STEREOCHEMISTRY OF BENZO[b]QUINUCLIDINES

IV.* SYNTHESIS AND CONFIGURATION OF SOME 3-MONO- AND 3,3-DISUBSTITUTED 6-METHOXYBENZO[b]QUINUCLIDINES

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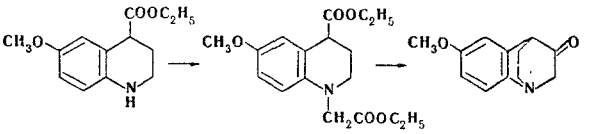
6-Methoxybenzo[b]quinuclidines, their 3-oxo derivatives, and a number of diastereomeric 3-mono- and 3,3-disubstituted derivatives were synthesized. The facile transformation of 3-hydroxy-3-(p-tolyl)-6-methoxybenzo[b]quinuclidine to 3-(p-tolyl)-6-methoxyquinoline was observed.

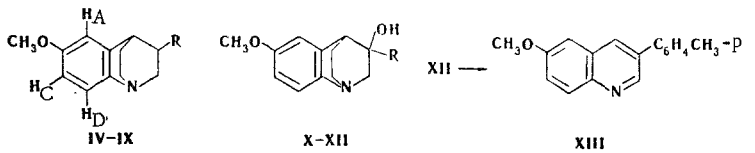
We have previously accomplished the synthesis of and established the configuration of some benzo-[b]quinuclidine derivatives [2, 3]. In the present paper we present data on the synthesis of unknown 6-methoxybenzo[b]quinuclidines and on the establishment of the structure of these compounds.

The starting material for the production of 6-methoxybenzo[b]quinuclidine (IV) was ethyl 1,2,3,4-tetrahydroquininate (I). Ester I was alkylated with ethyl bromoacetate. Intramolecular cyclization of the resulting 1-ethoxycarbonylmethyl-4-ethoxycarbonyl-6-methoxy-1,2,3,4-tetrahydroquinoline (II) under the conditions described in [2] gave 3-oxo-methoxybenzo[b]quinuclidine (III). Reduction of III by the Wolff–Kishner method gave 6-methoxybenzo[b]quinuclidine (IV). This compound, in contrast to the crystalline unsubstituted benzo[b]quinuclidine [6], is a highly mobile liquid. The high pK_a values of both compounds (7.1 and 6.94) constitute evidence for the low inductive effect of the 6-methoxy group on the capacity for protonation of the cyclic nitrogen atom.



I II III

The signals of the protons of the quinuclidine ring in the PMR spectrum of IV practically coincide with the signals of these protons in the unsubstituted benzo[b]quinuclidine [7]. The spectrum of IV is characterized by multiplets at 1.2-2 ppm (β protons) and 2.45-3.30 ppm (α and γ protons). The signals of the protons of the benzene ring are found at weak field: 6.78 (H_A), 6.75 (H_C), 7.08 (H_D); $J_{AC} \approx 2.5$ Hz, $J_{CD} \approx 8$ Hz. The singlet at 3.81 ppm is affiliated with the OCH_3 group.



IV–IX X–XII XIII

IV R=H; V R=OH; VI R=$OCOCH_3$; VII R=NOH; VIII R=NH_2; IX R=Cl; X R=CN; XI R=$COOC_2H_5$; XII R=p-$CH_3C_6H_4$.

*See [1] for communication III.

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Considerably greater stereospecificity than in the reduction under similar conditions of 3-oxobenzo-[b]quinuclidine is observed in the reduction of ketone III both catalytically and by complex metal hydrides. Thus the hydrogenation of III in the presence of platinum leads exclusively to syn-3-hydroxy-6-methoxy-benzo[b]quinuclidine (Vs),* while reduction with complex metal hydrides gives a mixture of diastereomeric alcohols Vs and Va containing 10-15% of the anti isomer. At the same time, the amount of anti-3-hydroxy-benzo[b]quinuclidine obtained from the 3-oxo derivative under similar conditions is 30-35% [2, 7]. The considerably more expressed stereospecificity of the reduction of III can apparently be explained by the additional orienting effect of the methoxy group due to the formation of a complex between the unshared pair of electrons of the 6 substituent and the catalyst or the metal hydrides.

