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PHENOL–TERPENE CONDENSATIONS IN AQUEOUS ACID MEDIA

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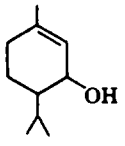
Abstract—Condensation of limonene and/or α-pinene with phenols such as orcinol or sesamol under mild aqueous acid conditions give high yields of phenolic terpenes.

The condensation of phenols with allylic alcohols in aqueous organic acid solutions provides a convenient method for the synthesis of a variety of nuclear alkylated compounds, and may serve as a biogenetic model for the formation of these types of natural products.[1-5] Cardillo *et al.* recently applied this procedure for the synthesis of new cannabinoid derivatives[6] by alkylation of resorcinols with piperitol (1) in aqueous citric acid, e.g., orcinol (2) and 1 gave a mixture (25% yield) of dialkylated orcinols and the cyclized phenolic terpenoids 3 and 4.



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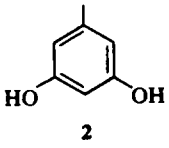

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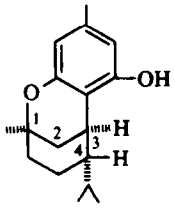

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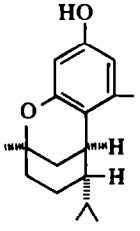

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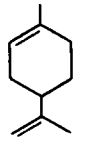
Since piperitol (1) and related terpene alcohols are not easily obtained in quantity, we investigated the synthesis of similar phenolic terpenoids by alkylation of phenols with commercially available terpene hydrocarbons such as limonene (5) and α-pinene (6). These hydrocarbons give high yields of cyclized condensation products. When orcinol was heated (18 h) with either limonene or α-pinene in 50% aqueous formic acid it gave an essentially identical reaction product (90% yield) consisting of the four isomers 3 (24%), 4 (24%), 7 (18%) and 8 (24%). With the exception of 3 (m.p. 144°) these isomers were obtained as oils after chromatographic separation on silicic acid. On the basis of their NMR spectra, products 3 and 4 are identical with those obtained by Cardillo *et al.* in the piperitol-orcinol reaction. Assignment of structure 3 to the crystalline isomer was confirmed by the appearance of the methyl group at C_1 as a 3H singlet at δ1·32, by its positive, deep blue color reaction with Gibbs reagent, and by irradiation of the aromatic Me resonance at δ2·16. This irradiation increased the intensity of both aromatic protons (at δ6·08 and δ6·15). The oily isomer 4 also shows the methyl group at C_1 as a 3H singlet δ1·30. It did not, however, give a color with Gibbs reagent and on irradiation of its aromatic Me resonance at δ2·14 it showed an increase in intensity of only one of the aromatic protons (at δ6·19). The two other isomeric condensation products have not been described. However, in accord with structures 7 and 8 the Me group appears as a 3H doublet at δ1·15 (J = 7·0 Hz), locating it at position 4, and the isopropyl group appears as a 6H doublet (J = 7·0 Hz) at δ0·95, locating the isopropyl group at position 1. In contrast to 7 and 8, the isopropyl group of 3 and 4 is attached to a secondary center of the cyclohexane ring and, therefore, the isopropyl group appears as a pair of doublets (J = 6·0 Hz) at δ1·03 and δ1·17. The isomer 7, unlike 8,



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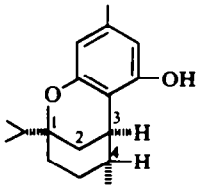

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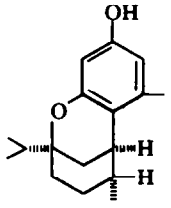

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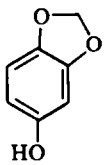
gives a positive Gibbs test and on irradiation at δ2·14 the intensity of both of its aromatic protons is increased.

Sesamol (**9**) condensed with limonene or α-pinene in aqueous formic acid to yield (87%) two isomeric products in approximately equal amounts. In acord with structure **10** one of these isomers showed the Me group at position 1 as a 3H singlet at δ1·29, and the isopropyl group as a pair of doublets (J = 6·0 Hz) at δ0·94 and δ1·03. The other isomer **11** showed a Me group (at position 4) as a doublet (J = 7·0 Hz) at δ1·09, the isopropyl group as a 6H doublet (J = 7·0 Hz) at δ0·95. In all of these condensation products, the benzylic methine proton at position 3 appears as a multiplet with a half-width of 8·0 Hz, e.g. at δ2·90 in **10**, indicating an H_3(eq.)–H_4(eq.) interaction, and, therefore, the 3,4-*trans* configurations shown[6].



