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Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 75th anniversary

Tandem Molecular Rearrangement in the Alkylation of Phenol with Camphene

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Abstract—The alkylation of phenol with camphene in the presence of boron trifluoride in glacial acetic acid was accompanied by tandem molecular rearrangement with formation of a mixture of *ortho*- and *para*-substituted phenols having 1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl and 5,5,6-trimethylbicyclo[2.2.1]hept-*exo*-2-yl substituents. The same products were obtained by rearrangement of 1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yloxybenzene under analogous conditions. Similar reactions performed in the presence of aluminum phenoxide as catalyst resulted in predominant formation of the corresponding *ortho*-substituted phenols.

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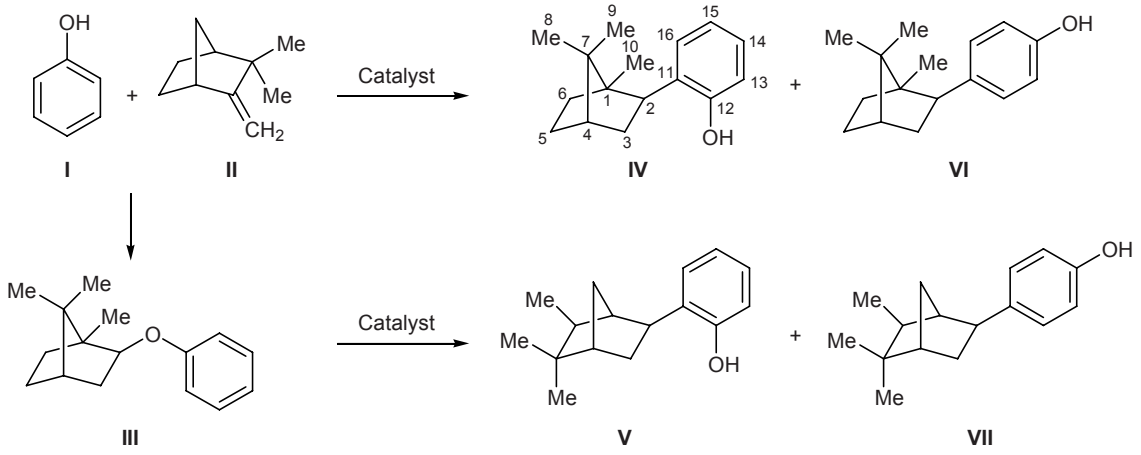
A large number of naturally occurring compounds, so-called terpenophenols, are products of mixed biogenesis of phenols and terpenoids [1, 2]. These compounds and structurally related phenols having bulky alkyl substituents have found application as intermediate products in the synthesis of fragrant substances [3, 4] and antioxidants [5]. Large-scale manufacture of alkylphenols is usually based on the alkylation of phenols with olefins in the presence of acid catalysts, which leads to complex mixtures of isomeric products [6]. Some homogeneous aluminum-based catalysts showed high *ortho*-selectivity in the alkylation of phenols; among these, the most active is aluminum phenoxide [7–9]. The use in such reactions of terpene derivatives that are characterized by very strong ability to undergo various skeletal rearrangements [10] adds much specificity to the alkylation process and highlights terpenophenols from other alkylphenols [11].

Scheme 1.



Alkylation of phenol (**I**) with camphene (**II**) and rearrangement of 1,7,7-trimethyl-*exo*-2-phenoxybicyclo[2.2.1]heptane (**III**)

Initial reactants (molar ratio)	Catalyst (10 wt %)	Temperature, °C	Reaction time, h	Conversion, %	Ratio of *ortho*/*para*-substituted phenols
I, **II** (1 : 1)	BF_3 in AcOH[a]	80	3	85	1 : 1
III	BF_3 in AcOH[a]	80	3	70	2 : 1
III	$(PhO)_3Al$	120	6	80	25 : 1
I, **II**, (1 : 1)	$(PhO)_3Al$	160	6	90	20 : 1

[a] A 35% solution of BF_3 in acetic acid.

The composition of alkylation products of phenol with camphene is very complex due to various types of isomerism [12–16]. Reactions of phenol with terpenes below 100°C resulted mainly in the formation of phenoxy-substituted terpenoids [12, 13, 17, 18].

