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RECYCLIZATION OF SPIRO[3*a*-HYDROXYPIPERIDIN-4,2′-OXIRANES] IN BASIC MEDIUM

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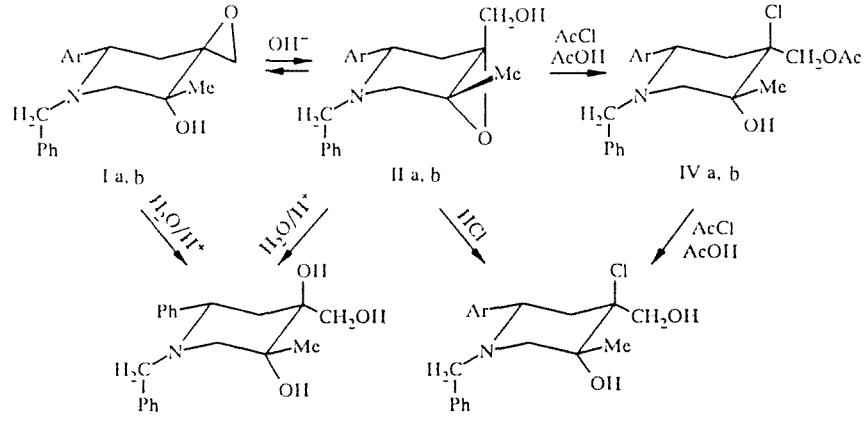
It is shown that heating spiro[3a-hydroxypiperidin-4,2'-oxiranes] in aqueous base gives rearrangement into derivatives of 3,4-epoxypiperidines. The structures of the latter were confirmed by spectral data and by chemical transformations.

Spiro[3α-hydroxypiperidin-4,2′-oxiranes] synthesized earlier by us [1] may serve as convenient predecessors for the preparation of derivatives of piperidines possessing biological activity (antiarrhythmic, local anesthetic, etc.) [2]. In a preceding work [3], it was shown that cleavage of the epoxide ring of spiro[3*a*-hydroxypiperidin-4,2′-oxiranes] by different nucleophiles takes place only on the side of the less substituted carbon atom. It might be expected that under conditions of basic catalysis, the presence in these compounds of a hydroxyl group would produce an intermediate with an internal nucleophile; the alcoholate ion. Intramolecular attack of the latter on the α- or β-carbon atoms should bring about the formation of the corresponding epoxi- or oxetanopiperidine.

In order to clarify the regioselectivity of the cleavage of the oxirane ring, we studied the behavior of compounds (Ia and b) with base upon heating in aqueous tetrahydrofuran and established that they partially transformed into 3,4-epoxypiperidines (IIa and b). This reaction is reversible, which confirms the formation of compound I from the previously-known example of II under the same conditions. It should be noted that recyclization of α-hydroxyepoxides under basic conditions was known earlier, including a series of nitrogen containing heterocycles [4], but as a rule it took place irreversibly.



I–IV a Ar = Ph, b Ar = *p*-$MeOC_6H_4$

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Epoxides IIa and IIb upon keeping in aqueous HCl, and even upon attempting to obtain their hydrochlorides with HCl in absolute ether, were transformed into the corresponding chlorohydrins (IIIa and b). The structure of compounds III conforms to data which indicates that in cleavage of an epoxide ring condensed with a six-membered ring, attack of the reagent proceeds from the axial direction [5]. Acylation of the chlorohydrins IIIa and b and the epoxyalcohols IIa and b with acetyl chloride in acetic acid leads to the 4e-acetoxymethyl-4*a*-chloropiperidines (IVa and b), respectively. Hydration of epoxide IIa in acidic medium gives the triol (Va), obtained earlier from epoxide Ia [1].

The structures of the synthesized compounds were conformed by spectral data. Thus, the ^{1}H NMR spectra of compounds II-IV showed signals of the aromatic nucleus, the methyl groups at C-3 of the piperidine ring, and also the methylene groups of the substituent on the nitrogen atom and at C-4. Interesting features of the ^{1}H NMR spectra of the epoxides II lie in the fact that the signals of the protons at C-5 and C-6 appear, not in the ABX-spin system as with compounds I [1], but in the form of an A_2B system with spin–spin coupling constants of 7.9-8.1 Hz. The reason for the degeneration of the spectra, apparently, is a preference for a twisted trough conformation for compounds II (which is confirmed by calculation of the optimum geometry of the IIa molecule using the PC MODEL program), as a result of which the dihedral angle between the (C-6)-H_a and (C-5)-H_a is near 90°, and the corresponding spin–spin coupling constant is near zero. At the same time, in recording the ^{1}H NMR spectrum of epoxide IIa in deuteromethanol, the 5-H_e, 5-H_a, and 6-H_a protons give signals in the form of AMX-spin system with spin–spin coupling constants $J_{5\text{-He-5-Ha}}$ = 15.4; $J_{5\text{-He-6-Ha}}$ = 5.5; $J_{5\text{-Ha-6-Ha}}$ = 10.3 Hz, which, evidently is connected with a change in the conformation of the molecule because of the formation of hydrogen bonds with the solvent.

