A SERIES OF CONTRIBUTIONS TO THE QUESTION OF THE RELATION BETWEEN CHEMICAL CONSTITUTION AND LOCAL ANESTHETIC ACTIVITY.*

II. SOME ALKOXY BENZOATES OF DIALKYLAMINO ALCOHOLS.

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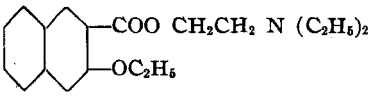
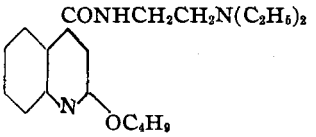
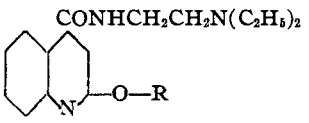
In considering the possibility of enhancing the anesthetic potency in the ester type anesthetic, one of the earliest questions to which our attention was directed was the effect of substituents other than the amino group in dialkylaminoalkyl benzoates. The fact that some ethoxy naphthoic acid esters of amino alcohols (1) such as



had proved to be effective local anesthetics, and the further fact that the butoxy group in Percaine (2)



not only contributed essentially to the anesthetic potency of that drug, but proved to have an optimum effect in a series of analogous compounds



in which R was varied from CH_3 to C_5H_{11}, led us to give further consideration to the fact that diethylaminoethyl *p*-methoxy benzoate was considerably less active than diethylaminoethyl *p*-amino benzoate. The fact that the methoxy group was an unsatisfactory replacement for the amino group in this pair of compounds had to be considered along with the further facts that it would be very improbable that any enhancement of activity to be had by para alkoxy substitution would be optimum in this first member of the homologous series, and that the physiological effect of the methyl group is so frequently out of line with the effect of its higher homologous groups.

Our conclusion that a study of the effect of alkoxy substitution in the benzoic acid residue of dialkylaminoalkyl benzoates might be fruitful was immediately confirmed by the fact that diethylaminoethyl *p*-ethoxy benzoate proved to be very much more active than diethylaminoethyl *p*-methoxy benzoate, and in fact somewhat more active than diethylaminoethyl *p*-amino benzoate (Procaine).

Before setting out upon a systematic variation of the alkoxy substituents it

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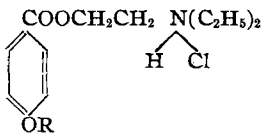
seemed desirable to have available a comparison of the anesthetic activity of the several isomers of the above *p*-ethoxy benzoate, and we therefore also prepared the diethylaminoethyl *o*-ethoxy benzoate and the diethylaminoethyl *m*-ethoxy benzoate. The activities of these isomers proved to be considerably less than that of the *p*-ethoxy benzoate, the ratio of activities of the three isomers being approximately of the order para = 1, meta = $^1/_8$, ortho = $^1/_{16}$ in the production of corneal anesthesia, and para = 1, meta = $^3/_4$ and ortho = $^1/_2$ in the production of intradermal anesthesia. We, therefore, selected as the scope of this study the para alkoxy benzoic esters of dialkylamino alcohols.

A series of *p*-alkoxy benzoates of diethylaminoethyl alcohol was first prepared and the compounds submitted to pharmacological test.[1] Because the summation of all considerations such as anesthetic potency, toxicity, etc., made the compound diethylaminoethyl *p*-ethoxy benzoate seem especially interesting, an additional series of esters was prepared in which all were derived from *p*-ethoxy benzoic acid but the alkylamino alcohol was varied in diverse manners. For analogous reasons a much smaller series of alkylaminoalkyl esters derived from *p*-butoxy benzoic acid was also prepared and studied.

After these several series of anesthetics had been prepared and the preliminary pharmacological studies had been completed, a paper by Rohmann and Scheurle (3) appeared, in which seven of the compounds prepared and studied by us were reported. These authors had evidently based their studies on a somewhat similar viewpoint as our own but had not extended their interest to so wide a variety of alterations in the ester molecules. In the descriptive tables of the compounds prepared by us, we have included the melting-point data obtained by Rohmann and Scheurle on their samples of the same compound in those instances in which their work has overlapped our own.

