The same procedure was used to obtain **N-(2,5-dichlorophenyl)-N'-(2-hydroxyethyl)ethylenediamine.** For analysis a sample was recrystallized from toluene, m.p. 95°.

Anal. Calcd. for $C_{10}H_{14}Cl_2N_2O$: C, 48.20; H, 5.66. Found: C, 48.5; H, 5.6.

D. 1-(4-Pyridyl)piperazine (51).—A solution of 1-benzyl-4-(4-pyridyl)piperazine[1] (25.33 g., 0.1 mole) in 100 ml. of 2 *N* HCl and 500 ml. of methanol was hydrogenated with 10 g. of palladium-on-charcoal catalyst (5% by wt.) at room temperature under atmospheric pressure. The theoretical amount of hydrogen was taken up in 3 hr. The catalyst was filtered and the filtrate was concentrated *in vacuo* on a rotary evaporator. The resulting white solid was taken up in water, and the solution was made alkaline with KOH. The precipitate was collected and dried to give **51** in nearly quantitative yield. It was recrystallized from heptane.

E and F. 1-(3,4-Dimethoxyphenethyl)-4-(2-pyridyl)piperazine (34).—A solution of 113 g. (0.46 mole) of 3,4-dimethoxyphenethyl bromide[7] and 150 g. (0.92 mole) of 1-(2-pyridyl)-piperazine in 1 l. of anhydrous xylene was refluxed for 10 hr. with stirring. After cooling, the mixture was filtered to remove 1-(2-pyridyl)piperazinium bromide (the solid was dried, yield 111 g.) and the filtrate was extracted with 500 ml. of 5% HCl. This solution was immediately made basic at 10–20°. The white solid which formed was collected, washed with water, and dried to give 138 g. (92%) of **34**. Recrystallization from 3 l. of heptane produced pure product.

1-(2,5-Dimethoxyphenethyl)-4-(2-pyridyl)piperazine Hydrochloride (33).—Following the same procedure, 1-(2,5-dimethoxy-phenethyl)-4-(2-pyridyl)piperazine was obtained as an oil after extraction with ether of the basic solution and concentration *in vacuo* of the dried extracts. To a solution of 16.35 g. (0.05 mole) of this base in 50 ml. of absolute ethanol was added 0.1 mole of 2 *N* absolute ethanolic HCl. The solvent was evaporated *in vacuo* and crude **33** was crystallized.

In method F, the above procedure was carried out for aralkyl chlorides, the solution being stirred under reflux for 24 hr.

G. 1-(3,4-Dimethoxyphenethyl)-4-(2-chlorophenyl)piperazine (6).—A solution of 120 g. (0.49 mole) of 3,4-dimethoxyphenethyl bromide and 98 g. (0.5 mole) of 1-(2-chlorophenyl)piperazine in 1 l. of 1-butanol was stirred at 105–110° for 15 hr. in the presence of 76 g. of anhydrous potassium carbonate. The mixture was filtered while hot and the filtrate was kept at 0° overnight to give colorless crystals; yield, 150 g. (84%). Recrystallization from 1.2 l. of isopropyl ether gave pure **6**.

H. 1-(3,4 Dimethoxyphenethyl)-4-(2-aminophenyl)piperazine (12).—A sample of 18.55 g. (0.05 mole) of 1-(3,4-dimethoxy-phenethyl)-4-(2-nitrophenyl)piperazine (11) in 300 ml. of ethanol was hydrogenated in the presence of platinum oxide catalyst at room temperature under atmospheric pressure. The calculated amount of hydrogen was taken up in 15 min. and the temperature was raised to 40–50°. The catalyst was removed while warm and a slow crystallization in the refrigerator of the filtrate afforded 14.1 g. (82.5%) of white crystals. Recrystallization from 50 ml. of 2-propanol gave pure **12**.

I. 1-(3,4-Dimethoxyphenethyl)-4-(2-acetylaminophenyl)-piperazine (13).—Acetyl chloride (7.85 g., 0.1 mole) was added slowly to a stirred solution of 6.8 g. (0.02 mole) of the above amine (**12**) in 75 ml. of toluene under anhydrous conditions. After refluxing for 1 hr., the solid was collected and dried to give 7.55 g. (90%) of **1-(3,4-dimethoxyphenethyl)-4-(2-acetylaminophenyl)piperazine hydrochloride,** m.p. 200–205°. For analysis, a sample was recrystallized from 2-propanol, m.p. 215°.

Anal. Calcd. for $C_{22}H_{29}N_3O_3 \cdot HCl$: Cl, 8.44. Found: Cl, 8.3.

A 5-g. finely ground sample of the above hydrochloride was suspended in 100 ml. of dry ether and treated with gaseous ammonia with stirring. After 15 min., the inorganic salt was filtered and the filtrate was concentrated *in vacuo* to yield a white solid. It was recrystallized from 150 ml. of heptane to give 4.05 g. (80%) of **13**.

