SYNTHESIS OF 2,5,5-TRIMETHYLCYCLOHEPTANONE

G. V. Kalechits and N. G. Kozlov   UDC 547.597.2

The synthesis of 2,5,5-trimethylcycloheptanone from 3-carene was described. It was demonstrated that hydrogenolysis of cis-*caran-trans-4-ol on nickel- and copper-containing catalysts occurred with cleavage of the internal C^1–C^6 bond of the cyclopropane ring and predomonant (up to 95%) formation of 2,5,5-trimethylcycloheptanone.*

3-Carene, which is the second most abundant component of turpentine, is used as starting material to prepare difficultly accessible trimethylcycloheptane derivatives owing to its availability.

An unsaturated group in the cyclohexane portion of carane compounds is known to have an important influence on the direction in which the cyclopropane ring opens [1-3]. Thus, in contrast with *cis*- and *trans*-caranes (3,7,7-trimethylbicyclo[4.1.0]heptanes), which undergo hydrogenolysis exclusively at the external C^1–C^7 and C^6–C^7 bonds of the three-membered ring [4], the internal C^1–C^6 bond opens preferentially in 3-carene and forms 1,1,4-trimethylcycloheptane [1, 2]. Only the external C^1–C^7 bond opens in caran-2-one, in which the three-membered ring is conjugated to the carbonyl. The principal products are isomeric 2-substituted *p*-menthane derivatives [3]. We demonstrated previously that *cis*-caran-*trans*-4-ol is converted over a Cu-carbon catalyst at 320°C in a stream of H_2 by 39% into a cyclic ketone, 2,5,5-trimethylcycloheptanone, as a result of the opening of the C^1–C^6 bond [5].

Herein we report results from an investigation of the transformations of *cis*-caran-*trans*-4-ol (**1**) under hydrogenolysis conditions over Cu- and Ni-containing catalysts in order to develop a preparative method for preparing difficultly accessible 2,5,5-trimethylcycloheptanone (**2**), which in turn can act as a convenient building block for the synthesis of more complicated compounds with the cycloheptane moiety.

Starting *cis*-caran-*trans*-4-ol (**1**) was prepared by oxidative hydroboration of 3-carene using the literature method [6]. Alcohol **1** underwent hydrogenolysis in a flow system in the presence of catalyst. We used Ni/CrO_3, Cu/ZnO, Cu/MgO, Cu/Al_2O_3, Cu/Ni, and Pd/C as catalysts. The catalyst was reduced beforehand, after which **1** was added at a volumetric flow rate of 0.2-0.4 h^{-1} without stopping the flow of H_2. The reaction temperature was varied in the range 230-270°C [7]. Qualitative and quantitative compositions of the products were monitored and identified by GC.

Table 1 gives the results, which indicate that the principal direction of the transformation under hydrogenolysis conditions was opening of the internal C^1–C^6 bond of the cyclopropane ring to form 2,5,5-trimethylcycloheptanone (**2**). Smaller amounts of *cis*- and *trans*- *m*- and *p*-carvomenthones (**3-6**) were formed. The reaction was most selective if Ni/CrO_3 catalyst was used. A complicated mixture of unsaturated and saturated hydrocarbons was produced with catalysts such as Cu/Al_2O_3 and Pd/C because of dehydration of **1**, isomerization, and subsequent partial or complete hydrogenation.

In order to study the sequence of transformations occurring during hydrogenolysis, we observed the change in the composition of the products with simultaneous hydrogenation—dehydrogenation over Cu/Ni catalyst, which is used in industry to dehydrogenate borneols into camphar [8]. Table 2 gives the product compositions.

The results show that **1** was dehydrogenated in the first step to *cis*-caran-4-one (**7**), subsequent hydrogenolysis of which at the internal unshielded C^1–C^6 bond of the cyclopropane ring formed **2**. Selective hydrogenolysis of the C^1–C^6 bond is probably due to the availability of this bond for adsorption on the catalyst.


