and 2 g. (0.02 mole) of triethylamine added. After 5 min. the precipitate was removed by filtration. To the filtrate was added 2.2 g. (0.00315 mole) of tricarbobenzoxy-L-arginine *p*-nitrophenyl ester. The solution was allowed to stand for 2 days at room temperature and was evaporated to an oil. The gum was washed repeatedly with water, ether, and ethyl acetate and was gradually solidified. The solid was crystallized from methanol–ethyl acetate; yield 2 g. (52%), m.p. 95–115°, $[\alpha]^{23}D$ −37° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{77}H_{94}N_{16}O_{20}$: C, 59.04; H, 6.05; N, 14.31; OAc, 2.75. Found: C, 58.47; H, 6.20; N, 14.45; OAc, 1.97.

Tricarbobenzoxy-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-*p*-fluoro-L-phenylalanylnitro-L-arginine Methyl Ester (VIIIb).—This compound was prepared according to the above described procedure. A 2.5-g. (0.00225 mole) run of the carbobenzoxyoctapeptide (VIIb) gave 3 g. (87%) of cream-colored solid, m.p. 145–147°, $[\alpha]^{23}D$ −47.5° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{77}H_{93}FN_{16}O_{20}\cdot 3H_2O$: C, 56.54; H, 6.10; N, 13.70; OAc, 2.72. Found: C, 56.20; H, 6.19; N, 13.57; OAc, 2.58.

Tricarbobenzoxy-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-O-acetyl-L-seryl-*p*-fluoro-D-phenylalanylnitro-L-arginine Methyl Ester (VIIIc).—From 2.3 g. (0.0033 mole) of tricarbobenzoxy-L-arginine *p*-nitrophenyl ester and 3.5 g. (0.0031 mole) of the *p*-fluoro-D-phenylalanine octapeptide (VIIc) a cream solid amounting to 3.5 g. (74%) was obtained, m.p. 120–125°, $[\alpha]^{23}D$ −36.1° (*c* 1, methanol).

Anal. Found: C, 56.59; H, 6.00; N, 14.22; OAc, 2.21.

Dicarbobenzoxy-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-D-phenylalanylnitro-L-arginine (IXa).—To a solution of 1 g. (0.00066 mole) of the tricarbobenzoxynonapeptide methyl ester (VIIIa) in 30 ml. of methanol was added 1 ml. of 2 *N* sodium hydroxide. The solution was stirred at room temperature for 25 min., water was added, and the solution remained clear. The solution was filtered and 1.5 ml. of 2 *N* hydrochloric acid was added. The precipitate was removed by filtration and the solid was crystallized from methanol–ether, yield 625 mg. (79%), m.p. 170–175° $[\alpha]^{23}D$ −38° (*c* 1, methanol).

Anal. Calcd. for $C_{66}H_{84}N_{16}O_{17}\cdot 2H_2O$: C, 56.21; H, 6.29; N, 15.90. Found: C, 56.27; H, 6.39; N, 15.98.

Dicarbobenzoxy-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-*p*-fluoro-L-phenylalanylnitro-L-arginine (IXb).—Hydrolysis of 2 g. (0.0013 mole) of the tricarbobenzoxynonapeptide methyl ester (VIIIb) with 1.6 ml. (0.0032 mole) of 2 *N* sodium hydroxide gave 1.2 g. (66%) of white solid, m.p. 155–160°, $[\alpha]^{23}D$ −62.5° (*c* 1, methanol).

Anal. Calcd. for $C_{66}H_{83}FN_{16}O_{17}\cdot 3H_2O$: C, 54.71; H, 6.19; N, 15.47; F, 1.37. Found: C, 54.46; H, 6.19; N, 15.37; F, 1.48.

Dicarbobenzoxy-L-arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-*p*-fluoro-D-phenylalanylnitro-L-arginine (IXc).—A similar hydrolysis of 2.5 g. of the corresponding tricarbobenzoxy *p*-fluoro-D-phenylalaninenonapeptide (VIIIc) gave 1.8 g. (80%) of tan solid, m.p. 160–165°, $[\alpha]^{23}D$ −31.3° (*c* 1, dimethylformamide).

Anal. Found: C, 54.24; H, 6.11; N, 15.84; F, 1.65.

L-Arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-D-phenylalanyl-L-arginine Triacetate Salt (Xa).—The dicarbobenzoxynonapeptide (IXa) (400 mg., 2.9×10^{-4} mole) was dissolved in 30 ml. of glacial acetic acid, and 200 mg. of palladium black catalyst and 20 ml. of methanol were added. The resulting mixture was hydrogenated for 24 hr. at room temperature and 2–3 lb. (0.14–0.21 kg./cm.^{2}) pressure. The catalyst was removed by filtration. The filtrate was evaporated *in vacuo*, the residue was dissolved in 50 ml. of water, the solution was filtered, shell frozen, and lyophilized leaving 333 mg. of white powder, m.p. 155–168°, $[\alpha]^{23}D$ −73° (*c* 0.89, water).

