[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. R. SCIENCE INSTITUTE, GUJARAT COLLEGE]

THE FRIES ISOMERIZATION OF ACETYL AND BENZOYL ESTERS OF UMBELLIFERONES

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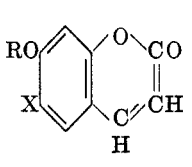
Since Limaye (1) applied the Fries migration for the first time to 7-acetoxy-4-methylcoumarin, considerable work has been published on the migration of 7-acyloxy-4-substituted coumarins (2). But the literature is very scanty with respect to the Fries reaction of umbelliferone esters, *i. e.* 7-acyloxycoumarins unsubstituted in the 4-position (3). The present investigation was, therefore, undertaken to study the Fries reaction of esters of umbelliferone and its various derivatives and to investigate the effect of different substituents on the course of the reaction. We have studied the Fries rearrangement of the acetyl and benzoyl esters of (i) 7-hydroxycoumarin (umbelliferone), (ii) 7-hydroxy-6-ethyl-, -6-chloro-, and -6-bromo-coumarins, and (iii) 7-hydroxy-3-acetyl- and -3-carbethoxy-coumarins. The migration was effected by baking a mixture of the coumarin ester (1 mole) and anhydrous aluminum chloride (3.3 moles) without any solvent; the latter was found to be unsuitable. All the coumarin esters mentioned above except (iii) underwent the rearrangement, the acetyl group migrating more easily than the benzoyl with better yields of the migration product.



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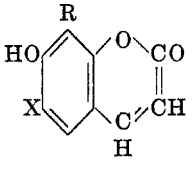

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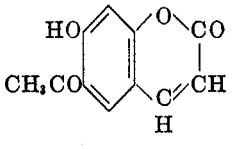

III

7-Acetoxy-coumarin (I, R = $COCH_3$; X = H) on rearrangement gave predominantly 7-hydroxy-8-acetylcoumarin (II, R = $COCH_3$; X = H), the isomeric 6-acetylcoumarin (III) being obtained also in minute quantity from the residue after isolation of the 8-acetyl isomer, confirming the results of Limaye and Joshi (3). The coumarin (II, R = $COCH_3$; X = H) on alkaline hydrolysis gave 2-acetylresorcinol, confirming the constitution assigned to it. It may be mentioned that this keto coumarin is unsuited for the preparation of 2-acetylresorcinol as the yield is extremely poor in comparison to 7-hydroxy-8-acetyl-4-methylcoumarin.

Attempts to synthesize 7-hydroxy-8-acetylcoumarin either by condensing 2-acetylresorcinol with malic acid in the presence of sulfuric acid or by the Perkin reaction on 2,4-dihydroxy-3-acetylbenzaldehyde (4) were unsuccessful. It is noteworthy that 2-acetyl group is eliminated during the condensation, leading to the formation of 7-hydroxycoumarin.

7-Benzoxycoumarin (I, R = COPh; X = H) gave only 7-hydroxy-8-benzoylcoumarin (II, R = COPh; X = H), not a trace of the 6-benzoyl isomer being obtained.

7-Acetoxy- and 7-benzoxy-6-ethylcoumarin (I, R = $COCH_3$ and COPh; X = Et) rearranged to 7-hydroxy-8-acetyl- and 7-hydroxy-8-benzoyl-6-ethylcoumarins (II, R = $COCH_3$ and COPh; X = Et) respectively. The rearrangement was smooth, the keto coumarins being obtained in good yield.

7-Acetoxy- and 7-benzoxy-6-chlorocoumarin (I, R = $COCH_3$ and COPh; X = Cl) on being subjected to rearrangement as before gave 7-hydroxy-8-acetyl- and 7-hydroxy-8-benzoyl-6-chlorocoumarin (II, R = $COCH_3$ and COPh; X = Cl) respectively. Similarly, 7-acetoxy- and 7-benzoxy-6-bromocoumarin (I, R = $COCH_3$ and COPh; X = Br) gave 7-hydroxy-6-bromo-8-acetyl- and -8-benzoyl-coumarin (II, R = $COCH_3$ and COPh; X = Br) respectively. A small quantity of the deacylated coumarin was obtained from the mother liquor after the removal of the keto coumarins in the case of each of the halogenated coumarins.

