SYNTHESIS OF 2,2,6,6-TETRAMETHYLQUINUCLIDINES WITH FUNCTIONAL SUBSTITUENTS IN THE QUINUCLIDINE RING

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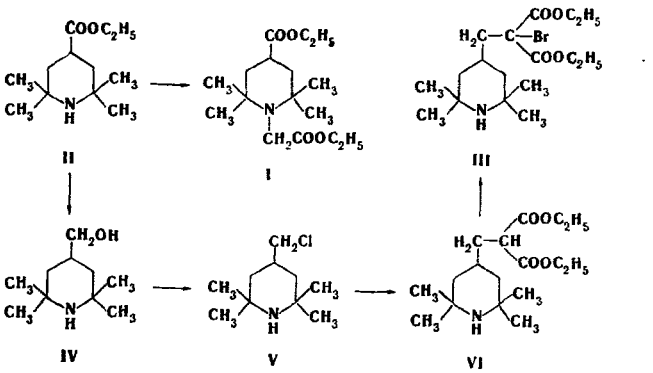
8-Carboxamido- and 8-phthalimido-2,2,6,6-tetramethylquinuclidines were synthesized. The effect of α,α'-gem-dimethyl groups, which shield the nitrogen atom, on the synthesis of functionally substituted quinuclidine compounds by classical methods was studied.

The stereochemistry of reaction centers and the degree of their steric shielding play a substantial role in the mechanism of the interaction of physiologically active substances with biochemical receptors.

We have previously shown that the introduction of shielding gem-dimethyl groups in the α,α' positions relative to the nitrogen atom considerably raises the ganglion-blocking activity of quinuclidine compounds, and this has made it possible to create the original and effective medicinals temekhin [1] and imekhin [2], which have been incorporated in medical practice. For the development of further research on α,α'-polyalkylquinuclidines it was necessary to develop methods for the synthesis of compounds of this type containing reactive functional substituents in other positions of the quinuclidine ring. One complication was the fact that the introduction of methyl groups that shield the nitrogen atom should sterically hinder reactions that are generally used for the synthesis of quinuclidine compounds with oxo and alkoxycarbonyl groups [3]. In fact, we were unable to arrive at the corresponding β-oxoquinuclidine derivative by Clemo cyclization [4], under various conditions, of 1-ethoxycarbonylmethyl-2,2,6,6-tetramethyl-4-ethoxycarbonylpiperidine (I), obtained by alkylation of 2,2,6,6-tetramethyl-4-ethoxycarbonylpiperidine (II) with bromoacetic ester [5]. Starting I was recovered in all cases in experiments with potassium metal, potassium ethoxide, and sodium hydride in refluxing toluene or xylene even when the reaction time was increased to 14 h. Ruvtsov–Dorokhova cyclization [6] of 2,2,6,6-tetramethyl-4-(2',2'-diethoxycarbonyl-2'-bromoethyl)piperidine (III), obtained from ester II through 2,2,6,6-tetramethyl-4-hydroxymethylpiperidine (IV), 2,2,6,6-tetramethyl-4-chloromethylpiperidine (V), and 2,2,6,6-tetramethyl-4-(2',2'-diethoxycarbonylethyl)piperidine (VI) via the following scheme, also did not give positive results:



An unsaturated monocyclic compound – 2,2,6,6-tetramethyl-4-(2'-ethoxycarbonylvinyl)piperidine (XI) – was formed instead of the expected alkoxycarbonyltetramethylquinuclidine during Grob cyclization [7] of 2,2,-6,6-tetramethyl-4-(2'-carboxyethyl)piperidine (VII), obtained from 2,2,6,6-tetramethyl-4-(2'-bromoethyl)-piperidine (VIII) [1] through 2,2,6,6-tetramethyl-4-(2'-cyanoethyl)piperidine (IX) and 2,2,6,6-tetramethyl-4-(2'-ethoxycarbonylethyl)piperidine (X).

