

THE REDUCTION OF 1,7-DIAZABICYCLO[4,3,0]NON-6-ENE AND OF 2,3-DIHYDROIMIDAZO-[1,2-a]PYRIDINE AS AZACYCLIC COMPOUNDS WITH AN AMIDINE STRUCTURE

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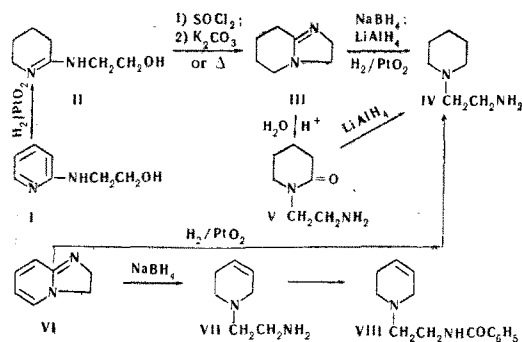
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It has been shown that the reduction of 1,7-diazabicyclo[4,3,0]non-6-ene and of 2,3-dihydroimidazo[1,2-a]pyridine takes place with the hydrogenolysis of the C=N bond and the formation of 1-(β-aminoethyl)piperidine or its 3,4-dehydro derivative.

It is known that the catalytic hydrogenation of 2-aminopyridine forms 2-iminopiperidine and, as a result of subsequent hydrogenolysis, piperidine [1]. The reduction of 2-benzylaminopyridine [2] and some lower 2-alkyl- and 2-dialkylaminopyridines [3] led to 2-benzylamino-3,4,5,6-tetrahydropyridine and the corresponding alkyl and dialkyl derivatives. However, in the case of 2-imino-1-(β-hydroxy-β-phenylethyl)-1,2-dihydropyridine, the absorption of 3 moles of hydrogen was observed with the formation of a derivative of 2-aminopiperidine [4]. 5,8-Dimethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine has been synthesized by the hydrogenation of 5,8-dimethylimidazo[1,2-a]pyridine [5].

We have studied the reaction of various 2-aminopyridines in order to pass to diazabicyclic compounds



In the hydrogenation of 2-(β-hydroxyethylamino)pyridine (I) over platinum oxide, 2 moles of hydrogen were absorbed with the formation of 2-(β-hydroxyethylamino)-3,4,5,6-tetrahydropyridine (II) which, after the replacement of the hydroxyl group by chlorine, cyclized to give 1,7-diazabicyclo[4,3,0]non-6-ene (III). The same compound was obtained by the vacuum distillation of II.

On further reduction of III with lithium aluminum hydride, sodium borohydride, or catalytically over platinum oxide, the hydrogenolysis of the C₆-N₇ bond took place with the formation of 1-(β-aminoethyl)piperidine (IV), identical with that obtained by independent synthesis [6].

The ease of cleavage of the C=N bond in the bicyclic compound III was also noted when III was heated with water, giving 1-(β-aminoethyl)-2-oxopiperidine (V), which was reduced by lithium aluminum hydride to the amine IV.

The reduction of 2,3-dihydroimidazo[1,2-a]pyridine (VI) [7], which is the cyclic form of a substituted 2-aminopyridine, was accompanied, just as in the case of III, by the hydrogenolysis of the C=N bond: the catalytic hydrogenation of the hydrochloride of VI gave the amine IV, and the reduction of the free base VI with sodium borohydride gave 1-(β-aminoethyl)-1,2,5,6-tetrahydropyridine (VII). The structure of the latter was confirmed by its synthesis by an independent route [8, 9]. The amine VII was converted into 1-(β-benzoylaminoethyl)-1,2,5,6-tetrahydropyridine (VIII).

EXPERIMENTAL

2-(β-Hydroxyethylamino)-3,4,5,6-tetrahydropyridine (II). A solution of 5 g of the hydrochloride of 2-(β-hydroxyethylamino)pyridine (I) in 50 ml of absolute ethanol was reduced with hydrogen in the presence of 0.2 g of platinum oxide.

After the absorption of 2 moles of hydrogen the reaction ceased. The platinum black was filtered off, the alcoholic solution was evaporated in vacuum, and the residue was treated with 50% potassium carbonate solution and extracted with chloroform. This gave 3.4 g (84%) of II in the form of a colorless viscous liquid soluble in organic solvents and in water. Found %: C 58.78; H 9.71; N 19.76. $C_7H_{14}N_2O$. Calculated %: C 59.12; H 9.92; N 19.70.

1,7-Diazabicyclo[4,3,0]non-6-ene (III). A) Compound II, obtained by the method described above from the reduction of 7 g of I was converted by the action of an ethanolic solution of hydrogen chloride with subsequent distillation of the ethanol in vacuum into the hydrochloride, which consisted of a noncrystallizing oily liquid. The hydrochloride was dissolved in 40 ml of chloroform, 6 ml of thionyl chloride was added, and the reaction mixture was boiled for 4 hr. The chloroform and the excess of thionyl chloride were driven off in vacuum, the residue was treated with 50% caustic soda solution, and the reaction products were extracted with ether. This gave 3 g (60%) of III. Colorless liquid readily soluble in organic solvents and in water. Bp 90°C (10 mm); n_D^{20} 1.5068. IR spectrum: 1628 cm^{-1} ($-\text{C}=\text{N}$). Found %: C 68.04; H 9.40; N 22.84. $C_7H_{12}N_2$. Calculated %: C 67.62; H 9.75; N 22.54. Picrate. Yellow crystals readily soluble in water and acetone, sparingly in ethanol, and insoluble in ether. Mp $143\text{--}146^\circ\text{C}$. Found %: C 44.13; H 4.23; N 20.10. $C_7H_{12}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 44.19; H 4.28; N 19.82.

