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Abstract

Full Text

Chemistry

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On the Mechanism of the Cyclization of Pseudoionone

(Presented by Academician B. A. Kazanskii, February 27, 1960)

In the course of studying the structural directionality of the cyclization of pseudoionone, we showed (1) that the primary product of this reaction is α-ionone, which, depending on the cyclization conditions (temperature, reaction time, and amount of cyclizing agent), is capable of isomerizing to a greater or lesser extent into β-ionone. A more detailed examination of the data we obtained showed that, under the conditions employed, the formation of β-ionone cannot be attributed entirely to isomerization of α-ionone, since the amount of the β-isomer in the mixture of ionones formed is always greater than in the direct isomerization of pure α-ionone under the same conditions, and this discrepancy exceeded the experimental error. In addition, it was shown that even under conditions in which isomerization of α-ionone into β-ionone practically does not occur ($-70°$), the formation of 10–12% of the β-isomer is invariably observed.

[scheme: cyclization leading to about 90% α-ionone and about 10% β-ionone, $R = H,\ CH_3$]

It turned out that a similar regularity is also observed in the cyclization of pseudoirone at $-70°$. In this case as well, predominantly the α-isomer is formed, with an admixture (about 7%) of β-irone. Pure β-irone can be obtained, like β-ionone, by isomerization of the α-isomer.

The conditions we used for the cyclization of pseudoionone and pseudoirone are conditions of stereospecific cyclization (2), and it was essential to determine to what extent the structural directionality of this reaction depends on the geometrical isomerism of the starting ketone. If such a dependence existed, then one could consider the formation of a small amount of the β-isomer to be the result of cyclization of the cis form, which may be present in the starting pseudoionone and pseudoirone. According to Shinz (3), cyclization of cis- and trans-pseudoionones gives the same mixture of ionones; however, the cyclization conditions he used compelled us to treat this conclusion with caution.

In order to resolve this question finally and unambiguously—a question very important for elucidating the mechanism of the cyclization reaction—we studied the cyclization of pure trans-pseudoionone, of a mixture of cis and trans isomers obtained from natural citral and containing 12% cis-pseudoionone (3), and of a synthetic mixture of cis and trans isomers (1:1) under conditions of stereospecific cyclization, and moreover under conditions that practically exclude the possibility of isomerization of α-ionone into β-ionone. It turned out that in all these cases completely identical mixtures of cyclization products are obtained, containing (according to UV-spectral data) 85–90% α-ionone and 10–12%

β-isomer. These data unambiguously show that the structural direction of the cyclization of pseudoionone does not depend on the cis- or trans-configuration at the 6–7 double bond of the starting ketone, and that the formation of the indicated amount of β-ionone is the result of an independent reaction occurring in parallel.

On the basis of Ruzicka' s ideas (4) concerning the role of the nonclassical cation in the cyclization reactions of isoprenoids, the scheme of the mechanism of pseudoionone cyclization that most fully accounts for all the regularities established above may be represented as follows:

Reaction scheme showing trans and cis pseudoionone pathways through nonclassical cations II and IIa, intermediates I and Ia, and products IV, III, and V, with arrows labeled H^+, A^-, 90%, and 10%.

Since it turned out that the structural direction of cyclization does not depend on the configuration of the starting ketones, formation of the final reaction products does not proceed through intermediate, spatially fixed forms (I and Ia), whose stabilization, in accordance with the general regularities of elimination reactions (5), should have given α-ionone from trans-pseudoionone and β-ionone from its cis-isomer. From this it is necessary to assume that the principal direction of stabilization of both possible nonclassical cations (II and IIa), corresponding to the trans- and cis-forms of pseudoionone, is direct ring closure with migration of the double bond into the α-position, by analogy with the Prins reaction and cationotropic rearrangements. This direction of the reaction makes understandable the initial and predominant formation of α-ionone (IV) and the independence of this result from the cis- and trans-configuration of the starting ketone.

