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BASIC AMIDES AS ANTISPASMODIC AGENTS. I

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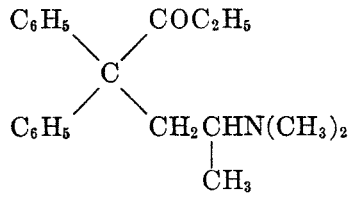
Methadone (amidone) (I) is a well-established recently developed analgesic (1). In an attempt to increase the potency and/or decrease the magnitude of undesirable side effects, extensive modifications of methadone have been under-



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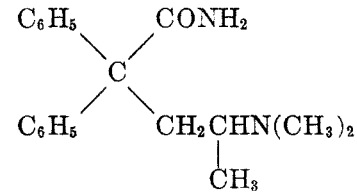
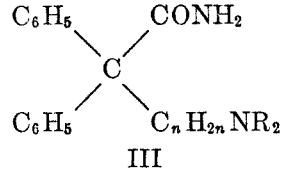


II

taken. It has been shown that imines and acylimines (2), and the secondary alcohols and their esters (3) related to methadone and its analogs possess analgesic activity to varying degrees. The dialkylaminodiarylnitriles from which methadone and its analogs are prepared through the action of an appropriate Grignard reagent have been reported to have antispasmodic properties (4). This spasmolytic action has been observed in our laboratory also. Of especial significance, however, is the discovery that hydrolysis of the basic nitriles to the basic amides markedly increases the antispasmodic potency (5).

Details of the pharmacology of the entire series of basic amides will be published elsewhere; it can be said here that the spasmolytic action of these dialkylaminodiarylamides is such that an extensive series of amides has been prepared. The amide related to methadone, γ-dimethylamino-α,α-diphenylvaleramide (II) is a powerful spasmolytic, approaching atropine in potency in *in vitro* tests against acetylcholine (5). This compound has recently been described by Walton, Ofner, and Thorp, but they mention only its lack of analgesic action (6). Related amides were prepared some time ago by Bockmühl and Ehrhart (7), but it was not until after the antispasmodic properties of the amides had been observed in our laboratories that information of the pharmacology of these earlier compounds became available (8).

Reference to a general formula (III) for these amides indicates the scope of



III

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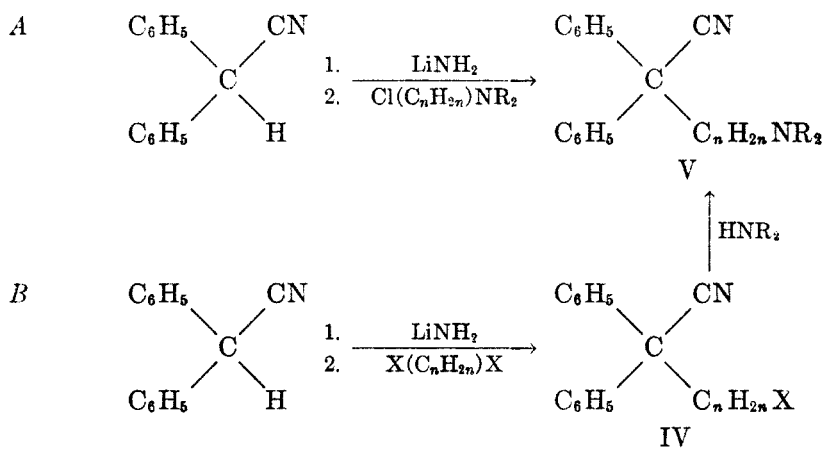
the variations reported in this communication. The basic moiety—NR_2 was varied to include acyclic and cyclic structures, and the length and structure of the alkylene chain —C_nH_{2n}— was changed. The effect of quaternization of the basic amides as well as the effect of substitution of the amide nitrogen was investigated.

