SYNTHESIS AND PHARMACOLOGICAL STUDY OF 1,2,2,6,6-PENTAMETHYL-4-(N-MORPHOLINOMETHYL)PIPERIDINE METHIODIDE

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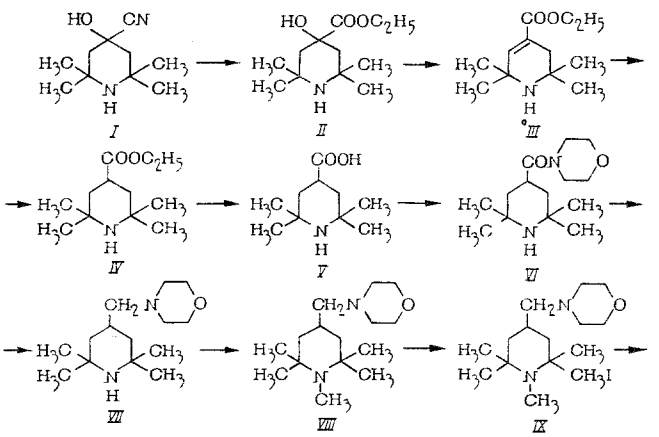
The problems of the interaction of physiologically active compounds with biochemical receptors are important for an understanding of the mechanism of medicinal therapy and the link between the structure and effect of medicinal substances. Moreover, the stereochemistry of the reaction centers and the degree of their steric shielding are of substantial importance in this respect.

We have previously examined the significance of the deshielding of nitrogen atoms for the high pharmacological activity of diverse quinuclidine derivatives as compared with the analogous monocyclic and aliphatic compounds [1]. It was shown that the introduction of shielding gem-dimethyl groups into the α- and α'-positions with respect to the nitrogen atom considerably increases the ganglion-blocking activity of quinuclidine and piperidine compounds [2, 3] but leads to complete loss of pharmacological action in the case of analgesic preparations of the piperidine series [4, 5].

The synthesis of the corresponding 1,2,2,6,6-pentamethyl-4-[β-(N-morpholino-ethyl]piperidine, which displayed ganglion-blocking activity in experiments, from 2,2,6,6-tetramethyl-4-carboxymethylpiperidine was reported [6] in the course of this research.

To obtain the lower homolog of this compound – 1,2,2,6,6-pentamethyl-4-(N-morpholinomethyl)piperidine (IX) – we used the scheme of synthesis from 2,2,6,6-tetramethylpiperidine-4-carboxylic acid (V) through its morpholide (VI), 2,2,6,6-tetramethyl-4-(N-morpholinomethyl)piperidine (VII), and its 1-methyl derivative (VIII).



The synthesis of the previously undescribed acid V was accomplished from the accessible triacetoneamine cyanohydrin (I) [7]. Alcoholysis of I made it possible to obtain hydroxy ester II in 80% yield, while dehydration of II under the influence of thionyl chloride gave unsaturated ester III. The yield of the latter was 84.5%, since dehydration of II with the participation of both the proton in the 3 position and the proton in the 5 position of the piperidine ring

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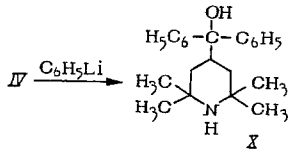
leads to the same compound (III). The catalytic hydrogenation of Δ^3-dehydropiperidine derivative III is accomplished smoothly under mild conditions; this made it possible to pass, in practically quantitative yield, to ethyl 2,2,6,6-tetramethylpiperidine-4-carboxylate (IV).

The synthesis of V is of interest not only for the preparation of IX but is also of independent significance, since this substance may be the starting material for the synthesis of a large number of diverse derivatives of 2,2,6,6-tetramethyl- and 1,2,2,6,6-pentamethyl-substituted piperidines. As an example, one should be referred to our synthesis of (2,2,6,6-tetramethyl-4-piperidyl)-diphenylcarbinol (X), which is the tetramethyl analog of the known ataractic azacyclonol (8-pipradrol, Frenquel). Compound X was obtained in 70% yield by reaction with phenyllithium.



