Chemistry of Natural Compounds, Vol. 44, No. 4, 2008

REACTION OF MENTHOL AND PHENOL IN THE PRESENCE OF ALUMINIUM ALKOXIDES

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UDC 547.562.1′596.2+548.737

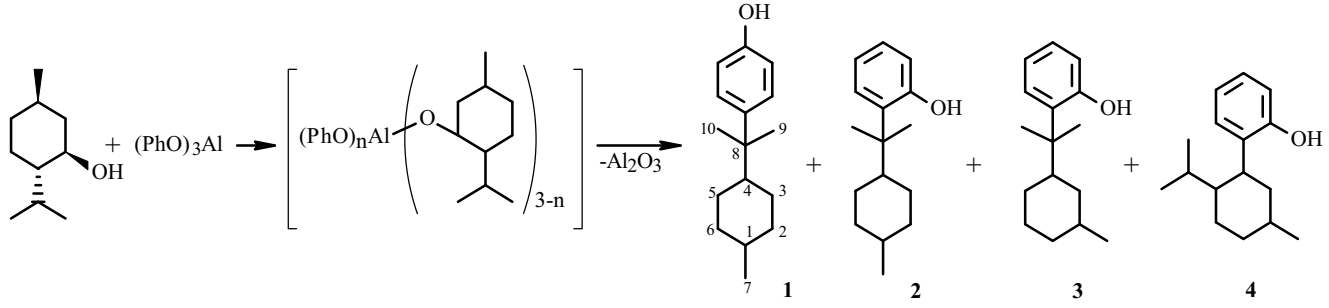
Phenol was alkylated with menthol in the presence of organoaluminium catalysts such as aluminium phenoxide and aluminium isopropoxide. Reaction products were isolated and characterized. Certain features of the process were determined.

Key words: phenol, menthol, organoaluminium catalysts, alkylation.

Natural terpenophenols possess a broad spectrum of biological activity [1]. Convenient synthetic pathways to analogs of these compounds are under investigation [2, 3]. Terpenophenols can be represented formally as products of C-alkylation of aromatic compounds by terpenes. Phenols are alkylated using Lewis acids, catalysts that are transition-metal complexes, or supercritical conditions [4-7].

Herein we report results from an investigation of the alkylation of phenol by menthol in the presence of the organoaluminium compounds aluminium isopropoxide [$(i\text{-PrO})_3$Al] and aluminium phenoxide [$(PhO)_3$Al]. Aluminium compounds are widely used as catalysts in organic reactions for structural isomerization, cracking, dehydrogenation of hydrocarbons, migration of C=C double bonds, alkylation of aromatic compounds, etc. The selectivity of the alkylation reaction on acid catalysts is related to the corresponding choice of reaction conditions and catalyst. Aluminium-containing homogeneous catalysts are highly *ortho*-selective in alkylation reactions, as was shown in previous studies of the alkylation of phenol by camphene [8-11].

The alkylation of phenol by menthol was carried out in the presence of equimolar amounts of organoaluminium compound, phenol, and menthol. Certain features of the process that were due to the nature of the aluminium alkoxide, the alkylating agent, and the reaction temperature were observed by studying the alkylation products. Use of organoaluminium compounds such as $(PhO)_3$Al and $(i\text{-PrO})_3$Al caused the formation of primarily C-alkylated products (Tables 1 and 2). However, the composition of the terpenophenols varied depending on the particular aluminium alkoxide. In particular, an array of C-alkylation products **1-4** was observed in the presence of aluminium phenoxide (Scheme 1) (atomic numbering is given for convenience of interpreting the NMR spectra).