In contrast to the reduction of III, the stereospecificity of the cyanohydrin synthesis and the Grignard reaction practically coincides with what is observed for 3-oxobenzo[b]quinuclidine [1, 3]. A mixture of diastereomeric 3-hydroxy-3-cyano-6-methoxybenzo[b]quinuclidines (Xs and Xa) in a ratio of ~3:2 is obtained in the reaction of the hydrochloride of ketone III with potassium cyanide (the reaction of ketone III with acetone cyanohydrin did not occur, apparently because of the low solubility of III in water). Both a steric factor – nucleophilic attack of the CN group from the least shielded side of the molecule – and a thermodynamic factor – predominance in the equilibrium reaction of the cyanohydrin synthesis of the isomer with a lower free energy – favor the predominant formation of the syn isomer in this case.

Diastereomeric 3-hydroxy-3-ethoxycarbonyl-6-methoxybenzo[b]quinuclidines (XIs and XIa) were obtained in the alcoholysis of a mixture of Xs and Xa. Crystallization of this mixture gave the individual syn-hydroxy ester (XIs) and a mixture of isomers enriched in XIa (75%).

As in the case of 3-oxobenzo[b]quinuclidine, the highest stereospecificity occurs in the reaction of III with p-tolyllithium [1], and only anti-3-hydroxy-3-(p-tolyl)-6-methoxybenzo[b]quinuclidine (XIIa) is formed. Such high stereospecificity in this case is probably associated with the formation of an unstable donor–acceptor complex of RLi with the methoxyphenyl portion of the III molecule, which hinders approach of the reagent to the reaction center from the phenyl ring side, as a consequence of which RLi interacts with the carbonyl group on the bridge fragment side of the molecule; this leads to anti isomer XIIa. Two singlets at 1.90 and 2.17 ppm are observed in the PMR spectrum of a mixture of VIs and VIa in the region of the signals of the protons of the acetyl groups. In conformity with the previously obtained data on the stereochemistry of benzo[b]quinuclidine derivatives [1, 7], the singlet at stronger field pertains to the isomer with a syn orientation of the substituent. Consequently, individual isomer VI, which has the signal of an $OCOCH_3$ group at 1.90 ppm, is the syn isomer of VI, and alcohol V, from which VIs is obtained, also has the syn configuration. The mixture of VIS and VIa that was richest in the anti isomer contained 35% VIs and 65% VIa.

Two singlets at 3.68 and 3.70 ppm with an intensity ratio of 3:2 are observed in the PMR spectrum of a mixture of cyanohydrins Xs and Xa. Alcoholysis of a mixture of Xs and Xa gave diastereomeric hydroxy esters XIs and XIa, the PMR spectrum of which is characterized by two singlets of the protons of the OCH_3 group at 3.77 and 3.78 ppm and two sets of signals of an ethyl group: triplets at 0.97 and 1.35 ppm, and quartets at 3.96 and 4.32 ppm. On the basis of a comparison of the intensities of the signals of the ethyl group at weak (anti orientation) and strong (syn orientation) fields [7], it was concluded that XIs: XIa ≈ 45:55. The chemical shifts of the protons of the ethyl group of $COOC_2H_5$ in the spectrum of the individual isomer attested to its syn configuration.

Only two singlets, which belong to the OCH_3 group (3.85 ppm) and the methyl part of the tolyl group (2.40 ppm), are observed in the PMR spectrum of XII. Consequently, the spectrum of XII corresponds to one isomer. The spectra of the protons of the quinuclidine rings in XII and in the previously studied 3-hydroxy-3-(p-tolyl)benzo[b]quinuclidine, for which anti orientation of the tolyl substituent was proved [1], practically coincide. The configuration of XII therefore corresponds to anti orientation of the tolyl group relative to the benzene ring.

In addition to the compounds described above, we also synthesized other 3-substituted 6-methoxy-benzo[b]quinuclidines: 3-amino-6-methoxybenzo[b]quinuclidine (VIIIs) – by reduction of the oxime of 3-oxo-6-methoxybenzo[b]quinuclidine (VII) – and 3-chloro-6-methoxybenzo[b]quinuclidine (IX) – by reaction of Vs with thionyl chloride. It was observed that the chlorine atom in IX is distinguished by its highly inert character. It cannot be completely replaced by an ethoxy group even on heating to 150° with a strong

*The letter s (or a) after the compound number indicates syn (or anti) orientation of substituent R relative to the benzene ring of benzo[b]quinuclidine.

nucleophilic agent such as sodium ethoxide, whereas it is known that the chlorine atom in 3-chloroquinuclidine is distinguished by its high lability: this compound readily forms a polyquaternary salt even at room temperature.

