formaldehyde (8 g.) at 100° for 18 hr. gave an amine, which readily formed the maleate VI (5.05 g.) in 61% over-all yield, m.p. 117–120°. A mixture melting point with the maleate obtained from the tosylate IIb was 115–119°. Their infrared and ultraviolet spectra were identical; λ_{max}^{EtOH} 270 mμ (ε 1960), 265 (2140), 259 (1700), and 252 (1400).

N-(1-Benzocyclobutenylmethyl)morpholine Hydrochloride (VII).—A solution of the tosylate IIb (10.1 g., 0.035 mole) and 8.7 g. (0.10 mole) of morpholine in 40 ml. of toluene was refluxed for 20 hr. under nitrogen. The precipitated salt was filtered, and the filtrate was evaporated. The residual oil was taken up in ether, which was shaken with water, dried (K_2CO_3), and saturated with dry HCl. The white needles weighed 6.4 g. (76%).

2-Bromo-4-methoxybenzyl chloride was synthesized from *m*-bromoanisole (293 g., 1.57 moles), 37% aqueous formaldehyde (270 g.), and HCl gas by a published procedure.[11] The product amounted to 259 g. (70%), b.p. 127–131° (3.8 mm.), lit.[11] b.p. 107° (1 mm.).

Ethyl 2-Bromo-4-methoxybenzylcyanoacetate.—To a solution of sodium ethoxide (1.55 moles) in 1 l. of absolute ethanol was added 860 g. (7.6 moles) of ethyl cyanoacetate. The milky solution was stirred for 1 hr. and then was treated with 358 g. (1.52 moles) of 2-bromo-4-methoxybenzyl chloride over a 2-hr. period with the temperature kept near 25°. After an additional hour of stirring at 25°, the solution was refluxed overnight. The solvent was removed under vacuum, and the organic residue was taken up in 500 ml. of ether, which was dried and evaporated. Distillation of the remaining liquid gave unchanged ethyl cyanoacetate, followed by 340 g. (72%) of product, b.p. 148–151° (0.05 mm.). A portion was redistilled for analysis, b.p. 143° (0.025 mm.).

Anal. Calcd. for $C_{13}H_{14}BrNO_3$: C, 50.01; H, 4.52; N, 4.49. Found: C, 50.11; H, 4.56; N, 4.37.

2-Bromo-4-methoxybenzylcyanoacetic Acid.—The ester (322 g., 1.03 moles) was added in 15 min. to 550 ml. of 10% NaOH kept near 20° by external cooling. The solution was stirred for 20 min. and then was acidified with 150 ml. of concentrated HCl. After the addition of the acid, the resulting mixture was stirred for 1 hr. The gummy solid was filtered, washed with water, and dried to give 238 g. (81%) of crude cyano acid. An analytical sample melted at 145.5–148.5° after several recrystallizations from benzene.

Anal. Calcd. for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.59; N, 4.93; neut. equiv., 284.12. Found: C, 46.38; H, 3.29; N, 4.98; neut. equiv., 281.14.

2-Bromo-4-methoxyhydrocinnamonitrile (VIII).—A solution of the crude cyano acid (207 g., 0.73 mole) in 400 ml. of dimethylacetamide was heated in a distillation apparatus until the vapor temperature reached 150°. At this point distillation was stopped, and the solution was refluxed for 2 hr., then cooled. After dilution with 250 ml. of water, the insoluble liquid was extracted with ether, which was dried and evaporated. Distillation of the residue afforded 159 g. (91%) of colorless liquid, b.p. 115–120° (0.15 mm.).

Anal. Calcd. for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.20; N, 5.84. Found: C, 50.08; H, 4.12; N, 5.74.

