A Simple Method for the Preparation of Desmethyl Derivatives of Some Organophosphorus Insecticides

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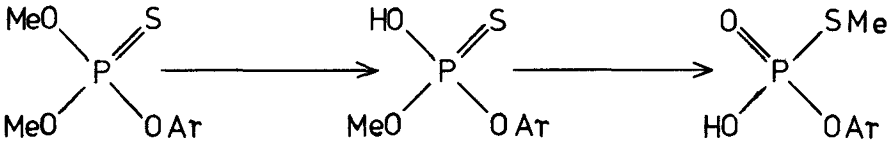
INTRODUCTION

For studies on the metabolic fate of a variety of O-aryl -O',O''-dimethyl phosphorothionate insecticides (I) in stored product pests, we required reference samples of the corresponding O-aryl-O'-methyl phosphorothionates (II) (desmethyl derivatives).

STENERSEN (1971) reported that the structures of commercial samples purported to be compounds (II) may not be in accordance with those specified on their labels, mainly as a result of isomerisation to O-aryl-S-methyl phosphorothionates (III) (isodesmethyl derivatives). He recommends the synthesis of desmethyl derivatives by the action of methanolic alkali on the aryl phosphorothiodichlorides, but we preferred to investigate their synthesis from the more readily available parent insecticides (I).



I demethylation II isomerisation III

Several direct methods have been employed in the past. For example, fenchlorphos (I; Ar = 2,4,5-trichlorophenyl) was demethylated by the action of an equimolar amount of potassium hydroxide in alcohol at 28°C for 16 hours (PLAPP and CASIDA 1958). DAUTERMAN *et al.* (1959) heated dimethoate, an aliphatic phosphorodithioate, with potassium dimethylphosphorodithioate in refluxing acetone for 2 hours to obtain desmethyl dimethoate. HOLLINGWORTH *et al.* (1967) made the desmethyl derivatives of parathion-methyl (I; Ar = 4-nitrophenyl) and fenitrothion (II; Ar = 3-methyl-4-nitrophenyl) by heating the latter compounds with sodium thiophenoxide in 95% ethanol at 58°C. Their attempts to make desmethyl compounds by heating insecticides with sodium iodide in acetone gave the isodesmethyl compounds. This was explained by reference to the kinetic data of

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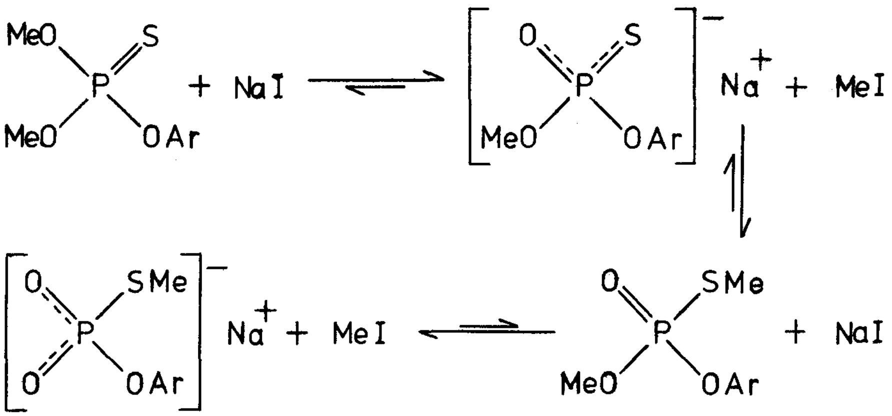
MILLER (1962). The methyl iodide formed methylates the desmethyl compound preferentially on the sulphur atom. This is then demethylated preferentially at the oxygen atom and the main product is the sodium salt of the isodesmethyl compound:



Presumably the methods involving potassium hydroxide, potassium dimethylphosphorodithioate, and sodium thiophenoxide give the required desmethyl compound because methanol, trimethylphosphorodithioate, and thioanisole respectively are not good methylating agents. Desmethyl fenitrothion (II; Ar = 3-methyl-4-nitrophenyl) has also been prepared by heating fenitrothion with 4-(4-nitrobenzyl)pyridine in acetone under reflux for 10 minutes (DYTE and ROWLANDS 1970).

We have made several attempts to prepare desmethyl bromophos (II; Ar = 4-bromo-2,5-dichlorophenyl). Bromophos treated with potassium hydroxide in molar ratio 1:1 or 1:2 in 95% alcohol at 28°C for 16 hours gave material which by thin layer chromatography and nuclear resonance spectrometry was shown to contain only 4-bromo-2,5-dichlorophenol *i.e.* no desmethyl bromophos. Bromophos was unaffected by treatment in refluxing acetone for 10 minutes with either 4-(4-nitrobenzyl)pyridine or with pyridine itself (molar ratio in both cases 1:1.2). Bromophos (0.55 mmol), heated for 2 hours with potassium dimethylphosphorodithioate (0.87 mmol) in refluxing acetone (10 ml), gave material from which desmethyl bromophos (37%) was isolated by column chromatography on Florisil (35 g) with methanol - chloroform (1:3). This sample was used for characterisation and comparison with desmethyl bromophos prepared by other methods (see later), but because potassium dimethylphosphorodithioate is not readily available and has a noxious odour we did not investigate this method further. For similar reasons we did not attempt to react bromophos with sodium thiophenoxide. Instead we decided to reinvestigate the intrinsically simple method of using an alkali metal halide to effect the demethylation.

