Dithiocarbamate Derivatives as Herbicide Safeners

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The growing environmental and toxicological concern about the dichloroacetamide type herbicide safeners prompted us to search for alternative safener types. Based on analogy considerations, a random screening of structurally unrelated bivalent sulphur compounds was performed, followed by successive structure optimization phases representing both speculative and empirical elements. Dithiocarbamate ester type compounds derived from 1,4-exazaspiro[4.5]decane revealed highest protecting potency both agains thiolcarbamate and chloracetanilide herbicides in corn (*Zea mays* L.), with the benzylic and allylic esters being the most active.

Introduction

The dichloroacetamide type safeners, representing the major part of herbicide safeners in current usage, became subject of growing toxicological and environmental concern. Accordingly a search for alternative safener types became a task of primary importance. A survey of the patent literature suggested that compounds containing bivalent sulphur are represented in increasing number amongst newly developed safener molecules. This led us to look into bivalent sulphur chemistry to find new safener structures.

Materials and Methods

We set up a sequence of phases in which gradual structure optimization with empirical and speculative elements play a part to variable extent.

The first phase was a random screening with an array of miscellaneous bivalent sulphur compounds, as presented by Fig. 1. Part of them are described in the chemical literature and were re-synthesized accordingly, such as **2, 3, 6, 7,** and **8** [1–4], some were obtained as a gift or from commercial sources (**1, 4, 9, 10**), while others, such as **5** and **11** were prepared by us as new compounds.

The compounds were tested on corn in glasshouse for preemergence safener activity. EPTC, representing the thiolcarbamate type herbicides, and acetochlor, representing the chloracetanilides (Fig. 2) were applied as herbicide components, using three herbicide dosages and two safener dosages. Activity was assessed both as corn height and corn yield. Only corn height data obtained with acetochlor as herbicide, and only one of the three

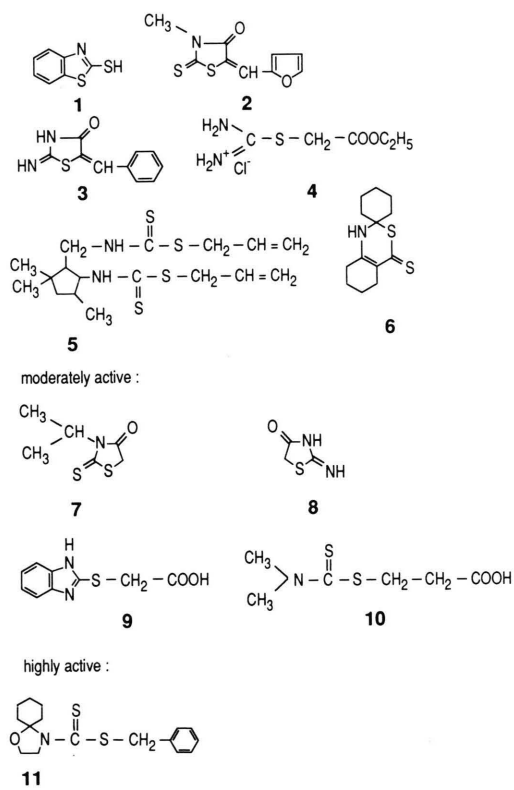

Fig. 1. Phase 1: random screening.

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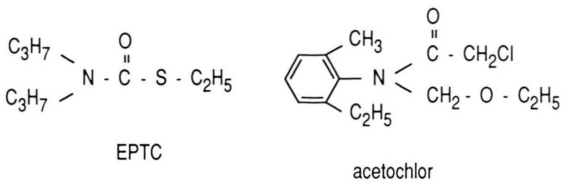

Fig. 2. Herbicides applied in the safener test.

herbicide dosages used, namely 1.5 kg/ha and one of the two safener dosages, 150 g/ha are documented in this communication.

Results and Discussion

Compounds **1–6** were inactive, compounds **7–10** were of moderate activity, while one of the compounds, **11,** representing a dithiocarbamate ester derived from 1,4-oxaza-spiro[4.5]decane revealed high safener potential.