(7) The necessary phenethyl halides were obtained according to literature methods: 3-methoxyphenethyl chloride, W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1533 (1935); 4-methoxyphenethyl bromide, J. B. Shoesmith and R. J. Connor, *ibid.*, 2230 (1927); 3,4-dimethoxyphenethyl bromide, S. Sugasawa, *J. Pharm. Soc. Japan*, **57**, 296 (1937); 2,5-dimethoxyphenethyl bromide, R. A. Barnes, *J. Am. Chem. Soc.*, **75**, 3004 (1953); 2,4-dimethoxyphenethyl bromide was prepared in 70% yield from 2-(2,4-dimethoxyphenyl)ethanol by the method used for 2,5-dimethoxyphenethyl bromide, b.p. 116–119° (0.3 mm.). *Anal.* Calcd. for $C_{10}H_{13}BrO_2$: Br, 32.60. Found: Br, 32.4.

p-Amino-N-[2-(substituted amino)ethyl]benzamides. Potential Antifibrillatory Drugs

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The alkylation of amines with 1-*p*-nitrobenzoylethylenimine has been studied. The *p*-nitro-N-[2-(substituted amino)ethyl]benzamides were readily hydrolyzed to N-substituted ethylenediamines. The *p*-nitrobenzamides were hydrogenated catalytically and a series of analogs of procaine amide were obtained. These analogs were screened for antifibrillatory activity in the rabbit heart and in the dog heart. Several of the compounds showed high activity.

Numerous drugs have been used to some extent in the treatment of the heart's rate and rhythm. However, only quinidine and *p*-amino-N-(2-diethylaminoethyl)-benzamide (procaine amide) are drugs of sufficient selectivity and specificity of action to be classified as antiarrhythmic and antifibrillatory agents. Fibrillation is a state of rapid, tremulous, and ineffective contractions of the atrial or ventricular muscle. In 1918 quinidine was reported to be the most effective antiarrhythmic agents among the cinchona alkaloids.[1] 2-Diethylaminoethyl *p*-aminobenzoate (procaine) had been reported to have some activity by Shen and Simon.[2] In 1951, procaine amide was shown to be effective in the treatment of cardiac arrhythmias.[3] This compound has cardiac actions essentially identical with those of quinidine.[4]

Although very useful, both quinidine and procaine amide may at times precipitate ventricular fibrillation or respiratory collapse.[5] Thus it was felt that the synthesis and study of the cardiac action of a series of

(1) W. Frey, *Berlin. klin. Wochschr.*, **55**, 849 (1918).

(2) T. C. R. Shen and M. A. Simon, *Arch. intern. pharmacodyn.*, **59**, 68 (1938).

(3) L. C. Mark, H. J. Kayden, J. M. Steele, J. R. Cooper, J. Berlin, E. A. Ronenshine, and B. B. Brodie, *J. Pharmacol. Exptl. Therap.*, **102**, 5 (1951).

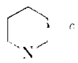
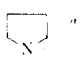
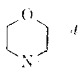
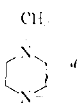
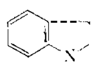
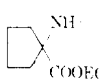
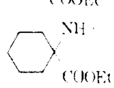
(4) J. Zapata-Diaz, C. E. Cabrera, and R. Mendez, *Am. Heart J.*, **43**, 854 (1952).

(5) S. P. Schwartz, S. Orloff, and C. Fox, *ibid.*, **37**, 21 (1949); B. M. Cohen, *New England J. Med.*, **246**, 225 (1952).

TABLE I

N-ALKYLAMINO- OR -ARYLAMINOETHYLAMINO-p-NITROBENZAMIDES

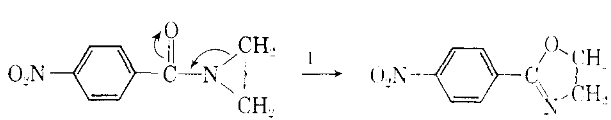
p-$O_2NC_6H_4CONHCH_2CH_2R$ (R = NHR, NR_2, NHAr)

