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Chemistry and Toxicology of Quinoxaline, Organotin, Organofluorine, and Formamidine Acaricides*

by Charles O. Knowles*

Quinoxaline, organotin, organofluorine, and formamidine compounds are among the newer pesticide chemicals used for acarine control. Included in these four classes are *some of the most selective synthetic organic toxicants currently in the* acaricide/insecticide arsenal. Oxythioquinox, Plictran (tricyclohexylhydroxytin), Nissol [2-fluoro-*N*-methyl-*N*-(1-naphthyl)acetamide], and chlordimeform are examples of quinoxaline, *organotin, organofluorine, and formamidine acaricides, respectively. The chemistry* and toxicology of these and related compounds are discussed.

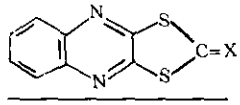
Several of the newer synthetic organic or "second generation" acaricides are widely used for control of phytophagous mites and ticks. Certain of these compounds also have insecticidal and fungicidal activity. This paper reviews some of the existing data derived from studies of the chemistry and toxicology of the quinoxaline, organotin, organofluorine, and formamidine compounds.

Quinoxaline Compounds

A systematic study of the sulfur-containing quinoxaline compounds conducted in Germany indicated that cyclic dithiocarbonates usually had higher initial toxicity to spider mites than trithiocarbonates (Table 1) *(1)*. The efficacy depended largely upon the nature of the substituents in the benzene nucleus of the quinoxaline skeleton. Thioquinox and oxythioquinox (Table 1) were the two most promising compounds; however, the former compound was not used primarily because of its skin sensitizing activity. Oxythioquinox or Morestan has a broad spectrum of miticidal activity and also is active against some insects and fungi *(1,2)*. It is prepared by the condensation of dimercaptomethylquinoxaline with phosgene; the product is a yellow crystalline powder melting at 172°C *(1)*. It hydrolyzes under alkaline conditions to yield a dithiol derivative, 6-methyl-2,3-quinoxalinedithiol or QDSH.

Carlson and DuBois *(3)* studied the mammalian toxicology of oxythioquinox and QDSH. They concluded that oxythioquinox had a relatively low acute toxicity; the acute intraperitoneal LD_{50} ranged from 95 to 192 mg/kg for adult male and female rats, respectively, and from 458 to 475 mg/kg, respectively, for adult male and female

Table 1. Toxicity of quinoxaline acaricides to two-spotted spider mites.[a]



R	X	Mortality at 24 hr. % [b] Motile forms	Eggs
H	O	> 90(0.002)[b]	16(0.001)
CH_3[c]	O	> 90(0.002)	99(0.001)
H	S	100(0.2)	47(0.001)
CH_3[d]	S	100(0.2)	—

[a]Data of Sasse *(1)*.
[b]Concentration (%) given in parentheses.
[c]Oxythioquinox.
[d]Thioquinox.

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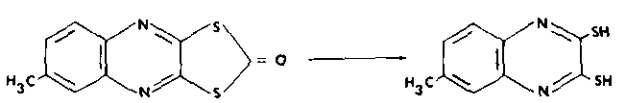
mice. QDSH was about twice as toxic as oxythioquinox. Acutely toxic doses caused decreased activity, diarrhea, increased hematocrit values, decreased urination, and a fall in blood pressure. The acute oral LD_{50} could not be accurately determined because of solubility limitations but was estimated to be greater than 1500 mg/kg for both oxythioquinox and QDSH. They also observed that oxythioquinox had a high cumulative toxicity when administered daily. For example, when various amounts were injected intraperitoneally into female rats for 60 days, 25 mg/kg was the highest level that was tolerated without mortality. Subacute dermal studies were conducted by applying oxythioquinox (250 mg/kg) to the clipped backs of male and female rats 5 days/week for 3 weeks. There were no grossly observable toxic effects. Treated male rats showed no inhibition of growth rate, but females weighed slightly less than their original body weight. Both sexes had enlarged livers, and histological changes were evident. Feeding oxythioquinox in the diet for 90 days at 500 ppm also resulted in decreased body weight and enlarged livers. Inhibition of acetoacetate synthesis and microsomal enzymes was observed. Oxythioquinox and QDSH also inhibited sulfhydryl enzymes including pyruvic dehydrogenase, succinic dehydrogenase, malate dehydrogenase, and > -keto glutare oxidase. Levels of glutathione and of nitroreductase activity were lower in liver. Carlson and DuBois (*3*) suggested that inhibition of sulfhydryl enzymes could be responsible for the mammalian toxicity of these compounds. The fact that cysteine and glutathione afforded some protection against the lethal action of oxythioquinox provided support for their hypothesis (*3*).

