SYNTHESIS OF 2,2,6,6-TETRAMETHYLQUINUCLIDINE

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A method was developed for the synthesis of the first representative of the previously unreported quinuclidine derivatives with four geminal substituents in the α-positions with respect to nitrogen, viz., 2,2,6,6-tetramethylquinuclidine, from triacetonamine. Two variants were studied for building up the chain from two CH_2 links in the γ-position of triacetonamine using the Reformatskii and Knoevenagel reactions.

Systematic investigations in recent years have led to the development of accessible methods for the synthesis of numerous quinuclidine derivatives which contain substituents in various positions of this bicyclic system [1]. However, quinuclidine compounds with four geminal substituents in the α-positions relative to nitrogen have not yet been described. Meanwhile, compounds of this type are of considerable interest for biological study. The 2,2,6,6-tetramethylquinuclidine that we synthesized in the form of various salts has considerable ganglion-blocking activity, and its hydrobromide (I), under the name temekhin, has been approved for medical application for hypertonic disease, gastric and duodenal ulcers, bronchial asthma, and for the elimination of spasms of the peripheral vessels [2].

2,2,6,6-Tetramethyl-4-piperidone (triacetonamine) (II) [3, 4] was used as the starting compound for the synthesis of I. The building up of the carbon chain in the γ-position of the piperidine ring by two carbon atoms is necessary for transition from II to the corresponding quinuclidine compound. This was achieved by Reformatskii condensation of II with bromoacetic ester or by Knoevenagel condensation of II with cyanoacetic ester.

The reaction of triacetonamine with ethyl bromoacetate under the conditions of the Reformatskii reaction gives 2,2,6,6-tetramethyl-4-hydroxy-4-(carbethoxymethyl)piperidine (III), which is dehydrated to the corresponding unsaturated ester (IVc) by reaction with thionyl chloride or phosphorus oxychloride. Compound IV in the form of the free acid (IVa) and its methyl ester (IVb) was also obtained from V – the product of the reaction of triacetonamine with cyanoacetic ester. Knoevenagel condensation of II with cyanoacetic ester proceeds readily in the presence of ammonium acetate in refluxing benzene with azeotropic distillation of the water formed and is complete in 1 h.

More prolonged heating in benzene or the use of higher-boiling solvents (toluene and xylene) leads to subsequent processes: N-acetylation of V and rearrangement of the VI formed to unsaturated piperidone VII [5], which lowers the yield of V. Selection of the optimum conditions made it possible to accomplish the synthesis of 2,2,6,6-tetramethyl-4-(carbethoxycyanomethylene)piperidine (V) in 97% yield. The PMR spectrum of the hydrochloride of V (in D_2O with tetramethylsilane as the internal standard) contains two singlets (12 proton units) at 1.80-1.84 ppm from the protons of the four paired equatorial and axial methyl groups in the α- and α'-positions of the piperdine ring, two singlets of two proton units (3.26 and 3.59 ppm) from the protons of the two CH_2 groups in the β- and β'-positions of the piperidine ring (which are shielded differently by the carbethoxycyanomethylene residue), in addition to signals from the protons of the carbethoxy group (triplet at 1.67 ppm and quartet at 4.63 ppm).

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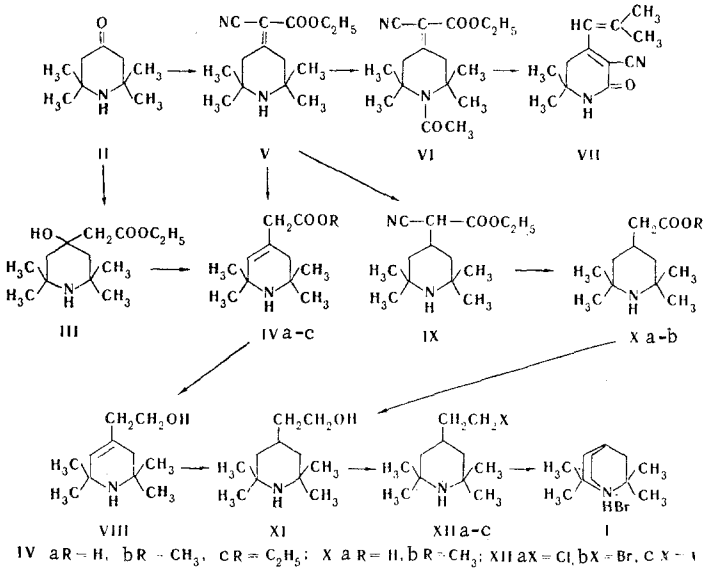