Compd.	R	Method	Time, min.	Liquid added	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I	$(C_2H_5)_2N$–[a]	A	60	Hexane	78	56–58[b]							
II	$(i\text{-}C_3H_7)_2N$–[c]	A	15	Hexane	79	94–96	$C_{15}H_{23}N_3O_3$	61.40	7.92	14.32	61.28	7.75	14.47
III	 [c]	A	10	Hexane	73	97–99	$C_{14}H_{19}N_3O_3$	60.62	6.92	15.15	60.79	7.06	14.98
IV	 [a]	A	15	Petr. ether	70	94–96	$C_{13}H_{17}N_3O_3$	59.29	6.52	15.96	59.18	6.36	16.09
V	 [d]	A	60	Hexane	96	120–122	$C_{13}H_{17}N_3O_4$	55.89	6.15	15.05	55.68	5.92	15.10
VI	 [d]	B	15		62	120–122	$C_{14}H_{20}N_4O_3$	57.51	6.91	19.17	57.68	7.05	19.00
VII	 [e]	B	720		71	193–196[f]	$C_{12}H_{12}N_4O_3$	55.37	4.66	21.53	55.58	4.73	21.40
VIII	C_6H_5NH–[g]	A	720	Ethanol–hexane	75	140–142	$C_{15}H_{15}N_3O_3$	63.14	5.31	14.73	63.29	5.50	14.52
IX	2,6-$(CH_3)_2C_6H_3$-NH–[g]	A	720	Ethanol–hexane	73	111–113	$C_{17}H_{19}N_3O_3$	65.15	6.12	13.41	64.95	5.97	13.27
X	$C_6H_5N(CH_3)$–[h]	A	60	Hexane	82	123–125	$C_{16}H_{17}N_3O_3$	64.13	5.74	13.81	64.19	5.73	14.04
XI	$(C_6H_5CH_2)(C_6H_5)N$–[i]	A	30	Hexane	73	126–128	$C_{22}H_{21}N_3O_3$	70.37	5.65	11.19	70.35	5.81	11.21
XII	 [e]	B	720		81	88–90	$C_{17}H_{17}N_3O_3$	65.57	5.51	13.50	65.41	5.34	13.51
XIII	$(C_6H_5)_2N$[j]	A	180[k]	Acetone–hexane	44	135–138	$C_{21}H_{19}N_3O_3$	69.78	5.31	11.63	69.70	5.40	11.39
XIV	 [c]	A	720	Hexane	67	88–89	$C_{17}H_{23}N_3O_5$	58.43	6.65	12.03	58.35	6.77	11.83
XV	 [e]	A	720	Hexane	68	102–103	$C_{18}H_{25}N_3O_5$	59.48	6.95	11.56	59.67	7.17	11.36

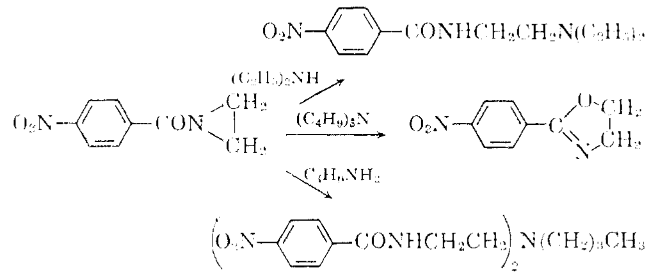
[a] Recrystallized from petroleum ether (30–60°). [b] M. Yamazaki, Y. Kitagawa, S. Hiraki, and Y. Tsukamoto [*J. Pharm. Soc. Japan*, **73**, 294 (1953)] report m.p. 53–54°. [c] Recrystallized from hexane. [d] Recrystallized from benzene. [e] Recrystallized from ethanol. [f] Sinters at 160°. [g] Recrystallized from ethanol–hexane. [h] Recrystallized from acetone–hexane. [i] Recrystallized from acetone. [j] Recrystallized from benzene–hexane. [k] Heated at 145°.

new analogs of procaine amide could possibly produce more active and specific drugs.

The procaine analogs were prepared by alkylating a number of primary and secondary amines with p-nitrobenzoylethylenimine. The latter can be prepared in good yields and is easily purified.[6] p-Nitrobenzoylethylenimine readily isomerizes to 2-(p-nitrophenyl)-2-oxazoline in acetone solution in the presence of sodium iodide or potassium thiocyanate.[6] In order to de-



termine whether the alkylation of amines with p-nitrobenzoylethylenimine would give both alkylation and isomerization products, the imine was treated in acetone solution with tributylamine, diethylamine, and n-butylamine, respectively. A good yield of 2-(p-nitrophenyl)-2-oxazoline was obtained when the solution in acetone was refluxed with tributylamine. With an equivalent of diethylamine, an exothermic reaction took place, and a good yield of N-(2-diethylaminoethyl)-p-nitrobenzamide was formed. An exothermic reaction was also observed with n-butylamine, but in this case a bis derivative was obtained, N,N-di(p-nitrobenzamidoethyl)butylamine.



The monosubstituted butylamine derivative could not be obtained by this method. Oxazoline formation does not appear to be a major competing reaction where primary or secondary amines are used. From these observations, 1-p-nitrobenzoylethylenimine appeared to be a promising alkylating agent for procaine amide analogs.

Satisfactory yields of substituted nitrobenzamides were obtained when p-nitrobenzoylethylenimine and the amine were heated on a steam bath without a solvent. However, when using more than 0.05-mole quantities, it was found advantageous to use acetone

(6) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).

