chlorine analyses were indicative of 0.5 mole of solvate ethanol which was lost on melting as shown by the following data.

Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found: C, 68.8; H, 8.8.

The filtrate and acetone washings (combined) from the 0.7 g of needles (above), left at 0° overnight, gave 0.5–0.6 g (64–78%) of prisms (**d-mandelate salt of (−)-II**), mp 190–193°[7] which, recrystallized from methanol–acetone, melted at 193–194°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.6; H, 8.0. Found: C, 72.8; H, 8.2.

Base (−)-II, prepared as (+)-II, melted at 217–219°, $[\alpha]^{25}D$ −61.5° (*c* 0.55, 95% EtOH).[8]

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7. Found: C, 78.7; H, 9.8.

The **hydrochloride of (−)-II** melted at 167–170° (froth), $[\alpha]^{25}D$ −37.4° (*c* 0.52, H_2O). It showed a correct analysis for the anhydrous material after melting.

(7) Occasionally, especially if the cooling time is 5 hr or less, the yield of (+)-II *d*-mandelate is only 0.5 g. If so, 0.9 g of a mixture, mp 170–190°, crystallizes from the filtrate and acetone washings. This mixture is dissolved in 2 ml of hot methanol and treated with 10 ml of acetone. Concentration of the solution to about half-volume and cooling at −5° for 1.5 hr gives 0.7 g (90%) of pure *d*-mandelate salt of (−)-II, mp 191–193°.

(8) Y. K. Sawa and J. Irisawa, *Tetrahedron*, **21**, 1129 (1965), prepared (+)-II from sinomenine and (−)-II from thebaine. We thank Dr. Sawa for sending us specimens of his bases for direct comparison.

Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found: C, 68.8; H, 8.8.

B. With (+)-3-Bromo-8-camphorsulfonic Acid.[9] A mixture of 2.5 g of (±)-II, 2.7 g of the ammonium salt of (+)-3-bromo-8-camphorsulfonic acid,[10] 0.85 ml of concentrated HCl, and 75–100 ml of water was heated to solution, which was treated with Norit. The filtrate was cooled slowly to room temperature where it was kept for 24 hr giving 1.9 g (71%) of heavy prisms, mp 238–241°. These were converted to 0.85 g of pure **(−)-II base** essentially as described above.

The filtrate from the 1.9 g of prisms was made basic with NH_4OH to give 1.3 g of solid. It was digested with 50–60 ml of boiling acetone. Filtration gave 0.3 g of (±)-II. On concentration of the filtrate to 10–15 ml, and cooling, 0.6 g of (+)-II, mp 212–216°, was obtained.

Acknowledgment.—Mrs. Louise Atwell of this laboratory performed the analgesic tests. Rotations were performed by Mrs. Evelyn Peake and microanalyses by Miss Paula Parisius both also of this laboratory.

(9) Initial experiments with this agent were performed by Dr. S. E. Fullerton; see S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(10) Sold by the Aldrich Chemical Co. as *d*-α-bromocamphor-π-sulfonic acid ammonium salt.

Central Nervous System Depressants. I. 1-Aminoalkyl-3-aryl Derivatives of 2-Imidazolidinone,[1a-c] 2-Imidazolidinethione, and Tetrahydro-2(1H)-pyrimidinone[1d]

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1-Aminoalkyl-3-aryl-2-imidazolidinones exhibit potent central nervous system depressant activity when tested in laboratory animals. Representative 1-aminoalkyl-3-aryl-2-imidazolidinethiones were less active and 1-aminoalkyl-3-aryltetrahydro-2(1H)-pyrimidinones were inactive in these tests. Several *m*-halo derivatives have been of particular interest and the compound, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (imidoline), has been chosen for evaluation in man.

In an earlier publication,[2] we described the preparation of a series of 1-aryl-3-methyl-2-imidazolidinones. The observation that some of these compounds exhibited low-potency CNS-depressant activity prompted us to extend this research to other 2-imidazolidinone derivatives and led to the discovery that many 1-aminoalkyl-3-aryl-2-imidazolidinones are potent CNS depressants.

The preparation of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone (I) and 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinethione (II) is illustrated in Chart I. The reaction of 2-bromoethylamine with *m*-chloroaniline gave N-(*m*-chlorophenyl)ethylenediamine (III), and further reaction with potassium cyanate resulted in a 55% overall yield of [2-(*m*-chloroanilino)ethyl]urea (IV). Cyclization to 1-(*m*-chlorophenyl)-2-imidazolidinone (V) was effected by heating IV in an oil bath at 220°. Compound V could also be prepared directly from III by reaction with N,N′-carbonyldiimidazole. Alkylation to I was accomplished by treating V in diglyme with sodium hydride and 2-chloroethyl-N,N-dimethylamine. Compound I was also prepared by reaction of 7-(*m*-chlorophenyl)-1,1-dimethyldiethylenetriamine (VI) with N,N′-carbonyldiimidazole. Compound VI was prepared from N,N-dimethylethylenediamine and N-(2-bromoethyl)-*m*-chloroaniline. When I was heated with phosphorus pentasulfide in xylene, II was obtained in 60% yield.

