

Heterocyclic Synthesis with β -Ketosulfoxides IV. Synthesis of 3-Substituted Chromones

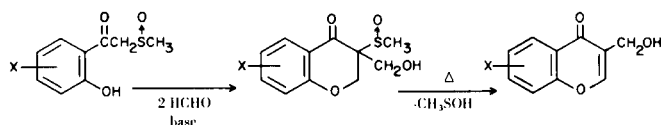
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Received December 3, 1973

A novel synthesis of 3-(hydroxymethyl)chromones from *o*-hydroxy- ω -(methylsulfinyl)acetophenones has been developed. These have been utilized in the synthesis of 3-formyl, 3-cyano, 3-carboxy, 3-carboxamido, 3-chloromethyl, 3-aminomethyl and 3-methoxymethylchromones.

A facile entry into the field of chromones was provided by our recent development of a new heterocyclic synthesis with β -ketosulfoxides (1). The method has now been extended to the preparation of 3-substituted chromones. This area has received little attention and, until recently, simple compounds such as 3-(hydroxymethyl)chromone and chromone-3-carboxylic acid remained undisclosed (2). The present report describes the preparation and chemical properties of these compounds.

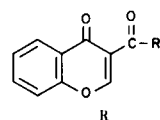
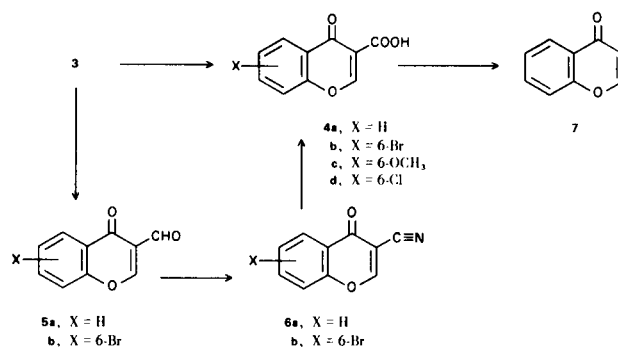


1a, X = H
b, X = 5'-Br
c, X = 5'-OCH₃
d, X = 6'-OCH₃
e, X = 3'-Ph
f, X = 5'-I
g, X = 4'-Cl
h, X = 5'-Cl

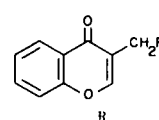
2a, X = H
b, X = 6-Br
c, X = 6-OCH₃
[d, X = 5-OCH₃]
[e, X = 8-Ph]
f, X = 6-I
[g, X = 7-Cl]
[h, X = 6-Cl]

3a, X = H
b, X = 6-Br
c, X = 6-OCH₃
d, X = 5-OCH₃
e, X = 8-Ph
f, X = 6-I
g, X = 7-Cl
h, X = 6-Cl

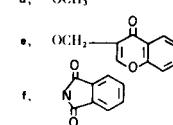
SCHEME 1



5a, Cl
b, OC₂H₅
c, NH₂
d, NHCH(CH₃)₂
e, N(CH₃)₂
f, NHPh
g, N(CH₃)OH
h, NHCONH₂



4a, Cl
b, H
c, OCOCH₃
d, OCH₃



4a, NH₂
b, NHCH(CH₃)₂
c, N(CH₃)₂
d, N(CH₃)OH
e, C≡N
f, CONH₂
g, COOH

When *o*-hydroxy- ω -(methylsulfinyl)acetophenones **1** were allowed to react with two moles of formaldehyde in the presence of base, 3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanones **2** were obtained. The intermediate 4-chromanones **2** were easily converted to 3-(hydroxymethyl)chromones **3** by thermal elimination of the elements of CH₃SOH in boiling toluene or xylene. In practice, the purification of intermediates **2** was not necessary and was often found impractical because of losses due to the facile elimination of methylsulfenic acid and the presence of diastereoisomers.

The availability of the new 3-(hydroxymethyl)chromones made possible the preparation of other simple 3-substituted chromones such as the acids, amides, nitriles, aldehydes, alkyl, aminoalkyl and carboxalkyl derivatives.

Oxidation of 3-(hydroxymethyl)chromones **3a-c** and **3h** with chromic acid in the form of Jones reagent (3) gave chromone-3-carboxylic acids **4a-d**. Compound **4a** was decarboxylated to chromone **7** as part of its structure proof.

Fair to poor yields of **4a-d** were attributed to decarboxylation and further oxidative degradation. An alternate procedure to the acids was devised whereby the alcohols **3a** and **3b** were first oxidized, with either concentrated nitric acid or sodium dichromate-acetic acid, to the aldehydes **5a** (4) and **5b** in good yields. Treatment of the aldehydes with hydroxylamine, formic acid and sodium formate gave a 51-

62% yield of nitriles **6a** and **6b**. Subsequent acid hydrolysis gave good yields of **4a** and **4b**.