TABLE II
HYDROCHLORIDES OF N-ALKYLAMINO- OR -ARYLAMINOETHYLAMINO-p-NITROBENZAMIDES[a]

Compd.	M.p., °C.	Formula	Cl, % Calcd.	Cl, % Found
I	164-166[b]			
II	202–204	$C_{15}H_{24}ClN_3O_3$	10.75	10.77
III	198–200	$C_{14}H_{20}ClN_3O_3$	11.30	11.45
IV	197–199	$C_{13}H_{18}ClN_3O_3$	11.83	11.80
V	233-234[c]	$C_{13}H_{18}ClN_3O_4$	11.23	11.08
VI	237–239[d]	$C_{14}H_{24}Cl_2N_4O_4$	18.50	18.53
VII	228-231	$C_{12}H_{13}ClN_4O_3$	11.95	11.70
VIII	237–240 dec.	$C_{15}H_{16}ClN_3O_3$	11.02	11.12
IX	215–229	$C_{17}H_{20}ClN_3O_3$	10.14	9.96
X	210–215 dec.	$C_{16}H_{18}ClN_3O_3$	10.56	10.44
XI	204–207 dec.	$C_{22}H_{22}ClN_3O_3$	8.61	8.65
XII	208–212	$C_{17}H_{18}ClN_3O_3$	10.19	10.32
XIII[e]				
XIV	206–208	$C_{17}H_{24}ClN_3O_5$	9.19	9.37
XV	236–237	$C_{18}H_{26}ClN_3O_5$	8.87	8.74

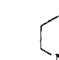
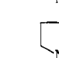
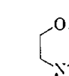
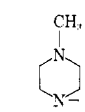
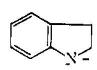
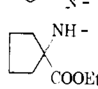
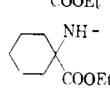
[a] Hydrochlorides prepared in ethanol–ether. [b] Ref. b, Table I gives m.p. 162–164°. [c] F. F. Blicke, H. C. Parke, and E. L. Jenner [*J. Am. Chem. Soc.*, **62**, 3316 (1940)] give m.p. 223–224°. [d] Dihydrochloride. [e] Not possible to prepare crystalline hydrochloride

The nitro compounds were hydrogenated in ethanol solution, over platinum as a catalyst, to the corresponding amino compounds. The latter are included in Table III and their hydrochlorides in Table IV.

Screening for Antifibrillatory Activity.—The pharmacological testing of the amino compounds was done with the aid of the personnel and facilities in the laboratory of Dr. Hadley L. Conn, Jr., of the University of Pennsylvania Medical School. The testing involved the measuring of a drug's ability to raise the threshold voltage necessary to produce atrial fibrillation in an isolated rabbit heart. Detailed information concerning these tests will be published elsewhere. Some of the pertinent data are shown in Tables V and VI. The other compounds which were synthesized had little or no activity and are not included in Tables V and VI.

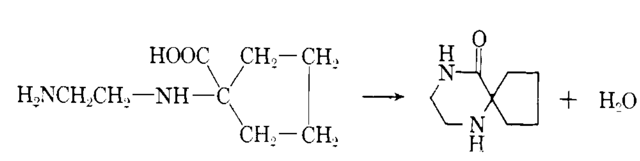
The N-alkylamino- or -arylaminoethylamino-p-nitrobenzamides are convenient starting materials for the preparation of N-substituted ethylenediamines. The benzamides are hydrolyzed by refluxing with 6 N HCl, and the N-substituted ethylenediamines are isolated as dihydrochlorides. Three examples of this procedure are summarized in Table VII. The free base of XXVIII was quite stable at room temperature, but when its aqueous solution was refluxed, it was converted to 6,9-diazaspiro[4,5]decan-10-one (XXXII).

TABLE III
N-ALKYLAMINO- OR -ARYLAMINOETHYLAMINO-p-AMINOBENZAMIDES
$p\text{-}H_2NC_6H_4CONHCH_2CH_2R$ (R = NHR, NR_2, NHAr)

Compd.	R	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
XVI	$(i\text{-}C_3H_7)_2N$–	49	236 (2.5 mm.)[a]	$C_{15}H_{25}N_3O$	68.39	9.59	15.95	68.24	9.60	15.93
XVII	 [b]	84	118–120	$C_{14}H_{21}N_3O$	67.97	8.57	16.99	67.86	8.51	16.73
XVIII	 [c]	61	139–140	$C_{13}H_{19}N_3O$	66.91	8.22	18.01	66.89	8.45	17.85
XIX	 [d]	61	159–160	$C_{13}H_{19}N_3O_2$	62.61	7.70	16.86	62.77	7.54	16.63
XX	 [e]	64	158–161	$C_{14}H_{22}N_4O$	64.08	8.47	21.36	63.97	8.64	21.19
XXI	C_6H_5NH – [f]	55	120–122	$C_{15}H_{17}N_3O$	70.55	6.72	16.46	70.42	6.79	16.40
XXII	$C_6H_5N(CH_3)$– [f]	78	139–141	$C_{16}H_{19}N_3O$	71.33	7.12	15.60	71.18	7.14	15.46
XXIII	 [g]	50	47–53	$C_{17}H_{19}N_3O$	72.56	6.82	14.94	72.32	7.09	14.67
XXIV	 [e]	80	105–107	$C_{17}H_{25}N_3O$	63.91	7.90	13.17	63.90	7.99	12.99
XXV	 [h]	60	218–220[i]	$C_{18}H_{28}ClN_3O$[i]	58.43	7.64	11.36	58.26	7.80	11.27

