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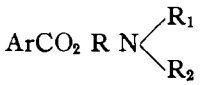
A SERIES OF CONTRIBUTIONS TO THE QUESTION OF THE RELATION BETWEEN CHEMICAL CONSTITUTION AND LOCAL ANESTHETIC ACTIVITY.

III. SUBSTITUTED CINNAMIC ACID ESTERS OF DIALKYLAMINO ALCOHOLS.

BY W. A. LOTT AND W. G. CHRISTIANSEN.

The first paper in this series dealt with the mechanism by which local anesthetics act and with hypotheses developed for use in orienting our efforts to produce new local anesthetics superior in one respect or another to existing ones. Particular emphasis was placed on the question of dual emulsions—systems which have water-in-oil and oil-in-water emulsions in equilibrium with each other and which can be altered or displaced in one direction or another by substances entering the system and having oil solubility as well as water solubility. Such substances would distribute themselves in accordance with their solubility coefficients and in so doing would alter the complex emulsion system. It is reasonable to expect that structural changes sufficient to significantly alter the oil solubility of a compound would modify the properties of the compound in so far as it is involved in complex emulsion systems.

Local anesthetics of the type studied in these researches may be represented by a general formula such as the following:



in which Ar represents an aromatic nucleus, R represents a polymethylene or substituted polymethylene group and R_1 and R_2 represent alkyl or substituted alkyl groups. These compounds may be described as esters obtained from aromatic acids and substituted amino alcohols. By appropriately altering the character of the acid or the alcohol one can change the oil-water solubility relationships.

The second paper was a report on anesthetics derived from alkoxy-benzoic acids. The character of the alkoxy group and other substituents in the benzene ring as well as the structure of the alkylaminoalkyl group were varied so as to produce substances having different distribution coefficients between oily and aqueous liquids and permit selection of the optimum combination of the acidic and alcoholic components.

It has long been known that the aromatic acid used for the preparation of a local anesthetic may be a cinnamic acid instead of a benzoic acid indicating that

in so far as local anesthetics are concerned the $C_6H_5CH = CH-$nucleus is qualitatively equivalent to the C_6H_5-nucleus. The cinnamic nucleus offers an excellent opportunity to study the effect of substitution, of the kind which would be expected to cause significant change in oil-water solubility relationships, on the behavior of the compounds as anesthetics. Thus, in addition to the benzene ring, the alpha and beta carbon atoms are available for the introduction of substituents. And whereas substitutions in the benzene ring are essentially the same in both the benzoate and cinnamate series so that in this respect the latter does not offer any opportunities fundamentally different from those found in the benzoate series, the possibility of substitution on the alpha and beta carbon atoms provided in the cinnamate series does not exist in the benzoate series. We are, therefore, able by working in the cinnamate series to study a factor which could not be investigated in the benzoate series. Consequently much of our work on the cinnamates has been directed toward determining the effect of substitution on the alpha and beta carbon atoms. By introducing alkyl groups at this point and gradually increasing the size of the alkyl substituent, one can appreciably change the oil solubility of the compound and do it gradually.

The compounds studied in the present work can be represented by the following formula:

$$C_6H_5CH = \underset{\displaystyle R}{\overset{\displaystyle |}{C}} - COOC_2H_4N(C_2H_5)_2 . HCl$$

$$C_6H_5CH = \underset{\displaystyle R}{\overset{\displaystyle |}{C}} - CONH . C_2H_4N(C_2H_5)_2 . HCl$$

R has been varied so that it has represented methyl, ethyl, propyl (both normal and iso), normal butyl and normal amyl. This covers a wide range and we have found that the lengthening of the group brings about a progressive increase in anesthetic potency and this is attributable to the increase in the organotropic portion of the molecule.

A number of analogous compounds were prepared in which the alkyl above designated by R was on the beta carbon. This did not influence the anesthetic activity very greatly. Neither did substitution in the ring by either $-Cl$, $-N(CH_3)_2$ or $-NH_2$.

