SYNTHESIS OF 6,7-DIMETHOXYBENZO[b]QUINUCLIDINE

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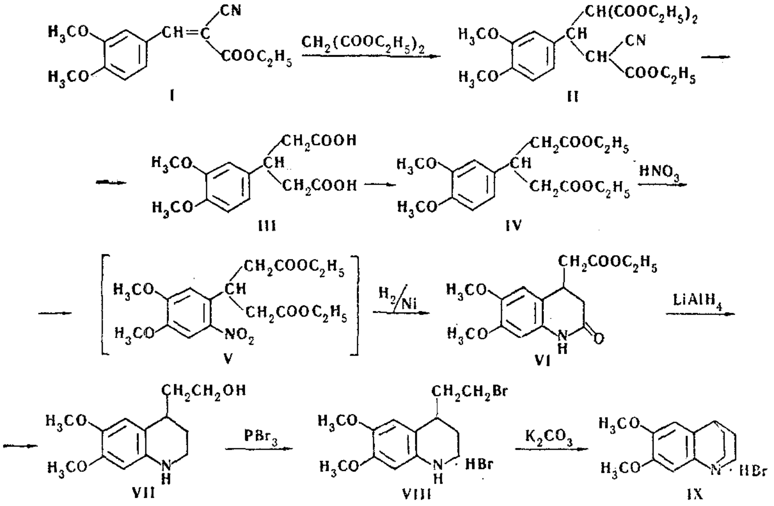
6,7-Dimethoxybenzo[b]quinuclidine was synthesized from ethyl veratrylidenecyanoacetate.

We have previously described the preparation and several reactions of benzo[b]quinuclidine [1,2]. In continuing the investigations in this field, we synthesized the unknown 6,7-dimethoxybenzo[b]quinuclidine. This compound was obtained via the following scheme:



Ethyl veratrylidenecyanoacetate (I) was converted to diethyl α-ethoxycarbonyl-β-(3,4-dimethoxyphenyl)-γ-cyanoglutarate (II) by reaction with the sodium salt of diethyl malonate (Michael condensation). β-(3,4-Dimethoxyphenyl)glutaric acid (III) was formed by refluxing II with a mixture of hydrochloric and acetic acids. Its diethyl ester (IV) was nitrated; the diethyl β-(3,4-dimethoxy-6-nitrophenyl)glutarate (V) obtained in the process was not isolated in the pure state but was subjected directly to reductive cyclization. The resulting 2-oxo-4-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (VI) was reduced with lithium aluminum hydride to 4-(2-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (VII), and the hydroxyl group in VII was replaced by bromine using phosphorus tribromide. A base, which was converted to 6,7-dimethoxybenzo[b]quinuclidine hydrobromide (IX), was isolated from 4-(2-bromoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline hydrobromide (VIII).

The structure of the synthesized tricyclic IX was confirmed by the PMR spectrum. The spectrum of IX contains two singlets at δ 7.08 and 7.15 ppm, which are affiliated with the two protons of the benzene ring in the para position relative to one another. Two singlets of methoxy groups lie at stronger field at 3.83 and 3.86 ppm. The signals of the protons of the quinuclidine ring form five multiplets. The syn-3-H and syn-10-H signals (with respect to the benzene ring) are situated at strongest field at 1.83 ppm, and the signals of the anti protons attached to these carbon atoms are found at 2.2 ppm. The signals of the syn-2-H and syn-9-H protons (3.15 ppm), anti-2-H and anti-9-H protons (3.70 ppm), and 4-H proton (3.45 ppm) are

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shifted to weaker field. The absence of signals at 4.5-7 ppm characteristic for olefin protons makes it possible to exclude the 4-vinyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline structure.

EXPERIMENTAL

Diethyl α-Ethoxycarbonyl-β-(3,4-dimethoxyphenyl)-γ-cyanoglutarate (II). Diethyl malonate [16 g (0.1 mole)] and 26 g (0.1 mole) of ethyl veratrylidenecyanoacetate (I) [3] were added to sodium ethoxide [obtained from 2.3 g (0.1 g-atom) of sodium and 50 ml of ethanol]. The reaction mass was heated at 60-65° for 2 h and poured over ice. The mixture was acidified with hydrochloric acid, and the reaction products were extracted with chloroform. The solvent was removed by distillation, and the residue was triturated with ethyl acetate and filtered to give 6 g of starting I. The filtrate was evaporated to give 24 g (74%) of ester II and a colorless, viscous liquid with bp 204-210° (0.4 mm). Found: C 59.9; H 6.3%. $C_{21}H_{26}NO_8$. Calculated: C 60.0; H 6.2%.

