415. *Studies on Phosphorylation. Part VI. The Reaction between Organic Bases and Esters of the Oxy-acids of Phosphorus. An Interpretation based on a Comparison of Certain Aspects of the Chemistry of Sulphur and Phosphorus.*

By V. M. Clark and A. R. Todd.

The monodebenzylation of neutral esters of phosphorous, phosphoric, and pyrophosphoric acids, containing one or more benzyl groups, by tertiary amines (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) has been extended to include all classes of amines. Debenzylation can also be brought about by base hydrochlorides. The influence of structure on the capacity of an amine to debenzylate such esters is discussed, and a general interpretation of the reactions involved is advanced based on a comparison with analogous reactions occurring among organic derivatives of the oxy-acids of sulphur.

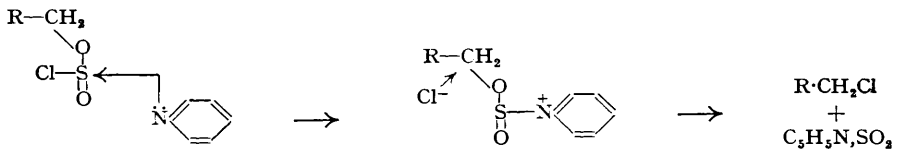
In Part V of this series (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) it was shown that neutral esters of phosphorous, phosphoric, and pyrophosphoric acids, containing one or more benzyl groups, can be selectively monodebenzylated by reaction with a tertiary amine. This reaction has since been studied in some detail and has been extended to include a variety of bases including primary and secondary amines. The results of this study, which covers both the influence of structure on the capacity of an amine to bring about this reaction and the debenzylating action of base hydrochloride are now reported. A comparison of the behaviour of certain derivatives of the oxy-acids of sulphur with that of the phosphorus compounds under discussion has led to a general interpretation of the debenzylation reaction. For convenience in presentation, it is desirable to consider at the outset some of the reactions of the sulphur compounds.

There are many examples of the selective removal of one alkyl group from an alkyl ester of an oxy-acid of sulphur resulting from the use of the ester to alkylate an amine, or from hydrolysis, *i.e.*, the alkylation of the water molecule or the hydroxyl ion. Such dealkylation can result from solvolysis or from a bimolecular nucleophilic displacement, though the latter is more frequent (McCleary and Hammett, *J. Amer. Chem. Soc.*, 1941, **63**, 2254; Morgan and Cretcher, *ibid.*, 1948, **70**, 375). In the displacement reaction, the attacking entity (*e.g.*, a nitrogenous base, an alkoxyl or hydroxyl ion) seeks an electron-deficient point in the sulphur-containing molecule, and in particular, for alkylation to occur, the alkyl group, and not the sulphur atom, must be the centre for this attack. It is convenient to discuss the behaviour of the various classes of sulphur compounds separately.

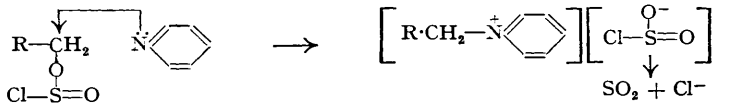
Quadrivalent Sulphur Compounds.—The dialkyl esters of sulphurous acid are very weak alkylating agents, being virtually unaffected by nitrogenous bases. Thus, Voss and Blanke (*Annalen*, 1931, **485**, 258) showed that aniline and pyridine were alkylated by dialkyl sulphites at room temperature only after several weeks, and even then the reaction was far from complete. By comparison, the alkyl chlorosulphinates (RO·SO·Cl), in which one of the alkoxyl groups of a dialkyl sulphite has been replaced by a chlorine atom, show greatly enhanced reactivity towards organic bases. The chlorine atom is a much more powerful electron-acceptor than the alkoxyl group it replaces and in consequence the central sulphur atom has an enhanced electrophilic character. Moreover, the inductive effect of the halogen atom is relayed to the α-carbon atom of the alkyl group, which thereby becomes a second centre for nucleophilic attack. This duality of positive centres in the chlorosulphinate molecule is implicit in the two mechanisms of decomposition which are observed in the presence of a tertiary base. Thus, Gerrard (*J.*, 1936, 688) observed that, on addition of pyridine to an alkyl chlorosulphinate in cold dry ether, a yellow oily mixture of 1-alkylpyridinium chloride and 1-alkylpyridinium chlorosulphinate separated in

quantity, leaving about 40% of alkyl chloride in the ethereal layer. To account for his observations, Gerrard put forward two mechanisms which are now represented thus:

Mechanism A



Mechanism B

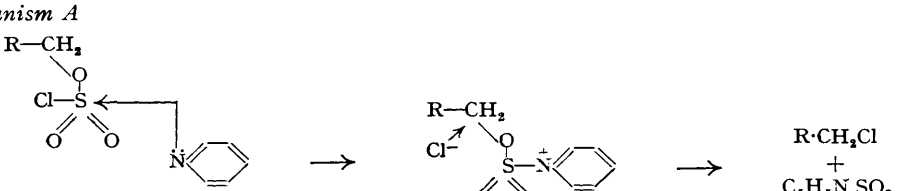


It should be noted that the above formulation of mechanism A represents the extreme case in which a chloride *ion* is actually liberated. The same products would be obtained were the attack of the chlorine atom on the alkyl group to be intramolecular and contemporaneous with the attack of the base on the sulphur atom. Mechanism A accounts for the formation of alkyl chloride and the liberation of sulphur dioxide, the base–SO_2 complex readily decomposing with continuous regeneration of the base. Such complexes have been isolated (Bateman, Hughes, and Ingold, *J.*, 1944, 243) and are known to decompose very readily into their components (Hoffman and Van der Werf, *J. Amer. Chem. Soc.*, 1946, **68**, 997; 1948, **70**, 262). This mechanism also receives support from the work of Kenyon, Lipscomb, and Phillips (*J.*, 1930, 415) on the replacement, by means of thionyl chloride, of the hydroxyl group in an optically active alcohol by a chlorine atom: in the absence of a tertiary base, optically active chlorosulphinates underwent decomposition to the chloride with retention of configuration, but, in the presence of a tertiary base, an intermediate was formed with liberation of chloride anions, these anions then taking up suitable positions for the production of the chloride with inversion of configuration. This is precisely what would be expected on the basis of mechanism A.

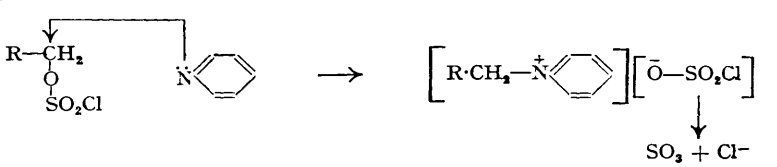
Mechanism B accounts for the isolation of the quaternary alkyl-pyridinium chloride, for it is inconceivable that this is formed by the addition of alkyl chloride to the base during the reaction. Combination of *iso*amyl chloride and pyridine in dry ether proceeds so slowly at room temperature that no deposit of salt occurs in three months, even when the solution is saturated with dry sulphur dioxide (Gerrard, *loc. cit.*).

Sexavalent Sulphur Compounds.—The alkyl chlorosulphonates would be expected to behave analogously to the alkyl chlorosulphinates, save that the sulphur atom, having an enhanced positive character relative to the α-carbon atom of the alkyl group, would be attacked in preference to, although not to the exclusion of, the alkyl group. Two reaction mechanisms are possible, *e.g.*, with pyridine:

Mechanism A



Mechanism B



In mechanism A, a base–SO_3 complex is formed, together with the alkyl chloride, whereas in mechanism B, the quaternary chlorosulphonate (or chloride) is formed. Both these mechanisms

have received experimental verification, for Willcox (*Amer. Chem. J.*, 1904, **32**, 446) obtained dimethylaniline–sulphur trioxide (in 83% yield), together with ethyl chloride, by treating ethyl chlorosulphonate with dimethylaniline in the cold (mechanism A) and also isolated a little of the quaternary dimethylethylanilinium chloride (mechanism B). Baumgarten (*Ber.*, 1926, **59**, 1166) obtained similar results using pyridine in place of dimethylaniline, and Binkley and Degering (*Proc. Indiana Acad. Sci.*, 1939, **49**, 117) found that they could obtain an alkyl halide and a base–SO_3 complex using dibutylamine; in the latter case, however, the complex, being in effect an amino-sulphonic acid, formed a salt with a further molecule of the secondary amine:

$$RO{\cdot}SO_2Cl + Bu_2NH \longrightarrow RCl + Bu_2NH,SO_3 \xrightarrow{Bu_2NH} [Bu_2NH_2^+][Bu_2N{\cdot}SO_3^-]$$

With respect to mechanism B, Traube (*Z. angew. Chem.*, 1925, **38**, 441) found that he could alkylate aniline using ethyl chlorosulphonate, and Delépine and Demars (*Bull. sci. pharmacol.*, 1923, **30**, 577) showed that methyl chlorosulphonate alkylated dimethylamine at 0°.