Other 2-imidazolidinone, 2-imidazolidinethione, and tetrahydro-2(1H)-pyrimidinone derivatives were similarly prepared. Details are given in the Tables I–VII and in the Experimental Section.

Pharmacological Methods.—The compounds described in this paper were screened by the following tests in an effort to select agents having an interesting or unique action on the central nervous system.

A. Ataxia (reduced rod-walking ability).—The agents studied were administered intraperitoneally in a 2% starch vehicle to groups of six mice at three or more graded dose levels. At 15- and 30-min intervals after treatment, each animal was placed on the midpoint of a horizontal steel rod (1.55 cm in diameter and about 6 dm in length), positioned 45.7 cm above the surface of the table, and forced to walk toward a platform at either end of the rod. The criterion of inability to perform this act was consistent slipping

(1) (a) American Cyanamid Co., Belgian Patent 623,942 (March 27, 1963); (b) Farbenfabriken Bayer, French Patent 2288M (Feb 17, 1964); (c) W. B. Wright and H. J. Brabander, U. S. Patent 3,196,152 (July 20, 1965); (d) presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4051 (1961).

Chart I

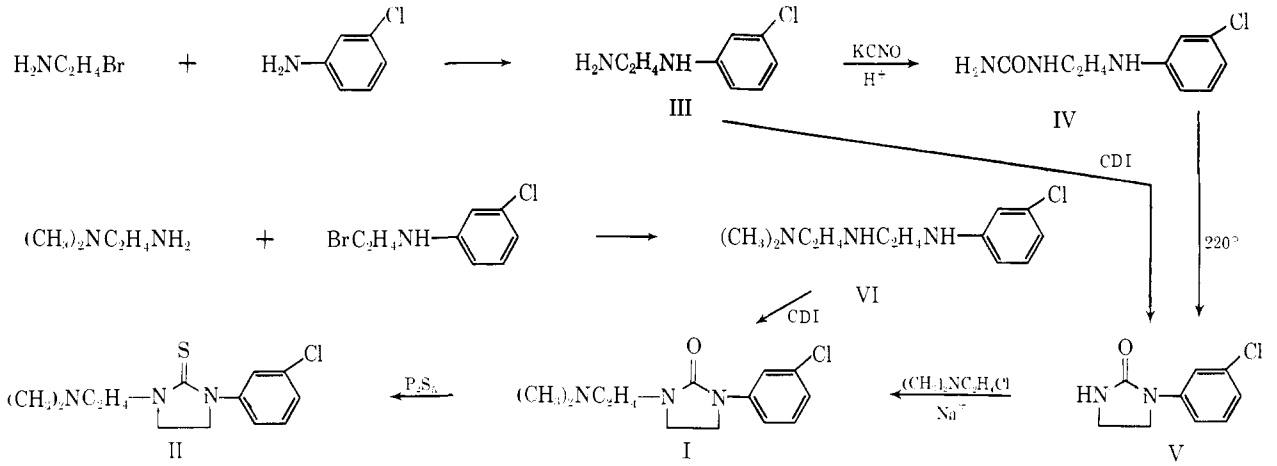
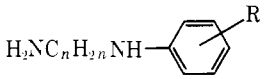


Table I

Alkylenediamine Derivatives[a]

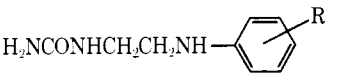


R	n	Yield, %	Bp, °C (mm)	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	2	67	90–95 (0.07)[b]	$C_8H_{12}N_2$	70.5	70.0	8.9	9.1			20.6	20.7
m-CH_3	2	65	85–90 (0.1)[c]	$C_9H_{14}N_2$	71.9	71.4	9.4	9.3			18.7	18.5
m-CF_3	2	71	80–83 (0.2)	$C_9H_{11}F_3N_2$[d]	53.0	53.6	5.4	5.7			13.7	13.5
m-Br	2	74	107–118 (0.2)	$C_8H_{11}BrN_2$	44.7	45.1	5.2	4.9	37.2	37.9	13.0	12.3
o-Cl	2	67	113–122 (1.2)	$C_8H_{11}ClN_2$[e]								
m-Cl	2	72	118–125 (0.1)	$C_8H_{11}ClN_2$	56.3	56.1	6.5	6.6	20.8	20.9	16.4	16.4
p-Cl	2	73	144–154 (1.3)	$C_8H_{11}ClN_2$	56.3	56.2	6.5	6.6	20.5	20.5	16.4	16.4
m-OCH_3	2	59	160–170 (0.3)	$C_9H_{14}N_2O$	65.0	65.2	8.5	8.7			16.9	16.7
m-SCH_3	2	49	125–130 (0.4)	$C_9H_{16}Cl_2N_2S$[g]	42.3	42.6	6.3	6.4	27.6	27.9	11.0	11.0
m-Cl	3	74	120–130 (0.05)[f]	$C_9H_{15}Cl_3N_2$[g]	42.0	41.9	5.9	5.5	41.3	41.5	10.9	11.3

