682. *Studies on Phosphorylation. Part XIV.* The Solvolysis by Phenols of Benzyl Phosphates.*

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The reaction between phenol and benzyl diphenyl phosphate leading to a mixture of *o*- and *p*-benzylphenol and diphenyl hydrogen phosphate has been studied; it is accelerated by the addition of acids. The similar reactions of dibenzyl phenyl phosphate and of tribenzyl phosphate are slower, whereas that of tetrabenzyl pyrophosphate is much faster. The process provides a useful method for the removal of benzyl protecting groups.

THE synthesis of numerous phosphates and polyphosphates has been achieved in this laboratory by use of benzylated intermediates (cf. the cognate series " Nucleotides " [1]). One reason for the selection of the benzyl group as a protection for phosphoric hydroxyl groups is the versatility of its reactions. Three main methods have been available hitherto for breaking the benzyl–oxygen link, namely, hydrogenolysis,[2] acidic hydrolysis,[3] and nucleophilic displacement.[4] A fourth method was discovered by Dr. A. S. Curry [5] during a repetition of the synthesis of adenosine-5′ triphosphate described by Baddiley, Michelson, and Todd.[6] Paper chromatography of the intermediates revealed that they had suffered

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* Part XIII, *J.*, 1956, 1231.

[1] Brown, Todd, and Varadarajan, *J.*, 1956, 2388; and preceding papers.

[2] Zervas, *Naturwiss.*, 1939, **27**, 317; Atherton, Openshaw, and Todd, *J.*, 1945, 382.

[3] Baddiley and Todd, *J.*, 1947, 648; Elmore and Todd, *J.*, 1952, 3681.

[4] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815; Clark and Todd, *J.*, 1950, 2023, 2031.

[5] Curry, Thesis, Cambridge, 1952.

[6] Baddiley, Michelson, and Todd, *J.*, 1949, 582.

extensive debenzylation and Dr. Curry's preliminary experiments, for information about which we are indebted to him, showed that this was caused by the phenolic solvents used. This paper records a study of the reaction as a preliminary to its use in synthesis. Some applications of the results have already been published.[7]

The products of reaction between benzyl diphenyl phosphate and phenol at 51° were diphenyl hydrogen phosphate, a little benzyl phenyl ether, and a mixture of *p*- and *o*-benzylphenol (ratio 1·22 : 1). As the ether proved to be stable under the reaction conditions, the principal course of reaction was clearly :

$$\mathrm{HOPh} + (\mathrm{CH_2Ph{\cdot}O})\mathrm{PO(OPh)_2} \longrightarrow \mathrm{HO{\cdot}C_6H_4{\cdot}CH_2Ph} + \mathrm{HO{\cdot}PO(OPh)_2}$$

The progress of this solvolysis could be followed by titration with aqueous sodium hydroxide and methyl-orange in presence of carbon tetrachloride, since diphenyl hydrogen phosphate was found to remain unesterified in phenol during four days at 51°. The amount of change in a given time was almost independent of the initial concentration of benzyl ester, as required by first-order kinetics. Autocatalysis was, however, apparent from the moderate acceleration caused by the addition of diphenyl phosphate. Toluene-*p*-sulphonic acid was, of course, a much more efficient catalyst, and convenient rates were obtained by using it at 20° in *m*-cresol instead of at 51° in phenol. Under these conditions, when the autocatalysis was masked, the velocity of reaction was proportional to the concentrations of benzyl ester and of added acid. Hydrogen chloride was also an effective catalyst with a constant about twice that of toluene-*p*-sulphonic acid. The ratio of *p*- to *o*-benzylphenol was lower (0·83 : 1) when the reaction in phenol at 51° was catalysed by toluene-*p*-sulphonic acid than when it was uncatalysed. On the other hand, the solvolysis of benzyl bromide by phenol at 51°, whether in the presence of added acid or not, gave much more of the *p*-isomer (ratios 2·50 : 1, 2·59 : 1, respectively). A closer analogy with the diphenyl phosphate reaction is provided by the work of Földi,[8] who isolated 25% of *p*- and 30% of *o*-benzylphenol from the solvolysis of benzyl benzenesulphonate in phenol at 150°; traces of benzyl phenyl ether were produced in this reaction also.