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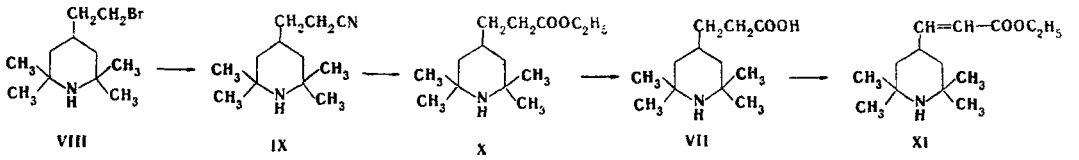
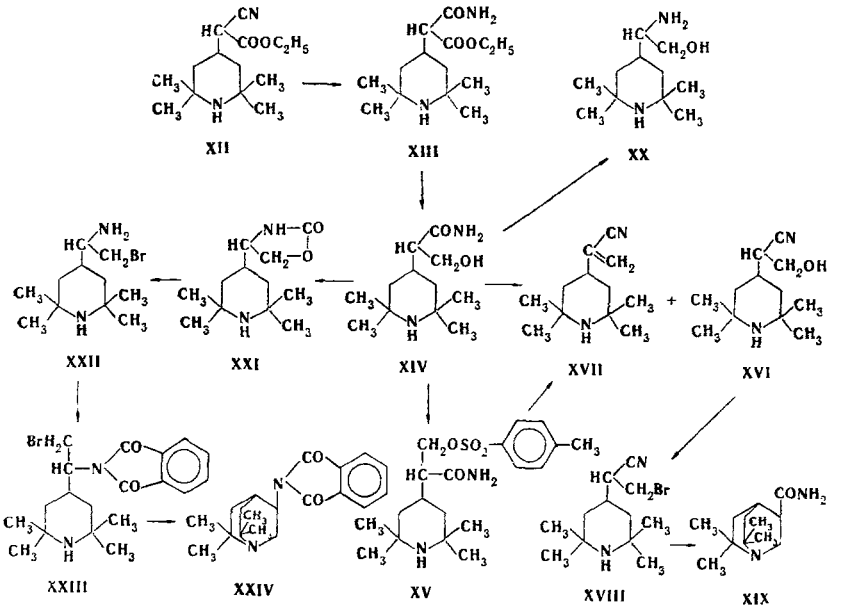


VIII IX X VII XI

We were able to accomplish the synthesis of 2,2,6,6-tetramethylquinuclidines with functional substituents in the quinuclidine ring via the following scheme:



XII XIII XX XXII XXI XIV XVII XVI XXIII XXIV XV XVIII XIX

The intermediates – 2,2,6,6-tetramethyl-4-(ethoxycarbonyl, cyanomethyl)piperidine (XII) [1] – in the industrial production of temekhin was used as the starting compound in this synthesis. Selective saponification of the nitrile group of this compound in 94% sulfuric acid made it possible to obtain amido ester XIII (in 71% yield), which was also obtained in 87% yield from XII through the corresponding imido ester derivative. Selective reduction with lithium aluminum hydride of the ester group in ester XIII gave hydroxy amide XIV in 81% yield. Difficulties were encountered in the replacement of the hydroxyl group in XIV by halogen: The reaction did not take place under mild conditions with hydrohalic (hydrochloric or hydrobromic) acids, whereas the amide group became involved under more severe conditions, and considerable resinification was observed; selective replacement of the hydroxyl group by chlorine also did not occur under the influence of thionyl chloride in refluxing chloroform. Treatment of XIV with p-toluenesulfonyl chloride in pyridine gave O-tosyl derivative XV, which, on refluxing in xylene, was converted to a mixture of products with different degrees of dehydration – 2,2,6,6-tetramethyl-4-(1'-cyano-2'-hydroxyethyl)piperidine (XVI) and 2,2,6,6-tetramethyl-4-(1'-cyanovinyl)piperidine (XVII). Compounds XVI and XVII were also obtained by treatment of hydroxy amide XIV with phosphorus tribromide. The ease of formation of vinyl derivative XVII is evidently associated with the energic advantageousness of the formation of a system of conjugated multiple bonds. We were, nevertheless, able to convert XVII to bromo nitrile XVIII and cyclize it to 2,2,6,6-tetramethylquinuclidine-8-carboxamide (XIX) by careful reaction of hydroxy nitrile XVI with PBr_3, although the process was ambiguous in this case and was accompanied by the formation of considerable amounts of unsaturated XVII.

