[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

BASIC AMIDES AS ANTISPASMODIC AGENTS. II.

W. B. WHEATLEY, W. F. MINOR, W. M. BYRD,[1] W. E. FITZGIBBON, JR.,[2] M. E. SPEETER,[3] L. C. CHENEY, AND S. B. BINKLEY[4]

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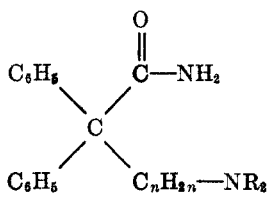
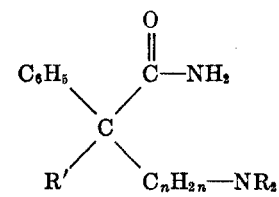
In a previous communication, the synthesis of a series of basic amides having marked antispasmodic action was reported (1). The general formula I represents these amides. We wish at this time to report extension of this work to include

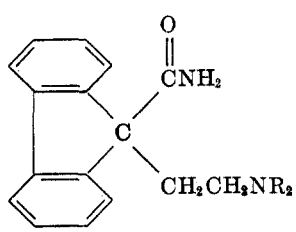


I

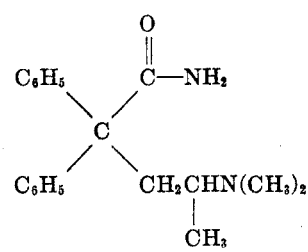


II

amides of the type II, where R′ represents hydrogen, alkyl, aralkyl, or heterocyclic structures. In addition, some fluorene analogs (III) and several polymethylene bis-quaternaries have been prepared.



III



IV

Sulfuric acid (90%) hydrolysis of the basic nitriles has continued to give consistently good yields of basic amides, which are summarized in Table II. In Table III are some fluorene amides which were prepared in a similar manner. It is of interest that the fluorene nitriles were hydrolyzed much more easily than the diphenyl nitriles. While the latter are hydrolyzed to amides in high yield in three hours on the steam-bath, even two hours heating was excessive for 9-β-dimethylaminoethyl-9-fluorenecarbonitrile, from which the amide was obtained in only 9% yield. Presumably hydrolysis proceeds beyond the amide stage with ease, producing acidic material. Optimum conditions were never

[1] Present address: Department of Chemistry, Antioch College, Yellow Springs, Ohio.
[2] Present address: Southern Research Institute, Birmingham, Alabama.
[3] Present address: The Upjohn Company, Kalamazoo, Michigan.
[4] Present address: Department of Biochemistry, University of Illinois, College of Medicine, Chicago, Illinois.

ascertained, but heating periods of 45 minutes gave the fluorene amides in 35 and 55% yields. Alkaline hydrolysis (2) failed to produce the desired amides.

In view of the high anticholinergic action of the racemic γ-dimethylamino-α,α-diphenylvaleramide (IV) (Centrine),[5] it was thought that one enantiomorph might be physiologically more active, as is the case with methadone. Preparation of the two optically active isomers of IV was therefore undertaken. Resolution of the DL-γ-dimethylamino-α,α-diphenylvaleronitrile according to the procedure of Pohland, Marshall, and Carney (3), followed by hydrolysis of the two nitriles afforded the *dextro* and *levo* amides. A difference in spasmolytic activity was indeed found, the *levo* isomer being about four times as potent as the *dextro* isomer with respect to antiacetylcholine activity in isolated muscle strips. Resolution of the racemic amide (IV) with *d*-tartaric acid has been accomplished by Dr. H. L. Dickison, and will be reported at an early date.

