

INSECTICIDE ANALOGS

Conversion of Phosphorothionates to Their Oxygen Analogs with Dinitrogen Tetroxide

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Some phosphorothionates can be readily converted to their oxygen analogs by a simple treatment with N_2O_4 gas of solutions in organic solvents at room temperature. Malathion and parathion give the best results, with yields up to 91%.

MANY PHOSPHOROTHIONATE TRIESTERS are important insecticides whose metabolism is of considerable interest. Since one metabolic path is invariably conversion to the oxygen analog, i.e., conversion of $P=S$ to $P=O$, and this analog is often the actual toxicant, simple chemical methods for preparing the oxygen analog from the phosphorothionate are desirable. This is particularly true in radioactive syntheses, where one needs to conserve time and radioactive starting material. A number of methods for particular phosphorothionates have appeared in the literature, usually for microgram quantities, but quantitative reports are rare. The reagents used have been bromine water (6), *N*-bromosuccinimide (4), nitric acid (3, 7, 8, 13, 14), peracetic acid (2, 9, 11), hydrogen peroxide (16), and potassium permanganate (16). Yield data are not usually given.

The present paper describes an extremely simple procedure for conversion of relatively large amounts.

Experimental

Malathion [S-1,2-bis(ethoxycarbonyl)-ethyl *O,O*-dimethyl phosphorodithioate] and parathion (*O,O*-diethyl *O-p*-nitrophenyl phosphorothioate) on the basis of vapor phase chromatography and other criteria were at least 98% pure. Methylene chloride was purified by shaking with concentrated sulfuric acid (15) and stored in a brown bottle kept in a dark cabinet. Ether was reagent grade anhydrous.

Conversion of Malathion. Malathion (3.30 grams, 0.01 mole) was dissolved in 30 ml. of methylene chloride or ether in a 100-ml. Minilab flask (Ace Glass, Inc., Vineland, N. J.) fitted with an all-glass hollow-bore stirrer, drying tube, and thermometer. Dinitrogen

Table I. N_2O_4 Oxidations of 3.30 Grams (0.01 Mole) of Malathion at 25° C.

Run	Time, Hours	Solvent	Weight of Product, Grams ^a	Product Composition, ^b %		Yield of Malaoxon, ^b %
				Malaoxon	Malathion	
1	4	Ether	2.40	47	0	36
2	16	Ether	2.22	75	0	53
3	1	CH ₂ Cl ₂	2.96	54	10	51
4	1.7	CH ₂ Cl ₂	2.84	52	11	47
5	4	CH ₂ Cl ₂	2.46	53	0	42
6	16	CH ₂ Cl ₂	2.31	80	0	59
7 ^c	4	CH ₂ Cl ₂	2.53	45	1	36

^a After bicarbonate wash. ^b Analysis was by vapor phase chromatography using a 10-ft. column packed with 20% silicone grease on Celite; column temperature, 206° C.; inlet temperature, 247° C. Bibenzyl was used as an internal standard. Analyses were performed by J. Cincotta, American Cyanamid Co., Stamford, Conn. ^c Reaction run at -70° C.

tetroxide (Matheson) was passed from the cylinder through two drying towers containing alternate layers of calcium chloride and indicating Drierite, and introduced at a standard steady rate, by means of the hollow stirrer, for 5 minutes. During the introduction of the gas, the stirred reaction mixture was maintained at a constant temperature by means of a cooling bath. The yellow-brown solution was allowed to stand at the original reaction temperature for a period of time as indicated in Table I. A gas was steadily evolved during this period. The solvent was then removed by disconnecting the tank of oxidant and drawing a slow stream of air (regulated by a pinch clamp on the Tygon tubing) through the stirred solution by means of an aspirator connected to the exit drying tube. The stripping time was $\frac{3}{4}$ to 1 hour, the temperature of the solution during the process being around -50° C. for methylene chloride solvent, lower for ether. The residual oil was blue or green in color. Its infrared spectrum was recorded, and it was taken up in 20 ml. of chloroform and washed with 5 ml. of 20% potassium bicarbonate solution.

The bicarbonate layer was extracted twice with 5 ml. of chloroform, and the three chloroform fractions were combined and dried over magnesium sulfate. After removal of the solvent on a rotary film evaporator, the product, a yellow oil, was analyzed by vapor phase chromatography.

Conversion of Parathion. The reaction was run on a 0.02 molar scale (3.66 grams) in essentially the same manner as for malathion. After 5 minutes of gas introduction at the standard rate, the flow was cut down to that sufficient to maintain a slow flow of brown NO_2 fumes from the end of the drying tube for an additional, variable period of time. A standing period followed, during which gas evolution was observed. Both solutions and crude and washed products were yellow to brown in color.

Results

In certain cases, dinitrogen tetroxide effects the conversion of P(S) to P(O) in good yield. The reaction was easily carried out in organic solvents, avoiding the problem of hydrolysis of sensitive

organophosphates inherent in the use of such oxidants as nitric acid and bromine water. Methylene chloride, chloroform, and ether were found to be satisfactory solvents. The dinitrogen tetroxide was used directly from the cylinder after passage through a Drierite-calcium chloride column.

Qualitative evidence (infrared) was obtained for at least partial conversion of P=S to P=O for six phosphorothionates. Of these, two—malathion and parathion—were studied in some detail with the aid of vapor phase chromatography. Although no attempt was made to isolate the phosphate ester products, chromatographic methods for separating phosphates from phosphorothionates are well known in the literature (12).

