Potassium phenolate was prepared from 9.4 g. of phenol, dissolved in 150 cc. of absolute ether. Seven and five-tenths grams of the acid chloride was added and the mixture heated for thirty minutes. Eleven and three-tenths grams of diphenyl phthalate was isolated; the calculated amount of ester is 12.3 g.

Sixteen grams of aluminum chloride was added, in portions, to a mixture prepared from 10 g. of the acid chloride, 9.4 g. of phenol and 100 cc. of carbon disulfide. The mixture was refluxed for one-half hour, when the evolution of hydrogen chloride stopped. The carbon disulfide, which was found to be free from organic compounds, was decanted and the residue, after decomposition with ice and hydrochloric acid, steam distilled to remove any unchanged phenol. The amorphous reaction product weighed 8.2 g. Two and five-tenths grams of this material was treated with 100 cc. of 2% sodium hydroxide solution. Two grams of an alkali-insoluble product was obtained which proved to be diphenyl phthalate; m. p. 74–75°. Upon acidification of the alkaline solution, 0.2 g. of phenolphthalein precipitated which melted at 254° after recrystallization from acetic acid.

Summary

2-Chloro-, 2-bromo- and 2-iodoanisole react with phthalyl chloride in the presence of aluminum chloride to yield 3′,3″-dihalophenolphthalein dimethyl ethers. Upon demethylation the phthaleins themselves were obtained.

From 2,6-dichloro- and 2,6-dibromoanisole, phthalyl chloride and aluminum chloride tetrahalodiphenyl phthalates were formed.

A practical method has been found for the preparation of 2,6-dichloro- and 2,6-dibromophenol.

Attempts to obtain diphenoxyphthalide are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

THE BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF -ONIUM COMPOUNDS. IX. DERIVATIVES OF HOMOLOGS OF BETAINE[1]

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The present paper deals with a continuation of the work[3] being done in coöperation with Reid Hunt, in an attempt to get some light on the basis for the action of substances on the nervous system and, along with that, the problem of discovering substances with highly selective actions on such tissues. In the latter endeavor some success has been attained.

[1] This problem is being carried out 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] This paper includes a portion of the material of a thesis presented by Martin E. McGreal, June, 1928, for the degree of Doctor of Philosophy at New York University.

[3] Renshaw and co-workers: (a) *Science*, **62**, 384 (1925); (b) THIS JOURNAL, **47**, 1904, (c) 2989 (1925); (d) *ibid.*, **48**, 517, (e) 1726, (f) 2146, (g) 2698 (1926); (h) *ibid.*, **51**, 953 (1929).

Hunt[4] has been able with these various products to obtain better control over the peripheral nervous system than has been possible before.

It has been shown[4g] that the physiologically inert betaine $(CH_3)_3N(CH_2COOH)X$ could be transformed into highly active substances by esterification. The methyl and ethyl esters gave the same type of action on the autonomic nervous system that the salts of choline, $(CH_3)_3N(CH_2CH_2OH)X$ give. Particularly intense was the "muscarine action," which caused a marked fall of blood pressure and, in larger doses, a slowing of the heart from a stimulation of the ending of the vagus nerve in the heart. We have prepared the esters of a number of homologs of betaine with other alkyl amine groups in place of the trimethylamine group in order to determine the effect of this variation on the muscarine and other actions. Hunt and Taveau[4a] had shown that in the choline series the muscarine action was most typical of those compounds having the trimethylamine group. Since that time, it has been shown largely through the work of Hunt and of Dale that many of these compounds also have a stimulating nicotine-like action on the ganglion cells of the autonomic nervous system.

Only a few of the -onium compounds investigated give but one of these effects. The greater number have both actions but in widely varying degree. It has, therefore, been impossible heretofore to bring out any very definite relationship between structure and the tendency to give on the one hand a stimulating nicotine effect and on the other the muscarine effect. It was previously found[4e] that betaine esters (the trimethyl compound) have an intense muscarine action and a moderate stimulating nicotine action. In this series of homologs the triethyl and the tripropyl betaine esters are substantially devoid of either of these actions. The tributyl and, to a greater extent, the triamyl, betaine ester has a very intense stimulating nicotine action but no muscarine action. It would seem, then, that these higher alkyl amine groups have no effect on the inhibitory nerve endings to the heart, but that they do act on the ganglion cells very intensely. This affords a striking case of compounds having similar gross structure (-onium) and similar chemical properties exhibiting a different but highly selective action on the nervous system.

Since Hunt[4f] had found that the substitution of a benzyl group for one of the methyl groups in tetramethylammonium salts seemed to increase the muscarine action, it was thought desirable to test similar substitutions in betaine esters. Several of these were, therefore, prepared. Contrary to the foregoing, it[4k] was found that the substitution of one methyl by one benzyl group lowered the activity in the case of the ethyl esters by

[4] Hunt and co-workers, (a) *Hygienic Lab. Bull.*, No. 73 (1911); (b) *Am. J. Physiol.*, **14,** 197 (1918); (c) *J. Pharmacol.*, **6,** 477 (1915); (d) *ibid.*, **7,** 301 (1915); (e) *ibid.*, **25,** 315 (1925); (f) *ibid.*, **28,** 367, (g) **29,** 17 (1926); (h) *ibid.*, **35,** 75, (i) 99 (1929); *ibid.*, **37,** (j) 177, (k) 309 (1929).

about fifty times and that the introduction of a second benzyl group further greatly diminished both the muscarine and stimulating nicotine action.

