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# ALKYLATION OF PHENOL BY β-PINENE IN THE PRESENCE OF ALUMINUM PHENOLATE

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*The alkylation of phenol by β-pinene using $Al(OPh)_3$ as a catalyst was studied. It was found that the composition of the products depended on the ratio of starting materials. The principal products were chromane-type ethers with an equimolar ratio of starting materials and an excess of phenol.* ortho-*Alkylated phenol and an ether with a terpene substituent of bornyl structure were formed with a two-fold excess of β-pinene.*

**Keywords:** phenol, β-pinene, alkylation, aluminum phenolate, terpenophenols.

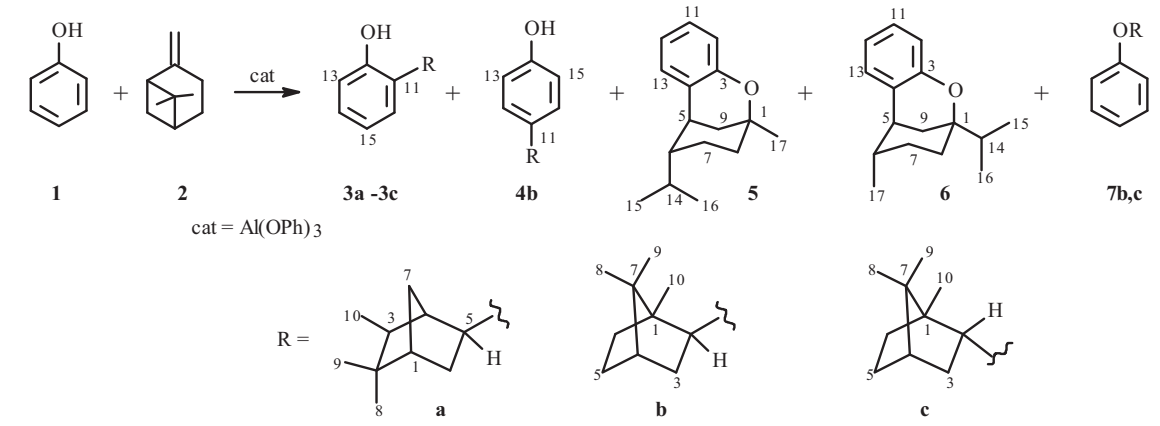
Pinenes are some of the most widely distributed natural terpenes and occur in turpentines and essential oils.

The useful properties of natural phenolic compounds with terpene substituents prompt the development of strategies for synthesizing their analogs and new derivatives. The application of aluminum alkoxides as catalysts is well known and enables selective alkylation of phenols to be conducted [1, 2].

We studied previously the alkylation of phenol by α-pinene using aluminum phenolate [$Al(OPh)_3$] as a catalyst [2]. The principal reaction products were chromane-type ethers **5** and **6**, the yields of which depended on the ratio of starting materials. *ortho*-Substituted phenols with isobornyl, bornyl, isocamphyl, and *para*-menthyl substituents were isolated from the phenolic fraction.

Herein results from a study of the alkylation of phenol (**1**) by the bicyclic monoterpene (1*S*)-(–)- β-pinene (**2**) are reported. Compound **2** differs from α-pinene by the presence of an exocyclic double bond. The reaction was catalyzed by $Al(OPh)_3$ at 100 and 160°C.

The alkylation product array depended on the ratio of starting materials and reaction temperature. A product array of O- and C-alkylation (**3**-**7**) with isocamphyl, isobornyl, and bornyl terpene substituents was observed in the presence of $Al(OPh)_3$ (Scheme 1, Table 1).




