[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE OF AGRICULTURE AND APPLIED SCIENCE]

Synthesis of Disodium Phenyl Phosphate

BY H. F. FREEMAN AND C. W. COLVER

Introduction

A rapid, accurate method for determining whether a supply of milk had been pasteurized properly is, from a public health standpoint, very important. Milk contains the enzyme phosphatase which is so resistant toward heat that when its activity is fully arrested, all pathogens likely to be present are destroyed. The presence or absence of active phosphatase in milk should be, therefore, a reliable test for effective pasteurization.

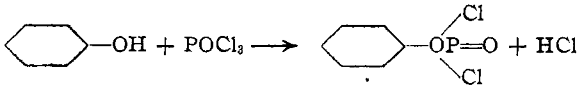
A method of Kay[1] and co-workers for the detection of phosphatase in milk makes use of disodium phenyl phosphate. This compound is hydrolyzed under certain conditions by phosphatase to give phenol. The amount of phenol liberated is accordingly a measure of the presence of phosphatase.

Dr. C. H. Whitnah and co-workers in this department have been carrying on investigations dealing with the relationship of enzymes to other constituents of milk and wanted recently disodium phenyl phosphate for their investigations in this field. At that time a commercial supply of disodium phenyl phosphate was not available in the United States. To supply the needs in our department we have prepared this compound with good results according to the following procedure.

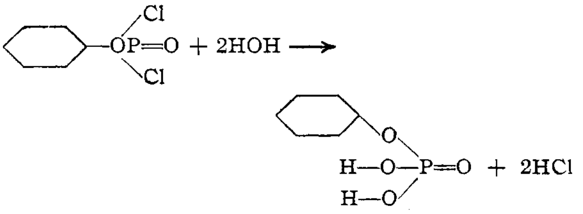
Monophenyl phosphoryl chloride was first formed by the action of phosphorus oxychloride upon phenol.[2] The monophenyl phosphoryl chloride was then hydrolyzed to give phenyl dihydrogen phosphate and this ester then neutralized to give the disodium phenyl phosphate.

Experimental

Monophenyl Phosphoryl Chloride.—Four hundred and seventy grams (5 moles) of phenol and 767 g. (5 moles) of phosphorus oxychloride were placed in a 2-liter round-bottomed flask fitted with a reflux condenser and heated to gentle boiling for ten hours. The reaction mixture, which contained mono- and diphenyl phosphoryl chlorides, and possibly some triphenyl phosphate, was transferred to a Claisen distilling flask and fractionally distilled under reduced pressure. The monophenyl phosphoryl chloride distilled over at 130–134° (21 mm.) and the diphenyl phosphoryl chloride at 212–215° (21 mm.). Yield of the crude monophenyl phosphoryl chloride was 785 g. (74.4%) and the yield of the crude diphenyl phosphoryl chloride which received no further purification was 110 g. (8.2%). Redistillation of the crude monophenyl phosphoryl chloride gave a yield of 744 g. (70.4%) boiling at 240° (760 mm.). Careful redistillation of the impure monophenyl phosphoryl chloride makes purification of the final product much easier.



Phenyl Dihydrogen Phosphate.—Two liters of water was placed in a 5-liter 3-necked flask fitted with a mechanical stirrer, condenser, and a separatory funnel. The upper end of the condenser was fitted with a tube to carry away the hydrogen chloride vapors for absorption. The 744 g. (3.52 moles) of monophenyl phosphoryl chloride obtained in the previous reaction was added slowly, with vigorous stirring, to the water. The hydrolysis at the start is slow but becomes violent if the addition is made too rapidly. The rate at which the acid chloride is hydrolyzed is indicated by the rate at which the hydrogen chloride is evolved. About three hours was required for the hydrolysis. The solution was then filtered and most of the hydrogen chloride was removed by warming it in a slow stream of air under reduced pressure. It was then evaporated further in a vacuum desiccator containing sodium hydroxide. Some of the phenyl dihydrogen phosphate separated in very large crystals and was filtered off and the filtrate further concentrated until free from hydrogen chloride. This solution and the crystals were used for making the salt.



Disodium Phenyl Phosphate.—Disodium phenyl phosphate was formed by adding solid sodium carbonate to a concentrated solution of the phenyl dihydrogen phosphate, which had been freed entirely from hydrogen chloride, until there was no further effervescence. The salt is formed with sodium carbonate rather than sodium hydroxide to prevent the formation of sodium phenolate. The solution obtained was clear and showed no pink coloration.

Crystals of disodium phenyl phosphate were obtained from a concentrated solution of this salt by adding a mixture of ethyl alcohol and diethyl ether until there was no further precipitation. The alcohol–ether mixture

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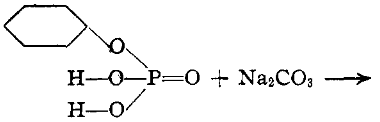
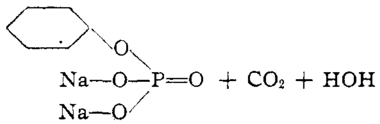
[1] Kay, *Can. Public Health J.*, **27**, 551–554 (1936); Kay and Neáve, *Dairy Ind.*, **2**, 5–7 (1937).

