence application. See Biological Methods section for complete rating table.

Table III. Structure, Chemical Properties, and Biological Activity of *N*-(1,1-Dimethyl-2-propargyl)-*N'*-phenylureas



| no. | X | % yield | mp, °C | herbicidal activity[a] pre B | pre G | post B | post G |
|---|---|---|---|---|---|---|---|
| 95 | 2-F | 95 | 170 | 3 | 2 | 6 | 3 |
| 96 | 3-$CH_3$ | 98 | 135 | 0 | 0 | 0 | 0 |
| 97 | 4-$C_4H_9$ | 94 | 113-115 | 0 | 0 | 0 | 0 |
| 98 | 4-$(CH_3)_3C$ | 98 | 174-175 | 0 | 0 | 0 | 0 |
| 99 | 2-Cl, 5-$CF_3$ | 95 | 174-175 | 0 | 0 | 0 | 0 |
| 100 | 2-F, 3-Cl | 92 | 137-139 | 2 | 0 | 5 | 6 |
| 101 | 2-F, 5-Cl | 83 | 161-162 | 0 | 0 | 0 | 0 |
| 102 | 2-F, 4-$CH_3$ | 73 | 130-131 | 0 | 0 | 0 | 0 |
| 103 | 2,4-$F_2$ | 90 | 157 | 2 | 2 | 2 | 2 |
| 104 | 2,5-$F_2$ | 95 | 142 | 5 | 2 | 6 | 5 |
| 105 | 2-F, 3,4-$Cl_2$ | 90 | 157 | 2 | 2 | 2 | 1 |

[a] 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 preemergence application and 80% for postemergence application. See Biological Methods section for complete rating table.

2 033 637, Disdier, Mocotte, Gonthier; *Chem. Abstr.* **75**, 48732, (1971)], 11.0 g (0.072 M), was reacted with 2.9 g (0.072 M) of sodium hydroxide dissolved in 10 mL of distilled water along with 80 mL of methyl alcohol. To this solution was added dropwise 8.5 g (0.072 M) of propargyl bromide in 15 mL of methyl alcohol. After all the bromide had been added, the solution was heated on a steam bath for 2 h. The solid that precipitated out on cooling was collected by vacuum filtration, washed with petroleum ether, and air-dried. There was isolated 6.0 g (44%) of solid which, when recrystallized from methyl alcohol, melted at 154–155 °C. The IR spectrum showed the NH band at 3.0 μm and the carbonyl band at 6.0 μm.

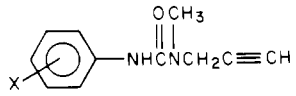
3-Amino-3-methyl-1-butyne prepared by the method of Hennion and Teach (1953) was reacted with the appropriately substituted phenyl isocyanate to give compounds **95–105**. Table III lists the compounds and the yield. A representative procedure is given for **104**.

***N*-(1,1-Dimethyl-2-propynyl)-*N'*-(2',5'-difluorophenyl)urea (104).** 2,5-Difluorophenyl isocyanate, 5.0 g (0.032 M), was reacted with 2.68 g (0.032 M) of 3-amino-3-methyl-1-butyne in 50 mL of dry benzene. After the exothermic reaction had subsided, the mixture was heated on a steam bath for 30 min. The solvent was distilled at reduced pressure and the residual solid recrystallized from benzene and petroleum ether to give 7 g (90%) of a white solid melting at 142 °C. The IR spectrum showed the NH band at 3.0 μm and the carbonyl band at 6.0 μm.

