Cyclic Organophosphorus Compounds as Possible Pesticides. Part II.[1] 1,3,2-Dioxaphosphorinans

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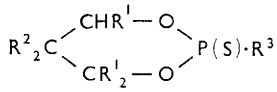
Some 2-*p*-nitrophenoxy- and 2-(*N*-substituted carbamoylmethyl)thio-1,3,2-dioxaphosphorinans have been prepared and shown to lack insecticidal properties.

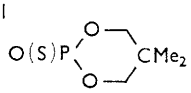
In the preceding Paper [1] we described the preparation of some 1,3,2-dioxaphospholans which are analogues of well established insecticides. Their lack of anticholinesterase activity may be explained by the facile hydrolytic cleavage of the five-membered ring. We were thus unable to examine the possible steric consequences of small, but relatively rigid systems, as opposed to those with mobile dialkoxy groups.

Like the 1,3,2-dioxaphospholans, the 1,3,2-dioxaphosphorinans present a disubstituted phosphoryl grouping with different steric potential from the conventional dialkyl phosphoryl groups. Unlike the dioxaphospholans, however, they provide a means of examining the behaviour of a group with an odd number of carbon atoms attached through oxygen to phosphorus, yet having a ring stability considerably greater than an isomeric dioxaphospholan.

We prepared a number of 2-carbamoylmethylthio- and 2-*p*-nitrophenoxy-2-thiono-1,3,2-dioxaphosphorinans by methods already explored for the dioxaphospholan series. The increased stability of the six-membered ring and reduced reactivity of exocyclic bonds to nucleophilic reagents is reflected in the ability to carry out some of the reactions in aqueous medium.

5,5-Dimethyl-2-mercapto-2-thiono-1,3,2-dioxaphosphorinan (I), as either the potassium salt in aqueous solution or as the free acid in acetone solution in the presence of anhydrous potassium carbonate, reacted readily with chloroacetamide, *N*-methylchloroacetamide, and *N*-chloroacetylmorpholine to give the esters (II), (III), and (IV), respectively, in good yields. In acetone, a high yield of a substance having m. p. 198—199·5° ($C_9H_{18}N_2O_4PS_2$) was also obtained from chloroacetamide. This was evidently not a ring-opened degradation product from the ester (II), since later experiments showed that the latter was stable to attack by nucleophilic reagents such as lithium chloride and pyridinium chloride. The compound (II) was, however, attacked at the exocyclic P–S bond by strong alkali, the ring being retained. Attempts to prepare the esters (II) and (III) by reaction between the phosphorochloridothionate (V) and either mercaptoacetamide or *N*-methylmercaptoacetamide in the presence of pyridine were unsuccessful, the end-product always being the di-cyclic dithiopyrophosphate (VI). This structure is supported by its



	R^1	R^2	R^3
(I)	H	Me	SH
(II)	H	Me	$S\cdot CH_2\cdot CO\cdot NH_2$
(III)	H	Me	$S\cdot CH_2\cdot CO\cdot NHMe$
(IV)	H	Me	$S\cdot CH_2\cdot CO\cdot$ morpholino
(V)	H	Me	Cl
(VI)	H	Me	
(VII)	H	Me	$O\cdot C_6H_4\cdot NO_2$-*p*
(VIII)	Me	H	$O\cdot C_6H_4\cdot NO_2$-*p*
(IX)	Me	H	Cl
(X)	H	H	$O\cdot C_6H_4\cdot NO_2$-*p*

infrared spectrum, and further confirmation has been obtained by treatment with cyclohexylamine, and by the synthesis of the *P*-thiono-*P*′-oxo-isomer.[2]

The two *p*-nitrophenoxy-esters (VII) and (VIII) were obtained from the corresponding phosphorochloridothionates (V) and (IX) and *p*-nitrophenol. Attempts to prepare 2-chloro-2-thiono-1,3,2-dioxaphosphorinan were not successful, and the ester (X) was therefore obtained directly from propane-1,3-diol and *p*-nitrophenyl phosphorodichloridothionate.

Determination of rates of hydrolysis indicated that for some of the esters, *e.g.*, the carbamoylmethylthio- and *p*-nitrophenoxy-derivatives, a reasonable degree of

[1] Part I, R. S. Edmundson and A. J. Lambie, preceding Paper.

