Fries Rearrangement of 1-Methoxy-4-(4-methyl-2- and -3-pentenoyloxy)benzenes[1)]

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Synopsis. Not only rearrangement but also cyclization occurred in a Fries rearrangement of 1-methoxy-4-(4-methyl-2- and -3-pentenoyloxy)benzenes and gave 5,8-dihydroxy-4,4-dimethyl-3,4-dihydro-1(2*H*)-naphthalenone. The reduction and oxidation of the dihydronaphthalenone gave 5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-1,4-naphthalenedione and 8,8-dimethyl-7,8-dihydro-1,4,5(6*H*)-naphthalenetrione, respectively.

Naphthoquinone compounds occur widely in nature among plants and fungi.[2)] They have been studied not only with regard to their pigment and structure[3)] but also concerning expectations of physiological activity.[4)] We have recently reported the total synthesis of shikalkin[(±)Shikonin], 5,8-dihydroxy-2-(1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone.[5)] This paper deals with a result of Fries rearrangements of phenolic esters, 1-methoxy-4-(4-methyl-2- and -3-pentenoyloxy)benzenes, as a model reaction for the introduction of the side chain of shikonin, 1-hydroxy-4-methyl-3-pentenyl moiety, to a phenolic nucleus. The product, 5,8-dihydroxy-4,4-dimethyl-3,4-dihydro-1(2*H*)-naphthalenone(**5**), was derived to 5-hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-1,4-naphthalenedione(**6**) and 8,8-dimethyl-7,8-dihydro-1,4,5(6*H*)-naphthalenetrione(**7**).

Results and Discussion

Following Caspi's procedure,[6)] a reaction of isobutyraldehyde with malonic acid in pyridine gave *trans*-4-methyl-2-pentenoic acid (**1**). This was then isomerized with alkali to 4-methyl-3-pentenoic acid (**2**). However, this isomerization did not proceed completely and gave an equilibrated isomeric mixture of **1** and **2**. The ^{1}H NMR spectrum of this mixture showed that it contained about 24% acid **1** and 76% of **2**. Since an attempted separation of these isomers was not successful, this acid mixture was used in the next step: treatment with thionyl chloride gave the corresponding acid chlorides, **3a** and **3b**.

p-Methoxyphenol was allowed to react with the acid chlorides to give a mixture of phenolic esters **4a** and **4b** in 68% yield. The ratio of **4a** and **4b** was about 3 : 1 by ^{1}H NMR. The treatment of an ester mixture **4a** and **4b** with a molten mixture of aluminum chloride and sodium chloride prepared at 180 °C, gave a crystalline product in 24% yield. The ^{1}H NMR spectrum showed two signals at δ 12.3 and 8.1 due to the phenolic hydroxyl groups; the former suggested the existence of a strongly hydrogen bonded OH. A single peak at δ 1.5 was due to two methyl groups and the signals of methine groups in the starting materials (**4a**: $-C\underline{H}=C(CH_3)_2$ and **4b**: $-C\underline{H}=C\underline{H}CH(CH_3)_2$) had disappeared. These spectral data could indicate only a cyclic ketone, **5**.

It can be concluded that the Fries rearrangement described here was accompanied with cyclization and demethylation. A Fries rearrangement of pure ester **4b**[7)] also resulted in the formation of cyclic ketone **5** in 16% yield. These results suggested that a rearrangement of the carbon-carbon double bond in the side chain of **4b** had occured. Ketone **5** was also prepared from **4** in 38% yield by using boron trifluoride etherate instead of a molten mixture of $AlCl_3$-NaCl.

