A New Class of Ultralong-Acting Local Anesthetics

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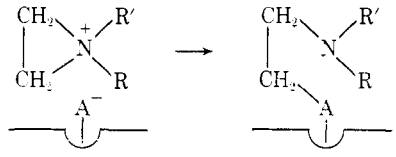
It has long been recognized that adrenergic blocking agents of the haloethylamine-type block those actions of norepinephrine mediated by the α receptor by a three-step process:[1] (1) cyclization to form an aziridinium ion, (2) formation of a reversible complex between the aziridinium ion and an anionic site on the receptor, and (3) reaction of the aziridinium ion with a nucleophilic group on the receptor to form a covalent bond. The last step may be represented by the following equation.

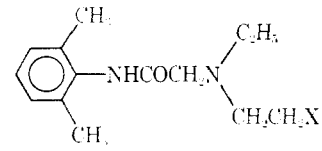


The activity of a given agent will depend upon its ability to penetrate to a biophase and to form the required aziridinium ions as well as upon its affinity for the receptor. The specificity for the α-adrenergic receptor should depend upon the ability of R and R′ to aid in formation of a reversible complex with the receptor. By proper choice of R and R′ it should be possible to make agents that can alkylate irreversibly other receptors that contain nucleophilic, anionic sites.

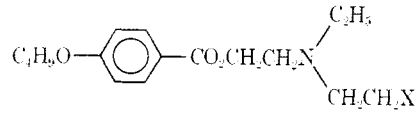
Although Baker[2] has reported extensive work toward development of specific alkylating agents for chemotherapy, there have been few attempts to exploit other monofunctional alkylating agents as pharmacodynamic agents. One successful application of this concept has been reported by Gill and Rang.[3] They found that the *N*-chloroethyl analog of benactazine possessed very long-acting anticholinergic activity.

In the present note the synthesis and pharmacological evaluation of two new long-acting local anesthetics is described. Ritchie and Greengard[4] have presented evidence that local anesthetics act in a cationic form once they have penetrated the nerve membrane. Therefore, it seemed reasonable that compounds known to have reversible local anesthetic activity could be modified to effect alkylation of the receptor.

The two local anesthetics chosen as models to test this hypothesis were lidocaine (Ia) and diethylaminoethyl 4-butoxybenzoate (IIa). The hydroxyethyl analog (Ib) of lidocaine was prepared by the method of Paabo.[5] Treatment of Ib with $SOCl_2$ gave the HCl salt of Ic. 2-[Ethyl(2-hydroxyethyl)amino]ethyl 4-butoxybenzoate (IIb), prepared by the method of Christiansen and Harris,[6] was treated similarly to give the HCl salt of IIc. This salt was very difficult to crystallize, and the crude material obtained was very hygroscopic. Repeated recrystallization was necessary to obtain a suitable solid product.



Ia, X = H
b, X = OH
c, X = Cl



IIa, X = H
b, X = OH
c, X = Cl

Pharmacological Results.—The HCl salt of Ic was examined for its ability to act as a local anesthetic on a variety of tissues. At a concentration of 0.5% in saline solution it produced corneal anesthesia in rabbits lasting for several hours. It blocked axonal conduction of squid nerves for many hours even after repeated washing, whereas the blockade from procaine was reversed readily upon wash. At the same concentration it abolished pain sensation for about 24 hr in the guinea pig intra-dermal wheal test. It also blocked the sciatic nerve of frog for an extended period of time, *i.e.*, up to 2 hr, unlike lidocaine blockade which reversed much more quickly. At 0.02–0.03% the compound blocked the indirectly elicited twitch of the rat phrenic nerve diaphragm preparation, and prolonged washing could not restore nerve transmission. Under similar conditions, blockade by procaine at 1% concentration was reversed within a few minutes. The compound blocked contractions of smooth muscles (rabbit aortic strip, guinea pig ileum, and rat stomach fundus strip) at concentrations of 0.1 mg/ml and below. This block lasted for up to 4 hr, the maximum period of survival of the tissues. Lidocaine at comparable concentrations was inert. The HCl salt of IIc acted in a manner similar to that of the first compound in several of these tests but was approximately 10–20-fold more potent in its blocking action.

