according to Gibson[12] was dissolved in 350 ml of CH_3OH containing 27.6 g of NaOH pellets. The mixture was heated under reflux for 5 hr and then cooled to room temperature. The supernatant liquid was poured off from the residue and brought to pH 7 with 20% HCl solution. After chilling this solution overnight, the light yellow crystals were collected on a filter and washed well with water. This material was recrystallized from ethyl alcohol–water (1:1) to give 16.0 g of white crystalline substance, mp 216–217°.

Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.57; H, 3.64; N, 11.32.

The following compounds were prepared in similar fashion.

1-Hydroxy-2-*p*-methoxyphenylbenzimidazole, mp 189–191°. *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; N, 11.66. Found: C, 70.22; H, 5.12; N, 11.42.

1-Hydroxy-6-nitro-2-phenylbenzimidazole, mp 273° dec. *Anal.* Calcd for $C_{13}H_9N_3O_3$: C, 61.17; H, 3.55; N, 16.46. C, 61.25; H, 3.70; N, 16.43.

6-Chloro-1-hydroxy-2-phenylbenzimidazole, mp 241°. *Anal.* Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.68; H, 3.69; N, 11.38.

General Procedures for Preparation of Compounds in Table I. 1-(2-Diethylaminoethoxy)-2-phenylbenzimidazole Dihydrochloride (8).—1-Hydroxy-2-phenylbenzimidazole (25.0 g, 0.119 mole) was dissolved in 200 ml of dimethylformamide (DMF) containing 50 ml of toluene. Six grams (0.131 mole) of NaH (53% suspension in mineral oil) was added to this solution with vigorous stirring and the mixture was heated at 50° for 30 min. At the end of this time, the solution was cooled to room temperature and then treated with 91 ml of a toluene solution containing 0.177 g of 2-dimethylaminoethyl chloride/ml of solution and the resulting solution was heated at 60° for 3 hr. After cooling the solution to room temperature, 50 ml of ethyl alcohol was added to decompose any unreacted NaH. To this solution there was added 1 l. of ether, and the resulting precipitate was removed. The filtrate was evaporated to a viscous residue *in vacuo*. This was dissolved in a small amount of ethyl alcohol and the solution in turn was treated with saturated ethanolic HCl. After chilling the solution overnight, the copious precipitate was collected on a filter, washed well with ether, and then recrystallized twice from ethyl alcohol–ethyl ether (1:1) to yield 17.5 g of white crystalline product.

1-(2-Dimethylaminoethoxy)-2-phenylbenzimidazole 3-Oxide (16).—A slurry of 3.0 g (0.0132 mole) of 1-hydroxy-2-phenylbenzimidazole 3-oxide in 30 ml of DMF was allowed to react with 0.64 g (0.014 mole) of 53% NaH at steam bath temperature for 15 min. The mixture was then cooled to room temperature and allowed to react with 2.1 g (0.0155 mole) of 2-diethylaminoethyl chloride for 24 hr. The solution was filtered, and the filtrate was evaporated *in vacuo* to an oil to which was then added H_2O. This mixture was extracted well with ether and the ether extract was dried (Na_2SO_4). Removal of the drying salt by filtration and concentration of the ether solution on the steam bath gave a light yellow oil. Ethanolic HCl was added to the oil and the solution was chilled overnight. The resulting precipitate was collected on a filter and recrystallized from ethyl alcohol–ethyl ether (1:1).

1-(2-Diethylaminoethoxy)-2-phenylindole (21).—1-Hydroxy-phenylindole (4.0 g, 0.019 mole) was dissolved in 150 ml of dry pyridine and the solution was then treated with 0.85 g (0.018 mole) of 53% NaH. The mixture was stirred at room temperature for 1 hr, the solution changing in color from light yellow to dark brown. A toluene solution (25 ml) of 2-diethylaminoethyl chloride (100 mg/ml) was added and the solution stirred at room temperature overnight. The reaction mixture was added to 300 ml of H_2O whereupon an oil precipitated from solution. The oil was separated and any excess water and pyridine were removed by heating the oil at 40° *in vacuo* for 4 hr. The oil was dissolved in ether and dried (Na_2SO_4). This salt was then filtered off and the ether solution was evaporated to dryness. Again an oil was obtained from which the maleate salt was prepared in an ethyl alcohol solution. The product was recrystallized from ethyl alcohol–ethyl ether (1:1).

(12) M. S. Gibson, *J. Chem. Soc.*, 1076 (1956).

A Series of Central Nervous System Stimulants Based on the 4-Substituted 3,3-Diphenyl-2-pyrrolidinone Skeleton. II

ALBERT D. CALE, JR., HERNDON JENKINS, BERNARD V. FRANKO, JOHN W. WARD, AND CARL D. LUNSFORD

Research Laboratories, A. H. Robins Company, Inc., Richmond, Virginia

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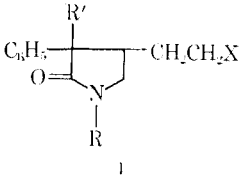
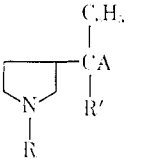
The previously described preparation of 4-(2-substituted ethyl)-3,3-diphenyl-2-pyrrolidinones by a rearrangement of (1-substituted 3-pyrrolidinyl)diphenylacetic acids has been expanded in order to observe structure-activity relationships. Variation of the ring and side-chain substituents has produced compounds of varying biological activity, generally central nervous system stimulants.

Part I[1] of this series described the synthesis of 1-alkyl-4-(2-substituted ethyl)-3,3-diphenyl-2-pyrrolidinones [I, R = lower alkyl, R′ = C_6H_5, X = Cl or Br (subsequently replaced by various basic residues)]. The key



I

intermediate 4-(2-haloethyl) compounds (I, X = Cl or Br, R′ = C_6H_5) were prepared from (1-alkyl-3-pyrrolidinyl)diphenylacetonitriles *via* a rearrangement of the corresponding acid chlorides (IIa → IIb → IIc → I; R = alkyl, R′ = C_6H_5, X = Cl or Br). In general



IIa, A = CN
b, A = COOH
c, A = COCl
d, A = $CONH_2$

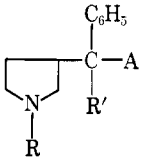
the compounds stimulated the central nervous system. 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone[2] (I, R = C_2H_5, R′ = C_6H_5, X = morpholino; VIa), selected for extensive study, proved to be a potent respiratory stimulant in animals and man.

Further variation of substituents on the 4-ethyl-2-pyrrolidinone nucleus is reported in the present work.

(1) C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964).

(2) Doxapram hydrochloride, Dopram®.

TABLE I

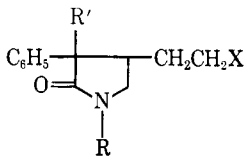


(R = i-C_3H_7 except as noted)

No.	R′	A	Method of prepn	% yield	Bp, °C (mm)	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	CH_3	CN	A	48	132–139 (0.09)	$C_{16}H_{22}N_2$	79.29	79.04	9.15	8.98	11.56	11.31
2	i-C_3H_7	CN	A	16	155–165 (0.25)	$C_{18}H_{26}N_2$	79.95	80.11	9.32	9.61	10.36	10.27
3	Cyclopentyl	CN	A	69	180–182 (0.25)	$C_{20}H_{28}N_2$	81.03	81.53	9.52	9.28	9.45	9.58
4	Cyclohexyl	CN	A	60	169–175 (0.001)	$C_{21}H_{30}N_2$	81.24	81.27	9.74	9.71	9.02	8.94
5[a]	3-Pyridyl	CN	A	57	168–171 (0.005)	$C_{19}H_{21}N_3$[b]						
6[a]	H	CN	A	46	128–135 (0.01)	$C_{14}H_{18}N_2$					13.08	12.80
7	i-C_3H_7	$CONH_2$	B	75	175–180 (0.05)[c]	$C_{18}H_{28}N_2O$	74.95	75.08	9.79	9.66	9.71	9.60
8	Cyclopentyl	$CONH_2$	B	66	221–225 (0.20)	$C_{20}H_{30}N_2O$	76.38	76.37	9.62	9.73	8.91	8.91
9	Cyclohexyl	$CONH_2$	B	65	208–216 (0.14)	$C_{21}H_{32}N_2O$	76.78	77.05	9.82	9.76	8.53	8.49

[a] R = C_2H_5. [b] *Anal.* Calcd: neut equiv, 146. Found: neut equiv, 150. [c] Mp 117–120°.