EXPERIMENTAL

Basic nitriles (*See Table I*). Alkylation of the substituted phenylacetonitriles with β-dialkylaminoethyl chlorides and sodium amide or lithium amide followed the procedures described for diphenylacetonitrile (1). The required nitriles were prepared as reported in the literature: α-phenylcapronitrile (4), cyclohexylidenephenylacetonitrile (5), 4-chlorodiphenylacetonitrile (6), and phenyl-α-pyridylacetonitrile (7). By analogy with the reaction of cyclohexylidenephenylacetonitrile with β-piperidylethyl chloride (8), we assumed that the product from β-dimethylaminoethyl chloride possessed the Δ^1-cyclohexenyl structure. Alkylation of phenylacetonitrile with β-piperidylethyl chloride according to the general procedure of Eisleb (9) yielded the desired α-phenyl-γ-piperidylbutyronitrile in 78% yield using lithium amide as the condensing agent, and in 82% yield using sodium hydride. This nitrile was earlier prepared by Anker and Cook *via* a four-step synthesis from phenylacetonitrile, the over-all yield being 19% (10).

Basic amides (*See Table II*). Hydrolysis of basic nitriles with 90% sulfuric acid on the steam-bath for about three hours yielded the amides (1). Acid addition salts and quaternary salts, prepared by standard procedures, are noted in the Table.

α-Cyclohexyl-γ-dimethylamino-α-phenylbutyramide was also prepared by partial hydrogenation of γ-dimethylamino-α,α-diphenylbutyramide. Glacial acetic acid containing a few drops of sulfuric acid was used as the solvent, platinum oxide the catalyst, and three moles of hydrogen were absorbed in six hours at 65° and three atmospheres pressure. The repeated recrystallization required to purify the product entailed such a loss that preparation of this amide by hydrolysis of the nitrile (obtained from cyclohexylphenylacetonitrile and β-dimethylaminoethyl chloride) was definitely superior.

Bis-quaternaries. 1,10-Decamethylene-bis(γ-carbamyl-γ,γ-diphenylpropyldiethylammonium) diiodide. A solution of 10.0 g. of γ-diethylamino-α,α-diphenylbutyramide (1) and 5.0 g. of 1,10-diiododecane in 50 ml. of benzyl alcohol was heated on the steam-bath for 88 hours. Dilution of the reaction mixture with 300 ml. of ether caused separation of a gum, from which the supernatant liquid was decanted. Fresh ether was added, and on cooling and scratching, the gum crystallized. Recrystallized from a mixture of ethanol and ethyl acetate, the bis-quaternary (10.0 g.) melted with decomposition at 133–141°.

Anal. Calc'd for $C_{50}H_{72}I_2N_4O_2$: C, 59.1; H, 7.2.

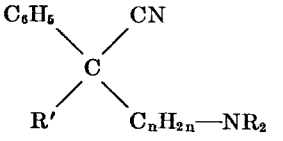
Found: C, 58.5; H, 7.1.

1,5-Pentamethylene-bis(γ-carbamyl-γ,γ-diphenylpropyldimethylammonium) diiodide. A solution of 14 g. of γ-dimethylamino-α,α-diphenylbutyramide (1) and 6.5 g. of 1,5-diiodo-

[5] "Centrine" is the trade mark name adopted by Bristol Laboratories Inc. for this compound which has been assigned the generic name aminopentamide.

TABLE I

BASIC NITRILES



R'[a]	$C_nH_{2n}NR_2$[b]	B.P., °C.	MM.	n_D^{25}	YIELD, %	FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
H	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	161–165	1.0	1.5150	67	$C_{18}H_{26}N_2$	79.9	80.1	9.7	9.8
C_4H_9	$CH_2CH_2N(C_2H_5)_2$	149–158	1.3	1.4970	44	$C_{18}H_{28}N_2$	79.4	78.7	10.4	10.5
C_6H_9	$CH_2CH_2N(CH_3)_2$	156–162	2.0	1.5334	69	$C_{18}H_{24}N_2$	80.5	80.0	9.0	9.2
p-Cl—C_6H_4	$CH_2CH_2NC_5H_{10}$	220–230	2.0	226–228[c]	32	$C_{21}H_{23}ClN_2 \cdot HCl$	67.2	67.6	6.4	6.6
C_5H_4N—	$CH_2CH_2N(CH_3)_2$	165–168	0.6	1.5548	81	$C_{17}H_{19}N_3$	77.0	78.0	7.2	7.6
C_5H_4N—	$CH_2CH_2N(C_2H_5)_2$	173–180	.9	1.5442	78	$C_{19}H_{23}N_3$	77.7	77.5	7.9	8.0

