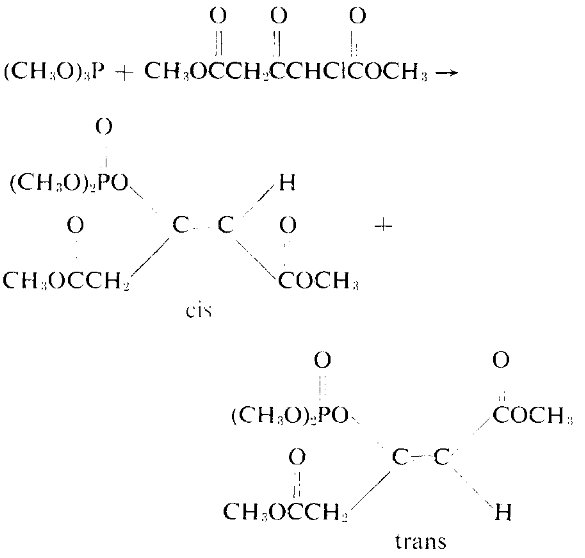
COMMUNICATIONS

Preparation and Biological Activity of the Isomers of Dimethyl-1,3-dicarbomethoxy-1-propen-2-yl Phosphate (Bomyl)

The insecticide, dimethyl-1,3-dicarbomethoxy-1-propen-2-yl phosphate (Bomyl), was prepared and the cis and trans isomers were separated. The insect toxicity and anticholinesterase activity of the two isomers were remarkably similar by contrast with the isomers of other vinyl phosphate insecticides.

A new vinyl phosphate, dimethyl-1,3-dicarbomethoxy-1-propen-2-yl phosphate (Bomyl insecticide, trademark of the Allied Chemical Corp.), has been synthesized which controls a wide variety of insects (Allied Chemical Corp., 1962) and is particularly effective against the housefly when formulated as a bait (Allied Chemical Corp., 1964). Casida (1955) and Casida *et al.* (1956) demonstrated that the cis and trans isomers of the related vinyl phosphate, Phosdrin, exhibited a wide difference in their biological properties. The authors, therefore, decided to investigate methods for the determination of the relative amounts of the two possible geometrical isomers in technical Bomyl and to evaluate each isomer for its biological activity.

Technical Bomyl is prepared by the Perkow reaction (Perkow *et al.*, 1955; Gilbert, 1959) and consists essentially of a mixture of cis and trans isomers as shown in the following equation:



$$(CH_3O)_3P + CH_3O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CHCl\overset{O}{\overset{\|}{C}}OCH_3 \rightarrow$$

The Schrader synthesis (Schrader, 1952) yields only the cis isomer and was carried out using the sodium salt of dimethyl acetonedicarboxylate and dimethyl phosphorochloridate. Rapid distillation of small quantities (5 grams) afforded the water-white cis isomer of very high purity as the middle cut. Attempts to distill larger quantities gave an impure product owing to decomposition. Small quantities of both isomers could be isolated from technical Bomyl by the use of the Craig liquid-liquid countercurrent technique (Spencer *et al.*, 1958), the most satisfactory solvent combination being ether-water.

EXPERIMENTAL

Preparation of Technical Bomyl. Sulfuryl chloride (473 grams, 3.5 moles) was added dropwise with stirring to the dimethyl acetonedicarboxylate (610 grams, 3.5 moles) maintaining a reaction temperature of 25° to 35° C. After the addition was completed, the reaction mixture was heated to 92° C. at 15 mm. for 10 minutes to remove the volatile materials. Trimethyl phosphite (435 grams, 3.5 moles) was then added dropwise maintaining the temperature in the 70° to 85° C. range. After heating the reaction mixture at 92° C. at 15 mm. for 30 minutes, 970 grams (98%) of technical Bomyl was obtained as an amber oil. Distillation gave a water-white liquid, b.p. 154° to 160° C. (2 mm.).

Anal. Calcd. for $C_9H_{15}O_8P$: C, 38.3; H, 5.32; P, 11.0. Found: C, 37.9; H, 5.22; P, 10.7.