Effect of the Variation of R *on the Interaction of Bases with* RO·SO·Cl and RO·SO_2·R′.—When R is an aryl group, the carbon atom carrying the chlorosulphinate residue is no longer a centre for nucleophilic attack. The electrophilic character of the sulphur atom is also reduced. Thus, although the alkyl chlorosulphinates are decomposed by tertiary amines at room temperature, phenyl chlorosulphinate does not react with pyridine or quinoline below 120° (Gerrard, *J.*, 1940, 218). However, when R is aralkyl the chlorosulphinates are much less stable since the α-carbon atom of, *e.g.*, the benzyl group is predisposed to nucleophilic attack (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627); benzyl chlorosulphinate decomposes at room temperature (Carré and Libermann, *Compt. rend.*, 1933, **196**, 1419).

In the light of the above evidence, the aryl esters of sulphonic acids would be expected to be very poor arylating agents, as indeed they are, the phenyl ester of toluene-*p*-sulphonic acid being unaffected by alcoholic ammonia at 190° (Freudenberg and Hess, *Annalen*, 1926, **448**, 121), whereas the corresponding methyl ester reacts in the cold (Autenreith and Bernheim, *Ber.*, 1904, **37**, 3800). However, by substituting the aryl nucleus with nitro-groups in the 2- and the 4-position, the carbon atom carrying the sulphonate residue becomes a centre for nucleophilic attack, and esters of this type are arylating agents (Ullmann and Nádai, *Ber.*, 1908, **41**, 1870). By increasing the nucleophilic character of the attacking reagent, it should be possible to cleave an aryl ester of a sulphonic acid without resorting to substitution with nitro-groups. In this case, the sulphur atom may be attacked in preference to the α-carbon atom, and Turner and his co-workers (*J.*, 1930, 928, 1853) showed that piperidine cleaved sulphonic esters with sulphonation rather than alkylation of the base:

$$Ar{\cdot}SO_2{\cdot}OR + C_5H_{10}NH \longrightarrow R{\cdot}OH + Ar{\cdot}SO_2{\cdot}N\langle\bigcirc\rangle$$

There is the interesting possibility of a mechanistic transition point inherent in these observations and, indeed, Bell (*J.*, 1931, 609) has reported that, whereas *o*-nitrophenyl toluene-*p*-sulphonate is cleaved by piperidine with acyl–oxygen fission, the corresponding 2 : 4-dinitrophenyl ester undergoes alkyl–oxygen fission (*cf.* Ullmann and Nádai, *loc. cit.*).

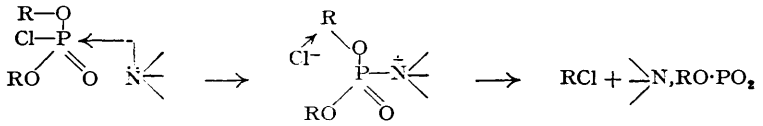
Phosphorus Compounds.—The decomposition of phosphorus compounds in the presence of bases has been examined in the light of the conclusions reached above regarding the behaviour of certain derivatives of the oxy-acids of sulphur. In Part V of this series (*loc. cit.*) we recorded experiments on the selective debenzylation of neutral esters of certain of the oxy-acids of phosphorus carried out in consequence of the observation of Atherton, Howard, and Todd (*J.*, 1948, 1106) that dibenzyl chlorophosphonate underwent rapid and complete decomposition with 4-methylmorpholine, leading to the formation of 4-benzyl-4-methylmorpholinium chloride, and, presumably, benzyl metaphosphate:

$$R_3N + (Ph{\cdot}CH_2{\cdot}O)_2POCl \longrightarrow [R_3N{\cdot}CH_2{\cdot}Ph]^+[Cl]^- + Ph{\cdot}CH_2{\cdot}O{\cdot}PO_2$$

On the other hand, Gerrard (*J.*, 1940, 1464), investigating the decomposition of alkyl chlorophosphonates and related compounds in the presence of tertiary bases, had obtained considerable yields of alkyl chloride. By analogy with the sulphur compounds, there are two mechanisms to be considered. The attacking nucleophilic reagent (the base) seeks an electrophilic centre which can be located either on the central phosphorus atom or on the α-carbon atom of one of the attached groups. If the phosphorus atom is the centre for the initial attack, then we have a

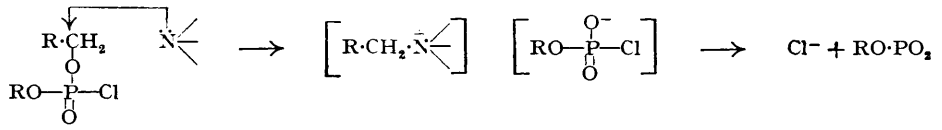
mechanism designated as type A, which results, in the case of a chlorophosphonate, in the formation of alkyl chloride and a base–metaphosphate complex (cf. Langheld, *Ber.*, 1911, **44**, 2076) :

