863. *Bis-*o-*phenylene Pyrophosphite: A New Reagent for Peptide Synthesis. Part I. The Preparation of Some* o-*Phenylene Pyrophosphites.*

By P. C. Crofts, J. H. H. Markes, and H. N. Rydon.

The usefulness of tetraethyl pyrophosphite as a reagent for peptide synthesis prompted a search for other, more readily accessible, pyrophosphites. The preparation of one such reagent, *viz.*, bis-*o*-phenylene pyrophosphite, from catechol by a two-stage process, in an overall yield of more than 80% is reported.

Tetraethyl pyrophosphite (IV; R = Et) was introduced as a reagent for the synthesis of peptides by Anderson, Blodinger, and Welcher[1] in 1952 and has since been used in several important syntheses;[2] it suffers, however, from the disadvantages that the yields, both in the preparation of the intermediate, diethyl phosphorochloridite, from phosphorus trichloride and ethanol in the presence of a tertiary base, and in the reaction of this phosphorochloridite with diethyl phosphite, are only moderate, and that purification, particularly of the phosphorochloridite, is difficult. The fact that *o*-phenylene phosphorochloridite (I) is readily prepared,[3] in excellent yield, from catechol and phosphorus trichloride without the use of tertiary base, suggested that *o*-phenylene pyrophosphites might be more readily accessible than the tetraethyl ester.

o-Phenylene phosphorochloridite (I) was at first prepared in ether, as described by Anschütz *et al.*,[3] but later, and more conveniently for large scale working, without a solvent. *o*-Phenylene phosphorochloridite with di-*n*-butyl phosphite and triethylamine in light petroleum gave a moderate yield of di-*n*-butyl *o*-phenylene pyrophosphite (II; R = Bu^n). A similar experiment with diethyl phosphite, however, yielded a mixture from which the two symmetrical compounds, tetraethyl pyrophosphite (IV; R = Et) and bis-*o*-phenylene pyrophosphite (III), were obtained. The expected unsymmetrical compound, diethyl *o*-phenylene pyrophosphite (II; R = Et), was probably also present, but was not isolated; it has recently been prepared from sodium diethyl phosphite and *o*-phenylene phosphorochloridite by Arbusov and Valitova,[4] who also isolated bis-*o*-phenylene pyrophosphite from the reaction product, indicating the occurrence of some

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[1] Anderson, Blodinger, and Welcher, *J. Amer. Chem. Soc.*, 1952, **74**, 5309.

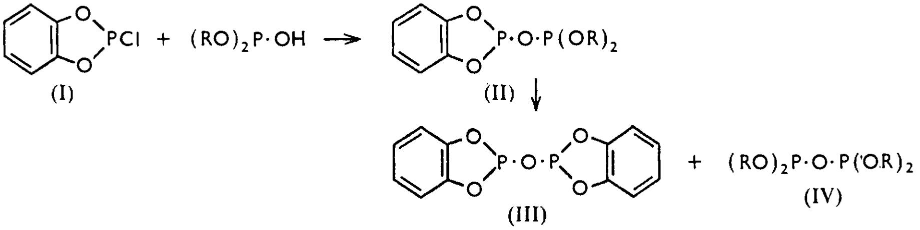
[2] *E.g.*, du Vigneaud, Ressler, Swan, Roberts, Katsoyannis, and Gordon, *J. Amer. Chem. Soc.*, 1953, **75**, 4879; Anderson, *ibid.*, 1953, **75**, 6081; du Vigneaud, Ressler, Swan, Roberts, and Katsoyannis, *ibid.*, 1954, **76**, 3115; Ressler and du Vigneaud, *ibid.*, 1957, **79**, 4511; Katsoyannis, Gish, and du Vigneaud, *ibid.*, p. 4516; Gish and du Vigneaud, *ibid.*, p. 3579.

[3] Anschütz, Broeker, Neher, and Ohnheiser, *Ber.*, 1943, **76**, 223.

[4] Arbusov and Valitova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1956, 681.

disproportionation. Disproportionations of this kind have been observed on several occasions with derivatives of pyro-acids containing quinquevalent phosphorus.[5]

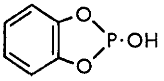
Attempts were made to confirm the structure of the symmetrical pyrophosphite (III) by preparing it by a different route, the most obvious being reaction between *o*-phenylene phosphite (V) and *o*-phenylene phosphorochloridite in the presence of a tertiary base.

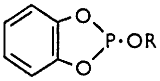


In fact, pure *o*-phenylene phosphite could not be isolated; the attempts to prepare it led, instead, to a very satisfactory preparation of the pyrophosphite (III).

