platinum oxide in 200 ml. of ethanol was shaken under 60 p.s.i. of hydrogen. The pressure drop was less than 1 p.s.i.; 3.5 hours after an additional 0.5 g. of catalyst had been added, the theoretical amount (23 p.s.i.) of hydrogen had been taken up. The reaction was worked up in the same manner as described for the reduction of 1-methyl-2-phenylpyridinium iodide. Distillation of the residual oil afforded 15.6 g. (75%) of yellow liquid, b.p. 103–105° at 4.5 mm. This was redistilled through a short Vigreux column to yield 14.8 g. of yellowish oil, $n^{24}D$ 1.5280, b.p. 98–99° at 3.5 mm.

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.30; H, 9.93; N, 7.29.

1,1-Dimethyl-2-*o*-tolylpiperidinium iodide was obtained as colorless fine crystals, m.p. 190–195°, from the reaction of 10.0 g. (0.053 mole) of the tertiary amine in 25 ml. of acetonitrile with 15 ml. of methyl iodide. The yield was 17.4 g. (99%).

A sample of this quaternary salt was recrystallized from acetonitrile–ether to a constant melting point of 206–208°. The mixed melting point of this with the methiodide V (223–225°) was 179–185°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.78; H, 6.70; N, 4.23. Found: C, 50.65; H, 6.72; N, 4.24.

1-Dimethylamino-5-*o*-tolylpentane (VI).—To a well-stirred hot solution of 16.4 g. (0.050 mole) of the above methiodide in 300 ml. of water there was added over 1 hr. 400 g. of 5% sodium amalgam. After an additional 26 hr. heating on steam, the reaction mixture was worked up as in the Emde reduction described above to afford 7.80 g. (77%) of the tertiary amine, b.p. 122–125° at 4.8 mm.

The picrate, m.p. 108–109°, and the methiodide, m.p. 125–126°, were prepared in the same manner as described above. A mixed m.p. of each of these derivatives with those of the amine obtained by reduction of V failed to show any depression.

Attempted Rearrangement of V.—The methiodide (20 g., 0.0605 mole) was added to 0.122 mole of sodium amide (from 2.8 g. of sodium metal) in 200 ml. of liquid ammonia. After 40 minutes stirring, the reaction was neutralized with 12 g. of solid ammonium chloride. The oil which was obtained when the reaction mixture was worked up in the usual manner was distilled through a short Vigreux column. At 2 mm., 2.72 g. of colorless liquid, b.p. 96–100°, was obtained; this was followed by 1.0 g., b.p. 100–110°; the residue (5.07 g.) had not yet come over when the bath temperature was 250°. The first fraction formed a picrate of m.p. 110–165°, which could not be recrystallized readily.

Substantially the same result was obtained with a reaction time of 5 hr. In this case, however, some ether-insoluble, rubber gum was obtained as well.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

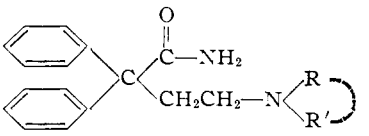
Antispasmodics. X. α,α-Diphenyl-γ-amino Amides[1]

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

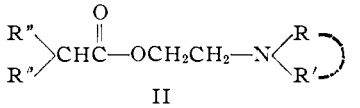
RECEIVED MARCH 25, 1957

A number of α,α-diphenyl-γ-amino amides, their salts and intermediate nitriles have been prepared and tested for anticholinergic activity. In several cases the same tertiary amino groups that previously gave highly active anticholinergics in the ester series also gave very active compounds when introduced into the γ-position of these amides. The effects of substitution or replacement of one of the phenyl groups and of branching the alkyl chain were also explored.

The reports of Bockmühl and Ehrhart[2] in which certain α,α-diphenylamino amides were shown to be powerful antispasmodic agents have stimulated considerable work[3] on this interesting type of compound. In our study of the relationship between structure and anticholinergic activity it seemed of interest to introduce, in the γ-position of these amides (I), some of the amino groups that gave good results in the ester type of anticholinergics[4] (II).



I



II

Table I lists the compounds tested in this study with their toxicities and antispasmodic and gastric antisecretory activities. For comparison the activities of atropine, Pamine,[5] and a few previously reported amides have also been included.

It would hardly be expected that any correlation would exist between the anticholinergic activity and the type of amino groups in molecules so fundamentally different, and indeed no *close* correlation was found. For example, esters containing dimethylamino and piperidyl groupings have not been very effective, whereas at least one amide with each of these groupings has been outstanding enough to market.[6] On the other hand, some pyrrolidine-containing amides are no better than the corresponding pyrrolidine-containing esters. However, the methyl-substituted pyrrolidine-containing esters III, IV and V had atropine indexes (in Thiry-vella dogs) of 2, 1 and 1, and antisecretory ED_{50}'s of 0.4, 0.5 and 0.1, respectively, while the

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

(2) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943); *Ann.*, **561**, 52 (1948).