## BIOLOGICAL METHODS

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

Table IV. Preemergence Herbicide Field Test



| compd | X | kg/ha | % crop injury[a] | | | | % weed control[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | soybean | corn | cotton | wheat | grass | broadleaves |
| 1 | H | 2.24[b] | 98 | 65 | 100 | 100 | 98 | 100 |
| | | 1.12 | 55 | 40 | 63 | 100 | 68 | 65 |
| | | 0.56 | 27 | 10 | 27 | 100 | 48 | 28 |
| | | 0.28 | 0 | 0 | 0 | 100 | 0 | 0 |
| 4 | 3-F | 2.24 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 1.12 | 100 | 97 | 100 | 100 | 99 | 100 |
| | | 0.56 | 98 | 63 | 62 | 100 | 92 | 70 |
| | | 0.28 | 30 | 17 | 10 | 60 | 52 | 25 |
| 11 | 4-Cl | 2.24 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 1.12 | 100 | 100 | 50 | 100 | 96 | 95 |
| | | 0.56 | 93 | 95 | 37 | 97 | 78 | 73 |
| | | 0.28 | 30 | 28 | 5 | 63 | 33 | 20 |
| 21 | 4-I | 4.48 | 65 | 77 | 63 | 100 | 90 | 89 |
| | | 2.24 | 33 | 25 | 28 | 100 | 76 | 76 |
| | | 1.12 | 7 | 0 | 8 | 100 | 70 | 60 |
| | | 0.56 | 0 | 0 | 0 | 100 | 0 | 0 |
| | | 0.28 | 0 | 0 | 0 | 93 | 0 | 0 |
| 51 | 2,5-$F_2$ | 2.24 | 100 | 67 | 97 | 100 | 100 | 100 |
| | | 1.12 | 100 | 67 | 75 | 82 | 84 | 80 |
| | | 0.56 | 67 | 67 | 67 | 67 | 84 | 67 |
| | | 0.28 | 67 | 43 | 67 | 67 | 84 | 64 |
| 56 | 3,4-$F_2$ | 2.24 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 1.12 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | 0.56 | 85 | 80 | 52 | 100 | 100 | 95 |
| | | 0.28 | 62 | 43 | 22 | 67 | 82 | 54 |
| 61 | 2-F, 5-Cl | 2.24 | 100 | 100 | 98 | 100 | 100 | 100 |
| | | 1.12 | 98 | 58 | 65 | 100 | 98 | 98 |
| | | 0.56 | 97 | 77 | 52 | 97 | 91 | 73 |
| | | 0.28 | 0 | 0 | 0 | 0 | 0 | 0 |
| 70 | 3,4-$Cl_2$ | 2.24 | 83 | 85 | 100 | 100 | 91 | 75 |
| | | 1.12 | 27 | 0 | 0 | 80 | 81 | 58 |
| | | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 0.28 | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Average weed control and crop injury of three replications (Pre-Plant Incorporated) using scale of 0-100 where 0 is a completely normal plant and 100 is complete destruction. [b] The 4.48 rate is omitted when the rating is 95% or greater.

(Rohm and Haas) X-155 surfactant. The resultant formulations contained 2080 ppm of test compound in 50% by volume of acetone–water and 0.025% by weight of surfactant. Lower concentrations were obtained by diluting the stock formulation with 50% aqueous acetone containing 0.025% surfactant.

The pre- and postemergence test was run in a 23 × 23 × 5 cm fiber pan containing 3.8 cm of composted soil. Seeds of redroot pigweed (*Amaranthus retroflexus*), velvetleaf (*Abutilon theophrasti*), mustard (*Brassica kaber*), red millet (*Panicum miliaceum*), green foxtail (*Setaria viridis*), and Japanese Millet (*Echinochloa frumentacea*) were planted about 1 cm deep in one-half of the tray. The tray was transferred to the greenhouse where the test species were allowed to grow until one true leaf was present on the slowest growing species (redroot pigweed). This required 7–14 days, depending on the time of the year. The other one-half of the tray was then planted with the same six species. The tray was sprayed with 40 mL of the stock test 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. The rating number relates to the applied dose, according to Scheme I. The rating numbers for each test compound are recorded in Tables I–III.