Preparation of the basic amides was accomplished by hydrolysis of the nitriles with 90% sulfuric acid. Direct alkylation of diphenylacetamide with basic alkyl chlorides was not feasible, since alkylation occurred on the nitrogen instead of on the tertiary carbon atom. A similar course of reaction has been reported by Swiss investigators (9). Several N,N-disubstituted diphenylacetamides were successfully alkylated using lithium amide and β-piperidylethyl chloride. Bockmühl and Ehrhart prepared several amides of the type III by hydrolyzing the nitriles with alcoholic potassium hydroxide (8). In a few experiments amides were obtained together with the hydroxamamide, by heating the nitrile in alcohol with hydroxylamine hydrochloride and sodium acetate. This synthesis of amides was reported by Lipp, who obtained some diphenylacetamide from diphenylacetonitrile under similar conditions (10). Sulfuric acid gave the most satisfactory results, and was thus used in the majority of cases. Ordinarily, heating the basic nitrile with 90% sulfuric acid on the steam-bath for three hours was sufficient to cause a high conversion to the basic amide. Those nitriles containing a neopentylene group between the quaternary carbon and the nitrogen required overnight (about 16 hours) heating; after three hours the nitriles could be recovered unchanged in high yield.

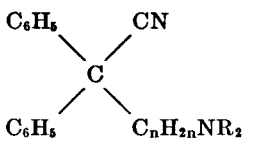
The required basic nitriles (V) were prepared in either of two ways, depending on the availability of the necessary intermediates:



Method B was followed where —C_nH_{2n}— represents tetra-, penta-, or hexamethylene groups; in all other cases method A was followed. The halonitriles (IV) were not isolated in a pure state, but were used in the form of the crude reaction products. The new basic nitriles which were prepared are to be found in Table I. Literature references to previously-reported nitriles may be found in Table II under the corresponding amide.

TABLE I

BASIC NITRILES



$C_nH_{2n}NR_2$[a]	METHOD	YIELD, %	B.P., °C.	MM.	M.P. OR n_D^{25}	FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
$(CH_2)_4N(C_2H_5)_2$	B	26	180–185	0.8	1.5412	$C_{22}H_{28}N_2$	82.4	82.4	8.8	8.7
$(CH_2)_4NC_4H_8$	B	31	195–200	1.0	1.5592	$C_{22}H_{26}N_2$	83.0	83.1	8.2	8.3
$(CH_2)_4NC_5H_{10}$	B	45	200–205	1.0	81.5–83.5[b]	$C_{23}H_{28}N_2$				
$(CH_2)_5N(C_2H_5)_2$	B	16	190–197	2.5		$C_{23}H_{30}N_2$				
$(CH_2)_5NC_5H_{10}$	B	43	211–217	1.5	63.0–65.0	$C_{24}H_{30}N_2$	83.2	83.1	8.7	8.7
$(CH_2)_6N(C_2H_5)_2$	B	27	197–204	1.0	1.5372	$C_{24}H_{32}N_2$	82.7	81.9	9.3	9.1
$(CH_2)_6NC_5H_{10}$	B	36	231–240	3.0		$C_{25}H_{32}N_2$	83.3	83.0	9.0	9.2
$CH_2C(CH_3)_2CH_2N(CH_3)_2$	A	73	[d]		139.0–141.5	$C_{21}H_{26}N_2 \cdot HCl$	73.6	73.3	7.9	7.8
$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	A	66	170–176	2.5	46.0–50.0[c]	$C_{23}H_{30}N_2$[e]	82.6	82.6	9.0	9.2
$CH_2C(CH_3)_2CH_2NC_5H_{10}$	A	61	183–186	2.0	66.0–68.0[c]	$C_{24}H_{30}N_2$[f]	83.2	83.0	8.7	8.9

