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SHAPIRO REACTION IN THE SERIES OF PIPERIDINE DERIVATIVES. SYNTHESIS OF 3-HYDROXY-1,2,3,6-TETRAHYDROPYRIDINES

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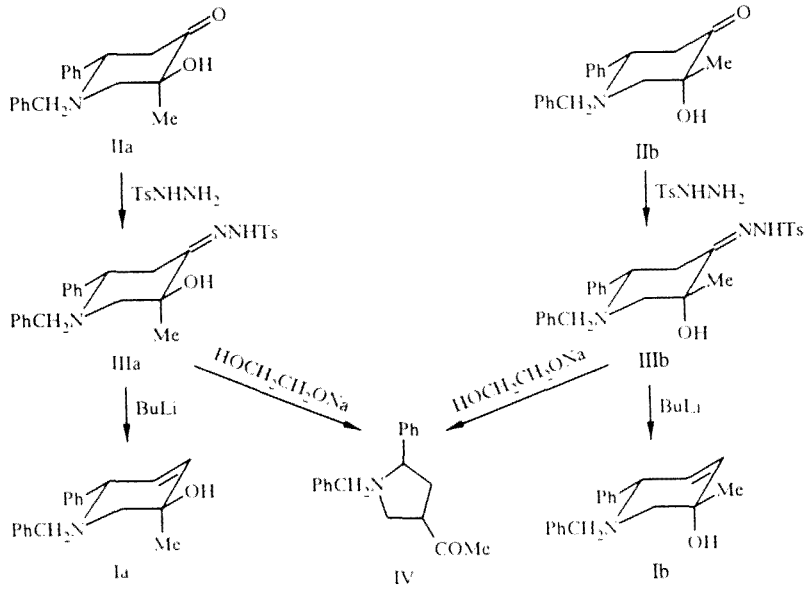
It is shown that the reaction of tosylhydrazones of 3-hydroxypiperidin-4-ones with bases, depending on the nature of the latter, results in a rearrangement with a narrowing of the heterocycle and formation of acetylpyrrolidines, or in the formation of 3-hydroxy-1,2,3,6-tetrahydropyridines.

Compounds of the 1,2,3,6-tetrahydropyridine series (also frequently referred to in the literature as 3-piperidines) began to attract increasing attention of researchers when the extremely high neurotoxic activity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was observed. The physiological properties of this compound and its analogs have been the subject of many studies, including a review [1]. At the same time, in the last few years, the literature has provided no data on the synthesis or biological activity of 3-piperidines hydroxylated in the ring.

We prepared diastereoisomeric 1-benzyl-3-hydroxy-3-methyl-6-phenyl-1,2,3,6-tetrahydropiperidines (Ia, b) via a two-step synthesis that included conversion of the corresponding 3-hydroxypiperidin-4-ones (IIa, b) with their subsequent treatment with butyllithium (the Bamford–Stevens reaction in the Shapiro modification). However, an attempt to carry out this conversion in the classical conditions of the Bamford–Stevens reaction (sodium in ethylene glycol) in the case of both IIIa and IIIb compounds resulted in the same mixture (1:1, ESR data) of epimeric acetylpyrrolidines (V) with a low yield. Isolation of the individual isomers from this mixture was found to be difficult in view of their equal chromatographic mobility. The result obtained correlates with reported data [2], according to which in an aprotic



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solvent, the reaction takes place via a carbene intermediate, and in a protic solvent, via a carbocation, considerably increasing the probability of a rearrangement. Note that the formation of the same mixture from isomers IIIa and IIIb does not prove the nonstereoselectivity of the rearrangement, since under the conditions of the reaction, the cis and trans isomers of compound IV should be readily converted into each other by enolization.