Thus, in the case of intramolecular nucleophilic cleavage of the epoxide rings of spiro(piperidin-4,2'-oxiranes), in contrast to the reaction with external nucleophiles, attack of the reagent is directed to the more substituted carbon atom of the epoxide.

EXPERIMENTAL

The ^{1}H NMR spectra were registered in $CDCl_3$ solution with a Tesla BS-567 A instrument with a working frequency of 100 MHz, using TMS as internal standard. The IR spectra were recorded with a Specord IR-75 spectrometer in CCl_4 solution. Analysis of reaction mixtures was monitored by TLC on Silufol plates. The starting materials Ia and Ib were synthesized by methods described in [1].

6-Aryl-1-benzyl-4*a*-hydroxymethyl-3e-methyl-3*a*,4e-epoxypiperidines (IIa, IIb). To a solution of 0.005 mole of compounds Ia or Ib in 20 ml of tetrahydrofurana was added 20 ml of 10% aqueous solution of* and 0.02 g of triethylbenzylammonium chloride. The mixture was boiled for 8-10 h under reflux while the reaction was followed by TLC. The mixture was then cooled to room temperature, the aqueous phase was separated and extracted with methylene chloride (2 × 30 ml). The extract was combined with the organic phase and dried with anhydrous sodium sulfate. The solvents were distilled and the residue was subjected to chromatographic separation on a column of aluminum oxide 40/100 (eluent = methylene chloride:hexane, 1:2-2:1), to isolate nonreacted Ia or Ib and product IIa or IIb.

IIa: $C_{20}H_{23}NO_2$. Yield = 32%, Oil. IR spectrum: 3434 cm^{-1} (OH). ^{1}H-NMR spectrum: 1.28 (3H, s, CH_3), 2,22 (2H, d, J = 7.9 Hz, 5-H_e and 5-H_a), 2.26 (1H, d, J = 12.1 Hz, 2-H_a), 2.54 (1H, s, OH), 2.82 (1H, d, J = 12.1 Hz, N–CH_2), 3.13 (1H, d, J = 12.1 Hz, 2-H_e), 3.25 (1H, t, J = 7.9 Hz, 6-H_a), 3.67 (2H, s, CH_2O), 3.74 (1H, d, J = 12.1 Hz, N–CH_2), 7.27 (10H, m, H_{Ph}).

IIb: $C_{21}H_{25}NO_3$. Yield = 28%, Oil. IR spectrum: 3440 cm^{-1} (OH). ^{1}H NMR spectrum: 1.26 (3H, s, CH_3), 2.20 (2H, d, J = 8.1 Hz, 5-H_e and 5-H_a), 2.25 (1H, d, J = 12.2 Hz, 2-H_a), 2.50 (1H, s, OH), 2.77 (1H, d, J = 12.7 Hz, N–CH_2), 3.10 (1H, d, J = 12.2 Hz, 2-H_e), 3.21 (1H, t, J = 8.1 Hz, 6-H_a), 3.59 (2H, s, CH_2O), 3.71 (1H, d, J = 12.7 Hz, N–CH_2), 3.79 (3H, s, OCH_3), 6.90 (2H, d, J = 8.5 Hz, H_{Ar}), 7.23 (5H, m, H_{Ph}), 7.35 (2H, d, J = 8.5 Hz, H_{Ar}).

6-Aryl-1-benzyl-3*a*-hydroxy-4e-hydroxymethyl-3e-methyl-4*a*-chloropiperidines (IIIa, IIIb). To a solution of 0.001 mole of epoxide IIa or IIb in 5 ml of 1,4-dioxane was added 10 ml of 10% HCl solution. The mixture was kept for 1-2 h at room temperature and then treated with 30 ml of 5% $NaHCO_3$ and extracted with methylene chloride (3 × 15 ml). The extract was dried with anhydrous sodium sulfate and the solvents were evaporated. Compound IIa crystallized from hexane, and compound IIb remained an oil.

*As in Russian Original – Publisher.

IIIa: $C_{20}H_{24}NO_2Cl$. Yield = 87%. mp 95-96°C. IR spectrum: 3395, 3310, 3244 cm^{-1} (OH). ^1H NMR spectrum: 1.24 (3H, s, CH_3), 2.00 (1H, dd, J = 14.6 and 3.1 Hz, 5-H_e), 2.50 (1H, d, J = 11/9 Hz, 2-H_a), 2.61 (1H, dd, J = 14.6 and 10.7 Hz, 5-H_a), 2.75 (1H, m, J = 11.9 Hz, 2-H_e), 2.98 (1H, d, J = 13.2 Hz, NCH_2), 3.69 (1H, d, J = 11.3 Hz, O−CH_2), 3.73 (1H, dd, J = 10.7 and 3.1 Hz, 6-H_a), 3.80 (1H, d, J = 13.2 Hz, N−CH_2), 4.06 (1H, d, J = 11.3 Hz, O−CH_2), 7.27 (10H, m, H_{Ph}).

