Studies of Aromatic Sesquiterpenes. IV.[1] The Synthesis of γ-Calacorene, Calamenene, and 4-Methoxyisocadalene

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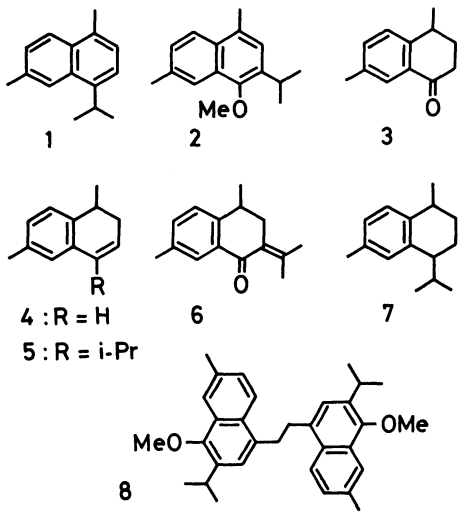
Synopsis. The Grignard reaction of 3,4-dihydro-4,7-dimethyl-1(2*H*)-naphthalenone with isopropylmagnesium bromide gave a 3 : 1 mixture of normal reaction product and α-isopropylidene ketone, from which, the title sesquiterpenes and 1,2-bis(3-isopropyl-4-methoxy-6-methyl-1-naphthyl)ethane were synthesized.

Some sesquiterpenes are dehydrogenated by heating with sulfur, selenium or palladium catalysts giving a parent hydrocarbon of the sesquiterpenes such as cadalene (**1**), which have been recently isolated[2] along with 4-methoxyisocadalene[3] (**2**) or other sesquiterpenes from *Heterotheca* species (Compositae). In the various path ways for synthesis of **1**, 3,4-dihydro-4,7-dimethyl-1(2*H*)-naphthalenone (**3**) have been employed as a key intermediate.[4] However, the isopropylated products of **3** by the Grignard reaction have not been investigated.

In this paper, it is described that the Grignard reaction products of **3** were dehydrated with formic acid giving a mixture of 1,2-dihydro-1,6-dimethylnaphthalene (**4**), γ-calacorene (**5**), and 3,4-dihydro-2-isopropylidene-4,7-dimethyl-1(2*H*)-naphthalenone (**6**). Calamenene (**7**) and 4-methoxyisocadalene (**2**) were synthesized from **5** and **6**, respectively.



The ketone **3** was allowed to react with isopropylmagnesium bromide, and the dehydration of the reaction products gave a mixture of four components (**4**, **5**, and **6** including **3**). The formation of two hydrocarbons **4** and **5** indicates that the corresponding alcohols were respectively prepared by reductive reaction and normal addition of the Grignard reagent on **3**. Furthermore, any other isomers of the *endo*-olefin **5** were not observed. Therefore, an intermediate in the synthesis of cadalene (**1**) from **3** is γ-calacorene (**5**), which has been isolated from the wood of *Juniperus rigida*[5] and the Japanese hop (*Humulus lupulus* L.).[6]

The structure of 3,4-dihydro-2-isopropylidene-4,7-dimethyl-1(2*H*)-naphthalenone (**6**) was confirmed by the comparison of its spectral data with those of 3,4-dihydro-2-isopropylidene-1(2*H*)-naphthalenone and the 4-methyl derivative.[7]

The catalytic hydrogenation of **5** afforded calamenene (**7**) in a mixture of diastereomers which consisted of *cis* (80%) and *trans* (20%) isomers on the basis of the ^{1}H-NMR (60 MHz), *i.e.*, the proton signals of two methyl groups in the isopropyl group indicated four pairs of doublets (d, at δ=0.74, 1.01, and 0.69, 0.98).[8] In the literature,[9] it has been reported that the reduction of α-calacorene afforded calamenene which consisted of about 40% of *cis*- and 60% of *trans*-isomers.

The unsaturated ketone **6** on isomerization with Pd–C catalysts and subsequent methylation with dimethyl sulfate afforded 4-methoxyisocadalene (**2**). The prism crystals (mp 165.5—166.0 °C) were obtained as a by-product of **2**, and its IR spectrum showed similar pattern with that of **2**. 1,2-Bis(3-isopropyl-4-methoxy-6-methyl-1-naphthyl)ethane (**8**) was proposed as the structure of this by-product on the basis of its NMR spectrum and the elementaly analysis. During the isomerization of **6**, a part of the reactant was dehydrogenatively dimerized to give **8**.

Experimental

The Grignard Reaction of Isopropylmagnesium Bromide on 3,4-Dihydro-4,7-dimethyl-1-(2H)-naphthalenone (3). The ketone **3** was synthesized from toluene in the same way as the synthesis of 3,4-dihydro-8-isopropyl-4,5-dimethyl-1(2*H*)-naphthalenone from *p*-cymene.[10]

A solution of **3** (10.0 g) in ether (25 ml) was added to the Grignard reagent prepared from Mg (4.2 g) and isopropyl bromide (23.0 g) in ether (150 ml). The reaction mixture was stirred for several hours in an ice bath, allowed to stand for over night, and then refluxed for 8 h. Acetone was added to destroy an excess reagent, and the reaction mixture was decomposed by adding a crushed ice and NH_4Cl. After removal of the solvent from the ethereal solution, the residue (14 g) was dehydrated by stirring with formic acid (70 ml) at 50 °C for 3 h. The reaction mixture was diluted with water and extracted with benzene. Removal of the solvent from the benzene extract and distillation of the residue gave 8.5 g of an oil, bp 94—146 °C/3 mmHg (1 mmHg=133.322 Pa), which was a mixture consisted of **4** (14.3%), **5** (54.8%), **3** (13.4%), and **6** (17.5%) (GC analysis). The oily mixture was separated into two fractions by successive elution with CCl_4 and ether through a silica-gel column. The hydrocarbon mixture eluted with CCl_4 was repeatedly distilled to separate **4** and **5**. The unsaturated ketone **6** in the ethereal eluates was freed from **3** over a silica-gel column chromatography.