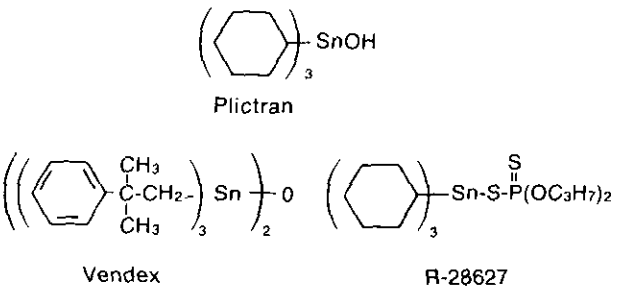


I II

Aziz and Knowles *(4)* studied the toxicity, action, and metabolism of oxythioquinox in two-spotted spider mites (*Tetrancychus urticae* Koch). Oxythioquinox and QDSH were highly toxic to the mites. Spider mites rapidly metabolized oxythioquinox-^{14}C to QDSH and to other unidentified polar metabolites *(5) in vivo* and *in vitro* [eq. (1)]. Using equilibrium dialysis it was shown that oxythioquinox was bound irreversibly to proteins in the mite homogenate, and in rat brain, liver, and blood. Binding was blocked by sulfhydryl reagents. Aziz and Knowles *(4)* concluded that binding of oxythioquinox to proteins probably involved a mechanism by which the sulfhydryl group of proteins initially attacked the carbonyl carbon of the acaricide and that acaricidal action of oxythioquinox was due, in part to disruption of the normal function of significant proteins by the parent compound itself and perhaps by QDSH.

Organotin Compounds

Three organotins that possess appreciable acaricidal activity are Plictran or tricyclohexylhydroxytin, the forerunner of this class of miticides; Vendex, a distannoxane; and R-28627, a di-*n*-propyl phosphorodithioate with tricyclohexyltin as the acid anhydride moiety.



Organotin Acaricides

Plictran is the only organotin currently in use for mite control. The compound is a white crystalline powder virtually insoluble in water (*6*). The acute oral LD_{50} of Plictran to white rats ranged from 235 to 650 mg/kg (*6*). Rats fed Plictran in the diet for 16 weeks at 200 ppm showed no adverse effects except for poor weight gains attributed to unpalatability of the diet preparation. Ahmad and Knowles *(7)* studied the toxicity of Plictran miticide and Du-Ter (triphenylhydroxytin) fungicide to mice, house flies (*Musca domestica* L.), and two-spotted spider mites (Table 2); the selective toxicity of Plictran to

Table 2. Toxicity of Plictran and Du-Ter to the mouse, house fly, and two-spotted spider mite.[a]

Organism	Route	Compound	Toxicity, ppm 24 hr	Toxicity, ppm 48 hr
Mouse	Intraperitoneal, LD_{50}	Plictran	2500	661
		Du-Ter	3900	700
House fly	Topical, LD_{50}	Plictran	640	630
		Du-Ter	1100	950
Spider mite	Contact, LC_{50}	Plictran	285	150
		Du-Ter	1000	355

[a]Data of Ahmad and Knowles (7).

mites was apparent. Plictran also possesses appreciable mite–mite selectivity *(8,9)*, and this organotin is probably the most selective compound currently in the miticide arsenal.

The mode of action of trisubstituted organotins, such as Du-Ter and Plictran, has been ascribed, at least in part, to inhibition of oxidative phosphorylation *(10)*. Both Du-Ter and Plictran inhibit ATPases in mice and house flies *(7)*. Moreover, Plictran was an outstanding inhibitor of oligomycin-sensitive (mitochondrial) Mg^{2+} ATPase from fish brain and spider mite homogenates with I_{50} values of $6.6 \times 10^{11} M$ and $6.2 \times 10^{-10} M$, respectively *(11)*. Studies with Plictran–^{119}Sn indicated that it degraded to inorganic tin compounds, predominantly stannic acid, presumably via successive decyclohexylation *(6)*. It was reported that Plictran presented no unusual problems as far as health or the environment was concerned *(12)*.

There is little published information on the chemistry and toxicology of Vendex and R-28627.

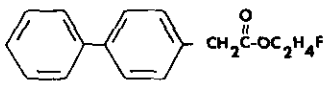
Organofluorine Compounds

Four different types of organofluorine miticides are fluenethyl, Nissol, fenazaflor, and R-10044.