TABLE II



(R = i-C_3H_7 except as noted)

No.	R′	X	Salt	Method of prepn	% yield	Mp, °C (recrystn solvent[a])	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Cl, % Calcd	Cl, % Found
10	Cyclopentyl	Cl		C	74	74.5–77.5[b] (a)	$C_{20}H_{28}ClNO$	71.93	72.15	8.45	8.16	4.20	4.31		
11	CH_3	Cl			11.5	102–104 (b)	$C_{16}H_{22}ClNO$	68.68	68.84	7.93	7.73	5.01	5.16	12.67	12.16
12	i-C_3H_7	Cl		C	16.5	95–96 (c)	$C_{18}H_{26}ClNO$	70.22	70.19	8.51	8.41	4.55	4.62	11.52	11.29
13	Cyclohexyl	Cl		C	61	118–119 (d)	$C_{21}H_{30}ClNO$	72.49	72.54	8.69	8.68	4.03	4.17		
14	Cyclopentyl	Morpholino	Maleate	D	66	173–177 (d)	$C_{28}H_{40}N_2O_6$	67.17	67.37	8.05	8.22	5.60	5.64		
15	Cyclopentyl	N-$(CH_3)_2$		D	79	94–98.5 (e)	$C_{22}H_{34}N_2O$	77.14	77.43	10.01	10.06	8.18	7.95		
16	i-C_3H_7	N-$(CH_3)_2$	HCl	D	62	208–210 (f)	$C_{20}H_{33}ClN_2O$	68.05	68.13	9.42	9.61	7.94	7.93	10.05	10.44
17	i-C_3H_7	Morpholino	HCl		25	173–176 (f)	$C_{22}H_{35}ClN_2O_2$	66.90	67.03	8.93	9.06	7.09	7.15		
18[c]	3-Pyridyl	Cl		J	29	100–103 (e)	$C_{19}H_{21}N_2ClO$	69.39	69.31	6.44	6.28	8.52	8.32		
19[c]	3-Pyridyl	Morpholino		L	57	127–129 (g)	$C_{23}H_{29}N_3O_2$	72.79	72.79	7.70	7.73	11.07	10.97		
20[c]	H	Morpholino	HI	E	65	*Ca.* 258 (h)									
21[c]	H	Morpholino		E	48	59.5–61.5 (e)	$C_{18}H_{26}N_2O_2$	71.49	71.50	8.67	8.84	9.26	9.05		
22[c]	2-Pyridyl	Morpholino	$HCl \cdot H_2O$	F	27	*Ca.* 230 (f)	$C_{23}H_{32}ClN_3O_3$	63.65	64.96	7.43	7.11	9.68	9.11	4.5[d]	2.48[d]
23[c]	2-Pyridyl	Morpholino		F		91–92 (e)	$C_{23}H_{29}N_3O_2$	72.79	72.67	7.70	7.75	11.07	10.93		
24[c]	4-Pyridyl	Morpholino		F	20	134–136 (g)	$C_{23}H_{29}N_3O_2$	72.79	72.54	7.70	7.77	11.07	10.79		

[a] Recrystallized from: (a) ligroin, (b) ethanol–water, (c) isooctane, (d) ethanol, (e) isopropyl ether, (f) methyl isobutyl ketone–methanol, (g) ethyl acetate–isopropyl ether, (h) water. [b] Bp 178–180° (0.03 mm). [c] R = C_2H_5. [d] H_2O.

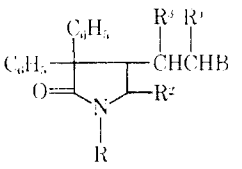
Because the 4-morpholinoethyl compound appeared to possess optimum activity among the amino derivatives, particular effort was made to hold this part of the molecule constant while varying the other substituents. For similar reasons the N substituent was maintained as lower alkyl (methyl, ethyl, or isopropyl). A summary of biological activities suggesting some structure–activity relationships is presented.

Chemistry.—Alkyl- (or cycloalkyl-) (1-substituted 3-pyrrolidinyl)phenylacetonitriles (Table I) were prepared by alkylation of the corresponding alkyl- (or cycloalkyl-) phenylacetonitriles with the appropriate 1-substituted 3-chloropyrrolidine in the presence of sodamide in toluene. Hydrolysis of these nitriles (IIa) in 70% sulfuric acid at 130° gave the corresponding amides (IId, R′ = i-C_3H_7, C_6H_{11}, C_5H_9; R = i-C_3H_7) except when the α-alkyl group was methyl. Hydrolysis of the methyl compound (IIa, R′ = CH_3, R = i-C_3H_7) under the same conditions gave the acid (IIb, R′ = CH_3, R = i-C_3H_7). When the amides were obtained they were readily converted to the acids with butyl nitrite and HCl. These crude acids, which were α,α disubstituted, on treatment with thionyl chloride underwent the rearrangement in the same manner as the diphenyl analogs. This was not realized with the α-monosubstituted compounds.

Clarke,[3] *et al.*, reported that treatment of γ-dialkylamino-α,α-disubstituted butyric acids with thionyl chloride gave ring closure (Table II) while the same treatment of analogs containing α-hydrogens produced sulfur-containing compounds. It was similarly observed in this laboratory that the desired rearrangement did not take place when the acid III was treated with thionyl chloride. The 1-ethyl-4-(2-iodoethyl)-3-phenyl-2-pyrrolidinone was, however, obtained by treatment of the acid III with acetic anhydride and a large excess of sodium iodide (Scheme I). Treatment of the iodide IV, without isolation, with morpholine gave the desired 2-morpholinoethyl derivative V. Phenylation of 1-ethyl-4-(2-morpholinoethyl)-3-phenyl-

(3) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, **71**, 2821 (1949).

TABLE III

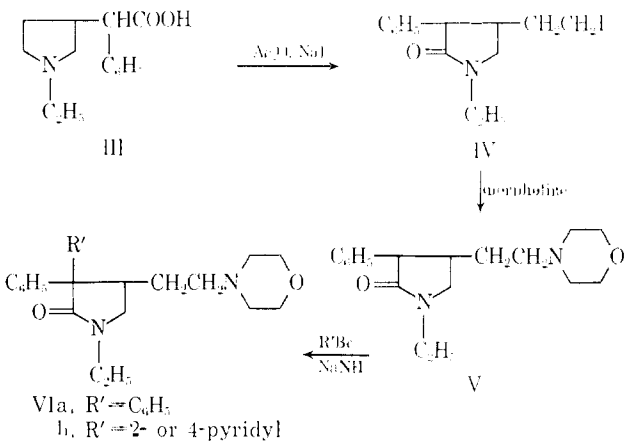


(R = C_2H_5 except as noted)

No.	R^2	R^3	R^4	B	Salt	Method of prepn	% yield	Mp, °C (recrystn solvent[a])	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
25	H	CH_3	H	Cl		J	53	150–153 (a)	$C_{22}H_{24}ClNO$	73.77	73.92	7.08	6.92	4.10	4.31
26	H	CH_3	H	Morpholino	HCl	L	70	255–261.5 (b)	$C_{26}H_{34}ClN_2O_2$	69.99	69.77	7.75	7.53	6.53	6.38
27	H	CH_3	H	$N(CH_3)_2$	HCl	D	64	251–253 (c)	$C_{24}H_{31}ClN_2O$	71.39	71.19	8.08	8.10	7.21	7.17
28	H	CH_3	H	CN		K	73	177–180 (d)	$C_{23}H_{28}N_2O$	79.18	78.96	7.28	7.27	8.49	8.09
29	H	H	CH_3	Cl		J		111–112 (a)	$C_{22}H_{24}ClNO$	73.77	73.60	7.08	7.31	4.10	4.23
30	H	H	CH_3	Morpholino	HCl	L	50	225–228 (c)	$C_{26}H_{34}ClN_2O_2$	69.99	70.09	7.75	7.87	6.53	6.45
31[b]	CH_3	H	H	Cl		J	45	150–153 (c)	$C_{23}H_{26}ClNO$	73.27	72.98	6.76	6.81	3.27	3.31
32[b]	CH_3	H	H	Morpholino	HCl·H_2O	L	38	165–168.5 (d)	$C_{27}H_{36}ClN_2O_3$	66.57	66.24	7.68	7.89	5.47	5.52

[a] Recrystallized from: (a) ethanol–isopropyl ether, (b) 2-propanol–acetone, (c) methyl isobutyl ketone, (d) methyl ethyl ketone, (e) 2-propanol. [b] R = CH_3.

