

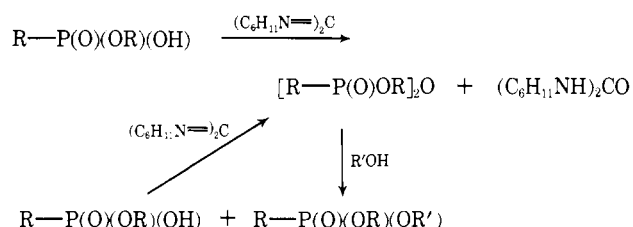
Preparation of Volatile Neutral Esters from Acidic Esters of Phosphoric Acid

A new method is described for the conversion of acid phosphate esters formed by the metabolic or hydrolytic decomposition of phosphatic pesticides into neutral esters sufficiently volatile to be determined by gas chromatography. In this method, the acids are reacted with dicyclohexylcarbodiimide to form

esters of pyrophosphoric acid, and these are decomposed with an alcohol or phenol. The reactions are simply and rapidly carried out and utilize stable, nontoxic reagents. The reactions are also useful for preparing neutral esters for analytical or biological purposes.

Acid esters of phosphoric and phosphorothioic acid represent important products in the hydrolytic and metabolic decomposition of many of the phosphatic pesticides. Although these compounds are usually conceded to be of low toxicity and of little physiological importance, it is desirable to be able to determine them as residues resulting from the treatment of soils, plants, or animals with pesticides. The low volatility of these compounds prevents their separation and identification by the gas chromatographic methods which have proved so valuable for the determination of the pesticides themselves. To overcome this difficulty, it has been customary to esterify the acid compounds and convert them into neutral esters which have sufficiently high vapor pressure to be characterized by gas chromatography. This esterification is usually accomplished by means of diazomethane, since the various silyl reagents and alcohol catalyzed by boron trifluoride are not effective. Diazomethane is unstable and must be prepared immediately before use and has a high acute and chronic toxicity which make its use undesirable. It is the purpose of this communication to describe another method of esterification which does not have these disadvantages.

Khorana and Todd (1953) described the reaction of dicyclohexylcarbodiimide (DCC) with mono- and di-esters of orthophosphoric acid to form esters of pyrophosphoric acid. Burger and Anderson (1957) showed that neutral phosphonates could be prepared by decomposing such pyro compounds with an alcohol or phenol. They pointed out that by using 1 mole of DCC per mole of starting ester, instead of the theoretical 0.5 mole, the acid ester regenerated by the alcoholysis of the pyro compound could be "recycled" and complete conversion to the neutral ester could be obtained:



This sequence of reactions is also applicable to the preparation of neutral phosphates and phosphorothioates from dialkyl hydrogen phosphates. By using appropriately larger amounts of dicyclohexylcarbodiimide, monoalkyl dihydrogen phosphates and even phosphorous and phosphoric acids can be

esterified completely. The reaction of the diimide with the acidic compounds is almost instantaneous at room temperature and the reaction of the resulting pyrophosphate with lower alcohols is quite rapid. With phenols and mercaptans it is somewhat slower and long standing, or heating under reflux may be required for good yields.

This reaction has been carried out many times with varying reactants. The experiments are outlined in Table I. In each case, the products of the reaction were identified gas chromatographically by comparing their retention times with those of samples of the neutral esters which have been prepared by conventional methods.

In a typical experiment, 28 g of commercial ethyl acid phosphate [an equimolar mixture of $(\text{C}_2\text{H}_5\text{O})_2\text{P}(\text{O})(\text{OH})$ and $(\text{C}_2\text{H}_5\text{O})\text{P}(\text{O})(\text{OH})_2$] was dissolved in 100 ml of methanol, and 41.2 g of DCC dissolved in 100 ml of tetrahydrofuran was added. Heat began to be evolved immediately and a white precipitate of dicyclohexyl urea formed. The reaction appeared to be complete in 15 min and the precipitate was filtered, washed with methanol, and dried. It weighed 42.6 g, 95% of the theoretical. The filtrate was examined by gas chromatography and two large peaks having the same retention times as authentic samples of dimethyl ethyl phosphate and methyl diethyl phosphate were found. Small peaks shown to be due to dissolved dicyclohexyl urea and to unreacted DCC were also observed. Since these and the methanol peak were the only peaks recorded, it would appear that no volatile by-products are formed.