Among the new compounds are:

(*a*) seven β-diethylaminoethyl α-alkyl-cinnamates.
(*b*) four ring substituted dialkylaminoalkyl α-ethyl-cinnamates.
(*c*) two β-diethylaminoethyl β-alkyl-cinnamates.
(*d*) five *N*-(β-diethylaminoethyl)-α-alkyl-cinnamamides.

In every instance the compounds had pronounced local anesthetic activity. The details of their pharmacological evaluation will be reported shortly in separate publications emanating from the Biological Laboratories of E. R. Squibb and Sons and from the Department of Pharmacology, University of Nebraska, Medical School.

EXPERIMENTAL.

Preparation of α-Alkyl-Cinnamic Acids.—These substances were prepared by the Claisen condensation (1) in which an ester was condensed with benzaldehyde, or substituted benzaldehyde in the presence of sodium

$$C_6H_5CHO + \underset{\underset{C_2H_5}{|}}{CH_2}COOCH_3 \longrightarrow C_6H_5CH = \underset{\underset{C_2H_5}{|}}{C} - COOCH_3$$

and the resulting α-alkyl-cinnamic ester hydrolyzed to give the free acid.

Preparation of β-Alkyl-Cinnamic Acids.—These acids were prepared by the Reformatsky synthesis (2) in which the appropriate homolog of acetophenone was condensed with ethyl bromo acetate in the presence of zinc wool.

$$C_6H_5\underset{\underset{CH_3}{|}}{C} = O + CH_2Br.COOC_2H_5 \longrightarrow C_6H_5\underset{\underset{CH_3}{|}}{C}(OH).CH_2COOC_2H_5$$

and the result β-hydroxy-β-alkyl-β-phenyl-propionic ester saponified to give the free acid. This acid was then dehydrated by means of concentrated sulfuric acid to give the corresponding β-alkyl-cinnamic acid.

$$C_6H_5.\underset{\underset{CH_3}{|}}{C}(OH).CH_2COOH \longrightarrow C_6H_5\underset{\underset{CH_3}{|}}{C} = CH.COOH$$

Preparation of Diethylaminoethyl α-Alkyl-Cinnamate Hydrochlorides.—Two methods were employed in the preparation of these anesthetic esters.

Method A.—The α-alkyl-cinnamic acid was converted to the corresponding acid chloride and the latter was digested with an equimolecular quantity of the diethylaminoethanol in an inert solvent. In those instances when the hydrochloride of the ester crystallized out of the solvent upon standing, it was purified by recrystallizing directly from a suitable solvent. However, when spontaneous crystallization of the product did not occur, the hydrochloride of the ester and any unreacted amino alcohol were extracted from the reaction solvent by means of acidulated water. The bases were then liberated by alkalinizing the aqueous solution. An ether solution of the liberated bases was then washed repeatedly with water to remove the diethylaminoethanol. Then, after thoroughly drying the ether solution by means of anhydrous potassium carbonate, the hydrochloride of the ester was precipitated by the addition of an ethereal solution of anhydrous HCl. This product was then recrystallized from a suitable solvent.

Method B.—The sodium salt of the α-alkyl-cinnamic acid was digested with diethylaminoethyl chloride in alcoholic solution. After the precipitated sodium chloride had been removed by filtration, the alcoholic solution was concentrated and the hydrochloride of the ester precipitated by the addition of an ethereal solution of hydrogen chloride. Purification of the product was effected by recrystallization from a suitable solvent.

Preparation of β-Diethylaminoethyl β-Alkyl-Cinnamate Hydrochlorides.—Method C.—The β-diethylaminoethyl β-alkyl-cinnamate hydrochlorides were all prepared by a method exactly analogous to the above mentioned *A*.

Preparation of β-Diethylaminoethyl α-Alkyl-Cinnamamide Hydrochlorides.—Method D.—The β-diethylaminoethyl α-alkyl-cinnamamide hydrochlorides were prepared by digesting the α-alkyl-cinnamyl chloride with unsymmetrical diethyl ethylene diamine in an inert solvent. The produet was isolated and purified in a manner exactly analogous to the above method *A*.

In Table I the eighteen new compounds are enumerated and the methods used for their preparation and purification indicated. Characterizing physical and chemical data for each individual is also presented therein.

TABLE I.

Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride.	Method.	M. P., ° C.	Solvent.	Formula.	Analyses, %. N. Calcd.	N. Found.	Cl. Calcd.	Cl. Found.
β-Diethylaminoethyl (α-methyl)	A	133–134.5	Acetone	$C_{16}H_{24}O_2NCl$	4.70	4.90	11.91	11.57
β-Diethylaminoethyl (α-ethyl)	A, B	145	Acetone-Abs. EtOH	$C_{17}H_{26}O_2NCl$	4.49	4.32	11.38	11.57
γ-Diethylaminopropyl (α-ethyl)	A	143.8–144.4	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.23	10.89	10.86
β-Diethylaminoethyl (α-n-propyl)	A	125–126	Acetone-Ether	$C_{18}H_{28}O_2NCl$	4.30	4.54	10.90	10.80
β-Diethylaminoethyl (α-isopropyl)	B	152–153	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.63	10.90	10.96
β-Diethylaminoethyl (α-n-butyl)	B	105.5–106.5	Acetone	$C_{19}H_{30}O_2NCl$	4.12	4.16	10.44	10.29
β-Diethylaminoethyl (α-n-amyl)	B	83–85	Acetone	$C_{20}H_{32}O_2NCl$	3.96	4.26	10.03	10.07
Ring Substituted Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride								
β-Diethylaminoethyl (α-ethyl)-o-chloro	A	127.5–128	Acetone	$C_{17}H_{25}O_2NCl_2$	4.04	4.32	10.25	9.72
β-Diethylaminoethyl (α-ethyl)-p-dimethylamino	B	170–171	Acetone-Abs. EtOH	$C_{19}H_{31}O_2N_2Cl$	7.87	7.95	9.97	9.35
γ-Diethylaminopropyl (α-ethyl)-p-amino	A	191–192	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	7.54	18.80	18.80
γ-Diethylaminopropyl (α-ethyl)-o-amino	A	170–170.5	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	..	18.80	18.80
Dialkylaminoalkyl (β-Alkyl)-Cinnamate Hydrochloride								
β-Diethylaminoethyl (β-methyl)	C	141–142	Abs. EtOH	$C_{16}H_{24}O_2NCl$	4.70	4.85	11.91	11.93
β-Diethylaminoethyl (β-propyl)	C		.....	$C_{18}H_{28}O_2NCl$	4.30	4.94	10.90	10.33
N-(Dialkylaminoalkyl) (α-Alkyl)-Cinnamamide Hydrochloride								
N-(β-Diethylaminoethyl)-(α-methyl)	D	111–112.5	Acetone-Benzene	$C_{16}H_{25}ON_2Cl$	9.44	9.62	11.95	11.84
N-(β-Diethylaminoethyl)-(α-n-propyl)	D	134.2–134.9	Methyl-Ethyl Ketone	$C_{18}H_{29}ON_2Cl$	8.62	8.71	10.92	10.89
N-(β-Diethylaminoethyl)-(α-ethyl)	D	163–164	Abs. EtOH	$C_{17}H_{27}ON_2Cl$	9.02	9.11	11.41	11.46
N-(β-Diethylaminoethyl)-(α-n-butyl)	D	124.5	Acetone	$C_{19}H_{31}ON_2Cl$	8.27	8.62	10.47	10.25
N-(β-Diethylaminoethyl)-(α-amyl)	D	92–95	.....	$C_{20}H_{33}ON_2Cl$	7.94	8.00	10.05	9.97

SUMMARY.

1. A series of compounds derived from α-alkyl- and β-alkyl-cinnamic acids designed to be local anesthetics were prepared. Included were:

β-diethylaminoethyl α-alkyl-cinnamate hydrochlorides.

β-diethylaminoethyl β-alkyl-cinnamate hydrochlorides.

N-(β-diethylaminoethyl)-α-alkyl-cinnamamide hydrochlorides.

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

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

IV. LOCAL ANESTHETICS CONTAINING AN EPHEDRINE-LIKE NUCLEUS.

BY W. A. LOTT AND W. G. CHRISTIANSEN.

Researches described in Parts II and III of this series have dealt primarily with the acidic component of local anesthetics—the term acidic as used here refers