SCHEME I



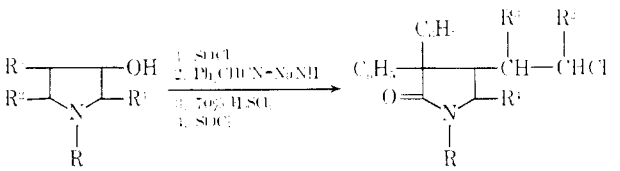
VIa, R′ = C_6H_5
b, R′ = 2- or 4-pyridyl

2-pyrrolidinone (V) using bromobenzene and sodamide in liquid ammonia gave 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone (VIa) (isolated and identified as the hydrochloride hydrate) which was identical with the substance derived from (1-ethyl-3-pyrrolidinyl)diphenylacetonitrile described above and reported in part I. Leake and Levine[4] reported phenylation of the esters and ketones by this method; however, we have been unable to find any previous report of an amide acting as the activating group for such a phenylation.

1-Ethyl-4-(2-morpholinoethyl)-3-phenyl-3-(3-pyridyl)-2-pyrrolidinone (I, R = C_2H_5, R′ = 3-pyridyl, X = morpholino) was prepared from the corresponding acid (IIb, R = C_2H_5, R′ = 3-pyridyl) in the same manner as described previously for the 3,3-diphenyl analogs. This route was not applicable, however, for the 2- or 4-pyridyl isomers because of the facile decarboxylation which occurred during acid hydrolysis of the (1-ethyl-3-pyrrolidinyl)phenyl-2- (or 4-) pyridylacetonitrile (IIa, R = C_2H_5, R′ = 2-pyridyl or 4-pyridyl). The desired compounds (VIb) were obtained by treatment of the monophenylpyrrolidinone V with 2- or 4-bromopyridine and sodamide in toluene.

Since similar reaction conditions can lead to pyridyne mechanisms and consequent changes of the location of substituents on the pyridine ring,[5] the nmr spectra of these products were studied. They showed that no rearrangement had occurred and that the 2-, 3-, and 4-pyridyl compounds had the expected pyridine ring substitution.

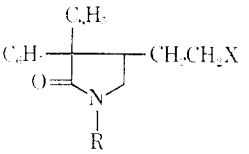
Methyl substitution on the ethyl side chain (VIII, R^2 or R^3 = CH_3) and at the 5 position in the ring (VIII, R^4 = CH_3) (Table III) was achieved by use of the appropriately substituted pyrrolidinols (VII, R^4, R^2, or R^3 = CH_3). Only one position was substituted in any one compound.



VII
R = CH or C_2H_5

VIII
R = CH or CH

Replacement of the chloride in the parent 1-alkyl-4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinones[1] (I, R′ = C_6H_5, X = Cl) by the cyano group and subsequent modification led to a large number of derivatives (Table IV) including the homologous 1-alkyl-4-(3-substituted propyl)-3,3-diphenyl-2-pyrrolidinones *via* the sequence IXa–f.

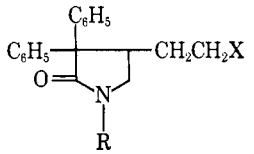


IXa, X = Cl
b, X = CN
c, X = COOH
d, X = COCl
e, X = CH_2OH
f, X = CH_2Cl

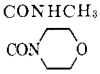
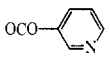
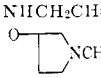
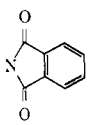
In order to study the pharmacological effect of substitution of sulfur for the ring carbonyl oxygen, direct substitution on two of the pyrrolidinones (IXa and b, R = *i*-C_3H_7) was carried out by treatment with a mixture of phosphorus pentasulfide and potassium sulfide.[6] Derivatives of the pyrrolidinethiones (Table V)

(4) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1169, 1627 (1959).
(5) H. J. den Hertog and H. C. van der Plas, *Adv. in Heterocyclic Chem.*, **4**, 126 (1965).
(6) R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 45 (1961).

TABLE IV



(R = *i*-C_3H_7 except as noted)

No.	X	Salt	Mp, °C (recrystn solvent[a])	Method of prepn	% yield	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
33	COOH		175–176 (a)	M	93	$C_{29}H_{29}NO_3$	75.18	74.99	7.17	7.29		
34	$CONH_2$		203.5–205 (a)		90	$C_{29}H_{30}N_2O_2$	75.40	75.55	7.48	7.68		
35	$CON(CH_3)_2$		149–150 (b)	N	92	$C_{31}H_{34}N_2O_2$	76.15	75.99	7.90	7.89		
36	$CONHCH_3$		170–171 (c)	N	84	$C_{30}H_{30}N_2O_2$	75.79	75.66	7.74	7.82		
37			157.5–158.5 (d)	N	94	$C_{36}H_{32}N_2O_3$	74.25	74.24	7.67	7.60		
38	$CONHC_6H_9$		113.5–114 (d)	N	95	$C_{36}H_{34}N_2O_2$	76.81	76.69	8.43	8.28		
39	$CON(CH_2)_5CH_2$		144–145 (b)	N	92.5	$C_{38}H_{36}N_2O_2$	77.74	77.54	8.39	8.20		
40	$CON(CH_2)_3CH_2$		179.5–180 (b)	N	91	$C_{36}H_{32}N_2O_2$	77.19	77.25	7.97	7.89		
41	$COOC_2H_5$		84–85 (e)	O	75	$C_{34}H_{29}NO_3$	75.96	76.14	7.70	7.85	3.69	3.79
42	CH_2OH		142–143 (e)		44	$C_{32}H_{27}NO_2$	78.30	78.24	8.07	8.03	4.15	4.20
43	$COOCH_2CH_2N(CH_3)_2$	HCl	172–173 (f)	P	75	$C_{36}H_{38}ClN_2O_3$	68.03	67.88	7.69	7.48		
44	CH_2Cl		85–86.5 (g)		72.5	$C_{32}H_{26}ClNO$	74.28	74.51	7.36	7.37	3.94	4.03
45		Maleate	155 (g)	R	58	$C_{36}H_{38}N_2O_6$	68.94	68.75	7.33	7.22	5.38	5.42
46	$OCOCH_2N(C_2H_5)_2$		91–92 (e)	Q	63.5	$C_{37}H_{36}N_2O_3$	74.27	74.16	8.31	8.15	6.42	6.24
47		HCl	203–204 (e)	Q	43	$C_{37}H_{35}ClN_2O_4$	66.58	66.44	7.24	7.21	5.75	5.75
48		2HCl	190–191 (h)	Q	68	$C_{38}H_{39}Cl_2N_3O_3$	62.68	62.27	7.33	7.30	7.83	8.07
49	$OCOCH_2N(CH_2)_3CH_2$		98–99 (e)	Q	51	$C_{37}H_{34}N_2O_3$	74.62	74.52	7.89	7.90	6.45	6.52
50	$OCOCH_2N(CH_2)_4CH_2$		107–108 (e)	Q	65	$C_{38}H_{36}N_2O_3$	74.96	75.10	8.09	8.14	6.25	6.09
51	$OCOCH_2N(CH_2)_5CH_2$		117–118 (e)	Q	52	$C_{39}H_{38}N_2O_3$	75.29	75.15	8.28	8.26	6.06	6.12
52		HCl	227–230 (g)	Q	52	$C_{38}H_{37}ClN_2O_4$	67.11	67.25	7.44	7.52	5.59	5.49
53	COC_2H_5		120–122.5 (a)		17	$C_{24}H_{29}NO_2$	79.30	79.47	8.04	8.07	3.85	4.06
54	CN		150.5–151 (j)		87	$C_{22}H_{24}N_2O$	79.48	79.21	7.28	7.08	8.43	8.27
55	CH_2NH_2	Fumarate	149–152 (r)		21	$C_{26}H_{32}N_2O_5$	69.00	69.08	7.13	7.24	6.18	6.19
56	CH_2CN		125–126 (j)	K	55	$C_{23}H_{26}N_2O$	79.73	79.53	7.56	7.38	8.09	7.95
57	$CH_2NHCOCH_3$		113–115 (k)		60	$C_{24}H_{30}N_2O_2$	76.15	76.25	7.99	7.85	7.40	7.26
58			104–105 (e)	S	67	$C_{27}H_{28}N_2O_3$	75.67	75.52	6.59	6.51	6.54	6.39
59	$OCOC_6H_4OH$-*o*		111–112 (g)	S	60	$C_{28}H_{29}NO_4$	75.82	75.65	6.59	6.57	3.16	3.25
60	$OCOCH_3$		83–84 (l)	S	94	$C_{22}H_{25}NO_3$	75.18	75.03	7.17	7.00		
61	$NHCH_2CH{=}CH_2$		103–105 (m)	D	63	$C_{24}H_{30}N_2O$	79.52	79.51	8.34	8.50	7.73	7.76
62			232–234 (0.1) [b]		69	$C_{28}H_{38}N_2O_2$	77.38	77.20	8.81	8.56	6.45	6.30
63	$COO(CH_2)_4N(CH_2)_4CH_2$	HCl	197–199 (i)	P	10	$C_{31}H_{43}ClN_2O_3$	70.63	70.30	8.22	8.27	5.32	5.49
64	$COOCH_2CH_2N^+(CH_3)_3 \cdot Br^-$		175–180 (d)		50	$C_{27}H_{37}BrN_2O_3$	62.66	62.55	7.21	7.26	5.41	5.52
65	$COOCH_2CH_2N^+(C_2H_5)_2CH_3I^-$		170–172 (n)		10	$C_{29}H_{41}IN_2O_3$					4.73	4.73
66[c]			152.5–154 (p)	*e*	83	$C_{28}H_{26}N_2O_3$	76.69	76.90	5.98	6.12		
67[c]	OH		190.5–191.5 (q)	*e*	93	$C_{26}H_{23}NO_2$	77.64	77.57	7.49	7.49		
68[d]	OC_6H_5		136–138 (k)	*e*	20	$C_{25}H_{23}NO_2$	80.83	80.72	6.78	6.83	3.77	4.01

