N-(2,6-Dihalobenzylidene)arenesulfinamide Herbicides and Analogous Compounds. 2. Structure–Activity Relationships

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The CAMSEQ-II processor was used to perform a fixed valence geometry conformational analysis of selected benzylidenearenesulfinamide herbicides and some congeneric compounds. The molecular mechanics MM method as formalized and parameterized in CAMSEQ-II gave an estimate of relative conformational energies and free-space statistical probabilities of minimum energy conformational states for each of the selected structures. The data suggest a qualitative relationship between statistical molecular conformational populations and observed biological activity. Only those compounds having planar conformation (within a 5° resolution of the methylidene carbon–phenyl carbon bond torsional angle) with statistical populations of 72% or greater were herbicidally active. Changes in the substitution pattern of the benzylidene phenyl ring, saturation of the nitrogen–carbon double bond, and the preparation of vinylogous compounds all resulted in a loss of herbicidal activity and low (20–30%) planar statistical populations.

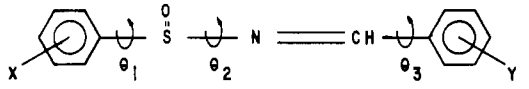
In part 1 of this series (Friedman, 1983), the synthesis and biological evaluation of compounds of type I and II,

I II

as well as some congeneric structures were described. With very few exceptions, only those compounds bearing substituents on the 2 and 6 positions of Ar′ and having general structure II were found to have any herbicidal activity. Furthermore, all attempted structural modifications of II (such as the preparation of a vinylogous analogue or reduction of the carbon–nitrogen double bond) also resulted in the loss of herbicidal activity. In order to elucidate those structural features required for herbicidal activity, a quantitative structure–activity analysis of the data base was performed, which included conformational studies of selected compounds. Certain structure–activity relationships have been identified and are reported.

COMPUTATIONAL METHODS

Conformational Analysis. The CAMSEQ-II processor (Potenzone et al., 1977) was used to perform a fixed valence geometry conformational analysis of selected N-(2,6-dihalobenzylidene)arenesulfinamides. Conformational freedom was expressed through the torsional rotation angles, θ_i, as defined in III.



III

Both E and Z isomers, with respect to the NC double bond, were considered. A series of congeners in which the —N=CH— group was replaced by alternate fragments was also investigated. "Standard" bond lengths and angles as built into CAMSEQ-II were used to construct the valence geometries of all compounds.

The molecular mechanics MM method (Hopfinger, 1973), as formalized and parameterized in CAMSEQ-II, was used to estimate relative conformational energies. Intramolecular energy minima were first located at a resolution of ±30° by scanning over all combinations of θ_1, θ_2, and θ_3 at 30° intervals. These crude minima were then used as starting points in precise energy minimizations. Once the intramolecular minima were precisely determined, conformational space (e.g., θ_1, θ_2, and θ_3) about a minimum was uniformly scanned at 5° intervals for ±30° about the location of the minimum. This then provided the necessary data to estimate the free-space statistical probability $P(i)$ of any minimum energy conformer state, i, by

$$P(i) = \frac{\sum_{\theta_1}^{\pm 10^\circ} \sum_{\theta_2}^{\pm 10^\circ} \sum_{\theta_3}^{\pm 10^\circ} \exp[-\Delta E_i/(RT)]\Delta\theta_1\Delta\theta_2\Delta\theta_3}{\sum_i [\sum_{\theta_1}^{\pm 30^\circ} \sum_{\theta_2}^{\pm 30^\circ} \sum_{\theta_3}^{\pm 30^\circ} \exp[-\Delta E_i/(RT)]\Delta\theta_1\Delta\theta_2\Delta\theta_3]} \quad (1)$$

where $\theta_1 = \theta_2 = \theta_3 = 5°$, the $\pm x°$ above each sum indicates that range of scanning about each minimum, E_i is the relative conformational energy, with respect to the energy of the global minimum, of the ith minimum energy conformer, and $RT = 0.56$ kcal/mol, i.e., the Boltzman factor at room temperature.

