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Abstract
Insecticidal activity of chloronitroalkanes was predicted on the basis of structure-activity relationships. Two series of new bis(substituted-phenyl) chloronitroalkanes were synthesized and evaluated for insecticidal activity. The synthetic pathway proceeded through phenylnitroethanols and diphenylnitroethanes as intermediates. Final products were 1,1-bis (substituted-phenyl)-2-chloro-2-nitroethanes and 1,1-bis(substituted-phenyl)-2,2-dichloro-2-nitroethanes. Aromatic substituents were selected from alkyl, alkoxy, and halogen moieties. Following purifications and confirmation of structures, the compounds were bioassayed against insects. The two series were compared for potency, as were various combinations of X and Y substituents. Adult female house flies (Musca domestica), mosquito larvae (Aedes aegypti), western corn rootworm (Diabrotica virgifera virgifera) and German cockroach (Blattellagermanica) have been tested. In general, the mono-chloro series is more toxic than the di-chloro series. Five of the mono-chloro analogs are 8-10 times more potent than pyrethrins and 6-7 times more toxic than methoxychlor to the house fly.

Disciplines
Entomology | Environmental Health | Environmental Microbiology and Microbial Ecology | Organismal Biological Physiology | Plant Sciences

Comments
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Chapter 20

Diphenylchloronitroethane Insecticides

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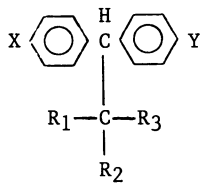
Insecticidal activity of chloronitroalkanes was predicted on the basis of structure-activity relationships. Two series of new bis(substituted-phenyl) chloronitroalkanes were synthesized and evaluated for insecticidal activity. The synthetic pathway proceeded through phenylnitroethanols and diphenylnitroethanes as intermediates. Final products were 1,1-bis (substituted-phenyl)-2-chloro-2-nitroethanes and 1,1-bis(substituted-phenyl)-2,2-dichloro-2-nitroethanes. Aromatic substituents were selected from alkyl, alkoxy, and halogen moieties. Following purifications and confirmation of structures, the compounds were bioassayed against insects. The two series were compared for potency, as were various combinations of X and Y substituents. Adult female house flies (Musca domestica), mosquito larvae (Aedes aegypti), western corn rootworm (Diabrotica virgifera virgifera) and German cockroach (Blattella germanica) have been tested. In general, the mono-chloro series is more toxic than the di-chloro series. Five of the mono-chloro analogs are 8-10 times more potent than pyrethrins and 6-7 times more toxic than methoxychlor to the house fly.

Insecticides of the "DDT-type" have potent excitatory activity in the peripheral nervous system of insects (Narahashi, 1979). For DDT, X = Y = R_1 = R_2 = R_3 = Cl in the structure below.



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Many analogs have been made since the initial disclosure of insecticidal activity (Müller, 1940). Major synthetic efforts have been made over the years (reviewed by Coats, 1982) and several commercially successful compounds were discovered, e.g., methoxychlor, perthane, rhothane, dicofol. The nitroalkanes prolan (or 1,1-bis-bis(p,p'-dichlorophenyl)-2-nitropropane), bulan and dilan were among the commercial products.