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TABLE 1. Products from Hydrogenolysis of *cis*-Caran-*trans*-4-ol (**1**)

Catalyst	Temperature, °C	Volumetric rate, h⁻¹	Product composition, % GC				
			1	**2**	**7**	**3+4**	**5+6**
Cu/MgO	250	0.2	10.0	62.5	7.1	14.6	5.4
	270	0.3	5.0	79.8	2.0	7.1	5.5
Cu/ZnO	250	0.2	4.9	74.3	3.4	14.5	2.8
	260	0.3	Tr.	86.0	1.5	9.4	3.1
Ni/Cr₂O₃	250	0.3	Tr.	85.6	1.2	2.2	1.0
	270	0.4	Tr.	94.6	Tr.	Tr.	Tr.
	290	0.4	Tr.	93.0	Tr.	Tr.	Tr.

TABLE 2. Products from Hydrogenolysis of *cis*-Caran-*trans*-4-ol (**1**) on Copper-Nickel Catalyst at 190°C

Reaction time, h	Reaction mixture composition, % GC				
	1	**7**	**2**	**3+4**	**5+6**
0.5	53.7	28.4	16.7	0.7	0.5
1.5	37.5	14.3	46.4	1.0	0.8
3.0	22.7	16.9	52.0	4.5	3.9
5.0	11.5	19.5	60.1	5.1	3.8
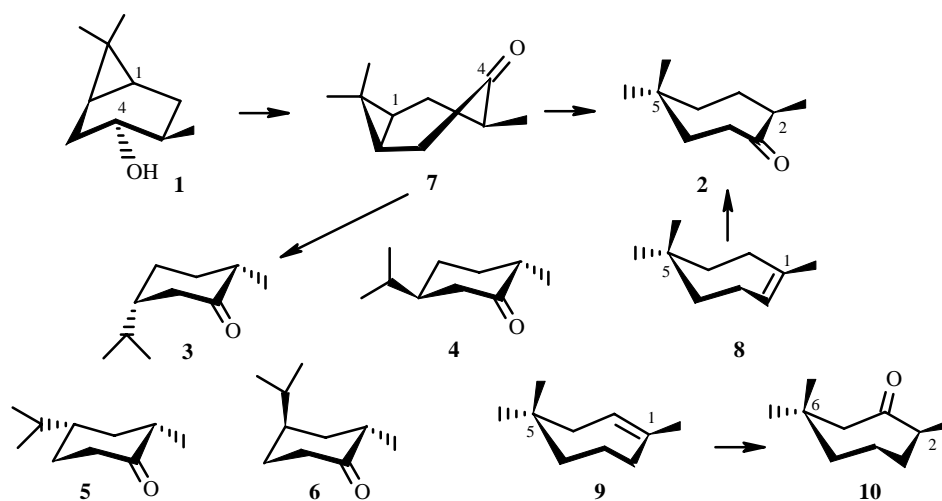
According to the literature [9], **7** exists in a conformation with the six-membered ring as a half-chair and an *e*-10-CH₃ group. This conformation is sterically unhindered for adsorption of the C^1–C^6 bond on the catalyst whereas the C^1–C^7 and C^6–C^7 bonds are shielded by the *gem*-dimethyl group on C^7. Compound **2** was isolated from the hydrogenolysis products of **1** over Ni/CrO₃ by fractional distillation through a column of 50 theoretical plates. Its structure was consistent with elemental analysis; IR, PMR, and ¹³C NMR spectra; and retrosynthesis. The IR spectrum contained a strong band at 1707 cm⁻¹ characteristic of carbonyl stretching vibrations. Deformations of the methyl next to the C=O appeared at 1155 and 1167, of the *gem*-dimethyl on C^5, at 1365 and 1390.

The PMR spectrum had signals for protons in the *α*-position to the carbonyl. A multiplet at 2.31-2.38 ppm belonged to the C^2 proton; a multiplet at 2.48-2.63 ppm, to two protons on C^7. Protons of the methyl on C^2 appeared as a doublet at 1.05 ppm with SSCC 7.1 Hz. Singlets for the *gem*-dimethyl protons were observed at 0.89 and 0.96 ppm. In the ¹³C NMR spectrum, the carbonyl C atom was observed at weak field at 216.8 ppm. The composition and structure of ketones **3-6** were confirmed by the fact that Wolff—Kishner reduction of them formed 1,1,4-trimethylcycloheptane and *cis-* and *trans- p-* and *m*-menthanes, respectively. The hydrocarbons were identified by GC with the appropriate standards [10].