In the present work we examined direct alkylation of phenol (**I**) with camphene (**II**) and rearrangement of phenoxybornane **III** catalyzed by boron trifluoride in glacial acetic acid and aluminum phenoxide (see table). The alkylation of phenol with camphene, as well as rearrangement of ether **III**, in the presence of BF_3 in AcOH gave a mixture of *ortho*- and *para*-substituted phenols **IV**–**VII** with different structures of the terpene substituent (Scheme 1). The product structure was unambiguously determined on the basis of their ^1H and ^{13}C NMR and IR spectra. The ratio of *ortho*-substituted phenols **IV** and **V** was 1 : 4, and the ratio of *para*-substituted phenols **VI** and **VII** was 1 : 2. The overall *ortho*/*para* ratio in the rearrangement of ether **III** was 2 : 1 (see table). In keeping with published data [13], this ratio suggests intermolecular mechanism of the rearrangement, i.e., alkylation of the aromatic ring is preceded by dissociation of the ether bond with formation of trimethylbicyclo[2.2.1]heptyl cation. The same mechanism is likely to be responsible for the formation of isomer mixture **IV**–**VII** in the reaction of camphene with phenol in the presence of BF_3; this means that alkyl phenyl ethers are not necessarily formed as precursors of alkylphenols. Thus the alkylation of phenol (**I**) with camphene (**II**) and rearrangement of ether **III** in acid medium give rise to the same set of products, and C-alkylation occurs under the same conditions as does the rearrangement of **III**.

However, different results were obtained in the reaction of phenol with camphene and in the rearrangement of ether **III** in the presence of aluminum phenoxide. The first process required a higher temperature, and the *ortho*/*para* isomer ratio was 25 : 1 against 20 : 1 in the rearrangement of **III**. Furthermore, no phenols **V** and **VII** were formed in the second reaction. According to our previous data [19], the ratio of *ortho*-substituted phenols **IV** and **V** in the alkylation of phenol (**I**) with camphene was 10 : 1.

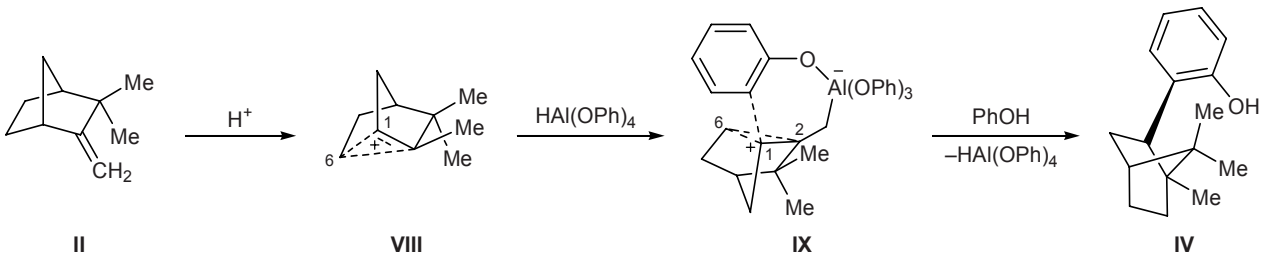
Our results indirectly indicate that the C-alkylation process in the presence of aluminum phenoxide involves preliminary etherification followed by rearrangement. In the first step, the aluminum atom in $Al(OPh)_3$ coordinates an additional phenol molecule with localization of proton in the vicinity of oxygen atoms, leading to the formation of ether **III**. When the reaction is carried out at low temperature, it may be stopped at the O-alkylation step with selective formation of ether **III**. Raising the temperature promotes rearrangement of **III** into C-substituted phenol.

The first step in the rearrangement of ether **III** in the presence of $Al(OPh)_3$ is coordination of the ether oxygen atom to aluminum. Next follows intramolecular tandem rearrangement of the ether into alkylphenol (in a way similar to Claisen rearrangement) and Wagner–Meerwein rearrangement of the terpene fragment.

Thus aluminum phenoxide as catalyst promotes selective alkylation of phenol (**I**) and rearrangement of ether **III** with predominant formation of *ortho* isomer **IV** with *exo* orientation of the benzene ring (80%).