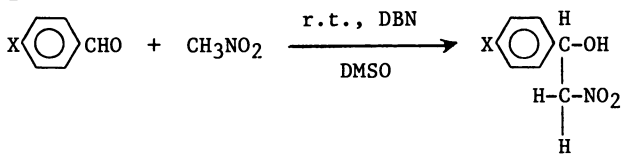
Structure-activity studies have indicated that X and Y groups of proper size and shape with appropriate combinations of R_1, R_2, and R_3 groups act as good insecticides. However, steric factors alone may not account for optimal potency. Neurotoxicological studies on insect nerve indicate that increasing electronegativity in the aliphatic moiety may enhance insecticidal activity (Brown et al., 1981). Nitroalkane analogs possess excellent activity as do chloro, dichloro, and trichloro alkanes, while pure alkanes are only moderately good compounds. Trifluoro, pentafluoro, or chlorodifluoro alkanes are rather poor insecticides, apparently too electronegative of an aliphatic moiety or too polar to penetrate the insect cuticle well (Abu-El-Haj et al., 1979). Combinations of nitro and halogen groups R_1, R_2, and R_3 have been attempted by Hass et al. (1951) and by Skerrett and Woodcock (1952). The latter group made 3 p,p'-dichlorophenyl haloalkanes with disappointing results: the 2-chloro-2-nitroethane and 2,2-dichloro-2-nitroethane were not insecticidal, but the 2-chloro-2-nitropropane was as effective as the 2-nitropropane. Deactivation via dehydrochlorination of the aliphatic moiety occurs more rapidly when the X and Y aromatic substituents are e^- withdrawing but occurs much more slowly with e^- donating aromatic groups (Metcalf and Fukuto, 1968). Electron donating substituents (at least one) on the rings also provide for greater insecticidal potency (Holan, 1969; Metcalf et al., 1971; Coats et al., 1977). Hence, the only 2-chloro-2-nitroethane synthesized by Skerrett and Woodcock lacked insecticidal activity, probably due to poor stability and low intrinsic toxicity, both resulting from the p,p'-dichloro substituents. Hass et al. (1951) also made some 2-chloro-2-nitroethanes with chlorophenyl-, tolyl-, or unsubstituted phenyl rings, but they gave no data on insecticidal activity.

Other synthesis and structure-activity progress with diphenylnitroalkane insecticides include work by Jacob et al., 1951; Holan 1971a; 1971b; Boehner et al., 1974; Kaufman and Strong, 1975; Lee et al., 1977; and Coats, 1983.

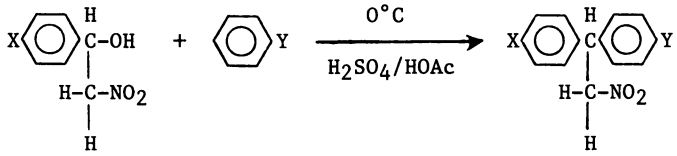
Synthesis Pathway

A 3-step reaction pathway was followed, using reactions previously described. Reactions I and II are described by Lee, et al., 1977. Reaction III was adapted from Tindall (1943; 1946).

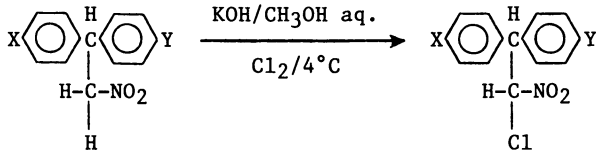
Reaction I



Reaction II



Reaction III



Series 1

In Reaction I, a large excess of nitromethane was added to maximize efficient use of the benzaldehyde and minimize clean up of the crude reaction mixture (an aqueous $NaHSO_3$ wash helped remove any unreacted benzaldehyde).

The base used by Lee et al. (1977) and Coats (1983) was 1,5-diazabicyclo-[4.3.0] non-5-ene (DBN); numerous other bases have also been utilized, e.g., sodium methoxide, sodium bicarbonate, triethylamine, KOH, pyridine (Worrall, 1934; Hass et al., 1951; Kamlet, 1939). The carbinol intermediates were not purified prior to use in the condensation reaction. The acid used was a mixture of conc. sulfuric and glacial acetic acids (ratios ranged from 4:1 to 1:3).

In Reaction II, the crude carbinol was mixed with a 3-6 fold excess of the substituted benzene and dripped into cold acid mixture, with stirring. A 4:1 ratio of sulfuric (conc.) and acetic (glacial) acids was determined to be optimal for most condensations attempted. The reaction was allowed to warm to room temperature after 1 h, and it was then poured over ice. Following extraction with diethyl ether, washing with $NaHCO_3$, drying with anhydrous Na_2SO_4, filtration, and rotary evaporation, the product was purified and characterized before further use.

Reaction III was initiated by dissolving the diphenyl-nitroethane in methanol and adding it to an aqueous solution of KOH. Chlorine gas was introduced at 4°C (Tindall, 1943; 1946), and was added until the pH of the reaction fell to 5-6. Mixtures of mono- and di-chloro nitroethanes were formed, often requiring separation by silica gel column chromatography.