The rôle of the phenol is complicated since it acts both as hydroxylic solvent of the phosphate fragment and as acceptor of the benzyl group. The rate of reaction is approximately the same in *m*-methoxyphenol as in phenol, but is considerably less in the cresols and in *p*-chlorophenol. No reaction could be detected in anisole even when much acid was added. Anisole is doubtless much less efficient than phenol both as a solvent and as a nucleophilic reagent : its bromination in acetic acid is slower by two powers of ten.[9] Dr. Curry's observation [5] that the reaction is inhibited by relatively small quantities of methyl cyanide has been confirmed. Methanol has the same effect. The similar inhibition by dioxan of the reaction between phenol and *tert.*-butyl chloride has been attributed [10] to the formation of hydrogen-bond complexes and consequent removal of the phenol from the reaction; an alternative explanation in the present instance is competition between the diluent and the benzyl phosphate for the acid catalyst.

The results of our experiments, which were largely aimed at practical improvement of the technique of debenzylation, agree with the following, admittedly speculative, ideas about the mechanisms of the reactions. Solvolysis can proceed through a slow ionisation producing a benzyl cation, which is accepted by phenol mainly at its *para*-position. When acid has been liberated by solvolysis or acid has been deliberately added, the mesomeric cation (I) and perhaps the cation (II) can be formed and undergo bimolecular substitution at the *ortho*- and, to a smaller extent, the *para*-position of the phenol.

Dibenzyl phenyl phosphate is more similar than benzyl diphenyl phosphate to the benzylated intermediates normally encountered in synthetical work, and its solvolysis by phenol was therefore examined. Phenyl dihydrogen phosphate was isolated as its mono*cyclo*hexylammonium salt in good yield, but the reaction was considerably slower than in the earlier example (19·5% complete in 1 hr. instead of 41%); the solvolysis of tribenzyl

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[7] Christie, Kenner, and Todd, *J.*, 1954, 46; Kenner, Todd, Webb, and Weymouth, *ibid.*, p. 2288.

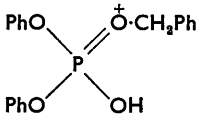
[8] Földi, *Ber.*, 1928, **61**, 1609.

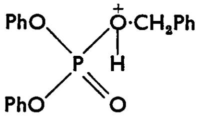
[9] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.

[10] Hart, Cassis, and Bordeaux, *J. Amer. Chem. Soc.*, 1954, **76**, 1639.

phosphate was slower still (8%). Evidently the reaction is accelerated by the withdrawal of electrons from the phosphate group by the aryl nucleus and the consequent increase in polarity of the benzyl–oxygen link. Other differences between the behaviours of phenyl and benzyl esters arising from the same cause have already been noted in Part X.[11] On

(I)





(II)

the other hand the solvolysis by *m*-cresol containing hydrogen chloride proceeded at about the same speed in all three cases. This difference between the reactions with and without added acid is reasonably explicable if the main mechanism of the first class is ionisation to a benzyl cation whilst that of the second class is nucleophilic attack on an ion such as (I) or (II). The above results refer to only the first step of a multiple debenzylation since titration to methyl-orange detects only primary phosphoric acid groups. The sum of the primary and secondary acidic groups can be determined by potentiometric titration in aqueous acetone. By this method it was possible to compare the acid-catalysed solvolysis by *m*-cresol of benzyl phenyl hydrogen phosphate with that of dibenzyl phenyl phosphate. This showed that the second step of a double debenzylation is appreciably slower than the first.