Anal. Calcd. for $C_{56}H_{85}N_{15}O_{17}\cdot H_2O$: C, 53.46; H, 6.97; N, 16.70: Found: C, 53.16; H, 7.07; N, 17.07.

L-Arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-*p*-fluoro-L-phenylalanyl-L-arginine Triacetate Salt (Xb).—The appropriate dicarbobenzoxynonapeptide IXb (200 mg.) was hydrogenated in the manner previously described. The catalyst was removed and lyophilization of the filtrate gave 194 mg. of fluffy white solid, $[\alpha]^{23}D$ −79° (*c* 0.696, water).

Anal. Calcd. for $C_{56}H_{84}FN_{15}O_{17}$: C, 53.45; H, 6.73; N, 16.70; F, 1.51. Found: C, 52.79; H, 6.79; N, 17.42; F, 1.61.

L-Arginyl-L-prolyl-L-prolylglycyl-L-phenylalanyl-L-seryl-L-prolyl-*p*-fluoro-D-phenylalanyl-L-arginine (Xc).—From 500 mg. of the dicarbobenzoxy 8-*p*-fluoro-D-phenylalanine nonapeptide (IXc) there was obtained after catalytic hydrogenation 470 mg. of light tan solid, $[\alpha]^{23}D$ −63.4° (*c* 1, water). The analytical sample was dried at 110° for 18 hr.

Anal. Found: C, 53.11; H, 6.64; N, 17.33; F, 1.19.

For the paper chromatography of the three bradykinin analogs, two different solvent systems were employed: (A) *t*-butyl alcohol–acetic acid–water (2:1:1) and (B) isopropyl alcohol–concentrated ammonium hydroxide–water (70:5:25). The spots were developed with bromophenol blue and Sakaguchi reagents. Single spots were obtained in each case. The R_f values obtained were: 8-D-phenylalanine bradykinin (A) 0.79, (B) 0.52; 8-*p*-fluoro-L-phenylalanine bradykinin (A) 0.72, (B) 0.49; 8-*p*-fluoro-D-phenylalanine bradykinin (A) 0.77, (B) 0.56. Paper electrophoresis of the three nonapeptides was carried out in acetate buffer, pH 5.6, using a constant current of 30 ma. for 3 hr. The mobilities of the analogs were found to be identical and could not be distinguished from bradykinin which moved a distance of 6.7 cm. from the point of origin.

Acknowledgment.—We wish to express our sincere appreciation to Mr. C. E. Childs and his staff for the microanalyses reported herein and to Dr. J. M. Vandenbelt, Mrs. Carola Spurlock, and Mrs. Vivien Lee for the determination of optical rotations.

The Anticonvulsant Properties of Some Substituted Benzamides

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Received November 5, 1962

A number of substituted aromatic amides have been prepared and their anticonvulsant properties are reported. Two compounds, 4-amino-N-cyclopropyl-3,5-dichlorobenzamide and 4-amino-N-cyclopropyl-3,5-dibromobenzamide, were shown to be potent antagonists to the convulsant action of strychnine.

During a routine search for compounds which might possess muscle relaxant properties, it was found that 4-amino-N-cyclopropyl-3,5-dichlorobenzamide (8) was outstanding. The muscle relaxant properties of this amide have been reported earlier.[1]

It is interesting to note that although 4-amino-3,5-dichlorobenzoic acid was first prepared by Elion[2] in 1923, no simple derivatives other than the methyl ester[3] and the acid chloride[4] were ever prepared. Elion prepared the acid in low yield by chlorination of *p*-amino-

(1) T. E. Lynes and G. M. Everett, *Federation Proc.*, **20**, 323 (1961). The substance of this Communication was presented before the Medicinal Chemistry Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 9–14, 1962.

(2) L. Elion, *Rec. trav. chim.*, **44**, 145 (1923).

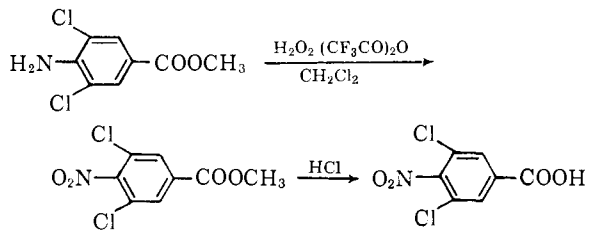
(3) E. Müller and E. Tietz, *Chem. Ber.*, **74B**, 807 (1941).