[2] R. S. Edmundson, *Tetrahedron*, 1965, **21**, 2379.

anticholinesterase activity might have been expected. Screening of the compounds against *Megoura viciae* and *Tetranychus telarius* indicated little, if any, contact or systemic activity.

2-Oxo-2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinan hydrolyses at about the same rate as diethyl *p*-nitrophenyl phosphate but exhibits negligible anticholinesterase activity. This has been attributed to a steric effect on the part of the enzyme.[3]

Many 4,5-benzo-1,3,2-dioxaphosphorinans, derivable from 2-hydroxybenzyl alcohol and phosphorodichloridates and related compounds,[4,5] or *in vivo* from tri-*o*-cresyl phosphate,[6,7] possess insecticidal activity, and they are notable in that the exocyclic group need have no electron-withdrawing properties. Thus, while steric effects of this bicyclic system are apparently insufficient to inhibit biological activity, the latter was modified by variation in the exocyclic group.[8]

A preliminary report of the material of this and the preceding Paper has appeared.[9]

EXPERIMENTAL

General experimental details were given in the preceding Paper.

2-Carbamoylmethylthio-5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan.—(a) *Preparation in acetone.* A solution of 5,5-dimethyl-2-mercapto-2-thiono-1,3,2-dioxaphosphorinan [2] (99 g.) and chloroacetamide (47 g.) in acetone (1200 ml.) was boiled with anhydrous potassium carbonate (50 g.) for 5 hr. The hot mixture was filtered, and the filtrate evaporated, to leave a yellow solid. This was extracted with boiling chloroform, leaving an insoluble *substance* (52 g.), m. p. 198—199·5° (from dimethylformamide–benzene, then acetone) (Found: C, 34·5; H, 5·7; N, 8·6; P, 10·4; S, 20·3. $C_9H_{18}N_2O_4PS_2$ requires C, 34·5; H, 5·8; N, 8·95; P, 9·9; S, 20·45%). The chloroform extract was evaporated, and the residue triturated with light petroleum, to give the required *ester* (60 g., 50%), m. p. 96—98° (from propan-2-ol) (Found: C, 33·45; H, 5·85; N, 5·65; P, 12·25; S, 25·5. $C_7H_{14}NO_3PS_2$ requires C, 33·2; H, 5·6; N, 5·55; P, 12·2; S, 25·4%).

(b) *Preparation in water.* A solution of the dithiophosphoric acid (19·8 g.) in potassium carbonate solution (6·9 g. of solid in 200 ml. of water) was heated at 90° with chloroacetamide (9·4 g.) for 2·5 hr. The cooled suspension was extracted with chloroform. Addition of light petroleum to the dried extract gave the dithio-ester (17·5 g., 60%), identical with that prepared above. No substance of m. p. 195—200° was found.

5,5-Dimethyl-2-(N-methylcarbamoylmethyl)thio-2-thiono-1,3,2-dioxaphosphorinan.—This *ester*, m. p. 135—137° (33·5 g., 83%), was prepared as in the previous synthesis [procedure (b)] from the dithio-acid (29·7 g.), *N*-methylchloroacetamide (16·2 g.), and potassium carbonate (10·4 g.) in water (200 ml.) (Found: N, 5·1; P, 11·5; S, 23·75. $C_8H_{16}NO_3PS_2$ requires N, 5·2; P, 11·5; S, 23·8%).

5,5-Dimethyl-2-(N-morpholinocarbonylmethyl)thio-2-thiono-1,3,2-dioxaphosphorinan.—This was prepared, according to procedure (b), from the dithio-acid (29·7 g.), *N*-chloroacetylmorpholine (24·5 g.), and potassium carbonate (10·4 g.) in water (200 ml.). The cyclic *dithio-ester* (36 g., 74%) had m. p. 123—124° (from propan-2-ol) (Found: N, 4·7; P, 9·35; S, 19·6. $C_{11}H_{20}NO_4PS_2$ requires N, 4·3; P, 9·5; S, 19·7%).

