Figure 1.—Blood levels of a dog that received an oral dose of 4.4 mg of brompheniramine-¹⁴C

If the ketone VII were formed, ¹⁴CO₂ should appear in the expired air. In order to investigate this possibility, a dog was administered an oral dose of brompheniramine-¹⁴C (I) and placed in a cage[4] so that expired CO₂ could be collected and counted for a 24-hr period. No radioactivity could be detected. Since both carbons of the ethyl chain are labeled with ¹⁴C, extensive metabolism of this portion of the moelcule does not appear to occur.

Blood levels and excretion were studied in a dog that received an oral dose of 4.4 mg of brompheniramine-¹⁴C (I). Samples were analyzed for radioactivity and by the chemical method. These results are shown in Table V and in Figure 1. The larger dose (7 mg/kg) was not administered in this case because it would have necessitated a large dilution of the samples for the chemical method of analysis. The total urinary excre-

(4) R. B. Bruce and J. H. Newman, *Intern. J. Appl. Radiation Isotopes*, in press.

TABLE V

EXCRETION OF BROMPHENIRAMINE MALEATE AND ITS METABOLITES IN THE URINE AND FECES OF A DOG FOLLOWING THE ADMINISTRATION OF 4.4 mg ORALLY

| | mg of brompheniramine maleate excreted | | |
| | Urine | | Feces |
Time after dosing, hr	Chemical method	Radioisotope method	Radioisotope method
0-24	0.492	0.667	0.026
24-48	0.409	0.608	0.011
48-72	0.286	0.388	0.456
72-144	0.445	0.668	0.259

tion in this dog agrees well with that found from the dog receiving the larger dose. In the case of the lower dose, 53% was excreted in the urine and 17% in the feces. The urine value also agrees with those found for humans.

The ratio of the results found for the excretion by the isotope method and chemical method is of interest. The chemical method determines only basic compounds, whereas the isotope method determines any compound that has the radioactive carbon present. Brompheniramine and its metabolites are slowly excreted over a long period and one would expect the ratio of the isotope to the chemical method to increase with time. However, this is not the case. The ratio remains constant for the 144-hr period. This would seem to indicate that the drug is readily absorbed into the tissues and is then slowly released to be metabolized and excreted. The blood levels (Figure 1) confirm this. Following an equilibration period, the curves remain almost parallel for the 144 hr. It is likely that the amine being slowly released by the tissues is not unchanged brompheniramine but one of its basic metabolites (II or III) since the half-life of the total basic compounds in the human is approximately twice that of unchanged brompheniramine (unpublished results).

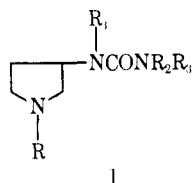# Synthesis and Biological Activity of Some 1-Substituted 3-Pyrrolidinylureas

GROVER C. HELSLEY, BERNARD V. FRANKO, WILLIAM J. WELSTEAD, AND CARL D. LUNSFORD

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A series of 1-substituted 3-pyrrolidinylureas was synthesized and evaluated for pharmacologic activity. Some of the activities observed were CNS depressant, antiarrhythmic, local anesthetic, and hypoglycemic.

It has been reported that alkyl, aryl, or aralkyl derivatives of urea possess anticonvulsant, hypnotic, sedative, and depressant activity.[1] This paper describes the synthesis and pharmacological properties of a series of 1-substituted 3-pyrrolidinylureas (I).

R₁
|
N-CONR₂R₃
|
N
|
R

I

Chemistry.—The general synthetic scheme utilized in preparing the urea derivatives is illustrated in Chart I.

The 3-aminopyrrolidines (II) were prepared by the reaction of the 3-chloropyrrolidines[2] with potassium phthalimide in dimethyl sulfoxide[3] and subsequent treatment of the resulting 3-phthalimidopyrrolidine (Table I) with hydrazine, or by the nucleophilic displacement of the tosylate of a 3-pyrrolidinol. The latter method of preparing 1-substituted 3-aminopyrrolidines has been reported.[4] The properties of the

(1) For references on this activity refer to P. Aeberli, J. Gogerty, and W. J. Houlihan, *J. Med. Chem.*, **10**, 636 (1967).

