dyl)-2-propen-1-ol, m.p. 74–75°. The n.m.r. spectrum was consistent with the proposed structure, with the expected hydrogen ratio of 2:2, peaks occurring at 3.06 (for $=CH_2$) and at 4.1 τ (for the methylene group of CH_2OH).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.61; H, 8.29; N, 5.77.

The **picrate,** formed in methanol on addition of a methanol solution of pieric acid, decomposed violently with a brilliant purple flash at 243°, with gradual darkening above 150°.

5-Cyano-6-hydroxy-4-methyl-2-phenylpyrimidine.—To a solution of 0.4 g. of sodium in 50 ml. of absolute ethanol was added 1.1 g. of benzamidine hydrochloride. After a few minutes, 1.3 g. of ethyl 3-ethoxy-2-cyanoacetate was added. The reaction mixture was heated under reflux for 2 hr. and then allowed to stand overnight at room temperature. After the addition of 25 ml. of water, the reaction mixture was neutralized with glacial acetic acid. A precipitate was deposited that amounted to 1 g. Dissolution of this material in concentrated ammonium hydroxide, followed by acidification with glacial acetic acid, afforded 0.8 g. of product, m.p. 290–291°.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.59; H, 4.42; N, 20.03.

5-Carbethoxy-4-hydroxy-2-phenylpyrimidine.—To a solution of 1.38 g. of sodium in 100 ml. of absolute ethanol was added 6.25 g. of benzamidine hydrochloride, followed by 5.1 g. of diethyl piperidylmethylenemalonate. The reaction mixture was heated under reflux with stirring for 2 hr. After filtering the reaction mixture, the ethanol was removed from the filtrate *in vacuo* and the residue was acidified with glacial acetic acid. The precipitate that was deposited amounted to 1 g. Recrystallization from ethanol afforded 0.9 g. of product, m.p. 214–215°. A mixture melting point with an authentic sample gave no depression.

Diethyl morpholinylmethylenemalonate (5.1 g.) reacted with 3.0 g. of benzamidine hydrochloride under the same conditions to give 0.5 g. of 5-carbethoxy-4-hydroxy-2-phenylpyrimidine, m.p. 214–215°, and 1.2 g. of 5-carboxy-4-hydroxy-2-phenylpyrimidine, m.p. 270.5–271.5°.

Formation of Benzimidazole from *o*-Phenylenediamine and Ethoxymethylenemalononitrile.—A solution of 6.1 g. of ethoxymethylenemalononitrile and 5.2 g. of *o*-phenylenediamine in 75 ml. of absolute ethanol was heated under reflux for 1 hr. After removal of the solvent *in vacuo* on a rotary evaporator, the residual solid was washed with petroleum ether and amounted to 7 g., m.p. 171–173°. Comparison of the infrared spectra and a mixture melting point with benzimidazole showed the two materials to be identical.

Formation of 2-Methylbenzimidazole from *o*-Phenylenediamine and Ethyl 3-Ethoxy-2-cyanocrotonate.—A solution of 27.5 g. of ethyl 2-cyano-3-ethoxycrotonate and 16.2 g. of *o*-phenylenediamine in 50 ml. of absolute ethanol was heated under reflux for 7.5 hr. The solvent was removed *in vacuo* on a rotary evaporator. The residue amounted to 24 g., m.p. 150–160°. Several recrystallizations from ethyl acetate–petroleum ether afforded pure 2-methylbenzimidazole, m.p. 176–177° (lit.[10] m.p. 176°).

Acknowledgments.—The authors are indebted to Messrs. Lee E. McCardle and Ronald D. Stewart for their able technical assistance, to Dr. Gordon Ellis and staff for the microanalyses, and to Dr. M. Gluckman for the pharmacological evaluation.

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Cyclic Analogs and Congeners of Succinyl Dicholine[1,2]

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Received June 30, 1963

Dicholine- and bis(N,N-dimethylhydraziniumethyl) esters of *cis*- and *trans*-cyclopropane- and cyclobutane-1,2-dicarboxylic acids have been prepared to study the effect of forcing the ester groups to assume a fixed conformation which would be similar to one of the conformations of succinyl dicholine. Biological test data are presented.