The subscript i indicates summing over all energy minima conformers. The choice of ±10° and ±30° is arbitrary and represents a compromise between extreme accuracy and reasonable calculation efficiency. $P(i)$ is relatively insensitive to the choice of ±10° and ±30° as long as θ is less than 10°.

Estimation of log P, F_{H_2O}, and F_{oct}. An attempt was made to consider the possible role of transport and the thermodynamics of binding to a receptor site in the structure–activity analysis. This was modeled through the estimation of the logarithm of the octanol/water partition coefficient, P, the free energy of aqueous solvation, F_{H_2O}, and the free energy of solvation in octanol, F_{oct}. These three quantities are related by the expression (Hopfinger and Battershell, 1976)

$$\log P = \frac{1}{RT}(F_{H_2O} - F_{oct}) \quad (2)$$

log P was estimated according to the Leo and Hansch empirical formalism (Hansch and Leo, 1979). F_{H_2O} was

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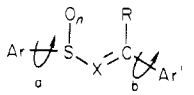
Table I. Statistical Populations of Extended Conformers of Sulfinamides and Related Compounds



compd no.	Ar	Ar'	R	n	X	torsional angle a, deg	torsional angle b, deg	statistical population, %	benzylidene total planar population, %
1	C_6H_5	2,6-Cl_2-C_6H_3-	H	0	N	0	0	37	37
2	C_6H_5	2,6-Cl_2-C_6H_3-	H	1	N	0	0	82	82
3	4-F-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	80	80
4	4-Cl-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	77	77
5	4-Br-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	79	79
6	4-CH_3-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	78	78
7a	2-CH_3CONH-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	43	
7b	2-CH_3CONH-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	180	0	38	81
8	4-CH_3CONH-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	72	72
9	2-pyridyl-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	90	90
10a	2-pyrimidyl-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	26	
10b	2-pyrimidyl-	2,6-Cl_2-C_6H_3-	H	1	N	90	0	49	75
11	2-benzothiazyl-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	83	83
12a	2-NO_2-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	28	
12b	2-NO_2-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	180	0	61	89
13	3-NO_2-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	N	0	0	84	84
14	3-NO_2-C_6H_4-	2,4-Cl_2-C_6H_3-	H	1	N	0	0	32	32
15	3-NO_2-C_6H_4-	3,4-Cl_2-C_6H_3-	H	1	N	0	0	21	21
16	3-NO_2-C_6H_4-	3,5-Cl_2-C_6H_3-	H	1	N	0	0	18	18
17	3-NO_2-C_6H_4-	2-F,6-Cl-C_6H_3-	H	1	N	0	0	57	57
18	3-NO_2-C_6H_4-	2,4,6-$(CH_3)_3$-C_6H_2-	H	1	N	0	0	82	82
19	2-NO_2-C_6H_4-	2,6-Cl_2-C_6H_3-	CH_3	1	N	0	90	71	
20	2-NO_2-C_6H_4-	2,6-Cl_2-C_6H_3-	H	1	CH	90	90	66	

determined from a set of additive values constructed from aqueous activity coefficient data (Forsythe and Hopfinger, 1980). F_{oct} was computed from eq 2.

Structure–Activity Analysis. log P, F_{H_2O}, and F_{oct} were calculated as described previously for compounds 44–62, and each of these three descriptors was used in conjunction with the planar conformational statistical populations in an attempt to generate a QSAR. Biological activity measures (rating numbers) of individual weed species were first used for the activity data base, then the separate sums of the broadleaf, grass, and crop activities were used, and finally the differences between weeds and crops (i.e., broadleaf – crops and grasses – crops) were used. The molecular descriptors were considered in both linear form and quadratic form in the regression analysis.

RESULTS AND DISCUSSION

Quantitataive Structure–Activity Relationships (QSAR). No correlation equation could be generated having a correlation coefficient greater than 0.80 and a standard deviation less than 1.8 rating numbers. In general, however, the statistical populations played the most important role in these poor correlations by about a factor of 10 over log P, F_{H_2O}, and F_{oct}. Although a true QSAR was not found, a qualitative relationship nevertheless appears to exist between conformational statistical populations and observed biological activity.