[a] C_6H_9 = Δ^1-cyclohexenyl; C_5H_4N = α-pyridyl. [b] —NC_5H_{10} = 1-piperidyl. [c] M.p. of hydrochloride (recrystallized from acetone).

pentane in 250 ml. of methanol was refluxed for 18 hours. Evaporation of the solvent left a semi-solid residue, which on boiling with isopropyl alcohol gave the crystalline bis-quaternary, m.p. 205.0–207.0°.

Anal. Calc'd for $C_{41}H_{54}I_2N_4O_2$: C, 55.4; H, 6.0.

Found: C, 55.4; H, 6.2.

1,5-Pentamethylene-bis(γ-carbamyl-γ,γ-diphenyl-α-methylpropyldimethylammonium) diiodide. A solution of 17.8 g. of γ-dimethylamino-α,α-diphenylvaleramide (1) and 6.8 g. of 1,5-diiodopentane in 250 ml. of methanol was refluxed for 50 hours. The solvent was evaporated and the crude residual solid was triturated with hot petroleum ether (b.p. 85–100°). A crystalline bis-quaternary, m.p. 138.0–140.0°, was thus obtained.

Anal. Calc'd for $C_{43}H_{58}I_2N_4O_2$: C, 56.3; H, 6.4.

Found: C, 56.6; H, 6.5.

9-Formylfluorene. The use of sodium hydride and a reflux time of 17.5 hours as modifications of the procedure of Von and Wagner (11) gave crude 9-formylfluorene in yields of 52–55%. The crude material was used directly in the preparation of the oxime.

9-Formylfluorene oxime. The following procedure, essentially that of Bachmann and Boatner (12) was employed. 9-Formylfluorene (50 g., 0.26 mole) and 36.0 g. (0.52 mole) of hydroxylamine hydrochloride were dissolved in a mixture of 150 ml. each of absolute ethanol and pyridine. After 1.5 hours at reflux, the solvents were distilled under reduced pressure and 300 ml. of water was added to the residual oil. Crystallization proceeded rapidly, giving 52.0 g. (97% yield) of crude oxime, m.p. 145–155°. Recrystallization from isopropyl alcohol gave oxime melting at 160–165° dec. [lit. (13) m.p. 166–167° for β-oxime].

9-Cyanofluorene. Dehydration of the oxime by thionyl chloride in ether (13) gave the nitrile in yields of 68–71%; lower yields were obtained if unrecrystallized oxime were used (*cf.* 14).

9-β-Dimethylaminoethyl-9-fluorenecarbonitrile. Alkylation of 9-cyanofluorene with β-dimethylaminoethyl chloride in the presence of lithium amide was carried out in the usual manner (1). The dried ether solution of the crude basic nitrile was chilled and saturated with dry hydrogen chloride. There was thus obtained 9-β-dimethylaminoethyl-9-fluorenecarbonitrile hydrochloride in 93% yield, m.p. 248–250°. An analytical sample, recrystallized from ethanol, melted at 250–251°.

Anal. Calc'd for $C_{18}H_{18}N\cdot HCl$: C, 72.4; H, 6.4.

Found: C, 71.9; H, 6.6.

9-β-Diethylaminoethyl-9-fluorenecarbonitrile. This nitrile was prepared in a similar manner, with a change in isolation method. When the toluene reaction solution was shaken with 6 *N* hydrochloric acid, the nitrile hydrochloride crystallized rapidly. It was collected and recrystallized from acetone, affording 9-β-diethylaminoethyl-9-fluorenecarbonitrile hydrochloride in 87% yield, m.p. 213.5–214.5° with sintering at 115–120°, [lit. (15) m.p. 205–206].

