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The Fries Rearrangement of Acetoxybenzofuran Derivatives and the Synthesis of Furochromenonecarboxylic Acids

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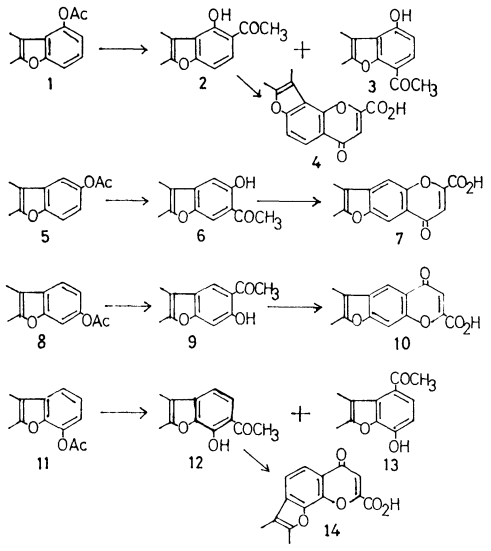
Synopsis. The Fries rearrangement of 4-, 5-, 6-, and 7-acetoxy-2,3-dimethylbenzofurans was studied and the *o*-hydroxy-ketones obtained were converted to dimethylfuro derivatives of 4*H*-chromen-4-one-2-carboxylic acid.

It has been reported that the Fries rearrangement of 6-acetoxy-3-methylbenzofuran gave a 2-acetyl compound[1] and that of 6-acetoxy-3-methylbenzofuran-2-carboxylic acid gave a 7-acetyl compound.[2] In the present experiments, the Fries rearrangement of *bz*-acetoxy-2,3-dimethylbenzofurans was studied, and the *o*-hydroxy-ketones obtained were converted to the corresponding furochromenonecarboxylic acid derivatives to test the pharmacological activity.

Four isomeric 4-, 5-, 6-, and 7-acetoxy-2,3-dimethylbenzofurans (**1**, **5**, **8**, and **11**) were heated with anhydrous aluminum chloride at 120 °C for 15 min and the reaction mixture was treated as usual to give the products, the structures of which were determined by comparing their melting points and IR spectra with those of authentic samples.[3,4] The products obtained from **5**, **8**, and **11** were the *o*-hydroxy-ketones **6**, **9**, and **12**, respectively, and a small amount of *p*-hydroxy-ketone (**13**) was also obtained in the case of **11**. But, in the case of **1**, the main product was *p*-hydroxy-ketone (**3**), as well as a small amount of the *o*-hydroxy-ketone (**2**). The same reaction in carbon disulfide at room temperature for 24 h gave some amounts of the *p*-hydroxy-ketone **3** or **13**, respectively, from **1** or **11**, while no reaction occured in the case of **5** and **8**. The *o*-hydroxy-ketones **2**, **6**, **9**, and **12** thus obtained were converted to furochromenonecarboxylic acid derivatives **4**, **7**, **10**, and **14**, respectively, by condensation with ethyl oxalate followed by hydrolysis and cyclization.[5,6]



Experimental

All the melting points and boiling points are uncorrected. IR spectra: Hitachi Model EPI-S. UV spectra: Hitachi Model 124. NMR spectra: JEOL Model JNM-MH-60 (60 MHz).

The Preparation of 4-, 5-, 6-, and 7-Acetoxy-2,3-dimethylbenzofurans (1, 5, 8, and 11). These compounds were prepared by heating the corresponding hydroxy-compounds[7] with acetic anhydride and sodium acetate. Compound **1**; bp 163—167 °C/22 Torr, ν_{CO} 1765 cm^{-1}. Found: C, 70.34; H, 6.05%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. Compound **5**; mp 60 °C (from *n*-hexane), ν_{CO}^{KBr} 1760 cm^{-1}. Found: C, 70.79; H, 5.84%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. Compound **8**; mp 54—55 °C (from *n*-hexane), ν_{CO}^{KBr} 1760 cm^{-1}. Found: C, 70.79; H, 5.84%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. Compound **11**; bp 165—167 °C/20 Torr, ν_{CO} 1770 cm^{-1}. Found: C, 70.69; H, 6.13%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

The Fries Rearrangement of the Acetoxybenzofurans.

