Synthesis and Structural Studies of Remirol

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One step cyclization of 2′,4′,6′-trihydroxyacetophenone with 1,4-dibromo-2-methyl-2-butene gave two 2-isopropenyl-2,3-dihydrobenzofuran-4,6-diols and a new 3-methyl-2,5-dihydro-1-benzoxepin-6,8-diol. The structure of natural remirol was confirmed by comparison with monomethylated compounds of the former products. Racemic remirol was synthesized from 3,5-dimethoxyphenol in three steps.

In 1969, Allan et al. isolated a new dihydrobenzofuran from *Remiria maritima* and proposed a structure of 5-acetyl-2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran-4-ol (**1**).[1] A positive Gibbs test was the only reason to propose the structure, and so some possibilities of other structure, 5-acetyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran-6-ol (**2**) or 7-acetyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran-6-ol (**3**), remained for remirol. In this paper, we describe a synthesis and structural reconsideration of remirol.

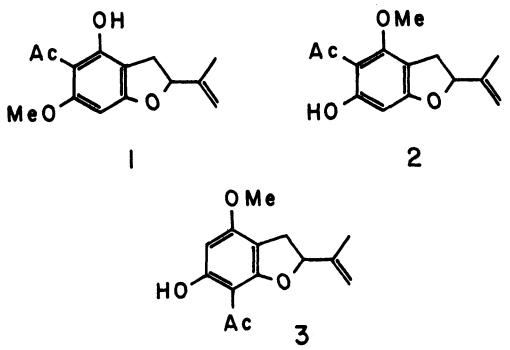

Chart 1.

Cyclization of 2′,4′,6′-trihydroxyacetophenone with 1,4-dibromo-2-methyl-2-butene was already reported by two groups.[2,3] Nickl obtained 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4,6-diol (**5**) in cyclization of the sodium salt of the phenol in cold methanol.[2] Bigi et al. isolated two dihydrobenzofurans, 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4,6-diol (**4**) and **5**, in cyclization of the potassium salt in refluxing toluene.[3] We have reinvestigated these two methods and found that Nickl's method gave a mixture, different from Bigi's, containing 9-acetyl-3-methyl-2,5-dihydro-1-benzoxepin-6,8-diol (**6**). This evidence shows that a different cyclization proceed in a different solvent; the cyclization in nonpolar toluene occurred at 2′- and 4′-hydroxyl groups, while the cyclization in polar methanol occurred mainly at the 2′-hydroxyl group. We have already reported that a similar cyclization of 2′,6′-dihydroxyacetophenone gave a mixture of corresponding dihydrobenzofuran and dihydrobenzoxepin in nonpolar toluene.[4] In these two cases dihydrobenzoxepin derivatives were obtained. Further studies are necessary to establish the formation mechanism of the dihydrobenzoxepin derivatives. In the ^{1}H NMR spectra, two isopropenyldihydrobenzofurans **4** and **5** showed ABX coupling patterns due to protons in their dihydrofuran ring, while **6** showed another coupling mode of the oxepin ring part. The spectral mode of **6** was similar to those of some natural 3-methyl-2,5-dihydro-1-benzoxepin derivatives.[5] Hydrogenation of **6** gave a mixture of 9-acetyl-3-methyl-2,3,4,5-tetrahydro-1-benzoxepin-6,8-diol (**7**) (mp 117—118 °C) and 2′,4′,6′-trihydroxy-3′-(3-methylbutyl)acetophenone (**8**). Nickl already reported that hydrogenation of **5** gave a dihydro compound (mp 153—156 °C) and **8**. The dihydro compound **7** derived from **6** showed only one doublet methyl at δ 0.94 in ^{1}H NMR sectrum. This evidence shows that **6** was not a dihydrobenzofuran derivative but a 3-methyl-2,5-dihydro-1-benzoxepin derivative. In their methylation with diazomethane, **4** gave two mono-methylated