Chromone-3-carboxylic acid **4a** was used to synthesize a variety of amide, ester and hydroxamic acid derivatives **8b-h** through its acid chloride **8a**.

Other reactions of the alcohol **3a** included etherification to **9d** with methanol and iodine (5) and fusion at 250° to give a low yield of the bis ether **9e**. Thionyl chloride with **3a** gave the corresponding 3-(chloromethyl)chromone **9a** which yielded a variety of aminomethyl derivatives **9f-k** by reaction with appropriate amines and hydroxylamines. Reduction of **9a** with zinc in acetic acid produced the known 3-methylchromone **9b** (6). The treatment of **9a** with potassium cyanide gave the chromone-3-acetonitrile **9l**. Acid hydrolysis of the nitrile resulted in either the acetamide **9m** or the chromone-3-acetic acid **9n** depending on reaction conditions.

EXPERIMENTAL

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 544 double beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

General Procedure A: Preparation of 2'-Hydroxy-2-(methylsulfinyl)acetophenones **1a-h**.

These intermediates were prepared by the reaction of salicylic esters with sodium methylsulfinylmethide (1,7) as follows: A quantity of 12.7 g. (0.3 mole) of 57% sodium hydride-mineral oil dispersion was added to a stirred solution of 150 ml. of dimethyl sulfoxide and 350 ml. of benzene under nitrogen. The mixture was heated at 75-80° for 1 hour until solution was essentially complete. The solution was cooled to 35° and a quantity of 0.1 mole of the appropriate ethyl or methyl salicylate was added. After the initial exotherm ($T = 50^\circ$) the solution was allowed to cool over the next 0.5 hour and ether (1500 ml.) was added. The resulting precipitate was filtered, washed well with ether and dissolved in 150 ml. of ice water. The solution was acidified with 24 g. (0.4 mole) of glacial acetic acid to precipitate the product in 43-88% yield. Recrystallization from absolute ethanol gave pure **1a-h**.

General Procedure B: Preparation of 3-(Hydroxymethyl)-3-(methylsulfinyl)-4-chromanones **2a-c** and **2f**.

A quantity of 24.3 g. (0.3 mole) of 37% aqueous formaldehyde was added to a warm (40°), stirred solution of 0.15 mole of the appropriate 2'-hydroxy-2-(methylsulfinyl)acetophenone (**1**), 90 g. of potassium carbonate and 600 ml. of water. After 0.5 hour the separated solid was filtered, washed with cold water and recrystallized from acetone. The oil which separated in the case of **2a** was isolated by extraction with 50% methylene chloride-ether.

General Procedure C: Preparation of 3-(Hydroxymethyl)chromones **3a-h** Directly from 2'-Hydroxy-2-(methylsulfinyl)acetophenones **1** Without Purification of the Intermediate Chromanones **2**.

The intermediate 3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanones **2** were prepared according to General Procedure B. The crude product was suspended in 300 ml. of toluene or xylene and boiled for 0.5 hour. The solution was filtered hot, cooled and the

separated crystals were filtered and recrystallized from absolute ethanol.

General Procedure D: Preparation of Chromone-3-carboxylic Acids **4a-d** via Jones Reagent Oxidation of the Corresponding 3-(Hydroxymethyl)chromones **3a-c** and **3h**.

A warm (50°) stirred solution of 0.047 mole of the alcohol **3** and 125 ml. of glacial acetic acid was treated with 0.072 mole of chromic oxide as Jones reagent (3) over a period of ca. 5 minutes. The temperature of the exothermic reaction was maintained at ca. 60° by the rate of addition of the oxidant. After 0.5 hour the solution was heated at 75° for 10 to 30 minutes when the excess acetic acid was removed at reduced pressure. Water (200 ml.) was added to the residue and the separated crude product was collected. On standing several days the filtrate yielded additional material for total yields of from 9 to 39%. Purification, if necessary, was effected by dissolution in 3% sodium bicarbonate solution at room temperature, filtration to remove insolubles and acidification with concentrated hydrochloric acid to recover the free acid. Recrystallization from ethyl acetate gave the pure chromone-3-carboxylic acids.

General Procedure E: Preparation of Chromone-3-carboxamides **8d-f**.

A solution of 0.05 mole of chromone-3-carbonyl chloride **8a** in 200 ml. of methylene chloride was added over a 5 minute period to a stirred mixture of 0.07 mole of the appropriate amine, 200 ml. of methylene chloride and 30 g. of powdered anhydrous potassium carbonate, keeping the temperature at 20 to 25° with cooling. After one hour the solids were filtered and the filtrate concentrated to give the crude product. In the case of **8f** additional insoluble product was recovered from the filter cake by trituration with water. Recrystallization was from ether in the case of **8d**, ethyl acetate for **8e** and chloroform-petroleum ether for **8f**.

