Some of the compounds prepared in this way had antifibrillant activity. An optimum effect was experienced when $n \geqq 3$ and $NR_2 = N(CH_2)_y$ where $y = 4, 5, 6$, or 7. In the case of quaternary salts the activity was lower or eventually absent (see Tables I and II).

Experimental

A. N-(β-Heptamethyleniminoethyl)phthalimide Hydrochloride (7).—A solution of N-(β-bromoethyl)phthalimide (254 g., 1 mole) in benzene (2000 ml.) was treated with heptamethylenimine (228 g., 2 moles) and refluxed 2 hr. The precipitated heptamethylenimine hydrobromide was separated by filtration, the filtrate was evaporated *in vacuo* on a water bath, and the residue was dissolved in a mixture of ethanol and ether. After clearing the solution with charcoal and acidifying the liquid, the precipitated crystals were filtered and recrystallized from ethanol; yield 257.75 g. (90%), m.p. 214–216°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2 \cdot HCl$: Cl, 10.98; N, 8.68. Found: Cl, 10.87; N, 8.65.

B. N-(β-Aminoethyl)heptamethylenimine.—N-(β-Heptamethyleniminoethyl)phthalimide (70 g., 0.244 mole) was refluxed 6 hr. with 12 *N* HCl (150 ml.). On cooling, phthalic acid precipitated from the reaction mixture; it was filtered, washed with cold water, and dried, yielding 37 g. (91.2%). The filtrate was made alkaline with concentrated NaOH and extracted with ether or benzene. The organic phase was separated, dried ($MgSO_4$), and after evaporating the solvent, distilled *in vacuo;* yield 30.64 g. (80.2%), b.p. 75° (0.8 mm.).

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.29; H, 12.92; N, 17.96. Found: C, 69.35; H, 12.98; N, 17.80.

C. N-(β-Heptamethyleniminoethyl)-4-nitrophthalimide (8).—4-Nitrophthalimide (14.3 g., 0.05 mole) was heated with N-(β-aminoethyl)heptamethylenimine (7.81 g., 0.05 mole) for 1 hr. in a metal bath at 150°. The reaction proceeded with liberation of ammonia. On cooling, the brown melt solidified. On recrystallization from ethanol, the yield was 12.92 g. (72%), m.p. 163–165°.

Anal. Calcd. for $C_{17}H_{21}N_3O_4$: N, 12.68. Found: N, 12.34.

On acidifying the solution of the base in ethanol–ether, the monohydrochloride of the base precipitated, m.p. 119–120°.

Anal. Calcd. for $C_{17}H_{21}N_3O_4 \cdot HCl$: Cl, 9.64; N, 11.43. Found: Cl, 9.54; N, 11.20.

D. N-(β-Heptamethyleniminoethyl)phthalimide Methiodide (21).—A solution of N-(β-heptamethyleniminoethyl)phthalimide (2.86 g., 0.01 mole) in acetone (20 ml.) was allowed to stand 3 hr. with methyl iodide (2.13 g., 0.011 mole) at room temperature. Then the precipitated crystals were filtered and recrystallized from ethanol, yielding 3.85 g. (90%), m.p. 227–228°.

Anal. Calcd. for $C_{18}H_{25}IN_2O_2$: I, 29.63; N, 6.54. Found: I, 29.26; N, 6.19.

E. N-(5-Phthalimidopentyl)pyridinium Bromide (20).—N-(5-bromopentyl)phthalimide (2.94 g., 0.1 mole) was refluxed for 2 hr. with pyridine (39.5 g. 0.5 mole), then cooled and poured into acetone. The precipitated white platelets were recrystallized from ethanol, yielding 29.65 g. (79%), m.p. 186–188°.

Anal. Calcd. for $C_{18}H_{19}BrN_2O_2$: Br, 21.30; N, 7.46. Found: Br, 21.57; N, 7.33.

The Synthesis of Ethyl α-(*p*-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate

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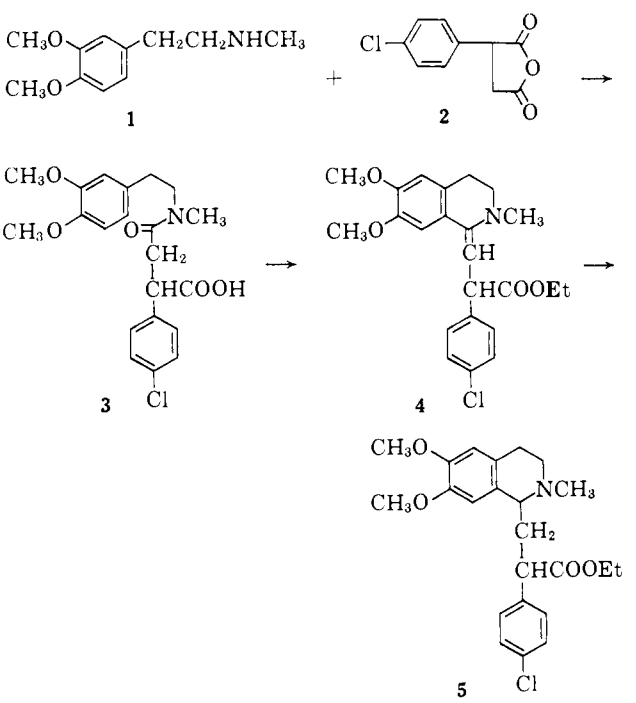
In view of our interest in ethyl 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate[1] and the report of the analgesic activity of 1-(*p*-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by Brossi,[2] we undertook the synthesis of ethyl α-(*p*-chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate (**5**).

