NEWS

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Structure-Activity Relationships Seen In Organophosphorus Compounds

High degree of acute toxicity appears among phosphates and phosphonates that profoundly inhibit cholinesterases

KANSAS CITY.—Despite considerable difficulty in the evaluation of structure-activity relationships among organophosphorus compounds reported in the literature, some progress is being made along these lines, according to Hamilton Anderson, University of California School of Medicine.

In speaking before the Division of Agricultural and Food Chemistry at the American Chemical Society's national meeting here, Dr. Anderson said that the toxicity of this type of compound is dependent upon one or more of the following effects: cholinesterase inhibition; selective degeneration of the central and peripheral nervous systems; stimulation and depression of the central nervous system; and irritation of the surface tissues.

Considerable difficulty arises in the evaluation of structure-action relationships among organophosphorus compounds reported in the literature, said Anderson, because of the lack of knowledge of exact structures, uncertain purity of some compounds, and possible metabolic transformations into more active compounds. The variety of species, the different routes of administration, and the sources of enzymes further complicate comparisons of the results of different investigators.

Among the organophosphorus compounds studied thus far, a high degree of acute toxicity has been found only among those phosphates and phosphonates that profoundly inhibit cholinesterases. Inhibition of the so-called true cholinesterase, which is found in erythrocytes, striated muscle, and motor cortex, results in the paralysis of striated muscle. Inhibition of the so-called pseudocholinesterase, found in blood serum and the autonomic and sensory ganglia, stimulates the glands of mucous secretion and the muscles of the eye and pulmonary tract.

A number of substituents confer active cholinesterase-inhibiting properties on the organophosphorus molecule. When one of the radicals is maintained as *p*-nitrophenyl, the diethyl group is more potent than the propyl, and the *n*-propyl is more active than the isopropyl. The substitution of amide groups seems to lower the anticholinesterase activity of the molecule, as does the substitution of sulfur for oxygen.

Discussing the degeneration of the central and peripheral nervous system by organosphosphorus compounds, Anderson indicated that triorthotolyl phosphate causes a characteristic paralysis in many species because of the selective demyelination of the peripheral nerves, degeneration of the anterior horn cells, and fatty degeneration in the white substance of the spinal cord.

In the case of a number of compounds, the chief toxic effect is stimulation and depression, or depression alone, of the central nervous system. These compounds occur in the class of phosphinates, phosphites, and phosphonates, as well as phosphates. In general, large doses are required to produce this nonspecific syndrome. Simple substituted trialkyl phosphates up to the hexyl derivatives characteristically produce this effect.

Among the few organophosphorus compounds that irritate surface tissues are those in which one or more hydroxyl

Betty Sullivan (left) of Russell-Miller Milling Co. is presented the Garvan Medal by Gladys Emerson of Merck.

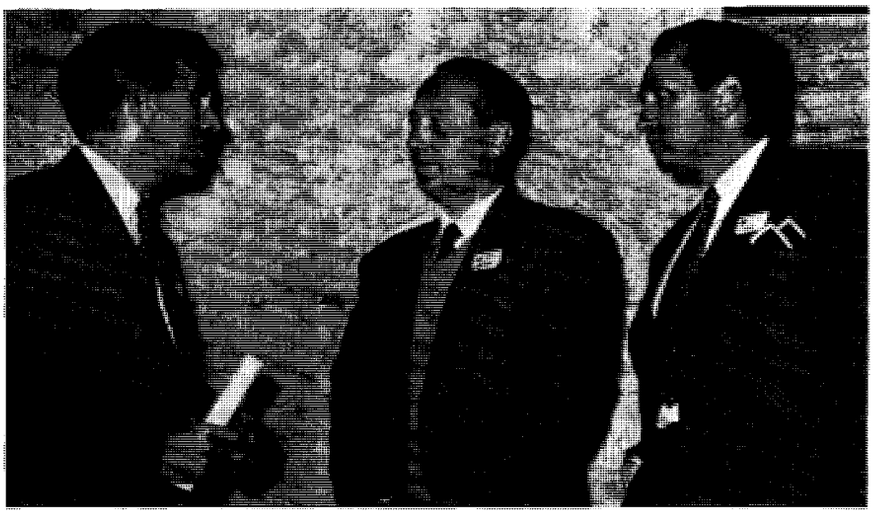
D. V. Josephson (left) of Pennsylvania State University receives Borden Award from J. H. McCain, Borden Foundation

