

Bioactive Chemical Bond Systems in Safeners and Prosafeners*

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Acetals and ketals involving a dichloromethyl group on their central carbon atom were found to be active or highly active as safeners of corn against thiocarbamate and chloroacetanilide herbicide injury. A mechanism for the biotransformation of these compounds as prosafeners to the actual dichloroacetic ester safeners is proposed.

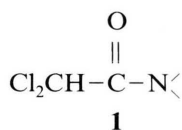
Similarly, S- and N-analogues of the cyclic acetals (ketals) which show safener activity can also be considered as prosafeners because they can be converted in the biophase by the same mechanism into actual safeners such as dichloroacetic thioesters or dichloroacetamides supporting the bioactivation hypothesis.

Characteristic bioactive chemical bond systems in safeners and prosafeners are suggested.

Introduction

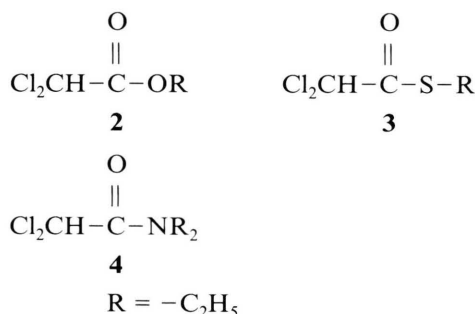
Chemical safeners are compounds decreasing or completely eliminating herbicide injury to crop plants without decreasing herbicidal potential. Prosafeners are chemicals which are bioinactive in their original form but are transformed into an active state by the plant organism.

Structure-activity relationship examinations with several chloroacetamides evaluated as corn safeners against thiocarbamate herbicide injury have been conducted by a number of investigators [1–6]. From all these studies it appeared that the dichloroacetamido group (**1**)

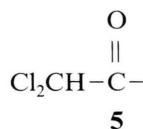


is the common structural feature of all molecules which are effective corn safeners against thiocarbamates. Principally, the safener activity could be attributed to this function.

Several years ago, however, it was found [7] that dichloroacetic esters (**2**) and thiol esters (**3**)



applied to corn plant under special conditions to prevent their chemical decomposition before getting to the biological target are also effective safeners: their activities are near to that of dichloroacetamides (**4**). This means that not the dichloroacetamido group but the dichloroacetyl function (**5**)



is responsible primarily for the safener activity.

Nevertheless, in other experiments dichloroacetaldehyde (**6**) and dichloroacetone (**7**)



also containing a dichloroacetyl group proved to be practically inactive as safeners even at high doses [8].

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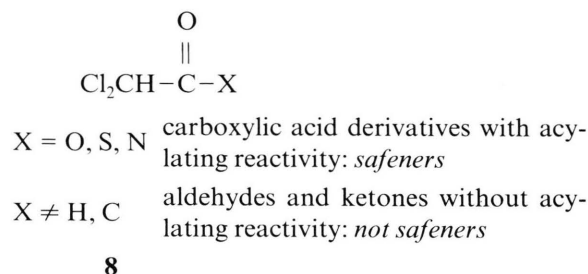
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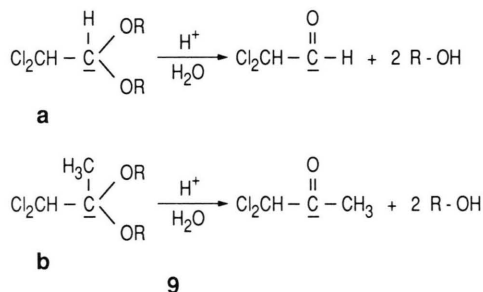
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From the comparative analysis of these results it emerges that the dichloroacetyl group is a necessary but not sufficient structural fragment for the safener potential. The fundamental criterion of the bioactive bond system in safeners is that in the general formula (8)



this basic group should be attached to O, S, or N (more electronegative than C) atom but not to H- or C-atom. Compounds of the former class are chemically acylating agents while those of the latter type are inactive in transacylation processes. These findings suggest that a relationship exists between chemical acylation reactivity and safener activity [5, 7].