[a] NC_4H_8 = 1-pyrrolidyl; NC_5H_{10} = 1-piperidyl. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from dilute methanol. [d] The free basic nitrile was not isolated, as the hydrochloride crystallized out or water on working up the reaction mixture. The m.p., formula, and analysis are those of the hydrochloride (recrystallized from isopropyl alcohol). [e] *Sulfate*, m.p. 220.5–222.5° (recrystallized from methanol-ether). *Anal.* Calc'd for $C_{23}H_{30}N_2 \cdot H_2SO_4$: C, 63.8; H, 7.5; N, 6.5. Found: C, 63.5; H, 7.3; N, 6.9. [f] *Hydrochloride:* m.p. 184.5–185.5° (recrystallized from isopropyl alcohol-Skellysolve B); *Anal.* Calc'd for $C_{24}H_{30}N_2 \cdot HCl$: C, 75.3; H, 8.2. Found: C, 75.3; H, 8.3. *Nitrate:* m.p. 145° dec. (recrystallized from isopropyl alcohol-Skellysolve B); *Anal.* Calc'd for $C_{24}H_{30}N_2 \cdot HNO_3$: C, 70.4; H, 7.6; N, 10.0. Found: C, 69.7; H, 8.0; N, 9.9.

EXPERIMENTAL

Basic alkyl chlorides. β-Dialkylaminoethyl and γ-dialkylaminoneopentyl chloride hydrochlorides were prepared by treatment of the corresponding aminoalcohols with thionyl chloride (11, 12). γ-Dimethyl- and γ-diethylaminoneopentyl alcohols were prepared according to reported procedures (1, 12, 13). The dialkylaminoalkyl chlorides were liberated from the hydrochlorides immediately before use by stirring with strong alkali and extracting into toluene. The toluene solutions were dried a short time over potassium carbonate.

Basic nitriles. Typical examples are given below for the preparation of the basic nitriles used in this work. Those which have not previously been reported in the literature are described in Table I. The yields given are based on the starting nitrile and thus represent an over-all yield for those prepared by route *B*.

Method A. This method, whereby diphenylacetonitrile is treated with sodium amide and subsequently a dialkylaminoalkyl chloride, has been well described in the literature (1, 2b). We have found lithium amide to be as satisfactory as sodium amide, and therefore prefer it because of its safety, low cost, and ease of handling.

Method B. A mixture of 212.5 g. (1.1 moles) of diphenylacetonitrile and 27.8 g. (1.21 moles) of lithium amide in 1.7 l. of toluene was heated under reflux for four hours. The resulting red suspension was added portionwise to a stirred and refluxing solution of 288 g. (2.27 moles) of 1,4-dichlorobutane in 300 ml. of toluene. After completion of the addition, the reaction mixture was stirred and refluxed overnight. The cooled mixture was washed several times with water and dilute hydrochloric acid. The toluene layer was shaken with saturated sodium chloride solution and filtered through anhydrous sodium sulfate. Evaporation of the toluene and excess 1,4-dichlorobutane, finally under reduced pressure, left 200 g. of crude ω-chloro-α,α-diphenylcapronitrile as a dark red oil. Purification was not possible *via* crystallization or distillation, so the crude chloronitrile was used directly in the subsequent reaction (14). In a similar manner, 1,5-dichloropentane yielded ω-chloro-α,α-diphenylenanthonitrile and 1,6-dibromohexane yielded ω-bromo-α,α-diphenylcaprylonitrile.

α,α-Diphenyl-ω-piperidylenanthonitrile. Crude ω-chloro-α,α-diphenylenanthonitrile (74.5 g., 0.25 mole) and 150 ml. (*ca.* 1.5 moles) of piperidine were heated together in 200 ml. of refluxing toluene for 24 hours. The cooled reaction mixture was washed with water, then extracted twice with 6 *N* hydrochloric acid. The aqueous extracts were made basic with potassium hydroxide and the liberated basic nitrile extracted into chloroform. The combined chloroform extracts were shaken with saturated sodium chloride solution and filtered through anhydrous potassium carbonate. Evaporation of the chloroform followed by distillation *in vacuo* gave 38.8 g. of α,α-diphenyl-ω-piperidylenanthonitrile, b.p. 211–217° at 1.5 mm. The distillate spontaneously crystallized: m.p. 63–65°.

When diethylamine was used in place of piperidine, it was found advisable to carry out the reaction in a sealed vessel in order to prevent loss of the amine.

