

174. *Studies on Phosphorylation. Part II. The Reaction of Dialkyl Phosphites with Polyhalogen Compounds in Presence of Bases. A New Method for the Phosphorylation of Amines.*

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Dibenzyl phosphite reacts with carbon tetrachloride in presence of excess ammonia the products being dibenzyl aminophosphonate, ammonium chloride and chloroform. Strong primary and secondary amines can replace ammonia in this reaction. With aniline no reaction occurs unless a tertiary base be added, whereupon dibenzyl anilinophosphonate is produced. Dialkyl phosphites undergo a similar reaction and in place of carbon tetrachloride pentachloroethane and hexachloroethane may be used.

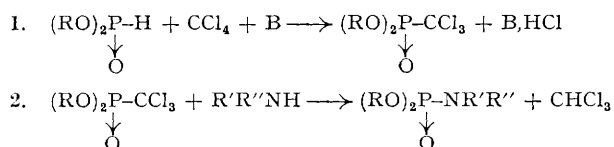
The mechanism of this reaction is discussed and it is suggested that where carbon tetrachloride is employed it proceeds by intermediate formation of a trichloromethylphosphonate which reacts with amines in the same way as trichloromethyl ketones.

In the course of experiments on the purification of dibenzyl phosphite required for the preparation of dibenzyl chlorophosphonate (Atherton, Openshaw, and Todd, this vol., p. 382), it was observed that when a solution of

the ester in carbon tetrachloride was washed with dilute aqueous ammonia a considerable amount of white solid separated. Examination of this solid revealed that it was dibenzyl aminophosphonate. This fortuitous and unexpected discovery led us to investigate the origin of the aminophosphonate and the results, which disclose a new method for the phosphorylation of amines, are now recorded.

When dibenzyl phosphite is dissolved in carbon tetrachloride no reaction occurs, but if gaseous ammonia be passed into the solution or if it be shaken with aqueous ammonia heat is evolved and dibenzyl aminophosphonate is produced in nearly theoretical yield, the other products being ammonium chloride and chloroform. An exactly similar reaction is brought about by strong primary and secondary bases, *e.g.*, cyclohexylamine, benzylamine, α -phenylethylamine, morpholine, the corresponding substituted aminophosphonates being produced. The reaction in these cases is best carried out under anhydrous conditions, but the presence of alcohol in the reaction mixture has little adverse effect on the yield. With weak bases, such as aniline, no reaction occurs, but reaction can be induced by adding a tertiary base. Thus on adding dibenzyl phosphite to a solution of equimolecular quantities of aniline and *NN*-dimethylcyclohexylamine in carbon tetrachloride at room temperature dibenzyl anilinophosphonate is formed in moderate yield. Reaction with carbon tetrachloride in presence of bases is not peculiar to dibenzyl phosphite although it occurs more readily with this ester than with others we have examined; it has also been observed with diethyl and di-*isopropyl* phosphites and is probably a general reaction. It does not occur, at any rate under the same conditions, with triethyl phosphite.

The most straightforward explanation of these facts is given by the assumption that reaction occurs in two stages. In the first of these carbon tetrachloride reacts with the phosphite in presence of a base to give a trichloromethylphosphonate; in the second stage the trichloromethylphosphonate reacts with a molecule of primary or secondary amine yielding chloroform and an amino- or substituted amino-phosphonate. The two stages can be expressed in general terms by the following equations:



where B = base, R = benzyl or alkyl, and R', R'' = hydrogen or organic radicals.