[a] Boiling point. [b] Recrystallized from acetone–ether. [c] Recrystallized from acetone–petroleum ether. [d] Recrystallized from acetone. [e] Recrystallized from acetone–hexane. [f] Recrystallized from chloroform. [g] Recrystallized from ethanol–cyclohexane (hygroscopic solid). [h] All attempts to prepare the pure base have failed. [i] Monohydrochloride. Cl: calcd., 9.59; found, 9.50.

as a solvent to dissipate the heat of reaction. The N-substituted ethylamino derivatives of p-nitrobenzamide are listed in Table I and their hydrochlorides in Table II. Most of the amines used in preparing the substituted p-nitrobenzamides were purified commercial products. Ethyl 1-aminocyclopentanecarboxylate and ethyl 1-aminocyclohexanecarboxylate were prepared by published methods. With aromatic primary amines, unlike aliphatic primary amines, both the monoalkylated and the dialkylated products can be prepared.



XXXII

TABLE IV

HYDROCHLORIDES OF N-ALKYLAMINO- OR -ARYLAMINOETHYL-AMINO-p-AMINOBENZAMIDES[a]

Compd.	M.p., °C.	Formula	Cl, % Calcd.	Cl, % Found
XVI[b]	222-228	$C_{15}H_{27}Cl_2N_3O$	21.08	21.04
XVII[c]	205-207	$C_{14}H_{22}ClN_3O$	12.49	12.61
XVIII[c]	194-196	$C_{13}H_{20}ClN_3O$	13.14	12.95
XIX[c]	201-202	$C_{13}H_{20}ClN_3O_2$	12.41	12.22
XX[d]	224-226	$C_{14}H_{24}Cl_2N_4O$	21.15	21.40
XXI	93	$C_{15}H_{18}ClN_3O$	12.15	12.14
XXII[e]	205-216 dec.	$C_{16}H_{20}ClN_3O$	11.59	11.64
XXIII[f]				
XXIV[b]	224-227	$C_{17}H_{27}Cl_2N_3O$	18.07	18.23
XXV[g]				

[a] Hydrochlorides were made in ethanol-ether. [b] Dihydrochloride. [c] Monohydrochloride. [d] Dihydrochloride was prepared by catalytic hydrogenation of the dihydrochloride of VI. [e] Monohydrochloride prepared by the catalytic hydrogenation of the hydrochloride of VIII (very hygroscopic). [f] Pure hydrochloride could not be isolated. [g] See XXV, Table III.

TABLE V

ANTIFIBRILLATORY EFFECTS ON ISOLATED RABBIT HEART[a]

Compd.	No. of expt.	Av. change from the control threshold voltage for atrial fibrillation, %
Procaine amide	3	65
XXII	5	>15,000
XXIII	3	452[b]
XVII	3	174
$(p\text{-}H_2NC_6H_4CONHCH_2CH_2)_2NC_4H_9$	2	150
XXI	4	46
XVI	2	24

[a] After the threshold values were established, aqueous solutions containing 5 mg. of the compound were infused into the heart. [b] This compound introduced irregularities in the heart rhythm.

Compound XXXII was also prepared by the procedure described by Freed and Day.[7]

Experimental

Infrared spectra of the free bases were obtained from potassium bromide disks. Ultraviolet spectra were measured in methanol solution. All melting points were determined in the Thomas-Hoover capillary melting point apparatus.

p-Nitrobenzoylethylenimine was obtained in good yields by a previously reported procedure,[6] m.p. 124-126°.

2-p-Nitrophenyl-2-oxazoline.—p-Nitrobenzoylethylenimine (3.84 g., 0.02 mole) and 3.70 g. (0.02 mole) of tributylamine were dissolved in 200 ml. of acetone. The solution was refluxed for 12 hr. After cooling, the white, crystalline precipitate was removed, washed with a little acetone, and dried, 88% yield, m.p. 180-181°.[6]

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.24; H, 4.20; N, 14.58. Found: C, 56.14; H, 4.08; N, 14.42.

N-Alkylamino- and -Arylaminoethylamino-p-nitrobenzamides. A.—p-Nitrobenzoylethylenimine (3.84-5.76 g., 0.02-0.03 mole) was carefully mixed with 0.02-0.06 mole of the amine. In general, the reactions were highly exothermic. After heating on the steam bath, a suitable organic liquid was added with stirring before removing the product by filtration. The solid was recrystallized from a suitable solvent with the aid of decolorizing carbon.