Furthermore, we performed hydroboration of 1,4,4-(**9**) and 1,5,5-(**8**), trimethylcycloheptenes isolated from the products of partial hydrogenation of 3-carene over Cu/Ni catalyst [2]. These were first reported by Cocker et al. [1]. For some time their structure assignments were not questioned [2, 10]. In the present work, hydroboration of **8** and **9** produced alcohols, subsequent oxidation of which formed the corresponding ketones **2** and **10**. As it turned out, **2**, which was isolated from the hydrogenolysis products of **1**, and the ketone synthesized from one of the trimethylcycloheptenes had identical physicochemical and spectral properties. Therefore, this hydrocarbon was 1,5,5-trimethylcycloheptene (**8**) and not 1,4,4-trimethylcycloheptene (**9**), as thought earlier [1]. From **9**, which was assigned [1] the 1,4,4-trimethylcycloheptene (**8**) structure, 2,6,6-trimethylcycloheptanone (**10**) was produced, the properties of which corresponded with the literature values [11] for the ketone produced from eucarvone.

Thus, we developed a preparative synthesis for 2,5,5-trimethylcycloheptanone and proved the positions of the double bonds in **8** and **9** using chemical methods.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer in the frequency range 400-3800 cm^{-1} as a thin layer between KBr plates. PMR spectra were recorded in CDCl$_3$ on a WM-360 spectrometer with TMS internal standard. ^{13}C NMR spectra were recorded on a WH-90 (Bruker) spectrometer at 22.62 MHz resonance frequency with full proton decoupling and TMS internal standard. GC was performed on a Vyrukhrom instrument with a FID, 2000×3 mm column, Chromaton N-AW-DMCS support, Reoplex-400 stationary phase, 100°C, and N$_2$ carrier gas at 50 mL/min. Preliminary separation was performed on a PAKhV-07 instrument, 3000×6 mm column packed with Chromaton N-AW-DMCS impregnated with 1,2,3-tris-(β-cyanoethoxy)-propane (20% of packing mass), 100°C, and He carrier gas.

2,5,5-Trimethylcycloheptanone (2). *cis*-Caran-*trans*-4-ol (**1**, 15.4 g, 0.1 mol) was passed in a H$_2$ stream through a catalyst (Cu/MgO, Cu/ZnO, Ni/Cr$_2$O$_3$) layer. The bulk weight of the catalyst was 15 mL. Catalyst was reduced beforehand and **1** was added at a volumetric flow rate of 0.2-0.4 h^{-1} without stopping the flow of H$_2$ (100-120 mL/min). The process temperature was 230-270°C. Table 1 gives the results. Fractional distillation through a column of 50 theoretical plates at 9 mm Hg afforded **2**, C$_{10}$H$_{18}$O, mp 85-86.5°C, n$_D^{20}$ 1.4600, d$_4^{20}$ 0.9065. IR spectrum (KBr, ν, cm^{-1}): 2960, 2870, 1707 (C=O), 1460, 1390, 1365, 1167, 1155. PMR spectrum (CDCl$_3$, δ, ppm, J/Hz): 0.89 and 0.96 (6H, s, 2CH$_3$), 1.05 (3H, d, J = 7.1, CH$_3$), 1.36-1.55 and 1.62-1.72 (6H, m, 3CH$_2$), 2.31-2.38 (1H, m, H-2), 2.48-2.63 (2H, m, H$_2$-7). ^{13}C NMR spectrum (CDCl$_3$, δ, ppm, TMS): 216.8 (C-1), 46.3 (C-2), 29.0 (C-3), 41.8 (C-4), 33.1 (C-5), 36.4 (C-6), 38.8 (C-7), 29.2 (C-8), 32.3 (C-9), 17.2 (C-10).

Transformation of 1 over Cu/Ni Catalyst at 190°C. Compound **1** (3.08 g, 0.02 mol) and catalyst (0.2 g) were heated at 190°C for 5 h taking samples and analyzing them by GC. Table 2 gives the composition of the products.

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