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The Fries Rearrangement of 2-Ethyl-5-acetyloxybenzofuran

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The reaction of acyl ester of phenol with aluminum chloride is known with respect to the conversion of ester into isomeric *o*- or *p*-hydroxy ketone. It is an important route in synthesis of ketones from phenols.[1] Fries discovered this rearrangement during his study on coumaranones.[2] Thereafter this type of rearrangement has been examined on coumarin derivatives. Little has been done, however, on the study of coumarones, *i.e.*, benzofuran derivatives[3] in which only one compound was separated as a rearrangement product. In the present paper we report the Fries reaction of 2-ethyl-5-acetyloxybenzofuran which resulted in the isolation of three new isomeric products.

2-Ethyl-5-acetyloxybenzofuran (I) in nitrobenzene was stirred in the presence of aluminum chloride at room temperature for 16 hr, the reaction mixture was decomposed with water, and submitted to steam distillation. After a run of nitrobenzene, a yellow oil was distilled to give a precipitate on standing. Recrystallization from petroleum ether gave yellow needles (II), mp 120—122°C. The mother liquor gave yellow plates (III), mp 75—76°C. The residue on steam distillation was recrystallized from ethanol to yield colorless prisms (IV), mp 177—178°C.

Elementary analysis revealed that the three compounds were the rearranged isomeric products of I. The IR measurement of the reaction products showed no absorption of ester. However, the absorption due to the presence of a ketonic group was distinctly observed. Absence of absorption due to hydroxyl group in II and III was explained by the influence of intramolecular hydrogen bonding to the ketonic group formed in the rearrangement reaction, whereas the absorption of hydroxyl group was observed with IV.

Signals of protons in benzofuran ring in the NMR spectra were assigned in the usual manner. The proton at position 3 in II was assigned δ 6.57 in a singlet, which appears to be a fine splitting peak due to a long range coupling of the protons at positions 3 and 7 in benzofuran ring.[4] The doublet peaks at δ 6.80 and δ 7.51 are of one proton respectively. A signal with fine splitting peak at lower magnetic field (δ 7.51) was assigned to proton at position 7. The relatively greater coupling constant ($J_{6,7}=9.0$ cps) indicates that the coupling is *o*-coupling,[5] and the doublet at higher magnetic field was assigned to proton at position 6.

The hydroxyl proton of position 5 was assigned to a singlet at δ 12.92, which supported the presence of intramolecular hydrogen bonding to adjacent carbonyl group.[6] Based on these evidences, the acetyl group in I is considered to be rearranged to position 4, and II is formed as the rearrangement product.

A singlet (δ 6.32) was assigned to the proton of position 3 in benzofuran ring of III and the remaining two peaks (δ 6.97 and δ 7.71) were assigned to two protons in the benzene ring, which showed scarcely any coupling with each other. Thus they

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[1] A. H. Blatt, "Organic Reactions," Vol I, John Wiley & Sons, New York (1942), p. 342.

[2] K. Fries and G. Finck, *Chem. Ber.*, **41**, 4271 (1908).

[3] N. M. Shan and P. M. Shan, *Chem. Ber.*, **92**, 2927 (1959); *ibid.*, **93**, 18 (1960). A. Mustafa, W. Asker, O. H. Hishmat, M. I. Ali, A. K. E. Mansour, N, M. Abed, K. M. A. Khalil and S. M. Samy, *Tetrahedron*, **21**, 849 (1965).

[4] J. A. Eluidge and R. G. Foster, *J. Chem. Soc.*, **1963**, 590.

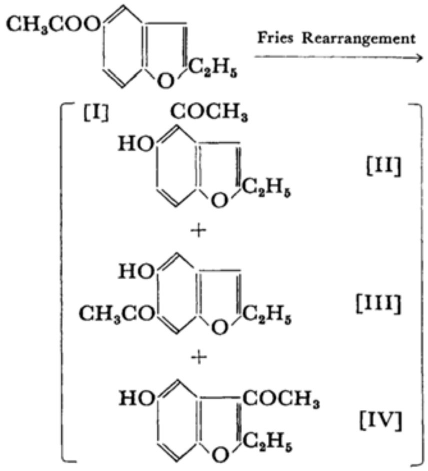
[5] "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, ed. by J. W. Emsley, J. Feeney and L. H. Sutchiffe, Pergamon Press Inc., Oxford (1966), p. 770.

[6] "Spectrometric Identification of Organic Compounds," R. M. Silverstein and G. C. Bassler, John Wiley & Sons, Inc., New York (1967), p. 122.

must be situated at *p*-position,[5] *i.e.*, positions 4 and 7. As the protons at positions 3 and 7 in the benzofuran ring show a long range coupling, a signal with a fine splitting peak at δ 7.71 was assigned to position 7. The assignment of the hydroxyl proton at position 5 of III (δ 12.12) was the same as in the case of II. From these results, it is concluded that the acetyl group in I is rearranged to position 6, resulting in the formation of III.

