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SYNTHESIS OF 1-(2-ETHOXYETHYL)-4-HYDROXY-4-[2-(1-HYDROXYCYCLOHEXYL)ETHYNYL]-PIPERIDINE AND HETEROCYCLIZATION UNDER THE CONDITIONS OF HYDRATION

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The reaction of 1-(2-ethoxyethyl)piperidin-4-one with ethynylcyclohexanol led to the synthesis of a glycol, the hydration of which gave a mixture of spirocyclic compounds with a carbonyl group at various positions in the furan ring.

Keywords: 1-ethynyl-1-hydroxycyclohexane, 3-(2'-ethoxyethyl)-14(15)-oxo-7-oxa-3-azadispiro-[5,1,5,2]pentadecane, 1-(2-ethoxyethyl)piperidin-4-one, hydration, Favorsky reaction.

Spirocyclic compounds can be obtained during the hydration of acetylenic glycols [1]. Substances capable of exhibiting high pharmacological activity have been found among the substituted spirocyclic compounds [2, 3].

1-(2-Ethoxyethyl)-4-hydroxy-4-[2-(1-hydroxycyclohexyl)ethynyl]piperidine (**3**) was obtained by the reaction of 1-(2-ethoxyethyl)piperidin-4-one (**1**) with 1-ethynylcyclohexanol (**2**) under the conditions of the Favorsky reaction. The reaction is complicated by a simultaneous reverse Favorsky reaction, leading to the formation of an appreciable amount of the glycol **4**.

After the usual treatment of the reaction mixture and distillation of the solvent the obtained glycol **3** crystallized and was characterized in the form of the base and the hydrochloride **3a**.

The hydration of the glycol **3** was conducted in 10% sulfuric acid in the presence of a catalytic amount of $HgSO_4$ at 90-95°C. The reaction can take place both at the first and at the second carbon atom of the acetylene bridge with the formation of the keto glycols **5** and **6** and their cyclization products **7** and **8**. After treatment of the reaction mixture the hydration product was isolated in the form of an oil, which according to the IR spectrum contained an uncyclized product (1720 cm^{-1}) as well as the spirocyclic products (1752 and 1720 cm^{-1}). After distillation twice under vacuum an oily product boiling at 170°C (1 mm Hg) was obtained. Its IR spectrum contained a strong absorption band for the spirocyclic carbonyl (1752 cm^{-1}) and a weaker band (1736 cm^{-1}), which can also be assigned to the spirocyclic structure.

In the ^1H NMR spectra of the hydration products there are two triplet signals for CH_3 of the ethoxyethyl substituent (1.18 and 1.19 ppm, J = 7.6 Hz) and also two singlets for the methylene protons of the tetrahydrofuran ring (2.44 and 2.43 ppm). In intensity the first of these signals is approximately twice as strong as the second, and together they correspond accordingly to three protons for the methyl group and two protons for the methylene group. The methylene protons of the ethoxyl fragment give one quartet (3.48 ppm. J = 7 Hz).