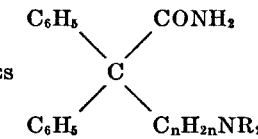
Basic amides. The following experiment is a typical example of the hydrolysis of the nitrile by means of sulfuric acid. γ-Dimethylamino-α,α-diphenylvaleronitrile (100 g., was added to a cooled mixture of 180 ml. of concentrated sulfuric acid and 18 ml. of water. After three hours on the steam-bath, the mixture was poured on ice and rendered strongly basic with ammonium hydroxide. The oil which separated solidified on standing. Recrystallization from isopropyl alcohol afforded 95 g. (89% yield) of γ-dimethylamino-α,α-diphenylvaleramide (II), m.p. 183.0–184.0° [lit. (6) m.p. 175–176°].

The amides listed in Table II were prepared in the same manner except that, as mentioned above, those containing the neopentylene grouping were heated on the steam-bath overnight. Most amides crystallized on cooling and scratching; those which did not were extracted into chloroform (these amides are only sparingly soluble in ether), and the chloroform solutions were dried and evaporated to dryness. The crude amides were then converted to salts and purified by recrystallization. Those few amides which yielded no crystalline salts were used in the crude form.

A number of nitriles were isolated in the form of the hydrochlorides. It was found that

TABLE II

BASIC AMIDES



$C_nH_{2n}NR_2$[a]	Y[a]	RECRYST. SOLVENT[b]	M.P., °C.	FORMULA	ANALYSES				Nitrile prep.
					C		H		
					Calc'd	Found	Calc'd	Found	
$CH_2CH_2N(CH_3)_2$[c]	—	Cyclohexane	138.0–140.0	$C_{18}H_{22}N_2O$	76.6	76.3	7.6	7.9	(14)
$CH_2CH_2N(CH_3)_2$	CH_3I	MeOH	207.0–208.0	$C_{19}H_{25}IN_2O$	53.8	53.2	5.9	5.9	(14)
$CH_2CH_2N(CH_3)_2$	C_2H_5I	*i*-PrOH	172.5–173.5	$C_{20}H_{27}IN_2O$	54.8	55.2	6.2	6.6	(14)
$CH_2CH_2N(C_2H_5)_2$	—	SSD	91.0– 92.0	$C_{20}H_{26}N_2O$	77.4	77.5	8.4	8.5	(7)
$CH_2CH_2N(C_2H_5)_2$	HCl	*i*-PrOH	176.0–177.5	$C_{20}H_{27}ClN_2O$	69.2	69.4	7.9	8.0	(7)