(*p*-Chlorophenyl)succinic anhydride (**2**), prepared from the corresponding dicarboxylic acid by treatment with acetyl chloride and thionyl chloride, was obtained as a crystalline solid, m.p. 64–65°.[3] Reaction of the anhydride with 3,4-dimethoxy-N-methylphenethylamine (**1**) gave the amide **3** as a sharp melting crystalline solid. After esterification, **3** was cyclized with phosphorus oxychloride to give the unsaturated amino ester **4** as a mixture of two geometric isomers as evidenced by the range in melting point. Catalytic reduction of **4** gave the dihydro derivative **5** as an oil (see Chart I). Conversion of **5** to a hydrochloride

CHART I



resulted in a wide-melting material which after fractional crystallization afforded one of the two possible stereoisomers.

Our synthetic route is not unequivocal since in the reaction between 3,4-dimethoxy-N-methylphenethylamine and (*p*-chlorophenyl)succinic anhydride the possibility exists for the formation of two isomeric acid amides depending on which carbonyl of the anhydride is attacked. The basis for our scheme is the work of Anschütz[4] who obtained 2-phenylsuccinamic acid from the reaction of ammonia with phenylsuccinic anhydride. Additional evidence for this mode of attack in our case was obtained by examination of the ultraviolet and proton nuclear magnetic resonance spectra of **4** (a mixture of two geometric isomers).

The p.m.r. spectrum of **4** shows the olefinic and allylic hydrogens as an AB quartet in one isomer and a singlet in the other. This absorption is not compatible with

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(4) R. Anschütz, *Ann.*, **354**, 117 (1907).

the alternate formula for **4** which would have arisen from attack at the other carbonyl in the first step, since it would be expected to give rise to a singlet at higher fields for each geometric isomer.

The ultraviolet spectrum of **4** shows a K band similar to that of styrene.[5] Again this absorption is not in agreement with that expected for the alternate structure which should display a K band similar to stilbene.[6]

Brossi[2] has shown the activity of 1-(*p*-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline to be comparable to codeine. In the phenylquinone writhing syndrome test[7] codeine has an ED_{50} of 10 mg./kg. *p.o.*; however, isomer A of **5** showed no analgesic activity at doses up to 200 mg./kg. *p.o.* in this test.

Experimental[8]

(*p*-Chlorophenyl)succinic Anhydride (2).—A mixture of 420 g. of (*p*-chlorophenyl)succinic acid,[9] 2800 ml. of acetyl chloride, and 135 ml. of thionyl chloride was refluxed for 5 hr. Removal of the excess acetyl chloride on the steam bath followed by distillation of the residue gave 354 g. (91%) of a colorless oil, b.p. 160–170° (0.4 mm.). Redistillation gave 338 g. of a colorless oil, b.p. 165° (0.4 mm.), which crystallized on standing. Recrystallization from petroleum ether (30–60°) gave an analytical sample: m.p. 64–65°; ν_{max}^{Nujol} 1780, 1860 cm.$^{-1}$; $\lambda_{max}^{CH_3CN}$ 220 mμ (ε 11,000), 252 (160), 258 (200), 265 (235), 275 (160).

Anal. Calcd. for $C_{10}H_7ClO_3$: C, 57.02; H, 3.35; Cl, 16.84. Found: C, 56.79; H, 3.52; Cl, 16.72.

2-(*p*-Chlorophenyl)-N-(3,4-dimethoxyphenethyl)-N-methylsuccinamic Acid (3).—To a solution of 52.5 g. of (*p*-chlorophenyl)-succinic anhydride in 1 l. of ether was added a solution of 107 g. of 3,4-dimethoxy-N-methylphenethylamine in 100 ml. of ether with cooling, such that the temperature remained between 20 and 25°. The mixture was then stirred for 1 hr. The ether was decanted from the precipitated gum, and 500 ml. of water was added followed by 40 ml. of 40% NaOH solution. The resulting solution was acidified by the dropwise addition of 10% HCl. The precipitate was taken up in benzene, washed with water, and dried (Na_2SO_4), and the solvent was removed. The residue was dissolved in 275 ml. of ethanol and on standing there was deposited 55 g. (55%) of a crystalline solid, m.p. 147–149°. Further recrystallization gave an analytical sample: m.p. 151.5–153°; ν_{max}^{Nujol} 1595, 1730 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1640, 1712 cm.$^{-1}$; λ_{max}^{EtOH} 221 mμ (ε 19,400), 275 (3000).