General Procedure F: Preparation of Secondary and Tertiary 3-(Aminomethyl)chromones **9h-j**.

A solution of 8.3 g. (0.043 mole) of 3-(chloromethyl)chromone **9a** in 50 ml. of methylene chloride was added gradually over ca. 5 minutes to a 7 to 10 fold excess of the amine. After the initial exotherm, the stirred mixture was maintained at reflux for one hour and concentrated to remove the excess amine. Saturated aqueous potassium carbonate solution (50 ml.) was added to the residue and the separated crude product was extracted into 100 ml. of ether. The dried (potassium carbonate) ether solution was stripped of solvent of traces of excess amine. In the case of **9i** and **9j** the excess amine was chased with xylene. The residue was again extracted into ether (methanol was used for **9j**) and the hydrochloride (dihydrochloride in the case of **9j**) was precipitated with hydrogen chloride and recrystallized from methanol-ether.

2'-Hydroxy-2-(methylsulfinyl)acetophenone (**1a**).

Prepared by General Procedure A; yield, 88%, m.p. 151-153°; reported m.p. 153° (8); ν (nujol), 1635 (C=O), 1015 cm^{-1} (S=O); nmr (deuteriochloroform): δ 11.85 (s, 1H, OH), 6.9-7.9 (m, 4H, aromatics), 4.42 (d, 2H, CH_2), 2.81 (s, 3H, CH_3).

5'-Bromo-2'-hydroxy-2-(methylsulfinyl)acetophenone (**1b**).

Prepared by General Procedure A; yield, 60%; m.p. 148-149°.

Anal. Calcd. for $\text{C}_9\text{H}_9\text{BrO}_3\text{S}$: C, 39.01; H, 3.27; S, 11.57. Found: C, 39.26; H, 3.36; S, 11.64.

2'-Hydroxy-5'-methoxy-2-(methylsulfinyl)acetophenone (**1c**).

Prepared by General Procedure A; yield, 58%; m.p. 153-155.5°.

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.05.
Found: C, 52.73; H, 5.42; S, 13.82.

2'-Hydroxy-6'-methoxy-2-(methylsulfinyl)acetophenone (**1d**).

Prepared by General Procedure A; yield, 57%; m.p. 123-125°.

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.05.
Found: C, 53.05; H, 5.33; S, 13.96.

2'-Hydroxy-2-(methylsulfinyl)-3'-phenylacetophenone (**1e**).

Prepared by General Procedure A; yield, 49%; m.p. 126-128°.

Anal. Calcd. for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69.
Found: C, 65.80; H, 5.09; S, 11.81.

2'-Hydroxy-5'-iodo-2-(methylsulfinyl)acetophenone (**1f**).

Prepared by General Procedure A; yield, 56% m.p. 144-145°.

Anal. Calcd. for $C_9H_9IO_3S$: C, 33.35; H, 2.80; S, 9.89.
Found: C, 33.51; H, 2.79; S, 10.14.

4'-Chloro-2'-hydroxy-2-(methylsulfinyl)acetophenone (**1g**).

Prepared by General Procedure A; yield, 43%; m.p. 142-144°.

Anal. Calcd. for $C_9H_9ClO_3S$: C, 46.46; H, 3.90; S, 13.78.
Found: C, 46.22; H, 3.81; S, 13.71.

5'-Chloro-2'-hydroxy-2-(methylsulfinyl)acetophenone (**1h**).

Prepared by General Procedure A; yield, 64% m.p. 144-147°.

Anal. Calcd. for $C_9H_9ClO_3S$: C, 46.46; H, 3.90; S, 13.78.
Found: C, 46.69; H, 3.85; S, 13.68.

3-(Hydroxymethyl)-3-(methylsulfinyl)-4-chromanone (**2a**).

Prepared by General Procedure B; yield, 69%; n_D^{26} 1.5868;
ir (film): 3400 (OH), 1670 (C=O), 1050 cm^{-1} (S=O).

Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03; S, 13.34.
Found: C, 55.06; H, 5.15; S, 13.09.

6-Bromo-3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanone (**2b**).

Prepared by General Procedure B; yield, 26%; m.p. 129-131°.
ir (nujol): 3200 (OH), 1670 (C=O), 1050 cm^{-1} (S=O).

Anal. Calcd. for $C_{11}H_{11}BrO_4S$: C, 41.39; H, 3.47; S, 10.05.
Found: C, 41.73; H, 3.43; S, 10.18.

3-(Hydroxymethyl)-6-methoxy-3-(methylsulfinyl)-4-chromanone (**2c**).

Prepared by General Procedure B; yield, 25%; m.p. 107-110°.

Anal. Calcd. for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86.
Found: C, 53.53; H, 5.22; S, 11.78.

