

3-(4-Cyclopropylphenyl)-1,1-dimethylurea, a Selective Herbicide for Weed Control in Cereal Grains

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The herbicidal effectiveness of 3-(4-cyclopropylphenyl)-1,1-dimethylurea (PH 40-51) was demonstrated in a number of field trials in the Netherlands and France, especially on monocotyledonous weeds in cereals. The effective dosage was

1.5–2.0 kg of ai/ha, while at 3.0 kg of ai/ha an excellent crop tolerance was found. Several routes for the preparation of PH 40-51 have been considered. None of them proved to be economically attractive.

In a number of laboratory tests for herbicidal activity, 3-(4-cyclopropylphenyl)-1,1-dimethylurea, coded PH 40-51, showed very promising results. This prompted us to investigate in detail the possible routes of synthesis of this compound, with the synthesis of 4-cyclopropylaniline as the main problem. In addition, the properties of this herbicide were tested both in the greenhouse and in the field. In this paper an account of this experimental work is presented.

CHEMICAL METHODS

In the literature two methods for the preparation of 4-cyclopropylaniline are cited (Figure 1, routes A and B). A third one is also described in Figure 1, route C.

Acetylation of cyclopropylbenzene (route A: Hahn *et al.*, 1968; Hart *et al.*, 1968) followed by a Schmidt rearrangement (Hahn *et al.*, 1968) of the resulting 4-cyclopropylacetophenone gives fair yields of 4-cyclopropylacetanilide. The latter compound can be hydrolyzed to 4-cyclopropylaniline.

Nitration of cyclopropylbenzene (route B: Hahn *et al.*, 1968; Ketcham *et al.*, 1963) gives very poor yields of the desired 4-cyclopropylnitrobenzene, as ortho substitution is strongly favored by the cyclopropyl ring system.

Route C. 1-Chloro-3-phenylpropane was nitrated (Iliceto *et al.*, 1960), which, after a crude distillation, resulted in a 1:1 mixture of 1-chloro-3-(2-nitrophenyl) and 1-chloro-3-(4-nitrophenyl)propane; 105.0 g (0.50 mol) of this mixture was dissolved in 200 ml of DMF. To the stirred solution was added 33.0 g of powdered potassium hydroxide (0.50 mol; KOH containing 15% water) at room temperature. The mixture was kept overnight and continuously stirred. The dark solution was poured onto crushed ice and the resulting mixture extracted three times with ether. The combined ether layers were washed successively with a 5% solution of sodium hydrogencarbonate and with water, and were finally dried over sodium sulfate. On distillation we obtained 34.6 g of 4-cyclopropylnitrobenzene (85%), bp 110–112° (2 mm). A sample of the distilled product was analyzed by glc on a 100-cm column containing 10% FFAP on Chromosorb W-HP (80–100 mesh); the column temperature was 160°. The analysis showed the product to contain 98.3% of the desired 4-cyclopropylnitrobenzene and 1.7% of the 2 isomer. 3-Chloro-1-(2-nitrophenyl)propane was dehydrochlorinated very slowly under the described conditions and was present in the distillation residue in large quantities. 4-Cyclopropylnitrobenzene was hydrogenated to 4-cyclopropylaniline as described by Hahn *et al.* (1968).

3-(4-Cyclopropylphenyl)-1,1-dimethylurea (PH 40-51). 4-Cyclopropylaniline (26.6 g, 0.20 mol) was dissolved in 100 ml of acetonitrile and 17 ml (0.21 mol) of pyridine.

24.7 g of dimethylcarbonylchloride (0.23 mol) was added, with the temperature rising to 35°. After stirring for 24 hr, the resulting deep red reaction mixture was concentrated *in vacuo* to 60 ml and poured into water. The resulting crystals were collected, dried, and recrystallized twice from benzene, affording 28.5 g (70%) of PH 40-51, white crystals with a mp of 152.0–153.0°: nmr (CDCl₃) δ 0.4–1.0 (cyclopropane, AA'BB' part of an AA'BB'X system), 1.84 (cyclopropane, X part of an AA'BB'X system, 2.98 [N(CH₃)₂], 7.25 (2,6-H₂, aromatic, AA' part of an AA'BB' system), 6.97 (3,5-H₂, aromatic, BB' part of an AA'BB' system), 6.31 (NH).

Anal. Calcd for C₁₂H₁₆N₂O (204.26): C, 70.56; H, 7.90; N, 13.72. Found: C, 70.6; H, 8.0; N, 13.7.

HERBICIDAL PROPERTIES

Greenhouse Trials. PH 40-51 was tested in the greenhouse in pre- and postemergence applications in comparison with methabenzthiazuron, 1-(2-benzothiazolyl)-1,3-dimethylurea, and with metoxuron, 3-(3-chloro-4-methoxyphenyl)-1,1-dimethylurea.

