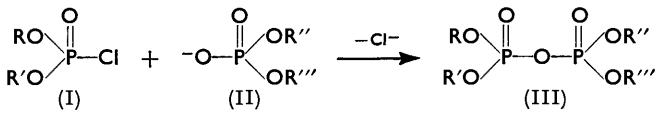
255. *Studies on Phosphorylation. Part XIII.* Ketoxime Sulphonates as Intermediates in Pyrophosphate Formation.*

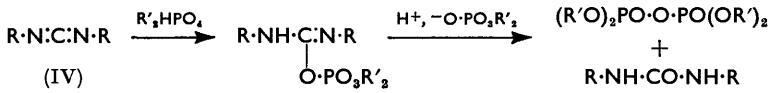
By G. W. Kenner, Sir Alexander R. Todd, and R. F. Webb.

Imidoyl phosphates (VIII) have been prepared by the Beckmann rearrangement of the arylsulphonyl derivatives (VI) of ketoximes in the presence of phosphate anions, and have been used for the preparation of pyrophosphates. These reactions constitute a general method likely to be useful in the coenzyme field.

Of the methods developed in the present series for the preparation of polyphosphates that which involves the reaction between a phosphorochloridate (I) and the salt of a phosphoric acid (II) has hitherto been the most widely used in the nucleotide series.[1-4] This method and those employing exchange reactions involving tetraphenyl pyrophosphate or trifluoroacetic anhydride [5,6] are, however, subject to the limitation that the sugar- and/or phosphate-hydroxyl residues in reactive nucleoside intermediates must be shielded during the condensation by hydrophobic protecting groups which are subsequently removed. The extreme lability of the fully esterified condensation products, and of many of the nucleotide coenzymes themselves, to both acid and alkali has stimulated the development of synthetic methods in which the requisite nucleotide intermediates do not require the usual protecting groups since the conditions under which these groups can be removed are often those which cause extensive destruction of the desired product.



The introduction of the carbodi-imide method [7] for the synthesis of P^1P^2-diesters of pyrophosphoric acid (III; R = R″ = H) from free monoalkyl phosphates or their pyridine salts, together with the demonstration that neither traces of water [7] nor certain free sugar-hydroxyl groups [6] seriously interfered with pyrophosphate formation, appeared to offer a route to many nucleotide coenzymes and it has since been used in the synthesis of uridine-diphosphate-glucose,[8] adenosine-5′ triphosphate,[9] and uridine-5′ triphosphate.[10] The formation of pyrophosphates by the interaction of carbodi-imides and phosphoric acids was represented [7] as proceeding by initial addition of the acid to the carbodi-imide (IV) followed by phosphorolysis of the adduct :

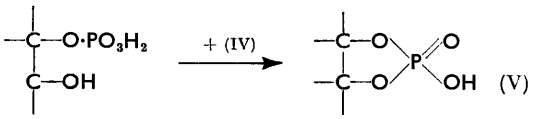


Isolation of the intermediate adduct was not possible, with the result that the coupling of two different phosphoric acids invariably gave mixtures of the two symmetrical pyrophosphates together with the unsymmetrical product, thus greatly complicating the isolation procedures.[8]

* Part XII, *J.*, 1954, 2381.

[1] Baddiley and Todd, *J.*, 1947, 648.
[2] Baddiley, Michelson, and Todd, *J.*, 1949, 582; Michelson and Todd, *ibid.*, p. 2487.
[3] Kenner, Todd, and Weymouth, *J.*, 1952, 3675; Kenner, Todd, Webb, and Weymouth, *J.*, 1954, 2288.
[4] Christie, Kenner, and Todd, *ibid.*, p. 46.
[5] Corby, Kenner, and Todd, *J.*, 1952, 1234.
[6] Christie, Elmore, Kenner, Todd, and Weymouth, *J.*, 1953, 2947.
[7] Khorana and Todd, *ibid.*, p. 2257.
[8] Kenner, Todd, and Webb, *J.*, 1954, 2843.
[9] Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3517.
[10] Hall and Khorana, *ibid.*, p. 5066.

