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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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NEW YORK UNIVERSITY]

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).

bases pyrroline, pyrrolidine and piperidine were condensed with one molar equivalent of phenoxyethyl bromide in alcohol solution by heating for two hours at 70°. The alcohol was then distilled, the residue made alkaline with aqueous potassium hydroxide, and the solution extracted with ether. From the ether extract, after drying, the phenyl ether of the tertiary base was separated from the secondary base by vacuum fractional distillation. The tertiary base was then converted into the quaternary compound by heating in a benzene or acetone solution for varying lengths of time and the resulting salt purified by recrystallization from acetone, chloroform or from butyl alcohol or ethyl alcohol and ether. The ease of alkylation of the phenyl ethers of the tertiary bases differed considerably.

Efforts to obtain esters of β-pyridine sulfonic acid failed, showing that this substance probably forms an unusually stable betaine.

TABLE I

COMPOUNDS PREPARED

-Onium compound	M. p. (corr.), °C.	Halogen, % Calcd.	Found	
$C_5H_{10}>NCH_2CH_2OC_6H_5(CH_3)I$[a]	121.2	36.45	36.54	36.73
$C_5H_{10}>NCH_2CH_2OC_6H_5(C_2H_5)Br$[b]	112–3	25.44	25.22	
$C_4H_8>NCH_2CH_2OC_6H_5(CH_3)I$[c]	86.5–7.5	38.10	37.94	37.99
$C_4H_8>NCH_2CH_2OC_6H_5(CH_3)I$[d]	119–21	38.34	38.20	38.23
$C_4H_8>NCH_2CH_2OC_6H_5(C_2H_5)I$[e]	97–9	36.77	36.54	36.38
$C_5H_5>NCH_2CH_2OC_6H_5Br$[f]	80–3	28.54	28.30	28.36
$3\text{-}HOC_5H_4>NCH_2CH_2OC_6H_5Br$[g]	126–7	26.98	26.82	26.89
$2\text{-}(NHCOCH_3)\text{-}C_5H_4>NCH_3I$[h]	177	45.66	45.80	46.09
$3\text{-}(NHCOCH_3)\text{-}C_5H_4>NCH_3I$[i]	220–1	45.65	45.44	45.29

[a] Thin rectangular plates from alcohol–ether. [b] Condensation nearly complete after two days' heating in benzene at 90°. Recrystallized from absolute butyl alcohol and ether as granular crystals. [c] The β-phenoxyethylpyrrolidine, b. p. 142–146° at 20 mm., condensed readily in benzene by heating for two hours at 70°. [d] β-Phenoxyethylpyrroline, b. p. 154–158° at 18 mm., condensed at once with methyl iodide at room temperature with evolution of heat; feathery aggregates of thin plates from chloroform–benzene. [e] With ethyl iodide the tertiary base condenses very much more slowly than the preceding, the condensation being complete after eight days at room temperature. Granules of ill-defined crystals from alcohol–ether. [f] This condensation required two days' heating at 70° in benzene. [g] The oily product formed after thirty hours' heating in dry toluene at 70° was finally obtained as thick, almost square plates from acetone–ether. [h] This acetaminopyridine methylates slowly with methyl iodide, the reaction being incomplete after twenty-four hours' heating at 90° in a sealed tube. Rectangular plates from alcohol–ether. [i] Long thin rectangular needles from acetone.

Summary

1. There is here reported the preparation of β-phenoxyethyl derivatives of the following: -methylpiperidinium iodide, -methylpiperidinium bromide, -methylpyrrolidinium iodide, -methylpyrrolinium iodide, -ethylpyrrolinium iodide, -pyridinium bromide, -3-hydroxypyridinium bromide,

and 3-hydroxy-N-phenoxyethylpyridinium bromide, 2- and 3-acetamino-N-methylpyridinium iodides.

2. Hunt has found that these derivatives of pyridine and piperidine in general have no pronounced effect on the autonomic nervous system. The β-phenoxyethyl-N-methylpyrrolidinium iodide, while giving no muscarine effect, produces an intense stimulating nicotine-like action.

NEW YORK CITY

[CONTRIBUTION FROM THE CHEMICAL DEPARTMENTS OF WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY, AND FROM THE CHIEF MEDICAL EXAMINER'S OFFICE, AND BELLEVUE HOSPITAL, NEW YORK CITY]

THE ISOLATION OF PURE, ANHYDROUS ETHYL ALCOHOL FROM NON-ALCOHOLIC HUMAN AND ANIMAL TISSUES

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The object of the present communication is to throw light on the question whether traces of ethyl alcohol are present in human and animal tissues. Some of the earlier workers, notably A. and J. Béchamp, Rajewsky, Vitali, Albertoni, M. Nicloux, Landsberg and Stocklasa,[1] claimed that ethyl alcohol is always present in animal tissues in very small traces, while Arnheim and Rosenbaum, Umber and others claimed that it is absent.[2]

One reason why this problem has not been solved to date is because, if alcohol is normally present at all in organs and tissues, its amount is extremely small. We shall show that distillates from organs contain only about 0.0025% of alcohol at the most and that this small amount is mixed with traces of numerous other volatile organic compounds.

Another reason for disagreement among investigators is the fact that there are no specific tests for alcohol in such dilute solutions. Methods based upon physical constants are all unreliable, both because of the extreme dilution and because of the intermixture of other volatile organic substances. The above experimenters applied the Moore, the Schiff or the Nessler reaction to their oxidized tissue distillates; or tested the distillates directly with Lieben's iodoform or with Nicloux's sulfuric acid-chromate reaction.

Because of the non-specificity of these tests, neither group should have made any claims as to the presence or absence of ethyl alcohol in tissues.

[1] (a) A. and J. Béchamp, *Compt. rend.*, **75**, 1830 (1872); **76**, 836 (1873); **89**, 573 (1879); (b) Rajewsky, *Arch. ges. Physiol.*, **2**, 122 (1875); (c) Vitali, *Ann. Chim. Farm.*, [4] **5**, 113 (1887); (d) Albertoni, *ibid.*, **6**, 250 (1887); (e) M. Nicloux, *Compt. rend. acad. sci.*, [10] **3**, 841 (1896); (f) Landsberg, *Z. physiol. Chem.*, **41**, 505 (1904); (g) Stocklasa, *Deut. med. Wochschr.*, **6**, 198 (1904).

[2] Arnheim and Rosenbaum, *Z. physiol. Chem.*, **40**, 220 (1904); Umber, *Z. klin. Med.*, **39**, 12 (1900).