3-(Hydroxymethyl)-6-iodo-3-(methylsulfinyl)-4-chromanone (**2f**).

Preparation by General Procedure B; yield, 36%; m.p. 122-124°.

Anal. Calcd. for $C_{11}H_{11}IO_4S$: C, 36.08; H, 3.03; S, 8.76.
Found: C, 36.30; H, 3.01; S, 8.86.

3-(Hydroxymethyl)chromone (**3a**).

Prepared by General Procedure C; yield, 50%; m.p. 108-110°;
ir (nujol): 3350 (OH), 1635 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.35-8.18 (m, 1H, H-5), 8.02 (s, 1H, H-2), 7.9-7.2 (m, 3H, H-6, 7, 8), 4.62 (s, 2H, CH_2), 3.32 (broad, 1H, OH).

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.20; H, 4.68.

6-Bromo-3-(hydroxymethyl)chromone (**3b**).

Prepared by General Procedure C; yield, 60%; m.p. 155-158°;
ir (nujol), 3400 (OH), 1630 cm^{-1} (C=O); nmr (DMSO- d_6): δ 8.35 (s, 1H, H-2), 8.2 (d, 1H, J = 2 Hz, H-5), 8.04 (q, 1H, J_{ortho} = 9 Hz, J_{meta} = 2 Hz, H-7), 7.71 (d, 1H, J = 9 Hz, H-8), 5.23 (t, 1H, OH),

4.46 (d, 2H, J = 5 Hz, CH_2).

Anal. Calcd. for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77. Found: C, 47.29; H, 2.81.

3-(Hydroxymethyl)-6-methoxychromone (**3c**).

Prepared by General Procedure C; yield 56%; m.p. 150-153.5°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.21; H, 4.86.

3-(Hydroxymethyl)-5-methoxychromone (**3d**).

Prepared by General Procedure C; yield, 25%; m.p. 155-156°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.81; H, 4.94.

3-(Hydroxymethyl)-8-phenylchromone (**3e**).

Prepared by General Procedure C; yield, 27% m.p. 105-107°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 76.18; H, 4.79. Found: C, 76.07; H, 4.83.

3-(Hydroxymethyl)-6-iodochromone (**3f**).

Prepared by General Procedure C; yield 28%; m.p. 134-137°.

Anal. Calcd. for $C_{10}H_7IO_3$: C, 39.76; H, 2.34. Found: C, 39.88; H, 2.40.

7-Chloro-3-(hydroxymethyl)chromone (**3g**).

Prepared by General Procedure C; yield, 47%; m.p. 157-159°.

Anal. Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35. Found: C, 57.06; H, 3.32.

6-Chloro-3-(hydroxymethyl)chromone (**3h**).

Prepared by General Procedure C; yield, 48%; m.p. 163-164°.

Anal. Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35. Found: C, 57.00; H, 3.23.

4-Oxo-4H-1-benzopyran-3-carboxylic acid (**4a**).

Prepared by General Procedure D; yield, 22%; m.p. 199-201°;
ir (nujol): 1740 (carboxylic C=O), 1620 cm^{-1} (pyrone C=O); nmr (DMSO- d_6): δ 9.17 (s, 1H, H-2), 8.26 (d, 1H, H-5), 7.4-8.1 (m, 3H, H-6,7,8).

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 62.93; H, 3.19.

Alternate Method for **4a**

Prepared by acid hydrolysis of nitrile **6a**. A solution of 3.1 g. (0.018 mole) of **6a** and 100 ml. of 55% sulfuric acid was heated at 130° for one hour. Ice water (100 ml.) was added to the cooled solution to precipitate 2.5 g. of crude **4a**. Purification was effected by stirring with 250 ml. of 3% sodium bicarbonate, filtration to remove undissolved solid and acidification with concentrated hydrochloric acid to precipitate the **4a**; wt. 1.9 g., m.p. 190-195° yield, 55%. Recrystallization from ethyl acetate gave pure **4a**; m.p. 199-201°.

6-Bromo-4-oxo-4H-1-benzopyran-3-carboxylic Acid (**4b**).

Prepared by General Procedure D; yield, 9%; m.p. 191-193°;
ir (nujol), 1735 (carboxylic C=O), 1610 cm^{-1} (pyrone C=O); nmr (DMSO- d_6): δ 9.06 (s, 1H, H-2), 8.17 (d, 1H, J = 2 Hz, H-5), 8.04 (q, 1H, J_{ortho} = 9 Hz, J_{meta} = 2 Hz, H-7), 7.73 (d, 1H, J = 9 Hz, H-8).

Anal. Calcd. for $C_{10}H_5BrO_4$: C, 44.64; H, 1.87. Found: C, 44.74; H, 1.82.

Alternate Method for **4b**

Prepared by hydrolysis of nitrile **6b** by method similar to alternate for **4a**; yield, 93%.