[2] Jacobsen, *Ber.*, **8**, 1521 (1875), and Rapp, *Ann.*, **224**, 157 (1884).

tends to hold any phenol in solution and to prevent hydrolysis of the salt. The product, when taken up in water and reprecipitated again with a mixture of alcohol and ether, showed in a water solution only a faint trace of phenol. The yield of the disodium phenyl phosphate after thorough drying in a vacuum desiccator was 700 g. (68.2%).





Summary

Disodium phenyl phosphate, which showed in a water solution only a faint trace of phenol, was obtained in good yields starting with phenol and phosphorus oxychloride.

MANHATTAN, KANSAS RECEIVED DECEMBER 31, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS]

Mercuration of Diphenyl Ether and Some of its Derivatives

BY W. D. SCHROEDER AND R. Q. BREWSTER

In continuation of the study of iodinated derivatives of diphenyl ether which is being conducted in this Laboratory,[1] it seemed that these iodine compounds might be obtained by mercuration of diphenyl ether, or some of its derivatives, and subsequent replacement of the mercuri group by iodine. It was particularly desirable to obtain compounds in which the mercury atom was joined to the nucleus at the position ortho to the oxygen since its replacement by iodine would then lead to the formation of 2-iodo derivatives which are not readily obtainable by direct iodination. This end, however, was not attained. In all cases 4-mercuri compounds were produced which upon heating with iodine chloride in acetic acid solution gave 4-iodo substituents. Nevertheless the mercury compounds themselves seem to warrant a brief description since they are easily prepared and in some instances heating of the mercurated diphenyl ethers with aryl halides leads to the precipitation of mercuric halides and the formation of a carbon–carbon bonding which is rather unusual for organic mercurials.

Experimental Part

Mercuration of Diphenyl Ether.—Mercuration with mercuric acetate in glacial acetic acid solution was found to give the best results. In order to obtain as large a proportion as possible of the monoacetoxymercuri diphenyl ether an excess of the diphenyl ether was necessary. One mole (216 g.) of mercuric oxide was dissolved in 800 cc. of glacial acetic acid and the solution made nearly anhydrous by the addition of 100 g. of acetic anhydride. Two moles (340 g.) of diphenyl ether was added, the solution was heated on the steam-bath until a test portion was free from ionic mercury (two and one-half to three hours) and poured into 2 liters of water. The pasty precipitate consisted of unchanged diphenyl ether, 4-acetoxymercuri diphenyl ether (I) and 4,4′-diacetoxymercuri diphenyl ether (III). The water solution was poured off and the precipitate washed several times with cold ligroin (b. p. 90–100°) to remove most of the unmercurated diphenyl ether. Separation of I from III was best accomplished by extraction with hot ligroin in which the former is moderately soluble and the latter practically insoluble. Ten such extractions with 1.5 liters of boiling ligroin each time gave 200 g. of 4-acetoxymercuri diphenyl ether (I), m. p. 150°, and recrystallization of the residue from 95% ethyl alcohol gave 175 g. of 4,4′-diacetoxymercuri diphenyl ether (III), m. p. 195–200°.

The mercuration proceeds slowly at room temperature and after about 3 weeks' standing the solution is free from ionic mercury. The proportion of I and III is about the same as when the reaction is conducted on the steam-bath.

Each of these substances in acetic acid solution reacts with inorganic reagents in the normal manner. Warm mineral acid converts I to diphenyl ether, sodium chloride solution gives 4-chloromercuri diphenyl ether (II), bromine produces 4-bromodiphenyl ether and iodine chloride (but not iodine) gives 4-iododiphenyl ether. Likewise the 4,4′-diacetoxymercuri diphenyl ether (III) with the above reagents yields, respectively, diphenyl ether, 4,4′-dichloromercuri diphenyl ether (IV), 4,4′-dibromodiphenyl ether and 4,4′-diiododiphenyl ether all of which were identical with known samples.

Mercuration of Diphenyl Ether Derivatives.—Molar proportions of 4-bromodiphenyl ether (or 4-iododiphenyl ether) and mercuric acetate combine in the foregoing manner to produce 4-bromo-4′-acetoxymercuri diphenyl ether (V) and the corresponding iodo derivative (VII). 4-Hydroxydiphenyl ether upon mercuration gave a mixture of poly-mercurated products which were inseparable. Analysis of the mixture showed 62% of mercury which corresponds approximately to the triacetoxymercuri-hydroxydiphenyl ether. Likewise no individual mer-

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(1) Brewster and Strain, THIS JOURNAL, 56, 117 (1934).