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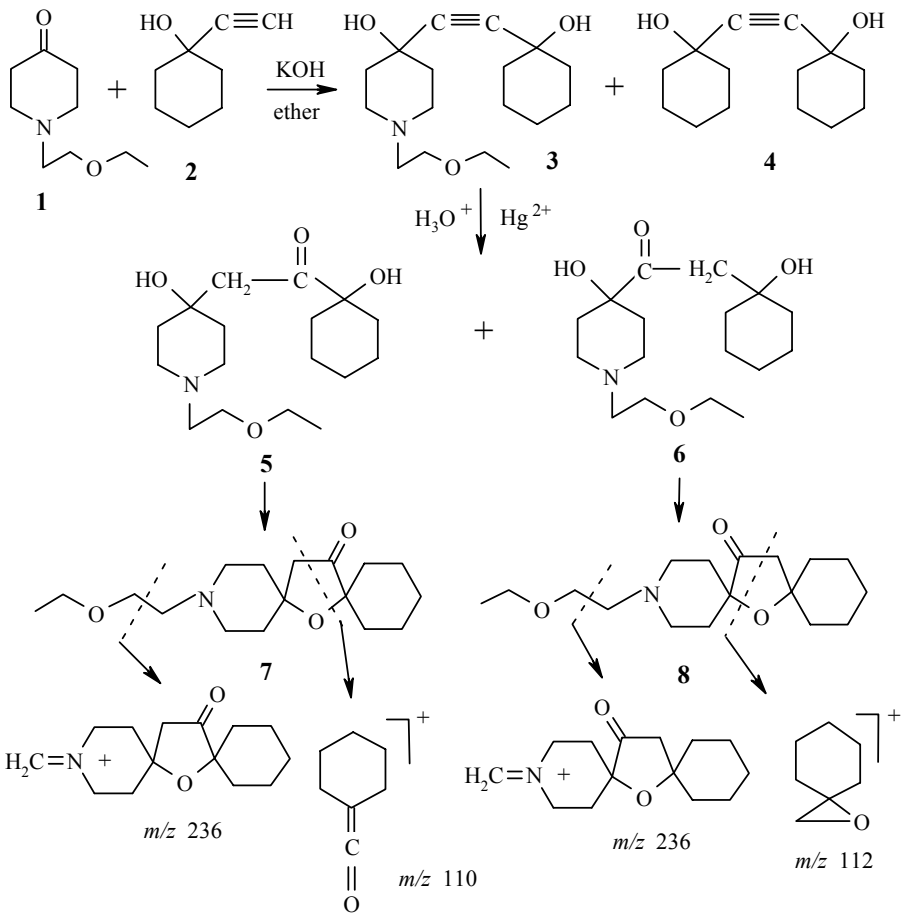

The protons of the cyclohexane ring appear as a multiplet in the region of 1.30-1.70 ppm, and the protons of the piperidine ring (H_a, H_e) give multiplets in the region of 1.70-1.85 (H-3,5) and 2.27-2.84 ppm (H-2,6).

In the ^{13}C NMR spectra there are signals for the two carbonyl groups (217.5 and 217.8 ppm). The shifts of the signals are consistent with data for tetrahydrofuranones [4].

The spirocyclic atoms C-2 and C-10 each give three signals, and it could therefore be supposed that there is a third product in the mixture of spiroketones **7** and **8**.

By recording the mass spectrum on a chromatomass spectrometer it was shown that the mixture of spiroketones contained three products in ratios of 9:4:6.5. All the substances had a molecular mass of 295. The strongest peaks (100%) with mass *m*/*z* 236 corresponded to the ion formed during β dissociation with elimination of the $MeCH_2OCH_2$ radical (in relation to the nitrogen atom).

For the isomer present in the mixture of spiroketones in the largest amount the second in intensity was the peak with *m*/*z* 110. The same peak was second in intensity (if the peaks with *m*/*z* 42, 44, etc. are disregarded) in the spectrum of the second isomer to emerge from the column, present in the mixture in the smallest amount.

The fragmentation of this isomer is similar to the fragmentation of the first isomer. In the third isomer the second in intensity was the peak with *m*/*z* 112, i.e., the fragmentation of the third isomer differed from the fragmentation of the first two. If the peak with *m*/*z* 110 corresponds to the $C_6H_{10}CH(O)$ fragment, formed during β-dissociation in relation to the carbonyl oxygen atom of structure **7**, the peak with *m*/*z* 112 may correspond to the $C_6H_{10}CH_2O$ fragment formed during β-dissociation in relation to the carbonyl oxygen of structure **8**. The isomers **7** with identical fragmentation obviously differ in the orientation of the oxygen atom of the tetrahydrofuran ring. In view of the large size of the substituent in the intermediate ketoglycols **5** and **6** we can

assume that its equatorial position and the axial position for the hydroxyl in relation to the piperidine ring will be more favorable. During heterocyclization this will lead to preferential formation of the products with the axial orientation of the C–O bond in relation to the piperidine ring. The mixture of isomers contains twice as much of the isomer **7** as of **8**, which can be explained by the stronger donating effect of the cyclohexyl substituent.