B) One gram of 2-(β -hydroxyethylamino)-3,4,5,6-tetrahydropyridine was heated in vacuum (10 mm) at $155\text{--}160^\circ\text{C}$, whereupon 0.7 g (94%) of III distilled over. Bp 90°C (10 mm); n_D^{20} 1.5068. Picrate. Mp $143\text{--}146^\circ\text{C}$. A mixture with a sample obtained by method (A) gave no depression of the melting point.

Reduction of 1,7-diazabicyclo[4,3,0]non-6-ene (III). A) A solution of 1.8 g of III in 30 ml of a mixture of ether and benzene (1:1) was poured into a suspension of 2 g of lithium aluminum hydride in 30 ml of the same mixture. The resulting mixture was heated at $55\text{--}60^\circ\text{C}$ for 20 hr, and was cooled and treated with 4 ml of water. The metal hydroxides were filtered off and washed with benzene, and 1.6 g (86%) of 1- β -aminoethylpiperidine (IV) was obtained. Mobile colorless liquid, soluble in organic solvents and in water. Bp $62\text{--}63^\circ\text{C}$ (8 mm); n_D^{20} 1.4783. Found %: C 65.28; H 12.34; N 21.58. $C_7H_{16}N_2$. Calculated %: C 65.52; H 12.57; N 21.83. Picrate. Mp 225°C [10].

B) At room temperature, 7 g of sodium borohydride was added in portions to a solution of 2 g of III in 50 ml of methanol. After 24 hr, the solution was evaporated, the residue was dissolved in 20 ml of water, and the reaction products were extracted with ether. This gave 1.4 g (70%) of IV.

C) A mixture of 1.2 g of III, 0.2 g of platinum oxide, and 40 ml of methanol was shaken with hydrogen. After the absorption of 2 moles of hydrogen the platinum black was filtered off, the ethanolic solution was evaporated, and the residue was distilled. This gave 0.85 g (67.5%) of IV.

1-(β -Aminoethyl)-2-oxopiperidine (V). A solution of 2 g of III in 20 ml of water was boiled for 6 hr. The reaction mixture was treated with 50% caustic potash solution and extracted with benzene, which gave 1.7 g (80%) of V in the form of a colorless liquid soluble in water and organic solvents. Bp $154\text{--}156^\circ\text{C}$ (13 mm). IR spectrum: 1638 cm^{-1} ($\text{CO}-\text{N}<$), 3310 cm^{-1} , 3360 cm^{-1} (NH_2). Found %: C 59.03; H 9.90; N 19.65. $C_7H_{14}N_2O$. Calculated %: C 59.11; H 9.92; N 19.70.

Reduction of 1-(β -aminoethyl)-2-oxopiperidine. By the method described above, 2 g of V in a mixture of 30 ml of ether and 30 ml of benzene was reduced with 3 g of lithium aluminum hydride. The reaction products were extracted with ether, giving 1.7 g (70%) of 1-(β -aminoethyl)piperidine (IV).

Reduction of 2,3-dihydroimidazo[1,2-*a*]pyridine (VI). A) Some 2.5 g of the hydrochloride of VI in 30 ml of methanol was subjected to hydrogenation with 0.2 g of platinum oxide. This gave 1.7 g (95%) of IV.

B) At $10\text{--}15^\circ\text{C}$, 15 g of sodium borohydride was added in portions to a solution of 5 g of VI in 100 ml of methanol. The reaction mixture was boiled for 10 hr and evaporated in vacuum, the residue was dissolved in 30 ml of water, and the reaction products were extracted with benzene. This gave 2.25 g (43.5%) of VII in the form of a mobile colorless liquid. Bp 100°C (36 mm); n_D^{20} 1.4887. Found %: C 65.98; N 11.40. $C_7H_{14}N_2$. Calculated %: C 66.62; H 11.18. Dipicrate. Yellow crystals soluble in acetone, insoluble in water and ether, sparingly soluble in ethanol. Mp $195\text{--}197^\circ\text{C}$ (from ethanol). Found %: C 39.18; H 3.48; N 19.48. $C_7H_{14}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 39.04; H 3.43; N 19.20.

1-(β -Benzoylaminoethyl)-1,2,5,6-tetrahydropyridine (VIII). At -1 to $+2^\circ\text{C}$, 1.12 g of benzoyl chloride was added to a solution of 1 g of VII in 3 ml of water containing 0.41 g of caustic soda. After 15 min, the reaction products were

extracted with benzene. This gave 1.45 g (79%) of VIII. Colorless viscous liquid readily soluble in benzene and sparingly soluble in ether. Mp 74-75°C (from a mixture of ether and petroleum ether); bp 168-170°C (0.7 mm). Found %: C 73.27; H 7.49; N 12.40. $C_{14}H_{18}ON_2$. Calculated %: C 73.01; H 7.88; N 12.16.

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