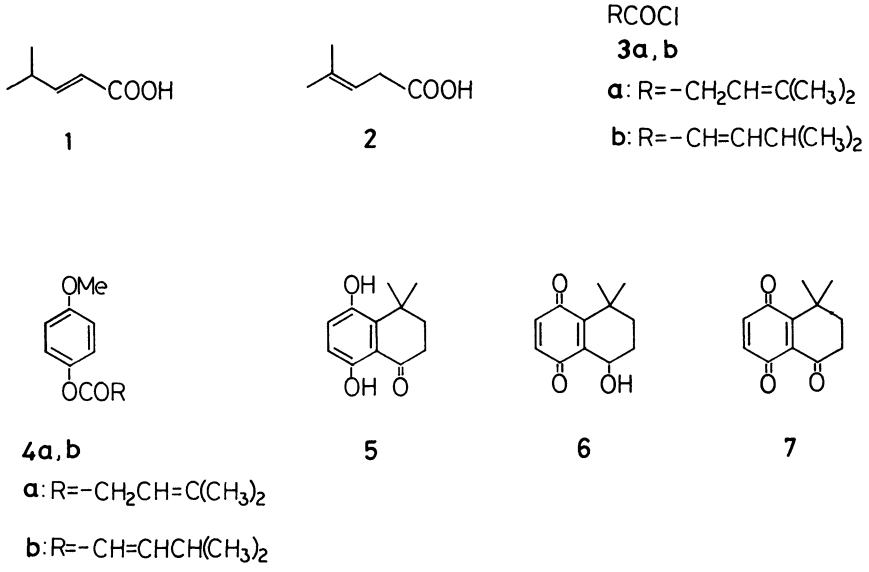

Fig. 1.

A reduction of **5** with lithium aluminum hydride in tetrahydrofuran and subsequent air-oxidation gave **6** in 37% yield.

A oxidation of **5** with ceric (IV) ammonium nitrate gave **7** in 79% yield.

Experimental

^{1}H NMR spectra were taken on a JEOL JNM-FX60 spectrometer using tetramethylsilane as an internal standard; the chemical shifts were reported in δ values. Mass spectral data were obtained with a JEOL DX-300. Infrared spectra were recorded on a Hitachi 260-30 infrared spectrometer and the UV spectra on a Shimadzu recording spectrometer UV-200S. Column chromatography was performed on silica gel (Wakogel C-200). Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected.

4-Methyl-3-pentenoyl Chloride (3a) and 4-Methyl-2-pentenoyl Chloride (3b) Mixture. 4-Methyl-3-pentenoic acid **2** (16.8 g, 0.147 mol, containing ca. 24% of **1**) was added dropwise to thionyl chloride (21.0 g, 0.176 mol) under reflux and the mixture was refluxed for another 30 min, then fractionally distilled under reduced pressure to give 14.6 g (75%) of an oil of **3** (**3a**:**3b**=3:1), bp 55—58 °C/22 mmHg (1 mmHg=133.322 Pa). IR (neat) 1795 (C=O), 1755 (C=O), 1625 (C=C), 1030, and 960 cm^{-1}; MS *m/z* 134(M^++2), 132 (M^+), 97, and 69; ^{1}H NMR ($CDCl_3$) **3a**: δ=1.64, 1.74 (6H, $2CH_3$), 3.61 (d, *J*=6.8 Hz, 2H, CH_2), and 5.28 (m, 1H, CH); **3b**: δ=1.04, 1.14 (6H, $2CH_3$), 2.41 (m, 1H, CH), 6.09 (dd, *J*=15.5 and 1.0 Hz, 1H, COCH=CH), and 7.32 (dd, *J*=15.5 and 6.0 Hz, 1H, COCH=CH).

1-Methoxy-4-(4-methyl-3-pentenoyloxy)benzene (4a) and 1-Methoxy-4-(4-methyl-2-pentenoyloxy)benzene (4b) Mixture. A mixture of *p*-methoxyphenol (9.2 g, 74.2 mmol) and the acid chloride mixture **3** (10 g, 75 mmol) was refluxed until the evolution of hydrogen chloride ceased. The reaction product was distilled under reduced pressure to give 11.2 g (68%) of an oil, **4** (**4a**:**4b**=3:1), bp 180—186 °C/20 mmHg. IR (neat) 2850 (OCH_3), 1760 (C=O), 1650 (C=C), 1250, 1196, and 1035 cm^{-1}; MS *m/z* 220 (M^+), 124, and 97; ^{1}H NMR ($CDCl_3$) **4a**: δ=1.69, 1.77 (6H, $2CH_3$), 3.23 (d, *J*=7.3 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 5.39 (m, 1H, CH), and 6.9 (m, 4H, ArH); **4b**: δ=1.03, 1.15 (6H, $2CH_3$), 2.58 (m, 1H, CH), 3.74 (s, 3H, OCH_3), 5.93 (dd, *J*=15.6 and 1.0 Hz, COCH=CH), 6.9 (m, 4H, ArH), and 7.1 (dd, *J*=15.6 and 7.2 Hz, 1H, COCH=CH). Found: C, 70.74; H, 7.45%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

