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

Hypotensive Agents. Pyridinecarboxamides and Piperidinecarboxamides[1]

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A series of pyridinecarboxamides and piperidinecarboxamides has been prepared. Certain of the latter have been reduced with lithium aluminum hydride to alkylaminomethylpiperidines, which were converted to bis-methiodides. 3-Pyrrolidinomethylpyridine, a structural isomer of nicotine, has been synthesized. Some of the piperidinecarboxamides showed moderate lowering of blood pressure in the anesthetized dog.

The high physiological activity of many substituted piperidines, combined with the availability of a convenient and facile method of preparation of pyridinecarboxamides, prompted the preparation for pharmacologic evaluation of a number of piperidinecarboxylic acid derivatives.

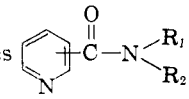
The use of alkyl carbonic–carboxylic acid mixed anhydrides for the preparation of amides[4] has become of increasing importance, especially in the synthesis of peptides.[5] This reaction was readily adapted to the synthesis of amides of pyridinecarboxylic acids. The reaction of the anhydrides of pyridinecarboxylic acids and ethyl chloroformate with amines proceeded smoothly in methylene chloride at 0–5°. A probable side-reaction was the interaction of the mixed acid anhydrides with the ethyl alcohol liberated in the final step, resulting in the formation of the corresponding ethyl esters. Although the yields of the amides were seldom much greater than 50% of theory, the ease of performance of the reaction made it an attractive method.

Quaternization of the pyridinecarboxamides with alkyl or aralkyl halides, followed by hydrogenation over platinum oxide catalyst, yielded the 1-substituted piperidinecarboxamides of Table III. Many of the quaternary ammonium salts did not crystallize, but satisfactory yields of the piperidinecarboxamides were obtained by hydrogenation of aqueous solutions of these crude products after removal of the unreacted halides. Some of the 1-methylpiperidinecarboxamides were reduced by lithium aluminum hydride to the corresponding 1-methylalkylaminomethylpiperidines which were converted to the bis-methiodides.

After the completion of our work Swain and Naegele[6] reported a series of 1-substituted-N,N-diethylisonipecotamides and 1-(3-indolylmethyl)-piperidinecarboxamides. Many of these compounds showed hypotensive activity in the dog.

Biel and co-workers[7] have published a paper describing a series of aminoalkyl esters of piperidinecarboxylic acids and their "reversed" ester derivatives. Some of these compounds displayed appreciable hypotensive activity when tested in

TABLE I

PYRIDINECARBOXAMIDES 

NR_1R_2	Position	B.p., °C.	B.p., Mm.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Diethylamino[a]	4	109	0.5	62	$C_{10}H_{14}N_2O$[g]				
Pyrrolidino	3	131–133	0.3	64	$C_{10}H_{12}N_2O$	68.1	67.6	6.9	7.0
Morpholino	2	142–143	1	59	$C_{10}H_{12}N_2O_2$	62.5	62.9	6.3	6.2
Morpholino	3	190–195	0.4	48	$C_{10}H_{12}N_2O_2$[g]				
Morpholino[b]	4	142–145	.4	55	$C_{10}H_{12}N_2O_2$[g]				
2,6-Dimethylmorpholino	3	138–140	.5	57	$C_{12}H_{16}N_2O_2$	65.4	64.8	7.3	7.3
2,6-Dimethylmorpholino	4	135–137	.3	50	$C_{12}H_{16}N_2O_2$	65.4	64.9	7.3	6.9
2,6-Dimethylpiperidino	4	73–74[d,h]		20	$C_{13}H_{18}N_2O$	71.5	71.6	8.3	8.1
4-Methylpiperazino	4	133–135	.4	39	$C_{11}H_{15}N_3O$	64.4	64.7	7.4	7.2
4-Ethoxyanilino[c]	3	170–175[d]		50	$C_{14}H_{14}N_2O_2$[g]				
4-Dimethylaminoanilino	2	227–230 d.[d,e]		60	$C_{14}H_{15}N_3O\cdot 2HCl$	53.5	53.8	5.4	5.6
4-Dimethylaminoanilino	3	185–187[d,i]		25	$C_{14}H_{15}N_3O$	69.7	69.6	6.2	6.3
4-Dimethylaminoanilino	4	175 dec.[d,f]		38	$C_{14}H_{15}N_3O\cdot 2HCl$	53.5	53.4	5.4	5.7

