[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, DIVISION OF BASIC HEALTH SCIENCES, EMORY UNIVERSITY]

# Substituted Piperidinecarboxamides[1]

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The synthesis of a series of mono- and bis[(N,N-diethylcarboxamido)piperidino]alkanes, and related compounds is described.

A considerable number of piperidinecarboxylic acid derivatives are known to have significant pharmacological effects, ranging from local anesthesia (cocaine) to analeptic activity (coramine). In the course of an investigation, directed toward the elucidation of the pharmacodynamic characteristics of this class of compounds, we have undertaken the synthesis of a series of piperidinecarboxylic acid derivatives. The first group of these compounds is reported in this communication. Their pharmacological evaluation is in progress.

## EXPERIMENTAL[3]

*Piperidine-3-carboxylic acid hydrochloride* (I) was prepared from nicotinic acid according to the method of McElvain and Adams.[4] The recrystallized product melted at 240.0–242.0°, in accordance with the literature.[4]

*Piperidine-4-carboxylic acid hydrochloride* (II) was prepared from isonicotinic acid in the same manner as I. The recrystallized product melted at 292.0–293.0° with decomposition, in accordance with the literature.[5]

*1-Methylpiperidine-3-carboxylic acid hydrochloride* (III) was prepared from I according to the method of Preobraschenski and Fisher.[6] The recrystallized product melted at 176.0–177.0°, in accordance with the literature.[6,7]

*1-Methylpiperidine-4-carboxylic acid hydrochloride* (IV) was prepared from II in the same manner as III. The recrystallized product melted at 226.5–228.5°, in accordance with the literature.[8]

*Piperidine-3-(N,N-diethylcarboxamide)* (V). Pyridine-3-(N,N-diethylcarboxamide) (100 g., 0.5612 mole) (VI) was dissolved in 150 ml. of water, and while cooling this solution, 54 ml. of aqueous 38% hydrochloric acid (equivalent to 0.5627 mole of HCl) was added. The solution was subjected to hydrogenation in the "Parr" pressure reaction apparatus, in the presence of 1.7 g. of platinum oxide (Adams' catalyst), at maximum pressures of 50–55 lbs/inch$^2$. The reaction went to completion in 34–39 hours. The platinum oxide was filtered off, the acidic filtrate neutralized to *p*H 6.4–6.8, and the water was removed under reduced pressure (max. pot temp. 50°). An excess of cold aqueous 40% potassium hydroxide was added to the residue and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, the solution filtered, the benzene removed, and the residue fractionated under reduced pressure. The product was obtained in 90–96% yields. It distilled at 100°/0.30–0.32 mm.; $n_D^{27}$ 1.4860.

*Anal.* Calc'd for $C_{10}H_{20}N_2O$: C, 65.16; H, 10.94; N, 15.20. Found: C, 65.28; H, 11.03; N, 15.00.

The *aurochloride* (Va) was prepared by dissolving 1 g. of V in water, rendering the solution slightly acid with hydrochloric acid, and adding an equivalent quantity of aqueous 10% gold chloride. The crystals, formed overnight under refrigeration, were recrystallized from aqueous 25% ethanol. The derivative melted at 111.5–112.0°.

*Anal.* Calc'd for $C_{10}H_{21}AuCl_4N_2O$: C, 22.91; H, 4.03; Au, 37.61. Found: C, 23.37; H, 4.04; Au, 37.50.

*1-Methyl-3-(N,N-diethylcarboxamido)pyridinium iodide* (VII). Compound VI (71 g., 0.395 mole), and 108.6 g. (0.765 mole) of methyl iodide were dissolved in 400 ml. of anhydrous benzene and refluxed for 5 hours. The precipitate formed during the reaction was filtered off. The air-dried crude product weighed 119 g. (94% yield). After two recrystallizations from an ethanol–ethyl acetate solvent system the crystals melted at 129.5–130.5°.

*Anal.* Calc'd for $C_{11}H_{17}IN_2O$: C, 41.26; H, 5.35; I, 39.64; N, 8.75. Found: C, 41.36; H, 5.29; I, 39.4; N, 8.65.