(2) B. V. Franko and C. D. Lunsford, *ibid.*, **2**, 523 (1960).

(3) G. C. Helsley, U. S. Patent 3,316,276 (April 25, 1967).

(4) W. J. Welstead, Jr., J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, Jr., *J. Med. Chem.*, **10**, 1015 (1967).

TABLE I
3-Phthalimidopyrrolidines
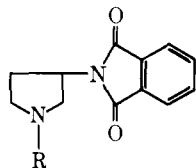
No.	R	% yield	Mp, °C	Recrystn solvent[a]	Formula[b]
1	C_2H_5	58	110–112	O	$C_{14}H_{16}N_2O_2$
2	c-C_6H_{11}	51	113–114	O–B	$C_{18}H_{22}N_2O_2$
3	CH_3	29	94–95.5	O–E	$C_{13}H_{14}N_2O_2$
4	$C_6H_5CH_2$	48	131–132	O–B	$C_{19}H_{18}N_2O_2$
5	i-C_3H_7	51	134–135.5	O–B	$C_{15}H_{18}N_2O_2$
6	C_6H_5	55	153–155	B–P	$C_{18}H_{16}N_2O_2$

[a] O = isooctane, B = C_6H_6, E = i-Pr_2O, P = petroleum ether (bp 60–110). [b] All compounds were analyzed for C, H, N.

were then injected intravenously. In this experimental situation the two 3-phthalimidopyrrolidines tested (1 and 2 in Table I) exhibited antiarrhythmic activity comparable to that of quinidine sulfate. These compounds are cyclic analogs of a group of N-(ω-aminoalkyl)phthalimidines that were reported to have antifibrillant activity.[8]

Testing for local anesthetic activity involved intradermal administration to guinea pigs and rabbits and application of painful stimuli to the skin overlying the injected area. Of the compounds tested only 2 was found to be active. Compounds 1 and 26 were inactive while 4–6 were considered borderline, primarily because of the inconsistency of the results.

Anesthetized dogs and conventional sensing and recording devices were used in a general screening procedure. Experimental compounds were given in

TABLE II
2-Aminopyrrolidines
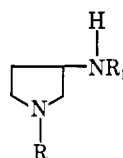
No.	R	R₁	Prepn method[a]	% yield	Mp or bp (mm), °C	Recrystn solvent[b]	Formula[c]
7	i-C_3H_7	H	I	69	199–200.5	I	$C_7H_{15}Cl_2N_2$[d]
8	c-C_6H_{11}	H	I	60	156–157	M–I	$C_{18}H_{28}N_2O_8$[e]
9	$C_6H_5CH_2$	H	I	62	174–175	M–I	$C_{13}H_{20}N_2O_4$[f]
10	C_6H_5	H	I	60	170–172	I–E	$C_{10}H_{15}ClN_2$[g]
11	$C_6H_5CH_2CH_2$	C_6H_5	I	46	173–174 (0.04)		$C_{18}H_{22}N_2$
12	CH_2=$CHCH_2$	C_6H_5	II	58	65–67	O	$C_{13}H_{18}N_2$

[a] See Experimental Section. [b] I = i-PrOH, M = MeOH, E = i-Pr_2O, O = isooctane. [c] All compounds were analyzed for C, H, N. [d] Dihydrochloride. [e] Difumarate. [f] Fumarate. [g] Hydrochloride.

compounds not previously described are given in Table II. In the case of the 1-phenylpyrrolidine compounds the tosylate procedure was necessary since 1-phenyl-3-pyrrolidinol gave only intractable tars when treated with thionyl chloride under the usual reaction conditions.

The substituent on the 1 position of the 3-anilinopyrrolidines was varied by catalytically hydrogenating the 1-benzyl-3-anilinopyrrolidine to the corresponding secondary amine[4] and alkylating with an appropriate alkyl halide.

