m-**Chlorophenylphenylacetonitrile.**—This was prepared essentially as described for diphenylacetonitrile[16] from 203.2 g. (2.0 moles) of *m*-chlorophenylacetonitrile, 110.3 ml. (2.2 moles) of bromine, 936 ml. of benzene and 267 g. (2.0 moles) of aluminum chloride. The product was distilled under reduced pressure, b.p. 145–148° (0.25 mm.), giving an oil which crystallized from 300 ml. of isopropyl alcohol, m.p. 50–52°; yield 230.3 g. (50.6%).

Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 73.95; H, 4.25; N, 6.09; Cl, 15.59.

KALAMAZOO, MICHIGAN

(16) C. M. Robb and E. M. Schultz, *Org. Syntheses*, **28**, 55 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

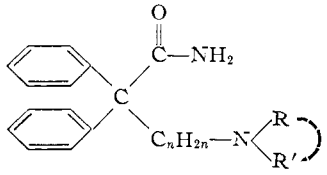
Antispasmodics. XI. α,α-Diphenyl-γ-amino-N-monosubstituted Amides[1]

BY ROBERT BRUCE MOFFETT, BROOKE D. ASPERGREN AND M. E. SPEETER

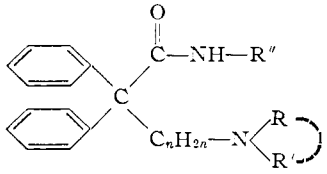
RECEIVED MARCH 25, 1957

Although α,α-diphenyl-γ-tertiaryamino amides (I) are well known as anticholinergics, no similar amides monosubstituted on the amide nitrogen (II) have been previously reported. A series of these have now been made but unexpectedly they have little if any anticholinergic properties. However, these tertiary amino amides were found to be powerful oxytocics and/or diuretics.

Amides of the general type I, unsubstituted on the amide nitrogen, are well known as anticholinergics.[2] In our study of the relationship of structure



I

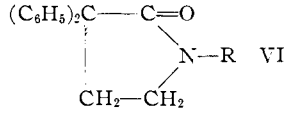


II

to anticholinergic activity it seemed desirable to prepare some amides substituted on the amide nitrogen. A search of the literature revealed that while many unsubstituted amides and a few disubstituted amides[3–5] of this type are known, none of the N-monosubstituted amides (II) have been reported.

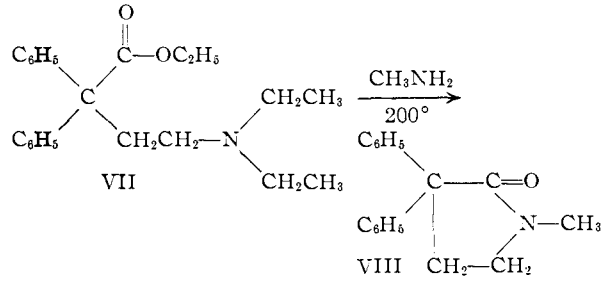
The simplest method for preparing these substituted amides would involve hydrolysis of the well known nitriles III, to the acids IV. These would then be converted to the acid chlorides V, and treated with the requisite primary amine.

This (method A) gave good results when $-C_nH_{2n}-$ was $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$ but when $-C_nH_{2n}-$ was $-CH_2CH_2-$ or $-CH(CH_3)CH_2-$ the cyclization reaction to give 3,3-diphenylpyrrolidones (VI)[6,7] took precedence and little if any of the desired amides were obtained.



VI

Likewise when the ethyl ester VII was heated with methylamine under sufficiently vigorous conditions to cause reaction, the only product isolated was a pyrrolidone (VIII). It is interesting that in this case the substituent on the nitrogen was methyl rather than ethyl.



VII VIII

An attempt to alkylate a diphenyl-N-monosubstituted acetamide with an amino alkyl chloride gave only N-alkylation even when a hindered amide (isopropyl) was used.

The amides (II, $-C_nH_{2n}-$ = $-CH_2CH_2-$ or $-CH(CH_3)CH_2-$) could, however, be obtained readily (with one exception) by alkylating the correspond

(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, at Miami, Florida, April, 1957. Abstracts p. 19-N.

(2) Paper X of this series and references given therein, THIS JOURNAL, **79**, 4451 (1957).

(3) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943).

(4) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

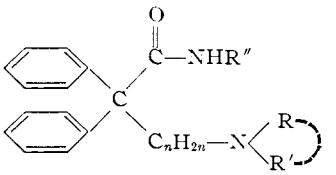
(5) P. Janssen, THIS JOURNAL, **78**, 3862 (1956).

(6) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2906 (1948).

(7) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, *ibid.*, **71**, 2821 (1949).