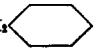
The compounds being reported in this paper are arranged in the three tables appearing below. In every case the compound has marked local anesthetic properties, the especial characteristics of which will be described elsewhere very shortly in separate papers emanating from the Biological Laboratories of E. R. Squibb & Sons, and the Department of Pharmacology of the University of Nebraska, School of Medicine.

TABLE I.—DIETHYLAMINOETHYL *p*-ALKOXY BENZOATE HYDROCHLORIDES.



Acid from Which Ester Is Derived.	R.	Method of Preparation —See Experimental Part.	R. & S. Melting Point of HCl Salt.	Melting Point of HCl Salt (Corrected).	Analysis. Found. %N.	Found. %Cl.	Calculated. %N.	Calculated. %Cl.
p-Methoxy benzoic	-OCH_3	1a		142° C.	5.07	12.52	4.87	12.33
p-Ethoxy benzoic	-OCH_2CH_3	1	174° C.	177.3° C.	4.62 4.62*	11.55 11.86*	4.64	11.76

[1] As has already been indicated in the previous paper, the results of these pharmacological studies will be reported elsewhere.

p-(n) propoxy benzoic	$-OCH_2CH_2CH_3$	1a	137° C.	137.6–138.1° C.	4.25 4.34*	11.22 10.93*	4.44	11.24
p-(iso) propoxy benzoic	$-OCH(CH_3)_2$	2	128° C.	125.5° C.	4.28	10.93	4.44	11.24
p-(n) butoxy benzoic	$-OCH_2CH_2CH_2.CH_3$	1	147° C.	146.5–147.5° C.	4.19	10.76	4.24	10.76
p-allyloxy benzoic	$-OCH_2.CH = CH_2$	1a	130° C.	130° C.	4.40	10.93	4.47	11.31
p-*β*-phenylethoxy benzoic	$-OCH_2CH_2$ 	1a	..	91–92° C.	3.76	9.30	3.72	9.42
p-*β*-ethoxy ethoxy benzoic	$-OCH_2CH_2OCH_2CH_3$	2	..	102–103.5° C.	4.03	9.80	4.05	10.03
p-*β*-bromo allyloxy benzoic	$-OCH_2CBr = CH_2$	3	..	81.5–83.5° C.	4.3	9.80	3.57	9.03
p-*β*-diethylamino ethoxy benzoic	$-OCH_2CH_2N(C_2H_5)_2$	1	..	Hygroscopic**	7.70	..	7.55	..

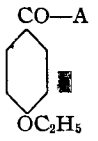
NOTE: Below are included also the single ortho and meta alkoxy benzoic acid esters of diethylaminoethyl alcohol.

o-ethoxy benzoic	$-OCH_2CH_3$	1	..	139–139.5° C.	5.0	11.55	4.64	11.76
m-ethoxy benzoic	$-OCH_2CH_3$	2	..	125–125.5° C.	4.96	11.21	4.64	11.76

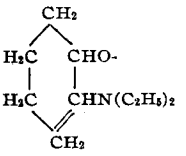
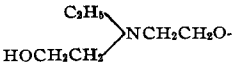
* Analytical data obtained on a separately prepared sample.

** R. & S. report m. p. 180° C. for the dihydrochloride.

TABLE II.—*p*-ETHOXY BENZOIC ESTER HYDROCHLORIDES OF VARIOUS ALKYL AMINO ALCOHOLS.