Type A



If, however, the α-carbon atom of an attached group is the centre for the initial attack, then we get a mechanism designated as type B, which results in the formation of a quaternary halide, the base becoming alkylated :

Type B



This distinction leads to the conclusion that alkylation by a phosphorus compound is to be attributed more to the nature of the alkyl group than to the valency state of the phosphorus atom. Thus, as reported in Part V of this series (*loc. cit.*), trialkyl and triaryl phosphates are virtually unaffected by tertiary bases but, in particular, tribenzyl phosphate is affected, since the benzyl group is very susceptible to nucleophilic attack (*cf.* Hughes, *loc. cit.*; Baker, *Trans. Faraday Soc.*, 1941, **37**, 632).

If the electrophilic character of the phosphorus atom is increased by the replacement of one alkoxyl group of a trialkyl phosphate by a chlorine atom, the alkylating properties of the molecule are not enhanced; instead, we facilitate mechanism A relative to mechanism B, *i.e.*, increase the possibility of decomposition to alkyl chloride. The further replacement of a second alkoxyl group by a chlorine atom results in mechanism A being even more prominent and more rapid. Thus butyl dichlorophosphonite, $BuO{\cdot}POCl_2$, reacts with pyridine at 0° to give 31% of butyl chloride, whereas dibutyl chlorophosphonate, $(BuO)_2POCl$ only reacts with pyridine on heating (Gerrard, *loc. cit.*), and tributyl phosphate is unaffected when refluxed with a tertiary base.

We do not wish to imply that structural factors influencing mechanisms of type A are completely independent of those influencing mechanisms of type B. They are not, for an increase in the electrophilic character of the phosphorus atom does produce an increase in the electrophilic character of the α-carbon atoms of the attached alkoxyl groups—through induction; but the resultant enhancement of mechanism A usually outweighs any facilitation of mechanism B.

In Part V of this series, the results of the variation of substrate in the base/substrate ester reaction were recorded and it was noted that the esters of aminophosphonic acid were virtually unaffected under the normal reaction conditions and could be recovered in high yield. Presumably the nitrogen atom in, say, dibenzyl aminophosphonate, by accession of electrons from its lone pair, depresses the electrophilic reactivity not only of the central phosphorus atom but also of the benzyl groups, so that debenzylation of an aminophosphonate under the usual conditions of reaction would only be possible if the tendency of the nitrogen atom to donate electrons to the phosphorus atom were reduced.

The removal of only one benzyl group from tribenzyl phosphate by reaction with a tertiary base is almost certainly related to the relative unreactivity of the aminophosphonates, the integral negative charge of the anion produced on monodebenzylation reducing the overall electrophilic character of the molecule and thereby inhibiting further reaction.

Atherton, Howard, and Todd (*loc. cit.*) investigated the stability of dibenzyl chlorophosphonate in the presence of various bases, estimating the unchanged material after a specified time by passing ammonia into the mixture and isolating the dibenzyl aminophosphonate produced. It was noted that the heterocyclic bases substituted in the 2-position were markedly better than pyridine for purposes of phosphorylation using dibenzyl chlorophosphonate. The present investigation has shown that the capacity of heterocyclic bases to cause debenzylation is markedly impaired by substitution in the α-positions to the heterocyclic nitrogen. Thus, in a series of experiments using tribenzyl phosphate as substrate and carrying out the reactions under standard conditions (2 hours at 100°) the following results were obtained :

Base.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
4-Methylmorpholine	65	10
Morpholine	50	10
Pyridine	62	2
Quinoline	63	22
2-Picoline	20	56
2 : 6-Lutidine	8	73
Quinaldine	5	83