(4) M. Schubert, *Ann.*, **558**, 31 (1947).

benzoic acid with potassium chlorate. The acid also has been prepared by the action of sulfuryl chloride[5] on *p*-aminobenzoic acid and more recently by the direct action of chlorine gas[6] on *p*-acetamidobenzoic acid. We have found it more convenient and also obtained the desired acid in much higher yield by treating sulfuryl chloride with ethyl *p*-aminobenzoate in chloroform and hydrolyzing the crude ester with dilute hydrochloric acid.

As a part of a study of structure–activity relationships in a group of synthetic agents, a number of 4-amino-3,5-dihalobenzamides were prepared. Several other mono-, di-, and trisubstituted benzamides were also prepared for comparison. An anilide, namely, N-(4-amino-3,5-dichlorophenyl)cyclopropanecarboxamide (**14**) was also prepared to establish the activity of the benzamide moiety. This compound was prepared by treating 2,6-dichloro-*p*-phenylenediamine with one equivalent of cyclopropanecarbonyl chloride as it is known that the monoacylation of 2,6-dichloro-*p*-phenylenediamine occurs more readily on the unhindered amino group.[7]

In order to prepare what was hoped would be a precursor of 4-amino-N-cyclopropyl-3,5-dichlorobenzamide, it was necessary to oxidize methyl 4-amino-3,5-dichlorobenzoate according to the procedure of Emmons.[8]



The cyclopropylamide of this hitherto unknown dichloronitrobenzoic acid was then prepared. The amides prepared and tested are listed in Table I.

Pharmacological Studies

Methods.—The anticonvulsant properties of these compounds were determined by methods patterned after those of Berger.[9] All test compounds were administered as suspensions in gum tragacanth by the intraperitoneal route to groups of ten albino mice (18–24 g.). Tests were run 1 hr. after treatment. Median effective doses were determined by the method of Bliss.[10] Median lethal doses (LD_{50}) were derived from screening procedures using only three animals per dose and can only be considered as estimates.

Strychnine antagonism was determined in groups of animals challenged with a certainly lethal dose of strychnine sulfate (2.0 mg./kg., s.c.) (LD_{99}). Pentamethylenetetrazol antagonism was determined in groups of animals challenged with a certainly lethal dose of pentamethylenetetrazol (120 mg./kg., s.c.) (LD_{99}). Only animals which did not convulse were considered to be protected from either of the chemical convulsants. Tonic extensor seizures were produced by electroshock administered through corneal electrodes. Parameters of stimulus were as follows: amplitude 140 v.; frequency 100/sec.; pulse duration 1 msec.; train duration 0.3 sec. Abolition of the tonic extensor phase of the seizure was used as the criterion for protection.

(5) S. Chiavarelli, *Gazz. chim. ital.*, **85**, 1405 (1955); *Chem. Abstr.*, **50**, 10025*d* (1956).
(6) C. Stelt and W. Th. Nauta, *Rec. trav. chim.*, **78**, 534 (1959).
(7) G. Morgan and D. Cleage, *J. Chem. Soc.*, **113**, 594 (1918).
(8) W. Emmons, *J. Am. Chem. Soc.*, **76**, 3470 (1954).
(9) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954).
(10) C. Bliss, *Ann. Appl. Biol.*, **22**, 134 (1935).

Results

Pharmacological results are reported in Tables II and III.

Strychnine Antagonism.—In this series of substituted benzamides only 4-amino-N-cyclopropyl-3,5-dichlorobenzamide (**8**) and its dibromo analog (**10**) were effective in prevention of convulsions produced by strychnine. The toxicity of strychnine was limited by all N-alkyl derivatives of 4-amino-3,5-dihalobenzamide except the *t*-butyl derivative (**11**) with maximum activity present in the cyclopropyl derivative (**8**).

Pentamethylenetetrazol Antagonism.—Convulsions produced by pentamethylenetetrazol were effectively antagonized by many of the compounds studied. The most active compound was 4-amino-N-cyclopropyl-3,5-dichlorobenzamide (**8**). The activity of N-cyclopropyl-3,5-dichlorobenzamide (**26**) suggested that the amino group in the 4-position has only slight influence on antipentamethylenetetrazol activity. The 4-amino-3,5-dichlorobenzamide (**1**) had no effect in this test. N-Alkyl substituents increased activity with maximum activity present when the cyclopropyl substituent (**8**) was used. Substitution on the aromatic nucleus indicated that the 3,5-dihalogenated derivatives were effective pentamethylenetetrazol antagonists. Protection against the lethal effects of pentamethylenetetrazol seemed to be correlated with protection from its convulsant effects.