Searching for new effective safeners we have demonstrated that acetals (9a) and ketals (9b) can

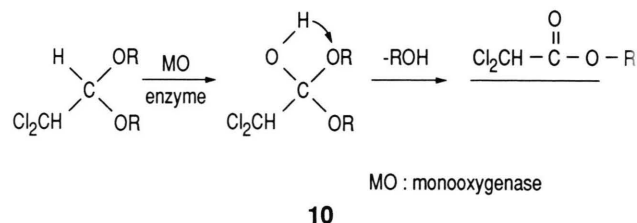


act as safeners against EPTC in corn especially if they have a dichloromethyl group bound to the central carbon atom. This was surprising because these compounds do not involve any of the molecular functions needed for safener activity (8). Though the central carbon atom of these mole-

cules is a "proacyl" carbon, since their hydrolysis leads to aldehyde or ketone involving dichloroacetyl group (9), these products are inactive as safeners (8).

Prosafener Concept and Bioactivation Mechanisms

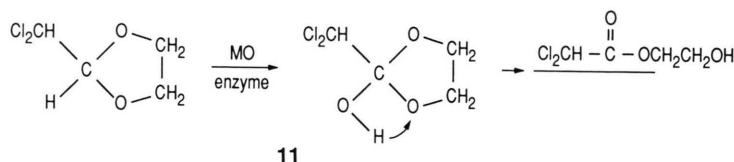
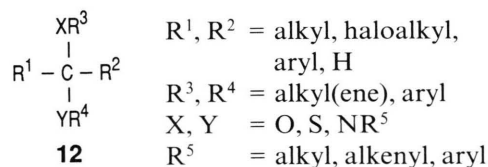
On the basis of these results it was interesting to speculate that dichloromethyl acetals and ketals are bioactivated to safeners in the plant organism by a chemical reaction other than hydrolysis. Such a possible transformation may be a two-step mechanism (10) [9]: by the action of monooxy-



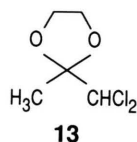
genase enzymes in the first step a disubstituted geminal triol is formed. This is not stable chemically and by the loss of an alcohol molecule is converted to dichloroacetic ester which is an active safener involving a bond system characteristic of safener potential (8).

The hypothetic mechanism of the biotransformation of cyclic acetals (2-dichloromethyl-1,3-dioxolane) is slightly different (11): after biooxidation and an intramolecular O→O transprotonation the dichloroacetic ester with safener activity is formed by a simple ring opening process.

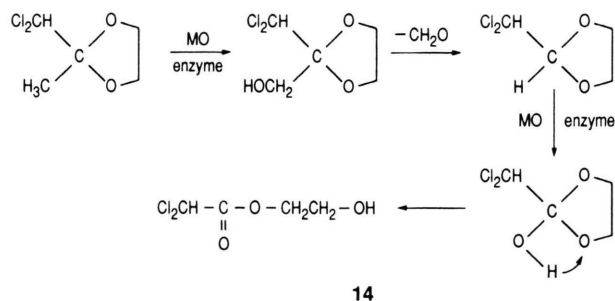
To examine the reliability of this hypothesis a great number of derivatives described by the general formula (12) was synthesized and analyzed for



safener potential in laboratory, greenhouse and field experiments. Variation in the structure resulted in different degrees of protecting effect. The compound MG-191 (**13**) (2-dichloromethyl-2-methyl-1,3-dioxolane) showed optimum biological activity [10, 11].



Concerning the hypothetical bioactivation mechanism of MG-191 (**14**) the first step is the enzymic oxidation of the methyl group to hydroxymethyl function which due to its special structural position easily releases a formaldehyde molecule forming the cyclic acetal. Furthermore the mecha-

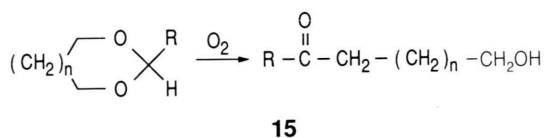


nism is quite identical with that of the 2-dichloromethyl-1,3-dioxolane producing the active safener dichloroacetic ester (**11**).

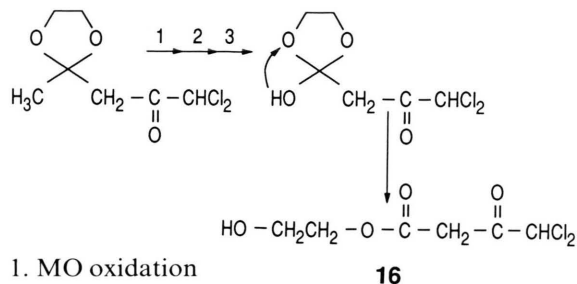
There are several experimental facts corroborating this theory:

1. Dichloroacetaldehyde and 1,1-dichloroacetone are not safeners (**8**) thus the hydrolysis (**9**) of their acetals (ketals) can not be the bioactivation process.