The results show that umbelliferone acetate gives 8- and 6-acetyl derivatives, both the *ortho* positions to the hydroxyl manifesting reactivity with the 8-acetyl derivative being predominantly formed; whereas, in case of the benzoyl derivative, only the 8-benzoyl derivative has been obtained.

In substituted coumarins, a 6-ethyl group in the coumarin nucleus does not inhibit or retard the rearrangement; whereas, chlorine or bromine in the same position has some retarding influence on the reaction. A similar observation has been made in case of the corresponding 4-methylcoumarins (5).

All the above migration products have been characterized by preparing their functional derivatives. They give positive color tests with alcoholic ferric chloride indicating the *ortho* position of the hydroxy and ketonic groups. These keto coumarins are useful starting materials for the synthesis of heterocyclic compounds such as furanocoumarins, dicoumarins, and chromonocoumarins by suitable reactions. The possibilities of these syntheses have been realized. These results will form the subject of a separate communication.

In order to investigate the effect of substituents in the 3-position of the coumarin ring, the rearrangement of 7-acetoxy-3-acetylcoumarin and of 7-acetoxy-3-carbethoxycoumarin was carried out under different conditions but only the deacetylated product was obtained. In the case of the 3-carbethoxy compound, the hydroxycoumarin acid was isolated, hydrolysis occurring during the reaction. Thus the acetyl and the carbethoxy group in 3-position of the coumarin nucleus completely inhibit the migration.

EXPERIMENTAL

Fries rearrangement of 7-acetoxycoumarin; formation of 7-hydroxy-8-acetyl- and -6-acetylcoumarin. An intimate mixture of 7-acetoxycoumarin (6) (6 g., 1 mole) and anhydrous aluminum chloride (12 g., 3.3 moles) was heated at 145–150° in an oil-bath for an hour, with a $CaCl_2$ guard tube to prevent access of moisture. HCl gas was copiously evolved. The reaction mixture when cold was treated with ice and concentrated HCl (10 cc.); the solid thus obtained was collected, washed with water, and crystallized from alcohol as needles, m.p. 169–170°. Yield, 2.8 g. Limaye and Joshi (3) give m.p. 167°. It gives a red-violet color with alcoholic ferric chloride and dissolves in alkali with a non-fluorescent yellow color.

The *acetyl derivative*, prepared by the use of the acetic anhydride and sodium acetate method, crystallized from alcohol as needles, m.p. 158–159°.

Anal. Calc'd for $C_{13}H_{10}O_5$: C, 63.41; H, 4.07.
Found: C, 63.30; H, 4.09.

The alcoholic mother liquors from several of the above rearrangements (after removal of 7-hydroxy-8-acetylcoumarin) were pooled. On evaporating off the alcohol, the solid that separated was collected and taken through several fractional crystallizations from alcohol. In this way a minute quantity of needles was obtained, m.p. 177°. Limaye and Joshi (3) record the same melting point for 6-acetyl-7-hydroxycoumarin; the melting point of its acetoxy derivative also was in agreement with that of Limaye and Joshi.

Fries rearrangement of 7-benzoxycoumarin; formation of 7-hydroxy-8-benzoylcoumarin. 7-Benzoxycoumarin was prepared by heating 7-hydroxycoumarin and benzoyl chloride in the presence of pyridine for four hours. The product thus obtained crystallized from acetic acid as white needles, m.p. 162°.

Anal. Calc'd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76.
Found: C, 71.94; H, 3.70.

The benzoyl coumarin (3 g., 1 mole) and anhydrous aluminum chloride (5 g., 3.3 moles) were mixed intimately and heated at 150–155° for two hours ($CaCl_2$ guard tube). When the reaction was worked up as before, a solid was obtained which crystallized from alcohol in clusters of needles, m.p. 195–196°. Yield, 1.7 g.

Anal. Calc'd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76.
Found: C, 71.96; H, 3.72.

No other product could be isolated from the mother liquors after the removal of 7-hydroxy-8-benzoylcoumarin.

The *semicarbazone* was prepared as usual, m.p. 268° (decomp.).