Purification

Every nitrocarbinol, nitroethane, chloronitroethane and dichloro-nitroethane synthesized was worked up to eliminate the solvent and

as much of the unreacted materials as possible. Diethyl ether/water extractions were utilized, with a $NaHSO_3$ wash of the carbinol to remove excess benzaldehyde, or a $NaHCO_3$ wash of the diphenyl-nitroethane to remove excess acetic acid. Anhydrous Na_2SO_4 was used to dry the ether extract. Column chromatography with silica gel and hexane/diethyl ether or hexane/benzene solvent systems were used to obtain pure samples of the insecticides in Series 1 and Series 2.

Characterization

Three techniques were used to determine the structure of each chemical made. For each new analog, an ^1H NMR (nuclear magnetic resonance) analysis of a 25 mg sample was run on a Nicolet 300 MHz NMR spectrometer. The sample was dissolved in $CDCl_3$ with tetramethylsilane (TMS) as a reference.

^1H-NMR information is provided here for the aliphatic protons on the central nitroethane skeleton, for 1-*p*-ethylphenyl-1-*p*-ethoxyphenyl-2-nitroethane, its monochloro derivative (compound 1e) and its dichloro derivative (compound 2e) as typical of the compounds synthesized. Ethylphenyl ethoxyphenyl-2-nitroethane: α-H at δ 4.7-4.9 (triplet), β-H's at δ 4.9-5.0 (doublet); 1e: α-H at δ 4.6-4.8 (2 doublets); β-H at δ 6.4 (doublet); 2e: α-H at δ 4.8 (singlet).

Two uncorrected melting points observed were for 1,1-bis(p-ethoxyphenyl)-2,2-dichloro-2-nitroethane at 75-77°C and for 1-(p-methylphenyl)-1-(p-ethoxyphenyl)-2,2-dichloro-2-nitroethane at 51-54°C.

After a chemical structure had been confirmed, TLC (thin layer chromatography) was used to monitor the purity of the chemicals. The TLC solvent systems hexane and diethyl ether (8:2) or hexane and benzene (1:1) best separated chemicals on F_{254} silica gel TLC plates. The Series 2 compounds had the highest R_fs, followed by the Series 1 compounds, and then the nitroethanes. The TLC plates were then sprayed with a solution made from zinc chloride and diphenylamine (1:1), dissolved in acetone. After the plates were sprayed, they were placed in a 125°C oven overnight. Generally, carbinols turned green, nitroethanes turned pink, Series 1 and Series 2 compounds turned purple. Color and R_f on the plate confirmed the identity of a product.

Mass spectrometry was also employed to confirm the structure of one Series 1 and one Series 2 compound, utilizing a Finnegan 4000 direct exposure probe mass spectrometer.

Bioassay

Toxicity of the compounds was examined in four types of insects: house fly (*Musca domestica*), mosquito (*Aedes aegypti*), corn rootworm beetles (*Diabrotica virgifera virgifera* and *Diabrotica undecimpunctata howardi*) and the German cockroach (*Blattella*

germanica). Topical toxicities were determined for adult female house flies (susceptible Orlando Regular stock) and field-collected adult western corn rootworms (D. v. virgifera). Toxicity to fourth instar Aedes aegypti (Liverpool strain) larvae was also investigated.

In examining topical toxicity, known concentrations of the compounds were applied in one µl of acetone solution to the abdominal venters of anesthesized insects using a syringe micro-applicator. Ten insects received each treatment, and treatments were replicated three times. The standards for comparison were pyrethrins and methoxychlor for house flies. Carbaryl and methoxychlor were used for rootworms, and chlorpyrifos was used against the cockroach. Mortality was recorded at 24 h following exposure. Insects were considered dead when a tactile stimulus produced no significant movement. LD_{50} values were computed using the Spearman-Karber procedure (Hamilton et al., 1977).

Toxicity to larval mosquitoes was examined by applying known concentrations of the compounds in one ml of acetone solution to 4-oz. glass jars containing 100 ml of distilled water and 20 early fourth-instar mosquito larvae. Treatments were replicated three times and chlorpyrifos was used as a standard for comparison. Mortality was recorded at 24 h following initial exposure to the compounds. Larvae were considered dead when tapping on the glass containers failed to elicit swimming movements. LC_{50} values were computed by the Spearman-Karber procedure.