Anal. Calc'd for $C_{20}H_{22}N\cdot HCl$: C, 73.5; H, 7.1.

Found: C, 73.2; H, 7.1.

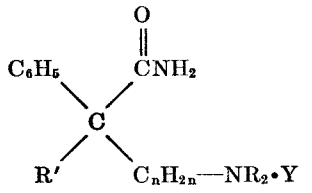
Basic amides (*See Table III*). The basic nitriles were heated with 90% sulfuric acid on the steam-bath for 45 minutes; longer heating resulted in drastically reduced yields.

Resolution of DL-*γ-dimethylamino-α,α-diphenylvaleronitrile.* Resolution by means of *d*-tartaric acid as described by Pohland, Marshall, and Carney (3) gave the *levo* nitrile in 68% yield, m.p. 102–103°, $[\alpha]_D^{24}$ −49.4° (*c*, 1 in ethanol) and the *dextro* nitrile in 69% yield, m.p. 101–102.5°, $[\alpha]_D^{23}$ +50.2° (*c*, 1 in ethanol).

dextro-γ-Dimethylamino-α,α-diphenylvaleramide. *dextro*-γ-Dimethylamino-α,α-diphenylvaleronitrile (15 g., 0.054 mole) was heated on the steam-bath for three hours in a mixture of 26.5 ml. of concentrated sulfuric acid and 2.7 ml. of water. The solution was poured on ice, rendered basic with ammonium hydroxide, and the oil which separated was extracted into chloroform. Evaporation of the solvent from the dried extracts left a gum, which solidified on trituration with petroleum ether (b.p. 28–38°). Recrystallization, first from cyclohexane and then twice from petroleum ether (b.p. 85–100°), gave 11.7 g. (73% yield) of the *dextro* amide, m.p. 136.5–137.5° (with previous sintering), $[\alpha]_D^{23}$ +98.9° (*c*, 1.0 in methanol).