B.—A solution of the reactants in acetone was heated on a steam bath. The acetone was removed under reduced pressure, and the residue was recrystallized as above.

N-(2-Diethylaminoethyl)-p-nitrobenzamide (I).—Infrared: 3335 (s), 1631 (s), 1592 (s), 1517 (s), 1339 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.06).

(7) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2108 (1960).

TABLE VI

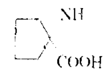
ANTIFIBRILLATORY EFFECTS ON INTACT DOG HEART[a]

Compd.	No. of expt.	Av. change from the control threshold voltage for atrial fibrillation, %
Procaine amide	2	75
XXII	2	200
XXIII	1	40
XVII	2	58
$(p\text{-}H_2NC_6H_4CONHCH_2CH_2)_2NC_4H_9$	1	160

[a] After the threshold values were established, aqueous solutions containing 150 mg. of the compound were infused through the femoral vein.

TABLE VII

N-SUBSTITUTED ETHYLENEDIAMINE DIHYDROCHLORIDES $RCH_2CH_2NH_2$

R	Yield, %	M.p., °C.
C_6H_5NH-	74	183-186[a]
$C_6H_5N(CH_3)$-	76	212[a]
	89	187-189

[a] Melting points check with published values.

N-(2-Diisopropylaminoethyl)-p-nitrobenzamide (II).—Infrared: 3270 (s), 1629 (s), 1593 (s), 1512 (s), 1342 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.07).

N-(2-Piperidinoethyl)-p-nitrobenzamide (III).—Infrared: 3380 (s), 1637 (s), 1594 (s), 1520 (s), 1342 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.06).

N-(2-Pyrrolidinoethyl)-p-nitrobenzamide (IV).—Infrared: 3355 (s), 1629 (s), 1590 (s), 1515 (s), 1342 (s), 1331 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.05).

N-(2-Morpholinoethyl)-p-nitrobenzamide (V).—Infrared: 3275 (s), 1638 (s), 1589 (s), 1510 (s), 1338 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.05).

N-[2-(4-Methyl-1-piperazino)ethyl]-p-nitrobenzamide (VI).—Infrared: 3285 (s), 1639 (s), 1597 (s), 1520 (s), 1346 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.11).

N-[2-(1-Imidazolyl)ethyl]-p-nitrobenzamide (VII).—Infrared: 3235 (m), 1648 (s), 1590 (s), 1511 (s), 1343 cm.$^{-1}$ (s); ultraviolet: λ_{max} 261 mμ (log ϵ_{max} 4.09).

N-(2-Anilinoethyl)-p-nitrobenzamide (VIII).—Infrared: 3371 (s), 1632 (s), 1591 (s), 1512 (s), 1345 cm.$^{-1}$ (s); ultraviolet: λ_{max} 248 mμ (log ϵ_{max} 4.32).

N-[2-(2,6-Dimethylanilino)ethyl]-p-nitrobenzamide (IX).—Infrared: 3298 (m), 1634 (s), 1595 (s), 1513 (s), 1343 cm.$^{-1}$ (s); ultraviolet: λ_{max} 249 mμ (log ϵ_{max} 4.13).

N-[2-(N-Methylanilino)ethyl]-p-nitrobenzamide (X).—Infrared: 3345 (s), 1648 (s), 1610 (s), 1515 (s), 1351 cm.$^{-1}$ (s); ultraviolet: λ_{max} 254 mμ (log ϵ_{max} 4.39).

N-[2-(N-Benzylanilino)ethyl]-p-nitrobenzamide (XI).—Infrared: 3372 (s), 1631 (s), 1589 (s), 1505 (s), 1497 (s), 1346 (s), 1338 cm.$^{-1}$ (s); ultraviolet: λ_{max} 254 mμ (log ϵ_{max} 442).

N-[2-(1-Indolino)ethyl]-p-nitrobenzamide (XII).—Infrared: 3360 (s), 1633 (s), 1595 (s), 1514 (s), 1339 cm.$^{-1}$ (s); ultraviolet: λ_{max} 257 mμ (log ϵ_{max} 4.31).

N-2-Diphenylaminoethyl-p-nitrobenzamide (XIII).—Extraction of the solid with acetone at room temperature left a 20-30% yield of 2-p-nitrophenyl-2-oxazoline. A mixture melting point determination with an authentic sample showed no depression. The acetone extract was evaporated and the residue was recrystallized from benzene-hexane to give pure XIII. It was not possible to prepare a crystalline hydrochloride.

Infrared: 3290 (s), 1638 (s), 1590 (s), 1513 (s), 1488 (s), 1355 (s), 1342 cm.$^{-1}$ (s); ultraviolet: λ_{max} 248 mμ (log ϵ_{max} 4.27), 260 (min.) (4.22), 275 (4.24).

