

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NEW YORK UNIVERSITY]

PHOSPHORIC ACID ESTER DERIVATIVES OF CHOLINE.
BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF -ONIUM
COMPOUNDS. VIII¹

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The phosphoric acid ester of choline and its derivatives are of interest not only because of their relationship to lecithin and because of a possible utilization of them in the synthesis of the latter substance, but also on account of the pharmacological properties that some of them may have.

Our earlier work on attempts to prepare phosphoric acid ester derivatives of choline² convinced us that these could not be obtained readily by double decomposition reactions with iodo- or bromo-ethyltrimethylammonium salts, nor by the action of phosphoric halides on choline. Much better prospects for obtaining these products as well as for the synthesis of the structure usually assigned to lecithin seemed possible by starting with β -chloro-ethyl phosphoryl dichloride $\text{ClCH}_2\text{CH}_2\text{OPOCl}_2$. This product was obtained in coöperation with Mr. Shott in this Laboratory in 1926, and during the winter of 1927-1928 the products herein described were prepared. We expected to extend this work before publishing, but since others have entered the field³ it seems desirable to present the material at this time.

β -Chloro-ethyl Phosphoryl Dichloride, $\text{ClCH}_2\text{CH}_2\text{OPOCl}_2$.—A mixture of 80.5 g. (1 mole) of ethylene chlorohydrin and 100 cc. of dry carbon tetrachloride was stirred vigorously while 153.5 g. (1 mole) of phosphoryl chloride was added through a dropping funnel over a period of one and one-half hours. The stirring was continued while the flask was heated on the water-bath for three hours. The mixture was then distilled very carefully under diminished pressure, with the temperature being kept below 60° until the carbon tetrachloride was removed and hydrogen chloride no longer was evolved. The product distilled at 108-110° (15 mm.) in a yield of 91 to 93 g. (46 to 47% of the theoretical). It is a colorless, mobile liquid of suffocating odor.

Anal. Calcd. for $\text{C}_2\text{H}_4\text{O}_2\text{Cl}_3\text{P}$: Cl, 53.86. Found: Cl, 54.14, 53.89.

This dichloride condensed readily with trimethylamine under anhydrous conditions to form a very hygroscopic product which was probably dichlorophosphato-ethyltrimethylammonium chloride, isomeric with the product isolated by the action of phosphoryl chloride on choline.

Dimethyl β -Chloro-ethyl Phosphate, $\text{ClCH}_2\text{CH}_2\text{OPO}(\text{OCH}_3)_2$.—To a rapidly stirred mixture of 29.5 g. (0.15 mole) of β -chloro-ethyl phosphoryl dichloride and 50 cc. of dry

¹ This problem is being carried on in coöperation with Dr. Reid Hunt of the Harvard Medical School. The physiological data are the basis of another series of papers published elsewhere by him.

² Renshaw and Ware, *THIS JOURNAL*, 47, 2993 (1925).

³ Our attention has just been called to a report of a paper on "Esters of Phosphoric Acid," presented before the Biochemical Society by Plimmer and Burch, in which they describe β -chloro-ethyl phosphoryl dichloride.

carbon tetrachloride contained in a flask surrounded by cold water, there was added drop by drop 12 g. (0.37 mole) of absolute methyl alcohol. The reaction mixture was refluxed gently for one to two hours until no more hydrogen chloride was evolved. The solvent was then removed by evaporation under a vacuum and the remaining liquid fractionated at a pressure of 4 mm. Considerable decomposition resulted at higher pressures. There was finally obtained 7 g. (25% yield) of the desired ester boiling at 95–96° (4 mm.). Dimethyl β -chloro-ethyl phosphate is a colorless, mobile liquid having a faint ester odor.

Anal. Calcd. for $C_4H_{10}O_4PCl$: Cl, 18.79. Found: Cl, 18.94, 18.70.

Dimethylphosphato-ethyltrimethylammonium Chloride (Choline Ester of Dimethyl Phosphoric Acid), $(CH_3O)_2POCH_2CH_2N(CH_3)_3Cl$.—A toluene solution of 3.0 g. (0.05 mole) of trimethylamine and 9.4 g. (0.05 mole) of dimethyl β -chloro-ethyl phosphate was allowed to stand overnight in a pressure bottle. The product was filtered off and washed with toluene and dry ether. It crystallized from a small volume of chloroform in fine needles, m. p. 136.5–137° (corr.). It is somewhat soluble in chloroform and acetic anhydride, very soluble in water and in ethyl alcohol, nearly insoluble in ether, toluene, petroleum ether and carbon tetrachloride. It is very hygroscopic.

Anal. Calcd. for $C_7H_{19}O_4NCIP$: Cl, 14.32. Found: Cl, 14.42, 14.37.

Dr. Reid Hunt has found this compound to have little muscarine action. It does have, however, a powerful stimulating nicotine action.

Conclusion

β -Chloro-ethyl phosphoryl dichloride has been prepared. It condenses with trimethylamine to form a quarternary salt. From it, too, dimethyl β -chloro-ethyl phosphate has been obtained. This forms with trimethylamine the choline ester of dimethylphosphoric acid. Hunt has found that the latter compound has the interesting property of giving a powerful stimulating nicotine action and yet has little muscarine action.

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NEW BOOKS

College Chemistry. By NEIL E. GORDON, Professor of Chemical Education, Johns Hopkins University. World Book Company, Yonkers-on-Hudson, New York, 1928. ix + 516 pp. 88 figs. 14 × 21 cm. Price \$2.96.

The book is written especially for students who have had high-school chemistry and therefore omits much of the descriptive material found in ordinary texts. It is divided into two general parts, the non-metals and the metals. Under each head certain units are taken up, since it is the idea of the author that for students who already have a reasonable amount of chemical information, the more advanced viewpoint is best given by the study of topics rather than by a description of the properties of individual elements. Like other Gordon texts, the subject is presented by means of laboratory exercises, on which the discussion is based. While this may make the book less generally useful than if it were cast in the usual form, yet it has advantages for those who wish to follow Dr. Gordon's