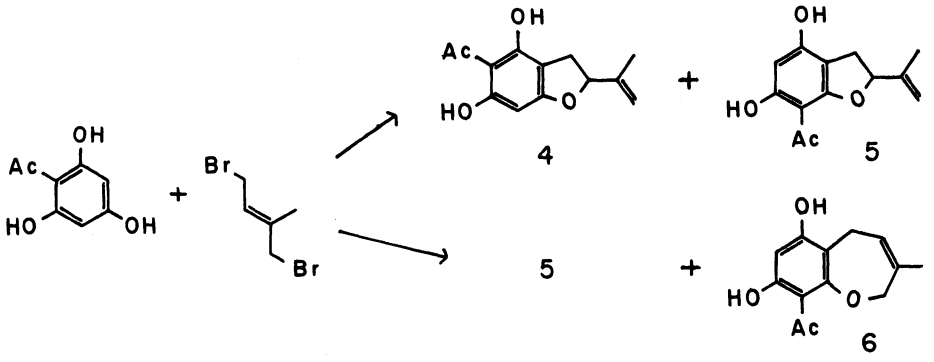

Chart 2.

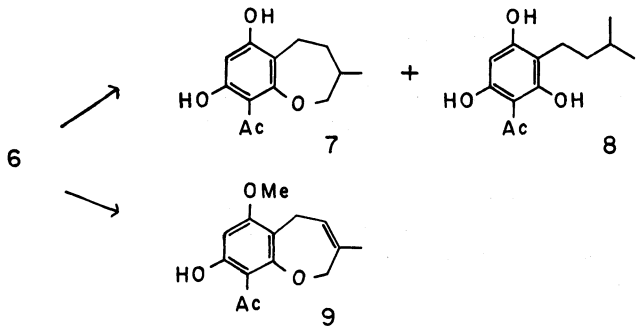

Chart 3.

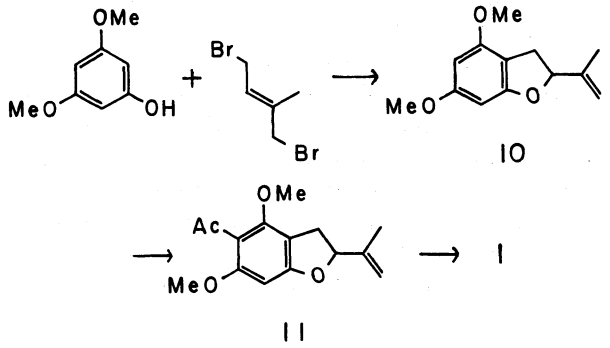

Chart 4.

compounds **1** and **2**, while **5** gave only one monomethylated compound **3**. The methylation of a dihydrobenzoxepin **6** gave one monomethylated compound, 9-acetyl-6-methoxy-3-methyl-2,5-dihydro-1-benzoxepin-8-ol (**9**). Each structure of these monomethylated dihydrobenzofurans **1**—**3** was confirmed by NOE measurements in their ^{1}H NMR spectra. In irradiations at methoxy protons, **1** and **3** showed 39 and 35% area increases, respectively, in their aromatic proton signals (7-H in **1** and 5-H in **3**), but **2** showed only +3 and +4% increases in the two methylene proton signals (3-H). In the UV spectra, **1** and **2** were comparable with 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4-ol and 5-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-6-ol, respectively, while **3** and **9** were comparable with 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-6-ol.[4,6] Thus, each structure of the four monomethylated compounds **1**—**3** and **9** was confirmed. The structure of natural remirol whose spectral data were identical with those of **1**, was confirmed to be 5-acetyl-2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran-4-ol.