(3) (a) J. B. Hoekstra and H. L. Dickison, *J. Pharmacol. Exptl. Therap.*, **98**, 14 (1950); R. J. Cozort, *ibid.*, **100**, 325 (1950). (b) O. Schaumann and E. Lindner, *Arch. Exper. Path. Pharmacol.*, **214**, 93 (1951). (c) 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); W. B. Wheatley, *ibid.*, **19**, 434 (1954); W. B. Wheatley, W. F. Minor, W. M. Byrd, W. E. Fitzgibbon, M. E. Speeter, L. C. Cheney and S. B. Binkley, *ibid.*, **19**, 794 (1954). (d) P. Janssen, D. Zivkovic, P. Demoen, D. K. deJongh and E. G. von Proosdij-Hartzema, *Arch. intern. pharmacodynamie*, **103**, 82 (1955).

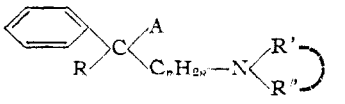
(4) R. B. Moffett, B. D. Aspergren and F. E. Visscher, THIS JOURNAL, **77**, 1565 (1955), and preceding papers.

(5) Pamine Bromide is the Upjohn brand of scopolamine methyl bromide.

(6) α,α-Diphenyl-γ-dimethylaminovaleramide hydrogen sulfate is being marketed by Bristol Laboratories as Centrine; α,α-diphenyl-γ-piperidylbutyramide methobromide is marketed by Farbwerke Hoechst as Resantin.

TABLE I

PHARMACOLOGICAL ACTIVITIES



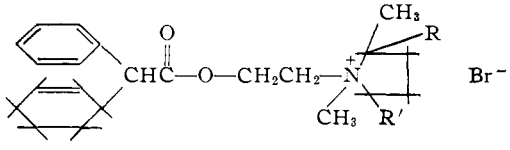
No. of base	R	$-C_nH_{2n}-N\begin{matrix}R'\\R''\end{matrix}$	A	Salt	Toxicity LD_{50} (mg./kg.)[a]	Anti-spasmodic activity At. I.[b]	Anti-secretory activity ED_{50} (mg./kg.)[c]
1	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	H_2SO_4[d]	233	<0.1	0.5
1	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[d]	167	1.0	0.3
2	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-C\equiv N$	HCl	..	<0.1	$\ll$1.0
3	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CONH_2$	HCl	200	0.1	0.2
3	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	167	3.5	0.08
4	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-C\equiv N$	HCl	200	<0.1	$\ll$1.0
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	$1/_2H_2SO_4$	200	0.1	0.4
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	77	4.0	0.003
5	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	$\rightarrow O$	533	0.2	1.0
6	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-C\equiv N$	HCl	167	<0.05	<1.0
7	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-CONH_2$	HCl	167	<0.1	0.2
7	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CHCH_3$	$-CONH_2$	CH_3Br	77	3.0	0.1
8	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-C\equiv N$	HCl	..	...	...
9	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-CONH_2$	HCl	..	<0.1	...
9	C_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	$-CONH_2$	CH_3Br	167	5.0	0.2
10	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-C\equiv N$	CH_3Br[e]	65	0.5	0.1–1.0
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	HCl[2]	167	1.0	0.1–0.2
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[e]	100	2.0	0.1
11	C_6H_5	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	$-CONH_2$	$\rightarrow O$	767	0.3	1.0
12	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CH_2$	$-CONH_2$	HCl[f]	167	0.5	0.2
12	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br[f]	77	3.0	0.2
13	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-C\equiv N$	Base[g]	..	...	...
14	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-CONH_2$	HCl	65	<0.2	<1.0
14	C_6H_5	$-CH_2CH_2-NCH(CH_3)CH_2CH_2CH_2CHCH_3$	$-CONH_2$	CH_3Br	200	1.0	0.2
15	C_6H_5	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CONH_2$	H_2SO_4	133	0.1	2.0
15	C_6H_5	$-CH_2CH_2-N[CH(CH_3)_2]_2$	$-CONH_2$	CH_3Br[3d]	65	3.0	0.1
16	C_6H_5	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CONH_2$	H_2SO_4[3a,3c,8]	133	1.0	0.5
16	C_6H_5	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CONH_2$	CH_3I[3a,3c]	150	0.5	5.0
16	C_6H_5	$-CH_2CH(CH_3)-N(CH_3)_2$	$-CONH_2$	$\rightarrow O\cdot HBr$	1000	<0.1	>1.0
17	C_6H_5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CONH_2$	HCl[3c]	..	<0.1	>1.0
17	C_6H_5	$-CH(CH_3)CH_2-N(CH_3)_2$	$-CONH_2$	CH_3Br	..	<0.1	$\gg$1.0
18	C_6H_5	$-CH_2C(CH_3)_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	HCl	175	<0.1	0.5
18	C_6H_5	$-CH_2C(CH_3)_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	100	3.0	0.1
19	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-C\equiv N$	HCl	..	...	...
20	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	HCl	200	0.12	>1.0
20	C_6H_5	$-CH_2CH_2CH_2-NCH_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	65	1.0	$\gg$1.0
21	C_6H_5	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	HCl	200	0.1	...
21	C_6H_5	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	CH_3Br	65	0.75	1.0
22	C_6H_5	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CONH_2$	HCl[h]	77	<0.1	...
22	C_6H_5	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	$-CONH_2$	CH_3Br[h]	167	0.5	...
23	m-ClC_6H_5	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-C\equiv N$	Base	..	...	...