As in the case of other 3-aryl-3-hydroxybenzo[b]quinuclidines [1], XIIa readily undergoes aromatization on heating with acetic anhydride: the dehydration of XIIa is accompanied by ejection of the ethylene bridge from the quinuclidine portion of the molecule to give 3-(p-tolyl)-6-methoxyquinoline (XIII).

The structure of XIII was confirmed by the PMR spectrum, which contains signals of only the aromatic protons and the methyl groups of the substituents at 8.87 (2-H), 7.95 (4-H), 6.90 (5-H), 3.84 (OCH_3), 7.22 (7-H), 7.90 (8-H), 7.17 and 7.46 (C_6H_4), and 2.40 ppm (p-CH_3); $J_{24} \approx 2.4$, $J_{57} \approx 2.8$, $J_{78} \approx 8.8$ Hz. The low chemical shifts and spin–spin coupling constants for the protons in XIII, the previously studied quinoline derivatives [1], and unsubstituted quinoline [8] confirm structure XIII.

EXPERIMENTAL

The PMR spectra were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. The solvents were $CDCl_3$ (IV, XI, and XII), CCl_4 (XIII), CD_3OD (VI·HCl), and C_5D_5N (X). Tetramethylsilane was used as the internal standard.

Ethyl 1,2,3,4-Tetrahydroquininate (I). A. A 9.1-g (45 mmole) sample of quininic acid [4] was added to a solution of 1.77 g (45 mmole) of sodium hydroxide in 100 ml of water, and the resulting sodium salt was hydrogenated [4] in the presence of 5 g of Raney nickel at 60° and an initial hydrogen pressure of 100 atm. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the reaction mixture was acidified with HCl (with respect to Congo red). The mixture was then evaporated, and the residue was dried and esterified by heating with 75 ml of ethanol and 12 ml of concentrated H_2SO_4. The alcohol was removed by vacuum distillation, and the residue was cooled, treated with sodium carbonate, and extracted with benzene to give 8.2 g (78%) of a product with bp 162-163° (0.8 mm). Found: C 66.4; H 7.5; N 6.1%. $C_{13}H_{17}NO_3$. Calculated: C 66.4; H 7.3; N 6.0%.

B. A 30-g (113 mmole) sample of ethyl 2-chloroquininate [4, 5] and 10 g of Raney nickel were added to a solution of 9.07 g (226 mmole) of sodium hydroxide in 200 ml of water, after which the mixture was hydrogenated at 40° and an initial hydrogen pressure of 70 atm. Workup as described in part A gave 22 g (83%) of ester I.

1-Ethoxycarbonylmethyl-4-ethoxycarbonyl-6-methoxy-1,2,3,4-tetrahydroquinoline (II). A mixture of 60 g (255 mmole) of ester I, 42.6 g (255 mmole) of ethyl bromoacetate, 27 g (255 mmole) of sodium carbonate, and 240 ml of anhydrous ethanol was refluxed for 5 h with vigorous stirring. The alcohol was then removed by vacuum distillation, and the residue was dissolved in 100 ml of water and extracted with ether to give 76.3 g (93.5%) of a product with bp 183-185° (3 mm). Found: C 63.7; H 7.3; N 4.3%. $C_{17}H_{23}NO_5$. Calculated: C 63.5; H 7.2; N 4.3%.

3-Oxo-6-methoxybenzo[b]quinuclidine (III). A solution of 53.2 g (165 mmole) of diester II in 120 ml of toluene was added with stirring to a refluxing solution of potassium ethoxide, obtained from 15.9 g (408 mg-atom) of potassium and 23.5 ml (408 mmole) of anhydrous ethanol in 240 ml of toluene, after which the mixture was refluxed for another 6 h. It was then cooled to 50-60° and treated with 180 ml of concentrated HCl. The acid solution was separated, and the toluene layer was extracted twice with 180-ml portions of hydrochloric acid. The combined acid solutions were refluxed for 6 h and evaporated. The residue was cooled and treated with 50% KOH, after which it was extracted with benzene. The benzene was removed, and the residue was vacuum-sublimed at 125-130° (3 mm) to give 25 g (74.4%) of a product with mp 82-84° (from hexane). Found: C 71.1; H 6.5; N 7.1%. $C_{12}H_{13}NO_2$. Calculated: C 70.9; H 6.4; N 6.9%. The hydrochloride had mp 210-211° (dec.). Found: Cl 14.7; N 6.0%. $C_{12}H_{13}NO_2 \cdot HCl$. Calculated: Cl 14.8; N 5.8%.