As stated earlier, the use of sodium iodide leads to isodesmethyl derivatives (III) because the first formed methyl iodide methylates the required desmethyl compound. We decided to try to remove the methyl iodide as it is formed by bubbling nitrogen through the reaction mixture. Additionally we chose to investigate the use of potassium bromide and sodium chloride because neither of the corresponding methyl halides is as good a methylating agent as methyl iodide, and both are more volatile than methyl iodide, suggesting that it might be easier to remove them from the reaction mixture [b.p. methyl iodide 42°C; methyl bromide 4°C; methyl chloride -24°C (HEILBRON and BUNBURY 1953)].

TABLE 1: Reactions using the General Method (see text)

Insecticide (Ar)	Halide	Yield of desmethyl compound
Bromophos (4-bromo-2,5-dichlorophenyl)	NaI	18%[*]
"	KBr	21%
"	NaCl	0%
Iodofenphos (2,5-dichloro-4-iodophenyl)	KBr	15%
Chlorpyrifos methyl (3,4,6-trichloro-2-pyridyl)	KBr	13%[†]
Fenitrothion[≠] (3-methyl-4-nitrophenyl)	KBr	19%

[*] With no nitrogen flow a mixture of desmethyl bromophos (15%) and isodesmethyl bromophos (13%) was obtained.

[†] Reaction mixture heated to only 40°C for 72 hours; heating to 60°C for 16 hours gave 2-hydroxy-3,4,6-trichloropyridine.

[≠] Dissolved in dimethylformamide not methanol.

EXPERIMENTAL

All reagents and solvents were dried before use. Merck pre-coated Kieselgel 60 HF_{254} plates (20 × 20 cm) were used for preparative thin layer chromatography (p.t.l.c.) directly, and were cut to 6.5 × 2 cm for use in analytical thin layer chromatography (t.l.c.). The eluant in all cases was isopropanol, and materials were located by u.v. light (254 nm). Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian EM 360 spectrometer using tetramethylsilane as internal standard. The elemental analysis was performed by Butterworth Microanalytical Consultancy Ltd.

General Method : Insecticide (200 mg) in methanol (5 ml) was added to a solution of alkali metal halide (1 mol equiv.) in glycerol (2 ml) in a flask equipped with a reflux condenser fitted with a swan-neck adapter and a silica gel drying tube. A stream of nitrogen (about 10 ml/min) was dried in a calcium chloride tower, then was passed in a glass capillary down the centre of the condenser, and was bubbled through the mixture. The mixture was stirred magnetically and heated to 60°C for 16 hours. After cooling to room temperature and removal of the methanol on a rotary film evaporator, *M*-hydrochloric acid (2.6 ml) was added. Extraction into chloroform (3 x 5 ml), washing (H_2O then brine), drying ($MgSO_4$), and removal of solvent *in vacuo* gave a light brown oil. T.l.c. usually showed the presence of three materials (insecticide, a small amount of ArOH, and desmethyl compound in order of decreasing R_F). P.t.l.c. and extraction of the least mobile u.v. active — band with methanol gave desmethyl compound.

The results obtained with four insecticides are recorded in TABLE 1. N.m.r. data of the products are listed in TABLE 2. Additionally, the synthesised desmethyl bromophos, in the form of its sodium salt, was subjected to elemental analysis: Found: C, 22.6; H, 1.45%. Calc. for $C_7H_5BrCl_2NaO_3PS$: C, 22.5; H, 1.35%.

TABLE 2: N.m.r. Spectra of the Reaction Products

Product	Solvent	Ar Signals[*]	MeO Signals[†]
Desmethyl bromophos	$CDCl_3$	2.42(m; H-3 & H-6)	6.24
Desmethyl bromophos	C_6D_6	2.19(d,*J* 2Hz; H-6) 2.80(s; H-3)	6.32
Isodesmethyl bromophos	DMSO-d_6	2.00 and 2.18 (both d,*J* 1Hz; H-3 & H-6)	7.92[≠]
Desmethyl iodofenphos	DMSO-d_6	2.18(m; H-3 & H-6)	6.50
Desmethyl chlorpyrifos methyl	$CDCl_3$	2.25(s; H-5)	6.20
Desmethyl fenitrothion	DMSO-d_6	1.92 - 2.15(m; H-5) 2.54 - 2.90(m; H-2) & H-6) 7.51(s; 3-CH_3)	6.50

[*] s = singlet, d = doublet, m = multiplet

[†] All signals in this column were of the form d,*J* 13Hz

[≠] MeS signal.

DISCUSSION

The two experiments in which bromophos was treated with sodium iodide demonstrate that a stream of nitrogen bubbled through the reaction mixture is effective in removing the methyl iodide formed, thereby preventing isomerisation of the desmethyl derivative to the isodesmethyl compound, and enabling the pure desmethyl compound to be readily isolated. The results in TABLE 1 show that further improvement is achieved by the use of potassium bromide rather than sodium iodide. Sodium chloride is ineffective, presumably because the chloride is insufficiently nucleophilic in the solvent used.

Treatment with potassium bromide and the use of a stream of nitrogen to remove methyl halide appear to constitute a generally applicable method for the demethylation of a variety of insecticides of type I. Thus iodofenphos reacted under the conditions used for bromophos (60°C / 16 hours), chlorpyrifos methyl, in which the aryloxy- moiety is readily displaced, was successfully demethylated under milder conditions (40°C / 72 hours), and fenitrothion, which is only slightly soluble in methanol, was demethylated in dimethylformamide - glycerol solution.

CONCLUSION

Desmethyl derivatives of a variety of O-aryl-O',O''-dimethyl phosphorothionate organophosphorus insecticides can be prepared from the parent insecticides by treatment with potassium bromide and with a stream of nitrogen bubbling through the reaction mixture. The yields are low and we have made no attempt to optimise them, but we feel that this disadvantage is outweighed by three factors: (i) the starting materials are readily available and cheap, (ii) the reaction is clean and simple, and (iii) the procedure does not involve malodorous compounds.

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