Base Rearrangement of Chromone-3-carboxylic Esters to 3-Acyl-4-hydroxycoumarins

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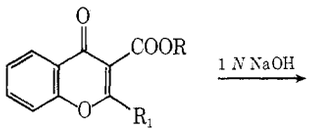
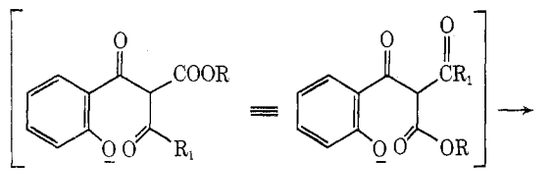
In the course of our work in chromone chemistry[1] the hydrolysis of chromone-3-carboxylic esters **1a** and **1b** was studied. It was found that acid condition gave the expected chromone-3-carboxylic acids **5a** and **5b** in good yields. Basic condition, however, resulted in facile rearrangement in high yields to the known 3-acyl-4-hydroxycoumarins[2,3] **3a** and **3b**.

This reaction may be looked upon as a "reverse" acyllactone rearrangement.[4] Its probable course would involve opening of the chromome ring system by base with subsequent ring closing through lactonization of the postulated triacyl intermediate **2**. In one experiment the sodium salt



1a, R = C_2H_5; R_1 = H
b, R = CH_3; R_1 = CH_3
c, R = CH_3; R_1 = C_2H_5



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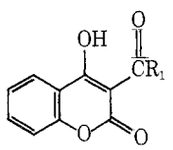


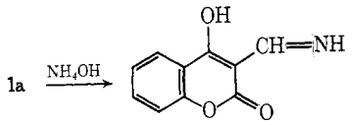
3a, R_1 = H
b, R_1 = CH_3
c, R_1 = C_2H_5

of the coumarin **3a** precipitated directly from solution, indicating that rearrangement occurred under basic conditions and before acidification of the reaction solution.

The two types of products, 3-acyl-4-hydroxycoumarins and chromone-3-carboxylic acids, could not be readily distinguished by ir or on the basis of their acidity, since both were found to be equally soluble in sodium bicarbonate. Differentiation was made by consideration of the following spectral data. Ultraviolet spectra of the coumarins **3a–c** displayed a band at about 300 nm with an intensity of ϵ 14,000 whereas the intensity of the corresponding bands for the acids **5a** and **5b** was less than half of this value. Nmr spectra showed signals for the methyl protons of **3b** and **5b** at δ 2.76 and 3.04 ($CDCl_3$), respectively. The broad signal for the OH proton of **3b** appeared at δ 17.70 ($CDCl_3$) whereas the carboxylic acid proton of **5b** appeared at δ 14.33. Mass spectra proved to be most useful for structure proof by showing the elimination of CO_2 (m/e 190 → 146 for **5a** and m/e 204 → 160 for **5b**) from the carboxylic acid molecular ions.

The rearrangement was seen also under conditions other than that of basic hydrolysis. Preparation of the 2-alkyl esters **1b** and **1c** under the basic conditions of a Kostanecki-type reaction on the recently reported methyl salicyloylacetate[5] with acetic or propionic anhydride resulted in rearrangement in varying degree. In the case of cyclization to **1b**, which was isolated in good yield, a minor amount of **3b** was obtained, whereas the attempted preparation of **1c** by the same method resulted mainly in rearrangement to **3c** in good yield.

An analogous transformation was observed when 3-carbethoxychromone **1a** was heated with concentrated ammonium hydroxide, giving rise to the known 3-(formimidoyl)-4-hydroxycoumarin (**4**).[6]



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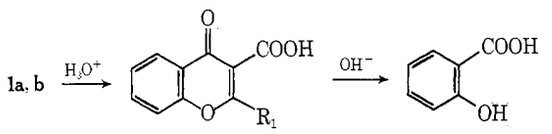
Rearrangement did not occur on treatment of the free carboxylic acid **5b** with base. There was either no reaction at 20° or degradation on warming to give a good yield of salicylic acid (**6**).



5a, R_1 = H
b, R_1 = CH_3

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These observations may explain the scarcity of chromone-3-carboxylic acids and esters in the literature, since most known methods of preparation are base catalyzed. The similarity of some physical and chemical properties between chromone-3-carboxylic acids and 3-acyl-4-hydroxycoumarins indicates that caution should be exercised in structure assignments in this area.