Treatment of *o*-phenylene phosphorochloridite (I) with the theoretical amount of water in the presence of triethylamine dried over potassium hydroxide led to an inseparable mixture of the desired phosphite (V) and catechol. A similar mixture was obtained by the ester-interchange between catechol and diethyl phosphite, although such reactions have been found satisfactory for the preparation of higher dialkyl phosphites.[6] Attempts to prepare the ester (V) by hydrogenolysis of benzyl *o*-phenylene phosphite (VI; R = $Ph{\cdot}CH_2$) were unsuccessful; this may be, at least partly, due to the use of non-hydroxylic solvents, rendered necessary by the susceptibility of the phosphite (VI) to solvolysis.

(V)





(VI)

A further attempt to synthesise bis-*o*-phenylene pyrophosphite was made by heating together the phosphorochloridite (I) and ethyl *o*-phenylene phosphite (VI; R = Et), but this was equally unsuccessful, although analogous reactions have been found very satisfactory for the preparation of pyrophosphates.[7]

When attempting to prepare *o*-phenylene phosphite by hydrolysis of the phosphorochloridite, it was noticed that a little triethylamine hydrochloride was precipitated when triethylamine was added to the ethereal solution of the phosphorochloridite; this was eventually traced to the presence of small amounts of water in the triethylamine dried over potassium hydroxide, no precipitate being formed with triethylamine dried over, and redistilled from, sodium. When this sodium-dried triethylamine was used in a hydrolysis of the phosphorochloridite with slightly less than the theoretical amount of water, the product had a lower melting point than the products of the earlier hydrolysis and was shown, by elementary analysis and by colour reactions, to be a mixture of the phosphite (V) and the pyrophosphite (III).

This result suggested that bis-*o*-phenylene pyrophosphite might be prepared by treatment of two mols. of the phosphorochloridite (I) with one of water, in a manner analogous to the preparation of pyrophosphates by the partial hydrolysis of phosphorochloridates;[8] this proved to be the case. Initially, bis-*o*-phenylene pyrophosphite was prepared in 72% yield by partial hydrolysis of the ester (I) in ether in the presence of triethylamine.

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[5] Corby, Kenner, and Todd, *J.*, 1952, 1234; Kosolapoff, *J. Amer. Chem. Soc.*, 1952, **74**, 5520.

[6] Kosolapoff, *J. Amer. Chem. Soc.*, 1951, **73**, 4989; Malowan, *Inorg. Synth.*, 1953, **4**, 61.

[7] Hall and Jacobsen, *Ind. Eng. Chem.*, 1948, **40**, 694; Toy, *J. Amer. Chem. Soc.*, 1949, **71**, 2268; 1950, **72**, 2065.

[8] Toy, *J. Amer. Chem. Soc.*, 1948, **70**, 3882.

Subsequently, the yield was raised to 87%, and the reaction made more suitable for large-scale operation, by carrying it out without solvent, introducing the water as vapour, and removing the hydrogen chloride under reduced pressure. Bis-*o*-phenylene pyrophosphite (III) is, in this way, readily prepared from catechol by a two-stage process with an overall yield of better than 80%; its use in the synthesis of peptides will be described in Part II of this series.

EXPERIMENTAL

To avoid hydrolysis, calcium chloride guard-tubes were fitted to all condensers and dropping funnels; manipulations were carried out, when necessary, in a dry-box; m. p. tubes were stored over phosphoric oxide. Except where otherwise stated, light petroleum denotes the fraction of b. p. 30—40°. Ether was dried over sodium.

In calculating molecular refractivities, Eisenlohr's values [9] have been used, with 1·643 for oxygen and Kabachnik's value [10] of 7·04 for phosphorus in phosphites.

o-*Phenylene Phosphorochloridite* (I).—Phosphorus trichloride (94 g.) was added, in one portion, to catechol (50 g.) to which water (0·585 g.) had previously been added. There was a brisk evolution of hydrogen chloride and the mixture became solid. After an hour, more phosphorus trichloride (39 g.) was added, and the mixture heated, with stirring, on the steam-bath for 2½ hr. Distillation gave the ester (I) (74·5 g., 94%), b. p. 91°/18 mm., m. p. 30°, n_D^{20} 1·5724 (supercooled liquid).

*Di-*n*-butyl* o-*Phenylene Pyrophosphite* (II; R = Bu^n).—*o*-Phenylene phosphorochloridite (43·6 g.) in light petroleum (150 ml.) was added, with vigorous stirring, during 10 min. to di-*n*-butyl phosphite (48·5 g.) and triethylamine (25·3 g.) in light petroleum (250 ml.). The mixture was refluxed for 15 min. and allowed to cool. Precipitated triethylamine hydrochloride was removed by rapid filtration and the filtrate kept at 0° for several days. The product was again filtered and distilled; light petroleum and unchanged starting materials were followed by the *pyrophosphite* (27·8 g., 33·5%), b. p. 140°/0·5 mm., n_D^{20} 1·5078, d_4^{20} 1·1760 whence $[R_L]_D$ 84·19 (Calc. 85·55) (Found: C, 49·9; H, 6·3; P, 18·2. $C_{14}H_{22}O_5P_2$ requires C, 50·6; H, 6·7; P, 18·6%).