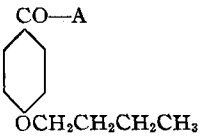


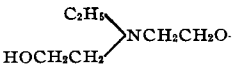
Alcohol from Which Ester Is Derived.	A.	Method of Preparation —See Experimental Part.	Melting Point of HCl Salt (Corrected).	Analysis. Found. %N.	Found. %Cl.	Calculated. %N.	Calculated. %Cl.
Ethyl amyl amino ethyl	C_5H_{11} C_2H_5 >NCH_2CH_2O-	1	108–110° C.	3.98	11.6	4.07	10.33
β-Di (n) butylamino ethyl	$(CH_3CH_2CH_2CH_2)_2NCH_2CH_2O-$	1	144.5–145.5° C.	4.08	9.26	3.91	9.90
γ-Di (n) butylamino propyl	$(CH_3CH_2CH_2CH_2)_2NCH_2CH_2CH_2O-$	1	85.5–86.5° C.	3.42	9.08	3.76	9.05
ββ-Dimethyl-*γ*-diethylaminopropyl	$(C_2H_5)_2NCH_2C(CH_3)_2.CH_2O-$	5	121–121.5° C.	7.78	9.47	7.81	9.89
γ-Diethylaminopropyl	$(C_2H_5)_2NCH_2CH_2CH_2O-$	4	149.9–150.4° C. (R. & S.) 148° C.	4.34 *4.31	11.27; *11.30 (R. & S.) 11.22	4.44	11.24
β-Diethylamino-*δ*-methyl (n) amyl	$(CH_3)_2CH.CH_2CH.CH_2O-$ $N(C_2H_5)_2$	3	Oil	4.11	..	4.36	..
αα-Di-dimethylamino-methyl *n*-propyl	$CH_2N(C_2H_5)_2$ CH_3CH_2 C O- $CH_2N(C_2H_5)_2$	5	121–121.5° C.	7.78	9.47	7.81	9.89
α-Methyl-*α*-diethyl-aminomethyl *n*-propyl	CH_3 CH_3CH_2 C O- $CH_2N(C_2H_5)_2$	3	122–124° C.	3.92	10.00	4.02	10.39
β-Diethylaminoeth-oxy ethyl	$(C_2H_5)_2NCH_2-CH_2OCH_2CH_2O$	5	112–115° C.	4.9	11.3	4.05	10.30

2-Diethylamino cyclohexyl		3	184–185° C.	4.04	9.98	3.94	9.77
1-Diethylamino 2,3-propanediol	$(C_2H_5)_2NCH_2.CHOH.CH_2O$	3	Not definite	4.34	10.76	4.22	10.70
N-Ethyl diethanolamine		3	Oil	4.94	..	4.98	..

* Analytical data obtained on a separately prepared sample.

TABLE III.—*p*-BUTOXY BENZOIC ESTER HYDROCHLORIDES OF VARIOUS ALKYL AMINO ALCOHOLS.



Alcohol from Which Ester Is Derived.	A.	Method of Preparation —See Experimental Part.	Melting Point of HCl Salt (Corrected).	Analysis. Found. %N.	Found. %Cl.	Calculated. %N.	Calculated. %Cl.
N-Ethyl diethanolamine		3	79.6° C.	3.93 4.05*	10.39 10.35*	4.04	10.27
1-Diethylamino 2,3-propanediol	$(C_2H_5)_2NCH_2CHOH.CH_2O$-	3	Indefinite	3.92	10.21	3.39	9.88
β-Dimethylamino ethyl	$(CH_3)_2NCH_2CH_2O$	1	132–133° C.	4.74	11.00	5.08	11.55

* Analytical data obtained on a separately prepared sample.

EXPERIMENTAL.

The methods involved in the preparation of the many anesthetic ester hydrochlorides reported by us were in no case difficult or involved. A number of well-known methods of preparing such esters of alkylated amino alcohols were used. These methods will be briefly described and numbered to correspond with the numbers in the several columns which indicate which of these esterification methods were used in preparing each of the individual compounds.