*1-Methylpiperidine-3-(N,N-diethylcarboxamide) hydrochloride* (VIII). *Method A.* Compound III (20 g., 0.111 mole) was dispersed in 150 ml. of anhydrous benzene, 132 g. (1.11 moles) of thionyl chloride was added, and the reaction mixture was heated gradually to and maintained at reflux temperature for 3 hours. The excess thionyl chloride and benzene were removed under reduced pressure (max. pot temp. 40°). The residual thionyl chloride was removed by azeotropic distillation under reduced pressure with two 100-ml. portions of anhydrous benzene. To the residue, approximately 200 ml. of anhydrous benzene was added and, while maintaining the contents of the reaction vessel at reflux temperature, 35 g. (0.48 mole) of diethylamine in 150 ml. of anhydrous benzene was added gradually. The reaction mixture was refluxed for additional 2 hours. Upon cooling, the reaction mixture was treated with cold aqueous 40% potassium hydroxide, and the benzene layer was removed, dried over magnesium sulfate, and filtered. The solvent was removed and the residue was fractionated under reduced pressure. The product distilled at 94°/0.15 mm.; $n_D^{29}$ 1.4752 (10.9 g., 49.5% yield). The base was converted to the hydrochloride in anhydrous ethyl ether and the salt was purified by recrystallization from an ethanol–ethyl acetate solvent system. The hydrochloride melted at 156.8–158.0°.

*Anal.* Calc'd for $C_{11}H_{23}ClN_2O$: C, 56.27; H, 9.87; Cl, 15.10; N, 11.93. Found: C, 56.04; H, 9.95; Cl, 15.20; N, 11.4.

*Method B.* Compound VII (89 g., 0.278 mole) was hy-

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(3) All melting points uncorrected. Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(4) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2745 (1923).

(5) V. Hanousek and V. Prelog, *Collection Czechoslov. Chem. Communs.*, **4**, 259 (1932). [*Chem. Abstr.*, **26**, 5302 (1932)].

(6) N. A. Preobraschenski and L. B. Fisher, *J. Gen. Chem. (USSR)*, **11**, 141 (1941). [*Chem. Abstr.*, **35**, 5505$^8$, (1941)].

(7) E. Winterstein and A. B. Weinhagen, *Z. physiol. Chem.*, **100**, 182 (1917).

(8) P. Lucas, R. C. Clarke, and A. Mooradian, U. S. Patent 2,555,333, June 5, 1951. [*Chem. Abstr.*, **46**, 142$^e$, (1952).

drogenated in an aqueous solution as described in the preparation of V, using 1.0 g. of the catalyst. The reaction went to completion in less than 22 hours. The platinum oxide was filtered off and the water was removed under reduced pressure. An excess of cold aqueous 40% potassium hydroxide was added to the residue and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, the solution was filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The hydrochloride was prepared by the procedure employed in *Method A*. A total of 41.4 g. (63.5% yield) of the salt was obtained. The product melted at 159.0–159.5°. The mixture melting point of the products prepared by *Methods A* and *B:* 158.5–159.4°.

*1-Methylpiperidine-4-(N,N-diethylcarboxamide) hydrochloride* (IX) was prepared from IV by *Method A* employed in the synthesis of VIII. The base distilled at 98°/0.50–0.55 mm.; $n_D^{30}$ 1.4755 (9.8 g., 44.5% yield). The hydrochloride melted at 196.0–196.5°.

*Anal.* Calc'd for $C_{11}H_{23}ClN_2O$: C, 56.27; H, 9.87; Cl, 15.10; N, 11.93. Found: C, 56.28; H, 9.70; Cl, 15.1; N, 11.8.

*1-Methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboxamide) hydrochloride* (X). 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid was prepared from arecoline according to Jahns procedure.[9] The compound was recrystallized from aqueous 65% ethanol and melted at 228.0–228.5°, which appears to be in agreement with the findings of Wohl and Johnson.[10] To 37 g. (0.232 mole) of the acid, 328 g. (2.76 moles) of thionyl chloride was added, and the mixture was heated gradually to reflux temperature and the resulting solution was refluxed for 19 minutes. The excess thionyl chloride was removed under reduced pressure (max. pot temp. 40°). The residue was dispersed in 400 ml. of anhydrous benzene and 107 g. (1.465 moles) of diethylamine was added gradually to the contents of the reaction vessel. Then an additional 200 ml. of anhydrous benzene was added and the mixture was heated at 50–55° for 9 hours, with vigorous agitation. The resulting slurry was treated with aqueous saturated sodium carbonate and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, filtered, and the benzene was removed under reduced pressure. The residue was extracted with cold, aqueous 10% hydrochloric acid, the acid solution was rendered alkaline with aqueous saturated sodium carbonate, and the base was extracted with ethyl ether. The ether extracts were combined, dried over magnesium sulfate, and the solution was filtered. The ether was removed on the steam-bath and the residue was fractionated under reduced pressure. The fraction distilling at 105–106°/0.08 mm.; $n_D^{24}$ 1.4915 (32.5 g., 71.5% yield) was identified as the base of X. The hydrochloride was prepared as described in the preparation of VIII, and melted at 195.0–196.0°.