TABLE I

PHARMACOLOGICAL ACTIVITIES

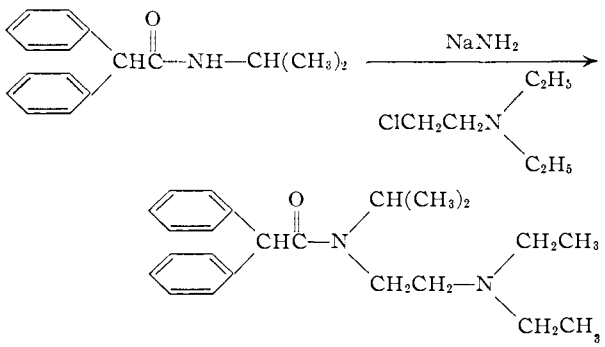


No. of base	$-C_nH_{2n}-N$	R″	Salt	Toxicity LD_{50} (mg./kg.)[a]	Oxytocic activity[b] at 1 mg./kg.	Diuretic activity[c] at 10 mg./kg.
1	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	HCl	200	Pronounced	Good
1	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	CH_3Br	100	Inactive	...
2	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CH_3$	HCl	65	Pronounced[d]	Excellent
3	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CH_3$	HCl	200	Moderate	Inactive
4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CH_3$	HCl	167	Slight	Good
4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CH_3$	CH_3I	..	Inactive	...
5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CH_3$	HCl	..	Inactive	Mild
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	HCl	65	Pronounced	Excellent
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	CH_3Br	100	Inactive	Inactive
6	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_3$	→ O	>1000	Inactive	Good
7	(*d*)-$CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	HCl	77	Moderate	Excellent
7	(*d*)-$CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	CH_3Br	..	...	...
7	(*d*)-$CH_2CH(CH_3)-N(CH_3)_2$[e]	$-CH_3$	→ O	650	Inactive	Excellent
8	(*l*)-$CH_3CH(CH_3)-N(CH_3)_2$[f]	$-CH_3$	HCl	..	Slight	Good
8	(*l*)-$CH_2CH(CH_3)-N(CH_3)_2$[f]	$-CH_3$	CH_3Br	..	...	...
9	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_3$	HCl	65	Pronounced	Excellent
9	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_3$	CH_3Br	200	Inactive	Inactive
10	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_3)_2$	HC.	65	Pronounced	Excellent
10	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_3)_2$	CH_3Br	233	Inactive	Inactive
11	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH=CH_2$	HCl	65	Pronounced	Fair
11	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH=CH_2$	CH_3Br	167	Inactive	...
12	$-CH_2CH(CH_3)-N(CH_3)_2$	$-(CH_2)_3CH_3$	CH_3Br	..	...	...
13	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_2)_5$	HCl	77	Good at 0.5	Fair
13	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH(CH_2)_5$	CH_3Br	100	Inactive	...
14	$-CH_2CH(CH_3)-N(CH_3)_2$	C_6H_5	HCl	200	Inactive	Slight
15	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2OH$	HCl	233	Slight	Good
15	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2OH$	CH_3Br	100	...	...
16	$-CH_2CH(CH_3)-N(CH_3)_2$	$-NH_2$	Base[g]	86[h]	Inactive	Fair
17	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	HCl	233	Slight	Inactive
17	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CH_3$	CH_3Br	65	Inactive	Inactive
18	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CH_3$	HCl	200	Inactive	...
18	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CH_3$	CH_3Br	65	Inactive	Inactive
19	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CH_3$	HCl[i]	100	Pronounced	Fair
20	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3CH_2$	2HCl	200	Inactive	Inactive
21	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$[j]	$-CH_3$	Base[k]	200	...	Fair
22	$(C_6H_5)_2CHCO-N[CH(CH_3)_2]CH_2CH_2N(CH_2CH_3)_2$		HCl	167	Pronounced	Mild
22	$(C_6H_5)_2CHCO-N[CH(CH_3)_2]CH_2CH_2N(CH_2CH_3)_2$		CH_3Br	65	Inactive	Inactive
	Oxytocin[l]		...	..	Pronounced	...
	Diamox[m]			1000	...	Excellent