[a] Reference 6, no physical constants given. [b] G. A. Langlois and A. M. Deloison, U. S. Patent 2,188,244 (Jan. 23, 1940), reported m.p. 70°. [c] F. Lafranchi, *Atti acad. italia, rend.*, [7] **4**, 190 (1942); L. J. Szabo, U. S. Patent 2,274,620 (Feb. 24, 1942). The former reported m.p. 169–170°. [d] Melting point. [e] The free amine had m.p. 131–132° after crystallization from methanol. [f] The free amine had m.p. 227–229°, as also reported by H. C. Byerman, *et al.*, *Rec. trav. chim.*, **73**, 109 (1954). Recrystallized from methanol. [g] Used as an intermediate without being analyzed. These compounds are characterized by their derivatives in Tables II and III. [h] Recrystallized from cyclohexane. Recrystallized from methanol.

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(2) E. I. du Pont de Nemours and Co., Camden, S. C.

(3) To whom inquiries concerning this publication should be addressed.

(4) D. A. Johnson, THIS JOURNAL, **75**, 3636 (1953); R. L. Barnden, *et al.*, *J. Chem. Soc.*, 3733 (1953).

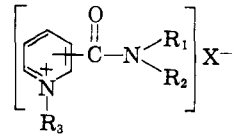
(5) R. A. Boisonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951); J. R. Vaughan, Jr., THIS JOURNAL, **73**, 3547 (1951); **73**, 5553 (1951); **74**, 675 (1952); V. du Vigneaud, *et al.*, *ibid.*, **75**, 4879 (1953); **76**, 3107, 3110, 3113, 3115 (1954).

(6) A. P. Swain and S. K. Naegele, *ibid.*, **79**, 5250 (1957).

(7) J. H. Biel, E. P. Sprengeler and H. L. Friedman, *ibid.*, **79**, 6184 (1957).

TABLE II

QUATERNARY AMMONIUM SALTS OF PYRIDINECARBOXAMIDES

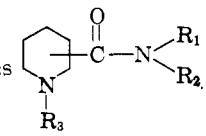


NR_1R_2	Position	R_3	X	M.p., °C.	Yield,[c] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Recrystn.[b] solvent
Pyrrolidino	3	CH_3	I	213.5–214.5	87	$C_{11}H_{15}IN_2O$	41.5	41.7	4 8	5.0	A
Morpholino	2	CH_3	I	175–176 d.	81	$C_{11}H_{15}IN_2O_2$	39.5	39.7	4.5	4.9	M
Morpholino	3	$C_6H_5CH_2CH_2$	Br	212–213	95	$C_{18}H_{21}BrN_2O_2$	57 3	57.6	5.6	5.8	M–E
Morpholino	4	$C_6H_5CH_2CH_2$	Br	214–215	97	$C_{18}H_{21}BrN_2O_2$	57.3	57.5	5.6	5.8	M–Ac
2,6-Dimethylmorpholino	4	$C_6H_5CH_2CH_2$	Br	227–228	94	$C_{20}H_{25}BrN_2O_2$	59.1	59.2	6.2	6.2	M–E
4-Ethoxyanilino	3	CH_3	I	194–196	92	$C_{15}H_{17}IN_2O_2$	46.9	47.0	4.5	4.6	M
4-Ethoxyanilino	3	$C_6H_5CH_2CH_2$	Br	243–244	88	$C_{22}H_{23}BrN_2O_2$	61.8	61.6	5.4	5.4	M
4-Dimethylaminoanilino	2	CH_3	I	229–230 d.	98	$C_{15}H_{18}IN_3O$	47.0	47.0	4.7	4.7	
4-Dimethylaminoanilino	3	CH_3[a]	I	230–235 d.	95	$C_{16}H_{21}I_2N_3O$	36.6	36.7	4.0	4.1	M
4-Dimethylaminoanilino	4	CH_3[a]	I	>200 d.	90	$C_{16}H_{21}I_2N_3O$	36.6	36.6	4.0	4 2	M

[a] Bis-methiodide. [b] A, acetonitrile; M, methanol; Ac, acetone; E, ether. [c] Yields are of unrecrystallized products.