The second variant of conversion of hydroxy amide XIV to an 8-substituted 2,2,6,6-tetramethylquinuclidine involved the use of the Hofmann reaction, as a result of which the side carbon chain is shortened, and the possibility of the formation of unsaturated piperidine compounds through the development of a conjugated system of multiple bonds vanishes. The Hofmann rearrangement of hydroxy amide XIV proceeds smoothly: Hydroxy amine XX is obtained in 95% yield in aqueous media, whereas 5-(2',2',6',6'-tetramethyl-4'-piperidyl)-2-oxazolone (XXI) is obtained in 93% yield in methanol. Oxazolone XXI was converted to bromo amine XXII in 93% yield by brief heating with 40% hydrobromic acid. The presence in XX and XXII of α,β-aminohydroxy and α,β-aminobromoethyl groupings facilitated their conversion to the corresponding piperazine derivatives. The N-acetyl protective group did not prevent this reaction. The introduction of the more stable phthalimide group insured the possibility of closing of the quinuclidine ring by conversion to 2,2,6,6-tetramethyl-8-phthalimidoquinuclidine (XXIV), despite the fact that steric hindrance substantially slowed down the cyclization process.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrometer. The PMR spectrum of a $CDCl_3$ solution of XIX was recorded with a Varian spectrometer with tetramethylsilane as the internal standard, and the PMR spectrum of XXIV was recorded with a JNM 4H-100 spectrometer with TMSO as the internal standard.

1-Ethoxycarbonylmethyl-2,2,6,6-tetramethyl-4-ethoxycarbonylpiperidine (I). A 16-g (75 mmole) sample of 2,2,6,6-tetramethyl-4-ethoxycarbonylpyridine (II) was dissolved in 40 ml of xylene, after which 12.4 g (90 mmole) of freshly calcined potassium carbonate and a solution of 15 g (90 mmole) of ethyl bromoacetate in 10 ml of xylene were added, and the mixture was stirred for 20 h. The xylene was vacuum evaporated, the residue was dissolved in 15 ml of water, and the solution was treated with 50% aqueous potassium carbonate solution to pH > 12. The liberated base was extracted with chloroform, and the extract was worked up to give 17.15 g (76.5%) of I as a viscous colorless liquid with bp 150-152° (2 mm). Found: C 64.5; H 9.5; N 4.6%. $C_{16}H_{29}NO_4$. Calculated: C 64.2; H 9.7; N 4.7%.

2,2,6,6-Tetramethyl-4-hydroxymethylpiperidine (IV). A 12.35-g (60 mmole) sample of II in 120 ml of refluxing ether was reduced by means of 2.2 g (60 mmole) of lithium aluminum hydride in the course of 3 h. The complex was decomposed with 4.4 ml of water, and the liberated base was extracted with chloroform. Workup of the extract gave 9.38 g (94.7%) of III as colorless crystals with mp 168-169° (from alcohol); the product was quite soluble in alcohol and chloroform but less soluble in ether. Found: C 70.4; H 12.2; N 8.3%. $C_{10}H_{21}NO$. Calculated: C 70.1; H 12.3; N 8.2%. The hydrochloride was obtained as a colorless crystalline powder, with mp 298-299°, that was quite soluble in water and alcohol. Found: Cl 17.2; N 6.7%. $C_{10}H_{21}NO \cdot HCl$. Calculated: Cl 17.1; N 6.7%.

2,2,6,6-Tetramethyl-4-chloromethylpiperidine (V). A solution of 50 ml of thionyl chloride in 50 ml of chloroform was added to 5 g (24 mmole) of the hydrochloride of IV, and the mixture was refluxed for 5 h. It was then vacuum evaporated, and the residue was neutralized with excess 50% potassium carbonate solution. The liberated base was extracted with chloroform, and the extract was worked up to give 4.9 g (89.4%) of V as a transparent liquid with bp 55-57° (4 mm). Found: C 63.1; H 10.5; Cl 19.0; N 7.4%. $C_{10}H_{20}ClN$. Calculated: C 63.4; H 10.5; Cl 18.7; N 7.4%. The hydrochloride was obtained as shiny crystals, with mp 246-247°, that were quite soluble in water and alcohol. Found: Cl 30.8; N 6.4%. $C_{10}H_{20}ClN \cdot HCl$. Calculated: Cl 30.9; N 6.2%.