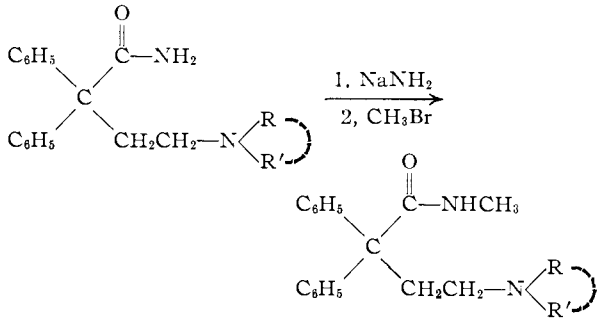
[a] Administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] Tested by intravenous administration in cats by a modification of the method of M. L. Clary, A. Cameron and B. N. Cramer, *Proc. Soc. Exp. Biol., Med.*, **77**, 778 (1951). [c] Administered orally to rats. [d] At 2 mg./kg. [e] This is the dextrorotating stereoisomer. [f] This is the levorotating stereoisomer. [g] Hydrazide. [h] This toxicity was by intravenous injection. [i] Preparation reported, THIS JOURNAL, **79**, 4451 (1957). [j] In this compound a *p*-chlorophenyl replaces one of the phenyl groups. [k] This base was dissolved in dilute hydrochloric acid and buffered to suitable *p*H for biological testing. [l] Oxytocic principle from the posterior lobe of the pituitary gland. It was given at 0.05 unit per kg. [m] The Lederle Laboratories brand of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide.

ing unsubstituted amides with sodium amide and an alkyl halide (method B). Methyl bromide was used in this work. The one exception noted was the case where R and R′ were methyls. In this case the attack was on the amino nitrogen and the quaternary salt was the principal product.

These amides in the form of their hydrochlorides and also their methobromides were tested as anti-



spasmodics in Thiry-Vella dogs and as gastric antisecretories in pyloric ligation rats. Surprisingly neither the tertiary amine nor quaternary salts showed any appreciable anticholinergic activity, being generally less than one-tenth as active as atropine sulfate as antispasmodic and inactive at 1 mg./kg. as antisecretory agents.



In the course of screening these compounds for a wide variety of biological activities it was found that the tertiary amine salts possessed a high order of oxytocic and/or diuretic activity. The quaternary salts were generally inactive in these respects. Table I lists the amides prepared in this study with their toxicities and an approximation of their oxytocic and diuretic activities. Several of these are considered to have sufficiently desirable properties to warrant clinical investigation.

Acknowledgments.—The authors are indebted to Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap, Mr. B. E. Graham and associates of our Department of Pharmacology for the pharmacological data. The authors also wish to express their appreciation to Dr. R. V. Heinzelman of our Department of Chemistry for guidance in this work.

Experimental

Method A (compounds no. 6–18 and 20 in Table II were made by this method).

α,α-Diphenyl-γ-dimethylamino-N-methylvaleramide.—To a cooled suspension of 207 g. (0.5 mole) of α,α-diphenyl-γ-dimethylaminovaleryl chloride acid sulfate[6] in 600 ml. of benzene was added slowly 78 g. of methylamine in 300 ml. of benzene with stirring. The mixture was allowed to warm to room temperature with stirring for 4 hours. It was then heated under reflux on a steam-bath for one-half hour. After cooling, the benzene solution was well washed with water and extracted with dilute hydrochloric acid. The acidic aqueous solution was made basic with sodium hydroxide and the free base was collected on a filter and dried. The product was recrystallized from isopropyl alcohol giving 138.5 g. (89.2%) of white crystals, m.p. 168–169°.

Hydrochloride.—To a warm solution of 62.1 g. (0.2 mole) of the above free base in 700 ml. of ethyl acetate was added a slight excess of ethanolic hydrogen chloride. On cooling, the hydrochloride crystallized giving 64.5 g. (93%) of white crystals, m.p. 217–219°.

Methobromide.—To a cold solution of 10 g. (0.032 mole) of the above free base in 100 ml. of benzene was added a large excess of cold methyl bromide. The flask was stoppered and allowed to stand at room temperature for 4 days. The product was collected on a filter, dried, m.p. 190–192°.

α,α-Diphenyl-γ-dimethylamino-N-methylvaleramide N'-Oxide.—A mixture of 31.0 g. (0.1 mole) of the above free base, 350 ml. of methanol and 25 ml. of 30% hydrogen peroxide was stirred rapidly at room temperature for 22 hours by which time all the solid had dissolved. After standing for 3 days the excess hydrogen peroxide was decomposed by adding a small amount of an aqueous slurry of platinum-on-charcoal and stirring for 5 hours. The solution was filtered through Supercel and distilled practically to dryness under reduced pressure below 50°. The crystalline residue was recrystallized from ethyl acetate giving white crystals, m.p. 141–144° after sintering at about 120°. This appeared to be a solvate which lost weight on drying at 50° (20 mm.) for 20 hours; yield 29.4 g. (90%); m.p. 147–148.5°.

***dextro*-α,α-Diphenyl-γ-dimethylaminovaleric Acid Acid Sulfate.**—A mixture of 138 g. (0.5 mole) of *dextro*-α,α,γ-dimethylaminovaleronitrile,[8] 175 ml. of concentrated sulfuric acid and 107 ml. of water was heated under reflux at 150° for 5 hours. After cooling it was poured onto ice and the white solid was collected on a filter. This was dissolved in 290 ml. of boiling absolute ethanol and diluted with an equal amount of ether. The product was collected and dried giving 322 g. (94%) of the acid sulfate salt; m.p. 195–198°; $[\alpha]^{22}D$ +74° (1.0% in methanol).