Reduction of 3-Oxo-6-methoxybenzo[b]quinuclidine (III). A. A mixture of 4.88 g (24 mmole) of ketone III and 0.3 g of platinum oxide in 100 ml of ethanol was shaken in a stream of hydrogen. The necessary amount of hydrogen was absorbed in 2 h. The mixture was then heated to the boiling point, and the platinum was removed by filtration. The filtrate was cooled, and the resulting crystals were removed by filtration and washed with ethanol to give 3 g of Vs. Evaporation of the alcohol solution gave another 1.2 g of Vs to give an overall yield of 4.2 g (86%) of a product with mp 187-189°. Found: C 70.2; H 7.3; N 6.7%. $C_{12}H_{15}NO_2$. Calculated: C 70.2; H 7.4; N 6.8%. The hydrochloride had mp 213-215°. Found: Cl 14.4; N 5.8%. $C_{12}H_{15}NO_2 \cdot HCl$. Calculated: Cl 14.7; N 5.8%.

B. A solution of 3 g (14.8 mmole) of III in 30 ml of ether was added to a suspension of 1 g (26 mmole) of lithium aluminum hydride in 50 ml of ether, and the mixture was refluxed for 3 h. It was then cooled and treated with 2 ml of water. The aqueous mixture was extracted with ether and chloroform. The chloroform solution yielded 2 g (66%) of Vs, while the ether solution yielded 0.6 g of a mixture of Vs and Va. Recrystallization of 0.6 g of the mixture from acetone gave 0.3 g of a mixture of isomers enriched in the syn form. The acetone solution gave 0.25 g of a mixture containing 35% Vs and 65% Va with mp 138-140°. Found: C 70.4; H 7.4; N 7.0%. $C_{12}H_{15}NO_2$. Calculated: C 70.2; H 7.4; N 6.8%.

C. A 6-g (158 mmole) sample of sodium borohydride was added in the course of 2 h to a solution of 6.1 g (30 mmole) of III in 70 ml of methanol, after which the mixture was refluxed for 5 h and then evaporated. The residue was treated with 25% K_2CO_3 and extracted with ether and chloroform. The overall yield of alcohols Vs and Va was 5.2 g (86.5%). Treatment of this mixture by the method described in part B gave 1.2 g of a mixture containing 65% Va and 3.2 g of Vs.

6-Methoxybenzo[b]quinuclidine (IV). A mixture of 3.04 g (15 mmole) of III, 6 ml of hydrazine hydrate, 6 g of potassium hydroxide, and 30 ml of anhydrous glycerol was heated at 165-170° for 7 h. The products were removed by steam distillation as the bath temperature was raised from 170 to 265°. The distillate was extracted with ether to give 0.8 g (28.6%) of a light-yellow mobile liquid with a sharp amine odor and bp 98-100° (0.7 mm). Found: N 7.4%. $C_{12}H_{15}NO$. Calculated: N 7.4%. The picrate had mp 193-195°. Found: C 51.4; H 4.2; N 13.6%. $C_{12}H_{15}NO \cdot C_6H_3N_3O_7$. Calculated: C 51.7; H 4.3; N 13.4%.

syn-3-Acetoxy-6-methoxybenzo[b]quinuclidine (VIs). A mixture of 2.05 g (10 mmole) of Vs and 10 ml of acetic anhydride was heated at 100° for 4 h, after which the solution was vacuum-evaporated, and the residue was treated with potassium carbonate and extracted with ether to give 2.35 g (96%) of a product with bp 142-144° (0.6 mm). Found: C 68.3; H 7.0%. $C_{14}H_{17}NO_3$. Calculated: C 68.0; H 6.9%. The hydrochloride had mp 245-246°. Found: Cl 12.4; N 5.1%. $C_{14}H_{17}NO_3 \cdot HCl$. Calculated: Cl 12.5; N 5.0%.

3-Oxo-6-methoxybenzo[b]quinuclidine Oxime (VII). A mixture of 5 g (245 mmole) of III, 1.7 g (245 mmole) of hydroxylamine hydrochloride, and 100 ml of ethanol was refluxed for 14 h, after which the precipitate was removed by filtration and washed with ethanol to give 5.8 g (92%) of the hydrochloride of VII with mp 201-202°. Found: C 56.8; H 5.7; Cl 14.0; N 11.0%. $C_{12}H_{14}N_2O_2 \cdot HCl$. Calculated: C 56.5; H 5.9; Cl 13.9; N 11.0%.

