SYNTHESIS AND REACTIONS OF 2,5-DIMETHYL-4-(3'-HYDROXY-3'-METHYL-1'-BUTYNYL)-4-PIPERIDINOL

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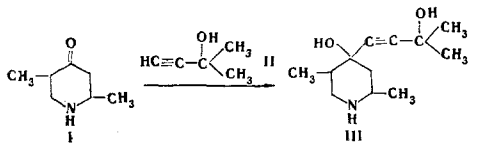
The addition of dimethyl ethynyl carbinol to the carbonyl group of 2,5-dimethyl-4-piperidinone under the conditions of the Favorskii reaction has been studied. It has been shown that the addition takes place stereo-selectively and leads to the formation of a single isomeric acetylenic glycol. The hydration of this glycol has given a heterocyclic tetrahydrofuran with a spiran structure. The exhaustive hydrogenation of the acetylenic glycol has yielded the corresponding saturated glycol. By its cyclization a tetrahydrofuran derivative has been synthesized.

Previously, 4-ethynyl-2,5-dimethyl-4-piperidinols and the corresponding vinyl and ethyl compounds have been synthesized, the configurations of the geometrical isomers of these compounds have been studied [2, 3], and various esters have been obtained from them, among which there are substances possessing a high physiological activity [4–6]. In all these investigations the acetylenic piperidinols were synthesized by condensing acetylene with 2,5-dimethyl-4-piperidinone under the conditions of the Favorskii reaction.

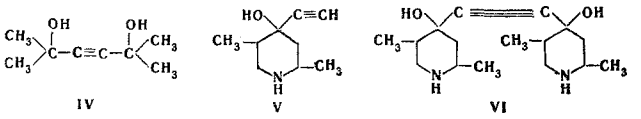
It was of interest to use this condensation also for the synthesis of an unsymmetrical piperidine acetylenic γ-glycol. Thanks to the presence of four reactive centers (the triple bond, the secondary amine group and the hydroxyl groups), this glycol may be an important subject of study and for the preparation of a whole series of promising physiologically active compounds. In the literature there is a communication [7] on the synthesis and properties of a piperidinic γ-glycol of analogous structure but containing a methyl radical on the ring nitrogen atom. In the present work we used 2,5-dimethyl-4-piperidinone (I) [8, 9] as the starting material. When this ketone was condensed with dimethyl ethynyl carbinol (II) in the presence of powdered caustic potash, the unsymmetrical acetylenic γ-glycol (III) was obtained with a yield of 62%.



Thin-layer chromatography on alumina showed the purity of III. It follows from this that the nucleophilic addition of II to the carbonyl group of I takes place with spatial orientation and leads to a single isomer of III. In this reaction, the piperidinone I condenses in its stable trans form with the equatorial arrangement of the methyl groups (the 2e5e conformation) [3, 10, 11].

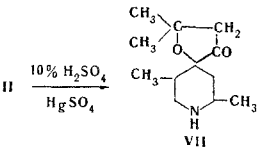
In the IR spectrum of III (dilute solution in carbon tetrachloride) there are absorption bands corresponding to an NH bond (3493 cm^{-1}) and an OH bond (3616 cm^{-1}).

The condensation of the acetylenic alcohol II with the piperidinone I is considerably complicated by simultaneous disproportionation reactions which take place with the formation of a mixture of various products. Thus, in addition to the acetylenic glycol III, we obtained tetramethylbutynediol (IV) with a yield of about 4%, 4-ethyl-2,5-dimethyl-4-piperidinol (V) with a yield of 3%, and the symmetrical piperidinic acetylenic glycol (VI) in small amount.



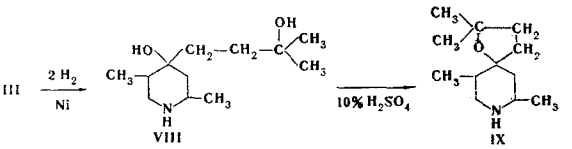
In order to determine the configurational relationship between the glycol (III) and the geometrical isomers of the acetylenic piperidols obtained previously, we cleaved III in the presence of small amounts of caustic potash by a known method [12]. It was found that under these conditions the reverse Favorskii reaction was accompanied mainly by the formation of the initial piperidinol I. The γ-isomer of 4-ethynyl-2,5-dimethyl-4-piperidol (V) [1–3] could be isolated in only low yield.

We also studied the hydration of III. Like aliphatic, alicyclic [13, 14], and heterocyclic [15] acetylenic γ-glycols, this hydration takes place with the formation of tetrahydrofuranones, i.e., in addition to the hydration of the triple bond water is split out with the involvement of the hydroxyls. When III was heated with 10% sulfuric acid in the presence of mercuric sulfate, the tetrahydrofuranone derivative VII was obtained in a yield of about 60%.



The IR spectrum of VII (pure substance) has absorption bands corresponding to the bonds C=O (1753 cm^{-1}), C–O–C (1163 cm^{-1}), and NH (3280 cm^{-1}).

The exhaustive hydrogenation of the acetylenic glycol (III) in the presence of an Ni catalyst gave an almost quantitative yield of the saturated glycol (VIII). When this was heated with 10% sulfuric acid, a good yield of the tetrahydrofuran derivative IX was obtained.



The IR spectrum of IX (pure substance) has absorption bands of a C—O—C bond (1162 cm^{-1}) and an NH bond (3270 cm^{-1}).