By a similar procedure,[7] 2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**10**) was prepared from 3,5-dimethoxyphenol and 1,4-dibromo-2-methyl-2-butene. Acylation of **10** with acetic acid and trifluoroacetic anhydride gave only one acylated product, 5-acetyl-2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**11**). Demethylation of **11** with magnesium iodide etherate gave only one demethylated product, the spectrum of which was identical with **1** and natural remirol. This shows that the acylation of **10** occurred only at the 5-position and the demethylation of **11** occurred only at the 4-methoxyl group. It is interesting that the demethylation of **11** occurred only at the 4-methoxyl group, while monomethylation of **4** occurred at two hydroxyl groups with almost equal probability. By this way, racemic remirol was effectively synthesized from 3,5-dimethoxyphenol in three steps.

Experimental

The boiling points (1 mmHg=133.322pa) and melting points are uncorrected. The IR spectra were measured on a Hitachi EPI-S2 spectrophotometer in KBr disks or liquid films, and UV spectra were taken on a Hitachi 220A spectrophotometer in ethanol. The ^{1}H NMR spectra were recorded on a JEOL JNM-MH-60 NMR spectrometer, a JEOL JNM-FX90Q FT NMR spectrometer, or Varian XL-200 FT NMR spectrometer, Mass spectra were determined on a JEOL JMS-OISG-2 mass spectrometer.

Cyclization of 2′,4′,6′-Trihydroxyacetophenone with 1,4-Dibromo-2-methyl-2-butene by Nickl's Procedure.[2] A solution of the sodium salts was prepared by mixing 2′,4′,6′-trihydroxyacetophenone monohydrate (9.95 g, 53.5 mmol) and sodium methoxide (prepared from 2.78 g, 121 mmol of sodium metal) in methanol (200 mL). To the solution , 1,4-dibromo-2-methyl-2-butene (15.5 g, 64.3 mmol) was added and the mixture was stirred at room temperature for 20 h. After removal of the methanol under reduced pressure, the mixture was acidified with 10% hydrochloric acid and extracted with ether. The ethereal layer was extracted with 10% sodium hydroxide solution. The sodium hydroxide solution was acidified with 10% hydrochloric acid and extracted with ether. After removal of the ether, the residue was chromatographed on a silica-gel column to give 7-acetyl-2-isopropenyl-2,3-dihydrobenzofuran-4,6-diol (**5**) (0.90 g, 7.2%) and 9-acetyl-3-methyl-2,5-dihydro-1-benzoxepin-6,8-diol (**6**) (1.48 g, 11.8%). The compounds isolated showed the following data. **5**: mp 185—186 °C (from benzene)(lit,[3] 178—182 °C); IR 1640 cm^{-1}; UV 228.5 (log ε=4.07), 286 (4.26), 327 nm (3.58); ^{1}H NMR (acetone-d_6) δ=1.8 (3H, broad s), 2.6 (3H, s), 3.0 (1H, dd, J=15 and 8 Hz), 3.2 (1H, dd, J=15 and 9.5 Hz), 5.0 (1H, broad s), 5.2 (1H, broad s), 5.5 (1H, dd, J=9.5 and 8 Hz), 6.0 (1H, s), 13.4 (1H, s); all spectra were identical with Bigi's. **6**: mp 192—193 °C (from benzene); IR 1630 cm^{-1}; UV 223.5 (log ε=4.05), 284 (4.11), 328 nm (3.66); ^{1}H NMR (acetone-d_6) δ=1.6 (3H, broad s), 2.7 (3H, s), 3.4 (2H, broad m), 4.6 (1H, broad s), 5.7 (1H, broad m), 6.3 (1H, s), 13.6 (1H, s); MS m/z 234 (M^+), 219, 201. Found: C, 66.56, H, 6.11%. Calcd for $C_{13}H_{14}O_4$: C, 66.65, H, 6.02%.