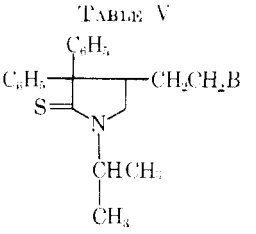
[a] Recrystallized from: (a) $CHCl_3$–ligroin, (b) ethyl acetate, (c) methanol–water, (d) methyl ethyl ketone, (e) isopropyl ether, (f) ethanol–ethyl acetate, (g) ethanol, (h) ethanol–ether, (i) ethanol–water, (j) 2-propanol, (k) isopropyl ether–ethyl acetate, (l) toluene–ligroin, (m) isooctane, (n) methyl isobutyl ketone, (p) methanol, (q) toluene, (r) water. [b] Bp, °C (mm). [c] R = C_2H_5. [d] R = CH_3. [e] Prepared according to the method of the 1-isopropyl analog.[1]

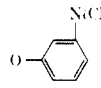
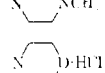
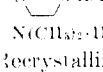
were prepared by methods analogous to the pyrrolidinones, that is, direct substitution for the chloride IXa or conversion of the nitrile IXb.

Many of the compounds reported in this paper may exist as diastereoisomers. Although generally no attempt was made to separate diastereoisomers, the compounds were recrystallized to constant melting point and consequently probably in most cases pure single diastereoisomers were obtained. It is, however, likely that some of the reported compounds are still mixtures of diastereoisomers (Table VI).

Pharmacology. Method.—The experimental procedure was identical with that described in the previous communication.[1]

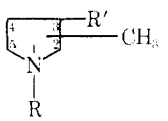
TABLE V



No.	B	Mp, °C (recrystn solvent[a])	Method of prepn	% yield	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	S, % Calcd	S, % Found
69	Cl	149–151 (a)	T	45	$C_{20}H_{22}ClNS$	70.46	70.32	6.76	6.47	3.91	3.98		
70	CN	166–167 (b)	T	57	$C_{22}H_{22}N_2S$	75.82	75.90	6.94	7.11	8.04	8.13	9.20	9.35
71	OC_6H_5	164–165 (a)	b	43	$C_{27}H_{29}NOS$	78.03	78.30	7.03	6.76	3.37	3.45		
72	COOH	191–194 (a)	M	80	$C_{22}H_{25}NO_2S$	71.90	71.78	6.86	6.68	3.81	3.97		
73	$CON(CH_3)_2$	109–111 (c)	N	37	$C_{24}H_{30}N_2OS$	73.05	73.22	7.66	7.51	7.10	6.91		
74	$COOC_2H_5$	148.5–151 (d)	O	54	$C_{24}H_{29}NO_2S$	72.87	72.75	7.39	7.20	3.54	3.63		
75	$COOCH_2CH_2N(CH_3)_2 \cdot HCl$	196–198 (e)	P	67	$C_{26}H_{35}ClN_2O_2S$	65.73	65.86	7.43	7.51	5.90	5.96		
76	SH	200–210 (0.005)[b]	b	24	$C_{21}H_{28}NS_2$	70.91	71.03	7.10	6.99	3.94	4.20		
77		104–105 (e)	b	18	$C_{29}H_{31}N_2OS$	75.94	75.65	7.47	7.39	6.11	6.13		
78	$OCOCH_3$	107–109 (f)	S	76	$C_{24}H_{27}NO_2S$	72.40	72.19	7.13	7.30	3.67	3.61		
79	OH	184–187 (f)	b	90	$C_{22}H_{25}NOS$	74.29	74.10	7.42	7.41	4.13	4.10		
80	$COOCH_2CH_2N^+(CH_3)_3I^-$	218–219 (g)		55	$C_{27}H_{37}IN_2O_2S$	55.85	55.74	6.13	6.17	1.83	1.83		
81		133–134 (c)		6	$C_{26}H_{36}N_2S$	74.96	74.11	8.37	8.28	9.97	9.85		
82		275 dec (f)	L	58	$C_{26}H_{33}ClN_2OS$	67.46	67.45	7.17	7.30	6.30	6.20		
83	$N(CH_3)_2 \cdot HCl \cdot H_2O$	196–197 (e)	D	38	$C_{23}H_{34}ClN_2SO$	65.61	65.88	7.90	7.70	6.65	6.59		

[a] Recrystallized from: (a) toluene, (b) 2-propanol, (c) isopropyl ether, (d) ethyl acetate, (e) methyl isobutyl ketone–methanol, (f) methanol, (g) ethanol. [b] Prepared by method of analogous 2-pyrrolidinone.[1] [c] Bp, °C (mm).

TABLE VI



B	B′	Position of methyl	Bp, °C (mm)	Yield, %	Method of prepn
CH_3[a]	Cl	2	64–66 (20)	66	H
C_2H_5	Cl	5	67–70 (25)	58.5	H
C_2H_5	Cl	4	71 (20)	91.5	H
C_2H_5	$(C_6H_5)_2CH(CN)$	4	175–190 (0.03–0.04)	64.7	A
C_2H_5[b]	$(C_6H_5)_2CH(CN)$	5	173–175 (0.02)	82	A
CH_3[c]	$(C_6H_5)_2C(CN)$	2	168–170 (0.1), 115–117[d]	25	A

[a] Pyrrolidinol was reported by C. W. Ryan and Ainsworth [*J. Org. Chem.*, **27**, 2901 (1962)]. [b] *Anal.* Calcd for $C_{29}H_{24}N_2$: neut equiv, 318. Found: neut equiv, 321. [c] *Anal.* Calcd for $C_{29}H_{22}N_2$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.87; H, 7.62; N, 9.51. [d] Mp., C.

Results.—Most of the compounds reported herein enhanced respiratory rate and amplitude, increased arterial blood pressure, and antagonized the CNS depressant action of the anesthetic agent (Table VII). In many instances the blood pressure and respiratory effects were elicited by doses that had little or no antianesthetic action; however, the latter effect was invariably produced with larger doses.

Several compounds (*e.g.*, **35**, **39**, **40**) increased respiratory rate and amplitude, even with the lowest dose tested. This effect was of relatively long duration. The pressor action of these compounds was pronounced initially and a good effect persisted for more than 60 min in some experiments. Also, these compounds caused considerable spontaneous movement of the head and limbs and the animals were then responsive to various stimuli, whereas they had been totally unresponsive prior to treatment.