Compound **11** was then selected as lead compound in the subsequent structure optimization phases. In the first of these phases modifications were carried out on the oxazolidine ring, as presented on Fig. 3. MG-191, a highly active safener developed by Dutka and Kőmíves [5] was used as standard in these thests. All compounds of this series showed a significantly reduced safener activity as compared to the lead compound, indicating that the rigid spiro structure with a fixed tetrahedral configuration is a stringent requirement of activity.

Based on these results the oxaza-spirodecane structure was maintained throughout the structural modifications of phase 3 and substitutions were carried out on the benzene nucleus (Fig. 4). These modification led to limited changes in safener activity. This finding is in accordance with the narrow range of structural variations carried out on the lead compound. Only the 1-naphthyl analogue of the lead compound revealed a slight increase of safener effect.

Considerable variations of activity were obtained in phase 4, where the S-benzylic moiety of the lead compound was replaced by various other groups (Fig. 5). This finding was again in accordance with expectations and the profound structural variations carried out in this phase comprehended increased probability both of sharp drop and of sharp enhancement of safener activity. High in-

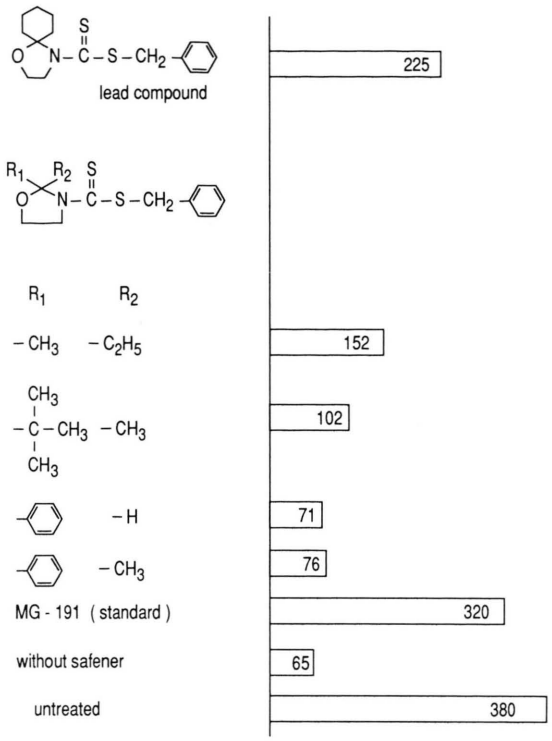

Fig. 3. Phase 2: modifications on the N-containing moiety; acetochlor 1,5 kg/ha, safener 150 g/ha corn height, mm, 14 days.

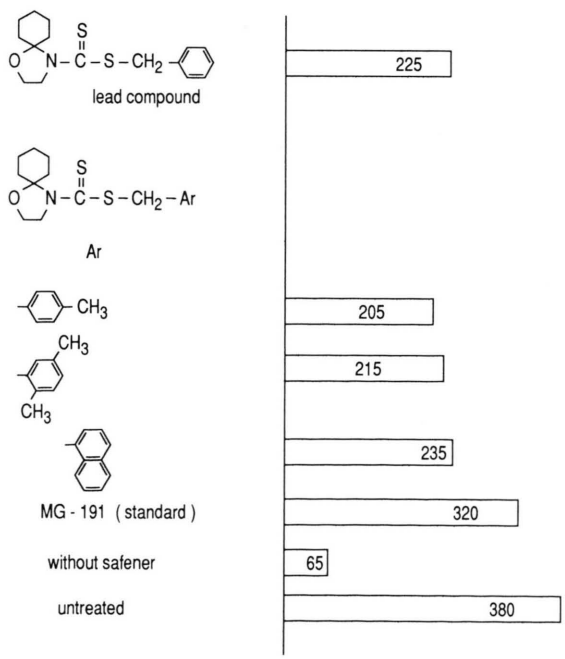

Fig. 4. Phase 3: modifications on the aromatic nucleus; corn height, mm, 14 days.