Saponification of V and subsequent partial decarboxylation is accompanied by migration of the double bond to the endocyclic position and results in the formation of (2,2,6,6-tetramethyl-Δ^3-dehydro-4-piperidyl) acetic acid (IVa), which is esterified by methanol with sulfuric acid to ester IVb. The PMR spectrum of ester IVb, obtained in $CDCl_3$ with tetramethylsilane as the internal standard, contains a singlet of two proton units from the methylene group in the β-position of the ring (1.74 ppm), a singlet from the proton on the double bond in the Δ^3-dehydropiperidine ring (5.45 ppm), a singlet of two proton units from the methylene group in the side chain next to the carbomethoxy group (2.82 ppm), in addition to signals from the three protons of the carbomethoxy group (3.55 ppm) and the 12 protons of the four methyl groups in the α- and α'-positions of the ring (0.86-1.2 ppm).

As would be expected, reduction of the exocyclic double bond in V proceeds considerably more readily than reduction of the double bond in the 3,4-position of the tetrahydropyridine ring of ester IVb. While reduction with a platinum catalyst (1% of the weight of the compound) is complete in 3-4 h in the first case, in the hydrogenation of ester IVb increasing the amount of platinum by a factor of 10 makes it possible to complete the process only in 30-40 h. The double bond in the product of the reduction of ester IVb with lithium aluminum hydride, viz., 2,2,6,6-tetramethyl-4-(2-hydroxyethyl)-Δ^3-dehydropiperidine (VIII), is also hydrogenated very slowly. It was not expedient to use palladium or nickel catalysts for the hydrogenation of VIII since the process is inhibited to an even greater degree, while selective reduction of the exocyclic double bond in V is readily achieved even during reduction with palladium on a support (carbon or calcium carbonate) at room temperature and 15-20 atm. Selective reduction could not be achieved with a nickel catalyst: the nitrile group is reduced along with the carbon–carbon double bond.

Subsequent saponification in the product of reduction of V, viz., 2,2,6,6-tetramethyl-4-(carbethoxycyanomethyl)piperidine (IX), of the nitrile and carbethoxy groups with partial decarboxylation of the substituted malonic acid formed, can be accomplished in one step by refluxing it with concentrated hydrochloric acid for 15 h. The high yields in the preparation of V, IX, and Xa make it possible to carry out all of these reactions without isolation of the pure products in the indicated steps and to obtain, after esterification of acid Xa, methyl (2,2,6,6-tetramethyl-4-piperidyl)acetate (Xb) immediately in an overall yield of 48.5%, based on triacetonamine (II). Reduction of ester Xb with lithium aluminum hydride gave a 93% yield of 2,2,6,6-tetramethyl-4-(2-hydroxyethyl)piperidine (XI), which is identical to the product of catalytic hydrogenation of alcohol VIII. This series of reactions accomplishes the building up into the triacetonamine chain of the two CH_2 links necessary for closing the quinuclidine ring. Subsequent transformations reduce to substitution in XI of the hydroxy group by halogen and cyclization of 2,2,6,6-tetramethyl-4-(2-haloethyl)-piperidine (XII) to the corresponding tetramethylquinuclidine (I).