$CH_2CH_2N(C_2H_5)_2$	CH_3Cl	*i*-PrOH-Et_2O	217.5–218.5	$C_{21}H_{29}ClN_2O$	69.9	69.8	8.0	8.1	(7)
$CH_2CH_2N(C_2H_5)_2$	CH_3I	*i*-PrOH	159.0–160.0	$C_{21}H_{29}IN_2O$	55.8	55.8	6.5	6.5	(7)
$CH_2CH_2N(C_2H_5)_2$	C_2H_5Cl	*i*-PrOH	204.5–206.0	$C_{22}H_{31}ClN_2O$	70.5	70.4	8.3	8.3	(7)
$CH_2CH_2N(C_2H_5)_2$	C_2H_5I	EtOH	182.0–183.5	$C_{22}H_{31}IN_2O$	56.6	56.8	6.7	6.9	(7)
$CH_2CH_2NC_4H_8O$	—	MIBK	184.0–185.0	$C_{20}H_{24}N_2O_2$	74.0	74.1	7.4	7.5	(2, 14)
$CH_2CH_2NC_4H_8O$	$(C_2H_5)_2SO_4$	EtOH-EtOAc	170.0–171.5	$C_{24}H_{34}N_2O_6S$	59.1	59.4	7.2	7.1	(2, 14)
$CH_2CH_2NC_4H_8$	—	*i*-PrOH	143.0–144.0	$C_{20}H_{24}N_2O$	77.9	77.5	7.8	7.8	(14)
$CH_2CH_2NC_4H_8$	CH_3I	EtOH-EtOAc	101.0–103.0	$C_{21}H_{27}IN_2O$	56.0	55.8	6.0	6.2	(14)
$CH_2CH_2NC_4H_8$	$(C_2H_5)_2SO_4$	EtOH-EtOAc	130.0–133.0	$C_{24}H_{34}N_2O_5S\cdot\frac{1}{2}H_2O$	61.1	61.3	7.5	7.1	(14)
$CH_2CH_2NC_5H_{10}$	H_2SO_4[d]	*i*-PrOH	185.0–187.0	$C_{21}H_{28}N_2O_5S$	60.0	59.8	6.7	6.8	(7, 8)
$CH_2CH_2NC_5H_{10}$	CH_3I	*i*-PrOH	201.0–202.0	$C_{22}H_{29}IN_2O$	56.9	56.8	6.3	6.2	(7, 8)
$CH_2CH_2NC_5H_{10}$	$C_6H_5CH_2Br$	H_2O	180.0–181.5	$C_{28}H_{33}BrN_2O\cdot H_2O$	65.7	66.1	6.9	6.4	(7, 8)
$CH_2CH_2NC_6H_{12}$	—	*i*-PrOH-SSC	165.0–166.5	$C_{22}H_{28}N_2O$	78.5	77.9	8.4	8.5	(14)
$CH_2CH_2NC_6H_{12}$	$C_7H_7SO_3CH_3$	EtOH-EtOAc	170.0–176.0	$C_{30}H_{38}N_2O_4S$	68.9	68.3	7.3	7.2	(14)
$CH_2CH_2CH_2N(CH_3)_2$	—	SSB	111.0–112.0	$C_{19}H_{24}N_2O$	77.0	76.6	8.2	8.0	(2c)
$CH_2CH_2CH_2N(CH_3)_2$	HCl	*i*-PrOH	197.0–198.0	$C_{19}H_{25}ClN_2O$	68.6	68.6	7.6	7.6	(2c)
$CH_2CH_2CH_2N(C_5H_{10})$	—	EtOAc	119.0–120.0	$C_{22}H_{28}N_2O$	78.5	78.3	8.4	8.3	(7, 8)
$CH_2CH_2CH_2NC_5H_{10}$	HCl	*i*-PrOH	223.0–224.0[e]	$C_{22}H_{29}ClN_2O$	70.8	70.6	7.8	7.8	(7, 8)
$CH_2CH(CH_3)N(CH_3)_2$	H_2SO_4[f]	*i*-PrOH-EtOAc	185.0–187.0	$C_{19}H_{26}N_2O_5S$	57.9	57.5	6.6	6.4	(1, 8)