The removal of benzyl groups from esters of pyrophosphoric acid is, if anything, of greater practical importance than the operation with orthophosphates. The solvolysis of tetrabenzyl pyrophosphate was much faster even than that of benzyl diphenyl phosphate whether the reaction studied was simple solvolysis by phenol at 51° (complete in 1 hr.) or the hydrogen chloride-catalysed reaction in *m*-cresol (1·59 equivalents of acid liberated under conditions which produced only 0·22 equivalent in the example studied earlier). The way in which this difference can be exploited for the synthesis of pyrophosphates has been pointed out elsewhere.[12] Only the first two stages of the tetradebenzylation could be detected by either of the titration techniques, but the last three stages were studied by paper chromatography, with one of the very efficient systems described by Ebel,[13] and colorimetric estimation of the phosphorus content of different portions of the paper. The results show that the final stages of debenzylation were still rapid but that the full yield of pyrophosphoric acid was never obtained because considerable breakdown to orthophosphoric acid occurred. This was evidently not caused by the cresol, since there was no sign on the chromatograms of *m*-tolyl dihydrogen phosphate and no loss of phosphate to unaccounted sources. Moreover the breakdown eventually ceased and must therefore have been caused by traces of water. The chromatograms of the later samples showed the presence of triphosphoric and, probably, tetraphosphoric acid in increasing and then constant amounts. These results are easily explained by the hypothesis that reactions of the following type took place :

$$2H_4P_2O_7 \rightleftharpoons H_5P_3O_{10} + H_3PO_4$$
$$H_4P_2O_7 + H_5P_3O_{10} \rightleftharpoons H_6P_4O_{13} + H_3PO_4$$
$$2H_5P_3O_{10} \rightleftharpoons H_6P_4O_{13} + H_4P_2O_7$$

It should be remarked that these reactions were slower than the hydrolysis, which in turn was slower than the debenzylation. The phenolic debenzylation method is therefore likely to be useful, particularly if water can be excluded, provided that the reaction is not prolonged excessively.

It would have been interesting to examine the phenolic debenzylation of pentabenzyl triphosphate, but we were unable to prepare a satisfactory sample of this presumably unstable substance from dibenzyl phosphorochloridate and triethylammonium tribenzyl pyrophosphate.

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[11] Corby, Kenner, and Todd, *J.*, 1952, 1236.
[12] Christie, Kenner, and Todd, *J.*, 1954, 47.
[13] Ebel, *Bull. Soc. chim. France*, 1953, 991.

EXPERIMENTAL

M. p.s are corrected.

*4-Benzyl-2-*p*-nitrophenylazophenol.*—A 0·32N-solution of *p*-nitrobenzenediazonium chloride (15 c.c.; prepared according to Saunders[14]) was added slowly to a stirred solution of *p*-benzylphenol[15] (0·505 g.) in 0·1N-sodium hydroxide (5 c.c.). A portion of the *azo-compound*, which was precipitated by acidification, was purified by chromatography in benzene on alumina and crystallised from aqueous ethanol in orange-red crystals, m. p. 173—174°, $\varepsilon_{max.}$ 21,180 at 340 mμ in C_6H_6 (Found, in material dried at 90°: C, 69·1; H, 4·7; N, 12·8. $C_{19}H_{15}O_3N_3$ requires C, 68·5; H, 4·5; N, 12·6%).

Coupling of o-*Benzylphenol with Diazotised* p-*Nitroaniline.*—Dilute hydrochloric acid was added to *o*-benzylphenol[16] (0·05 g.) in sodium hydroxide solution until a very slight turbidity was produced. The diazonium solution (1 c.c.; as above) was then added and followed by acid to precipitate a mixture of dyes, which was separated by chromatography in benzene on alumina into a rapidly moving purple band and a slow pink band. The latter consisted of *2-benzyl-4-*p*-nitrophenylazophenol* which, eluted by chloroform and crystallised from aqueous ethanol, had m. p. 150—152°, $\varepsilon_{max.}$ 22,900 at 376—378 mμ in C_6H_6 (Found, in material dried at 90°: C, 68·4; H, 4·6; N, 12·7%). When a greater quantity (4 c.c.) of the diazonium solution was used together with sufficient sodium hydroxide to maintain the alkalinity, the purple band was more intense and it yielded *2-benzyl-4 : 6-bis-*p*-nitrophenylazophenol* as a brown amorphous solid, m. p. 214—215°, $\varepsilon_{max.}$ 41,000 at 366—370 mμ (Found, in material dried at 90°: C, 62·5; H, 3·9; N, 17·5. $C_{25}H_{18}O_5N_6$ requires C, 62·2; H, 3·8; N, 17·4%).

