SYSTEMIC INSECTICIDES

Development of Organic Phosphates As Systemic Insecticides

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Historical Review of the Work of Gerhard Schrader

SYSTEMICS SYMPOSIUM

CERTAIN DERIVATIVES OF β-FLUOROETHYL ALCOHOL were found by Gerhard Schrader, of Farbenfabriken Bayer, in Germany, about 1935, to have strong insecticidal action (*1*, *3*, *8*). Outstanding compounds are shown in Table I.

Compounds A and B, because of their high volatility, were limited in their application as agricultural pesticides.

Schrader then prepared condensation products of aldehydes with β-fluoroethyl alcohol and its derivatives (C and D). These readily prepared acetals were distinguished by their strong contact-insecticidal effect. Surprisingly, they also showed a new kind of effect. Schrader and his entomologist coworker, Kuekenthal (*1*, *3*, *8*), were able to show that the acetals penetrated into young growing plants, and there remained unchanged in the systems of the plants for several weeks. The plants were either sprayed or the ground in which they were growing was watered with the solutions of these acetals. This is believed to be the first discovery of systemic action of an organic insecticide.

The methylals of β-fluoroethyl alcohol later proved to be so toxic to mammals that they were not developed much further.

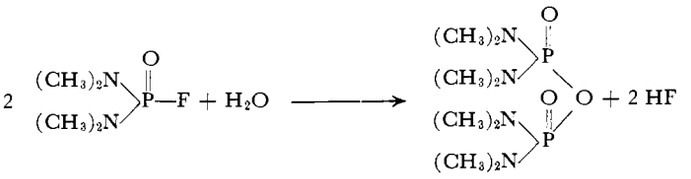
Soon thereafter, Schrader produced the fluorides of organic phosphorus compounds. This very soon proved to be a promising virgin chemical field. It was intensively followed from 1936 on, and over 2000 new compounds were synthesized up to 1936 (*1*, *3*, *8*).

In 1941, compound E, showing a pronounced systemic effect, was synthesized. This was compound 13/28 (*2*), the fluorophosphoric acid bisdimethylamide. Compound E was considered by Schrader and Kuekenthal to be too toxic to mammals to be used commercially. However, Pest Control, Ltd., of England, now uses it as the principal active ingredient of Hanane, in the control of cocoa "swollen shoot" disease, transmitted by mealy bugs.

Schrader questioned whether fluorine was necessarily a part of a systemically active molecule. He found that if the molecule were doubled, with simultaneous dehydration, octamethylpyrophosphoramide, OMPA, was formed, which besides having pronounced contact-insecticide properties, also had a systemic reaction.

Compound F (13/163), was recognized in 1941 as being systemically active. It definitely showed that fluorine was not a necessary part of a systemic insecticide. Using chemically pure preparations, and unfed male rats weighing 200 to 250 grams, Wirth, Farbenfabriken Bayer, showed the toxicity of compound F, OMPA, to be as high as that of compound E.

OMPA was not released for sale in Germany because of its toxic effect on mammals. It has since been marketed in England by Pest Control, Ltd., as Pestox 3, or schradan, and in a limited



Compound E — Compound F

Table I. Esters of β-Fluoroethyl Alcohol Showing Insecticidal Action

Compound	Chemical Composition	Boiling Point, °C./Mm. Hg	LD_{100}, Aphis, %
A	$F.CH_2.CH_2.O)_2SO$	108/17	0.1[a]
B	$F.CH_2.CH_2.O)_2CO$	89–90/14	0.1
C	$CH_2(O.CH_2.CH_2.F)_2$	43/11	0.1
D	$CH_2(O.CH_2.CH_2.O.CH_2.CH_2.F)_2$	120/ 3	0.1
E[a]	$(CH_3)_2N)_2P(=O)F$	67/ 4	0.05

[a] 0.1 gram of material in 100 grams of solution.
[b] Water-soluble.

way, for ornamental plant use in the United States. OMPA proved to be the stimulant in the search for systemically active organic phosphates of lower mammal toxicity. Some compounds prepared later are shown in Table III.

These new compounds, which on the one hand resemble tetraethyl pyrophosphate (TEPP) and on the other hand resemble octamethyl pyrophosphoramide (OMPA), show a distinct systemic effect. Preparation 15/8, which was very interesting, was tested extensively, but was supplanted by later discoveries. It continues to be interesting in the treatment of the muscular disease of man, *Myanstaenia gravis* (*1*, *3*, *8*). Surprisingly, it does not seem to be able to reach the brain centers of man, and does stimulate the nerves in much the same manner as prostigmine.

Dialkyl Thiophosphoric Esters

Eventually Schrader considered the esters of the dialkyl thiophosphoric acids, which are derived from the glycol ethers. Table IV gives a survey.

