Thermal Rearrangement of 1-(3-Methylbut-2-enyloxy)-4-prop-1-enyl-benzene (Feniculin) : a New Synthesis of Anisoxide and Re-investigation of the Constituents of Star Anise Oil [1]

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At 153 °C feniculin (1) undergoes Claisen rearrangement to the 1,1-dimethylallylphenol (3), which is slowly converted into the 1,2-dimethylallylphenol (4) ; the products of abnormal Claisen rearrangement, phenol (4) and anisoxide (2), are formed at 185 °C. Anisoxide was shown by g.l.c. analysis to be absent in star anise oil and in the seeds of *Illicium verum* and *Foeniculum vulgare*, and is believed to have been obtained previously as a result of prolonged distillation of anise oil.

ANISOXIDE (2) is a 1,2-dimethylallyl derivative, which was first isolated by Jackson and Short [2] from star anise oil obtained from the seeds of *Illicium verum*. The structure of anisoxide was established by Barton and co-workers [3] by degradation and by synthesis from 1-(2-hydroxy-4-methylphenyl)-3-methylbutan-2-one. Although anisoxide contains a chiral centre, the compound was obtained from anisole oil as a racemate, and therefore may be an artifact formed during the isolation procedure. Since the 3,3-dimethylallyl ether (1) (feniculin) is a known constituent of star anise oil,[4] anisoxide could originate from an abnormal Claisen rearrangement of feniculin followed by cyclisation of the resultant 1,2-dimethylallylphenol (4). We sought to resolve this question, first by studying the thermal rearrangement of feniculin, and secondly by carrying out a new investigation of the constituents of star anise oil.

RESULTS AND DISCUSSION

4-Prop-1-enylphenol, required for the preparation of feniculin (1), was obtained conveniently by cleavage of the corresponding methyl ether, anethole; the phenol derived from reaction of anethole with thiophenoxide [5] was difficult to purify, but the older lower-yield method using methylmagnesium iodide was successful.[6] Reaction of 4-prop-1-enylphenol with 3,3-dimethylallyl bromide and potassium carbonate in acetone gave feniculin (80%); the structure of the product was confirmed by n.m.r. and mass spectroscopy (see Experimental section).

Schmid and co-workers [7] studied the rearrangement of 3,3-dimethylallyl phenyl ether in dimethylformamide (DMF) and we used the same solvent to effect rearrangement of feniculin (1). At 185 °C two isomeric products were formed and were separated by chromatography. One product (28% yield) was the 1,2-dimethylallyl-phenol (4); although this compound was sparingly soluble in aqueous base, the presence of the hydroxy-group was indicated by i.r. absorption at 3 470 cm⁻¹, by an n.m.r. resonance at τ 4.30 disappearing on addition of D₂O, and by formation of a crystalline 3,5-dinitro-benzoate. The structure of the C₅ side-chain of phenol (4) was established from the n.m.r. spectrum, which showed a two-proton broad singlet at τ 4.70 (=CH₂) and

a one-proton quartet at τ 6.33. The second rearrangement product was anisoxide (2) (29% yield); its structure was confirmed by n.m.r. spectroscopy, the one-proton quartet at τ 6.80 (MeCH<) being particularly diagnostic, and by its formation from the 1,2-dimethyl-allylphenol (4) by treatment with hydrogen bromide-acetic acid at ambient temperature.

It was apparent that at 185 °C only the products of abnormal Claisen rearrangement of feniculin were
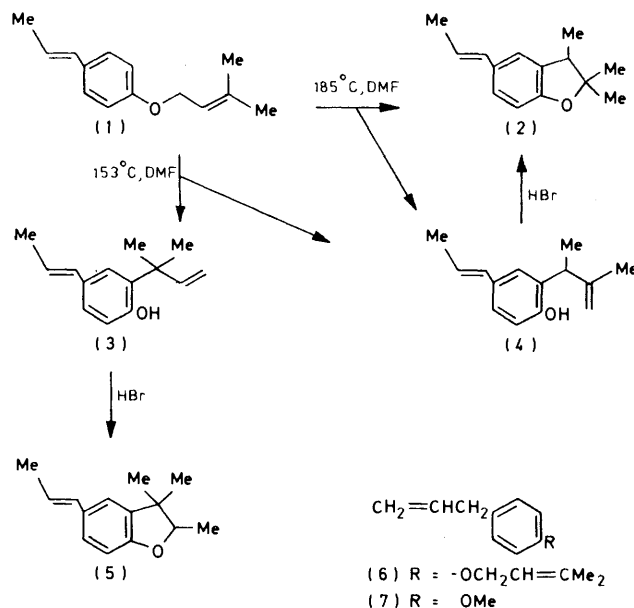
formed. At a lower temperature, however, the major component was the normal Claisen product (3). Thus, heating feniculin in DMF at 153 °C for 55 h gave 4-prop-1-enylphenol from the alkali-soluble fraction, and chromatography of the remainder afforded feniculin (24%), the 1,2-dimethylallylphenol (4) (26%), and the 1,1-dimethylallylphenol (3) (43%). The structure of the latter compound was indicated by its i.r. absorptions at 3 470 (OH) and 920 cm⁻¹ (>C=CH₂) and from the n.m.r. spectrum in which resonances at τ 4.47 (-CH=CH₂) and 4.72 (-CH=CH₂) constituted an ABX system with J_{AX} 6, J_{BX} 2 Hz; the crystalline 3,5-dinitrobenzoate did not give a satisfactory elemental analysis, but the

