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The Synthesis of Racemic Dihydroageratone. Efficient Demethylation by Magnesium Iodide Etherate

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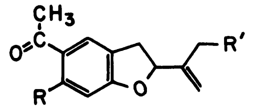
Synopsis. 2-Isopropenyl-6-methoxy-2,3-dihydrobenzofuran, prepared from *m*-methoxyphenol and 1,4-dibromo-2-methyl-2-butene, was converted to racemic dihydroageratone *via* oxidation with selenium dioxide, the acetylation with acetic acid–trifluoroacetic anhydride, and the demethylation with magnesium iodide etherate.

Some syntheses of 2-isopropenyl-2,3-dihydrobenzofuran derivatives were reported. They mainly consisted of two methods; one was the dehydration of 2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofurans and the other was our one-step cyclization of the phenols and 1,4-dibromo-2-methyl-2-butene.[1] We have already reported the synthesis of 5-acetyl-2-[1-(hydroxymethyl)vinyl]-2,3-dihydrobenzofuran (**1**) having an oxidized isopropenyl group.[2] Dihydroageratone (**2**), isolated from *Ageratum houstnianum* by Anthonsen and Chanthrasakul, also exhibited an oxidized side chain.[3] Here, we describe the synthesis of the dihydroageratone (**2**) having an oxidized isopropenyl and a phenolic hydroxyl group.



1 R=H, R'=OAc
2 R=OH, R'=OAc
3 R=OH, R'=H

Chart 1.

For the synthesis of **2**, a key step was to remove the protection of the phenolic hydroxyl group. In the syntheses of hydroxytremetone (**3**), Oda *et al.* used alkaline hydrolysis for the removal of the acetyl group[4] and Harada *et al.* used hydrogenolysis for the removal of the benzyl group.[5] However, in our one-step cyclization using sodium metal, the protection by *O*-acetylation was unsuitable, and the deprotection of a benzyl group by hydrogenolysis or acidic cleavage might have caused a hydrogenation or an isomerization on the isopropenyl side chain. However, we were able to remove the protection by demethylation with magnesium iodide etherate without affecting the isopropenyl group.

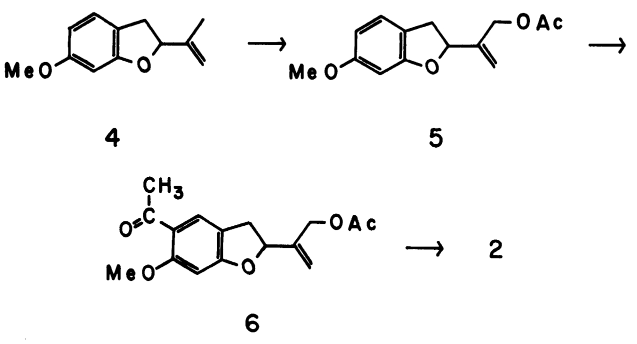


Chart 2.

We have already described the preparation of 2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran (**4**) from *m*-methoxyphenol and 1,4-dibromo-2-methyl-2-butene.[1] When the dihydrobenzofuran **4** was heated with selenium dioxide in refluxing acetic anhydride for 7 h, 2-[1-(acetoxymethyl)vinyl]-6-methoxy-2,3-dihydrobenzofuran (**5**) was obtained in 7.1% yield. A carbonyl absorption at 1740 cm^{-1} in the IR spectrum and a methyl signal at δ 1.9 in the ^{1}H NMR spectrum showed the exsistence of an acetoxyl group. Further, a methylene signal at δ 4.6 showed that the acetoxyl group was on the methyl carbon in the isopropenyl group. Acylation of the acetate **5** with acetic acid–trifluoroacetic anhydride at room temperature for 3 h gave 2-[1-(acetoxymethyl)vinyl]-5-acetyl-6-methoxy-2,3-dihydrobenzofuran (**6**) in 48.3% yield. A new carbonyl absorption in the IR spectrum and two singlets at δ 6.5 and 7.7 in the ^{1}H NMR specturm indicated that the acetylation was at position 5. Refluxing the keto-acetate **6** with magnesium iodide etherate in dry benzene for 3 h gave the corresponding demethylated product **3** in 20.5% yield without any isomerization. Carbonyl absorption at 1635 cm^{-1} in the IR specturum and a signal at δ 13.0 in the ^{1}H NMR indicated the formation of intramolecular hydrogen bonding. This reagent was very useful for the demethylation of a methoxyl group in the ortho position of an acyl group in mild conditions. The spectral data of this demethylated product **3** were identical with reported data of natural dihydroageratone.[3]