Other members of this series (*e.g.*, **10**–**12**) apparently had no direct respiratory stimulating action. The increased respiratory effort was probably induced reflexly as a result of their hypotensive action. Still other compounds (**48**, **64**) decreased respiratory rate and/or amplitude. These also were depressor. All compounds having no direct respiratory stimulating action were essentially void of antianesthetic activity.

As previously reported,[1] substitution at the nitrogen of the pyrrolidinone ring was essential for producing the pharmacologic effects in question; activity was optimum with the smaller alkyl groups. Quaternization virtually eliminated activity (**64**, **39***[7]). All members of the present series have lower alkyl on the pyrrolidinone nitrogen.

In agreement with, and extending previously reported results,[1] the present study showed that certain variations of the β substituent of the 4-ethyl group do not seriously diminish pharmacologic activity. Among the most active of the present series were several tertiary amino acetates (**46**, **47**, **49**–**51**); an exception within this group was the N′-methylpiperazine analog (**48**). Three amides were active with the results suggesting increasing potency in going from a primary (**34**) through a secondary (**36**) to a tertiary (**35**). Other variations of the β substituent, particularly amines (**15**, **16**, **61**, **75**, **83**), produced definite hypotension and probably had no direct stimulating effect on respiration. Also causing a lowering of blood pressure were 2-methyl substitution in the chain of a chloro compound (**29**) [similar substitution in a morpholino compound

[7] A number with an asterisk refers to the compound of this number in ref 1.

Table VII

No. (solvent[a])	Min dose obsd to stim resp, mg/kg iv	Predominant blood pres effects	Antianesthetic effects[b]
10 (b)	8[c]	Depressor	±
11 (b)	8[c]	Depressor	+
12 (b)	8[c]	Depressor	++
13 (b)	2	Pressor	++
14 (c)	4	Pressor[d]	+++
15 (c)	2[c]	Depressor	+
16 (c)	16[c]	Depressor	−
17 (c)	4	Pressor	±
18 (b)	2	Pressor	+++
19 (c)	2	Pressor[d]	++
21 (c)	16[c]	Depressor	−
22 (c)	8	Pressor	++
24 (c) (HCl salt)	2	Pressor	++
25 (b)	2	Pressor	+++
26 (c)	8	Pressor	++
27 (c)	8[c]	Depressor	±
29 (b)	2[c]	Depressor	++
30 (c)	2	Pressor	+
32 (d)	4[c]	Depressor	−
33 (b)	8	Pressor	−
34 (a)	4	Pressor	++
35 (b)	1	Pressor	++++
36 (b)	2	Pressor	++
38 (a)	2	Pressor	+++
39 (b)	1	Pressor	++++
40 (b)	1	Pressor	++++
41 (b)	1	Pressor	++++
42 (b)	4	Pressor	++
43 (c)	2	Pressor	+++
44 (b)	1	Pressor	++
45 (c)	2	Pressor	+++
46 (c) (HCl salt)	1	Pressor	++
47 (c)	1	Pressor	+++
48 (c)	Resp depressant	Depressor	−
49 (c) (HCl salt)	2	Pressor	+++
50 (c) (HCl salt)	1	Pressor	++++
51 (c) (HCl salt)	1	Pressor	+++
52 (c)	1	Pressor	++
53 (b)	1	Pressor	+++
54 (a)	1	Pressor	++++
55 (b)	4	Pressor[d]	−
56 (b)	2	Pressor	+++
58 (b)	1	Pressor	++
59 (a)	2	Pressor	++
60 (a)	2	Pressor	+++
61 (c) (HCl salt)	2[c]	Depressor	±
62 (c) (HCl salt)	2[c]	Depressor	±
63 (c)	2	Pressor	+
64 (c)	Resp depressant	Depressor	−
66 (a)	1	Pressor	++++
69 (a)	1	Pressor	++++
70 (b)	1	Pressor	+++
71 (a)	2	Pressor	++++
74 (b)	2	Pressor	+++
75 (c)	2[c]	Depressor	±
76 (b)	4	Pressor	++
78 (a)	2	Pressor	++
79 (a)	2	Pressor[d]	++
81 (b)	2[c]	Depressor	−
82 (c)	1	Pressor	++++
83 (b)	4[c]	Depressor	−

[a] Solvents: (a) PEG-300, (b) propylene glycol, (c) water, (d) dimethylformamide. [b] −, no activity; ±, questionable; +, very slight; ++, slight; +++, moderate; ++++, marked. [c] Respiratory stimulation coincided with hypotensive period. [d] High doses were depressor.

(**30**) did not eliminate pressor activity] and methyl substitution at the 5 position of the pyrrolidinone ring (**32**). It was interesting to note in comparing two amines that increasing the chain length by a methylene group seemed to introduce a qualitative change in biological activity. The 4-(2-aminoethyl) member of the previously reported series (**37***) depressed respiration and failed to raise blood pressure regardless of dose, but lower doses of the 4-(3-aminopropyl) compound (**55**) were pressor and slightly increased respiratory rate. A similar change in activity was not seen with the analogous chloro (**44**, **3***), hydroxy (**42**, **17***), morpholino (**45**, **26***), or cyano (**54**, **56**) compounds.

In comparing certain members of the present series to each other or to particular compounds in the previous study,[1] several examples show that replacing the oxygen of the pyrrolidinone ring with sulfur does not materially impair biologic activity. Of approximately equal potency in the present series were **70** and **54**, **74** and **41**, **78** and **60**. Compounds of the present series (first number in each set) that were comparable to members of the previous series[1] were **69** and **3***, **71** and **16***, **79** and **17***, **82** and **26***, and **83** and **7***. There were three examples in which this equality did not hold but most of the compounds involved (**75** and **43**, **76** and **21***, **81** and **24***) were among the less effective.

The results of the present study (with some comparisons to previously reported results[1]) stress the importance of the two phenyl substituents at the 3 position of the pyrrolidinone ring. Among the 4-(2-morpholinoethyl) compounds, activity was decreased when a phenyl group was replaced with isopropyl (**17**), cyclopentyl (**14**), or pyridyl (2-pyridyl, **22**; 3-pyridyl, **19**; 4-pyridyl, **24**). Activity was abolished by replacing a phenyl with hydrogen (**21**). Likewise, in comparing 4-(2-dimethylaminoethyl) compounds, the 3-phenyl-3-isopropyl (**16**) and the 3-phenyl-3-cyclopentyl (**15**) compounds were less potent than the 3,3-diphenyl compound (**8***). Also, the 3,3-diphenyl compound in the 4-(2-chloroethyl) group (**3***) increased blood pressure, stimulated respiration, and exerted antianesthetic effects. The corresponding compounds in which a phenyl was replaced with methyl (**11**), isopropyl (**12**), or cyclopentyl (**10**) were depressor and relatively ineffective respiratory-stimulating and antianesthetic agents. Only the cyclohexyl compound (**13**) exhibited activity comparable to that of the analogous diphenyl compound.

Experimental Section

Melting points were determined in glass capillaries and are corrected. Boiling points are uncorrected. Microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., Galbraith Microanalytical Laboratories, Knoxville, Tenn., Micro-Tech Laboratories, Skokie, Ill., and Mrs. Ruby Higgins of these laboratories.

Method A was previously described for the preparation of (1-isopropyl-3-pyrrolidinyl)diphenylacetonitrile.[1]

Method B. 2-Cyclopentyl-2-(1-isopropyl-3-pyrrolidinyl)-phenylacetamide (7).—A solution of 150 g (0.50 mole) of 2-cyclopentyl-2-(1-isopropyl-3-pyrrolidinyl)phenylacetonitrile in 800 g of 70% H_2SO_4 was stirred at 130–140° for 48 hr. The solution was poured on ice, made basic with 50% NaOH, and extracted ($CHCl_3$). The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated, and the residue was distilled, yield 105 g (66%), bp 221–225° (0.2 mm). The infrared spectrum showed a strong absorption at 6.1 and none near 4.45 μ. The material was taken to the next step without further characterization.

