Proceedings 1979 British Crop Protection Conference - Pests and Diseases

AMIDINOHYDRAZONES - A NEW CLASS OF INSECTICIDES

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Summary Laboratory studies have demonstrated the potential of a novel class of compounds, the amidinohydrazones, as insecticides. The amidinohydrazones show selective toxicity based on foliar treatments for the control of lepidopterous larvae. Members of this class of compounds are highly active by ingestion (suggesting stomach poison), exhibit delayed toxicity, and provide short residual activity on plants. They are considered to be only slightly to moderately toxic to mammals based on acute oral studies in mice. The amidinohydrazones appear to possess the unique properties required for utility in pest management programs.

One of the amidinohydrazones, AC 217,300, is being developed under an Experimental Use Permit in the U.S.A. for the control of imported fire ants. Current data confirm its effective control of imported fire ants.

INTRODUCTION

Recently, a new class of insecticides, the amidinohydrazones, was discovered in the random insecticidal screening program at American Cyanamid's Agricultural Center, Princeton, NJ, U.S.A. Following months of testing, specific compounds within the series were found to be quite selective depending on the method of application used. By foliar treatment the amidinohydrazones were more toxic to lepidopterous larvae than malathion and compared favorably with methyl parathion. They showed little or no toxicity by foliar treatment to other orders of insects, especially those with piercing-sucking mouthparts. Used in bait form they showed excellent activity when ingested by the red imported fire ant (Solenopsis invicta), the American cockroach (Periplaneta americana), the German cockroach (Blattella germanica), the oriental cockroach (Blatta orientalis), and the adult housefly (Musca domestica). The amidinohydrazones proved to be only slightly to moderately toxic to mammals based on acute oral tests, in which single dosages were administered to mice. The remarkable toxicity of these unique compounds and the commercial possibility of their use as insecticides prompted us to report their insecticidal properties.

CHEMISTRY

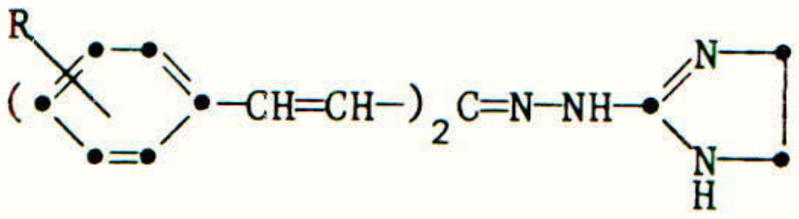
The amidinohydrazones (Table 1) are yellowish, odourless solids which are practically insoluble in water and are of low solubility in most organic solvents.

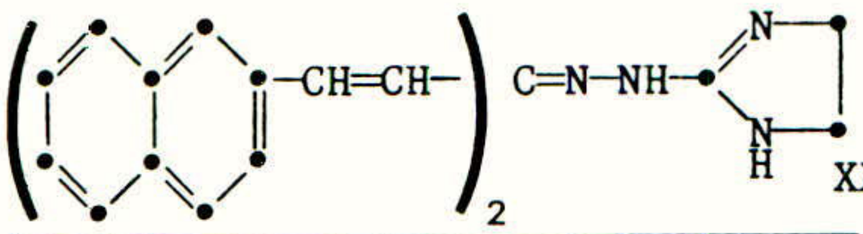
RELATION OF STRUCTURE TO ACTIVITY

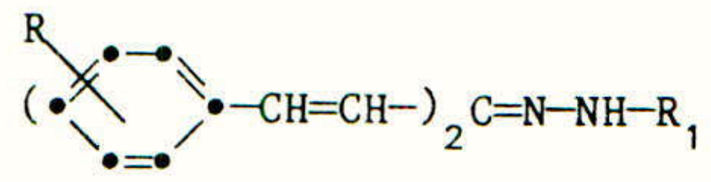
The effectiveness of the amidinohydrazones against third-instar larvae of three lepidopterous insects, the tobacco budworm (Heliothis virescens), the southern armyworm (Spodoptera eridania), and the cabbage looper (Trichoplusia ni) are presented in Table 2. Malathion and methyl parathion are also included as reference standards.