groups remain unsubstituted, such as monobutyl phosphite, and compounds whose substituted halogen radicals are easily hydrolyzed to release a halide acid. The acidity of these agents approaches that of strong inorganic acids. The irritation is produced by the presence of hydrogen ions and is not a specific action of the phosphorus atom, said Anderson.

Determination of Aldrin. A number of analytical methods have been developed for the determination of aldrin residues of the order of 0.1 p.p.m. in agricultural crop materials. The two approaches of most immediate promise for the determination of microgram quantities of aldrin are the phenyl azide photometric method and the combustion chloride ion titration method, according to a report by A. E. O'Donnell, M. M. Neal, and coworkers at Shell Development.

The determination of 0.08 p.p.m. or less of aldrin in many plant materials is possible, based on the analysis for chlorine. In this test, the insecticide is separated from the plant matrix by solvent extraction and then treated chromatographically to remove biological extractives and naturally occurring halogen.

Before the photometric method could be used, a detailed investigation was necessary to overcome its critical deficiencies. The reliability of the method has been improved, and the determination of 0 to 40 micrograms with a standard deviation of 1 microgram has now been made possible. The modified method is applicable to the determination of 0.05 p.p.m. or less of aldrin in a wide variety of plant materials when the insecticide is first separated and purified as in the chlorine method. A number of common chloride-containing insecticides interfere in the over-all chlorine method, but no appreciable interference in the photometric method has been found with any of the insecticides tested.



Chatting in between sessions of the Division of Agricultural and Food Chemistry are: (left to right) L. W. Hazelton of Hazelton Laboratories, H. H. Anderson of the University of California School of Medicine, and J. A. Noone, NAC Association

Residual Pesticides Give Excellent Control, Despite Poor Application

Spreading properties of liquid formulations compensate for inadequate coverage

KANSAS CITY.—A pesticide is effective because of its ability to enter into the required biological reactions and also because of a hydrophile-lipophile balance that permits the pesticide to penetrate to the reaction site, said Lloyd L. Isenhour of Rohm & Haas, speaking before the ACS Division of Agricultural and Food Chemistry. With such a toxicant, adequate dispersement must be achieved without interference with the desired properties of the pesticide.

Residual pesticides, acting as surface, systemic, or subcuticular toxicants, give excellent pest control, frequently in spite of inadequate application techniques. This creates bad habits in commercial practice, Isenhour emphasized. At present, there is increasing commercial use of liquid formulations. Their spreading properties, as compared to dry dusts, compensate to some extent for poor distribution and coverage.

In technical circles, much discussion has centered around the need for improving toxicant penetration through formulation. More emphasis, he said, should be placed on not interfering with the basic penetrating properties of the toxicant itself. Past reports on pesticides have given only minor attention to the water solubility of toxicants. This factor, just as much as lipid solubility, is important in classifying the activity of a pesticide.

Chemical Formulations. The effectiveness of insecticides in the field is dependent not only on the inherent toxicity of chemicals but also upon their preparation before application, said N. F. Hardman of Stauffer Chemical. The chemical properties of diluents, either liquid or solid, may be such that reaction with toxicants occurs with reduction of effectiveness. Furthermore, wetting agents, dispersing agents, and adhesive agents must be compatible with toxicants and diluents.

The physical properties of diluents are equally as important. Diluents and surfactants in spray formulations may

J. D. Wilson (center) of the Ohio Agricultural Experiment Station discusses his report on the field performance of fungicides with N. F. Hardman (left) of Stauffer Chemical and R. M. Thomas of Mathieson at Agricultural and Food Chemistry session