1,2-Dihydro-1,6-dimethylnaphthalene (4): Oil, bp 96—97 °C/9 mmHg; IR: 1605, 1490, 1445, 880, 810, 695, and 670 cm^{-1}; NMR (CCl_4): δ=1.18 (3H, d, J=7 Hz, CH_3), about 2.2 (2H, m, CH_2), 2.23 (3H, s, CH_3), 2.78 (1H, m, J=7 Hz, >CH–),

5.81 (1H, dt, J=9 and 4 Hz), 6.32 (1H, dt, J=9 and 2 Hz), 6.73 and 6.88 (3H, each br, s).

γ-Calacorene (1,2-Dihydro-4-isopropyl-1,6-dimethylnaphthalene) (5): Oil, bp 125—126 °C/9 mmHg; IR: 1605, 1485, 1455, 1445, 1380, 1360, 880, 815, and 805 cm^{-1}; NMR (CCl_4): δ= 1.14 (9H, d, J=7 Hz, three CH_3), 2.17 (2H, m, CH_2), 2.30 (3H, s, CH_3), 2.82 (2H, m, J=7 Hz, two >CH–), 5.70 (1H, t, J=5 Hz, =CH–), 6.93 and 7.05 (3H, each br. s).

3,4-Dihydro-2-isopropylidene-4,7-dimethyl-1(2H)-naphthalenone (6): Oil, bp 127—128 °C/3 mmHg; IR: 1665, 1605, 1495, 1450, 1365, 1290, 1175, 820, and 785 cm^{-1}; NMR (CCl_4): δ= 1.24 (3H, d, J=7 Hz, CH_3), 1.90 (3H, br. s, vinyl-CH_3), 2.18 (3H, br. s, vinyl-CH_3), 2.35 (3H, s, CH_3), 2.73 (2H, br, CH_2), 3.00 (1H, m, >CH–), 7.02 (1H, d, J=8 Hz), 7.18 (1H, dd, J=8 and 2 Hz) and 7.82 (1H, br. s). Found: C, 84.01; H, 8.45%. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%.

Calamenene (7). A solution of **5** (2.0 g) in ethanol (50 ml) was shaken with Pd–C (10%, 0.5 g) under a hydrogen atmosphere for 8 h. The catalysts were then removed by filtration, and the filtrate was evaporated to give an oil, which was distilled to afford **7** (1.9 g), bp 127—130 °C/10 mmHg, n_D^{20} 1.5262, d_4^{20} 0.9305; IR: 1615, 1495, 1455, 1380, 1370, 1360, and 815 cm^{-1}; NMR (CCl_4): δ=0.69 and 0.74 (3H, each d, J=7 Hz, CH_3), 0.98 and 1.01 (3H, each d, J=7 Hz, CH_3), 1.21 (3H, d, J=7 Hz, CH_3), 1.67 (4H, m), 2.23 (3H, s, CH_3), about 2.58 (3H, m, three >CH–) and 6.87 (3H, m). The resulting calamenene (**7**) showed a single peak on GC (a 2 m×3 mm Apiezon Grease L 30% on Cellite 545 column, He), but its NMR spectrum showed the presence of two isomers, *cis*-**7**: *trans*-**7**=4 : 1.

4-Methoxyisocadalene (2) and Its Dimerized Product (8). A mixture of the unsaturated ketone **6** (1.0 g) and Pd–C (10%, 0.5 g) in xylene (10 ml) was refluxed for 12 h. The catalysts were removed by filtration and the filtrate was evaporated. The residual oil was refluxed with K_2CO_3 (2.0 g) and dimethyl sulfate (1.6 g) in acetone (20 ml) for 8 h. After removal of the solvent, ammonia water (2 ml) was added and stirred to destroy an excess dimethyl sulfate at 50 °C for 30 min. The reaction mixture was diluted with water and then extracted with benzene. The benzene extract was washed with water, dried and evaporated to give an oil which was chromatographed over an alumina column. The hexane eluate wa evaporated to give an oil (0.9 g), from which, the precipitated crystals (0.3 g) of **8** were removed by filtration and the filtrate was purified by distillation to afford **2** (0.4 g), bp 128—130 °C/ 10 mmHg, n_D^{20} 1.5587. The IR and NMR spectra of **2** were superimposable with those of the authentic specimen.[1] *Picrate*: Orange brown needles, mp 90.5—91.5 °C (lit,[1] mp 90.5—91.5 °C).

1,2-Bis(3-isopropyl-4-methoxy-6-methyl-1-naphthyl)ethane (8): Prisms from petroleum ether, mp 165.5—166.0 °C; IR (KBr): 1620, 1600, 1565, 1510, 1455, 1440, 1405, 1350, 1225, 1195, 1090, 1060, 985, 880, and 815 cm^{-1}; NMR (CCl_4): δ=1.14 (12H, d, J=7 Hz, two $\langle^{CH_3}_{CH_3}$), 2.52 (6H, s, two CH_3), 3.35 (4H, s, two CH_2), 3.45 (2H, m, J=7 Hz, two >CH–), 3.80 (6H, s, two OCH_3), 6.85 (2H, s), 7.16 (2H, dd, J=9 and 2 Hz), 7.78 (2H, br. s) and 7.79 (2H, d, J=9 Hz). Found: C, 84.50; H, 8.42%. Calcd for $C_{32}H_{38}O_2$: C, 84.54; H, 8.43%.

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