Reaction of Diethyl Phosphite with o-*Phenylene Phosphorochloridite.*—The phosphorochloridite (43·6 g.) in light petroleum (150 ml.), was added with vigorous stirring during 10 min. to diethyl phosphite (34·5 g.) and triethylamine (25·3 g.) in light petroleum (250 ml.), and the whole refluxed for 15 min. Precipitated triethylamine hydrochloride was filtered off; further hydrochloride was however precipitated slowly and the mixture was refluxed overnight, kept for a few hours, and again filtered. The filtrate, which now remained quite clear, was distilled. The later fractions solidified in the condenser and, on redistillation, gave *bis-*o*-phenylene pyrophosphite* (16·9 g., 46%), b. p. 122—126°/0·15 mm., m. p. 72° [Found: C, 48·7; H, 3·1; P, 20·6%; *M* (cryoscopic, in benzene), 276. $C_{12}H_8O_5P_2$ requires C, 49·0; H, 2·7; P, 21·0%; *M*, 294]. Several redistillations of the lower-boiling fractions afforded tetraethyl pyrophosphite, b. p. 99—100°/9 mm., n_D^{20} 1·4386 (lit.,[1] n_D^{26} 1·4313) (Found: C, 36·9; H, 7·7; P, 23·2. Calc. for $C_8H_{20}O_5P_2$: C, 37·2; H, 7·8; P, 24·0%).

Ethyl o-*Phenylene Phosphite* (VI; R = Et).—*o*-Phenylene phosphorochloridite (34·9 g.) in ether (50 ml.) was added with rapid stirring during 28 min. to ethanol (9·2 g.) and diethylaniline (30·0 g.) in ether (150 ml.). After being stirred for a further 30 min., the mixture was kept overnight at 0° and filtered. Distillation of the filtrate gave the phosphite (32·7 g., 89%), b. p. 97°/14 mm., n_D^{20} 1·5196, d_4^{20} 1·1954, whence $[R_L]_D$ 46·80 (Calc., 46·41) (lit.,[11] b. p. 86°/11 mm., n_D^{17} 1·5085) (Found: C, 52·2; H, 4·9; P, 16·4. Calc. for $C_8H_9O_3P$: C, 52·2; H, 4·9; P, 16·8%).

There was no reaction, below 200°, when this compound was heated with *o*-phenylene phosphorochloridite, even in the presence of iodine, sodium iodide, or copper powder.

Benzyl o-*Phenylene Phosphite* (VI; R = $Ph{\cdot}CH_2$).—*o*-Phenylene phosphorochloridite (34·9 g.) in ether (100 ml.) was added with stirring during 30 min. to benzyl alcohol (21·6 g.) and diethylaniline (30·0 g.) in ether (200 ml.). The mixture was stirred and refluxed for 30 min., then kept at 0° for several days. Filtration, followed by two distillations, afforded the

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[9] Eisenlohr, *Z. phys. Chem.*, 1910, **75**, 585.

[10] Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1948, 219.

[11] Arbusov and Valitova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1940, 529.

phosphite (35·0 g.; 71%), b. p. 97°/0·13 mm., n_D^{20} 1·5761, d_4^{20} 1·2313, whence $[R_L]_D$ 66·18 (Calc. 65·90) (Found: C, 63·9; H, 4·8; P, 12·8. $C_{13}H_{11}O_3P$ requires C, 63·4; H, 4·5; P, 12·6%).

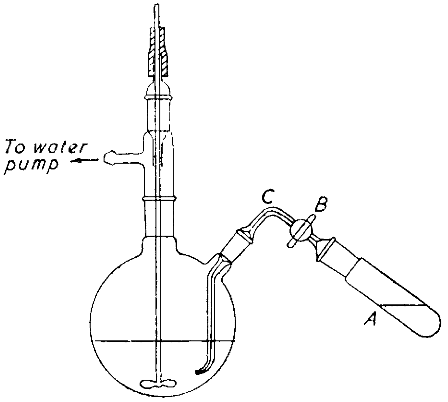
Attempted Preparations of o-*Phenylene Phosphite*.—(a) *By hydrogenolysis.* No hydrogen was absorbed when benzyl *o*-phenylene phosphite was shaken with hydrogen in ether over palladised barium sulphate, palladised calcium carbonate, or Adams platinic oxide catalyst, or in dioxan or chloroform over Adams catalyst.