However, alongside this principal reaction there occurs recombination of the nonclassical cations (II and IIa) into one and the same classical cation (III), whose most probable stabilization takes place as a result of elimination of a tertiary hydrogen atom with formation of the conjugated system of the β-isomer (V). This side direction of the cyclization reaction explains the appearance of β-ionone in the mixture, the amount of which should depend only on the ratio of the rate of formation of cation (III) and the rate of direct cyclization of the nonclassical cations into α-ionone (IV).

It does not appear possible to study the kinetics of this side reaction, occurring in parallel, since the isomerization of α-ionone into β-ionone should also proceed through the intermediate formation of the classical cation (III). The only possibility of influencing the rate of recombination of the π-complex into the classical cation might have been a change in the nature of the solvent in which the low-temperature acid cyclization of pseudoionone is to be carried out. However, an attempt to replace nitroparaffins with other solvents (hydrocarbons, alkyl halides, liquid ···

SO_2, simple and complex esters, fatty acids, etc.) was not successful, because at low temperature these solvents either dissolved sulfuric acid poorly or almost completely suppressed its acidic properties.

Extensive material on the cyclization of isoprenoid compounds (6) shows that the exclusive or predominant formation of α-isomers is a general regularity of this reaction, and therefore the proposed scheme of the cyclization mechanism apparently has a general character. The schemes of the cyclization mechanism discussed previously, using pseudoionone as an example, (7,8) cannot be considered satisfactory, since they do not reflect this basic regularity.

Experimental Part*

In the cyclization reaction the following were used: 1) pseudoionone obtained from natural citral; 2) trans-pseudoionone obtained from pure geraniol (regenerated from crystalline diphenylurethane with m.p. 80° and purified from the diphenylamine impurity by chromatography on alumina) by oxidation and simultaneous condensation with acetone (3). The trans-pseudoionone used had b.p. 112–114°/1 mm, n_D^{20} 1.5308, and gave, in 90% yield, 2,4-dinitrophenylhydrazone, m.p. 148–149° (methanol-dioxane) (3); 3) a mixture of trans- and cis-pseudoionones, obtained as follows. Purified geraniol was isomerized to nerol** in the presence of caustic soda (10). Unreacted geraniol was separated by two treatments with calcium chloride. The residue not reacting with calcium chloride was converted into diphenylurethane, and a certain amount of geraniol diphenylurethane was also isolated from the mother liquor of the diphenylurethane. The noncrystallizing residue after saponification was converted into the alcohol, which, after chromatography on alumina, gave diphenylurethane with m.p. 54–60° (11). Oxidation of this alcohol with simultaneous condensation with acetone led to a mixture of trans- and cis-pseudoionones, the composition of which was estimated by fractional crystallization of their 2,4-dinitrophenylhydrazones (methanol-dioxane). In this way it was shown that the mixture obtained contains equal amounts of trans- and cis-pseudoionones, whose 2,4-dinitrophenylhydrazones melt at 148–149° (methanol-dioxane) and 118–120° (methanol), respectively (3).

Cyclization of pseudoionones. a. To a solution of 3.0 ml of 100% sulfuric acid in 10 ml of nitropropane at −70°, over 4 min, was added a cooled mixture of 2.0 g of trans-pseudoionone and 5 ml of nitropropane. After stirring for 1 h, the reaction mixture was decomposed by pouring (with stirring) into a mixture of 40 ml of water with ice and 30 ml of hexane. The aqueous part was extracted three times with hexane; the hexane solution was washed with water, with sodium bicarbonate solution, again with water, and dried over potash. After distillation of the hexane and nitropropane, the residue was distilled in vacuo. There were obtained 1.55 g of substance with b.p. 75–78°/1 mm and n_D^{20} 1.500; residue, 0.3 g. The UV spectrum of this cyclization product has λ_{max}227 mμ, ε 13400, and λ_{max}294 mμ, ε 1300, which corresponds to a content of 90% α-ionone and 12% β-ionone.