The *oxime* crystallized from alcohol in plates, m.p. 260° (decomp.).

Fries rearrangement of 7-acetoxy-6-ethylcoumarin; formation of 7-hydroxy-8-acetyl-6-ethylcoumarin. 7-Hydroxy-6-ethylcoumarin was prepared by condensing 4-ethylresorcinol with malic acid in the presence of sulfuric acid (7). On acetylating the compound with acetic anhydride-sodium acetate, the acetoxy derivative was obtained and was crystallized from dilute alcohol as long needles, m.p. 100°.

Anal. Calc'd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.17.
Found: C, 67.19; H, 5.16.

The acetoxycoumarin (3 g., 1 mole) and anhydrous aluminum chloride (6 g., 3.3 moles) were mixed and the mixture was baked as before at 110–115° for one hour ($CaCl_2$ guard tube). The product, on working up as before, crystallized from alcohol as lustrous white needles, m.p. 138°. Yield, 1.3 g.

Anal. Calc'd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.17.
Found: C, 67.15; H, 5.1.

The *acetyl derivative* of the keto-coumarin crystallized from alcohol as needles, m.p. 122°.

Anal. Calc'd for $C_{15}H_{14}O_5$: C, 65.70; H, 5.11.
Found: C, 65.52; H, 4.97.

The *semicarbazone* crystallized from alcohol as small, pale green needles, m.p. 225° (decomp.).

Fries rearrangement of 7-benzoxy-6-ethylcoumarin; formation of 7-hydroxy-6-ethyl-8-benzoylcoumarin. 7-Benzoxy-6-ethylcoumarin (m.p. 115–116°, 3 g.) mixed with aluminum chloride (4.5 g.) was baked at 155–160° for two hours. The product was isolated as before; it crystallized from alcohol in needles, m.p. 151°. Yield, 1.2 g.

Anal. Calc'd for $C_{18}H_{14}O_4$: C, 73.48; H, 4.76.
Found: C, 73.3; H, 4.66.

The *semicarbazone* prepared as usual had m.p. 265° (decomp.).

Fries rearrangement of 7-acetoxy-6-chlorocoumarin; formation of 7-hydroxy-8-acetyl-6-chlorocoumarin. 7-Acetoxy-6-chlorocoumarin (8) was rearranged as before at 160–170°. The product thus obtained was crystallized from acetic acid as small needles, m.p. 162–163°. Yield, 1.3 g.

Anal. Calc'd for $C_{11}H_7ClO_4$: Cl, 14.88. Found: Cl, 14.64.

A quantity of the deacetylated product was obtained from the mother liquor after the removal of the above keto coumarin.

The *acetyl derivative* crystallized from dilute alcohol, m.p. 142°.

The *semicarbazone* crystallized from acetic acid as clusters of needles, m.p. 300°.

Fries rearrangement of 7-benzoxy-6-chlorocoumarin; formation of 7-hydroxy-6-chloro-8-benzoylcoumarin. 7-Benzoyloxy-6-chlorocoumarin, prepared as usual, crystallized from acetic acid as needles, m.p. 187°.

A mixture of the 7-benzoxy derivative (3 g.) and anhydrous aluminum chloride (4.5 g.) was heated at 165–170° for two hours. On working up the reaction mixture as before, the product obtained was crystallized from acetic acid as long needles, m.p. 176°. Yield, 1.3 g.

Anal. Calc'd for $C_{16}H_9ClO_4$: Cl, 11.81. Found: Cl, 11.68.

A small quantity of 7-hydroxy-6-chlorocoumarin was obtained from the mother liquor after the removal of the keto coumarin.

The *semicarbazone* crystallized from alcohol, m.p. 257° (decomp.).

7-Hydroxy-6-bromocoumarin. To an intimate mixture of 4-bromoresorcinol (3 g.) and malic acid (3 g.), concentrated sulfuric acid (12 g.) was added and the mixture was heated until it began to show the signs of frothing. The heating was continued for a few minutes more and the mixture then was left aside. On adding ice-cold water, a solid was obtained which was collected and crystallized from alcohol as shining needles, m.p. 283°. Yield, 2.3 g.