When the temperature of reaction was raised to 115—116°, the yield of monodebenzylated material afforded by 4-methylmorpholine rose to 87%, whereas the yield afforded by pyridine remained virtually constant at 61—62%. The marked difference in behaviour between pyridine and quinoline and their 2-substituted homologues cannot be attributed to any difference in basic strength in the generally accepted sense, *i.e.*, basic strength determined with respect to hydrogen ion, for with this as the reference acid, 2 : 6-lutidine ($K_b = 1 \times 10^{-7}$) is a stronger base than pyridine ($K_b = 2{\cdot}3 \times 10^{-9}$), yet its power to debenzylate tribenzyl phosphate is very much less. This contrast in the behaviour of pyridine and 2 : 6-lutidine parallels that observed by Brown, Schlesinger, and Cardon (*J. Amer. Chem. Soc.*, 1942, **64**, 325), who showed that, although 2 : 6-lutidine is a stronger base than pyridine when competing for hydrogen chloride, it is displaced by pyridine from its boron trifluoride adduct. Moreover, whereas pyridine forms an adduct with trimethylboron, 2 : 6-lutidine fails to do so even at temperatures as low as −80°. In the same way, 2-picoline, a stronger base than 4-picoline, is nevertheless much less effective as a debenzylating agent. This is in keeping with the lower stability of its trimethylboron adduct (Brown and Barbaras, *ibid.*, 1947, **69**, 1137). The American workers attribute their results to a steric effect (*cf.* also Van der Werf, Davidson, and Michaelis, *ibid.*, 1948, **70**, 908) and we consider that the same factors operate in the debenzylation reaction, *i.e.*, that the reluctance of the *ortho*-substituted pyridines and quinolines to participate is mainly due to steric strain in the transition complex.

It is of interest to compare the relative efficacies of aniline and its *N*-methyl derivatives as debenzylating agents. There is little difference between the basic strengths of aniline, methylaniline and dimethylaniline, but whereas the product of the reaction of tribenzyl phosphate with the tertiary amine is a quaternary salt the products formed in the cases of aniline and methylaniline are salts of weak bases with a strong acid, *i.e.*, as the reaction progresses in aniline or methylaniline solution, hydrogen ions may be formed and may facilitate solvolysis of the phosphate ester. Such an explanation would account for the anomalous behaviour of dimethylaniline, for, whereas tribenzyl phosphate is debenzylated to give dibenzyl hydrogen phosphate in high yield in aniline or methylaniline solution (after 2 hours at 100° the yields are 79% and 75% respectively), in dimethylaniline solution after the same length of time at 100°, 65% of the starting material can be recovered unchanged.

All our experimental observations are, of course, qualitative; detailed conclusions about subtleties in the reaction mechanism cannot be drawn since all reactions were carried out using the basic component as solvent. Moreover, the isolation of product and recovery of starting material are procedures which do not lend themselves easily to exact analysis. Again, side reactions may creep in and obscure certain details. For example, in pyridine solution, the yield of dibenzyl hydrogen phosphate from tribenzyl phosphate after 15 minutes at 100° is 55%, after 1 hour 85%, and after 2 hours only 62%. This must mean that dibenzyl hydrogen phosphate is itself affected by base, and indeed, when this acid is refluxed in pyridine solution for 6 hours, only 44% of the acid is recoverable unchanged, at least 22% of the original phosphorus being isolated as inorganic phosphate. Similarly, if dibenzyl hydrogen phosphate is heated for 2 hours at 100° in dimethylaniline, only 70% is recoverable unchanged and, if the period of heating is extended to 6 hours, the recovery drops to 58%. This debenzylation of dibenzyl hydrogen phosphate in tertiary base solution is probably due to factors similar to those which operate in the reaction between tribenzyl phosphate and aniline or methylaniline. Despite their qualitative nature, however, our results do give a general picture of the main reactions involved since, although the differences observed in the behaviour of various bases may really only be differences in degree, they are so large as to be tantamount in practice to differences in kind. From a practical standpoint it would appear that, although amines of all types may be used, the tertiary aliphatic amines give the highest yields in monodebenzylation reactions. Moreover, in phosphorylation reactions using dibenzyl chlorophosphonate, decomposition of the reagent by the base is reduced to a minimum if 2 : 6-lutidine is employed.

In the course of the investigations described in this series of papers, reference has been made

on occasion to the possibility of debenzylation by the action of a base hydrochloride; in particular, it has been suggested that the extensive decomposition of dibenzyl chlorophosphonate during certain phosphorylation reactions carried out with pyridine or 2 : 6-lutidine as solvent was in part attributable to the base hydrochloride produced in the course of the reaction.

In the decomposition of chlorophosphonates we should, as mentioned above, expect a mechanism of type A to play a more important part than it does in the decomposition of triaralkyl phosphates. Moreover, the attacking chloride anion in the postulated second stage of mechanism A need not arise from within the molecule undergoing decomposition—it could be introduced from an external source.