A further complication arises when carbodi-imides are used to form pyrophosphates from esters of phosphoric acid bearing a hydroxyl group in a vicinal position to the phosphate since here cyclic phosphate (V) formation may predominate : [8]

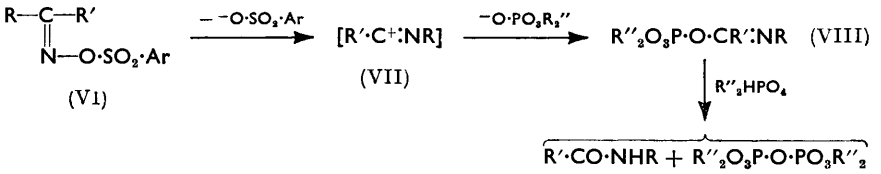


(V)

Finally, neither trialkylammonium nor tetra-alkylammonium salts of phosphates, which may have convenient solubilities in organic solvents, can be used in the carbodi-imide process.

In attempts to overcome some of these restrictions, we investigated the use of imidoyl phosphates. Dr. F. R. Atherton had already shown that dibenzyl *N*-phenylbenzimidoyl phosphate (VIII; R = R′ = Ph, R″ = CH_2Ph) undergoes phosphorolysis when treated with either dibenzyl or diphenyl hydrogen phosphate, yielding the pyrophosphate and benzanilide; [11] this reaction is analogous to the hypothetical second step in the carbodi-imide reaction sequence.

The imidoyl phosphate (VIII; R = R′ = Ph, R″ = CH_2Ph) was prepared by Dr. Atherton from *N*-phenylbenzimidoyl chloride and silver dibenzyl phosphate. It occurred to us that a wider series of imidoyl phosphates might be made accessible by the Beckmann rearrangement of oximes. The current view is that the first step of rearrangement in non-hydroxylic media is ionisation with simultaneous intramolecular alkyl or aryl migration, yielding an ion such as (VII). Consequently rearrangement in presence of a phosphate anion could lead to an imidoyl phosphate (VIII) by union of the added anion with the intermediate cation (VII) instead of the normal reunion of the latter with the anion generated in the first rearrangement step.



In a preliminary experiment it was demonstrated that the diphenyl phosphoryl derivative of acetoxime gave the imidoyl phosphate (VIII; R = R′ = Me, R″ = Ph) by straightforward Beckmann rearrangement during distillation at 120°. The product was allowed to react with dibenzyl hydrogen phosphate, and the resulting neutral material was then examined for the presence of pyrophosphates by treatment with *cyclo*hexylamine and detection of the *N-cyclo*hexylphosphoramidate and *cyclo*hexylammonium phosphates (cf. Part X [5]).

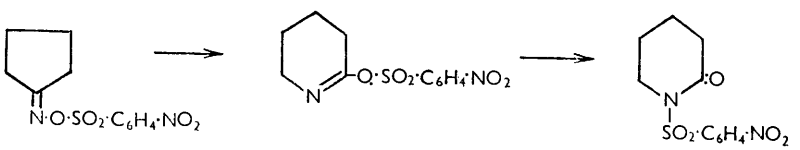
As starting materials for the synthetic method proper the arenesulphonyl derivatives of ketoximes (VI) were selected, since the arenesulphonate ion should not compete effectively with the added phosphate ion for the intermediate cation (VII) and a series of these compounds had been described by Oxley and Short [12] who had used them for the preparation of amidines. In the present investigation the ketoxime sulphonates required were those which could readily be obtained pure, could be stored without spontaneous rearrangement, and would rearrange at a suitable rate in a polar solvent. The suitability of various oxime esters in the synthesis of tetrabenzyl pyrophosphate was determined by reaction of the oxime ester (1 mol.) in a suitable solvent with dibenzyl hydrogen phosphate (2 mols.) in the presence of various tertiary amines (1 mol.). The yield of tetrabenzyl pyrophosphate produced in each experiment was estimated by the *cyclo*hexylamine assay previously

