General Rearrangement of 3-Substituted Chromones. Rearrangement to 1-Benzoxepins and 4-Chromanones

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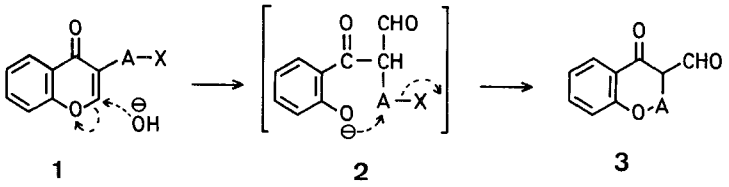
We wish to report that base treatment of 3-haloacylchromones and 3-pyridiniummethylchromones results in a rearrangement to give derivatives of 4-formyl-1-benzoxepin and 3-(hydroxymethylene)-4-chromanone, respectively. We suggest that these conversions are examples of a general reaction of chromones. Chromones **1** containing a leaving group X at C-3, linked directly or indirectly (via A) to the pyrone ring, undergo base rearrangement resulting in ring expansion, ring contraction or retention of ring size, depending on the presence and size of the group A.



1 **2** **3**

The reaction is initiated by a nucleophilic displacement at C-2 of the phenolate anion through hydroxide (or amine) with concomitant ring cleavage[1] to give **2**. This is followed by an intramolecular nucleophilic displacement of the leaving group X by the phenolate anion resulting in recyclization to the new ring **3**. The net effect is a replacement of C-2 by the carbon atom (in A) originally bonded to the leaving group X. The C-2 moiety now becomes an exocyclic carbonyl function of the new ring.

Our first reported example of this rearrangement was the base catalyzed conversion of 3-alkoxycarbonylchromones to 3-acyl-4-hydroxycoumarins[2]. The literature reveals examples of reactions which apparently fall into the general scheme. For example, 3-chloroflavone undergoes ring contraction to 2-benzoyl-3-benzofuranone[3]. Concurrent with our work, rearrangements of 3-ethoxycarbonylchromone and of a dihydro-γ-pyrone were observed as isolated parts of studies on different subjects[4, 5].

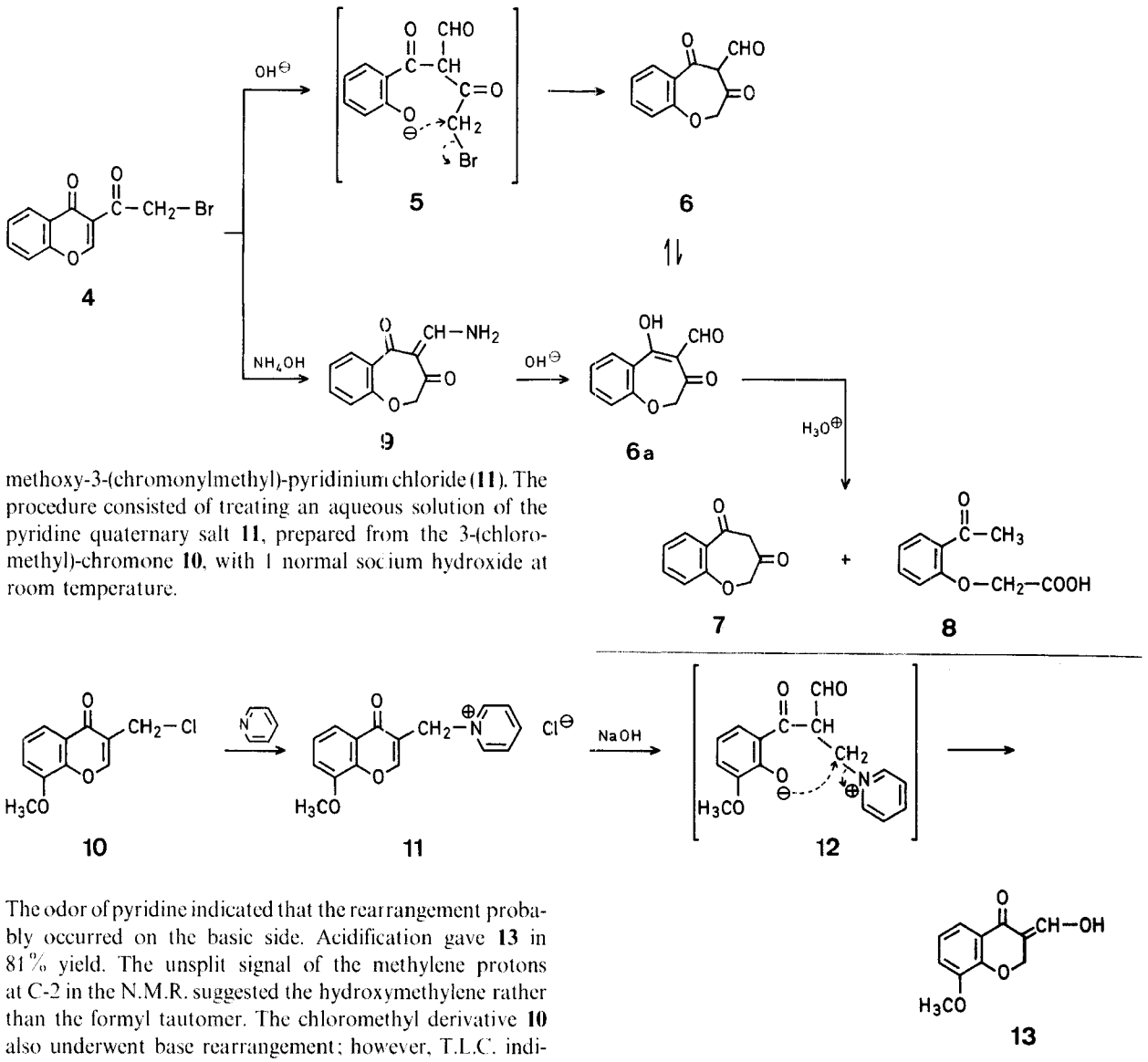
Warming of 3-(bromoacetyl)-chromone (**4**) with 1 normal sodium hydroxide gave, on acidification, 2,3-dihydro-3,5-dioxo-1-benzoxepin-4-carboxaldehyde (**6**) in 45% yield. This tricarbonyl structure probably exists in the enol form **6a** as suggested by its acidic nature (i.e. solubility in 1% sodium hydrogen carbonate), and exchangeable OH proton in the N.M.R.: N.M.R. ($CDCl_3$) $\delta = 4.6$ (2H singlet, CH_2), 9.85 (1H singlet, CHO) and 17.4 ppm (1H broad, OH).