The structure of the dialkyl phosphites is not known with certainty, but we believe that most of the reactions of dibenzyl phosphite, which is insoluble in alkali, are best explained on the basis of the phosphonate structure used in Equation 1, and that it is in the phosphonate form that it and other phosphites react with carbon tetrachloride. It is of interest that dibenzyl phosphite in which the phosphonate character is most marked reacts more easily than diethyl phosphite which can, with difficulty, form a sodium salt. Formulation of the carbon tetrachloride reaction on the basis of the phosphonate structure also emphasises the difference between it and the production of alkylphosphonic esters from triaryl (Michaelis and Kähne, *Ber.*, 1898, **31**, 1050) or trialkyl phosphites (Arbusow, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687; *C.*, 1906, **II**, 1640) and alkyl halides, which generally requires the use of elevated temperatures and proceeds by intermediate formation of phosphonium halides. The mechanism proposed here seems very much more likely than one involving intermediate formation of a chlorophosphonate, and the first stage is analogous to other reactions of carbon tetrachloride (*e.g.*, Reimer-Tiemann reaction) in which a positive centre is attacked with expulsion of a proton. The second stage would be expected by analogy with the behaviour of other compounds containing trichloromethyl groups, *e.g.*, trichloromethyl ketones. Thus ω -trichloroacetophenone benzoylates alcohols in presence of sodium alkoxides, potassium and magnesium hydroxides, or potassium acetate (Houben and Fischer, *Ber.*, 1931, **64**, 240, 2636) and chloral was introduced as a formylating agent for amines by Hofmann (*Ber.*, 1872, **5**, 247). For purposes of comparison with the phosphite reaction we have examined the behaviour of ω -trichloroacetophenone as an acylating agent. This substance reacts readily with ammonia to give benzamide and with strong primary and secondary amines to give substituted benzamides; with aniline only traces of benzanilide are formed even on long standing. ω -Trichloroacetophenone does not react with methanol alone, but in presence of a tertiary base reaction occurs on refluxing and methyl benzoate is produced in good yield. Reaction with an alcohol in presence of a tertiary base to give an ester could not be realised in the case of dibenzyl phosphite and carbon tetrachloride although this may have been due to decomposition of the trichloromethylphosphonate in other directions on heating the mixture so that any ester formed could not readily be isolated. In any case, the fact that no ester was isolated when the reaction was carried out at room temperature is a strong argument against the formation of dibenzyl chlorophosphonate as an intermediate in the reaction since this compound reacts readily with alcohols in presence of tertiary bases (Atherton, Openshaw, and Todd, *loc. cit.*).

Various attempts have been made to isolate the trichloromethylphosphonates postulated as intermediates in the above scheme of reaction by reacting dibenzyl or di-*isopropyl* phosphite with carbon tetrachloride in presence of one molar proportion of *N*-methylmorpholine. These attempts have so far been unsuccessful. The product from dibenzyl phosphite in carbon tetrachloride solution decomposed when attempts were made to distil it; in acetonitrile solution a considerable amount of debenzylation occurred even at room temperature

and *N*-benzyl-*N*-methylmorpholinium chloride separated. With di-*isopropyl* phosphite the product also decomposed on attempted distillation and some di-*isopropyl* chlorophosphonate was isolated. These failures were not wholly unexpected since there was already evidence that the initial reaction product in such cases is unstable. If either of these phosphites be mixed with carbon tetrachloride and a tertiary base and treated at once with, e.g., cyclohexylamine, a fair yield of the corresponding cyclohexylaminophosphonate is obtained. Delay in adding the cyclohexylamine causes a progressive and rapid decrease in the yield and purity of the cyclohexylaminophosphonate.

In the cases so far described carbon tetrachloride was used but the reaction is not confined to this substance. In preliminary experiments it has been found that although chloroform and tetrachloroethane do not appear to react under comparable conditions, pentachloroethane and hexachloroethane react in the same way as carbon tetrachloride. The reaction is being further studied both to find out how generally it can be applied to polyhalogen compounds and to elucidate its mechanism more thoroughly. Meanwhile the main practical interest in the results so far obtained is that the reaction with carbon tetrachloride offers a convenient method for phosphorylating amines, since it proceeds under mild conditions and if dibenzyl phosphite is employed the benzyl residues can be removed from the product by hydrogenolysis.

EXPERIMENTAL.