Table 1

Text designation and chemical structure of amidinohydrazones



R	
I	p-Cl free base
II	3,4-Cl,Cl ·HBr salt
III	p-Br ·HBr salt
IV	o-Cl ·HBr salt
V	p-CH_3 ·HBr·n-C_3H_7OH
VI	m-CH_3 ·HBr salt
VII	o-CH_3 ·HBr salt
VIII	p-$(CH_3)_2CH$ ·HBr salt
IX	p-CH_3S ·HBr salt
X	p-NO_2 ·HBr salt
XI	p- ·HBr·n-C_3H_7OH
XII	p-F_3C free base
XIII	 ·HBr
XIV	p-Cl free base
XV	p-F free base
XVI	p-F_3C free base
XVII	m-F_3C free base
XVIII	o-F_3C free base
XIX	malathion
XX	methyl parathion



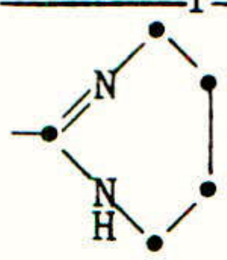
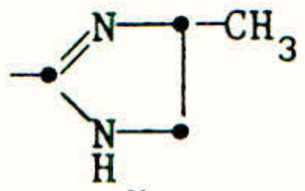
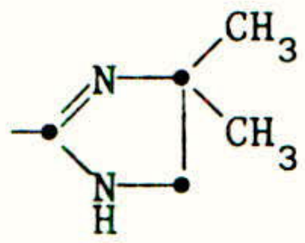
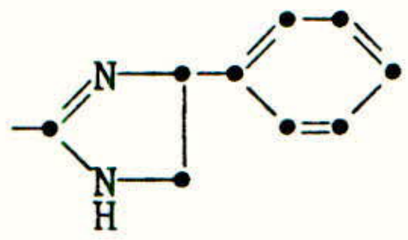
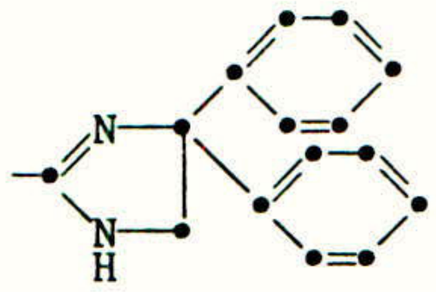
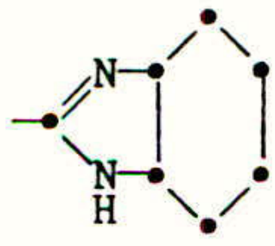
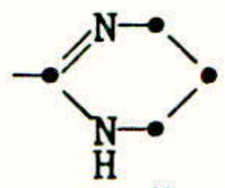
R	R_1	
XXI	p-F_3C	 ·HCl salt
XXII	p-F_3C	" free base
XXIII	p-Cl	" free base
XXIV	p-Cl	 free base
XXV	p-F_3C	" free base
XXVI	p-Cl	 free base
XXVII	p-Cl	" ·HCl salt
XXVIII	p-Cl	 free base
XXIX	p-Cl	 free base
XXX	p-Cl	 free base
XXXI	p-F_3C	" free base
XXXII	p-Cl	 free base
XXXIII	p-F_3C	" free base