2. Oxidation of cyclic acetals is a preparative method of diol monoester production (**15**) in the synthetic organic chemistry [12].

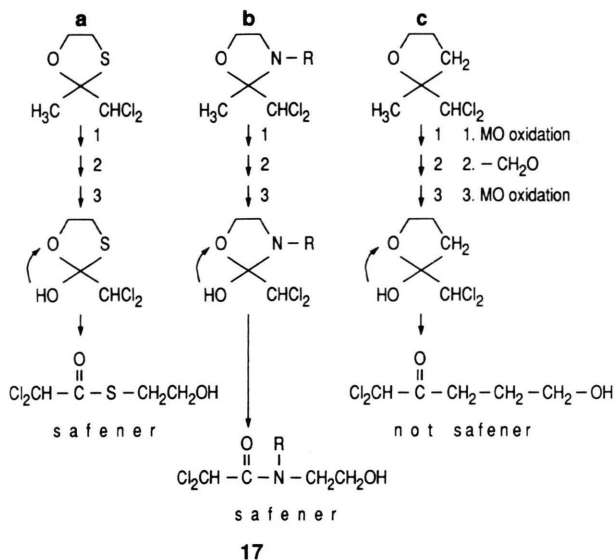


3. If the dichloroacetyl group is involved in the side chain the cyclic ketal (**16**) is inactive as safener even if it is oxidized enzymatically. This is in agreement with the observation that C-dichloroacetyl compounds possess no safener potential (**8**).



1. MO oxidation
2. $-\text{CH}_2\text{O}$
3. MO oxidation

4. Exchanging one of the oxygen atoms in the dioxolane ring of MG-191 (**13**) by sulfur (**17a**) or nitrogen (**17b**) results to molecules that are also active safeners since they can be bioactivated to dichloroacetic thiolester and dichloroacetamide, respectively:

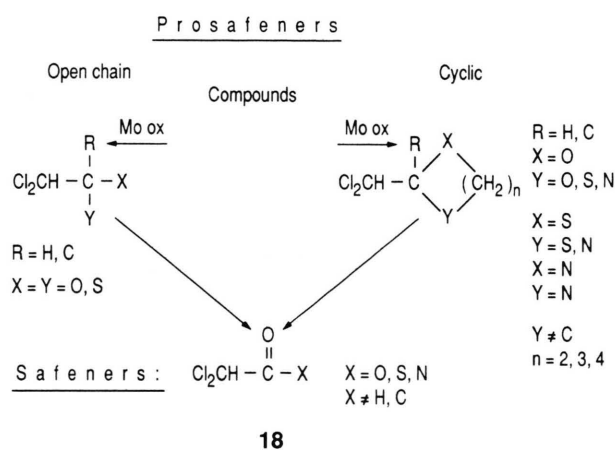


5. On the other hand, substitution of one of the oxygens in the cyclic ketal (**13**) by a carbon atom (**17c**) yields a compound (2-dichloromethyl-2-methyl-tetrahydrofuran) showing no safener action. This is because its biooxidation followed by ring opening results to a ketone involving a bioinactive C-dichloroacetyl group (**8**).

Our results demonstrate that some types of compounds analyzed chemically and biologically behave as prosafeners [13, 14] being activated in the plant organism rapidly to esters, thioesters or amides of dichloroacetic acid (**8**) which are the actual safeners of corn against injury from the herbicide EPTC (N,N-di-*n*-propyl-S-ethyl thiocarbamate). These prosafeners have characteristic bioactive chemical bond systems (**18**).

The highest safener activity appeared when both X and Y were oxygen atoms. Generally, ketal derivatives proved to be more efficient safeners than the corresponding acetals.

Examination of **18** shows that contrary to safeners, prosafeners do not necessarily contain an



active dichloroacetyl group. Even the presence of oxygen atom is not necessary because oxygen is incorporated into the safeners enzymatically during the bioactivation of prosafeners (**10**, **11**, **14**).

Conclusion

The concept of prosafeners is of great importance because it provides an alternative way for in-

creasing the selectivity of safeners. Differences in the ability of crop and weed plants in biotransforming prosafeners to actual safeners could be exploited to advantage and enhance the practical usefulness of this concept [13]. In addition, the bioavailability by plants and the transport mobility in the biophase of prosafeners may be preferred to that of safeners improving the protective activity.