Method A: A mixture of the acetoxybenzofuran (4.1 g) and powdered anhydrous aluminum chloride (3.2 g) was heated with stirring at 120 °C for 15 min. The cooled mixture was treated with diluted hydrochloric acid, extracted with ether, and the ethereal layer was extracted with dilute aqueous sodium hydroxide solution. The product obtained from the ethereal solution was *o*-hydroxy-ketone, and the precipitate obtained by the acidification of the alkaline extract was *p*-hydroxy-ketone. In the case of **1**, 0.04 g (1% yield) of 5-acetyl-2,3-dimethyl-4-hydroxybenzofuran (**2**), mp 47—50 °C (lit,[4] mp 58.5—60 °C), and 1.6 g (40% yield) of 7-acetyl isomer (**3**), mp 204—206 °C (lit,[4] mp 206—208 °C), were obtained. In the case of **5**, 1.8 g (45% yield) of 6-acetyl-2,3-dimethyl-5-hydroxybenzofuran (**6**), mp 139—142 °C (lit,[3] mp 141 °C) was obtained. In the case of **8**, 1 g (24% yield) of 5-acetyl-2,3-dimethyl-6-hydroxybenzofuran (**9**), mp 119—121 °C (lit,[3] mp 122 °C) was obtained. In the case of **11**, 2 g (49% yield) of 6-acetyl-2,3-dimethyl-7-hydroxybenzofuran (**12**), mp 129—130 °C (lit,[3] mp 130 °C) and 0.01 g (0.3% yield) of 4-acetyl-2,3-dimethyl-7-hydroxybenzofuran (**13**), mp 164—165 °C (lit,[3] mp 169 °C) were obtained.

Method B: A mixture of the acetoxybenzofuran (4.1 g), anhydrous aluminum chloride (3.2 g) and carbon disulfide (20 g) was stirred at room temperature for 24 h. The reaction mixture was treated similarly to the method described for method A. In the case of **1**, 0.6 g (15% yield) of **3** was obtained, and in the case of **11**, 0.4 g (10% yield) of **13** was obtained. In the cases of **5** and **8**, almost all of the starting compounds were recovered.

The Preparation of Furochromenonecarboxylic Acids. The *o*-hydroxy-ketone (1 g) and ethyl oxalate (2 g) were added to a suspension of powdered sodium metal (0.5 g) in xylene (75 ml) and the mixture was refluxed for 1 h. The cooled mixture was treated with ethanol to destroy the excessive

sodium metal and then with water. The alkaline aqueous layer was separated and acidified with dilute hydrochloric acid. The precipitate formed was crystallized from acetic acid to give the following furochromenone-carboxylic acids: 1,2-Dimethyl-6*H*-furo[2,3-*h*]chromen-6-one-8-carboxylic acid (**4**) was obtained from **2** in a 29% yield; mp 300—302 °C; ν_{CO}^{KBr} cm^{-1}: 1730 (COOH) and 1640 (γ-pyrone); λ_{max}^{EtOH} nm (log ε): 220 (4.54), 252 (4.41), and 322 (3.65); δ (DMSO-d_6): 2.18 (3H, s, 1-CH_3), 2.31 (3H, s, 2-CH_3), 6.70 (1H, s, 7-H), 7.27 (1H, d, J=9 Hz, 4-H), and 7.57 (1H, d, J=9 Hz, 5-H). Found: C, 65.30; H, 4.18%. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90%. 2,3-Dimethyl-8*H*-furo[2,3-*g*] chromen-8-one-6-carboxylic acid (**7**) was obtained from **6** in a 47% yield; mp 293—295 °C; ν_{CO}^{KBr} cm^{-1}: 1740 (COOH) and 1630 (γ-pyrone); λ_{max}^{EtOH} nm (log ε): 220 (4.39), 242 (4.22), and 325 (4.20); δ (DMSO-d_6): 2.15 (3H, s, 3-CH_3), 2.41 (3H, s, 2-CH_3), 6.83 (1H, s, 7-H), 7.65 (1H, s, 4-H), and 7.88 (1H, s, 9-H). Found: C, 64.84; H, 3.79%. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90%. 2,3-Dimethyl-5*H*-furo[3,2-*g*]chromen-5-one-7-carboxylic acid (**10**) was obtained from **9** in a 42% yield; mp 310—312 °C, ν_{CO}^{KBr} cm^{-1}: 1730 (COOH) and 1640 (γ-pyrone); λ_{max}^{EtOH} nm (log ε): 211 (4.57), 251 (4.54), and 343 (3.82); δ (DMSO-d_6): 2.15 (3H, s, 3-CH_3), 2.40 (3H, s, 2-CH_3), 6.80 (1H, s, 6-H), 7.70 (1H, s, 9-H), and 7.96 (1H, s, 4-H). Found: C, 64.88; H, 3.86%. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90%. 2,3-Dimethyl-6*H*-furo[3,2-*h*]chromen-6-one-8-carboxylic acid (**14**) was obtained from **12** in a 31% yield; mp 275—277 °C; ν_{CO}^{KBr} cm^{-1}: 1730 (COOH) and 1640 (γ-pyrone); λ_{max}^{EtOH} nm (log ε): 214 (4.30), 261 (4.36), and 327 (3.90); δ (DMSO-d_6): 2.21 (3H, s, 3-CH_3), 2.57 (3H, s, 2-CH_3), 6.97 (1H, s, 7-H), 7.57 (1H, d, J=8 Hz, 4-H), and 7.90 (1H, d, J=8 Hz, 5-H). Found: C, 64.35; H, 4.04%. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90%.

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