If the possible conformations of the succinic acid portion of succinyl dicholine are considered, it would be expected that *in vitro* a staggered conformation would be favored. The question then arises as to whether this conformation would also be favored for adsorption at an *in vivo* receptor surface. It was the purpose of the research reported herein to limit the degrees of rotational freedom about the two carbons alpha to the carboxyls of certain succinic acid congeners, thus forcing the ester groups to assume a fixed conformation which would be similar to one of the extreme conformations of succinyl dicholine. Inspection of Dreiding models of the dicholine esters of *cis*-cyclopropane- and of *cis*-cyclobutane-1,2-dicarboxylic acids indicates that they coincide (as regards the carbonyl groups) with the *eclipsed* form of the succinate ester. The *trans* isomers are nearly superimposable on the *staggered* conformation of the succinate ester. Since the cyclopropane and the cyclobutane rings are small, there should be a minimum of steric interference by the ring with the receptor surfaces involved, and it might be possible to evaluate the biological effects induced by the enforcement of specific conformations.

Tammelin[4] has prepared analogs of dicholine esters of saturated alkyl dicarboxylic acids from oxalic through adipic, in which one nitrogen-methyl of each choline was replaced by a primary amino group, forming a hydrazinium structure. These hydrazine analogs of choline esters possessed neuromuscular blocking activity, but they were in general less potent than the corresponding dicholine esters.[5] Nevertheless, it appeared that comparative studies of ammonium and hydrazinium

(1) Presented to the Division of Medicinal Chemistry of the American Chemical Society, Los Angeles, California, April 1–4, 1963. Abstracted in part from a thesis submitted by John F. McCarthy in partial fulfillment of the requirements of the degree of Doctor of Philosophy, University of Wisconsin, 1962.

(2) The investigation at the University of Wisconsin was supported by Fellowship Grant MF-11,607, National Institutes of Health.

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groups were incomplete, and that further studies were indicated.

Due to low yields and to the lengthy procedures involved in the literature methods leading to *cis*- and *trans*-cyclopropane-1,2-dicarboxylic acids, it was attempted to prepare them using the method employed by Simmons and Smith[6] for the preparation of ethyl cyclopropanecarboxylate, namely treatment of ethyl acrylate with methylene iodide in the presence of a zinc–copper couple. Presumably, a carbene intermediate is involved, and it would be expected that there should be retention of configuration in such a reaction. It was found that treatment of methyl fumarate with methylene iodide in the presence of a zinc–copper couple in tetrahydrofuran gave rise to a 5% yield of methyl *trans*-cyclopropane-1,2-dicarboxylate. Side products predominated, which will be the subject of a future communication.

The quaternary esters were prepared from the corresponding bis(2-bromoethyl) esters by treatment with trimethylamine or with 1,1-dimethylhydrazine. Acetonitrile appeared to be the solvent of choice; a reaction time of 24 to 48 hr. was possible using acetonitrile, as compared to a 1–2 week period with ethereal solvents. Paper chromatographic analysis indicated that the products of the quaternization reactions were homogeneous. Several of the quaternary bromides were isolated as glasses which could not be induced to crystallize.

Recently, Burger and Bedford[7] have reported synthesis of dicholine esters of *cis*- and *trans*-cyclopropane-1,2-dicarboxylic acids. Biological test data reported by Burger and Bedford for these esters parallel the data reported herein.

Experimental[8]

Mono(2-bromoethyl) *cis*-Cyclopropane-1,2-dicarboxylate (I).—*cis*-Cyclopropane-1,2-dicarboxylic acid anhydride[9] (3.0 g., 0.027 mole) and 3.35 g. (0.027 mole) of 2-bromoethanol (Eastman White Label, redistilled) were dissolved in 50 ml. of sodium-dried, thiophene-free benzene and the solution was allowed to stand at room temperature for 48 hr. in a well closed container. The benzene solution was diluted with 50 ml. of ether and was washed with two 50-ml. portions of cold water. The ether–benzene solution was dried over anhydrous magnesium sulfate and the solvent was removed on a steam bath in a stream of dry nitrogen. After removal of the last traces of solvent under reduced pressure, 5.6 g. (89%) of a viscous oil remained. The infrared spectrum (film) showed typical H-bonded OH of a carboxylic acid at 3.0 to 3.2 μ (broad) and at 3.6 to 3.8 μ (broad). Bands were also present at 5.75 μ (ester carbonyl) and at 5.85 μ (carboxyl carbonyl). Attempts to crystallize this material failed, and it was used without further purification.

