block β-receptors which varies in different tissues and preparations (Table III). The importance of the terminal substituent on the nitrogen atom for closeness of fit to this receptor is at once apparent.

The demonstration of antagonism to the effects of histamine in inhibiting motility of rat uterus, and in causing a flow of acid gastric juice in three species reveals a new degree of antihistamine activity. The active compounds so far examined are disubstituted and Br > Cl. The activity of the ethyleneiminium picrylsulfonate relative to its parent compound 11 agrees with a previous finding for the E^+ of classical halogenoalkylamines.[11] The duration of the blockade produced by these compounds is less than that of phenoxybenzamine. If it is assumed that in the latter case an ester is formed by alkylation of the α-receptor, the hydrolysis which is necessary for regeneration may be anchimerically aided by the N,N-dimethylamino moiety in this series, which has a greater nucleophilic driving force than N,N-dialkyl groups of greater complexity. The new feature is that the antagonism is not merely brief but is surmountable; it is possible that this is due to easy reversibility of alkylating power.

Acknowledgments.—All compounds and the chemical and physical data relating to them were supplied by N. B. Chapman and his colleagues of the Department of Chemistry, University of Hull, England. We are glad to acknowledge technical assistance from Mr. Peter Jones. Supplies of D.C.I. were given by Eli Lilly and Co.

Quaternary Ammonium Compounds. III. Antiacetylcholinesterase Activity and Charge Distribution in Aromatic Quaternary Ammonium Compounds

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A series of trimethylphenylalkylammonium compounds has been prepared and examined for antiacetylcholinesterase activity. The results indicate that quaternary ammonium compounds in which the quaternized nitrogen atom is adjacent to an aromatic ring are more active than those in which the quaternary ammonium group is removed from the benzene ring and is of the aliphatic type. This phenomenon is discussed and explained in terms of charge delocalization and stereochemistry of the two types of quaternary ammonium ion.

It is generally accepted that acetylcholinesterase contains two functional entities in its active site, the esteratic site and the anionic site.[1] The substrate, usually acetylcholine, is considered to unite with the enzyme at these two points; the quaternary ammonium group at the anionic site and the acyl carbon of the ester group at the esteratic site. Reversible antiacetylcholinesterases such as eserine and neostigmine are considered to unit with the same active sites but to differ from the substrates in being hydrolyzed either not at all or only very slowly. However, many simple quaternary ammonium compounds which contain no other polarized group possess antiacetylcholinesterase activity. It is considered that the quaternary ammonium ion becomes adsorbed onto the anionic site and then the adsorbed onium ion hinders the approach of substrate molecules by one or both of two factors: (a) the electrostatic repulsion between the positively charged centers of acetylcholine and the inhibitor, and (b) the bulk of the quaternary ammonium ion prevents access to the esteratic site of the enzyme. If the substrate and inhibitor molecules are sufficiently small steric interaction at the esteratic site is not sufficient to achieve complete inhibition.[2] It follows, therefore, that there is a relationship between the forces of adsorption of quaternary ammonium compounds onto acetylcholinesterase and the antiacetylcholinesterase activity of these compounds. This has been shown to be the case by Myers.[3]

The total adsorption force between acetylcholinesterase and quaternary ammonium compounds is comprised of the following constituent forces[4,5]: (a) coulombic interaction between the positive charge of the quaternary ammonium group and the anionic site of the enzyme; (b) van der Waals forces between the hydrocarbon moiety of the quaternary ammonium ion and the enzyme suface. A third factor which is involved in the antiacetylcholinesterase activity of quaternary ammonium ions is the surface activity of amphipathic molecules or ions. As the lyophobic to lyophylic ratio is increased in an homologous series of quaternary ammonium compounds, such as *n*-alkyltrimethylammonium, so the antiacetylcholinesterase activity will increase because of (a) the increased forces of attraction between the enzyme and inhibitor, and (b) the increased concentration of onium ions at the interface of the water and enzyme due to the effect of water on the amphipathic ions. This effect will be called the "distribution effect" in the following discussion.

Thomas[6] postulated that with aliphatic quaternary ammonium ions the major contribution to the coulombic force was between the fractional positive charge on the α-carbon atoms of the quaternary ammonium group and the anionic site rather than between the positive charge on the nitrogen atom and the site. He came to this conclusion after a consideration of the charge distribution and stereochemistry of the quaternary nitrogen group and a study of the antiacetylcholinesterase activities of a series of stereospecific quaternary ammonium spiran compounds.

