was chromatographed in C_6H_6 on 100 g of acid-washed alumina. Elution with C_6H_6 gave 14 g of oil which was crystallized by the addition of 150 ml of hexane. Recrystallization (C_6H_6–petroleum ether) gave 6.0 g (32%) of **33**, mp 110–111°. *Anal.* ($C_{18}H_{16}ClNO_2$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole (26).—A mixture of 1.16 g (3.7 mmoles) of **33**, 10 ml of diethylene glycol, 1.0 ml of hydrazine hydrate (85% aqueous), and 0.70 g of KOH was heated to about 160–180° for 2 hr, cooled to 100°, and poured onto ice. The cold mixture was extracted with three portions of ether. The ether extracts were washed (H_2O, dilute HCl, saturated NaCl) and concentrated to 1.17 g of residual oil. The oil was chromatographed on 5 g of acid-washed alumina in benzene and gave 1.05 g of oil which, when crystallized from 2 ml of C_6H_6 and 8 ml of petroleum ether, gave 700 mg (63%) of **26**, mp 91–92°. *Anal.* ($C_{18}H_{18}ClNO$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxygramine (34).—By a procedure similar to that used for the synthesis of **14**, 31.3 g (0.104 mole) of **26** was converted into 27.4 g of crude **34**. Recrystallization from 150 ml of hexane gave 18.6 g (50%) of **34**, mp 92–94°. *Anal.* ($C_{21}H_{25}ClNO$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole-3-acetonitrile (35).—By the procedure used for the synthesis of **16**, 15.7 g (44 mmoles) of **34** was converted with MeI to the methiodide which when treated with KCN gave 9.7 g of crude **35** along with 7.8 g of recovered starting methiodide. Chromatography of the crude product on alumina in benzene followed by crystallization from C_6H_6–petroleum ether gave 3.9 g (52% based on starting methiodide not recovered) of **35**, mp 108–110°. *Anal.* ($C_{20}H_{19}ClN_2O$) C, H, Cl.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole-3-acetic Acid (6).—By hydrolysis with hot aqueous–ethanolic KOH, 3.9 g of **35** was converted into 3.9 g of crude **6**. Recrystallization gave 3.3 g of **6**.

Methyl 2-Acetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (37).—To 1 g of methyl 1-*p*-chlorobenzyl-5-methylindole-3-acetate[1] and 0.5 g of fused $ZnCl_2$ was added 10 ml of AcCl and the light yellow mixture was stirred at room temperature for 5 min and poured onto ice. The semisolid obtained was extracted into 100 ml of $CHCl_3$ and washed twice with 10% $KHCO_3$ and several times with water. Concentration of the $CHCl_3$ gave 1 g of solid. Recrystallization from Et_2O (25 ml) gave 0.52 g (45%) of **37**, mp 125–128°. *Anal.* ($C_{21}H_{20}ClNO_3$) C, H, Cl, N.

2-Acetyl-1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid (8).—Three grams of **37** was hydrolyzed in hot aqueous–ethanolic KOH. Recrystallization of the crude product gave 1.2 g of **8**.

Methyl 2-Chloroacetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (38).—Methyl 1-*p*-chlorobenzyl-5-methylindole-3-acetate[1] (1 g) dissolved in 10 ml of chloroacetyl chloride was refluxed for 5 hr with stirring. The dark brown solution was poured onto ice, and an oil separated. The aqueous mixture was extracted twice with $CHCl_3$, and the combined $CHCl_3$ extracts were washed (H_2O) until neutral and dried ($MgSO_4$). The solvent was removed and the residual oil solidified after the addition of a few drops of petroleum ether. The solid was recrystallized from Et_2O–petroleum ether and 0.4 g (33%) of **38**, mp 110–112°, was obtained. *Anal.* ($C_{21}H_{19}Cl_2NO_3$) C, H, Cl, N.

2-Chloroacetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetic Acid (9).—To a suspension of 300 mg of **38** in 3 ml of glacial AcOH was added 0.2 ml of concentrated HCl and the mixture was refluxed for 11 hr. The solvent was removed and the residue was dissolved in ether and washed (H_2O) until neutral. Concentration of the dried ether solution gave a residue (280 mg) of product. Recrystallization left 105 mg of **9**.

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Synthesis and Biological Activity of Some 3-Substituted Amino-1-carbamoyl- and -thiocarbamoylpyrrolidines

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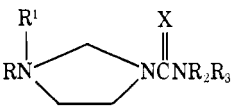
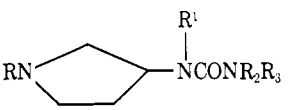
This paper describes the synthesis and pharmacological properties of a series of 3-amino-1-carbamoyl- and -thiocarbamoylpyrrolidines (I). These compounds are structurally related to the 1-substituted 3-pyrrolidinylureas (II), some of which show CNS depressant activity.[1]



I, X = O, S



II

Chemistry.—The carbamoyl- and thiocarbamoylpyrrolidines (Table I) were prepared by the reaction of the 3-substituted aminopyrrolidines with (1) alkyl or aryl isocyanates, (2) potassium cyanate, (3) substituted carbamoyl chlorides, or (4) alkyl or aryl isothiocyanates. The general procedure for the preparation of the intermediate 3-aminopyrrolidines has been reported.[2] The preparation of compounds not previously described is given in the Experimental Section.

