COMMUNICATIONS

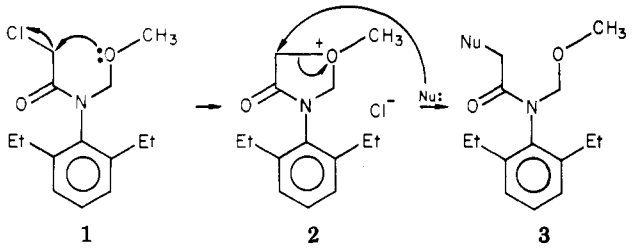
Design, Synthesis, and Biological Activity of Rigid Acetanilide Herbicides

A series of rigid acetanilide compounds was synthesized to test the hypothesis of the intermediacy of an oxonium ion in the mechanism of action of the known acetanilide herbicides. The compounds did react with nulceophiles, although unexpected ring-opened products were obtained. The compounds prepared did not exhibit any significant biological activity in either preemergence or postemergence screens.

The class of chloroacetamide and chloroacetanilide preemergence herbicides has grown significantly since the commercial introduction of Randox by Monsanto in 1956. Between 1965 and 1970 Monsanto added three additional herbicides to the armamentarium: Ramrod, Lasso (1) and Machete.

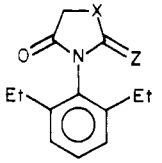
Several investigations directed toward the metabolism of these compounds by plants and soils have demonstrated the reactive nature of the α-chloro moiety (Jaworski, 1975). Various metabolites of these herbicides have been isolated which have been shown to possess different functionalities in place of the α-chloro group. These results have led to speculation concerning a possible mechanism of action of these compounds. It has been suggested that these herbicides may act as alkylating agents in vivo by reacting with biological nucleophiles.

It has also been suggested that in a series of *N*-formylhaloacetanilides, anchimeric assistance by the formyl oxygen promotes the lability of the halogen atom (Chupp et al., 1969). This suggests the additional possibility of formation of the oxonium chloride **2** as an intermediate in alkylation by Lasso-type compounds. Further reaction of this intermediate with a biological nucleophile would then be possible, giving rise to **3** (eq 1).



1 2 3 (1)

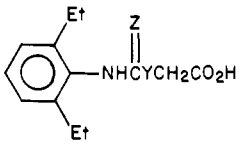
Based on the demonstrated herbicidal activity of the chloroacetanilides and their presumed mechanism of action as alkylating agents, it was proposed that rigid acetanilides, related to the commercial herbicide Lasso, be prepared and screened for biological activity. The proposed compounds, of general structure **4**, represent a series which incorporates



4a–j
X, Z = NR, O, S

a latent leaving group X analogous to the oxonium ion in

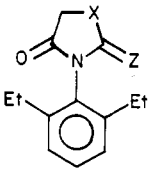
Table I. Acyclic Precursors of Rigid Acetanilide Analogues[a]



compd no.	Y	Z	mp, °C
7a	NH	O	210 dec
7b	NH	S	108–110
7c	O	O	165–167
7d	S	S	137–138
7e	S	O	126–128

[a] All compounds were characterized by ^{1}H NMR and IR spectroscopy and elemental analyses.

Table II. Rigid Acetanilide Analogues[a]



compd no.	X	Z	mp, °C
4a	NH	O	153–154
4b	$NCOCH_3$	O	152–153
4c	$NCOCF_3$	O	115–117
4d	$NCOCH_2CH_2CH_3$	O	105–106
4e	NH	S	164–166
4f	$NCOCH_3$	S	152–153
4g	NCH_2CO_2H	S	86–88
4h	O	O	99–101
4i	S	S	112–113
4j	S	O	87–89
10	S	NH	77–78

[a] All compounds were characterized by ^{1}H NMR and IR spectroscopy and elemental analyses. See Buchman and Komoroski (1980) for a ^{13}C NMR analysis.

2. Substituent Z enhances the capability of X to function as a leaving group. If the mechanism of action of the acetanilide herbicides does involve the formation of an oxonium salt, a change in the nucleofugality of X would result in a change in the reactivity of the rigid analogues toward nucleophiles.

The synthesis of compounds of general structure **4** and the results of their biological evaluation are presented in this report.