TABLE I (*Continued*)

No. of Base	R	$-C_{n2n}-N\langle^{R'}_{R''}$	A	Salt	Toxicity LD_{50} (mg./kg.)[a]	Anti-spasmodic activity At. I.[b]	Anti-secretory activity ED_{50} (mg./kg.)[c]
24	*m*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	100	<0.1	...
24	*m*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	65	3.0	...
25	*p*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	167	<0.1	...
25	*p*-ClC_6H_4	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	..	2.0	...
26	$-CH(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	HCl	200	<0.1	≫0.1
26	$-CH(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	$-CONH_2$	CH_3Br	53	0.2	>0.1
27	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-C\equiv N$	HCl	..	<0.1	≫0.1
28	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	HCl	200	<0.1	>0.1
28	$-CH(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$-CONH_2$	CH_3Br	77	0.5	>0.1
29	Atropine			$^1/_2H_2SO_4$	150	1.0	0.07
30	Scopolamine			CH_3Br[5]	150	6.0	0.003

[a] The compounds were administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] The antispasmodic activity was determined in Thiry-Vella dogs [O. H. Plant, *J. Pharmacol. Exp. Therap.*, **16**, 311 (1921)]. The results are expressed as the ratio of the activity to that of atropine sulfate (Atropine Index). [c] The gastric antisecretory activity was determined in pyrolic ligration rats [F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exp. Therap.*, **110**, 188 (1954)]. It is expressed as the effective dose necessary to reduce the gastric secretion by approximately 50%. [d] The corresponding free base, methiodide, and ethosulfate have been reported previously.[3c] [e] This compound was reported by us before the Division of Medicinal Chemistry, A.C.S., at Los Angeles, California, March, 1953. [f] The corresponding free base and methyl *p*-toluenesulfonate quaternary salt have been reported.[3c] [g] Preparation by a different method reported by D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 506 (1949). [h] Preparation reported in paper IX of this series, THIS JOURNAL, **79**, 3186 (1957).

corresponding amides had atropine indexes of 3.5, 4 and 3 and ED_{50}'s of 0.08, 0.003 and 0.1. Another grouping occurring in active compounds in both series was the diisopropylamino group. An



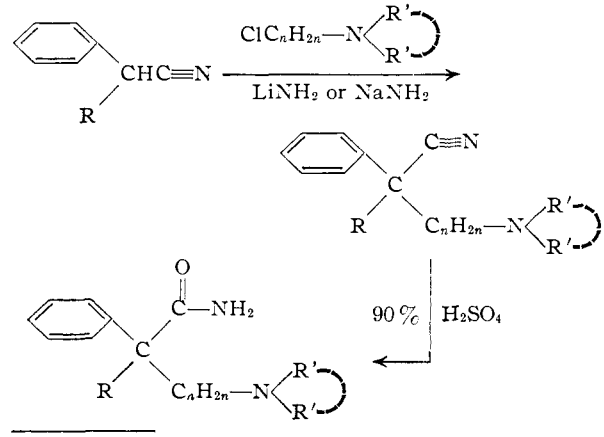
III, R and R' = H
IV, R = CH_3, R = H
V, R = H, R' = CH_3

ester containing this group, 2-(diisopropylamino)-ethyl-9-xanthine carboxylate methobromide is on the market[7] and the corresponding amide (No. 15 (CH_3Br), Table I) has been extensively studied by Dr. Paul Janssen and associates.[3d] One compound, α,α-diphenyl-γ-(2,2,4-trimethyl-1-pyrrolidyl)-butyramide methobromide (Table I, no. 9) showed exceptionally high antispasmodic activity but only moderate gastric antisecretory activity. The esters containing this trimethylpyrrolidyl group[4] were not outstanding. Therefore, whereas broadly speaking, a surprising number of groups previously found in active esters are also present in our most active amides, considerable variation is apparent between parallel members of the two classes. In addition, it is clear that ED_{50}'s do not go hand-in-hand with atropine indexes.

The amide series (Table I) has been extended by the preparation of a few compounds in which one of the phenyl groups is replaced by an isopropyl group. These were found to be less active than the corresponding diphenyl amides. Substitution of a chlorine atom in the *meta* or *para* positions of one of the phenyl rings tended to decrease the anticholinergic activity. Compounds with the amino group on the δ-carbon atom had very little activity. α,α-Diphenyl-γ-amino amides with a methyl group on the γ-carbon atom are well known.[3a,b,c] Aminopentamide[8] (Table I, no. 16) is of this type. In one case in which two methyl groups were substituted on the γ-carbon atom, the product (Table I, no. 18, MeBr) was considerably more active than the corresponding compound with no methyls on the γ-carbon.

In general, the quaternary salts (methobromides) were more active both as antispasmodics and as antisecretories than the corresponding tertiary amine salts. Aminopentamide[9] is an exception, being more active than its methiodide.[3a] The amine oxides of a few of these amino amides were prepared. They were considerably less toxic than the parent amines but also less active.