6-Methoxy-4-oxo-4H-benzopyran-3-carboxylic Acid (4c).

Prepared by General Procedure D; yield, 8%; m.p. 167-169°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.94; H, 3.67.

6-Chloro-4-oxo-4H-1-benzopyran-3-carboxylic Acid (4d).

Prepared by General Procedure D; yield 7%; m.p. 225-227°.

Anal. Calcd. for $C_{10}H_5ClO_4$: C, 53.48; H, 2.24; Cl, 15.78. Found: C, 53.37; H, 2.24; Cl, 15.60.

4-Oxo-4H-1-benzopyran-3-carboxaldehyde (5a).

A quantity of 35.2 g. (0.2 mole) of **3a** was dissolved in 250 ml. of 70% nitric acid with stirring at 25°. There was no initial heat of reaction but the temperature gradually rose to 30° (caution) over the next several minutes and was kept there for about five minutes with good cooling. Water (600 ml.) was added to the reaction solution and the separated crude **5a** was filtered; wt. 25 g.; m.p. 145-148°. Purification to remove a minor, slow-moving spot on tlc was effected by filtration of a methylene chloride solution through a layer of silica gel. Concentration of the filtrate gave 20 g. (63%) of pure aldehyde **5a**; m.p. 151-152°; reported m.p. 152° (4).

Anal. Calcd. for $C_{10}H_6O_3$: C, 68.97; H, 3.47. Found: C, 68.76; H, 3.19.

6-Bromo-4-oxo-4H-1-benzopyran-3-carboxaldehyde (5b).

A warm (40°) solution of 29.8 g. (0.1 mole) of sodium dichromate dihydrate in 80 ml. of glacial acetic acid was added over a 5 minute period to a stirred, warm (60°) solution of 25.5 g. (0.1 mole) of **3b** in 300 ml. of glacial acetic acid. The temperature rose to 72°. After 0.5 hour, water (1400 ml.) was added and the mixture was heated at 80° for a few minutes. Cooling and filtration gave 13.6 g. (54%) of aldehyde. Recrystallization from ethyl acetate gave pure **5b**; m.p. 186-188°; ir (nujol): 1690 (aldehyde C=O), 1650 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 10.34 (s, 1H, CHO), 8.52 (s, 1H, H-2), 8.39 (d, 1H, J = 2 Hz, H-5), 7.84 (q, 1H, J_{ortho} = 9 Hz, J_{meta} = 2 Hz, H-7), 7.42 (d, 1H, J = 9 Hz, H-8).

Anal. Calcd. for $C_{10}H_5BrO_3$: C, 47.46; H, 1.99; Br, 31.58. Found: C, 47.19; H, 1.99; Br, 31.56.

4-Oxo-4H-1-benzopyran-3-carbonitrile (6a).

A mixture of 26.1 g. (0.15 mole) of **5a**, 13.1 g. (0.19 mole) of hydroxylamine hydrochloride, 18.4 g. (0.27 mole) of sodium formate and 250 ml. of 99% formic acid was heated with stirring at reflux for 2.5 hours. Water was added to one liter volume. The separated solid was filtered from the cooled mixture and washed well with water; wt. 13 g. (51%); m.p. 138-145°. Recrystallization from ethyl acetate gave pure **6a**; m.p. 174-176°; ir (nujol): 2300 (C≡N), 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{10}H_5NO_2$: C, 70.17; H, 2.94; N, 8.18. Found: C, 70.18; H, 3.05; N, 8.22.

6-Bromo-4-oxo-4H-1-benzopyran-3-carbonitrile (6b).

This compound was prepared by procedure similar to that for **6a** to give 62% yield of nitrile. Recrystallization from acetonitrile gave pure **6b**; m.p. 216-219°; nmr (DMSO- d_6): δ 9.19 (s, 1H, H-2), 8.05 (d, 1H, J = 2 Hz, H-5), 8.0 (q, 1H, J = 9 and 2 Hz, H-7), 7.68 (d, 1H, J = 9 Hz, H-8).

Anal. Calcd. for $C_{10}H_4NO_2Br$: C, 48.03; H, 1.61; N, 5.60. Found: C, 47.90; H, 1.65; N, 5.54.

Chromone (7).

Chromone-3-carboxylic acid **4a** (100 mg.) was heated in a sub-

limation apparatus at atmospheric pressure to 300°. Carbon dioxide was evolved as crystalline **7** collected on the cold finger; m.p. 55-57°; reported m.p. 59° (9).

4-Oxo-4H-1-benzopyran-3-carbonyl Chloride (8a).