Scheme 1

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TABLE 1. Conditions and Products of Phenol Alkylation by β-Pinene in the Presence of $Al(OPh)_3$

| Phenol–β-pinene ratio | Reaction conditions | Conversion, % | Reaction product composition, % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **3a** | **3b** | **3c** | **4b** | **5** | **6** | **7b** | **7c** | Mixture of ethers |
| 1:1 | 160°C, 6 h | 89 | – | 14 | 9 | – | 60 | 17 | – | – | – |
| 1:1 | 100°C, 6 h | 86 | 9 | 35 | – | 11 | 21 | 19 | – | – | 5 |
| 1:2 | 160°C, 6 h | 74 | 2 | – | 48.5 | – | 6 | 2 | – | 35 | 6.5 |
| 1:2 | 100°C, 6 h | 71 | – | – | 22 | – | 23 | 9 | – | 46 | – |
| 2:1 | 160°C, 6 h | 76 | 3 | 19 | – | – | 40 | 34 | – | 4 | – |
| 2:1 | 100°C, 6 h | 70 | – | – | 3 | – | 35 | 20 | 6 | 32 | 4 |

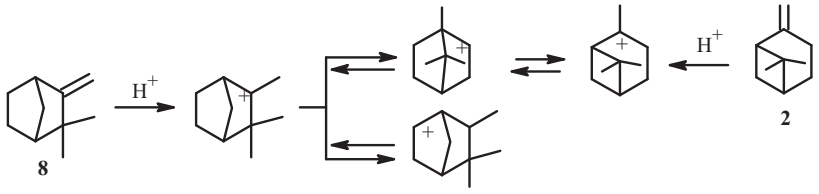
Chromane-type ethers (**5** and **6**) in total yield 77% (Scheme 1, Table 1) in addition to C-alkylation products such as *ortho*-substituted phenols with isobornyl (**3b**) (14%) and bornyl (**3c**) (9%) terpene substituents were the principal products with an equimolar ratio of starting materials in the presence of $Al(OPh)_3$ (reaction temperature 160°C). At 100°C and a 1:1 phenol:β-pinene ratio, the total yield of chromane-type ethers **5** and **6** was slightly less (40%) and the yield of *ortho*-isobornylphenol (**3b**) increased (35%). Furthermore, *ortho*-isocamphylphenol (**3a**) (9%) and *para*-isobornylphenol (**4b**) (11%) were isolated. The amount of *para*-substituted phenol was uncharacteristic of alkylation in the presence of $Al(OPh)_3$ and at a rather low temperature. The formation of chromane-type ethers was explained by the fact that heating the reaction mixture to 160°C assisted opening of the 4-membered ring of β-pinene and further production of **5** and **6**.

A feature of the alkylation of phenol by an excess of β-pinene in the presence of $Al(OPh)_3$ was the formation of compounds with a terpene substituent of bornyl structure whereas this was not observed for alkylation of phenols by camphene [2]. Thus, the principal products at 160°C were 2-substituted phenol with a terpene substituent of bornyl structure (**3c**, 48.5%) and phenylbornylether (**7c**, 35%). Side products included 2-isocamphylphenol (**3a**, 2%), chromane-type ethers (**5** and **6**, 8%), and a difficultly separated mixture of ethers (6.5%). Alkylation of phenol by a two-fold excess of β-pinene at 100°C also produced compounds with a terpene substituent of bornyl structure (**3c**, 22%; **7c**, 46%). Furthermore, chromane-type ethers (**5** and **6**) were isolated in total yield 32%.

The product mixture from alkylation of a two-fold excess of phenol by β-pinene depended on the reaction temperature. The principal products at 160°C (like for alkylation with a 1:1 ratio of starting materials) were chromane-type ethers in total yield 74%. Side products of this reaction were *ortho*-isobornylphenol (**3b**, 19%), *ortho*-isocamphylphenol (**3a**, 3%), and phenylbornylether (**7c**, 4%). The reaction of an excess of phenol with β-pinene at 100°C gave chromane-type ethers (**5** and **6**) in addition to an ether with a terpene substituent of bornyl structure (**7c**, 32%).