[a] These compounds were used in the next step without further purification. [b] J. P. Fourneau and Y. de Lestrange [*Bull. Chem. Soc. France*, 827 (1947)] report bp 143–145° (15 mm). [c] Lit.[b] bp 168° (28 mm). [d] *Anal.* Calcd: F, 27.9. Found: F, 28.3. [e] Not analyzed. [f] G. F. Deebel [U. S. Patent 2,953,490 (Sept. 20, 1960)] reports bp 128° (0.1–0.25 mm). [g] Dihydrochloride.

Table II

(2-Anilinoethyl)urea Derivatives



R	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	49	102–104	A	$C_9H_{13}N_3O$	60.3	60.0	7.3	7.5			23.5	23.6
m-CH_3	86	126–127	B	$C_{10}H_{15}N_3O$	62.2	61.8	7.8	7.9			21.7	21.8
m-CF_3	70	89–92	B	$C_{10}H_{12}F_3N_3O$	48.4	48.3	5.3	4.9	23.0	23.0	16.9	16.7
o-Cl	83	126–130	C	$C_9H_{12}ClN_3O$	50.6	50.5	5.7	5.8	16.6	16.7	19.7	19.2
m-Cl	76	115–117	A	$C_9H_{12}ClN_3O$	50.6	50.5	5.7	6.0	16.6	16.6	19.7	19.8
p-Cl	75	124–126	A	$C_9H_{12}ClN_3O$	50.6	50.4	5.7	5.9	16.6	16.8	19.7	19.6
m-OCH_3	44	97–98	D	$C_{10}H_{15}N_3O_2$	57.4	57.3	7.2	7.3			20.1	19.8
m-SCH_3	66	104–105	D	$C_{10}H_{15}N_3OS$[b]	53.3	53.4	6.7	6.6			18.7	18.1

[a] A, ethyl acetate; B, chloroform–petroleum ether (bp 30–60°); C, acetone; D, ethanol. [b] *Anal.* Calcd: S, 14.2. Found: S, 13.9.

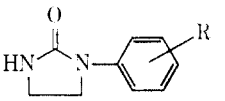
to the side or falling off the rod. Effective doses for reduced rod-walking ability (RWD_{50}) were calculated or approximated from the data, and the time of peak effect was estimated from the data.

B. Reduced Locomotor Activity.—One-half of the RWD_{50} dose was given intraperitoneally to each mouse in groups of 5. At the time of peak effect, as determined above, each group of mice was put into the actophotometer for a period of 5 min and the motor activity counts were recorded and compared to controls. Those compounds that appeared to reduce motor activity by 50% were administered to additional groups of five mice at graded doses and tested similarly. The dose (MDD_{50}) that caused a 50% reduction in motor activity was estimated.

C. Paralysis.—Groups of ten mice for each of three or more graded dose levels were placed on an inclined screen (60°) for a period of 20 min or more, immediately after receiving the agents studied. The proportions of mice falling off the screen at each dose were recorded, and effective doses (ISD_{50}) were calculated.

TABLE III

1-ARYL-2-IMIDAZOLIDINONES



R	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	60	162–163[b]	A	$C_9H_{10}N_2O$	66.7	66.5	6.2	6.3			17.3	17.5
m-CH_3	60	143–144[c]	A	$C_{10}H_{12}N_2O$	68.2	68.0	6.9	6.8			15.9	15.9
m-CF_3	65	139–140	B	$C_{10}H_9F_3N_2O$	52.2	52.2	3.9	4.0	24.8	25.1	12.2	12.1
m-Br	32	135–136	C	$C_9H_9BrN_2O$	44.8	44.9	3.8	3.8	33.2	33.0	11.6	11.9
o-Cl	56	182–185[d]	C	$C_9H_9ClN_2O$	55.0	55.3	4.6	4.7	18.0	18.4	14.3	14.1
m-Cl	76	124–126[e]	C	$C_9H_9ClN_2O$	55.0	54.6	4.6	4.6	18.0	18.2	14.3	14.0
p-Cl	57	181–183[f]	D	$C_9H_9ClN_2O$	55.0	55.3	4.6	4.9	18.0	18.3	14.3	14.5
m-OCH_3	57	134–135	D	$C_{10}H_{12}N_2O_2$	62.4	62.1	6.3	6.3			14.6	14.6
m-SCH_3	88	140–141	E	$C_{10}H_{12}N_2OS$	57.7	58.2	5.8	6.2			13.5	13.3