A number of the intermediate nitriles were also tested but were found to be much less active as anticholinergics than the corresponding amides.



(7) Probanthine, G. D. Searle and Company.

(8) Centrine, Bristol Laboratories, Inc.

TABLE II

INTERMEDIATE NITRILES

No. of base (Table I)	Salt or base	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	M.p., °C.	Empirical formula	Carbon Calcd.	Carbon Found[a]	Hydrogen Calcd.	Hydrogen Found[a]	Nitrogen Calcd.	Nitrogen Found[a]	Halogen Calcd.	Halogen Found[a]
2	Base	70	173	0.2	1.5600	.....	$C_{21}H_{24}N_2$	82.85	82.68	7.95	7.76	9.24	9.39	.....	.....
2	HCl	..	..	...	....	189–191[b]	$C_{21}H_{25}ClN_2$	73.99	73.64	7.39	7.26	8.22	8.40	Cl, 10.40	Cl, 10.31
4	HCl[c]	76	..	...	....	209–211	$C_{22}H_{27}ClN_2$	74.45	74.70	7.67	7.98	7.89	8.09	Cl, 9.99	Cl, 9.69
6	Base[d]	79	170	0.12	1.5538	.....	$C_{22}H_{26}N_2$	82.97	82.82	8.23	8.00	8.79	8.99	.....	.....
6	HCl	..	..	...	....	177–179[b]	$C_{22}H_{27}ClN_2$	74.45	74.37	7.67	7.68	7.89	7.67	Cl, 9.99	Cl, 9.99
8	Base	35	150	0.05	1.5473	.....	$C_{23}H_{28}N_2$	83.08	81.99	8.49	8.85	8.43	8.91	.....	.....
8	HCl	72[e]	..	...	....	188-190	$C_{23}H_{29}ClN_2$	74.87	73.90	7.92	7.60	7.59	7.54	Cl, 9.61	Cl, 9.36
10	CH_3Br[f]	..	..	...	....	205.5–207.5	$C_{22}H_{27}BrN_2$	...	...	...	..	7.02	6.95	Br, 20.01	Br, 20.43
13	Base[g]	58	170	0.005	1.5568	.....	$C_{23}H_{28}N_2$	83.08	82.70	8.48	8.50	8.43	8.70	.....	.....
19	HCl[h]	68	..	...	....	157–158	$C_{21}H_{25}ClN_2$	73.99	74.01	7.39	7.69	8.22	8.07	Cl, 10.40	Cl, 9.76
22	Base	56	160	0.025	1.5619	... ..	$C_{22}H_{25}ClN_2$	74.87	74.75	7.14	6.95	7.94	7.99	Cl, 10.05	Cl, 10.23
26	Base[i]	45	112	0.02	1.5002	.....	$C_{17}H_{26}N_2$	79.01	78.73	10.14	9.70	10.84	11.22	.....	.....
26	HCl	..	..	...	....	167–169[j]	$C_{17}H_{27}ClN_2$	69.24	68.98	9.23	9.04	9.50	9.70	Cl, 12.02	Cl, 11.94

[a] Analyses are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. [b] Crystallized from isopropyl alcohol. [c] Prepared from 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, R. B. Moffett, J. L. White, B. D. Aspergren and F. E. Visscher, THIS JOURNAL, **77,** 1565 (1955). The addition of hydrochloric acid to the toluene solution of the free base caused the precipitation of the hydrochloride. It was collected, dried and recrystallized from a mixture of ethanol and methyl ethyl ketone. [d] This was prepared from 2-(2,5-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70,** 3100 (1948). [e] Yield based on the reaction of diphenylacetonitrile without isolation of the free base. A sample was recrystallized from ethyl acetate. [f] This methobromide was prepared from the known base[2] by Mr. John L. White in these laboratories. It was recrystallized from methanol plus methyl ethyl ketone. [g] This was prepared from 2-(2,6-dimethyl-1-piperidyl)-ethyl chloride hydrochloride, J. W. Cusic and R. A. Robinson, *J. Org. Chem.*, **16,** 1921 (1951). (See Table I, footnote *g*.) [h] The addition of hydrochloric acid to the toluene solution of the crude free base caused the precipitation of the hydrochloride. It was collected, dried and recrystallized from methyl ethyl ketone. [i] Prepared from α-phenyl-β-methylbutyronitrile (Table III, footnote *k*) by the general procedure described in the Experimental part except sodium amide was used in place of lithium amide. [j] Recrystallized from ethanol plus ethyl acetate.

