1-Phenylcarbamoyl-2-pyrazolines: A New Class of Insecticides. 2. Synthesis and Insecticidal Properties of 3,5-Diphenyl-1-phenylcarbamoyl-2-pyrazolines

Rolf van Hes,* Kobus Wellinga, and Arnold C. Grosscurt

The syntheses and biological activities of a selected group of 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines are reported. The structures of these compounds have been confirmed by NMR. Their insecticidal properties were evaluated with the larval stages of *Aëdes aegypti* L., *Pieris brassicae* L., and *Leptinotarsa decemlineata* Say.

In Part 1 of this series of articles from our laboratories (Wellinga et al., 1977) we reported on the syntheses and insecticidal properties of a number of 3-phenyl-1-phenylcarbamoyl-2-pyrazolines. In the present article we wish to demonstrate that substitution at the 5 position in the pyrazoline nucleus of the above-mentioned compounds with another phenyl ring gives rise to products with comparable or enhanced insecticidal activities.

CHEMICAL METHODS

Microanalyses were carried out in the Analytical Department of the Institute for Organic Chemistry TNO, Utrecht, the Netherlands, under the supervision of W. J. Buis. Nuclear magnetic resonance spectra were measured on a Varian HA 100 spectrometer, with tetramethylsilane as the internal reference. The melting points are uncorrected.

For the preparation of the compounds mentioned in the Tables I and II, one general method was used. They were prepared according to the reaction shown in Scheme I.

3,5-Bis(4-chlorophenyl)-2-pyrazoline. To a solution of 13.85 g of 4,4′-dichlorobenzalacetophenone (0.05 mol) in 35 mL of ethanol was added 5 mL of hydrazine hydrate (0.11 mol). After refluxing for 1 h, the ethanol was distilled off at reduced pressure. The residue was dissolved in ether and washed with water. Evaporation of the solvent gave the crude pyrazoline (14.0 g), which can be used without further purification. The pyrazolines were not very stable and required storage under nitrogen in the refrigerator.

3,5-Bis(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline. [Table I, Compound 7 (I,7)]. To a solution of 5.82 g of 3,5-bis(4-chlorophenyl)-2-pyrazoline (0.02 mol) in 50 mL of dry ether, 3.07 g of 4-chlorophenyl isocyanate (0.02 mol) and four drops of triethylamine were added. After stirring for 2 h, the crystals formed were collected, washed with ether, and dried, affording 8.0 g (90%) of compound I,7, mp 226–228 °C.

Anal. Calcd for $C_{22}H_{16}Cl_3N_3O$ (444.74): C, 59.41; H, 3.63; Cl, 23.92; N, 9.45. Found: C, 59.4; H, 3.6; Cl, 24.1; N, 9.3.

3,5-Bis(4-chlorophenyl)-1-[*N*-(4-chlorophenyl)-*N*-methyl]carbamoyl-2-pyrazoline (II,1). To a stirred suspension of 4.45 g of 3,5-bis(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline (0.01 mol) and 1 g of potassium carbonate in 20 mL of DMF, 0.7 g of powdered potassium hydroxide (0.0125 mol) was added. After 15 min at 0 °C, 0.7 mL of methyl iodide was added. The mixture was stirred 0.5 h at 0 °C, then 16 h at room temperature, and then poured into ice–water. The precipitate was collected, dried, and washed with 20 mL of methanol and 30 mL of petroleum ether: yield, 3.1 g (67%); mp 123–128 °C.

