Reinvestigation of the Nazarov cyclization of 1-(3-hydroxypropynyl)cyclododecan-1-ol to bicyclo[10.3.0]pentadec-1(12)-en-13-one

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Reinvestigation of the acid-catalyzed cyclization of 1-(3-hydroxypropynyl)cyclododecan-1-ol under the conditions of the Nazarov reaction demonstrated that this conversion yields two isomeric bicyclic ketones, namely, bicyclo[10.3.0]pentadec-1(12)-en-13-one and bicyclo[10.3.0]pentadec-1-en-3-one. The latter compound is thermodynamically less stable.

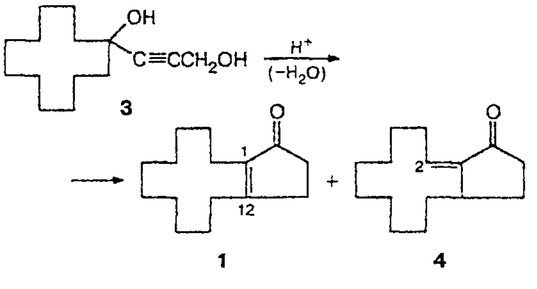
Key words: 1-(3-hydroxypropynyl)cyclododecan-1-ol, acid-catalyzed cyclization, Nazarov reaction, unsaturated bicyclic ketones.

Bicyclo[10.3.0]pentadec-1(12)-en-13-one (**1**) is a key intermediate in the commercial synthesis of valuable perfumes, namely, cyclopentadecanone (exaltone) and muscone, from cyclododecanone (**2**).[1,2]

Ketone **1** was first synthesized from **2** in 1957.[3] Ketone **2** was condensed with diethyl succinate according to the Stobbe reaction. The reaction product was subjected to cyclization and decarboxylation. Crystalline ketone **1** was isolated in a yield of 47% (m.p. 28—29 °C). Other cyclization products were not studied. This method of preparation of ketone **1** was often used in the synthesis of cyclopentadecanone and muscone.[1,2,4] In 1976, a simpler method for the synthesis of a bicyclic ketone (the authors believed that it was ketone **1**) was reported.[5] The method involved the reaction of ketone **2** with the lithium derivative of propyn-2-ol in liquid NH_3 and cyclization of acetylenic alcohol (**3**) obtained under the action of H_2SO_4 in a methanol solution. At the stage of cyclization of **3**, the yield of the target ketone was 76%. However, this bicyclic ketone, unlike the ketone described in Ref. 3, was obtained as a yellow oil, and its structure was not established.

We have demonstrated[6] that addition of propargyl alcohol to ketone **2** proceeds readily under the action of KOH in THF at 20 °C by the Favorskii reaction to form alcohol **3**, while cyclization of alcohol **3** in a solution of acetic acid in the presence of a KU-2 cation exchanger or H_2SO_4 gave (after crystallization from hexane) ketone **1** in yields of 73% and 60%, respectively. Cyclization in ethanol in the presence of H_2SO_4 gave ketone **1** in a 53% yield. Other possible cyclization products were not studied.

In our studies, we needed ketone **1**, and we decided to prepare **1** by cyclization of acetylenic alcohol **3** according to the procedures reported in Refs. 5 and 6. We noted that ketone **1** reported in Ref. 5 is a viscous liquid, whereas in Refs. 3 and 6, ketone **1** was described as a crystalline compound with a melting point of 29—30 °C. A more detailed study of the cyclization of acetylenic alcohol **3** demonstrated that under various reaction conditions, a mixture of two isomeric α,β-unsaturated bicyclic ketones, namely, crystalline ketone **1** and liquid ketone **4**, form. The ratio of these ketones depends on the solvent, the nature of the acid catalyst, and the reaction temperature. Crystalline ketone **1** obtained by us is identical with the ketone reported in Refs. 3 and 6. According to the results of elemental analysis, ketone **4** has a composition ($C_{15}H_{24}O$) identical to that of ketone **1**. According to the data of IR spectroscopy, it is an α,β-unsaturated ketone whose refraction index differs from that of ketone **1**. The dinitrophenylhydrazone of **4** with the dinitrophenylhydrazone of ketone **1** gave melting point depression. It was confirmed by ^1H NMR spectroscopy that ketone **4** is bicyclo[10.3.0]pentadec-1-en-13-one. In addition to the complex multiplet in the δ 0.6—2.3 region, the ^1H NMR spectrum of liquid ketone **4** has a singlet at δ