N-[2-(1-Carbethoxycyclopentylamino)ethyl]-p-nitrobenzamide (XIV).—Infrared: 3275 (s), 1630 (s), 1712 (s), 1589 (s), 1508 (s), 1338 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.09).

N-[2-(1-Carbethoxycyclohexylamino)ethyl-p-nitrobenzamide (XV).—Infrared: 3275 (m), 1639 (s), 1705 (s), 1588 (s), 1508 (s), 1336 cm.$^{-1}$ (s); ultraviolet: λ_{max} 262 mμ (log ϵ_{max} 4.09).

N-Alkylamino- and -Arylaminoethylamino-p-aminobenzamides.—A mixture of the corresponding nitro compound (0.01

mole,) 200 mg. of platinum oxide, and 150 ml. of ethanol was hydrogenated in a Parr apparatus. The catalyst was removed by filtration, the ethanol was evaporated under reduced pressure, and the residue was purified by vacuum distillation or by recrystallization from suitable solvents. The monohydrochlorides were obtained by catalytically hydrogenating the hydrochlorides of the corresponding nitro compounds. In many cases the monohydrochlorides were prepared first and the pure free base then was obtained by neutralization and recrystallization.

N-(2-Diisopropylaminoethyl)-p-aminobenzamide (XVI).—Infrared: 3345 (s), 3225 (s), 1620 (s), 1600 (s), 1495 (s), 1292 cm.$^{-1}$ (s); ultraviolet: λ_{max} 283 mμ (log ϵ_{max} 4.23).

N-(2-Piperidinoethyl)-p-aminobenzamide (XVII).—Infrared: 3330 (s), 3217 (m), 1620 (s), 1600 (s), 1508 (s), 1289 cm.$^{-1}$ (s); ultraviolet: λ_{max} 280 mμ (log ϵ_{max} 4.24).

N-(2-Pyrrolidinoethyl)-p-aminobenzamide (XVIII).—Infrared: 3375 (s), 3345 (s), 3220 (s), 1623 (s), 1590 (s), 1485 (s), 1288 (s), 1270 cm.$^{-1}$ (s); ultraviolet: λ_{max} 280 mμ (log ϵ_{max} 4.20).

N-(2-Morpholinoethyl)-p-aminobenzamide (XIX).—Infrared: 3392 (s), 3322 (s), 3228 (s), 1622 (s), 1595 (s), 1505 (s), 1285 cm.$^{-1}$ (s); ultraviolet: λ_{max} 280 mμ (log ϵ_{max} 4.23).

N-[2-(4-Methyl-1-piperazino)ethyl]-p-aminobenzamide (XX).—Infrared: 3450 (s), 3385 (s), 3338 (s), 1622 (s), 1600 (s), 1500 (s), 1290 (s), 1280 cm.$^{-1}$ (s).

N-(2-Anilinoethyl)-p-aminobenzamide (XXI).—Infrared: 3468 (s), 3412 (s), 3328 (s), 1618 (s), 1595 (s), 1492 (s), 1295 cm.$^{-1}$ (s); ultraviolet: λ_{max} 248 mμ (log ϵ_{max} 414), 258 (4.11), 282 (4.27).

N-[2-(N-Methylanilino)ethyl]-p-aminobenzamide (XXII).—Infrared: 3440 (s), 3428 (s), 3351 (s), 1630 (s), 1600 (s), 1495 (s), 1279 cm.$^{-1}$ (s); ultraviolet: λ_{max} 255 mμ (log ϵ_{max} 4.31), 266 (4.25), 280 (4.27).

N-[2-(1-Indolino)ethyl]-p-aminobenzamide (XXIII).—Infrared: 3425 (s), 3340 (s), 3223 (m), 1622 (s), 1598 (s), 1492 (s), 1285 cm.$^{-1}$ (s).

N-[2-(1-Carbethoxycyclopentylamino)ethyl]-p-aminobenzamide (XXIV).—Infrared: 3465 (s), 3419 (s), 3355 (s), 3325 (s), 1620 (s), 1695 (s), 1598 (s), 1495 (s), 1293 cm.$^{-1}$ (s); ultraviolet: λ_{max} 280 mμ (log ϵ_{max} 4.23).

N-[2-(1-Carbethoxycyclohexylamino)ethyl]-p-aminobenzamide Monohydrochloride. (XXV).—All attempts to prepare the pure free base have failed. The monohydrochloride was hygroscopic.

N,N-Di(p-nitrobenzamidoethyl)butylamine (XXVI). A.—The time of heating was 5 min., the liquid added was ethanol. The product was recrystallized from benzene, 71% yield, m.p. 123-125°, light yellow solid.

Anal. Calcd. for $C_{22}H_{27}N_5O_6$: C, 57.75; H, 5.96; N, 15.31. Found: C, 57.92; H, 6.15; N, 15.18.

Infrared: 3300 (m), 3260 (m), 1652 (m), 1596 (m), 1520 (s), 1342 cm.$^{-1}$ (s); ultraviolet: λ_{max} 261 mμ (log ϵ_{max} 4.34).