The replacement of the hydroxy group in alcohol XI by chlorine is readily accomplished by heating with thionyl chloride. However, the cyclization of the thus-formed 2,2,6,6-tetramethyl-4-(2-chloroethyl)-piperidine (XIIa) met with difficulty because of the relatively low lability of the chlorine during the alkylation of the nitrogen shielded by the four methyl groups in the α- α'-positions of the piperidine ring. Chlo-

rine is replaced by iodine by heating chloride XIIa with excess sodium idodide in acetone, and the 2,2,6,6-tetramethyl-4-(2-iodoethyl)piperidine (XIIc) formed is partially cyclized even on heating in acetone.

The replacement of the hydroxy group in alcohol XI by bromine is quite fully accomplished by refluxing with 40% hydrobromic acid with simultaneous distillation of the more dilute hydrobromic acid formed during the reaction or by refluxing XI in benzene with phosphorus tribromide. 2,2,6,6-Tetramethyl-4-(2-bromoethyl)piperidine (XIIb) is readily cyclized by refluxing in xylene to form 2,2,6,6-tetramethylquinuclidine hydrobromide.

EXPERIMENTAL

2,2,6,6-Tetramethyl-4-hydroxy-4-(carbethoxymethyl)piperidine (III). Zinc dust [15.1 g (250 mg-atom)] and 45 ml of dry benzene were added to 12 g (77 mmole) of triacetonamine (II) and 45 ml of anhydrous ether, nitrogen was bubbled through the mixture, and 25.2 g (150 mmole) of ethyl bromoacetate was added. After this, several crystals of iodine were added, and the mixture was stirred at 60 deg for 30 min. Then, at intervals of 30 min, two 7.38-g (110 mg-atom) portions of zinc dust and two 10-ml portions of ether–benzene (1:1) were added, the mixture was stirred at 60 deg for 3.5 h, and 17 ml of absolute alcohol was added. The reaction mass was cooled to 5-10 deg, 17 ml of acetic acid was added, the zinc dust was filtered, and the filtrate was acidified with hydrochloric acid. The aqueous layer was separated, and the benzene–ether solution was additionally extracted with hydrochloric acid. The hydrochloric acid solutions were combined, made alkaline with excess 50% potassium carbonate solution, and extracted with dichloroethane to give 13.45 g (71%) of piperidine III as a light-yellow liquid with bp 127-129 deg (8 mm) which was soluble in the usual organic solvents. Found %: C 64.1; H 10.2; N 5.7. $C_{12}H_{25}NO_3$. Calc. %: C 64.2; H 10.4; N 5.8.

Ethyl (2,2,6,6-Tetramethyl-Δ^3-dehydro-4-piperidyl)acetate (IVc). A) Piperidine III [3.72 g (15 mmole)] was dissolved in 15 ml of absolute ether, an ether solution of hydrogen chloride was added until the mixture gave an acid reaction to Congo red, and the ether was removed by vacuum distillation. The residue was dissolved in 40 ml of chloroform, 40 ml of thionyl chloride was added, and the mixture was heated at 45-50 deg (bath temperature) for 10 h. The excess thionyl chloride and chloroform were removed by vacuum distillation, and the residue was dissolved in 20 ml of water. The aqueous solution was made alkaline with excess 50% potassium carbonate solution and extracted with ether to give 2.2 g (63%) of ester IVc as a colorless liquid with bp 92-94 deg (1 mm) which was soluble in the usual organic solvents. Found %: C 69.2; H 10.0; N 6.3. $C_{13}H_{23}NO_2$. Calc. %: C 69.3; H 10.3; N 6.2.

B) Phosphorus oxychloride [2.64 g (17 mmole)] was added to 4.1 g (17 mmole) of III in 10 ml of dry benzene, and the mixture was refluxed for 1.5 h. The reaction mass was cooled and poured into 40 ml of water, and the benzene layer was separated and washed with hydrochloric acid. The combined acid extracts were made alkaline with excess 50% potassium carbonate solution and extracted with ether to give 2.63 g (62%) of ester IVc.

