SYNTHESIS OF 5,6-BENZO-1,2-DIAZABICYCLO[2.2.2]OCTANE

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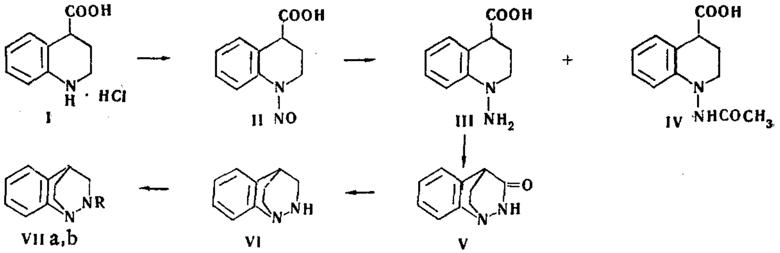
5,6-Benzo-1,2-diazabicyclo[2.2.2]octane was synthesized by nitrosation of 1,2,3,4-tetrahydrocinchoninic acid, reduction of the 1-nitroso derivative to 1-amino-1,2,3,4-tetrahydrocinchoninic acid, cyclodehydration of it to 3-oxo-5,6-benzo-1,2-diazabycyclo[2.2.2]octane, and reduction of the oxo group to a methylene group with lithium aluminum hydride.

We have previously described [1-3] a method for obtaining a number of 1,2-diazabicycloalkanes. The proposed scheme for the synthesis of this class of compounds has been extended to the preparation of the previously unreported condensed systems including a benzene ring in addition to a 1,2-diazabicycloalkane. In particular, we have synthesized 5,6-benzo-1,2-diazabicyclo[2.2.2]octane starting from 1,2,3,4-tetrahydrocinchoninic acid (I). Nitrosation of I gave 1-nitroso-1,2,3,4-tetrahydrocinchoninic acid (II), which was subsequently reduced with zinc in a mixture of aqueous ethanol or methanol and acetic acid to 1-amino-1,2,3,4-tetrahydrocinchoninic acid (III). An appreciable quantity of 1-acetamido-1,2,3,4-tetrahydrocinchoninic acid (IV) was also formed along with III.



VII a $R = CH_3$; b $R = COC_6H_5$

The mixture of products obtained in the previous step from II was heated in vacuo (10-20 mm) at 260-270°C. Under these conditions, only amino acid III undergoes intermolecular cyclodehydration to form 3-oxo-5,6-benzo-1,2-diazabicyclo[2.2.2]octane (V); IV remains unchanged. Cyclic hydrazide V was then reduced with lithium aluminum hydride to 5,6-benzo-1,2-diazabicyclo[2.2.2]octane (VI), from which 2-methyl and 2-benzoyl derivatives (VIIa, b) were obtained. Compound VI forms a monohydrochloride, which is characteristic for both hydrazine derivatives and 1,2-diazabicycloalkanes [3]. This property was noted for VIIa, for which a monohydrochloride and a monomethiodide were obtained. Protonation of the hydrochlorides and addition of a methyl group to the quaternary salt apparently proceeds via the most shielded angular nitrogen atom, as is the case for 2-methyl-1,2-diazabicyclo[2.2.2]octane derivatives [2].

The 1-acetamido-1,2,3,4-tetrahydrocinchoninic acid (IV) isolated as a side product was converted to ethyl 1-amino-1,2,3,4-tetrahydrocinchoninate (VIII) by heating with an ethanol solution of hydrogen chloride.

Ester VIII displayed high thermal stability on heating in biphenyl up to 220° and also on distillation in vacuo at 243-245° (85 mm). Compound VIII was also stable under conditions of alkaline hydrolysis. Acid III was isolated from sodium 1-amino-1,2,3,4-tetrahydrocinchoninate, obtained in the process by the action

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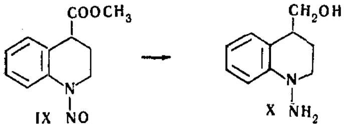
of an equimolecular amount of hydrochloric acid. Compounds III, IV, and VIII, as well as 1-amino-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline (X), obtained by reduction of methyl 1-nitroso-1,2,3,4-tetrahydrocinchoninate (IX) with lithium aluminum hydride, displayed high lability under the influence of a number of acidic reagents.



Thus IV and VIII, on heating with 17% hydrochloric acid, and III and X, on treatment with thionyl chloride, undergo pronounced resinification, which is apparently associated with the instability of the 3,4-dihydroquinoline derivatives formed during cleavage of the 1-amino group in the form of ammonium chloride. The ease in the elimination of the 1-amino group, probably due to the inductive effect of the benzene ring, was noted on heating X with a Raney nickel catalyst in aqueous ethanol. 1,2,3,4-Tetrahydroquinoline forms under these conditions, apparently due to cleavage of formaldehyde and ammonia with subsequent reduction of the dihydro derivative to 1,2,3,4-tetrahydroquinoline.