Method C. 4-(2-Chloroethyl)-3-cyclopentyl-1-isopropyl-3-phenyl-2-pyrrolidinone (10).—Anhydrous HCl was introduced slowly into a stirred solution of 73 g (0.232 mole) of **7** in 200 ml of glacial acetic acid over 25 min. This was followed by the subsurface addition of 47.9 g (0.464 mole) of butyl nitrite over a 2-hr period. There was a slight exothermic reaction during this addition. The temperature was held at 26–30° by intermittent application of an ice bath. The mixture was stirred overnight at 25° and then heated for 3 hr on a steam bath. The acetic acid was removed *in vacuo*, and the residue was taken into about 400 ml of $CHCl_3$, washed with water, and concentrated. This residue was then dissolved in approximately 500 ml of $SOCl_2$ and heated at reflux for 2 hr. The excess $SOCl_2$ was removed *in vacuo*. The residue was taken into 200 ml of $CHCl_3$, washed twice with water, dried (Na_2SO_4), concentrated, and distilled: bp 178–180° (0.03 mm). The product was crystallized from ligroin (bp 65–110°).

4-(2-Chloroethyl)-1-isopropyl-3-methyl-3-phenyl-2-pyrrolidinone (11).—To 150 g of 70% H_2SO_4 was added 30 g (0.124 mole) of 2-(1-isopropyl-3-pyrrolidinyl)-2-phenylpropionitrile. The solution was heated at 130–135° for 48 hr, poured on ice, and made basic (NaOH). The solution was concentrated to dryness and the residue was extracted twice with 400-ml portions of boiling absolute ethanol. The ethanolic solution was concentrated and $CHCl_3$ was added to the residue. HCl was passed into the mixture until it was acidic, and the $CHCl_3$ was removed. The residue was dissolved in 300 ml of $SOCl_2$ and refluxed for 40 min. The excess $SOCl_2$ was removed, and the residue was treated with 45 g of KOH in 300 ml of ethanol and 100 ml of water.[8] The solution was concentrated, and the residue was partitioned between 300 ml of H_2O and 300 ml of $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated. The residue solidified on standing and was recrystallized three times from ethanol–water and once from isopropyl ether.

Method D was previously described as a general procedure for the preparation of 1-substituted 4-(2-aminoethyl)-3,3-diphenyl-2-pyrrolidinones.[1]

Method E. 1-Ethyl-4-(2-morpholinoethyl)-3-phenyl-2-pyrrolidinone (21).—A solution of 198 g (0.91 mole) of (1-ethyl-3-pyrrolidinyl)phenylacetonitrile in 850 g of 70% H_2SO_4 was heated at 130° for 48 hr, cooled, poured onto crushed ice, and made strongly basic with 50% NaOH. Chloroform was added forming three layers. The bottom ($CHCl_3$) layer was removed and combined with the top layer; the middle (H_2O) layer was discarded. The chloroform–oil combination was concentrated *in vacuo*, and the residue was dissolved in 1 l. of absolute ethanol. The ethanolic solution was treated with HCl gas until the pH was about 6 and then filtered. The filtrate was concentrated and the residue was treated with dry toluene which was removed *in vacuo* several times to remove traces of H_2O and ethanol. The residue solidified and was left under reduced pressure (30 mm) overnight. About 1 l. of dry ethyl methyl ketone was added followed by 410 g (2.73 moles) of NaI. The mixture was brought to reflux with stirring, and 93 g (0.91 mole) of acetic anhydride was added over a period of 10 min. Refluxing was continued 0.5 hr and an additional 93 g (0.91 mole) of acetic anhydride was added. After another hour of refluxing, 36 ml of H_2O was added slowly to the hot solution. The mixture was concentrated *in vacuo* and partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with dilute HCl followed by dilute NaOH, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in 500 ml of morpholine, refluxed 1 hr, and concentrated *in vacuo*, and the residue was dissolved in 1600 ml of hot dilute HCl. To this solution was added 50 g of NaI in 200 ml of H_2O. Crystals formed on cooling, yield 253 g (65%). The hydriodide salt on further purification by recrystallization from water melted at about 258°. (This melting point was dependent on rate of heating since the compound decomposed at lower temperatures when heated slowly.[8])

The salt was partitioned between $CHCl_3$ and dilute NaOH. The $CHCl_3$ was concentrated, and the residue distilled, yield 134 g (48.5%), bp 215–220° (0.2 mm). The distillate crystallized on standing and was recrystallized twice from isopropyl ether by cooling in Dry Ice–acetone bath, mp 59.5–61.5°.

3,3-Diphenyl-1-ethyl-4-(2-morpholinoethyl)-2-pyrrolidinone Hydrochloride Hydrate by Phenylation of 1-Ethyl-4-(2-morpholinoethyl)-3-phenyl-2-pyrrolidinone.—A catalytic amount of $FeCl_3$ was added to 1.31 g (0.043 g-atom) of Na in 100 ml of liquid NH_3, and the solution was stirred until the blue color disappeared. Ten grams (0.021 mole) of 1-ethyl-4-(2-morpholinoethyl)-3-phenyl-2-pyrrolidinone hydriodide was partitioned between dilute NaOH and $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was added, over a period of 2 min, to the ammoniacal $NaNH_2$. The mixture was stirred for 10 min, and 1.7 g (0.011 mole) of bromobenzene was added. A vigorous reaction ensued. After 10 min of stirring 2.7 g (0.050 mole) of NH_4Cl was added, the NH_3 was allowed to evaporate, and the residue was partitioned between 100 ml of $CHCl_3$ and 100 ml of 2 *N* HCl. The $CHCl_3$ layer was washed with dilute NaOH and concentrated. The residue was dissolved in 25 ml of boiling 2 *N* HCl, treated with activated carbon, and filtered. On cooling, the product crystallized, yield 1 g (23%), mp 216–218°; mixture melting point with authentic 3,3-diphenyl-1-ethyl-4-(2-morpholinomethyl)-2-pyrrolidinone hydrochloride hydrate[1] gave no depression.

Method F. 1-Ethyl-4-(2-morpholinoethyl)-3-phenyl-3-(2-pyridyl)-2-pyrrolidinone Hydrochloride Hydrate (22).—1-Ethyl-4-(2-morpholinoethyl)-3-phenyl-2-pyrrolidinone (3.0 g, 0.0033 mole), 2.7 g (0.0066 mole) of $NaNH_2$, and 5.2 g (0.0330 mole) of 2-bromopyridine in 100 ml of dry toluene were refluxed for 1 hr. Water (100 ml) was added, and the layers were separated. The toluene solution was extracted with dilute HCl, the acid layer was made basic (NaOH) and extracted ($CHCl_3$). The $CHCl_3$ was dried (Na_2SO_4) and concentrated. The residue was dissolved in isobutyl methyl ketone and about 1 g of HCl in isobutyl methyl ketone was added. Enough CH_3OH was added to bring about solution when boiling and on cooling crystals were obtained which were recrystallized from isobutyl methyl ketone–methanol, mp *ca.* 230–232° (sample in a bath preheated to the temperature which brings about rapid melting), yield 3.9 g (27%). The salt was dissolved in H_2O, made basic (NaOH), and extracted ($CHCl_3$). The $CHCl_3$ was concentrated and the residue was crystallized from a mixture of isopropyl ether and ligroin; mp 91–92°.

Method G. 1-Ethyl-2-methyl-4-pyrrolidinol. A solution of 127 g (1.00 mole) of 1-ethyl-2-methyl-4-pyrrolidinone,[9] bp 90–91° (22 mm), in 800 ml of H_2O was treated with 83 g (2.2 moles) of $NaBH_4$ in approximately 2-g portions over a period of 30 min at 20°. The solution was stirred at 30° for 2 hr and cooled to 0°, and 600 g of K_2CO_3 was added with stirring while the temperature rose to 25°. The mixture was filtered, and the filtrate was extracted five times ($CHCl_3$). The $CHCl_3$ solution was concentrated and distilled; yield 100 g (81%), bp 104–106° (25 mm).

Anal. Calcd for $C_7H_{15}NO$: neut equiv, 129.2. Found: neut equiv, 128.

1-Ethyl-4-methyl-3-pyrrolidinol was prepared by method G in 40% yield, bp 105–108° (20 mm), from 1-ethyl-4-methyl-3-pyrrolidinone which was made by the method of Cavalla, *et al.*[9]

Method H has been previously described for the preparation of 1-alkyl-3-chloropyrrolidines.[10]

Method J. 4-(1-Chloro-2-propyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone (25).—A solution of 50 g (0.158 mole) of diphenyl(1-ethyl-3-methyl-4-pyrrolidinyl)acetonitrile in 300 g of 70% H_2SO_4 was heated at 135° for 48 hr, poured onto ice, and made basic with 50% NaOH while keeping the temperature below 50°. The solution was extracted with $CHCl_3$, forming three layers. The $CHCl_3$ (bottom) and middle layers were drawn off together and acidified (HCl). A small aqueous layer was again formed which was discarded. The $CHCl_3$ was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 50 ml of $SOCl_2$, refluxed 2 hr, and concentrated *in vacuo*. This residue was crystallized three times from ethanol–isopropyl ether.