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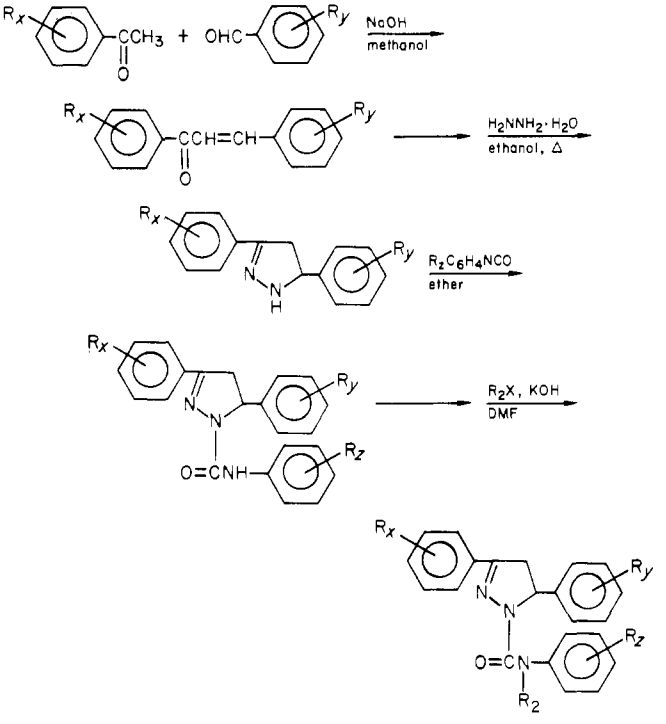
Scheme I. Preparation of Substituted 3,5-Diphenyl-1-phenylcarbamoyl-2-pyrazolines



Anal. Calcd for $C_{23}H_{18}Cl_3N_3O$ (mol wt, 458.79): C, 60.21; H, 3.95; N, 9.16; Cl, 23.19. Found: C, 59.9; H, 3.9; N, 9.1; Cl, 23.0.

The compounds 4–8 of Table II were prepared according to the procedure described for compound I, 7. The compound below has been prepared for comparison with compound I, 7 (see Results and Discussion section).

3,5-Bis(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)pyrazole. The synthesis of 3,5-bis(4-chlorophenyl)pyrazole is described in the literature (Lipp et al., 1958). To a suspension of 1 g of 3,5-bis(4-chlorophenyl)pyrazole (0.0035 mol) in 25 mL of acetone, 0.56 g of 4-chlorophenyl isocyanate (0.0036 mol) and two drops of triethylamine were added. After refluxing for 1 h the reaction mixture was filtered and then cooled. The precipitate was collected and dried, yielding 0.7 g (45%): mp 242 °C; NMR (Me_2SO) δ 7.20 (1, s, CH), 7.57 (12, m, aromatic), 8.80 (1, s, NH).

Anal. Calcd for $C_{22}H_{14}Cl_3N_3O$ (mol wt, 442.75): C, 59.68; H, 3.19; Cl, 24.03; N, 9.49. Found: C, 59.4; H, 3.3; Cl, 24.3; N, 9.7.

NMR SPECTRA

The NMR proton chemical shift data of the 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines are summarized in Table III. All the chemical shifts are as may be expected. The N-alkyl derivatives (R_2 = alkyl) have the same

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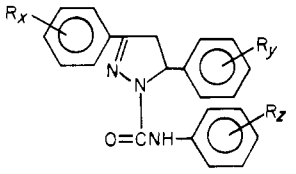
Table I. Insecticidal Activities of:



Compd no.	R_x	R_y	R_z	Lowest test concentration with ≥90% mortality[a] *L. decemlineata* Say	*P. brassicae* L.	*A. aegypti* L.	Mp, °C
		a. R_x = halogen; R_y = halogen; R_z = miscellaneous					
I,1	2-Cl	4-Cl	4-Cl	100	>300	>1	161
I,2	4-Cl	2-Cl	4-Cl	30	>300	>1	237
I,3	4-Cl	2,4-Cl_2	4-Cl	3	10	0.3	166
I,4	4-Cl	3-Cl	4-Cl	100	100	>1	207
I,5	4-Cl	4-Cl	2-Cl	>300	30	1	226
I,6	4-Cl	4-Cl	3-Cl	100	100	>1	192
I,7	4-Cl	4-Cl	4-Cl	3	3	0.03	228
I,8	4-Cl	4-Cl	4-Br	1	10	0.01	233
I,9	4-Cl	4-Cl	4-CF_3	1	1	>1	207
I,10	4-Cl	4-Cl	4-C_2H_5	3	10	>1	182
I,11	4-Cl	4-Cl	4-*i*-C_3H_7	3	3	>1	152
I,12	4-Cl	4-Cl	4-O-*i*-C_3H_7	3	1	1	159
I,13	4-Cl	4-Cl	4-SO_2CH_3	3	30	0.1	170
		b. R_x = halogen; R_y = H; R_z = halogen, alkyl					
I,14	3-Cl	H	4-Cl	30	>300	>1	196
I,15	4-Cl	H	4-Cl	30	30	>1	174
I,16	4-Cl	H	4-Br	10	30	0.1	187
I,17	4-Cl	H	4-I	10	30	0.03	156
I,18	4-Cl	H	4-C_2H_5	30	100	>1	143
		c. R_x = halogen; R_y = miscellaneous; R_z = halogen					
I,19	4-Cl	4-C_2H_5	4-Cl	3	30	>1	235
I,20	4-Cl	4-*i*-C_3H_7	4-Cl	10	10	>1	190
I,21	4-Cl	4-$N(CH_3)_2$	4-Cl	30	30	1	189
I,22	4-Cl	4-$N(C_2H_5)_2$	4-Cl	10	1	>1	158
I,23	4-Cl	4-O-*i*-C_3H_7	4-Cl	3	3	0.1	166
I,24	4-Cl	4-SCH_3	4-Cl	100	300	>1	225
I,25	4-Cl	4-SO_2CH_3	4-Cl	300	>300	>1	266
		d. R_x = miscellaneous; R_y = halogen; R_z = halogen					
I,26	H	4-Cl	4-Cl	10	>300	>1	160
I,27	4-CF_3	4-Cl	4-Cl	3	3	>1	206
I,28	4-*t*-C_4H_9	4-Cl	4-Cl	30	30	>1	204
I,29	4-$N(CH_3)_2$	4-Cl	4-Cl	10	3	0.03	130
I,30	4-O-*i*-C_3H_7	4-Cl	4-Cl	100	30	>1	116
I,31	4-SCH_3	4-Cl	4-Cl	30	100	>1	188
I,32	4-SO_2CH_3	4-Cl	4-Cl	>300	>300	>1	228
I,33	4-C_2H_5	4-Cl	4-Cl	30	>300	>1	206

[a] Applied concentrations, in parts per million: *Aëdes aegypti* L., 1, 0.3, 0.1, 0.03, etc.; *Pieris brassicae* L., 300, 100, 30, 10, 3, etc.; *Leptinotarsa decemlineata* Say, 300, 100, 30, 10, 3, etc.

anomalous proton chemical shift behavior as the 1-(*N*-alkylphenylcarbamoyl)-3-phenyl-2-pyrazolines (Wellinga et al., 1977).

The proton spin coupling constants of the 2-pyrazoline protons ($J_{4,4'}$ = −18 Hz; $J_{4,5}$ = 6 Hz; $J_{4',5}$ = 12 Hz) are in accordance with those of 1,3,5-triphenyl-2-pyrazolines ($J_{4,4'}$ = −16 Hz; $J_{4,5}$ = 8 Hz; $J_{4',5}$ = 12 Hz; Batterham, 1973).

BIOLOGICAL METHODS

The methods for the insecticidal evaluation are described in Part 1 of this series of papers (Wellinga et al., 1977).

RESULTS AND DISCUSSION

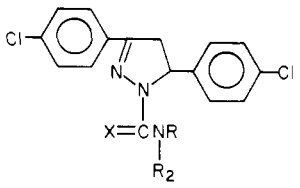
In a previous paper (Wellinga et al., 1977) we pointed out the overwhelming number of substitution possibilities in the 3-phenyl-1-phenylcarbamoyl-2-pyrazolines. It is obvious that the same applies still more strongly to the 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines with another phenyl ring at the 5 position in the pyrazoline nucleus. From the several hundreds of compounds prepared in this series we wish to draw attention to the activities of a representative selection. The following discussion as to this selection, however, is conclusive for the whole series prepared so far.