In a triplicate postemergence greenhouse trial, young plants of 14 species, generally in the two-leaf stage, were potted and sprayed at rates of 0.25, 0.5, and 1.0 kg of ai/ha using 1000 l. of water/ha. Three weeks later the results were evaluated by assessing the phytotoxicity on a scale of 0 (no damage) to 5 (plants dead). The results are given in Table I. From these data it is found that a number of important weeds were effectively controlled in the greenhouse at the level of 1.0 kg of ai/ha. In comparison to methabenzthiazuron and metoxuron, which are both used in practice in cereal crops, PH 40-51 showed a similar level of activity, justifying further evaluation in the field. The observed phytotoxic effects were identical with those of many other phenylurea herbicides which are known to interfere with the photosynthetic Hill reaction.

In a triplicate preemergence greenhouse trial, *Avena fatua*, *Alopecurus myosuroides*, and wheat, *Triticum vulgare* cv. Peco, were sown in flats and sprayed immediately after sowing at rates of 1.0, 3.0, and 6.0 kg of ai/ha using 1000 l. of water/ha. Three weeks after emergence the phytotoxicity was assessed in the same way as in the postemergence trial. Then the plants were cut off and *Lepidium sativum* was sown in order to establish the residual activity of the compounds. Eight weeks later the phytotoxicity was determined again. The results are presented in Table II. PH 40-51 showed a good preemergence activity at a rate of 3.0 kg of ai/ha against *Alopecurus myosuroides* and a moderate activity against *Avena fatua*. Wheat showed some tolerance at a dose of 3.0 kg of ai/ha.

In Table III the results are given of an additional greenhouse trial to determine the tolerance of a number of cereals to a postemergence treatment in the three- to four-leaf stage. Wheat proved to be slightly more tolerant for PH 40-51 than for metoxuron.

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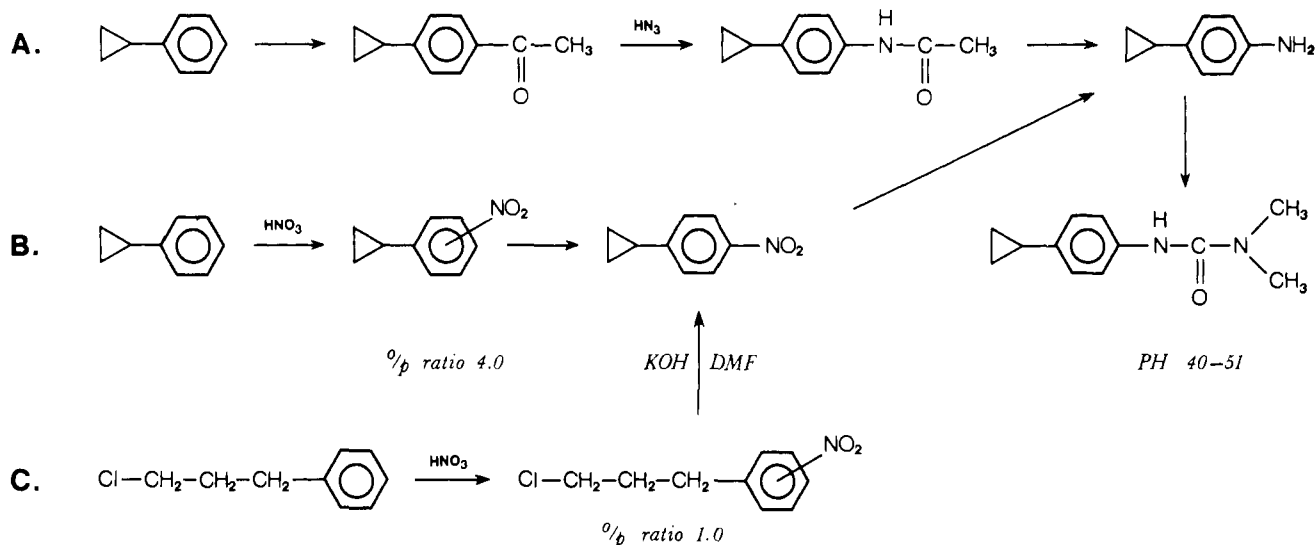


Figure 1. Three methods for the preparation of PH 40-51.

