[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

AROMATIC PROPERTIES OF SOME ALIPHATIC COMPOUNDS LOCAL ANESTHETICS DERIVED FROM ALIPHATIC CARBOXYLIC ACIDS

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Introduction

The differences between aromatic and corresponding aliphatic compounds are largely of degree and not of kind. There are probably no rigidly exclusive aromatic characteristics. Functional groups that have the so-called aromatic properties are almost invariably attached to a tertiary carbon atom that has some degree or other of unsaturation. A fair basis of comparison would restrict correlation to aliphatic compounds that have functional groups of a related type. When this condition is met, in part or in whole, one observes that practically all the so-called distinctive aromatic properties are shown by varied aliphatic compounds.[1]

The present work extends such correlation to include the comparative physiological action of some aromatic compounds with related aliphatic types. Previously, Gilman and Pickens[2] showed a correlation, based on physiological action, between some aromatic heterocyclic types (furan, thiophene and pyrrole) and benzene. For comparative purposes the same physiological action, namely, local anesthetic action, has been studied. It has been found that the diethylamino-ethyl esters of carboxylic acids (where the carboxyl group is attached to an *unsaturated* carbon atom, $RCH{=}CHCO_2CH_2CH_2N(C_2H_5)_2$) show a distinct, although small, local anesthetic action. Where the same grouping is attached to a saturated carbon atom there is no local anesthetic action.

For comparative purposes it is interesting to observe that when the unsaturated acid contains also a phenyl radical, as in cinnamic acid, the anesthetic action is increased. Also, the cinnamic acid ester of diethylaminopropyl alcohol ("Apothesin") is distinctly active. Its high potency is no doubt partly due to the introduction of the phenyl radical into the acrylic acid and partly to the fact that the amino-alcohol part of the molecule contains an additional carbon atom.

Experimental Part

The hydrochlorides of the diethylamino-ethyl esters were prepared by a standard technique involving the interaction of the acid chloride

[1] Space does not permit of reference to the many works in this field. A general and leading account of some such correlations is to be found in Johnson and Hahn's translation of Henrich's "Theories of Organic Chemistry," John Wiley and Sons, Inc., New York, **1922**, in particular see pages 182–183, 232 and 234–235.

[2] Gilman and Pickens, THIS JOURNAL, **47**, 245 (1925).

with diethylamino-ethanol in an inert medium, generally benzene or ether.

Diethylamino-ethyl Acrylate Hydrochloride, $CH_2{=}CHCO_2CH_2CH_2N(C_2H_5)_2.HCl$.—Eight g. or 0.088 mole of acrylic acid chloride[3] in 50 cc. of dry benzene was added dropwise to 11 g. or 0.094 mole of β-diethylamino-ethanol in 50 cc. of benzene. The hygroscopic hydrochloride of diethylamino-ethyl acrylate melted at 93° when crystallized from benzene.

Anal. Calcd. for $C_9H_{18}O_2NCl$: Cl, 17.07; N, 6.70. Found: Cl, 16.89, 16.53; N, 6.30.

Preliminary to the above synthesis, β-chloro-ethyl α,β-dibromopropionate, $CH_2BrCHBrCO_2CH_2CH_2Cl$, was prepared by passing hydrogen chloride into a mixture of α,β-dibromopropionic acid and ethylene chlorohydrin. The yield of ester boiling at 153° (20 mm.) was 92.9%; $n^{30} = 1.9080$; $d_4^{20} = 1.5241$.

Anal. Calcd. for $C_5H_7O_2Br_2Cl$: Br, 54.31; Cl, 12.03. Found: Br, 54.20; Cl, 12.02.

Diethylamino-ethyl β,β-Dimethylacrylate Hydrochloride, $(CH_3)_2C{=}CHCO_2CH_2CH_2N(C_2H_5)_2.HCl$.—This compound was prepared from dimethylacrylic acid chloride and diethylamino-ethanol in ether. When crystallized from acetone it melted at 128.5–130°.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: Cl, 15.07. Found: Cl, 15.2.