(1) D. Nachmansohn and I. B. Wilson, *Advan. Enzymol.*, **12**, 259 (1951).
(2) I. B. Wilson, *J. Biol. Chem.*, **197**, 215 (1952).
(3) D. K. Myers, *Arch. Biochem.*, **27**, 341 (1950).
(4) F. Bergmann, *Discussions Faraday Soc.*, **20**, 126 (1955).
(5) S. A. Bernhard, *J. Am. Chem. Soc.*, **77**, 1966 (1955).
(6) J. Thomas, *J. Med. Pharm. Chem.*, **3**, 309 (1961).

TABLE I. TRIMETHYLPHENYLALKYLAMMONIUM SALTS

Compounds	Amine used	Alkyl halide used	Reaction solvent	Reaction time and cond.	Solv. for recrystn.	M.p., °C. Found	M.p., °C. Lit.	Analysis, % Calcd. C	Calcd. H	Calcd. Br	Calcd. I	Found C	Found H	Found Br	Found I
Trimethylphenyl-ammonium iodide	N,N-Dimethylaniline (26.6 g., 0.21 mole)	Methyl iodide (30.5 g., 0.22 mole)	Chloroform (100 ml.)	30 min. reflux	Ethanol	219.5–220.5	218[9] 224[10]	41.1	5.4		48.2	41.3	5.5		48.2
Trimethylbenzyl-ammonium iodide	N,N-Dimethylbenzyl-amine[11] (10.7 g., 0.08 mole)	Methyl iodide (15.0 g., 0.1 mole)	Ether (100 ml.)	1 hr. reflux	Acetone–ethanol	179.5–180.5	178–179[12]	43.3	5.8		45.8	43.4	6.0		45.8
Trimethylphenethyl-ammonium bromide	Trimethylamine[a] (16.5 ml., 0.08 mole)	2-Phenylethyl bromide (14.0 g., 0.08 mole)	No solvent [b]	2 hr., 110° in autoclave	Ethanol	238.0–239.0	220[13] 238–239[14]	54.1	7.4	32.7		53.9	7.2	32.6	
Trimethyl-(3-phenyl-propyl) ammonium bromide	Trimethylamine[a] (18.0 ml., 0.1 mole)	3-Phenylpropyl bromide (19.9 g., 0.1 mole)	Ethanol (75 ml.)	10 hr., 45°	Ethanol	152.0–152.5	143[13] 151[15]	55.8	7.8	31.0		55.8	7.8	31.0	
Trimethyl-(4-phenyl-butyl) ammonium bromide[c]	Trimethylamine[a] (38.5 ml., 0.2 mole)	4-Phenylbutyl bromide (32.6 g., 0.15 mole)	Ethanol (50 ml.) [b]	10 hr., 45°	Ethanol	181.5–182.5		57.4	8.2	29.4		57.4	8.0	29.3	
Trimethyl-(5-phenyl pentyl) ammonium bromide[d]	Trimethylamine[a] (38.5 ml., 0.2 mole)	5-Phenylpentyl bromide (30.0 g., 0.13 mole)	Ethanol (50 ml.) [b]	3 hr., 45°	Ethanol	163.5–165.5	162–163[15]	58.7	8.5	27.9		58.8	8.5	28.0	

[a] 33% ethanolic solution of trimethylamine used. [b] Product precipitated from the cooled reaction mixture by the addition of ether. [c] Picrate salt, yellow plates from ethanol (50%), m.p. 99.5–100.5°. *Anal.* Calcd. for $C_{19}H_{24}N_4O_7$: C, 51.3; H, 5.8. Found: C, 54.3; H, 5.8. [d] Picrate salt, yellow plates from ethanol (50%), m.p. 86–87°. *Anal.* Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.2; H, 6.3. Found: C, 55.3; H, 6.3.

However, it was indicated by the results of the antiacetylcholinesterase studies of Thomas[7] on spiran quaternary ammonium compounds that factors other than those discussed above are involved in the activities of onium ions containing an aromatic system. In the series of compounds reported[7] there were two pairs of isomers I, II and III, IV included. The more active one in each pair was the one with the nitrogen atom adjacent to the aromatic ring. Since the pairs of compounds are isomers, then with each pair, the van der Waals and "distribution effect" components of the total binding force should be constant. Hence it appears that the difference in binding force, and therefore in antiacetylcholinesterase activity, is due to differences in the coulombic forces of attraction between the quaternary ammonium ions and the enzyme. However, since with each pair of isomers there is a considerable difference in shape it is impossible to decide how crucial this is.