Results and Discussion

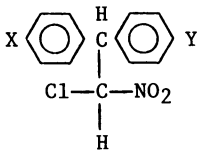
The results of the insect bioassay trials are presented in Tables I and II. The data show that the monochloro derivatives (Series 1 - Table I) are much more active than the dichloro compounds (Series 2 - Table II). In both series, the p,p'-dichlorophenyl analogs, made earlier by other investigators, listed above, were the poorest insecticides of the series. Deployment of an ethoxy group on one ring resulted in insect toxicity increases of 10-20 fold. The best compounds were the Cl-OC_2H_5, the CH_3-OC_2H_5, the C_2H_5-OC_2H_5, and the C_2H_5O-OC_2H_5 analogs. The poorest insecticides, other than the Cl-Cl derivatives, were the F-OC_2H_5 analogs.

Comparison of the monochloro series with standard compounds indicate that several of the new chemicals possess insecticidal activity comparable or superior to some commercial products.

Toxicity to house fly is obviously quite good. Moderate efficacy is demonstrated against the corn rootworm beetles and mosquito larvae. For an insecticide of the prolan/DDT class, the potency demonstrated against the wild strain German cockroach is quite remarkable. Preliminary tests on the larval stage corn rootworm revealed soil activity of a monochloro compound, unlike most previously reported chemicals in this class. Overall, the spectrum of activity is quite broad, although other categories of insect pests must still be tested (e.g., lepidopteran larvae).

The physical properties of these compounds are somewhat different from prolan, DDT, methoxychlor, perthane, and other related chemicals. Water solubility and polarity are considerably

Table I. Toxicity of monochloronitroethanes to insects by topical application or in water

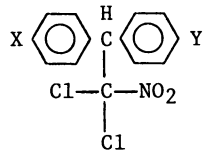


Series 1

No.	X	Y	24 h-LD_{50} (µg/insect) House fly	Corn rootworm beetle	Cockroach	24 h-LC_{50} (ppm) Mosquito larva
1a	F	OC_2H_5	0.20	2.71	34	0.22
1b	Cl	OC_2H_5	0.08	0.58	6.3	0.04
1c	Br	OC_2H_5	----	----	---	0.02
1d	CH_3	OC_2H_5	0.07	0.54	6.3	0.03
1e	C_2H_5	OC_2H_5	0.08	0.25	1.5	0.01
1f	$CH(CH_3)_2$	OC_2H_5	0.07	0.29	2.5	0.03
1g	$C(CH_3)_2$	OC_2H_5	0.54	----	---	0.46
1h	OC_3H_3	OC_2H_5	0.05	0.18	2.0	0.03
1i	Cl	Cl	1.8	2.55	---	----
	pyrethrins		0.69	----	0.89	------
	methoxychlor		0.50	0.35	>100	------
	chlorpyrifos		----	----	0.86	0.0026
	carbaryl		>10	0.02	>100	------

Table II. Toxicity of bis(substituted phenyl) dichloronitroethanes to insects by topical application or in water

Series 2



No.	X	Y	24 h-LD_{50} (μg/insect) House fly	Corn rootworm beetle	Cockroach	24 h-LC_{50} (ppm) Mosquito larva
2a	F	OC_2H_5	10	100	>100	0.46
2b	Cl	OC_2H_5	0.55	59	>100	0.38
2c	Br	OC_2H_5	1.71	23	>100	0.19
2d	CH_3	OC_2H_5	0.63	5.4	>100	0.07
2e	C_2H_5	OC_2H_5	0.86	4.0	>100	0.06
2f	$CH(CH_3)_2$	OC_2H_5	1.13	4.3	>100	1.13
2g	OC_2H_5	OC_2H_5	0.50	4.3	>100	0.06
2h	Cl	Cl	2.95	24	---	----
	pyrethrins		0.69	----	0.89	------
	methoxychlor		0.50	0.35	100	------
	chlorpyrifos		----	----	0.86	0.0026
	carbaryl		10	0.02	100	------

higher, with lower lipophilicity apparent as well. These properties may approach a more effective optimum for rapid and thorough penetration through insect cuticle, combined with charge distribution and steric dimensions for excellent insecticidal potency at the site of action (sodium gate in the peripheral nervous system).

Research remains to be done on the residual activity and mammalian toxicity of the chloronitroethane insecticides, but our initial studies on design, directed synthesis, and bioassay indicate there is clearly potential for those compounds in insect control.

Acknowledgments

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