Bis(2-bromoethyl) *cis*-Cyclopropane-1,2-dicarboxylate (II).—I (4.7 g., 0.02 mole) was dissolved in 50 ml. of sodium-dried, thiophene-free benzene, and the solution was cooled to 5–10°. Oxalyl chloride (Eastman White Label, redistilled, 3.0 ml., 0.035 mole) was added in one portion, and the solution was stirred for 1 hr. at 5–10°. The solution was allowed to come to room temperature and stirring was continued for 1 hr. The benzene and unreacted oxalyl chloride were removed under reduced pressure. Benzene (50 ml.) was added to the residue and was subsequently removed under reduced pressure; this procedure was repeated and the residue was redissolved in 50 ml. of dry benzene and was cooled to 5°. A solution of 5 ml. (8.75 g., 0.07 mole) of 2-bromoethanol in 50 ml. of dry benzene was added from a dropping funnel over a period of 10 min. to the rapidly stirred cold solution. The reaction mixture was maintained at 5° for an additional 5 min., allowed to warm to room temperature, and stirred for 1 hr. Ether (100 ml.) was added, and the ether–benzene solution was washed successively with 30 ml. of ice–water, two 30-ml. portions of cold, saturated sodium bicarbonate solution, and two 30-ml. portions of ice–water. After drying over anhydrous magnesium sulfate, the solvents were removed under reduced pressure and the viscous residue was distilled at 0.05 mm. in a short path distillation apparatus which provided no opening for a thermometer; total yield of distillate, 4.1 g. (60%).

Anal. Calcd. for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.52; Br, 46.46. Found: C, 31.55; H, 3.50; Br, 46.41.

The infrared spectrum (film) showed no absorption in the OH region, but had an ester carbonyl band at 5.75 μ; $n^{25}D$ 1.5150.

***dl*-Bis(2-bromoethyl) *trans*-Cyclopropane-1,2-dicarboxylate (III).**—A solution of 3.45 g. (0.028 mole) of *trans*-cyclopropane-1,2-dicarbonyl chloride[10] and 10 g. (0.08 mole) of 2-bromoethanol in 75 ml. of sodium-dried, thiophene-free benzene was refluxed for 24 hr. and the product was isolated as described in the preparation of II. The crude product (8.3 g.) yielded 5.2 g. (54%) of material boiling at 184–186° (1.5 mm.).

Anal. Calcd. for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.52; Br, 46.46. Found: C, 31.59; H, 3.16; Br, 46.60.

The infrared spectrum contained a band at 5.80 μ (ester carbonyl).

Mono(2-bromoethyl) *cis*-Cyclobutane-1,2-dicarboxylate (IV).—This compound was prepared in the same manner as described for I. A viscous oil (9.4 g., 90%) was obtained from 5.04 g. (0.04 mole) of *cis*-cyclobutane-1,2-dicarboxylic acid anhydride[11] and 5.16 g. (0.041 mole) of 2-bromoethanol. The product showed OH absorption typical of a carboxylic acid and two bands in the carbonyl region of the infrared spectrum. No anhydride bands were present at 5.40 and 5.65 μ. This material was used in subsequent operations without further purification.

Bis-(2-bromoethyl) *cis*-Cyclobutane-1,2-dicarboxylate (V).—This material was prepared from 8.2 g. (0.033 mole) of IV in the same manner as described for II. A yield of 7.2 g. (60%) of material boiling at 124–126° (0.03 mm.) was obtained.

Anal. Calcd. for $C_{10}H_{14}Br_2O_4$: C, 33.54; H, 3.94; Br, 44.64. Found: C, 34.42; H, 3.97; Br, 43.55; $n^{24}D$ 1.5101.

***dl*-Bis(2-bromoethyl) *trans*-Cyclobutane-1,2-dicarboxylate (VI).**—A solution of *trans*-cyclobutane-1,2-dicarboxylic acid[11] (3.8 g., 0.026 mole) in a mixture of 75 ml. of sodium-dried, thiophene-free benzene, 10 ml. of purified[12] dioxane, and 5.1 ml. (0.06 mole) of oxalyl chloride (Eastman White Label, redistilled) was stirred at room temperature for 3 hr. and then was refluxed 0.5 hr. Removal of the excess oxalyl chloride was accomplished by distilling 50 ml. of the solvent at atmospheric pressure. Dry benzene (50 ml.) was added to the residue; 12.5 g. (0.1 mole) of 2-bromoethanol in 100 ml. of dry benzene was added over a period of 15 min., and the mixture was stirred at room temperature for 16 hr. The solution, diluted with 200 ml. of ether, was washed successively with 50 ml. of cold water, two 50-ml. portions of cold, saturated sodium bicarbonate solution, and with two 50-ml. portions of cold water. The ether–benzene solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. An infrared spectrum (film) of the viscous residue (9.9 g.) showed no OH absorption bands, but there was present a broad band at 5.75 μ (ester carbonyl). The crude material was fractionated twice; the second distillation gave 5.1 g. (56%) of material boiling at 140–142° (0.05 mm.).