Conformational Studies. CAMSEQ II calculations have shown that the lowest energy conformation (and presumably the active one) in N-(2,6-dihalobenzylidene)arenesulfinamides is planar within a 5° resolution of the torisonal angles (Figure 1A). All of the sulfenamides studied and all of the sulfinamides except the 2,6-dihalobenzylidene analogues had very low statistical populations for the active planar conformation—usually on the order of 20% (Table I). In the case of the 2,6-dichloro-substituted compounds, however, the "active" conformation was populated to the extent of 75–90%, as

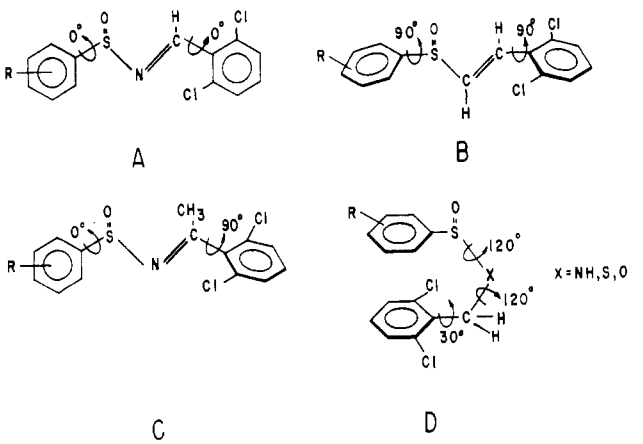


Figure 1. Conformational preference for N-(2,6-dichlorobenzylidene)arenesulfinamides and related compounds.

shown in Table I. A plot of conformational energy [$E(\theta)$] as a function of rotation about the benzylidene carbon–phenyl carbon bond (Figure 2) indicates that in the unsubstituted benzylidene case, the small energy barrier (approximately 1.3 kcal/mol) between the lowest energy benzylidene planar ($\theta = 0°$) conformation and the highest energy orthogonal ($\theta = 90°$) conformation allows for nearly free rotation about that bond.

In the case of the 2,4-dichlorobenzylidene analogue, the rotational barrier is nearly twice as great as in the previous example; however, the planar statistical population is still only 32%. Finally the 2,6-dichlorobenzylidene analogue has a rotational barrier of nearly 4 kcal/mol with a correspondingly high planar population of 89%.

It appears that such high statistical populations are necessary for biological activity, although the molecule need not be all planar (Figure 1), as shown in Table I. For example, compound 1 has a statistical population in the all-planar conformation of only 37% and is herbicidally

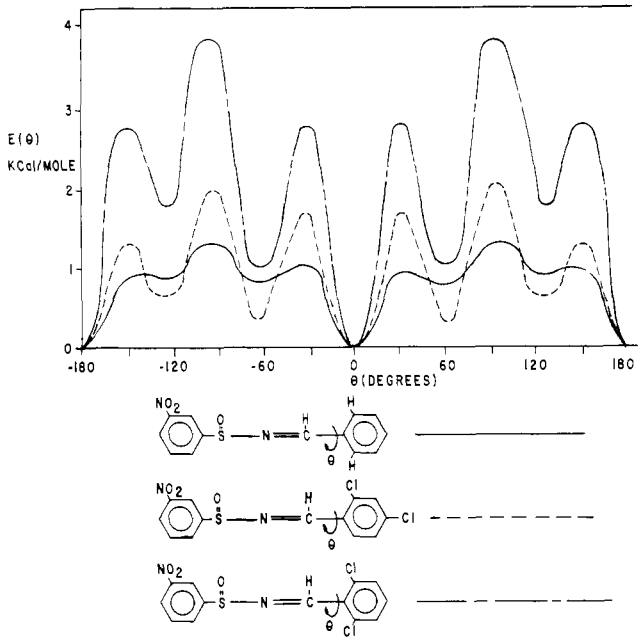


Figure 2. Conformational energy, $E(\theta)$, as a function of torsional angle, θ, for unsubstituted and 2,4-dichlorophenyl- and 2,6-dichlorophenyl-substituted sulfinamides.

inactive. Compound **10** has two energy minima corresponding to the all-planar (0°,0°) conformation. The first of these has a statistical population of only 26% and the second 49%. Apparently, only coplanarity of the benzylidene ("b") portion of the molecule and the R′—C=N plane is a necessary (but not sufficient) condition for herbicidal activity (i.e., torsional angle b is critical but angle a is not). On this basis the total "b" coplanar population is 75%, and thus the molecule is highly populated in the "active" conformation and has good herbicidal activity.