Since IV is slightly soluble in chloroform, the corresponding acetate was derived to use in NMR measurement. No absorption at about δ 6.4 proved the absence of proton at position 3. One-proton peaks belonging to the benzene ring were recognized at δ 7.67, 7.01 and 7.43, respectively. A quartet at δ 7.01 was assigned to the proton at position 6 which arose through unequal coupling with protons at positions 4 and 7. The proton at position 7 was assigned to the doublet at δ 7.43 which has a greater *o*-coupling constant with proton at position 6 (*o*-coupling: $J_{6,7}=9.0$ cps). The remaining signal which appeared at δ 7.67 was assignable to the proton at position 4 (*m*-coupling: $J_{4,6}=2.1$ cps). Thus it is concluded that the acetyl group of I is rearranged to position 3 to produce IV.

Based on these results, a scheme of the rearrangement is presented as follows:



One interesting point in the Fries reaction is that the variation in the ratio of both ortho- and para-isomers depends on experimental conditions. In order to investigate the variation, we performed gas chromatography on benzofuran derivatives.[7] Raw products obtained on decomposition with water for 5 hr and 16 hr were submitted to gas chromatography. Intensity of the peaks on gas chromatogram indicated the preparation ratio of II : III : IV to be approximately 1 : 1 : 1.5 at 5 hr and 1 : 1 : 1 at 16 hr. A peak appearing immediately after the peak of IV was recognized to be due to 2-ethyl-3-acetyl-5-acetyloxybenzofuran (V). The compounds are not known. Hence we synthesized them through another route, and used them for standard sample on gas chromatography. Formation of V during the reaction suggested that the present rearrangement was intermolecular.

It has been reported[8] that under high reaction temperature in the usual Fries reaction the production rate of an *o*-derivative is predominant. Accordingly we conducted the rearrangement reaction at 110°C for 1 hr, but the ratio of II : III : IV in reaction products as estimated by gas chromatography was 1 : 1 : 1 or the same as that in the previous reaction.

Experimental

Apparatus and gas chromatographic conditions. A Shimadzu Model GC-1C gas chromatograph fitted with hydrogen flame ionization detector was employed. The U-shaped stainless steel column 1.1 m × 3 mm i.d. containing 20% Apiezon GL by weight on 40/60 Neosorb NC. Conditions for chromatography: Column temperature, 190°C. Nitrogen (carrier), 20 m*l*/min.

2-Ethyl-5-acetyloxybenzofuran (I). To 2-ethyl-5-hydroxybenzofuran[9] (16.2 g) in pyridine (40 m*l*) was added dropwise acetic anhydride (20.4 g) with ice-cooling and stirring. After being stirred at room temperature for about 3 hr, the reaction mixture was poured with vigorous stirring into HCl-containing ice-water. The white precipitate thus formed was filtered and recrystallized from petroleum ether to give colorless needles (17 g), mp 54—55°C: IR (KBr) showed C=O arylacetate at 1758 cm^{-1}.

Found: C, 70.49; H, 6.10%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92%.

2-Ethyl-4-acetyl-5-hydroxybenzofuran (II). To 2-ethyl-5-acetyloxybenzofuran (5 g) in nitrobenzen (50 ml) was added by portions anhydrous $AlCl_3$ (10 g) with ice-cooling and stirring. After being stirred at room temperature (20—25°C) for about 16 hr, the mixture was poured into ice-water to decompose. Steam distillation gave, after a run of nitrobenzene, a yellow precipitate, which was filtered and recrystallized from petroleum ether to yield yellow needles (0.8 g), mp 120—122°C. IR (KBr) showed no hydroxyl band, but intramolecular chelated aryl-ketone band at 1620 cm^{-1}.

Found: C, 70.61; H, 5.91%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92%.

2-Ethyl-5-hydroxy-6-acetylbenzofuran (III). Removal of most of the mother liquor (petroleum ether) caused precipitation of yellow plates (III) (0.2 g), mp 75—76°C (from ethanol). IR (KBr) showed no hydroxyl absorption, but intramolecular chelated aryl-ketone band at 1630 cm^{-1}.

Found: C, 70.63; H, 5.75%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92%.

2-Ethyl-3-acetyl-5-hydroxybenzofuran (IV). The residue on steam distillation was collected to recrystallize from ethanol to give colorless prisms (IV) (1.3 g),

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[7] T. Nakanishi *et al.*, to be published.

[8] K. W. Rosenmund and W. Sehnurr, *Ann.*, **460**, 56 (1928).

[9] M. Bisagni, Ng. Ph. Buu-Hoi and R. Royar *J. Chem. Soc.*, **1955**, 3688.

177—178°C. IR (KBr) showed hydroxyl band at 3200 cm^{-1}, and intermolecular hydrogen bonded aryl-ketone band at 1625 cm^{-1}.

Found: C, 70.65; H, 6.07%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92%.

2-Ethyl-3-acetyl-5-acetyloxybenzofuran (V). 2-Ethyl-5-hydroxybenzofuran (2.4 g) in CS_2 (40 m*l*) was cooled at 0—5°C, and to this was added acetyl chloride (2.4 g), and then dropwise $SnCl_4$ (8.1 g) with stirring. After being stirred at 5—10°C for about 5 hr, the reaction mixture was poured into HCl-containing ice-water and stirred vigorously. The CS_2 layer was dried, evaporated, and the residue was recrystallized from petroleum ether to give colorless needles (2.7 g), mp 88—89°C: arly-ketone at 1645 cm^{-1}, aryl-acetate at 1740 cm^{-1}.

Found: C, 68.45; H, 5.94%. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

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