The malathion results are given in Table I. The highest yield of malaxon [the P(O) analog] was obtained in Run 6. The 16-hour ether run (Run 2) was nearly as good. It is not clear why the 4-hour runs in both solvents gave lower yields since in each case no malathion remained at the end of the reaction. A possible explanation for the 4-hour ether run lies in a sudden strong exotherm and evolution of NO₂ that occurred during the removal of the solvent from the crude, unwashed reaction mixture. Decomposition could have taken place at this point. Although it was not tried, this difficulty could probably have been avoided by washing the crude reaction mixture with base before removing the solvent.

Besides the two well-separated bands for malathion and malaxon, the vapor phase chromatograms of the reaction products exhibited a complex of narrow bands with low retention times. The structures of these volatile materials are not known. Infrared spectra of the reaction products all exhibited weak bands in the region of nitro group absorption at 1560 and/or 1580 cm⁻¹. In addition, several spectra showed weak bands in the 1610-1650 cm⁻¹ region (double bond) not present in the spectra of either malathion or malaxon.

Parathion was converted to paraoxon [its P(O) analog] in straightforward fashion. The results are shown in Table II. The vapor phase chromatograms of the reaction products showed, in most cases, only bands for parathion and paraoxon. A few chromatograms showed a single minor impurity band.

Table II. N₂O₄ Oxidations of 3.66 Grams (0.02 Mole) of Parathion at 25° C.

Run	Duration of Gas Flow, Min.	Standing Time, Hours	Solvent	Weight of Product, Grams ^a	Product Composition, ^b %		Yield of Paraoxon, %
					Paraoxon	Parathion	
1	30	0	Ether	3.38	28	73	28
2	15	4	Ether	3.63	29	39	31
3	30	16	Ether	3.29	93	6	91
4	30	0	CH ₂ Cl ₂	3.11	57	36	53
5	15	4	CH ₂ Cl ₂	2.49	84	2	63

^a After bicarbonate wash. ^b Same as in Table I.

In Runs 2 and 5, an appreciable amount of material was not eluted from the column, presumably representing high-boiling impurities. Recoveries, as parathion plus paraoxon, of material placed on the VPC column in the other three runs ranged from 93 to 101%. The same difficulty with unexpected evolution of heat and NO₂ previously mentioned in connection with the malathion reaction occurred in Run 2 and could account for the low recovery experienced in that case.

The parathion-paraoxon conversion exhibited a solvent effect, as shown by comparison of Runs 1 and 2 with Runs 4 and 5. In each case, the ether reactions resulted in a higher recovery of unreacted parathion than did those carried out in methylene chloride. This is in agreement with other evidence that the oxidizing action of dinitrogen tetroxide is moderated by complex formation with electron donor solvents (7, 10).

The following compounds were also treated with dinitrogen tetroxide: dimethoate (CH₃O)₂P(S)SCH₂C(O)NH-CH₃, dimethoate acid (CH₃O)₂P(S)-SCH₂COOH, diethyl pyrazinyl phosphorothionate, and (CH₃O)₂P(S)SCH₃. The reactions were carried out in chloroform or methylene chloride in a fashion similar to the malathion runs. In each case, the infrared spectrum of the crude reaction product exhibited P=O absorption in the 1250 cm⁻¹ region. It was not shown that the phosphoryl band in fact belonged to the desired oxygen analog. In the case of dimethoate, the simple oxygen analog was definitely not obtained, the infrared spectrum, with the carbonyl band at 1740 cm⁻¹ and a strong band at 1513 cm⁻¹, being indicative of an N-nitrosoamide (17). This product exploded on attempted vacuum distillation. Previous work has indi-

cated that N₂O₄ probably does give the oxygen analog of dimethoate acid (5).

Literature Cited

- Addison, C. C., Sheldon, J. C., *J. Chem. Soc.*, **1957**, 1937.
- Casida, J. E., Ahmed, M. K., *J. Econ. Entomol.* **52**, 111 (1959).
- Cassaday, J. T., Fletcher, J. H., Hamilton, J. C., Hechenbleikner, I., Hoegberg, E. I., Sertl, B. J., Thurston, J. T., *Advan. Chem. Ser.* **1**, p. 148 (1950).
- Cook, J. W., *J. Assoc. Offic. Agr. Chemist* **38**, 826 (1955).
- Dauterman, W. C., Viado, G. B., Casida, J. E., O'Brien, R. D., *J. Agr. Food Chem.* **8**, 117 (1960).
- Fallscheer, H. O., Cook, J. W., *J. Assoc. Agr. Chemist* **39**, 691 (1956).
- Giang, P. A., Hall, S. A., *Anal. Chem.* **23**, 1830 (1951).
- Johnson, G. A., U. S. Patent **2,713,018** (1955).
- Krueger, H. R., Casida, J. E., Niedermeier, R. P., *J. Agr. Food Chem.* **7**, 182 (1959).
- Levy, N., Scaife, C. W., *J. Chem. Soc.* **1946**, 1093, 1100.
- Miskus, R., Hassan, S., *J. Econ. Entomol.* **52**, 353 (1959).
- O'Brien, R. D., "Toxic Phosphorus Esters," Academic Press, N. Y., pp. 352, 359-64 (1960).
- Plapp, F. W., Jr., Bigley, W. S., Darrow, D. I., Eddy, G. W., *J. Econ. Entomol.* **54**, 389 (1961).
- Plapp, F. W., Jr., Casida, J. E., *J. Agr. Food Chem.* **6**, 662 (1958).
- Riddick, J. A., Toops, E. E., "Organic Solvents," Vol. VII, in A. Weissberger's "Technique of Organic Chemistry," 2nd ed., p. 409, Interscience, N. Y. (1955).
- Santi, R., de Pietri-Tonelli, P., *Nature* **183**, 398 (1959).
- White, E. H., *J. Am. Chem. Soc.* **77**, 6008 (1955).

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