Determination of p- *and* o-*Benzylphenol in a Mixture with Phenol.*—Phenol (0·153 g.), *p*-benzylphenol (0·0617 g.), and *o*-benzylphenol (0·0526 g.) were dissolved in ethanol (25·0 c.c.). A portion (5·0 c.c.) of this solution was stirred with water (5 c.c.) and magnesium oxide (2 g.; " AnalaR ") in an ice-cooled flask. *p*-Nitrobenzenediazonium chloride solution (5 c.c.; as above) was slowly added, followed, 10 min. later, by concentrated hydrochloric acid (10 c.c.). Immediate addition of water (200 c.c.) precipitated an amorphous brown powder, which was collected, washed with dilute hydrochloric acid and water, and dried (0·2438 g.). A portion (5·0 c.c.) of a solution of this powder (0·0215 g.) in benzene (100·0 c.c.) was concentrated to about 2 c.c. and applied to a column (12 × 1 cm.) of alumina (Spence " H," deactivated by 2% of water). Washing the column with benzene eluted 4-benzyl-2-*p*-nitrophenylazophenol [50 c.c. of solution, optical density in 1 cm. cell (*D*) 0·123 at 337 mμ], followed by 2-benzyl-4 : 6-bis-*p*-nitrophenylazophenol (81 c.c., *D* 0·100 at 370 mμ). Ether then removed the 2-benzyl-4-*p*-nitrophenylazophenol, which was recovered by evaporation and redissolved in benzene (5 c.c., *D* 0·171 at 378 mμ). The dyes formed from the phenol remained strongly adsorbed at the top of the column. Calculation, with the previously determined extinction coefficients, shows that the eluted dyes correspond to 0·0607 g. of *p*- and 0·0491 g. of *o*-benzylphenol, 98 and 93% respectively of the amounts used.

Stability of Benzylphenols in Phenol.—A solution of *p*-benzylphenol (0·210 g.; m. p. 82—83°) in phenol (5 c.c.) was kept at 51° during 96 hr. The *p*-benzylphenol was recovered unchanged (m. p. 82—83°) on sublimation of the phenol at $20°/10^{-2}$ mm. until the residue reached constant weight (0·213 g.). *o*-Benzylphenol (0·192 g.; m. p. 50—52°) was treated in the same way and recovered (0·192 g.; m. p. 49—52°).

A solution of *p*-benzylphenol (0·245 g.) in phenol (5 c.c.) containing toluene-*p*-sulphonic acid (0·0116N) was kept at 51° during 48 hr. and then diluted with benzene (15 c.c.) before extraction with saturated sodium hydrogen carbonate solution (2 × 5 c.c.) and water (5 c.c.). The benzene solution was frozen and evaporated to constant weight (0·248 g.); the m. p. of the residue was 82—83°. *o*-Benzylphenol (m. p. 48—52°) was likewise recovered in quantitative yield.

Stability of Benzyl Phenyl Ether in Phenol.—A solution of benzyl phenyl ether (1 g.; m. p. 39°) in phenol (10 c.c.) was kept at 51° during 22 hr. and then diluted with carbon tetrachloride (35 c.c.) before three extractions with N-sodium hydroxide. Evaporation of the dried (Na_2SO_4) carbon tetrachloride, finally at 80°/2 mm., left unchanged benzyl phenyl ether (0·986 g.; m. p. 39° after crystallisation from ethanol).

A mixture of benzyl phenyl ether (1·018 g.), diphenyl hydrogen phosphate (0·740 g.), and

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[14] Saunders, " Aromatic Diazo Compounds," Arnold, London, 1949, 2nd edn., p. 6.

[15] Short and Stewart, *J.*, 1929, 553.

[16] Claisen, *Annalen*, 1925, **442**, 238.

phenol (10 c.c.) yielded 0·920 g. of unchanged ether after being kept for 17 hr. at 51°. A mixture of the ether (1·058 g.), toluene-*p*-sulphonic acid (0·693 g.), and phenol (10 c.c.) gave 0·672 g. of unchanged ether after 2 hr. at 51°.