TABLE III

1-SUBSTITUTED PIPERIDINECARBOXAMIDES



NR_1R_2	Position	R_3	B.p. °C.	B.p. Mm.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Diethylamino	3	$C_6H_5CH_2CH_2$[a]	173	0 3[o]	86	$C_{18}H_{28}N_2O$	75.0	74.9	9.8	10.0
Diethylamino	3	$C_6H_5CH{=}CHCH_2$	184–187	0.4	90	$C_{19}H_{28}N_2O$	76 0	75.9	9.4	9.6
Diethylamino	3	$(C_6H_5)_2CH$[a]	[d]		20	$C_{23}H_{30}N_2O{\cdot}HBr$	64.0	64.1	7.3	7.2
Diethylamino	3	$4\text{-}NO_2C_6H_4$	[e]		99	$C_{16}H_{23}N_3O_3$	63.0	63.0	7.6	7.6
Diethylamino	3	$4\text{-}NH_2C_6H_4$	[f]		50	$C_{16}H_{25}N_3O{\cdot}2HCl$	55.1	55.9	7.5	7.9
Diethylamino	3	$C_6H_5CH(OH)CH_2$	228–230	3.5	70	$C_{18}H_{28}N_2O_2$	71.0	70.9	9.3	9.0
Diethylamino[b]	4	$C_6H_5CH_2$[a]	173–175	0.7	87	$C_{17}H_{26}N_2O$	74.4	74.6	9.6	9.6
Pyrrolidino	3	CH_3	111–114	.3	89	$C_{11}H_{20}N_2O$	67.3	66.8	10.3	10.4
Pyrrolidino	3	$C_6H_5CH_2CH_2$[a]	181–183	.1[p]	62	$C_{18}H_{26}N_2O$	75.5	75.7	9.1	9.1
Morpholino[c]	2	H	143–145	1.5	65	$C_{10}H_{18}N_2O_2$	60.6	60.8	9.2	9.2
Morpholino[c]	2	CH_3	121–123	0.8[q]	87	$C_{11}H_{20}N_2O_2$	62.2	62.0	9.5	9.8
Morpholino[c]	2	$C_6H_5CH_2CH_2$[a]	192–195	.4[r]	16	$C_{18}H_{26}N_2O_2$	71.5	71.5	8.7	8.6
Morpholino	3	CH_3[a]	118	.2[s]	72	$C_{11}H_{20}N_2O_2$	62.2	62.0	9.5	9.6
Morpholino	3	$C_6H_5CH_2$[a]	183–186	.3	80	$C_{17}H_{24}N_2O_2$	70.8	71.0	8.4	8.4
Morpholino	3	$C_6H_5CH_2CH_2$	188–192	.2[t]	85	$C_{18}H_{26}N_2O_2$	71.5	71.5	8.7	9.0
Morpholino	3	$C_6H_5CH_2CH_2CH_2$[a]	203–206	.3	71	$C_{19}H_{28}N_2O_2$	72.1	72.3	8.9	8.9
Morpholino	4	$C_6H_5CH_2CH_2$	[g]		85	$C_{18}H_{26}N_2O_2{\cdot}HBr$	56.4	56.4	7.1	7.2
2,6-Dimethylmorpholino	3	$C_6H_5CH_2CH_2$[a]	188–190	.2[u]	50	$C_{20}H_{32}N_2C_2$	72.2	72.5	9.7	9.4
	4	$C_6H_5CH_2CH_2$	[h]		78	$C_{20}H_{32}N_2O_2{\cdot}HBr$	58.1	58.1	8.1	7.9
4-Ethoxyanilino	3	CH_3	[i]		77	$C_{15}H_{22}N_2O_2$	68.7	69.0	8.5	8.5
4-Ethoxyanilino	3	$C_6H_5CH_2CH_2$	[j]		82	$C_{22}H_{28}N_2O_2{\cdot}HBr$	61.0	60.8	6.8	7.0
4-Dimethylamino-anilino	2	H	[k,l]		93	$C_{14}H_{21}N_3O{\cdot}2HCl$	52.5	52.8	7.2	7.4
	4	H	[m,n]		90	$C_{14}H_{21}N_3O{\cdot}2HCl$	52.5	52.6	7.2	7.3