[11] Atherton, personal communication; Atherton, Morrison, Cremlyn, Kenner, Todd, and Webb, *Chem. and Ind.*, 1955, 1183.
[12] Oxley and Short, *J.*, 1948, 1514.

described, the yield of the tetraester produced being based on the weight of *cyclo*hexylamine salt isolated. The validity of this procedure was checked in certain cases by subsequent isolation of the *N-cyclo*hexylphosphoramidate also produced in the *cyclo*hexylamine treatment and also by isolation of tetrabenzyl pyrophosphate in separate experiments. The results may be summarised as follows.

As previously shown by Oxley and Short,[12] acetoxime benzenesulphonate did not undergo the Beckmann rearrangement except at elevated temperature and was therefore unsuitable for the present study. Acetophenone oxime toluene-*p*-sulphonate could not be obtained pure since the solid ester rearranged rapidly at room temperature. The crude material, however, gave some tetrabenzyl pyrophosphate (16%) when allowed to react with dibenzyl hydrogen phosphate and triethylamine in benzene at 18° for 16 hr. The use of a more polar solvent, methyl cyanide, under the same conditions doubled the yield of pyrophosphate. Ethyl methyl ketoxime benzenesulphonate also gave fair yields (20—38%) of tetrabenzyl pyrophosphate under various conditions; the use of methyl cyanide as solvent again improved yields of the pyrophosphate in comparison with benzene. The use of 2 : 6-lutidine in place of triethylamine as base had no marked effect on yields. *cyclo*-Pentanone oxime benzenesulphonate was prepared as a low-melting solid but the material could be stored at −40° without spontaneous rearrangement. The rate of rearrangement of the compound in chloroform and methyl cyanide was determined. In chloroform rearrangement was slow (about 25% in 200 min. at 25°); in methyl cyanide it was virtually complete in 95 min. at 25°. However, in the presence of 2 : 6-lutidine (1 mol.) and dibenzyl hydrogen phosphate (2 mols.) in methyl cyanide at 18° for 16 hr. only a 40% yield of tetrabenzyl pyrophosphate was obtained, probably owing to some inhibition by this base. Markedly more pyrophosphate was obtained when nitromethane replaced methyl cyanide as solvent. *cyclo*Pentanone oxime *p*-nitrobenzenesulphonate was found to be the most suitable reagent for the synthesis of tetrabenzyl pyrophosphate, yields up to 90% being obtained with nitromethane as solvent at room temperature; the reagent, moreover, can be stored indefinitely at 0°. In methyl cyanide at 25° its rearrangement was complete in 50 min., whereas in chloroform only 40% of the ester had rearranged after 200 min. Comparison of these rates, together with those for the corresponding benzenesulphonates reveals the well-recognised influences of acid strength in the oxime ester and polarity of the solvent on the rate of the Beckmann rearrangement.[13,14]

Another possible route to imidoyl phosphates (VIII) involves phosphate–sulphonate anion-exchange on an imidoyl sulphonate which may itself be produced by the Beckmann rearrangement of a ketoxime sulphonate.[13] In the present investigation only a preliminary examination of imidoyl sulphonates was undertaken; a more detailed consideration will be presented in a later paper. *cyclo*Pentanone oxime *p*-nitrobenzenesulphonate rearranged spontaneously in nitromethane to the enol *p*-nitrobenzenesulphonate (IX) of valerolactam which was then treated with dibenzyl hydrogen phosphate (2 mols.) and triethylamine (1 mol.). The yield of the pyrophosphate (27%; assayed as above) was much lower than