1-Cyano-5-methoxybenzocyclobutene (IX).—The nitrile VIII (36 g., 0.15 mole) was allowed to react with 0.6 mole of commerical sodamide in 500 ml. of liquid ammonia for 3.5 hr. The reaction mixture was neutralized with excess ammonium nitrate, and the ammonia was allowed to evaporate. Water (150 ml.) was added to the residue, and the crude product was taken up in two 150-ml. portions of chloroform. After drying (Na_2SO_4), the solvent was removed under vacuum. Distillation of the remaining liquid provided 13.2 g. (55%) of the bicyclic nitrile, b.p. 101–105° (0.6 mm.). A redistilled sample, b.p. 93° (0.1 mm.), was used for analysis.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.44; H, 5.70; N, 8.80. Found: C, 75.52; H, 5.52; N, 8.78.

1-Aminomethyl-5-methoxybenzocyclobutene hydrochloride (X) was synthesized by reduction of 9.6 g. (0.06 mole) of the nitrile IX with $LiAlH_4$ (2.88 g., 0.076 mole) in anhydrous ether. Distillation of the crude product provided 5.8 g. of a colorless liquid, b.p. 90–105° (1 mm.). An ethereal solution of the material was treated with dry HCl to afford 2.3 g. (19% over-all) of white granules.

(11) B. Lythgoe, S. Trippett, and J. C. Watkins, *J. Chem. Soc.*, 4060 (1956).

N-Carbethoxy-1-aminobenzocyclobutene (XI) was prepared by the reaction of 3 g. (0.019 mole) of the amine hydrochloride III in a solution of triethylamine (3.9 g.) and chloroform with 2.1 g. (0.019 mole) of ethyl chloroformate. The yield of white needles was 3.4 g. (94%), m.p. 76–77.5° after recrystallization from Skelly B.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.67; N, 7.41.

N′-(1-Benzocyclobutenylmethyl)-5-oxo-2-pyrrolidinecarboxamide (XII).—To the mixed anhydride prepared from 1.55 g. (0.012 mole) of 5-oxo-2-pyrrolidinecarboxylic acid and equivalent amounts of triethylamine and ethyl chloroformate in 50 ml. of methylene dichloride at −10° was added a mixture of amine hydrochloride IV (2 g., 0.012 mole) and triethylamine (1.2 g.) in methylene dichloride. Elution of the crude product (1.2 g.) from a column of alumina (30 g.) with chloroform–methanol (2:1) gave 0.9 g. (31%) of a white, powdery material, m.p. 103–108° after recrystallization from chloroform–Skelly B.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.62. Found: C, 68.70; H, 6.89.

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A New Group of Antifibrillants. N-(ω-Aminoalkyl)phthalimides

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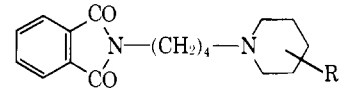
In earlier communications[1,2] the synthesis of a new group of antifibrillant N-(ω-aminoalkyl)phthalimides was reported. Of these, N-[4-(3-methylpiperidino)-butyl]phthalimide (Ia) and N-[4-(4-methylpiperidino)-butyl]phthalimide (Ib) has the highest activity. The 3-methylpiperidine compound (Ia) proved to be 1.6 times as potent in auricular and 2.5 times as potent in ventricular fibrillation as quinidine, while its toxicity was only 1.6 times higher than that of quinidine.[3]



Ia, R = 3-CH_3
b, R = 4-CH_3

In the present communication the nature of the amino group and the number of the members of the alkyl chain were varied. The synthesis of the new compounds was carried out by the following methods.

A. $o\text{-}C_6H_4(CO)_2N(CH_2)_nBr \xrightarrow{2HNR_2}$

$o\text{-}C_6H_4(CO)_2N(CH_2)_nR_2 + NR_2H_2{}^+Br^-$

(1) (a) K. Hideg and H. O. Hankovszky, *Acta Chim. Acad. Sci Hung.*, **39**, 391 (1963); (b) K. Hideg, L. Szekeres, H. O. Hankovszky, and J. Papp, 2nd International Pharmacological Meeting, Prague, August 20–23, 1963, *Biochem. Pharmacol., Suppl.*, **12**, 171 (1963).