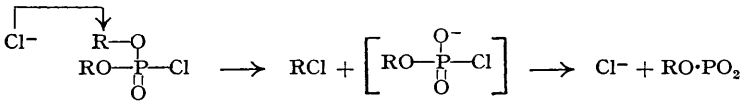
On examining the action of pyridine and 2 : 6-lutidine on tribenzyl phosphate in the absence and presence of their respective hydrochlorides it was found that the yield of monodebenzylated material was markedly increased by the introduction of 2 : 6-lutidine hydrochloride into the 2 : 6-lutidine reaction mixture. Thus, with a reaction time of 2 hours at 100° the following results were obtained :

Debenzylating agent.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
Pyridine	62	2
Pyridine + its hydrochloride	61	4
2 : 6-Lutidine	5	75
2 : 6-Lutidine + its hydrochloride	31	46

Similar experiments in which the phosphate was heated in ethoxyethanol solution with base hydrochloride alone gave the following results :

Debenzylating agent.	Yield (%) of dibenzyl hydrogen phosphate.	Recovery (%) of tribenzyl phosphate.
Pyridine hydrochloride	52	32
2 : 6-Lutidine hydrochloride	55	28

These results show quite definitely that debenzylation occurs, not only as a result of attack by a nitrogenous base, but also by the attack of chloride ion, and this being so it is apparent that the decomposition of chlorophosphonate, according to a mechanism of type A, is catalysed by traces of base hydrochloride. Thus,



On the basis of the above considerations, it is clearly advantageous to work up phosphorylation reactions using dibenzyl chlorophosphonate as soon as possible.

The preparation of dibenzyl hydrogen phosphate (Atherton, Howard, and Todd, *loc. cit.*) has been re-examined in the light of our present knowledge, and a new and more convenient method has been devised for its preparation in bulk by adaptation of the phosphorylation method using dibenzyl phosphite in carbon tetrachloride solution in presence of a tertiary base (Atherton and Todd, *J.*, 1947, 674). In this adaptation the substance to be phosphorylated is replaced by the water molecule, and the tertiary amine by sodium hydroxide; the virtual insolubility of sodium dibenzyl phosphate in excess of sodium hydroxide solution greatly facilitates isolation of the product.

It is of interest that the system dibenzyl phosphite–carbon tetrachloride–aqueous caustic alkali can give either tetrabenzyl pyrophosphate (when N-potassium hydroxide is used) or sodium dibenzyl phosphate (when 10N-sodium hydroxide is used).

Experimental.

Action of Various Bases on Tribenzyl Phosphate (Experiments at 100° for 2 Hours).—All the bases were freshly distilled over solid potassium hydroxide, and in each experiment 1 g. of tribenzyl phosphate and 10 c.c. of anhydrous base were employed. All reaction mixtures were worked up in the same manner. A typical example follows :

A solution of tribenzyl phosphate (1 g.) in freshly distilled 4-methylmorpholine (10 c.c.) was heated at 100° for 2 hours. Excess of base was removed under reduced pressure and the residual gum shaken with a mixture of aqueous sodium hydroxide (20 c.c. of 5%) and ether (30 c.c.). The alkaline aqueous layer was separated, washed with a further quantity of ether (30 c.c.), acidified with sulphuric acid (20 c.c. of 3N.), and rapidly extracted with chloroform (2 × 75 c.c.). (The acidification always produces an opalescence if debenzylation has proceeded to any considerable extent.) The chloroform extracts were combined, washed twice with water, dried (Na_2SO_4), and evaporated under reduced pressure. The

residual oil crystallised on addition of ether; the product (0·49 g., 65%) had m. p. 77°, undepressed on admixture with an authentic specimen of dibenzyl hydrogen phosphate (m. p. 78°).

The ethereal extract and washings of the original alkaline solution were combined, washed with hydrochloric acid (2 × 20 c.c. of 3N.), then with water (2 × 25 c.c.), and dried (Na_2SO_4). Evaporation gave a colourless oil (0·103 g.) which when rubbed set to a mass of crystals, m. p. 61°, undepressed on admixture with an authentic specimen of tribenzyl phosphate (m. p. 63—64°); hence recovery of starting material = 10%.

From a series of experiments similar to that outlined above but using morpholine, pyridine, 2-picoline, 2 : 6-lutidine, quinoline, and quinaldine as the base the results quoted in the Introduction were obtained. It is of interest to note that, if 10% sodium hydroxide solution is used in place of the 5% solution indicated in the isolation procedure, three layers are formed and sodium dibenzyl phosphate may crystallise out and so interfere with the separation and the determination of the yield.

Three experiments were carried out at the boiling points of the bases concerned, *viz.*, with 4-methylmorpholine (116°), pyridine (115°), and with triethylamine (89°). The yields of dibenzyl hydrogen phosphate were 87%, 61%, and 26% respectively. In the experiment using triethylamine, recovery of crystalline tribenzyl phosphate amounted to 58%.