Tautomers of **6a** in which either the 4-aldehyde or the C-3 ketone are enolized were ruled out on the basis of N.M.R. evidence. The aldehyde shows a typical formyl proton at $\delta = 9.85$ ppm whereas the proton of the corresponding enol form (=CH—OH) would be expected to appear more upfield as exemplified by the spectrum of the (hydroxymethylene)-4-chromanone **13** in which this proton appears at $\delta = 7.69$ ppm. The ketone at C-3 is apparently not enolized because the signal for the adjacent C-2 protons ($\delta = 4.6$ ppm) is approximately the same as that for the similar carbonyladjacent C-2 protons ($\delta = 4.5$ ppm) in compound **7**.

Additional proof for the 1-benzoxepin skeleton was obtained through acid hydrolysis and ring cleavage which yielded the degradation products 1-benzoxepin-3,5-dione (**7**) and *o*-acetylphenoxyacetic acid (**8**). The N.M.R. of structure **7** in deuterated chloroform indicated that it exists in the diketo form as is reported for some related benzoxepin-3,5-diones[6, 7]. The C-2 protons appear as a singlet at $\delta = 4.50$ ppm and the C-4 protons as a singlet at $\delta = 4.28$ ppm.

The rearrangement of **4** using concentrated ammonium hydroxide as the base gave **9** in 86% yield. Treatment of **9** at 40° for 10 minutes with 1 normal sodium hydroxide gave rise to the aldehyde **6a** in 97% yield. This sequence was the preferred method of preparation of **6a** in high overall yields.

Another example of a rearrangement following the general scheme (**1**→**3**) was the preparation of 3-(hydroxymethylene)-8-methoxy-4-chromanone (**13**) by base rearrangement of 8-



methoxy-3-(chromonylmethyl)-pyridinium chloride (**11**). The procedure consisted of treating an aqueous solution of the pyridine quaternary salt **11**, prepared from the 3-(chloromethyl)-chromone **10**, with 1 normal sodium hydroxide at room temperature.

The odor of pyridine indicated that the rearrangement probably occurred on the basic side. Acidification gave **13** in 81% yield. The unsplit signal of the methylene protons at C-2 in the N.M.R. suggested the hydroxymethylene rather than the formyl tautomer. The chloromethyl derivative **10** also underwent base rearrangement; however, T.L.C. indicated a complex reaction mixture.

3-(Bromoacetyl)-4*H*-1-benzopyran-4-one (4):
A solution of bromine (1.6 g, 0.01 mol) in chloroform (10 ml) was added over a period of 5 min to a stirred solution of 3-acetylchromone[8] (1.88 g, 0.01 mol) in chloroform (10 ml). After 0.5 h, the solvent was removed; crude yield: 1.9 g (70%); m.p. 140–145°. Recrystallization from ethyl acetate gave pure **4**; yield: 1.4 g (52%); m.p. 151–153°.