Free Basic Acid.—A sample of the above salt was dissolved in dilute sodium hydroxide and made just acid with acetic acid. The product was collected and dried; m.p. 219–221° dec.; $[\alpha]^{22}D$ +115° (1.0% in methanol).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.74; H, 7.70; N, 4.76.

***dextro*-α,α-Diphenyl-γ-dimethylaminovaleryl Chloride Acid Sulfate.**—A mixture of 105 g. (0.265 mole) of the above *dextro* acid sulfate salt, 120 ml. of thionyl chloride and 150 ml. of benzene was heated under reflux with stirring for 45 minutes. All the acid dissolved and later the product crystallized. The excess thionyl chloride was removed by distillation under reduced pressure and an additional 100 ml. of benzene was added and distilled. The crystalline product was collected, washed with benzene and absolute ether and dried in a vacuum desiccator; yield 104 g. (95%).

***levo*-α,α-Diphenyl-γ-dimethylaminovaleric Acid Acid Sulfate.**—This was prepared as described above for the *dextro* isomer; yield 81%; m.p. 195–198°, $[\alpha]^{22}D$ −76° (1.0% in methanol).

Free Basic Acid.—Prepared as described for the *dextro* isomer; m.p. 219–221° dec., $[\alpha]^{22}D$ −111° (1.0% in methanol).

Hydrochloride.—Prepared as described for the *dextro* isomer; m.p. 228–230°, $[\alpha]^{22}D$ −90° (1.0% in methanol).

***levo*-α,α-Diphenyl-γ-dimethylaminovaleryl Chloride Acid Sulfate.**—This was prepared in 96% yield as described above for the *dextro* isomer.

α,α-Diphenyl-γ-(1-pyrrolidyl)-valeric Acid Acid Sulfate.—This was prepared from 50 g. (0.146 mole) of α,α-diphenyl-γ-(1-pyrrolidyl)-valeronitrile[2] by a procedure similar to that described above for the *dextro*-α,α-diphenyl-γ-dimethylaminovaleric acid acid sulfate. The product was recrystallized twice from alcohol plus ether giving 50 g. (82%) of white solid, m.p. 180–185° dec.

Anal. Calcd. for $C_{21}H_{27}NO_6S$: C, 59.83; H, 6.45; N, 3.33; S, 7.61. Found: C, 60.16; H, 6.71; N, 3.50; S, 7.52.

β-Pyrrolidylethylamine.[9]—To 853 g. (12 moles) of dry pyrrolidine, in a 5-l. flask, was added slowly 499 g. (2.44 moles) of β-bromoethylamine hydrobromide with vigorous stirring and cooling by an ice-bath. The addition was carried out at such a rate that the temperature did not rise

(8) A. Pohland, F. J. Marshall and T. P. Carney, THIS JOURNAL, **71**, 460 (1949).

(9) This compound has been previously reported, J. J. van Alphen, *Rec. trav. chim.*, **58**, 1105 (1939), and R. H. Reitsema and J. H. Hunter, THIS JOURNAL, **70**, 4009 (1948), but the present method appears to be more convenient.