The criterion for passing the preemergence test was 50% control of any one of the test species are compared to the untreated check. Eighty percent control of the test species

Scheme I

| test rate | rating number | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| kg/ha | 17.92 | 8.96 | 4.48 | 2.24 | 1.12 | 0.56 | 0.28 | 0.14 | 0.07 |

was required for passage of the postemergence test. For example, a compound that gave 50% preemergence control of the broadleaf weeds at 4.48 kg/ha and less than 50% control at 2.24 kg/ha would receive a 3 rating. An increase of 1 rating number corresponds to a twofold increase in activity in any given test.

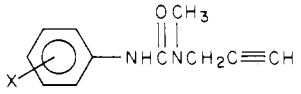
Field evaluations were run in plots which had been cleared of all annual weeds and sown with the following crop and weed plants: crops—corn (*Zea mays*), soybean (*Glycine max*), cotton (*Gossypium hirsutum*), and wheat (*Triticum aestivum*); broadleaf weeds—redroot pigweed (*Amaranthus retroflexus*), cocklebur (*Xanthium pensylvanicum*), annual morningglory (*Ipomoea purpurea*), and velvetleaf (*Abutilon theophrasti*); grasses—barnyardgrass (*Echinochola crus-galli*), and greenfoxtail (*Setaria viridis*). On the day before sowing, the field was treated with aqueous suspensions prepared from 50% wettable 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, 0.56, and 0.28

Table V. Preemergence Herbicide Field Test Standards

| standard | kg/ha | % crop injury[a] | | | | % weed control[a] | |
|---|---|---|---|---|---|---|---|
| | | soybean | corn | cotton | wheat | grass | broadleaves |
| monuron | 2.24 | 100 | 100 | 92 | 100 | 100 | 100 |
| | 1.12 | 100 | 100 | 87 | 100 | 100 | 100 |
| | 0.56 | 100 | 100 | 58 | 100 | 100 | 100 |
| | 0.28 | 100 | 100 | 67 | 100 | 96 | 99 |
| diuron | 2.24 | 100 | 100 | 48 | 100 | 100 | 100 |
| | 1.12 | 100 | 100 | 48 | 100 | 100 | 100 |
| | 0.56 | 90 | 100 | 23 | 100 | 92 | 85 |
| | 0.28 | 30 | 60 | 17 | 100 | 81 | 44 |
| linuron | 2.24 | 90 | 100 | 92 | 100 | 100 | 98 |
| | 1.12 | 90 | 98 | 85 | 100 | 100 | 100 |
| | 0.56 | 50 | 50 | 25 | 100 | 84 | 80 |
| | 0.28 | 48 | 50 | 40 | 92 | 60 | 56 |
| fluometuron | 2.24 | 100 | 100 | 77 | 100 | 100 | 100 |
| | 1.12 | 100 | 100 | 28 | 100 | 100 | 100 |
| | 0.56 | 85 | 100 | 13 | 100 | 100 | 98 |
| | 0.28 | 62 | 37 | 0 | 100 | 81 | 82 |
| alachlor | 2.24 | 0 | 0 | 0 | 70 | 100 | 45 |
| | 1.12 | 0 | 0 | 0 | 45 | 98 | 30 |
| | 0.56 | 0 | 0 | 0 | 33 | 92 | 26 |
| | 0.28 | 0 | 0 | 0 | 0 | 16 | 4 |
| check | | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Average weed control and crop injury of three replications (Pre-Plant Incorporated) using scale of 0-100 where 0 is a completely normal plant and 100 is complete destruction.