The structure of the synthesized compounds is confirmed by spectroscopic data. Thus, the ESR spectra of tosylhydrazones III contain, in addition to the signals characteristic of piperidinones II [3], signals of the protons of the methyl group bound to the aromatic ring (around 2.4 ppm) and of the protons of the p-disubstituted aromatic ring, and their IR spectra show absorption bands of the hydroxyl group at 3470-3490, of the N–H bond at 3200 and 3295 cm^{-1}, and of the C=N bond at 1650 cm^{-1}. The ESR spectra of the mixture of acetylpyrrolidines IV show two signals of the protons of acetyl groups at 2.07 ppm and 2.13 ppm, similar in strength, and the IR spectrum of this mixture shows the absorption band of the carbonyl group at 1715 cm^{-1}.

A characteristic feature of the ESR spectra of tetrahydropyridines Ia, b is the presence of two "far" spin–spin interaction constants $J_{4\text{-H},6\text{-Ha}}$ (1.6-2.0 Hz) and $J_{4\text{-H},2\text{-He}}$ (0.8-1.3 Hz). The IR spectra of compounds Ia,b show absorption bands of the C=C double bond at 1630 cm^{-1} and of the hydroxyl group at 3595 cm^{-1} (Ia) or 3545 cm^{-1} (Ib).

Thus the splitting of tosylhydrazones of 3-hydroxypiperidin-4-ones takes place differently under action of butyllithium and sodium in ethylene glycol: in one case, derivatives of 3-hydroxy-1,2,3,6-tetrahydropyridine are obtained, and in the other case, the chief transformation is a rearrangement with ring contraction and formation of acetylpyrrolidines.

EXPERIMENTAL

The ESR spectra were recorded with a Tesla BS-567 A instrument with an operating frequency of 100 MHz in $CDCl_3$ solutions and TMS as the internal standard. The IR spectra were recorded with a 75 IR Specord spectrometer in CCl_4 or $CDCl_3$ solutions. The reaction mixtures were analyzed by thin-layer chromatography on Silufol plates, with ether–hexane as the eluent.

Tosylhydrazones of 1-Benzyl-3-hydroxy-3-methyl-6-phenylpiperidin-4-ones (IIIa, b). Compound IIa, b in the amount of 2.95 g (0.01 mole) and 1.86 g (0.01 mole) of tosylhydrazine were boiled in 20 ml of ethanol for 0.5 h, then the reaction mixture was cooled to room temperature, and the precipitate of product III was separated and recrystallized from ethanol.

Tosylhydrazone IIIa. Yield, 84%; mp 175-176°C. ESR spectrum: 1.50 (3H, s, 3-Me); 2.14 (1H, d, J = 11.8 Hz, 2-H_a); 2.17 (1H, d.d, J = 14.6 Hz, 10.6 Hz, 5-H_a); 2.42 (3H, s, Me_{Ts}); 2.72 (1H, d.d, J = 14.6 Hz, 4.1 Hz, 5-H_e); 2.94 (1H, d, J = 11.8 Hz, 2-H_e); 2.98 and 3.61 (2H, d, J = 13.6 Hz, $PhCH_2$); 3.33 (1H, d.d, J = 10.6 Hz, 4.1 Hz, 6-H_a); 4.07 (1H, br.s, OH); 7.30 (12H, m, H_{arom}); 7.77 (2H, d, J = 8.0 Hz, H_{arom}). Found, %: C 67.29; H 7.07; S 6.44. $C_{26}H_{29}N_3O_3S$. Calculated, %: C 67.35; H 6.31; S 6.92.

Tosylhydrazone IIIb. Yield, 86%, mp 179-181°C. ESR spectrum: 1.18 (3H, s, 3-Me); 2.15 (1H, d, J = 11.9 Hz, 2-H_a); 2.38 (3H, s, Me_{Ts}); 2.41 (1H, d.d, J = 15.0 Hz, 11.3 Hz, 5-H_a); 2.69 (1H, d.d, J = 14.6 Hz, 4.1 Hz, 5-H_e); 2.86 (1H, d, J = 11.8 Hz, 2-H_e); 2.95 and 3.61 (2H, d, J = 13.6 Hz, $PhCH_2$), 3.32 (1H, d.d, J = 10.6 Hz, 4.1 Hz, 6-H_a); 7.26 (12H, m, H_{arom}); 7.75 (2H, d, J = 8.4 Hz, H_{arom}). Found, %: C 66.70; H 7.05; S 6.27. $C_{26}H_{29}N_3O_3S$. Calculated, %: C 67.35; H 6.31; S 6.92.