In some instances (squid axon, smooth muscles, and phrenic nerve diaphragm preparation) application of Ic in the presence of procaine or lidocaine was accompanied by reversal upon wash. Thus both reversible local anesthetics could protect the sites of reaction of these tissues against the irreversible action of the alkylating drug. Therefore, it would appear that the new compounds react in an irreversible manner with a nucleophilic group on the receptor and constitute a new class of long-acting local anesthetic agents.

(1) M. Nickerson, *Pharmacol. Rev.*, **9**, 246 (1957).
(2) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley & Sons, Inc., New York, N. Y., 1967.
(3) E. W. Gill and H. P. Rang, *Mol. Pharmacol.*, **2**, 284 (1966).
(4) J. M. Ritchie and P. Greengard, *J. Pharmacol. Exp. Ther.*, **133**, 241 (1961).
(5) G. Paabo, U. S. Patent, 3,042,720 (1962).
(6) W. G. Christiansen and S. E. Harris, U. S. Patent, 2,404,691 (1946).

Experimental Section[7]

2-[(2-Chloroethyl)ethylamino]-2′,6′-acetoxylidide Hydrochloride.—2-[Ethyl(2-hydroxyethyl)amino]-2′,6′-acetoxylidide (13.8 g, 0.055 mol) in 50 ml of $CHCl_3$ was cooled in an ice bath. A solution of $SOCl_2$ (13.1 g, 0.110 mol) in 50 ml of $CHCl_3$ was added slowly with stirring. The mixture was warmed on a water bath for 2 hr at 50–60°. The excess $SOCl_2$ and $CHCl_3$ were removed *in vacuo*, and the residual oil was triturated with dry C_6H_6 until crystallization occurred. The solid material was removed by filtration and recrystallized repeatedly from C_6H_6–$CHCl_3$. The yield was 6.2 g of product melting at 152–154°. *Anal.* ($C_{14}H_{22}Cl_2N_2O$): C, H, N.

2-[(2-Chloroethyl)ethylamino]ethyl 4-Butoxybenzoate·HCl.—2-[Ethyl-(2-hydroxyethyl)amino]ethyl 4-butoxybenzoate (6.2 g, 0.02 mol) was dissolved in 20 ml of $CHCl_3$. A solution of $SOCl_2$ (6.0 g, 0.05 mol) in 20 ml of $CHCl_3$ was added in small portions with stirring. The mixture was heated for 4 hr at 65–70° on a water bath. The mixture was concentrated *in vacuo* to a thick oil. The residue was cooled and triturated with petroleum ether to induce crystallization. The product was recrystallized repeatedly from a C_6H_6–petroleum ether mixture. The yield of pure material melting at 103–105° was 0.9 g. *Anal.* ($C_{17}H_{27}Cl_2NO_3$): C, H, N.

(7) Melting points were taken in a Thomas–Hoover Unimelt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Radioopaque Contrast Media. XVIII.[1] Derivatives of 2-(3-Amino-2,4,6-triiodophenyl)alkanoic Acids

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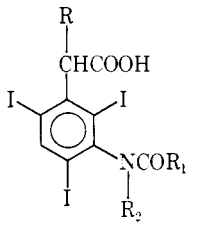
In connection with our studies concerning X-ray contrast media and particularly with the search for new oral cholecystographic agents[2] a number of derivatives of 2-(3-amino-2,4,6-triiodophenyl)alkanoic acids have been synthesized for biological evaluation.

