

826. *Studies on Phosphorylation. Part XX.* The Oxidation of Mono- and Di-alkyl Phosphites.*

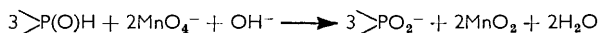
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Permanganate, periodate, iodate, and hypochlorite oxidise dialkyl phosphites to the corresponding phosphates. Of these reagents, permanganate alone oxidises monoalkyl phosphites.

AMONG the phosphorylation methods developed in this Laboratory, one¹ in which alkyl benzyl phosphite intermediates are employed has been of considerable value. There is sometimes a need for a mild method of converting these into the corresponding phosphates, applicable when the alkyl residue is a complex, sensitive grouping. While a number of reagents, such as mercuric oxide and manganese dioxide,² hydrogen peroxide,³ hypochlorite,⁴ and dinitrogen tetroxide,⁵ have been used successfully with trialkyl phosphites, it has been stated⁶ that both the primary and the secondary esters of phosphorous acid are quite resistant to oxidation. This is evidently not so. The oxidation of dialkyl phosphites by iodine has been studied kinetically (although the products were not isolated) and they have been converted into dialkyl phosphates by reaction with *N*-chlorosuccinimide to yield the phosphorochloridate, followed by the hydrolysis of the latter.¹ Difficulties have sometimes been experienced with the latter route, possibly due to the instability of benzyl phosphorochloridates, and a direct oxidation applicable to aqueous solutions would be valuable. The present study arose from the observation that phosphites rapidly decolorised permanganate. Since then, Dimroth and Ploch⁸ have described an investigation of the permanganate oxidation of mono-, di-, and tri-alkyl phosphites, and we confirm their results in so far as our experiments correspond.

Using ammonium monobenzyl phosphite and dibenzyl phosphite as models, we studied a number of mild oxidants, initially by paper-chromatographic examination of the products. Dibenzyl phosphite was unaffected by benzoyl peroxide, perbenzoic acid, and active manganese dioxide. Mercuric acetate and oxide slowly converted the phosphite into a crystalline mercury derivative from which the phosphite appeared to be regenerated by hydrogen sulphide.

Potassium permanganate in aqueous dioxan under basic conditions was an effective reagent, oxidising mono- and di-benzyl phosphite according to the scheme



Good yields were obtained. Too rapid addition of the reagent caused oxidation of the benzyl group, to give small amounts of benzaldehyde and benzoic acid. None of the other reagents studied oxidised the monobenzyl ester.

With hypochlorite at pH 8—9 rapid and quantitative oxidation of dibenzyl phosphite to the phosphate occurred.

Periodate and iodate in mildly acid medium (~pH 3—4) gave high yields of dibenzyl phosphate from the phosphite, with generation of iodine. Extraction and estimation

* Part XIX, *J.*, 1960, 1155.

¹ Corby, Kenner, and Todd, *J.*, 1952, 3669; Kenner, Todd, and Weymouth, *J.*, 1952, 3675.

² Ayres and Rydon, *J.*, 1957, 1109.

³ Stetter and Steinacker, *Chem. Ber.*, 1952, **85**, 451; cf., however, ref. 5.

⁴ B.P. 737,431.

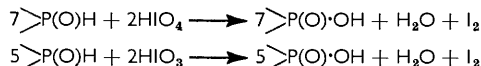
⁵ Cox and Westheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5441.

⁶ Van Wazer, "Phosphorus and Its Compounds," Interscience Publ. Inc., New York, 1958, Vol. I, p. 381.

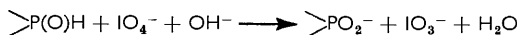
⁷ Nylén, *Z. anorg. Chem.*, 1938, **235**, 161.

⁸ Dimroth and Ploch, *Chem. Ber.*, 1957, **90**, 801.

of the latter (80% recovery) indicated a stoichiometry for the reactions approximating to:



The preferred reagent, however, was periodate in weakly basic solution. Sodium hydrogen carbonate or 2,6-lutidine was used as base, since pyridine was oxidised under these conditions. Besides the lack of side reactions and the isolation of pure products, the very soluble periodic acid could be adapted to solutions of low water content for phosphites of high molecular weight. A titrimetric study of the reaction showed that it followed the course



and, moreover, iodate was not reduced in basic solution.