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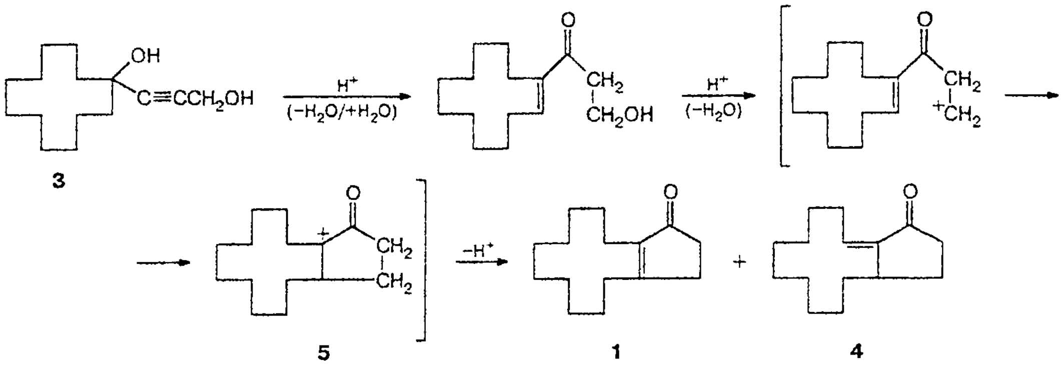
Scheme 1



4.86, which was assigned to the signal of the proton at the double =CH bond of the twelve-membered ring of ketone **4**. The ratio of ketones **1** and **4** formed in the course of cyclization of the mixture was determined from the change in the refraction index and by separating ketones **1** and **4** by low-temperature crystallization.

Therefore, cyclization of acetylenic alcohol **3** under the action of acid catalysts yields two isomeric unsaturated bicyclic ketones **1** and **4** rather than one ketone **1** as was reported previously.[5,6]

We believe that cyclization of alcohol **3** proceeds according to Scheme 1, which was suggested by Nazarov[7] and confirmed in Ref. 8.

The intermediate carbocation **5** that forms by elimination of a proton gives two isomeric unsaturated ketones **1** and **4**. Ketone **4** is completely converted to ketone **1** by isomerization of the double bond of ketone **4** under the action of catalytic amounts of $RhCl_3 \cdot 4H_2O$ in ethanol. Therefore, ketone **1** is thermodynamically more stable than ketone **4**:

$$\mathbf{4} \xrightarrow[C_2H_5OH,\ \Delta]{RhCl_3 \cdot 4H_2O} \mathbf{1}$$

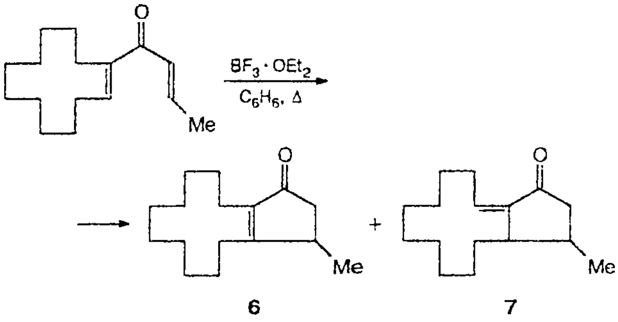
In the presence of a rhodium catalyst, the mixture of ketones **1** and **4** formed by cyclization of alcohol **3** undergoes isomerization to give ketone **1** in high yield.

From the data obtained it follows that the ratio of ketones **1** and **4** obtained by cyclization of alcohol **3** depends on a number of factors such as the solvent, the nature of the acid catalyst, and the temperature.

Previously,[9] analogous formation of two isomeric bicyclic ketones, namely, 15-methylbicyclo[10.3.0]pentadec-1(12)-en-13-one (**6**) and 15-methylbicyclo[10.3.0]pentadec-1-en-13-one (**7**), was observed in the cyclization of 1-propenylcyclododecen-1-ylketone under the action of $BF_3 \cdot OEt_2$ in benzene.

In this mixture, ketone **7** was also isomerized to ketone **6** under the action of a rhodium catalyst.

The published data[9] and our studies demonstrated that cyclization of divinylketones containing one vinyl group in the ring, which proceeds by the Nazarov reaction, can yield a mixture of bicyclic isomeric α,β-unsaturated ketones containing the keto group in a five-membered ring.



Experimental

The ¹H NMR spectra were recorded on a Bruker WP-200-SY instrument in $CDCl_3$. The IR spectra were obtained on a UR-20 spectrometer using KBr pellets. The purities of ketones **1** and **4** were established by GLC on a quartz capillary column (32 m×0.24 mm); FFAP was used as the stationary phase; the thickness of the film was 0.12 μ; helium was used as the carrier gas (1.7 bar); and the temperature was 180 °C. The Raman spectra were recorded on a laser Jobin Yvon U-1000 spectrometer using the argon excitation line of a ILA-120 laser at 514.5 nm and a laser power of 100 W.

1-(3-Hydroxypropynyl)cyclododecan-1-ol (3). A solution of propargyl alcohol (13.6 g, 0.24 mol) in dry THF (100 mL) was added dropwise with stirring to a mixture of cyclododecanone (40 g, 0.22 mol) and KOH (91 g, 1.6 mol) in THF (300 mL) at –20 °C. After 2 h, the mixture began to harden, which made further stirring difficult. The reaction mixture was kept for 12 h and then diluted with H_2O (400 mL). The precipitate was filtered off, washed on a filter with water (2×100 mL) and THF (2×50 mL), and dried *in vacuo* with the use of a water jet pump at 50—60 °C. Alcohol **3** was obtained in a yield of 40.6 g (78%), m.p. 124—125 °C (*cf.* Ref. 1: m.p. 126—127 °C).