The various substituted ureas described in Table III were prepared (Chart I) by the reaction of the 3-aminopyrrolidine with (1) alkyl or aryl isocyanates, (2) carbamoyl chlorides, (3) nitrourea,[5] (4) potassium cyanate, or (5) p-toluenesulfonyl carbamide.[6]

Pharmacologic Studies.—Most of the compounds described in this paper (Tables I–III) were included in at least one of a battery of pharmacologic tests. The more noteworthy findings are summarized below.

Antiarrhythmic activity was investigated using a method described by Winbury, et al.[7] Cardiac arrhythmias were produced in two ways: (a) an area in the region of the sinoatrial node was crushed and then stimulated electrically, and (b) aconitine was injected into the wall of the right atrium. Test materials

increasing intravenous doses, usually until lethality was reached. In this experimental situation 9, 10, 12, and 42 elevated and 1–3, 7, 17, 26, 39, 43, 46, and 53 lowered arterial blood pressure. These changes were never marked and they persisted only with 12. Compounds 1, 2 (low doses), and 10 caused tachycardia, an effect of long duration with the last compound; the opposite effect was produced by 2 (other than low doses), 3, 43, 46, and 53. Respiratory effort was enhanced by two compounds (9, 12) that elevated blood pressure. Compounds 6, 58, and 59 were essentially without pharmacologic action in these experiments. When administered in doses below the lethal range, no compound caused meaningful changes in venous blood pressure, the pattern of the electrocardiogram, activity of the small intestine, urine flow, or autonomic nervous system function.

Effects on the central nervous system were investigated in mice that were observed for gross changes in behavior following intraperitoneal administration of test compounds. Evidence of CNS depression was seen with 14, 18, 19, 24–28, 31, 33, 43, and 58; 15, 22, 23, and 29 had the opposite effect. The results with 30 suggested skeletal muscle relaxant activity.
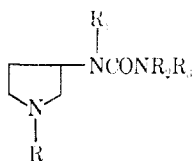
Acute intraperitoneal LD_{50} estimates (mouse) encompassed a wide range with the compounds investigated. Compounds 20, 21, 23, 28, and 50 were among

(5) J. S. Buck and C. W. Ferry, J. Am. Chem. Soc., 58, 854 (1936).
(6) E. Haack and R. Jacob, East German Patent 9,688 (April 21, 1955).
(7) M. M. Winbury, M. L. Hemmer, and D. Calhoun, Acta Physiol. Pharmacol. Neerl., 5, 468 (1957).
(8) K. Hideg and H. O. Hankovszky, J. Med. Chem., 8, 257 (1965).