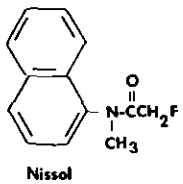
Fluenethyl has not been used for mite control in the United States but is used abroad. The pure compound is a white, odorless, crystalline material with a melting point of 60.5°C *(13)*. It is prepared by reacting the sodium salt of biphenylacetic acid with 2-fluoroethyl *p*-toluenesulfonate *(14)*. Acute toxicity studies of purified fluenethyl administered orally in 0.1% olive oil to warm-blooded animals gave the following LD_{50} values *(13)*: mouse, 57 mg/kg; rat, 8.7 mg/kg; guinea pig, 0.7 mg/kg; rabbit, 0.7 mg/kg; dog, 1.5—2.0 mg/kg; cat, 1.0 mg/kg; chicken, 16 mg/kg; monkey, 75 mg/kg; quail, 54 mg/kg; and pheasant, 80 mg/kg. Percutaneous toxicity studies revealed LD_{50} values of 10 and 4 mg/kg of fluenethyl to the rat at 4 hr and 10 days posttreatment, respectively *(13)*. The LD_{50} of fluenethyl administered intravenously to rats at 1.0% in dimethylacetamide was 43 mg/kg. When administered via intramuscular injection to chickens in 1% olive oil the LD_{50} was 32 mg/kg, and when administered via intraperitoneal injection to rats the LD_{50} was 5.5 mg/kg *(13)*.

The chronic toxicity of fluenethyl to rats was determined by feeding groups of 20 rats 0.04 and 0.4 mg of fluenethyl/kg per day for a period of 6 months *(13)*. There were no apparent lesions or abnormalities at the lower dosage level. The higher dose brought about, in some cases, a moderate reduction in splenic tissue, cessation of spermatogenesis and possible testicular atrophy (in one of nine rats analyzed) *(13)*.

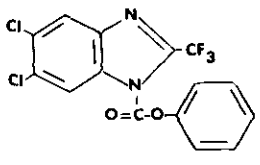
Johannsen and Knowles *(15,16)* studied the toxicity, action, and metabolism of fluenethyl and several other monofluorine-containing compounds in mice, house flies, and two-spotted spider mites. Of the compounds examined, fluenethyl, monofluoroacetic acid, and monofluoroethanol were the most toxic (Table 3). Intoxicated mice and house flies exhibited classical symptoms of organofluorine poisoning; mites exhibited a brief period of hyperactivity. Ethanol, isoniazid, triazole, acetamide, sodium acetate, and monoacetin afforded some protection against the toxicity of fluenethyl and monofluoracetic acid, suggesting that metabolic transformation of these two compounds was essential for toxicity. Further, mice, house flies, and spider mites poisoned with fluenethyl and other fluorine-containing compounds accumulated high levels of citrate as compared to controls, providing evidence that the enzyme aconitase was attacked *(15)*.



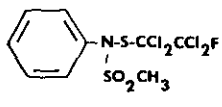
fluenethyl



Nissol



fenazaflor

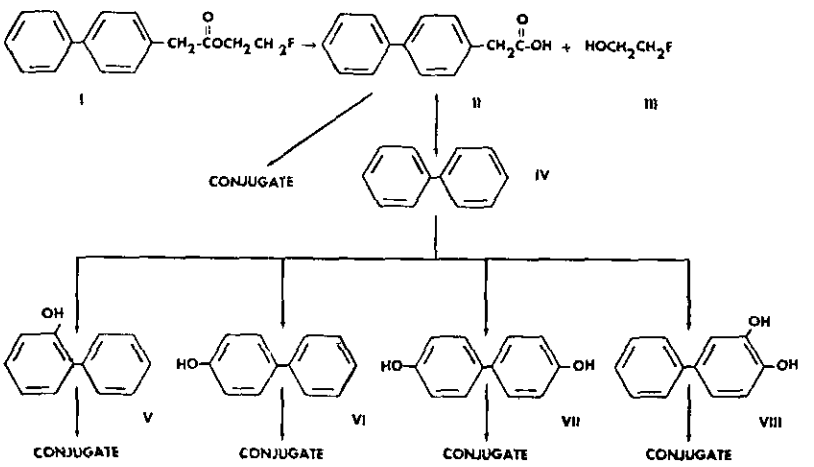


R-10044

Table 3. Acute toxicity of fluenethyl and related compounds to the mouse, house fly, and two-spotted spider mite.[a]

Compound	Toxicity: Mouse LD_{50}, mg/kg[b]	House fly LD_{50}, mg/kg[c]	Spider mite LC_{50}, ppm[d]
Fluenethyl	42	13; 300	284
Fluoroacetic acid	15	17; 230	231
Fluorethanol	20	17; 350	163
Fluoroacetamide	110	27; 235	1971

[a]Data of Johannsen and Knowles *(15)*.
[b]Intraperitoneal injection,
[c]Intrathoracic injection and topical application,
[d]Slide-dip technique.