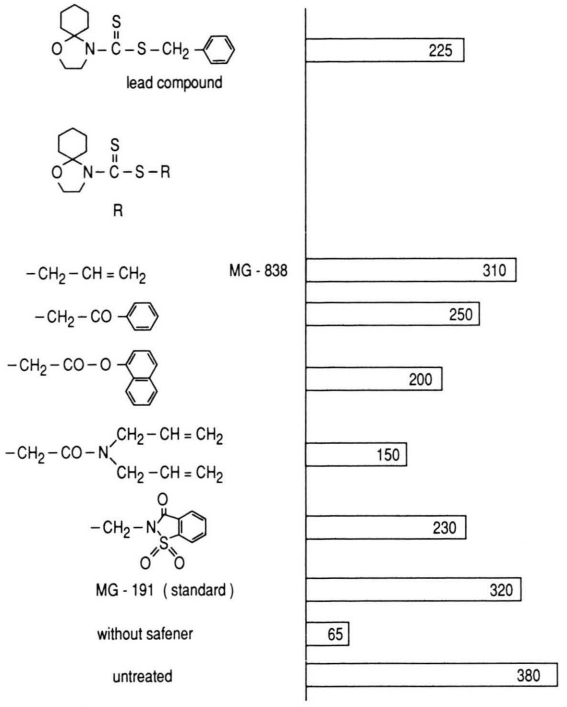

Fig. 5. Phase 4: replacement of the benzene ring by other moieties; corn height, mm, 14 days.

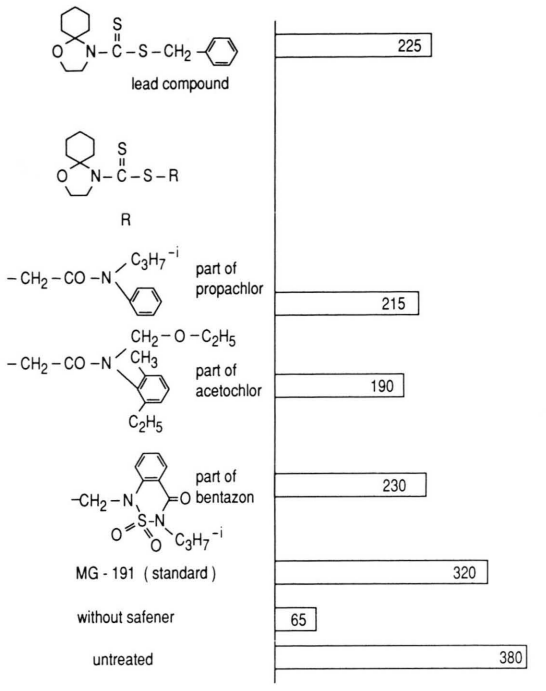

Fig. 6. Phase 5: insertion of moieties present in herbicide molecules; corn height, mm, 14 days.

crease of safener effect was observed when the benzylic group was exchanged for allylic group. This product, marked with the code number MG-838, was selected for practical development, along with the lead compound. Neither of the bivalent sulphur compounds investigated within this study has reached the activity of MG-191, the standard used in our tests, but the allylic derivative was just slightly behind it. Fair safener potential was obtained also when the benzene ring was exchanged for benzoyl- or a saccharine moiety. Other structural modifications in this phase led to decreased activity.

These compounds can be easily obtained by the condensation of cyclohexanone with ethanolamine to yield 1,4-oxaza-spiro[4.5] decane. Reacting this intermediate with carbon-disulfide in aqueous alkaline media leads to the corresponding dithiocarbamic acid salt, which is then alkylated (*e.g.*, with benzyl- or allyl-chloride, respectively) to yield the final product.

The compounds prepared and tested in phase 5 were designed according to the finding of Stephenson and co-workers [6] that in some cases active safeners can be rationally designed by incorporating molecular fragments present also in the herbicide molecule which they antagonize (Fig. 6). Two compounds prepared within this series, containing moieties present in the chloroacetanilide type herbicides propachlor and acetochlor, respectively, revealed only moderate activity in our tests. The compound containing part of the bentazon molecule proved to be of medium safening activity against acetochlor. Its safener activity against bentazon is under investigation.

Field tests with some selected members of this new safener type are in progress and further derivatives are being prepared in order to optimize safener activity and selectivity. No final conclusion can be drawn as yet on the practical value of the compounds prepared hitherto. Yet the high activity data obtained in the glasshouse tests and the wide range of possible further structural variations render this new group of herbicide safeners a promising, environmentally acceptable alternative to the dichloroacetamide type compounds.

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