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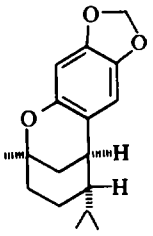

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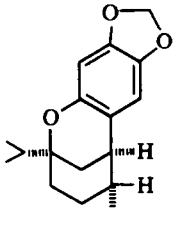

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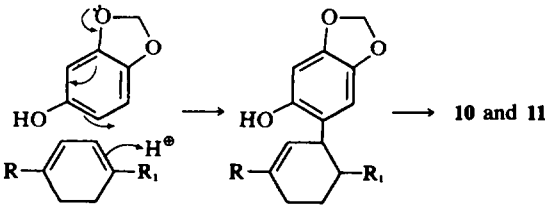
A priori, the formation of identical condensation products from limonene and α-pinene was unexpected. It is known that in acid solutions limonene undergoes sequential protonation–deprotonation reactions to give terpinenes and other products.[7] The identical products formed in α-pinene condensations suggested that in aqueous formic acid α-pinene must rapidly form a mixture of terpenes similar to those from limonene. This has now been demonstrated. α-Pinene was heated alone in 50% aqueous formic acid. GLC-mass spectral analysis of the reaction product established the presence of α-terpinene (22·9%), terpinolene (26·5%), γ-terpinene (19·25%) and minor amounts of α-pinene (2·1%), β-pinene (0·92%), 1,4-cineole (2·1%), p-cymene (6·9%), limonene (9·8%) and 1,8-cineole (7·3%). The phenolic condensation reaction of α-pinene (and of limonene) can be retionalized, therefore, as involving condensation with intermediate protonated terpinenes and terpinolene, e.g. sesamol (**9**) and α-terpinene (**12**) to give the non cyclic intermediate which then reacts further to give final products. By employing these relatively mild aqueous conditions more complex rearrangement products, e.g. such as occur in the reaction of phenol with camphene in the presence of boron trifluoride,[8] are avoided.



12: R = Me, R_1 = $CHMe_2$
R = $CHMe_2$, R_1 = Me

EXPERIMENTAL

Condensation of limonene with orcinol. A mixture of limonene (68 g, 0·5 mole), orcinol (71 g, 0·5 mole) and 500 ml of 50% formic acid was refluxed for 18 h then cooled to room temp. The solvent was then poured off and an NMR spectrum of the resulting oil showed four closely related compounds present in a ratio of **3** (24%), **4** (24%), **7** (18%) and **8** (24%). Chromatography on silica gel (heptane/ether, 80:20) gave the four isomers. Compound **3** (m.p. 144°, ether–hexane) had NMR ($CDCl_3$) spectrum: δ1·03 (d, 3H, J = 6·0 Hz); δ1·17 (d, 3H, J = 6·0 Hz); δ1·32 (S, 3H); δ2·16 (S, 3H); δ3·34 (m, 1H); δ6·08 (S, 1H); δ6·25 (S, 1H). Calc. for $C_{17}H_{24}O_2$, m.w. = 260·1776; Found: 260·1756. Compound **4** (oil) had NMR ($CDCl_3$) spectrum: δ1·03 (d, 3H, J = 6·0 Hz); δ1·17 (d, 3H, J = 6·0 Hz); δ1·30 (S, 3H); δ2·14 (S, 3H); δ2·16 (S, 3H); δ3·12 (m, 1H); δ6·28 (S, 2H). Compound **7** (oil) had NMR ($CDCl_3$) spectrum: δ0·95 (d, 6H, J = 7·0 Hz); δ1·15 (d, 3H, J = 7·0 Hz); δ2·16 (S, 3H); δ2·98 (m, 1H); δ6·08 (S, 1H); δ6·25 (S, 1H). Compound **8** (oil) had NMR ($CDCl_3$) spectrum: δ0·95 (d, 6H, J = 7·0 Hz); δ1·15 (d, 3H, J = 7·0 Hz); δ2·16 (S, 3H); δ2·79 (m, 3H); δ6·28 (S, 2H).

Condensation of limonene with seasamol. A mixture of **9** (13·8 g, 0·1 mole), **5** (13·6 g, 0·1 mole) and 500 ml of 50% formic acid was refluxed for 24 h then cooled to room temp. Extraction with ether gave an oil which distilled at 140–145°/150μ giving 23·8 g (87%) of a mixture of two compounds which were separated by chromatography on activity 3 alumina (Skelly F/ether, 95:5). Compound **11** was eluded as an oil with an NMR ($CDCl_3$, 100 MHz) spectrum as follows: δ0·95 (d, 6H, J = 7·0 Hz); δ1·09 (d, 3H, J = 7·0 Hz); δ2·57 (m, 1H, 8 Hz half width); δ5·80 (S, 2H); δ6·35 (S, 1H); δ6·42 (S, 1H). Calc. for $C_{17}H_{22}O_3$, m.w. = 274·1569. Found: 274·1567 Compound **10** gave NMR ($CDCl_3$) spectrum: δ0·94 (d, 3H, J = 6 Hz); δ1·03 (d, 3H, J = 6·0 Hz); δ1·29 (S, 3H); δ2·90 (m, 1H, 8 Hz half width); δ5·78 (S, 2H); δ6·34 (S, 1H); δ6·39 (S, 1H).

REFERENCES

[1]L. Jurd, *Experientia* **24**, 858 (1968)
[2]L. Jurd, *Tetrahedron Letters* 2863 (1969)
[3]S. Mageswaran, W. D. Ollis, R. J. Roberts and I. O. Sutherland, *Ibid.* 2897 (1969)
[4]L. Jurd, K. Stevens and G. Manners, *Ibid.* 2275 (1971)
[5]G. Manners, L. Jurd and K. Stevens, *Tetrahedron* **28**, 2949 (1972)
[6]B. Cardillo, L. Merlini and S. Servi, *Tetrahedron Letters* 945 (1972)
[7]J. Verghese, *Perfumery and Essential Oil Record* **58** (12), 868 (1967) and ref therein
[8]W. F. Erman, *J. Org. Chem.* **86**, 2887 (1964)