(2)

Metabolism studies of fluenethyl-^{3}H in mice, house flies, and mites showed that initial attack on the molecule occurred at the ester linkage *in vitro* and *in vivo*; this attack was hydrolytic in nature, and the products were biphenylacetic acid and monofluorethanol. Several mono- and dihydroxylated biphenyls and their conjugates also were present *in vivo (16)*. The metabolic paths for fluenethyl *(5)* are summarized in the reaction scheme (2).

It was concluded that the monofluorethanol released upon esteratic cleavage of fluenethyl was oxidized to monofluoroacetic acid which, after conversion to fluorocitrate, inhibited aconitase. This appeared to be the mechanism for the toxic action of fluenethyl and the other monofluoroethyl esters in the three species examined *(15)*.

Nissol or MNFA is an *N*-substituted fluoroacetamide with a melting point of 86–87°C *(17)*. It is prepared by reacting *N*-methyl-1-naphthylacetanilide with potassium fluoride *(18)*. Johannsen and Knowles *(19)* studied the toxicity of Nissol to mice, house flies, and two-spotted spider mites (Table 4). Selectivity of this organofluorine miticide was evident. Taniguchi *(20)* earlier reported that Nissol possessed superior selective toxicity. In another study *(21)*, with different mammals as test organisms, it was observed that the acute toxicity of Nissol varied markedly with the species. For example, guinea pigs, rabbits, dogs, and cats were extremely sensitive to Nissol with acute oral LD_{50} values of less than 5 mg/kg, while mice, rats, and monkeys were appreciably more tolerant, with LD_{50} values greater than 200 mg/kg in most cases. Subacute toxicity studies of Nissol in rats revealed two interesting phenomena *(21)*. Aspermatogenesis was observed in some tubules of testes of rats receiving 5.0 or 10.0 mg/kg of Nissol daily for 6 months. Destruction of the germinal epithelium was more pronounced in mature cell series than in immature cell series. Lower doses of Nissol did not produce significant changes in the testes. It was suggested that the effects on rat testes may have resulted from monofluoroacetic acid, a Nissol metabolite. An inverse relationship was noted between Nissol dosage and systolic arterial blood pressure in male rats. Cardiac depression occurred, and electrocardiagrams indicated various kinds of effect *(22)*. Additional pharmacological properties of Nissol also were described *(22)*. Mammals *(23,24)* accumulated citrate following treatment with Nissol citric acid levels in brain, heart, kidney, and liver of mice 12 hr following intraperitoneal injection of Nissol (100 mg/kg) are shown in Figure 1 *(24)*. House flies and two-spotted spider mites treated with Nissol also accumulated citrate *(19,24)*.

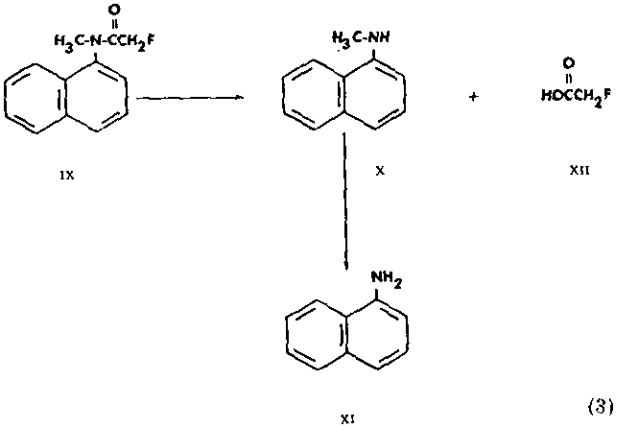
Nissol metabolism was examined in rats, guinea pigs, house flies and two-spotted spider mites *(5,25,26)*. It was converted initially to *N*-methyl-1-napthylamine [compound X, eq. (3)], and

Table 4. Toxicity of Nissol to the mouse, house fly, and two-spotted spider mite[a]

Organism	Route	Toxicity, ppm
Mouse	Intraperitoneal, LD_{50}	200
House fly	Topical, LD_{50}	525
	Injected, LD_{50}	14
Spider mite	Contact, LC_{50}	250

[a]Data of Johannsen and Knowles *(19)*.

monofluoracetic acid [compound XII, eq. (3)]. 1-Naphthylamine (XI) and unidentified polar metabolites also were present.