TABLE III

AMIDES

No. of base (Table I)	Salt or base	Yield, %	M.p., °C.[a]	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	H_2SO_4	77	115–118	MeEtCO	$C_{20}H_{26}N_2O_5S$	59.09	59.09	6.45	6.34	6.89	7.12	S, 7.89	S, 7.60
1	CH_3Br	75	228–230	MeOH + *i*-PrOH	$C_{21}H_{27}BrN_2O$	62.52	62.95	6.75	6.77	6.95	7.52	Br, 19.81	Br, 19.90
3	Base	74	142–144	*i*-PrOH	$C_{21}H_{26}H_2O$	78.22	78.60	8.13	8.08	8.69	9.10	.....	.....
3	HCl	..	207–209	MeEtCO	$C_{21}H_{27}ClN_2O$	70.27	70.56	7.58	7.67	7.87	7.92	Cl, 9.88	Cl, 9.72
3	H_2SO_4	..	185–187	EtOH	$C_{21}H_{28}N_2O_5S_{1/2}$	59.97	60.43	6.71	6.73	6.66	6.84	S, 7.62	S, 7.87
3	CH_3Br	98	231–233	MeOH + *i*-PrOH	$C_{22}H_{29}BrN_2O$	63.30	63.36	7.00	7.08	6.71	6.90	Br, 19.15	Br, 19.27
5	Base[c]	72	164-165	*i*-PrOH	$C_{22}H_{28}N_2O$	78.53	78.35	8.39	8.06	8.33	8.21	.....	.....
5	$^1/_2H_2SO_4$	83	173–174	EtOH + MeEtCO	$C_{22}H_{29}N_2O_5S$	68.54	67.84	7.58	7.77	7.27	7.24	S, 4.16	S, 4.22
5	CH_3Br	87	231–233	EtOH	$C_{23}H_{31}BrN_2O$	64.03	64.12	7.24	7.18	6.50	6.57	Br, 18.52	Br, 18.45
5	→ O	33	146.5–148	*i*-PrOH + MeEtCO + Et_2O	$C_{22}H_{28}N_2O_2$	74.96	74.44	8.01	8.06	7.95	7.89	.....	.....
7	Base	66	129–131	*i*-PrOH + H_2O	$C_{22}H_{28}N_2O$	78.53	78.65	8.39	8.43	8.33	8.34	.....	.....

7	HCl	..	222–224	EtOH + EtOAc	$C_{22}H_{28}ClN_2O$	70.85	70.73	7.84	7.71	7.51	7.76	Cl, 9.51	Cl, 9.12
7	CH_3Br	95	231–235	EtOH + EtOAc + MeEtCO	$C_{23}H_{31}BrN_2O$	64.03	64.36	7.24	7.09	6.50	6.59	Br, 18.52	Br, 18.28
9	Base	82	124–126	*i*-PrOH + H_2O	$C_{23}H_{30}N_2O$	78.81	78.77	8.63	8.39	8.00	8.29	.....	.....
9	HCl	..	221–223	EtOH + MeEtCO	$C_{23}H_{31}ClN_2O$	71.38	70.87	8.08	7.99	7.24	7.17	Cl, 9.16	Cl, 9.36
9	CH_3Br	96	225–226	Benzene	$C_{24}H_{33}BrN_2O$	64.71	64.73	7.46	7.76	6.29	6.13	Br, 17.94	Br, 17.50
11	CH_3Br[d]	87	216–216.5	*i*-PrOH + EtOAc	$C_{22}H_{29}BrN_2O$	63.29	63.33	7.00	6.85	..	..	Br, 19.15	Br, 19.14
11	→ O	98	167.5–168.5	Me_2CO	$C_{21}H_{28}N_2O_2$	74.52	74.44	7.74	7.56	8.30	8.16	.....	.....
12	HCl[c]	55	208–210	EtOH + MeEtCO	$C_{22}H_{28}ClN_2O$	70.85	70.86	7.84	7.74	7.51	7.69	Cl, 9.51	Cl, 9.37
12	CH_3Br[c]	95	209–210	Benzene	$C_{23}H_{31}BrN_2O$	64.02	63.73	7.24	7.07	6.49	6.46	Br, 18.52	Br, 18,27
14	HCl[e]	..	225–227	MeEtCO	$C_{23}H_{31}ClN_2O$	71.38	71.23	8.08	8.26	7.24	7.16	Cl, 9.16	Cl, 8.87
14	CH_3Br	93[e]	224–225	*i*-PrOH	$C_{24}H_{33}BrN_2O$	64.71	64.62	7.47	7.36	6.29	6.60	Br, 17.94	Br, 17.52
15	H_2SO_4[c]	..	178–180	*i*-PrOH + Et_2O	$C_{22}H_{32}N_2O_5S$	60.52	60.56	7.39	7.43	6.42	6.70	S, 7.35	S, 7.45
16	→ O	75	152–154	*i*-PrOH + H_2O	$C_{19}H_{24}N_2O_2 \cdot H_2O$	69.06	68.39	7.93	7.76	8.48	8.56	.....	.....
16	→ O·HBr	83	156–158.5	MeEtCO + EtOAc	$C_{19}H_{25}BrN_2O_2$	58.02	57.74	6.41	6.52	7.12	6.89	Br, 19.45	Br, 21.05
17	CH_3Br[f]	78	194–186	MeOH + *i*-PrOH	$C_{20}H_{27}BrN_2O \cdot H_2O$[g]	58.68	59.32	7.14	7.07	6.84	6.83	Br, 19.52	Br, 19.47
18	HCl[h]	40	220–224	MeOH + *i*-PrOH	$C_{22}H_{29}ClN_2O$	70.85	71.62	7.84	7.70	7.51	7.59	Cl, 9.51	Cl, 9.65
18	CH_3Br	55	167–168	EtOH	$C_{23}H_{31}BrN_2O$	64.03	63.87	7.24	7.24	6.49	6.24	Br, 18.52	Br, 18.73
20	Base	75	125–127	*i*-PrOH	$C_{21}H_{26}N_2O$	78.22	78.55	8.13	8.12	8.69	8.37	.....	.....
20	HCl	100	217–219	EtOH + MeEtCO	$C_{21}H_{27}ClN_2O$	70.27	70.62	7.58	7.59	7.81	7.57	Cl, 9.88	Cl, 9.59
20	CH_3Br	100	215–218	MeEtCO	$C_{22}H_{29}BrN_2O$	63.30	63.66	7.00	7.04	6.71	6.70	Br, 19.15	Br, 18.77
21	HCl[i,e]	73	210–211	*i*-PrOH	$C_{21}H_{29}ClN_2O$	69.88	69.44	8.10	8.18	7.76	7.99	Cl, 9.82	Cl, 9.63
21	CH_3Br	87[e]	187–189	MeEtCO	$C_{22}H_{31}BrN_2O$	63.00	63.34	7.45	7.10	6.68	6.45	Br, 19.06	Br, 18.98
23	Base	54	156–157.5	EtOH	$C_{22}H_{27}ClN_2O$	71.23	70.99	7.34	7.31	7.55	7.65	Cl, 9.56	Cl, 9.56
23	HCl	83	218–220	MeOH + *i*-PrOH	$C_{22}H_{28}Cl_2N_2O$	64.86	65.06	6.93	6.89	6.88	6.82	Cl, 17.41	Cl, 17.03
23	CH_3Br	83	226–228	EtOH	$C_{23}H_{30}BrClN_2O$	59.29	59.31	6.49	6.70	6.01	5.78	Br, 17.16	Br, 17.31
24	Base[j]	68	140–142	EtOH	$C_{22}H_{27}ClN_2O$	71.23	71.36	7.34	8.22	7.55	7.54	Cl, 9.56	Cl, 9.64
24	HCl	79	216–218	EtOH + EtAOc	$C_{22}H_{28}Cl_2N_2O$	64.86	64.72	6.93	6.61	6.88	6.73	Cl, 17.41	Cl, 17.54
24	CH_3Br	60	226–228	MeEtCO	$C_{23}H_{30}BrClN_2O$	59.29	59.55	6.49	6.36	6.01	5.88	Br, 17.06	Br, 17.08
25	HCl[k]	..	225–228	*i*-PrOH	$C_{19}H_{21}Cl_2NO$	67.33	67.03	9.22	8.91	8.27	8.29	Cl, 10.46	Cl, 10.25
25	CH_3Br[e]	82	178–180	MeEtCO	$C_{21}H_{33}BrN_2O$	60.44	61.02	8.37	8.24	7.05	6.84	Br, 20.11	Br, 19.67
27	HCl	..	174–176	EtOH + MeEtCO	$C_{17}H_{29}ClN_2O$	65.25	65.26	9.33	9.19	8.95	8.77	Cl, 11.33	Cl, 11.45
27	CH_3Br	..	164–166	EtOH + EtOAc	$C_{18}H_{31}BrN_2O$	58.41	58.40	8.20	8.56	7.54	7.30	Br, 21.52	Br, 21.20