The low-contact insecticidal action of these compounds did not encourage continuation of work in this field. However, the corresponding sulfur compounds, the esters of the dialkyl thiophosphoric acids with thioglycol ethers, were prepared and examined.

These proved to be very effective contact insecticides and their systemic effect surpassed the activity of all previous compounds tested when their mammal tolerance was also considered. Table V gives a survey of the insecticidal and mammal tolerance of some of these new thiophosphoric acid esters (*6*, *7*).

These new thiophosphoric acid esters, prepared for the first time by Schrader, were tested entomologically by Unterstenhoefer and Kuekenthal. Unterstenhoefer drew the attention to the systemic action of the new compounds.

The diethyl thiophosphoric acid ester of ethyl thioglycol ether was finally found to be one of the most valuable compounds. It was given the trade name Systox (trademark of Chemagro Corp., New York, N. Y.) (*7*, *9*). It is readily absorbed from aqueous solutions by the roots and leaves of living plants, as well as through the bark of some trees, such as citrus and avocados. It exhibits a high contact as well as systemic action, and has already become of economic importance in the control of aphis and mites of cotton. It has been found sufficiently labile to be destroyed, if it should occur in cottonseed, by the treatment to which cottonseed is subjected in order to destroy the normally occurring gossypol. Therefore, it became the first organic phosphate, systemically active, to reach commercial use in the United States. Some of its isomers are also very interesting.

In Table VI a survey is given of isomeric compounds of components of Table V.

A survey of the systemics without the inclusion of the very interesting selenium compounds (*4*, *10*) that are related to Systox would be incomplete (Table VII).

These compounds are very active systemic insecticides. The harmful residual effect from the possible inclusion of selenium in food will limit their further development.

Acknowledgment

Credit is hereby given to the valuable contributions to Schrader's work by R. A. Muehlmann, who determined the boiling points listed herein, and prepared chemically pure 15/8.

Summary

During the investigation of certain derivatives of β-fluoroethyl alcohol, the methylals of this alcohol were recognized to be the carriers of systemic properties.

Table II. Comparison of Vapor Pressures of OMPA and Compound E

OMPA		Compound E	
Pressure, mm. Hg	Temp., °C.	Pressure, mm. Hg	Temp., °C.
0.02	66	0.4	30
0.05	74	1.0	43
0.1	87	1.5	49
0.15	94	2.0	55
0.2	98	2.5	60
0.45	110	3.0	63
0.6	116	4.0	67
1.0	126	5.0	70
1.5	136	10.0	80
2.0	142	18.0	92

Table III. Significant Organic Phosphates Which Followed OMPA

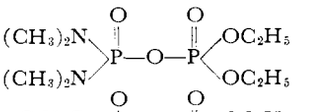
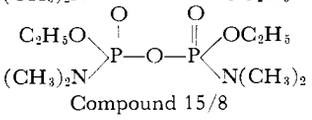
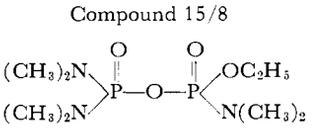
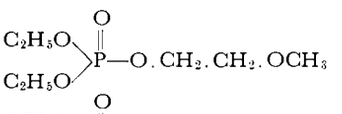
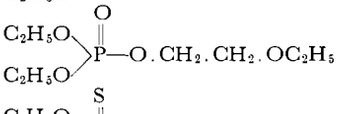
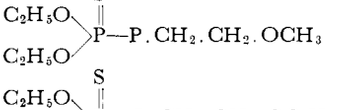
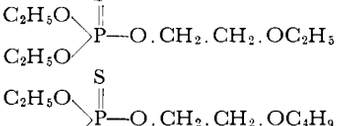
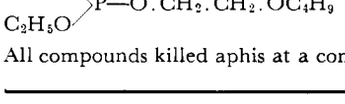
Composition	Boiling Point, °C./Mm. Hg	Solubility in Water	Approx. LD_{100} Aphis, %
	147/2	Limited	0.05
 Compound 15/8	135/2	Limited	0.05 0.02
	145/3	Soluble	0.05

Table IV. Toxicities of Esters of Dialkyl Thiophosphoric Acids

Composition	Boiling Point, °C./Mm. Hg	Toxicity to Mice, Subcutaneous Injection	
		Mg./Kg.	Result
	103/2	100	No symptoms
	109/1	50	Dead
	130/15	500	Dead
	110/2	1000	Dead
	149/0.5	500	Dead

All compounds killed aphis at a concentration of 0.2%.

The first preparation with systemic properties found among the great number of fluorophosphorus compounds prepared was the fluorophosphoric acid dimethylamide.

The presence of fluorine in organic phosphorus compounds is not necessary in order to achieve a systemic effect. This is clearly proved by the synthesis and the mechanism of action of octamethylpyrophosphoramide (OMPA).