The observed regio- and stereoselectivity in the alkylation of phenol (**I**) with camphene (**II**) may be rationalized in terms of intramolecular mechanism of the process with participation of aluminum coordination sphere (Scheme 2). Initially, addition of phenol to aluminum phenoxide gives $HAl(OC_6H_5)_4$ [20, 21]. Protonation of camphene with $HAl(OC_6H_5)_4$ generates cation **VIII**. The latter reacts with the catalyst, yielding intermediate cyclic complex **IX**. Spatial proximity of the electrophilic C^1 center to the *ortho*-carbon atom in the aromatic ring favors intramolecular *ortho*-alkylation which is accompanied by Wagner–Meerwein rearrangement [22]. A small amount of phenol **V** may be formed via alkylation of **I** with the corresponding cation generated by the action of $HAl(OC_6H_5)_4$ or as a result of secondary isomerization processes.

Scheme 2.



II **VIII** **IX** **IV**

Our experimental data on the rearrangements of ether **III** in the presence of BF_3 in acetic acid and in the presence of aluminum phenoxide led us to presume that in the first case the process follows intermolecular mechanism, and in the second, intramolecular.

Unlike isotope mass spectrometry, quantitative ^{2}H NMR spectroscopy provides a unique possibility for studying selective intramolecular isotope distribution which is very important for analysis of mechanisms of chemical reactions and paths of formation of organic compounds [23]. The results of ^{2}H NMR study on the molecular rearrangements in the alkylation of phenol with camphene will be reported later.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples prepared as KBr pellets or thin films (neat). The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM instrument at 300.13 and 75.03 MHz, respectively, using chloroform-*d* as solvent and reference (δ 7.26 ppm, δ_C 77.0 ppm). Signals were assigned using JMOD, COSY, NOESY, and HETCOR ^{13}C–^{1}H techniques.

The initial compounds and products were analyzed by GLC on a Kristall-2000 chromatograph (30-m×0.3-mm capillary column, stationary phase PEG 20; oven temperature programming from 100 to 240°C at a rate of 6 deg/min; carrier gas argon). Thin-layer chromatography was performed on Silufol UV-254 plates using diethyl ether–hexane (3:1) as eluent; spots were detected by treatment with a solution of vanillin, followed by heating to 110°C, or with a saturated solution of $KMnO_4$ at room temperature. Preparative column chromatography was performed on silica gel L (100–250 μm) or aluminum oxide (neutral, Brockmann activity grade I). The melting points were determined on a Kofler hot stage.

According to the GLC data, initial camphene (**II**, racemate) contained 5% of tricyclene; ether **III**: n_D^{20} = 1.5247, bp 190°C (0.98 atm).

Alkylation of phenol (I) with camphene (II) in the presence of aluminum phenoxide. Phenol, 5.6 g (59.5 mmol), was heated to 160°C, 0.06 g (2.2 mmol) of aluminum turnings was added in small portions, the resulting solution was cooled to 40°C, and 7.2 g (52.8 mmol) of camphene was added. The mixture was heated at 160–170°C until complete consumption of camphene (GLC), cooled, diluted with diethyl ether, treated with dilute hydrochloric acid to decompose the catalyst, and washed with water until neutral reaction. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. According to the GLC data, the residue contained 93 wt % of *orto*-substituted phenols. The product mixture was separated by column chromatography on aluminum oxide using hexane–diethyl ether as eluent (gradient elution) to isolate 80% of **IV**, 3% of **III**, 4% of **V**, and 8% of **VI**.