EXPERIMENTAL

The IR spectra of the compounds were recorded on a Specord M-80 spectrometer in thin layers (for the liquids) and in tablets with potassium bromide (for the crystalline samples). The ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform on a Mercury-300 spectrometer (300 and 75 MHz respectively) with HMDS as internal and external standard (δ 0.05 ppm). Thin-layer chromatography was conducted on Silufol UV-254 plates with a mixture of 2-propanol and 20% ammonia solution (9.9:0.7) as eluant and with development in iodine vapor. The mass spectra were recorded on a Hewlett Packard gas chromatograph with an MSD HP-5972 mass-selective detector at 70 eV ionization energy.*

1-(2-Ethoxyethyl)-4-hydroxy-4-[2-(1-hydroxycyclohexyl)ethynyl]piperidine (3). To a flask containing powdered potassium hydroxide (12.09 g, 0.216 mol) and anhydrous ether (50 ml) with cooling to -4°C and vigorous stirring we added dropwise a mixture of 1-(2-ethoxyethyl)piperidin-4-one (**1**) (13.30 g, 0.07 mol) and ethynylcyclohexanol (**2**) (8.94 g, 0.07 mol). The mixture was stirred with cooling in iced water, left overnight, and stirred the next day at room temperature for a further 7 h. The reaction was monitored by TLC. At the end of the reaction the mixture was cooled to -4°C and decomposed with water. The ether layer was separated, and the aqueous layer was extracted with ethyl acetate. The extracts were dried with anhydrous magnesium sulfate. After distillation of the greater part of the solvent the precipitate that separated was removed and washed with petroleum ether. We obtained 13.0 g (53%) of the glycol **3**; mp 109-111°C. Found %: C 69.01; H 9.90; N 4.98. $C_{17}H_{29}NO_3$. Calculated %: C 69.11; H 9.89; N 4.73.

Hydrochloride 3a. Compound **3a** (mp 130-132°C, ethanol–ether) was obtained by treating a solution of the base **3** in ether with a solution of HCl in propanol. IR spectrum (in potassium bromide), ν, cm^{-1}: 3336 (OH), 2700-2580 (NH^+), 2144 (C≡C), 1120 (C–O–C), 1072 (C–O). Found %: C 66.66; H 9.36; Cl 10.72; N 3.43. $C_{17}H_{29}ClNO_3$. Calculated %: C 61.52; H 9.11; Cl 10.68; N 3.21.

After evaporation of the mother solutions and washing (the acidic solutions were first neutralized) and distillation of the unreacted ketone **1** 3.5 g of the glycol **4** was isolated. It did not differ in melting point (106-107°C) and spectral data from an authentic sample [5].

3-(2'-Ethoxyethyl)-14(15)-oxo-7-oxa-3-azadispiro[5,1,5,2]pentadecane (7) and (8). A mixture of the glycol **3** (4.95 g, 0.016 mol) and $HgSO_4$ (1.0 g) in 10% sulfuric acid (50 ml) was stirred at 90°C for 10 h. At the end of the reaction the precipitate was filtered off, and the solution was neutralized with potassium carbonate and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate. The ethyl acetate was distilled, the residue was distilled under vacuum, the fraction boiling at 164-172°C (1 mm Hg) was collected, and 3 g (65.7%) of an oily substance was obtained. After redistillation it boiled at 170°C (1 mm Hg). IR spectrum (in potassium bromide), ν, cm^{-1}: 3336 (OH), 1720 (C=O), 1120 (C–O–C). Found %: C 69.20; H 9.90; N 7.41. $C_{17}H_{29}NO_3$. Calculated %: C 69.11; H 9.89; N 4.73.

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