Several experiments were carried out in pyridine solution to determine the speed of debenzylation at 100°. After a pyridine solution of tribenzyl phosphate had been heated at 100° for 15 minutes, the yield of dibenzyl hydrogen phosphate amounted to 55%, together with a recovery of 39% of tribenzyl phosphate. After 1 hour at 100°, the yield was 85% and the recovery 4%, and after 2 hours at 100° the yield was 62%, the recovery being 2%.

Comparison of 2- and 4-Picoline in Their Reaction with Tribenzyl Phosphate.—These reactions were carried out by using 1 g. of the substrate in 10 c.c. of the anhydrous base. Heating was at 100° for 1 hour and the reaction mixture worked up as described above. In the case of 2-picoline, the yield of dibenzyl hydrogen phosphate was 9% and the recovery of unchanged tribenzyl phosphate 72%. The corresponding figures for 4-picoline were 74% and 15%.

Reactions with Aniline and Its Methyl Derivatives.—These reactions were carried out at 100° for 2 hours and the reaction mixtures worked up as before. With aniline a 79% yield of crystalline dibenzyl hydrogen phosphate was obtained, and with methylaniline a 75% yield. In each case the amount of tribenzyl phosphate recovered was negligible. With dimethylaniline the debenzylated product was obtained in 15% yield only and did not crystallise, whereas 65% of the starting material was recovered crystalline.

Action of Bases on Dibenzyl Hydrogen Phosphate.—(a) *Pyridine.* Dibenzyl hydrogen phosphate (10 g.) was dissolved in anhydrous pyridine (75 c.c.), and the solution refluxed for 6 hours, moisture being excluded throughout. Excess of pyridine was removed under reduced pressure in a stream of dry air, and the residual oil was dissolved in water (30 c.c.). The solution was acidified with sulphuric acid (30 c.c. of 3N.) and extracted with chloroform (3 × 50 c.c.). The chloroform extract was washed twice with water, dried (Na_2SO_4), and evaporated at atmospheric pressure to leave a colourless oil which solidified when seeded with dibenzyl hydrogen phosphate (4·41 g., 44% recovery).

The aqueous acidic residue remaining after chloroform extraction was neutralised with excess of barium carbonate and left overnight. The solid was filtered off and then boiled with excess of dilute sulphuric acid for 30 minutes. The acid solution so obtained was freed from barium sulphate, and the total inorganic phosphate in the filtrate determined as phosphomolybdate. The weight of phosphorus so determined was 245 mg., *i.e.*, at least 22% of the phosphorus originally present in the dibenzyl hydrogen phosphate was liberated as inorganic phosphate.

(b) *Dimethylaniline.* Dibenzyl hydrogen phosphate (4·0 g.) was dissolved in freshly distilled dimethylaniline (30 c.c.), and the solution divided into two equal portions. One was worked up immediately to provide a check on the procedure, while the other was heated at 100° for 2 hours before being worked up by the following method.

The reaction mixture was diluted with ether (50 c.c.) and the whole extracted with aqueous sodium hydroxide (2 × 30 c.c. of 5%). The alkaline extracts were combined and acidified with sulphuric acid (40 c.c. of 3N.). The opalescent acid solution was now extracted with chloroform (3 × 100 c.c.), and the chloroform extract washed with water, dried (Na_2SO_4), and evaporated yielding dibenzyl hydrogen phosphate. Recovery in the case where isolation of the acid was carried out immediately after dissolution in the base was 1·924 g. (96%). This was converted into its *cyclo*hexylamine salt (Part V of this series, *loc. cit.*) which was obtained in a yield of 90% based on the weight of acid originally dissolved in the base.

In the case where the dimethylaniline solution of dibenzyl hydrogen phosphate had been heated to 100° for 2 hours, the recovery (as *cyclo*hexylamine salt) was 1·905 g. (70%). Extension of the period of heating to 6 hours caused the amount of material recovered to fall to 58%.

Effect of Pyridine Hydrochloride on the Reaction between Pyridine and Tribenzyl Phosphate.—Tribenzyl phosphate (1 g., 1 mol.) and freshly prepared pyridine hydrochloride (315 mg., 1 mol.), dissolved in freshly distilled pyridine (10 c.c.), were heated at 100° for 2 hours. The base was then removed under reduced pressure and the residue worked up as described above for the reaction of tribenzyl phosphate with 4-methylmorpholine. The yield of dibenzyl hydrogen phosphate was 0·46 g. (61%). The neutral fraction, usually tribenzyl phosphate, was an oil smelling of benzyl chloride. This oil was repeatedly evaporated with water until no longer lachrymatory. The residue weighed 40 mg. (4%).