$C_{11}H_7BrO_3$ (267.1) calc. C 49.47 H 2.64 Br 29.92
found 49.57 2.88 30.20

I.R. (Nujol): ν_{max} = 1710 (acyl C=O), 1650 cm^{-1} (pyrone C=O).

U.V. (ethanol): λ_{max} = 207 sh (ε = 17000), 227 (17000), 286 sh (8200), 296 nm (9000).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.67 (s, 1H, H-2), 8.28 (q, 1H, H-5), 7.9–7.25 (m, 3H, H-6,7,8), 4.75 ppm (s, 2H, CH_2Br).

5-Hydroxy-3-oxo-2,3-dihydro-1-benzoxepin-4-carboxaldehyde (6a) from 4:
A mixture of **4** (12.0 g, 0.045 mol) and 1 normal sodium hydroxide (400 ml) was heated with stirring on the steam bath. The resulting dark solution was kept at 65–70° for 5 min. Ice (500 g) was added and the solution was acidified with concentrated hydrochloric acid to precipitate the product; yield: 4.1 g (45%); m.p. 110–112° (from isopropyl ether).

$C_{11}H_8O_4$ (204.2) calc. C 64.70 H 3.95
found 64.88 4.08

I.R. (Nujol): ν_{max} = 1660 cm^{-1} (C=O).

U.V. (ethanol): λ_{max} = 207 (ε = 13700), 246 (8100), 306 nm (11700).

Mass spectrum: m/e = 204 (M$^{\oplus}$, 100%), 189 (50%), 176 (67%), 162 (40%), 161 (60%), 147 (31%), 134 (27%), 121 (100%).

1-Benzoxepin-3,5(2*H*,4*H*)-dione (7):
A mixture of **6a** (14.28 g, 0.07 mol), methanol (250 ml), and concentrated hydrochloric acid (120 ml) was maintained at reflux for 0.5 h. The resulting solution was concentrated to ca. one-half volume and ice (200 g) was added. The semi-solid material which separated was extracted into dichloromethane (200 ml) to give 10 g of crude solid. Purification was effected by dissolution in ether and removal, by extraction, of the more acidic component **8** with 3% sodium hydrogen carbonate solution. The ether phase was concentrated to give crude dione **7**; yield: 7.2 g (58%); m.p. 75–78°. Recrystallization from ether gave the pure 1-benzoxepin-3,5-dione; yield: 3.0 g (24%); m.p. 81–83°.

$C_{10}H_8O_3$ (176.2) calc. C 68.18 H 4.58
found 68.14 4.71

I.R. (Nujol): ν_{max} = 1730 (C=O at C-3), 1680 cm^{-1} (C=O at C-5).

U.V. (ethanol): λ_{max} = 248 (ε = 5800), 294 (7900), 310 nm, sh (7100).

Mass spectrum: m/e = 176 (M$^{\oplus}$, 99%), 134 (83%), 118 (28%), 105 (100%), 90 (16%), 76 (70%), 63 (26%).

2-Acetylphenoxyacetic acid (8):
This compound was isolated as a by-product in low yield from the above preparation of compound **7**. It was obtained by acidifica-

tion of the sodium hydrogen carbonate wash. Purification was effected by use of silica gel column chromatography using ethyl acetate as eluent; m.p. 110–112° (Lit.[9] m.p. 119–120°[9]).

$C_{10}H_{10}O_4$	calc.	C 61.85	H 5.19	
(194.2)	found	61.74	5.35	

I.R. (Nujol): ν_{max} = 3100–2500 (OH), 1740 (carboxy C=O), 1665 cm^{-1} (acetyl C=O).

5-Hydroxy-3-oxo-2,3-dihydro-1-benzoxepin-4-carboxaldehyde (6a) from 9:

A quantity of **9** (70.0 g, 0.35 mol) was added to 1 normal sodium hydroxide (1400 ml) with stirring. The mixture was warmed to 40°. The solid gradually dissolved as ammonia was liberated. The dark, reddish-brown solution was kept at 40° for 10 min and filtered to remove traces of solid. Ice (500 g) was added and the solution was acidified with concentrated hydrochloric acid to precipitate product; crude yield: 68 g (97%); m.p. 108–110°. Recrystallization from isopropyl ether gave pure **6a**; yield: 54.4 g (76%); m.p. 110–112°.

4-(Aminomethylene)-1-benzoxepin-3,5(2*H*,4*H*)-dione (9):

Concentrated ammonium hydroxide (1300 ml) was added to a stirred mixture of **4** (108 g, 0.41 mol) and methanol (500 ml). All solid went into solution. There was a mildly exothermic reaction. After several minutes the product which separated was filtered, washed with water and dried; crude yield: 70 g (86%); m.p. 149–151°. Recrystallization from ethyl acetate gave pure orange-colored crystals; yield: 59.5 g (73%); m.p. 151–153°.