The most effective systemic insecticides were obtained by the esterification of thioglycol ethers with dialkyl thiophosphoric acids. The new substances have a tolerable toxic action on warm-blooded animals and are at the same time used in a concentration which is, in some cases, only one-tenth of that of the preparations previously known. (The corresponding thiolphosphoric esters are also efficient systemic insecticides.)

Esters of the thioglycol ethers with certain selenol phosphoric acids also show a strong systemic effect.

Wirth (*10*), Farbenfabriken Bayer Pharmacological Laboratories, has recently advanced a hypothesis regarding the cholinesterase inhibition properties of various organic phosphates. He maintained that Systox, parathion, and some other organic phosphates, that do not contain fluorine as part of their molecule, do not, in vivo, irreversibly inhibit choline esterase. He believes that the enzyme-phosphate combination that results in the inhibition splits apart, and the enzyme resumes its normal functions. He cites the relatively fast recovery of cholinesterase levels in rats treated with Systox, contrary to diisopropyl fluorophosphate (DFP). This might explain the rather low rate of fatal poisonings in connection with the widespread agricultural use of parathion and Systox in this country. The freeing of inhibited cholinesterase in affected men may be the cause of good survival in cases of rather severe poisonings.

Table V. Toxicities of Thiophosphoric Acid Esters of Thioglycol Ethers

Composition	Boiling Point, °C./Mm. Hg	LD_{100} Aphis, %	Toxicity to Mice, Subcutaneous Injection, Mg./Kg.
$(CH_3O)_2P(S)—O.CH_2.CH_2.SCH_3$	108/2	0.005	200
$(C_2H_5O)_2P(S)—O.CH_2.CH_2.SCH_3$	119/2	0.005	25
$(C_2H_5O)_2P(S)—O.CH_2.CH_2.SC_2H_5$	128/1.2	0.001	25
$(C_2H_5O)_2P(S)—O.CH_2.CH_2.SC_3H_7(n)$	139/2	0.005	50
$(C_2H_5O)_2P(S)—O.CH_2.CH_2.SC_4H_9(n)$	161/3	0.001	25
$(C_2H_5O)_2P(S)—O.CH_2.CH_2.SC_5H_{11}(n)$	147/2	0.005	50

Table VI. Toxicities of Thiophosphoric Acid Esters

Composition	Boiling Point, °C./Mm. Hg	LD_{100}, Aphis, %	Toxicity to Mice, Subcutaneous Injection, LD, Mg./Kg.
$(CH_3O)_2P(O)—S.CH_2.CH_2.SCH_3$	83/0.07	0.001	100
$(C_2H_5O)_2P(O)—S.CH_2.CH_2.SCH_3$	135–140/4	0.0005	2.5
$(C_2H_5O)_2P(O)—S.CH_2.CH_2.SC_2H_5$	128/1	0.0005	10
$(C_2H_5O)_2P(O)—S.CH_2.CH_2.S—C_6H_4—CH_3$	Not distillable	0.05	500

Table VII. Toxicities of Selenolphosphoric Acid Esters

Composition	Boiling Point, °C./Mm. Hg	LD_{100}, Aphis, %	Toxicity to Mice, Subcutaneous Injection, LD, Mg./Kg.
$(C_2H_5O)_2P(O)—Se.CH_2.CH_2.SCH_3$	152/3	0.005	5
$(C_2H_5O)_2P(O)—Se.CH_2.CH_2.SC_2H_5$	153/3	0.0005	10

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(1) Schrader, Gerhard, *BIOS Final Rept.* **1095,** 30 (1947).
(2) *Ibid.*, p. 46.
(3) Schrader, Gerhard, "Die Entwicklung neuer Insektizide auf Grundlage organischer Fluor- und Phosphor-Vergindungen," Monographie 62, Parts 1 and 2, Weinheim/Bergstr., Germany, Verlag Chemie.
(4) Schrader, Gerhard, German Patent 824,046 (Sept. 7, 1949).
(5) *Ibid.*, 830,262 (Oct. 11, 1949).
(6) *Ibid.*, 836,349 (May 10, 1950); U. S. Patent 2,571,989 (Nov. 17, 1950).
(7) Schrader, Gerhard, German Patent 850,677 (Oct. 11, 1949); French Patent 998,052; Argentine Patent 78,639; Spanish Patent 194,511; Belgian Patent 498,167.
(8) Schrader, Gerhard, *Z. angew. Entomol.*, **33,** 329 (1951).
(9) Wirth, W., and Hecht, G., *Arch. exptl. Path. Pharmakol.*, **211,** 215 (1950).
(10) *Ibid.*, **217,** 144–52 (1953).

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