[a] The intermediate quaternary ammonium salt did not crystallize and was used in the crude form as described in B of the Experimental section. [b] Reference 6 reported m.p. 221–222° for the hydrochloride. [c] Prepared by hydrogenation of the corresponding pyridinecarboxamide in glacial acetic acid over platinum oxide. [d] Isolated as the hydrobromide salt, m.p. 234.5–235° when recrystallized from methanol. [e] Recrystallized from ethanol, m.p. 99.5–101.5°. [f] Dihydrochloride, m.p. 227.5–228.5° after recrystallization from methanol–ethyl acetate. [g] Hydrobromide, m.p. 279–280°; recrystallized from methanol. [h] Hydrobromide, m.p. 252–254° from water. [i] Recrystallized from methanol–water; m.p. 122–123°. [j] Hydrobromide, m.p. 108–110° dec. after recrystallization from acetone. [k] Dihydrochloride, m.p. 248–250° dec. from methanol. [l] The free amine had m.p. 127–130° after recrystallization from methanol–water. [m] Dihydrochloride, recrystallized from methanol; m.p. 252–254° dec. [n] Free amine was recrystallized from methanol, m.p. 187–188°. [o] $n^{27}D$ 1.5221. [p] $n^{25}D$ 1.5431. [q] $n^{32}D$ 1.5013. [r] $n^{24}D$ 1.5426. [s] $n^{25.5}D$ 1.5065. [t] $n^{34}D$ 1.5406. [u] $n^{24.5}D$ 1.5327.

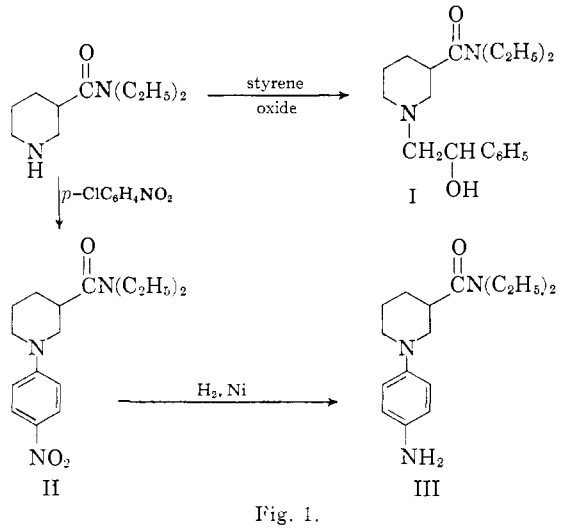
the dog in the form of their bis-quaternary ammonium salts.

An amide where the carboxamido group is separated from the piperidine nucleus by an ethylene chain was prepared from 3-pyridinecarboxaldehyde by the following sequence of reactions. Reaction of this aldehyde with malonic acid gave β-(3-pyridyl)-acrylic acid,[8] which was converted to the morpholide by a mixed anhydride reaction with ethyl chloroformate and morpholine. Catalytic hydrogenation of this morpholide over palladium-on-

(8) L. Pannizon, *Helv. Chim. Acta*, **24**, 24E (1941).

carbon gave the morpholide[9] of β-(3-pyridyl)-propionic acid, which was quaternized with phenethyl bromide and subsequently reduced over platinum oxide to yield 4-[3-(1-phenethyl-3-piperidyl)-propionyl]-morpholine.

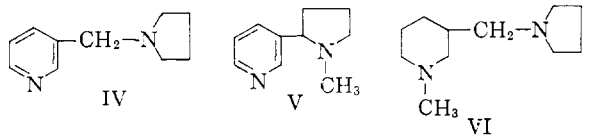
Two alternative preparations of 1-substituted piperidinecarboxamides were accomplished by the reaction of N,N-diethylnipecotamide with styrene oxide and 4-chloronitrobenzene (Fig. 1). Since the reaction of styrene oxide with secondary amines[10] has been shown to give chiefly secondary alcohols the compound I was assigned such a structure without formal proof. It is possible that this product may be a mixture of I and the primary alcohol resulting from attack at the α-carbon of styrene oxide.[11,12]



II III

Fig. 1.