Pharmacology.—These carbamoylpyrrolidines, when tested in the general behaviorial screen in mice,[3] showed mainly CNS depression. Several compounds showed activity in the fighting mice test.[4] Compounds **5**, **8**, **11**, **19**–**21** blocked the aggressive behavior of at least two of the five mice tested at a dose of 20 mg/kg ip. The acute intraperitoneal LD_{50} estimates (mouse) of these compounds ranged from 500 to 1800 mg/kg.

Three compounds (**8**, **20**, **21**) also suppressed the toxic effect of amphetamine in aggregated mice[5] at a dose of 10 mg/kg ip and in the anesthetized dog produced a transient lowering of the blood pressure. None of these compounds was effective in protecting against thiosemicarbazide-induced convulsions in mice.[6]

Experimental Section

General procedures, in most instances, are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in Table I and significant variations in the procedure are noted in the table footnotes. Temperatures are uncorrected. Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.

3-Amino-1-carbamoylpyrrolidines. Procedure 1. By Reaction of 3-Aminopyrrolidine and Alkyl or Aryl Isocyanates.—

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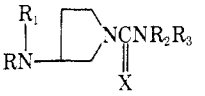
TABLE I

1-CARBAMOYL- AND 1-THIOCARBAMOYLPYRROLIDINES



No.	R	R_1	R_2	R_3	X	Prepn method[a]	% yield	Mp, °C	Purifien[b] solvent	Formula	Analyses
1	C_6H_5	H	H	H	O	2	57	133–135	W	$C_{11}H_{15}N_3O$	C, H, N
2	C_6H_5	CH_3	H	H	O	2	62	130–132	B–O	$C_{12}H_{17}N_3O$	C, H, N
3	C_6H_5	CH_3	CH_3	H	O	1	97	126–128	B–O	$C_{13}H_{19}N_3O$	C, H, N
4	C_6H_5	CH_3	C_2H_5	H	S	4	82	82–84	B–E	$C_{14}H_{21}N_3S$	C, H, N
5	C_6H_5	CH_3	*m*-C_4H_9	H	S	4	68	176–178	I	$C_{16}H_{26}ClN_3S$[d]	C, H, N
6	C_6H_5	H	C_2H_5	C_2H_5	O	3	84	102–104	O	$C_{15}H_{23}N_3O$	C, H, N
7	C_6H_5	CH_3	C_2H_5	C_2H_5	O	3	81	154–160	I–E	$C_{16}H_{27}Cl_2N_3O$[c]	C, H, N
8	C_6H_5	CH_3	C_6H_5	H	O	1	81	142–144	B–O	$C_{18}H_{21}N_3O$	C, H, N
9	C_6H_5	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	O	1	89	176–178	I–E	$C_{21}H_{28}ClN_3O_4$[d]	H, N; C[e]
10	C_6H_5	CH_3	*p*-$CH_3OC_6H_4$	H	O	1	69	107–109	B–O	$C_{19}H_{23}N_3O_2$	C, H, N
11	C_6H_5	CH_3	*m*-$CF_3C_6H_4$	H	S	4	54	137–138	M–W	$C_{19}H_{20}F_3N_3S$	C, H, N
12	C_2H_5	C_2H_5	*m*-ClC_6H_4	H	O	1	81	187–190	I	$C_{15}H_{23}Cl_2N_3O$[d]	C, H, N
13	C_2H_5	C_2H_5	*m*-$CF_3C_6H_4$	H	O	1	60	212–214	I	$C_{16}H_{23}ClF_3N_3O$[d]	C, H, N
14	C_6H_5	CH_3	C_6H_5	H	S	4	79	61–63	B–O	$C_{18}H_{21}N_3S$	N
15	C_6H_5	CH_3	*m*-$CF_3C_6H_4$	H	O	1	75	196–198	B–O	$C_{19}H_{21}ClF_3N_3O$[d]	C, H, N
16	C_6H_5	CH_3	C_6H_5	*m*-C_3H_7	O	3	33	132–135	I	$C_{21}H_{28}ClN_3O$[d]	C, H, N
17	C_2H_5	C_2H_5	C_6H_5	CH_3	O	3	59	162–164	I–E	$C_{16}H_{26}ClN_3O$	C, H, N
18	C_2H_5	C_2H_5	C_6H_5	C_6H_5	O	3	40	137–140	I	$C_{25}H_{31}N_3O_9$[e]	C, H, N
19	*o*-$CH_3OC_6H_4$	H	C_6H_5	C_6H_5	O	3	77	72–74	B–O	$C_{24}H_{25}N_3O_2$	C, H, N
20	C_6H_5	H	C_6H_5	C_6H_5	O	3	81	125–126	B–O	$C_{24}H_{25}N_3O$	C, H, N
21	C_6H_5	CH_3	C_6H_5	C_6H_5	O	3	85	124–126	B–O	$C_{23}H_{23}N_3O$	C, H, N

[a] See Experimental Section. [b] B = C_6H_6, E = *i*-Pr_2O, I = *i*-PrOH, M = MeOH, W = H_2O, O = isooctane. [c] Dihydrochloride. [d] Hydrochloride. [e] Dioxalate. [f] C: calcd, 59.78; found, 59.16.

