daily protein supply of individuals or of a population, the point hardly seems to warrant further investigation.

The nitrogen contents of the two air-dried breads containing cottonseed flour were 2.54 and 2.45%. Air-dried samples of six whole wheat breads purchased in local markets contained 2.25, 2.48, 2.51, 2.41, 2.27, and 2.32% nitrogen. As both the color and the nitrogen content of the breads containing cottonseed flour more nearly approached that of whole wheat bread than white bread, a comparison of the protein quality of the two breads would perhaps be of value. The results of the present study show that the incorporation in white bread of either 10 parts of cottonseed flour or 4 parts of milk solids will improve, to about the same extent, the protein quality as measured by rat growth. Where protein supplies are limited and where milk solids are not available, cottonseed flour of the quality used in these experiments might prove useful to enhance the protein quality of bread.

Acknowledgment

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Tailor-Making an Insecticide; Potential Market for Chemicals as Rodent Repellents

CHEMICAL STRUCTURE–ACTIVITY RELATIONSHIP

Chemical Structure of a Series of Organic Sulfites And Its Toxicity to the Two-Spotted Spider Mite

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Following the discovery by this laboratory that 2-chloroethyl dodecyl sulfite is highly toxic to the two-spotted spider mite (*Tetranychus bimaculatus* Harvey), related unsymmetrical sulfites were studied. The relationships between chemical structure and toxicity to the two-spotted spider mite are discussed. This study led to the conclusion that the sulfite radical is the "toxic" group and the rest of the molecule serves to modify chemical and physical properties. Substitution of aryloxy radicals for a portion of the long-chain alkyl radical produced a flexible new series of sulfites which made it possible to tailor a compound of optimum activity which is free from the undesirable side effects often associated with insecticides. The effect of size, shape, and location of various substituents on the toxicity to two-spotted spider mites is discussed.

ESTERS OF SULFUROUS ACID were mentioned as insecticides as early as 1929 by workers of I. G. Farbenindustrie. Two esters, bis(2-chloroethyl) sulfite glycol sulfite, were disclosed as being toxic to grain weevils (*3*). Hechenbleikner (*2*) later described several sulfites as being toxic to mites, aphids, and thrips. His data indicate that dialkyl sulfites such as dilauryl sulfite and di-2-ethylhexyl sulfite are especially toxic to mites, and to a lesser extent to aphids.

The writers' interest in the organic sulfites began as a result of the discovery that 2-chloroethyl *p*-chlorobenzenesulfonate is toxic to the two-spotted spider mite (*Tetranychus bimaculatus* Harvey). Among the chemicals tested in following up this lead was 2-chloroethyl dodecyl sulfite (*1*). This compound exhibited an LD_{95} of about 150 p.p.m. It was roughly eight times more toxic to two-spotted spider mites than the sulfonate and over thirty times as toxic as the compounds of the prior art, as shown in Table I.

It is obvious from Table I that in the sulfite series toxicity to mites is greatly affected by the nature of the organic radicals. A program was initiated to study the relationships between structure and activity in this series as the first step in the development of a practical control for mites.

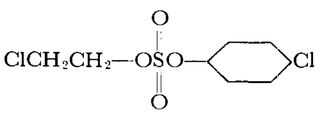
2-Chloroethyl dodecyl sulfite is an unsymmetrical ester of sulfurous acid. This class of compounds can be represented by the generalized formula

$$\mathrm{R{-}O\overset{\displaystyle O}{\overset{\|}{S}}O{-}R'}$$

Both R and R′ can be varied to produce a large number of compounds with any desired gradation in properties. Table II compares the activity of a group of 2-chloroethyl *n*-alkyl sulfites in which the length of hydrocarbon chain is varied.

Activity increases rapidly with increasing chain length up to about 10 carbon atoms, changes little between 10 and 12 carbon atoms, and decreases with further increase in chain length. Branching of the chain has little or no effect on activity. Table III shows the effect of variation of the R radical if R′ is a long-chain alkyl radical—namely, *n*-decyl ($C_{10}H_{21}$).

Table I. Toxicity of a Group of Compounds to Two-Spotted Mites

Compound	LD_{95}, P.P.M.
	1250
$ClCH_2CH_2\text{—}O\overset{O}{\overset{\|}{S}}\text{—}C_{12}H_{25}$	150
$ClCH_2CH_2\text{—}O\overset{O}{S}O\text{—}CH_2CH_2Cl$	5000
$C_{12}H_{25}\text{—}O\overset{O}{S}O\text{—}C_{12}H_{25}$	10,000

Mite-infested bean plants were sprayed to run off with aqueous emulsions of the various chemicals and mortalities were determined after 48 hours. All data shown in this paper are in terms of parts per million required to kill 95% of the two-spotted spider mites on bean plants within 48 hours (LD_{95}).

Halogen substitution on the small alkyl radical greatly increases activity. In this series the chloro- and bromoethyl and the dichloropropyl members were the most active.

The relationships are somewhat different in series having either longer or shorter alkyl chain length, as shown in Table IV.