4-(2',2'-Diethoxycarbonylethyl)-2,2,6,6-tetramethylpiperidine (VI). A mixture of 5.5 g (30 mmole) of V and 8.1 g (50 mmole) of malonic ester was added to sodium alkoxide, prepared from 1.15 g (50 mg-atom) of sodium and 28 ml of absolute alcohol, and the mixture was stirred and refluxed for 20 h. The alcohol was then removed in vacuo, and the residue was dissolved in 10 ml of water. The solution was treated with 10 ml of 50% aqueous potassium carbonate solution and extracted with ether. Workup of the extract gave 3.92 g (43.1%) of VI as a transparent viscous liquid with bp 140-142° (6 mm). Found: C 65.2; H 9.8; N 4.4%. $C_{17}H_{31}NO_4$. Calculated: C 65.1; H 9.9; N 4.5%. The hydrochloride was obtained as colorless crystals, with mp 179-180°, that were quite soluble in water, alcohol, and chloroform. Found: C 58.3; H 9.2; Cl 9.9; N 4.0%. $C_{17}H_{31}NO_4 \cdot HCl$. Calculated: C 58.4; H 9.2; Cl 10.1; N 4.0%.

4-(2',2'-Diethoxycarbonyl-2'-bromoethyl)-2,2,6,6-tetramethylpiperidine (III). A solution of 2.5 g of bromine (15.5 mmole) in 32 ml of chloroform was added dropwise in the course of 5 h to a solution of 5.45 g (15.5 mmole) of the hydrochloride of VI in 50 ml of chloroform, after which the mixture was allowed to stand overnight. The resulting colorless solution was vacuum evaporated, and the residue (5.8 g) was recrystallized from alcohol–ether to give 5.25 g of the hydrochloride of III as a colorless crystalline powder with mp 146-147°. The product was quite soluble in alcohol, chloroform, and water. Found: Cl' 8.5; N 3.4%. $C_{17}H_{30}BrNO_4 \cdot HCl$. Calculated: Cl' 8.3; N 3.3%.

A 5.25-g sample of the hydrochloride of III was dissolved in 10 ml of water, and the solution was neutralized with excess 50% aqueous potassium carbonate solution and extracted with chloroform. Workup of the extract gave 4.9 g (80%) of base III as a transparent liquid with bp 168-170° (4 mm). Found: C 52.3; H 7.7; Br 20.4; N 3.7%. $C_{17}H_{30}BrNO_4$. Calculated: C 52.0; H 7.7; Br 20.4; N 3.7%.

2,2,6,6-Tetramethyl-4-(2'-cyanoethyl)piperidine (IX). A 2.48-g (10 mmole) sample of VIII and 0.65 g (10 mmole) of potassium cyanide were refluxed in 20 ml of alcohol for 30 h, after which the mixture was cooled, and the alcohol was removed by distillation. The residue was dissolved in water, and the solution was treated with 10 ml of 50% aqueous potassium carbonate solution and extracted with ether. Workup of the extract gave 1.38 g (71.2%) of colorless needles of IX with mp 52-53° (from petroleum ether) and bp 138-140° (18 mm). IR spectrum, ν, cm^{-1}: 2260 (CN) and 3200-3400 (NH). Found: C 74.0; H 11.2; N 14.6%. $C_{12}H_{22}N_2$. Calculated:

Calculated: C 74.2; H 11.5; N 14.4%. The hydrochloride was obtained as colorless crystals with mp 200-201° (from alcohol). Found: Cl 15.5; N 12.1%. $C_{12}H_{22}N_2 \cdot HCl$. Calculated: Cl 15.4; N 12.1%.

2,2,6,6-Tetramethyl-4-(2'-ethoxycarbonylethyl)piperidine (X). A mixture of 19.4 g (100 mmole) of IX, 190 ml of hydrochloric acid, and 380 ml of acetic acid was refluxed for 30 h, after which it was vacuum evaporated and traces of moisture were removed by azeotropic distillation with benzene. The residue was esterified by refluxing with 200 ml of a 10% alcohol solution of hydrogen chloride for 6 h. Workup gave 10.4 g (42.2%) of X as a transparent liquid with bp 102-102.5° (1 mm). The product hydrolyzed readily on standing to the corresponding acid VII. Found: C 69.8; H 10.9; N 5.9%. $C_{14}H_{27}NO_2$. Calculated: C 69.7; H 11.3; N 5.8%.