Table 2

Insecticidal screening results

Compound	Percent mortality: Southern armyworm concn (ppm) 1000	100	10	1	Tobacco budworm concn (ppm) 1000	100	10	Cabbage loopers concn (ppm) 1000	100	10
I	100	60			0			100	0	
II	0									
III	100	60			30	0		0		
IV	0									
V	0									
VI	0									
VII	0									
VIII	100	10			0			20		
IX	0				0			0		
X	0									
XI	0									
XII	100	100	20		100	60				
XIII	0				0			0		
XIV	100	100	100	0	100	100	10	100	100	10
XV	100	40	0		0			90	0	
XVI	100	100	40	0	100	95	0	100	100	0
XVII	90	0			0			90	30	
XVIII	0									
XIX	100	70	0		100	0		70	0	
XX	100	100	0		100	65	0	100	100	0
XXI	100	100	100	0	100	100	0	100	100	0
XXII	100	100	100	40	100	100	0	100	100	30
XXIII	100	100	35	0	60	0		95	15	
XXIV	100	100	0		20			100	0	
XXV	100	100	95	0	100	100	0	100	100	0
XXVI	100	100	30	0	50	10		100	60	
XXVII	100	100	80	0	80	0		100	100	0
XXVIII	100	95	0		100	70	0	100	70	0
XXIX	0				0			0		
XXX	100	100	50		80	0		100	50	0
XXXI	90	0			70	0		10	0	
XXXII	100	100	0		20			100	50	0
XXXIII	100	100	70		100	100	0	100	100	20

Test procedures - lepidopterous larvae The test materials were dispersed in a 65% acetone-water solution. For both Spodoptera and Trichoplusia, primary leaves of Sieva lima bean plants (Phaseolus limensis) were dipped for 3-5 s. After the leaves were dry, each leaf was placed in a 10 cm petri dish with moist Whatman No. 1 filter paper on the bottom. Each dish contained ten third-instar larvae. For the Heliothis larvae, leaves from cotton plants (Gossypium sp. var. Stoneville 213) were used. After each leaf was treated and dried, it was cut into five sections. Each section was placed in a 21 ml plastic cup containing one third-instar larva and a 2.5 cm cotton dental wick saturated with water. Mortality counts were made after 3 d. In some cases the test results in Table 2 are averages of more than one test.

RESULTS

The original active lead compound XXI, which has a p-trifluoromethyl group on the benzaldehyde portion and a tetrahydrodiazepine on the hydrazone end, had excellent activity against the three species of lepidopterous larvae. Compound XXII, the free base of the original lead, was equally as effective as compound XXI, but compound XXIII, in which p-chloro was substituted for p-trifluoromethyl, was substantially less active than compounds XXI and XXII.

In another series of compounds, a comparison of activity was made among various substituted benzaldehydes (compounds I-XIII) when the amidine was itself a substituted imidazoline. The p-trifluoromethyl substituent (compound XII) was the most effective in this group. Compounds I, III, and VIII showed some activity whereas the performance was nil for the other compounds in this group.

The activity of the p-chloro and p-trifluoromethyl substituted benzaldehydes was compared with various substituents on the imidazolinyl moiety. In most of the comparisons, the p-trifluoromethyl substituent afforded a more active compound than did the p-chloro substituent. The phenylimidazolinyl moiety was more effective than either the methyl or dimethylimidazolinyl moieties which were equally effective. The hexahydrobenzimidazolyl moiety (compound XXX) was slightly more effective than the methyl and dimethylimidazolinyls.

Comparisons among p-halo and p-trifluoromethyl substituted benzaldehydes were made with tetrahydropyrimidinyl moieties on the hydrazone (compounds XIV-XVII; XXXII-XXXIII). The trifluoromethyl substituent lent more activity in the p-position than in the m- > o-position. The p-trifluoromethyl and p-chloro were more effective than the p-fluoro substituent. Compound XXXIII showed that the p-trifluoromethyl was more effective than p-chloro (compound XXXII).

During this study, compounds XXI, XXII, and XIV emerged as the most active compounds against southern armyworm larvae and gave excellent control of tobacco budworm larvae and cabbage loopers. Additional studies proved compounds XVI (AC 217,300) and XXV were extremely active against red imported fire ants as well as being substantially effective against lepidopterous larvae.

TOXICOLOGY

The acute toxicities of some of the more active technical amidinohydrazones are presented in Table 3.

Table 3

Toxicity of technical amidinohydrazones to laboratory mice

Compound	Acute oral LD50 (mg/kg)
XIV	812
XVI	>1600
XXI	696
XXII	429
XXIII	330
XXIV	660
XXV	272
XXX	871
XXXIII	1124

The technical materials were slightly to moderately toxic to mice by oral administration. The dermal LD50 to rabbits was greater than 200 mg/kg, with no skin irritation for the compounds tested. Slight eye irritation occurred when 100 mg of the technical materials tested were introduced in the eye of a rabbit.