Anal. Calcd. for $C_{10}H_{14}Br_2O_4$: C, 33.54; H, 3.94; Br, 44.64. Found: C, 33.84; H, 3.91; Br, 44.231; $n^{25}D$ 1.4938.

The infrared spectrum showed a single sharp symmetrical band at 5.78 μ. A low boiling fraction from these distillations crystallized on standing and was identified as bis(2-bromoethyl) oxalate.

Quaternary Salts.—The appropriate bis(2-bromoethyl) ester was dissolved (A) in a convenient amount of acetonitrile, or (B)

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Table I

Cyclic Analogs and Congeners of Succinyl Dicholine, $(R'(CH_3)_2NCH_2CH_2OCO)_2R\cdot 2Br^-$

No.	R	R'	M.p., °C.[a]	Yield, %[b]	Formula	% Calcd. C	H	N	Br	% Found C	H	N	Br
1	*cis*-1,2-Cyclopropane	CH_3	Glass[c]	50	$C_{15}H_{30}Br_2N_2O_4$	38.97	6.49	6.06	34.58	38.39	6.05	5.96	34.68
2	*trans*-1,2-Cyclopropane	CH_3	234–235 dec.[d]	95	$C_{15}H_{30}Br_2N_2O_4$	38.97	6.49	6.06	34.58	39.24	6.46	6.00	34.35
3	*cis*-1,2-Cyclobutane	CH_3	Glass[c]	90	$C_{16}H_{32}Br_2N_2O_4$	40.35	6.73	5.88	33.60	40.04	6.11	5.48	34.02
4	*trans*-1,2-Cyclobutane	CH_3	190–192 dec.[d]	90	$C_{16}H_{32}Br_2N_2O_4$	40.35	6.73	5.88	33.60	39.95	6.58	5.75	33.22
5	*cis*-1,2-Cyclopropane	NH_2	196–198 dec.[d]	69	$C_{13}H_{28}Br_2N_4O_4$	33.65	6.06	12.04	34.50	33.58	6.23	12.10	33.92
6	*trans*-1,2-Cyclopropane	NH_2	175–177 dec.[d]	92	$C_{13}H_{28}Br_2N_4O_4$	33.65	6.06	12.04	34.50	34.03	5.99	11.92	34.27
7	*cis*-1,2-Cyclobutane	NH_2	Glass[c]	80	$C_{14}H_{30}Br_2N_4O_4$	35.16	6.32	11.72	33.42	35.42	6.51	11.59	33.90
8	*trans*-1,2-Cyclobutane	NH_2	Glass[e]	96	$C_{14}H_{30}Br_2N_4O_4$	35.16	6.32	11.72	33.42	35.35	6.60	12.09	33.68

[a] Taken in a silicone oil bath which was preheated to 10° below the m.p. Temperature was increased at the rate of 2°/min. [b] Calcd. on the basis of crude product obtained. [c] From 2-propanol–ether. [d] From 2-propanol–ethanol (2:1). [e] From 2-propanol.

in sodium dried ether, and a 100% excess of trimethylamine (prepared by heating trimethylamine hydrochloride with solid potassium hydroxide) or of 1,1-dimethylhydrazine (Eastman Yellow Label, redistilled) was added. The mixture was placed in a well closed container and was allowed to stand at room temperature in a desiccator for 48 hr. (A), or for 1 week (B). The solvent was decanted from the gummy precipitate which was washed with several portions of dry ether. Attempts to recrystallize the crude quaternary salts resulted, in the majority of experiments, in isolation of noncrystalline products. All of the quaternary salts were extremely hygroscopic, with the exception of the dicholine ester of *trans*-cyclopropane-1,2-dicarboxylic acid (see Table I).