TABLE II

AMIDES

No. of base (Table I)	Salt (or base)	Yield, %[a]	M.p., °C.	Crystallizing solvent	Empirical formula	Carbon Calcd.	Carbon Found[b]	Hydrogen Calcd.	Hydrogen Found[b]	Nitrogen Calcd.	Nitrogen Found[b]	Other element Calcd.	Other element Found[b]
1	HCl	23[c]	185–187	EtOH	$C_{21}H_{29}ClN_2O$	69.88	69.72	8.10	7.81	7.76	7.61	Cl, 9.82	Cl, 9.81
1	CH_3Br	..	216–217	EtOH + EtOAc	$C_{22}H_{31}BrN_2O$	63.00	63.38	7.45	7.73	6.68	6.56	Br, 19.05	Br, 18.70
2	HCl	..	202–204	MeEtCO + Et_2O	$C_{23}H_{33}ClN_2O$	71.02	70.99	8.55	8.24	7.20	7.15	Cl, 9.12	Cl, 9.00
3	HCl	..	195–198	MeEtCO + EtOH	$C_{22}H_{29}ClN_2O$	70.85	70.70	7.84	7.61	7.51	7.49	Cl, 9.51	Cl, 9.61
4	HCl	73[c]	214–216	EtOAc	$C_{23}H_{31}ClN_2O$	71.38	71.38	8.08	8.35	7.24	7.13	Cl, 9.16	Cl, 9.30
4	CH_3I	98[d]	122–125	Benzene	$C_{24}H_{33}IN_2O$	58.53	58.89	6.75	7.18	5.69	5.69	I, 25.77	I, 23.83
5	HCl	64[e]	248–250	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.66	7.85	7.85	8.08	7.55	Cl, 10.22	Cl, 10.08
6	Base	89	168–169	*i*-PrOH	$C_{20}H_{26}N_2O$	77.38	77.71	8.44	8.46	9.03	9.22	.....	.....
6	HCl	93	217–219	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.17	7.85	7.59	8.08	8.31	Cl, 10.22	Cl, 10.10
6	CH_3Br	..	190–192	Benzene	$C_{21}H_{29}BrN_2O$	62.21	62.16	7.21	7.03	6.91	6.90	Br, 19.71	Br, 19.65
6	→ O	90	147–148.5	MeOH + EtOAc	$C_{20}H_{26}N_2O_2$	73.75	73.66	8.03	8.23	8.58	8.49	O, 9.80	O, 9.86
7	Base	89	114–116[e]	*i*-PrOH + H_2O	$C_{20}H_{26}N_2O$	77.38	77.26	8.44	8.13	9.03	9.21	.....	.....
7	HCl	95	223–224[f]	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.11	7.85	7.63	8.08	8.44	Cl, 10.22	Cl, 9.94
7	CH_3Br	96	184–186[g]	MeEtCO	$C_{21}H_{29}BrN_2O$	62.21	62.03	7.21	6.89	6.91	6.74	Br, 19.71	Br, 19.68
7	→ O	..	154–155	EtOAc	$C_{20}H_{26}N_2O_2$	73.75	73.57	8.03	7.72	8.58	8.56	.....	.....
8	Base	95	116–117[h]	*i*-PrOH + H_2O	$C_{20}H_{26}N_2O$	77.38	77.78	8.44	8.12	9.03	9.06	.....	.....
8	HCl	98	221–223[i]	EtOH + EtOAc	$C_{20}H_{27}ClN_2O$	69.24	69.49	7.85	7.71	8.08	7.89	Cl, 10.22	Cl, 10.22
8	CH_3Br	100	181–182[j]	MeEtCO	$C_{21}H_{29}BrN_2O$	62.21	62.21	7.21	7.56	6.91	6.43	Br, 19.71	Br, 19.91
9	Base	84	133–135	*i*-PrOH	$C_{20}H_{28}N_2O$	77.73	78.01	8.70	8.40	8.64	8.42	.....	.....
9	HCl	86	197–199	EtOH + EtOAc	$C_{21}H_{29}ClN_2O$	69.88	69.69	8.10	7.83	7.76	7.63	Cl, 9.82	Cl, 9.66
9	CH_3Br	98	176–178	*i*-PrOH	$C_{22}H_{31}BrN_2O$	63.00	62.86	7.45	7.16	6.68	6.78	Br, 19.06	Br, 18.83
10	Base	48	116–118	Cyclohexane	$C_{22}H_{30}N_2O$	78.06	78.16	8.93	8.89	8.28	8.29	.....	.....
10	HCl	90	216–218	EtOH + MeEtCO	$C_{22}H_{31}ClN_2O$	70.47	70.22	8.33	8.37	7.47	7.73	Cl, 9.46	Cl, 9.50
10	CH_3Br	..	155–158	EtOAc + Et_2O	$C_{23}H_{33}BrN_2O$	63.73	64.09	7.62	7.71	6.46	6.36	Br, 18.44	Br, 18.27
11	Base	84	99–101	*i*-PrOH + H_2O	$C_{22}H_{28}N_2O$	78.53	78.78	8.39	8.32	8.33	8.59	.....	.....
11	HCl	72	167–170	EtOH + EtOAc	$C_{22}H_{29}ClN_2O$	70.85	70.55	7.84	7.59	7.51	7.25	Cl, 9.51	Cl, 9.53
11	CH_3Br	98	167–169	*i*-PrOH	$C_{23}H_{31}BrN_2O$	64.03	63.94	7.24	7.18	6.50	6.29	Br, 18.53	Br, 18.76
12	CH_3Br	76[k]	175–177	EtOAc + Et_2O	$C_{24}H_{35}BrN_2O$	64.42	64.61	7.88	7.73	6.28	6.25	Br, 17.56	Br, 17.89
13	Base	..	94–97	*i*-PrOH + H_2O	$C_{25}H_{34}N_2O$	79.32	79.66	9.05	8.91	7.40	7.48	.....	.....
13	HCl	..	188–191	EtOAc	$C_{25}H_{35}ClN_2O$	72.35	72.07	8.50	8.64	6.75	6.22	Cl, 8.54	Cl, 8.40
13	CH_3Br	..	130–135	EtOAc + Et_2O	$C_{26}H_{37}BrN_2O$	65.95	66.73	7.88	7.98	5.92	5.67	Br, 16.88	Br, 16.38
14	Base	..	169–171	MeOH	$C_{27}H_{28}N_2O$	80.59	80.63	7.57	7.31	7.52	7.47	.....	.....
14	HCl	..	243–244.5	EtOH	$C_{25}H_{29}ClN_2O$	...	...	..	..	6.84	6.86	.....	.....
15	Base	77	149.5–151.5	Benzene + cyclohexane	$C_{21}H_{28}N_2O_2$	74.08	74.55	8.29	8.27	8.23	8.17	.....	.....
15	HCl	77	198–201	EtOH + EtOAc	$C_{20}H_{29}ClN_2O_2$	66.91	66.59	7.75	7.74	7.43	7.15	Cl, 9.41	Cl, 9.39
15	CH_3Br	94	170–171	*i*-PrOH + EtOAc	$C_{22}H_{31}BrN_2O_2$	60.68	60.63	7.18	7.00	6.44	6.40	Br, 18.36	Br, 18.19
16	Base	..	156–158	EtOAc	$C_{19}H_{25}N_3O$	73.27	73.34	8.09	8.01	13.49	13.51	.....	.....