IIIb: $C_{21}H_{26}NO_3Cl$. Yield = 90%, oil. IR spectrum: 3400, 3312, 3241 cm^{-1} (OH). ^1H NMR spectrum: 1.27 (3H, s, CH_3), 2.01 (1H, dd, J = 15.0 and 3.1 Hz, 5-H_e), 2.55 (1H, d, J = 11.9 Hz, 2-H_a), 2.68 (1H, dd = 15.0 and 10.9 Hz, 5-h_a), 2.79 (1H, d, J = 11.9 Hz, 2-H_e), 3.04 (1H, d, J = 13.1 Hz, N−CH_2), 3.70 (1H, d, J = 12.2 Hz, O−CH_2), 3.74 (1H, dd, J = 10.9 and 3.1 Hz, 6-H_a), 3.78 (3H, s, OCH_3), 3.89 (1H, d, J = 13.1 Hz, N−CH_2); 4.10 (1H, d, J = 12.2 Hz, O−CH_2), 6.92 (2H, d, J = 8.4 Hz, H_{Ar}), 7.23 (5h, m, H_{Ph}), 7.40 (2H, d, J = 8.4 Hz, H_{Ar}).

6-Aryl-4e-acetoxymethyl-1-benzyl-3a-hydroxy-3e-methyl-4a-chloropiperidines (IVa, b). A. To a solution of 0.001 mole of epoxide IIa or IIb in 5 ml of glacial acetic acid was added 0.5 ml (0.007 mole) of acetyl chloride. The mixture was kept for 4-5 h at room temperature and then neutralized with 100 ml of 5% $NaHCO_3$ and extracted with methylene chloride (3 × 15 ml). The combined extracts were dried with sodium sulfate, the solvents were evaporated, and the residue was crystallized from hexane.

B. The above conditions were also used for the acetylation of compounds IIIa and IIIb.

IVa: $C_{22}H_{26}NO_3Cl$. Yield = 70% (A), mp = 98-99°C. IR spectrum: 3433 cm^{-1} (OH), 1736 cm^{-1} (C=O). ^1H NMR spectrum: 1.24 (3H, s, CH_3), 1.57 (1H, s, OH), 2.03 (3H, s, CH_3CO), 2.17 (1H, dd, J = 11.2 and 5.0 Hz, 5-H_e), 2.25 (1H, dd, J = 11.2 and 9.1 Hz, 5-H_a), 2.51 (1H, d, J = 12.1 Hz, 2-H_a), 2.82 (1H, d, J = 12.1 Hz, 2-H_e), 2.96 (1H, d, J = 13.2 Hz, N−CH_2), 3.67 (1H, dd, J = 9.1 and 5.0 Hz, 6-H_a), 3.78 (1H, d, J = 13.2 Hz, N−CH_2), 4.47 (2H, s, CH_2O), 7.27 (10H, m, H_{Ph}).

IVb: $C_{23}H_{28}NO_4Cl$. Yield = 67% (A), mp = 100-102°C. IR spectrum: 3430 cm^{-1} (OH), 1736 cm^{-1} (C=O). ^1H NMR spectrum: 1.25 (3H s, CH_3), 1.59 (1H, s, OH), 2.04 (3H, s, CH_3CO), 2.19 (1H, dd, J = 11.4 and 5.3 Hz, 5-H_e), 2.26 (1H, dd, J = 11.4 and 9.1 Hz, 5-H_a), 2.51 (1H, d, J = 11.9 Hz, 2-H_a), 2.83 (1H, d, J = 11.9 Hz, 2-H_e), 2.97 (1H, d, J = 13.2 Hz, N−CH_2), 3.67 (1H, dd, J = 9.1 and 5.3 Hz, 6-H_a), 3.79 (3H, s, OCH_3), 3.80 (1H, d, J = 13.2 Hz, N−CH_2), 4.49 (2H, s, CH_2O), 6.90 (2H, d, J = 8.4 Hz, H_{Ar}), 7.24 (5H, m, H_{Ph}), 7.37 (2H, d, J = 8.4 Hz, H_{Ar}).

1-Benzyl-4e-hydroxymethyl-3*a*,4*a*-dihydroxy-3e-methyl-5e-phenylpiperidine (Va). To a solution of 0.155 g (0.0005 mole) of epoxide IIa in 5 ml of 1,4-dioxane was added 10 ml of 10% aqueous $HClO_4$. The reaction mixture was kept at room temperature for 20-30 h, neutralized with 40 ml of 5% $NaHCO_3$ and extracted with methylene chloride (3 × 10 ml). The combined extracts were dried with sodium sulfate and concentrated. The residue was crystallized from hexane to give 0.11 g (67%) of product, the spectral data and melting point of which were identical with those of compound Va [1].

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