Paper Chromatographic Determinations.—The method was a modification of that of Augustinsson and Grahn.[13] Whatman No. 4 filter paper was used, and a solvent system consisting of 1-butanol, ethanol, acetic acid, and water (8:2:1:3) was employed. Solutions of the compounds to be chromatographed were prepared immediately before application to the paper by dissolving 10–15 mg. in 0.5 ml. of methanol or methanol–water. These solutions (2.0 μl.) were then delivered 10 cm. from the edge of a rectangle of paper which was placed in the chromatography chamber arranged for descending flow. The solvent was allowed to descend 35–40 cm., which required 5 hr. The papers were dried at 120° for 1 hr., and the spots were located by spraying the dried chromatograms with 1% iodine solution[14] and with a hydroxylamine–ferric chloride reagent.[15] Modifications in the use of the latter reagent were as follows. A saturated ethanolic potassium hydroxide solution was mixed with the hydroxylamine hydrochloride solution (1:2); the potassium chloride was removed by filtration and the clear filtrate was sprayed on the dried chromatograms. After 5 min., the papers were sprayed with the ferric chloride reagent.

Dimethyl *trans*-Cyclopropane-1,2-dicarboxylate.—Zinc–copper couple[16] (4.5 g., 0.07 mole) was added to 50 ml. of purified tetrahydrofuran.[17] To this mixture was added a crystal of iodine and stirring was continued until the iodine color faded. A solution of 5 g. (0.035 mole) of dimethyl fumarate and 19 g. (0.071 mole) of methylene iodide in 150 ml. of purified tetrahydrofuran was added and the mixture was refluxed with stirring for 48 hr. After approximately 2 hr., a vigorous reaction occurred and the gray color of the zinc–copper couple was replaced by a red-brown color. The reaction mixture was cooled to room temperature and was passed through a fine grade filter paper. The clear filtrate was diluted with 400 ml. of ether, and the ether–tetrahydrofuran solution was washed successively with three 50-ml. portions of saturated ammonium chloride solution, two 50-ml. portions of saturated sodium bicarbonate solution, and two 50-ml. portions of water. The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed on a steam bath under reduced pressure. An amber liquid (6.1 g.) remained, whose infrared spectrum lacked the characteristic bands of the starting material (5.80, 6.08, and 10.2 μ), but contained a carbonyl band at 5.75 μ. Distillation at 0.02 mm. gave 0.30 g. (5%) of a product boiling at 35° whose infrared spectrum was superimposable upon one of an authentic sample of dimethyl *trans*-cyclopropane-1,2-dicarboxylate. Saponification of the product of the reaction gave rise to a white solid (m.p. 175–178°) which, when recrystallized from acetonitrile, was shown, by mixture melting point determination with an authentic sample, to be identical with *trans*-cyclopropane-1,2-dicarboxylic acid.[18]

Table II

Neuromuscular Blocking Activity of Succinyl Choline and Its Congeners

No.	No. of cats	Threshold dose (mg./kg.)	Duration of action (min.)	Change in blood pressure (mm.)
1	2	1.5	2	+12
2	4	0.02	20	+2 to +50
3	2	10.0	11	+42
4	3	0.9	2	+40
5	2	2.5	2	+15
6	3	0.04	24	+25
7	2	10.0	6	+10
8	3	2.5	4	+12
Succinyl choline	16	0.04	4	+12

Pharmacology. Methods.—All compounds were screened for neuromuscular blocking activity in cats anesthetized with α-chloralose and urethane (30 mg./ml. of α-chloralose in 25% urethane solution, 1.83 ml./kg.). The right posterior tibial nerve was separated from the peroneal nerve for a distance of 2–3 cm. and the right femoral nerve severed. The tibial nerve was ligated at a distance of 4–5 cm. from its union with the peroneal nerve and cut distal to the ligature. The bony tubercle on the medial edge of the foot was detached and the tendon of the tibialis anticus muscle ligated just above the tubercle and attached to a muscle lever recording system. Platinum electrodes were fixed around the intact peroneal nerve and the nerve bathed in warm mineral oil maintained between 35 and 38°. Blood pressure was recorded from a carotid artery *via* a mercury manometer. A Grass stimulator (Model SD5) delivered 0.8 to 1.0 v. square wave impulses every 6 sec., and the contractions of the tibialis anticus muscle were recorded on a smoked kymograph. The experimental compounds or succinyl choline were administered *via* a femoral vein, and the approximate minimal dose producing 100% blockade (threshold dose) was determined for each compound.

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(14) G. Brante, *Nature*, **163**, 651 (1949).
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(16) R. D. Smith and H. E. Simmons, *Org. Syn.*, **41**, 72 (1961).
(17) Eastman White Label tetrahydrofuran (2 l.) was refluxed over 250 g. of potassium hydroxide pellets for 4–5 hr. and was distilled. This distillate was twice redistilled from 15 g. of lithium aluminum hydride. The final distillate was stored in a glass-stoppered flask over a bright copper wire. Aliquots used in the zinc–copper couple reactions were again distilled from lithium aluminum hydride 15–30 min. before use.
(18) Furnished through the kindness of Professor Layton L. McCoy, Columbia University, to whom our thanks are extended.