17	HCl[i]	68	178–180	EtOH + EtOAc	$C_{22}H_{31}ClN_2O$	70.47	70.50	8.33	8.43	7.47	6.97	Cl, 9.46	Cl, 9.26
17	CH_3Br	65[d]	190–192	MeEtCO	$C_{23}H_{33}N_2O$	63.73	63.94	7.67	7.59	6.46	6.38	Br, 18.44	Br, 18.42
18	Base	63[m]	122–124	Cyclohexane	$C_{22}H_{28}N_2O$	78.53	78.62	8.39	8.25	8.33	8.51	.....	.....
18	HCl	77	147–149	EtOH + MeEtCO	$C_{22}H_{29}ClN_2O$	70.85	71.02	7.84	7.72	7.51	7.79	Cl, 9.51	Cl, 9.50
18	CH_3Br	98	238–240	MeEtCO	$C_{23}H_{31}BrN_2O$	64.03	64.41	7.24	7.12	6.49	6.55	Br, 18.52	Br, 18.31
20	2HCl	62	160–163	EtOH + EtOAc	$C_{25}H_{37}Cl_2N_3O$	64.37	64.68	8.00	8.19	9.01	9.12	.....	.....
21	Base	26	121–123	Hexane	$C_{23}H_{29}ClN_2O$	71.76	71.57	7.59	7.68	7.28	7.51	Cl, 9.21	Cl, 9.09
22	HCl	..	180–182	Dioxane	$C_{23}H_{33}ClN_2O$	71.02	70.93	8.52	8.43	7.20	7.35	Cl, 9.12	Cl, 8.95
22	CH_3Br	..	161–163	MeEtCO	$C_{24}H_{35}BrN_2O$	64.42	64.69	7.88	7.92	6.26	6.55	Br, 17.86	Br, 17.92

[a] Unless otherwise indicated the yields of the salts are calculated from the corresponding free bases. The yields of the bases are calculated from the acid chlorides (method A used for numbers 6 to 18 inclusive and for number 20) or the amides (method B, used for numbers 1 to 5 inclusive and for number 21). [b] Analyses and rotations are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. [c] This yield is based on the corresponding unsubstituted amide. The free base was not isolated in pure form. [d] This yield is based on the corresponding purified hydrochloride. [e] $[\alpha]^{22}D$ +100° (1% in MeOH). [f] $[\alpha]^{22}D$ +66° (1.5% in MeOH). [g] $[\alpha]^{22}D$ −98° (0.7% in MeOH). [h] $[\alpha]^{22}D$ +28° (1.5% in MeOH). [i] $[\alpha]^{22}D$ −64° (0.7% in MeOH). [j] $[\alpha]^{22}D$ −29° (1.0% in MeOH). [k] This yield is based on the corresponding acid chloride acid sulfate salt. The free base was not isolated in pure form. [l] This was prepared from the acid sulfate of α,α-diphenyl-δ-diethylaminovaleric acid (D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949)) *via* the acid chloride, and free basic amide, neither of which were obtained crystalline. The procedure was similar to that described in the Experimental section for the corresponding pyrrolidyl compounds. [m] This was prepared from the acid sulfate salt of the corresponding basic acid (Experimental section) *via* the acid chloride which, however, was not isolated.

above 10°. Most of the excess pyrrolidine was then distilled through an efficient column and recovered. To the residue was added with stirring 240 g. (6 moles) of sodium hydroxide in 240 ml. of water. The oil was decanted and dried over solid potassium hydroxide. The sodium bromide and potassium hydroxide residues were extracted with absolute ether which was added to the oil and dried over potassium carbonate. After filtration the solution was carefully distilled though an efficient column. The product distilled at 164–167° giving 220 g. (80%) of colorless liquid; $n^{25}D$ 1.4672.