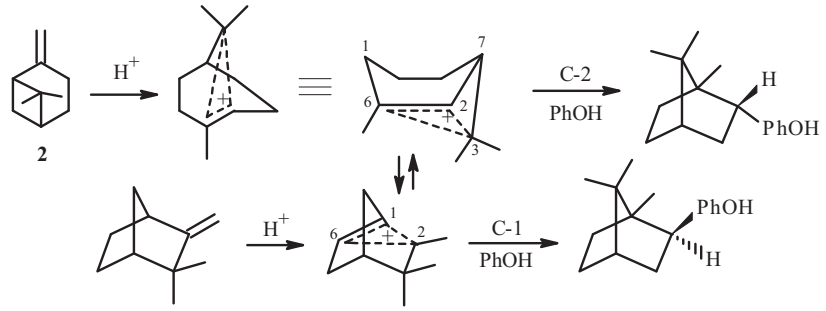
The formation of a carbonium ion when an excess of phenol was used was due to the proton-donating properties of phenol. In this instance, the catalytic effect of $Al(OPh)_3$ on the alkylation process was less significant.

The variety of structures for the terpene substituent is completely explainable by intramolecular rearrangements characteristic of terpenes. These include the Wagner–Meerwein, 6,2-hydride shift, and 2,6-methyl shift [2, 3]. These rearrangements can be represented as equilibria between classical cations (Scheme 2). A scheme for classical ions of camphene (**8**) and β-pinene (**2**) is given for comparison. The formation of products **3a** and **3b** can be explained from this viewpoint for alkylation of phenol by both camphene and β-pinene.




Scheme 2

However, these classical representations cannot explain why *ortho*-bornylphenol was formed during alkylation of phenol by β-pinene. In this instance, an examination of the reaction of phenol with the non-classical ion formed from the starting terpene β-pinene would be more definitive (Scheme 3). Scheme 3 shows that attack of phenol from the side opposite the bridge bond to form bornylphenol is sterically more preferred.




Scheme 3

HPLC on a chiral column and NMR spectroscopy using a chiral shift reagent found that *ortho*-bornylphenol (**3c**) and phenylbornylether (**7c**) were obtained as pure enantiomers.

Thus, the selectivity and direction of the alkylation of phenol by *β*-pinene using $Al(OPh)_3$ as a catalyst depended on the ratio of starting materials and the temperature. It was found that the principal alkylation products with an equimolar ratio of starting materials and with a two-fold excess of phenol were chromane-type ethers **5** and **6** and *ortho*-isobornylphenol (**3b**). A feature of the alkylation of phenol by an excess of *β*-pinene rather than by camphene was the formation of optically active compounds with a terpene substituent of bornyl structure (**3c** and **7c**).

## EXPERIMENTAL

PMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Bruker Avance II 300 spectrometer (300.17 and 75.5 MHz). Resonances of $CD(H)Cl_3$ ($\delta_H$ 7.26 ppm, $\delta_C$ 76.90 ppm) were used as internal standards. Resonances in $^{13}C$ NMR spectra were assigned using the JMOD method. The shift reagent was *tris*[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III). Specific rotation (+22°C) was measured on a Kruss Optronic P3002RS automated digital polarimeter.

The purity of the terpenophenols was monitored and volatile reaction products were analyzed using GC on a Shimadzu GC-2010AF chromatograph with an HP-1 capillary column (60 m × 0.25 mm × 0.25 μm, 100–240°C, 6°C/min), a flame-ionization detector, and He carrier gas.

The optical purity of enantiomerically enriched terpenophenols was determined by HPLC on an Agilent 1100 instrument (UV detector, λ = 219 and 254 nm, 20°C) using a column packed with Chiralcel OD-H hexane-IPS chiral stationary phase (99/1, 1 mL/min).

The course of reactions was followed by TLC on Sorbfil plates. Spots on plates were detected using vanillin in EtOH with subsequent heating to 100–150°C or $KMnO_4$ (15 g $KMnO_4$, 300 mL $H_2O$, 0.5 mL conc. $H_2SO_4$). Reaction products were separated using column chromatography over $SiO_2$ (packed wet, Alfa Aesar, 70/230 μm) with elution by petroleum ether:$Et_2O$ with an increasing fraction of the latter.