Method K. 4-(1-Cyano-2-propyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone (28). A mixture of 20 g (0.059 mole) of **25** and 2.88 g (0.059 mole) of NaCN in 50 ml of DMF was stirred and heated at 120° for 4.5 hr, cooled, and partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with 150 ml of H_2O, dried (Na_2SO_4), and concentrated to dryness *in vacuo*. The resulting tan crystals were dissolved in hot 2-propanol, treated with Norit, and filtered. Upon cooling, crystals formed, mp 176–179°; after several recrystallizations from ethyl methyl ketone, mp 177–180°.

(8) If this step is omitted the product as formed does not come up to the melting point given even on repeated recrystallizations.

(9) J. F. Cavalla, J. Duvoll, M. J. Dean, C. S. Franklin, and D. M. Temple, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

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

Method L. 3,3-Diphenyl-1-ethyl-4-(1-methyl-2-morpholinoethyl)-2-pyrrolidinone Hydrochloride (26).—A mixture of 20 g (0.059 mole) of 3,3-diphenyl-4-(2-chloro-1-methylethyl)-1-ethyl-2-pyrrolidinone and 80.2 g (0.92 mole) of morpholine was stirred and heated at 110° for 3 hr. The excess morpholine was removed *in vacuo* at steam-bath temperature, and the residue was partitioned between $CHCl_3$ and aqueous NaOH. The $CHCl_3$ layer was washed twice with 75 ml of H_2O, dried (Na_2SO_4), and concentrated *in vacuo* at steam-bath temperature. The light tan solid residue was dissolved in isobutyl methyl ketone, and the hydrochloride salt was precipitated by passing in anhydrous HCl. The dried, white solid turned brown at 243° and softened and decomposed from 248–258°. The material was then crystallized from 2-propanol and acetone; mp 255–261.5° dec.

Method M. 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]-propionic Acid (33).—A mixture of 94 g (0.28 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionitrile and 500 ml of 70% H_2SO_4 was heated with stirring at 80–90° for 24 hr and was poured onto ice. The precipitated while solid was separated, washed, and recrystallized from a 1:1 chloroform–ligroin mixture.

3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl Chloride.—To a suspension of 144 g (0.41 mole) of **33** in 500 ml of dry C_6H_6 was added, dropwise at 20–25° with stirring, 97.5 g (0.82 mole) of $SOCl_2$. The solution was refluxed 1 hr and concentrated *in vacuo* to one half volume. On cooling, 131 g (86%) of white crystals was obtained.

3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionamide (34).—To a cold aqueous NH_3 solution (37%) was added, in small portions with vigorous stirring, 54 g (0.15 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl chloride. The stirring was continued 0.5 hr after the addition was complete. The mixture was filtered and the solid was washed with water and recrystallized from a chloroform–ligroin mixture.

Method N. N,N-Dimethyl-3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionamide (35).—A C_6H_6 solution of 6.2 g (0.137 mole) of dimethylamine was added dropwise at 15–20° to a suspension of 25 g (0.068 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl chloride in C_6H_6. The reaction mixture was warmed to reflux for 1 hr. The solvent was removed and the residue was dissolved in 95% ethanol. Addition of small amounts of ice produced a white solid, mp 145–148°. An additional crystallization from ethyl acetate yielded a product melting at 149–150°.

Method O. Ethyl 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionate (41).—To 200 ml of dry ethanol was added 2.05 g (0.090 g-atom) of Na. When solution was complete 30 g (0.081 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]-propionyl chloride in 300 ml of dry ethanol was added rapidly. The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated and the residue was partitioned between 250 ml of $CHCl_3$ and 250 ml of H_2O. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated. The residue was crystallized from 70% ethanol.

3,3-Diphenyl-4-(3-hydroxypropyl)-1-isopropyl-2-pyrrolidinone (42). Procedure a.—To a boiling solution of 5 g (0.013 mole) of **41** in 50 ml of absolute ethanol[11] was added as rapidly as possible 2 g (0.09 g-atom) of sodium. The unreacted ester was then hydrolyzed by adding 30 ml of H_2O and refluxing 1 hr. The solvent was removed and the residue was partitioned between 100 ml of H_2O and 100 ml of $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated, and the residue crystallized, yield 1.6 g (36%), mp (after recrystallization from 50% ethanol) 140–141.5°. The product was identical with that made by procedure b.

Procedure b.—To a suspension of 10 g of $NaBH_4$ in 100 ml of dry dioxane[12] was added rapidly and with stirring 25 g (0.068 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl chloride in 200 ml of dry dioxane. The mixture was stirred at reflux for 4 hr and cooled to room temperature, and 100 ml of H_2O was added carefully.[13] The mixture was partitioned between 500 ml of H_2O and 300 ml of $CHCl_3$. The H_2O layer was extracted with another 300 ml of $CHCl_3$; the $CHCl_3$ solutions were combined, dried (Na_2SO_4), and concentrated. The residue was crystallized from 70% ethanol and recrystallized twice from isopropyl ether; yield 10 g (44%), mp 142–143°. A mixture melting point with a sample from procedure a gave no depression.

Method P. Dimethylaminoethyl 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionate Hydrochloride (43).—A warm solution of 25.0 g (0.068 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl chloride in 200 ml of C_6H_6 was added at a rapid drop with stirring to a 15° solution of 6.1 g (0.068 mole) of dimethylaminoethanol in 100 ml of C_6H_6. After addition the mixture was allowed to warm to room temperature, then refluxed for 1 hr. The benzene was evaporated under reduced pressure and the residue was dissolved in dry ethyl acetate. Chilling produced a white, crystalline solid, mp 162–167°, which was recrystallized from the same solvent (using a small volume of dry ethanol to effect solution).

4-(3-Chloropropyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (44).—A solution of 7.4 g (0.062 mole) of $SOCl_2$ in 50 ml of $CHCl_3$ was added dropwise to a solution of 10.5 g (0.031 mole) of **42** and 4.9 g (0.062 mole) of pyridine in 100 ml of $CHCl_3$ with stirring and ice-bath cooling. When the addition was complete the mixture was heated to reflux and maintained there for 5 hr, and then cooled. Water (100 ml) was added with stirring followed by 50 ml of 3 *N* HCl. The $CHCl_3$ layer was separated, dried (Na_2SO_4), and concentrated *in vacuo*, and the residue crystallized from 60% ethanol.

Method Q. 4-[2-(Diethylaminoacetoxy)ethyl]-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (46).—To 25 g (0.077 mole) of 3,3-diphenyl-4-(2-hydroxyethyl)-1-isopropyl-2-pyrrolidinone and 200 ml of dry benzene was added dropwise a solution of 8.65 g (0.077 mole) of chloroacetyl chloride in 50 ml of dry C_6H_6 with stirring and cooling at 15°. The mixture was allowed to stir at 40° for 12 hr and concentrated under reduced pressure to remove any unreacted chloroacetyl chloride. The residue was redissolved in 200 ml of dry C_6H_6 in the same flask and a solution of 16.8 g (0.23 mole) of diethylamine in 40 ml of dry C_6H_6 was added, maintaining the temperature below 40°. The mixture was then heated at 40° for 12 hr. The C_6H_6 solution was extracted in the cold with dilute HCl and several times with H_2O. The combined aqueous acid extracts were washed with ether, made basic with 6 *N* NaOH, and extracted several times with ether. On evaporation of the ether the product began to crystallize. The product was treated with decolorizing carbon in hot isopropyl ether and the product was filtered and vacuum dried.

Method R. 3,3-Diphenyl-1-isopropyl-4-(3-morpholinopropyl)-2-pyrrolidinone Maleate (45).—Compound **44** (5 g, 0.014 mole) was dissolved in 35 ml of morpholine and refluxed for 17 hr. The solution was concentrated *in vacuo*, and the residue was partitioned between 100 ml of $CHCl_3$ and 100 ml of 1 *N* HCl. The $CHCl_3$ solution was washed with 100 ml of 1 *N* NaOH and concentrated *in vacuo*. The residue was dissolved in 100 ml of ethyl acetate, and the solution was extracted with 200 ml of 1 *N* HCl. The aqueous layer was made basic (dilute NaOH) and extracted with 100 ml of $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from isopropyl ether; yield 3.3 g (58%). To a solution of 2.7 g (0.0066 mole) of the base in 25 ml of ethanol was added 0.78 g (0.0067 mole) of maleic acid with boiling to effect solution. The crystals resulting from cooling were recrystallized from ethanol; yield 1.4 g.