Table I. Postemergence Greenhouse Trial

Dosages, kg of ai/ha	PH 40-51			Metabenz- thiazuron			Metoxuron		
	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0
<i>Avena fatua</i>	2-3 ^a	3-4	4-5	2	2-3	3			
<i>Alopecurus myosuroides</i>	1	3	4	0	2-3	3	1	3-4	4
<i>Poa annua</i>	2-3	4	5	3	3-4	4	4-5	4-5	5
<i>Echinochloa cruss-galli</i>	1	1	2	1	2	3-4	1	1	2
<i>Galium aparine</i>	0	0	1	0	1	2	3-4	4	4-5
<i>Polygonum convolvulus</i>	0	2	4	4-5	5	5	5	5	5
<i>Polygonum persicaria</i>	3-4	5	5	4-5	5	5	4	4-5	4-5
<i>Matricaria chamomilla</i>	4-5	4-5	5	4-5	5	5	4	4-5	4-5
<i>Galinsoga parviflora</i>	4	5	5	4-5	5	5	3-4	4	4-5
<i>Stellaria media</i>	3	4	4-5	5	5	5	3-4	4-5	5
<i>Plantago media</i>	2	2	4	4	4-5	5	2	2	3
<i>Capsella bursa- pastoris</i>	3-4	4-5	5	3	4	5	3-4	5	5
<i>Urtica urens</i>	5	5	5	4-5	5	5	4-5	5	5
<i>Chenopodium album</i>	4-5	5	5	4	4-5	4-5	4	4-5	4-5

^a 0 = no damage; 5 = plants dead.

Field Trials. In 1970 and 1971, a number of field trials were carried out with PH 40-51 in the Netherlands and in France, mainly aimed at the control of black grass (*Alopecurus myosuroides*) in autumn-sown wheat. The product was applied postemergence (in spring) in dosages ranging from 0.5 to 3.0 kg of ai/ha. In the Netherlands a comparison was made with the standard dose of metoxuron, i.e., 4.0 kg of ai/ha. In triplicate trials with metoxuron, an average 82% kill was attained, while PH 40-51 at dosages of 1.5 to 2.0 kg of ai/ha gave comparable or better results. In five trials in France, 4.0 kg of "Cyflanit" (a formulation containing 31.2% dichlobenil and 11.2% monolinuron) served as the standard. Dosages of 1.0 to 2.0 kg of PH 40-51 ai/ha gave results comparable with those of the standard mixture "Cyflanit."

The effectiveness of PH 40-51 against broad-leaved weeds was assessed in a number of the above-mentioned

Table II. Preemergence Greenhouse Trial

Dosages, kg of ai/ha	PH 40-51			Methabenz- thiazuron			Metoxuron		
	1.5	3.0	6.0	1.5	3.0	6.0	1.5	3.0	6.0
<i>Avena fatua</i>	0 ^a	2	3	0	1	2-3	0	2	3-4
<i>Alopecurus myosuroides</i>	3-4	4-5	5	3	4	5	2	3	3-4
<i>Triticum vulgare</i> cv. Peco (wheat)	0	1	2	0	1	2-3	0	2	3
<i>Lepidium sativum</i> (residual effect after 8 weeks)	1	4	4-5	1	2-3	4	0	0	2

^a 0 = no damage; 5 = plants dead.

Table III. Tolerance of Cereals in a Postemergence Greenhouse Trial

Dos- ages, kg of ai/ha	PH 40-51			Methabenz- thiazuron			Metoxuron		
	1.0	2.0	4.0	1.0	2.0	4.0	1.0	2.0	4.0
Wheat	1 ^a	1-2	2-3	0	1	2	1	3	3-4
Barley	1	1-2	2-3	0	1	2-3	1	1-2	2
Oats	2-3	3-4	4-5	1	1-2	3	1	2	2-3
Rice	2	3-4	4-5	2	3-4	4-5			

^a 0 = no damage; 5 = plants dead.

trials. At a dosage of 2.0 kg of ai/ha, the control averaged about 85%, and at 3.0 kg of ai/ha was about 95%. In the present field trials the following weeds proved to be sensitive: *Matricaria*, *Stellaria*, *Sinapis*, *Ranunculus*, and *Anthemis* spp. Moderately sensitive were: *Polygonum*, *Raphanus*, and *Myosotis* spp., while *Veronica*, *Fumaria*, *Galium*, *Viola*, and *Senecio* spp. were found to be moderately resistant.

In a limited number of trials on autumn-sown wheat in France, the effectiveness of PH 40-51, applied postemergence against wild oats (*Avena fatua*) was assessed. The results indicate a good control at dosages of 2.0-2.5 kg of ai/ha.

With postemergence applications of PH 40-51, no phytotoxicity or growth depression of autumn-sown wheat was noted at dosages up to 3.0 kg of ai/ha. In the limited number of trials where this dosage was used, 4.0 kg of ai/ha proved to be slightly phytotoxic.