Scheme 1

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 0009-3130/08/4404-0450

TABLE 1. Alkylation of Phenol by Menthol in the Presence of $(PhO)_3Al$

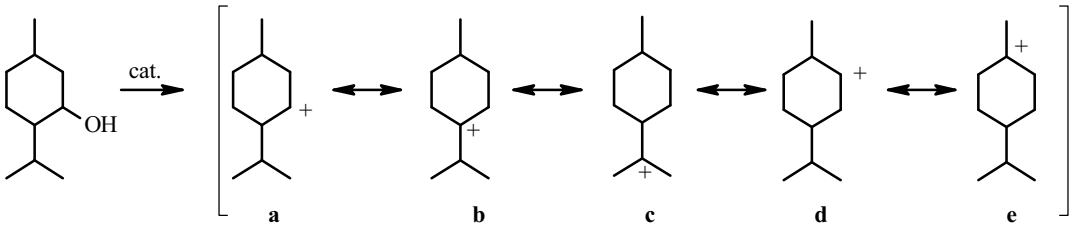
T, °C	Time, h	Menthol conversion, %	Reaction products, %						
			1	**2**	**3**	**4**	**5**	**6**	**7***
160	6	92	46.6	13.5	9.6	9.6	8.4	8.2	-
180	2	100	32.0	16.0	1.0	1.0	7.5	35.5	7.5
180	6	100	60	3	4	8	-	19	-

*Difficultly separable mixture of ethers.

TABLE 2. Alkylation of Phenol by Menthol in the Presence of $(i\text{-PrO})_3Al$

T, °C	Time, h	Phenol conversion, %	Reaction products, %			
			8	**9**	**10**	**11**
120	15	100	64.0	23.0	3.0	10.0
160	15	88	37.0	26.0	37.0	-

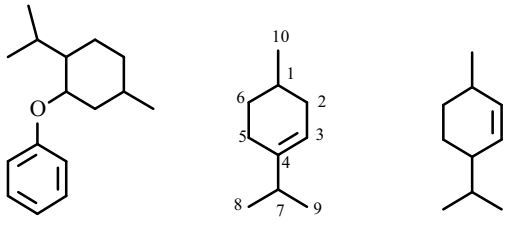
The structural variation of the phenol substituents was explained by the terpene nature of the alkylating agent. A whole array of carbocations **a**-**e** can form through the action of the catalyst on the monocyclic saturated alcohol menthol.



a **b** **c** **d** **e**

The most stable of these is tertiary carbocation **c**, which is stabilized by the gem-dimethyl group. Namely this reacts with the aromatic core, which is confirmed by the formation of the main product (**1**) and the side products (**2** and **3**). The possibility of forming **3** is entirely explained by an intramolecular Wagner—Meerwein rearrangement [12], during the course of which a 1,2-CH_3 shift from position C1 to position C2 occurs. Compound **4** forms from reaction of phenol with carbocation **a**.

The alkylation products of phenol by menthol included phenylmenthol ether **5**, a mixture of 2- and 3-menthenes (**6a** and **6b**), and a difficultly separable mixture of ethers (**7**).



5 **6a** **6b**

It is noteworthy that a significant amount of *para*-substituted phenol **1** forms in the presence of *ortho*-selective aluminium phenoxide. This may be due to steric factors of the *p*-menthane carbocation that affect the composition of the alkylation products.

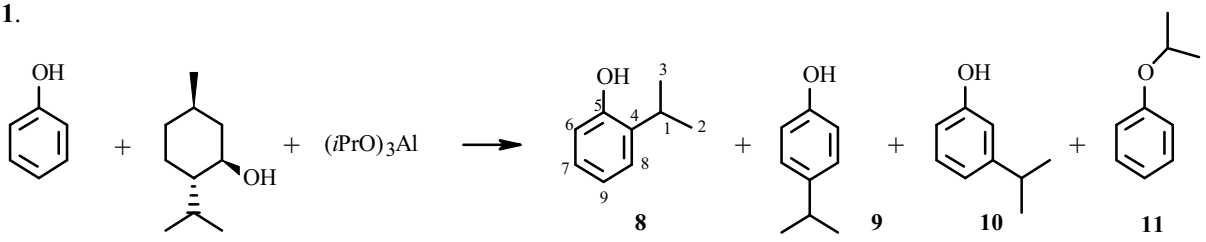
Carrying out the reaction at different temperatures showed that the optimum temperature for the alkylation was above 160°C. Menthol was completely converted in 2 h at 180°C. The principal reaction products were a mixture of 2- and 3-menthenes and **1**. Increasing the reaction time at this temperature decreased the selectivity of the process as the result of structural isomerization of the starting menthol.