TABLE III

3-UREIDOPYRROLIDINES

No.	R	R₁	R₂	R₃	Prepn method[a]	%, yield	Mp or bp (mm), °C	Recrystn solvent[b]	Formula[c]
13	CH₃	H	H	H	V	35	154–156	EA	C₆H₁₃N₃O
14	C₂H₅	H	H	H	V	53	129–130	EA–E	C₇H₁₅N₃O
15	c-C₆H₁₁	H	H	H	V	49	176–177	I–E	C₁₁H₂₁N₃O
16	C₆H₅	H	H	H	VI	71	195–197	M–W	C₁₁H₁₅N₃O
17	C₆H₅	CH₃	H	H	VI	36	124–126	N–E	C₁₂H₁₇N₃O
18	C₂H₅	H	p-CH₃OC₆H₄	H	III	82	129–130	B–O	C₁₄H₂₁N₃O₂
19	c-C₆H₁₁	H	p-CH₃OC₆H₄	H	III	85	163–164	B	C₁₈H₂₅N₃O₂
20	c-C₆H₁₁	H	i-C₃H₇	H	III	82	151–152	B–O	C₁₄H₂₅N₃O
21	c-C₆H₁₁	H	C₆H₅	C₆H₅	IV	44	185–187	I–M	C₂₃H₂₉N₃O[e]
22	CH₃	H	C₆H₅	C₆H₅	IV	45	105–107	O	C₁₈H₂₁N₃O
23	C₆H₅CH₂	H	p-CH₃OC₆H₄	H	III	91	133–134	B–O	C₁₉H₂₃N₃O₂
24	H	H	p-CH₃OC₆H₄	H	VIII	59	130–132	B	C₁₂H₁₇N₃O₂
25	C₆H₅CH₂	H	C₆H₅	H	III	84	175–176	B–O	C₁₈H₂₁N₃O
26	CH₃	H	p-CH₃OC₆H₄	H	III	88	159–160	B–O	C₁₃H₁₉N₃O₂
27	C₆H₅CH₂	H	C₆H₅	C₆H₅	IV	76	90–92	B–O	C₂₄H₂₅N₃O
28	H	H	C₆H₅	C₆H₅	IV	60	208–209	I–B	C₁₇H₂₀ClN₃O[e]
29	C₆H₅CH₂	H	3,4,5-(CH₃O)₃C₆H₂	H	III	80	112–114	I–B	C₂₁H₂₇N₃O₄
30	H	H	3,4,5-(CH₃O)₃C₆H₂	H	VIII	82	148–150	B	C₁₄H₂₁N₃O₄
31	i-C₃H₇	H	p-CH₃OC₆H₄	H	III	87	143–145	B	C₁₅H₂₃N₃O₂
32	i-C₃H₇	H	C₆H₅	C₆H₅	IV	69	178–179	I–E	C₂₀H₂₅N₃O₂[d]
33	C₆H₅	CH₃	C₆H₅	C₆H₅	IV	52	123–125	O	C₂₄H₂₅N₃O
34	CH₃	H	p-ClC₆H₄	H	III	96	183–184	I–B	C₁₄H₁₆ClN₃O
35	C₆H₅	CH₃	CH₃	H	III	70	149–151	B	C₁₃H₁₉N₃O
36	C₆H₅	CH₃	C₆H₅	H	III	86	176–179	B–O	C₁₈H₂₁N₃O
37	C₆H₅	CH₃	p-CH₃OC₆H₄	H	III	83	165–167	B–O	C₁₉H₂₃N₃O₂
38	C₆H₅	H	p-CH₃OC₆H₄	H	III	92	179–181	B	C₁₈H₂₁N₃O₂
39	C₆H₅	CH₃	C₃H₅	C₃H₅	IV	23	156–158 (0.01)		C₂₆H₂₅N₃O[e]
40	C₆H₅	H	C₆H₅	H	III	89	185–187	B	C₁₇H₁₉N₃O
41	C₆H₅	H	C₆H₅	C₆H₅	IV	87	166–168	B–O	C₂₃H₂₃N₃O
42	C₆H₅	CH₃	m-CF₃C₆H₄	H	III	67	162–164	B	C₁₉H₂₀F₃N₃O
43	H	H	C₆H₅	H	VIII	84	148–149	I–B	C₁₁H₁₅N₃O
44	i-C₃H₇	C₆H₅	C₄H₉	H	III	66	137–139	I–E	C₂₁H₃₃N₃O₂[d]
45	C₂H₅	C₆H₅	C₄H₉	H	III	63	110–112	I–E	C₂₁H₃₁N₃O₂[d]
46	CH₃	C₆H₅	C₆H₅	H	III	72	87–88	E	C₁₈H₂₁N₃O
47	i-C₃H₇	C₆H₅	CH₃	H	III	61	85–87	P	C₁₅H₂₃N₃O
48	i-C₃H₇	C₆H₅	C₆H₅	H	III	71	75–76	E	C₂₀H₂₅N₃O
49	i-C₃H₇	C₆H₅	C₂H₅	H	III	59	134–136	I–E	C₁₆H₂₅N₃O[e]
50	C₆H₅CH₂CH₂	C₆H₅	CH₃	H	III	65	115–117	I–E	C₂₁H₂₅N₃O[d]
51	CH₃	C₆H₅	CH₃	H	III	84	97–99	B–O	C₁₃H₁₉N₃O
52	CH₃	C₆H₅	p-CH₃OC₆H₄	H	III	46	129–131	I	C₁₉H₂₃N₃O₂
53	CH₃	H	3,4,5-(CH₃O)₃C₆H₂	H	III	84	161–163	B–O	C₁₅H₂₃N₃O₄
54	C₆H₅CH₂CH₂	C₆H₅	C₆H₅	H	III	84	130–131	I–E	C₂₆H₂₉N₃O
55	C₃H₅	C₆H₅	C₆H₅	H	III	47	45–48	O–E	C₂₀H₂₃N₃O
56	CH₂=CHCH₂	C₆H₅	C₆H₅	H	III	88	136–138	I–E	C₂₀H₂₃N₃O[e]
57	C₂H₅	H	p-CH₃C₆H₄SO₂	H	VII	96	179–180	M–E	C₁₄H₂₁N₃O₃S
58	c-C₆H₁₁	H	p-CH₃C₆H₄SO₄	H	VII	84	182–183	M–E	C₁₈H₂₇N₃O₃S
59	CH₃	H	p-CH₃C₆H₄SO₂	H	VII	78	192–193	M–W	C₁₃H₁₉N₃O₃S