Benzyl Diphenyl Phosphate.—Diphenyl phosphorochloridate (50 g.) was added during 2 hr. to pyridine (25 g.) and benzyl alcohol (20·1 g.), stirred at 0°. After 4 hr. further, the neutral product was extracted by ether (2 × 100 c.c.) after addition of water (100 c.c.) and was washed with N-sulphuric acid, N-sodium hydrogen carbonate solution, and water. The oil remaining after evaporation of the dried ether crystallised : recrystallisation from light petroleum (b. p. 40—60°) afforded *benzyl diphenyl phosphate*, m. p. 48° (54·5 g., 86%) (Found : C, 67·0; H, 5·3. $C_{19}H_{17}O_4P$ requires C, 67·1; H, 5·0%). Preparation of the oil has been recorded.[17]

Solvolysis of Benzyl Diphenyl Phosphate.—(1) *Acidic product.* A solution of the ester (0·615 g.) in phenol (10 c.c.) was kept at 51° during 72 hr. before dilution with benzene (25 c.c.). The solution was extracted with saturated sodium hydrogen carbonate solution (5 × 4 c.c.). The aqueous extracts were passed through a column (10 × 1 cm.) of Zeo-Karb 215 cation-exchange resin (hydrogen-ion form), which was washed with water until the eluate was neutral. *cyclo*-Hexylamine (0·4 c.c.) was added to the combined eluate, which was then evaporated to dryness. Addition of light petroleum (b. p. 40—60°) to the acetone solution of the residue precipitated crystalline *cyclo*hexylammonium diphenyl phosphate (0·510 g. 86%), m. p. 200° undepressed by an authentic sample.[20]

(2) *Neutral product.* A solution of benzyl diphenyl phosphate (0·315 g.) in phenol (5 c.c.) was kept at 51° during 70 hr. and then diluted with carbon tetrachloride (30 c.c.). After extraction with 1·5N-sodium hydroxide (5 × 40 c.c.) and water (3 × 40 c.c.), the solvent was evaporated. Two crystallisations of the residue from light petroleum afforded crude benzyl phenyl ether (0·01 g., 6%), m. p. 32—34° undepressed by an authentic specimen of m. p. 39°.

(3) *Phenolic product.* (*a*) Qualitative tests. The carbon tetrachloride solution of the solvolysis products, obtained as in (2) above, was extracted first with sodium hydrogen carbonate solution and then with sodium hydroxide solution, from which the phenols were recovered by acidification and ether-extraction. When an ethanolic solution of 2 : 6-dichloroquinone chloroimine was added to a dilute alkaline solution of this material, a deep blue colour was produced and this became bluish-pink on dilution. *o*-Benzylphenol behaved in the same way, but *p*-benzylphenol gave a brownish-blue colour, fading to slate-grey and becoming grey on dilution.[18] The dyes obtained by coupling the phenolic product with diazotised sulphanilic acid were dissolved in ethanol and applied to Whatman No. 3 paper, previously soaked in 1% sodium hydrogen carbonate solution and dried.[19] Ascending development of the paper with butan-1-ol–ethanol (50 : 13 v/v), saturated with water, gave a chromatogram pattern similar to that from a mixture of equal weights of *p*- and *o*-benzylphenol and phenol. *p*-Benzylphenol alone gave a strong pink spot (R_F 0·72), whereas *o*-benzylphenol gave a strong orange spot (R_F 0·58) together with three faint spots (orange R_F 0·48, orange R_F 0·42, mauve R_F 0·36). Phenol gave a yellow spot (R_F 0·32).

. (*b*) Quantitative analysis. A solution of benzyl diphenyl phosphate (0·615 g.) in phenol (3 c.c.) was kept at 51° during 72 hr. and then diluted with benzene (25 c.c.), which was extracted with saturated sodium hydrogen carbonate solution (5 × 4 c.c.). The residue from evaporation of the benzene and sublimation at 10^{-2} mm. (10 hr.) of the phenol was dissolved in ethanol (10·0 c.c.). A portion (2·0 c.c.) of this solution was converted, as previously described, into the *p*-nitrophenylazo-derivatives, which were separated chromatographically and estimated photometrically in the standard fashion. They corresponded to 0·156 g. of *p*- and 0·129 g. of *o*-benzylphenol, making a total yield of 85·5% whereas the extent of debenzylation, as determined by titration, was 94%.