To a stirred solution of 0.1 mole of the 3-aminopyrrolidine in 100 ml of dry C_6H_6 at room temperature was added slowly 0.1 mole of the alkyl or aryl isocyanate in 20 ml of dry C_6H_6. After the addition was complete, the mixture was stirred for several minutes and the solvent was evaporated at reduced pressure. Crude products were purified by recrystallization.

Procedure 2. By Reaction of 3-Aminopyrrolidine and Potassium Cyanate.—A solution of 0.03 mole of 3-substituted aminopyrrolidine in 31 ml of 1 *N* HCl was treated all at once with 0.03 mole of KNCO in 5 ml of H_2O. The mixture was stirred for 4–16 hr at room temperature, then the resulting precipitate was separated by filtration, washed (H_2O), and purified by recrystallization.

Procedure 3. By Reaction of 3-Aminopyrrolidine and Substituted Carbamoyl Chlorides.—A solution of 0.045 mole of the 3-substituted aminopyrrolidine in 50 ml of $CHCl_3$ was added to a solution of 10 g of K_2CO_3 in 50 ml of H_2O. The stirred mixture was then treated dropwise with 0.045 mole of the substituted carbamoyl chloride in 50 ml of $CHCl_3$ and stirring was continued for 1–16 hr. The $CHCl_3$ layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by recrystallization.

3-Amino-1-thiocarbamoylpyrrolidines. Procedure 4. By Reaction of Alkyl or Aryl Isothiocyanate and 3-Substituted Aminopyrrolidine.—The general procedure was essentially the same as procedure 1 except in some cases the reactants were stirred at room temperature for 2–16 hr or heated at reflux for several hours.

1-Benzyl-3-diethylaminopyrrolidine Difumarate.—A mixture of Et_2NH (250 g) and 170 g (0.61 mole) of 1-benzyl-3-pyrrolidinol benzenesulfonate ester was placed in a bomb and heated at 100° for 16 hr. After the excess amine was evaporated, the residue was treated with 200 ml of 6 *N* HCl and extracted (Et_2O). The acidic layer was made basic and then extracted (Et_2O). The combined extracts were washed (H_2O) and dried ($MgSO_4$) and the solvent evaporated. The residual oil was distilled at reduced pressure and the fraction boiling at 88–90° (0.10 mm) was collected. The nonviscous oil weighed 87.5 g (62% yield).

A portion of the free base (11.7 g, 0.05 mole) was added to a solution of 11.6 g (0.01 mole) of fumaric acid in warm *i*-PrOH. The salt which separated on cooling was recrystallized from *i*-PrOH–EtOH. The white product melted at 159.5–162° and weighed 13.6 g. *Anal.* ($C_{23}H_{32}N_2O_8$) C, H, N.

3-Diethylaminopyrrolidine Dihydrochloride.—A solution of 72 g (0.31 mole) of 1-benzyl-3-diethylaminopyrrolidine, 150 ml of absolute EtOH and 50 ml of 12 *N* HCl was shaken with 8 g of Pd–C catalyst at about 70° until 1 equiv of H_2 was absorbed. After cooling, the suspension was filtered and the solvent was evaporated at reduced pressure. The residual oil was made basic with 50% NaOH and the resulting suspension was filtered. The organic layer was separated, dried (NaOH pellets), and distilled at reduced pressure. The fraction boiling at 82–84° (12 mm) was collected. The water white, nonviscous oil weighed 21.2 g (49% yield). A portion of the free base was converted to the hydrochloride and recrystallized (*i*-PrOH). The white product melted at 181.5–183.5°. *Anal.* ($C_8H_{20}Cl_2N_2$) C, H, N.

S-2-Aminoethyl S′-ω-Carboxyalkyl Dithiocarbonate Hydrochlorides as Potential Antiradiation Agents[1]

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The synthesis of S-2-aminoalkyl S′-ω-carboxyalkyl dithiocarbonate hydrochlorides (V) was undertaken as an extension of previous modifications of the radioprotective agent 2-aminoethanethiol in which the mercapto group is combined in dithiocarbonate esters.[2] Two of the previously prepared dithiocarbonates (I and II)[2a] afforded "fair" protection to mice exposed

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

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