4-(β-Substituted ethyl)-3,3-diphenyl-2-pyrrolidinones. A New Series of CNS Stimulants[1]

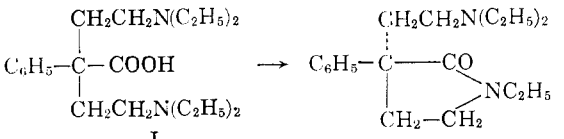
By CARL D. LUNSFORD, ALBERT D. CALE, JR., JOHN W. WARD, BERNARD V. FRANKO, AND HERNDON JENKINS

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

Received October 11, 1963

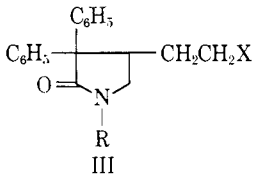
The conversion of α-(1-substituted 3-pyrrolidinyl)-α,α-diphenylacetic acids (IVb) to the corresponding acid chlorides (IVc) is followed by the facile "rearrangement" of the latter to 1-substituted 4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinones (III, X = Cl). Several such compounds have been prepared and this series has been extended by replacement of the halogen with a variety of bases. Proof that the materials have the 2-pyrrolidinone structure and evidence that their formation from the acid chlorides (IVc) proceeds through a transitory quaternary amide (VI) are presented. The starting acids are prepared by hydrolysis of the corresponding nitriles (IVa) which, in turn, are obtained by alkylation of diphenylacetonitrile with an appropriate 1-substituted 3-chloropyrrolidine. Members of this series of pyrrolidinones fall into two pharmacological activity classes—those which exhibit pronounced central nervous system (CNS) and respiratory stimulation in the dog, usually accompanied by varying degrees of pressor activity, and those which exhibit depressor activity with little or no CNS stimulation. One compound, 3,3-diphenyl-1-ethyl-4-(2-morpholinoethyl)-2-pyrrolidinone hydrochloride hydrate (XII), selected for extensive evaluation, produces prolonged respiratory stimulation and marked analeptic signs in the phenobarbital anesthetized dog at doses significantly below the convulsive dose.

The conversion of γ-dimethylamino-α,α-diphenyl-β-methylbutyryl chloride to 1,4-dimethyl-3,3-diphenyl-2-pyrrolidinone was reported by Gardner, *et al.*,[2] in 1948, and this type of reaction was subsequently studied by others.[3] A typical example, observed by Clark,[3b] is the formation of 3-(2-diethylaminoethyl)-1-ethyl-3-phenyl-2-pyrrolidinone (II) from α,α-bis(diethylaminoethyl)phenylacetic acid (I) through the corresponding acid chloride.



I II

The utility of this reaction has been increased to allow the formation of a 1-substituted 3,3-diphenyl-2-pyrrolidinone having a β-substituted ethyl group in the 4-position (III).

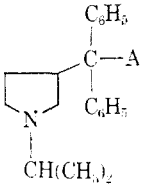


III

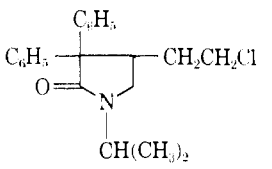
X = Cl, Br (subsequently replaced by various basic residues)
R = alkyl, cycloalkyl, benzyl

Many members of this new series of compounds are centrally acting respiratory stimulants and selected ones appear to be among the most potent compounds ever described for antagonizing phenobarbital anesthesia in the dog. It is the purpose of this report to describe the chemistry of the compounds and to present in summary form the salient features of their biological activity. The detailed pharmacology of selected members of the series will be presented elsewhere.

Chemistry.—The reaction sequence leading to the 1-substituted 4-(2-haloethyl)-3,3-diphenyl-2-pyrrolidinones (III, X = Cl or Br) is illustrated by the route used for the preparation of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (IIIa).



IVa, A = CN
b, A = COOH
c, A = COCl



IIIa, R = $CH(CH_3)_2$, X = Cl

The starting nitrile (IVa) was obtained by alkylating diphenylacetonitrile with 3-chloro-1-isopropylpyrrolidine using sodamide, and toluene as a solvent. The preparation of the 1-alkyl-3-chloropyrrolidines has been described[4] and the properties of those not previously reported are given in Table I. Hydrolysis of the nitrile (IVa) in 70% sulfuric acid at 130–140° yielded α-(1-isopropyl-3-pyrrolidinyl)-α,α-diphenylacetic acid (IVb). This acid, usually without isolation in a purified form, was converted to its hydrochloride salt and treated with thionyl chloride, effecting formation of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (IIIa) through the acid chloride (IVc). In no case was IVc isolated since rearrangement to the pyrrolidinone occurred readily when solutions of it were heated or isolation was attempted. However, appearance of the carbonyl chloride absorption in the infrared spectrum at 5.62 μ[5] and the formation of derivatives indicate clearly the existence of this intermediate. The entire course of the reaction, from

(1) Presented in part before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) J. H. Gardner, N. R. Easton, and J. R. Stevens, *J. Am. Chem. Soc.*, **70**, 2906 (1948).

(3) (a) D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949); (b) R. L. Clark, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, **71**, 2821 (1949); (c) P. Lucas, R. L. Clark, and A. Mooradian, U. S. Patents 2,555,353, 2,555,354 (1951).

(4) B. V. Franko and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960).

(5) All spectra reported were obtained in chloroform on a Beckman IR-4 spectrophotometer.

TABLE I

1-SUBSTITUTED 3-CHLOROPYRROLIDINES

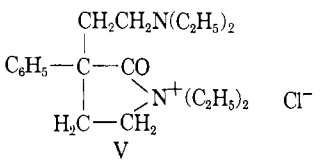
R	M.p. [b.p. (mm.)], °C.	$n^{25}D$	Empirical formula	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found
CH_3	[135 (760)]	1.4572	$C_5H_{10}ClN$			11.71
						11.50
(Picrate)	211–214		$C_{11}H_{13}ClN_4O_7$	37.88	3.76	
				37.95	3.65	
C_2H_5	[155 (760)]	1.4598	$C_6H_{12}ClN$			10.48
						10.47
(Picrate)	153		$C_{12}H_{15}ClN_4O_7$	39.73	4.17	15.45
				39.99	4.12	15.31
i-C_3H_7	[174 (760)]	1.4621	$C_7H_{14}ClN$			9.49
						9.58
(Picrate)	172–173		$C_{13}H_{17}ClN_4O_7$	41.44	4.55	14.87
				41.50	4.66	15.18
i-C_4H_9[a]	[99–105 (39)]	1.4538	$C_8H_{16}ClN$	59.43	9.98	8.66
				60.01	10.07	8.95
(Picrate)	119–120		$C_{14}H_{19}ClN_4O_7$	43.03	4.90	
				43.15	4.87	
CH_2—C_4H_8—CH	[68 (0.02)]	1.4962	$C_{10}H_{18}ClN$	63.98	9.66	7.46
				64.26	9.87	7.44
(Picrate)	158–159		$C_{16}H_{21}ClN_4O_7$	46.10	5.08	
				46.35	5.18	
$C_6H_5CH_2$	[139 (20)]	1.5384	$C_{11}H_{14}ClN$			7.16
						7.21
(HCl salt)	131–132		$C_{11}H_{15}Cl_2N$			Cl, 15.27
						15.22
(Picrate)	133–137		$C_{17}H_{17}ClN_4O_7$	48.06	4.03	
				47.61	3.88	

[a] See ref. 4.

nitrile to pyrrolidinone, was easily monitored without intermediate isolation by observing the absorption in the nitrile and carbonyl regions of the infrared spectra.