(3)

Fenazaflor contains a trifluoromethyl moiety; thus it is considered along with the organofluorines. It possesses residual contact and stomach activity against a wide range of phytophagous mite species *(27)*. Its toxicity to vertebrates varies with the species. The acute oral LD_{50} of the formulated material (Lovozal 20 W) was 283 mg/kg for rats, 1600 mg/kg for mice, 258 mg/kg for hamsters, 59 mg/kg for guinea pigs, 50 mg/kg for dogs and cats, 30 mg/kg for pigs (young) and lambs, and 28 mg/kg for rabbits *(27)*. Dermal absorption rate and dermal toxicity of the formulated material were both low; the acute dermal

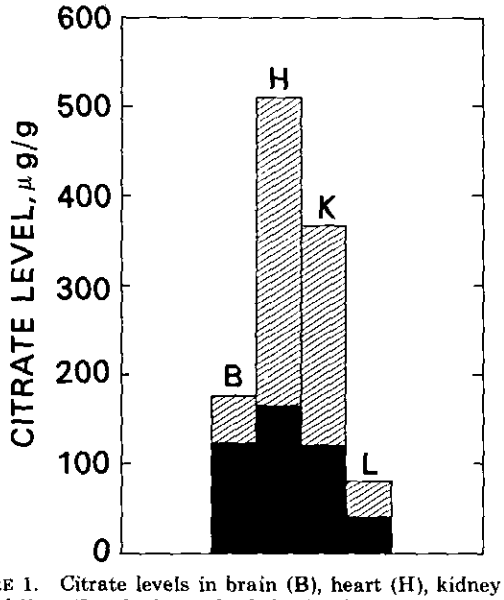
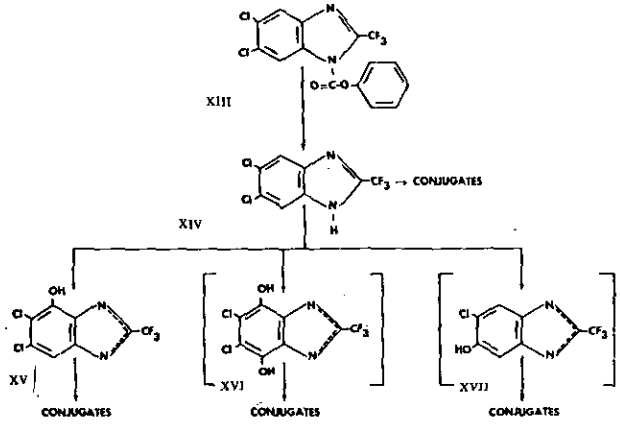


FIGURE 1. Citrate levels in brain (B), heart (H), kidney (K), and liver (L) of mice 12 hr following intraperitoneal injection of Nissol (100 mg/kg). Solid portion of bars indicate control levels of citrate in respective tissues. Data of Johannsen and Knowles. *(19)*.

LD_{50} values for the rat and rabbit were greater than 4000 and 2000 mg/kg, respectively, expressed as the active ingredient *(27)*.

Bowker and Casida *(28)* studied the metabolism of fenazaflor in mammals, insects, and plants, and these reactions are summarized in eq. (4). An important reaction was the conversion of fenazaflor [compound XIII, eq. (4)], to 5,6-dichlorotrifluoromethylbenzimidazole [compound XIV, eq. (4)]. Ilivicky and Casida *(29)* had shown earlier that the benzimidazole was an uncoupler of oxidative phosphorylation in insects and mammals, and Corbett and Wright *(30)* showed that fenazaflor, after conversion to the benzimidazole, uncoupled oxidative phosphorylation in intact mites and in



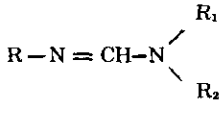
(4)

isolated mite mitochondria. This latter observation *(30)* was especially significant, as it apparently was the first report of the isolation of mite mitochondria.

Formamidine Compounds

There are five types of formamidines of current commercial interest as acaricides and insecticides (Table 5). In each case R is aryl and is either 4-chloro-*o*-tolyl or 2,4-xylyl. R_1 is alkyl and is always

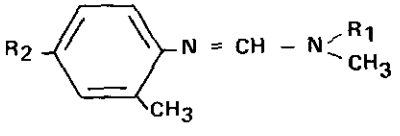
Table 5. Types of formamidines of current commercial interest as acaricides and insecticides.