It is of interest that 3-pyrrolidinomethylpyridine (IV), prepared by the reduction of 1-nicotinoylpyrrolidine with lithium aluminum hydride, is an isomer of nicotine (V) and possesses comparable physiological properties.



IV V VI

The corresponding 1-methyl-3-pyrrolidinomethylpiperidine (VI) is an analog of 1-methyl-3-(4-dimethylaminobutyl)-piperidine, which was reported by Norton and Phillips[13,14] to possess potent hypotensive activity. However, VI has little or no hypotensive activity.

Pharmacology.—All of the compounds reported in this communication were tested for hypotensive activity in the anesthetized dog. When so tested none of the pyridinecarboxamides of Table I gave more than slight lowering of blood pressure. The quaternary ammonium salts of Table II likewise showed very little hypotensive activity and in general were more toxic than the pyridinecarboxamides from which they were derived. The piperidinecarboxamides of Table III usually gave significant lowering of blood pressure only at levels approaching the toxic doses. The most active of these compounds was 4-(1-phenethylnipecotoyl)-morpholine. This compound, as well as many others of its type, caused central nervous system disturbances in unanesthetized test animals at approximately the same dose required to lower blood pressure. Many of these compounds exhibited slight adrenergic blockade.[15]

None of the three 1-methylalkylaminomethylpiperidines showed significant hypotensive activity. 1, 1 - Dimethyl - 3 - morpholinomethylpiperidinium iodide methiodide had appreciable activity but was quite toxic. Neither of the other two quaternary ammonium salts of this type showed significant hypotensive activity. 3-Pyrrolidinomethylpyridine had a pronounced nicotine-like activity.

4-[3-(3-Pyridyl)-acrylyl]-morpholine had slight hypotensive activity and was relatively non-toxic. Its reduction product was less active but more toxic, while 4-[3-(1-phenethyl-3-piperidyl)-propionyl]-morpholine had even less activity and greater toxicity.

A more comprehensive report of the pharmacology of these compounds will be given elsewhere.

Acknowledgments.—We are indebted to Dr. Justin B. Hoekstra for the pharmacological data reported herein. The microanalyses were performed by Mr. Richard M. Downing.

Experimental[16]

A. **Pyridinecarboxamides.**—The following example illustrates the general method used. To a stirred and cooled mixture of 100 g. (0.80 mole) of nicotinic acid in 2 liters of methylene chloride there was gradually added 81 g. (0.80 mole) of triethylamine. The resulting clear solution was maintained at 0–5° during the addition of 95 g. (0.88 mole) of ethyl chloroformate (U. S. Industrial Chemicals Co.). This addition required 15–20 minutes. After the mixture had been maintained at 0° for 30 minutes there was added 57 g. (0.80 mole) of pyrrolidine while maintaining the temperature at 0–5°. The mixture was allowed to warm to room temperature and after two hours was washed twice with 150-ml. portions of water and distilled. There was obtained 90 g. (64%) of 1-nicotinoylpyrrolidine distilling at 131–133° (0.3 mm.); see Table I for analysis.

In some cases the residues crystallized after removal of the methylene chloride and were recrystallized from suitable solvents.

B. **Piperidinecarboxamides.**—The quaternary ammonium salts of the pyridinecarboxamides were prepared in methanol or acetonitrile, usually by refluxing for 24 hours in one of these solvents with 10–20% excesses of the halides. Whenever possible the quaternaries were isolated and recrystallized from the solvents indicated in Table II. The piperidinecarboxamides were prepared by hydrogenation of the quaternaries in water or ethyl alcohol over platinum oxide (0.3 g. per 0.1 mole) at 50–60 p.s.i. Hydrogenation times varied from 15 to 30 hours. The catalyst was removed and the aqueous solutions were made strongly basic with 50% sodium hydroxide and extracted with ether. After drying over anhydrous potassium carbonate the ether solutions were distilled. When the hydrogenations were performed in ethyl alcohol the solutions were freed of catalyst, the solvents removed *in vacuo*, the residues dissolved in water and then treated as above.

(9) The morpholide of β-(2-pyridyl)-propionic acid was prepared by F. H. McMillan and J. A. King, THIS JOURNAL, **73**, 3165 (1951).