[a] A, benzene; B, ether–petroleum ether; C, acetone; D, benzene–hexane; E, ethanol. [b] H. Najer, R. Giudicelli, J. Menin, and C. Morel [*Compt. Rend.*, **253**, 2369 (1961)] report mp 162.5°. [c] Lit.[b] mp 138–139°. [d] Lit.[b] mp 181–182°. [e] Lit.[b] mp 121°. [f] Lit.[b] mp 178–179°.

D. Lethality.—Agents that appeared to specifically inhibit motor activity ($RWD_{50}/MDD_{50} \geq 2$) were administered intraperitoneally to ten mice at a dose of $10 \times MDD_{50}$, and agents that did not significantly reduce motor activity were similarly administered at a dose of $4 \times RWD_{50}$. If more than 50% of the mice died within 24 hr, the compound was rejected for reasons of toxicity or low margin of safety. If $\leq 50\%$ of the mice died, the compound was considered interesting for further study.

Pharmacological Results.—The most interesting compounds as determined by these test procedures are described in Table VII. When judged by reduced locomotor activity, the 1-aminoethyl-3-(*m*-chlorophenyl)-2-imidazolidinones and the corresponding *m*-bromo analogs were the most active compounds in this series and compared favorably with chlorpromazine in activity. The spread between reduced motor activity and ataxia or paralysis was greater for our series than for chlorpromazine. Compounds containing other *meta* substituents including trifluoromethyl were less active, and those containing a *p*-chloro substituent were much less active or inactive and are not included in the table. In regard to the amine function, the pyrrolidino group appeared to impart the most reduced locomotor activity, followed closely by the diethylamino, ethylmethylamino, dimethylamino, and piperidino groups. When the alkylene group was extended to trimethylene, the activity was greatly reduced. The corresponding 2-imidazolidinethione derivatives were less active and were toxic. The 1-aminoalkyl-3-*m*-chlorophenyltetrahydro-2(1H)-pyrimidinones were inactive in this test.

Based on these and other pharmacological tests, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (imidoline), has been selected for study in human subjects.

Experimental Section

General procedures are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in the tables and critical variations in the procedures are noted in the table footnotes. Temperatures are uncorrected.

Alkylenediamine Derivatives (Table I).—A mixture of 1 mole of 2-bromoethylamine hydrobromide, 2 moles of the aniline derivative, and 400 ml of toluene was heated at reflux temperature for 16 hr and cooled. A mixture of 600 ml of water and 200 ml of 50% aqueous KOH was added and the layers were separated. The water layer was saturated with NaCl and extracted twice with benzene. The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and distilled.

(2-Anilinoethyl)urea Derivatives (Table II).—One mole of KCNO was added to a solution of 1 mole of the diamine in 400 ml of 2.5 *N* HCl, and the mixture was heated at reflux temperature for 4 hr. The reaction mixture was cooled, and the crystalline product was filtered off, washed with cold water, and dried at 60°. The mother liquor was extracted with chloroform for some additional material. The combined product was further purified by recrystallization from a suitable solvent.

1-Aryl-2-imidazolidinones (Table III).—The (2-anilinoethyl)urea derivative was placed in a flask and heated for 5 hr in a Wood's metal bath at 215–225°. The flask was cooled and the product was recrystallized from a suitable solvent.

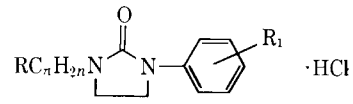
1-(*m*-Chlorophenyl)-2-imidazolidinone was also prepared directly from N-(*m*-chlorophenyl)ethylenediamine. A solution of 5.6 g (0.033 mole) of 95% N,N'-carbonyldiimidazole in 50 ml of tetrahydrofuran (THF) was added to a solution of 6.4 g (0.03 mole) of N-(*m*-chlorophenyl)ethylenediamine in 30 ml of benzene. The clear solution was allowed to stand at room temperature for 18 hr and was then heated for 2 hr at reflux temperature. The solvent was evaporated off, and the crystalline residue was warmed with 50 ml of water, filtered, washed with water, and dried. The product (5.9 g) was recrystallized from benzene and hexane. The yield of 1-(*m*-chlorophenyl)-2-imidazolidinone, mp 124–126°, was 4.9 g (83%).