Experimental Section[7]

Base Rearrangement of Ethyl 4-Oxo-4*H*-1-benzopyran-3-carboxylate (1a) to 4-Hydroxy-2-oxo-2*H*-1-benzopyran-3-carboxaldehyde (3a). A mixture of 6.4 g (0.029 mol) of **1a**[1] and 100 ml of 1 *N* NaOH was stirred at room temperature for 15 min. Partial solution took place as the sodium salt of **3a** separated. Water (800 ml) was added to dissolve all solid and the solution was acidified with concentrated HCl to precipitate **3a**, 4.6 g (83%), mp 135–137°. Recrystallization from 2-propanol gave pure **3a**: mp 137–139° (reported[2] mp 136–137°); ir (Nujol) 1715 (formyl C=O), 1615 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 238 nm (ϵ 15,100), 304 (14,250); mass spectrum m/e (rel intensity) 190 (50), 162 (100), 121 (50), 120 (70), 92 (30).

In one run the insoluble sodium salt of **3a** was filtered in 58% yield. Recrystallization from methanol–water gave the pure sodium salt: mp 375° dec; ir (Nujol) 1690 (formyl C=O), 1615 cm^{-1} (2-pyrone C=O).

Anal. Calcd for $C_{10}H_5O_4Na$: C, 56.62; H, 2.38; Na, 10.84. Found: C, 56.90; H, 2.55; Na, 10.59.

Methyl 2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate (1b). A stirred mixture of 22.0 g (0.112 mol) of methyl salicyloylacetate,[5] 600 ml of xylene, 60 g of powdered anhydrous potassium carbonate, and 60 ml of acetic anhydride was heated to 80°. After evolution of CO_2 was complete the temperature was raised to 125–130° for 1 hr. The mixture was filtered (filter cake was retained for isolation of **3b**) and the filtrate was stirred for 2 hr with 200 ml of water, washed well with water, dried (Na_2SO_4), and concentrated to give 15 g (62%) of crude ester. Recrystallization from ethyl acetate gave pure **1b**: mp 116–118°; ir (Nujol) 1725 (ester C=O), 1640 cm^{-1} (pyrone C=O); nmr ($CDCl_3$) δ 8.22 (q, 1, H-5), 7.3–7.8 (m, 3, H-6, -7, -8), 3.97 (s, 3, $COOCH_3$), 2.53 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.03; H, 4.59.

3-Acetyl-4-hydroxy-2*H*-1-benzopyran-2-one (3b). A. Isolated in the Preparation of 1b. The above K_2CO_3 filter cake from the xylene reaction mixture was dissolved in 500 ml of water and aci-

dified with concentrated HCl to precipitate 1.1 g (5%) of **3b**, mp 133–135° (reported[3] mp 134°).

B. From Base Rearrangement of 1b. A mixture of 1.0 g (0.005 mol) of **1b** and 100 ml of 1 *N* NaOH was warmed on the steam bath for 5 min or until complete solution took place. The cooled solution was acidified with concentrated HCl to precipitate **3b**: 0.80 g (86%); mp 133–135°; ir (Nujol) 1730 (acetyl C=O), 1615 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 212 nm (ϵ 23,000), 300 (14,000), 320 sh (9600); mass spectrum *m/e* (rel intensity) 204 (60), 189 (40), 162 (20), 121 (60), 120 (60), 105 (10), 93 (15), 92 (50), 77 (25), 43 (100).

4-Hydroxy-3-(1-oxopropyl)-2*H*-1-benzopyran-2-one (3c). A mixture of 5.5 g (0.028 mol) of methyl salicyloylacetate, 150 ml of xylene, 19.5 g (0.15 mol) of propionic anhydride, and 30 g of powdered potassium carbonate was heated with stirring at 135° for 0.5 hr. Ether (300 ml) was added to the cooled mixture and the solids were filtered and washed with ether. The filter cake was stirred with 500 ml of water, the insoluble portion was filtered, and the filtrate was acidified with concentrated HCl to precipiate 4.8 g (78%) of **3c**: mp 122–124° (reported[3] mp 123°); ir (Nujol) 1720 (acyl C=O), 1610 cm^{-1} (2-pyrone C=O); uv max (95% EtOH) 226 nm sh (ϵ 15,200), 301 (13,300); mass spectrum *m/e* (rel intensity) 218 (50), 200 (15), 189 (100), 162 (17), 121 (50), 120 (25), 105 (12), 93 (12), 92 (25), 77 (25), 43 (5).

In this reaction the 3-carbomethoxy-2-ethylchromone **1c** could not be isolated from work-up of the above xylene–ether reaction filtrate as was the case in the preparation of **1b**.