(10) W. S. Emerson, *ibid.*, **67**, 516 (1945).

(11) C. L. Browne and R. E. Lutz, *J. Org. Chem.*, **17**, 1877 (1952).

(12) A. J. Castro, *et al.*, *ibid.*, **19**, 1444 (1957).

(13) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953).

(14) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).

(15) A. Calò and V. Evdokimoff [*Gazz. chim. ital.*, **80**, 456 (1950)] reported a series of nicotinamides which had slight hypotensive activity and adrenergic blocking effect.

(16) All melting points and boiling points are uncorrected.

In the instances where the quaternaries did not crystallize from solution the solvents were removed *in vacuo*. The residual oils were dissolved in water, extracted with ether, and after being heated on the steam-bath until all ether was expelled the aqueous solutions were hydrogenated under the conditions stated above.

1-Cinnamyl-N,N-diethylnipecotamide.—A mixture of 19 g. (0.10 mole) of N,N-diethylnipecotamide, 20 g. (0.10 mole) of cinnamyl bromide and 20 g. (0.15 mole) of anhydrous potassium carbonate in 200 ml. of toluene was stirred and refluxed for 3 hours. The mixture was cooled, washed with water and dried over anhydrous potassium carbonate. Distillation yielded 27 g. (90%) of product, b.p. 184–187° at 0.4 mm.

C. **Alkylaminomethyl-1-methylpiperidines.**—Reduction of the 1-methylpiperidinecarboxamides (from procedure A) with lithium aluminum hydride by the procedure of Sommers[17,18] and co-workers gave the desired 1-methylalkylaminomethylpiperidines[19] as recorded below.

1-Methyl-3-pyrrolidinomethylpiperidine, b.p. 59° at 0.3 mm., yield 93%. *Anal.* Calcd. for $C_{11}H_{22}N_2$: C, 72.5; H, 12.2. Found: C, 72.2; H, 12.1.

1-Methyl-2-morpholinomethylpiperidine, b.p. 79–82° at 0.4 mm., yield 63%. *Anal.* Calcd. for $C_{11}H_{22}N_2O$: C, 66.6; H, 11.2. Found: C, 66.4; H, 11.2. $n^{32.5}D$ 1.4793.

1-Methyl-3-morpholinomethylpiperidine, b.p. 87–88° at 0.8 mm., $n^{25.5}D$ 1.4819. *Anal.* Calcd. for $C_{11}H_{22}N_2O$: C, 66.6; H, 11.2. Found: C, 66.4; H, 11.1.

3-Pyrrolidinomethylpyridine.—The reduction of 1-nicotinoylpyrrolidine in ether with lithium aluminum hydride[17,18] gave 3-pyrrolidinomethylpyridine in 44% yield, b.p. 75–77° at 0.2 mm., $n^{25.5}D$ 1.5202. *Anal.* Calcd. for $C_{10}H_{14}N_2$: C, 74.0; H, 8.7. Found: C, 73.3; H, 9.3.

D. **Bis-methiodides of Alkylaminomethyl-1-methylpiperidines.**—Treatment of acetonitrile or methanol solutions of the alkylaminomethyl-1-methylpiperidines with methyl iodide in excess yielded the bis-methiodides as specifically recorded below.

1,1-Dimethyl-3-pyrrolidinomethylpiperidinium iodide methiodide was prepared in acetonitrile at 25°, yield 94%. Recrystallization from methanol gave a product of m.p. 264–266° dec.

Anal. Calcd. for $C_{13}H_{28}I_2N_2$: C, 33.6; H, 6.1. Found: C, 33.5; H, 6.2.

1,1-Dimethyl-2-morpholinomethylpiperidinium Iodide Methiodide.—A solution of the diamine and methyl iodide in acetonitrile was refluxed for 6 hr. to yield this product. After two recrystallizations from water–methanol there was obtained 55% of product of m.p. 255–256° dec.

Anal. Calcd. for $C_{13}H_{28}I_2N_2O$: C, 32.4; H, 5.9. Found: C, 32.8; H, 6.1.