The test results obtained with the different types of substituted 3,5-diphenyl derivatives are listed in Table I, subdivided into sections a, b, c, and d, and Table II.

Table Ia presents the activities of the 3,5-diphenyl derivatives with both rings ("ring 3" and "ring 5") substituted with chloro atoms. The phenyl ring in the carbamoyl group ("ring 1") has a miscellaneous substitution pattern. The most striking compounds of Table Ia appear to be compound **7** and **8**, showing a high activity on the larvae of the three species involved. Displacement of a chloro atom of compound **7** to an ortho or a meta position in the different phenyl rings brings about a sharp decrease in activity (I: **1**, **2**, **4**, **5**, and **6**).

Substitution of the chloro atom in ring 1 of compound **7** by electron-donating or electron-attracting groups leads

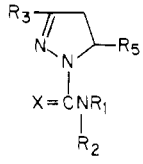
Table II. Insecticidal Activities of:



Compd no.	X	R_1	R_2	Lowest test concentration with ≥90% mortality[a]			Mp, °C
				L. decemlineata Say	*P. brassicae* L.	*A. aegypti* L.	
II,1	O	4-ClC_6H_4	CH_3	10	10	0.03	128
II,2	O	4-ClC_6H_4	C_2H_5	3	30	0.1	136
II,3	O	4-ClC_6H_4	n-C_3H_7	30	100	0.3	Oil
II,4	O	CH_3	H	>300	>300	>1	148
II,5	O	n-C_4H_9	H	300	>300	>1	Oil
II,6	O	c-C_6H_{11}	H	30	100	>1	102
II,7	O	n-$C_{11}H_{23}$	H	>300	>1	>1	Oil
II,8	S	4-ClC_6H_4	H	300	>1	>1	194

[a] Applied concentrations, in parts per million: *Aëdes aegypti* L., 1, 0.3, 0.1, 0.03, etc.; *Pieris brassicae* L., 300, 100, 30, 10, 3, etc.; *Leptinotarsa decemlineata* Say, 300, 100, 30, 10, 3, etc.

Table III. Proton NMR Data of:



	Substituents				Average chemical shifts in δ value[a,b]												
					Pyrazoline			Phenyl R_1			R_2	Phenyl R_3			Phenyl R_5		
X	R_1	R_2	R_3	R_5	H_4	H_4'	H_5	Ortho	Meta	Para	NH	Ortho	Meta	Para	Ortho	Meta	Para
S	Phenyl	H	Phenyl	Phenyl	3.20	3.96	6.05	7.56	7.25		10.07	7.93	7.42		7.15	7.26	
O	Phenyl	H	Phenyl	Phenyl	3.16	3.90	5.55	7.58	7.18	6.89	9.02	7.87	7.40	7.39	7.22	7.28	7.29
O	Alkyl	H	Phenyl	Phenyl	3.05	3.81	5.44				6.63 7.00	7.73	7.30		7.14	7.24	
O	Phenyl	Alkyl	Phenyl	Phenyl	2.92	3.69	5.47	7.16 7.25	7.22 7.13			7.11 7.34	7.31 7.08		7.22	7.25	

[a] Solvent Me_2SO. [b] The chemical shifts of the phenyl and NH protons were calculated for the unsubstituted derivatives with the help of the aromatic substituent shifts (Wellinga et al., 1977; Table IV). The standard deviation for the aromatic and pyrazoline protons was 0.05 and for the NH protons 0.07.

to derivatives highly active on *Leptinotarsa* and *Pieris* (I: **9**, **10**, **11**, **12**, and **13**).