I

II

III

IV

In order to obtain further and less ambiguous evidence that there is a difference in coulombic force of attraction between aromatic and aliphatic quaternary ammonium compounds and acetylcholinesterase, a series of trimethylphenylalkylammonium compounds $C_6H_5(CH_2)_nN^+(CH_3)_3$ ($\bar{V}$, n = 0–5), has now been prepared and their antiacetylcholinesterase activities have been determined.

Experimental[8]

The trimethylphenylalkylammonium salts which were prepared are listed in Table I together with details of the preparation and analytical data.

4-Phenyl-1-butanol was prepared from 3-phenylpropyl bromide (80 g.) by the method of Gilman and Catlin,[16] yield 41.2 g. (71%), b.p. 136–138° (14.5 mm.). **Phenylurethane,** long white needles from (40–60°) petroleum ether, m.p. 53–53.5° (lit.[17] 51–52°).

4-Phenylbutyl Bromide.—4-Phenyl-1-butanol (38.6 g., 0.26 mole) was refluxed with 60% hydrobromic acid (24.6 ml., 031 mole) and sulfuric acid (14 m.) for 2 hr. The mixture was diluted with water (50 ml.), the product separated and then washed in turn with sulfuric acid (15 ml.), water (50 ml.) and sodium carbonate solution (50 ml., 10%). The product was dried over

(7) J. Thomas, *J. Med. Pharm. Chem.*, **3**, 45 (1961).

(8) All melting points were determined on a Kofler block and are corrected.

(9) R. W. D. Preston and H. O. Jones, *J. Chem. Soc.*, **101**, 1930 (1912).

(10) H. McCrombie and T. H. Reade, *ibid.*, **123**, 141 (1923).

(11) H. P. Clarke, H. B. Gillespie, and S. Z. Weishauss, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(12) M. Tiffeneau and K. Fuhrer, *Bull. soc. chim. France*, [4] **15**, 162 (1914).

(13) J. von Braun, *Ber.*, **43**, 3209 (1910).

(14) W. H. Saunders and D. H. Edison, *J. Am. Chem. Soc.*, **82**, 138 (1960).

(15) T. Kato, T. Morikawa, and Y. Suzuki, *J. Pharm. Soc. Japan*, **72** 1177 (1952).

(16) H. Gilman and W. E. Catlin, *Org. Syn.*, **Coll. Vol. 1**, 182 (1949).

(17) J. von Braun, *Chem. Ber.*, **44**, 2876 (1914).

calcium chloride and distilled under reduced pressure, b.p. 132–134° (13 mm.), yield 33.7 g. (61.8%).

Phenylthiuronium picrate was prepared by the method of Thomas and Baker,[18] lemon yellow crystals from ethanol (50%), m.p. 149–150°.

Anal. Calcd. for $C_{23}H_{23}N_5O_7S$: C, 53.8; H, 4.5. Found: C, 53.9; H, 4.5.

5-Phenyl-1-pentanol.—A Grignard reagent was prepared from 3-phenylpropyl bromide (80 g., 0.42 mole) by the standard technique. The mixture was cooled to 0° and then ethylene oxide (19.8 g., 0.45 mole) dissolved in ether (150 ml.) was added and the mixture stirred until it reached room temperature. The mixture was then refluxed for 1 hr. after which time 150 ml. of ether was distilled out. This was replaced by benzene (150 ml.) and distillation continued until the temperature of the vapor reached 65° and then the mixture refluxed for a further hr. After cooling, the mixture was poured onto ice and the precipitated magnesium hydroxide dissolved by the addition of sulfuric acid. The mixture was steam distilled and the distillate extracted with ether. The extract was dried and the product distilled under reduced pressure, b.p. 154–156° (20 mm.), lit.[19] 155° (20 mm.), yield 39.8 g. (56.7%).

Phenylurethane, long white needles from (40–60°) petroleum ether, m.p. 69–70°.

Anal. Calcd. for $C_{18}H_{21}O_2$: C, 76.3; H, 7.4. Found: C, 75.7; H, 7.2.