Three of the higher homologs of betaine were prepared. As was to be expected these showed marked inactivity.[4k] The inactivity of the betaines has been discussed.[3g]

Experimental Part

Homologs of Betaine and Betaine Esters.—The esters were prepared by condensing molecular quantities of methyl or ethyl bromoacetate with the corresponding tertiary amine. The reaction mixtures, sometimes mixed with an equal volume of toluene, were allowed to stand at −10 to +60° for from several hours to several days. With the higher homologs of trimethylamine there is a greater tendency to form the tertiary amine hydrohalide at the higher temperatures. The solid products formed were purified by recrystallizing from alcohol or acetone or by fractionally precipitating the alcoholic or acetone solutions with absolute ether. The higher homologs were surprisingly soluble in alcohol–ether mixtures, much less soluble in acetone–ether mixtures.

The betaines were prepared by the hydrolysis of the corresponding esters. The hydrolysis was brought about by boiling the esters with aqueous hydrobromic acid. The solutions were then evaporated to dryness and the products purified by precipitating either the alcohol or acetone solution with ether. The slight physiological activity Hunt[4k] found for these products when injected in very large amounts was probably due to the presence of very small quantities of the intensely active esters.

TABLE I

MELTING POINTS AND ANALYSES

-Onium compound	M. p., °C.	Halogen, % Calcd.	Found	
$CH_3OOCCH_2N(C_2H_5)_3Br$	132	31.50	31.60	31.59
$C_2H_5OOCCH_2N(C_2H_5)_3Br$	104	29.85	29.95	29.87
$CH_3OOCCH_2N(n\text{-}C_3H_7)_3Br$	138	27.02	26.80	26.97
$C_2H_5OOCCH_2N(n\text{-}C_3H_7)_3Br$	134	25.80	25.87	25.77
$CH_3OOCCH_2N(n\text{-}C_4H_9)_3Br$	113	23.64	23.74	23.60
$C_2H_5OOCCH_2N(n\text{-}C_4H_9)_3Br$	83	22.72	22.68	22.65
$C_2H_5OOCCH_2N(iso\text{-}C_5H_{11})_3Br$	99.5	20.28	20.37	20.47
$C_6H_5HNOCCH_2N(iso\text{-}C_5H_{11})_3Br$	169	18.12	18.00	17.91
$CH_3OOCCH_2N(CH_3)_2C_6H_5Br$	99	29.26	29.27	29.20
$CH_3OOCCH_2N(CH_3)_2CH_2C_6H_5Br$	151	27.74	27.61	27.65
$C_2H_5OOCCH_2N(CH_3)_2CH_2C_6H_5Br$	114.5	26.49	26.55	26.58
$CH_3OOCCH_2N(CH_2C_6H_5)_2CH_3Br$	128	21.97	21.93	22.03
$C_2H_5OOCCH_2N(CH_2C_6H_5)_2CH_3Br$	148	21.13	20.86	21.03
$HOOCCH_2N(C_2H_5)_3Br$	190	33.29	33.20	33.36
$HOOCCH_2N(n\text{-}C_3H_7)_3Br$	177	28.33	28.24	28.39
$HOOCCH_2N(iso\text{-}C_5H_{11})_3Br$	144	21.83	21.83	21.80

Summary

1. Salts of three of the higher homologs of betaine have been prepared. Hunt has found that they, like betaine itself, are markedly inactive on the autonomic nervous system.

2. A number of esters and one phenylcarbamido derivative of the higher homologs of betaine have been prepared. The physiological activity of these esters, as found by Hunt, affords a striking example of the varying effect of different alkyl groups when combined with nitrogen. The trimethyl compound has an intense muscarine action and a moderate stimulating nicotine action. The triethyl and tripropyl have neither of these effects. The tributyl and to a greater extent the tri-isoamyl ester has a very intense stimulating nicotine-like action and no muscarine action.

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BASIS FOR THE PHYSIOLOGICAL ACTIVITY OF -ONIUM COMPOUNDS. X. HETEROCYCLIC -ONIUM COMPOUNDS[1,2]

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The general problem of determining the basis for the physiological activity of -onium compounds has been discussed in earlier papers.[4] It seemed desirable to continue the work by preparing some of the simple heterocyclic -onium compounds with the reduced or partially reduced pyridine and pyrrole type of ring structures such as occur in the simpler alkaloids, nicotine and arecoline, for the latter, especially, has a very specific and strong action on the autonomic system.

Of the types of compounds so far prepared and investigated, the phenyl ethers of the cholines were outstanding in their activity. For this reason we have confined ourselves in the present work largely to the preparation of the phenyl ethers.

The bases pyrrole, pyrroline, pyrrolidine, 3-hydroxypyridine, and 2- and 3-aminopyridines, were prepared in this Laboratory by the best methods available.

The following procedure was used in the preparation of these -onium compounds. Somewhat more than two molar equivalents of the secondary

[1] This problem is being carried out 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] This paper is constructed from a portion of a thesis presented by Edward W. Shand, June, 1930, for the degree of Doctor of Philosophy at New York University.

[3] The authors wish to express their appreciation to Parke, Davis & Co. for a Fellowship which has made this work possible.

[4] For earlier references see THIS JOURNAL, **53**, 1471 (1932).