In the course of the subsequent synthesis of IX, acid V, under the influence of thionyl chloride, was converted to the acid chloride, which was converted to morpholide VI in 85% yield by reaction with morpholine under mild conditions. The reduction of VI with lithium aluminum hydride required severe conditions (refluxing for 24 h in benzene–ether) but made it possible to obtain VII in 94.2% yield. Subsequent methylation at a shielded nitrogen atom of the piperidine ring and quaternization by means of methyl iodide did not cause any difficulties. A pharmacological study of IX showed that it not only has lower toxicity but also lower ganglion-blocking activity than its 4-morpholinoethyl homolog.

EXPERIMENTAL

2,2,6,6-Tetramethyl-4-hydroxy-4-carbethoxypiperidine (II). A 10 g sample of I [7] was dissolved in 100 ml of a 10% alcohol solution of hydrogen chloride, and the solution was refluxed while dry hydrogen chloride was bubbled into it for 5 h. The excess alcohol was removed, and the residue was neutralized with excess 50% aqueous potassium carbonate solution and extracted with chloroform to give 10.5 g (80%) of colorless crystals of II with mp 95-96° (from ethyl acetate). The product was quite soluble in alcohol and chloroform but less soluble in ether. Found (%): C 62.58; H 9.95; N 6.31. $C_{12}H_{23}NO_3$. Calculated (%): C 62.84; H 10.01; N 6.18. The hydrochloride was obtained as colorless crystals with mp 208-209°. It was quite soluble in water, alcohol, and chloroform. Found (%): Cl 13.53; N 5.37. $C_{12}H_{22}NO_3 \cdot HCL$. Calculated (%): Cl 13.34; N 5.27.

2,2,6,6-Tetramethyl-4-carbethoxy-Δ^3-dehydropiperidine (III). A mixture of 22.9 g of II and 150 ml of thionyl chloride in 150 ml of dry benzene was heated at 70° for 5 h. The solvent was then removed by vacuum evaporation, and the residue was dissolved in water. The aqueous solution was neutralized with excess 50% aqueous potassium carbonate and extracted with ether. The ether was removed by distillation to give 17.2 g (81.5%) of III as a colorless liquid with bp 100-102° (4 mm). Found (%): C 68.25; H 10.27; N 6.93. $C_{12}H_{21}NO_2$. Calculated (%): C 68.28; H 10.02; N 6.63. The hydrochloride was obtained as colorless crystals with mp 219-220°. It was quite soluble in water, alcohol, and chloroform. Found (%): Cl 14.31; N 5.71. $C_{12}H_{21}NO_2 \cdot HCl$. Calculated (%): Cl 14.31; N 5.66.

2,2,6,6-Tetramethyl-4-carbethoxypiperidine (IV). A 21.1 g sample of III was dissolved in 200 ml of absolute alcohol, after which an alcohol solution of hydrogen chloride was added until the mixture was acidic to Congo Red. It was then hydrogenated in the presence of 1 g of platinum oxide at room temperature and an excess pressure of 20-30 cm (water gage) to give 24.8 g (99%) of the hydrochloride of IV as a colorless powder with mp 181-182°. The product was quite soluble in water and alcohol. Found (%): Cl 14.04; N 5.92. $C_{12}H_{23}NO_2 \cdot HCl$. Calculated (%): Cl 14.19; N 5.61.

Base IV was obtained by alkalization of an aqueous solution of the hydrochloride of IV with 50% aqueous potassium carbonate solution and extraction with ether. The substance was obtained as a colorless liquid with bp 90-91° (4 mm). Found (%): C 67.50; H 10.74; N 6.63. $C_{12}H_{23}NO_2$. Calculated (%): C 67.60; H 10.87; N 6.57.