5-Phenylpentyl Bromide.—5-Phenyl-1-pentanol (38.6 g., 0.26 mole) was added to a mixture of sulfuric acid (14 ml.) and 60% hydrobromic acid (24.6 ml., 0.31 mole), the mixture was refluxed for 2 hr., then cooled and diluted with water. The crude product was separated, washed in turn with sulfuric acid (20 ml.), water (50 ml.) and sodium carbonate solution (50 ml., 10%). After drying over calcium chloride the product was distilled under reduced pressure, b.p. 132–134° (13 mm.), yield 33.7 g. (61.5%).

Thiuronium picrate, orange yellow plates from ethanol (50%), m.p. 134–135°.

Anal. Calcd. for $C_{18}H_{21}N_5O_7S$: C, 47.9; H, 4.7. Found: C, 48.0; H, 4.7.

Measurement of Antiacetylcholinesterase Activity.—An electrically heated, thermostatically controlled water bath adjusted to 37° was used. A small beaker (50 ml.) was supported in the water bath and into it were placed a glass electrode, a glass stirring rod, one arm of an agar bridge and the tip of a microburet. The other arm of the agar bridge dipped into a saturated potassium chloride solution into which also dipped the calomel electrode. Both the glass and calomel electrodes were connected to a pH meter, the temperature compensator of which was set at 37°.

A solution of the inhibitor (x ml., concentration arbitrarily selected) was pipetted into the beaker, then distilled water ($13-x$ ml.), magnesium chloride (5 ml., 0.2 M) and sodium chloride (5 ml. 0.5 M). The enzyme preparation (2 ml.) was added and the solution adjusted to pH 7.4 by the addition of 0.02 N sodium hydroxide solution. The system was allowed to incubate for 30 min. and then acetylcholine perchlorate (5 ml., 0.06 M) was added. The mixture was maintained at pH 7.4 for 15 min. by the addition of 0.02 N sodium hydroxide solution. The volume was recorded. Throughout the determination the solution in the beaker was stirred frequently. The determination was repeated using different concentrations of inhibitor and the I_{50} values were calculated from graphs drawn with ordinates representing the $-\log$ of concentration of inhibitor and the abscissas representing per cent inhibition. The results quoted were corrected for non-enzymic hydrolysis. The non-enzymic hydrolysis rate was determined by repeating the experiment but substituting a buffer solution (pH 7.4, 2 ml.) for the enzyme preparation.

Source of Acetylcholinesterase.—Ox erythrocyte stromata prepared according to Augustinsson[20] was used. All determinations were made using the same preparation which was stored in a refrigerator at 4°. No deterioration in enzyme activity was observed during the course of the work. The concentration of substrate used was that found to be optimal for the particular enzyme preparation used.

(18) J. Thomas and W. A. Baker, *J. Pharm. Pharmacol.*, **12**, 460 (1960).
(19) J. von Braun and H. Deutsch, *Chem. Ber.*, **45**, 2171 (1912).
(20) K. B. Augustinsson, *Act. Physiol. Scand.*, **15**, Suppl., 52 (1948).

TABLE II

Antiacetylcholinesterase activities of trimethylphenylalkylammonium compounds. I_{50} values in g./M/l. Ox erythrocytes used as source of enzyme. Temp. 37°. Substrate concentration 0.012 M (acetylcholine perchlorate), sodium chloride 0.1 M, magnesium chloride 0.04 M.

Compound	I_{50}	n
Trimethylphenylammonium iodide	5.90×10^{-4}	0
Trimethylbenzylammonium iodide	3.10×10^{-3}	1
Trimethylphenethylammonium bromide	1.64×10^{-2}	2
Trimethyl(3-phenylpropyl)ammonium bromide	2.34×10^{-2}	3
Trimethyl(4-phenylbutyl)ammonium bromide	7.91×10^{-3}	4
Trimethyl(5-phenylpentyl)ammonium bromide	7.80×10^{-3}	5

Results and Discussion

The antiacetylcholinesterase activities of the trimethylphenylalkylammonium series of compounds are given in Table II and shown graphically in Fig. 1. where activity is plotted against the number of carbon atoms separating the phenyl group and the quaternized nitrogen atom. Also on Fig. 1 are the results obtained