Action of (1) *Pyridine Hydrochloride and* (2) *Lithium Chloride on 2-Carbamoylmethylthio-5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan.*—(1) The ester (13·0 g.) was boiled for 3 hr. with a dried solution of pyridine hydrochloride (4·4 g.) in chloroform (200 ml.). Addition of light petroleum to the water-washed and dried chloroform solution gave a quantitative recovery of the ester. The water washings responded negatively to tests for SH groups.

(2) A solution of the cyclic dithio-ester (5·1 g.) in 2-ethoxyethanol (50 ml.) was heated at 100° with lithium chloride (2·6 g.). Working-up of the solution led to a quantitative recovery of the ester.

N-Methylmercaptoacetamide.—Aqueous methylamine (25% w/v; 405 ml.) was added dropwise to methyl thioglycollate (212 g.) at 0—5°. The mixture was stirred for 4 hr. and set aside for 2 days. The solution was evaporated, dried azeotropically with propanol, and distilled, giving the *compound*, b. p. 112°/0·3 mm., n_D^{23} 1·5245 (184 g., 88%) (Found: C, 34·1; H, 7·1; N, 13·0; S, 30·8. C_3H_7NOS requires C, 34·2; H, 6·7; N, 13·3; S, 30·4%).

Reaction between 2-Chloro-5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan and Mercaptoacetamide [10] *or N-Methylmercaptoacetamide, in the Presence, and Absence of Pyridine.*—These experiments have been repeated and reported elsewhere.[2] From experiments in which undried solvents were used, di-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) oxide, m. p. 230°, was isolated.

5,5-Dimethyl-2-p-nitrophenoxy-2-thiono-1,3,2-dioxaphosphorinan.—A solution of 2-chloro-5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan (20·1 g.) [2] in dry chlorobenzene (150 ml.) was refluxed with potassium *p*-nitrophenoxide (17·7 g.) for 1 hr. The hot solution was filtered, and, on cooling, the required *ester*, m. p. 157·5—159·5° (from chlorobenzene) (15·0 g., 74%), crystallised (Found: N, 4·7; P, 10·1; S, 10·4. $C_{11}H_{14}NO_5PS$ requires N, 4·7; P, 10·2; S, 10·6%). The yield was appreciably more when the reaction was carried out with triethylamine to remove hydrogen chloride.

2-Chloro-2-thiono-4,4,6-trimethyl-1,3,2-dioxaphosphorinan.—A mixture of 2-methylpentane-2,4-diol (11·8 g.) and pyridine (15·8 g.) was added dropwise during 3 hr. to thiophosphoryl chloride (16·9 g.) in benzene (500 ml.) maintained at *ca.* 60° and then at 70—80° for 1·5 hr. The solution was cooled, filtered, washed with water, dried, and evaporated, giving the *phosphorochloridothionate* (53%) as a straw-coloured oil, n_D^{20} 1·5129, which would not crystallise (Found: P, 14·95; S, 14·8. $C_6H_{12}ClO_2PS$ requires P, 14·4; S, 14·9%).

2-p-Nitrophenoxy-2-thiono-4,4,6-trimethyl-1,3,2-dioxaphosphorinan.—The above phosphorochloridothionate

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[10] P. Klason and T. Carlson, *Ber.*, 1906, **39**, 732, 738.

(42·9 g.), *p*-nitrophenol (27·8 g.), and triethylamine (35 g.) were heated together in boiling toluene (200 ml.) for 3 hr. Working-up of the mixture in the usual way gave an oil (54 g.) which crystallised. The solid crystallised from chlorobenzene–light petroleum, and then from ethyl acetate-petroleum ether, giving the *ester*, m. p. 107·5—109° (30 g., 48%) (Found: N, 4·4; P, 9·75; S, 10·0. $C_{12}H_{16}NO_5PS$ requires N, 4·4; P, 9·7; S, 10·1%).

2-p-*Nitrophenoxy*-2-*thiono*-1,3,2-*dioxaphosphorinan*.—A solution of triethylamine (20·5 g.), *p*-nitrophenyl phosphorodichloridothionate (27·2 g.),[11] and propane-1,3-diol (7·6 g.) in toluene (100 ml.) was heated at 100° for 1·5 hr. and worked up in the usual way, to give the required *ester*, m. p. 165·5—166·5° (12·0 g.) (Found: P, 11·5; S, 11·7. $C_9H_{10}NO_5PS$ requires P, 11·3; S, 11·65%).

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