Hydrogenation of 6. A solution of **6** (330 mg, 1.41 mmol) in ethyl acetate (20 mL) was stirred with Adams catalyst (100 mg) under a hydrogen atmosphere. After the absorption of hydrogen ceased, the catalyst was filtered off. After removal of the ethyl acetate, the residue was chromatographed on a silica-gel column to give 9-acetyl-3-methyl-2,3,4,5-tetrahydro-1-benzoxepin-6,8-diol (**7**) (106 mg, 32%) and 2′,4′,6′-trihydroxy-3′-(3-methylbutyl)acetophenone (**8**) (84 mg, 25%). These two compounds showed following data. **7**: mp 117—118.5 °C (from cyclohexane-benzene); IR 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.94 (3H, d, 3-CH_3), 1.22 (1H, m, 4-Hax), 1.96 (1H, m, 4-Heq), 2.18 (1H, m, 3-Hax), 2.50 (1H, dd, 5-Hax), 2.66 (3H, s, -$COCH_3$), 3.05 (1H, dd, 5-Heq), 3.38 (1H, dd,

2-Hax), 4.29 (1H, dd, 2-Heq), 6.14 (1H, s, 7-H), 6.96 (1H, broad s, 6-OH), 13.54 (1H, s, 8-OH), J=15 (5a-5e), 14 (4a-4e), 12 (2a-2e, 3a-4a, 4a-5a), 9 (2a-3a), 7 (3a-Me, 4e-5e), 4 (2a-3a, 3a-4e), 2 (4a-5e, 4e-5a), 1 Hz (2e-4e); MS m/z 236 (M^+), 221, 181, 165. Found: C, 66.37, H, 6.77%. Calcd for $C_{13}H_{16}O_4$: C, 66.08, H, 6.38%. **8**: mp 190—192 °C (from benzene lit,[2] 185 °C); IR 1640 cm^{-1}; ^1H NMR (acetone-d_6) δ=0.95 (6H, d, J= 6 Hz), 1.2—1.7 (3H, m), 2.57 (2H, t, J=7 Hz), 2.58 (3H, s), 6.00 (1H, s), 8.83 (1H, s), 9.30 (1H, broad s), 13.8 (1H, s).

Methylation of 4—6 with Diazomethane. A solution of **4**, **5**, or **6** in methanol was treated with an ethereal solution containing excess diazomethane at room temperature for one night. After removal of the solvents and the excess of diazomethane, the residual oil was chromatographed. Methylation of **4** gave two monomethyl ether **1** and **2** in 21 and 24%, respectively. 5-Acetyl-2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran-4-ol (racemic remirol) (**1**): mp 72—72.5 °C (from hexane) (natural remirol:[1] 76.5—77 °C); IR 1635 cm^{-1}; UV 238 (log ε=4.11), 293 nm (4.28), (natural remirol:[1] 239 and 294 nm); ^1H NMR ($CDCl_3$) δ=1.76 (3H, s), 2.60 (3H, s), 2.95 (1H, dd, J=15, 8 Hz), 3.30 (1H, dd, J=15, 10 Hz), 3.86 (3H, s), 4.92 (1H, broad s), 5.07 (1H, broad s), 5.29 (1H, broad dd, J=10, 8), 5.97 (1H, s), 14.08 (1H, s); MS m/z 248 (M^+), 233. Found: C, 67.50, H, 6.63%. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50% **2**: mp 70.5—71 °C (from hexane); IR 1625 cm^{-1}; UV 233 (log ε=4.12), 241 sh (4.01), 288 (4.20), 323 sh nm. (3.67); ^1H NMR ($CDCl_3$) δ=1.77 (3H, s), 2.62 (3H, s), 3.09 (1H, J=15, 7 Hz), 3.46 (1H, dd, J=15, 9 Hz), 3.94 (3H, s), 4.95 (1H, broad s), 5.08 (1H, broad s), 5.22 (1H, dd, J=9, 7 Hz), 6.15 (1H, s), 13.86 (1H, s); MS m/z 248 (M^+), 233. Found: C, 67.81, H, 6.50%. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50%. Methylation of **5** and **6** gave corresponding monomethyl ethers **3** and **9** in 75.4 and 27.6%, respectively. 7-Acetyl-2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran-6-ol (**3**): mp 61—62 °C (from hexane); IR 1640 cm^{-1}; UV 230 (log ε=4.14), 283.5 (4.30), 337 nm (3.52); ^1H NMR ($CDCl_3$) δ=1.82 (3H, s), 2.58 (3H, s), 2.92 (1H, dd, J=15, 8 Hz), 3.17 (1H, dd, J=15, 9 Hz), 3.88 (3H, s), 5.02 (1H, braod s), 5.18 (1H, broad s), 5.38 (1H, dd, J=9, 8 Hz), 6.00 (1H, s), 13.57 ppm (1H, s); MS m/z 248 (M^+), 233. Found: C, 67.90, H, 6.61%. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50%. 9-Acetyl-6-methoxy-3-methyl-2,5-dihydro-1-benzoxepin-8-ol (**9**): mp 152—153 °C (from hexane) IR 1630 cm^{-1}. UV 230.5 (log ε=3.99), 280 (4.06), 328 nm (3.84); ^1H NMR ($CDCl_3$) δ=1.55 (3H, broad s), 2.68 (3H, s), 3.37 (2H, broad m), 3.83 (3H, s), 4.45 (2H, broad m), 5.65 (1H, broad m), 6.27 (1H, s), 13.67 (1H, s); MS m/z 248 (M^+), 233. Found: C, 67.93, H, 6.44%. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50%.