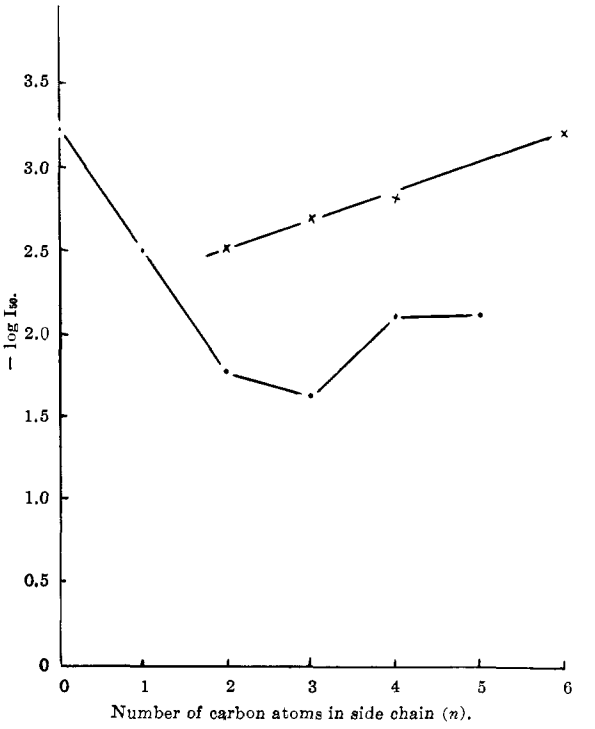

Fig. 1.—Antiacetylcholinesterase activities of trimethylphenylalkylammonium and n-alkyltrimethylammonium compounds: trimethylphenylalkylammonium compounds, —·—; n-alkyltrimethylammonium compounds, —x— (values taken from Bergmann and Shimoni[21]).

by Bergmann and Shimoni[21] on the antiacetylcholinesterase activities of the homologous series of n-alkyltrimethylammonium salts. Since the method used to determine activity by Bergmann and Shimoni[21] was not the same as the one used in the present work, the activities reported in the two series are not necessarily comparable. But within each series they are comparable, and since it is the pattern of change within each series which is compared, rather than absolute I_{50} values, then differences in the techniques used to

(21) F. Bergmann and A. Shimoni, *Biochim. Biophys. Acta*, **10**, 49 (1953).

determine I_{50} values are of no consequence to the interpretation of the results.

It can be seen from Fig. 1 that there is a fundamental difference in the change in activity as the two homologous series are ascended. In the case of the *n*-alkyltrimethylammonium series the activity increases, as the size of the *n*-alkyl group increases, in the normal and anticipated manner. This is due to van der Waals forces and "distribution effect" increasing with increasing length of the alkyl chain while the coulombic component of the total adsorption force remains constant from one compound to the next.

When the trimethylphenylalkylammonium series is considered it can be seen that as the homologous series is ascended activity first drops and then after passing through a minimum begins to rise. Since the addition of methylene groups *per se* should have the same type of effect on both the van der Waals forces and "distribution effect" in both series of compounds, it appears that the "abnormal" pattern of results obtained with the trimethylphenylalkylammonium series is due to a fundamental change in the coulombic component of the total adsorption force of attraction. It is possible to interpret these results in terms of charge delocalization and stereochemistry of the trimethylphenylalkylammonium compounds.

In a discussion of electrophilic aromatic substitution Ingold[22] came to the view that the trimethylammonium group withdraws π-electrons from the aromatic ring by what he describes as a negative-inductive effect. The intensity of the effect at the aromatic nucleus is diminished by relay through a chain of saturated carbon atoms, so that it becomes barely appreciable with the trimethyl(3-phenylpropyl)ammonium compound.

Charge Delocalization, Stereochemistry and Antiacetylcholinesterase Activity.—In an analysis of charge delocalization and antiacetylcholinesterase action in aliphatic quaternary ammonium compounds, Thomas[6] came to the conclusion that electrostatic attraction between the fractional positive charge on the α-carbon atoms of the quaternary ammonium group and the anionic site of the enzyme provided the major contribution to the total coulombic attractive forces. It was considered that the charge carried on the nitrogen atom provided only a minor contribution. The positive charge in aliphatic quaternary ammonium compounds is distributed, to the first approximation, equally among the nitrogen and the four α-carbon atoms[23,24] and hence each carries approximately 0.2 of a unit positive charge. Therefore with an aliphatic compound such as *n*-alkyltrimethylammonium bromide, something in the order of 0.5 to 0.75 of the unit positive charge is utilized in contributing to the coulombic attraction between the quaternary ammonium ion and the enzyme (see Fig. 2).