A decrease in activity is observed with derivatives bearing an unsubstituted ring 5 (I: **15** vs. **7**; **16** vs. **8** and **18** vs. **10**).

Introduction of strong electron-donating groups at the para position of ring 5 gives rise to some highly active compounds (I: **22** and **23**).

An electron-attracting group such as the sulfon group seems to be less favorable (I: **25**), and when this group is moved to ring 1 we get a less active compound too (I: **32**). On the other hand, compound **27** with the electron-attracting para CF_3 group in ring 1 is highly active against *Leptinotarsa* and *Pieris*. Compound **29** with the electron-donating dimethylamino group in ring 1 is highly active on all three species involved.

Several alterations in the basic molecule are disadvantageous to insecticidal activity, as is shown in Table II. Compound **7**, one of the outstanding representatives, when converted to its sulfur (II:**8**) or in its 4,5-dehydro derivative (the pyrazole analogue: not presented in the tables), becomes practically inactive. The same holds true if ring 1 is replaced by an alkyl group (II:**4**,**5**,**7**). However, the cyclohexyl group appears to be favorable to a moderate activity except against Aëdes (II:**6**). N-Alkylation of the carbamoyl function with lower alkyl groups brings about a less radical change in the insecticidal properties (II: **1**, **2**, **3** vs. I,**7**).

At present the toxicological data of several substituted 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines on vertebrates have been obtained. When administered orally the LD_{50} values of the following compounds toward mice are known to exceed 1000 mg/kg: **2**, **5**, **7**, **9**, **13**, **21**, **24**, and **32**.

CONCLUSION AND REMARKS

Among the compounds mentioned in Table I there are several, e.g., **7**, **8**, **23**, **29**, with a promising insecticidal activity. From the economic and practical aspects 3,5-bis(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline (I:**7**) appears to be one of the most promising compounds in these series.

ACKNOWLEDGMENT

The proton NMR spectra were measured and interpreted by Hans Schiereck. The structural analyses were coordinated by Frits W. van Deursen, of the Analytical Department of Philips-Duphar B. V.

The authors wish to express their gratitude to Jacobus Tipker, of the Biochemical Department, for his suggestions regarding structure–activity relationship.

Supplementary Material Available: A listing of microanalyses (1 page). Ordering information is given on any current masthead page.

LITERATURE CITED

Batterham, T. J., "NMR Spectra of Simple Heterocycles", Wiley, New York, N.Y., 1973, 206.

Lipp, M., Dallacker, F., *Justus Liebigs Ann. Chem.* **618**, 110 (1958).

Wellinga, K., Grosscurt, A. C., van Hes, R., *J. Agric. Food Chem.* **25**, 987–92 (1977).

Received for review September 12, 1977. Accepted January 17, 1978.

Decamethrin Metabolism in Rats

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On oral administration to male rats, the pyrethroid insecticide decamethrin [(*S*)-α-cyano-3-phenoxybenzyl (1*R*, 3*R*)-*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate] and various metabolites derived from its acid and alcohol fragments are almost completely eliminated from the body within 2–4 days. Metabolites of the cyano substituent are eliminated more slowly, especially from the skin and stomach, due in the latter case to temporary retention of thiocyanate which is formed from released cyanide. The excreted metabolites include: esters monohydroxylated at the 2′, 4′, and 5 positions of the alcohol moiety; 2,2-dimethyl-3-(2,2-dibromovinyl)cyclopropanecarboxylic acid and its glucuronide and glycine conjugates and a hydroxylated derivative of this acid, with the hydroxymethyl group trans to the carboxyl, and its glucuronide; 3-phenoxybenzoic acid and its glucuronide and glycine conjugates, 3-(4′-hydroxyphenoxy)benzoic acid and its glucuronide and sulfate conjugates, and 3-(2′-hydroxyphenoxy)benzoic acid sulfate; thiocyanate and 2-iminothiazolidine-4-carboxylic acid. The trans isomer of decamethrin is also rapidly metabolized in rats.