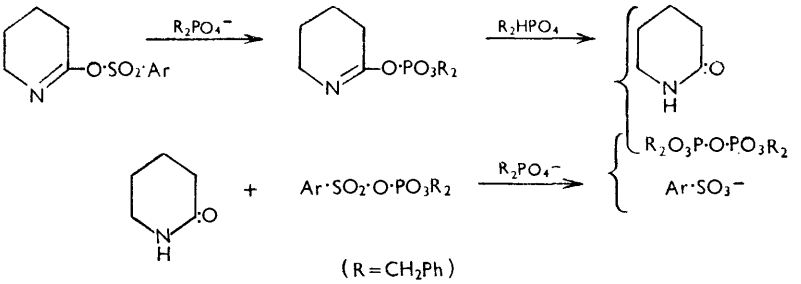


(IX) (X)

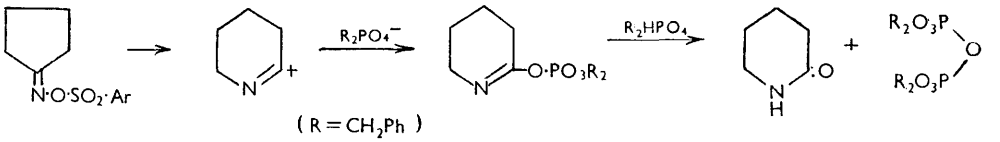
when the phosphate was present during the step involving Beckmann rearrangement (80%), under otherwise standard conditions. Further, the reaction involving the imidoyl sulphonate, in contrast to that with the ketoxime sulphonate, was apparently base-catalysed since an increase in the proportion of triethylamine (to 3 mols.) in the above experiment

[13] Kuhara, "The Beckmann Rearrangement," Komatsu, Tokyo, 1926.
[14] Chapman, *J.*, 1934, 1550.

raised the yield of tetrabenzyl pyrophosphate (to 44%). The lower yield of tetrabenzyl pyrophosphate in the reaction involving the preformed imidoyl sulphonate was not due to further rearrangement of the imidoyl sulphonate to the *N*-acylsulphonamide (X), *i.e.*, Chapman change,[15] since the Chapman change is itself probably base-catalysed (cf. the use of pyridine in preparation of *N*-acylureas from carbodi-imides and carboxylic acids [16]) and



also since the imidoyl sulphonate solution, even after 20 hr. at room temperature, still liberated 1 mol. of *p*-nitrobenzenesulphonic acid when treated with water; the *N*-acylsulphonamides would not liberate acid under these conditions. Also, the choice of *cyclo*pentanone oxime esters for the rearrangement largely precludes any intramolecular sulphonyl or phosphoryl migration in the piperidone derivative (cf. the effect of ring size on the analogous rearrangement of *N*-nitrosolactams [17]). We therefore consider that two possible mechanisms may account for the formation of pyrophosphates from imidoyl sulphonates, one involving sulphonate–phosphate anion-exchange followed by a phosphorolytic step; the other involving the formation of a mixed anhydride between *p*-nitrobenzenesulphonic and dibenzyl phosphoric acids which may then undergo phosphate exchange (cf. Part X [5]). We further conclude that this reaction differs from that involving the ketoxime sulphonate where the exchange of anions occurs during the Beckmann rearrangement, thus affording further evidence for the intermolecular migration of the anion in the Beckmann rearrangement of ketoxime esters (cf. Brodskii and Miklukin [18]):



Having established the reaction conditions and the preferred ketoxime ester we investigated the synthesis of an unsymmetrical pyrophosphate derivative. In the synthesis of tetrabenzyl pyrophosphate from trialkylammonium dibenzyl phosphates no intermediate imidoyl phosphate could be isolated. The Beckmann rearrangement of *cyclo*pentanone oxime *p*-nitrobenzenesulphonate was therefore conducted in the presence of tetraethylammonium dibenzyl phosphate; at this stage no tetrabenzyl pyrophosphate had been formed. Further treatment of the imidoyl phosphate solution with diphenyl hydrogen phosphate, with or without added tertiary amine, in a polar solvent (nitromethane) gave a mixture of pyrophosphates as judged by the *cyclo*hexylamine assay. However, in a non-polar solvent (benzene), the unsymmetrical pyrophosphate, dibenzyl diphenyl pyrophosphate, was formed almost exclusively. It is apparent from this, and from work to be reported later, that in a polar solvent the imidoyl phosphate may undergo two competing reactions, namely, phosphorolysis to the pyrophosphate and the amide, and exchange of phosphate leading ultimately to mixtures of pyrophosphates.