In the case of trimethylphenylammonium, because of the charge delocalization around the aromatic system, the situation is different. With this compound practically the whole of the unit positive charge may be utilized as can be seen from Fig. 3. The fact

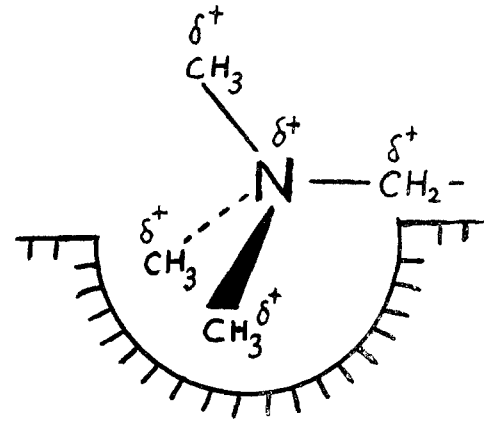

Fig. 2.—Anionic site.

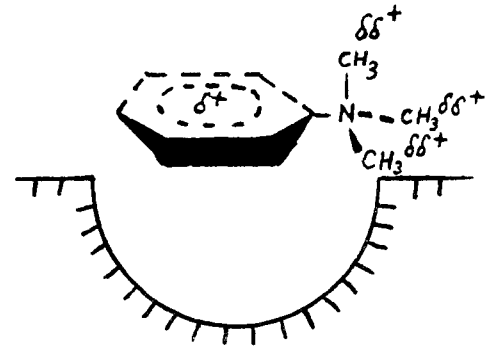

Fig. 3.—Anionic site.

that the charge is spread over a larger area with aromatic compounds than with aliphatic ones appears to have less effect than the increase in the fraction of the charge which is available.

If the trimethylphenylalkylammonium series of compounds is now examined with these considerations in mind, the pattern of results obtained becomes explicable. It was shown at the beginning of the discussion that the difference between the pattern of results obtained with (a) the trimethylphenylalkylammonium and (b) the alkyltrimethylammonium series of compounds appears to lie in the coulombic component of the total adsorption force. As discussed above with trimethylphenylammonium, practically the whole of the unit positive charge may be utilized. In the case of trimethyl(5-phenylpentyl)-ammonium the quaternary ammonium group is now aliphatic in type with only a fraction of the positive charge being available, and even though it has five carbon atoms more than trimethylphenylammonium, and therefore the van der Waals' forces and "distribution effect" will be greater, nevertheless its overall activity is less than the aromatic type onium ion.

It has been discussed above that as carbon atoms are introduced between the quaternized nitrogen atom and the benzene ring, the interaction between these two will diminish. Consequently, as the homologous series is ascended two factors, acting in opposite directions, will exert their influence on the overall activity of the compounds. The first factor which will tend to reduce activity will be the change from aromatic type quaternary ammonium compound to the aliphatic type. The second factor which will tend to increase

(22) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, p. 232.

(23) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1948, p. 71.

(24) D. B. Taylor, *Pharmacol. Rev.*, **3**, 412 (1951).

activity will be the progressive increase in van der Waals forces and "distribution effect." As the homologous series is ascended, therefore, the activity should first fall because of factor (1) but there will come a point where factor (2) becomes more significant than factor (1) and at that point activity will begin to increase. This is exactly the pattern of results which was obtained.

The Synthesis and Antitussive Properties of Some Cyclopentane Derivatives

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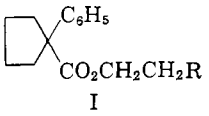
A number of derivatives of 1-hydroxycyclopentane-1-carboxylic acid has been synthesized; these include compounds in which one or both of the functional groups of the hydroxy acid carry basic substituents. The resulting compounds are mono- or diesters or ester-amides. A few compounds derived from 1-aminocyclopentane-1-carboxylic acid also were synthesized. The compounds were tested for antitussive properties in the cat; activity equal to one half of that of codeine is exhibited by several compounds. The relationship between chemical structure and antitussive potency is discussed briefly.