In a related experiment, the reaction rate and the yield obtained were determined by dissolving 0.203 g of ethyl acid phosphate in 10 ml of ethanol and adding 1 g (100% excess) of solid DCC. Samples from the reacting solution were injected into the gas chromatograph at 10 min intervals and the size of the peak due to triethyl phosphate was measured and compared with peaks given by known solutions of triethyl phosphate. The yields at 10, 20, and 30 min after mixing were 60, 75, and 88% of that calculated.

This reaction has been used in our laboratory as a means of identifying and measuring ethyl dihydrogen phosphate in extracts of plants grown in soils treated with *O*-ethyl-*S,S*-dipropyl phosphorodithioate (MOCAP). To achieve this, the plant extract was chromatographed on a silica column and the acid phosphate fraction eluted with methanol. The methanolic solution was then treated directly with about 50 mg of solid DCC, stirred, and allowed to stand 30 min. No

Table I. Preparation of Neutral Esters from Acid Phosphates

Acid	Hydroxyl Compound	Product Obtained	% Yield
(CH ₃ O) ₂ P(O)OH	CH ₃ OH	(CH ₃ O) ₃ P(O)	90
(C ₂ H ₅ O) ₂ P(O)OH + C ₂ H ₅ OP(O)(OH) ₂	CH ₃ OH	(C ₂ H ₅ O) ₂ P(O)OCH ₃ + C ₂ H ₅ OP(O)(OCH ₃) ₂	88
C ₄ H ₉ OP(O)(OH) ₂	CH ₃ OH	C ₄ H ₉ OP(O)(OCH ₃) ₂	80
(C ₄ H ₉ O) ₂ P(O)OH	CH ₃ OH	(C ₄ H ₉ O) ₂ P(O)OCH ₃	85
(CH ₃ O) ₂ P(O)H	CH ₃ OH	No reaction	...
H ₃ PO ₃	CH ₃ OH	(CH ₃ O) ₂ P(O)H	...
H ₃ PO ₄	CH ₃ OH	(CH ₃ O) ₃ PO	...
(C ₂ H ₅ O) ₂ P(O)OH + C ₂ H ₅ OP(O)(OH) ₂	C ₆ H ₅ OH ^a	(C ₂ H ₅ O) ₂ P(O)OC ₆ H ₅ +	...
(C ₆ H ₅ O) ₂ P(O)OH + C ₆ H ₅ OP(O)(OH) ₂	C ₆ H ₅ OH	(C ₆ H ₅ O) ₂ P(O)(OC ₆ H ₅) ₂	...
(C ₂ H ₅ O) ₂ P(O)OH	<i>p</i> -NO ₂ C ₆ H ₄ OH ^a	(C ₂ H ₅ O) ₂ P(O)(OC ₆ H ₄ NO ₂)	30
(C ₂ H ₅ O) ₂ P(O)OH	2,4-Cl ₂ C ₆ H ₃ OH ^a	(C ₂ H ₅ O) ₂ P(O)(OC ₆ H ₃ Cl ₂)	40
(C ₂ H ₅ O) ₂ P(O)(OH)	C ₃ H ₇ SH ^a	(C ₂ H ₅ O) ₂ P(O)(SC ₃ H ₇)	25

^a Reflux 8 hr.

visible precipitate formed, but gas chromatography of the solution indicated the presence of the reaction product, dimethyl ethyl phosphate.

The reaction can also be used as a convenient method of synthesizing small amounts of other types of neutral esters for analytical standards or toxicological study. The last three entries in Table I outline the preparation of derivatives of three commercial pesticides—the oxygen analogs of parathion and V-C 1-13, and the diethyl analog of prophos.

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