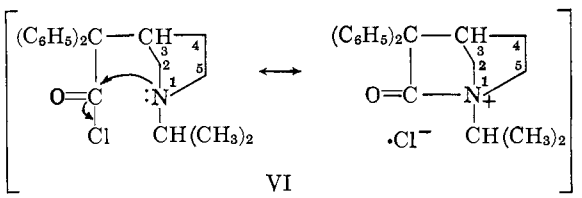
The starting nitriles are given in Table II, and the 2-pyrrolidinones which resulted from the reaction sequence are listed in Table III.

Clark[3b] has described the conditions for the general reaction and indicates that the rearrangement of the acid chloride corresponding to the acid (I) appears to go through a transitory quaternary ammonium ion (V) which then decomposes with the elimination of a molecular equivalent of alkyl halide.



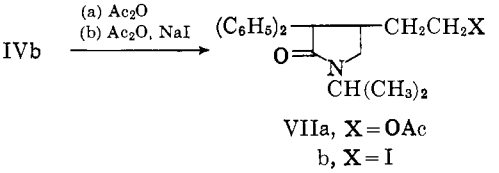
V

In the conversion of the acid chlorides analogous to IVc to the corresponding pyrrolidinones (IIIa; III, X = Cl), evidence supports the formation of such an intermediate quaternary amide which in this case would have the formula VI



VI

The pyrrolidinone (IIIa) would then result from this intermediate by displacement of the nitrogen atom from C-5 by chloride ion. The mild conditions required for this bond cleavage strongly suggest a greatly weakened 1–5 bond of the pyrrolidine ring. This activation may be attributed to formation of the proposed intermediate. If the quaternary (VI) is, in fact, an intermediate then other nucleophiles should be capable of reaction at position 5 which would result in various 4-(β-substituted ethyl)-2-pyrrolidinones where the 4-β-substituent corresponds to the reacting ion. In fact, when the acid (IVb) was treated with acetic anhydride under conditions required for the formation of the mixed anhydride, 4-(2-acetoxyethyl)-1-isopropyl-3,3-diphenyl-2-pyrrolidinone (VIIa) resulted and under the same conditions addition of an excess of sodium iodide resulted in the formation of the 4-(2-iodoethyl) compound (VIIb). This iodo compound, which was identical with that obtained from IIIa by displacement of the chloro group



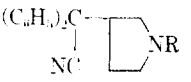
VIIa, X = OAc

b, X = I

by iodide, was not formed from the acetate (VIIa) under conditions identical with those required for its formation from the acid (IVb). This indicates that the acetate (VIIa) was not an intermediate and that the iodo compound was formed by attack of iodide ion on

TABLE II

α-(1-SUBSTITUTED 3-PYRROLIDINYL)-α,α-DIPHENYLACETONITRILES

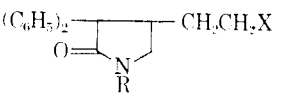


R	M.p. [b.p. (mm.)], °C.	Empirical formula	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found
CH_3	81–82[a]	$C_{19}H_{20}N_2$	82.57	7.29	10.14
	[183–186 (0.75)]		82.82	7.45	9.72
C_2H_5	83–84[a]	$C_{20}H_{22}N_2$	82.72	7.64	9.65
	[170–180 (0.15)]		82.83	7.78	9.47
(Picrate)	174–175[d]	$C_{26}H_{25}N_5O_7$	60.11	4.85	
			60.06	4.96	
i-C_3H_7	73–74[a]	$C_{21}H_{24}N_2$	82.85	7.95	9.20
	[175–177 (0.25)]		82.88	7.89	9.05
(Picrate)	215	$C_{27}H_{27}N_5O_7$	60.78	5.10	
			61.04	4.99	
i-C_4H_9	76–77[b]	$C_{22}H_{26}N_2$	82.97	8.23	8.80
	[190–200 (0.15)]		83.21	8.12	8.62
(Picrate)	213–214	$C_{28}H_{29}N_5O_7$	61.42	5.34	
			61.70	5.10	
CH_2—C_4H_8—CH	90[c]	$C_{24}H_{28}N_2$	83.67	8.19	8.13
	[195–200 (0.005)]		83.23	8.33	7.78
(Picrate)	228–229	$C_{30}H_{31}N_5O_7$	62.81	5.45	
			62.93	5.43	
$C_6H_5CH_2$	[215–218 (0.01)]	$C_{25}H_{24}N_2$	85.19	6.86	7.95
			84.93	6.93	7.75
(Picrate)	164–165	$C_{31}H_{27}N_5O_7$	64.02	4.68	
			63.76	4.56	

[a] Recrystallized from isooctane. [b] Recrystallized from ethanol–water. [c] Recrystallized from propylene glycol. [d] All picrates were recrystallized from ethanol or ethanol–water. [e] D. E. Ames, *J. Chem. Soc.*, 2780 (1960).

TABLE III

1-SUBSTITUTED 4-(β-SUBSTITUTED ETHYL)-3,3-DIPHENYL-2-PYRROLIDINONES



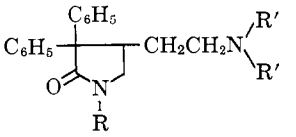
Compound	R	X	M.p., °C.	Empirical formula	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found	% X Calcd. Found
2	CH_3	Cl	140–141[a]	$C_{19}H_{20}ClNO$	72.71	6.42	4.46	Cl, 11.30
					72.87	6.44	4.48	11.05
1	C_2H_5	Cl	117–119[a]	$C_{20}H_{22}ClNO$	73.27	6.76	4.27	Cl, 10.82
					73.50	6.82	4.35	10.68
11	C_2H_5	Br	129–130[b]	$C_{20}H_{22}BrNO$	64.52	5.96	3.76	Br, 21.47
					64.26	5.99	3.96	21.39
3	i-C_3H_7	Cl	106–108[a]	$C_{21}H_{24}ClNO$	73.77	7.08	4.10	Cl, 10.37
					73.52	6.79	4.16	10.10
	n-C_8H_{17}	Cl	54–56.5[d]	$C_{28}H_{34}ClNO$			3.40	
							3.61	
	i-C_4H_9	Cl	113.5–114.5[a]	$C_{22}H_{26}ClNO$	74.24	7.36	3.94	Cl, 9.96
					74.37	7.45	3.98	9.78
4	CH_2—C_4H_8—CH-	Cl	151–152[c]	$C_{24}H_{28}ClNO$	75.47	7.39	3.67	Cl, 9.28
					75.50	7.86	3.82	9.05
5	$C_6H_5CH_2$	Cl	110[a]	$C_{25}H_{24}ClNO$	77.05	6.18	3.59	Cl, 9.10
					77.28	5.99	3.69	8.95
35	i-C_3H_7[e]	I	147–149[c]	$C_{21}H_{24}INO$	58.20	5.58		I, 29.29
					58.05	5.37		29.04

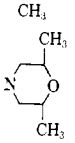
[a] Recrystallized from isopropyl ether. [b] Recrystallized from methanol–water. [c] Recrystallized from isopropyl ether–ethyl acetate. [d] Recrystallized from petroleum ether. [e] Prepared from the corresponding Cl compound.

the proposed intermediate quaternary amide (VI, where Cl is replaced by OAc).

