

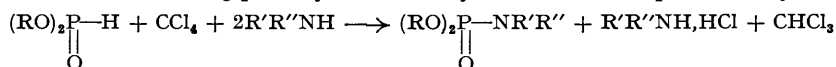
**129.** *Studies on Phosphorylation. Part III. Further Observations on the Reaction of Phosphites with Polyhalogen Compounds in Presence of Bases and its Application to the Phosphorylation of Alcohols.*

By F. R. ATHERTON and A. R. TODD.

The reaction between dialkyl phosphites and carbon tetrachloride in presence of bases described in Part II of this series (Atherton, Openshaw, and Todd, *J.*, 1945, 660) has been further studied using a variety of polyhalogen compounds. In general the reactivity of halogen compounds is decreased by introduction of fluorine and increased by bromine or iodine, and the reaction can also be used with diphenyl phosphite. In using the reaction as a preparative phosphorylation procedure, trichlorobromomethane appears to be the reagent of choice. A mixture of this substance with a phosphite will phosphorylate even aromatic amines directly, and in presence of a suitable tertiary base will phosphorylate ethyl alcohol.

The mechanism of the reaction is considered in the light of these further studies, and it is concluded that contrary to the view expressed earlier the main pathway of reaction involves intermediate formation of a halogenophosphonate which then acts as a phosphorylating agent.

IN Part II (*loc. cit.*) a reaction between dialkyl phosphites with carbon tetrachloride in presence of bases was described, which could be utilised for the phosphorylation of amines; the overall reaction in the case of a strong primary or secondary base could be represented by the equation



In the case of weakly basic amines (*e.g.*, aniline) addition of a strong tertiary base was necessary to induce reaction. In the same paper it was noted that this unusual reaction was not confined to carbon tetrachloride for, although chloroform and *s*-tetrachloroethane could not replace it, pentachloroethane and hexachloroethane reacted smoothly. The present communication

describes some further studies designed to test the general applicability of the reaction, to find the most suitable polyhalogen compound for general use in phosphorylation, and to gain further insight into its mechanism.

As a preliminary a number of further polyhalogenated hydrocarbons containing chlorine, or both chlorine and fluorine, were examined as substitutes for carbon tetrachloride. The results of a qualitative survey are given in the following table; the production of base hydrohalide on mixing dibenzyl phosphite, halogen compound, and ammonia or *cyclohexylamine* was taken as a criterion, controls being carried out in the absence of phosphite. Some of the reactions listed in the table were studied in a more quantitative fashion, the amino-phosphonate being isolated from the resulting mixture; details of two such experiments are given in the Experimental part. In general, reactivity in chlorofluoro-compounds decreased with increasing fluorine content, and in each case chloride ions were liberated with at most only traces of fluoride. The fact that tetrachloro-1:2-difluoroethane can take the place of carbon tetrachloride suggests that the failure of *s*-tetrachloroethane to do so may be due simply to preferential dehydrohalogenation in presence of bases.

*Reactivity of polyhalogen compounds with cyclohexylamine in presence of dibenzyl phosphite.*

Compound.	Reaction.	Compound.	Reaction.
CH <sub>3</sub> ·CCl <sub>3</sub> .....	—	CHCl <sub>2</sub> ·CF <sub>2</sub> Cl .....	Reacts with base alone
CH <sub>2</sub> Cl·CCl <sub>3</sub> .....	+ <sup>1</sup>	CFCl <sub>2</sub> ·CFCl <sub>2</sub> .....	+ <sup>1</sup>
CF <sub>2</sub> Cl·CCl <sub>3</sub> .....	+ <sup>1</sup>	CCl <sub>2</sub> ·CCl <sub>2</sub> .....	—
( <i>p</i> -Cl·C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CH·CCl <sub>3</sub> .....	—	CHCl·CCl <sub>2</sub> .....	—
CH <sub>2</sub> Cl·CHCl <sub>2</sub> .....	— <sup>2</sup>	CCl <sub>3</sub> ·CCl <sub>2</sub> ·CCl <sub>3</sub> .....	+
CH <sub>2</sub> Cl·CFCl <sub>2</sub> .....	+ <sup>1</sup>	CCl <sub>3</sub> ·CCl <sub>2</sub> ·CCl <sub>2</sub> ·CCl <sub>3</sub> .....	+
CH <sub>2</sub> Cl·CF <sub>2</sub> Cl .....	—	CCl <sub>2</sub> ·CCl·CCl <sub>3</sub> .....	+
CF <sub>2</sub> Cl·CFCl <sub>2</sub> .....	+ <sup>1</sup>	CCl <sub>2</sub> ·CCl·CCl·CCl <sub>2</sub> .....	—

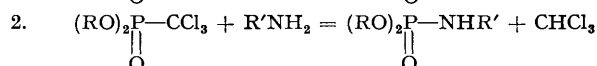
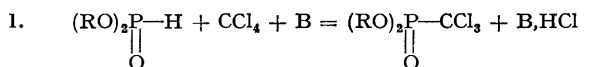
<sup>1</sup> No reaction when ammonia was substituted for *cyclohexylamine*.