5,8-Dihydroxy-4,4-dimethyl-3,4-dihydro-1(2*H*)-naphthalenone (5). A. 5 from 4 (4a and 4b Mixture) by Using Aluminum Chloride and Sodium Chloride Molten Mixture. A mixture of anhydrous aluminum chloride (30 g) and sodium chloride (10 g) was melted at 180 °C, and to this was added dropwise the ester **4** (7.8 g, 35 mmol) under vigorous stirring. After 10 min, the obtained pasty mass was decomposed by the addition of dil. hydrochloric acid and extracted with ether. The ether solution was washed with water, dried, and evaporated. The crude product was recrystallized from hexane-tetrahydrofuran to give 1.70 g (24%) of **5** as yellow crystals, mp 239—240 °C. IR (KBr) 3300 (OH), 2950, 1623 (C=O), 1475, and 1240 cm^{-1} (OH); MS *m/z* 206 (M^+), 191, and 163; ^{1}H NMR ($(CD_3)_2CO$) δ=1.53 (s, 6H, CH_3), 1.91 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 6.62 (d, *J*=9.2 Hz, 1H, ArH), 7.08 (d, *J*=9.2 Hz, 1H, ArH), 8.11 (s, 1H, OH), and 12.34 (s, 1H, OH); UV (dioxane) 264 (ε 13800) and 368 nm (ε 7900). Found: C, 69.68; H, 6.78%. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%.

B. 5 from 4b by Using Aluminum Chloride and Sodium Chloride Molten Mixture. The reaction of **4b**[7] (5.18 g, 24 mmol) with a molten mixture of aluminum chloride (15 g) and sodium chloride (1.3 g) was carried out by the procedure described above and gave 0.80 g (16%) of **5**, mp 238—240 °C. All the spectral data agreed with those of **5** prepared from method A.

C. 5 from 4 (4a and 4b Mixture) by Boron Trifluoride Etherate. Boron trifluoride etherate (1.2 ml, 9.6 mmol) was added dropwise to the ester **4** (680 mg, 3.2 mmol) at 140 °C, and after 10 min, was decomposed by addition of dil hydrochloric acid and extracted with chloroform. The usual work-up and chromatography on silica gel with chloroform gave 250 mg (38%) of a sample of **5**. Recrystallization from ligroine-benzene gave an analytical sample, mp 239—241 °C. All the spectral data agreed with those of **5** prepared from method A.

5-Hydroxy-8,8-dimethyl-5,6,7,8-tetrahydro-1,4-naphthalenedione (6). Lithium aluminum hydride (36 mg, 0.97 mmol) was added to a solution of the ketone **5** (100 mg, 0.485 mmol) in tetrahydrofuran (2 ml), stirred at room temperature for 1 h, decomposed with ice water, and extracted with chloroform. The usual work-up and chromatography on silica gel with chloroform gave 37 mg (37%) of a sample of **6** as a semisolid, mp 69—73 °C. IR (KBr) 3410 (OH) and 1645 cm^{-1} (C=O); MS *m/z* 206 (M^+), 188, 173, 151, and 123; HRMS *m/z* calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0945; ^{1}H NMR ($CDCl_3$) δ=1.29 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.6—2.0 (m, 4H, $2CH_2$), 3.18 (d, *J*=2.6 Hz 1H, OH), 4.72 (m, 1H, CH), and 6.67 (s, 2H, quinonoid ring H).

8,8-Dimethyl-7,8-dihydro-1,4,5(6*H*)-naphthalenetrione (7). A solution of ceric(IV) ammonium nitrate (800 mg, 1.46 mmol) in water (5 ml) was added dropwise to a solution of **5** (100 mg, 0.49 mmol) in tetrahydrofuran (5 ml) at room temperature, stirred for 1 h, diluted with water, and extracted with chloroform. The usual work-up and chromatography on silica gel with chloroform gave 78 mg (79%) of a sample of **7**. Recrystallization from hexane gave an analytical sample, mp 120—121 °C. IR (KBr) 1705 (C=O), 1660 (C=O), 1285, and 855 cm^{-1}; MS *m/z* 204 (M^+), 189, 161, and 149; ^{1}H NMR ($CDCl_3$) δ=1.47 (s, 6H, $2CH_3$), 1.94 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), and 6.71 (s, 2H, quinonoid ring H). Found: C, 70.58; H, 5.92%. Calcd for $C_{12}H_{12}O_3$: C, 69.92; H, 6.18%.

References

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7) Treatment of **3b** with *p*-methoxyphenol gave **4b**, bp 176—179 °C/27 mmHg. **3b** was prepared from the reaction of the acid **1** and thionyl chloride.