2,2,6,6-Tetramethyl-4-(carbethoxycyanomethylene)piperidine (V). Compound II (31.1 g (200 mmole)] and 22.6 g (200 mmole) of ethyl cyanoacetate were dissolved in 100 ml of benzene, 6.22 g (80 mmole) of ammonium acetate was added, and the mixture was refluxed for 1 h with azeotropic distillation of the water. The reaction mixture was then treated with 50 ml of 50% potassium carbonate solution and extracted with benzene. Drying of the extract and removal of the benzene by distillation gave 50 g (97%) of crude nitrile V. The pure nitrile V was obtained as colorless crystals with mp 57-58 deg (from ethyl acetate) and bp 128-130 deg (1.5 mm). The compound was quite soluble in the usual organic solvents. Found %: C 67.2; H 8.8; N 11.0. $C_{14}H_{22}N_2O_2$. Calc. %: C 67.2; H 8.9; N 11.2. The hydrochloride was obtained as colorless crystals with mp 210-211 deg. Found %: Cl 12.3; N 10.0. $C_{14}H_{22}N_2O_2 \cdot HCl$. Calc. %: Cl 12.3; N 9.8.

Methyl (2,2,6,6-Tetramethyl-Δ^3-dehydro-4-piperidyl)acetate (IVb). A mixture of 50 g of crude nitrile V and 375 ml of hydrochloric acid was refluxed for 15 h. The mixture was vacuum-evaporated with subsequent drying of the residue by azeotropic distillation with benzene. The residual crystalline mass, which is a mixture of the hydrochloride of acid IVa and ammonium chloride, was dissolved in 64 ml of methanol. The solution was cooled to 5-10 deg, 24 ml of sulfuric acid was added dropwise to it with stirring, and the mixture was refluxed for 8 h. The reaction mass was cooled to 25 deg and poured into a mixture of ice and dichloroethane. The mixture was made alkaline with excess 50% potassium carbonate solution and extracted with dichloroethane to give 26.4 g (62% based on triacetonamine) of ester IVb with bp 100-103 deg (9 mm) as a colorless liquid which was soluble in the usual organic solvents. Found %: C 67.8; H 9.9; N 6.7. $C_{12}H_{21}NO_2$. Calc. %: C 68.3; H 10.0; N 6.6.

2,2,6,6-Tetramethyl-4-(2-hydroxyethyl)-Δ^3-dehydropiperidine (VIII). Compound IVc [26.4 g (0.12 mole)] was reduced with 4.72 g (0.12 mole) of lithium aluminum hydride in 265 ml of dry ether. The usual workup gave 19.4 g (90%) of alcohol VIII as colorless crystals with mp 84-84.5 deg (from ethyl acetate) which were quite soluble in the usual organic solvents. Found %: C 72.4; H 11.6; N 7.7. $C_{11}H_{21}NO$. Calc. %: C 72.1; H 11.6; N 7.6. Compound IVb was similarly reduced.

2,2,6,6-Tetramethyl-4-(carbethoxycyanomethyl)piperidine (IX). Platinum oxide (0.15 g) was added to 15 g of crude nitrile V in 90 ml of alcohol, and the nitrile was hydrogenated at room temperature and 20-30 cm (water column). The catalyst was removed by filtration, and the solution was vacuum-evaporated to give 14.5 g (97%) of crude ester IX as a dark-red, viscous liquid. Pure ester IX was obtained as colorless crystals with mp 56-58 deg (from ethyl acetate) and bp 135-140 deg (4 mm). The compound was quite soluble in the usual organic solvents. Found %: C 66.5; H 9.4; N 11.0. $C_{14}H_{24}N_2O_2$. Calc. %: C 66.6; H 9.6; N 11.1. The hydrochloride was obtained as colorless crystals with mp 217-218 deg which were soluble in water and alcohol. Found %: Cl 12.5; N 10.0. $C_{14}H_{24}N_2O_2 \cdot HCl$. Calc. %: 12.4; N 9.7.