The structures of the alkylation products were studied by spectral methods.

The *para*-substitution of the aromatic ring of **1** was confirmed by an absorption band at 826 cm^{-1} in the IR spectrum that is characteristic of C–H vibrations of an aromatic ring. Furthermore, the PMR contained resonances of aromatic protons as an AB-system at 6.76-7.20 ppm. Addition to the *p*-menthane fragment at the isopropyl group was confirmed using NMR spectroscopy. The PMR spectrum of **1** contained a doublet at 0.83-0.85 ppm that was characteristic of a methyl on C7 and a singlet at 1.24 ppm that was characteristic of two methyls (C10 and C9). The *ortho*-substitution of the benzene ring in **2-4** was confirmed by the presence in the PMR spectrum of resonances for asymmetric aromatic protons from 6.63 to 7.27 ppm.

The ^{13}C NMR spectrum of menthene (**6a**) contained a resonance for quaternary C atom C4 of the double bond in the cyclohexane ring (142.77 ppm) and for menthene (**6b**), resonances characteristic of methine carbons at 117.44 and 133.56 ppm. The PMR spectra of **6a** and **6b** exhibited multiplets at 5.37 and 5.53 ppm that were characteristic of protons in double bonds. The IR spectra did not show vibrations of an aromatic ring.

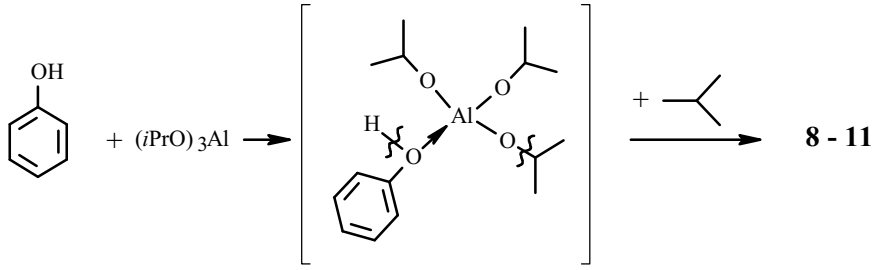
Performing the reaction in the presence of aluminium isopropoxide led to alkylation of phenol by the isopropyl moiety without any products from reaction of menthol and phenol (Scheme 2). This formed isopropylphenols **8-10** and isopropylphenol ether **11**.



Scheme 2

This can be explained by the fact that free phenol was present in the reaction mixture and coordinated to aluminium isopropoxide because it is a stronger acid than menthol. The stable isopropyl cation thus formed alkylates phenol.

The principal reaction product at 120°C was *ortho*-isopropylphenol (64% of the total products). Carrying out the reaction at 160°C gave a mixture of compounds formed by thermal rearrangement of the initially formed *ortho*-substituted phenol **8** (Table 2).



The lack of menthane resonances in NMR spectra of **8-11** confirmed that they were obtained.

The study of alkylation of phenol by menthol showed that the composition of the reaction products depended to a large extent on the organoaluminium catalyst. The reaction temperature was also important. Alkylation in the presence of aluminium phenoxide at 160°C for 6 h is the optimum method for preparing terpenophenols.