1,1-Dimethyl-3-morpholinomethylpiperidinium iodide methiodide was isolated from methanol after six hours at reflux and recrystallized from water–methanol; m.p. 281–282° dec.

Anal. Calcd. for $C_{13}H_{28}I_2N_2O$: C, 32.4; H, 5.9. Found: C, 32.5; H, 5.9.

(17) A. H. Sommers, *et al.*, THIS JOURNAL, **75**, 57 (1953).

(18) A. W. Weston, A. H. Sommers and K. M. Beck, U. S. Patent 2,684,965 (July 27, 1954).

(19) See also W. M. Mićović and M. Lj. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

N,N-Diethyl-1-(2-hydroxy-2-phenylethyl)-nipecotamide.—A mixture of 27.6 g. (0.15 mole) of N,N-diethylnipecotamide and 18.2 g. (0.15 mole) of styrene oxide was heated on the steam-bath for 18 hours. The mixture was dissolved in ether and extracted with 6 *N* HCl. Neutralization of the extracts with sodium hydroxide, ether extraction, drying of the extracts over anhydrous potassium carbonate and distillation yielded 32.2 g. (70.5%) of viscous yellow oil, b.p. 228–230° at 3.5 mm.; see Table III for analysis. Attempts to prepare a methiodide of this compound were unsuccessful.

N,N-Diethyl-1-(4-nitrophenyl)-nipecotamide.—A mixture of 27.6 g. (0.15 mole) of N,N-diethylnipecotamide, 23.6 g. (0.15 mole) of 1-chloro-4-nitrobenzene and 20.2 g. (0.20 mole) of triethylamine was heated for 20 hours on the steam-bath.[20] When cooled, the mixture crystallized and was triturated with water and filtered. The bright yellow product weighed 45.1 g. (99%) and had m.p. 99–100°. Recrystallization of an analysis sample from absolute ethyl alcohol gave m.p. 99.5–101.5°; see Table III for analysis.

N,N-Diethyl-1-(4-aminophenyl)-nipecotamide.—A suspension of 15.3 g. (0.30 mole) of N,N-diethyl-1-(4-nitrophenyl)-nipecotamide in 200 ml. of ethyl alcohol was hydrogenated over Raney nickel catalyst at room temperature and 50 p.s.i. The reaction was complete in 15 minutes as evidenced by uptake of the theoretical amount of hydrogen. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. An ethereal solution of the residual purple oil was saturated with dry hydrogen chloride. The resultant dihydrochloride had m.p. 227.5–228.5° after two recrystallizations from ethyl alcohol–ethyl acetate; see Table III for analysis.

4-[3-(1-Phenethyl-3-piperidyl)-propionyl]-morpholine.—β-(3-Pyridyl)-acrylic acid was prepared in 79% yield from 3-pyridinecarboxaldehyde and malonic acid by the method of Pannizon.[8] By a mixed anhydride reaction between this acid, ethyl chloroformate and morpholine in methylene chloride there was obtained 4-[3-(3-pyridyl)-acrylyl]-morpholine in a yield of 79%. This was recrystallized from acetonitrile: m.p. 141–143°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5. Found: C, 66.2; H, 6.6.

This amide was hydrogenated at 60 p.s.i. in methanol over 5% palladium-on-carbon, giving an 87% yield of 4-[3-(3-pyridyl)-propionyl]-morpholine, b.p. 188–190° at 1 mm., $n^{24.5}D$ 1.5457.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3. Found: C, 65.2; H, 7.5.

By heating a solution of the above morpholide and a 10% excess of phenethyl bromide in acetonitrile at reflux for 18 hr. there was obtained the phenethyl quaternary salt. Removal of the solvent *in vacuo* left an oil which could not be crystallized. An aqueous solution of this oil was hydrogenated over platinum oxide at 60 p.s.i. and 50°. Work-up of the reaction mixture as for similar hydrogenations in method B gave 84% of 4-[3-(1-phenethyl-3-piperidyl)-propionyl]-morpholine, b.p. 217–219° at 0.3 mm.

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.7; H, 9.2. Found: C, 72.8; H, 9.1.

SYRACUSE 1, N. Y.

(20) The general procedure of J. E. LuValle, D. B. Glass and A. Weissberger, THIS JOURNAL, **70**, 2223 (1948).