From a mixture of the ester (0·388 g.) and phenol (3 c.c.) containing toluene-*p*-sulphonic acid (0·1N), which had been kept for 3 hr. at 51°, there were likewise obtained dyes corresponding to 0·0819 g. of *p*- and 0·0985 g. of *o*-benzylphenol (total yield 86%).

Solvolysis of Benzyl Bromide.—A mixture of benzyl bromide (0·719 g.) and phenol (3 c.c.) was kept at 51° during 48 hr., hydrogen bromide being released at intervals. The yellowish-brown solution, treated as in the preceding experiment, gave dyes corresponding to 0·524 g. of *p*- and 0·2025 g. of *o*-benzylphenol (total yield 94%).

A solution of benzyl bromide (0·719 g.) in phenol (3 c.c.) containing toluene-*p*-sulphonic acid

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[17] Lora Tamayo and Gregorio Ramon, *Anal. Fis. Quim.*, 1949, **45**, *B*, 1123.

[18] Cf. Gibbs, *J. Biol. Chem.*, 1927, **72**, 649.

[19] Cf. Hossfeld, *J. Amer. Chem. Soc.*, 1951, **73**, 852.

[20] Lecocq and Todd, *J.*, 1954, 2384.

(0·142N) was kept at 51° during 5 hr.; it gave dyes corresponding to 0·497 g. of *p*- and 0·199 g. of *o*-benzylphenol (total yield 90%).

Solvolysis of Dibenzyl Phenyl Phosphate.—The acidic product was recovered from a mixture of the ester (0·0816 g.) and phenol (3 c.c.), which had been kept for 68 hr. at 51°, in the same way as from benzyl diphenyl phosphate. *cyclo*Hexylammonium phenyl hydrogen phosphate (0·052 g., 82%), m. p. 211° undepressed by an authentic specimen,[21] was precipitated from aqueous solution by addition of acetone.

Kinetics of the Solvolysis of Benzyl Diphenyl Phosphate.—(1) *At* 51°. The solution of the ester in phenol (20·0 c.c.) was contained by a 50 c.c. flask with a water-jacketed neck (10 × 1 cm.). During the run cold water was circulated in the jacket, but, immediately before each sample was taken, hot water was circulated in order to melt the sublimed phenol and return it to the flask. The sample (1 or 2 c.c.) was run into cold water (about 5 c.c.) containing carbon tetrachloride (about 5 c.c.) and 2 drops of methyl-orange, and was titrated with 0·0648N-sodium hydroxide. In calculations of the extent of reaction the change in volume caused by dissolution of the ester in phenol was neglected.

(*a*) Order of the reaction with respect to the ester. In a series of runs the percentage change in a given time was found to be independent of the initial ester concentration, as required by first-order kinetics, *e.g.*, at initial ester concentrations of 0·257 and 0·086M the percentage changes were respectively 22·2 and 21·0 at 30 min., 41·4 and 41·0 at 60 min., 59·2 and 58·4 at 90 min.

(*b*) Autocatalysis and the effect of diphenyl hydrogen phosphate. A run with an initial ester concentration of 0·246M was made and then repeated with added diphenyl hydrogen phosphate (0·119M). Results are tabulated.

Time (min.)	5	10	15	20	30	45	60	90	120
Change (%) (without acid)	4·08	7·28	11·40	14·98	22·18	32·44	41·46	59·20	70·40
Change (%) (acid added)	2·74	10·10	15·10	20·48	39·60	44·80	55·60	71·60	82·20

(*c*) Catalysis by toluene-*p*-sulphonic acid. The reaction was complete in less than 5 min. when a run was made with initial concentrations of 0·257M-ester and 0·137M-acid, and complete in 15 min. with concentrations of 0·514 and 0·023M respectively. A run with 0·275M-ester and 0·00639M-acid was 78·8% complete in 30 min.

(*d*) Comparison of different phenols. In one series of runs with 0·257M-ester the change in 30 min. was 26·2% in *m*-methoxyphenol, 22·2% in phenol, and 10·4% in *p*-chlorophenol. In a second series with 0·275M-ester, toluene-*p*-sulphonic acid was added at the concentration shown in parentheses and the change in 30 min. was 78·8% (0·00639) in phenol, 78·0% (0·00620) in *m*-methoxyphenol, 53·2% (0·00642) in *m*-cresol, 32·5% (0·00639) in *p*-cresol, 23·2% (0·00564) in *o*-cresol and 0·0% (0·0308) in anisole.