Maxima Electroshock Seizure Antagonism.—Tonic extensor seizures produced by supramaximal electroshock can be abolished by many compounds in this series. The most active compounds were N-cyclopropyl-2,4-dichlorobenzamide (**27**) and 3-amino-N-cyclopropyl-2,5-dichlorobenzamide (**17**). In the 4-amino-3,5-dichlorobenzamide group, the most active compound was the simple benzamide (**1**). The N-cyclopropyl substitution did not cause a decrease in activity, but any other change in this position profoundly decreased potency. It is of interest to note the differences in activity produced by unsaturation in the N-3-carbon chain compounds **4**, **6**, and **7**. The N-cyclobutyl derivative (**12**) had about the same potency as the N-*n*-propyl derivative (**4**), but the *t*-butyl derivative (**11**) is much less active. 4-Amino-N-phenyl-3,5-dichlorobenzamide (**13**) was inactive.

Discussion

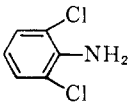
This study was designed to evaluate the muscle relaxant activity of a series of substituted benzamides using the antagonism of strychnine-induced convulsions as a criterion of such activity. In this series of compounds, only two, 4-amino-N-cyclopropyl-3,5-dichlorobenzamide and 4-amino-N-cyclopropyl-3,5-dibromobenzamide, have significant activity in protecting mice from the convulsant action of strychnine. It is worthwhile to note that to our knowledge no other compounds are known to antagonize strychnine-induced convulsions at doses which produce little or no neurological symptoms.[1] These two compounds have a spectrum of anticonvulsant action against strychnine, pentamethylenetetrazol, and electroshock which is different from the spectrum of diphenylhydantoin, phenobarbital, and meprobamate.

When the anticonvulsant action of these benzamide

TABLE I

AROMATIC AMIDES

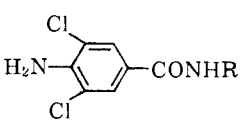
RCONHR'

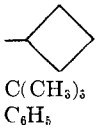
No.[a]	R	R'	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	3,5-Cl_2-4-$NH_2C_6H_2$	H	152–153	$C_7H_6Cl_2N_2O$	41.00	2.95	13.66	41.22	3.20	13.63
2	3,5-Cl_2-4-$NH_2C_6H_2$	CH_3	185–186	$C_8H_8Cl_2N_2O$	43.86	3.68	12.79	43.72	3.73	12.78
3	3,5-Cl_2-4-$NH_2C_6H_2$	CH_2CH_3	148–149	$C_9H_{10}Cl_2N_2O$	46.37	4.32	12.02	46.24	4.36	11.85
4	3,5-Cl_2-4-$NH_2C_6H_2$	$CH_2CH_2CH_3$	98–99	$C_{10}H_{12}Cl_2N_2O$	48.59	4.89	11.34	48.59	5.09	11.17
5	3,5-Cl_2-4-$NH_2C_6H_2$	$CH(CH_3)_2$	185–186	$C_{10}H_{12}Cl_2N_2O$	48.59	4.89	11.34	48.85	5.01	11.33
6	3,5-Cl_2-4-$NH_2C_6H_2$	$CH_2CH{=}CH_2$	142–143	$C_{10}H_{10}Cl_2N_2O$	49.00	4.12	11.43	49.06	4.28	11.21
7[b]	3,5-Cl_2-4-$NH_2C_6H_2$	$CH_2C{\equiv}CH$	173–174	$C_{10}H_8Cl_2N_2O$	49.40	3.32	11.53	49.78	3.38	11.24
8	3,5-Cl_2-4-$NH_2C_6H_2$		174–175	$C_{10}H_{10}Cl_2N_2O$	49.00	4.12	11.43	49.07	4.26	11.61
9[c]	C_6H_5		103–104							
10[d]	3,5-Br_2-4-$NH_2C_6H_2$		162–163	$C_{10}H_{10}Br_2N_2O$	35.95	3.02	8.39	35.90	2.88	8.30
11	3,5-Cl_2-4-$NH_2C_6H_2$	$C(CH_3)_3$	144–145	$C_{11}H_{14}Cl_2N_2O$	50.54	5.90	10.73	50.75	5.62	10.48
12[e]	3,5-Cl_2-4-$NH_2C_6H_2$		189–190	$C_{11}H_{12}Cl_2N_2O$	50.99	4.67	10.81	51.20	4.75	10.84
13	3,5-Cl_2-4-$NH_2C_6H_2$		159–160	$C_{13}H_{10}Cl_2N_2O$	55.53	3.57	9.96	55.40	3.23	10.09
14			224–225	$C_{10}H_{10}Cl_2N_2O$	48.99	4.11	11.43	48.76	3.82	11.39
15[f]	3,5-Cl_2-2-$NH_2C_6H_2$		179–180	$C_{10}H_{10}Cl_2N_2O$	48.99	4.12	11.43	48.30	4.56	11.23
16[g]	3,5-Cl_2-2-$NH_2C_6H_2$	CH_2CH_3	161–162							
17[h]	2,5-Cl_2-3-$NH_2C_6H_2$		162–163.5	$C_{10}H_{10}Cl_2N_2O$	49.19	4.13	11.48	49.42	4.06	11.56
18[h]	4-NH_2-C_6H_4		151–152	$C_{10}H_{12}N_2O$	68.15	6.86	15.90	68.45	6.89	15.81
19[h]	3-NH_2-4-ClC_6H_3		145	$C_{10}H_{11}Cl_2N_2O$	57.01	5.26	13.31	57.24	5.35	13.42
20[h]	2-NH_2-4-ClC_6H_3		135.5–137	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.31	56.66	5.25	12.76
21	4-$NO_2C_6H_4$		178–179	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.58	58.33	4.78	13.34
22[i]	4-Cl-3-$NO_2C_6H_4$		129–130	$C_{10}H_9ClN_2O_3$	49.91	3.76	11.64	50.01	3.72	11.52
23[j]	4-Cl-2-$NO_2C_6H_4$		164–165	$C_{10}H_9ClN_2O_3$	49.91	3.76	11.64	50.09	3.74	11.92
24[k]	2,5-Cl_2-3-$NO_2C_6H_2$		170–171	$C_{10}H_8Cl_2N_2O_3$	43.66	2.94	10.18	43.53	2.92	10.23
25	3,5-Cl_2-4-$NO_2C_6H_2$		167–168	$C_{10}H_{12}Cl_2N_2O_3$	43.66	2.94	10.18	43.73	3.00	10.09
26[l]	3,5-$Cl_2C_6H_3$		138–139	$C_{10}H_9Cl_2NO$	52.21	3.94	6.08	52.45	4.06	5.95
27[m]	2,6-$Cl_2C_6H_3$		191–192	$C_{10}H_9Cl_2NO$	52.21	3.94	6.08	52.35	4.17	5.96