More than 25 years of research on optimization of pyrethroids for high insecticidal activity culminated recently in discovery of the most potent pyrethroid, (*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (decamethrin) (Elliott, 1977; Elliott et al., 1974, 1975a,b; Owen, 1975), which is currently under development by Roussel-Uclaf-Procida (Paris, France) for control of insect pests of crops, livestock, and man. The (1*R*,3*R*,α*S*) configuration is essential for this remarkable potency (Figure 1).

The metabolic fate of the (1*R*,3*R*) and (1*R*,3*S*) isomers of the related pyrethroid permethrin (dichlorovinyl replacing dibromovinyl group, no cyano substituent) is well defined in rats (Elliott et al., 1976; Gaughan et al., 1977a) and other organisms (Gaughan et al., 1977b; Shono et al., 1978). On analogy with (1*R*,3*R*) permethrin metabolism in rats (Gaughan et al., 1977a), decamethrin is expected to undergo hydroxylation at the *trans*-methyl group of the acid moiety and the 2′ and 4′ positions of the alcohol moiety and to cleave at the ester linkage, resulting ultimately in a series of carboxylic acids in free and conjugated form. However, the permethrin isomers are rapidly metabolized by mouse liver microsomal esterases (1*R*,3*S*) and oxidases (1*R*,3*R* and 1*R*,3*S*) whereas each of the structural modifications introduced in decamethrin confers enhanced stability to microsomal metabolism (Soderlund and Casida, 1977a,b). On the other hand, the toxicity of decamethrin to mice is synergized by piperonyl butoxide and *S*,*S*,*S*-tributyl phosphorotrithioate, suggesting the importance of both oxidases and esterases in decamethrin detoxification (Ruzo et al., 1977; Soderlund et al., 1977b).

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An understanding of decamethrin metabolism is important in developing this new insecticide and more generally in expanding the knowledge of detoxication of novel pyrethroids. The present study considers the distribution and metabolic fate of decamethrin labeled with ^{14}C in three positions when administered orally to male rats at 0.64–1.6 mg/kg.

MATERIALS AND METHODS

Chromatography and Radiocarbon Analyses. Thin-layer chromatography (TLC) utilized silica gel 60 F-254 20 × 20 cm chromatoplates with 0.25-mm layer thickness (EM Laboratories, Inc., Elmsford, N.Y.) and the following solvent systems: A, butanol–acetic acid–water (6:1:1); B, benzene (saturated with formic acid)–ether (10:3), two developments; C, benzene–ethyl acetate (6:1); D, hexane–ether (4:1), three developments; E, hexane–ether (1:1), two developments; F, chloroform (saturated with formic acid)–ether (10:3); G, ethyl acetate–methanol–water (2:1:1); H, benzene–carbon tetrachloride (1:1), two developments. R_f values for decamethrin derivatives are given in Table I. In referring to solvent systems for two-dimensional development, (A, B) indicates development in the first direction with solvent system A and in the second direction with solvent system B. Unlabeled standard compounds were detected first with ultraviolet light (254 nm) and then by spraying with either $PdCl_2$ (0.5% w/v in 12 N HCl) or phosphomolybdic acid (20% w/v in ethanol) and heating at 110 °C for up to 30 min. Procedures for radioautography, ^{14}C quantitation, and cochromatography of ^{14}C metabolites or their derivatives with unlabeled standards are given by Ueda et al. (1975).

Chemicals. *^{14}C Compounds.* The following ^{14}C preparations (provided by Roussel-Uclaf-Procida; radiochemical purity > 99%) were used: decamethrin labeled in the dibromovinyl (^{14}Cv), benzylic carbon ($^{14}C\alpha$) and cyano (^{14}CN) substituents (Figure 1) with sp act. of 5.0, 60.0, and 51.5 mCi/mmol, respectively; the acid moiety (Br_2CA, Figure 2) labeled in the dibromovinyl substituent

0021-8561/78/1426-0918$01.00/0