Methyl (2,2,6,6-Tetramethyl-4-piperidyl)acetate (Xb). A mixture of 14.5 g of crude ester IX and 110 ml of hydrochloric acid was refluxed for 15 h. The mixture was worked up as described in the synthesis of IVb to give 67 g (48% based on triacetonamine) of ester Xb as a light-yellow liquid with bp 114-116 deg (11 mm). Found %: C 67.7; H 10.5; N 6.6. $C_{12}H_{23}NO_2$. Calc %: C 67.6; H 10.9; N 6.6. The hydrochloride was obtained as colorless crystals with mp 206-207 deg which were soluble in water and alcohol. Found %: Cl 14.5; N 5.9. $C_{12}H_{23}NO_2 \cdot HCl$. Calc. %: Cl 14.2; N 5.6.

2,2,6,6-Tetramethyl-4-(2-hydroxyethyl)piperidine (XI). A) A solution of 19.3 g (105 mmole) of dehydropiperidine VIII in 300 ml of absolute alcohol was acidified with an alcohol solution of hydrogen chloride until it gave an acid reaction to Congo red, 1.93 g of platinum oxide was added, and VIII was hydrogenated at room temperature and 20-30 cm (water column). The catalyst was removed by filtration, and the filtrate was vacuum-evaporated to give 23 g (97%) of the hydrochloride of piperidine XI as colorless crystals with mp 236-238 deg which were quite soluble in alcohol and water and insoluble in ether. Found %: C 59.5; H 10.4; Cl 16.0; N 6.4. $C_{11}H_{22}NO \cdot HCl$. Calc. %: C 59.6; H 10.9; Cl 16.0; N 6.3.

B) Ester Xb [6.7 g (31 mmole)] was reduced with 1.19 g (31 mmole) of lithium aluminum hydride in a mixture of 25 ml of ether and 50 ml of benzene to give 5.38 g (93%) of alcohol XI as colorless crystals with mp 67-68 deg which were quite soluble in the usual organic solvents. Found %: C 71.4; H 12.3; N 7.6. $C_{11}H_{23}NO$. Calc. %: C 71.3; H 12.5; N 7.6.

2,2,6,6-Tetramethyl-4-(2-bromoethyl)piperidine (XIIb). A) A mixture of 20.8 g (93 mmole) of the hydrochloride of XI and 200 ml of 68% hydrobromic acid was heated for 8 h at 60-65 deg (bath temperature). The excess hydrobromic acid was removed by vacuum distillation, 25 ml of water was added to the residue, and the resulting precipitate was filtered to give 22.4 g of yellowish crystals with mp 186-188 deg (a mixture of the hydrochloride and hydrobromide of XIIb). The crystals were mixed with 20 ml of water, and the mixture was made alkaline with excess 50% potassium carbonate solution and extracted with ether to give 10 g (43%) of bromide XIIb as a colorless liquid with bp 118-120 deg (9 mm) which was soluble in the usual organic solvents. Found %: C 53.4; H 9.1; Br 32.2; N 5.8. $C_{11}H_{22}BrN$. Calc. %: C 53.2; H 8.9; Br 32.2; N 5.6.

B) A mixture of 5.38 g (29 mmole) of XI and 20.3 g of 40% hydrobromic acid was heated with stirring. When the temperature in the mass was 110 deg, the dilute hydrobromic acid that formed began to distill. Distillation was continued until the temperature of the reaction mass rose to 127-129 deg, at which time 11-12 ml of acid had distilled. The flask contents were cooled to 70 deg, 5.4 ml of water was added, and the mixture was stirred thoroughly and allowed to crystallize for 8-10 h. The precipitate was removed by filtration and washed with water to give 7.89 g (82%) of the hydrobromide of XIIb in the form of a grayish crystalline substance with mp 194-196 deg. Crystallization from water gave a product which melted at 210-212 deg. Found %: Br 48.9; N 4.5. $C_{11}H_{22}BrN \cdot HBr$. Calc. %: Br 48.7; N 4.3

C) A solution of 5.12 g (19 mmole) of phosphorus tribromide in 16 ml of dry benzene was added to a solution of 5.38 g (29 mmole) of XI in 43 ml of dry benzene at 18-20 deg. The reaction mass was heated at 90-95 deg (bath temperature) for 1.5 h, cooled to 15-20 deg, and poured into ice water. An excess of 50% potassium carbonate solution was added, and the mixture was extracted with benzene to give 5.1 g (71%) of bromide XIIb with bp 118-120 deg (9 mm).