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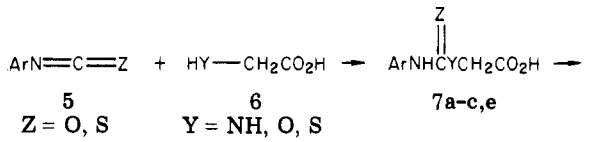
Table III. Preemergence and Postemergence Herbicidal Activity of Lasso

	% control for weed species					
	broadleaves			grasses		
method of application (rate)	pigweed	velvet-leaf	mustard	millet	foxtail	barnyard grass
preemergence (0.22 lb/acre)	78	<10	31	77	85	91
postemergence (1.76 lb/acre)	12	<10	10	18	28	40

CHEMICAL METHODS

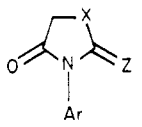
The general route utilized for the preparation of the desired compounds entailed the reaction of an aryl isocyanate or isothiocyanate, **5**, with an appropriate acetic acid derivative, **6**. Cyclodehydration of the resulting acyclic intermediates **7** furnished the rigid acetanilide derivatives **4**. This general synthetic route was utilized successfully to prepare the 3-(2,6-diethylphenyl)-substituted hydantoin, 2-thiohydantoin, rhodanine, thiazolidine-2,4-dione, and oxazolidine-2,4-dione (eq 2; Tables I and II). Preparation



5 **6** **7a-c,e**

Z = O, S Y = NH, O, S

Ar = 2,6-diethylphenyl



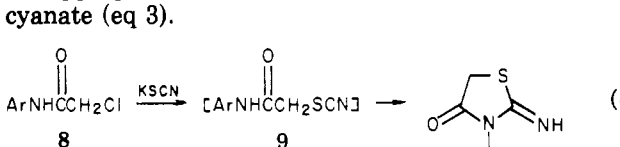
(2)

4a-j

X = NR, O, S

of intermediate **7d**, where Y, Z = S, was accomplished by reaction of 2,6-diethylaniline with CS_2/NH_4OH followed by addition of $ClCH_2CO_2H$.

An exception to the general synthesis outlined above was the preparation of 3-(2,6-diethylphenyl)pseudothiohydantoin **10**. This compound was prepared by reacting the appropriate chloroacetanilide **8** with potassium thiocyanate (eq 3).



(3)

8 **9**

Ar = 2,6-diethylphenyl

10

RESULTS AND DISCUSSION

The rigid acetanilides were tested for preemergence and postemergence herbicidal activity against three grass weed species and three broadleaf weed species. The broadleaf species included red root pigweed (*Armanthus retroflexus* L.), velvetleaf (*Abutilon theophrasti* Medic.), and common mustard [*Brassica kober* (DC.) L. C. Wheeler]. The grass species included red millet (*Panicum miliaceum* L.), green foxtail [*Setaria viridis* (L.) Beauv.], and barnyard grass [*Echinochloa crusgalli* (L.) Beauv.].

The rigid acetanilide compounds were completely devoid of both preemergence and postemergence activity against all broadleaf and grass species at an application rate of 4 lb/acre. In control experiments, Lasso demonstrated significant preemergence control against grasses (Table III). A lower, but still significant, level of control was exhibited against broadleaves. Meaningful postemergence activity was confined to grasses.

Due to the lack of biological activity, an investigation of the reactivity of the rigid acetanilides toward nucleophiles was undertaken. Lasso is known to undergo an exothermic reaction at ambient temperature with benzyl mercaptan (Phillips, 1973, 1975). The product obtained from this reaction, 2-benzylthio-2′,6′-diethyl-*N*-(methoxymethyl)acetanilide, results from nucleophilic displacement of the chlorine atom by benzyl mercaptan.

Initial experiments with the model 3-phenylrhodanine and benzyl mercaptan were conducted in refluxing acetone, absolute EtOH, CH_3CN, and CH_3NO_2. These attempts afforded only recovered starting material. When DMF/K_2CO_3 was used, however, a crystalline product was isolated. Spectroscopic analysis of this material identified it as benzyl *N*-phenyldithiocarbamate. The predicted nucleophilic ring opening of 3-phenylrhodanine would have yielded 2-(benzylthio)acetanilide.

These experiments demonstrate the potential reactivity of the rigid acetanilides toward nucleophiles. Although 3-phenylrhodanine did not afford the predicted product, it did undergo nucleophilic ring opening. The mechanism of this reaction, however, has not been investigated. Additional study is also required to determine why the rigid acetanilides did not exhibit any significant herbicidal activity.

ACKNOWLEDGMENT

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