3-Amino-6-methoxybenzo[b]quinuclidine (VIII). A solution of 10 g (40 mmole) of the hydrochloride of VII in 300 ml of methanol was reduced in the presence of 0.3 g of platinum oxide. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, the solution was acidified with HCl (with respect to Congo red), and vacuum-evaporated. The residue was triturated with acetone to give 8.1 g (74.2%) of the dihydrochloride of VIII with mp 184-186° (dec., from ethanol). Found: C 51.8; H 6.5; Cl 25.0; N 10.1%. $C_{12}H_{16}N_2O \cdot 2HCl$. Calculated: C 52.0; H 6.5; Cl 25.6; N 10.1%.

3-Chloro-6-methoxybenzo[b]quinuclidine (IX). A mixture of 3 g (14.6 mmole) of Vs and 30 ml of thionyl chloride was refluxed for 25 h, after which the solution was vacuum-evaporated, and the residue was dissolved in water. The aqueous solution was made alkaline with potassium carbonate and extracted with benzene to give 2.27 g (70%) of a product with bp 125-127° (0.6 mm). Found: C 64.6; H 6.4; Cl 15.4; N 6.3%. $C_{12}H_{14}ClNO$. Calculated: C 64.3; H 6.3; Cl 15.8; N 6.3%.

3-Hydroxy-3-cyano-6-methoxybenzo[b]quinuclidines (Xs and Xa). A solution of 1.4 g (21.5 mmole) of potassium cyanide in 5 ml of water was added dropwise to a cooled (0°) solution of 4.4 g (18.3 mmole) of the hydrochloride of III in 30 ml of water, after which the mixture was stirred and cooled for 4 h. The precipitate was removed by filtration and washed with water to give 4.2 g (quantitative yield) of a product with mp 145-147° (from ethyl acetate). Found: C 67.8; H 5.8; N 12.4%. $C_{13}H_{14}N_2O_2$. Calculated: C 67.8; H 6.1; N 12.1%.

3-Hydroxy-3-ethoxycarbonyl-6-methoxybenzo[b]quinuclidines (XIs and XIa). Dry hydrogen chloride was passed for 5 h into a stirred refluxing solution of 3.9 g (17 mmole) of a mixture of Xs and Xa in 60 ml of ethanol. The alcohol was then removed by vacuum distillation, and the residue was dissolved in water. The aqueous solution was made alkaline with potassium carbonate and extracted with chloroform. The chloroform solution was dried with magnesium sulfate, the chloroform was removed by distillation, and the residue was dissolved in 10 ml of ether. The ether solution was cooled at +4° for 20 h to precipitate 2.8 g (59.5%) of a mixture of XIs and XIa, which was recrystallized from acetone to give 0.7 g of XIs with mp 142-144°. Found: C 65.2; H 6.8; N 4.7%. $C_{15}H_{19}NO_4$. Calculated: C 65.0; H 6.9; N 5.0%.

The acetone mother liquor yielded 1.55 g of a mixture of XIs and XIa containing 70% of the anti isomer of XIa.

3-Hydroxy-3-(p-tolyl)-6-methoxybenzo[b]quinuclidine (XII). A solution of 5 g (24.3 mmole) of III in 120 ml of ether was added at 2-5° to a solution of p-tolyllithium [from 6.3 g (35.8 mmole) of p-bromotoluene and 0.52 g (73.5 mg-atom) of lithium] in 80 ml of ether. The mixture was refluxed for 6 h, after which it was cooled and treated with 30 ml of water. The precipitate was removed by filtration and washed with water to give 3.7 g (51%) of a product with mp 191-192° (from ethanol). Found: C 77.3; H 7.2; H 4.8%. $C_{19}H_{21}NO_2$. Calculated: C 77.3; H 7.2; N 4.7%.

Reaction of 3-Hydroxy-3-(p-tolyl)-6-methoxybenzo[b]quinuclidine (XII) with Acetic Anhydride. A mixture of 1 g (3.4 mmole) of XII and 10 ml of acetic anhydride was refluxed for 7 h, after which the solution was vacuum-evaporated, and the residue was recrystallized from acetone to give 0.5 g (60%) of 3-(p-tolyl)-6-methoxyquinoline (XIII) with mp 97-99°. Found: C 82.3; H 6.2; N 5.7%. $C_{17}H_{15}NO$. Calculated: C 81.9; H 6.1; N 5.6%.

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