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NEW ROUTE TO THE SYNTHESIS OF OCTAHYDROPYRROLO[1,2-a]PYRAZINES

A. M. Likhosherstov, V. P. Peresada, and A. P. Skoldinov

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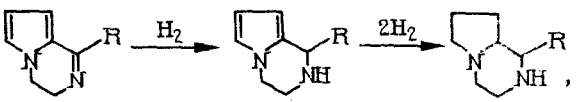
Octahydropyrrol[1,2-a]pyrazines are structural fragments of several drugs [4, 9], the synthesis of which were brought about through the difficultly available chloropentanoic acid using lithium aluminum hydride [1]. In the present work we examine a new route to octahydropyrrolo[1,2-a]pyrazine (Ia) and its homologs, starting form the 3,4-dihydropyrrolo[1,2-a]pyrazines (II), which is easily accessible [5-7].

It was established earlier that the reduction of the azomethine bond in compounds II proceed easily [8], and thus the possibility of the complete hydrogenation of the 3,4-dihydropyrrolo[1,2-a]pyrazine system is defined by the possibility of hydrogenation in this pyrrole ring.

We showed that the hydrogenation of IIa with catalysis by precious metals with the formation of Ia proceeds in acidic medium and at room temperature and atmospheric pressure [2].



II III I

where R=H(a), CH_3(b), C_6H_5(c), C_6H_{11} (hexyl) (2)

The process is carried out in glacial acetic acid, with Pt or Pd catalysis.

It also is possible to conduct the hydrogenation of IIa hydrochloride in aqueous solution, but with this process takes place significantly more slowly. It was established that the rate of the absorption of the first gram-mole of hydrogen was far faster than subsequent ones, and according to the GLC data, resulted in the formation of the intermediate 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine IIIa. Direct hydrogenation of this compound under the above conditions also led to Ia.

Hydrogenation of 1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine IIIb with Pt catalysis in glacial acetic acid gave 1-methyloctahydropyrrolo[1,2-a]-pyrazine Ib in the form of two stereoisomers in the ratio of 1:1, according to mass-spectral data.

The hydrogenation of 1-phenyl-1,2,3,4-tetrahydropyrrrolo[1,2-a]pyrazine IIIc with Pt catalysis in glacial acetic acid was studied. If the hydrogenation was carried out to the disappearance of the starting compound, a mixture of two compounds, 1-phenyl-octahydropyrrolo[1,2]-a-pyrazine Ic and 1-cyclohexyloctahydropyrrolo[1,2-a]pyrazine (Id), was formed in a ratio of 5:1, according to the GLC and PMR data. According to the GLC-MS data the bicycle Id was formed as a mixture of two stereoisomers (whose ratio was 2:1), while the presence of stereoisomers of the bicycle Ic, isolated from the mixture in 31.5% yield, was not established.

The hydrogenation of the bicycle IIIc to full termination of hydrogen uptake led to the formation of a mixture of bicycles Ic and Id in a ratio of 2:1 (according to GLC and ^{1}H NMR data) and carrying out the process to the end was unsuccessful. Thus, the rate of hydrogenation of the benzene ring in the bicycle IIc is significantly less than the rate of hydrogenation of the pyrrole ring.

The bicycle Id in the form a mixture of two stereoisomers (ratio 2:1) was obtained by hydrogenation of 1-cyclohexyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (IIId) under the indicated conditions.

The high cost of the platinum group catalysts, the duration of the hydrogenation process, and the complexity of isolating the product from its salt limits the use of this method for obtaining octahydropyrrolo[1,2-a]pyrazines on an industrial scale.

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It would be extremely desirable to use nickel catalysts for this purpose. According to literature data [10], the hydrogenation of the pyrrole ring with nickel catalysis takes place easily under high temperature and pressure.

We established that the bicycle Ia formed upon hydrogenation of compound IIa with Rainey nickel catalysis (30-50% on the weight of the material to be reduced) under autoclave conditions at a temperature of 150-180°C and a pressure of 150-180 atm [3].

The process is complete after 2-3 h, the catalyst is filtered off, washed with solvent, and the isolated bicycle is distilled under vacuum. The yield of the desired product when triethylamine or pentane is used as solvent is 78 to 80%, respectively, while in the absence of solvent the yield does not exceed 63%. Use of isopropanol as solvent allows the relative amount of catalyst to be lowered to 5% and the bicycle Ia is obtained in a yield on the order of 80%.

Under analogous conditions the hydrogenation with Rainey nickel was carried out with the bicycles IIb and IIc, from which the products of complete hydrogenation were formed, as with reduction in acidic medium with platinum group catalysts, as a mixture of two stereoisomers, the ratio of which for bicycle Ib was 1:1, and for bicycle Id, 3:1.