EXPERIMENTAL

1-Nitroso-1,2,3,4-tetrahydrocinchoninic Acid (II). A solution of 7.35 g (107 mmole) of sodium nitrite in 20 ml of water was added with stirring in the course of 30 min to a solution of 18.9 g (89 mmole) of 1,2,3,4-tetrahydrocinchoninic acid hydrochloride (I) in 35 ml of water. The mixture was stirred for another 30 min, and the precipitate was filtered and washed with water to give 18 g (98.5%) of II. The product was obtained in the form of colorless crystals which were quite soluble in the lower alcohols, acetone, chloroform, and insoluble in water, and had mp 124-125° (decomp., from 50% ethanol). Found %: C 58.03; H 4.86; N 13.48. $C_{10}H_{10}N_2O_3$. Calculated %: C 58.24; H 4.88; N 13.58.

Methyl 1-Nitroso-1,2,3,4-tetrahydrocinchoninate (IX). A solution of 3.6 g (52 mmole) of sodium nitrite in 15 ml of water was added in the course of 10 min to a solution of 10 g (52 mmole) of methyl 1,2,3,4-tetrahydrocinchoninate in 58 ml (58 mmole) of 1 N hydrochloric acid. The mixture was stirred for 10 min, and the oily substance which separated was extracted with chloroform. The chloroform solution was dried with magnesium sulfate, and the chloroform was removed in vacuo to give 10.5 g (91.2%) of IX. Found %: C 59.73; H 5.87; N 12.53. $C_{11}H_{12}N_2O_3$. Calculated %: C 60.00; H 5.49; N 12.72.

3-Oxo-5,6-benzo-1,2-diazabicyclo[2.2.2]octane (V). Glacial acetic acid (64 ml) was added in the course of 1.5 h at 25-30° to a suspension of 10 g (51 mmole) of II and 28 g (435 mmole) of zinc dust in 70 ml of methanol and 8 ml of water. The mixture was stirred at the same temperature for another 3 h and filtered. The residue was washed with 20 ml of water, and the mother liquors were evaporated in vacuo. The residue was heated in vacuo (10-20 mm) at 190-200, 220-230, and 265-270°, each for 30 min. The cooled mass was dissolved in 50 ml of water, 50 ml of 50% potassium carbonate was added, and the mixture was extracted with chloroform. The chloroform solution was evaporated, and the residue was triturated with ether to give 1.1 g (13%) of V with mp 186-188° (from ethyl acetate) in the form of light-yellow crystals, which were quite soluble in chloroform and alcohol, but slightly soluble in water and ethyl acetate, and insoluble in ether. Found %: C 68.65; H 5.88; N 16.02. $C_{10}H_{10}N_2O$. Calculated %: C 68.95; H 5.78; N 16.07.

The alkaline mother liquor, after removal of V, was acidified with concentrated hydrochloric acid with Congo red as the indicator. The resulting crystalline precipitate was removed after 24 h, washed with water, and recrystallized from aqueous alcohol to give 2.75 g (24.2%) of 1-acetamido-1,2,3,4-tetrahydrocinchoninic acid (IV). The colorless crystals were moderately soluble in methanol and ethanol, slightly soluble in water, and insoluble in ethyl acetate and ether, and had mp 204-206° (decomp.). Found %: C 61.46; H 6.12; N 11.98. $C_{12}H_{14}N_2O_3$. Calculated %: C 61.53; H 6.02; N 11.95.

5,6-Benzo-1,2-diazabicyclo[2.2.2]octane (VI). Cyclic hydrazide V [2.8 g (16 mmole)] was sprinkled in the course of 20 min into a suspension of 1.22 g (32 mmole) of lithium aluminum hydride in 100 ml of anhydrous benzene and ether (1 : 1). The reaction mass was stirred under reflux for 20 h, cooled, and treated with 3 ml of water. The inorganic precipitate was filtered and washed with chloroform. The combined extracts were evaporated, and the residue was distilled in vacuo to give 1.1 g (42.7%) of VI in the form of a light-yellow viscous liquid with bp 95-98° (0.6 mm) which was quite soluble in the usual organic solvents and insoluble in water. Found %: C 75.13; H 7.58; N 17.48. $C_{10}H_{12}N_2$. Calculated %: C 74.96; H 7.54; N 17.48. The hydrochloride was obtained in the form of colorless crystals and had mp 191-192° (decomp.). Found %: C 60.71; H 6.53; Cl 18.23; N 14.44. $C_{10}H_{12}N_2 \cdot HCl$. Calculated %: C 61.09; H 6.66; Cl 18.03; N 14.24.