EXPERIMENTAL

IR spectra in thin layers and KBr disks were recorded on a Shimadzu IR Prestige 21 IR-Fourier spectrometer; PMR and ^{13}C NMR spectra in $CDCl_3$, on a Bruker AM spectrometer (operating frequency 300 and 75 MHz, respectively) with $CDCl_3$ resonances as standards (δ_H 7.21 ppm, δ_C 76.90 ppm). Resonances were assigned using ^{13}C NMR spectra recorded in JMOD mode and two-dimensional NMR spectroscopy. The purity of the starting compounds was monitored and the reaction products were analyzed using GC on a Kristall 2000M chromatograph with a capillary column (25 × 0.22), FFAP phase, temperature

range 70-230°C, 6°C/min, a flame-ionization detector, and He carrier gas. The course of the reactions was monitored by TLC on Sorbfil plates. Plates were developed by $KMnO_4$ solution and vanillin solution with subsequent heating to 100-150°C.

Column chromatography used silica gel 70/230 μm.

Alkylation of Phenol by Menthol in the Presence of Organoaluminium Catalysts. Phenol (0.60 g, 0.006 mol) and menthol (1 g, 0.006 mol) were placed in a 100-mL two-necked flask equipped with a thermometer and reflux condenser and heated in the presence of $(PhO)_3Al$ or $(i\text{-}PrO)_3Al$ (0.006 mol) until the conversion was complete (GC and TLC monitoring). When the reaction was finished, the reaction mixture was cooled, diluted with diethylether, treated with dilute HCl solution to decompose the aluminium alkoxide, and washed with NaOH solution (5%) and water until the rinsings were neutral. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated.

The reaction products were separated by column chromatography over silica gel 70/230 μm with elution by petroleum ether:diethylether with increasing amounts of the latter to isolate the phenol alkylation products.

4-(2-(4-Methylcyclohexyl)propane-2-yl)phenol (1). IR spectrum (KBr, ν, cm^{-1}): 3329 (phenol ν OH), 1612 and 1595 (benzene ν C=C), 1367 and 1382 (δ_s *gem*-dimethyl), 1450 (δ_{as} CH_3), 1242 (δ OH), 1180 (benzene δ CH), 826 (*p*-substituted benzene δ CH [13, 14].

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83-0.85 (d, J = 6, CH_3-7), 0.87-0.90 (m, $1H_e$-3, $1H_e$-5), 0.92-0.95 (m, $1H_e$-2, $1H_e$-6), 0.96-0.97 (m, 1H-4), 1.24 (s, CH_3-10, CH_3-9), 1.31-1.40 (tt, J - 3, 11, 1H-1), 4.9 (s, 1H, OH), 6.7-6.79 (d, J = 9, 2H-13,15), 7.17-7.20 (d, J = 9, 2H-12,16).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 21.6 (C-7), 25.5 (C-10,9), 27.7 (C-3,5), 32.8 (C-1), 35.8 (C-2,6), 49.6 (C-4), 51.7 (C-8), 114.5 (C-13,15), 127.3 (C-12,16), 142.7 (C-11), 152.9 (C-14).

2-(2-(4-Methylcyclohexyl)propane-2-yl)phenol (2). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79-0.81 (d, J = 6, CH_3-7), 0.88-1.0 (m, $1H_e$-3, $1H_e$-5), 1.15-1.24 (m, 1H-1), 1.18-1.3 (m, $1H_e$-2, $1H_e$-6), 1.34 (s, CH_3-10, CH_3-9), 1.43-1.48 (m, $1H_a$-2, $1H_a$-6), 1.63-1.68 (m, $1H_a$-3, $1H_a$-5), 2.05-2.15 (tt, J = 11.7, 2.7, 1H-4), 4.74 (s, 1H, OH), 6.64-6.67 (dd, J = 7.83, 1.28, 1H-13), 6.85-6.90 (dt, J = 7.55, 1.26, 1H-15), 7.05-7.10 (dt, J = 7.76, 1.62, 1H-14), 7.19-7.22 (dd, J = 7.78, 1.56, 1H-12).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 22.3 (C-7), 24.3 (C-9), 24.4 (C-10), 28.0 (C-3,5), 33.0 (C-1), 35.9 (C-2,6), 40.7 (C-7), 43.6 (C-4), 116.6 (C-15), 120.3 (C-13), 126.7 (C-12), 128.5 (C-14), 135.9 (C-11), 159.9 (C-16).