Type	R	R_1	R_2
I	Aryl	Alkyl	Alkyl
II	Aryl	Alkyl	Alkylthioalkyl
III	Aryl	Alkyl	H
IV	Aryl	Alkyl	Aryl-N=CH–
V	Aryl	Alkyl	Thioaryl

methyl. In type I R_2 is methyl; in type II, R_2 is methylthiomethyl; in type III, R_2 is hydrogen; in type IV, R_2 is aryl-N=CH- and the aryl moiety is 4-chloro-*o*-tolyl or 2,4-xylyl; and in type V R_2 is thioaryl (usually thiophenyl). Examples of the different types are given in Figure 2. Type I is represented by chlordimeform; type II is represented by Hokupanon; type III is represented by C-8520 or demethylchlordimeform and by BTS-27271; type IV is represented by BTS-23376 and by BAAM or amitraz (BTS-27419, U-36059); and type V is represented by U-42558 and by U-42564.

Extensive structure-activity relationship studies have been conducted within each of the five formamidine types (Table 5) *(31–39)*. Generally, formamidines exhibit a unique activity spectrum being toxic to all life stages of mites and ticks and to eggs and early instar larvae of certain insects, particularly some of the Lepidoptera *(33,40–43)*. Knowles and Roulston *(33)* indicated that the essential moiety for maximum formamidine toxicity to cattle ticks, *Boophilus microplus* (Canestrini), has the structure XVIII. Each formamidine listed



XVIII

in Figure 2 possesses this moiety. Further, it can be concluded that the structure requirements for activity are more stringent for aryl substitutent R_2 than for nitrogen substitutent R_1.

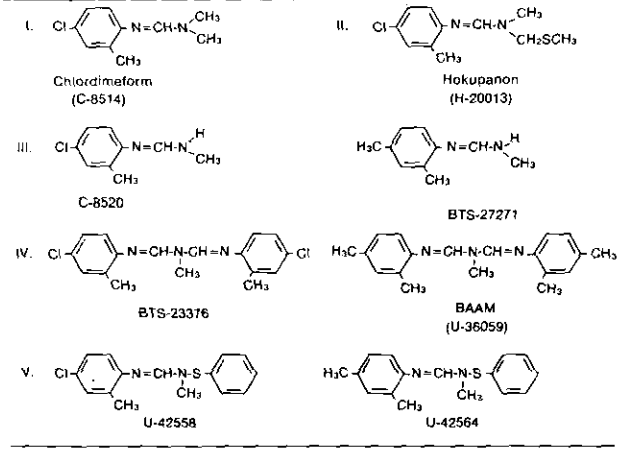
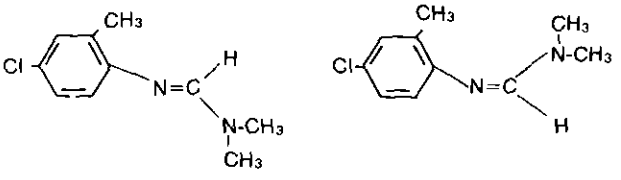


FIGURE 2. Examples of formamidine acaricides and insecticides.

Chlordimeform is the forerunner of this interesting class of compounds. Although several methods for synthesis of aryl dialkylformamidines have been described, chlordimeform is conveniently prepared by the reaction of dimethylformamide with 4-chloro-*o*-toluidine by using phosphorus oxychloride as the condensing agent *(31)*. Chlordimeform is a medium strength base with a pK_a 7.2 and will form crystalline salts with strong acids *(44)*. Studies at Schering A.G. in Germany *(45)* have revealed that both base and salt forms of chlordimeform exist exclusively in the E-form or *trans* configuration; this also was the case for several aryl *N*-monomethylformamidines.

CHLORDIMEFORM



E Form (*trans* isomer) Z Form (*cis* isomer)

The acute oral LD_{50} of chlordimeform base is about 250 mg/kg for rats and 625 mg/kg for rabbits *(46)*. Chlordimeform hydrochloride has acute oral and dermal LD_{50} values for rats of 335 and 4000 mg/kg, respectively *(46)*. Thus this formamidine has moderate mammalian toxicity.

In the United States chlordimeform is marketed as Galecron by CIBA-Geigy and as Fundal by NOR-AM Agricultural Products, Inc. Other names include Spike in Australia *(47)* and Spanone in Japan *(41)*. Both free base and hydrochloride salt forms are used in agricultural practice *(44)*.

The metabolic fate of radiolabeled chlordimeform was studied in plants *(48–52)*, insects *(53,54)*, acarines *(32,55,56)*, microorganisms *(57)*, and mammals *(58–61)*, and much of this material was recently reviewed *(5,43)*. Equations (5) show the paths for chlordimeform metabolism in mammals. *N'*-(4-Chloro-*o*-tolyl) formamidine (XXI) is a novel metabolite and was tentatively identified in the urine of rats treated orally with radiolabeled demethylchlordimeform *(62)*. The paths for chlordimeform metabolism in plants, insects, acarines, and microorganisms were similar qualitatively to those for mammals, except the *N'*-(4-chloro-*o*-tolyl) formamidine (XXI), and the two anthranilic acids (XXIV and XXV) were not detected in nonmammalian species.