2,2,6,6-Tetramethyl-4-(2-chloroethyl)piperidine (XIIa). Thionyl chloride (60 ml) was added to 6 g of the hydrochloride of XI in 30 ml of dry chloroform, and the mixture was heated at 65-70 deg (bath temperature) for 3 h. The excess thionyl chloride and chloroform were removed by vacuum distillation, and 6 ml of water and excess 50% potassium carbonate solution were added to the residue. The liberated base was extracted with chloroform to give 4.56 g (83%) of chloride XIIa with bp 80-82 deg (7 mm) as a colorless liquid which was quite soluble in organic solvents. Found %: C 64.9; H 10.4; Cl 17.2; N 6.7. $C_{11}H_{22}ClN$. Calc. %: C 64.8; H 10.9; Cl 17.4; N 6.9.

2,2,6,6-Tetramethylquinuclidine (I). A) Bromide XIIb [5.1 g (20.4 mmole)] was dissolved in 40.8 ml of xylene and the solution was refluxed for 6 h. The precipitated crystals were removed by filtration and recrystallized from absolute ethanol or isopropyl alcohol to give 4.15 g (81%) of hydrobromide I as colorless crystals with mp 270-272 deg. Found %: C 52.9; H 8.7; Br 31.9; N 5.6. $C_{11}H_{21}N \cdot HBr$. Calc. %: C 53.2; H 8.9; Br 32.2; N 5.6.

B) The hydrobromide of XII [7.89 g (23.9 mmole)] was mixed with 8 ml of water, treated with excess 40% sodium hydroxide, and extracted with xylene. The xylene extract was dried with calcined magnesium sulfate, decolorized with activated charcoal, and refluxed for 6 h. The precipitated crystals were removed by filtration and recrystallized from absolute ethanol or isopropyl alcohol to give 4.15 g (70%) of hydrobromide I with mp 270-272 deg. The base was liberated from the hydrobromide by the usual method and was a colorless, mobile liquid with bp 92-95 deg (12 mm) which crystallized on prolonged standing in the refrigerator. Found %: C 78.4; H 12.4; N 8.2. $C_{11}H_{21}N$. Calc. %: C 79.0; H 12.6; N 8.4. The hydrochloride was obtained as colorless crystals with mp 239-240 deg. Found %: C 64.6; H 10.7; Cl 17.3; N 7.0. $C_{11}H_{21}N \cdot HCl$. Calc. %: C 64.8; H 10.9; Cl 17.4; N 6.9. The p-toluenesulfonate was obtained as colorless crystals with mp 130-132 deg. Found %: N 4.03; S 9.4. $C_{11}H_{21}N \cdot C_7H_8O_3S$. Calc. %: N 4.1; S 9.4.

2,2,6,6-Tetramethylquinuclidine Hydriodide. Sodium iodide [5 g (33 mmole)] was added to 4.56 g (22 mmole) of chloride XIIb in 60 ml of acetone, and the mixture was refluxed for 30 h. The acetone was removed by distillation, and the residue was treated with excess 50% potassium carbonate solution and extracted with xylene. The xylene extract was dried, decolorized with activated charcoal, and refluxed for 6 h. The precipitated crystals were removed by filtration and recrystallized from ethanol or isopropyl alcohol to give 4.62 g (70%) of 2,2,6,6-tetramethylquinuclidine hydriodide as colorless crystals with mp 270-272 deg. Found %: C 44.3; H 7.3; N 4.6; I 43.1. $C_{11}H_{21}N \cdot HI$. Calc. %: C 44.7; H 7.5; N 4.7; I 43.0.

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