(2,2,6,6-Tetramethyl-4-piperidyl)diphenylcarbinol (X). A solution of 4 g of IV in 30 ml of absolute ether was added at 0-3° to a solution of phenyllithium (prepared from 0.84 g of lithium and 9.45 g of bromobenzene in 42 ml of ether), and the mixture was stirred at 20° for 6 h, after which it was cooled with ice, and 37 ml of water and concentrated hydrochloric acid were added dropwise until it was acidic to Congo Red. The resulting precipitate of the hydrochloride of X, which was only slightly soluble in water, was removed by filtration, triturated with acetone, and recrystallized from ether–alcohol to give 5.1 g (70%) of the hydrochloride of X as colorless crystals with mp ∿ 305° (dec.). Found (%): C 73.50; H 8.33; Cl 10.09. $C_{22}H_{29}NO \cdot HCl$. Calculated (%): C 73.41; H 8.40; Cl 9.85.

2,2,6,6-Tetramethylpiperidine-4-carboxylic Acid (V). A 20.2 g sample of the hydrochloride of IV was heated on a boiling-water bath with 200 ml of 15% hydrochloric acid for 30 min, after which the solution was vacuum evaporated to dryness, and the residue was triturated with ether and acetone to give 17.8 g (99.4%) of the hydrochloride of V as colorless crystals with mp ∿ 350° (from alcohol). The product was quite soluble in water and alcohol. Found (%): Cl 16.06; N 6.14. $C_{10}H_{19}NO_2 \cdot HCl$. Calculated (%): Cl 15.99; N 6.32.

2,2,6,6-Tetramethylpiperidine-4-carboxylic Acid Morpholide (VI). A mixture of 4 g of hydrochloride of V and 80 ml of thionyl chloride was refluxed and stirred for 4 h, after which it was vacuum evaporated. The residue was treated with 50 ml of chloroform and 20 ml of morpholine, after which it was stirred at 85-90° for another 5 h. The solvent and excess morpholine were removed in vacuo, and the residue was dissolved in a small amount of water. The aqueous solution was neutralized with excess 50% potassium carbonate solution and extracted with chloroform. The chloroform was removed to give 3.7 g (80.5%) of colorless crystals of VI with mp 173-174° (from ethyl acetate). The product was quite soluble in alcohol and chloroform but less soluble in ether. Found (%): C 66.48; H 10.06; N 11.22. $C_{14}H_{26}N_2O_2$. Calculated (%): C 66.10; H 10.30; N 11.02.

2,2,6,6-Tetramethyl-4-(N-morpholinomethyl)piperidine (VII). A 5 g sample of VI was reduced by the action of 1.5 g of lithium aluminum hydride in a mixture of 70 ml of benzene and 20 ml of ether by refluxing the mixture for 24 h. Workup of the mixture gave 4.45 g (94.2%) of colorless crystals with mp 76-77° (from ethyl acetate). The product was quite soluble in the usual organic solvents. Found (%): C 69.68; H 11.81; N 11.70. $C_{14}H_{28}N_2O$. Calculated (%): C 69.94; H 11.74; N 11.65.

1,2,2,6,6-Pentamethyl-4-(N-morpholinomethyl)piperidine (VIII). A mixture of 4.3 g of VII, 3 ml of 26% aqueous formalin, 5.5 ml of formic acid, and 5 ml of water was refluxed on a boiling-water bath for 15 h, after which it was cooled, made alkaline with excess 40% sodium hydroxide solution, and extracted with chloroform. Removal of the chloroform gave 3.76 g (83%) of colorless crystals of VIII with mp 70-71° (from ethyl acetate). The product was quite soluble in the usual organic solvents. Found (%): C 71.08; H 11.89; N 11.36. $C_{15}H_{30}N_2O$. Calculated (%): C 70.81; H 11.88; N 11.01.

Methiodide of VIII (IX). This compound was obtained as colorless crystals with mp 226-227°. It was quite soluble in alcohol and water. Found (%): I 32.36; N 6.76. $C_{16}H_{33}IN_2O$. Calculated (%): I 32.02; N 7.06.

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