(*e*) Inhibition of the solvolysis by methyl cyanide and methanol. The reaction in phenol without added catalyst or inhibitor was 22% complete in 30 min., but was only 16·4, 13·4, and 5·1% complete in 30 min. when methyl cyanide was added in concentrations of 0·936, 1·79, and 3·75M respectively to 0·245, 0·239, and 0·206M-solutions of the ester. A mixture which was 2·23M in methanol and 0·234M in ester showed 10·6% complete reaction in 30 min.

(2) *At* 20° *in* m-*cresol.* The procedure was the same as described in (1) except that a simple stoppered flask was used.

(*a*) Order of catalysis by toluene-*p*-sulphonic acid. Results are tabulated, the percentage change being $100x/a$, and $k = \{2{\cdot}303 \log [a/(a - x)]\}/15h$. The results are reasonably compatible with the assumption that velocity = k[Ester][Acid] as shown by the values of k (mean 0·295 min.$^{-1}$ mol.$^{-1}$ l.) calculated on this assumption. An alternative way of deriving k from the complete results of a single run is to plot time against log $[a/(a - x)]$ and then use $k = 2{\cdot}303/(h, \text{slope})$; the run with 0·197M-ester gave 0·282 for k in this way.

Molarity (a) of ester	0·119	0·135	0·150	0·178	0·197	0·237
Molarity (h) of acid	0·0392	0·0308	0·0479	0·0366	0·0528	0·0857
Change (%) in 15 min.	16·9	14·5	18·6	14·5	19·8	28·8
k	0·314	0·340	0·288	0·286	0·278	0·264

(*b*) Catalysis by hydrogen chloride. In this case a straight-line graph of time against log $[a/(a - x)]$ was not obtained because appreciable amounts of hydrogen chloride were lost from

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[21] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 818.

the bulk of solution during the withdrawal of samples. A control experiment showed that 10 c.c. of 0·0452M-hydrogen chloride in *m*-cresol lost 8·3% of its acidity during 3 minutes' exposure to air. The initial slopes of the graphs were therefore used and gave a mean *k* value of 0·575. In a typical run with 0·141M-ester and 0·069M-acid the change was 46·9% in 15 min. and 62·9% in 30 min.

(*c*) Catalysis by trichloro- and trifluoro-acetic acid. Reaction was 53·8% complete in 20 hr. when 0·131M-trichloroacetic acid was used with 0·120M-ester, and 78·5% complete in 17 hr. when 0·0556M-trifluoroacetic acid was used with 0·131M-ester.

Kinetics of the Solvolysis of Dibenzyl Phenyl Phosphate, Benzyl Phenyl Hydrogen Phosphate, Tribenzyl Phosphate, and Tetrabenzyl Pyrophosphate.—(1) *Followed by indicator titration.* (*a*) In phenol at 51° without added acid. Solvolysis of dibenzyl phenyl phosphate (0·136M) produced titratable acid in the following amounts (expressed as mols. % of the ester concentration), 8·3% in 30 min., 19·5% in 60 min., 50·6% in 150 min. Tribenzyl phosphate (0·131M) gave 8% in 1 hr., 20·2% in 3 hr., 92·5% in 68 hr. Tetrabenzyl pyrophosphate (0·084M) gave 160% in 30 min., 190% in 60 min., 190% in 180 min.

(*b*) At 20° in *m*-cresol containing hydrogen chloride. Solvolysis of dibenzyl phenyl phosphate (0·149M) in *m*-cresol, 0·0269M in hydrogen chloride, produced 43·6% of acid in 30 min., 73·7% in 17 hr. Tribenzyl phosphate (0·158M) in 0·0328M-acid gave 44·7% in 30 min., 66% in 79 hr. Tetrabenzyl pyrophosphate (0·090M) in 0·042M-acid gave 157% in 30 min. and 171% in 17 hr.