Two methoxy ketones, 5-acetyl-2-isopropenyl-4-methoxy- and -6-methoxy-2,3-dihydrobenzofuran (**7** and **8**) have already been reported.[1] They were similarly demethylated with magnesium iodide etherate to give corresponding hydroxy ketones, **9** and **3**. The spectral data of the hydroxyketone **3** were identical with those of natural hydroxytremetone.[6] However, the other hydroxy ketone, 5-acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran (**9**), did not agree with the natural compound[7] in the spectral data. Both samples showed intramolecular hydrogen bonding in their IR and ^{1}H NMR spectra. However, in the ^{1}H NMR spectra, our synthetic sample showed aromatic signals at δ 6.3 and 7.5, while the natural sample showed them at δ 6.81 and 6.99. This indicated that the natural compound had another structure, 4-acetyl-5-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran or 7-acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran, having a hydrogen-bonding between a phenolic hydroxyl group and an acetyl group and no aromatic proton in ortho position of an acetyl group.[8]

Experimental

The boiling points were uncorrected (in boiling points:

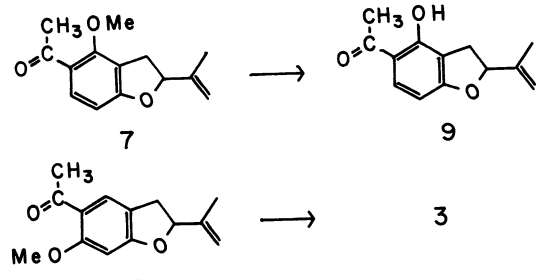


Chart 3.

1 mmHg=133.322 Pa). The IR spectra were measured on a Hitachi EPI-S2 spectrophotometer in a liquid film and the UV spectra were taken on a Hitachi 220 A spectrophotometer in an ethanolic solution. The ^{1}H NMR spectra were recorded on a JEOL JNM-MH-60 NMR spectrometer and the mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

2-[1-(Acetoxymethyl)vinyl]-6-methoxy-2,3-dihydrobenzofuran (5). To a solution of 2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran (**4**)[1] (1.08 g, 5.68 mmol) in acetic anhydride (15 ml), powdered selenium dioxide (578 mg, 5.21 mmol) was added, and the mixture was refluxed for 7 h. After cooling, the mixture was diluted with ether and filtered. The ether and the excess acetic anhydride was removed from the filtrate under reduced pressure. The residue was dissolved in ether and the ethereal solution was washed with saturated sodium hydrogencarbonate solution and then with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After the removal of the ether, the residual oil was purified on a silica-gel column. Fractions eluted with benzene gave pure 2-[1-(acetoxymethyl)vinyl]-6-methoxy-2,3-dihydrobenzofuran (**5**) (100 mg, 7.1%) as an oil; IR (neat) 1740 cm^{-1}. ^{1}H NMR (CCl_4) δ=2.0 (3H s), 3.0 (1H, dd, J=16 and 9 Hz), 3.3 (1H, dd, J=16 and 9 Hz), 3.7 (3H, s), 4.6 (2H, broad s), 5.1 (1H, broad s), 5.2 (1H, t, J=9 Hz), 5.3 (1H, broad s), 6.3 (2H, m), and 6.9 (1H, d, J=9 Hz).

Found: C, 67.57; H, 6.73%; M^+ 248. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%; M^+ 248.

2-[1-(Acetoxymethyl)vinyl]-5-acetyl-6-methoxy-2,3-dihydrobenzofuran (6). By a method similar to one described in our previous parer,[1] 2-[1-(acetoxymethyl)vinyl]-6-methoxy-2,3-dihydrobenzofuran (**5**)(200 mg, 0.806 mmol) was acetylated with acetic acid (97 mg, 1.6 mmol) and trifluoroacetic anhydride (500 mg, 2.38 mmol) at room temperature for 3 h, and gave a crude oil (229 mg). The crude oil was purified on a silica-gel column. Fractions eluted with chloroform gave pure 2-[1-(acetoxymethyl)vinyl]-5-acetyl-6-methoxy-2,3-dihydrobenzofuran (**6**) (113 mg, 48.3%) as an oil; bp 230—250 °C/15 mmHg (bath temp). IR (neat) 1740 and 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.1 (3H, s), 2.6 (3H, s), 3.2 (1H, dd, J=16 and 9 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 3.9 (3H, s), 4.7 (2H, s), 5.3 (1H, broad s), 5.4 (1H, broad s), 5.4 (1H, t, J=9 Hz), 6.5 (1H, s), and 7.7 (1H, s).