(b) *By ester interchange.* Catechol (22·0 g.) and diethyl phosphite (55·2 g.) were heated together with stirring for 56 hr., the pressure being reduced from atmospheric to 4 mm. until distillation of ethanol ceased. The distillate, collected in a trap at −70°, contained some diethyl phosphite and was estimated from the refractive index to contain 12·7 g. of ethanol (theor., 18·4 g.). Distillation of the residue afforded diethyl phosphite and a solid, b. p. *ca.* 110°/0·3 mm. (Found: P, 15·6. Calc. for $C_6H_5O_3P$: P, 19·8%), which, after recrystallisation from ether–light petroleum, had m. p. 98—106°, depressed to 70—100° on admixture with catechol (m. p. 105°). Addition of ethereal ferric chloride to an ethereal solution gave a deep red-brown colour which faded rapidly to reveal a cream-coloured precipitate; addition of more ethereal ferric chloride gave a permanent red-brown colour. With ethereal ferric chloride, catechol and diethyl phosphite give a red colour and a cream-coloured precipitate respectively. It was concluded that the product was a mixture of catechol and the required phosphite.

(c) *By hydrolysis.* (i) Addition of the theoretical amount of water, in ether, to *o*-phenylene phosphorochloridite and triethylamine (dried over potassium hydroxide and redistilled) in ether, filtration, and distillation of the filtrate gave a white solid, b. p. 160—170°/12 mm., m. p. 103—104°, depressed to *ca.* 85° on admixture with catechol; this material contained phosphorus (Found: P, 14·9%) and behaved towards ethereal ferric chloride in the same way as the product of the previous experiment.

(ii) Water (1·4 g., 0·078 mole) in ether (150 ml.) was added with stirring during 30 min. to *o*-phenylene phosphorochloridite (14·1 g., 0·081 mole) and triethylamine (dried and distilled over sodium) (9·1 g., 0·090 mole) in ether (270 ml.), and the mixture was stirred and refluxed for a further 30 min. Next day, triethylamine hydrochloride was removed and the filtrate distilled, affording a fraction (3·1 g.), b. p. 130—144°/0·25 mm., m. p. 54—55°, after softening at 44°; the product gave, with ethereal ferric chloride, a pale buff precipitate, and then, on addition of more ferric chloride, a brown oil, but not the intense red-brown solution characteristic of catechol. These reactions, together with elementary analysis (Found: C, 48·4; H, 3·2; P, 20·4. Calc. for $C_6H_5O_3P$: C, 46·2; H, 3·2; P, 19·8. Calc. for $C_{12}H_8O_5P$: C, 49·0; H, 2·7; P, 21·0%), indicated that the product was a mixture of *o*-phenylene phosphite and bis-*o*-phenylene pyrophosphite.

*Apparatus for preparation of bis-*o*-phenylene pyrophosphite.*



*Bis-*o*-phenylene Pyrophosphite* (III).—(a) *With added base.* Water (1·15 g.) in ether (150 ml.) was added with rapid stirring during 45 min. to *o*-phenylene phosphorochloridite (22·7 g.) and triethylamine (dried and distilled over sodium) (14·5 g.) in ether (250 ml.), and the mixture stirred and refluxed for a further 2½ hr. Next day, triethylamine hydrochloride was filtered off and the filtrate evaporated to dryness under reduced pressure, further amounts of hydrochloride being removed by filtration from time to time. The residue (15·6 g.) was recrystallised from light petroleum (b. p. 40—60°), giving the pyrophosphite (13·5 g., 72%), m. p. 72°, not depressed on admixture with material obtained from the phosphorochloridite and diethyl phosphite.

(b) *Without base or solvent* (*preferred procedure*). The apparatus used is shown in the Figure. *o*-Phenylene phosphorochloridite (144 g.) was placed in the flask and warmed to 30—35°. Water (6·80 g.) was placed in the vessel *A*, the apparatus was evacuated by means of a water-pump, and the tap *B* opened to allow the introduction of water-vapour through tube *C* (1 mm. internal diameter), which occupied 5½ hr. (N.B.: If the water is added too rapidly, the yield is reduced.) Vigorous stirring was maintained throughout. Distillation gave recovered phosphorochloridite (20·4 g.) and the pyrophosphite (90·7 g., 87%), b. p. 156°/0·25 mm., m. p. 72°, n_D^{20} 1·5090, d_4^{20} 1·4134 (supercooled liquid), whence $[R_L]_D$ 70·13 (Calc. 70·51); the product obtained by Arbusov and Valitova[4] had n_D^{20} 1·5502, d^{20} 1·3107 (whence $[R_L]_D$ 71·50), was too hygroscopic for the m. p. to be determined and appears to have been impure.

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Manchester College of Science and Technology,
Manchester, 1.

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