1-Aminoalkyl-3-aryl-2-imidazolidinones (Table IV). Procedure A. By Alkylation of the 1-Aryl-2-imidazolidinone. The 1-aryl-2-imidazolidinone (0.3 mole) was dissolved in about 400 ml of diglyme (dry purified) and added dropwise to a mixture of 17.3 g (0.36 mole) of 50% NaH (in mineral oil) and 400 ml of diglyme. The reaction mixture was stirred for about 1 hr longer, and 0.38 mole of the aminoalkyl chloride dissolved in ether or diglyme was added. The mixture was stirred at room temperature for 2 hr and then heated at reflux temperature (ether was boiled off) for 5 hr. The salt was filtered off, and the mother liquor was concentrated to remove most of the diglyme. The residue was treated with a mixture of 76 ml of 5 *N* aqueous HCl and 100 ml of water, and the mineral oil and uncharged starting material were extracted into ether or benzene. The aqueous layer was made alkaline by the addition of 76 ml of 5 *N* NaOH, and the desired product was extracted into ether. The hydrochloride salt was obtained when ethanolic HCl was added to the ether solution.

Procedure B. By Dehalogenation of the Corresponding Chloro Derivative.—A mixture of 0.05 mole of the 1-aminoalkyl-3-(*m*-chlorophenyl)-2-imidazolidinone, 1.0 g of 10% Pd-C catalyst, and 150 ml of 95% ethanol was shaken in a Parr hydrogenator under about 3.05 kg/cm² of hydrogen pressure until reduction was complete. The catalyst was filtered off and the mother liquor was concentrated to remove the solvent. The residue was recrystallized from a suitable solvent.