[a] See Experimental Section. [b] B = C₆H₆, E = i-Pr₂O, I = i-PrOH, EA = EtOAc, M = MeOH, N = MeCN, O = isooctane, W = H₂O. [c] All compounds were analyzed for C, H, N. [d] Fumarate. [e] Hydrochloride. [f] C: calcd, 69.78; found, 68.93. [g] Oxalate.
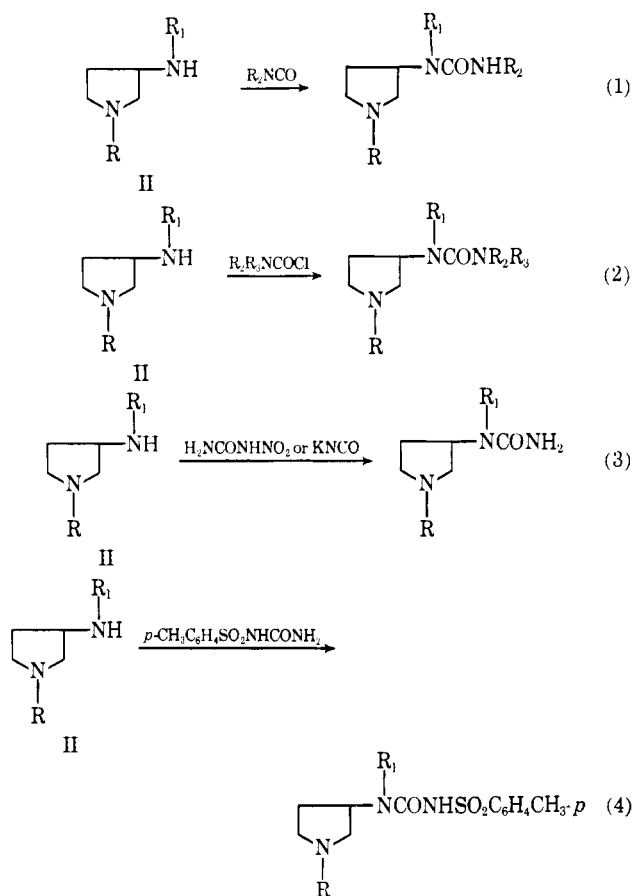
the more toxic (LD₅₀'s < 150 mg/kg) while **33, 57,** and **58** were the least toxic (LD₅₀'s > 1800 mg/kg). Included within these extremes were the LD₅₀'s for **2, 14, 15, 18, 19, 22, 24–27, 29, 30, 31, 43–46, 51, 52,** and **56.**

The toluenesulfonylureas were tested in rats for hypoglycemic activity. Compounds **57** and **58** were about 40% as potent as tolbutamide in lowering blood sugar and **59** showed very little activity.