Compounds IV, XVI, XXI, and XXII were evaluated in the Ames mutagenicity test (Ames et al, 1975) and were nonmutagenic.

BIOLOGICAL ACTIVITY OF FOLIAR TREATMENTS

Selectivity The results of the tests of the amidinohydrazones in comparison to malathion and methyl parathion against lepidopterous larvae are presented in Table 2. It is seen that approximately 25% of the amidinohydrazones tested were equal to or more effective than malathion and methyl parathion. Laboratory contact tests demonstrated that this series was generally inactive at 100 ppm on insects with piercing-sucking mouthparts, such as bean aphids (Aphis fabae), common malaria mosquitoes (Anopheles quadrimaculatus), tarnished plant bugs (Lygus lineolaris), and western potato leafhoppers (Empoasca abrupta). They showed little or no ovicidal activity on eggs of the common malaria mosquito and tobacco budworm. The lack of performance against insects with piercing-sucking mouthparts is an excellent indication of selective activity. Thus, the amidinohydrazones should be most suitable for pest management insect control programs.

Phytotoxicity No phytotoxicity was observed on young cotton and lima bean plants for any of the amidinohydrazones tested at rates up to 1000 ppm.

Stomach poison test to southern armyworm larvae Stomach poison and contact activity were compared by subjecting southern armyworm larvae to a three-layer leaf "sandwich" in which only the centre leaf was treated with the compound. Thus, the larvae could not come in contact with the toxicant except by ingestion. Contact activity was measured by exposing larvae for 2 d to compound XXI applied only on a glass surface. Dose-response curves showed that compound XXI was five to six times more potent by ingestion than by contact. The absence of high levels of contact toxicity also should reduce deleterious effects on beneficials under field conditions.

Delayed toxicity and residual activity Compound XVI (also designated as AC 217,300) was compared with methyl parathion (compound XX) for rapid toxicity and residual activity. The technical materials were dispersed in 65% acetone-water and applied to young cotton plants as an atomized spray for 45 seconds. After the treated

leaves dried, they were excised and each leaf was placed in a 10 cm petri dish. The bottom of the dish which had been lined with moist Whatman No. 1 filter paper was then infested with five third-instar tobacco budworm larvae. Two leaf samplings were made; one on the day of treatment and the second, one day posttreatment. Mortality counts were made at 1, 2 and 3 d after the first sampling (rapid toxicity) and 4 d after the second sampling (residual activity). The results (Table 4) showed that AC 217,300 was several days slower acting than methyl parathion at the lower concentration, 60 ppm. However, as the concentration was increased from 60 to 240 ppm the delayed toxic action of AC 217,300 was reduced.

In the residual portion of this test, a sampling of plants from the initial toxicity test was placed in the greenhouse under high intensity discharge lamps for 16 h. These lamps give off ultraviolet rays which are approximately equivalent to those emitted by the sun during a day in mid-June in New Jersey, U.S.A. The results (Table 4) showed that AC 217,300 was more persistent than methyl parathion at 60 ppm. However, at 240 ppm the residual activity for the two compounds was not significantly different.

Table 4

Initial and residual comparative toxicity of compound XVI (AC 217,300) and methyl parathion to third-instar tobacco budworm larvae

Compound	Concn (ppm)	Sampled on day of treatment % Mortality after 1 day	2 days	3 days	Sampled 1 day posttreatment % Mortality after 4 days
AC 217,300	60	0	60	100	25
methyl parathion	60	100			0
AC 217,300	240	0	100		55
methyl parathion	240	100			80

BIOLOGICAL ACTIVITY OF BAIT FORMULATIONS

Toxicity to adult houseflies Technical compound XXII was added to a homogeneous mixture of 50% dry powdered milk and 50% sugar to yield the test concentration. 100 g of the treated bait were placed in a cage with 200 housefly pupae. Flies started to emerge 5 d later and thereafter had continuous exposure to the treated bait. The results (Table 5) showed that compound XXII formulated in a sugar bait effectively controlled flies at rates down to 100 ppm.