Cyclization of 1-(3-hydroxypropynyl)cyclododecan-1-ol (3). **A.** A solution of alcohol **3** (18.5 g, 0.077 mmol) and 92% H_2SO_4 (3 mL) in CH_3COOH (70 mL) was boiled for 10 h. After cooling, water was added to the reaction mixture. The oil that formed was extracted with ether. The ethereal solution was washed with a solution of $NaHCO_3$ and dried with Na_2SO_4. After the removal of ether, a mixture of ketones **1** and **4** was obtained in a ratio of 7 : 3 in a yield of 10.6 g (62%), b.p. 145—147 °C (1 Torr), n_D^{25} 1.5195. IR (KBr), ν/cm^{-1}: 1670 (CO), 1600 (C=C), 1620 (C=C). Crystalline ketone **1** precipitated after storage of the mixture of ketones. The liquid was carefully decanted. The solid phase was crystallized from pentane, and ketone **1** was obtained, m.p. 27—28 °C, n_D^{25} 1.5230. IR (KBr), ν/cm^{-1}: 1700 (C=O), 1600 (C=C). 2,4-Dinitrophenylhydrazone: m.p. 189—190 °C (from AcOEt), *cf.* Ref. 3: m.p. 27—28.5 °C, n_D^{25} 1.5838; 2,4-dinitrophenylhydrazone: m.p. 192—193 °C. After repeated freezing of crystals, liquid ketone **4** was obtained from the liquid fraction, n_D^{25} 1.5100. IR (KBr), ν/cm^{-1}: 1703 (C=O), 1620 (C=C). ^{1}H NMR ($CDCl_3$), δ: 4.86 (s, 1 H, =CH). Raman spectrum, ν/cm^{-1}: 1700 (C=O), 1636 (C=C in conjugation). Found (%): C, 81.15: H, 10.71. $C_{15}H_{24}O$. Calculated (%): C, 81.70; H, 10.90. 2,4-Dinitrophenylhydrazone, m.p. 184—185 °C (from AcOH). Found (%): C, 62.91; H, 7.13; N, 14.11. $C_{21}H_{28}N_4O_4$. Calculated (%): C, 63.00; H, 7.00; N, 14.00. A sample mixed with 2,4-dinitrophenylhydrazone of ketone **1** gave melting point depression (178—179 °C).

B. A solution of alcohol **3** (28 g, 0.12 mol) in CH_3COOH (100 mL) was heated in the presence of a KU-2 (H^+) cation exchanger (12 g) with stirring according to the procedure reported previously.[6] The corresponding workup and distillation gave a mixture of ketones **1** and **4** in a ratio of 7 : 3 in a yield of 20.5 g (79%), n_D^{25} 1.5195. This mixture hardened upon storage. Recrystallization of the mixture from pentane gave ketone **1** in a yield of 14.4 g (68%), m.p. 28—29 °C, n_D^{25} 1.5232. The pentane was evaporated, the liquid residue was frozen out, and ketone **4** was obtained in a yield of 5.1 g (25%), n_D^{25} 1.5100.

C. To a solution of alcohol 3 (4 g, 0.017 mol) in EtOH (40 mL) 92% H_2SO_4 (1.2 mL) was added. The reaction mixture was boiled for 40 h. Distillation gave a mixture of ketones **1** and **4** in a ratio of 75 : 25 in a yield of 1.85 g (50%), n_D^{25} 1.5190.

Isomerization of ketone 4 to ketone 1. To a solution of ketone **4** (8.1 g, 0.037 mmol) in anhydrous EtOH (20 mL) $RhCl_3 \cdot 4H_2O$ (0.2 g) was added. The reaction mixture was boiled for 14 h. The product was poured into water and extracted with benzene. The benzene solution was washed with a solution of $NaHCO_3$ and dried with Na_2SO_4. After the removal of the solvent, the residue was distilled, b.p. 143 — 144 °C (1 Torr). Ketone **1** was obtained in a yield of 7.3 g (90%), m.p. 27—28 °C (from pentane), n_D^{25} 1.5238. IR (KBr), ν/cm^{-1}: 1700 (C=O), 1620 (C=C). Found (%): C, 81.68; H, 11.03. $C_{15}H_{24}O$. Calculated (%): C, 81.82; H, 10.90.

Isomerization of a mixture of ketones 1 and 4 to ketone 1. A 60 : 40 mixture of ketones **1** and **4** (20 g, 0.09 mol) was treated as described previously. Distillation gave ketone **1** in a yield of 16.5 g (82%), n_D^{25} 1.5238. IR (KBr), ν/cm^{-1}: 1700 (C=O), 1620 (C=C).

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