I. *Reactions with Ammonia*.—*Dibenzyl aminophosphonate*. (1) When a stream of gaseous ammonia was passed through a solution of dibenzyl phosphite (2.6 g.) in dry carbon tetrachloride (50 c.c.) reaction set in rapidly and the mixture became warm. After 20 mins. the gas stream was stopped and the mixture heated to boiling and filtered, the residue being extracted with a further quantity of hot carbon tetrachloride. The combined filtrate and extract were concentrated to small volume, light petroleum added and the crystalline dibenzyl aminophosphonate which separated, washed with light petroleum and recrystallised from aqueous alcohol (yield, 92%). The product had m. p. 103–104°, undepressed by an authentic specimen. (2) A solution of dibenzyl phosphite (1.3 g.) in carbon tetrachloride (2 c.c.) was shaken with aqueous ammonia (5 c.c., *d* 0.880) for 10 minutes. The mixture was evaporated to dryness, water added and the water again removed *in vacuo*. The residue was washed with water (5 c.c.) and dried giving crude dibenzyl aminophosphonate (90%, m. p. 101°). (3) In order to obtain all the products with as little loss as possible dibenzyl phosphite (52.4 g., 1 mol.) was dissolved in xylene (500 c.c.) containing carbon tetrachloride (31 g., 1 mol.), the solution cooled in ice and gaseous ammonia passed slowly through it for 1 hour. The solid (A) which separated was filtered off and washed with xylene, the filtrate and washings being combined (B).

The solid (A) was extracted with boiling carbon tetrachloride (600 c.c.) and filtered hot. The extract, on cooling, deposited dibenzyl aminophosphonate and a further quantity was obtained by a second extraction of the solid. The product (41.5 g., 75%) had m. p. 102–103.5° undepressed by an authentic specimen (m. p. 103–104°). The fraction of solid (A) insoluble in carbon tetrachloride proved to be ammonium chloride (8 g., 75%) (Found: Cl, 66.1. Calc.: Cl, 66.4%). The xylene solution (B) was distilled through a 2 ft. Vigreux column, an initial fraction, b. p. 60–138° (30 c.c.) being collected. The fraction was washed with dilute hydrochloric acid to remove ammonia, dried over sodium sulphate and refractionated. The fraction (16.5 g.) boiling at 60–64°, was again redistilled giving ultimately chloroform (12 g., 50%), b. p. 61–61.5°.

The rather low yield of dibenzyl aminophosphonate in this experiment was due to incomplete reaction under the conditions employed. When the xylene solution left after the initial fractionation of (B) was evaporated under reduced pressure and the residual oil dissolved in carbon tetrachloride and shaken with concentrated aqueous ammonia a further quantity of dibenzyl aminophosphonate (8 g., 14% on original material) was obtained.

Di-isopropyl Aminophosphonate.—Gaseous ammonia was passed slowly through a water-cooled solution of di-*isopropyl* phosphite (83 g., 1 mol.) and carbon tetrachloride (77 g., 1 mol.) in xylene (250 c.c.) for 16 hrs. The ammonium chloride (24 g., 90%) which separated was collected, washed with xylene and dried (Found: Cl, 66.6. Calc.: Cl, 66.4%). The mother liquor was distilled up to 138° and the distillate after several refractionations yielded pure chloroform, b. p. 61–61.4° (39 g., 65%).

The residual xylene solution after removal of the chloroform was concentrated to small volume and ligroin added. Fine colourless needles (77.5 g., 86%) of di-*isopropyl aminophosphonate*, m. p. 56–57°, unchanged by recrystallisation, separated (Found: C, 40.0; H, 9.1; N, 8.0. $C_8H_{16}O_3NP$ requires C, 39.8; H, 8.8; N, 7.7%).

Diethyl Aminophosphonate.—Diethyl phosphite (1 mol.) and carbon tetrachloride (1 mol.) dissolved in xylene and treated with ammonia as above gave diethyl aminophosphonate (92%) as colourless deliquescent needles, m. p. 50–51°, from carbon tetrachloride-cyclohexane (Found: C, 31.0; H, 8.1; N, 9.3. $C_4H_{12}O_3NP$ requires C, 31.4; H, 7.9; N, 9.2%). Pistschimuka (*J. prakt. Chem.*, 1911, [2], 84, 753) described a substance, m. p. 146°, which he obtained by heating triethyl thiophosphate with ammonia as diethyl aminophosphonate but his claim was unsupported by analysis and would appear to be unjustified.