3,3-Diphenyl-1-isopropyl-4-(3-oxopentyl)-2-pyrrolidinone (53).—To 2.4 g (0.10 g-atom) of Mg shavings in 200 ml of dry ether was added 10.9 g (0.10 mole) of ethyl bromide in 100 ml of dry ether at such a rate as to maintain reflux. When the addition was complete the mixture was refluxed for 2 hr. The mixture was cooled and 10 g (0.055 mole) of $CdCl_2$ was added over a period of 5 min. The temperature was raised to reflux and maintained for 1 hr. The ether was distilled leaving a syrupy oil. To this was added 200 ml of dry toluene, and the temperature was raised to 90° for 30 min. The slurry was cooled to 60° and 30 g (0.081 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionyl chloride in 150 ml of dry toluene was added at a rapid drop. The mixture was stirred at 85° for 2 hr and cooled, and 100 ml of H_2O was added followed by 100 ml of 6 *N* HCl. The toluene layer was separated and washed with dilute NaOH, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was distilled, bp 220–250° (0.2 mm). The distillate was crystallized from 60% ethanol; yield 8 g (27%). After three recrystallizations the yield was 5 g.

4-(3-Aminopropyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone Fumarate (55).—A mixture of 25 g (0.068 mole) of 4-(2-cyano-

(11) Dried with $Mg(OCH_3)_2$: see "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 249, note 2.

(12) Dried by shaking with NaOH followed by refluxing with $LiAlH_4$ for 24 hr.

(13) Water must be added very slowly due to excessive foaming.

ethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone and 2 teaspoons of Raney nickel in 300 ml of absolute ethanol was shaken in a hydrogen atmosphere for 54 hr during which time 0.12 mole of hydrogen was absorbed. The mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was distilled, bp 210–215° (0.2 mm), yield 13 g. This distillate, together with 5 g of fumaric acid was dissolved in 100 ml of ethanol, and the solvent was removed on the steam bath. The residue was dissolved in 400 ml of hot water, treated with activated charcoal, and filtered. The filtrate was concentrated to about 200 ml. The resulting precipitate was recrystallized from 200 ml of H_2O.

4-(3-Acetamidopropyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (57).—The above fumarate (2 g, 0.0044 mole) was partitioned between 100 ml of $CHCl_3$ and 100 ml of 1 *N* NaOH. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated to 50 ml. Acetyl chloride (0.84 g, 0.011 mole) was added, and the solution was refluxed for 15 hr, allowed to stand for 24 hr at room temperature, washed (dilute NaOH), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was crystallized from isopropyl ether containing about 5% ethyl acetate.

Method S. 3,3-Diphenyl-1-isopropyl-4-(2-nicotinoyloxyethyl)-2-pyrrolidinone (58).—To 17.1 g (0.050 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 250 ml of DMF was added 7.25 g (0.059 mole) of sodium nicotinate, and the mixture was refluxed for 24 hr. The NaCl was removed by filtration. Evaporation of the DMF gave the product which was crystallized from isopropyl ether.

1-Isopropyl-4-[2-(1-isopropyl-3-pyrrolidinyloxy)ethyl]-3,3-diphenyl-2-pyrrolidinone (62).—Sodamide (1.24 g, 0.032 mole) was suspended in 30 ml of dry toluene and stirred at room temperature while 8.24 g (0.064 mole) of 1-isopropyl-3-pyrrolidinol was added dropwise, and the mixture was stirred for 1.5 hr at 100°. After cooling to 30°, 10 g (0.029 mole) of 4-(2-chloroethyl)-1-isopropyl-3,3-diphenyl-2-pyrrolidinone was added portionwise. The mixture was heated and stirred at 100° overnight and cooled, and the product was extracted into 40 ml of 6 *N* HCl. The aqueous layer was made strongly basic with 50% NaOH. The resulting oil was extracted into 100 ml of ether, dried (Na_2SO_4), concentrated, and distilled at reduced pressure. The fraction taken at 220–230° (0.07 mm) was redistilled, bp 232–234° (0.1 mm).

Dimethylaminoethyl 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionate Methobromide (64).—To an ether solution of 10 g (0.024 mole) of dimethylaminoethyl 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)]propionate was added 3.4 g (0.027 mole) of CH_3Br in ether. White crystals formed which were recrystallized three times from ethyl methyl ketone containing a few drops of CH_3OH.

Diethylaminoethyl 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinone)]propionate Methiodide (65).—A stream of HCl was bubbled through a refluxing solution of 20 g (0.057 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinone)] propionic acid and 8 g (0.068 mole) of diethylaminoethanol in 250 ml of $CHCl_3$ for 5 hr. The solution was washed with three 200-ml portions of water followed by 200 ml of dilute NaOH. The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in 75 ml of isobutyl methyl ketone, and 8.0 g (0.057 mole) of CH_3I was added. The resulting crystals were recrystallized once from isobutyl methyl ketone containing a small amount of CH_3OH and once from 2-propanol.

Method T. 4-(2-Chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinethione (69).—Potassium sulfide (25 g, 0.23 mole) and P_2S_5 (23.3 g, 0.105 mole) were ground together and placed in a solution of 150 g (0.44 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 700 ml of dry toluene, and the mixture was refluxed with stirring for 24 hr, filtered while hot, treated with decolorizing carbon, filtered again, and allowed to cool, giving a crystalline precipitate, yield 88 g (56%), mp 148–150°. On recrystallization from toluene, mp 149–151°.

3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinethione)]propionyl Chloride.—To a stirred refluxing solution of 30 g (0.082 mole) of 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinethione)]propionic acid in 400 ml of dry C_6H_6 was added dropwise 10.7 g (0.090 mole) of $SOCl_2$ and refluxing was continued for 1 hr after addition. The product was used without further characterization in the preparation of **73**–**75**.

Dimethylaminoethyl 3-[4-(3,3-Diphenyl-1-isopropyl-2-pyrrolidinethione)]propionate Methiodide (80).—Dimethylaminoethyl 3-[4-(3,3-diphenyl-1-isopropyl-2-pyrrolidinethione)]propionate hydrochloride (5.0 g, 0.0105 mole) was partitioned between 75 ml of isobutyl methyl ketone and 50 ml of dilute NaOH. The organic layer was dried (Na_2SO_4) and 1.6 g (0.011 mole) of CH_3I was added. The resulting crystals were recrystallized from ethanol.

3,3-Diphenyl-1-isopropyl-4-[2-(4-methyl-1-piperazinyl)ethyl]-2-pyrrolidinethione (81).—To a solution of 20 g (0.056 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinethione in 300 ml of boiling toluene was added 11.2 g (0.112 mole) of 1-methylpiperazine. The solution was refluxed 20 hr during which time an oil separated. The mixture was washed with 300 ml of dilute NaOH followed by 300 ml of H_2O. Sufficient $CHCl_3$ was added to bring about complete solution (some precipitation from the toluene had occurred). The solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from isopropyl ether; yield 16 g (68%), mp 115–130°. Three crystallizations from isopropyl ether yielded 7 g with unchanged melting range. The solid was dissolved in 100 ml of isobutyl methyl ketone and treated with 3 g of HCl in 100 ml of isobutyl methyl ketone. An oil separated which was dissolved by adding a little CH_3OH to the boiling mixture. The crystals obtained on cooling were partitioned between 100 ml of $CHCl_3$ and 100 ml of dilute NaOH. The $CHCl_3$ was dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was crystallized from isopropyl ether.

Correction.—We would like to take this opportunity to correct an error in part I[1] of this series. In Table IV the structure of compounds **29** and **33** are reversed; therefore, the data reported in Tables IV and VI for **29** are for 4-[2-(2,6-dimethylmorpholino)ethyl]-3,3-diphenyl-1-isopropyl-2-pyrrolidinone, and the data reported for **33** are for 4-[2-(3,5-dimethylmorpholino)ethyl]-3,3-diphenyl-1-isopropyl-2-pyrrolidinone.

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