mass spectrum showed the presence of the molecular ion and a fragmentation ion at m/e 201 formed by cleavage of the ester function. Acid-catalysed cyclisation of phenol (3) apparently gave the dihydrobenzofuran derivative (5); although this compound was not obtained in a pure state, the structure was indicated by the n.m.r. spectrum in which a one-proton quartet at τ 5.58 shows that the methine proton is more strongly deshielded, as expected, than the methine proton of anisoxide (2). A g.l.c.-time study of the rearrangement of feniculin at 153 °C showed that the (1,1-dimethyl-allyl)phenol (3) was formed first and then converted into the 1,2-dimethylallylphenol (4), in accord with the accepted mechanism of the abnormal Claisen rearrangement of allyl ethers.[8]

The availability of synthetic anisoxide enabled us to re-examine the constituents of star anise oil. Monoterpenes and most of the anethole were removed from the commercial oil by fractional distillation. Chromatography of the residue on alumina and then preparative t.l.c. gave feniculin (1). Since feniculin and anisoxide are of very similar polarity on alumina, chromatography fractions containing feniculin were analysed by g.l.c.; mixed injection with anisoxide gave no coincidence of peaks in any fraction, showing that anisoxide is not a detectable constituent of anise oil. Preparative g.l.c. resulted in the isolation of the prop-2-enyl derivative (6); the structure was established by an i.r. absorption at 920 cm^{-1} (=CH$_2$) and by the n.m.r. spectrum (see Experimental section). Compound (6) is reported to be a constituent of *Dictamnus gymnostylis*;[9] it has not been identified previously in star anise oil, although the prop-2-enyl isomer of anethole (7) is present.[10] In case anisoxide was removed from star anise oil during refining, we studied the constituents of the fruits of *Illicium verum* from which the oil is obtained; anisoxide was not detected (g.l.c.), although it was apparent that a high proportion of the less volatile components are indeed removed during the production of anise oil. Seeds of *Foeniculum vulgare*, which contains feniculin, were also examined, but again anisoxide was shown to be absent. In order to simulate the isolation of anisoxide described by Jackson and Short, star anise oil enriched with feniculin was heated at 180 °C; g.l.c. analysis showed that anisoxide was present. We conclude that anisoxide is an artifact, probably formed by rearrangement of feniculin during 'protracted fractionation'[2] of star anise oil.

EXPERIMENTAL

N.m.r. spectra were determined with Perkin-Elmer R10A and R12 spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on an AEI MS902 spectrometer. Gas–liquid chromatography (g.l.c.) was carried out with a Perkin-Elmer F11 instrument with a $2\frac{1}{2}\%$ SE30 column at 150 °C and with a carrier gas pressure of 15 lb in^{-2}, unless stated otherwise; a Perkin-Elmer F21 instrument was used for preparative g.l.c. with a similar column. Silica plates and benzene–light petroleum (b.p. 60—80 °C) (2 : 3) were used for thin-layer chromatography

(t.l.c.). Star anise oil (BP grade 1) was supplied by Digby Chemical Service.

4-Prop-1-enylphenol.—Reaction of anethole with methylmagnesium iodide, chromatography of the product on silica, and elution with ether–light petroleum (b.p. 40—60 °C) gave the phenol (13% yield) as prisms, m.p. 89—92 °C (lit.,[10] m.p. 93—94 °C), R_F 0.14; $\nu_{max.}$ (Nujol) 3 230 (OH) and 965 cm^{-1} (*trans* CH=CH).