[a] Melting points are uncorrected. [b] See Table II, footnote *a*. [c] The free base and several quaternary salts of this amide have been reported by Janssen, *et al.*[3d] [d] Some samples of this compound which crystallized from the reaction mixture (tetrahydrofuran) had a melting point of 177.5–178.5°. These had the correct analysis (Found: Br, 19.23) and the same infrared spectrum in chloroform solution although different in a mull. The two forms must therefore be dimorphic. See Table I, footnote *e*. [e] The free base could not be obtained crystalline. The hydrochloride was prepared from the crude free base. The yield for the methobromide is based on the pure hydrochloride from which it was prepared. [f] The free base is reported by Cheney, *et al.*[3c] [g] Water determination by the Karl Fischer method indicated approximately one molecule of water of crystallization. [h] The intermediate nitrile was distilled, b.p. 174° (0.03 mm.), but was not obtained in analytical purity. The yield is the over-all yield from diphenylacetonitrile. [i] Prepared from the corresponding nitrile, D. J. Dupre, J. Elks, B. A. Heins, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949). [j] The intermediate α-(*p*-chlorophenyl)-α-phenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyronitrile was prepared from α-(*p*-chlorophenyl)-α-phenylacetonitrile [M. E. Speeter, L. C. Cheney and S. B. Binkley, THIS JOURNAL, **72**, 1659 (1950)] in 55% yield, b.p. 170° (0.1 mm.), but not obtained in analytical purity. [k] The intermediate α-phenyl-α-isopropyl-γ-(2,2-dimethyl-1-pyrrolidyl)-butyronitrile was prepared from α-phenyl-β-methylbutryonitrile (D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 252) in 44% yield by the general procedure described in the Experimental Part, except sodium amide was used in place of lithium amide. The yield was 44%, b.p. 120° (0.015 mm.). It was not obtained in analytical purity but was hydrolyzed to the amide and converted to the hydrochloride.