<sup>2</sup> Slow reaction occurs with base alone.

None of the active compounds listed in the table showed any practical advantages over carbon tetrachloride as a reagent, and attention was next directed to the use of accessible bromo- and iodo-compounds. Carbon tetrabromide reacted vigorously with dibenzyl phosphite in presence even of such weak bases as aniline, giving the corresponding substituted amino-phosphonates in excellent yield. A noteworthy feature of this reagent is that the bromoform produced reacts further being itself converted into methylene bromide, so that 1 mol. of carbon tetrabromide will effect complete phosphorylation of 2 mols. of an amine. Iodoform behaved very like bromoform, although the reaction products were contaminated with iodine, and dichlorobromomethane could also be used successfully. The very high degree of reactivity shown by carbon tetrabromide was also observed in tetrachloro-1:2-dibromoethane, which was converted on reaction into a mixture of tetrachloroethylene and trichlorobromoethylene.

From a practical standpoint the use of carbon tetrabromide in phosphorylating compounds by the reaction under discussion has the disadvantage that the methylene bromide produced has rather a high boiling point. It seemed, therefore, that the reagent of choice might well be trichlorobromomethane, which would be converted into chloroform during reaction. Difficulty was at first encountered in preparing this substance in bulk, but a convenient method was found in the vapour-phase bromination of chloroform. Our expectations as to its usefulness were entirely fulfilled, and a mixture of it with dibenzyl phosphite was found to phosphorylate weak bases such as aniline and *N*-methylaniline directly. Moreover, in presence of a tertiary base the same mixture successfully phosphorylated ethyl alcohol. Trichlorobromomethane is considered to be the best polyhalogen compound for general use in the phosphorylation of amines and alcohols by this method; examples of its application are given in the Experimental section. A point of practical interest is that not only dialkyl phosphites but also diphenyl phosphite can be used in the reaction with polyhalogen compounds and bases.

In Part II (*loc. cit.*) the mechanism of the phosphorylation of amines by carbon tetrachloride and dialkyl phosphites in the presence of strong bases was discussed, and it was suggested that the reaction proceeded in two stages with intermediate formation of a trichloromethylphosphonate as indicated below:





encountered in purifying the products when other fluorine-containing compounds were employed in the reaction.

*Reaction of Dibenzyl Phosphite with Ammonia and cycloHexylamine in Presence of Bromo- and Iodo-compounds.*—The reactions were carried out at room temperature in the usual manner (reaction time, 30 minutes) and the products isolated as described above. For convenience the results are tabulated. In each case the amount of dibenzyl phosphite used was 0.01 mole and methylene chloride was employed as a diluent.

Amount of diluent (c.c.).	Halogen compound.	Quantity used (moles).	Yield of dibenzyl amino-phosphonate (%).	Yield of dibenzyl cyclohexyl-aminophosphonate (%).
20	CHI <sub>3</sub>	0.01	81	83
20	CHBr <sub>3</sub>	0.012	90	80
20	CHBrCl <sub>2</sub>	0.015	43 <sup>1</sup>	87
25	CCl <sub>2</sub> Br·CCl <sub>2</sub> Br	0.01	91	90
50	CBr <sub>4</sub>	0.005	—	84

<sup>1</sup> Low yield due to incomplete reaction in 30 minutes.

*Reaction of Various Phosphites with Aniline in Presence of Carbon Tetrabromide.*—Carbon tetrabromide was added to a mixture of the dialkyl or dibenzyl phosphite and aniline at room temperature and the product worked up next day. Yields of anilinophosphonate: from dibenzyl phosphite, 91%; diethyl phosphite, 88%; diisopropyl phosphite, 40%.

*Isolation of Halogenated Reaction Products.*—The method employed was to pass a slow stream of gaseous ammonia for several hours through an ethereal solution containing equimolar quantities of diisopropyl phosphite and the appropriate polyhalogen compound. The ammonium halide was filtered off, the ether removed, and the residue steam distilled under reduced pressure. The product was separated from the distillate and fractionated. Treated in this way hexachloroethane gave tetrachloroethylene (70%, b. p. 120—121°), iodoform gave methylene iodide (80%, b. p. 90°/42 mm.), bromoform gave methylene bromide (59%, b. p. 96—97°), and tetrachloro-1:2-dibromoethane gave a mixture of tetrachloroethylene (54%, b. p. 121°) and trichlorobromoethylene (6.5%, b. p. 145—147°).

*Trichlorobromomethane.*—The vapour from a refluxing mixture of dry chloroform (400 c.c.) and bromine (320 g.) was carried by a stream of nitrogen through a vertical silica tube heated to 250° and then through an efficient condenser, the condensate being returned to the flask containing the refluxing mixture. Hydrogen bromide was rapidly evolved and when, after 3 hours, the bromine colour had disappeared, the mixture was allowed to cool, washed with dilute sodium carbonate, and dried (Na<sub>2</sub>SO<sub>4</sub>). Fractionation using a 20 cm. Fenske column gave trichlorobromomethane, b. p. 104° (yield: 294 g.; 74%); the distillation residue which solidified on cooling consisted almost entirely of hexachloroethane.