Found: C, 66.42; H, 6.31%; M^+ 290. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25%; M^+ 290.

2-[1-(Acetoxymethyl)vinyl]-5-acetyl-6-hydroxy-2,3-dihydrobenzofuran (Racemic Dihydroageratone) (2). To magnesium metal (21 mg, 0.80 mmol) in dry ether (0.24 ml) and dry benzene (0.5 ml), iodine crystals (108 mg, 0.850 mmol) were added in small portions. The mixture was stirred until the iodine color disappeared (*ca.* 3 h). A solution of 2-[1-(acetoxymethyl)vinyl]-5-acetyl-6-methoxy-2,3-dihydrobenzofuran (**6**) (165 mg, 0.638 mmol) in dry benzene was added to the benzene solution of magnesium iodide etherate prepared previously. The mixture was then refluxed for 3 h. After cooling, the mixture was poured onto 10% hydrochloric acid and extracted with ether. The ethereal solution was washed with a saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After the removal of the ether and benzene, the residual oil was purified on a silica-gel column. Fractions eluted with chloroform gave pure 2-[1-(acetoxymethyl)vinyl]-5-acetyl-6-hydroxy-2,3-dihydrobenzofuran (**2**) as an oil; bp 247—255 °C/15 mmHg. IR (neat) 1740 and 1635 cm^{-1}. UV (EtOH) 238 (log ε 4.47), 277 (4.29), and 325 nm 4.11). ^{1}H NMR (CCl_4) δ=2.0 (3H, s), 2.5 (3H, s), 3.1 (1H, dd, J=16 and 9 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 4.5 (2H, s), 5.4 (2H, broad s), 5.4 (1H, t, J=9 Hz), 6.5 (1H, s), 7.5 (1H, s), and 13.0 (1H, s). Mass m/z 276 (M^+), 216 ($M^+-C_2H_4O_2$), and 176 ($M^+-C_5H_8O_2$).

Found: C, 65.29; H, 6.06%; M^+ 276. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%; M^+ 276.

Those spectral data agreed with the reported data of natural dihydroageratone.[3]

Demethylation of 5-Acetyl-2-isopropenyl-4-methoxy- and -6-methoxy-2,3-dihydrobenzofuran (7 and 8). By a method similar to that described for the preparation of **2**, 5-acetyl-2-isopropenyl-4-methoxy- or -6-methoxy-2,3-dihydrobenzofuran (**7** or **8**) was demethylated with magnesium iodide etherate to give 5-acetyl-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran (**9**); yield 42.1%; bp 190—215 °C/15 mmHg (bath temp); IR (neat) 1645 cm^{-1}; UV (EtOH) 234 (logε 3.94), 241 (3.94), and 288 nm (4.19); ^{1}H NMR (CCl_4) δ=1.8 (3H, broad s), 2.5 (3H, s), 3.0 (1H, dd, J=16 and 10 Hz), 3.3 (1H, dd, J=16 and 10 Hz), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.3 (1H, t, J=10 Hz), 6.3 (1H, d, J=10 Hz), 7.5 (1H, d, J=10 Hz), and 12.7 (1H, s); Mass m/z 218 (M^+) and 203 ($M^+ -CH_3$). Found: C, 71.35; H, 6.38%; M^+ 218. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%; M^+ 218; and 5-acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran (**3**); yield 44.7%; IR (neat) 1640 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.7 (3H, broad s), 2.4 (3H, s), 2.9 (1H, dd, J=16 and 9 Hz), 3.2 (1H, dd, J=16 and 9 Hz), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.2 (1H, t, J=9 Hz), 6.2 (1H, s), 7.4 (1H, s), and 12.7 (1H, s).

The hydroxy ketone **3** was identical to natural hydroxytremetone[6] in their IR and ^{1}H NMR spectra, but the other hydroxy ketone **9** did not agreed with that of the natural compound (reported by Bohlmann *et al.*).[7,8]

We wish to thank Professer Dr. Ferdinand Bohlmann for providing copies of the IR and ^{1}H NMR spectra of natural compound.

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8) Recentry, we found, this natural compound had 4-acetyl-5-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran, by another preparation. It will be reported soon.