With the evidence supporting the formation of this intermediate (VI) or an alternative concerted reaction mechanism, which the evidence does not eliminate, it becomes obvious that there are three ways the reaction can proceed from this point: attack by the chloride ion can occur (1) at position 2 of the original pyrrolidine ring forming a 2-piperidinone (VIII); or (2) at the N-alkyl substituent, resulting in its elimination as an equivalent of alkyl halide and the formation of an azabicycloheptane; or (3) at position 5 form-

TABLE IV: 1-SUBSTITUTED 4-(β-AMINOETHYL)-3,3-DIPHENYL-2-PYRROLIDINONES

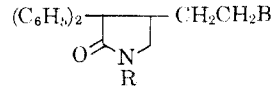


R (compound)	NR′R′	Salt	M.p., °C.	Recryst. solvent	Empirical formula	% C Calcd. Found	%H Calcd. Found	%N Calcd. Found	Misc. Calcd. Found
C_2H_5 (8)	N-$(CH_3)_2$	HCl·H_2O	161–164	[a]	$C_{22}H_{31}ClN_2O_2$	67.58 67.75	8.00 8.05	7.17 7.27	Cl, 9.07 9.04 H_2O, 4.60 4.80
C_2H_5 (43)	NH-CH_2CH_2OH	HCl	209.5–211.5	[b]	$C_{22}H_{29}ClN_2O_2$	67.94 67.87	7.51 7.56	7.20 7.36	
C_2H_5	N-$(CH_2CH_2OH)_2$	HCl	196–198	[b]	$C_{24}H_{33}ClN_2O_3$	66.57 66.63	7.68 7.74		
C_2H_5 (15)	N-$(n\text{-}C_4H_9)_2$		b.p. 205–210(0.05)		$C_{28}H_{40}N_2O$	79.95 79.82	9.59 9.45	6.66 6.41	
C_2H_5 (12)	Pyrrolidino	HCl·H_2O	169–172	[c]	$C_{24}H_{33}ClN_2O_2$	69.13 69.23	7.97 8.75	6.72 6.73	Cl, 8.50 8.58
C_2H_5 (14)	Piperidino		89	[d]	$C_{25}H_{32}N_2O$	79.74 79.89	8.57 8.60	7.44 7.70	
$i\text{-}C_3H_7$ (37)	NH_2		102–103.5	[e]	$C_{21}H_{26}N_2O$	78.22 78.38	8.13 8.05	8.69 8.57	
$i\text{-}C_3H_7$ (22)	$NHCH_3$	HCl	237–239	[a]	$C_{22}H_{29}ClN_2O$	70.85 70.93	7.84 7.99	7.51 7.56	Cl, 9.51 9.79
$i\text{-}C_3H_7$	N$(CH_2CH_2OH)_2$	HCl	197–200	[b]	$C_{26}H_{35}ClN_2O_3$	67.17 66.95	7.89 7.89	6.27 7.56	
$i\text{-}C_3H_7$ (24)	N′-methylpiperazino	2HCl·$2H_2O$	185–189	[a]	$C_{26}H_{41}Cl_2N_3O_3$	60.69 59.92	8.03 7.64	8.17 8.26	Cl, 13.78 13.89 H_2O, 7.00 7.60
$i\text{-}C_3H_7$ (25)	N′-phenylpiperazino	HCl·$2H_2O$	145–151	[f]	$C_{31}H_{42}ClN_3O_3$	68.92 68.95	7.84 7.31	7.78 7.77	Cl, 6.57 6.78 H_2O, 6.67 6.66
$i\text{-}C_4H_9$ (7)	$N(CH_3)_2$	HCl	154–155	[g]	$C_{24}H_{33}ClN_2O$	71.88 72.08	8.29 8.42	6.99 7.25	Cl, 8.84 8.53
$i\text{-}C_4H_9$ (9)	$N(CH_3)_2$	CH_3Br	218–219	[c]	$C_{25}H_{35}BrN_2O$	65.35 65.49	7.68 7.87	17.39 17.30	Br, 6.10 6.25
$C_6H_5CH_2$ (6)	$N(CH_3)_2$	HCl·H_2O	181–183	[a]	$C_{27}H_{33}ClN_2O_2$	71.58 71.90	7.34 7.65	6.19 6.29	Cl, 7.83 8.05 H_2O, 3.98 3.80
$i\text{-}C_3H_7$ (30)	$N(C_2H_5)_2$	Fumarate	156–159	[c]	$C_{29}H_{38}N_2O_5$	70.42 70.66	7.74 7.76	5.65 5.65	
$i\text{-}C_3H_7$ (32)	Hexamethyleneimino	Fumarate	163–165	[h]	$C_{31}H_{40}N_2O_5$	71.51 71.51	7.74 7.50	5.38 5.38	
$i\text{-}C_3H_7$ (20)	CH_3NCOCH_3		120–121	[i]	$C_{24}H_{30}N_2O$	76.15 76.01	7.99 7.97	7.40 7.54	
$i\text{-}C_3H_7$ (34)	Phthalimido		164–166	[j]	$C_{29}H_{28}N_2O_3$	76.97 76.74	6.24 6.29	6.19 6.11	
H (41)	Morpholino		200–202.5	[k]	$C_{22}H_{28}N_2O_2$	75.40 75.41	7.48 7.18	7.99 8.23	
CH_3	Morpholino		130–131	[j]	$C_{23}H_{28}N_2O_2$	75.79 75.89	7.74 7.79	7.69 7.58	
C_2H_5 (13)	Morpholino	HCl·H_2O	217–219	[e]	$C_{24}H_{33}ClN_2O_3$	66.57 66.60	7.68 7.53	6.47 6.52	Cl, 8.19 8.22
C_2H_5	Morpholino	Benzoate	123–124		$C_{31}H_{36}N_2O_4$	74.37 74.55	7.25 7.16	5.60 5.59	
C_2H_5 (39)	Morpholino	CH_3Br	247–250	[b]	$C_{25}H_{33}BrN_2O_2$	63.42 63.31	7.03 7.03	5.92 6.05	
$i\text{-}C_3H_7$ (26)	Morpholino	HCl·H_2O	182–185	[a]	$C_{25}H_{35}ClN_2O_3$	66.87 67.08	8.31 7.79	6.24 6.10	Cl, 7.90 8.18
$n\text{-}C_8H_{17}$ (40)	Morpholino	HCl·H_2O	150.5–152.5	[m]	$C_{36}H_{45}ClN_2O_3$			5.42 5.61	
$C_6H_5CH_2$ (42)	Morpholino		97–98	[n]	$C_{29}H_{32}N_2O_2$	79.05 78.81	7.32 7.33	6.36 6.34	
$i\text{-}C_3H_7$ (38)		HCl·H_2O	225–230	[b]	$C_{25}H_{35}ClN_2O_2S$	64.84 65.94	7.62 7.57	6.05 6.05	Cl, 7.67 7.76 H_2O, 3.89 3.3
$i\text{-}C_3H_7$ (29)		Maleate	177–178	[h]	$C_{31}H_{40}N_2O_6$	69.39 69.29	7.51 7.62	5.22 5.22	
$i\text{-}C_3H_7$ (33)		Maleate	149–150	[h]	$C_{31}H_{40}N_2O_6$	69.39 69.40	7.51 7.46	5.22 5.24	

[a] Isobutyl methyl ketone. [b] Isobutyl methyl ketone–methanol. [c] Ethyl methyl ketone. [d] Methanol–water. [e] Isopropyl ether. [f] Ethanol–hydrochloric acid. [g] Toluene–isobutyl methyl ketone. [h] Ethanol–ether. [i] Isopropyl ether–ethyl acetate. [j] Ethanol–water. [k] Ethyl acetate. [l] 2N Hydrochloric acid. [m] Ethyl alcohol–Ligroin.