2-Methyl-5,6-benzo-1,2-diazabicyclo[2.2.2]octane (VIIa). A mixture of 1.9 g (12 mmole) of VI, 1.2 g (13 mmole) of 35% formalin, 1.65 g (36 mmole) of formic acid, and 1 ml of water was heated for 17 h at 100°. The reaction mass was diluted with 10 ml of water, made alkaline with 50% potassium carbonate, and extracted with chloroform. After removal of the chloroform the residue was distilled to give 0.95 g (45.8%) of VIIa in the form of a viscous liquid with bp 67-70° (0.6 mm). Found %: C 76.01; H 8.08. $C_{11}H_{14}N_2$. Calculated %: C 75.82; H 8.09. The hydrochloride was obtained in the form of colorless crystals with mp 153-155°. Found %: C 62.80; H 6.94; Cl 17.08. $C_{11}H_{14}N_2 \cdot HCl$. Calculated %: C 62.70; H 7.17; Cl 16.82. The methiodide had mp 92-93° (from isopropyl alcohol). Found %: I 40.32; N 9.11. $C_{12}H_{15}IN_2$. Calculated %: I 40.14; N 8.86.

2-Benzoyl-5,6-benzo-1,2-diazabicyclo[2.2.2]octane (VIIb). A mixture of 0.75 g (4.7 mmole) of VI, 0.66 g (4.7 mmole) of benzoyl chloride, 0.47 g (4.7 mmole) of triethylamine, and 10 ml of anhydrous benzene was refluxed for 5 h. The mass was cooled, 10 ml of water was added, and the mixture was stirred until the precipitate dissolved, and the solution was acidified with hydrochloric acid. The benzene was removed, and the acid solution was extracted with benzene. The benzene solutions were evaporated, and the residue was triturated with ether, filtered, and recrystallized from acetone to give 0.8 g (67.3%) of VIIb in the form of colorless crystals with mp 150-151°. Found %: C 77.65; H 6.18; N 10.63. $C_{17}H_{16}N_2O$. Calculated %: C 77.25; H 6.10; N 10.59.

Ethyl 1-Amino-1,2,3,4-tetrahydrocinchoninate (VIII). A mixture of 3.3 g (14 mmole) of 1-acetamido-1,2,3,4-tetrahydrocinchoninic acid (IV) and 33 ml of a 10% ethanolic solution of hydrogen chloride was refluxed for 10 h. The reaction mixture was evaporated in vacuo, and the residue was treated with 25% potassium carbonate and extracted with benzene to give 2.5 g (80.6%) of VIII in the form of a colorless, viscous liquid with bp 148-149 (0.6 mm). Found %: C 65.64; H 6.99; N 13.00. $C_{12}H_{16}N_2O_2$. Calculated %: C 65.43; H 7.32; N 12.71.

1-Amino-1,2,3,4-tetrahydrocinchoninic Acid (III). A mixture of 10.75 g (49 mmole) of VIII, 49 ml (49 mmole) of 1 N sodium hydroxide, and 50 ml of ethanol was refluxed for 7 h. The reaction mixture was decolorized with charcoal, evaporated to one-third of its original volume, and treated with 49 ml (49 mmole) of 1 N hydrochloric acid. The precipitate was filtered and washed with water to give 8.45 g (90%) of III in the form of colorless crystals with mp 153-155° (decomp., from isopropyl alcohol). Found %: C 62.40; H 6.45; N 14.29. $C_{10}H_{12}N_2O_2$. Calculated %: C 62.48; H 6.29; N 14.57. The hydrochloride had mp 177-179° (decomp.). Found %: Cl 15.32; N 12.06. $C_{10}H_{12}N_2O_2 \cdot HCl$. Calculated %: Cl 15.50; N 12.25.

1-Amino-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline (X). A solution of 8.5 g (45 mmole) of methyl 1-nitroso-1,2,3,4-tetrahydrocinchoninate (IX) and 100 ml of anhydrous ether was added to a suspension of 5.8 g (152 mmole) of lithium aluminum hydride in 100 ml of anhydrous benzene. The mixture was refluxed for 5 h and treated as described above to give 4.6 g (58%) of X in the form of a light-yellow, viscous liquid with bp 166-167° (0.4 mm). Found %: C 67.10; H 8.15; N 15.56. $C_{10}H_{14}N_2O$. Calculated %: C 67.40; H 7.91; N 15.72. The hydrochloride had mp 154-156°. Found %: Cl 16.58; N 12.75. $C_{10}H_{14}N_2O \cdot HCl$. Calculated %: Cl 16.51; N 13.04.

Reductive Cleavage of 1-Amino-4-hydroxymethyl-1,2,3,4-tetrahydroquinoline. A mixture of 4.7 g (26.5 mmole) of X, 10 g of Raney nickel catalyst, 6 ml of ethanol, and 60 ml of water was heated with stirring with distillation of water. Water was simultaneously added from a dropping funnel in order to maintain a constant level of liquid in the flask. The distillate was extracted with benzene. The benzene solution yielded 0.8 g (23%) of 1,2,3,4-tetrahydroquinoline in the form of a light-yellow liquid with bp 108-110° (8 mm). Found %: C 81.0; H 7.90; N 10.36. $C_9H_{11}N$. Calculated %: C 81.16; H 8.32; N 10.51.

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