Preparation of *cis*-Bomyl. Sodium metal (11.5 grams, 0.5 mole) was added over a 1-hour period to a solution of dimethyl acetonedicarboxylate (87 grams, 0.5 mole) in 500 ml. of anhydrous ethyl ether. Cooling was applied during the addition and the mixture was stirred for an additional 2 hours. A solution of dimethyl phosphorochloridate (72.3 grams, 0.5 mole) in 200 ml. of anhydrous ether was then added dropwise with stirring over a 1/2-hour period. The reaction mixture was heated at reflux for 6 hours, washed with water, and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure left 68 grams (48%) of a dark amber oil. The crude product was distilled and the fraction boiling at 148° to 150° C. (1.0 mm.) was collected. An analytical sample was obtained by redistillation of a 5-gram sample, b.p. 148° to 149° C. (1.0 mm.).

Anal. Calcd. for $C_9H_{15}O_8P$: C, 38.3; H. 5.32; P, 11.0. Found: C, 38.2; H, 5.27; P, 10.8.

The assignment of the configuration of the geometrical isomers could be made on the basis of their infrared and NMR spectra (Stothers and Spencer, 1961; Fukuto *et al.*, 1961; Stiles *et al.*, 1961; Thompson, 1965). The infrared spectrum of the cis isomer has characteristic absorption bands at 1655, 1370, 1325, 980, 945, and 895 cm.$^{-1}$, while the trans isomer has bands at 1760, 1345, and 950 cm.$^{-1}$ Both isomers have a common absorption band at 915 cm.$^{-1}$

NMR spectroscopy provided the best means for the assignment of the configuration of the two isomers as well as for the determination of the relative amounts of each isomer. The Bomyl samples were examined as neat liquids and in carbon tetrachloride solution with a Varian A-60 spectrometer. The pertinent chemical shifts are reported in parts per million from tetramethylsilane. The NMR spectrum of the product obtained from the Schrader synthesis showed a doublet centered at 5.95 p.p.m. for the vinyl proton and was assigned the cis configuration. This was identical to the first isomer obtained by the Craig countercurrent method. The second isomer obtained by the Craig method was then the trans isomer which had a single vinyl proton peak at 5.50 p.p.m. The position of the vinyl resonances and the difference in their chemical shift values (0.45 p.p.m.) are consistent with results obtained for other vinyl phosphates.

Examination of several technical Bomyl samples by NMR indicated an isomer ratio of 3 to 2 with the cis isomer predominating. Initial fractions obtained on distillation of technical material were enriched in the cis isomer while later fractions contained more of the trans isomer. No significant separation of the isomers by distillation was realized. The use of a packed or spinning band column resulted in extensive decomposition owing to the longer heating periods required.

Pure cis isomer was isolated from technical Bomyl by column chromatography. A column 18 inches long and 1 inch in diameter was filled with benzene followed by the addition of approximately 100 grams of silica gel (Fisher S-157). A solution of 5 grams of Bomyl in 10 ml. of benzene was added, followed by elution with ethyl ether. A total of 3600 ml. of ether was used and 300 ml. of eluent were collected for each fraction. Combination of the first six fractions gave approximately 1.2 grams of the cis isomer, while fractions 10 to 12 gave approximately 0.2 gram of Bomyl containing 80% of the trans isomer.

The most effective separation of the two isomers was accomplished by liquid-liquid countercurrent distribution in an ether-water system (Spencer *et al.*, 1958). A 5-gram freshly distilled Bomyl sample was resolved in a 60-tube automatic Craig fractionator with 10-ml. phases. After 60 transfers, the fractions were located by phosphorus determination of suitable aliquots. Tubes 11 to 27 gave the cis isomer (2.7 grams), b.p. 130–31° C. at 0.05 mm. and tubes 34 to 54 the trans isomer (1.4 grams), b.p. 130-31° C. at 0.05 mm.

Gas chromatography was utilized in an attempt to analyze and purify Bomyl. Best results were obtained with a 6-foot, 1/4-inch U-column packed with 10% Dow Corning 200 (12,500 centistokes) on Gas Chrom Q (100- to 120-mesh). Resolution of Bomyl was excellent when isothermal conditions at 200° C. and a helium flow of 30 ml. per minute were employed. Under these conditions, a sharp symmetrical peak was obtained having a retention time of 7 minutes. The impurities in Bomyl could be readily detected; however, no resolution of the isomers was observed. Collection of Bomyl from the analytical experiments, followed by reinjection, indicated a high degree of purity. Preparative-scale gas chromatography, however, gave impure Bomyl.