TABLE II—*Cont.*

$CH_2CH(CH_3)N(CH_3)_2$	CH_3I	MeOH	203.0–204.0	$C_{20}H_{27}IN_2O$	54.8	55.0	6.2	6.3	(1, 8)
$CH_2CH(CH_3)N(CH_3)_2$	C_2H_5I	MeOH	192.0–192.5	$C_{21}H_{29}IN_2O$	55.8	56.4	6.5	6.6	(1, 8)
$CH(CH_3)CH_2N(CH_3)_2$	—	*i*-PrOH	151.0–152.5	$C_{19}H_{24}N_2O$	77.0	76.6	8.2	8.1	(7, 8)
$CH(CH_3)CH_2N(CH_3)_2$	HCl	*i*-PrOH	229.0–230.0	$C_{19}H_{25}ClN_2O$	68.6	68.3	8.6	8.7	(7, 8)
$CH_2CH(CH_3)N(C_2H_5)_2$	—	*i*-PrOH	161.5–163.0	$C_{21}H_{28}N_2O$	77.7	78.0	8.7	8.8	(15)
$CH(CH_3)CH_2N(C_2H_5)_2$	—	EtOAc	135.0–137.0	$C_{21}H_{28}N_2O$	77.7	77.7	8.7	8.7	(15)
$CH_2CH(CH_3)NC_5H_{10}$	—	SSC	158.5–160.0	$C_{22}H_{28}N_2O$	78.5	78.8	8.4	8.4	(15)
$CH(CH_3)CH_2NC_5H_{10}$	—	MeOH-SSC	155.0–157.0	$C_{22}H_{28}N_2O$	78.5	78.3	8.4	8.4	(15)
$(CH_2)_4N(C_2H_5)_2$	HCl	*i*-PrOH	222.0–224.0	$C_{22}H_{31}ClN_2O$	70.5	70.0	8.3	8.8	[a]
$(CH_2)_4NC_4H_8$	—	EtOAc	153.0–155.0	$C_{22}H_{28}N_2O$	78.5	78.4	8.4	8.5	[a]
$(CH_2)_4NC_5H_{10}$	—	SSC	89.0–90.0	$C_{23}H_{30}N_2O$	78.8	78.5	8.6	8.7	[a]
$(CH_2)_5NC_5H_{10}$	HCl	Acetone	178.0–180.0	$C_{24}H_{33}ClN_2O\cdot\frac{1}{2}H_2O$	70.3	70.0	8.4	8.4	[a]
$CH_2C(CH_3)_2CH_2N(CH_3)_2$	—	Cyclohexane	128.0–129.0	$C_{21}H_{28}N_2O$	77.7	77.7	8.7	8.8	[a]
$CH_2C(CH_3)_2CH_2N(CH_3)_2$	CH_3I	MeOH-Et_2O	211.0–212.5	$C_{22}H_{31}IN_2O$	56.6	56.7	6.7	6.7	[a]
$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	H_2SO_4	H_2O-*i*-PrOH	192.0–193.0	$C_{23}H_{34}N_2O_5S$	61.3	61.2	7.6	7.8	[a]
$CH_2C(CH_3)_2CH_2NC_5H_{10}$	HNO_3	EtOH-Et_2O	188.0–189.0 dec.	$C_{24}H_{33}N_3O_4$	67.4	67.4	7.8	7.7	[a]

[a] NC_4H_8O = *4*-morpholinyl; NC_4H_8 = *1*-pyrrolidyl; NC_5H_{10} = 1-piperidyl; NC_6H_{12} = *1*-(α-pipecolyl). [b] SSB = petroleum ether, b.p. 60–71°; SSC = petroleum ether, b.p. 85–100°; SSD = petroleum ether, b.p. 77–115°; MIBK = methyl isobutyl ketone. [c] Bockmühl and Ehrhart report the hydrochloride, m.p. 169–170°; our hydrochloride, m.p. 185–187°. [d] The free basic amide (6, 8) and its hydrochloride (8) have been reported. [e] Bockmühl and Ehrhart report 175–176° (8). [f] Walton, Ofner, and Thorp (6) report the free basic amide, m.p. 175–176°, and the hydrochloride, m.p. 190–191°. Our base, m.p. 183–184°. [g] See Table I.

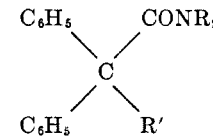
the hydrochloride could be used with the same ease as the free basic nitrile in the hydrolysis; hydrogen chloride was evolved at once and the hydrolysis proceeded as usual.

Hydroxylamine reacted with the basic nitriles to give both the expected hydroxamamide and the amide. Yields of the amide were inferior, however, to those obtained with sulfuric acid. To illustrate this reaction, one example is given. A solution of 98 g. (0.35 mole) of γ-dimethylamino-α,α-diphenylvaleronitrile, 112 g. (1.4 moles) of anhydrous sodium acetate, and 98 g. (1.4 moles) of hydroxylamine hydrochloride in 800 ml. of 95% ethanol was refluxed for 18 hours. The cooled reaction mixture was poured into three liters of water and made basic with sodium hydroxide. The oil which separated solidified on chilling and was collected. Recrystallization gave 57 g. (55% yield) of amide II, m.p. 183.0–184.0°. The mother liquors were concentrated and taken up in ethyl acetate. Crystallization proceeded slowly. The solid thus obtained, after five recrystallizations, alternately from ethyl acetate and ethanol, gave 2.5 g. of material melting at 174.5–176.0°. The analytical data are in agreement with those calculated for the hydroxamamide.

Anal. Calc'd for $C_{19}H_{25}N_3O$: C, 73.3; H, 8.1; N, 13.5.
Found: C, 73.4; H, 8.2; N, 13.4.