Table 5

Toxicity of compound XXII in a bait to adult houseflies

Concn (ppm)	% Mortality after indicated days of continuous exposure 2	8
1000	100	100
300	64	100
100	22	98
30	7	7
0	2	2

Toxicity to cockroaches The test compounds were mixed with peanut butter (creamy consistency) and offered continously to ten oriental cockroaches and ten American cockroaches in a 10 x 20 cm diameter cage. 5 g of treated bait, 5 g of untreated bait, and a source of water were placed in each cage. For the German cockroaches the compounds were formulated in a commercial bait with untreated peanut butter as a choice.

The results (Table 6) showed delayed toxicity, which is one of the characteristic properties of the amidinohydrazones. In the tests with the oriental cockroaches at the 2.0% concn, 20 and 36 d were required for AC 217,300 and compound XIV, respectively, to be as effective as propoxur at 3 d. Against American cockroaches at the 0.5% concn, AC 217,300 required 14 d to give greater than 90% control. In tests with German cockroaches at the lowest concn of 0.125%, compound XIV, AC 217,300 and the standard (propoxur) afforded 100% control after 8 d.

Table 6

Comparative toxicity of amidinohydrazones to oriental, American and German cockroaches

		% Mortality after indicated days								
		Oriental			American			German		
Compound	Concn (%)	3	20	36	7	14	21	1	5	8
AC 217,300	2.0	0	90	100				0	100	
XIV	2.0	0	100					0	95	100
propoxur	2.0	100						35	90	100
AC 217,300	0.5	0	50	90	17	92	92	0	100	
XIV	0.5	0	80	100	75	75	92	0	75	100
proproxur	0.5	40	60	70						
AC 217,300	0.125							0	65	100
XIV	0.125							0	60	90

Toxicity to imported fire ants The worker form of red imported fire ants was tested with the method described by Banks et al (1977). The results (Table 7) again showed the delayed toxicity possessed by the amidinohydrazones, as well as their outstanding effectiveness against imported fire ants. Delayed toxicity is one of the criteria required for an effective imported fire ant control agent applied by broadcast application. AC 217,300 is currently in a full-scale development program to obtain a registration in the U.S.A. for its use to control imported fire ants.

Table 7

Comparative toxicity of two amidinohydrazones and mirex to imported fire ants

		% Knockdown and mortality after indicated number of days			
Compound	Concn (%)	1	3	10	14
AC 217,300	1.0	23	95	98	100
AC 217,300	0.1	0	7	88	95
AC 217,300	0.01	0	0	0	5
XXV	1.0	22	93	100	
XXV	0.1	0	0	57	81
XXV	0.01	0	0	0	2
mirex	1.0	0	93	100	
mirex	0.1	0	11	96	100
mirex	0.01	0	0	0	43

CONCLUSION

The amidinohydrazones represent a novel class of compounds showing promise as insecticides. In a series of parallel tests using three species of lepidopterous larvae, many of the amidinohydrazones were equally, and in some cases, more effective than the standards, malathion and methyl parathion. In bait formulations they provided control of cockroaches, houseflies, and ants.

The amidinohydrazones appear to have several added advantages. (1) Insects resistant to organophosphorus, carbamate, and pyrethroid insecticides are not anticipated to exhibit cross-resistance to the amidinohydrazones because of the unique mode of action of this class of compounds; (2) they exhibit selective activity, which suggests they may not be harsh on many beneficial insects and therefore should be suitable for incorporation into pest management programs; (3) they are only slightly to moderately toxic to mammals in acute dosing; (4) their residual life is short on plants; and (5) they are effective at low application rates. The unique chemistry and insecticidal activity demonstrated with the amidinohydrazones warrant continued laboratory, greenhouse, and field evaluation.

Acknowledgement

The author is indebted to Dr. Andrew S. Tomcufcik and colleagues of Cyanamid's Medical Research Division and Dr. Roger W. Addor and colleagues of the Agricultural Research Division for synthesis of the compounds and to Robert J. Little, Jr. and colleagues of the Agricultural Research Division for biological information incorporated into this paper.

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