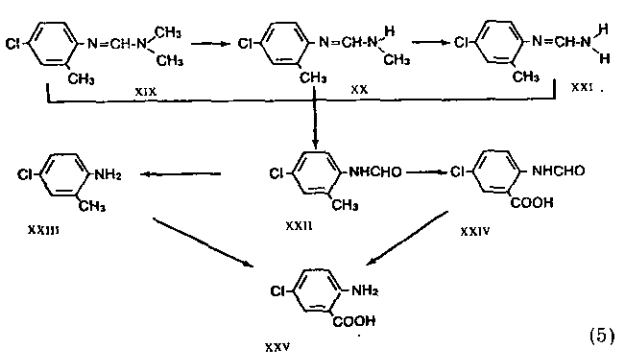
Table 6. Antagonism of chlordimeform toxicity to cattle tick larvae by piperonyl butoxide (PB) and sesamex[a]

Chlordimeform (0.02%) + modifier at following concentration (%)	Ratio modifier: chlordimeform	Relative antagonism at 48 hr, %	
		By PB	By sesamex
0.4	15:1	100.0	100.0
0.2	10:1	100.0	100.0
0.1	5:1	100.0	100.0
0.05	2.5:1	89.9	100.0
0.025	1.25:1	55.0	100.0
0.0125	0.63:1	9.5	98.2
0.0063	0.31.1	0.7	82.5
0.0031	0.16:1	0	43.2
0.0016	0.08:1	0	16.6

[a]Data of Knowles and Roulston *(33,63)*.
[b]Average mortality for chlordimeform alone was 85%; 100% antagonism corresponds to 0% mortality. There was no mortality of tick larvae in the presence of 0.4% modifier alone.

Piperonyl butoxide inhibited chlordimeform metabolism in house flies *(53)*, cabbage looper larvae *Trichoplusia ni* (Hubner) *(54)*, and cattle ticks *(55)*. In the case of house flies chlordimeform toxicity was slightly synergized *(53)*, but with cattle ticks toxicity was abolished *(33,63,64)*. An example of this marked antagonism of chlordimeform toxicity by piperonyl butoxide and sesamex is given in Table 6. These and other data prompted Knowles and Roulston *(63)* to suggest that chlordimeform was not the actual toxicant, at least in cattle tick larvae.

Several studies of the biochemical effects of chlordimeform have been conducted in ticks, insects, and mammals. Though the primary lesion has yet to be determined, there exists much information that points to involvement with biogenic amine regulatory mechanisms. Chlordimeform inhibited monoamine oxidase (MAO) from rat liver *(65,66)*, rat brain *in vitro* and *in vivo* *(67)*, cattle tick larvae *(68)*, and cockroach heads *(69)*. Several chlordimeform metabolites also inhibited MAO *(67,70)*, and 4′-chloro-*o*-formotoluidide was the most potent inhibitor (Table 7). In the case of chlordimeform, demethylchlordimeform, and 4′-chloro-*o*-formotoluidide, inhibition of rat brain



(5)

MAO was competitive and reversible *(67)*. Serotonin and norepinephrine accumulated in chlordimeform-poisoned rats *(66)* and cockroaches *(69)*, and chlordimeform synergized the toxicity of tryptamine to cockroaches *(69)*. Also 4-chloro-*o*-toluidine, a chlordimeform metabolite, interfered with the binding of norepinepherine to rat cardiac receptors *(70)*. Moreover, certain of the symptoms of chlordimeform poisoning in rats were sympathomimetic *(66,70)*. Other studies, especially those with the cattle tick, also suggested an involvement with biogenic amine regulatory mechanisms *(64,68,71–73)*. This interaction is doubtlessly involved in some of the atypical behavioral responses manifested by chlordimeform-poisoned organisms *(41,54,64,71–73)* and possibly in its killing action, although evidence is mounting against the MAO theory in the latter case *(64)*. In any event, this is the first insecticide or acaricide known to influence the biogenic amine system, thus this system is a potential target for the design of novel insecticides. Other workers have demonstrated that chlordimeform uncoupled oxidative phosphorylation in rats *(74)* and cockroaches *(75)*; that chlordimeform inhibited synthesis of DNA, RNA, and