These tables demonstrate the fact that toxicity to mites is associated with no particular alkyl or haloalkyl radical.

Table II. Toxicity of Alkyl 2-Chloroethyl Sulfites to Two-Spotted Spider Mites

$$ClCH_2CH_2\text{—}O\overset{O}{S}O\text{—}R$$

R	LD_{95}, P.P.M.	R	LD_{95}, P.P.M.
n-C_4H_9	10,000	n-$C_{11}H_{23}$	150
n-C_7H_{15}	1,000	n-$C_{12}H_{25}$	125
n-C_8H_{17}	500	n-$C_{14}H_{29}$	400
n-$C_{10}H_{21}$	170	n-$C_{16}H_{33}$	600

There is not the sharp relationship between structure and activity that is encountered among the isomers of benzene hexachloride or DDT, yet the best members of the series are many times as active as the simple dialkyl sulfites. When phytotoxicity and costs are considered, the 2-chloroethyl group is generally the most practical of the haloalkyls.

It seemed to the writers, therefore, that toxicity to mites is associated with the sulfite radical and that the other groups serve merely to impart to the compound the physical properties to enable it to arrive at the proper place in the mite and the right degree of stability to whatever chemical reactions are involved in the toxic action.

Although these sulfites were very toxic to mites, there was a narrow margin between the dosage required to control mites and that which sometimes injured plants. Other types were explored

Table III. Toxicity of Decyl Haloalkyl Sulfites to Two-Spotted Spider Mites

$$R\text{—}O\overset{O}{S}O\text{—}C_{10}H_{21}$$

R	LD_{95}, P.P.M.
C_2H_5—	2500
$ClCH_2CH_2$—	170
$BrCH_2CH_2$—	125
CCl_3CH_2—	1000
$ClCH_2CH_2CH_2$—	600
$ClCH_2CH(CH_3)$—	500
$Cl_2C_3H_5$[a]	50
C_4H_9—	5000
$ClCH_2CH_2CH_2CH_2$—	400

[a] Prepared from a commercial mixture known as "glycerol dichlorohydrin," which is stated to contain 75% $ClCH_2CHClCH_2OH$ and 25% $(ClCH_2)_2CHOH$.

in an effort to find ones which could be safely used on plants. As molecular shape did not seem critical, it was of interest to study the effect of various aromatic radicals in place of the alkyl chain. The monoaromatic ethers of the alkylene glycols were attractive intermediates, since they offered a convenient group for study and many were potentially inexpensive. A large series of chloroalkyl aryloxyalkyl sulfites of the type

$$\text{Chloroalkyl}\ \text{—}O\overset{O}{\overset{\|}{S}}O\text{—}C_nH_{2n}O\text{—aromatic}$$

was then studied, with most gratifying results. For the sake of brevity, the discussion is limited to the 2-chloroethyl series, although others were also very active.

Table IV. Toxicity of Certain Alkyl Haloalkyl Sulfites to Two-Spotted Spider Mites

$$RO\overset{O}{S}OR'$$

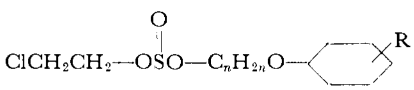
R	R′	LD_{95}, P.P.M.
$ClCH_2CH_2$—	n-C_7H_{15}—	1000
$ClCH_2CH_2CH_2$—	n-C_7H_{15}—	625
$Cl_2C_3H_5$—[a]	n-C_7H_{15}—	125
$ClCH_2CH_2$—	n-$C_{12}H_{25}$	125
$ClCH_2CH_2CH_2$—	n-$C_{12}H_{25}$	125
$Cl_2C_3H_5$—[a]	n-$C_{12}H_{25}$	75

[a] See Table III.

The center alkylene radical has a very strong influence on activity. The most active compounds are those in which it is propylene ($\text{–}CH(CH_3)CH_2\text{–}$). Table V illustrates this point.

That more is involved than just molecular weight is shown by a comparison of the compounds in Table VI. These compounds are isomeric. In effect, a methyl has been moved from the propylene radical to the alkyl substituent of the ring. The propylene derivative is invariably at least twice as effective as the ethylene analog having the same aromatic radical.

Table V. Toxicity of Substituted Aryloxyalkyl 2-Chloroethyl Sulfites to Two-Spotted Spider Mites



C_nH_{2n}	R	LD_{95}, P.P.M.
$\text{—}CH_2CH_2\text{—}$	H	1250
$\text{—}CH(CH_3)CH_2\text{—}$	H	600
$\text{—}CH_2CH_2\text{—}$	p-Cl	250
$\text{—}CH(CH_3)CH_2\text{—}$	p-Cl	60
$\text{—}CH_2CH_2\text{—}$	p-$C(CH_3)_3$	50
$\text{—}CH_2CH_2CH_2\text{—}$	p-$C(CH_3)_3$	20
$\text{—}CH(CH_3)CH_2\text{—}$	p-$C(CH_3)_3$	10

The effect of substitution on the benzene ring is even more dramatic, as shown in Table VII. The simplest member of the series exhibits an LD_{95} of 600 p.p.m. (Table V) compared with an LD_{95} of 10 p.p.m. for the most active members. Activity increases rapidly with increase in size of substituent up to four carbon atoms, then drops. The position and shape of the substituent are relatively unimportant.