Anal. Calc'd for $C_9H_5BrO_3$: Br, 33.20. Found: Br, 33.10.

The *acetyl derivative* crystallized from alcohol as flat plates, m.p. 185°.

Anal. Calc'd for $C_{11}H_7BrO_4$: Br, 28.27. Found: Br, 28.15.

Fries rearrangement of 7-acetoxy-6-bromocoumarin; formation of 7-hydroxy-6-bromo-8-acetylcoumarin. Anhydrous aluminum chloride (5.5 g.) and 7-acetoxy-6-bromocoumarin (3.5 g.) were mixed and heated at 170–175° for one hour. The product crystallized from acetic acid as needles, m.p. 176°. Yield, 1.7 g.

Anal. Calc'd for $C_{11}H_7BrO_4$: Br, 28.27. Found: Br, 28.1.

The *acetyl derivative* crystallized from alcohol as needles, m.p. 165°.

Anal. Calc'd for $C_{13}H_9BrO_5$: Br, 24.61. Found: Br, 24.57.

The *oxime* crystallized from alcohol as granules, m.p. 233–234°.

Fries rearrangement of 7-benzoxy-6-bromocoumarin; formation of 7-hydroxy-6-bromo-8-benzoylcoumarin. 7-Benzoxy-6-bromocoumarin prepared by the benzoyl chloride-pyridine method, was crystallized from acetic acid as shining needles, m.p. 205°.

An intimate mixture of aluminum chloride (4.5 g.) and the 7-benzoxy derivative (3.5 g.) was baked at 170–175° for two hours as before. The solid obtained after working the reaction up was collected and crystallized from alcohol (animal charcoal) and recrystallized from benzene as plates, m.p. 271°.

Anal. Calc'd for $C_{16}H_9BrO_4$: Br, 23.2. Found: Br, 23.01.

The *semicarbazone* was obtained as pale green needles, m.p. 259° (decomp.).

7-Hydroxy-3-acetylcoumarin. A mixture of β-resorcylaldehyde (5 g.) and ethyl acetoacetate (5 g.) was cooled in an ice-bath and piperidine (1 cc.) was added; after an hour it was left overnight at room temperature. Then it was treated with cold acidulated water. The solid obtained was crystallized from alcohol as greenish lustrous needles, m.p. 240°. Yield, 3.3 g.

Anal. Calc'd for $C_{11}H_8O_4$: C, 64.71; H, 3.92.
Found: C, 64.67; H, 3.91.

Attempted Fries rearrangement of 7-acetoxy-3-acetylcoumarin. 7-Acetoxy-3-acetylcoumarin, obtained by the acetic anhydride-pyridine method, was crystallized from alcohol as needles, m.p. 115°.

Anal. Calc'd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.07.
Found: C, 63.27; H, 4.03.

To a nitrobenzene solution (30 cc.) of aluminum chloride (6 g., 3.3 moles), 7-acetoxy-3-acetylcoumarin (3 g., 1 mole) was added at once and the mixture was heated for one hour at 90° on a water-bath ($CaCl_2$ guard tube). After treating it with concentrated HCl (10

cc.), nitrobenzene was steam-distilled off. The solid thus obtained was crystallized from alcohol, m.p. 239°; the mixture melting point with 7-hydroxy-3-acetylcoumarin was not depressed.

The rearrangement was repeated without using any solvent, the de-acetylated product again being obtained.

The attempted Fries rearrangement of 7-acetoxy-3-carbethoxycoumarin. 7-Acetoxy-3-carbethoxycoumarin was prepared by the acetylation of 7-hydroxy-3-acetoxycoumarin (9) by the acetic anhydride-pyridine method; it crystallized from alcohol in plates, m.p. 152°.

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.52; H, 4.27.

Found: C, 61.34; H, 4.22.

The rearrangement was carried out as before. The solid obtained was treated with sodium bicarbonate solution and filtered. On acidification, the filtrate gave a solid which was crystallized from hot water, m.p. 271° (decomp.), the mixture melting point with 7-hydroxy-3-carboxylcoumarin prepared according to Pechmann and Graeger (9) remaining undepressed.

The same rearrangement in nitrobenzene (22 cc.) at 100–110° for one hour also gave the same acid.

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