In order to confirm the presence of secondary amino groups in compounds VII and IX, their N-acetyl derivatives were synthesized.

EXPERIMENTAL

2,5-Dimethyl-4-(3'-methyl-1'-butynyl)-4-piperidinol (III). A 3-necked round-bottomed flash fitted with a stirrer, reflux condenser, thermometer, and dropping funnel was charged with 84 g of powdered caustic potash and 750 ml of absolute ether. With vigorous stirring at −4° C, a mixture of 63.5 g of the piperidone I and 46.2 g of the carbinol II in 300 ml of absolute ether were gradually added. The reaction mixture was stirred with ice cooling for another 20 hr and then 10 ml of water was added at −4° C and it was stirred for another half an hour. The white precipitate of VI that deposited on the bottom of the flask was filtered off. It was insoluble in ether, benzene, and acetone. Weight 0.9 g, mp 275° C. The ethereal layer was separated off and the aqueous layer was carefully extracted with ether. The ethereal extract was neutralized with carbon dioxide and dried with calcined potassium carbonate. After the ether had been driven off, the viscous dark red reaction product was distilled in vacuum. The following fractions were obtained: 1st—70–75° C (2 mm), 2.84 g; 2nd—115–118° C (2 mm), 2.3 g; 3rd—165–167° C (2 mm), 65.1 g. The 1st fraction crystallized, mp 91–92° C (IV), and gave no depression of the melting point with an authentic sample of tetramethylbutynediol. After recrystallization from benzene, the 2nd fraction yielded 1.8 g of the γ-isomer of V with mp 93–94° C. After two redistillations, the third fraction yielded 59 g of the pure acetylenic glycol III in the form of a vitreous mass; bp 166–167° C (2 mm), mp 50–51° C. On thin-layer chromatography, a single spot was found: R_f 0.55 (Al_2O_3, activity grade II, acetone—methanol, 1 : 1). Found, %: N 6.37. Calculated for $C_{12}H_{21}NO_2$, %: N 6.63. The hydrochloride of III was obtained by adding an ethereal solution of dry hydrogen chloride to an ethereal solution of 0.5 g of the glycol and recrystallizing from ethanol the hydrochloride that precipitated. Yield 0.55 g (92%), mp 175–176° C (hygroscopic). Found, %: N 5.19. Calculated for $C_{12}H_{21}NO_2 \cdot HCl$, %: N 5.54.

Cleavage of the acetylenic glycol III. A carefully ground mixture of 6.33 g of III and 50 mg of caustic potash was melted in a distillation flask and subjected to vacuum. Redistillation of the decomposition product gave 2.47 g (65%) of the piperidinone I and 0.5 g (11%) of the piperidinol V with bp 114–116° C (2 mm), mp 93–94° C after recrystallization from benzene.

2,2,6,9-Tetramethyl-1-oxa-8-azaspiro[4,5]decan-4-one (VII). A flask with a stirrer was charged with 4.22 g of the acetylenic glycol III, 60 ml of 10% sulfuric acid, and 2 g of mercuric sulfate and was heated in the boiling water bath for 6 hr. The solution was filtered and evaporated in vacuum, and the residue was dried with potassium carbonate and repeatedly extracted with ether. The extract was dried with potassium carbonate, the ether was driven off, and the product was distilled in vacuum to give 2.99 g (71%) of VII with bp 134–135° C (2 mm), n_D^{20} 1.4840. Found, %: N 6.53. Calculated for $C_{12}H_{21}NO_2$, %: N 6.63.

N-Acetyl derivative of VII. 2.11 g of VII was mixed with 5.4 g of acetic anhydride, and after the end of the exothermic reaction the mixture was treated with dilute sodium carbonate solution. The oil that separated out was extracted with ether and the extract was dried with sodium sulfate. Distillation of the ether yielded 2.97 g (90%) of VII with mp 30–31° C (from petroleum ether). Found, %: N 5.74. Calculated for $C_{14}H_{23}NO_3$, %: N 5.53.

2,5-Dimethyl-4-(3"-methylbutyl)-4-piperidinol (VIII). In the presence of Raney nickel (0.5 g), 6.33 g of III was hydrogenated in 100 ml of ethanol at 30° C. After the absorption of the calculated amount of hydrogen, the ethanol was driven off and the residue was distilled. This gave 5.79 g (90%) of VIII with bp 159–160° C (4 mm), n_D^{20} 1.4880. Found, %: N 6.36. Calculated for $C_{12}H_{25}NO_2$, %: N 6.51.

2,2,6,9-Tetramethyl-1-oxa-8-azaspiro[4,5]decane (IX). A mixture of 2.12 g of VIII and 30 ml of 10% sulfuric acid was heated in the boiling water bath with stirring for 3 hr. At the end of the reaction, the solution was evaporated in vacuum, and the residue was saturated with potassium carbonate and extracted with ether. The ethereal extract was dried with calcined potassium carbonate and, after the ether had been driven off, the reaction product was distilled in vacuum to give 1.62 g (82%) of IX with bp 98–99° C (2 mm), n_D^{20} 1.4790. Found, %: N 6.76. Calculated for $C_{12}H_{23}NO$, %: N 7.10.

The N-acetyl derivative of IX was obtained by the reaction of 1 g of IX with acetic anhydride. The yield was 1.4 g (89%), mp 27–28° C (from petroleum ether). Found, %: N 4.81. Calculated for $C_{14}H_{25}NO_2$ g, %: N 5.40.

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