Chlorine substitution presents a slightly different relationship, as shown in Table VIII. A molecular weight increase

Table VI. Relationship Between Position of a Methyl Group and Toxicity to Two-Spotted Spider Mites

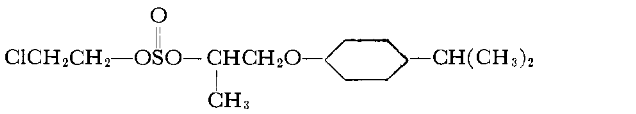
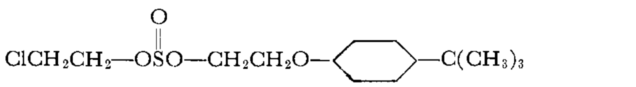
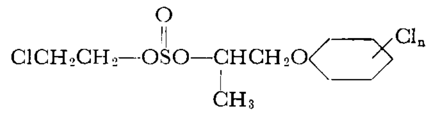
Compound	*LD_{95},P.P.M.*
	20
	50

Table VIII. Effect of Ring Chlorine Substitution of Aryloxyisopropyl 2-Chloroethyl Sulfites on Toxicity to Two-Spotted Spider Mites

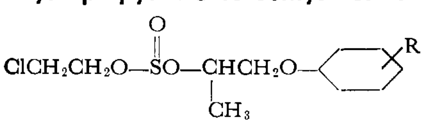


Cl_n	*LD_{95}*
H	600
p-Cl	60
2,4-Di-Cl	20
2,4,5-Tri-Cl	50
Penta-Cl	150

due to chlorine is roughly equivalent biologically to the same increase due to an alkyl radical.

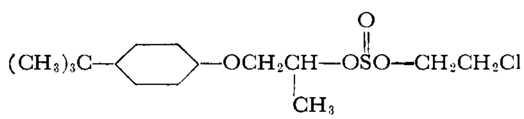
As in the long-chain alkyl series, there is a nice relationship between structure and activity in the aryloxy alkyl sulfites.

Table VII. Effect of Ring Substitution on Toxicity to Two-Spotted Spider Mites in a Series of Aryloxyisopropyl 2-Chloroethyl Sulfites



R	*LD_{95}, P.P.M.*
H	600
p-CH_3	100
p-$CH(CH_3)_2$	20
o-$CH(CH_3)_2$	20
p-$CH(CH_3)C_2H_5$	10
p-$C(CH_3)_3$	10
p-$C(CH_3)_2C_2H_5$	16
p-Cyclohexyl	25

From the simplest member of the series to the most active there is approximately a 125-fold increase in activity. Many other types have been tested; although many are very toxic to mites, none is more toxic than 2-(*p-tert*-butylphenoxy) isopropyl 2-chloroethyl sulfite, which is marketed commercially as Aramite (*1*).



The great activity of this compound on many species of mites, coupled with its low toxicity to predatory insects, its low mammalian toxicity (oral LD_{50} for rats and guinea pigs, 3.9 grams per kilogram of body weight), its high ovicidal activity, and its safety on plants makes it an ideal miticide.

While many sulfites are extremely toxic to the two-spotted spider mite, many others are not. Almost any of the simple symmetrical ones which a chemist would tend to try first are so inactive that they would not pass a screening test. Some others which are active cause injury to a wide variety of plants at the dosage required to kill mites. It is, therefore, necessary to try several members of a series before a valid conclusion can be reached.

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RODENT CONTROL

A Review of Chemical Repellents for Rodents

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Emphasis on chemical repellents as a means of reducing damage by rodents and other animal pests has been increased in recent years, though the deterrent approach to rodent control is not new.

The need for such protective materials is generally recognized. It has been estimated that the annual economic loss due to rats and other rodents in the United States may amount to between one and two billion dollars. Part of this is loss to orchards, field crops, poultry, and other farm products, part is loss to buildings and equipment, and a considerable portion involves damage to or contamination of packaged goods in transit or storage.

The most satisfactory method for preventing these losses would be the elimination of the rodent populations through extermination campaigns and by use of rodent-proof construction. The importance of these measures cannot be minimized and every effort should be made to increase their application where feasible. However, such methods may not be completely successful in all cases and may be impossible or impractical to carry out in the vicinity of temporary storage dumps or the wharf areas of large ports. The supplementary use of rodent-repellent containers would be of material advantage in reducing the economic loss due to rodent depredations on packaged goods.

Although there is a definite relationship between the physical hardness or toughness of a barrier and its resistance to rodent attack, additional resistance may be afforded by an effective chemical repellent. Such material should prevent or minimize damage by rodents upon paperboard, fabrics, or other materials impregnated, coated, or other-