b. Cyclization of a mixture of trans- and cis-pseudoionones (1 : 1) was carried out under strictly analogous conditions; 0.8 g of product was obtained, with b.p. 81–84°/1 mm and n_D^{19} 1.4990; residue, 0.5 g. The UV spectrum of the cyclization product has λ_{max}227 mμ, ε 12080, and λ_{max}294 mμ, ε 1275, which corresponds to a content of 83% α-ionone and 11% β-ionone.

c. Cyclization of pseudoionone obtained from natural citral under the same conditions led to 1.5 g of product with b.p. 78–81°/1 mm with n_D^{19}1.5000; residue 0.3 g. The UV spectrum has λ_{max}227 mμ, ε12790, and λ_{max}294 mμ, ε1306, which corresponds to a content of 86% α-ionone and 12% β-ionone.

An attempt to isomerize α-ionone into β-ionone under conditions strictly analogous to those described above led to the isolation of practically unchanged α-ionone. Isomerization under these conditions proceeds extremely slowly, and over 10 hours the content of β-ionone increased from 5% in the initial α-ionone to 8% in the reaction product. The UV spectrum of the initial α-ionone had λ_{max}227 mμ, ε13300, and λ_{max}297 mμ, ε564, which corresponds to a content of 93% α-ionone and 5% β-ionone; after the reaction had been carried out, the ionone obtained had λ_{max}227 mμ, ε12600, and λ_{max}297 mμ, ε830, i.e., contained 87% α-ionone and 8% β-ionone.

Cyclization of pseudoirone. The 3-methyllinalool required for the synthesis of pseudoirone was obtained by the addition of hydrogen bromide to 2,3-dimethylbutadiene, condensation of the bromide with sodium acetoacetic ester, subsequent acetylene-synthesis reaction, selective hydrogenation, and conversion into the primary alcohol by analogy with the synthesis of linalool ([9]). Oxidation of 3-methyllinalool with simultaneous condensation with acetone gave pseudoirone with b.p. 105-116°/1 mm and $n_D^{18.5}$1.5340.

To a solution of 15 ml of 100% sulfuric acid in 50 ml of nitropropane at −70°, over 20 min, was added a cooled solution of 10 g of pseudoirone in 25 ml of nitropropane. After stirring for 1 hour, the reaction mixture was decomposed by pouring it (with stirring) into a mixture of 200 ml of water with ice and 150 ml of hexane. The aqueous portion was extracted three times with hexane; the hexane solution was washed with water, sodium bicarbonate solution, again with water, and dried over potassium hydroxide. After distilling off the hexane

* Carried out with the participation of T. N. Chernova.

** The data available in the literature (9) on the possibility of isolating nerol by chromatography on alumina of the reaction product of geranyl bromide with potassium acetate in dimethylformamide solution proved to be erroneous.

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and nitropropane, the residue was distilled in vacuo. This gave 7.3 g of cyclization product with b.p. 99-103°/1 mm and $n_D^{20}1.5020$. Its UV spectrum has $\lambda_{\text{max}}226.5$ mμ, $\varepsilon13610$, and $\lambda_{\text{max}}294$ mμ, $\varepsilon912$, which corresponds to a content of 85% α-irone and 7% β-irone.

Addition of one equivalent of hydrogen to the cyclization product did not lead to a compound giving an individual semicarbazone, on the basis of which it must be assumed that the irone obtained is apparently a mixture of stereoisomeric α-irones ([12]). Special tests of the irone showed that the low-temperature cyclization of pseudoirone gives a product with very valuable perfumery properties.

Isomerization of α-irone into β-irone. To a solution of 3.0 ml of 100% sulfuric acid in 10 ml of nitromethane at −20°, over 3 min, was added a mixture of 2.0 g of the α-irone obtained and 5 ml of nitromethane. During the next 3 min the temperature of the mixture was brought to +10°, and the reaction mixture was stirred for a further 10 min. Decomposition and isolation were carried out in the usual manner. This gave 1.75 g of isomerization product with b.p. 90-94°/1 mm and $n_D^{18}1.5140$. From 0.8 g of the product, 0.4 g of the semicarbazone of β-irone was obtained, m.p. 167-168° (from alcohol) ([12]).

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