[a] The acid chlorides of most of the acids were prepared with thionyl chloride and used as crude materials. In the case of compounds **15** and **16,** the acid chloride was prepared with phosphorus pentachloride, according to F. Sheibly, *J. Org. Chem.*, **12,** 743 (1947). [b] The propargylamine used for this amide was prepared according to K. Schulte and M. Goes, *Arch. Pharm.*, **290,** 118 (1957); *Chem. Abstr.*, **51,** 12817e (1957), but was isolated as the fumarate salt. This salt was used along with aqueous alkali instead of triethylamine as described in the Experimental for compound **8**. [c] This compound was described by M. Schlatter, *J. Am. Chem. Soc.*, **63,** 1733 (1941). [d] The acid for this compound was prepared according to Elion.[2] The acid chloride in this case melted at 178–180°. [e] Cyclobutylamine was prepared according to G. Heisig, *J. Am. Chem. Soc.*, **63,** 1698 (1941). [f] The acid for the amide was obtained from the Dow Chemical Co. [g] This compound was reported by F. Sheibly, *J. Org. Chem.*, **12,** 743 (1947). [h] These amides were prepared from the corresponding nitro compounds by catalytic reduction as described in the Experimental. [i] The acid for this amide was obtained from D.P.I. [j] This acid is available from Aldrich Chemical Co. [k] A sample of this acid was obtained from Am Chem. Co. [l] The acid is available from Aldrich Chemical Co. [m] The acid in this case was obtained from the DuPont Co.