We have not studied the reaction mechanisms involved in these oxidations, but the fact that permanganate alone oxidises the monobenzyl phosphite anion suggests that it reacts by a radical mechanism. In support of this view it was noted that, during oxidation of dibenzyl phosphite in glacial acetic acid in a suitable apparatus, oxygen was absorbed, a characteristic of some other free-radical oxidations.⁹

The permanganate, periodate, and hypochlorite reagents were successfully applied to the oxidation of 2',3'-*O*-isopropylideneadenosine 5'-(benzyl phosphite) and 1,2-*O*-isopropylidenglycerol benzyl phosphite, details being given in the experimental section. Further use of the reagents in the synthesis of phosphatidic acids will be described in a forthcoming paper.

EXPERIMENTAL

Paper Chromatography.—Ascending chromatograms were run on Whatman No. 1 paper with the solvent systems, (A) butan-1-ol-acetic acid-water (5:2:3) and (B) propan-2-ol-ammonia-water (7:1:2). Phosphates and phosphites were detected by the molybdate reagent.¹⁰

Oxidation of Dibenzyl Phosphite.—(a) *Periodic acid.* (i) Basic conditions. Dibenzyl phosphite (2.62 g.), in dioxan (50 ml.) and 2,6-lutidine (5 ml.), was treated with periodic acid (2.50 g. of HIO₄) in water (50 ml.), and the solution stirred at room temperature for 1 hr. Chromatography showed complete conversion into dibenzyl phosphate. A quarter part of the solution was removed for titration, and to the remainder was added sodium hydrogen carbonate. Lutidine was extracted with chloroform (5 × 20 ml.), the aqueous phase acidified, and dibenzyl hydrogen phosphate extracted into chloroform (3 × 10 ml.). The dried (Na₂SO₄) solution was evaporated. The crystalline residue had m. p. 71–73° raised to 79.5° on recrystallisation from ether (Found: C, 60.3; H, 5.4; P, 11.5. Calc. for C₁₄H₁₅O₄P: C, 60.4; H, 5.4; P, 11.2%).

(ii) Acid conditions. Dibenzyl phosphite (4.0 g.) was suspended in 1:1 aqueous dioxan (40 ml.) and to the stirred solution periodic acid (2.0 g.) in water (20 ml.) was added during 30 min. Sodium hydrogen carbonate was added to pH 8, the iodine extracted with chloroform, and then after acidification dibenzyl hydrogen phosphate (3.65 g., 86%), m. p. 71°, was isolated as above. One crystallisation gave the acid, m. p. 78°.

(b) *Iodic acid.* The phosphite (4.0 g.) was dispersed in dioxan (50 ml.) and water (20 ml.) containing 20% acetic acid (1 ml.). Potassium iodate (1.5 g.) in water (30 ml.) was added with stirring to the warm (50°) solution during 10 min. and stirring was continued for a further 0.5 hr. Iodine was extracted, and the dibenzyl hydrogen phosphate then isolated as above. The crude yield was 94%.

Iodate under basic conditions was ineffective.

(c) *Sodium hypochlorite.* 0.5N-Sodium hypochlorite (35 ml.) was added during 15 min. to a stirred solution of the phosphite (2.0 g.) in dioxan (25 ml.) containing sodium hydrogen carbonate (4.0 g.). Stirring was continued for 30 min., and after acidification the dibenzyl hydrogen phosphate (1.95 g., 92%) was isolated as before.

⁹ Waters, *Trans. Faraday Soc.*, 1946, **42**, 188.

¹⁰ Hanes and Isherwood, *Nature*, 1949, **164**, 1107.

(d) *Potassium permanganate*. The phosphite (26.2 g.) and sodium hydrogen carbonate (3.0 g.) were suspended in 1:1 aqueous dioxan (100 ml.) and potassium permanganate (10.5 g.) in water (150 ml.) added with stirring during 1 hr. Next morning the coagulated manganese dioxide was removed, and after acidification the product was isolated. The crude product (26.0 g., 94%) had m. p. 68° and was conveniently crystallised from benzene–light petroleum.

Pyridine was used satisfactorily in place of sodium hydrogen carbonate, as base.

Oxidation of Ammonium Benzyl Phosphite.—Potassium permanganate (1.05 g.) in water (30 ml.) was added slowly to a solution of the phosphite (1.89 g.) and sodium hydrogen carbonate (2.0 g.) in water (30 ml.). After removal of manganese dioxide the solution was evaporated to dryness under reduced pressure. The residue was stirred with a suspension of Dowex-50 (H form) resin in water (20 ml.), and the solution was percolated through a column of the same resin (20 g.) into cyclohexylamine (2.5 g.). The solution was concentrated to 20 ml., and hot acetone (100 ml.) added; dicyclohexylammonium benzyl phosphate¹¹ (3.0 g., 78%), m. p. 232–234°, separated (Found: C, 56.8; H, 9.3; N, 7.1. Calc. for C₁₇H₃₃O₄N₂P: C, 56.4; H, 9.2; N, 6.9%).