Thus, the catalytic hydrogenation of 3,4-dihydropyrrolo[1,2-a]pyrazines may be successfully used for the preparation of octahydropyrrolo[1,2-a]pyrazines under laboratory or industrial conditions.

EXPERIMENTAL

The ^1H NMR spectra on the ppm scale were obtained on a Varian T-60 instrument in CCl_4, with TMS as internal standard, gas-liquid chromatography was carried out with an LKhM-8MD chromatograph with a 0.25 mm × 30 m steel capillary column, liquid phase SE-30, injector temperature 300°C. Condition 1 (τ^1 = retention time, min): oven temperature = 95°C, gas carrier (nitrogen) inlet pressure = 0.13 kg/cm. Condition 2 (τ^2): 150°C, 0.3 kg/cm. GLC–MS studies were carried out with the aid of a Varian MAT-112 instrument, ionization current 70 eV, injector temperature = 200°C, gas carrier (helium) pressure = 0.8 kg/cm, with oven temperature programmed from 100 to 200°C at a rate of 4° per min. A 30 m × 0.25 mm capillary steel column, coated with polyethylene glycol 6000, was used. The found values for the elemental analysis agreed with calculations.

Octahydropyrrolo[1,2-a]pyrazine (Ia). 1. Hydrogenation in Acetic Acid. A solution of 1.2 g (0.01 mole) of IIa in 20 ml of glacial acetic acid containing 0.1 g of platinum oxide prepared according to Adams was hydrogenated to uptake of the theoretical amount of hydrogen (10 h). The catalyst was filtered off, the filtrate was evaporated, the residue was dissolved in 10 ml of CH_2Cl_2 and the solution was saturated with ammonia. The resulting precipitate was filtered off, the CH_2Cl_2 was evaporated, and the residue was distilled to give Ia, 0.8 g (63.5%), bp 65-66°C (10 mm Hg), n_D^{20} 1.4960, τ 3.5 min. Lit. [5]: bp 65-66.5°C (10 mm Hg), n_D^{20} 1.4922. Hydrogenation of IIa over platinum oxide on barium sulfate or IIIa over platinum oxide under analogous conditions gave Ia in yields of 64 and 65%, respectively.

2. Hydrogenation in Aqueous Solution. A solution of 3.13 g (0.02 mole) of IIa hydrochloride in 10 ml of water was hydrogenated over 0.2 g of PtO_2 until the uptake of the theoretical amount of hydrogen (50 h). The catalyst was filtered off, the filtrate was evaporated, and the residue was evaporated with benzene. This residue was dissolved in 25 ml of $CHCl_3$ and saturated with ammonia. The precipitate was filtered off, the $CHCl_3$ was evaporated, and the residue was distilled to give Ia, 1.2 g (47.5%).

3. Hydrogenation with Selective Nickel Catalyst. In a 0.5 liter rotating steel autoclave was placed 24 g (0.2 mole) of IIa, 1.2 g of selective nickel catalyst, and 50 ml of 90% isopropanol. Initial pressure = 150 atm. The stirred autoclave was gradually heated to 150°C and kept at 150-160°C for 2 h. After cooling, the catalyst was filtered off, the filtrate was concentrated, and the residue was distilled to give Ia, 20.2 g (80%), bp 85-88°C (23 mm Hg), n_D^{20} 1.4960. Hydrogenation of IIa under analogous conditions in Et_3N, heptane, or without solvent gave IIa in yields of 77.7, 80, and 63%, respectively, but required a significantly larger amount of catalyst (on the order of 30-50% of the weight of the starting compound).

1-Methyloctahydropyrrolo[1,2-a]pyrazine (Ib). 1. Hydrogenation with PtO_2. A solution of 1.36 g (0.01 mole) of IIIb in 20 ml of glacial acetic acid was hydrogenated over 0.2 g of PtO_2 to uptake of the theoretical amount of hydrogen (8 h). The catalyst was filtered off, the AcOH was evaporated, the residue was dissolve in 10 ml of CH_2Cl_2, and the solution was saturated with ammonia. The precipitate was filted off, the filtrate was evaporated, and the residue was distilled to give Ib, $C_8H_{16}N_2$, 0.98 g (70%), bp = 95-100°C (25 mm Hg), n_D^{20} 1.4940. Compound Ib was formed, according to GLC–MS data, as a mixture of equal amounts of stereoisomers having different retention times (τ = 4.5 and 6 min), and identical M^+ values (140).