1-(3-Methylbut-2-enyloxy)-4-prop-1-enylbenzene (*Feniculin*).—3-Methylbut-2-enyl bromide (13 g) in acetone (10 ml) was added during 30 min to 4-(prop-1-enyl)phenol (12 g), acetone (100 ml), and anhydrous potassium carbonate (7.5 g), and the mixture was refluxed for 12 h. The acetone solution was evaporated, and the residue in ether was washed with 2N-sodium hydroxide and evaporated. Chromatography of the product on alumina and elution with ether–light petroleum (b.p. 40—60 °C) (1 : 9) gave feniculin as an oil (12.9 g, 79%), homogeneous on g.l.c. (retention time, 9 min), R_F 0.70; $\nu_{max.}$ (liquid film) 961 cm^{-1} (*trans* CH=CH); τ(CDCl$_3$), 4.35 (1 H, t, J 6 Hz, CH$_2$CH=CMe$_2$); m/e 202 (M^+, 10%) and 134 (M^+ − C$_5$H$_8$, 100%).

Rearrangement of Feniculin (1).—(a) A solution of feniculin (2 g) in dimethylformamide (20 ml) in a sealed tube was kept at 185 °C for 80 h. The product was added to 2N-hydrochloric acid (10 ml) and extracted into ether. The ether solution was extracted with 2N-sodium hydroxide and evaporated to give a yellow oil showing two spots on t.l.c., R_F 0.29 and 0.59. Chromatography on alumina and elution with ether–light petroleum (b.p. 40—60 °C) (1 : 9) gave anisoxide (2) as an oil (0.57 g, 29%), R_F 0.59, g.l.c. retention time 9.0 min (120 °C); $\nu_{max.}$ (liquid film) 962 cm^{-1} (*trans* CH=CH); τ(CDCl$_3$) 2.60—3.40 (3 H, m, Ar-H), 3.59—3.78 (2 H, m, CH=CH), 6.80 (1 H, q, J 7 Hz, CH–Me), 8.15 (3 H, d, J 5 Hz, =CH–Me), 8.51 (3 H, s), 8.70 (3 H, s), and 8.78 (3 H, d, J 7 Hz, CH–Me); m/e 202.135 8 (M^+, 100%, Calc. for C$_{14}$H$_{18}$O; M, 202.135 585), 187 (M^+ − Me, 30), and 158 (M^+ − C$_3$H$_7$, 11).

Elution with ether–light petroleum (b.p. 40—60 °C) (4 : 1) gave 2-(1,2-dimethylprop-2-enyl)-4-prop-1-enylphenol (4) as an oil (0.55 g, 28%), R_F 0.29, g.l.c. retention time 6.6 min; $\nu_{max.}$ (liquid film) 3 470 (OH) and 885 cm^{-1} (C=CH$_2$); τ(CDCl$_3$) 2.40—3.15 (3 H, m, Ar-H), 3.50—3.70 (2 H, m, CH=CH), 4.30 (1 H, OH), 4.70 (2 H, br s, C=CH_2), 6.33 (1 H, q, J 7 Hz, CH–Me), 8.18 (3 H, d, J 6 Hz, =CH–Me), 8.35 (3 H, s, =C–Me), and 8.62 (3 H, d, J 7 Hz, CH–Me); this was further characterised as its 3,5-dinitrobenzoate, orange prisms (from hexane), m.p. 104—105 °C (Found: C, 63.4; H, 5.0; N, 6.9. C$_{21}$H$_{20}$N$_2$O$_6$ requires C, 63.0; H, 5.1; N, 7.0%).

The alkali-soluble fraction gave 4-prop-1-enylphenol (0.12 g, 8%), identical (i.r. and t.l.c.) with an authentic sample.

(b) Rearrangement of feniculin (2 g) in dimethylformamide (20 ml) refluxing under nitrogen was followed by g.l.c. analysis; after 55 h, when *ca.* 30% feniculin remained, the solution was worked up as described in (a) to give a yellow oil (1.8 g), showing three spots on t.l.c. Chromatography on alumina and elution with ether–light petroleum (b.p. 40—60 °C) (1 : 19) gave feniculin (0.47 g, 24%), R_F 0.70, identical (i.r.) with an authentic sample. Elution with ether–light petroleum (b.p. 40—60 °C) (1 : 1) gave 2-(1,1-dimethylprop-2-enyl)-4-prop-1-enylphenol (3) as an oil, (0.85 g, 43%), R_F 0.32, g.l.c. retention time 7.4 min; $\nu_{max.}$ (liquid film) 3 470 (OH) and 920 cm^{-1} (CH=CH$_2$); τ(CDCl$_3$) 2.60—3.20 (3 H, m, Ar-H), 3.60—3.75 (2 H, m,