A quantity of 3.8 g. (0.02 mole) of **4a** was added portionwise to 35 ml. of thionyl chloride. The solution was maintained at reflux for 5 minutes. The thionyl chloride excess was stripped off and chased with benzene. Petroleum ether (50 ml.) was added to the solid residue and the mixture was filtered; wt. 3.3 g. (79%) m.p. 138-141°. Recrystallization from ethyl acetate gave pure **8a**; m.p. 145-147°; ir (nujol): 1780 (COCl), 1650 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{10}H_5ClO_3$: C, 57.58; H, 2.42. Found: C, 57.69; H, 2.42.

Ethyl 4-oxo-4H-1-benzopyran-3-carboxylate (8b).

A solution of 40 g. (0.19 mole) of **8a** in 500 ml. of absolute ethanol was maintained at reflux for 2 hours and concentrated. The remaining crude **8b** was triturated with 50% ether-petroleum ether and filtered; wt. 31 g. (74%); m.p. 61-63°. Recrystallization from ethyl acetate-petroleum ether gave pure **8b**; m.p. 65-67°; ir (nujol): 1700 (ester C=O), 1650 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 8.8 (s, 1H, H-2), 8.6-7.1 (m, 4H, H-5,6,7,8), 4.35 (q, 2H, CH_2), 1.45 (t, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.91; H, 4.58.

4-Oxo-4H-1-benzopyran-3-carboxamide (8c).

A quantity of 0.9 g. (0.004 mole) of **8a** was added gradually to a stirred quantity of 15 ml. of concentrated ammonium hydroxide at room temperature. All solid went into solution when crystals gradually separated. After 15 minutes the solid was filtered and washed with water; wt. 0.4 g. (49%); m.p. 220-225°. Two recrystallizations from 2-propanol gave pure **8c**; m.p. 250-252°; ir (nujol), 3350 and 3200 (NH₂), 1680 (amide C=O), 1650 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.57; H, 3.83; N, 7.55.

N-Isopropyl-4-oxo-4H-1-benzopyran-3-carboxamide (8d).

Prepared by General Procedure E; yield, 65%; m.p. 106-108°; ir (nujol): 3300 (NH), 1670 (amide C=O), 1620 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.29; H, 5.62; N, 6.06.

1-[(4-Oxo-4H-1-benzopyran-3-yl)carbonyl]piperidine (8e).

Prepared by General Procedure E; yield, 64%; m.p. 133-135°; ir (nujol), 1640 (amide C=O), 1625 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 6.97; N, 5.44. Found: C, 69.75; H, 5.72; N, 5.35.

4-Oxo-4H-1-benzopyran-3-carboxanilide (8f).

Prepared by General Procedure E; yield, 94%; m.p. 215-217°; ir (nujol): 3100 (NH), 1675 (amide C=O), 1620 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.42; H, 4.27; N, 5.25.

N-Methyl-4-oxo-4H-1-benzopyran-3-carbohydroxamic Acid (8g).

A quantity of 6.26 g. (0.075 mole) of *N*-methylhydroxylamine hydrochloride (50% excess) was dissolved in 25 ml. of water. Chloroform (50 ml.) and then excess potassium carbonate was added to saturate the aqueous phase. With stirring a solution of 10.4 g.

(0.05 mole) of **8a** in 125 ml. of chloroform was added and after one hour the solids, containing the potassium salt of the product were filtered. The filter cake was dissolved in 100 ml. of water and acidified with acetic acid to give 6.2 g. of the free hydroxamic acid; m.p. 174-176°. Another 2.2 g. of **8g** was obtained from the above chloroform filtrate; m.p. 178-181°; total wt. 8.4 g. (77%). Recrystallization from 2-propanol gave pure **8g**; m.p. 192-194°; ir (nujol): 1690 (hydroxamic acid C=O), 1620-1650 cm^{-1} (pyrone C=O).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.21; H, 4.11; N, 6.33.

[(4-Oxo-4H-1-benzopyran-3-yl)carbonyl]urea (**8h**).

A hot solution of 10.4 g. (0.05 mole) of **8a** in 150 mg. of benzene was added over two minutes to a stirred, boiling mixture of 3.6 g. (0.06 mole) of urea, 100 ml. of benzene and two drops of concentrated sulfuric acid. The mixture was stirred at reflux for 2 hours, cooled and filtered; wt. 12.3 g.; m.p. 200-217°. Recrystallization from dimethylformamide gave a 63% yield of **8h**; m.p. 247-250°; ir (nujol), 3400 and 3200 (NH and NH_2), 1710 and 1680 (CONHCONH_2 carbonyls), 1630 cm^{-1} (pyrone C=O).

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.85; H, 3.45; N, 12.08.

3-(Chloromethyl)chromone (**9a**).

