## QUATERNARY AMMONIUM SALTS OF DIALKYLAMINOALKYL ESTERS OF 4-AMINO- AND 4-NITRO-2-CHLOROBENZOIC ACID

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The quaternary ammonium salts of dialkylaminoalkyl esters of 4-amino-2-hydroxybenzoic acid previously prepared by us [1] were examined for their anticholinesterase activity and evaluated as short-acting muscle relaxants [2]. It is known [3] that the introduction of a chlorine atom into the molecule in a series of derivatives of dialkylaminoalkyl esters of 4-aminobenzoic acid will occasionally result in compounds of greater activity and broader chemotherapeutic spectrum.

To extend the study of the relationship between chemical structure and pharmacological activity in this group of compounds, we have now synthesized quaternary ammonium salts of dialkylaminoalkyl esters of 4-substituted-2-chlorobenzoic acid of the following general type:

 $R \rightarrow OOO(CH_2)_n \stackrel{*}{\bigwedge} R'R'R''X'$ in which  $R = NO_2$  or  $NH_2$ ; R', R", and R''' = Hor a lower alkyl group; n = 2 or 3; and X = Br, Cl, or I (see Table 1).

The starting point of all these preparations was 2-chloro-4-nitrobenzoic acid. The dialkylaminoalkyl esters of this acid can be obtained by a variety of methods [4-7], but we prepared them by the interaction of the acid chloride with the appropriate dialkylaminoalkanol [7]. This procedure furnished products of a higher degree of purity and gave better yield.

Reduction of the dialkylaminoalkyl esters of 2-chloro-4-nitrobenzoic acid to the corresponding 4aminobenzoic esters has been attempted by several different methods [6-12]. Thus, catalytically, the diethylaminoethyl ester cannot be reduced at all [8], even though the free acid itself is readily reduced by this means, i.e., by gaseous hydrogen at atmospheric pressure in the presence of Raney nickel. (Presumably the ester resists reduction because the increased electron density in the nitro group, induced therein by the electron-donating effect of the ester group, lowers its adsorbability on the catalyst surface [9]). Again, although attempts to reduce the nitro esters (I), (II), and (III) with mixtures of hydrochloric acid and (a) metallic iron, (b) metallic tin, or (c) stannous chloride do furnish the corresponding amino esters (IV), (V), and (VI) respectively, the yields are low and the products difficult to purify [6, 7, 10-12].

We have successfully employed a more satisfactory method of reducing the three dialkylaminoalkyl esters, (I), (II), and (III), of 2-chloro-4-nitrobenzoic acid. This consisted in the use of hydrazine hydrate in the presence of Raney nickel, the course of the reduction being controlled by thin layer chromatography. The resulting amino esters, (IV), (V), and (VI) respectively, were characterized as hydrochloride salts, the free bases being recovered from these by means of aqueous ammonia, followed by extraction with ether. For this discharge of the bases to ether, the pH was adjusted to a value of at least 10, as at lower pH values, e.g., at pH 8 or 9, only some 20-30% of the basic product can be transferred to the organic layer [13].

The quaternary ammonium salts, (VII)-(XIV), of the dialkylaminoalkyl esters, not only of 4-amino-[(IV), (V), and (VI)], but also of unreduced 4-nitro-2-chlorobenzoic acid [(I), (II), and (III)], were obtained by

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TABLE 1. Di	monium Salts

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in error in the Russian original - Consultants Bureau. System 1: dichloroethane-ethanol (17.5:2.5); system 2: dichloroethane-ethanol (16.5:3.5). pe pe \* Some of the calculated values appear to Note.

the action on these six tertiary bases of the appropriate alkyl halides in anhydrous alcohol or acetone.

The chromatographic behavior of all these nitro and amino esters, both tertiary and quaternary, was examined. The experiments were carried out in unfixed layers of grade IV-activity  $Al_2O_3$ . The  $R_f$  values of the tertiary dialkylaminoalkyl esters of 4-nitrochlorobenzoic acid were greater than those of the corresponding 4-amino esters (see Table 1); this can be attributed to the fact that the adsorption mobility of the amino group is lower than that of the nitro group. In the case of the quaternary salts, the value of  $R_f$  is determined in part by the identity of the alkyl groups at the quaternary nitrogen atom, but in part also by the distance of this atom from the oxygen atom of the ester grouping [14].

The biological properties of the compounds described in this paper have been examined in the Pharmacological Laboratory (Director: Professor M. Ya. Mikhel'son) of the Evolutionary Physiology and Biochemistry Institute of the Academy of Sciences of the USSR. Of all the compounds, (XII) proved to have the most pronounced effect on the cholinoreceptors of skeletal muscle. In experiments with the smooth muscle of frog's intestine, a concentration of  $2 \cdot 10^{-5}$  of the same compound could elicit contractions amounting to 50% of the maximal possible effect, while doses of 2.5 µg/kg administered intravenously to anesthetized cats could elicit a depolarization-type blockade in the nervemuscle communication system of the animal.

## EXPERIMENTAL

Dialkylaminoalkyl Esters of 2-Chloro-4-Nitrobenzoic Acid. 2-Chloro-4-nitrobenzoyl chloride (0.01 mole) was dissolved in 30 ml of absolute alcohol or benzene. To this solution, cooled in ice and constantly stirred, was added the appropriate dialkylaminoalkanol (0.03 mole) in 10 ml of anhydrous solvent. The resulting precipitate was filtered off after 30 min and recrystallized from absolute alcohol.

Dialkylaminoalkyl Esters of 2-Chloro-4-Aminobenzoic Acid. A solution of a dialkylaminoalkyl ester of 2-chloro-4-nitrobenzoic acid (0.01 mole) in ethanol (10 ml) was treated with hydrazine hydrate (0.05 mole) and heated to boiling. About 0.1 g of Raney nickel catalyst was then added and the mixture boiled for 1.5 h. During this time, the course of the reaction was checked every 15 min by TLC, using an unfixed layer of grade V-activity Al<sub>2</sub>O<sub>3</sub> and the solvent system dichloroethane-ethanol (16:4). When the reaction was complete, the excess of hydrazine hydrate was decomposed by adding a further amount of catalyst (about 0.05 g) and boiling the mixture for 5 min. The catalyst was then filtered off and the filtrate concentrated down to a volume of about 5 ml. On passing in hydrogen chloride gas, a precipitate was obtained which was filtered off and crystallized from absolute alcohol.

[4-Amino- and 4-Nitro-2-Chlorobenzoyloxyalkyl] -Trialkylammonium Salts. A solution of a dialkylaminoalkyl ester of 4-amino- or 4-nitro-2-chlorobenzoic acid (0.01 mole) in 15 ml of absolute alcohol or acetone was treated with a solution of an alkyl halide (0.05 mole) in 5 ml of the corresponding solvent and the mixture maintained at the boiling point for 15-60 min. The resulting precipitate of quaternary ammonium salt was filtered off and crystallized from absolute alcohol.

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