Experimental Section

Chart I

$$\text{II} \xrightarrow{\text{R}_2\text{NCO}} \text{NCONHR}_2 \quad (1)$$

$$\text{II} \xrightarrow{\text{R}_2\text{R}_3\text{NCOCl}} \text{NCONR}_2\text{R}_3 \quad (2)$$

$$\text{II} \xrightarrow{\text{H}_2\text{NCONHNO}_2 \text{ or KNCO}} \text{NCONH}_2 \quad (3)$$

$$\text{II} \xrightarrow{p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCONH}_2} \text{NCONHSO}_2\text{C}_6\text{H}_4\text{CH}_3\text{-}p \quad (4)$$

3-Phthalimidopyrrolidines (Table I).—A rapidly stirred suspension of 0.80 mole of potassium phthalimide, 0.80 mole of the 3-chloropyrrolidine, and 700 ml of DMSO was heated at 110–113° for 16 hr and filtered while hot to remove the inorganic salt. The crystalline product which usually formed when the filtrate was cooled and treated with H_2O was separated by filtration and recrystallized from the appropriate solvent.

3-Aminopyrrolidines (Table II). Procedure I. By Reaction of 3-Phthalimidopyrrolidines with Hydrazine.—A mixture of 0.10 mole of the phthalimidopyrrolidine, 0.11 mole of 85% hydrazine hydrate, and 100 ml of 95% EtOH was heated at reflux for 2 hr, cooled, and treated with concentrated HCl until the solution was strongly acidic. The voluminous precipitate of phthalhydrazide was filtered off and washed with four 15-ml portions of 95% EtOH. The filtrate was concentrated to 50 ml and 50 ml of H_2O was added to the flask; any insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. After the residue was treated with 50% NaOH, the oil which formed was separated and dried over NaOH pellets.

The free base was fractionally distilled and converted to a solid addition salt.

Procedure II. By Alkylation of 3-Anilinopyrrolidine.—A solution of 0.123 mole of alkyl bromide in 50 ml of absolute EtOH was added dropwise to a stirred mixture of 0.123 mole of 3-anilinopyrrolidine[4] and 30 g of K_2CO_3 in 100 ml of absolute EtOH under N_2. After stirring overnight at room temperature the mixture was treated with 200 ml of H_2O and the resulting suspension was extracted into $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated to an oil. The crude product was purified by distillation or column chromatography.

3-Ureidopyrrolidines (Table III). Procedure III. By Reaction of the 3-Aminopyrrolidine with Alkyl or Aryl Isocyanates.—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 (solid free bases or addition salts) were purified by recrystallization.

Procedure IV. By Reaction of 3-Aminopyrrolidines with Carbamyl Chlorides.—To a stirred suspension of 0.3 mole of Na_2CO_3 in 100 ml $CHCl_3$ were added 0.1 mole of the 3-aminopyrrolidine and 0.1 mole of the carbamyl chloride. The mixture was heated at gentle reflux for 16 hr and then treated with 100 ml of H_2O. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The products in the form of free bases or acid addition salts were purified by recrystallization.

Procedure V. By Reaction of the 3-Aminopyrrolidine with Nitrourea.—A mixture of 0.05 mole of the 3-aminopyrrolidine, 0.06 mole of the nitrourea, and 50 ml of EtOH was heated gently until the evolution of gas ceased (15–20 min) and then the solvent was evaporated at reduced pressure. The product was purified by recrystallization.

Procedure VI. By Reaction of the 3-Aminopyrrolidine with Potassium Cyanate.—A solution of 0.03 mole of the 3-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 hr at room temperature, then the resulting precipitate was filtered, washed (H_2O), and purified by recrystallization.

Procedure VII. By Reaction of the 3-Aminopyrrolidine with p-Toluenesulfonylcarbamide.—A mixture of 0.05 mole of the 3-aminopyrrolidine, 0.05 mole of p-toluenesulfonylcarbamide, and 150 ml of dry dioxane was stirred and heated at reflux for 5 hr. NH_3 was evolved during the first hour of heating and a precipitate began to form. The crystalline product was separated by filtration and purified by recrystallization.

Procedure VIII. By Catalytically Hydrogenating 1-Benzyl-3-pyrrolidinylureas.—A solution of 0.035 mole of the 1-benzyl-3-pyrrolidinylurea in 250 ml of 95% EtOH was reduced catalytically with 5 g of 10% Pd–C. The mixture was heated at ca. 70° and shaken with H_2 until 1 equiv of H_2 was absorbed (about 2 hr). After cooling, the suspension was filtered and the solvent was evaporated. The crude product was purified by recrystallization.