Table IV

1-Aminoalkyl-3-aryl-2-imidazolidinones

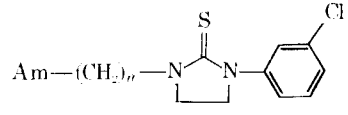


R	n	R_1	Yield, %	Procedure	Mp, °C	Recrystn solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found
Methylamino	2	H	80	B	221–223	A	$C_{12}H_{18}ClN_3O$	56.4	56.0	7.1	7.2	13.9	14.0	16.4	16.3
Dimethylamino	2	H	52	B	191–193	B	$C_{13}H_{20}ClN_3O$	57.9	57.9	7.5	7.8	13.1	13.3	15.6	15.3
Dimethylamino	2	*m*-CH_3	9	A	214–215	A	$C_{14}H_{22}ClN_3O$	59.3	59.1	7.8	8.1	12.5	12.4	14.8	14.6
Dimethylamino	2	*m*-CF_3	69	A	168–170	B	$C_{14}H_{19}ClF_3N_3O$[b]	49.8	49.9	5.6	6.1	10.5	10.6	12.4	12.6
Dimethylamino	2	*m*-Br	60	A	227–229	A	$C_{13}H_{19}BrClN_3O$[c]	44.8	45.2	5.5	5.6	10.2	10.3	12.1	12.1
Dimethylamino	2	*o*-Cl	62	A	197–199	A	$C_{13}H_{19}Cl_2N_3O$	51.3	51.7	6.3	6.5	23.3	23.1	13.8	14.0
Dimethylamino	2	*m*-Cl	79	A	217–219	A	$C_{13}H_{19}Cl_2N_3O$	51.3	51.5	6.3	6.2	23.3	23.4	13.8	14.0
Dimethylamino	2	*p*-Cl	46	A	211–212	A	$C_{13}H_{19}Cl_2N_3O$	51.3	51.0	6.3	6.3	23.3	23.2	13.8	13.8
Dimethylamino	2	*m*-OCH_3	32	A	220–222	A	$C_{14}H_{22}ClN_3O_2$	56.1	56.5	7.4	7.3	11.8	11.9	14.0	13.8
Dimethylamino	2	*m*-OH	41	D	200–203	A	$C_{13}H_{20}ClN_3O_2$	54.6	54.5	7.1	7.0	12.4	11.8	14.7	14.2
Dimethylamino	2	*m*-SCH_3	70	A	148–150	B	$C_{14}H_{22}ClN_3OS$[d]	53.2	52.4	7.0	7.3	11.2	11.3	13.3	13.1
Dimethylamino	3	H	56	B	186–187	B	$C_{14}H_{22}ClN_3O$	59.3	59.2	7.8	7.9	12.5	12.5	14.8	14.9
Dimethylamino	3	*m*-CH_3	57	A	164–165	A	$C_{15}H_{24}ClN_3O$	60.5	59.9	8.1	8.1	11.9	12.1	14.1	14.2
Dimethylamino	3	*m*-CF_3	47	A	155–157	B	$C_{15}H_{21}ClF_3N_3O$[e]	51.2	50.8	6.0	6.3	10.1	10.1	11.6	11.8
Dimethylamino	3	*m*-Br	53	A	168–169	B	$C_{14}H_{22}BrClN_3O_{1.5}$[f]	45.2	45.2	6.0	6.2	9.5	10.0	11.3	11.1
Dimethylamino	3	*m*-Cl	87	A	175–177	C	$C_{14}H_{21}Cl_2N_3O$	52.8	52.7	6.7	7.0	22.3	22.6	13.2	13.4
Dimethylamino	3	*p*-Cl	48	A	177–178	A	$C_{14}H_{21}Cl_2N_3O$	52.8	53.3	6.7	7.1	22.3	22.0	13.2	13.2
Dimethylamino	3	*m*-SCH_3	58	A	144–146	A	$C_{15}H_{24}ClN_3OS$[g]	54.6	54.8	7.3	7.4	10.8	10.6	12.7	12.9
Ethylmethylamino	2	H	45	B	163–164	C	$C_{14}H_{22}ClN_3O$	59.3	59.3	7.8	7.8	12.5	12.8	14.8	14.8
Ethylmethylamino	2	*m*-Cl	48	A	172–174	A	$C_{14}H_{21}Cl_2N_3O$	52.8	52.9	6.7	6.8	22.3	22.7	13.2	13.2
Ethylmethylamino	2	*m*-Br	65	A	186–188	A	$C_{14}H_{21}BrClN_3O$[h]	46.4	46.5	5.8	5.8	9.8	9.7	11.6	11.5
Diethylamino	2	H	74	B	149–151	D	$C_{15}H_{24}ClN_3O$	60.5	60.3	8.1	8.2	11.9	11.8	14.1	14.0
Diethylamino	2	*m*-Cl	79	A	144–145	A	$C_{15}H_{23}Cl_2N_3O$[i]	54.2	53.9	7.0	7.0	21.3	21.5	12.7	12.6
Diethylamino	2	*m*-Br	64	A	140–142	A	$C_{15}H_{23}BrClN_3O$[i]	47.8	47.1	6.1	6.2	9.4	9.3	11.2	11.1
Benzylmethylamino	2	*m*-Cl	51	A	188–190	B	$C_{19}H_{23}Cl_2N_3O$	60.0	59.9	6.1	6.2	18.6	18.8	11.1	11.1
Pyrrolidinyl	2	H	75	B	220–221	A	$C_{15}H_{22}ClN_3O$	60.9	60.8	7.5	7.6	12.0	12.4	14.2	14.1
Pyrrolidinyl	2	*m*-Cl	64	A	191–192	A	$C_{15}H_{21}Cl_2N_3O$	54.6	54.7	6.4	6.7	21.5	21.8	12.7	12.7
Pyrrolidinyl	2	*m*-Br	69	A	199–200	A	$C_{15}H_{21}BrClN_3O$[i]	48.1	48.1	5.7	5.6	9.5	9.3	11.2	11.2
Piperidino	2	H	13	A	219–220	B	$C_{16}H_{24}ClN_3O$	62.0	61.0	7.8	8.0	11.4	11.5	13.6	13.9
Piperidino	2	*m*-Cl	21	A	212–214	A	$C_{16}H_{23}Cl_2N_3O$	55.8	55.8	6.7	6.8	20.6	20.5	12.1	12.1
Morpholino	2	*m*-Cl	49	A	219–221	A	$C_{15}H_{21}Cl_2N_3O_2$	52.0	51.9	6.1	6.2	20.5	20.2	12.1	11.9
Methylpiperazinyl	3	H	54	A	278–280	E	$C_{17}H_{28}Cl_2N_4O$[k]	54.4	54.1	7.5	7.4	18.9	18.9	14.9	14.9
Methylpiperazinyl	3	*m*-Cl	70	A	277–278	E	$C_{17}H_{27}Cl_3N_4O$	49.8	49.6	6.6	6.6	26.0	25.9	13.7	13.5

[a] A, ethanol; B, ethanol-ether; C, acetone; D, acetone-ether; E, methanol. [b] *Anal.* Calcd: F, 16.9. Found: F, 16.6. [c] *Anal.* Calcd: Br, 22.5. Found: Br, 22.7. [d] *Anal.* Calcd: S, 10.2. Found: S, 10.2. [e] *Anal.* Calcd: F, 16.2. Found: F, 15.5. [f] Hemihydrate. *Anal.* Calcd: Br, 21.5. Found: Br, 21.7. [g] *Anal.* Calcd: S, 9.7. Found: S, 9.7. [h] *Anal.* Calcd: Br, 22.0. Found: Br, 22.0. [i] *Anal.* Calcd: Br, 21.2. Found: Br, 21.3. [j] *Anal.* Calcd: Br, 21.3. Found: Br, 21.4. [k] Dihydrochloride.