Except as noted in the experimental part or in the tables, the amides were prepared by alkylating the appropriate disubstituted nitrile with the requisite amino alkyl halide and hydrolyzing with 90% sulfuric acid. An example is given in the Experimental part.

Acknowledgments.—The authors are indebted to Dr. F. E. Visscher, Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap 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

Unless otherwise indicated all the nitriles, amides and their salts were prepared essentially as described in the following examples.

α,α-Diphenyl-γ-(2-methyl-1-pyrrolidyl)-butyronitrile.—To a suspension of 13.8 g. (0.6 mole) of lithium amide in 900 ml. of dry toluene, was added slowly with stirring 96.62 g. (0.5 mole) of diphenylacetonitrile. The mixture was heated and stirred under reflux for four hours. A solution of 2-(2-methyl-1-pyrrolidyl)-ethyl chloride was prepared by adding an excess of 40% aqueous sodium hydroxide to 92.1 g. (0.5 mole) of the corresponding hydrochloride[9] and extracting with 500 ml. of toluene in several portions. The toluene solution was dried over potassium carbonate and slowly added to the hot suspension of the lithium derivative of diphenylacetonitrile. After heating under reflux with stirring for 18 hours the mixture was cooled and 300 ml. of water was cautiously added. The toluene layer was extracted with dilute hydrochloric acid, and this aqueous acid solution was washed with ether and made basic with 20% sodium hydroxide solution. The free base was extracted with several portions of benzene which were washed with water and dried over sodium sulfate. After removal of the solvent the product was distilled under reduced pressure giving 107 g. (70.3%) of nearly colorless oil; b.p. 173–175° (0.2 mm.).

Hydrochloride.—A sample of the above nitrile in ethyl acetate was acidified with ethanolic hydrogen chloride. The product was recrystallized from isopropyl alcohol giving white crystals, m.p. 189–192°.

α,α-Diphenyl-γ-(2-methyl-1-pyrrolidyl)-butyramide.—A mixture of 126 ml. of concentrated sulfuric acid, 12.6 ml. of water and 67 g. (0.22 mole) of the above nitrile free base[10] was heated with stirring on a steam-bath for four hours. The mixture was cooled, poured onto ice and made strongly basic with ammonium hydroxide. The product separated as a gum which crystallized on standing. It was collected, dried and recrystallized from 400 ml. of isopropyl alcohol giving 52.2 g. (74%) of white crystals, m.p. 142–144°.

Hydrochloride.—A sample of the above amide in ethyl acetate was acidified with ethanolic hydrogen chloride. The resulting gum was recrystallized from methyl ethyl ketone; m.p. 207–209°.

Acid Sulfate.—A sample of the above amide free base in methanol was treated with one molar equivalent of concentrated sulfuric acid. The acid sulfate was precipitated by the addition of absolute ether and was recrystallized from ethanol; m.p. 185–187°.

Methobromide.—A large excess of cold methyl bromide was added to a cold solution of 20 g. (0.062 mole) of the above amide free base in 100 ml. of benzene.[11] The flask (round) was tightly stoppered, and allowed to stand at room temperature for three days. The product was collected giving 25.5 g. (98.5%) of crystals, m.p. 230–233°. This was recrystallized from a mixture of methyl and isopropyl alcohols giving 22.8 g. of white crystals, m.p. 231–233°.

α,α-Diphenyl-γ-(1-piperidyl)-butyramide N-Oxide.—To a suspension of 19.7 g. (0.061 mole) of α,α-diphenyl-γ-(1-piperidyl)-butyramide[2] in about 1 l. of methanol was added 35 ml. of 30% hydrogen peroxide. The mixture was shaken for three days during which time the solid dissolved. The excess hydrogen peroxide was decomposed by adding an aqueous slurry of platinum-on-charcoal and shaking for five hours. The solution was filtered and distilled below 50° under reduced pressure. The residue was dissolved in boiling ethyl acetate and on cooling an oil separated which soon crystallized. The crystalline solid was collected and air dried; weight 22 g., m.p. 70–75°. This appears to be a hydrate containing about 1.5 molecules of water.

Anal. Calcd. for $C_{21}H_{26}N_2O_2 \cdot 1\frac{1}{2}H_2O$: C, 69.0; H, 8.00; N, 7.67; H_2O, 7.40. Found: C, 68.94, 69.95; H, 8.18, 7.82; N, 7.61; H_2O, 8.88 by Karl Fischer method.[12]

A sample of this hydrate was mixed with 75 ml. of boiling acetone. Most of it dissolved and then immediately began to precipitate as a white crystalline solid. After boiling a few minutes and cooling the anhydrous material was obtained, m.p. 167.5–168.5°.

α,α-Diphenyl-γ-(dimethylamino)-valeramide N-Oxide Hydrate.—This was prepared by a procedure similar to the above from 14.8 g. (0.05 mole) of the corresponding free base[3c] and 10 ml. of 30% hydrogen peroxide in 190 ml. of methanol. The product was crystallized from 80% aqueous isopropyl alcohol and appears to contain approximately one molecule of water as a hydrate.