2-(1,7,7-Trimethylbicyclo[2.2.1]hept-*exo*-2-yl)-phenol (IV). Colorless crystals, mp 100°C (from hot hexane). IR spectrum (KBr), ν, cm^{-1}: 3560, 3476 (OH); 1152 (C–O); 1604, 1588, 1458 (C=C); 754, 828 (δCH). ^{1}H NMR spectrum, δ, ppm: 0.85 s (3H, C^{10}H$_3$), 0.90 s (3H, C^{8}H$_3$), 0.96 s (3H, C^{9}H$_3$), 1.36–1.45 m (1H, 6-H$_\alpha$), 1.47–1.55 d.d.d (1H, 6-H$_\beta$, J = 6.4, 9.0 Hz), 1.63–1.72 m (2H, 3-H), 1.74–1.97 m (2H, 5-H), 2.23–2.32 m (1H, 4-H), 3.18 t (1H, 2-H, J = 8.9 Hz), 4.80 s (1H, OH), 6.78–6.81 d.d (1H, 13-H, J = 1.3, 6.6 Hz), 6.92–6.98 t.d (1H, 15-H, J = 1.2, 6.4 Hz), 7.08–7.14 t.d (1H, 14-H, J = 1.5, 6.0 Hz), 7.37 br.d (1H, 18-H, J = 7.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.38 (C^{10}), 20.34 (C^9), 21.49 (C^8), 27.57 (C^5), 33.95 (C^3), 39.99 (C^6), 45.44 (C^2), 45.65 (C^4), 48.04 (C^7), 49.80 (C^1), 114.99 (C^{16}), 120.24 (C^{14}), 126.47 (C^{15}), 128.13 (C^{13}), 129.54 (C^{11}), 154.62 (C^{12}). Found, %: C 84.09; H 9.31. $C_{16}H_{22}O$. Calculated, %: C 83.43; H 9.63.

1,7,7-Trimethyl-*exo*-2-phenoxybicyclo[2.2.1]-heptane (III). Oily liquid, n_D^{20} = 1.5255. IR spectrum (neat), ν, cm^{-1}: 1604, 1592, 1458 (C=C); 754, 692 (δC–H); 1248 (C–O–C); 1084 (O–C). ^{1}H NMR spectrum, δ, ppm: 1.32 s (3H, C^{10}H$_3$), 1.19 s and 1.41 s (3H

each, C^8H_3, C^9H_3), 1.46–1.61 m (2H, 5-H, 6-H), 1.87–1.94 m (1H, 6-H), 2.06 m (2H, 5-H, 4-H), 2.12–2.2 m (2H, 3-H), 4.32 q (1H, 2-H, J = 3.7, 3.3 Hz), 7.13–7.20 m (3H, H_{arom}), 7.50–7.55 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.93 (C^{10}), 20.26 (C^9), 20.45 (C^8), 27.50 (C^5), 34.32 (C^6), 39.61 (C^3), 45.38 (C^4), 47.09 (C^7), 49.23 (C^1), 84.39 (C^2), 115.46 (C^{13}, C^{15}), 120.08 (C^{14}), 129.38 (C^{12}, C^{16}), 158.00 (C^{11}).

4-(1,7,7-Trimethylbicyclo[2.2.1]hept-*exo*-2-yl)-phenol (VI). Colorless crystals, mp 150°C (from hot heptane). IR spectrum (KBr), ν, cm^{-1}: 3276 (OH); 1620, 1604 (C=C); 824 (δC–H); 1244 (C–O). ^1H NMR spectrum, δ, ppm: 0.75 s (3H, $C^{10}H_3$), 0.81 s (3H, C^8H_3), 0.84 s (3H, C^9H_3), 1.25–1.39 m (2H, 6-H), 1.59–1.69 m (2H, 3-H), 1.74–1.87 m (2H, 5-H), 2.25 d.d.d.d (1H, 4-H, J = 3.5, 4.0, 4.5 Hz), 2.85 t (1H, 2-H, J = 9.0 Hz), 4.75 s (1H, OH), 6.74–6.77 d.t (2H, 12-H, 16-H, J = 3.0, 2.0, 6.8 Hz), 7.14 s and 7.16 s (1H each, 13-H, 15-H). ^{13}C NMR spectrum, δ_C, ppm: 14.66 (C^{10}), 20.11 (C^9), 21.44 (C^8), 27.64 (C^5), 33.68 (C^3), 40.53 (C^6), 45.68 (C^2), 47.84 (C^7), 49.46 (C^1), 51.73 (C^4), 114.39 (C^{13}, C^{15}), 130.36 (C^{12}, C^{16}), 135.59 (C^{11}), 153.15 (C^{14}). Found, %: C 83.60; H 9.10. $C_{16}H_{22}O$. Calculated, %: C 83.43; H 9.63.