$C_{11}H_9NO_3$	calc.	C 65.02	H 4.46	N 6.89
(203.2)	found	65.03	4.56	6.88

I.R. (Nujol): ν_{max} = 3420 (NH_2), 1660 (C=O), 1610 cm^{-1} (C=C).

U.V. (ethanol): λ_{max} = 210 sh (ε = 16100), 252 sh (11300), 271 (12200), 309 nm (15700).

1-[(8-Methoxy-4-oxo-4*H*-1-benzopyran-3-yl)methyl]pyridinium Chloride Monohydrate (11):

A solution of 3-(chloromethyl)-8-methoxychromone[10] (22.4 g, 0.1 mol) in pyridine (200 ml) was heated with stirring to the boiling point. After 5 min the mixture was cooled and the separated solid was filtered, washed with pyridine and then with ether; yield: 30.3 g (94%); m.p. 225–230°. Recrystallization from 2-propanol/ether gave pure quaternary salt **11** as a monohydrate; yield: 25.8 g (80%); m.p. 233–235°.

$C_{16}H_{14}NO_3^{\oplus}Cl^{\ominus}\cdot H_2O$	calc.	C 59.73	H 5.01	N 4.35	
(321.7)	found	59.50	5.05	4.48	

I.R. (Nujol): ν_{max} = 3400 (H_2O), 1640 cm^{-1} (C=O).

U.V. (ethanol): λ_{max} = 220 (ε = 20300), 252 (13500), 300 nm, sh (3200).

2,3-Dihydro-3-(hydroxymethylene)-8-methoxy-4*H*-1-benzopyran-4-one (13):

A solution of **11** hydrate (15.5 g, 0.048 mol) in water (50 ml) was treated with 1 normal sodium hydroxide (200 ml). Pyridine was liberated as indicated by odor. After 5 min, conc. hydrochloric acid was added to pH 1 to precipitate a yellow solid; yield: 8.5 g (86%); m.p. 75–77°. Recrystallization from isopropyl ether gave pure **13**; yield: 5.0 g (51%); m.p. 76–78°.

$C_{11}H_{10}O_4$	calc.	C 64.08	H 4.89
(206.2)	found	64.31	5.10

I.R. (Nujol): ν_{max} = 2870 (OH), 1645 (C=O), 1615 cm^{-1} (C=C).

U.V. (ethanol): λ_{max} = 216 (ε = 17600), 256 sh (7000), 318 nm (6400).

^{1}H-N.M.R. ($CDCl_3$): δ = 12.3 (broad, 1H, C=CHOH), 7.69 (s, 1H, C=CHOH), 7.48 (q, 1H, H-5), 7.1–6.9 (m, 2H, H-6,7), 4.92 (s, 2H, CH_2) and 3.87 ppm (s, 3H, OCH_3).

Received: September 15, 1976

[1] Usually the β-dicarbonyl system resulting from base ring opening of chromones undergoes further cleavage to salicyclic acids or *o*-hydroxyacetophenones; S. Wawzonek in *Heterocyclic Compounds*, Vol. 2, R. C. Elderfied, Ed., John Wiley & Sons New York, 1951, p. 258.

[2] S. Klutchko, J. Shavel, Jr., M. von Strandtmann, *J. Org. Chem.* **39**, 2436 (1974).
[3] J. R. Merchant, D. V. Rege, *Tetrahedron Lett.* **1969**, 3589.
[4] K. Sato, S. Inoue, M. Ohashi, *Bull. Chem. Soc. Jpn.* **46**, 1289 (1973).
[5] K. Okumura, K. Kondo, T. Oine, I. Inoue, *Chem. Pharm. Bull.* **2**, 333 (1974).
[6] J. H. P. Tyman, R. Pickles, *Tetrahedron Lett.* **1966**, 4993.
[7] H. Hofmann, *Angew. Chem.* **77**, 864 (1965); *Angew. Chem. Int. Ed. Engl.* **4**, 872 (1965).
[8] F. Eiden, H. Haverland, *Arch. Pharm.* **300**, 806 (1967).
[9] J. Moszew, J. Mikulski, *Roczn. Chem.* **29**, 536 (1955).
[10] This compound, m.p. 144–146°, was prepared from 3-(hydroxymethyl)-8-methoxychromone, *U.S. Patent* 3,887,584, by a procedure similar to that described for making 3-(chloromethyl)-chromone: S. Klutchko, M. P. Cohen, J. Shavel, Jr., M. von Strandtmann, *J. Heterocycl. Chem.* **11**, 183 (1974).