TABLE V

1-(*m*-CHLOROPHENYL)-2-IMIDAZOLIDINETHIONE DERIVATIVES

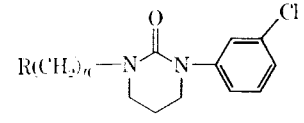


Am	*n*	Yield, %	Salt	Mp, °C	Recrystn solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found
Dimethylamino	2	48	Base	57–59		$C_{13}H_{18}ClN_3S$	55.0	55.4	6.4	6.2	12.5	12.5	14.8	14.9	11.3	11.4
			Hydrochloride	177–179	A	$C_{13}H_{19}Cl_2N_3S$	48.7	48.8	6.0	6.1	22.1	21.8	13.1	13.3	10.0	10.0
Diethylamino	2	60	Base	Oil		$C_{15}H_{22}ClN_3S$	57.8	57.5	7.1	7.3	11.4	11.7	13.5	13.6	10.3	10.3
			Tartrate	135–136	B	$C_{19}H_{28}ClN_3O_6S$	49.4	49.5	6.7	6.7	7.7	7.7	9.1	9.2	6.9	7.1
Pyrrolidinyl	2	58	Base	78–79	C	$C_{15}H_{20}ClN_3S$	58.1	58.4	6.5	6.5	11.6	11.6	13.6	13.7	10.3	10.6
			Hydrochloride	180–182	A	$C_{15}H_{21}Cl_2N_3S$	52.0	51.9	6.1	6.3	20.5	20.2	12.1	11.8	9.3	9.3
Dimethylamino	3	50	Base	Oil		$C_{14}H_{20}ClN_3S$	56.4	56.0	6.8	6.8	11.9	11.9	14.1	14.4	10.8	10.9
			Hydrochloride	210–212	B	$C_{14}H_{21}Cl_2N_3S$	50.3	50.6	6.4	6.3	21.3	21.3	12.3	12.6	9.8	9.8

[a] A, ethanol–ether; B, ethanol; C, ethyl acetate.

TABLE VI

TETRAHYDRO-2-PYRIMIDINONE DERIVATIVES

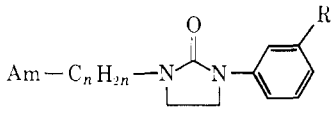


R	*n*	Yield, %	Salt	Mp, °C	Recrystn solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
H	0	61[b]		188–190	A	$C_{10}H_{11}ClN_2O$	57.0	56.7	5.3	5.4	16.8	16.9	13.3	13.2
Dimethylamino	2	32[c]	HCl	190–192	B	$C_{14}H_{23}Cl_2N_3O$	52.8	52.5	6.3	6.7	22.3	22.3	13.2	13.0
Ethylmethylamino	2	47[c]	HCl	149–151	C	$C_{15}H_{25}Cl_2N_3O$	54.2	54.0	7.0	6.9	21.3	21.4	12.6	12.6
Pyrrolidinyl	2	36[c]		Oil		$C_{16}H_{23}ClN_3O$	62.4	62.0	7.2	7.4	11.5	11.9	13.7	13.4

[a] A, ethanol; B, ethanol–ether; C, acetone–ether. [b] Over-all yield from N-(*m*-chlorophenyl)-1,3-propanediamine (Table I). [c] By alkylation of the first compound.

Table VII

CNS Testing Results[a]



Am	n	R	MDD_{50},[b] mg/kg	RWD_{50},[c] mg/kg	ISD_{50},[d] mg/kg
Pyrrolidinyl	2	Br	0.8	22	
	2	Cl	1.0	35	89
	2	H	2.5	49	130
Diethylamino	2	Br	1.3	22	
	2	Cl	1.4	12	45
Ethylmethylamino	2	Cl	1.2	44	100
	2	H	2.0	30	90
	2	Br	2.4	54	
Dimethylamino	2	Cl	2.5	60	100
	2	Br	4.0	60	135
	2	SCH_3	6.0	62	138
	2	OCH_3	6.0	100	165
	2	CH_3	9.0	104	
	2	OH	22.0	274	280
	2	H	34.0	25	172
	3	Br	25.0	75	150
	3	Cl	45.0	49	158
Piperidino	2	Cl	4.0	21	38
	2	H	16.0	81	100
Morpholino	2	Cl	24.0	138	120
Chlorpromazine			2.0	6	10

[a] The ratio between CNS depression and lethality was favorable for all of these compounds. All doses were administered intraperitoneally. [b] The dose estimated to reduce motor activity in mice to 50% of controls. [c] The dose estimated to cause 50% of the mice to be incapable of walking across a horizontal rod in a normal manner. [d] The dose estimated to cause 50% of the mice to fall off a screen inclined at 60°.