α,α-Diphenyl-γ-dimethylamino-N-[2-(1-pyrrolidyl)-ethyl]-valeramide Dihydrochloride.—A solution of 70 g. (0.61 mole) of β-pyrrolidylethylamine in 250 ml. of benzene was cooled in an ice-bath and 82.8 g. (0.2 mole) of α,α-diphenyl-γ-dimethylaminovaleryl chloride acid sulfate[6] was added in small portions with stirring during one-half hour. After stirring for 2 hours at room temperature and 15 minutes under reflux the mixture was cooled and filtered. The filtrate was washed well with water and extracted with dilute hydrochloric acid. The aqueous acid solution was washed with ether and made basic with sodium hydroxide. The free base was extracted with benzene which was washed with water and the solvent was distilled.

The residual free base was dissolved in ethyl acetate and a slight excess of ethanolic hydrogen chloride was added. After cooling the product was collected giving 57.4 g. (62%) of white crystals, with the properties given in Table II.

Method B (compounds no. 1–5 and 21 in Table II were prepared by this method from amides previously described[2]).

α α-Diphenyl-γ-diethylamino-N-methylbutyramide Hydrochloride.—A mixture of 63.5 g. (0.205 mole) of α,α-diphenyl-γ-diethylaminobutyramide,[4] 8 g. (0.205 mole) of sodium amide and 500 ml. of dry toluene was heated under reflux for 2.5 hours. After cooling, a solution of 19.5 g. (0.205 mole) of methyl bromide in 100 ml. of dry toluene was added slowly. After stirring for 1 hour more water was added. The organic layer was extracted with dilute hydrochloric acid and this acid solution was again made basic with dilute sodium hydroxide. The free base was extracted with benzene and the solvent was distilled leaving 40 g. of yellow oil. This was dissolved in 400 ml. of methyl ethyl ketone and a slight excess of ethanolic hydrogen chloride was added. The hydrochloride separated as a white solid; m.p. 175–185°. This product contained a small amount of the hydrochloride of the starting material which was removed by repeated crystallizations from isopropyl or ethyl alcohol. The over-all yield was 23%. The infrared spectrum[10] indicated that this was monosubstituted amide essentially free from unsubstituted or disubstituted amides.

Reaction of Ethyl α,α-Diphenyl-γ-diethylaminobutyrate with Methylamine.—A solution of 25 g. (0.074 mole) of ethyl α,α-diphenyl-γ-diethylaminobutyrate[11] and 47.5 g. (1.53 moles) of methylamine in 75 ml. of ethylene glycol gave no reaction at room temperature or at 100°, but reacted when heated in an autoclave at 200° for 15 hours. On standing, crystals separated which were collected, washed with water and dried; m.p. 140–145°. After two recrystallizations from benzene–cyclohexane, it gave a product, m.p. 144–146°. This was found by mixed melting point and comparison of the infrared spectrum[10] with that of an authentic sample to be 1-methyl-3-diphenylpyrrolidone-2.[12]

α,α-Diphenyl-N-isopropylacetamide.—A mixture of 72.6 ml. (1.0 mole) of thionyl chloride, 106.1 g. (0.5 mole) of diphenylacetic acid and 100 ml. of benzene was heated under reflux for 45 minutes. The benzene and excess thionyl chloride were distilled under reduced pressure and 75 g. (1.26 moles) of isopropylamine in 200 ml. of dry benzene was added slowly with cooling. After stirring for 2 hours, the mixture was heated to the boiling point, filtered and cooled. The crystalline amide was collected and recrystallized from benzene giving 89 g. (70%) of white solid, m.p. 158–159°.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.89; H, 7.48; N, 5.81.

α,α-Diphenyl-N-isopropyl-N-(2-diethylaminoethyl)-acetamide Hydrochloride.—To a suspension of 12.5 g. (0.32 mole) of sodium amide in 700 ml. of dry toluene was added

(10) The infrared spectra are by Dr. James L. Johnson and associates of our Department of Physics.

(11) M. Bockmühl and G. Ehrhart, U. S. Patent 2,230,774 (1941).

(12) D. J. Dupre, J. Elks, B. A. Hens, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

78.49 g. (0.31 mole) of α,α-diphenyl-N-isopropylacetamide and the mixture was heated under reflux with stirring for 3 hours. A solution of 44.7 g. (0.33 mole) of β-diethylaminoethyl chloride in 100 ml. of dry toluene was added slowly with stirring at reflux temperature and the heating was continued for 20 hours. The toluene solution was washed with water, and extracted with dilute hydrochloric acid. The aqueous solution was washed with toluene and made basic with sodium hydroxide. The free base was extracted with benzene which was washed with water, dried over sodium sulfate and the solvent distilled. A yellow oil remained which could not be crystallized.