[15] Chapman and Howis, *J.*, 1933, **806**.
[16] Zetsche and Fredrich, *Ber.*, 1939, **72**, 1735.
[17] Huisgen and Reinertshofer, *Annalen*, 1952, **575**, 197.
[18] Brodskii and Miklukin, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **32**, 588.

The method outlined above employing ketoxime sulphonates as intermediates in the formation of tetraesters of pyrophosphoric acid is therefore complementary to that employing phosphorochloridates [19] in non-polar media; however, in polar media the products are similar to those obtained by the use of carbodi-imides (Part XI [7]).

Experimental

Diphenyl Phosphorylation of Acetoxime and Partial Thermal Rearrangement of the Product.—Acetoxime (3·4 g.) in pyridine (4 c.c.) at 0° was treated with diphenyl phosphorochloridate [20] (11·6 g.) in pyridine (20 c.c.). The solution was kept at 0° for 18 hr., then poured into ice-water (150 c.c.), the precipitated oil was collected and dissolved in chloroform (20 c.c.), and the solution washed with saturated potassium hydrogen carbonate solution, water, saturated sodium hydrogen carbonate solution, and water. The dried (Na_2SO_4) solution was evaporated *in vacuo* and the residual oil (7·76 g., 72%) distilled in small portions (*ca.* 2 g.) when required, affording a colourless oil, b. p. 120° (bath-temp.)/1·0 × 10^{-4} mm., which was a mixture of acetoxime diphenyl phosphate and diphenyl *N*-methylacetimidoyl phosphate as shown by the following experiment.

Pyrophosphate formation from the above crude product. A solution of the crude product (0·5 g.) and dibenzyl hydrogen phosphate (0·52 g., 1·1 mol.) in dry carbon tetrachloride (2 c.c.) was refluxed for 4 hr., washed with saturated sodium hydrogen carbonate solution then with water, dried ($CaCl_2$), and evaporated *in vacuo*. The residue was shown to contain pyrophosphates by treatment with *cyclo*hexylamine (Part X [5]) as follows. The residue was dissolved in ethyl methyl ketone (5 c.c.), the solution evaporated under reduced pressure, the residue redissolved in ethyl methyl ketone (5 c.c.), *cyclo*hexylamine (1 c.c.) added, and the mixture kept at 20° for 16 hr. The precipitate (0·1 g., 20%) was filtered off, washed with benzene (2 c.c.) and ether (2 c.c.), and when dried *in vacuo* over phosphoric oxide had m. p. 174—182°. Recrystallisation (twice) from ethanol afforded *cyclo*hexylammonium diphenyl phosphate (0·04 g.), m. p. and mixed m. p. 199—200°. The filtrate and washings from the *cyclo*hexylamine fission were evaporated *in vacuo*, the residue was dissolved in benzene (4 c.c.) and washed with N-hydrochloric acid (3 × 4 c.c.), water (8 c.c.), saturated sodium hydrogen carbonate solution (2 × 4 c.c.), and again with water (2 × 4 c.c.). The dried (Na_2SO_4) solution was evaporated *in vacuo* and the semi-solid residue (0·19 g.) pressed on a porous tile. The solid residue (0·11 g., 20%) had m. p. 68—70°, and after crystallisation from *cyclo*hexane gave dibenzyl *N*-cyclohexylphosphoramidate (0·06 g.), m. p. and mixed m. p. 78—80°.

Preparation of Ketoxime Sulphonates.—The ketoxime sulphonates were prepared by the general method of Oxley and Short,[12] as illustrated by the following.