TABLE II

BASIC AMIDES



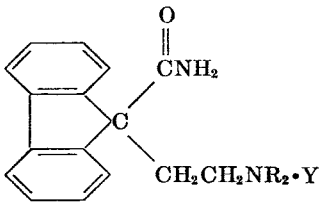
R[a]	$C_nH_{2n}NR_2$	Y	RECRYST. SOLVENT[b]	M.P., °C.	YIELD,[c] %	FORMULA	ANALYSES C Calc'd	ANALYSES C Found	ANALYSES H Calc'd	ANALYSES H Found	NITRILE PREP.
H	$CH_2CH_2N(CH_3)_2$	—	Cyclohexane	89.0–90.0	85	$C_{12}H_{18}N_2O$	69.9	69.9	8.8	9.0	(16)
H	$CH_2CH_2N(CH_3)_2$	HCl	—	202.5–204.0	—	$C_{12}H_{19}ClN_2O$	59.4	59.2	7.9	7.8	
H	$CH_2CH_2N(C_2H_5)_2$	—	SSB	81.0–82.0	91	$C_{14}H_{22}N_2O$	71.8	72.0	9.5	9.6	(9, 16)
H	$CH_2CH_2N(C_2H_5)_2$	HCl	*i*-PrOH	178.5–180.0	—	$C_{14}H_{23}ClN_2O$	62.1	62.2	8.6	8.6	
H	$CH_2CH_2N(C_2H_5)_2$	CH_3I	MeOH-Et_2O	172.0–173.0	96	$C_{15}H_{25}IN_2O$	47.9	47.8	6.7	6.7	
H	$CH_2CH_2N(C_2H_5)_2$	C_2H_5I	MeOH-Et_2O	186.5–187.5	74	$C_{16}H_{27}IN_2O$	49.2	49.1	7.0	7.1	
H	$CH_2CH_2NC_5H_{10}$	—	EtOAc	104.0–105.5	73	$C_{15}H_{22}N_2O$	73.1	72.8	9.0	9.0	[d]
H	$CH_2CH_2NC_5H_{10}$	HCl	MeOH-Et_2O	229.0–233.0	—	$C_{15}H_{23}ClN_2O$	63.7	63.8	8.2	8.0	
H	$CH_2CH_2NC_5H_{10}$	CH_3I	*i*-PrOH	188.0–190.0	71	$C_{16}H_{25}IN_2O$	49.5	50.1	6.5	6.6	
H	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	—	MeOH	77.0–79.0	83	$C_{18}H_{28}N_2O$	74.9	73.9	9.8	10.0	[e]
H	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	CH_3I	MeOH-Et_2O	219.0–220.0	57	$C_{19}H_{31}IN_2O$	53.0	53.1	7.3	7.4	
H	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	$C_6H_5CH_2Cl$	EtOH-EtOAc	160.0–167.0	64	$C_{22}H_{29}ClN_2O•H_2O$	67.6	67.2	8.0	7.8	
CH_3	$CH_2CH_2N(CH_3)_2$	—	Cyclohexane	95.0–96.5	73	$C_{13}H_{20}N_2O$	70.9	71.1	9.2	9.2	(17)
CH_3	$CH_2CH_2N(CH_3)_2$	CH_3I	*i*-PrOH-H_2O	243.5–245.5	64	$C_{14}H_{23}IN_2O$	46.4	46.8	6.4	6.3	
C_2H_5	$CH_2CH_2N(C_2H_5)_2$	—	—	Oil	84	$C_{16}H_{26}N_2O$	73.2	72.8	10.0	10.2	(18)
C_2H_5	$CH_2CH_2N(C_2H_5)_2$	CH_3I	EtOH-EtOAc	169.5–172.0	75	$C_{17}H_{29}IN_2O•H_2O$	48.4	48.2	7.4	7.3	
C_2H_5	$CH_2CH_2N(C_2H_5)_2$	C_2H_5I	MeOH-EtOAc	190.5–192.5	68	$C_{18}H_{31}IN_2O$	51.7	51.9	7.5	7.6	
C_4H_9	$CH_2CH_2N(C_2H_5)_2$	—	—	Oil	61	$C_{18}H_{30}N_2O$	74.4	74.6	10.4	10.1	[e]
C_6H_9	$CH_2CH_2N(CH_3)_2$	—	—	Glass	69	$C_{18}H_{26}N_2O$	75.5	75.4	9.2	9.0	[e]
C_6H_{11}	$CH_2CH_2N(CH_3)_2$	—	EtOAc	138.0–140.0	67	$C_{18}H_{28}N_2O$	75.0	74.9	9.8	9.7	(19)

C_6H_{11}	$CH_2CH_2N(CH_3)_2$	HCl	Acetone	195.0–197.0	—	$C_{18}H_{29}ClN_2O$	65.5	65.3	9.0	8.8	
C_6H_{11}	$CH_2CH_2N(CH_3)_2$	C_2H_5I	H_2O	187.0–191.0	66	$C_{20}H_{33}IN_2O$	54.1	54.2	7.5	7.6	
p-ClC_6H_4—	$CH_2CH_2NC_5H_{10}$	—	EtOH	190.0–193.0	55	$C_{21}H_{25}ClN_2O$	70.7	70.6	7.1	6.8	[e]
p-ClC_6H_4—	$CH_2CH_2NC_5H_{10}$	CH_3I	*i*-PrOH-Et_2O	Indef.	30	$C_{22}H_{28}ClIN_2O$	53.0	52.9	5.7	5.8	
$C_6H_5CH_2$	$CH_2CH_2NC_5H_{10}$	—	*i*-PrOH-H_2O	159.5–161.0	25	$C_{22}H_{28}N_2O$	78.5	78.7	8.4	8.2	(9)
C_5H_4N	$CH_2CH_2N(CH_3)_2$	—	—	Oil	76	$C_{17}H_{21}N_3O$	72.0	70.8	7.5	7.6	[e]
C_5H_4N	$CH_2CH_2N(CH_3)_2$	CH_3I	*i*-PrOH-H_2O	178 dec.	78	$C_{18}H_{24}IN_3O$	50.8	51.1	5.7	5.9	
C_5H_4N	$CH_2CH_2N(CH_3)_2$	C_2H_5I	MeOH-EtOAc	141.5–142.5	83	$C_{19}H_{26}IN_3O$	51.9	51.9	6.0	6.1	
C_5H_4N	$CH_2CH_2N(C_2H_5)_2$	—	Cyclohexane	63.0–67.0	72	$C_{19}H_{25}N_3O$	73.3	73.3	8.1	8.3	[e]
C_5H_4N	$CH_2CH_2N(C_2H_5)_2$	CH_3I	*i*-PrOH-H_2O	158 dec.	91	$C_{20}H_{28}IN_3O$	53.0	53.1	6.2	6.3	