The free base was dissolved in methyl ethyl ketone, acidified with a slight excess of ethanolic hydrogen chloride and evaporated. A gum was obtained which crystallized from dioxane giving white crystals, with the properties given in Table II.

Methobromide.—An aqueous solution of 10 g. of this hydrochloride was made basic with sodium hydroxide and extracted with benzene. A portion of the benzene was distilled to remove water and cooled. Then 30 g. of cold methyl bromide was added, the flask was stoppered, clamped and allowed to stand at room temperature for 3 days. Concentration of the solution caused an oil to separate which solidified on trituration with ether. It was recrystallized from ethyl acetate and a little ethanol giving crystals, m.p. 76–78°. Recrystallization of this material gave a different modification, m.p. 161–163°.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

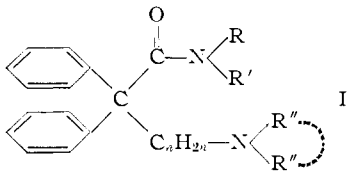
Antispasmodics. XII. α,α-Diphenyl-tertiaryamino-N,N-disubstituted Amides[1]

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED MARCH 25, 1957

A series of α,α-diphenyl-γ-tertiaryamino-N,N-disubstituted amides (I, R and R′ = alkyl) have been prepared. In general they have been found to have little if any anticholinergic properties, but, like the monosubstituted amide series, the acid addition salts are oxytocics and/or diuretics.

Amides of the general type I (R and R′ = H), unsubstituted on the amide nitrogen, are well known as anticholinergics.[2]

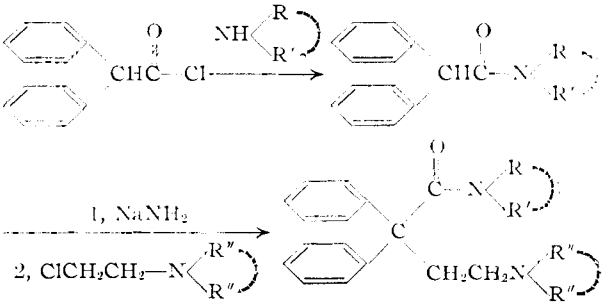


I

The preceding paper of this series[3] reported monosubstituted amides (I, R = H, R′ = alkyl). These were found to have little, if any, anticholinergic properties, but were powerful oxytocics and/or diuretics. It was therefore of interest to determine what type of activity would be shown by the disubstituted amides (I, R and R′ = alkyl). A very few of these disubstituted amides have been reported in the literature.[4–6] The first of these were reported in articles[4,5] dealing with antispasmodics but no pharmacology was given. Recently certain ones were reported to have high analgetic activity.[6]

A considerable number of these disubstituted amides have now been made and are listed in Table I. Like the monosubstituted amides[3] neither the hydrochlorides nor the methobromides had much antispasmodic activity in the Thiry-Vella dogs or gastric antisecretory activity in pyloric ligation rats but the hydrochlorides were generally oxytocics and/or diuretics.

In cases where $-C_nH_{2n}-$ (I) was $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$ the dimethylamides (no. 15–18 in the table) were prepared from the corresponding acid chloride by a procedure essentially like procedure A described in the preceding paper[3] using dimethylamine in place of monomethylamine. When C_nH_{2n} = $-CH_2CH_2-$ or with large or hindered secondary amines pyrrolidones[7,8] were the chief products. Where $-C_nH_{2n}-$ was $-CH_2CH_2-$ the disubstituted amides were prepared by the method



This method is illustrated by an example in the Experimental part and the physical properties of the amides are listed in Table II (no. 1–14).

Acknowledgments.—The authors are indebted to Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap, Mr. B. E. Graham and associates of our Department of Pharmacology for the pharmacological data. The authors also wish to express their appreciation to Dr. R. V. Heinzelman of our Department of Chemistry for guidance in this work.

Experimental

α,α-Diphenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-N,N-dimethylbutyramide.—A mixture of 54 g. (0.226 mole) of diphenyl-

(1) Presented in part before the Division of Medicinal Chemistry, A.C.S., at Miami, Florida, April, 1957. Abstracts, p. 19-N.

(2) R. B. Moffett and B. D. Aspergren, THIS JOURNAL, **79**, 4451 (1957), and references given therein.

(3) R. B. Moffett, B. D. Aspergren and M. E. Speeter, *ibid.*, **79**, 4457 (1957).

(4) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943).

(5) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

(6) P. Janssen, THIS JOURNAL, **78**, 3862 (1956).

(7) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2960 (1948).

(8) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, *ibid.*, **71**, 2821 (1949).