II. *Reaction with α -Phenylethylamine, Benzylamine, cycloHexylamine, and Morpholine*.—Method 1. A slight excess of the amine was added to a solution of dibenzyl phosphite in carbon tetrachloride at room temperature without external cooling and the mixture left overnight then washed with dilute acid and water. Evaporation of the carbon tetrachloride solution gave the crude product; yields, dibenzyl α -phenylethylaminophosphonate 90%, dibenzyl benzylaminophosphonate 95%, dibenzyl cyclohexylaminophosphonate 90%, identified in each case by m. p. and mixed m. p.

Method 2. A slight excess of the amine was added to a solution of dibenzyl phosphite in a mixture of carbon tetrachloride and alcohol and the mixture left overnight, evaporated and the residue washed with water and recrystallised; yields, dibenzyl α -phenylethylaminophosphonate 88%, dibenzyl benzylaminophosphonate 87%, dibenzyl cyclohexylaminophosphonate 79%.

Dibenzyl morpholinophosphonate, prepared by Method I, crystallised from warm cyclohexane in prisms (86%), m. p. 71–72° (Found: C, 62.1; H, 6.5; N, 4.2. $C_{18}H_{22}O_4NP$ requires C, 62.2; H, 6.3; N, 4.0%).

III. *Reaction with Aniline*.—Dibenzyl phosphite (2.62 g., 1 mol.) in carbon tetrachloride (3 c.c.) was added dropwise to a solution of aniline (0.93 g., 1 mol.) and *NN*-dimethylcyclohexylamine (1.27 g., 1 mol.) in carbon tetrachloride (20 c.c.). Heat was evolved and crystalline material separated rapidly. After 24 hours, water was added, the mixture shaken and the aqueous layer discarded. The carbon tetrachloride layer was washed with dilute acid then with sodium bicarbonate, dried and evaporated. Recrystallisation of the residue from hexane-ethylene chloride gave needles (62%) of dibenzyl anilinophosphonate (m. p. and mixed m. p. 91–92.5°).

IV. *ω -Trichloroacetophenone as an Acylating Agent*.— ω -Trichloroacetophenone (5.6 g., 1 mol.) was dissolved in hexane

(25 c.c.) and cyclohexylamine (2.23 g., 1 mol.) added. Heat was evolved and a crystalline precipitate formed immediately. After 30 minutes the mixture was filtered and the *N*-cyclohexylbenzamide (97%) washed with hexane. It had m. p. 148—149° (lit., m. p. 149°).

N-Benzybenzamide was prepared in 91% yield as above, using benzylamine.

N- α -Phenylethylbenzamide was also prepared in 94% yield, as above, using α -phenylethylamine.

N-Morpholinobenzamide. Morpholine reacted less vigorously than the above primary amines and the yield (87%) was slightly less.

Benzamide. On passing gaseous ammonia into a solution of ω -trichloroacetophenone in hexane, benzamide (92%) was formed very rapidly.

Methyl benzoate. A solution of ω -trichloroacetophenone (22.4 g.) and *N*-methylmorpholine (5 g.) in methanol (100 c.c.) was boiled for 5 hours, evaporated and the residue distilled. The main fraction gave on redistillation methyl benzoate (73%), b. p. 196—200°.

V. Reactions with Tertiary Bases.—*N*-Methylmorpholine required for the following experiments was conveniently prepared by adding paraformaldehyde (1 mol.) to morpholine (1 mol.) and allowing the mixture to stand 30 mins. By this time the paraformaldehyde had dissolved and formic acid (1 mol.) was added to the stirred liquid at a rate sufficient to maintain vigorous reaction. When all had been added the mixture was heated on the steam bath for 3 hours, cooled, made alkaline with potassium hydroxide and the base (80%, b. p. 116°) worked up in the usual manner.