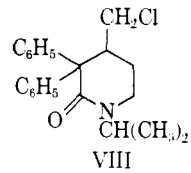
TABLE V

1-SUBSTITUTED 4-(β-SUBSTITUTED ETHYL)-3,3-DIPHENYL-2-PYROLIDINONES



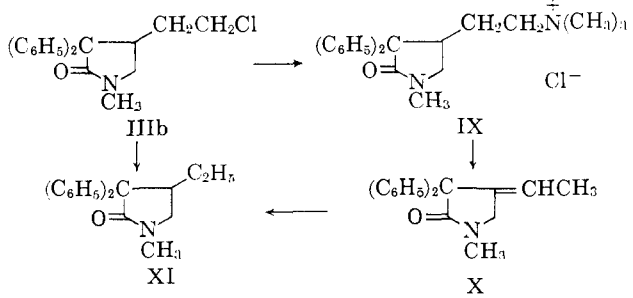
R (Compound)	B	M.p., °C.	Empirical formula	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found	Misc. Calcd. Found
i-C_3H_7	$OCOCH_3$	91–94[a]	$C_{23}H_{27}NO_3$	75.58	7.45	3.83	
(18)				75.75	7.32	3.90	
i-C_3H_7	SH	104–107[b]	$C_{21}H_{25}NOS$	74.29	7.42	4.13	S, 9.44
(21)				74.54	7.54	4.23	9.73
i-C_3H_7	SCH_3	123–125[b]	$C_{22}H_{27}NOS$	74.74	7.70	3.96	S, 9.07
(23)				74.87	7.91	4.15	8.65
i-C_4H_9	OCH_3	86–87[a]	$C_{23}H_{29}NO_2$	78.59	8.32	3.99	
(27)				78.58	8.21	4.04	
i-C_3H_7	OCH_3	105–106[a]	$C_{22}H_{27}NO_2$	78.30	8.07	4.15	
(10)				78.10	7.90	4.17	
i-C_3H_7	OC_6H_5	104–106[b]	$C_{27}H_{29}NO_2$	81.17	7.32	3.51	
(16)				81.32	7.40	3.53	
i-C_3H_7	OH	180–182[b]	$C_{21}H_{25}NO_2$	77.98	7.79	4.33	
(17)				78.25	7.90	4.32	
i-C_3H_7		135–137[b]	$C_{28}H_{31}NO_3$	78.29	7.28	3.26	
(19)				78.03	7.50	3.42	

[a] Recrystallized from methanol–water. [b] Recrystallized from ethanol–water.



VIII

ing a 2-pyrrolidinone (IIIa) as has proven to be the case. The second possibility can be eliminated since the actual product is isomeric with the starting acid chloride. To establish that the 2-pyrrolidinone (IIIa) and not the 2-piperidinone (VIII) was, in fact, the product of the reaction, the following sequence of reactions was completed.



IIIb was converted to the 4-(β-trimethylammonium) compound (IX) which was then degraded under the Hofmann conditions. The infrared spectrum indicated that the resulting double bond shifted from the terminal position giving the 4-ethylidene-2-pyrrolidinone (X). This was catalytically reduced to 3,3-diphenyl-4-ethyl-1-methyl-2-pyrrolidinone (XI) which was also obtained by zinc–acetic acid reduction of IIIb. The infrared spectrum of XI corresponded closely to those of 3,3-diphenyl-1-methyl-2-pyrrolidinone[3a] and 1,4-dimethyl-3,3-diphenyl-2-pyrrolidinone,[2] with the lactam carbonyl absorption occurring in each case at 5.89 μ. The similar six-membered ring lactam, 3,3-diphenyl-1-methyl-2-piperidinone, prepared from δ-dimethylamino-α,α-diphenylvaleric acid, absorbs at the longer wave length 6.08 μ. This infrared evidence, which corresponds to published work,[6] is taken as proof that the rearrangement in the present series, *i.e.*, the acid chloride (IVc) to the 2-pyrrolidinone (IIIa), occurs in the manner indicated. By analogy and the fact that they all show carbonyl absorption at 5.89–5.92 μ it is concluded that all members of the series of lactams reported have this 2-pyrrolidinone structure.

The 4-(β-halogen) of the 2-pyrrolidinones (III, X = Cl or Br) has been replaced by a variety of amines and other bases resulting in the compounds presented in Tables IV and V, respectively.

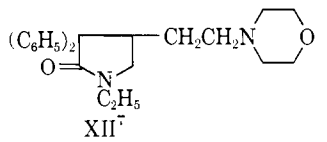
Pharmacology.—Some of the 2-pyrrolidinones of Tables III, IV, and V were found to be unusually effective in stimulating respiration in the phenobarbital anesthetized dog. The frequency and amplitude of breathing was increased markedly and the duration of these effects was often in excess of 60 min. even after relatively small intravenous doses. The strong respiratory stimulants were also found (a) to be powerful antagonists to the barbiturate anesthetic and (b) to produce prolonged pressor effects (Table VI). In general, respiratory stimulation and pressor activity were the first effects observed and were quite apparent at doses which did not cause pronounced antianesthetic activity.

Other compounds of this series produced only depressor effects (Table VI). In general, the depressor agents (a) had little or no direct effect on respiration and (b) caused little or no antagonism to the anesthetic. Only two compounds (**10** and **27**) caused convulsions. Although it may be coincidental, it is interesting to note that in each case the β-substituent of the 4-ethyl group is methoxyl.

It is difficult to differentiate the degree of activity of many of the 2-pyrrolidinones where the β-substituent of the 4-ethyl group is varied, *i.e.*, chloro, mercapto, phenoxy, and acetoxy. More specificity does exist in the amine compounds. When this group (NR_2',

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 214.

Table IV) is dimethylamino and the N-substituent is ethyl (**8**), the compound produces a marked and prolonged hypotension in the anesthetized dog; however, the corresponding morpholino compound (XII, **13**) has proven to be one of the most interesting pressor



XII[7]

agents, respiratory stimulants, and CNS stimulants of the series. This compound has undergone extensive pharmacological evaluation which will be the subject of separate reports. It is currently being studied clinically[8] for various conditions involving hypoventilation or respiratory arrest.

Nikethamide, studied for comparison, required intravenous doses of 40–80 mg./kg. to produce a modest effect on respiration. This effect was extremely brief in nature no matter what dose was used. In contrast, it was possible to stimulate respiration for several hours following a single injection of XII. It was impossible to elicit any observable analeptic effects with nikethamide at doses up to lethal.

It can be seen from Table VI that the 4-(2-morpholinoethyl) compounds are unique among the amino-substituted derivatives. Substitution with other heterocyclic amines [*e.g.*, pyrrolidine (**12**), piperidine (**14**), and hexamethyleneimine (**32**)] causes a marked diminution in activity. Hindrance of the nitrogen of the morpholino substituent, a probable site of metabolism, by methyl substitution in the morpholine nucleus (**29**, and **33**) produced an increase in duration of effect.

Substitution at the nitrogen of the pyrrolidinone ring was necessary for antianesthetic activity and was optimum for the smaller alkyl groups. The N-unsubstituted compound (**41**) and the N-octyl derivative (**40**) were void of activity. Quaternization of XII produced an inactive compound (**39**).