(2) *Followed by potentiometric titration.* The samples were run into water (about 10 c.c.) and sufficient acetone (about 5 c.c.) to maintain homogeneity during the titration. This was conducted with a glass electrode–calomel electrode pH-meter, the nominal pH being read as each small portion of alkali was added. A plot of ΔpH/Δvol. against vol. of alkali added showed a series of peaks corresponding to the different acidic species. The position of the last peak was taken as giving the total acid present except for the tertiary dissociation of orthophosphoric acid and the two secondary dissociations of pyrophosphoric acid. All the runs were made in *m*-cresol at 20°. Dibenzyl phenyl phosphate (0·129M) together with 0·0309M-hydrogen chloride gave 118 mols.% of acid in 1 hr. and 179% in 2 hr., whereas benzyl phenyl hydrogen phosphate (0·128M) with 0·0309M-acid gave 29·4% in 1 hr. and 75% in 7 hr. Tetrabenzyl pyrophosphate (0·0804M) with 0·0336M-acid gave 172% in 1 hr.; a final value of 185% was obtained when the mixture was heated at 55° for 1 hr. after 13 hr. at 20°.

Chromatographic Investigation of the Degradation of Tetrabenzyl Pyrophosphate by m-*Cresol and Toluene*-p-*sulphonic Acid.*—Freshly distilled *m*-cresol (5 c.c.) and dry toluene-*p*-sulphonic acid (0·0515 g.) were placed in a test-tube, fitted by a ground-glass joint with an adaptor which had a side-arm and a sampling-tube reaching to the bottom of the test-tube and closed by a tap. The cresol was boiled until vapour issued freely from the side-arm, which was closed with a calcium chloride drying-tube before the solution was allowed to cool to room temperature (24°). While the adaptor was momentarily removed, tetrabenzyl pyrophosphate (0·199 g.) was added and then dissolved by shaking of the tube. Samples of about 0·1 c.c. were blown through the tap by applying air pressure to the drying-tube. A micro-syringe was used to apply 0·03 c.c. of each sample along a 10 cm. line at the base of a strip of Whatman No. 1 paper, which had been dried after being washed with N-hydrochloric acid and water. Development of the ascending paper chromatogram in propan-2-ol (75 c.c.)–water (25 c.c.)–trichloroacetic acid (5 g.)–ammonia solution (0·25 c.c.; *d* 0·88) was begun immediately and was continued for 12—24 hr. The paper was then dried and the phosphorus-containing bands were located by the molybdate reagent.[22] Six different bands were obtained from the various samples and four of them were identified by direct comparison with known compounds: mean R_F 0·40 triphosphoric acid, 0·54 pyrophosphoric acid, 0·66 orthophosphoric acid, 0·85 P^1P^2-dibenzyl dihydrogen phosphate. The two remaining bands were believed to contain tetraphosphoric acid (mean R_F 0·27) and benzyl trihydrogen phosphate (mean R_F 0·73). Each band was cut out and the strips of paper were digested with hot 60% perchloric acid (2·2 c.c.) until a colourless solution resulted. The phosphate content of this was then estimated by Allen's method,[23] allowance being made for the " blank " given by the same area of paper which had been irrigated with the solvent but had not been treated with phosphate. The total phosphorus content (158 μg.) of 0·03 c.c. of the cresol solution was estimated directly, with 0·03 c.c. of cresol for the " blank "; determination of the phosphorus content of a longitudinal, instead of a lateral, strip of paper which had been

[22] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.

[23] Allen, *Biochem. J.*, 1940, **34**, 858.

developed gave a similar value (156 µg.). Hence the cresol solution was initially 0·085M-tetrabenzyl pyrophosphate and 0·069M-toluene-*p*-sulphonic acid. The percentages of the total phosphorus content found in the various bands are tabulated.

Time of sampling (hr.)	½	1	2	4	6	9	12
Tetraphosphoric acid	—	—	2·8	2·3	3·1	2·8	2·5
Triphosphoric acid	—	4·5	9·5	6·6	15	15·8	14·6
Pyrophosphoric acid	60	62	51	34	29	31	29
Orthophosphoric acid	6·8	22	35	44	42	44	45
Monobenzyl pyrophosphate	14·5	1·9	—	—	—	—	—
Dibenzyl pyrophosphate	4·6	1·5	—	—	—	—	—
Phosphorus accounted for (%)	87	92	98	87	89	94	92

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