Dibenzyl phosphite, carbon tetrachloride, and N-methylmorpholine. A mixture of *N*-methylmorpholine (3 c.c.) and carbon tetrachloride (2.5 c.c.) was added to a solution of dibenzyl phosphite (5.24 g.) in dry acetonitrile (15 c.c.) and allowed to stand for 1 hour. The separated solid was collected (1.75 g.), more *N*-methylmorpholine (2 c.c.) added to the solution and, after 24 hours, a second crop of solid (1.55 g.) was collected. Concentration of the solution gave a further amount (0.43 g.) of the same solid material. Recrystallisation of the combined solid fractions gave *N*-benzyl-*N*-methylmorpholinium chloride, m. p. 236° (decomp.) after shrinking at 230° (Found: Cl, 15.6. $C_{12}H_{18}ONCl$ requires Cl, 15.6%). The product was identical with that obtained by direct reaction of benzyl chloride with *N*-methylmorpholine.

Di-isopropyl phosphite, carbon tetrachloride, and N-methylmorpholine. On adding *N*-methylmorpholine (50.5 g., 1 mol.) to a solution of di-isopropyl phosphite (83 g., 1 mol.) in carbon tetrachloride (150 c.c.) no apparent reaction took place, but on heating under reflux a crystalline solid began to separate. After 3 hours the solvent was removed *in vacuo* (distillate contained chloroform), the residue stirred with light petroleum (200 c.c.) and the solid material collected, washed with light petroleum and dried. From its properties and analysis the solid (28 g.) appeared to be *N*-methylmorpholine hydrochloride (Found: Cl, 25.7. Calc. for C_3H_7ON, HCl : Cl, 25.8%). After separation of this hydrochloride the ligroin solution was evaporated on the water bath and the residue distilled under reduced pressure. The main fraction (70 g.) contained traces of solid and on filtration and re-distillation afforded a colourless liquid (58 g.), b. p. 49°/1 mm., which tended to explode on heating and whose chlorine content suggested that it was largely di-isopropyl chlorophosphate (Found: Cl, 16.9. Calc. for $C_6H_{14}O_3ClP$: Cl, 17.7%). On treating the product with aniline (2 mols.) it gave aniline hydrochloride and di-isopropyl anilinophosphate (m. p. and mixed m. p. 121°).

VI. Reactions Using Other Polyhalogen Compounds.—*Dibenzyl phosphite and pentachloroethane*. A solution of dibenzyl phosphite (1.3 g.) in pentachloroethane (5 c.c.) was shaken with aqueous ammonia (5 c.c., d 0.880). As no rapid reaction occurred pyridine (15 c.c.) was added to facilitate mixing. Heat was evolved and after 30 minutes the mixture was evaporated under reduced pressure and the residue washed with water. Recrystallisation gave dibenzyl aminophosphate (0.9 g., 66%).

Dibenzyl phosphite and hexachloroethane. Rapid reaction took place on mixing dibenzyl phosphite (1.3 g.), hexachloroethane (5 c.c.), pyridine (20 c.c.), and aqueous ammonia (5 c.c., d 0.880). After 30 minutes the mixture was worked up as above giving dibenzyl aminophosphate (1.25 g., 90%).

Di-isopropyl phosphite and pentachloroethane. Ammonia was passed in a slow stream through a water-cooled solution of di-isopropyl phosphite (83 g.) in pentachloroethane (260 g.) for several hours. Benzene (100 c.c.) was added to the pasty mixture and passage of ammonia continued (total time 15 hours). The separated solid (70.5 g.) was identified as ammonium chloride (Found: Cl, 66.6. Calc.: Cl, 66.4%). Distillation of the liquid gave, in addition to recovered solvent and unidentified material, tetrachloroethylene (b. p. 120—121°) and unchanged di-isopropyl phosphite (60 g.) The distillation residue on trituration with ligroin yielded di-isopropyl aminophosphate (16 g.), m. p. 56—57°. The rather unsatisfactory result in this case was not unexpected in view of the ease with which hydrogen chloride is eliminated from pentachloroethane.

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