2. Hydrogenation with Selective Nickel Catalyst. In a 0.5 liter rotating steel autoclave was placed 13 g (0.843 mole) of IIb, 3.4 g of selective nickel catalyst washed with Et_3N. Initial pressure = 150 atm. The stirred autoclave was gradually heated to 150°C and kept at 150-160°C for 2 h. After cooling the catalyst was filtered off, the solvent was evaporated, and residue was distilled to give I, 10 g (84%), which consisted of a mixture of stereoisomeners in a ratio of 3:1 (GLC).

1-Phenyloctahydropyrrolo[1,2-a]pyrazine (Ic). 1. Hydrogenation to the Disappearance of Starting Material. A solution of 4.95 g (0.025 mole) of IIIc in 20 ml of glacial acetic acid was hydrogenated over 0.3 g of PtO_2 until disappearance of starting material (followed by GLC). After uptake of 1450 ml (0.065 mole) of hydrogen in 30 h, the catalyst was filted off, the filtrate was evaporated, and the residue was dissolved in 10 ml of water, treated with 25% aqueous ammonia, and extracted with benzene. The benzene was evaporated, the residue was distilled under vacuum, and the fraction with bp 194-196°C (2 mm Hg), n_D^{20} 1.5610 was collected. Weight 3.5 g, containing (GLC–MS) a mixture of Ic (M^+ 202, τ^2 = 4.5 min), and Id (M^+ 208, τ^2 = 3.5 and 6 min) in a ratio of 5:1 (^{1}H NMR).

An alcoholic solution of the mixture (3.5 g in 10 ml) was added to a solution of maleic acid (4.4 g in 10 ml), and the resulting precipitate (6.5 g) was filtered off, crystallized from ethanol, dissolved in 5 ml of water, treated with 25% aqueous ammonia, extracted with benzene, the benzene evaporated, and the residue distilled to give Ic, $C_{13}H_{18}N_2$, 1.6 g (31.5%), bp 119-120°C (1 mm Hg), n_D^{22} 1.5645, mp 42-43°C, τ^2 = 4.5 min, M^+ 202. ^{1}H NMR spectrum: 1.1-3.3 (11 H, m, protons of the pyrrolidine and pyrazine rings); 2.7 (1 H, NH); 4.1 (1 H, d, 1-H); 7.1-7.6 (5 H, m, benzene). Dimaleate, $C_{13}H_{15}B_2 \cdot 2C_4H_4O_4$, mp 169-170°C (from ethanol).

2. Hydrogenation to Essentially Complete Hydrogen Uptake. A solution of 4.95 g (0.025 mole) of IIIb in 20 ml of glacial acetic acid was hydrogenated over 0.3 g of PtO_2. After uptake of 1700 ml (0.077 mole) of hydrogen (60 h), further uptake was extremely slow, even after addition of a fresh portion (0.2 g) of catalyst. The catalyst was filtered off, the AcOH was evaporated, the residue was dissolved in 10 ml of water and treated with 25% aqueous ammonia. The mixture was extracted with benzene, the benzene was evaporated, and the residue was distilled to give a mixture consisting of compounds Ic and Id in a ratio of 2:1 (^{1}H NMR and GLC).

1-Cyclohexyloctahydropyrrolo[2,2-a]pyrazine (Id). A solution of 2.04 g (0.01 mole) of 1-cyclohexyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine in 20 ml of glacial acetic acid was hydrogenated over 0.2 g of PtO_2 to uptake of the theoretical amount of hydrogen (24 h). The catalyst was filtered off, the AcOH was evaporated, and the residue was dissolved in 5 ml of water. The solution was treated with 25% aqueous ammonia, extracted with benzene, the benzene was evaporated, and the residue was distilled to give Id, $C_{13}H_{24}N_2$, 1.3 g (63%), bp 121-122°C (1 mm Hg), n_D^{20} 1.5160. Compound Id contained, according to GLC–MS data, a mixture of stereoisomers having different retention times (τ^2 = 3.5 and 6 min) and identical mass spectra (M^+ 208). The ratio of stereoisomers was 2:1 by GLC.

In a 0.5 liter rotating steel autoclave, 21.3 g (0.108 mole) of IIc, 11 g of Et_3N-washed selective nickel catalyst, and 70 ml of Et_3N were introduced. The initial pressure was 147 atm. The autoclave was gradually heated to 170°C and kept at 160-170°C for 2 h. After cooling, the reaction mass was poured out, the catalyst was filtered off, the solvent was removed, and the residue was distilled to give 20 g (89%) of Id, which was formed as a mixture of stereoisomers in a ratio of 1:1 (GLC).

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