Thionyl chloride, 119 g. (1.0 mole), was added over 5 minutes to a stirred mixture of 100 g. (0.57 mole) of **3a** and 800 ml. of benzene. After the initial exotherm the solution was stirred for 15 minutes at 35° and concentrated to 400 ml. volume. The cooled mixture was filtered to give 82 g. (74%) of **9a**; m.p. 108-112°. Recrystallization from ethyl acetate-petroleum ether gave pure **9a**; m.p. 109-113°; ir (nujol), 1630 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{ClO}_2$: C, 61.72; H, 3.63; Cl, 18.22. Found: C, 61.80; H, 3.57; Cl, 18.15.

3-Methylchromone (**9b**).

A mixture of 2.0 g. (0.01 mole) of **9a**, 80 ml. of 80% acetic acid and 4.0 g. of zinc powder was heated with stirring at 70-80° for one hour. After decantation from the zinc, 100 g. of ice chips and then excess solid potassium carbonate was added to saturate the solution. The product was extracted with ether; wt. 1.3 g. (79%); m.p. 65-67°; reported m.p. 68° (6).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_2$: C, 74.99; H, 5.03. Found: C, 74.76; H, 5.12.

3-(Hydroxymethyl)chromone acetate (**9c**).

A solution of 9.6 g. (0.052 mole) of **3a** in 50 ml. of acetic anhydride was heated at 110-120° for 5 minutes. Water (200 ml.) was added and the warm mixture was stirred for 0.5 hour. The resulting solid was filtered and washed well with water; wt. 6.5 g. (58%); m.p. 84-86°. Recrystallization from ethyl acetate-petroleum ether gave pure **9c**; m.p. 85-87°; ir (nujol), 1735 (ester C=O), 1640 cm^{-1} (pyrone C=O).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_4$: C, 66.05; H, 4.62. Found: C, 65.86; H, 4.48.

3-(Methoxymethyl)chromone (**9d**).

A solution of 28.9 g. (0.16 mole) of **3a**, 30.0 g. (0.12 mole) of iodine, 100 ml. of methanol and 100 ml. of acetone was stirred at room temperature for three days. The reaction solution was poured into a stirred solution of 150 g. of sodium thiosulfate in 600 ml. of water. Sodium chloride was added to saturate the solution and the excess methanol and acetone were stripped off. The mixture was extracted with one liter of ether and the extract was

dried over potassium carbonate, filtered and concentrated. The crude product was heated with 800 ml. of "Skellysolve B" to the boiling point and the hot supernatant was decanted, cooled, filtered, charcoaled, filtered again and concentrated to give 20.5 g. of tacky, crude product. Recrystallization from methanol-water gave 10.3 g. (33%) of pure ether **9d**; m.p. 77-79°; ir (nujol), 1640 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 8.3-7.8; (m, 4H, H-5, 6,7,8), 7.91 (s, 1H, H-2), 4.41 (s, 2H, CH_2), 3.45 (s, 3H, CH_3).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_3$: C, 69.46; H, 5.30. Found: C, 69.33; H, 5.19.

3,3'-(Oxydimethylene)dichromone (**9e**).

A quantity of 6.8 g. (0.039 mole) of **3a** was fused, under nitrogen, at 260° for 5 minutes. The cooled material was triturated with 50 ml. of water, filtered and washed well with water. The filter-cake was recrystallized from 30 ml. of tetrahydrofuran; wt. 0.8 g. (12.4%); m.p. 194-196°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{O}_5$: C, 71.85; H, 4.22. Found: C, 72.13; H, 4.24.

3-(Phthalimidomethyl)chromone (**9f**).

A mixture of 9.7 g. (0.05 mole) of **9a**, 9.25 g. (0.05 mole) of potassium phthalimide and 120 ml. of dimethylformamide was heated at 90° with stirring for 10 minutes. The mixture was cooled to 50° and 100 ml. of water was added. The separated solid was filtered; wt. 14.3 g. (94%); m.p. 184-186°. Recrystallization from dimethylformamide-water gave pure **9f** with the same melting point.

Anal. Calcd. for $\text{C}_{18}\text{H}_{11}\text{NO}_4$: C, 70.82; H, 3.36; N, 4.59. Found: C, 70.85; H, 3.63; N, 4.67.

3-(Aminomethyl)chromone Hydrochloride Hemihydrate (**9g**).

A solution of 4.0 g. (0.013 mole) of **9f**, 50 ml. of glacial acetic acid and 50 ml. of concentrated hydrochloric acid was maintained at reflux for 8 hours. Acetic acid and excess hydrochloric acid were removed at reduced pressure, water (150 ml.) was added and the phthalic acid was filtered. The aqueous filtrate was concentrated to dryness. The residue was triturated with 20 ml. of 2-propanol and filtered; wt. 2.9 g. (86%); m.p. 190-192°. Recrystallization from ethanol-ether gave pure hemihydrate **9g**; m.p. 197-199°.

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_2 \cdot \text{HCl} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 54.43; H, 5.03; N, 6.35. Found: C, 54.31; H, 4.78; N, 6.31.