TABLE III

N,N-DISUBSTITUTED AMIDES



R'	NR_2	M.P., °C.	RECRYST. SOLVENT	YIELD, %	FORMULA	ANALYSES			
						C		H	
						Calc'd	Found	Calc'd	Found
H	$N(CH_3)_2$	134.5–135.5	EtOAc	84	$C_{16}H_{17}NO$	80.3	80.0	7.2	7.0
H	NC_5H_{10}	120.0–121.0	Benzene	73	$C_{19}H_{21}NO$	81.7	81.8	7.6	7.5
$CH_2CH_2NC_5H_{10}$	$N(CH_3)_2$	167.5–169.0	*i*-PrOH	32	$C_{23}H_{30}N_2O$	78.8	78.8	8.6	8.6
$CH_2CH_2NC_5H_{10}$	NC_5H_{10}	152.0–154.0	SSC[a]	15	$C_{20}H_{34}N_2O$	80.0	80.2	8.8	8.8

[a] SSC = petroleum ether, b.p. 85–100°.

A mixture of the amide and assumed hydroxamamide melted at 148–170°.

N,N-Disubstituted basic amides. A solution of 49.5 ml. (42.6 g., 0.5 mole) of piperidine in 100 ml. of benzene was added dropwise to a solution of 50 g. (0.217 mole) of diphenylacetyl chloride in 150 ml. of benzene. The solution became very hot, and after the addition had been complete, it was refluxed for one hour. The cooled reaction mixture was washed several times with water and the benzene concentrated. The diphenylacetopiperidide crystallized out and was collected. There was obtained 44.0 g. of amide.

A mixture of 39.0 g. (0.14 mole) of diphenylacetopiperidide and 3.44 g. (0.15 mole) of lithium amide in 150 ml. of benzene was stirred and refluxed for five hours. To this hot mixture was added dropwise a solution of 1-(2-chloroethyl)piperidine in 250 ml. of benzene, which had been prepared from 35 g. (0.19 mole) of the hydrochloride. The reaction mixture was refluxed for 18 hours, then cooled and poured into water. The benzene layer was separated and extracted with 400 ml. of 6 *N* hydrochloric acid. On basification of the acid extract with sodium hydroxide, a solid formed. Recrystallization of this crude solid gave 8.0 g. (15% yield) of α,α-diphenyl-γ-(1-piperidyl)butyropiperidide. From the benzene solution following acid extraction, there was recovered 21 g. of unreacted diphenylacetopiperidide by concentration.

By substituting dimethylamine for piperidine, analogous basic amides were prepared. These amides are summarized in Table III.

Derivatives of basic amides: Acid addition salts and quaternary ammonium halides. Acid addition salts of the basic amides were prepared by treating a solution of the amide in an inert solvent with an excess of dry hydrogen chloride, or concentrated sulfuric or nitric acid. Quaternary ammonium halides were prepared by treating a solution of the amide in isopropyl alcohol or acetone with an excess of the desired alkyl halide or alkyl sulfate. The quaternary chlorides were prepared by shaking a hot methanol solution of the quaternary iodide with freshly-prepared silver chloride, chilling, filtering off the silver iodide formed, and recovering the quaternary chloride from the filtrate by dilution with ether.

Pharmacology. A number of the basic amides have atropine indices against acetylcholine of 0.5 or better. Those amides containing the dimethylamino basic function are more active if branching of the fundamental chain is present; *e.g.* II is more active than the related butyramide. With other basic groups, the general rule is that branching is deleterious to antispasmodic activity. Quaternaries are often superior to the parent bases (or acid addition salts). Detailed pharmacological studies with these amides will be reported elsewhere.

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SUMMARY

A series of basic amides has been prepared as potential antispasmodic drugs; high activity was found in certain members. The amides were most conveniently prepared by hydrolysis of the nitriles with 90% sulfuric acid at steam-bath temperature. These amides bear a formal relationship to methadone and its homologs, having two *alpha*-phenyl groups and the basic moiety at or adjacent to the end of the carbon chain of the amide.

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