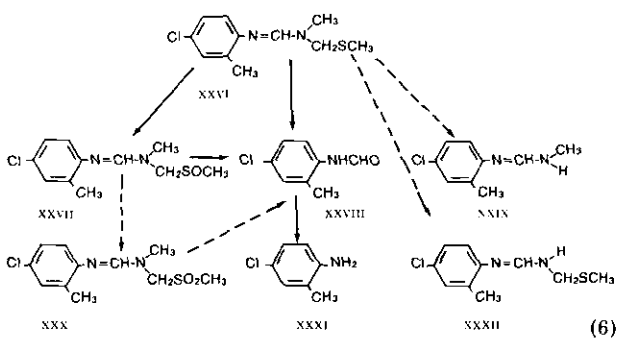
Table 7. Inhibition of rat brain tyramine oxidation by chlordimeform and metabolites[a]

	Compound[b]	I_{50}, *M*
XIX	Chlordimeform	6.0×10^{-5}
XX	Demethylchlordimeform	3.3×10^{-5}
XXI	Didemethylchlordimeform	7.5×10^{-5}
XXII	4′-Chloro-*o*-formotoluidide	2.6×10^{-6}
XXIII	4-Chloro-*o*-toluidine	1.0×10^{-4}
XXIV	*N*-Formyl-5-chloroanthranilic acid	$>1.0 \times 10^{-4}$
XXV	5-Chloroanthranilic acid	$>1.0 \times 10^{-4}$

[a]Data of Benezet and Knowles *(67)*.
[b]Structures for compounds are given in eqs. (5).

proteins *(76)*; and that chlordimeform had an effect on frog nerve-muscle preparations *(77,78)*. Therefore, the mechanisms of action of chlordimeform are complex, and more work is required before a clear picture emerges.

Hokupanon or Hokko-20013 is prepared by condensing 4-chloro-*o*-toluidine with methyl methylthiomethylformamide in the presence of phosphorus oxychloride *(79)*. It is subsequently converted to the hydrochloride salt and marketed in that form in Japan *(80)*. The metabolism of radiolabeled Hokupanon in rice plants was investigated *(79)* and is summarized in eqs. (6). The major metabolite was the sulfinyl derivative (XXVII). Other than studies of Hokupanon with the cattle tick *(33)* and the observation that it was a weak inhibitor of rat MAO *(65,67)* there is little published information on this compound.



(6)

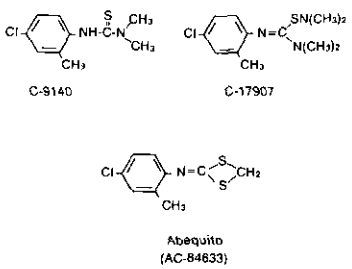
C-8520 or demethylchlordimeform and BTS-27271 are of interest primarily because they are metabolites and/or degradation products of several of the other formamidines. These formamidines can be prepared by reacting 4-chloro-*o*-toluidine or 2,4-dimethylaniline with *N*-methylformamide in the presence of a suitable condensing agent *(31,34)*. Both compounds are toxic. They inhibited MAO and elicited atypical behavior in acarines *(64,71–73)*.

BTS-23376 and BAAM are formamidines of more complex structure, and several procedures have been described for their preparation. For example, they can be prepared by heating the respective *N*-aryl *N*-methyl formamidine with methyl amine *(37)*. BAAM is being developed in the United States by The Upjohn Co. for use as an insecticide and acaricide. Acute oral toxicity studies of the technical material yielded the following LD_{50} values: > 1600 mg/kg for the mouse, 600 mg/kg for the rat, 488–800 mg/kg for the guinea pig, > 100 mg/kg for the rabbit, and 100 mg/kg for the dog *(81)*. These compounds also elicited atypical behavioral response *(64,71–73)* and inhibited MAO *(65,67,68,70)*.

The arylthioformamidines are the most recent addition to this class of compounds. U-42558 and U-42564 can be prepared by reacting the appropriate *N'*-aryl *N*-methylformamidine with phenylsulfenyl chloride in the presence of a tertiary amine in a suitable solvent *(38)*. U-42558 and U-42564 have rat acute oral LD_{50} values of 132 and 100–300 mg/kg, respectively *(82,83)*. They, too, inhibited rat brain MAO *in vitro (67)*.

Miscellaneous Compounds

The structural resemblance of C-9140, C-17907, and Abequito to the formamidines is as striking as are certain aspects of their toxicology *(33,67,72,73)*.



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Equations(1)–(4) are reproduced from a chapter which appeared in the book, *Survival In Toxic Environments (5)*. I am grateful to Academic Press, New York, for permission to include them in this paper.

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