Table VI. Postemergence Herbicide Field Test



| compd | X | kg/ha | % crop injury[a] | | | | % weed control[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | soybean | corn | cotton | rice | grass | broadleaves |
| **1** | H | 4.48 | 67 | 12 | 63 | 67 | 50 | 62 |
| | | 2.24 | 27 | 3 | 5 | 33 | 30 | 27 |
| | | 1.12 | 33 | 0 | 7 | 25 | 28 | 23 |
| | | 0.56 | 33 | 0 | 0 | 0 | 0 | 0 |
| **4** | 3-F | 4.48 | 100 | 57 | 97 | 100 | 97 | 100 |
| | | 2.24 | 100 | 43 | 68 | 100 | 77 | 99 |
| | | 1.12 | 8 | 0 | 17 | 33 | 31 | 16 |
| | | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| **11** | 4-Cl | 4.48 | 90 | 33 | 63 | 100 | 86 | 100 |
| | | 1.12 | 7 | 5 | 3 | 33 | 23 | 23 |
| | | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| 21 | 4-I | 4.48 | 17 | 17 | 22 | 67 | 58 | 55 |
| | | 2.24 | 0 | 0 | 0 | 33 | 11 | 15 |
| | | 1.12 | 0 | 0 | 0 | 33 | 21 | 12 |
| | | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| **51** | 2,5-$F_2$ | 4.48 | 100 | 30 | 100 | 100 | 99 | 100 |
| | | 2.24 | 100 | 10 | 67 | 100 | 89 | 99 |
| | | 1.12 | 53 | 3 | 25 | 67 | 43 | 64 |
| | | 0.56 | 33 | 0 | 0 | 0 | 0 | 11 |
| **56** | 3,4-$F_2$ | 4.48 | 100 | 90 | 97 | 100 | 100 | 100 |
| | | 2.24 | 100 | 23 | 57 | 100 | 91 | 94 |
| | | 1.12 | 47 | 0 | 12 | 67 | 63 | 66 |
| | | 0.56 | 7 | 0 | 0 | 0 | 0 | 0 |
| **61** | 2-F, 5-Cl | 4.48 | 100 | 47 | 63 | 67 | 70 | 70 |
| | | 2.24 | 67 | 30 | 23 | 67 | 55 | 57 |
| | | 1.12 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| **70** | 3,4-$Cl_2$ | 4.48 | 100 | 77 | 47 | 100 | 100 | 100 |
| | | 2.24 | 92 | 33 | 10 | 100 | 88 | 88 |
| | | 1.12 | 3 | 0 | 0 | 33 | 32 | 33 |
| | | 0.56 | 0 | 0 | 0 | 33 | 17 | 26 |

[a] Average weed control and crop injury of three replications (Pre-Plant Incorporated) using scale of 0-100 where 0 is a completely normal plant and 100 is complete destruction. [b] The 0.28 rate is omitted because it gave all 0's.

kg/ha. Eight weeks after treatment, the degree of damage to the test plants was subjectively assessed on a scale of 0–100, 0 denoting a completely normal plant and 100 denoting complete destruction. The degree of damage to the crops, broadleaf weeds, and grasses, in the field evaluations are summarized in Tables IV and V.

**In Vitro Activity.** The relative activity of a number of propargyl ureas as inhibitors of the Hill reaction was determined using chloroplasts isolated from the spinach leaves according to the procedure published previously by