*Anal.* Calc'd for $C_{11}H_{21}ClN_2O$: C, 56.74; H, 9.09; Cl, 15.28; N, 12.04. Found: C, 56.82; H, 8.92; Cl, 15.46; N, 11.7.

*(+)-2-(N,N-Diethylcarboxamido)-3-benzoxytropane hydrochloride* (XI). *l*-3-Benzoxytropane-2-carboxylic acid was prepared from cocaine according to Einhorn's procedure.[11] The product, crystallized from water, melted at 194–195°; $[\alpha]_D^{28}$ (in aqueous 50% ethanol) −45.39°.

*Anal.* Calc'd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.20; H, 6.61; N, 4.81.

To 30 g. (0.104 mole) of the acid, 164 g. (1.38 moles) of thionyl chloride was added. The solution was gradually heated to 70° and maintained at 70–72° for 10 minutes. The excess thionyl chloride was removed under reduced pressure (max. pot temp. 30°). The reddish viscous residue was dispersed in 400 ml. of anhydrous benzene, and to the mixture 110 g. (1.5 moles) of diethylamine was added gradually, while maintaining the reaction temperature below 40°. The slurry-like reaction mixture was stirred vigorously for an additional hour at 50° and subsequently was refluxed for 1½ hours. Upon cooling, the reaction mixture was treated with cold aqueous 25% potassium carbonate and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, filtered, and the benzene was removed under reduced pressure. The residue was dissolved in cold aqueous 10% hydrochloric acid, treated with charcoal, filtered, and the acid solution was rendered alkaline with cold aqueous 25% potassium carbonate and the base was extracted with ethyl ether. The ether extracts were combined, dried over magnesium sulfate, filtered, the solvent was removed on the steam-bath, and the residue was fractionated under reduced pressure. The fraction distilling at 132–134°/0.25 mm.; $n_D^{13}$ 1.5118 (3.6 g.) was identified as 2-(N,N-diethylcarboxamido)tropidine (XII). The aurochloride (XIIa) was prepared as described in the preparation of Va and the product was recrystallized from aqueous 95% ethanol. The derivative melted at 178.5–180.0°.

*Anal.* Calc'd for $C_{13}H_{23}AuCl_4N_2O$: C, 27.76; H, 4.12; Au, 35.06; N, 4.98. Found: C, 27.90; H, 4.17; Au, 34.8; N, 4.84.

The fraction distilling at 192–198°/0.08–0.10 mm. (2.6 g.) was identified as the base of XI. The hydrochloride was prepared as described in the preparation of VIII. The salt melted at 224–226°; $[\alpha]_D^{18}$ +41.2° (in aqueous 50% ethanol).[12] In the course of this work XI was obtained in a maximum yield of 19.7%.

*Anal.* Calc'd for $C_{20}H_{29}ClN_2O_3$: C, 63.06; H, 7.67; Cl, 9.31; N, 7.36. Found: C, 62.72; H, 7.63; Cl, 9.17; N, 7.1.

The *aurochloride* (XIa) was prepared as described in the preparation of XIIa. The derivative melted at 160.5–161.0°.

*Anal.* Calc'd for $C_{20}H_{29}AuCl_4N_2O_3$; C, 35.09; H, 4.27; Au, 28.81; N, 4.09. Found: C, 35.16; H, 4.45; Au, 28.80; N, 3.84.

*1-Propylpiperidine-3-(N,N-diethylcarboxamide) hydrobromide* (XIII). Compound VI (36 g., 0.202 mole) and 74 g. (0.601 mole) of 1-bromopropane were refluxed for a total of 27 hours. The excess of 1-bromopropane was removed under reduced pressure (max. pot temp. 50°). The residue was dissolved in 230 ml. of aqueous 42% ethanol, and the solution was filtered and hydrogenated as described in the preparation of V, using 1.0 g. of the catalyst. The reaction went to completion in 4¼ hours. The platinum oxide was filtered off and the solvents were removed under reduced pressure. The residual moisture was removed by azeotropic distillation under reduced pressure with anhydrous benzene (max. pot temp. 50°). The product was purified by recrystallization from the ethanol–ethyl acetate solvent system.

(9) E. Jahns, *Arch. Pharm.*, 229, 680 (1891).
(10) A. Wohl and A. Johnson, *Ber.*, 40, 4718 (1907).
(11) A. Einhorn, *Ber.*, 21, 48 (1888).