On the other hand, highly effective safeners which are very reactive chemically are not usable in the practice since they are consumed partially or completely before reaching the sensitive active site(s) of action. However, these chemicals can be transported at critical concentrations as far as the biological target by their chemically stable prosafeners.

As mentioned above, the bioactivation mechanism described should be considered as a hypothesis. Further research could well yield proof for the theory outlined. Nevertheless, this mechanism has some realistic features since our earlier suggestions that

- the dichloroacetamido group is essential part of molecules of effective safeners [5],
- a transacylation reaction is probably involved in the biological activity of safeners [7],
- the dichloroacetyl moiety rather than dichloroacetamide group may be responsible for safening activity [10],

proved to be correct as a working hypothesis with the discovery and recent development of the “safener” MG-191 (**13**) which protects corn from thiocarbamate and chloroacetanilide herbicide injury [10, 11, 15–17].

On the basis of present results, however, MG-191 is a prosafener, whose bioactivation to the actual safener by grass plants can be explained by the proposed mechanism (**14**).

- [1] F. M. Pallos, R. A. Gray, D. R. Arneklev, and M. E. Brokke, *J. Agric. Food Chem.* **23**, 821 (1975).
- [2] F. M. Pallos, R. A. Gray, D. R. Arneklev, and M. E. Brokke, in: *Chemistry and Action of Herbicide Antidotes* (F. M. Pallos and J. E. Casida, eds.), p. 15, Academic Press, Inc., New York 1978.
- [3] G. R. Stephenson, J. J. Bunce, R. I. Makowski, M. D. Bergsma, and J. C. Curry, *J. Agric. Food Chem.* **26**, 137 (1978).
- [4] G. R. Stephenson, J. J. Bunce, R. I. Makowski, M. D. Bergsma, and J. C. Curry, *J. Agric. Food Chem.* **27**, 543 (1979).
- [5] F. Dutka, T. Kőmives, A. F. Márton, Á. Hulesch, K. Fodor-Csorba, and M. Kárpáti, *Proc. Hung. Ann. Biochem.* **19**, 253 (1979).
- [6] J. Nagy and K. Balogh, *Proc. Brit. Crop Prot. Conf. – Weeds* **1**, 107 (1985).
- [7] F. Dutka and T. Kőmives, in: *Pesticide Chemistry: Human Welfare and the Environment* (J. Miyamoto and P. C. Kearney, eds.), **Vol. 3**, p. 213, Pergamon, Oxford 1983.
- [8] F. Dutka and T. Kőmives, unpublished work.
- [9] F. Dutka, *Conf. of Hungarian Chemists (Vegyész-konferencia)*, Program, p. 9, Debrecen, Hungary 1987.
- [10] F. Dutka and T. Kőmives, in: *Pesticide Science and Biotechnology* (R. Greenhalgh and T. Roberts, eds.), p. 204, Blackwell Sci. Publ., Oxford 1986.
- [11] F. Dutka, T. Kőmives, E. Tömördi, and Cs. Söptei, *Proc. Brit. Crop Prot. Conf. – Weeds* **1**, 77 (1987).
- [12] E. M. Kuramshin, L. G. Kulak, M. N. Nazarov, S. S. Zlotsky, and D. L. Rakhmankulov, *J. prakt. Chem.* **331**, 591 (1989).
- [13] K. K. Hatzios, in: *Crop Safeners for Herbicides* (K. K. Hatzios and R. E. Hoagland, eds.), p. 3, Academic Press, Inc., San Diego 1989.
- [14] B. Rubin and O. Kirino, in: *Crop Safeners for Herbicides* (K. K. Hatzios and R. E. Hoagland, eds.), p. 317, Academic Press, Inc., San Diego 1989.
- [15] E. Széll, I. Csala, F. Fodor, T. Kőmives, and F. Dutka, *Cereal Res. Commun.* **13**, 55 (1985).
- [16] E. Széll, I. Csala, F. Fodor, Á. Hulesch, T. Kőmives, and F. Dutka, *Cereal Res. Commun.* **14**, 397 (1986).
- [17] E. Széll, I. Csala, Á. Hulesch, T. Kőmives, and F. Dutka, *Cereal Res. Commun.* **16**, 245 (1988).