2-(2-(3-Methylcyclohexyl)propane-2-yl)phenol (3). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87-0.88 (d, J = 5, CH_3-10), 1.02-1.09 (m, $1H_e$-3, $1H_e$-2), 1.22-1.24 (m, $1H_e$-5), 1.27-1.28 (m, 1H-1), 1.34-1.35 (m, $1H_e$-6), 1.39 (s, CH_3-8,9), 1.46-1.49 (m, $1H_a$-6), 1.59-1.69 (m, $1H_a$-5), 1.94-1.96 (d, J = 6, $1H_a$-2), 4.73 (s, 1H, OH), 6.63-6.65 (dd, J = 7.83, 1.28, 1H-13), 6.87-6.90 (d, J = 7.55, 1.26, 1H-15), 7.05-7.08 (dt, J = 7.76, 1.62, 1H-14), 7.24-7.7 (dd, J = 7.78, 1.56, 1H-12).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 21.10 (C-10), 29.00 (C-9,8), 32.90 (C-6), 34.10 (C-2), 35.9 (C-4), 37.90 (C-3), 38.2 (C-5), 44.20 (C-7), 47.2 (C-1), 116.3 (C-13), 120.5 (C-15), 126.9 (C-12), 128.1 (C-14), 135.0 (C-11), 154.2 (C-16).

(2-Isopropyl-5-methylcyclohexyl)phenol (4). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.69-0.71 (d, J = 6, CH_3-10), 0.81-0.83 (d, J = 6, CH_3-9), 0.89-0.91 (d, J = 6, CH_3-7), 1.01-1.05 (m, 1H-1), 1.06-1.11 (m, $1H_a$-2), 1.17-1.22 (m, $1H_a$-6, $1H_e$-6), 1.38-1.40 (m, $1H_e$-2), 1.51-1.53 (m, $1H_a$-4, 1H-8), 1.80-1.85 (m, $1H_a$-5, $1H_e$-5), 2.88-2.96 (t, J = 12, $1H_a$-3), 4.68 (s, 1H, OH), 6.74-6.76 (m, 1H-15), 6.89-6.94 (m, 1H-14), 7.02-7.07 (m, 1H-13), 7.14-7.17 (m, 1H-12).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 15.8 (C-7), 19.9 (C-9), 21.6 (C-10), 24.7 (C-5), 27.5 (C-1), 33.3 (C-3), 35.3 (C-6), 44.6 (C-2), 46.8 (C-4), 115.3 (C-15), 121.0 (C-13), 126.2 (C-14), 126.7 (C-12), 127.4 (C-11), 155.6 (C-16).

(2-Isopropyl-5-methylcyclohexyloxy)benzene (5). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75-0.77 (d, J = 6, CH_3-7), 0.89-0.91 (s, CH_3-10), 0.94-0.96 (d, CH_3-9), 0.98-0.99 (m, $1H_e$-6), 1.02-1.03 (m, $1H_e$-2) 1.10-1.12 (m, $1H_a$-5), 1.25-1.27 (m, $1H_e$-1), 1.46-1.54 (tt, J = 3, 6.6, 1H-2), 1.68-1.70 (m, $1H_e$-6), 1.73-1.74 ($1H_e$-5), 2.18-2.22 (m, $1H_a$-2), 2.23-2.27 (m, $1H_a$-8), 4.00-4.07 (dt, J = 6, 10, 1H-3), 6.90-6.95 (m, 1H-12,14,16), 7.25-7.30 (m, 1H-13,15).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 16.5 (C-7), 21.3 (C-9), 22.5 (C-10), 23.7 (C-5), 26.0 (C-8), 34.5 (C-6), 31.4 (C-1), 40.3 (C-2), 48.1 (C-4), 74.4 (C-3), 115.8 (C-12,16), 120.4 (C-14), 129.4 (C-13,15).