*cyclo*Pentanone (4·2 g.) was added dropwise to a stirred solution of hydroxylammonium chloride (3·5 g., 1 mol.) in aqueous 4·5N-potassium hydroxide (25 c.c.) at 0°. The solution was stirred at 0° for a further 40 min. and then a solution of *p*-nitrobenzenesulphonyl chloride [21] (11·1 g., 1·02 mol.) in acetone (35 c.c.) was slowly added, the mixture being kept at 0—5°. The mixture was stirred at 0—5° for a further 30 min., the precipitate filtered off, washed with ice-cold aqueous potassium hydroxide (50 c.c. of 5%) and with ice-cold water (100 c.c.), and the solution dried (K_2CO_3), filtered, and evaporated *in vacuo* at room temperature until solid began to separate. Light petroleum (110 c.c.; b. p. 60—80°) was added, and the mixture set aside at 0° for 30 min. and filtered. Recrystallisation from chloroform–light petroleum (b. p. 60—80°) gave cyclo*pentanone oxime* p-*nitrobenzenesulphonate* (11·0 g., 77%), m. p. 69° (decomp.) (Found: C, 46·5; H, 4·1; N, 9·8. $C_{11}H_{12}O_5N_2S$ requires C, 46·5; H, 4·3; N, 9·9%).

Similarly prepared were acetoxime benzenesulphonate,[22] m. p. 53°, acetophenone oxime toluene-*p*-sulphonate,[12] m. p. *ca.* 30°, ethyl methyl ketoxime benzenesulphonate,[22] m. p. 48° (Found: C, 52·4; H, 5·7. Calc. for $C_{10}H_{13}O_3NS$: C, 52·8; H, 5·8%), and *cyclo*pentanone oxime benzenesulphonate [12] (Found: C, 54·0; H, 5·8; N, 6·1%; sap. equiv., 241. Calc. for $C_{11}H_{13}O_3NS$: C, 55·2; H, 5·5; N, 5·9%; equiv., 239).

Rate of Rearrangement of cyclo*Pentanone Oxime Sulphonate.*—0·2M-Solutions of *cyclo*pentanone oxime benzenesulphonate and *p*-nitrobenzenesulphonate in methyl cyanide (10 c.c.) and chloroform (10 c.c.) were kept at 25°. Aliquot parts (1 c.c.) were withdrawn at intervals

[19] Toy, *J. Amer. Chem. Soc.*, 1950, **72**, 2065.
[20] Brigl and Müller, *Ber.*, 1939, **72**, 2121.
[21] Barber, *J.*, 1943, 102.
[22] Wege, *Ber.*, 1891, **24**, 3538.

and added to excess of 0·1N-sodium hydroxide, the mixtures diluted with water, and the excesses of alkali back-titrated with 0·0911N-hydrochloric acid. The results are tabulated.

Solvent	cyclo*Pentanone oxime benzenesulphonate* Time (min.)	Rearrangement (%)	cyclo*Pentanone oxime* p-*nitrobenzenesulphonate* Time (min.)	Rearrangement (%)
$CHCl_3$	90	18	90	28
,,	200	24	200	42
MeCN	30	46	25	66
,,	50	57	50	99
,,	90	93	200	99
,,	—	—	20 hr.	99