Procedure C. By Reaction of 1-(*m*-Chlorophenyl)-7,7-dimethyldiethylenetriamine with N,N′-Carbonyldiimidazole.—A mixture of 31.5 g of 2-(*m*-chloroanilino)ethyl bromide hydrobromide, 24.6 g of N,N-dimethylethylenediamine and 100 ml of toluene (exothermic) was heated on the steam bath for 20 hr. The reaction mixture was treated with 100 ml of 3 *N* NaOH and the layers were separated. The organic layer was washed with water and distilled. The yield of 1-(*m*-chlorophenyl)-7,7-dimethyldiethylenetriamine, bp 130–135° (0.03 mm), was 13.6 g (56%). This product contained a little 2-(*m*-chloroanilino)ethanol and was further purified by conversion to the dihydrochloride, mp 167–169°.

Anal. Calcd for $C_{12}H_{22}Cl_3N_3$: C, 45.8; H, 7.5; Cl, 33.8; N, 13.4. Found: C, 45.8; H, 7.2; Cl, 33.9; N, 13.5.

A solution of 2.1 g (0.01 mole) of 77% N,N′-carbonyldiimidazole in 25 ml of dry THF was added to a solution of 2.42 g (0.01 mole) of 1-(*m*-chlorophenyl)-7,7-dimethyldiethylenetriamine, prepared from the above dihydrochloride, in 10 ml of benzene. The mixture was allowed to stand at room temperature for 2 hr and was then heated at reflux temperature for 2 hr. The solvent was distilled and the residue was triturated with 20 ml of water and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated to an oil, 2.3 g. The oil was redissolved in ether and 5.6 ml of 1.6 *N* ethanolic HCl was added. The product was filtered off and recrystallized twice from ethanol. The yield of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride, mp 215–218°, was 1.4 g (53%).

Procedure D. 1-(2-Dimethylaminoethyl)-3-(*m*-hydroxyphenyl)-2-imidazolidinone Hydrochloride.—A mixture of 1.0 g of 1-(2-dimethylaminoethyl)-3-(*m*-methoxyphenyl)-2-imidazolidinone hydrochloride, 20 ml of 48% HBr, and 20 ml of acetic acid was heated at reflux temperature for 72 hr and then diluted with 75 ml of water. Potassium carbonate was added to pH 8, and the reaction mixture was extracted with chloroform. The chloroform layer was dried ($MgSO_4$) and concentrated to remove the solvent. The oil that remained was dissolved in ethanol, and 2.2 ml of 1.8 *N* ethanolic HCl and ether were added. The precipitate was filtered off and recrystallized from ethanol.

1-(*m*-Chlorophenyl)-2-imidazolidinethione Derivatives (Table V).—A mixture of 25 g of the 1-(aminoalkyl)-3-(*m*-chlorophenyl)-2-imidazolidinone hydrochloride, 100 ml of xylene, and 100 ml of benzene was heated in an oil bath until most of the benzene was distilled off, and 25 g of P_2S_5 was added. The bath temperature was held at 155–160° for 28 hr. The reaction mixture was cooled to about 60°, and 350 ml of 2 *N* NaOH and 200 ml of benzene were added. The mixture was heated until the glassy lower layer dissolved and the organic layer was separated. The aqueous layer was extracted with benzene and then discarded. The combined organic layers were washed twice with water and then extracted with 250 ml of 1 *N* HCl. The acid layer was extracted once with ether and then made alkaline by the addition of 60 ml of 5 *N* NaOH. The product was extracted into ether, and the ether layer was dried ($MgSO_4$) and then concentrated. Salts were prepared by addition of the appropriate acid to a solution of the base in ether or ethanol.

Tetrahydro-2(1H)-pyrimidinone Derivatives (Table VI).—The 1-aminoalkyl-3-(*m*-chlorophenyl)tetrahydro-2(1H)-pyrimidinones were prepared from 3-bromopropylamine hydrobromide, *m*-chloroaniline, and the appropriate aminoalkyl halide by a three-step process similar to that used in the preparation of the 2-imidazolidinones. Yields in the first step were lower than in the 2-imidazolidinone series and products were more difficult to purify. Properties of the intermediates and final products are given in the tables.

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