Method No. 1.—The acid chloride was refluxed for several hours with slightly more than the equivalent amount of the amino alcohol in a medium of anhydrous benzene. The reaction mixture was then treated with a dilute solution of sodium hydroxide and thoroughly washed with water to remove the excess of diethylaminoethyl alcohol. The benzene solution of the ester base was then dried over sodium sulfate and treated with a very slight excess of a solution of dry hydrochloric acid in absolute alcohol. In some instances the ester salt immediately separated in crystalline form and was recrystallized from acetone, mixtures of alcohol and ether, or some other suitable solvent. In other instances the crude ester salt was first obtained by evaporating the benzene solution to dryness and then recrystallized from a suitable solvent as indicated.

The acid chloride was refluxed for several hours with an equivalent quantity of the amino alcohol in dry benzene, and the reaction mixture allowed to stand over night in a cool place. The crude ester hydrochloride which thus crystallized from the benzene solution was filtered off and dissolved in water. This aqueous solution was then alkalinized with dilute sodium hydroxide solution and the ester base extracted with benzene. The benzene solution was washed thoroughly with water and dried over potassium carbonate. The benzene was then boiled off and the residual ester base distilled in high vacuum.

Method No. 2.—The acid chloride was refluxed for several hours with *two* equivalents of the amino alcohol in a medium of dry benzene. When the reaction mixture was allowed to stand in the cold the excess amino alcohol crystallized out as the hydrochloride leaving the ester base in solution. This amino alcohol hydrochloride was filtered off and the benzene solution of the product evaporated to dryness. The residue was then taken up in anhydrous ether and treated with a very slight excess of dry hydrochloric acid. The ester hydrochloride crystallized out and was recrystallized out of the solvent which proved to be most suitable. Dry acetone, or mixtures of either acetone or alcohol with anhydrous ether have usually given excellent results.

Method No. 3.—Equivalent quantities of the acid chloride and the amino alcohol were refluxed several hours in a benzene solution while an excess of powdered anhydrous potassium carbonate was kept suspended throughout the reaction mixture by means of efficient agitation. The solid mixture of potassium carbonate and potassium chloride was then filtered off and the benzene solution treated with a very slight excess of dry alcoholic hydrochloric acid. The benzene was then boiled off and the crude residue recrystallized by taking up in a minimum amount of absolute alcohol to dissolve it and adding sufficient anhydrous ether to cause incipient precipitation. Standing in a cool place or rubbing with a stirring rod usually produced crystallization.

Method No. 4.—The acid chloride was added to a solution of the amino alcohol in water containing an excess of sodium hydroxide and the mixture shaken for one-half hour. After the heat which developed had been dissipated the crude ester base which separated out as a thick oil was taken up in benzene and washed with several portions of dilute sodium hydroxide and finally with several portions of water. The benzene was boiled off and the residual ester base taken up in a minimum volume of absolute alcohol and treated with just sufficient dry alcoholic hydrochloric acid to convert it to the ester hydrochloride. Sufficient dry ether was then added to induce crystallization of the product.

Method No. 5.—The acid chloride was refluxed with an equivalent quantity of the amino alcohol in a small volume of anhydrous chloroform. When the hydrochloride of the amino alcohol which first separated had completely disappeared and the solution was clear it was cooled and admixed with sufficient anhydrous ether to induce crystallization of the ester hydrochloride.

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It should be further commented that there was no systematic basis for our choice of the methods used in the individual preparations. These preparations represented some of our earliest work and it was desirable to try out various esterification methods for purposes of comparison. Yields have been omitted from our discussion entirely for the reason that in our preparation of small quantities of the various ester hydrochlorides for preliminary evaluation no attempts were made to obtain the best yields obtainable and very often much of the product remained unisolated in cruder crops of crystalline material or even in mother liquors.

SUMMARY.

1. Several series of alkoxy benzoic esters of alkyl amino alcohols were prepared and isolated as their hydrochlorides.

2. These compounds have all proved to be local anesthetics in preliminary pharmacological tests and the details of these studies are to be presented shortly.

REFERENCES.

(1) Hill, A. J., and Smith, Spring 1929 meeting, A. C. S.
(2) Miescher, *Helv. Chim. Acta*, 15, 163 (1932).
(3) Rohmann and Scheurle, *Arch. Pharm.*, 274, 110 (1936).