Experimental[9]

Synthesis.—The **1-substituted 3-chloropyrrolidines** were prepared by the method previously described[4] for 3-chloro-1-isobutylpyrrolidine. The bases were characterized as their picrate or hydrochloride salts. Properties and analyses are detailed in Table I.

α-(1-Isopropyl-3-pyrrolidinyl)-α,α-diphenylacetonitrile.—This method is typical of that used for each of the compounds of Table II in which the properties and analyses are reported. A suspension of the sodium salt of diphenylacetonitrile was formed by the addition of 193 g. (1.0 mole) of diphenylacetonitrile to a stirred suspension of 43 g. (1.1 moles) of sodamide in 1 l. of dry toluene. The mixture was refluxed for 4 hr., and then to the refluxing mixture 148 g. (1.0 mole) of 3-chloro-1-isopropylpyrrolidine was added at a rapid dropwise rate with continuous stirring. After addition was complete, stirring and refluxing were continued for 3 hr. The mixture was then cooled and extracted with 1 *N* hydrochloric acid. The aqueous layer together with the insoluble oily hydrochloride was separated, made basic with dilute sodium hydroxide, and extracted with ether. The ethereal solution was dried over sodium sulfate and concentrated, and the residue was distilled *in vacuo;* yield, 238 g. (78%).

TABLE VI

EFFECTS OF 1-SUBSTITUTED 4-(β-SUBSTITUTED ETHYL)-3,3-DIPHENYL-2-PYRROLIDINONES ADMINISTERED INTRAVENOUSLY TO ANESTHETIZED DOGS

Compound	Minimum dose observed to stimulate respiration, mg./kg.	Predominant blood pressure effects	Antianesthetic[e] effects
1[a]	2	Pressor	++
2[a]	2	Pressor	+++
3[a]	2	Pressor	+++
4[b]	2	Pressor	++
5[a]	5	Pressor	++
6[c] (HCl salt)	<1[d]	Depressor	+
7[c]	<1[d]	Depressor	+
8[c]	<1[d]	Depressor	+
9[c]	(Respiratory depressant)	Depressor	−
10[a]	1	Pressor	++
11[a]	1	Pressor	++
12[c]	5	Depressor	+
13[c]	<1	Pressor	++++
14[c] (HCl salt)	8	Pressor	±
15[a]	2	Pressor	+
16[a]	1	Pressor	++
17[a]	2	Pressor	++
18[a]	1	Pressor	+++
19[a]	1	Pressor	+++
20[a]	1	Pressor	+++
21[a]	1	Pressor	+++
22[c]	8	Depressor	+
23[a]	1	Pressor	+++[f]
24[c]	4	Pressor	±
25[a]	4	Depressor	±
26[c]	<1	Pressor	+++
27[a]	2	Pressor	+++
28[a]	4	Pressor	+
29[a]	1	Pressor	+++[f]
30[c]	2	Pressor	+
31[a]	16	Depressor	−
32[a]	4	Pressor	−
33[a]	<1	Pressor	++++[f]
34[a]	<1	Pressor	++++[f]
35[a]	1	Pressor	+++[f]
36[c]	4	Pressor	+
37[a]	(Respiratory depressant)	Depressor	−
38[c]	1	Pressor	++
39[a]	4[g]	Pressor	−
40[a]	16	Pressor	−
41[c] (HCl salt)	8	Depressor	−
42[a]	8	Pressor	+
43[c]	16	Depressor	−
Nikethamide	40	Depressor	−

[a] Administered as a solution in propylene glycol. [b] Dimethylacetamide. [c] Water. [d] At high doses, respiratory stimulation coincides with hypotensive period. [e] − No activity; ± Questionable; + Very slight; ++ Slight; +++ Moderate; ++++ Marked. [f] Long duration of activity. [g] Respiratory effects coincided with blood pressure effects which were depressor followed by pressor at lower doses and pressor at higher doses.

The picrate salt crystallized from an ethanolic solution of equimolar quantities of acid and base.

α-(1-Isopropyl-3-pyrrolidinyl)-α,α-diphenylacetic Acid.—A solution of 36 g. (0.12 mole) of α-(1-isopropyl-3-pyrrolidinyl)-α,α-diphenylacetonitrile in 120 g. of 70% sulfuric acid was heated at 128–134° for 64 hr. The hot solution was poured onto 100 g. of ice and this mixture was made strongly basic with 50% sodium

(7) Nonproprietary name of HCl salt hydrate is doxapram hydrochloride.

(8) See, for example, A. J. Wasserman and D. W. Richardson, *J. Clin. Pharmacol. Therap.*, **4**, 321 (1963); H. G. Canter, *Am. Rev. Respirat. Diseases*, **87**, 830 (1963).

(9) Melting points are corrected and were determined with a Drechsel apparatus. Boiling points are uncorrected.

hydroxide. The water was removed at reduced pressure and the residue was extracted with two 250-ml. portions of boiling absolute alcohol. The alcoholic extracts were dried at reduced pressure and the combined residue was dissolved in 400 ml. of water. Glacial acetic acid was added until no more precipitate formed. The precipitated solid was collected and dried; yield, 34.1 g. (88%). The material was recrystallized from dimethylformamide; m.p. 248–250° dec.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.79; H, 7.99; N, 4.13.

α-(1-Ethyl-3-pyrrolidinyl)-α,α-diphenylacetic acid was prepared in an analogous manner and was recrystallized from an ethanol–benzene mixture; m.p. 136–139° dec.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.41; H, 7.33.

The **1-substituted 4-(2-haloethyl)-3,3-diphenyl-2-pyrrolidinones** were generally prepared from the nitriles of Table II without isolation of the intermediate acid (Method A). This method is typical of that used for each of the 4-(2-chloroethyl) compounds of Table III in which the properties and analyses are reported. Method B illustrates the conversion of the purified acids to the pyrrolidinones.

4-(2-Chloroethyl)-3,3-diphenyl-1-isobutyl-2-pyrrolidinone (III, X = Cl, R = Isobutyl). A.—A solution of 100 g. (0.314 mole) of α-(1-isobutyl-3-pyrrolidinyl)-α,α-diphenylacetonitrile in 500 g. of 70% sulfuric acid was heated at 130–140° for 48 hr., poured onto ice, made strongly basic with sodium hydroxide, and extracted with chloroform. (Depending on the concentration and on the substituent on nitrogen, the sodium salt of the amino acid may either dissolve in the chloroform layer or form a separate third layer between the water and chloroform.) The aqueous layer was discarded and the chloroform extract was acidified with hydrogen chloride gas, dried over sodium sulfate, and concentrated. The residue was refluxed in 500 ml. of thionyl chloride for 3 hr. The resulting solution was concentrated *in vacuo* and the residue was crystallized from isopropyl ether; yield, 69 g. (62%).

4-(2-Chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone [III, X = Cl, R = C_2H_5 (1)]. B.—A suspension of 2.5 g. (0.0081 mole) of α-(1-ethyl-3-pyrrolidinyl)-α,α-diphenylacetic acid in 100 ml. of dry chloroform was treated with dry HCl gas until solution was complete. Two ml. of thionyl chloride was added and the mixture was refluxed for 2 hr. and concentrated *in vacuo*. The residue was crystallized from isopropyl ether; yield, 2 g. (75%); m.p. 118–120°.