[a] C_6H_9 = Δ^1-cyclohexenyl, C_6H_{11} = cyclohexyl, C_5H_4N = α-pyridyl. [b] SSB = Skellysolve B (petroleum ether, b.p. 60–71°). [c] Yields of basic amides refer to hydrolysis of nitrile; yields of quaternaries are based on basic amide. [d] See Experimental. [e] See Table I.

TABLE III

BASIC AMIDES



R	Y	RECRYST. SOLVENT	M.P., °C.	YIELD, %	FORMULA	ANALYSES			
						C		H	
						Calc'd	Found	Calc'd	Found
CH_3	—	EtOAc	131–132.5	35	$C_{18}H_{20}N_2O$	77.0	76.8	7.17	7.48
CH_3	HCl	EtOH	232.5–233 dec.	—	$C_{18}H_{21}ClN_2O \cdot C_2H_5OH$	66.2	66.8	7.50	7.11
CH_3	CH_3I	EtOH	221–222	95	$C_{19}H_{23}IN_2O \cdot H_2O$	51.8	51.2	5.71	5.95
CH_3	C_2H_5Br	EtOH	228–228.5 dec.	64	$C_{20}H_{25}BrN_2O$	61.7	61.9	6.47	6.63
C_2H_5	—	*i*-PrOH	115.5–117.5	55	$C_{20}H_{24}N_2O$	77.9	78.0	7.82	7.99
C_2H_5	HCl	*i*-PrOH	234.5–235.5 dec.	—	$C_{20}H_{25}ClN_2O$	69.6	69.7	7.30	7.48
C_2H_5	C_2H_5Br	EtOH	218.5–219.5 dec.	61	$C_{22}H_{29}BrN_2O \cdot C_2H_5OH$	61.9	62.2	7.61	7.48
C_2H_5	CH_3I	EtOH	202.5–204.5 dec.	65	$C_{21}H_{27}IN_2O$	56.0	56.2	6.05	6.26

Anal. Calc'd for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2.
Found: C, 77.2; H, 8.4.

levo-γ-Dimethylamino-α,α-diphenylvaleramide. Hydrolysis of 15 g. of *levo*-γ-dimethylamino-α,α-diphenylvaleronitrile in a similar manner gave 14.2 g. (88% yield) of the *levo* amide, m.p. 136.5–137.5° (with previous sintering), $[\alpha]_D^{23}$ −101.9° (*c*, 1.0 in methanol).

Anal. Calc'd for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2.
Found: C, 77.2; H, 8.3.

Acknowledgment. The authors are indebted to Dr. H. L. Dickison and coworkers for the pharmacological information reported and to Mr. R. M. Downing for the microanalyses.

SUMMARY

A number of basic amides having antispasmodic action are reported.

The enantiomorphic γ-dimethylamino-α,α-diphenylvaleramides have been prepared, the *levo* isomer having been found to be more potent than the *dextro* isomer as an antispasmodic agent.

SYRACUSE 1, NEW YORK

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