β-(3,4)-Dimethoxyphenyl)glutaric Acid (III). A mixture of 24 g (0.057 mole) of ester II, 200 ml of acetic acid, and 100 ml of hydrochloric acid was refluxed for 16 h. The reaction mass was decolorized with charcoal and evaporated in vacuo. The residue was recrystallized from 200 ml of water to give 10 g (61%) of acid III as colorless crystals with mp 173-175°. Found: C 57.7; H 6.3%. $C_{13}H_{16}O_6$. Calculated: C 58.2; H 6.0%.

Diethyl β-(3,4-Dimethoxyphenyl)glutarate (IV). A mixture of 10 g (0.036 mole) of acid III, 100 ml of ethanol, and 10 ml of concentrated sulfuric acid was refluxed for 4 h. The mixture was cooled and poured over ice, and the reaction products were extracted with benzene to give 8.5 g (70%) of ester IV as a colorless liquid with bp 165-167° (0.4 mm). Found: C 63.1; H 7.4%. $C_{17}H_{24}O_6$. Calculated: C 62.9; H 7.5%.

2-Oxo-4-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (VI). Fuming nitric acid (13.4 ml) was added in the course of 15 min at 0° to a solution of 8 g (0.025 mole) of ester IV in 25 ml of glacial acetic acid. The reaction mass was poured over ice and extracted with chloroform. The chloroform extract was washed with water, sodium bicarbonate solution, and water, and dried with magnesium sulfate. The chloroform was removed by vacuum distillation, and the residue was dissolved in 100 ml of ethanol and reduced in the presence of 7 g of a nickel catalyst. After the required amount of hydrogen had been absorbed, the catalyst was removed by filtration, the alcohol was removed by vacuum distillation, and the residue was triturated with ethyl acetate to give 2 g (34%) of VI as colorless crystals with mp 122-124°. Found: C 61.3; H 6.6; N 5.7%. $C_{15}H_{19}NO_5$. Calculated: C 61.4; H 6.5; N 5.8%.

4-(2-Hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (VII). Lithium aluminum hydride [2 g (0.052 mole)] was added to a solution of 1.6 g (57 mmole) of ester VI in 20 ml of anhydrous ether in 30 ml of anhydrous benzene, and the mixture was refluxed with stirring for 25 h. The mixture was cooled, and 4 ml of water was added. The resulting mixture was filtered, the hydroxide was washed with benzene, and the ether–benzene solution was vacuum-evaporated to give 0.8 g (58%) of VII as a colorless liquid with bp 180-184° (0.6 mm). Found: C 65.9; H 8.0; N 6.2%. $C_{13}H_{19}NO_3$. Calculated: C 65.8; H 8.0; N 5.9%.

4-(2-Bromoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline Hydrobromide (VIII). Phosphorus tribromide [0.91 g (34 mmole)] was added in the course of 10 min at 0° to a solution of 0.8 g (34 mmole) of alcohol VII in 20 ml of dry chloroform. The reaction mass was allowed to stand at room temperature for 24 h and was then vacuum-evaporated. The residue was triturated with ethanol–ether to give 0.6 g (45%) of hydrobromide VIII as colorless crystals with mp 161-162°. Found: Br 39.9%. $C_{13}H_{18}BrNO_2 \cdot HBr \cdot H_2O$. Calculated: Br 40.4%.

6,7-Dimethoxybenzo[b]quinuclidine (IX). A solution of 0.5 g (13 mmole) of bromo derivative VIII in 10 ml of water was treated with 10 ml of 50% potassium carbonate solution, and the base of the bromide was extracted with xylene. The xylene solution was shaken with calcined potassium carbonate, filtered, and refluxed for 5 h. Crystals of hydrobromide IX precipitated during the reflux period and, after cooling of the mass, were removed by filtration to give 0.27 g (68%) of colorless crystals with mp 234-235° (from ethanol). Found: C 51.9; H 5.7; Br 26.4; N 4.6%. $C_{13}H_{17}NO_2 \cdot HBr$. Calculated: C 52.0; H 6.0; Br 26.6; N 4.7%. Base IX was isolated from the hydrobromide by the usual method to give colorless crystals with mp 98-101° (from hexane). Found: C 71.2; H 8.0; N 6.2%. $C_{13}H_{17}NO_2$. Calculated: C 71.2; H 7.8; N 6.4%. The picrate was obtained as yellow crystals with mp 227-228°. The methiodide was obtained as colorless crystals with mp 245-246°. Found: I 35.6; N 3.5%. $C_{14}H_{20}INO_2$. Calculated: I 35.1; N 3.9%.

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