2,2,6,6-Tetramethyl-4-(2'-carboxyethyl)piperidine (VII) Hydrochloride. A mixture of 10.4 g (43 mmole) of X and 100 ml of 18% hydrochloric acid was heated at 100° for 5 h, after which it was vacuum evaporated to dryness, and the residue was triturated with ether. The resulting colorless crystalline solid was removed by filtration to give 8.6 g (80%) of the hydrochloride of VII with mp 238-240°. Found: Cl 14.5; N 5.3%. $C_{12}H_{23}NO_2$ HCl. Calculated: Cl 14.2; N 5.6%.

2,2,6,6-Tetramethyl-4-(2'-ethoxycarbonylvinyl)piperidine (XI). A mixture of 3.15 g (12.5 mmole) of the hydrochloride of VII and 32 ml of thionyl chloride was stirred at 70° for 3 h, after which the excess thionyl chloride was removed in vacuo, and the residue was dissolved in 15 ml of dry chloroform. A solution of 2.1 g (13 mmole) of bromine in 15 ml of dry chloroform was added gradually at 60° to this solution, after which the mixture was stirred at 60° for 8 h and allowed to stand overnight. The resulting colorless solution was vacuum evaporated, and the residue was dissolved in 48 ml of water. The aqueous solution was added to a heated (to 70°) 10% solution of sodium hydroxide (168 ml), after which the mixture was stirred at 100° for 5 h. The water was vacuum evaporated, and the residue was dried by azeotropic removal of traces of water by distillation with benzene and esterified with an alcohol solution of hydrogen chloride for 10 h. The usual workup gave 1.05 g (35%) of XI as a transparent mobile liquid with bp 103-105° (2 mm). The product gave a positive reaction for a double bond with potassium permanganate. Found: C 69.6; H 10.8; N 5.9%. $C_{14}H_{25}NO_2$. Calculated: C 70.2; H 10.5; N 5.9%.

The hydrochloride was obtained as colorless crystals with mp 172-173° and was quite soluble in water and alcohol. Found: Cl 12.6; N 5.1%. $C_{14}H_{25}NO_2 \cdot HCl$. Calculated: Cl 12.9; N 5.1%.

2,2,6,6-Tetramethyl-4-(ethoxycarbonylaminocarbonylmethyl)piperidine (XIII). A) A total of 24.2 ml of 94% sulfuric acid was added with cooling and stirring to 7.56 g (30 mmole) of XII, and the mixture was allowed to stand at 60° for 2 h. It was then cooled to 5-10° and neutralized with excess 50% aqueous potassium carbonate solution. The liberated base was extracted with chloroform, the solvent was removed from the extract, and the residue was recrystallized from ethyl acetate to give 5.8 g (71.5%) of colorless crystals of XIII with mp 139-140°. The product was quite soluble in alcohols and chloroform, less soluble in dioxane, and slightly soluble in ether and benzene. IR spectrum, ν, cm^{-1}: 1730 ($COOC_2H_5$) and 1663 ($CONH_2$). Found: C 62.1; H 9.5; N 10.3%. $C_{14}H_{26}N_2O_3$. Calculated: C 62.2; H 9.7; N 10.4%. The hydrochloride was obtained as colorless crystals, with mp 246-247°, that were quite soluble in alcohol, chloroform, and water. Found: Cl 11.4; N 9.0%. $C_{14}H_{26}N_2O_3 \cdot HCl$. Calculated: Cl 11.5; N 9.1%.

B) An 8.65-g (30 mmole) sample of the hydrochloride of XII and 1.38 g (30 mmole) of ethanol were dissolved in 87 ml of anhydrous chloroform, and the solution was saturated with dry hydrogen chloride (the gain in weight was ~25 g). The mixture was then allowed to stand at 0 to −5° for 10 days, after which it was vacuum evaporated, and the residue was triturated with ether. The mixture was then filtered to give 11 g of the imido ester dihydrochloride with mp 95-100° (dec.). Found: Cl 19.1%. $C_{16}H_{30}N_2O_3 \cdot 2HCl$. Calculated: Cl 19.2%. The product was heated on an oil bath at 120-130° for 4 h, after which it was cooled and dissolved in water. The aqueous solution was neutralized with excess 50% aqueous potassium carbonate solution and extracted with chloroform. Workup of the extract gave 7.05 g (86.8%) of XIII with mp 139-140° (from acetone). No melting point depression was observed for a mixture of samples of XIII obtained by methods A and B.