Results

The neuromuscular blocking activity of the cyclic analogs and congeners of succinyl dicholine is summarized in Table II. Compound **2** was the most active compound in this current series and was approximately twice as potent as succinyl choline, having a duration of action 5 times that of succinyl choline. Compound **6** was approximately equipotent to succinyl choline, although the duration of action was approximately 6 times that of succinyl choline. In each instance, the *trans* derivative was much more potent than the *cis* derivative. For example, **2** was approximately 75 times more potent than **1**, and **6** was approximately 60 times more potent than **5**. The *trans*-1,2-cyclopropane derivatives were much more potent than the *trans*-1,2-cyclobutane derivatives. For example, **2** was approximately 45 times as potent as **4**, and **6** was approximately 60 times as potent as 8. All of the compounds produced mild to marked pressor responses.

Quaternary Ammonium Compounds. V. Antiacetylcholinesterase Activity of a Series of N-*t*-Alkylpyridinium Compounds

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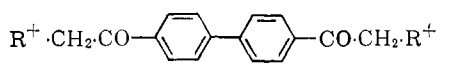
Received September 2, 1962

A series of N-*t*-alkylpyridinium compounds has been synthesized and the antiacetylcholinesterase activity of the compounds determined. The activities of the compounds are compared with those of an isosteric series of trimethylphenylalkylammonium compounds previously reported.[2] From these studies quaternary ammonium compounds are classified into two types, "aliphatic" and "aromatic," from the point of view of charge delocalization and stereochemistry.

Thomas and Marlow[2] have reported the antiacetylcholinesterase activities of a series of trimethylphenylalkylammonium compounds. It was found that the pattern of results obtained, as the homologous series was ascended, was fundamentally different from a "normal" series such as *n*-alkyltrimethylammonium (see Fig. 1). The fact that activity was reduced as saturated carbon atoms were introduced between the trimethylammonium group and the aromatic ring was explained in terms of the charge delocalization and stereochemistry of the compounds. From an antiacetylcholinesterase activity point of view, quaternary ammonium compounds were classified into two types, "aromatic" and "aliphatic."

A priori it might be anticipated that in a series of quaternary ammonium compounds in which the only difference between them was the structure of the onium group, the one containing the trimethylammonium group would be the most active antiacetylcholinesterase. There are two reasons for this; one is that acetylcholine, the natural substrate, contains the trimethylammonium group and in terms of "stereochemical fit" it could be expected that the enzyme surface could accommodate this group better than any other. The second reason is that in terms of the importance of the availability of the α-carbon atoms, as suggested by Thomas,[3] the trimethylammonium group is ideal. Since the evidence for the relative importance of shape and charge availability of a quaternary ammonium group has been mainly obtained from the trimethylphenylalkylammonium series in which each compound contained the trimethylammonium group, then it would be of value to examine the antiacetylcholinesterase activities of "aromatic" type compounds which did not contain this group.

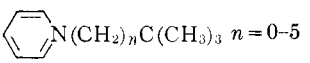
There is some evidence reported in the literature which supports the view that charge availability is more important than shape. A particularly interesting series of antiacetylcholinesterase activities, from this point of view, is one reported by Long and Schueler,[4] who determined the activities of a series of bisquaternary ammonium compounds of the type I. The compound



I

containing the trimethylammonium groups (I_{b0}, 6×10^{-5}) had next to the lowest activity and the 2-methylpyridinium compound (I_{b0}, 8×10^{-10}) the highest. Although the compounds reported are not strictly comparable, from the "distribution effect"[2] and potential van der Waals forces points of view, the results suggest that there is some basic difference in binding forces between "aromatic" and "aliphatic" quaternary ammonium compounds and the anionic site of acetylcholinesterase.

In order to obtain further evidence that there is a difference in the coulombic component of the total force of adsorption between "aliphatic" and "aromatic" quaternary ammonium compounds, a homologous series of pyridinium compounds (II) has now been examined. The pyridinium series of compounds (II) are isosteric with the trimethylphenylalkylammonium series reported previously[2] and so any differences in the pattern of change of activity between the two series of compounds, as the homologous series are ascended, should be a reflection of differences in the coulombic component of the total adsorption force of the two series.



II

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