*Direct Phosphorylation of Aniline and other Weak Bases by Means of Trichlorobromomethane and a Phosphite.*—A mixture of the dibenzyl or other phosphite with trichlorobromomethane, diluted with an inert solvent (benzene or ethyl acetate), was allowed to react with the appropriate amine at room temperature. After 18 hours the products were worked up in the usual way. In this way were prepared the known diethyl anilinophosphonate (yield, 88%), diisopropyl anilinophosphonate (yield, 62%) and dibenzyl anilinophosphonate (yield, 92%) as well as the following: *dibenzyl β-naphthylaminophosphonate*, colourless prisms, m. p. 75.5—76.5°, from cyclohexane-ether (Found: C, 71.1; H, 5.2; N, 3.5. C<sub>24</sub>H<sub>22</sub>O<sub>3</sub>NP requires C, 71.5; H, 5.4; N, 3.5%) (yield, 93%); *dibenzyl p-toluidinophosphonate*, colourless prisms, m. p. 89.5—90.5°, from light petroleum (Found: C, 68.0; H, 6.0; N, 3.8. C<sub>21</sub>H<sub>22</sub>O<sub>3</sub>NP requires C, 68.5; H, 6.0; N, 3.8%) (yield, 89%); *dibenzyl N-methylanilinophosphonate*, colourless prisms, m. p. 86—87°, from light petroleum (Found: C, 68.0; H, 6.0; N, 3.7. C<sub>21</sub>H<sub>22</sub>O<sub>3</sub>NP requires C, 68.5; H, 6.0; N, 3.8%) (yield, 64%).

*Barium Ethyl Phosphate.*—A mixture of dibenzyl phosphite (5.24 g.), ethyl alcohol (3 c.c.), 2:6-lutidine (5 c.c.), trichlorobromomethane (5 c.c.), and dry ether (25 c.c.) was set aside at room temperature for 2½ hours. The oil obtained by working up in the usual manner was evaporated with water to remove traces of lachrymatory material, dissolved in alcohol, and boiled for a few minutes with charcoal. The filtered solution (100 c.c.) was hydrogenated at atmospheric pressure using palladium oxide catalyst. When absorption of hydrogen was complete (10 minutes; 750 c.c.) the mixture was filtered and neutralised to phenolphthalein with barium hydroxide, and the alcohol removed under reduced pressure. The residue was dissolved in water, and the solution filtered, concentrated, and brought to crystallisation by adding alcohol. Barium ethyl phosphate separated as its crystalline hydrate, and was converted to the anhydrous salt (2.7 g.; 51%) by drying at 100° (Found: Ba, 52.1. Calc. for C<sub>2</sub>H<sub>5</sub>O<sub>4</sub>PBa: Ba, 52.6%).

*Diphenyl Aminophosphonate.*—Ammonia was passed through a solution of diphenyl phosphite (2.34 g.) in carbon tetrachloride (25 c.c.) for 15 minutes. The product (2.05 g.; 82%), recrystallised from chloroform-light petroleum, had m. p. 149—150°, undepressed in admixture with authentic diphenyl aminophosphonate (m. p. 149—150°).

*Tetraphenyl Pyrophosphate.*—A mixture of dibenzyl phosphite (26.2 g.), carbon tetrachloride (30 c.c.), and aqueous potassium hydroxide (250 c.c. of N) was stirred at room temperature for 9½ hours. The phases were then separated, the aqueous phase being washed with carbon tetrachloride. The combined carbon tetrachloride solutions were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated, and the residual oil was dissolved in a small amount of ether (ca. 50 c.c.) and cyclohexane added until slightly turbid. On standing, tetraphenyl pyrophosphate separated in colourless needles (16.5 g.; 61%), m. p. 60—61° undepressed by a sample (m. p. 60—61°) prepared according to Deutsch and Fernö (*loc. cit.*). From the aqueous phase, acidification and recrystallisation gave dibenzyl phosphate (2.6 g.; 9%), m. p. and mixed m. p. 78—79°, while fractionation of the distillate from the isolation of the tetraphenyl pyrophosphate gave chloroform (5 g.; 42%).

A similar experiment was carried out using trichlorobromomethane in place of carbon tetrachloride.

In this case difficulty was experienced in crystallising the oily tetrabenzyl pyrophosphate, and it was therefore identified by treatment with ammonia; it then yielded the expected mixture of dibenzyl aminophosphonate and dibenzyl phosphate.

It may be observed in passing that tetrabenzyl pyrophosphate is a satisfactory phosphorylating agent—with ammonia it gave in a trial experiment dibenzyl aminophosphonate (93%) and dibenzyl phosphate (90%)—and the fact that it can readily be prepared and stored in a crystalline condition gives it certain advantages as a reagent.

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