CH=CH), 4.15 (1 H, s, OH), 4.47 (2 H, CH=CH$_2$), 4.72 (1 H, CH=CH$_2$), 8.13 (3 H, d, J 5 Hz, =CH-Me), and 8.55 (6 H, s, CMe$_2$). The 3,5-dinitrobenzoate, which separated from hexane as yellow needles, m.p. 97—99 °C, m/e 396.131 0 (M^+, 97%; C$_{21}$H$_{20}$N$_2$O$_6$ requires M, 396.126 1) and 201.126 8 (M^+ — C$_7$H$_3$N$_2$O$_7$, 98%; C$_{14}$H$_{17}$O requires 201.126 9) did not give a satisfactory analysis.

Elution with ether–light petroleum (b.p. 40—60 °C) (3 : 2) afforded the phenol (4) (0.52 g, 26%), identical with the compound obtained in (a).

Cyclisation of Phenols (3) *and* (4).—(a) The phenol (3) (0.16 g) in 12% hydrogen bromide in acetic acid (8 ml) was kept at 20 °C for 22 h. The solution was evaporated and the residue in ether was washed with water and evaporated to give 5-prop-1-enyl-2,3,3-trimethyl-2,3-dihydrobenzofuran (5) as an oil; τ(CDCl$_3$) 2.60—3.45 (3 H, m, Ar-H), 3.63—3.88 (2 H, m, CH=CH), 5.58 (1 H, q, J 7 Hz, CH-Me), 8.13 (3 H, d, J 5 Hz, =CH-Me), 8.63 (3 H, d, J 7 Hz, CH-Me), 8.70 (3 H, s), and 8.91 (3 H, s). The compound was shown by g.l.c. analysis to be 95% pure; chromatography on alumina resulted in decomposition.

(b) Phenol (4) (0.15 g) was cyclised as in (a); filtration through a short column of alumina gave anisoxide (2) (0.13 g), identical (g.l.c., n.m.r., and i.r.) with a sample obtained by rearrangement of feniculin.

Constituents of Star Anise Oil.—(a) Commercial star anise oil (2.5 l) was fractionally distilled *in vacuo* until most of the anethole was removed; chromatography of the residue (15.0 g) on alumina and elution with ether–light petroleum gave a number of fractions containing feniculin (1), which was isolated by preparative t.l.c. Fractions containing feniculin were submitted to g.l.c.; mixed injection with anisoxide gave no coincidence of peaks in any fraction. Preparative g.l.c. at 90 °C with nitrogen as carrier gas at 420 ml min^{-1} gave 1-(3-methylbut-2-enyloxy)-4-prop-2-enyl-benzene (6) as an oil; $\nu_{max.}$ (liquid film) 920 cm^{-1} (C=CH$_2$); τ(CDCl$_3$) 2.88—3.20 (4 H, m, Ar-H), 3.98—4.20 (1 H, CH$_2$-CH=CH$_2$), 4.48—4.60 (1 H, m, OCH$_2$CH=), 5.54 (2 H, d, J

9 Hz, $^-$OCH$_2$CH=), 6.79 (2 H, d, J 8 Hz, Ar-CH$_2$CH=), 8.20 (3 H, s), and 8.32 (3 H, s); m/e 202.135 90 (M^+, 17%; Calc. for C$_{14}$H$_{18}$O, M, 202.135 85), 134 (M^+ — C$_5$H$_8$, 100), 133 (M^+ — C$_5$H$_8$, 53), and 107 (20).

(b) Crushed seeds of *Illicium verum* (200 g) were boiled with light petroleum (b.p. 60—80 °C) for 24 h; evaporation of the solution gave a yellow oil (5.5 g), shown by g.l.c. to contain feniculin (1) (8%) but no anisoxide. A similar result was obtained with seeds of *Foeniculum vulgare*.

Formation of Anisoxide in Star Anise Oil.—Star anise oil (1.3 g) enriched with feniculin (0.3 g) was kept at 180 °C under nitrogen for 24 h. G.l.c. at 120 °C gave a new peak (retention time 9 min), shown to be due to the presence of anisoxide by mixed injection with an authentic sample; this was confirmed by g.l.c. on a 10% tris(cyanoethoxy)-propane column at 160 °C with carrier gas at 40 lb in^{-2} (retention time, 33.2 min).

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