Table I. Insecticidal Activity of Bomyl Isomers

	Mortality, %[a]				
Sample	**MBBL, 11.7 p.p.m.**	**PAA, 7.8 p.p.m.**	**SAL, 18.8 p.p.m.**	**TSSM, 5.9 p.p.m.**	**HFA, 5.9 p.p.m.**
cis/trans = 1.5 (technical)	80	47	73	78	78
cis (98%)	87	96	53	97	91
trans (80%)	67	83	73	87	90

[a] MBBL – Mexican bean beetle; PAA – pea aphid adult; SAL – Southern armyworm larvae; TSSM – two-spotted spider mite; HFA – housefly adult.

Table II. Toxicity and Anticholinesterase Activity of Bomyl Isomers to the Fly

Isomer	**LD_{50}, Mg./Kg.**[a]	I_{50}[b]
cis	2.3	3.2×10^{-9}
trans	2.4	3.2×10^{-9}

[a] LD_{50} determined by topical application in acetone to 3-day old female housefly. Mortality was recorded after 24 hours.

[b] Concentration of the organophosphate to product 50% inhibition for a flyhead cholinesterase preparation at 25° C. in 30 minutes. Manometric determination (Vardanis and Crawford, 1964).

The effect of Bomyl irradiation with ultraviolet light on stability and isomer distribution was determined. The irradiation was carried out with a 450-watt Hanovia lamp in an aluminum reflector at a distance of 8 inches. After irradiation of samples containing 80% trans or 95% cis isomer for 7 hours, their final cis content was 76 and 79%, respectively. Comparable results were obtained using sunlamps at a distance of 7 inches for 24 hours. Apparently irradiation of Bomyl gives an equilibrium mixture of cis to trans isomers of 4 to 1.

In view of the previously reported (Casida, 1955; Casida *et al.*, 1956) differences in biological activity of the Phosdrin isomers, the present authors decided to compare the insecticidal activity of cis and trans Bomyl. Table I shows that technical Bomyl and its cis and trans isomers showed essentially the same degree of activity. Further work on the anticholinesterase activity and toxicity of the isomers also showed little difference between the isomers (Table II). These results are in striking contrast to the dramatic difference in toxicity of the Phosdrin isomers (Spencer, 1961).

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LITERATURE CITED

Allied Chem. Agr. Tech. Bull. No. **3702-02-1004** (1964).
Allied Chem. Agr. Tech. Bull. No. **3707-01-811** (1962).
Casida, J. E., *Science* **122,** 597 (1955).
Casida, J. E., Gotterdam, P. E., Getzin, L. W., Chapman, R. K., J. AGR. FOOD CHEM. **4,** 236 (1956).
Fukuto, T. R., Hornig, E. O., Metcalf, R. L., Winton, M. Y., *J. Org. Chem.* **26,** 4620 (1961).
Gilbert, E. E. (to Allied Chemical Corp.), U. S. Patent **2,891,887** (June 23, 1959).
Perkow, W., Krockow, E. W., Knoevenagel, K., *Chem. Ber.* **88,** 662 (1955).
Schrader, G., *Angew. Chem. Monograph* No. **62,** 48 (1952).
Spencer, E. Y., *Can. J. Biol.* **39,** 1790 (1961).
Spencer, E. Y., Todd, A. R., Webb, R. F., *J. Chem. Soc.* **1958,** p. 2968.
Stiles, A. R., Reilly, C. A., Pollard, G. R., Tieman, C. H., Ward, L. F., Phillips, D. D., Soloway, S. B., Whetstone, R. R., *J. Org. Chem.* **26,** 3960 (1961).
Stothers, J. B., Spencer, E. Y., *Can. J. Chem.* **39,** 1389 (1961).
Thompson, J. E., *J. Org. Chem.* **30,** 4276 (1965).
Vardanis, A., Crawford, L. G., *Econ. Entomol.* **57,** 136 (1964).

P. E. NEWALLIS[1]
P. LOMBARDO[2]
E. E. GILBERT

Allied Chemical Corp.
Morris Township, N. J.

E. Y. SPENCER
A. MORELLO

Research Institute
Canada Department of Agriculture
London, Ontario, Canada

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[1] Present address, Chemagro Corp., Kansas City, Mo.

[2] Present address, Food and Drug Administration, Pesticide Branch, Washington, D.C.