2-(5,5,6-Trimethylbicyclo[2.2.1]hept-*exo*-2-yl)-phenol (V). Colorless crystals, mp 70°C (from hot hexane). IR spectrum (KBr), ν, cm^{-1}: 3345 (OH); 1609, 1591 (C=C); 750 (δC–H); 1208 (C–O). ^1H NMR spectrum, δ, ppm: 1.02 s (3H, C^8H_3), 1.04 d (3H, $C^{10}H_3$, J = 2.6 Hz), 1.17 s (3H, C^9H_3), 1.37–1.45 m (3H, 1-H, 6-H, 7-H), 1.76–1.84 m (2H, 7-H, 4-H), 2.02 s (1H, 3-H), 2.26–2.34 m (1H, 6-H), 2,90 t (1H, 5-H, J = 7.4 Hz), 4.83 s (1H, OH), 6.79 d (1H, 13-H, J = 6.5 Hz), 6.91 t (1H, 14-H, J = 3.7 Hz), 7.16 t (1H, 15-H, J = 6.0 Hz), 7.29 d (1H, 16-H, J = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.23 (C^8), 24.77 (C^{10}), 27.67 (C^9), 32.52 (C^6), 33.47 (C^7), 39.63 (C^2), 40.61 (C^5), 48.82 (C^1), 49.82 (C^4), 50.75 (C^3), 115.13 (C^{13}), 120.44 (C^{14}), 125.79 (C^{15}), 126.48 (C^{16}), 133.02 (C^{11}), 153.31 (C^{12}). Found, %: C 83.80; H 9.35. $C_{16}H_{22}O$. Calculated, %: C 83.43; H 9.63.

Rearrangement of 1,7,7-trimethyl-*exo*-2-phenoxybicyclo[2.2.1]heptane (III) in the presence of aluminum phenoxide. The catalyst (10 wt % with respect to ether **III**) was preliminarily prepared according to the procedure described above. Compound **III** was then added, and the mixture was heated for 6 h at 120°C (conversion 80%). The procedure for treatment of the reaction mixture and isolation of products was the same as above.

Alkylation of phenol (I) with camphene (II) in the presence of boron trifluoride in glacial acetic acid. A 35% solution of BF_3 in glacial acetic acid (10 wt % with respect to the initial phenol) was slowly added at room temperature to a mixture of 5.0 g (53.1 mmol) of phenol (**I**) and 7.23 g (53.1 mmol) of camphene (**II**). The mixture was heated to 80°C, stirred for 3 h at that temperature, cooled, diluted with diethyl ether, and washed first with a solution of $NaHCO_3$ and then with a solution of NaCl until neutral reaction. The organic phase was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was distilled in a vacuum, a fraction boiling at 135°C (3 mm) being collected. The *ortho* and *para* isomers were separated by column chromatography on silica gel L (100–160 μm) using benzene–hexane as eluent. A mixture of *para*-substituted phenols **V** and **VII** was thus isolated. The NMR spectra contained signals typical of the corresponding terpene fragments. The data for phenol **VII** coincided with those reported in [24].

4-(5,5,6-Trimethylbicyclo[2.2.1]hept-*exo*-2-yl)-phenol (VII). ^1H NMR spectrum, δ, ppm: 0.98 s (3H, C^8H_3), 1.02 d (3H, $C^{10}H_3$, J = 2.6 Hz), 1.14 s (3H, C^9H_3), 1.50–1.56 m (3H, 3-H, 6-H, 7-H), 1.81–1.94 m (2H, 7-H, 1-H), 1.97 m (1H, 4-H), 2.28–2.32 m (1H, 6-H), 2.80 t (1H, 5-H, J = 7.4 Hz), 6.66 s (1H, OH), 6.96–6.97 m (2H, 12-H, 16-H), 7.18 s and 7.20 s (1H each, 13-H, 15-H). ^{13}C NMR spectrum, δ_C, ppm: 16.38 (C^{10}), 24.88 (C^8), 27.74 (C^9), 32.68 (C^6), 33.57 (C^7), 39.66 (C^2), 40.67 (C^5), 48.83 (C^3), 49.89 (C^1), 50.87 (C^4), 115.29 (C^{16}), 120.59 (C^{14}), 125.97 (C^{15}), 126.52 (C^{13}), 133.40 (C^{11}), 153.35 (C^{12}).

The rearrangement of ether **III** in the presence of BF_3 in acetic acid was performed in a similar way.

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