2,2,6,6-Tetramethyl-4-(1'-aminocarbonyl-2'-hydroxyethyl)piperidine (XIV). A solution of 1 g (3.7 mmole) of XIII in 25 ml of dioxane was added dropwise at 15-20° to a suspension of 0.16 g (4.2 mmole) of lithium aluminum hydride in 10 ml of ether, after which the mixture was stirred at 20° for 4 h. The complex was destroyed with 0.5 ml of water, and the precipitated hydroxides were removed by filtration and washed thoroughly with hot chloroform. The organic solutions were combined, and the solvents were removed by vacuum distillation. The residue was recrystallized from isopropyl alcohol to give 0.685 g (81.4%) of colorless crystals of XIV with mp 170-171°. The product was only slightly soluble in alcohol, acetone, and chloroform and insoluble in ether and water. IR spectrum, ν, cm^{-1}: 1670 ($CONH_2$) and 3100-3350 (OH, NH). Found: C 62.9; H 10.6; N 12.5%.

$C_{12}H_{24}N_2O_2$. Calculated: C 63.1; H 10.6; N 12.3%. The hydrochloride was obtained as colorless crystals with mp 290-291° (dec.) and was quite soluble in alcohol, chloroform, and water. Found: Cl 13.1; N 10.4%. $C_{12}H_{24}N_2O_2 \cdot HCl$. Calculated: Cl 13.4; N 10.6%.

2,2,6,6-Tetramethyl-4-[1'-aminocarbonyl-2'-(p-tosyloxyethyl)]piperidine (XV). A solution of 4.6 g (24 mmole) of p-toluenesulfonyl chloride in 15 ml of pyridine was added gradually at 10-12° to a solution of 2.75 g (12 mmole) of XIV in 15 ml of pyridine, and the mixture was allowed to stand at 20-25° for 3 days. The pyridine was then removed by vacuum distillation, and 15 ml of water and 15 ml of ether were added to the residue. The resulting white precipitate was removed by filtration, dried in a desiccator, and recrystallized twice with acetone to give 1 g (15%) of p-tosylate XV as colorless crystals with mp 152-153° that were quite soluble in water, alcohol, and chloroform. Found: N 4.8; S 11.2%. $C_{19}H_{30}N_2O_4 \cdot C_7H_8O_3S$. Calculated: N 5.0; S 11.5%.

A 1-g sample of p-tosylate XV was dissolved in 5 ml of water, 5 ml of a 50% aqueous potassium carbonate solution was added, and the liberated base was extracted with chloroform. Workup of the extract gave 0.55 g (80%) of XV as a colorless powder with mp 165-166° [from alcohol–cyclohexane (1:1)]. Found: C 59.7; H 7.7; N 7.1; S 8.3%. $C_{19}H_{30}N_2O_4S$. Calculated: C 59.7; H 7.9; N 7.3; S 8.3%.

2,2,6,6-Tetramethyl-4-(1'-cyano-2'-hydroxyethyl)piperidine (XVI) and 2,2,6,6-Tetramethyl-4-(1'-cyanovinyl)piperidine (XVII). A solution of 6.6 g (35 mmole) of p-toluenesulfonyl chloride in 40 ml of pyridine was added at 10° to a solution of 4 g (17.5 mmole) of XIV in 40 ml of pyridine, and the mixture was allowed to stand at 20-25° for 4 days. The pyridine was removed by vacuum distillation, 15 ml of water was added to the residue, and the mixture was neutralized with excess 50% potassium carbonate solution. The liberated base was extracted with xylene, and the xylene extract was dried with magnesium sulfate, refluxed for 7 h, and vacuum evaporated. The residue was dissolved in water, and the aqueous solution was neutralized with excess 50% aqueous potassium carbonate solution and extracted with chloroform.