4-Oxo-4*H*-1-benzopyran-3-carboxylic Acid (5a). A solution of 1.09 g (0.005 mol) of **1a**[1] and 100 ml of concentrated HCl was heated at 100° for 1 hr. Ice water (100 ml) was added and the mixture was filtered to give **5a**, 0.90 g (95%), mp 198–200°. Recrystallization was effected by dissolution in 100 ml of ethyl acetate and concentration to 25-ml volume to give pure crystals of **5a**: mp 199–201° (reported[1] mp 199–201°); ir (Nujol) 1740 (carboxylic C=O), 1620 cm^{-1} (pyrone C=O); uv max (95% EtOH) 213 nm (ϵ 18,000), 238 sh (11,000), 300 (5600); mass spectrum *m/e* (rel intensity) 190 (10), 173 (5), 146 (100), 120 (20), 104 (30), 92 (15), 63 (15), 53 (20).

2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxylic Acid (5b). A solution of 10.0 g (0.046 mol) of **1b** in 100 ml of concentrated HCl was heated at 80–90° for 20 min. Ice (400 g) was added to precipitate a tacky solid. The crude product was dissolved in 300 ml of 5% $NaHCO_3$ and the insoluble portion was extracted away with ether. The aqueous phase was acidified with concentrated HCl to give 6.4 g (68%) of **5b**, mp 120–135°. Recrystallization from 2-propanol gave pure **5b**: mp 145–147°; ir (Nujol) 1725 (carboxylic C=O), 1618 cm^{-1} (pyrone C=O); uv max (95% EtOH) 232 nm (ϵ 21,300), 298 (5660); mass spectrum *m/e* (rel intensity) 204 (57), 186 (22), 160 (100), 131 (5), 120 (98), 92 (32); nmr ($CDCl_3$) δ 14.33 (broad, 1, COOH), 8.35 (q, 1, H-5), 7.3–8.0 (m, 3, H-6, -7, -8), 3.04 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.79; H, 4.11.

Base Degradation of 5b to Salicylic Acid (6). A solution of 2.5 g (0.012 mol) of **5b** in 100 ml of 1 *N* NaOH was heated at 100° for 1 min. The cooled solution was acidified with concentrated HCl to precipitate **6**, 1.5 g (88%), mp 157–159° [reported (Lange Handbook) mp 158.3°].

4-Hydroxy-3-(iminomethyl)-2*H*-1-benzopyran-2-one (4). A mixture of 2.0 g (0.009 mol) of **1a** was heated with 5 ml of concentrated NH_4OH on the steam bath. The ester soon dissolved and after 5 min crude **4** separated, 1.5 g (81%), mp 223–225°. Recrystallization from ethanol gave pure **4**, mp 236–238° (reported[6] mp 240–242°).

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Registry No.—**1a**, 51085-94-0; **1b**, 51751-33-8; **3a**, 51751-34-9; **3a** sodium salt, 51751-35-0; **3b**, 2555-37-5; **3c**, 4139-73-5; **4**, 51751-36-1; **5a**, 39079-62-4; **5b**, 51751-37-2; **6**, 69-72-7; methyl salicyloylacetate, 20349-86-4.

References and Notes

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(7) Melting points were determined with the Thomas-Hoover capillary melting point apparatus, which was calibrated against known standards. Infrared spectra were determined with a Baird Model 455 double-beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

Selective Demethylation of 2,5-Dimethoxybenzaldehyde to 5-Hydroxy-2-methoxybenzaldehyde

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The selective demethylation of 2,5-dimethoxybenzaldehyde (**1**) with boron trichloride to give 2-hydroxy-5-methoxybenzaldehyde (**2**) is well known.[1] This reaction proceeds by a cyclic process involving the boron trichloride complex of 2,5-dimethoxybenzaldehyde. However, 5-hydroxy-2-methoxybenzaldehyde (**3**), the isomer of **2**, has not been synthesized previously.

Utilization of the complexing ability of the aldehydic group with the o-methoxy group could be used to advantage to block the approach of the demethylating agent, providing that the complexing agent does not cleave the neighboring ether group as observed with boron trichloride or aluminum trichloride. In the Gattermann reaction of 1,4-dimethoxybenzene with hydrogen cyanide in the presence of aluminum chloride, an iminium complex **4** is produced in which the aluminum chloride in fact could coordinate with the neighboring methoxy group. A cyclic ether cleavage process analogous to the boron trichloride demethylation is not operative, as evidenced by the fact that **2** was not isolated on hydrolysis of **4**. The approach of a