(2) K. Hideg and H. O. Hankovszky, *Acta Chim. Acad. Sci. Hung.*, in press.

(3) L. Szekeres, K. Hideg, H. O. Hankovszky, and J. Papp, *Acta Physiol. Acad. Sci. Hung.*, in press.

B. $o\text{-}C_6H_4(CO)_2N(CH_2)_2\underline{N(CH_2)_7} \xrightarrow{HCl}$

$$o\text{-}C_6H_4(CO_2H)_2 + H_2N(CH_2)_2\underline{N(CH_2)_7}$$

C. $4\text{-}NO_2C_6H_3\text{-}1,2\text{-}(CO)_2NH + H_2N(CH_2)_2\underline{N(CH_2)_7} \xrightarrow{-NH_3}$

$$4\text{-}NO_2C_6H_3(CO)_2N(CH_2)_2\underline{N(CH_2)_7}$$

D. $o\text{-}C_6H_4(CO)_2N(CH_2)_nNR_2 \xrightarrow{CH_3I}$

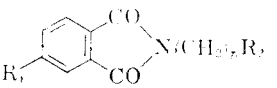
$$o\text{-}C_6H_4(CO)_2N(CH_2)_nN^+(CH_3)R_2\cdot I^-$$

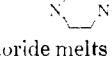
E. $o\text{-}C_6H_4(CO)_2N(CH_2)_5Br \xrightarrow{\text{pyridine}}$

$$o\text{-}C_6H_4(CO)_2N(CH_2)_5\overset{+}{N}\langle\bigcirc\rangle\cdot Br^-$$

TABLE I

N-(ω-AMINOALKYL)PHTHALIMIDE

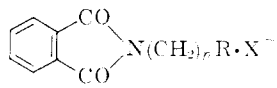


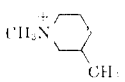
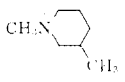
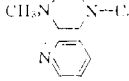
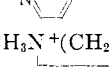
No.	R_1	R_2	n	Method	M.p., °C.	Formula	Calcd., % Cl	Calcd., % N	Found, % Cl	Found, % N
1	H	$\underline{N(CH_2)_4}$	4	A	166–169	$C_{16}H_{20}N_2O_2\cdot HCl$	11.49	9.07	11.30	8.76
2	H		3	A	144–146	$C_{17}H_{22}N_2O_2\cdot HCl$	10.98	8.68	10.75	8.84
3	H		4	A	47–51[a]	$C_{18}H_{24}N_2O_2$	...	9.33	...	9.18
4	H		5	A	156–158	$C_{19}H_{26}N_2O_2\cdot HCl$	10.11	7.98	10.35	8.54
5	H	$\underline{N(CH_2)_6}$	2	A	233–234	$C_{16}H_{20}N_2O_2\cdot HCl$	11.48	9.07	11.65	9.26
6	H	$\underline{N(CH_2)_6}$	4	A	186–187	$C_{18}H_{24}N_2O_2\cdot HCl$	10.52	8.32	10.22	7.80
7	H	$\underline{N(CH_2)_7}$	2	A	214–216	$C_{17}H_{22}N_2O_2\cdot HCl$	10.98	8.68	10.87	8.65
8	NO_2	$\underline{N(CH_2)_7}$	2	C	163–165	$C_{17}H_{21}N_3O_4$	...	12.68	...	12.34
					119–120	$C_{17}H_{21}N_3O_5\cdot HCl$	9.64	11.43	9.54	11.20
9	H	$\underline{N(CH_2)_7}$	4	A	185–186	$C_{19}H_{26}N_2O_2\cdot HCl$	10.11	7.98	10.45	7.50
10	H	$CH_3NCH_2C_6H_5$	4	A	81–83	$C_{20}H_{22}N_2O_2\cdot HCl$	9.88	7.80	9.63	7.72
11	H		4	A	210–213	$C_{22}H_{25}N_3O_2\cdot 2HCl$	16.25	9.63	16.05	9.38

[a] The hydrochloride melts at 192–194°.