CONCLUSIONS

At rates of application ranging from 1.5 to 3.0 kg of ai/ha, PH 40-51 proved to be an effective and safe black grass herbicide in autumn-sown wheat. At these dosages, a number of important broad-leaved weeds are also satisfactorily controlled. The apparent effectiveness against wild oats in cereals merits further evaluation. Studies on the synthesis of PH 40-51 have so far not resulted in a process which is economically acceptable.

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Received for review May 29, 1973. Accepted August 23, 1973.

Homeosterically Related Plant Growth Regulators.¹ I. Synthesis

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Four structurally related series of potential plant growth-regulating compounds have been synthesized containing $-\text{OCH}_2-$, $-\text{NHCH}_2-$, $-\text{CH}_2\text{CH}_2-$,

and $-\text{S}-$ in the same relative structural position in the molecules.

In conjunction with the biological response produced by synthetic plant growth regulators, considerable efforts have been made to correlate these activities with the chemical structures of the compounds (Wain and Fawcett, 1969); the published data have often been concerned with correlations using the aryl and aryloxy acids and their derivatives as model compounds (Osborne and Wain, 1951; Wain, 1958). In addition to studies concerning the overall structure, attempts have also been made to correlate biological activity with variations in benzene ring substituents, including the number and position of the substituents (Fawcett *et al.*, 1953). It has generally been observed that biological activity of the compounds may be increased by the addition of halogen (usually chlorine) on the aromatic nucleus. However, even with the vast amount of information collected concerning structure-activity relationships, the molecular basis of their mode of action has been indicated in only a few instances (Barth and Michel, 1969; Overbeek, 1961; Wain and Wightman, 1957).

Attempts to correlate chemical structure with plant growth activity were made by Koepfli *et al.* (1938) and were subsequently modified by Went (1949) to the effect that an unsaturated ring system and a side chain adjacent to the ring double bond containing at least two carbon atoms ending in a carboxyl group were all that was necessary for plant growth-regulating activity. While there are many exceptions, it is of interest to note that many synthetic compounds which are active in affecting plant growth still meet these criteria.

A recent compilation of organic herbicidal compounds which are presently in commercial use included 75 structures, of which 9% possessed a carbamate linkage, 5% a thiolcarbamate, 17% a ureido, and 12% contained an

amide function (Ashton and Crafts, 1973). Assuming all other structural features to be equivalent in an analogous series of derivatives, the indicated moieties are homeosterically related, *i.e.*, $-\text{OCH}_2-$, $-\text{NHCH}_2-$, $-\text{CH}_2\text{CH}_2-$, and $-\text{S}-$ with relative mass units of 30, 29, 28, and 32, respectively. Since few systematic attempts have been made to correlate physiological activity of plant growth-regulating compounds on the basis of homeosteric relationships, four types of derivatives have been synthesized which incorporate these functional groups into a series of analogous compounds. Their relative biological activities have been determined in several plant systems using both physical and chemical assay procedures, and some biochemical results are presented in an accompanying paper.

EXPERIMENTAL SECTION

Organic Synthesis. *O*-[(*Substituted*)carbamoyl]-3-hydroxypropionitriles (Table I). All of these derivatives were prepared in a similar manner using the method of Beaver *et al.* (1963). A mixture consisting of 0.033 m of the appropriate isocyanate and 0.033 m of 3-hydroxypropionitrile was heated in an oil bath at 80° for 6 hr under anhydrous conditions. Upon cooling to room temperature the reaction mixture solidified and was then recrystallized from the solvent system indicated in Table I. The products were dried in a vacuum desiccator over calcium chloride prior to elemental analysis.

O-[(*Substituted*)carbamoyl]-3-hydroxypropionic Acids. These derivatives were prepared in a comparable fashion. A suspension of 0.01 m of the appropriate hydroxypropionitrile derivative in 50 ml of 6 *N* hydrochloric acid was magnetically stirred and heated under reflux for 2-4 hr. Upon cooling to room temperature, a precipitate formed which was filtered, washed with water, and air dried. This material was dissolved in a dilute solution of sodium hydroxide and extracted twice with 10-15-ml portions of ether. The aqueous phase was adjusted to pH 2 with a dilute solution of hydrochloric acid to produce a precipitate which was filtered, washed with water, air dried, and recrystallized from either water or 95% ethanol, as indicated in Table II. These products were dried in a vacuum desiccator heated to 50-60°.

3-[*N*³-(*Substituted*)ureido]propionic Acids. Using the general procedure of Runti and Ulian (1963), a sample of

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¹In view of the confusion which exists between the concepts of classical and nonclassical isosteric replacements in chemical analogs, the authors suggest the term "homeosteric," homoios (Gr) meaning similar. The term homeosteric would thus be defined as two or more chemical moieties which are similar in mass or shape and valence bond angles.