Anal. Calcd. for $C_{21}H_{24}ClNO_5$: C, 62.15; H, 5.92; Cl, 8.73; N, 3.45. Found: C, 62.17; H, 6.08; Cl, 8.93; N, 3.28.

Ethyl α-(*p*-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-Δ$^{1,\beta}$-isoquinolinepropionate (4).—A solution of 24.3 g. of 2-(*p*-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-N-methylsuccinamic acid and 1 ml. of sulfuric acid in 200 ml. of ethanol was refluxed for 3 hr. After removal of the solvent *in vacuo* on the steam bath, the residue was treated with 100 ml. of saturated sodium bicarbonate solution and benzene. The solvent was removed from the benzene layer, and the residue was refluxed in a solution of 25 ml. of phosphorus oxychloride and 100 ml. of xylene for 2 hr. The reaction mixture was poured into 500 ml. of ether with stirring, the ether was decanted, and the precipitate was treated with 500 ml. of water. The solution was filtered, made basic with NH_4OH, and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4), and the solvent was removed. There remained 6.5 g. (27%) of a viscous gum which crystallized on long standing. Recrystallization from ethanol gave an analytical sample: m.p. 134–139°; ν_{max}^{Nujol} 1600, 1620, 1730 cm.$^{-1}$; λ_{max}^{EtOH} (pH 11) 246–270 mμ plateau (ε 4000); λ_{max}^{EtOH} (0.1 *N* HCl) 219 mμ (ε 17,000), 247 (12,800), 308 (5200), 360 (7700); $\delta_{TMS}^{CDCl_3}$ = 4.75, 4.95 (*J* = 9 c.p.s.), 5.75 p.p.m. (*J* = 9 c.p.s.).

Anal. Calcd. for $C_{23}H_{26}ClNO_4$: C, 66.42; H, 6.30; Cl, 8.53; N, 3.37. Found: C, 66.38; H, 6.33; Cl, 8.51; N, 3.34.

Ethyl α-(*p*-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate Hydrochloride (5).—To a solution of 6.5 g. of ethyl α-(*p*-chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-Δ$^{1,\beta}$-isoquinolinepropionate in 50 ml. of acetic acid, was added 100 mg. of platinum oxide, and the mixture was hydrogenated. After 0.02 equiv. of hydrogen had been absorbed, uptake ceased. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was dissolved in 100 ml. of water, made basic with NH_4OH, and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4), and the solvent was removed. The residue was dissolved in 15 ml. of ethanol and made acidic with HCl. There was deposited 5.1 g. (85%) of a crystalline solid, m.p. 174–181°. Two more recrystallizations from ethanol gave an analytical sample of a mixture of two stereoisomers: m.p. 179–185°; ν_{max}^{Nujol} 1720, 1728, 2420 cm.$^{-1}$; λ_{max}^{EtOH} 224 mμ (ε 18,600), 283 (4000), 290 sh (3200).

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_4$: C, 60.79; H, 6.43; Cl, 15.61; N, 3.08. Found: C, 60.67; H, 6.20; Cl, 15.58; N, 3.17.

Isomer A was obtained by fractional crystallization from ethanol as a crystalline solid: m.p. 190–191.5°; ν_{max}^{Nujol} 1728, 2420 cm.$^{-1}$; λ_{max}^{EtOH} 224 mμ (ε 18,600), 283 (3700), 289 sh (3200).

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_4$: C, 60.79; H, 6.43; Cl, 15.61; N, 3.08. Found: C, 61.00; H, 6.45; Cl, 15.81; N, 3.17

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(8) Since this work was carried out prior to the establishment of journal policy, the melting points were taken on a Mel-Temp apparatus and are uncorrected. The authors are indebted to Mr. A. Lewis and his associates, Mr. R. Pucbalski for the spectral data, and Mrs. U. Zeek for analytical determinations. The n.m.r. spectra were determined on deuteriochloroform solutions with internal tetramethylsilane using a Varian Associates A-60 spectrometer.

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Synthesis and Biological Activities of Certain Short-Chain Mono- and Bisquaternary Ammonium Compounds[1a,b]

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Plummer and co-workers[2] compared the ganglionic blocking activities of a number of bisquaternary compounds derived from halogenated N-aminoalkylisoindolines. The most potent member of the series and the one possessing the longest duration of action was that in which the two nitrogen atoms were separated by a chain of two methylene units.

The fact that C_2 bisquaternary ammonium compounds block nerve impulses at autonomic ganglia tends to discount the prime importance of interquaternary distance for maximum ganglionic activity in α,ω-bisquaternary ammonium drugs. Biel and DiPierro[3] and Neumeyer, *et al.*,[4] have demonstrated that inser-

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