TABLE II

QUATERNARY N-(ω-AMINOALKYL)PHTHALIMIDE



No.	R	n	Method	M.p., °C.	Formula	Calcd., % X	Calcd., % N	Found, % X	Found, % N
12	$CH_3N^+\underline{(CH_2)_4}$	4	D	277–280	$C_{17}H_{23}IN_2O_2$	30.63	6.76	30.12	6.34
13		4	D	257–260	$C_{19}H_{27}IN_2O_2$	28.69	6.33	28.43	6.68
14		5	D	186–188	$C_{20}H_{29}IN_2O_2$	27.81	6.14	27.52	6.05
15	$CH_3N^+\underline{(CH_2)_6}$	2	D	247–248	$C_{17}H_{23}IN_2O_2$	30.64	6.76	30.84	6.84
16	$CH_3N^+\underline{(CH_2)_6}$	4	D	260–261	$C_{19}H_{27}IN_2O_2$	28.69	6.33	28.76	6.26
17	$CH_3N^+\underline{(CH_2)_7}$	4	D	231–232	$C_{20}H_{29}IN_2O_2$	27.81	6.14	28.00	6.23
18	$(CH_3)_2N^+—CH_2—C_6H_5$	4	D	202–203	$C_{21}H_{25}IN_2O_2$	27.34	6.03	27.05	5.98
19		4	D	194–196	$C_{23}H_{28}IN_3O_2$	25.11	8.32	24.85	8.39
20		5	E	186–188	$C_{18}H_{19}BrN_2O_2$	21.30	7.46	21.57	7.33
21	$CH_3N^+\underline{(CH_2)_7}$	2	D	227–228	$C_{18}H_{23}IN_2O_2$	29.63	6.54	29.26	6.69

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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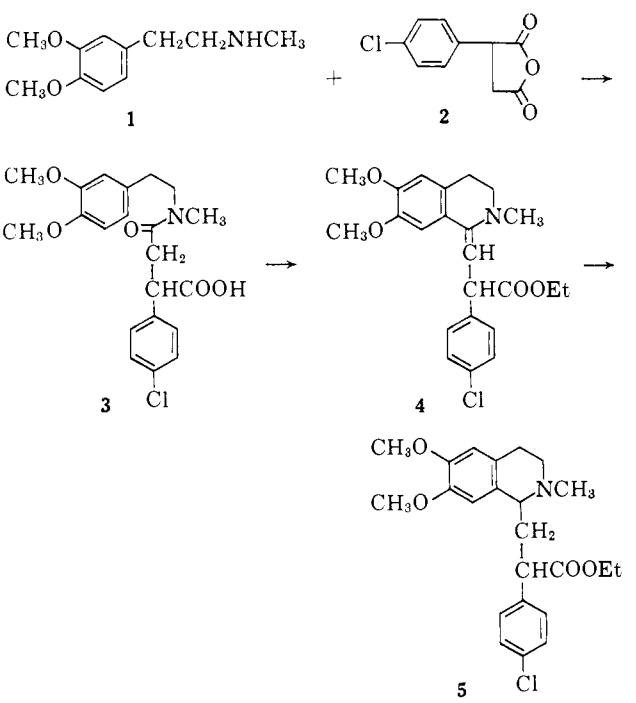
In view of our interest in ethyl 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate[1] and the report of the analgesic activity of 1-(*p*-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by Brossi,[2] we undertook the synthesis of ethyl α-(*p*-chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate (**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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(2) A. Brossi, H. Besendorf, B. Pellmont, M. Water, and O. Schnider, *Helv. Chim. Acta*, **43**, 1459 (1960).

(3) M. A. Wali, A. K. Khalil, R. L. Bhatia, and S. S. Ahmad [*Proc. Indian Acad. Sci.*, **14A**, 139 (1941)] previously reported m.p. 80°.

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