Mixture of Δ2- and Δ3-*p*-methenes (6). IR spectrum (KBr, ν, cm^{-1}): 2951 and 2924 (ν CH_3, CH_2), 1597 (ν CH=CH), 1367 and 1382 (*gem*-dimethyl δ_s), 1450 (δ_{as} CH_3), 1375 (*gem*-dimethyl δ CH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89-0.91 (d, J = 6, CH_3-10, CH_3-9), 0.93-0.95 (d, J = 6, CH_3-10′, CH_3-9′), 0.98-1.00 (d, J = 6, CH_3-7, CH_3-7′), 1.23-1.27 (m, 2H-5, 2H-6, 2H-5′, 2H-6′), 1.53-1.67 (m, 1H-8,8′), 1.97-2.18 (m, 1H-1,1′), 5.36-5.37 (m, 1H-3′), 5.53 (s, 1H-2, 1H-3).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 18.83 (C-7′), 19.15 (C-7), 20.83 (C-9), 21.19 (C-10), 21.42 (C-10,9), 25.59 (C-2′), 28.31 (C-8), 30.52 (C-8′), 31.01 (C-5′), 31.56 (C-5), 31.75 (C-1′), 33.49 (C-1), 35.8 (C-6), 41.5 (C-4), 117.44 (C-2), 129.48 (C-3′), 133.57 (C-3), 142.77 (C-4′).

2-Isopropylphenol (8). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.28-1.31 (d, J = 9, CH_3-2,3), 3.20-3.27 (m, 1H-1), 4.83 (s, 1H, OH), 6.75-6.78 (m, 1H-6), 6.92-6.97 (m, 1H-7) 7.07-7.10 (m, 1H-8), 7.22-7.24 (m, 1H-9).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 22.6 (C-2,3), 27.0 (C-1), 115.3 (C-6), 121.0 (C-8), 126.4 (C-9), 126.7 (C-7), 134.4 (C-4), 152.7 (C-5).

4-Isopropylphenol (9). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.21-1.23 (d, J = 6, CH_3-2, CH_3-3), 2.84-2.88 (m, 1H-1), 4.95 (s, 1H, OH), 6.78-6.80 (d, J = 6, 1H-6, 1H-8), 7.09-7.11 (d, J = 6, 1H-5, 1H-9).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 23.9 (C-2,3), 33.3 (C-1), 115.1 (C-8,9), 127.4 (C-5,9), 141.2 (C-4), 153.5 (C-7).

3-Isopropylphenol (10). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.22-1.25 (d, J = 9, CH_3-2, CH_3-3), 3.12-3.15 (m, 1H-1), 4.73 (s, 1H, OH), 6.75-6.78 (m, 1H-5,7), 7.07-7.10 (m, 1H-8), 7.07-7.09 (m, 1H-8,9).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 23.9 (C-2,3), 27.2 (C-1), 113.4 (C-5), 119.0 (C-7), 124.5 (C-8), 126.2 (C-9).

Isopropoxybenzene (11). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.34-1.36 (d, J = 6, CH_3-2, CH_3-3), 4.56-4.60 (m, 1H-1), 6.90-6.96 (m, 1H-5,7,9), 7.29-7.30 (m, 1H-6,8).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): 22.1 (C-2), 23.9 (C-3), 69.8 (C-1), 115.9 (C-5), 120.6 (C-7), 121.3 (C-9), 123.4 (C-8), 129.4 (C-6), 133.6 (C-4).

ACKNOWLEDGMENT

The work was supported by the Russian Foundation for Basic Research (Project No. 07-03-01132), the President of the Russian Federation (Program of Support for Leading Scientific Schools, Grant NSh-4028.2008.3), and a grant from the Urals Division of the Russian Academy of Sciences.

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