Formation and Assay of Tetrabenzyl Pyrophosphate from cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate.*—In a typical experiment a solution of dibenzyl hydrogen phosphate (0·556 g., 0·002 mole) and 2 : 6-lutidine (0·11 c.c., 0·001 mole) was prepared in nitromethane (5 c.c.), *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·284 g., 0·001 mole) added, the whole kept at room temperature for 16 hr. and then evaporated under reduced pressure. The residue was dissolved in chloroform (40 c.c.), the solution washed with water (20 c.c.), saturated sodium hydrogen carbonate solution (20 c.c.), and water (20 c.c.), then dried (Na_2SO_4) and evaporated. The neutral residue was assayed for tetrabenzyl pyrophosphate in the following way. The residue was dissolved in benzene (10 c.c.), and *cyclo*hexylamine (0·5 c.c., 0·005 mole) added; precipitation began almost immediately. The mixture was set aside overnight, then filtered, and the solid washed with benzene (5 c.c.) and ether (5 c.c.) and dried at 60° *in vacuo* over phosphoric oxide. The product, *cyclo*hexylammonium dibenzyl phosphate (0·299 g., 80%), had m. p. 170—172°. Crystallisation from ethanol gave the pure salt (0·21 g.), m. p. and mixed m. p. 173°. The filtrate and washings from the *cyclo*hexylamine fission were combined and successively washed with 0·1N-sodium hydroxide (5 c.c.), water (5 c.c.), 0·1N-hydrochloric acid (5 c.c.), and water (5 c.c.), dried (Na_2SO_4), and evaporated under reduced pressure. The residue crystallised from *cyclo*hexane, giving dibenzyl *N-cyclo*hexylphosphoramidate (0·14 g., 39%), m. p. and mixed m. p. 78—80°.

In this and subsequent experiments involving the *cyclo*hexylamine assay the yield of tetrabenzyl pyrophosphate was based on the amount of *cyclo*hexylammonium dibenzyl phosphate isolated from the neutral fraction.

The above experiment was repeated with different solvents and varying proportions of base : the results are tabulated.

Solvent	Reaction time (hr.)	Base	Yield of pyrophosphate (%)
Nitromethane	16	Triethylamine (1 mol.)	80
,,	,,	,, (3 mol.)	75
,,	,,	2 : 6-Lutidine (1 mol.)	80
,,	,,	,, (3 mol.)	35
Pyridine	20	None	0

Tetrabenzyl Pyrophosphate from cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate and Dibenzyl Hydrogen Phosphate.*—To a solution of dibenzyl hydrogen phosphate (11·12 g., 0·04 mole) and triethylamine (2·6 c.c., 0·02 mole) in dry nitromethane (50 c.c.), *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (5·68 g., 0·2 mole) was added. The solution warmed spontaneously from 17° to *ca.* 25° and was kept overnight at room temperature. The solution was then diluted with chloroform (100 c.c.) and washed with saturated sodium hydrogen carbonate solution (100 c.c.) and with water (2 × 100 c.c.), then dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in acetone (10 c.c.) and poured into water. The gummy precipitate was collected and dried at room temperature *in vacuo* over phosphoric oxide. Recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded tetrabenzyl pyrophosphate (9·22 g., 86%), m. p. and mixed m. p. 59—61°.

Beckmann Rearrangement of cyclo*Pentanone Oxime* p-*Nitrobenzenesulphonate followed by Reaction with Dibenzyl Hydrogen Phosphate.*—A solution of *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·284 g., 0·001 mole) in nitromethane (5 c.c.) was kept at room temperature for 2 hr.; rearrangement to the *O-p*-nitrobenzenesulphonate of valerolactam was then complete. Triethylamine (0·13 c.c., 0·001 mole) and dibenzyl hydrogen phosphate (0·556 g., 0·002 mole) were added, and the solution was set aside at room temperature for 16 hr. The neutral fraction was isolated as described above and assayed with *cyclo*hexylamine. The yield of tetrabenzyl

pyrophosphate was 27%. In a similar experiment where the amount of triethylamine added after the Beckmann rearrangement was increased to 0·003 mole the yield of pyrophosphate was increased to 44%.

Preparation of Tetrabenzyl Pyrophosphate from cyclo*Pentanone Oxime Benzenesulphonate.*—The reactions involving the formation of tetrabenzyl pyrophosphate and its subsequent assay by treatment with *cyclo*hexylamine and isolation of *cyclo*hexylammonium dibenzyl phosphate were repeated as described above, but with *cyclo*pentanone oxime benzenesulphonate in place of *p*-nitrobenzenesulphonate, and 2 : 6-lutidine (1 mol.) in place of triethylamine. When 1 mol. of oxime ester was employed, the yield of tetrabenzyl pyrophosphate was 41% in methyl cyanide and 55% in nitromethane; with nitromethane as solvent but with 2 mols. of oxime ester yields of 75—80% were obtained.