Hydrobromide.—To a solution of 11.2 g. (0.04 mole) of the above free base in 50 ml. of methanol was added 4 ml. (0.041 mole) of 48% hydrobromic acid. The solution was distilled nearly to dryness below 40° under reduced pressure. The resulting sirup was dissolved in 25 ml. of methyl ethyl ketone and diluted to turbidity at the b.p. with ethyl acetate. After cooling in the refrigerator the crystals were collected and dried for a short time in a vacuum desiccator. Too much drying causes the material to turn red; yield 10.94 g. (82.5%). It appears to contain a small amount (about 1/4 molecule) of water of crystallization.

2-(2,2,4-Trimethyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a solution of 42 g. (0.267 mole) of 2-(2,2,4-trimethyl-1-pyrrolidyl)-ethanol[13] in 200 ml. of benzene, with stirring and cooling by an ice-bath, until it tested strongly acid. While still cooled by the ice-bath, 24.5 g. (0.4 mole) of thionyl chloride was added dropwise with stirring. The solution was then gently heated under reflux for two hours during which sulfur dioxide and hydrogen chloride were evolved. About 50 ml. of solvent was removed by distillation and the mixture was cooled. The crystalline product was collected and washed with absolute ether; yield 55.3 g. (98%), m.p. 162–165°. Recrystallization from isopropyl alcohol raised the melting point to 164–166°.

Anal. Calcd. for $C_9H_{19}Cl_2N$: C, 50.95; H, 9.03; Cl, 33.42; N, 6.60. Found: C, 51.29; H, 9.19; Cl, 33.22; N, 6.96.

2-Methyl-2-(1-pyrrolidyl)-propyl Chloride Hydrochloride. This was prepared by a procedure similar to the above from 104 g. (0.728 mole) of 2-methyl-2-(1-pyrrolidyl)-propanol,[14] 65 ml. of thionyl chloride and 500 ml. of benzene. The product was recrystallized from a mixture of ethanol and ethyl acetate; yield 138 g. (96%), m.p. 145–147°.

Anal. Calcd. for $C_8H_{17}Cl_2N$: C, 48.49; H, 8.65; N, 7.07; Cl, 35.79. Found: C, 48.79; H, 8.74; N, 6.78; Cl, 35.58.

3-(1-Pyrrolidyl)-propyl Chloride Hydrochloride.—This was prepared by a similar procedure from 200 g. (1.55 moles) of 3-(1-pyrrolidyl)-propanol,[15] 135 ml. of thionyl chloride and 1 l. of benzene. The product was recrystallized from a mixture of isopropyl alcohol and ethyl acetate; yield 250 g. (88%), m.p. 140–142°.

Anal. Calcd. for $C_7H_{15}Cl_2N$: C, 45.66; H, 8.21; Cl, 38.52; N, 7.61. Found: C, 46.13; H, 8.40; Cl, 38.87; N, 7.78.

(9) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, THIS JOURNAL, **71**, 3988 (1949).

(10) Hydrochlorides or other salts may be used equally well for this hydrolysis.

(11) In general methyl ethyl ketone was found to be a superior solvent for the preparation of quaternary salts.

(12) The Karl Fischer water determination tends to give high results with amine oxide hydrates probably due to reaction of the N-oxide with the reagent.

(13) R. B. Moffett and J. L. White, *J. Org. Chem.*, **17**, 407 (1952).

(14) R. B. Moffett, *ibid.*, **14**, 862 (1949).

(15) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, THIS JOURNAL, **70**, 3862 (1948).

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]

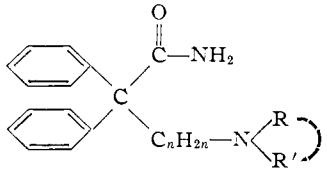
Antispasmodics. XI. α,α-Diphenyl-γ-amino-N-monosubstituted Amides[1]

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

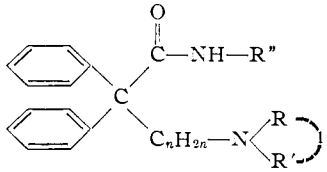
RECEIVED MARCH 25, 1957

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

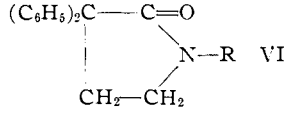


II

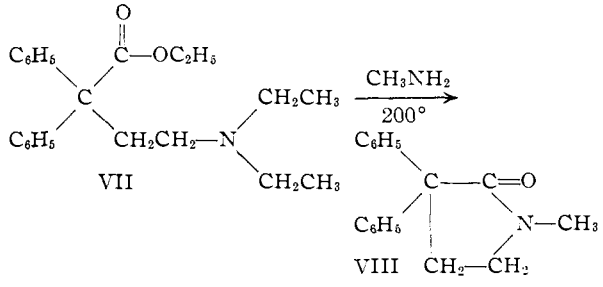
to anticholinergic activity it seemed desirable to prepare some amides substituted on the amide nitrogen. A search of the literature revealed that while many unsubstituted amides and a few disubstituted amides[3–5] of this type are known, none of the N-monosubstituted amides (II) have been reported.

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.



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.



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).