4-(2-Bromoethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone [III, X = Br, R = C_2H_5 (11)]. C.—A solution of 31.5 g. (0.091 mole) of crude α-(1-ethyl-3-pyrrolidinyl)-α,α-diphenylacetic acid hydrochloride and 42.8 g. (0.21 mole) of thionyl bromide in 70 ml. of chloroform was refluxed for 7 hr. The infrared spectrum, carbonyl region, indicated formation of the acyl bromide but no rearrangement to the pyrrolidinone. The solution was treated with 50 ml. of morpholine dropwise with stirring and then extracted with dilute hydrochloric acid, concentrated, and the residue was dissolved in 200 ml. of boiling 90% methanol. The solution was decolorized with Norite, filtered, and 25 ml. of water was added. On cooling the product precipitated and was recrystallized from a methanol–water mixture; yield, 4.0 g. (12%); m.p. 129–130°.

D.—A solution of 31.5 g. (0.091 mole) of crude α-(1-ethyl-3-pyrrolidinyl)-α,α-diphenylacetic acid hydrochloride in 20 ml. of phosphorus tribromide and 70 ml. of chloroform was refluxed for 13 hr. and concentrated *in vacuo*. The residue was crystallized from 90% methanol; yield, 5.2 g. (15%); m.p. 129–130°. The mixture of the two samples respectively prepared by methods C and D also melted at 129–130°.

4-(2-Acetoxyethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (VIIa; 18). E.—A mixture of 2.5 g. (0.0077 mole) of α-(1-isopropyl-3-pyrrolidinyl)-α,α-diphenylacetic acid and 20 ml. of acetic anhydride was refluxed 5 hr. Water (60 ml.) was then added cautiously. An oil separated which crystallized on cooling. The solid was collected and recrystallized from methanol–water (2:1); yield, 1.65 g. (59%); m.p. 94–95°.

F.—A mixture of 18 g. (0.22 mole) of sodium acetate and 70 g. (0.205 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 500 ml. of dimethylformamide was stirred and refluxed for 15 hr., partitioned between 500 ml. of water and 500 ml. of chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* and the residue crystallized from 85% aqueous methanol; yield, respectively, by Methods E and F showed no depression of the melting point. Infrared spectra of the two were identical.

3,3-Diphenyl-4-(2-iodoethyl)-1-isopropyl-2-pyrrolidinone [III, X = I, R = i-C_3H_7 (35)]. G.—A mixture of 2.30 g. (0.0071 mole) of α-(1-isopropyl-3-pyrrolidinyl)-α,α-diphenylacetic acid and 2.1 g. (0.014 mole) of sodium iodide was refluxed in 25 ml. of dry butanone and 1.0 ml. (0.011 mole) of acetic anhydride was added. Refluxing was continued for 30 min. and an additional 1.0 ml. (0.011 mole) of acetic anhydride was added. After an additional 1 hr. of reflux the solvent was removed at reduced pressure and the residue was dissolved in 25 ml. of 95% ethanol. Chilling produced a white solid which was collected and recrystallized from 95% alcohol; yield, 2.15 g. (70%); m.p. 143–146°.

H.—A mixture of 25.0 g. (0.073 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone and 12.5 g. (0.083 mole) of sodium iodide in 200 ml. of acetone was stirred and refluxed for 18 hr. About 75% of the acetone was distilled and 400 ml. of water was added slowly to the cooled mixture. The precipitated solid was recrystallized from 400 ml. of 95% ethanol; yield, 24.9 g. (79%); m.p. 144–147.5°. A mixture of the two samples prepared by methods G and H respectively, showed no depression of melting point.

The **1-substituted 4-(2-aminoethyl)-3,3-diphenyl-2-pyrrolidinones** were generally prepared from the corresponding 4-(2-chloroethyl) compounds of Table III by heating at 90–120° with an ethanolic solution of 2 *M* equiv. of the amine for a period of at least 8 hr. When the compounds were isolated as hydrochloride salts, hydrates of the salts were usually obtained. The following procedure is typical. The properties and analyses are detailed in Table IV.

4-(2-Dimethylaminoethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone Hydrochloride Hydrate (8).—A solution of 40 g. (0.122 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone and 11 g. (0.244 mole) of dimethylamine in 250 ml. of absolute ethanol was heated for 16 hr. at 100° in a sealed system and concentrated *in vacuo*. The residue was dissolved in dilute hydrochloric acid and extracted with ethyl acetate. The acid extract was made basic with sodium hydroxide and again extracted with ethyl acetate. This ethyl acetate extract was concentrated *in vacuo* and the residue was dissolved in butanone and acidified with hydrogen chloride which caused precipitation of the product; yield, 32 g. (67%); m.p. 162–166°. Drying at 125° produced the anhydrous salt which on standing at room temperature for 0.5 hr. reabsorbed its water of hydration.

Anal. Calcd. for $C_{22}H_{29}ClN_2O$ (anhydrous salt): C, 70.85; H, 7.84; N, 7.51; Cl, 9.51. Found: C, 70.50; H, 8.15; N, 7.17; Cl, 9.30.

4-[2-(N-Acetyl-N-methylamino)-ethyl]3,3-diphenyl-1-isopropyl-2-pyrrolidinone (20).—3,3-Diphenyl-1-isopropyl-4-(2-methylaminoethyl)-2-pyrrolidinone hydrochloride (27 g., 0.0725 mole) was partitioned between aqueous sodium hydroxide and chloroform. The chloroform extract was dried over anhydrous sodium sulfate, 9 g. (0.088 mole) of acetic anhydride was added, and the resulting solution was refluxed for 2 hr. and concentrated *in vacuo*. The residue was crystallized from isopropyl ether containing a little ethyl acetate; yield, 24.5 g. (89%); m.p. 120–121°.

3,3-Diphenyl-1-isopropyl-4-(2-phthalimidoethyl)-2-pyrrolidinone (34).—A mixture of 34.2 g. (0.10 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone, 20.4 g. (0.11 mole) of the potassium salt of phthalimide, and 200 ml. of dimethylformamide was stirred and refluxed for 3 hr., then cooled and left standing overnight at room temperature. The reaction mixture was then poured into 600 ml. of hot water whereupon an oil separated and solidified. This solid was collected and recrystallized from 1 l. of 95% methanol; yield, 36.3 g. (80%); m.p. 164–166°.

4-(2-Aminoethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone (37).—A solution of 176 g. (0.39 mole) of 3,3-diphenyl-1-isopropyl-4-(2-phthalimidoethyl)-2-pyrrolidinone and 15.2 g. (0.45 mole) of 95% hydrazine in 3.7 l. of 95% ethanol was refluxed 58 hr. and concentrated *in vacuo*. The residue was partitioned between 3 *N* hydrochloric acid and ether. The acid extract was made basic with concentrated sodium hydroxide and extracted with ether. The ethereal layer was washed, dried over sodium sulfate, and concentrated. The residue was crystallized from isopropyl ether; yield, 75 g. (60%); m.p. 100–102°.

3,3-Diphenyl-4-(2-morpholinoethyl)-2-pyrrolidinone (41).—To a stirred suspension of 5.0 g. (0.011 mole) of 1-benzyl-3,3-di-

phenyl-4-(2-morpholinoethyl)-2-pyrrolidinone in 200 ml. of liquid ammonia at reflux were added small pieces of sodium until a blue color persisted for 10 min. This required 0.1 g. (0.026 g.-atom) of sodium. After addition of 1.6 g. of ammonium chloride, the ammonia was allowed to evaporate and the residue was partitioned between 200 ml. of dilute sodium hydroxide and 200 ml. of chloroform. The chloroform was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crystalline residue was recrystallized from ethyl acetate; yield, 2.8 g. (73%); m.p. 201–203°.