1,2-O-Isopropylidenglycerol Benzyl Phosphite.—A solution of *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride¹ [prepared from monobenzyl phosphite (17.1 g.), diphenyl phosphorochloridate (26.7 g.), and dry pyridine (8.0 ml.) in dry benzene (250 ml.)] was added to *O*-isopropylidenglycerol (10.85 g.) and 2,6-lutidine (9.35 ml.). The solution was stirred with exclusion of moisture for 1 hr., lutidine hydrochloride then removed by filtration, and the solution evaporated under reduced pressure. The residue, dissolved in chloroform (100 ml.), was washed with water and sodium hydrogen carbonate solution, and the solution evaporated. The phosphite was obtained as a colourless oil (18.95 g., 79%) and gave one well-defined spot on chromatograms, with R_F 0.95 (in *A*) and 0.7 (in *B*).

1,2-O-Isopropylidenglycerol Benzyl Phosphate.—(a) The above phosphite (3.0 g.) was dissolved in 2,6-lutidine (15 ml.) and water (10 ml.), and periodic acid (2.42 g.) in water (10 ml.) added to the stirred solution during 10 min. Stirring was continued for 1 hr. and then solid hydrated-barium hydroxide (6.0 g.) was added and the lutidine extracted with chloroform (5 × 10 ml.). The aqueous phase was neutralised with carbon dioxide, the solution boiled, filtered, and evaporated, and the barium salt (2.2 g., 57%) collected. Recrystallisation from 95% ethanol or, better, dimethylformamide–ethyl acetate afforded the *phosphate* in needles (Found: C, 41.8; H, 4.4. C₂₆H₃₆BaO₁₂P₂ requires C, 42.2; H, 4.8%). Infrared absorption bands were present at 1383, 1373 (Me₂C), and 1501 cm.⁻¹ (aromatic).

(b) The phosphite (1.6 g.) in 2:1 dioxan–water (60 ml.) and pyridine (5 ml.) was treated with potassium permanganate (0.58 g.) during ½ hr. After basification, pyridine was extracted with chloroform, the solution was acidified with hydrochloric acid to pH 3, and the products were extracted with chloroform. Careful evaporation gave the free acid as a gum which was converted into the solid barium salt (1.56 g., 75%).

The oxidation could also be carried out with sodium hypochlorite and by reaction with *N*-chlorosuccinimide followed by hydrolysis of the intermediate phosphorochloridate.

Hydrogenation of the benzyl phosphate in water containing a little triethylamine over palladium black was rapid and yielded barium 1,2-*O*-isopropylidenglycerol phosphate¹² as a white powder. It gave a single spot, R_F 0.19, when run on chromatograms in solvent *B* (Found: C, 19.2; H, 3.6. Calc. for C₈H₄BaO₆P₂H₂O: C, 19.7; H, 3.6%).

The isopropylidene derivative was hydrolysed by 10% acetic acid under reflux for 30 min. Glycerol 1-(benzyl phosphate) was conveniently isolated as the cyclohexylammonium salt, m. p. and mixed m. p. 123°, R_F 0.55 in solvent *B* (Found: P, 8.8. Calc. for C₁₆H₂₆NO₆P: P, 8.6%).

Adenosine 5'-(Benzyl Hydrogen Phosphate).—(a) Benzyl 2',3'-*O*-isopropylideneadenosine 5'-phosphite (1.87 g.; crude) was dissolved in pyridine (10 ml.), and potassium permanganate (0.428 g.) in water (25 ml.) added during 30 min. with stirring. Manganese dioxide was removed. The filtrate was made alkaline with barium hydroxide solution and extracted with chloroform, and the aqueous phase neutralised with carbon dioxide. The isopropylidene derivative was isolated after removal of barium carbonate and evaporation, and then boiled under reflux for 1 hr. with 0.03*N*-hydrochloric acid (120 ml.). Adenosine 5'-(benzyl hydrogen phosphate)¹³

¹¹ Chase, Kenner, Todd, and Webb, *J.*, 1956, 1375.

¹² Fischer and Pfähler, *Ber.*, 1920, 53, 1606.

¹³ Baddiley and Todd, *J.*, 1947, 648.

(0.79 g., 45%) separated from the cooled solution. Recrystallised from water, it had m. p. and mixed m. p. 234°.

The oxidation was also carried out successfully with the periodate-lutidine reagent, and the product isolated as above.

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