1-Benzyl-3-hydroxy-3-methyl-6-phenyl-1,2,3,6-tetrahydropyridines (Ia, b). To a suspension of 0.232 g (0.0005 mole) of tosylhydrazone IIIa, b in 15 ml of absolute ether is added 2.3 ml of a 1.09 M solution of butyllithium in hexane, and the mixture is stirred in a stream of dry argon for 3 h, then allowed to stand overnight at room temperature. To the reaction mixture is added 10 ml of saturated NaCl solution, the ether layer is separated out, and 10 ml of ether is extracted from the aqueous phase. The combined extracts are dried with sodium sulfate and evaporated. Compounds Ia, b are purified by flush chromatography on silica gel (eluent, 1:2 ether–hexane).

Ia. Yield, 71%. Oil. ESR spectrum: 1.39 (3H, s, Me); 1.49 (1H, br.s, OH); 2.31 (1H, d, J = 10.8 Hz, 2-H_a); 2.83 (1H, d.d, J = 10.8, 0.8 Hz, 2-H_e); 3.27 and 3.51 (2H, d, CH, J = 13.5 Hz, $PhCH_2$); 4.06 (1H, d.d, J = 2.3 Hz, 1.6 Hz, 6-H_a); 5.55 (1H, d.d, J = 10.0 Hz, 2.3 Hz, 5-H); 5.73 (1H, d.d.d, J = 10.0 Hz, 2.3 Hz, 0.8 Hz, 4-H); 7.30 (10H, m, H_{arom}). Found, %: C 81.22; H 7.21. $C_{19}H_{21}NO$. Calculated, %: C 81.68; H 7.58.

Ib. Yield, 62%. Oil. ESR spectrum: 1.18 (3H, s, Me); 2.30 (1H, d, J = 11.2 Hz, 2-H_a); 2.78 (1H, br.s, OH); 2.81 (1H, d.d, J = 11.2, 1.3 Hz, 2-H_e); 3.12 and 3.84 (2H, d.d, J = 13.3 Hz, $PhCH_2$); 3.87 (1H, d.d, J = 2.0 Hz, 1.6 Hz, 6-H_a);

5.52 (1H, d.d, J = 10.2 Hz, 1.6 Hz, 5-H); 5.73 (1H, d.d.d, = 10.2 Hz, 2.0 Hz, 1.3 Hz, 4-H); 7.30 (10H, m, H_{arom}). Found, %: C 82.22; H 7.39. $C_{19}H_{21}NO$. Calculated, %: C 81.68; H 7.58.

Splitting of Tosylhydrazones IIIa, b by the Bamford–Stevens Reaction. To a solution of 0.035 g (0.0015 mole) of sodium in 10 ml of ethylene glycol is added 0.466 g (0.001 mole) of tosylhydrazone IIIa, b. The mixture is heated on an oil bath for 125-135°C for 30 min, then poured into 100 ml of cold water and extracted with ether (3 × 15 ml). The combined extracts are dried with sodium sulfate and evaporated, and the residue is dissolved in a 1:2 ether–hexane mixture and filtered through a 40/100 layer of silica gel. The solvent is driven off, and an oil mixture (~ 1:1) of cis and trans 3-acetyl-1-benzyl-5-phenylpyrrolidines IV is separated out. Yield, 33% (from IIIa), 39% (from IIIb). For the mixture of compounds IV, we found, %: C 82.22; H 7.39. $C_{19}H_{21}NO$. Calculated, %: C 81.68; H 7.58.

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