CXLIV. THE PREPARATION OF PHENYL PHOSPHORIC ESTERS

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THE phosphoric esters of simple phenols have been prepared through the action of phosphorus oxychloride on the phenol. Thus Rapp [1884] and Jacobsen [1875] prepared monophenyl phosphoryl chloride; monophenyl phosphoric acid was prepared by Iwatsura [1926] and the phosphoric esters of several phenols by Asakawa [1929]. A method for making disodium phenyl phosphate was recently described by Freeman & Colver [1938]. The procedures used by these authors have been essentially the same, i.e. a prolonged refluxing of phosphorus oxychloride with the phenol at a high temperature. The final reaction mixture consists of unchanged phosphorus oxychloride and the mono-, di- and tri-esterification products. These are separated by fractional distillation under diminished pressure. The phenyl phosphoryl chlorides are decomposed with water to give the phosphoric acid esters.

The introduction of phenyl phosphoric ester for the study of phosphatase activity in blood serum [King & Armstrong, 1934] and in milk [Kay & Graham, 1935], and the use of phosphoric esters of several phenols for studying the kinetics of phosphatase hydrolysis [King & Delory, 1938; 1939] have made desirable the description of a simple procedure for preparing phenyl phosphoric esters. The reaction of phenols with phosphorus oxychloride in pyridine solution takes place quickly and without the necessity for prolonged heating. When the phenol and the oxychloride are mixed in molecular proportions there is only one product of the reaction, namely the primary ester, and this is usually uncontaminated by unesterified phosphoric acid. The separation of the free ester from ether solution, or of its salts from aqueous alcohol is easily accomplished. The following esters have been prepared by this method: phenyl phosphate, *o*-methylphenyl phosphate, *p*-bromophenyl phosphate, *p*-nitrophenylphosphate and cyclohexanol phosphate.

EXPERIMENTAL

Barium phenyl phosphate

To 10 ml. of phosphorus oxychloride (17.1 g.) in a 1 l. beaker is added, slowly and with stirring, a solution of 10.5 g. of phenol in 50 ml. of dry pyridine. The mixture becomes hot and a crystalline precipitate of pyridine hydrochloride separates. The beaker is covered with a watch glass and the mixture is boiled gently for 10 min. The hot solution solidifies on cooling. The phenyl phosphoryl chloride is decomposed with water (5 ml.) added dropwise and slowly. It is advisable to cool the beaker under the cold water tap during this process, as the reaction may be somewhat violent and much heat is developed. Hot saturated aqueous barium hydroxide is added until the mixture is pink to phenolphthalein. The barium salt of phenyl phosphoric ester separates as a heavy flocculent precipitate. This is increased by adding alcohol, with stirring, to the capacity of the beaker and leaving in the ice chest overnight. The barium phenyl phosphate

is filtered by suction, washed first with 50 %, then with absolute alcohol, and is dried *in vacuo* over H_2SO_4 . Yield of crude barium salt 29.4 g. and 30.2 g. in two typical experiments (85 and 87 % of theoretical). Crystallized from hot aqueous alcohol barium phenyl phosphate separates as small glancing platelets. (Found: P, 8.95, 8.97%; Ba, 40.4, 40.0%. Calc. for $\text{BaC}_6\text{H}_5\text{PO}_4 \cdot 2\text{H}_2\text{O}$: P, 8.98; Ba, 39.9%.)

Disodium phenyl phosphate

This salt is generally used for the phosphatase determinations and for other enzymic studies. For that reason its preparation is described. 10 g. of the Ba salt are dissolved in 300 ml. of 0.2 *N* HCl, and the solution shaken out with 6 changes of 100 ml. of ether. The combined ether extracts are diluted with half their volume of alcohol and 40 % aqueous NaOH added with stirring until the mixture is alkaline. The precipitate of disodium phenyl phosphate is filtered, washed with alcohol and dried *in vacuo* over H_2SO_4 .

o-Methylphenyl phosphate

5 g. of *o*-cresol in 25 ml. of pyridine were added to 4.15 ml. of phosphorus oxychloride. The reaction mixture was heated for 1 hr., cooled and diluted slowly with water to a total volume of 100 ml. The solution was neutralized with 40 % NaOH. 9.5 g. of barium chloride (a 50 % excess over the theoretical), dissolved in 50 ml. of water, were added with stirring, followed by 2 vol. alcohol. The heavy precipitate which separated on standing was filtered, and extracted with hot water (500 ml.). On adding 2 vol. alcohol to the filtered extract, the barium *o*-methylphenyl phosphate separated as a precipitate of small plate-like crystals. Analysis: P, 8.97%; Ba, 40.2%. Calc. for $\text{C}_7\text{H}_7\text{O}_4\text{PBa} \cdot \text{H}_2\text{O}$: P, 9.09%; Ba, 40.2%.

p-Bromophenyl phosphate

A solution of 17.3 g. of *p*-bromophenol in 50 ml. of pyridine was added slowly and with stirring to 9 ml. of phosphorus oxychloride. The mixture was allowed to cool spontaneously and deposited crystals of pyridine hydrochloride. Water was added dropwise, until the initial violent reaction had subsided, and then in amount sufficient to make a final volume of about 150 ml. Hot saturated aqueous barium hydroxide was added until the mixture was alkaline, followed by an equal volume of alcohol. The barium salt of *p*-bromophenyl phosphate separated as a sheeny white crystalline precipitate. (Found: P, 7.69%; Ba, 36.6%. Recrystallized from aqueous alcohol the product analysed: P, 8.02, 7.98%; Ba, 35.2, 35.8%. Calc. for $\text{C}_6\text{H}_4\text{O}_4\text{PBrBa}$: P, 7.99%; Ba, 35.3%.)

p-Nitrophenyl phosphate

13.9 g. of *p*-nitrophenol were dissolved in 50 ml. of pyridine and added to 9 ml. of phosphorus oxychloride. The mixture was diluted with water to a final volume of 150 ml. Hot saturated barium hydroxide and alcohol were added as in the case of the bromophenyl phosphate. The barium salt was obtained as pale yellow plate-like crystals. (Found: P, 7.97, 7.99%. Calc. for $\text{C}_6\text{H}_4\text{O}_6\text{NPBa} \cdot 2\text{H}_2\text{O}$: P, 7.95%.)

cycloHexanol phosphate

5.7 ml. of *cyclohexanol* were added to 5 ml. of phosphorus oxychloride in 50 ml. of pyridine. The product was treated with water, diluted with aqueous alcohol and precipitated with barium hydroxide. The crude barium salt was only slightly soluble in water. It was shaken with alcoholic *N* H_2SO_4 in amount

equivalent to the barium present (determined by analysis). A small excess of H_2SO_4 in the filtrate was removed with benzidine, and the *cyclohexanol* phosphate precipitated with alcoholic potassium hydroxide. (Found: P, 11.9%; K, 31.1%. Calc. for $\text{K}_2\text{C}_6\text{H}_{10}\text{PO}_4$: P, 12.1%; K, 30.6%.)

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