Table VII. Postemergence Herbicide Field Test Standards

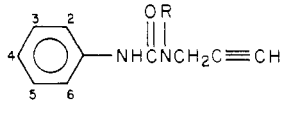
| standard | kg/ha | % crop injury[a] soybean | corn | cotton | rice | % weed control[a] grass | broadleaves |
|---|---|---|---|---|---|---|---|
| monuron | 4.48 | 100 | 100 | 37 | 100 | 100 | 100 |
| | 2.24 | 100 | 100 | 33 | 100 | 100 | 100 |
| | 1.12 | 97 | 82 | 15 | 100 | 100 | 100 |
| | 0.56 | 73 | 23 | 7 | 67 | 66 | 66 |
| diuron | 4.48 | 100 | 97 | 13 | 100 | 100 | 100 |
| | 2.24 | 100 | 97 | 3 | 100 | 100 | 100 |
| | 1.12 | 100 | 70 | 0 | 100 | 100 | 100 |
| | 0.56 | 67 | 15 | 0 | 67 | 67 | 65 |
| linuron | 4.48 | 43 | 17 | 40 | 100 | 97 | 94 |
| | 2.24 | 0 | 0 | 20 | 67 | 66 | 62 |
| | 1.12 | 0 | 7 | 0 | 67 | 58 | 60 |
| | 0.56 | 0 | 0 | 3 | 67 | 64 | 63 |
| flumeturon | 4.48 | 100 | 62 | 33 | 100 | 94 | 98 |
| | 2.24 | 100 | 33 | 0 | 100 | 81 | 92 |
| | 1.12 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0.56 | 0 | 0 | 0 | 0 | 0 | 0 |
| paraquat | 4.48 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 2.24 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 1.12 | 100 | 97 | 98 | 100 | 99 | 92 |
| | 0.56 | 38 | 65 | 67 | 100 | 95 | 83 |
| | 0.28 | 0 | 13 | 43 | 100 | 92 | 70 |
| check for 5 reps | | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Average weed control and crop injury of three replications (Pre-Plant Incorporated) using scale of 0-100 where 0 is a completely normal plant and 100 is complete destruction.

Holm and Stallard (1974).

## RESULTS AND DISCUSSION

**Greenhouse Testing Results.** From the herbicidal screening results found in Tables I, II, and III, the most active compounds on broadleaf weed species, both in the post- and preemergence tests, are summarized below using the following Markush structure:



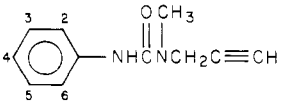

Generally, the activity was decreased by the subtle change in alkyl substitution at nitrogen, i.e., R = $C_2H_5$ > $CH_3$ > $i$-$C_3H_7$. The phenyl group containing a halogen (F, Cl, Br, I, or a $C_2HF_2CF_2O$-) in the 3 or 4 position or both led to active derivatives. Substituted ureas with fluorine atoms in the 2 or 2,5 position of the phenyl ring were also active both as post- and preemergence herbicides on broadleaf weeds.

Three of the most active compounds against broadleaf weeds in postemergence tests were *N*-ethyl-*N*-propargyl-*N'*-(3,4-dichlorophenyl)urea (**71**), *N*-methyl-*N*-propargyl-*N'*-(3-chloro-4-methoxyphenyl)urea (**80**), and *N*-methyl-*N*-propargyl-*N'*-(3-chloro-4-fluorophenyl)urea (**77**). Three of the most active compounds against broadleaf weeds in the preemergence tests were *N*-methyl-*N*-propargyl-*N'*-(2,5-difluorophenyl)urea (**51**), **71**, and **77**.

The most active compounds on the grassy weed species both post- and preemergence are summarized by the previously given Markush structure. Again, the following decrease in activity was observed: R = $C_2H_5$ > $CH_3$ > $C_3H_7$(i). Substitution of the phenyl moiety in the 3 or 4 position or both with a halogen, i.e., F, Cl, Br, or I or with an electron donating group, i.e., isopropyl in the 4 position, resulted in very active postemergence control of grasses. The most active compounds postemergence on grassy weeds were **53**, **71**, and **80**.

Three of the most active compounds preemergence on grassy weeds were **51**, *N*-methyl-*N*-propargyl-*N'*-(4-chlorophenyl)urea (**12**), and *N*-methyl-*N*-propargyl-*N'*-(3-methoxyphenyl)urea (**30**).