(12) Lieberman and Giesel[13] advanced the theory that the *l*-3-hydroxytropane-2-carboxylic acid (*l*-ecgonine) derivatives are transformed partially into the corresponding *d*-configurations, upon exposure to hot aqueous hydrochloric acid.[14] Einhorn and Marquardt, who reported the base-catalyzed transformation of optical properties in *l*-ecgonine derivatives in an earlier communication,[15] do not share this belief,[16] and feel that the change in the optical activity of these moieties was affected by their subsequent exposure to alkali in the course of Lieberman and Giesel's procedure.[14] It should be noted that F. Hoffmann-La Roche reported[17] the preparation of *l*-benzoylecgonyl chloride, using considerably less thionyl chloride and lower reaction temperatures than we did. The nature of the change in the optical activity will be further investigated.

(13) G. Lieberman and F. Giesel, *Ber.*, 23, 508 (1890).
(14) G. Lieberman and F. Giesel, *Ber.*, 21, 3196 (1888).
(15) A. Einhorn and A. Marquardt, *Ber.*, 23, 468 (1890).
(16) A. Einhorn and A. Marquardt, *Ber.*, 23, 981 (1890).
(17) F. Hoffmann-La Roche and Co., Swiss Patent 111,994; September 16, 1925.

The white crystals (33.2 g., 53.5% yield) melted at 151.0–152.1°.

*Anal.* Calc'd for $C_{13}H_{27}BrN_2O$: C, 50.81; H, 8.86; Br, 26.01; N, 9.12. Found: C, 50.89; H, 8.91; Br, 26.1; N, 9.14.

*1-Butylpiperidine-3-(N,N-diethylcarboxamide) hydrobromide* (XIV). Compound VI (18 g., 0.101 mole) and 99 g. (0.721 mole) of 1-bromobutane were heated on the steam-bath for a total of 22¼ hours. The excess of 1-bromobutane was removed under reduced pressure (max. pot temp. 50°). The residue was dissolved in 250 ml. of aqueous 48% ethanol, and the solution was filtered and hydrogenated as described in the preparation of V, using 1.0 g. of the catalyst. The reaction went to completion in 1½ hours. The product was isolated and purified as described in the preparation of XIII. The white crystals (9 g., 27.8% yield) melted at 172.0–174.0°.

*Anal.* Calc'd for $C_{14}H_{29}BrN_2O$: C, 52.33; H, 9.10; Br, 24.88; N, 8.72. Found: C, 52.45; H, 9.15; Br, 24.8; N, 8.45.

*1-Amylpiperidine-3-(N,N-diethylcarboxamide) hydrobromide* (XV). A mixture of 36 g. (0.202 mole) of VI and 101.6 g. (0.672 mole) of 1-bromopentane was heated on the steam-bath for a total of 36 hours. Upon cooling, the supernatant liquid was decanted from the semisolid material formed in the course of the reaction. The latter was washed with anhydrous ether and the residual ether was removed under reduced pressure. The reaction product was dissolved in water, and the solution was filtered and hydrogenated as before, using 1.7 g. of the catalyst. The reaction went to completion in 6–8 hours. The product was isolated and purified as described in the preparation of XIII (crude yield: 62.3 g., 92%). The white crystals melted at 186.0–187.3°.

*Anal.* Calc'd for $C_{15}H_{31}BrN_2O$: C, 53.72; H, 9.32; Br, 23.83; N, 8.36. Found: C, 53.90; H, 9.37; Br, 23.76; N, 8.25.

*Spiro[3-(N,N-diethylcarboxamido)piperidine-1,1'-pyrrolidinium]bromide* (XVI). Compound V (23 g., 0.125 mole) and 6.7 g. (0.031 mole) of 1,4-dibromobutane were refluxed in 200 ml. of anhydrous benzene for 16 hours. The white crystalline precipitate formed during the reaction was filtered off (3.8 g., 39.6% yield). The product was purified by crystallization from an ethanol–ethyl acetate solvent system. The white crystals melted at 173.0–174.0°.

*Anal.* Calc'd for $C_{14}H_{27}BrN_2O$: C, 52.66; H, 8.53; Br, 25.03; N, 8.78. Found: C, 52.81; H, 8.66; Br, 24.9; N, 8.7.

*1,1'-Spiro-3-(N,N-diethylcarboxamido)bipiperidinium bromide* (XVII). Compound V (12 g., 0.065 mole) and 4 g. (0.0174 mole) of 1,5-dibromopentane were refluxed in 400 ml. of anhydrous benzene for 5 hours. The white crystals formed during the reaction were filtered off (5.4 g., 93% yield). The product was purified by crystallization from benzene-ethanol. The white crystals melted at 197.0–198.0°.