4,6-Dimethoxy-2-isopropenyl-2,3-dihydroxybenzofuran (10). By a method described in our previous paper,[7] **10** was obtained from 3,5-dimethoxyphenol (25.0 g, 163 mmol) and 1,4-dibromo-2-methyl-2-butene (37.3 g, 163 mmol) in the presence of sodium hydride (7.8 g, 326 mmol) in dry ether (300 mL). After distillation and chromatography, **10** was obtained in pure state in 27% yield. **10**: bp 138—140 °C (3 mmHg); mp 53.5—54.5 °C (from hexane); UV 234 sh (log ε=3.86), 273 nm (3.20); ^1H NMR (CCl_4) δ=1.72 (3H, s), 2.80 (1H, dd, J=15, 8 Hz), 3.03 (1H, dd, J=15, 9 Hz), 3.62 (3H, s), 3.65 (3H, s), 4.73 (1H, broad s), 4.92 (1H, broad s), 4.98 (1H, dd, J=9, 8 Hz), 5.72 (1H, d, J=2 Hz), 5.80 (1H, d, J=2 Hz); MS m/z 220 (M^+), 205. Found: C, 71.15, H, 7.52%. Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32%.

5-Acetyl-2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (11). By the method described in our previous paper,[7] **10** (3.45 g, 15.7 mmol) was acylated with acetic acid (1.90 g, 31.7 mmol) and trifluoroacetic anhydride (6.60 g, 31.4 mmol) to give **11** (1.19 g, 28.3%); bp 225—240 °C (16 mmHg); IR 1685 cm^{-1}; UV 234 sh: 4.02), 274 nm (3.70); ^1H NMR (CCl_4) δ=1.78 (3H, s), 2.33 (3H, s), 3.03 (1H, dd, J=16, 8 Hz), 3.27 (1H, dd, J=16, 9 Hz), 3.78 (6H, s), 4.87 (1H, broad s), 5.05 (1H, broad s), 5.12 (1H, dd, J=8,9 Hz), 6.10 (1H, s); MS m/z 262 (M^+), 245. Found: C, 68.77, H, 6.88%. alcd for $C_{15}H_{18}O_4$: C, 68.68, H, 6.92%.

Demethylation of 11 to Racemic Remirol (1). By the method described in our previous paper,[6] **11** (1.00 g 3.83 mmol) was demethylated with magnesium iodide etherate in refluxing benzene. After purification by silica-gel column chromatography, fractions eluted with hexane-benzene (8:2) gave **1** (431 mg, 42.7%) as colorless crystals (mp 72—72.5 °C). All spectral data were identical with those of **1** obtained from monomethylation of **4** and natural remirol reported by Allan et al.[1]

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