CYCLIZATION OF DEHYDRONEROLIDOL ACETATE – A ROUTE FOR THE SYNTHESIS OF CYCLIC ISOPRENOIDS

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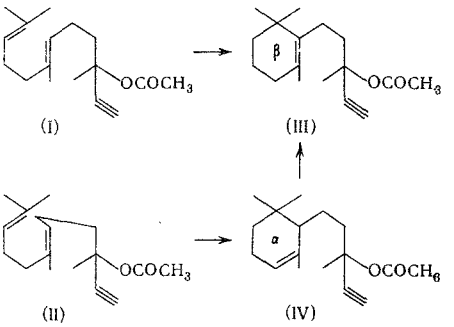
The α- and β-ionones are usually the starting materials in the synthesis of monocyclic isoprenoids. As is known [1], the cyclization of geranylacetone leads to the formation of the chromene derivative, i.e., a bicyclic system, instead of the dihydroionone desired in the given case. Numerous attempts to effect the cyclization of geranylacetone to dihydroionone, with prior protection of the carbonyl group, have proved unsuccessful, since the protective grouping was cleaved under the conditions of the cyclization reaction.

In this paper we studied the reaction for the cyclization of the geometric isomers of the acetate of the acetylenic alcohol obtained from geranylacetone (i.e., the acetate of dehydronerolidol), with the thought in mind of obtaining the monocyclo derivative. The starting trans- and cis-acetates of dehydronerolidol (I) and (II) were obtained in good yields from the corresponding geranylacetone derivatives [1] by the acetylene synthesis reaction (Favorskii–Nazarov reaction) and acetylation with acetic anhydride in the presence of phosphoric acid [2]. The acetates of the α- and β-cyclodehydronerolidols (IV) and (III), needed for identification of the cyclization products, were obtained by the same route, starting with the α- and β-dihydroionones. The cyclization reaction was run by the previously described [1] procedure using 100% sulfuric acid, at −70°, in nitropropane solution. Analysis of the reaction products, as well as control of the quality of the starting materials, was accomplished by gas-liquid chromatography (GLC). It was found that the cyclization of (I) gives a 90% pure (III) in good yield (up to 70%).



Running the cyclization reaction under milder conditions (greater dilution), with the periodic removal of samples, makes it possible to follow the rate of formation of (III) with time. A comparison of the data of such an experiment with the experiment on the isomerization of the α-acetate (IV) to the β-isomer (III), run under strictly analogous conditions, indicates that the isomerization goes much more slowly, which means that the β-isomer (III) is the primary reaction product formed in the cyclization of (I). The picture for the cyclization of the cis-dehydronerolidol acetate (II) proved to be much more complicated. Together with the α-isomer, the β-isomer is always formed in the cyclization of (II), in which connection its formation is mainly explained by the isomerization of the α-isomer to the β-isomer under the conditions of running the cyclization, which was proved by a special series of experiments on the isomerization of (IV) under these conditions. Although the isomerization reaction goes somewhat more slowly than the cyclization reaction also in this case, still we were unable (the same as in the case of the cyclization of the isomers of 2,6-dimethyl-2,6-undecadiene [3]), despite numerous experiments on modifying the reaction conditions, to obtain the pure α-cyclodehydronerolidol acetate (IV). The mixtures

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of the reaction products, richest in the α-isomer, contained only up to 65% of (IV). An attempt to avoid the isomerization by replacing the sulfuric acid by other cyclization agents, such as boron trifluoride and its etherate, proved unsuccessful. Here products were obtained that in their chromatographic parameters were quite different from the desired compounds, which is probably explained by the transformations of the acetylenic bond in the presence of these reagents.

Despite the isomerization, which interfered with following the course of the "pure" cyclization reaction, the obtained data unequivocally indicate that (IV) is predominantly formed in the cyclization of (II), which is then easily isomerized to the β-isomer, whereas the β-isomer is formed directly from the trans-acyclic derivative. As a result, also on the example of such compounds we again observe a dependence of the stereospecificity of the cyclization reaction on the configuration of the isolated 6,7 double bond of the acyclic molecule [3]. The easy isomerization of (IV) to (III) makes it possible to obtain (III) in good yield, starting with a mixture of the cis- and trans-acyclic derivatives. In other words, a mixture of the cis-trans geranylacetones can be used in the syntheses of β-monocyclic isoprenoids.