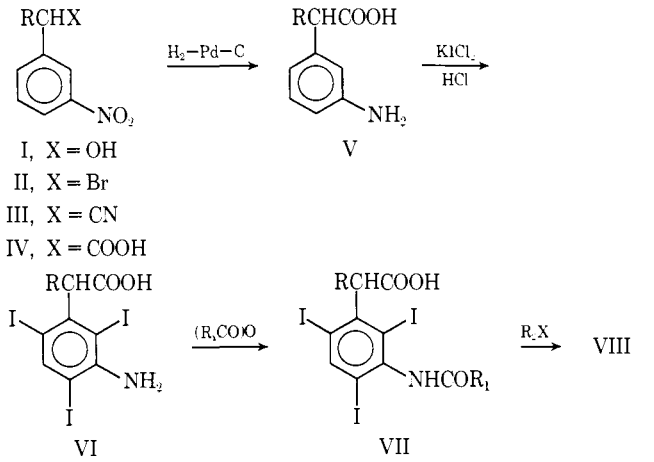


VIII

We were specially interested in the relationship between structure and biological activity such as intestinal absorption, toxicity, and biliary and urinary excretion within a homogenous group of substances.

The synthetic steps leading to the title compounds are outlined in Scheme I.

SCHEME I



(1) (a) XVI, E. Felder, D. Pitrè, L. Fumagalli, H. Suter, and H. Zutter, *Helv. Chim. Acta*, **52**, 1339 (1969); (b) XVII, D. Pitrè and L. Fumagalli, *Chim. Ther.*, in press.

(2) (a) D. Pitrè and L. Fumagalli, *Farmaco, Ed. Sci.*, **18**, 33 (1963); (b) D. Pitrè and L. Fumagalli, *ibid.*, **17**, 340 (1962); (c) L. Fumagalli and D. Pitrè, *ibid.*, **24**, 568 (1969).

Pharmacology.—The compounds were tested by Dr. G. Rosati for acute toxicity and biliary and urinary excretion.

For determination of intravenous and oral acute toxicity aqueous solutions of the Na salts were administered in mice and the LD_{50} was determined after 3 days following the method of Litchfield and Wilcoxon.[3] Excretion studies were done in the rabbit, collecting bile and urine through catheters for 3 hr after intravenous injection of 100 mg/kg of the aqueous solution of the Na salts. Total I_2 was determined, after digestion, by the Sandell–Kolthoff reaction[4] with a Technikon autoanalyzer[5] and results calculated as per cent of administered dose.

TABLE I
1-(3-NITROPHENYL)ALKANOLS (I)

No.	R	Mp or bp (mm), °C	Yield, %	Formula	Analyses
1	CH_3	62.5[a]	80[a]	$C_8H_9NO_3$	
2	C_2H_5	163 (2)[b]	95[b]	$C_9H_{11}NO_3$	
3	C_3H_7	173 (4)	92	$C_{10}H_{13}NO_3$	C, H, N

[a] Lit.[8] mp 62.5°; yield 76%. [b] Lit.[9] bp 170–172° (12 mm).

TABLE II
1-(3-NITROPHENYL)ALKYL BROMIDES (II)

No.	R	Mp or bp (mm), °C	Yield, %	Formula	Analyses
4	CH_3	42	55	$C_8H_8BrNO_2$	C, H, Br, N
5	C_2H_5	153 (3)	58	$C_9H_{10}BrNO_2$	C, H, Br, N
6	C_3H_7	150 (2)	55	$C_{10}H_{12}BrNO_2$	Br[a]

[a] Br: calcd, 30.96; found, 30.18.

The 2-(3-amino-2,4,6-triiodophenyl)alkanoic acids (Table VI) and their acyl derivatives (Table VII) showed predominantly urinary excretion; N-alkylation (Table VIII) enhanced biliary excretion.

For comparison iopanoic acid was tested under the same conditions giving LD_{50} p.o. = 1540 mg/kg and LD_{50} i.v. = 285 mg/kg (mouse), biliary excretion 28%, urinary excretion 13% (rabbit). For further investigation 200 mg/kg of compounds **37**, **38**, and **40** in suspension in 5% arabic gum solution were administered orally to dogs. Opacification of the gallbladder and of bile

(3) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

(4) E. B. Sandell and J. M. Kolthoff, *J. Amer. Chem. Soc.*, **56**, 1426 (1939).

(5) Technikon Instruments Corporation "N" Method File N-56.