The chloroform was removed to give 2 g of a viscous semicrystalline mass, which was triturated with ether and filtered to give 1.1 g (30%) of colorless crystals of XVI with mp 161-162° (from alcohol). The product was quite soluble in alcohol and chloroform. IR spectrum, ν, cm^{-1}: 2245 (CN) and 3290 (OH). Found: C 68.2; H 10.5; N 13.2%. M (mass spectrometrically) 210. $C_{12}H_{22}N_2O$. Calculated: C 68.5; H 10.5; N 13.3%.

The ether mother liquor (after separation of XVI) was applied to a 20× 2 cm column filled with activity II aluminum oxide and eluted with petroleum ether to give 0.6 g (18%) of colorless crystals with mp 74-75°. The product sublimed readily (at 100° and 5 mm) and was quite soluble in ordinary organic solvents. IR spectrum, ν, cm^{-1}: 2220 (CN) and 1625 (C=C). Found: C 75.2; H 10.5; N 14.7%. M (mass spectrometrically) 196. $C_{12}H_{20}N_2$. Calculated: C 75.0; H 10.5; N 14.6%. The hydrochloride was obtained as colorless crystals, with mp 250° (dec.), that were quite soluble in water and alcohol. Found: Cl 15.4; N 12.1%. $C_{12}H_{20}N_2 \cdot HCl$. Calculated: Cl 15.5; N 12.2%.

The fraction that was subsequently eluted from the column with petroleum ether–chloroform (1:3) contained 0.1 g (2.5%) of starting XIV.

2,2,6,6-Tetramethylquinuclidine-8-carboxamide (XIX). Phosphorus tribromide (5 ml) was added to a solution of 1 g (4.75 mmole) of XVI in 10 ml of anhydrous toluene, and the mixture was stirred at 100° for 6.5 h. It was then cooled, 10 ml of water was added, and the mixture was neutralized with excess 50% aqueous potassium carbonate solution and extracted with chloroform. The extract was vacuum evaporated, 200 ml of xylene was added to the residue, and the mixture was refluxed for 10 h. The xylene was removed by vacuum distillation, 10 ml of 50% aqueous potassium carbonate solution was added, and the mixture was extracted with chloroform. The extract was dried, and the chloroform was removed by distillation to give 1.05 g of a thick viscous mass, which was triturated with ether and filtered to give 0.15 g (15%) of colorless crystals of XIX with mp 206-207° (from acetone). IR spectrum, ν, cm^{-1}: 1682-1686 ($CONH_2$) and 3115-3270 (NH_2). PMR spectrum, δ, ppm: 1.36 s, 1.41 s, 1.44 s, 1.38 s (4-CH_3); 1.12-1.76 m (β-CH_2, β'-CH_2); 2.04-2.44 m (2H attached to C_4 and C_8), 3.2 q; 3.63 q (2H attached to C_7); and 5.5 s (NH_2). Found: C 68.1; H 10.3; N 13.5%. $C_{12}H_{22}N_2O$. Calculated: C 68.5; H 10.5; N 13.3%. According to the results of thin-layer chromatography (TLC), the ether mother liquor (after separation of XIX) contained 20-25% XVII, 25-30% XVI, 10-15% XIV, and two other unidentified substances.

2,2,6,6-Tetramethyl-4-(1'-amino-2'-hydroxyethyl)piperidine (XX). A 3.3-g (14.5 mmole) sample of XIV was added gradually to a solution containing 1.4 ml of bromine and 25.5 g of potassium hydroxide in 500 ml of water, and the mixture was heated to 70° and stirred at this temperature for 1 h. The initially formed flocculent precipitate dissolved at the end of the reaction. The mixture was vacuum evaporated to 100 ml, and the base was extracted with chloroform. The chloroform was vacuum evaporated, and the residue was fractionated to give 2.75 g (95%) of XX, with bp 130-133° (4 mm), in the form of a viscous transparent liquid that crystallized

on standing to give colorless crystals with mp 85-86° (from cyclohexane). Found: C 66.0; H 12.2; N 13.7%. $C_{11}H_{24}N_2O$. Calculated: C 66.0; H 12.1; N 14.0%. The dihydrochloride was obtained as colorless crystals with mp 310° (dec.) and was quite soluble in water and alcohol. Found: Cl 23.5; N 9.9%. $C_{11}H_{24}N_2O \cdot 2HCl$. Calculated: Cl 23.6; N 10.3%.