EXPERIMENTAL

The starting cis- and trans-geranylacetones were obtained by the fractional distillation in vacuo of a mixture of the isomers through a column with an efficiency of 120 theoretical plates [1]. The GLC analyses were run on a chromatograph equipped with a glass vaporizer, a 200×0.5 cm column, filled with Chromosorb W, not washed with alkali, impregnated with 2% neopentyl glycol succinate, and a flame-ionization detector; temperature 125°; carrier gas – helium, 50 ml/min.

Preparation of trans- and cis-Dehydronerolidols. With water cooling, a solution of 80 g of trans-geranylacetone in 0.5 liter of ether was added under an acetylene pressure of 10 atm to a stirred suspension of 200 g of powdered KOH in 1.5 liters of absolute ether in a steel reactor. The mixture was stirred for another 3 h. The ether layer was washed with water and dried over Na_2SO_4. After distilling off the ether and vacuum-distillation of the reaction product we obtained 75 g (83%) of trans-dehydronerolidol with b.p. 110-112° (3 mm); n_D^{20} 1.4803. In a similar manner, from 20 g of cis-geranylacetone and 60 g of KOH we obtained 18.3 g (81%) of cis-dehydronerolidol with b.p. 104-106° (1 mm); n_D^{20} 1.4800. Using the same method, the α- and β-cyclodehydronerolidols were obtained respectively from the dihydro-α- and dihydro-β-ionones.

Preparation of Acetates of trans- and cis-Dehydronerolidols (I) and (II). A mixture of 74 g of trans-dehydronerolidol, 54 g of acetic anhydride and 3.4 g of a 10% solution of H_3PO_4 in acetic anhydride was kept at room temperature overnight. Then water was added, the mixture was extracted with ether, and the ether solution was washed with $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. After distilling off the ether the product was vacuum-distilled. We obtained 64.7 g (73%) of (I) with b.p. 128-130° (2 mm); n_D^{20} 1.4718. Found %: C 78.02, 77.77; H 10.07, 10.02. $C_{17}H_{26}O_2$. Calculated %: C 77.82; H 9.99. In a similar manner, from 16 g of cis-dehydronerolidol, 11.7 g of acetic anhydride and 0.75 g of a 10% solution of H_3PO_4 in acetic anhydride we obtained 14.8 g (78%) of (II) with b.p. 118-120° (2 mm); n_D^{20} 1.4710. Found %: C 77.56, 77.30; H 9.89, 9.99. $C_{17}H_{26}O_2$. Calculated %: C 77.82; H 9.99. (IV) and (III) were obtained in a similar manner from the α- and β-cyclodehydronerolidols.

Cyclization of Acetates of trans- and cis-Dehydronerolidols (I) and (II). To a vigorously stirred mixture of 2.0 g of (I) and 10 ml of nitropropane at −75° was added a solution of 1.2 ml of 100% H_2SO_4 in 2 ml of nitropropane. After stirring for 30 min at −70° the reaction mass was decomposed by pouring with stirring into a mixture of water, ice and hexane. After the usual workup the product was distilled. We obtained 1.45 g (72%) of (III) (90% pure) with b.p. 105-107° (2 mm). The product (0.65 g) was purified by preparative chromatography in a thin layer on a plate 24×24 cm^2, thickness of Al_2O_3 (II activity) layer 2 mm, solvent – hexane:benzene 1:2. We obtained 0.5 g of (III). Found %: C 78.30, 78.34; H 10.30, 10.15. $C_{17}H_{26}O_2$. Calculated %: C 77.81; H 9.99. The infrared spectrum of the substance has an intense absorption band at 1740 cm^{-1} (carbonyl of ester group), and a band of medium intensity at 3300 cm^{-1} (≡C−H). The GLC analysis and a comparison of the complete infrared spectra of the cyclization product and the (III) obtained from dihydro-β-ionone disclosed that they were identical. In a similar manner from 2.0 g of (II) and 0.6 ml of H_2SO_4 in 15 ml of nitropropane, with stirring for 1 h, we obtained 1.5 g (75%) of a mixture of (IV) and (III) in a ratio of approximately 2:1, with b.p. 106-108°

(2 mm). Under the conditions of the preceding cyclization for 1 h this mixture is converted almost completely to pure (III), which was shown by the GLC data and a comparison of the complete infrared spectra.

CONCLUSIONS

1. The low-temperature cyclization of the dehydronerolidol acetates goes smoothly to give the monocyclo derivative, in which connection in harmony with the previously found rule, the cyclization of the trans-isomer leads to β-cyclodehydronerolidol, while the cis-isomer forms predominantly α-cyclodehydronerolidol.

2. The easy isomerization of α-cyclodehydronerolidol to the β-isomer offers a new way of synthesizing cyclic isoprenoids from a mixture of the geranylacetone isomers.

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