Table VIII. Comparison of Inhibitor Activity of *N*-Methyl-*N*-propargyl-*N'*-phenylureas in the Hill Reaction




| no. | 2 | 3 | 4 | 5 | 6 | $I_{50}$, M | log (1/$C$) |
|---|---|---|---|---|---|---|---|
| diuron[a] | | | | | | $1.55 \times 10^{-7}$ | 6.81 |
| **70** | H | Cl | Cl | H | H | $1.44 \times 10^{-7}$ | 6.84 |
| **21** | H | H | I | H | H | $4.78 \times 10^{-7}$ | 6.33 |
| **12** | H | H | Cl | H | H | $1.44 \times 10^{-6}$ | 5.83 |
| **4** | H | F | H | H | H | $1.55 \times 10^{-6}$ | 5.77 |
| **56** | H | F | F | H | H | $1.61 \times 10^{-6}$ | 5.79 |
| **1** | H | H | H | H | H | $1.06 \times 10^{-5}$ | 4.90 |
| **61** | F | H | H | Cl | H | $1.99 \times 10^{-5}$ | 4.70 |
| **51** | F | H | H | F | H | $2.32 \times 10^{-5}$ | 4.63 |

[a] *N,N*-Dimethyl-*N'*-(3,4-dichlorophenyl)urea.

Probably the best overall compounds would range as follows: **71 = 77 > 12 = 42 = 80 > 13 = 51 > 7 = 73 = 78 > 20 = 26 = 70**.

Replacing the phenyl moiety of the propargylureas with a sulfolanyl, piperidinyl, or naphthyl group gave ureas which were completely inactive as herbicides.

**Field Testing Results.** In this series, **70** was the best preemergence compound (Tables IV and V). It gave the best crop tolerance, while still controlling both broadleaf and grassy weeds.

Compound **56** was the most active compound in this series in the postemergence testing, showing good weed control on both broadleaf and grasses with good tolerance to corn and cotton (Tables VI and VII). When evaluated in the Hill reaction, these compounds were highly effective inhibitors of electron transport with **70** being as active as diuron (Table VIII). The results of the log (1/$C$) values obtained in the Hill reaction studies correlates roughly with the values obtained on grasses in the postemergence test in the greenhouse, compound **70** being the most active and **51** being the least active.

LITERATURE CITED

Beaver, D. J., Hamm, P. C., Stoffel, P. J., Monsanto Chemical Co., U.S. Patent 2867520 (1959).
Disdier, A., Mocotte, J., Gonthier, B., Progil SA, French Patent 2033637; *Chem. Abstr.* **75**, 48732 (1971).
Hennion, G. F., Teach, E. G., *J. Am. Chem. Soc.* **75**, 1653 (1953).
Holm, R. E., Stallard, D. E., *Weed Sci.* **22**, 20 (1974).
Kearney, P. C., Kaufman, D. D., "Herbicides", 2nd ed, Marcel Dekker, New York, 1975, pp 216–217.
Peters, L. R., Hennion, G. F., *J. Med. Chem.* **7** (3), 390 (1964).

Received for review August 24, 1978. Accepted January 8, 1979.

# Structure–Activity Relationships for Antidotes to Thiocarbamate Herbicides in Corn

Gerald R. Stephenson,* Nigel J. Bunce, Ruth I. Makowski, Michael D. Bergsma, and James C. Curry

Seventeen different amides and one carbamate were synthesized as possible antidotes for six different thiocarbamate herbicides in corn. Only six of the 18 compounds failed to show significant antidote activity for at least one thiocarbamate herbicide. In quartz sand nutrient culture, dichloroacetamides were significantly more active than monochloro or trichloro analogues as antidotes for molinate (*S*-ethyl hexahydro-1*H*-azepine-1-carbothioate) or cycloate (*S*-ethyl *N*-ethylthiocyclohexanecarbamate). In quartz sand nutrient culture, various dichloroacetamides varying in N substituents were highly effective as antidotes for particular thiocarbamate herbicides with essentially identical N substituents. However, when applied to soil, R25788 (*N,N*-diallyl-2,2-dichloroacetamide) was the most effective antidote for at least five different thiocarbamates, apparently due to greater availability for uptake from the soil. We conclude that amides that are closely similar in structure to various thiocarbamate herbicides are often effective antidotes to these herbicides in corn.