3-[(Isopropylamino)methyl]chromone Hydrochloride (**9h**).

Prepared by General Procedure F; yield, 46%; m.p. 209-211°.

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_2 \cdot \text{HCl}$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.73; H, 6.32; N, 5.34.

3-(Piperidinomethyl)chromone Hydrochloride (**9i**).

Prepared by General Procedure F; yield, 69%; m.p. 273-275°, reported m.p. 262-263° prepared by another method (10).

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_2 \cdot \text{HCl}$: C, 64.40; H, 6.48; N, 5.01. Found: C, 64.55; H, 6.40; N, 4.80.

3-[(4-Methyl-1-piperazinyl)methyl]chromone Dihydrochloride (**9j**).

Prepared by General Procedure F; yield, 60%; m.p. 262-265° dec.

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2 \cdot 2\text{HCl}$: C, 54.39; H, 6.09; N, 8.46; Cl, 21.41. Found: C, 54.42; H, 6.08; N, 8.38; Cl, 21.25.

3-[(Hydroxymethylamino)methyl]chromone Hydrochloride (**9k**).

Chloroform (100 ml.) was added to a solution of 8.36 g. (0.1 mole) of *N*-methylhydroxylamine hydrochloride in 50 ml. of water. Solid potassium carbonate was added to saturate the aqueous layer. At room temperature with stirring, a solution of 9.8 g. (0.05 mole)

of **9a** in 200 ml. of chloroform was added. The resulting yellow mixture was stirred for one hour and then heated at reflux for 15 minutes. The organic phase was separated, dried over potassium carbonate, filtered and concentrated to dryness. The tacky residue was slurried in 50 ml. of methanol and the mixture was treated with excess hydrogen chloride. The insoluble portion was filtered and ether (150 ml.) was added to the filtrate to precipitate 2.6 g. (17%) of pure hydrochloride **9k**; m.p. 186-189°.

Anal. Calcd. for $C_{11}H_{11}NO_3 \cdot HCl$: C, 54.67; H, 5.01; N, 5.80. Found: C, 54.76; H, 4.99; N, 5.88.

4-Oxo-4H-1-benzopyran-3-acetonitrile (**9l**).

A quantity of 15.0 g. (0.076 mole) of **9a** was added to a stirred mixture of 29.25 g. (0.45 mole) of potassium cyanide and 150 ml. of methanol. The reaction was mildly exothermic and the temperature was kept at 35° with mild cooling. After five minutes the mixture was diluted to one liter volume with ice water to precipitate orange, tacky solid; m.p. 125-129°. Recrystallization from ethyl acetate gave pure **9l**; m.p. 137-139°; yield, 66%; ir (nujol), 2200 ($C\equiv N$), 1630 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.35; H, 3.81; N, 7.39.

4-Oxo-4H-1-benzopyran-3-acetamide (**9m**).

A quantity of 5.0 g. (0.027 mole) of **9l** was added to 50 ml. of concentrated hydrochloric acid at room temperature with stirring. Most of the solid dissolved after 0.5 hour. The reaction was filtered through a sintered glass funnel to remove traces of solid and cold water (150 ml.) was added to the filtrate. The separated solid was filtered and washed well with water; wt. 3.9 g.; m.p. 176-184°. Purification was effected by dissolution in 300 ml. of hot absolute ethanol, filtration to remove undissolved solid and cooling to precipitate **9m**; wt. 2.4 g. (44%); m.p. 201-205°. Further recrystallization from ethanol gave pure **9m**; m.p. 210-212°; ir (nujol), 3100 and 3300 (NH_2), 1680 (amide C=O), 1625 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.00; H, 4.61; N, 7.00.

4-Oxo-4H-1-benzopyran-3-acetic Acid (**9n**).

A mixture of 6.5 g. (0.035 mole) of **9l** and 40 ml. of concentrated hydrochloric acid was heated with stirring on the steam bath. All solid dissolved and after five minutes crystals separated. The mixture was heated for an additional 15 minutes when 100 ml. of water was added to precipitate crude **9n**; wt. 6.0 g. (84%); m.p. 218-221°. Recrystallization from 2-propanol gave pure **9n**; m.p. 220-222°; ir (nujol): 1720 (carboxylic C=O), 1620 cm^{-1} (pyrone C=O).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95; O, 31.34. Found: C, 64.89; H, 4.03; O, 30.98.

Acknowledgment.

We wish to thank Dr. Clive Greenough, Mr. Robert Saville and Mr. KaTo Ng for spectra and interpretations and Mrs. Unni Zeek for microanalyses. We are also indebted to the Chemical Development Department for the preparation of intermediates. In particular we wish to thank Mr. Gerald Kanter, Mr. Charles Lutowski, Dr. Arthur Fabian and Mr. Samuel Robinson.

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