The hydrochloride melted at 196–198°.

Anal. Calcd. for $C_{22}H_{28}ClN_5O_6$: Cl, 7.18. Found: Cl, 7.11.

N,N-Di(p-nitrobenzamidoethyl)aniline (XXVII). A.—When 2 equiv. of p-nitrobenzoylethylenimine and 1 equiv. of aniline were used a bis derivative was obtained. The time of heating was 12 hr., the liquid added was hexane. The product was recrystallized from acetone, m.p. 190-191°.

Anal. Calcd. for $C_{24}H_{23}N_5O_6$: C, 60.36; H, 4.86; N, 14.67. Found: C, 60.24; H, 4.75; N, 14.69.

Infrared: 3300 (m), 3260 (m), 1652 (m), 1596 (m), 1520 (s), 1342 cm.$^{-1}$ (s); ultraviolet: λ_{max} 256 mμ (log ϵ_{max} 4.56).

The hydrochloride had m.p. 228–232° dec.

Anal. Calcd. for $C_{24}H_{24}ClN_5O_6$: Cl, 6.90. Found: Cl, 6.83.

N,N-Di(p-aminobenzamidoethyl)butylamine (XXVIII).—This compound was prepared from XXVI by catalytic hydrogenation over platinum. The product was recrystallized from chloroform–ether and obtained as a yellow, hygroscopic solid, m.p. 64–68°.

Anal. Calcd. for $C_{22}H_{31}N_5O_2$: C, 66.46; H, 7.88; N, 17.62. Found: C, 66.52; H, 7.67; N, 17.54.

Ethyl 1-Aminocyclopentanecarboxylate (XXIX).—Cyclopentanone was converted to hydantoin-5-spirocyclopentane.[8] The latter was hydrolyzed with barium hydroxide to form 1-aminocyclopentanecarboxylic acid.[9] The ethyl ester hydrochloride was prepared in the usual manner, m.p. 228°. It was suspended in ether and treated with triethylamine to form the free ester, b.p. 80° (10 mm.); this agrees with the boiling point reported in the literature.[10]

Ethyl 1-Aminocyclohexanecarboxylate (XXX).—This compound was made from cyclohexanone by the same procedures used for making XXIX.[10–12] The free ester had b.p. 97° (14 mm.) which agrees with the literature value.

N-Substituted Ethylenediamines.—A stirred suspension of 0.01 mole of the corresponding substituted p-nitrobenzamide (VIII, X, XIV) in 50 ml. of 6 N HCl was refluxed for 12 hr. After cooling, the p-nitrobenzoic acid was removed by filtration and the solvent was distilled under reduced pressure. The residual dihydrochloride was then recrystallized from ethanol with the aid of decolorizing carbon. The results are shown in Table VII. The new compound XXXI was converted to the free base. A solution of the dihydrochloride (0.01 mole) in 25 ml. of water was passed through a 30-ml. column of IR-4B Amberlite weakly basic ion-exchange resin. The column had previously been washed with aqueous ammonia and distilled water. The column was then eluted with distilled water until the eluent no longer gave a ninhydrin test. After removing the water under reduced pressure, the residue was recrystallized from water–acetone to yield pure 1-(2-aminoethylamino)cyclopentanecarboxylic acid, 65% yield, m.p. 194–196° (sinters at 185°).

Anal. Calcd. for $C_8H_{16}N_2O_6$: C, 55.78; H, 9.38; N, 16.25. Found: C, 55.59; H, 9.43; N, 16.03.

6,9-Diazaspiro[4,5]decan-1-one.—1-(2-Aminoethylamino)-cyclopentanecarboxylic acid (0.5 g., 0.0029 mole) was dissolved in 35 ml. of water and the solution refluxed for 12 hr. Cooling and addition of acetone caused the recrystallization of the diazaspiro compound, m.p. 158-159°, 69% yield. The infrared spectrum showed a strong lactam carbonyl absorption at 1635 cm.$^{-1}$. The series of broad bands in the 3000–2000-cm.$^{-1}$ region, characteristic of amino acids, were not present.

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.55; H, 9.35; N, 18.16.

The hydrochloride, prepared by passing HCl into an ethanol solution of the base, showed an interesting behavior on recrystallization. When recrystallized from ethanol–ether, it melted at 229–230°, but when recrystallized from ethanol–ether with the aid of decolorizing carbon, it melted at 239–240°. When the higher melting form was recrystallized from ethanol–ether without the aid of charcoal, the lower melting form was again obtained. This process was repeated several times. The two interconvertible forms showed no differences in their infrared spectra nor in their analyses.

Anal. Calcd. for $C_8H_{15}ClN_2O$: C, 50.38; H, 7.95; Cl, 18.59; N, 14.69. Found: C, 50.50; H, 7.93; Cl, 18.78; N, 14.65.

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