TABLE II

PHARMACOLOGICAL ACTIVITY OF SOME N-SUBSTITUTED 4-AMINO-3,5-DICHLOROBENZAMIDES

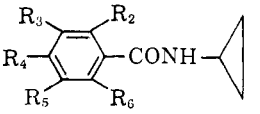


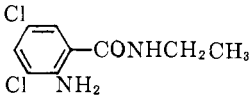
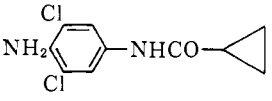
Compound	R	Electroshock[a]	Pentamethylenetetrazol[a] Convulsions	Pentamethylenetetrazol[a] Death	Strychnine[a] Convulsions	Strychnine[a] Death	Est. LD_{50}, mg./kg.
1	H	50 (42–57)	>200	>200	>200	168 (136–233)	200
2	CH_3	153 (123–188)	>300	>300	>300	98 (72–111)	250
3	CH_2CH_3	78 (65–90)	112 (96–139)	67 (58–74)	>300	107 (69–137)	350
8		59 (46–72)	17 (14–20)	6 (4.8–7.2)	34 (26–42)	22 (18–26)	265
5	$CH(CH_3)_2$	118 (96–179)	33 (23–43)	18 (15–21)	>200	86 (66–106)	250
4	$CH_2CH_2CH_3$	131 (105–154)	114 (94–143)	69 (54–79)	>300	107 (69–137)	350
6	$CH_2CH{=}CH_2$	153 (125–183)	139 (111–167)	114 (90–150)	>300	170 (146–196)	600
7	$CH_2C{\equiv}CH$	>300	>300	262 (222–302)	>300	220 (180–260)	550
12		121 (100–142)	59 (55–63)	22 (20–24)	>300	242 (190–800)	500
11	$C(CH_3)_3$	226 (186–266)	47 (41–56)	18 (15–20)	>300	>300	800
13	C_6H_5	>300	>300	>300	>300	>300	>1500

[a] ED_{50} mg./kg. and 95% confidence limits.

TABLE III

PHARMACOLOGICAL ACTIVITY OF SOME DERIVATIVES OF N-CYCLOPROPYL BENZAMIDE AND SOME MISCELLANEOUS COMPOUNDS



Compound	R_2	R_3	R_4	R_5	R_6	Electroshock[a]	Pentamethylenetetrazol[a] Convulsions	Pentamethylenetetrazol[a] Death	Strychnine[a] Convulsions	Strychnine[a] Death	Est. LD_{50}, mg./kg.
27	Cl	H	H	H	Cl	36 (30–45)	>200	67 (15–85)	>300	150 (120–180)	400
17	Cl	NH_2	H	Cl	H	37 (31–44)	>300	>300	>300	>300	600
26	H	Cl	H	Cl	H	80 (68–92)	31 (22–40)	16 (12–20)	>200	>200	250
10	H	Br	NH_2	Br	H	88 (80–96)	37 (31–43)	11 (8–14)	53 (32–74)	39 (26–52)	500
18	H	H	NH_2	H	H	139 (111–170)	>300	>300	>300	>300	600
20	NH_2	H	Cl	H	H	139 (113–161)	>300	>300	>300	>300	800
19	H	NH_2	Cl	H	H	215 (195–241)	>300	>300	>300	>300	750
15	NH_2	Cl	H	Cl	H	>300	200 (169–232)	100 (81–119)	>300	>300	1200
25	H	Cl	NO_2	Cl	H	>300	>300	>300	>300	>300	1200
9	H	H	H	H	H	>300	>300	>300	>300	>300	600
16						95 (75–115)	>300	140 (105–175)	>500	>500	600
14						>300	>300	>300	>300	>300	>2000
	Diphenylhydantoin					8 (6.7–9.3)	>500	>500	>500	>500	
	Phenobarbital					17 (14.3–19.7)	21 (15–27)	7 (5.7–8.3)	145 (115–175)	67 (57–67)	
	Meprobamate					114 (99–129)	110 (99–121)	37 (30–44)	460 (372–548)	257 (209–305)	

[a] ED_{50} mg./kg. and 95% confidence limits.

derivatives is analyzed it is apparent that structural requirements for anticonvulsant activity against the three test systems are not related. In the 4-amino-3,5-dichlorobenzamide series, the simple benzamide and the N-cyclopropylbenzamide are equally active as electroshock seizure antagonists, but the cyclopropyl substitution produces profound activity against pentamethylenetetrazol and strychnine. It is worthwhile to note that the unsubstituted benzamide as well as the methyl and ethyl benzamides are more active as electroshock antagonists than as pentamethylenetetrazol antagonists. The opposite is true for the isopropyl, cyclopropyl, *n*-propyl, allyl, cyclobutyl, and *t*-butyl benzamides.

It is difficult to see a pattern in the effect of alterations of the substituents on the aromatic nucleus of the cyclopropylbenzamides. Dihalogenation of the 2,6-positions produces effective antagonists to electroshock, while dihalogenation in the 3,5-positions increases the antipentamethylenetetrazol activity. Alteration in the position of the amino group produces changes in all tests as shown by a comparison of 4-amino-N-cyclopropyl-3,5-dichlorobenzamide and 2-amino-N-cyclopropyl-3,5-dichlorobenzamide. Oxidation of the 4-amino group completely abolishes activity in all of the tests.