5-(2,2,6,6-Tetramethyl-4-piperidyl)-2-oxazolone (XXI). A solution of 4 g (17.5 mmole) of XIV in 100 ml of methanol was added to a solution of 0.8 g (35 mg-atom) of sodium in 30 ml of methanol, and the mixture was cooled to 10°, after which 1 ml of bromine was added slowly dropwise. The mixture was then heated to the boiling point and refluxed for 1.5 h. The methanol was removed by vacuum distillation, the residue was dissolved in water, and the base was extracted from the aqueous solution with chloroform. Workup of the extract gave 3.7 g (93.5%) of XXI as colorless crystals with mp 166-167° (from ethyl acetate). The product was quite soluble in alcohol and chloroform but only slightly soluble in ether. IR spectrum, ν, cm^{-1}: 1725-1740 (CO); 3145, 3255 (NH). Found: C 64.0; H 9.9; N 12.5%. $C_{12}H_{22}N_2O_2$. Calculated: C 63.7; H 9.8; N 12.4%. The hydrochloride was obtained as colorless crystals with mp 273-274° and was quite soluble in water and alcohol. Found: Cl 13.3; N 10.3%. $C_{12}H_{22}N_2O_2 \cdot HCl$. Calculated: Cl 13.5; N 10.6%.

2,2,6,6-Tetramethyl-4-(1'-amino-2'-bromoethyl)piperidine (XXII) Dihydrobromide. A 2.3-g (10 mmole) sample of XXI was dissolved in 25 ml of 40% hydrobromic acid, and the solution was heated to 100° for 1 h, after which the dilute hydrochloric acid was removed from the mixture by distillation until the vapor temperature reached 130° (the distillation process averaged 1.5 h). The residual hydrobromic acid was removed in vacuo, and the product was dried by azeotropic removal of traces of water by distillation with benzene. The residue was triturated with ether and filtered to give 4 g (92.6%) of the dihydrobromide of XXII with mp 246-247° (dec.). The product was quite soluble in water and alcohol. Found: Br 56.4%. $C_{11}H_{23}BrN_2 \cdot 2HBr$. Calculated: Br 56.6%.

2,2,6,6-Tetramethyl-4-(1'-phthalimido-2'-bromoethyl)piperidine (XXIII). A mixture of 3 g (7 mmole) of dihydrobromide of XXII and 1.25 g (8.5 mmole) of phthalic anhydride was stirred throughly and heated at 180° for 1 h. It was then cooled and dissolved in 10 ml of water, and the excess phthalic anhydride was extracted with ether. The aqueous solution was made alkaline with excess 50% aqueous potassium carbonate solution, and the base was extracted with chloroform. Workup of the extract gave 1.6 g of a yellowish viscous mass. Anhydrous ether (5 ml) was added to the viscous mass, and the mixture was filtered to give 0.7 g (27%) of XXIII as colorless crystals with mp 173-174°. The product was quite soluble in alcohol, chloroform, and acetone. IR spectrum, ν, cm^{-1}: 1771, 1708 (CO), and 1610 (C_6H_4). Found: C 58.1; H 6.4; Br 19.6; N 7.0%. $C_{19}H_{25}BrN_2O_2$. Calculated: C 58.0; H 6.4; Br 20.3; N 7.1%.

2,2,6,6-Tetramethyl-8-phthalimidoquinuclidine (XXIV). A solution of 0.7 g (1.75 mmole) of XXIII in 40 ml of anhydrous xylene was refluxed for 18 h, after which it was cooled. The small amount of precipitate that formed on the walls of the flask was removed by filtration, washed with xylene, and dried to give 0.045 g (6.4%) of the hydrobromide of XXIV as colorless crystals with mp 221-222° (dec.). The hydrobromide was quite soluble in water but only slightly soluble in ordinary organic solvents. PMR spectrum, δ, ppm (CD_3OD): 1.36 s, 1.38 s, 1.40 s, 1.46 s (4-CH_3); 1.25-1.77 m (β-CH_2, β'-CH_2); 2.16-2.41 m (2H attached to C_4 and C_8); 4.14 m (2H attached to C_7); 7.82 s (4H of the phenyl ring). Evaporation of the xylene solution yielded 0.6 g of starting XXIII with mp 171-172°; no melting-point depression was observed for a mixture of this product with an authentic sample of XXIII.

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