A variety of chemical structures exhibit antitussive activity. Several of the non-narcotic type of antitussive compounds contain a cyclopentane ring, for example, the (2-diethylaminoethoxy)ethyl ester (carbetapentane, Ia) and 2-diethylaminoethyl ester (caramiphen as the ethanedisulfonate salt, Ib) of 1-phenylcyclopentane-1-carboxylic acid. Of the analogs of carbetapentane in which the size of the alicyclic ring only was varied between cyclopropane and cyclohexane, that with the cyclopentane ring was the most active compound.[1] A compound (II) containing two cyclopentane rings has been evaluated.[2] The presence of the cyclopentane ring in these compounds suggested the synthesis of a series of derivatives of 1-hydroxycyclopentane-1-carboxylic acid for examination of their antitussive properties.



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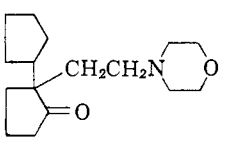
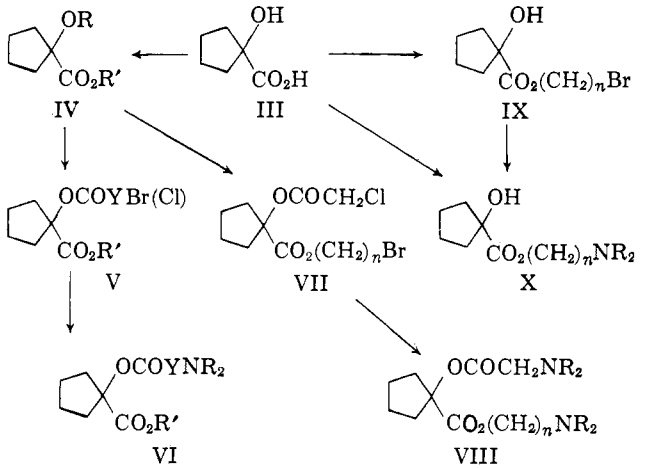


II

a. R = $OCH_2CH_2N(C_5H_5)_2$
b. R = $N(C_2H_5)_2$

Although the starting material, 1-hydroxycyclopentane-1-carboxylic acid, is readily available,[3] relatively little work has been published on its derivatives. The diethylaminoethyl esters of 1-hydroxycyclopentane-1-carboxylic acid and three of its O-acyl derivatives have been prepared[4] and tested for local anesthetic activity. Other simple derivatives of the hydroxy acid have been described[5] but no systematic study has been made of the effect on pharmacological properties of varying the substituent groups.

The present investigation has been concerned with the synthesis of (a) substituted aminoacyl derivatives of the parent hydroxyacid esters, (b) substituted aminoalkyl esters of 1-hydroxycyclopentane-1-carboxylic acid and (c) a series of compounds in which the features of both of these types are combined by preparing substituted aminoacyl derivatives of substituted aminoalkyl 1-hydroxycyclopentane-1-carboxylates. In addition the mono- or bisquaternary derivatives of several of these compounds have been prepared. The work is summarized in the accompanying scheme. A few derivatives of 1-aminocyclopentane-1-carboxylic acid have been prepared and tested in order to compare their properties with those of the corresponding compounds derived from the hydroxy acid.



The starting material for this investigation, 1-hydroxycyclopentane-1-carboxylic acid (III), was prepared by the cyanohydrin synthesis from cyclopentanone by a modification of Tchoubar's method.[3] The esters (IV, R = H, R′ = alkyl, aralkyl; IX, n = 2 or 3) were prepared by azeotropic esterification of the acid (III) in benzene with the appropriate alcohol using a little sulfuric acid as catalyst.[6] Yields were about 80–90% (Table I). The hydroxyesters (IV, R = H) were esterified with the appropriate halogeno acid halide in chloroform using pyridine as the acid-binding agent. The haloesters (V, Y = CH_2, $CHCH_3$, CH_2CH_2. Table I) were treated with various secondary amines

(1) S. Levis, S. Preat, and F. Moyersoons, *Arch. intern. pharmacodynamie*, **103**, 200 (1955).

(2) D. W. Archibald, L. B. Slipp, and S. J. Shane, *Can. Med. Assoc. J.*, **80**, 734 (1959).

(3) B. Tchoubar and C. Collin, *Bull. soc. chim. France*, 680 (1947); B. Tchoubar, *ibid.*, 160 (1949).

(4) R. Giuliano and M. L. Stein, *Il Farmaco* (Pavia), *Ed. sci.*, **11**, 3 (1956).

(5) R. Giuliano and G. Leonardi, *Farm. sci. e tec.* (Pavia), **7**, 29 (1952).

(6) J. Leon, W. F. Barthel, and S. A. Hall, *J. Org. Chem.*, **19**, 490 (1954).