The alkylating agent was the bicyclic monoterpene (1*S*)-(–)- *β*-pinene (Alfa Aesar, 99%), $[\alpha]_D^{20}$ –21° (pure). The catalyst was $Al(OPh)_3$, which was synthesized *in situ*. Phenol was commercially available (Alfa Aesar) and was used without further purification.

**Alkylation of Phenol by (1*S*)-(–)- *β*-Pinene in the Presence of $Al(OPh)_3$ (General Method).** A two-necked flask equipped with a thermometer and reflux condenser was charged with phenol (**1**, 2 g, 21 mmol) and heated to 160°C. Aluminum granules (0.017 g, 0.21 mmol) were added in small portions. After the Al was completely dissolved in the phenol, the solution was cooled to 40°C, treated with *β*-pinene (**2**, 2.89 g, at different phenol:*β*-pinene molar ratios 1:1, 1:2, and 2:1), and heated at 160°C or 100°C for 6 h. The reaction mixture was separated using column chromatography (eluent petroleum ether:$Et_2O$ with a gradual increase of the latter).

**1,7,7-Trimethyl-2-*endo*-(2-hydroxyphenyl)bicyclo[2.2.1]heptane (3c).** Yellow crystalline solid, $C_{16}H_{22}O$, $[\alpha]_D^{23}$ +52.6° (*c* 0.1, $CHCl_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.82 (3H, s, $CH_3$-10); 0.98 (3H, s, $CH_3$-8); 1.13 (3H, s, $CH_3$-9); 1.81–1.84 (2H, m, H-5, 6); 1.88–1.94 (2H, m, H-3, 6); 2.01–2.11 (2H, m, H-4, 5); 2.57–2.64 (1H, m, H-3); 3.52 (1H, ddd,

J = 3.1, 5.6, 11.8, H-2); 4.82 (1H, s, OH); 6.81–6.84 (1H, dd, J = 1.3, 6.6, H-13); 6.92–6.98 (1H, td, J = 1.2, 6.4, H-15); 7.08–7.14 (1H, td, J = 1.5, 6, H-14); 7.19 (1H, d, J = 7, H-16).

$^{13}$C NMR spectrum (75 MHz, $CDCl_3$, δ): 15.09 (C-10); 18.75 (C-9); 19.88 (C-8); 28.33 (C-5); 28.94 (C-3); 35.21 (C-6); 41.93 (C-4); 45.60 (C-2); 50.41 (C-1); 50.58 (C-7); 115.06 (C-13); 119.06 (C-15); 125.41 (C-16); 127.96 (C-11); 130.04 (C-14); 154.76 (C-12).

**1,7,7-Trimethyl-2-*endo*-2-phenoxybicyclo[2.2.1]heptane (7c).** Colorless oily liquid, $C_{16}H_{22}O$, $[\alpha]_D^{23}$ –101.1° (*c* 0.5, $CHCl_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.99 (3H, s, $CH_3$-10); 1.01 (3H, s, $CH_3$-8); 1.16 (3H, s, $CH_3$-9); 1.16–1.22 (2H, m, H-5, 6); 1.34–1.44 (2H, m, H-3, 6); 1.80–1.84 (2H, m, H-4, 5); 2.32–2.43 (1H, m, H-3); 4.35 (1H, br.d, J = 9.0, H-2); 6.90–6.99 (3H, m, H-12, 14, 16); 7.30–7.35 (2H, m, H-13, 15).

$^{13}$C NMR spectrum (75 MHz, $CDCl_3$, δ): 13.79 (C-10); 19.00 (C-9); 19.78 (C-8); 26.84 (C-5); 28.00 (C-3); 36.90 (C-6); 45.24 (C-4); 45.25 (C-2); 47.60 (C-1); 49.54 (C-7); 82.72 (C-11); 115.06 (C-12, 16); 120.13 (C-14); 129.36 (C-13, 15); 159.23 (C-12).

The spectral characteristics of **3a,b–6** and **7b** agreed with those in the literature [4, 5].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