*Tetrabenzyl Pyrophosphate from Acetophenone Oxime Toluene-*p*-sulphonate.*—From acetophenone oxime toluene-*p*-sulphonate (0·289 g., 0·001 mole), dibenzyl hydrogen phosphate (0·55 g., 0·002 mole), and triethylamine (0·13 c.c., 0·001 mole) in benzene (5 c.c.) at 18° for 16 hr. the yield of tetrabenzyl pyrophosphate was 16%. The use of methyl cyanide (5 c.c.) increased the yield to 22%.

Tetrabenzyl Pyrophosphate from Ethyl Methyl Ketoxime Benzenesulphonate.—In a typical experiment ethyl methyl ketoxime benzenesulphonate (0·227 g., 0·001 mole) was added to a solution of dibenzyl hydrogen phosphate (0·556 g., 0·002 mole) and triethylamine (0·13 c.c., 0·001 mole) in methyl cyanide (10 c.c.), the solution kept at 18° for 16 hr., and the isolated neutral fraction assayed for tetrabenzyl pyrophosphate with *cyclo*hexylamine in the usual manner. The results are tabulated for 0·001 mole of base in 10 c.c. of solvent.

Solvent	Base added	Temp.	Reaction time (hr.)	Yield of pyrophosphate (%)
$MeNO_2$	Triethylamine	18°	16	38
,, ...	2 : 6-Lutidine	18	60	34
,, ...	,,	80	2	35
C_6H_6	,,	18	16	20

Preparation of Dibenzyl Diphenyl Pyrophosphate from cyclo*Pentanone Oxime* p*-Nitrobenzenesulphonate.*—An aqueous solution of diphenyl hydrogen phosphate (0·25 g., 0·001 mole) was titrated to pH 7 with tetramethylammonium hydroxide solution, the solution then evaporated under reduced pressure and dried by repeated evaporation with benzene. The residue was dissolved in benzene (10 c.c.), *cyclo*pentanone oxime *p*-nitrobenzenesulphonate (0·284 g., 0·001 mole) added, and the solution refluxed for 45 min. during which an oil was precipitated which solidified on cooling. The supernatant solution was decanted from the solid which was extracted with benzene (3 c.c.). The combined benzene solutions were refluxed for 2 hr. with dibenzyl hydrogen phosphate (0·278 g., 0·001 mole), cooled, washed with water (5 c.c.), and dried (Na_2SO_4). The solution was treated with *cyclo*hexylamine (0·5 c.c., 0·004 mole) and kept at room temperature for 16 hr.; then the precipitate formed (0·235 g., 71%), m. p. 172—179°, was filtered off. After crystallisation from ethanol the precipitate gave *cyclo*hexylammonium diphenyl phosphate (0·2 g.), m. p. and mixed m. p. 190°. The benzene filtrate from the *cyclo*hexylamine treatment was washed with N-hydrochloric acid (3 × 5 c.c.), water (5 c.c.), N-sodium hydroxide (3 × 5 c.c.), and water (5 c.c.). The dried (Na_2SO_4) solution was evaporated, and the residue dissolved in ethanol (2 c.c.) and poured into water (45 c.c.). The precipitate (0·172 g.), m. p. 70—73°, after crystallisation from *cyclo*hexane gave dibenzyl *N-cyclo*hexylphosphoramidate (0·11 g.), m. p. and mixed m. p. 78—80°.

Use of methyl cyanide instead of benzene in the above reaction of tetraethylammonium diphenyl phosphate with the oxime sulphonate gave a mixture of pyrophosphate tetraesters as judged by the *cyclo*hexylamine fission of the isolated neutral fraction. Similarly, treatment of tetraethylammonium dibenzyl phosphate with the oxime sulphonate in nitromethane followed by reaction with diphenyl hydrogen phosphate gave mixtures of pyrophosphate derivatives.

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