Effect of 2 : 6-Lutidine Hydrochloride on the Reaction between 2 : 6-Lutidine and Tribenzyl Phosphate.—2 : 6-Lutidine hydrochloride is sparingly soluble in 2 : 6-lutidine, but is soluble in hot ethoxyethanol.

Ethoxyethanol was therefore used as diluent and solvent. A blank experiment using tribenzyl phosphate (1 g.) in a mixture of ethoxyethanol (10 c.c.) and 2 : 6-lutidine (10 c.c.) showed that the ethoxyethanol had no apparent effect on the base–phosphate ester reaction.

Tribenzyl phosphate (1 g., 1 mol.) and 2 : 6-lutidine hydrochloride (390 mg., 1 mol.), dissolved in a mixture of 2 : 6-lutidine (10 c.c.) and ethoxyethanol (10 c.c.), were heated at 100° for 2 hours. Excess of base and of diluent was then removed under reduced pressure, and the residue worked up in the usual manner. The yield of dibenzyl hydrogen phosphate obtained was 0·23 g. (31%). The recovered material, an oil, was a potent lachrymator, but, on its evaporation with water, the lachrymatory material (benzyl chloride) was removed and the residue then crystallised (0·46 g., 46%), having m. p. 61°, undepressed on admixture with an authentic specimen of tribenzyl phosphate.

Action of Base Hydrochlorides on Tribenzyl Phosphate.—(a) *Pyridine hydrochloride.* Pyridine hydrochloride (530 mg., 1 mol.) and tribenzyl phosphate (1·70 g., 1 mol.), dissolved in ethoxyethanol (25 c.c.), were heated at 100° for 2 hours, moisture being excluded by a silica-gel tube. The resulting solution was worked up in the usual manner, yielding dibenzyl hydrogen phosphate (0·67 g., 52%); tribenzyl phosphate (0·54 g., 32%) was recovered.

(b) 2 : 6-*Lutidine hydrochloride.* With 2 : 6-lutidine hydrochloride in place of pyridine hydrochloride in the above experiment, the yield of dibenzyl hydrogen phosphate was 55% and the recovery of tribenzyl phosphate 28%.

Sodium Dibenzyl Phosphate.—Crude dibenzyl phosphite (52 g., purity 71%) was dissolved in carbon tetrachloride (250 c.c.) and the solution cooled in ice. A solution of sodium hydroxide (80 g.) in water (160 c.c.) was added slowly with vigorous stirring during 30 minutes. Heat was evolved and a copious white precipitate of sodium dibenzyl phosphate formed almost immediately. Stirring was continued for 5 hours at room temperature and the reaction was then completed by refluxing the mixture on the water-bath with stirring for 2 hours to convert any tetrabenzyl pyrophosphate present into sodium dibenzyl phosphate. The mixture was cooled and the crude sodium salt collected. The salt was washed with carbon tetrachloride, then with dilute sodium hydroxide solution, and finally dried at room temperature *in vacuo* over phosphoric oxide. The salt so obtained was the stable *tetrahydrate* (46·5 g., 88%) (Found: C, 44·9; H, 5·7; loss at 140°/0·2 mm., 19·5. $C_{14}H_{14}O_4PNa,4H_2O$ requires C, 45·1; H, 5·9; H_2O, 19·3%). It can be recrystallised from chloroform from which it separates as colourless plates, m. p. 63°, resolidifying between 70° and 80° as a monohydrate. The tetrahydrate shows an interesting behaviour with ethyl acetate. It is immediately soluble in the cold ester but is rapidly redeposited, the product now melting at 295° (decomp.); presumably the salt is dehydrated by the solvent.

Conversion of Crude Sodium Dibenzyl Phosphate into Silver Dibenzyl Phosphate.—The crude sodium salt (100 g.) was dissolved in water (1750 c.c.) with gentle heating. The solution was cooled and brought to neutrality by the addition of dilute nitric acid (phenolphthalein). To this solution was added, slowly with stirring, a solution of silver nitrate (63·0 g.) in water (600 c.c.), the system being protected from light as much as possible. White crystals of silver dibenzyl phosphate separated immediately. After the addition was complete, the product was filtered off, washed well with distilled water, and dried *in vacuo* over phosphoric oxide. The yield was 85 g.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance, to Gonville and Caius College for the award of the Dunlop Studentship, and to the University of Cambridge for the award of the W. A. Meek Scholarship (to V. M. C.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 1st,* 1950.]