*Anal.* Calc'd for $C_{15}H_{29}BrN_2O$: C, 54.06; H, 8.77; N, 8.41; Br, 23.98. Found: C, 54.02; H, 8.76; N, 8.35; Br, 24.1.

*1,3-Bis[3-(N,N-diethylcarboxamido)piperidino]propane dihydrochloride* (XVIII). A mixture of 37 g. (0.201 mole) of V and 10.1 g. (0.05 mole) of 1,3-dibromopropane were refluxed in 250 ml. of anhydrous benzene for 3 hours. The benzene was removed under reduced pressure (max. pot temp. 50°). The residue was treated with cold aqueous 40% potassium hydroxide and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, filtered, and the benzene was removed and the residue was fractionated under reduced pressure. The fraction distilling at 249–251°/0.85–0.90 mm.; $n_D^{29}$ 1.4994 (12.7 g., 62% yield) was identified as the base of XVIII. The hydrochloride was prepared as described in the preparation of VIII. The salt melted at 263.0–264.0°.

*Anal.* Calc'd for $C_{23}H_{46}Cl_2N_4O_2$: C, 57.36; H, 9.63; Cl, 14.73; N, 11.64. Found: C, 57.24; H, 9.58; Cl, 14.5; N, 11.6.

*1,4-Bis[3-(N,N-diethylcarboxamido)pyridinium]butane dibromide* (XIX). Compound VI (18 g., 0.101 mole) and 10.8 g. (0.05 mole) of 1,4-dibromobutane were refluxed in 200 ml. of anhydrous benzene for a total of 50½ hours. Upon cooling, the supernatant benzene layer was decanted from the amorphous solid formed in the course of the reaction and the latter was purified by crystallization from ethanol–ethyl acetate. The white crystals (4.8 g., 16.8% yield) melted at 196.0–198.0°.

*Anal.* Calc'd for $C_{24}H_{36}Br_2N_4O_2$: C, 50.36; H, 6.34; Br, 27.93; N, 9.79. Found: C, 50.26; H, 6.20; Br, 27.9; H, 9.64.

*1,4-Bis[3-(N,N-diethylcarboxamido)piperidino]butane dihydrochloride* (XX). Crude XIX, prepared from 35.7 g. (0.20 mole) of VI and 21.6 g. (0.10 mole) of 1,4-dibromobutane, was dissolved in aqueous 14–15% ethanol, and the solution was filtered and hydrogenated as described in the preparation of V, using 1.0 g. of the catalyst. Hydrogen absorption ceased after 3 hours. The platinum oxide was filtered off and the solvents were removed under reduced pressure (max. pot temp. 50°). The residue was treated with cold aqueous 40% potassium hydroxide and the base was extracted with benzene. The combined benzene extracts were dried over magnesium sulfate, the solution was filtered, and the benzene was removed under reduced pressure. The residue was dissolved in anhydrous ethyl ether, converted to the hydrochloride, and the crude XX was purified by crystallization from ethanol–ethyl acetate. A total of 4.8 g. (9.7% yield) of the hydrochloride was obtained. The white crystals melted at 275.0–275.5°.

*Anal.* Calc'd for $C_{24}H_{48}Cl_2N_4O_2$: C, 58.15; H, 9.76; Cl, 14.31; N, 11.31. Found: C, 57.97; H, 9.76; Cl, 14.25; N, 11.1.

*1,5-Bis[3-(N,N-diethylcarboxamido)piperidino]pentane dihydrochloride* (XXI). A mixture of 54 g. (0.303 mole) of VI and 35 g. (0.152 mole) of 1,5-dibromopentane was refluxed in 300 ml. of anhydrous benzene for a total of 30 hours. The solvent was removed under reduced pressure (max. pot temp. 50°), the residue was dissolved in water, and the solution was filtered and hydrogenated in two portions as described in the preparation of V, using in each instance 2 g. of the catalyst. The base of XXI was isolated as described in *Method B* employed in the synthesis of VIII. It distilled at 259–263°/0.10–0.15 mm.; $n_D^{24}$ 1.4985 (20.6 g., 26.6% yield). The hydrochloride was prepared as described in the preparation of VIII. The salt melted at 247.0–250.0°.

*Anal.* Calc'd for $C_{25}H_{50}Cl_2N_4O_2$: C, 58.93; H, 9.89; Cl, 13.92; N, 10.99. Found: C, 58.71; H, 9.87; Cl, 13.75; N, 10.8.

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