Experimental

4-Amino-3,5-dichlorobenzoic Acid.—To a refluxing solution of 330 g. (2 moles) of ethyl *p*-aminobenzoate in 2600 ml. of chloroform there was added 603 g. (4.5 moles) of sulfuryl chloride in 500 ml. of chloroform over a 3-hr. period. After addition was complete, the reaction mixture was cooled and extracted with three 500-ml. portions of cold water. The solvent was removed by distillation and the oily residue was dissolved in 250 ml. of hot glacial acetic acid. To the acetic acid solution 200 ml. of water and 500 ml. of concentrated hydrochloric acid were added and the mixture was stirred and refluxed for **16–18** hr. The hot mixture was diluted with 500 ml. of water, stirred for 15 min., and the product was collected by filtration and washed well with water. The solid then was suspended in 2 l. of chloroform and stirred for 15 min. The solid was collected by filtration and washed with 1 l. of fresh chloroform. After drying 366 g. (89%) was obtained, m.p. 292–295°; lit.[2] m.p. 293–295°.

4-Amino-3,5-dichlorobenzoylchloride.—A mixture of 309 g. (1.5 moles) of 4-amino-3,5-dichlorobenzoic acid, 768 g. (464 ml.; 6.45 moles) of thionyl chloride, and 1158 ml. of dry benzene was heated under reflux for 3.25 hr. without stirring. At the end of this time, 200–250 ml. of the reaction mixture was removed by distillation. The reaction mixture was allowed to cool and the product was removed by filtration. The product was washed well with pentane to remove excess thionyl chloride and benzene. After air drying, 306.4 g. (91%) of fine light tan needles was obtained which melted at 160–161°; lit.[4] m.p. 160°. When this acid chloride was prepared on a developmental scale, the thionylamine derivative was occasionally obtained. This did not occur during laboratory preparation.

Methyl 4-Amino-3,5-dichlorobenzoate.—A mixture of 224.5 g. (1 mole) of 4-amino-3,5-dichlorobenzoyl chloride, 1 l. of methanol, and 1 ml. of dry pyridine was refluxed overnight (*ca.* 18 hr.). The next day the very dark reaction mixture was concentrated and the resulting dark residue was taken up in ether. The ethereal solution was filtered through a bed of decolorizing carbon (Darco) and the almost colorless solution was washed three times with dilute alkali, then with water, dilute hydrochloric acid, and again with water. After drying over magnesium sulfate, filtering, and concentrating the ether solution, the light straw-colored oil was poured into an evaporating dish and the remaining ether was allowed to evaporate. The resulting solid, 213 g. (97%), melted at 83–84°; lit.[3] m.p. 82°.

Methyl 3,5-Dichloro-4-nitrobenzoate.—Peroxytrifluoroacetic acid was prepared by adding 161.6 ml. (1.52 moles) of trifluoroacetic anhydride to a mixture of 26.4 ml. (0.96 mole) of 90% hydrogen peroxide in 800 ml. of methylene chloride in one portion with stirring. After an induction period of about 2 min., the reaction mixture began to reflux gently. The mixture was stirred for *ca.* 15 min. after reflux had subsided. To this mixture was added 52.8 g. (0.24 mole) of methyl 4-amino-3,5-dichlorobenzoate in 160 ml. of methylene chloride dropwise at such a rate as to maintain gentle reflux. After addition was complete, the clear reaction mixture was refluxed for 1.5 hr. The cooled reaction

mixture was washed twice with 800-ml. portions of water, twice with 800-ml. portions of 10% sodium carbonate, and once again with water. The solvent was removed by distillation and the residue solidified on cooling. The slightly yellow solid, obtained in quantitative yield, melted at 82–84°. This material, when recrystallized from a minimum amount of methanol, melted at 86–87°.

Anal. Calcd. for $C_8H_5Cl_2NO_4$: C, 38.42; H, 2.07; N, 5.60. Found: C, 38.55; H, 2.20; N, 5.39.

3,5-Dichloro-4-nitrobenzoic Acid.—The crude ester was used for hydrolysis. Sixty grams (0.24 mole) of the crude ester was treated with 110 ml. of glacial acetic acid, 40 ml. of water, and 100 ml. of concentrated hydrochloric acid. The mixture was refluxed with stirring for 20 hr. The reaction mixture was then poured into about 600 ml. of water and stirred for 15 min. The resulting solid was filtered and washed well with water. The acid was dissolved in dilute potassium hydroxide and the alkaline solution was extracted twice with ether. The alkaline solution was acidified and the acid was collected by filtration again. After drying, 55 g. of acid (97%) was obtained, m.p. 208–210°; it was recrystallized from methanol–water mixture, yielding 51 g. as a first crop, m.p. 210–211°.

Anal. Calcd. for $C_7H_3Cl_2NO_4$: C, 35.63; H, 1.28; N, 5.94. Found: C, 35.90; H, 1.45; N, 5.94.