The following two procedures are typical of those used for the oxygen ethers of Table V.

3,3-Diphenyl-1-isopropyl-4-(2-methoxyethyl)-2-pyrrolidinone (10).—A solution of 34 g. (0.10 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 150 ml. of absolute methanol in which 2.5 g. (0.11 g.-atom) of sodium had been dissolved was heated in a closed system for 16 hr. at 140°. Addition of 50 ml. of water to the resulting mixture yielded 27.5 g. (81%) of material which was recrystallized from a methanol–water mixture; m.p. 105–106°.

3,3-Diphenyl-1-isopropyl-4-(2-phenoxyethyl)-2-pyrrolidinone (16).—Sodium phenoxide was formed by adding a solution of 8.3 g. (0.088 mole) of phenol in 100 ml. of absolute ethanol to 200 ml. of absolute ethanol in which had been dissolved 2.0 g. (0.087 g.-atom) of sodium, and 30 g. (0.088 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 100 ml. of absolute ethanol was added. The resulting solution was refluxed for 7 hr., concentrated *in vacuo*, and the residue was partitioned between water and chloroform. The chloroform layer was dried with anhydrous sodium sulfate and concentrated *in vacuo* and the residue crystallized from an ethanol–water mixture; yield, 17 g. (49%); m.p. 104–106°.

3,3-Diphenyl-1-isopropyl-4-(2-mercaptoethyl)-2-pyrrolidinone (21).—A solution of 16.2 g. (0.176 mole) of sodium hydrogen sulfide dihydrate and 30 g. (0.088 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone in 400 ml. of 85% ethanol was refluxed for 7 hr. and concentrated *in vacuo*. The residue was partitioned between chloroform and water and the chloroform layer dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was distilled; yield, 17 g. (57%); b.p. 220–230° (0.05 mm.). The distillate was crystallized from an ethanol–water mixture; m.p. 104–107°.

3,3-Diphenyl-1-isopropyl-4-(2-methylmercaptoethyl)-2-pyrrolidinone (23).—A solution of 11.5 g. (0.12 mole) of methyl bromide in 200 ml. of absolute ethanol was added to a solution of 20 g. (0.059 mole) of 3,3-diphenyl-1-isopropyl-4-(2-mercaptoethyl)-2-pyrrolidinone in 200 ml. of absolute ethanol in which 1.5 g. (0.065 g.-atom) of sodium had been dissolved. The solution was stirred at room temperature for 4 hr., concentrated *in vacuo*, and the residue was partitioned between water and chloroform. The chloroform was concentrated *in vacuo* and the residue was crystallized from 70% ethanol; yield, 20 g. (96%); m.p. 123–125°.

3,3-Diphenyl-4-(2-hydroxyethyl)-1-isopropyl-2-pyrrolidinone (17).—A solution of 34 g. (0.093 mole) of 4-(2-acetoxyethyl)-3,3-diphenyl-1-isopropyl-2-pyrrolidinone and 4.0 g. (0.10 mole) of sodium hydroxide in 450 ml. of ethanol and 10 ml. of water was stirred and refluxed for 1 hr. and concentrated *in vacuo*. The residue was partitioned between chloroform and water and the chloroform layer was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue crystallized and was recrystallized from aqueous ethanol; yield, 22 g. (73%); m.p. 180–182°.

3,3-Diphenyl-4-ethylidene-1-methyl-2-pyrrolidinone (X).—4-(2-Dimethylaminoethyl)-3,3-diphenyl-1-methyl-2-pyrrolidinone methochloride was prepared by heating an ethanolic solution of 7.0 g. (0.022 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-methyl-2-pyrrolidinone and 3.0 g. (0.051 mole) of trimethylamine at 110° for 16 hr. The solution was concentrated and the residue was crystallized from acetone; yield, 6.5 g. (79%); m.p. 122–127°. Without further purification 2.0 g. (0.0054 mole) of this quaternary was dissolved in 100 ml. of water and stirred with silver oxide (freshly prepared from 5.0 g. (0.29 mole) of silver nitrate and aqueous potassium hydroxide) for 30 min. at 50°. The mixture was filtered and the filtrate concentrated. The residual oil was heated under water aspirator vacuum on a steam bath for 1.5 hr., and crystallized from isopropyl ether; yield, 0.5 g. (33%); m.p. 106–108°.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.10; H, 6.96; N, 5.01.

The principal infrared absorptions[5] occurred at 3.30, 5.85, 5.93, 6.65, and 14.20 μ.

3,3-Diphenyl-4-ethyl-1-methyl-2-pyrrolidinone (XI). J.—A solution of 0.50 g. (0.0018 mole) of 3,3-diphenyl-4-ethylidene-1-methyl-2-pyrrolidinone in 50 ml. of ethanol and 0.2 g. of 10% palladium-on-charcoal were shaken in an atmosphere of hydrogen for 1 hr., filtered, and the filtrate was concentrated. The residue was crystallized from isopropyl ether and melted at 91–93°. A mixture of this product with that prepared according to method K which had also been crystallized from isopropyl ether melted at 91–92°. When this product or that prepared according to method K was crystallized from 50% ethanol the m.p. was 100–102°.

K.—A solution of 10 g. (0.032 mole) of 4-(2-chloroethyl)-3,3-diphenyl-1-methyl-2-pyrrolidinone, 10 g. of potassium bromide, and 25 ml. of 48% hydrobromic acid in 150 ml. of acetic acid was stirred and refluxed for 2 hr. followed by addition of 20 g. of zinc dust in small portions. Another 25 ml. of 48% hydrobromic acid was added dropwise over a 2-hr. period to the refluxing solution. The mixture was cooled and filtered, the filtrate was concentrated *in vacuo*, and the residue was partitioned between chloroform and dilute sodium hydroxide. The chloroform layer was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was crystallized from 50% aqueous ethanol; yield, 6.5 g. (73%); m.p. 101–102°. When crystallized from isopropyl ether the m.p. was 91–92°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.66; H, 7.55; N, 5.21.

The principal infrared absorptions[5] occurred at 3.30, 5.89, 6.65, 14.36, and 15.51 μ.

3,3-Diphenyl-4-ethyl-1-isobutyl-2-pyrrolidinone.—This was prepared by both methods J and K. After recrystallization from aqueous ethanol, the m.p. was 94–96.5° for each product and for a mixture of the two.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.46; H, 8.58; N, 4.40.

3,3-Diphenyl-4-ethyl-1-isopropyl-2-pyrrolidinone.—This was prepared by both methods J and K. After recrystallization from aqueous ethanol, the m.p. was 95–97° for each product and for a mixture of the two.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.78; H, 8.10; N, 4.69.

5-Dimethylamino-2,2-diphenylvaleric Acid.—A solution of 60.0 g. (0.216 mole) of 5-dimethylamino-2,2-diphenylvaleronitrile in 200 ml. of 75% (wt./wt.) sulfuric acid was heated for 16 hr. at 130–135°. The cooled solution was poured onto ice and the resulting mixture made basic with excess 50% sodium hydroxide solution. When this mixture was extracted with toluene in a separatory funnel, three layers were formed. The dark center layer was removed and concentrated *in vacuo* on a steam bath until it crystallized. The sodium salt of the amino acid was extracted from this residue with 350 ml. of boiling alcohol. The alcohol was evaporated *in vacuo* on a steam bath and the residue was dissolved in 200 ml. of warm water. The solution was made slightly acidic with acetic acid, causing a white solid to precipitate. This was washed with alcohol and acetone and dried overnight; yield, 34.5 g. (54%); m.p. 211–215° dec. An analytical sample recrystallized from water (80% recovery) had m.p. 215–217.5° dec.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 75.95, 76.17; H, 7.53, 7.53; N, 4.70.