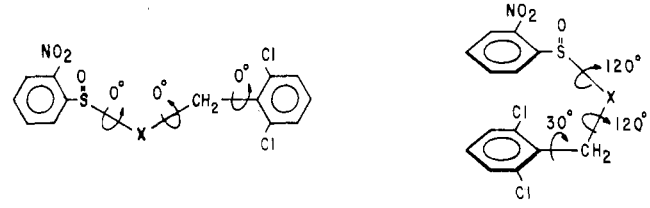
The one exception to the planar/active hypothesis appears to be compound **21** which (based on statistical population alone) should be herbicidally active but is not. It may be that the 4-methyl substituent changes the overall length of the extended planar conformation enough to interfere with fit of the molecule in a receptor site, thus eliminating activity.

When the methylidene hydrogen of **12** is replaced with a methyl group (**19**), the effect on conformation is that the benzylidene "b" ring is orthogonal to the R′—C=N plane in the lowest energy state (Figure 1B). Such a conformation should not be active if coplanarity is a necessary conformatinal feature, yet **19** does in fact possess a high level of activity against broadleaf weed species.

Furthermore, this activity is not due to aqueous decomposition, because the hydrolysis products, 2-nitrobenzenesulfinamide and 2,6-dichloroacetophenone, are herbicidally inactive. Since the activity of **19** is considerably different than that of **12** or other *N*-(2,6-dichlorobenzylidene)arenesulfinamides, it seems reasonable that **19** is acting through a different mechanism than sulfinamides **2**–**15**.

The vinylogue of **12**, compound **20**, is "a" and "b" orthogonal in the lowest energy conformation (Figure 1C) with the vinylic hydrogen on the carbon β to the sulfinyl moiety encountering considerable steric interactions with

Table II. Comparison of Folded vs. Extended Conformational Populations of Sulfinamides, Thiosulfinates, and Sulfinates



extended, all planar folded

compd no.	X	extended, all planar statistical population, %	folded statistical population, %
21	NH	29	63
22	S	18	72
23	O	48	50

both rings in the all-planar state. This compound, as would be predicted, is totally devoid of herbicidal activity at the tested rates of application.

Finally, when the C=N bond of **12** is saturated to give **22**, the inactive folded conformation shown in Figure 1D is energetically favored, with the extended planar conformation only populated to the extent of 29% (Table II). Compound **22**, its sulfenamide precursor, and its chalcogen analogues **23** and **24** have similar folded conformations (Table II) and are also inactive, as expected from the previous argument.

While a good quantitative structure–activity relationship could not be developed, the benzylidene planar hypothesis developed herein gives a qualitative explanation that seems to be in agreement with the biological data. Since very small structural modificatons have been shown to induce very significant conformational changes, it appears unlikely that close analogues having high degrees of both thermal stability and herbicidal activity will be found.

Registry No. 1, 83364-37-8; 2, 83364-77-6; 3, 83364-78-7; 4, 83364-79-8; 5, 83364-80-1; 6, 83364-81-2; 7, 83364-82-3; 8, 83364-83-4; 9, 83364-84-5; 10, 83364-85-6; 11, 83365-25-7; 12, 83364-86-7; 13, 83364-87-8; 14, 83364-91-4; 15, 83364-92-5; 16, 83364-93-6; 17, 83364-94-7; 18, 83364-99-2; 19, 83365-11-1; 20, 83365-26-8; 21, 83365-13-3; 22, 83365-16-6; 23, 83365-19-9.

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Received for review March 29, 1892. Accepted September 1, 1982.