*N,N*-Diallyl-2,2-dichloroacetamide (R-25788) was developed as a selective antidote to either EPTC (*S*-ethyl *N,N*-dipropylthiocarbamate) or butylate (*S*-ethyl *N,N*-diisobutylthiocarbamate) in corn (*Zea mays* L.) by Pallos et al. (1977) in 1972. Although extensive research of a practical and mechanistic nature has been conducted [see reviews by Blair et al. (1976) and Pallos and Casida (1978)], there is not yet full agreement on the actual mechanisms involved for the action of either the thiocarbamate herbicides or the dichloroacetamide antidotes for these herbicides in corn. Lay and Casida (1978) have proposed that the sulfur atom of EPTC or other thiocarbamates is highly important for phytotoxicity because of the production of the EPTC-sulfoxide, a highly toxic oxidizing metabolite within corn. They propose that glutathione-SH complexes with and detoxifies these sulfoxides and that glutathione-SH production is enhanced by the dichloroacetamide antidotes. Wilkinson (1978a) has shown that EPTC effects on fatty acid synthesis in several plants can be reversed by R-25788. In a more recent report, Wilkinson (1978b) has shown that EPTC influences the synthesis of kaurene, an intermediate in the production of gibberellic acid. Thus it is possible that the antidote may be acting at the hormone level as well.

In an earlier study (Stephenson et al., 1978), it was established that amides closely similar in structure to EPTC were even more effective than R-25788 as antidotes for EPTC in corn grown in a "soil free" system. The purpose of the study reported herein was to determine whether similar structure–activity relationships could be observed among series of analogues "closely similar" to other thiocarbamate herbicides.

## MATERIALS AND METHODS

**Synthesis of Amide Analogues.** The amide antidote analogues were synthesized from the appropriate acid chlorides and amines as previously described (Stephenson et al., 1978). Overall yields were typically 50–60% (see Supplementary Material Available paragraph).

**Quartz Sand Nutrient Culture Bioassay.** Corn (*Zea mays* L. United Hybrid 106, Stewart 2501, Golden Beaver) was germinated in petri dishes at 24 °C and then transferred to quartz sand nutrient culture in styrofoam cups as previously described (Stephenson et al., 1978). The plants were maintained in a growth room with a 16-h photoperiod with 46 klux light intensity at 24 °C and an 8-h dark period at 20 °C. Appropriate combinations of herbicide and antidote solutions were added simultaneously in 20-mL volumes of nutrient solution to the quartz sand. Treatments were applied twice at 2 and 4 days after transplanting. The plants were maintained with half-strength Hoagland's nutrient solution until harvested 10–11 days after transplanting.

**Bioassays in Soil.** Some bioassays were repeated in soil. Most conditions were the same except that the pregerminated seeds were transferred to soil in 10-cm peat pots. The appropriate treatments were applied in 50-mL volumes of $H_2O$ when the corn seedlings began to emerge. After treatment a thin layer of soil was added to the surface of each pot to prevent losses by volatilization. Ten days later, this treatment procedure was repeated. Fertility was maintained by weekly watering with soluble 20-20-20 fertilizer until the plants were harvested 20 days after transplanting. The soil was 10% clay, 56% sand, 30% silt, and 4% organic matter and had a pH of 7.4.

**Statistical Procedures.** All individual experiments were conducted twice with at least four replicates per treatment. Corn shoot weights were obtained after oven drying. Data were subjected to analysis of variance and Duncan's Multiple Range Tests to facilitate comparisons of antidote activity.

## RESULTS AND DISCUSSION

**Antidotes for Molinate.** Six different dichloroacetamides varying in N substituents were synthesized as possible antidotes for molinate (*S*-ethyl hexahydro-1*H*-

Departments of Environmental Biology and Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1.

0021-8561/79/1427-0543$01.00/0 