3,3-Diphenyl-1-methyl-2-piperidinone (VIII).—A suspension of 4.9 g. (0.016 mole) of 5-dimethylamino-2,2-diphenylvaleric acid in 50 ml. of chloroform was acidified with anhydrous hydrogen chloride. The chloroform was evaporated *in vacuo* and the residue refluxed 18 hr. in 50 ml. of thionyl chloride. The thionyl chloride was removed *in vacuo* on a steam bath. The residue was heated an additional 15 min. on a steam bath and dissolved in 30 ml. of alcohol. The solution was filtered, diluted with 20 ml. of water, chilled, and the crystals which formed were filtered and dried: yield, 3.35 g. (77%); m.p. 119.5–121.5°. Recrystallization from isooctane did not change the melting point.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.34; H, 7.10; N, 5.28.

The principal infrared absorptions[5] occurred at 3.30, 6.08, 6.65, 7.37, and 14.25μ.

Pharmacology. Method.—Mongrel dogs of either sex were anesthetized by the intravenous administration of phenobarbital sodium, usually 125 mg./kg. Sufficient anesthetic was always

given to abolish the corneal reflex. A carotid artery was cannulated for direct and continuous recording of the arterial blood pressure. The trachea was cannulated for continuous recording of amplitude and frequency of respiration. Recordings were made with conventional apparatus. A femoral vein was exposed for the administration of all compounds. Generally, 1 dog was used per compound. After blood pressure and respiration had stabilized, an initial dose of 1 mg./kg. of the experimental compound was given. Thereafter, each succeeding dose was doubled until it was impractical to continue. The time between doses usually varied from 15 to 60 min., depending upon response to the preceding dose.

Antianesthetic effects were determined by testing for the integrity of various reflexes including corneal, blink, and proprioceptive (limb withdrawal to a pinch on the toes). Increased skeletal muscular tone, spontaneous movement of head, trunk, limbs and tail, intact drink reflex, eyeball movement, etc. were additional responses which indicated CNS stimulation or antagonism to the anesthetic.

Acknowledgment.—The authors thank Josephine L. Garber, Richard P. Mays, John A. Richman, and Edward K. Rose for technical assistance, and Mrs. Ruby Higgins for the nitrogen analyses.

6-Amino Derivatives of 5H-Dibenzo[*d*,*f*][1,3]diazepine

W. E. KREIGHBAUM AND H. C. SCARBOROUGH

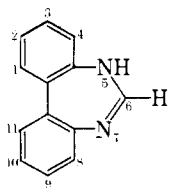
Mead Johnson Research Center, Evansville, Indiana

Received October 30, 1963

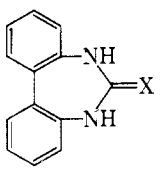
6-Amino and substituted-amino derivatives of 5H-dibenzo[*d*,*f*][1,3]diazepine (I) have been prepared by replacement of the corresponding alkylthio function or by ring closure of 2,2′-diaminobiphenyl with N,N′-dialkylcarbodiimides or S-methylisothiourea.

Compounds containing a 7-membered ring are known to exhibit diverse biological activities. These actions include cardiovascular (*e.g.*, azapetine)[1] and psychopharmacologic (amitriptyline,[2] diazepam,[3] and chlordiazepoxide[4]). We wish to report a series of 6-amino derivatives of 5H-dibenzo[*d*,*f*][1,3]diazepine (I),[5] incorporating a bulky near-planar aromatic moiety as in amitriptyline with a 7-membered cyclic guanidine system. These 6-amino compounds were considered of interest as potential psychotropic agents.

Other derivatives of I, substituted in the 6-position, have been reported to include alkyl,[5–8] aryl,[9–11] alkoxy,[11] hydroxy,[12] and sulfhydryl[13] compounds, the last two existing primarily as the keto and thione forms (IIb,a) respectively.



I



IIa, X=S
IIb, X=O

The simplest member of the series, 6-amino-5H-dibenzo[*d*,*f*][1,3]diazepine (IV), was prepared in one step from 2,2′-diaminobiphenyl (III) by fusion with S-methylisothiourea sulfate (method A).

In that Hungar, *et al.*,[14] have recently employed carbodiimides in the synthesis of 2-(substituted amino)-benzimidazoles, it was of interest to investigate the applicability of similar reagents in the preparation of 7-membered cyclic guanidines such as the 6-monoalkylamino derivatives of I. Two alkylamino derivatives were prepared from III and the appropriate carbodiimide; thus, heating III with N,N′-dicyclohexyl- or N,N′-diisopropylcarbodiimide at 160–200° gave 6-cyclohexylamino- (VIa) and 6-isopropylamino-5H-dibenzo[*d*,*f*][1,3]diazepine (VIb) (method B).

Compounds of type VI were also prepared by another route involving replacement of an alkylthio function by amines (method C). The intermediate methylthio compound(V) was produced in excellent yield by treatment of the 6-thione derivative (IIa) with methyl iodide in tetrahydrofuran. Preparation of VI(c–g, j–t) was accomplished by heating the methylthio compound with the appropriate amine or amine hydrochloride (in some cases, as with high-boiling amines, V was effectively employed as the free base; however, the use of the hydrohalide salt of either the methylthio compound or the amine reagent appeared to be more suitable in the case of low-boiling amines). Reaction temperatures varied from 70–200°, depending upon the reactivity of the amine function and the fusion temperature of the mixture (Table I). The temperature at which the reaction commenced was clearly observable by the evolution of mercaptan. The strong odor lessened considerably as the reaction neared completion, but never disappeared entirely. Yields were generally between 50–90% of analytically pure material; lower yields were usually due to losses in successive recrystallizations.

(1) Ilidar®, 6-allyl-6,7-dihydro-5H-dibenz[*c*,*e*]azepine.
(2) Elavil®, 3-(3-dimethylaminopropylidene)[1:2, 4:5]dibenzocyclohepta-1,4-diene.
(3) Valium®, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.
(4) Librium®, 7-chloro-2-methylamino-5-phenyl-3H-1,3-benzodiazepine 4-oxide.
(5) S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.*, **6**, 263 (1932); *Chem Abstr.*, **26**, 3246 (1932).
(6) P. T. Charlton, G. Maliphant, P. Oxley, and D. Peak, *J. Chem. Soc.*, 485 (1951).
(7) Y. V. Levin, A. P. Mokhova, and V. A. Kukhtin, *Zh. Obshch. Khim.*, **31**, 1460 (1961).
(8) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 873 (1957).
(9) A. E. S. Fairfull, V. Petrow, and W. F. Short, *J. Chem. Soc.*, 3549 (1955).
(10) German Patent 865,305; *Chem. Abstr.*, **52**, P20201 (1958).
(11) W. Ried and W. Storbeck, *Ber.*, **95**, 459 (1962).
(12) St. von Niementowski, *ibid.*, **34**, 3325 (1901).
(13) R. J. W. Le Fevre, *J. Chem. Soc.*, 733 (1929).
(14) A. Hungar, J. Kebrle, A. Rossi, and K. Hoffman, *Helv. Chim. Acta*, **44**, 1273 (1961).