4-Amino-N-cyclopropyl-3,5-dichlorobenzamide (8).—Unless otherwise indicated, most of the amides in Table I are prepared in the following manner. A mixture of 28.5 g. (0.5 mole) of cyclopropylamine and 50.5 g. (0.5 mole) of triethylamine in 180 ml. of dimethylacetamide was cooled in an ice bath. While stirring, 112.3 g. (0.5 mole) of 4-amino-3,5-dichlorobenzoyl chloride in 250 ml. of warm dimethylacetamide was added dropwise. After addition was complete, the reaction mixture was stirred for 0.5 hr. At the end of this time, 700–800 ml. of cold water was added while cooling and stirring was continued for 0.5 hr. longer. The product was removed by filtration and 111 g. (90%) was obtained, m.p. 173–175°. Upon recrystallization from alcohol and water, the colorless product melted at 175–176°. Almost all of the amides of Table I were recrystallized from alcohol and water, except **18**, which was somewhat soluble in water.

4-Amino-N-cyclopropylbenzamide (18).—This amide was prepared from the corresponding nitro amide (**21**) by catalytic hydrogenation. A solution of 26.5 g. (0.128 mole) of N-cyclopropyl-*p*-nitrobenzamide in 250 ml. of absolute ethanol was hydrogenated in the presence of 1 g. of 5% palladium on charcoal under a pressure of 8.12 kg./cm.^{2} at room temperature. Hydrogen uptake was complete in 35–40 min. The reaction mixture was filtered, the catalyst was washed with alcohol, and the combined filtrate and washes were concentrated under reduced pressure until the product began to crystallize. Upon further cooling and filtering, 18.7 g. (83%) was obtained after drying, m.p. 151–152°.

Compounds **17**, **19**, and **20** were prepared in a similar manner from **24**, **22**, and **23**, respectively, using platinum on carbon as the catalyst. Due to the insolubility of the nitroamides **23** and **24**, Methyl Cellosolve was used as a solvent.

N-(4-Amino-3,5-dichlorophenyl)cyclopropanecarboxamide (14).—To a refluxing mixture of 26.5 g. (0.15 mole) of 2,6-dichloro-*p*-phenylenediamine[11] and 15.15 g. (0.15 mole) of triethylamine in 250 ml. of dry acetone, there was added dropwise with stirring 15.7 g. (0.15 mole) of cyclopropanecarbonyl chloride[12] in 50 ml. of dry acetone. The reaction mixture was refluxed for 1 hr. longer. The acetone was removed by distillation and the dark residue was treated with water, yielding 31 g. of product, m.p. 219–221°. After several recrystallizations from dimethylacetamide and water almost colorless blades were obtained, m.p. 224–225°.

Cyclopropylamine.[13]—A mixture of 94 g. (0.75 mole) of N-cyclopropyl cyclopropanecarboxamide,[14] 83.5 g. (1.49 moles) of potassium hydroxide in 90 ml. of water, and 300 ml. of ethylene glycol were heated under a 25-cm. Vigreux column. The temperature of the vapors was kept at 85–90°. The distillate was collected over a 3–4 hr. period. The distillate was then cooled and completely saturated with potassium hydroxide pellets. The resulting amine was distilled from the mixture and 35 g. (82%), b.p. 49–51°, $n^{25}D$ 1.4198, was obtained. By removing the excess ethylene glycol, the potassium salt of cyclopropanecarboxylic acid can be isolated and converted to the acid.

Acknowledgments.—The authors thank Mr. F. E. Fischer and Mr. F. W. Miller for the preparation of some intermediates used in the synthesis of some of these compounds. Mr. M. Freifelder graciously carried out a number of hydrogenations. Chemical analyses were carried out by Mr. E. Shelberg and his staff. Miss N. Fullmer and Mrs. G. Teeters were extremely helpful in the pharmacological studies.

(11) This intermediate is reported by G. Morgan and D. Cleage, *J. Chem. Soc.*, **113**, 594 (1918). It was found more convenient, however, to prepare it from 2,6-dichloro-4-nitroaniline (Koppers Co.). It was obtained in good yield by catalytic reduction of this nitro compound in ethanol, using platinum on carbon at 24.6 kg./cm.^{2}

(12) L. Smith and E. Rogier, *J. Am. Chem. Soc.*, **73**, 4048 (1951).

(13) This is essentially the procedure reported by J. Roberts and V. Chambers, *ibid.*, **73**, 3176 (1951), and W. Emmons, *ibid.*, **79**, 6522 (1957), using other intermediates.

(14) H. Hart and O. Curtis, *ibid.*, **78**, 115 (1956).