Diethylamino-ethyl Trichloro-acetate Hydrochloride, $CCl_3CO_2CH_2CH_2N(C_2H_5)_2.HCl$.—The same general conditions were followed here as in the preparation of the β,β-dimethylacrylate ester hydrochloride. The compound melted at 144–145°.

Anal. Calcd. for $C_8H_{15}O_2NCl_4$: N, 4.68. Found: N, 4.76.

Diethylamino-ethyl Acetate, $CH_3CO_2CH_2CH_2N(C_2H_5)_2.HCl$, melted at 116–117°.

Anal. Calcd. for $C_8H_{18}O_2NCl$: Cl, 18.12. Found: Cl, 18.09, 18.14.

Some preliminary reactions were carried out between diethylamino-ethanol and the acid chlorides of fumaric and monochloro-acetic acids. From these the hydrochloride of β-diethylamino-ethanol was obtained.

Pharmacological Tests

The authors are indebted to Dr. Oliver Kamm of Parke, Davis and Company of Detroit for the results of the pharmacological tests. The method of testing was that described earlier.[2] Cocaine was selected arbitrarily as a standard and given a weight of 10. On a scale of this kind, the relative and rather approximate ratings of the hydrochlorides are as follows: diethylamino-ethyl dimethylacrylate is 1; diethylamino-ethyl acrylate is also 1; diethylamino-ethyl trichloro-acetate is slightly less than 1; and diethylamino-ethyl acetate is zero. "Apothesin," diethylaminopropyl cinnamate, has a rating of approximately 8 on this basis.

Diethylamino-ethyl trichloro-acetate was selected in this study because trichloro-acetic acid has, among other properties, a conductivity that places it nearer to aromatic compounds than acetic acid.

It is interesting to note that the comparative effectiveness of the diethylamino-ethyl esters of acrylic and dimethylacrylic acids places them

[3] Prepared according to directions of Moureu, *Ann. chim. phys.*, [7] **2**, 161 (1894).

not far from two of the aromatic types previously reported,[2] namely, diethylamino-ethyl 2-thiophenecarboxylate (with a rating of 1) and diethylamino-ethyl 2-furancarboxylate (with a rating of less than 1).

Summary

A study of the local anesthetic action of some diethylamino-ethyl esters of aliphatic carboxylic acids shows that the chemical correlation of aromatic compounds with some related aliphatic compounds can be extended to include physiological action.

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THE TAUTOMERISM OF HYDROXY QUINONES

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It is the purpose of this paper to apply to the problem named in the title certain of the principles governing chemical equilibria, and to present the results of experiments which were carried out with the view of testing and applying this theoretical treatment of the subject.

1. The General Theory

Hydroxynaphthoquinone is typical of the compounds under consideration. While only one form of the substance is known in the solid state,[1] it is necessary to recognize the presence of two tautomeric forms in its solutions in order to account for the course of the hydrolysis of 2-alkoxy-1, 4-naphthoquinones and 4-alkoxy-1,2-naphthoquinones, for a single solid substance results in each case.[2] Among the reactions which demonstrate the presence of hydroxy-α-naphthoquinone in the equilibrium mixture is that with diazomethane,[2] while the ready, reversible reaction of hydroxynaphthoquinone with sodium bisulfite must involve a β-naphthoquinone derivative. Thus these tautomers, which may be referred to as the α and β forms of hydroxynaphthoquinone, must be present in all solutions of the substance and the constant of the tautomeric equilibrium may be defined by the following equation

$$K = [\alpha\text{-Form}]/[\beta\text{-Form}] \quad (1)$$

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[1] Miller's statement to the contrary, *J. Russ. Phys.-Chem. Soc.*, **43**, 440 (1911), must be discounted. It is possible that the change in his sample on storage and the variation of the point of decomposition of this substance are both due in part to a reaction of the material with glass. Some of the samples which Miller prepared by different methods undoubtedly contained impurities. Dr. Samuel C. Hooker has informed me that, by following with the microscope the crystallization of a red sample of this quinone, he found the red color to be due to the presence of impurities removed only after numerous crystallizations.

[2] Fieser, THIS JOURNAL, **48**, 2922 (1926).