Synthesis *via* Pummerer Intermediates. IV (1). Synthesis of 1-(4-Hydroxy-2-oxo-2*H*-1-benzopyran-3-yl)pyridinium Hydroxide Inner Salt Derivatives and 3-(2*H*)Benzofuranones by the Action of Phosgene in Pyridine on 2-Hydroxy-1-[(methylsulfinyl)acetyl]benzene Derivatives

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The treatment of ketosulfoxide **1** with phosgene in pyridine gave a mixture of 1-(4-hydroxy-8-methoxy-2-oxo-2*H*-1-benzopyran-3-yl)pyridinium hydroxide inner salt (**4**) and 7-methoxy-2-(methylthio)-3-(2*H*)benzofuranone (**7**). Ketosulfoxides **8** and **11** behaved similarly. The inner salt structure assigned to compounds **4**, **10**, and **13** was confirmed by the unambiguous synthesis of **10** and **13** from hydroxycoumarins **15** and **18**.

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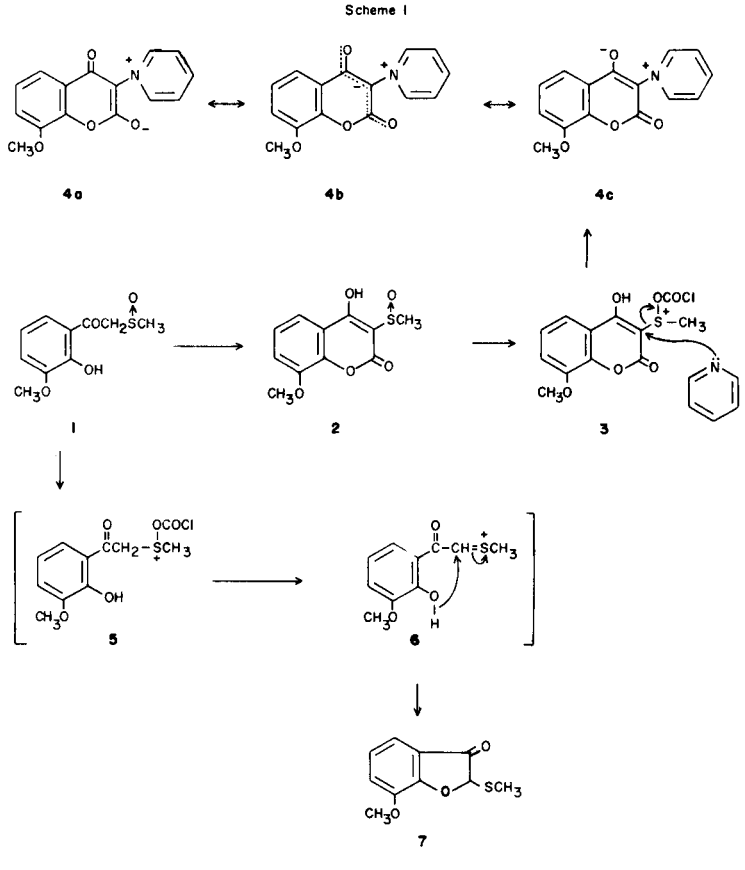
Our continuing interest in the synthesis of heterocyclic systems *via* β-ketosulfoxides (2) and contemporary interest in 3-substituted-4-hydroxycoumarins as antiallergy agents (3) encouraged us to attempt the synthesis of 4-hydroxy-3-methylsulfinylcoumarins by the condensation of 1-(2-hydroxyphenyl)-2-(methylsulfinyl)ethanones with phosgene in pyridine.

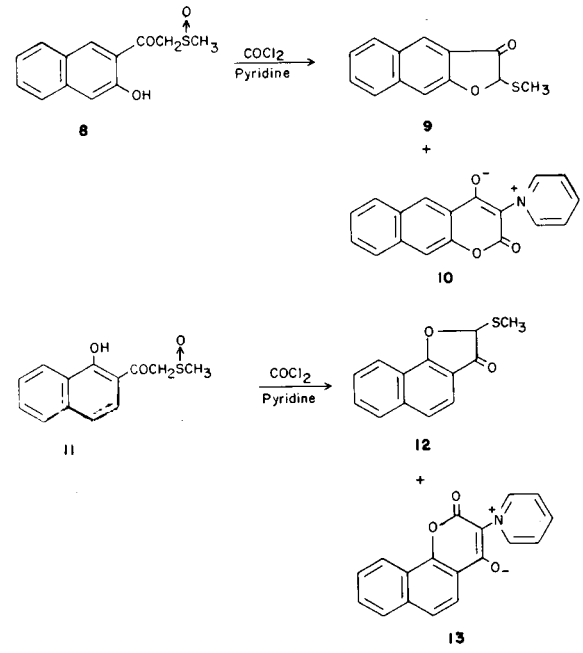
The reaction of sulfoxide **1** with phosgene in pyridine gave a mixture of two products (**4** and **7**). Compound **4**, obtained as yellow crystals, m.p. 295-297°, contains nitrogen but no sulfur by elemental analysis. The infrared spectrum showed carbonyl bands at 1675, 1625 (sh) and 1615 cm^{-1} due to delocalization of the negative charge over carbons 2, 3, and 4 and over the carbonyl oxygens. The ^1H nmr

Scheme I

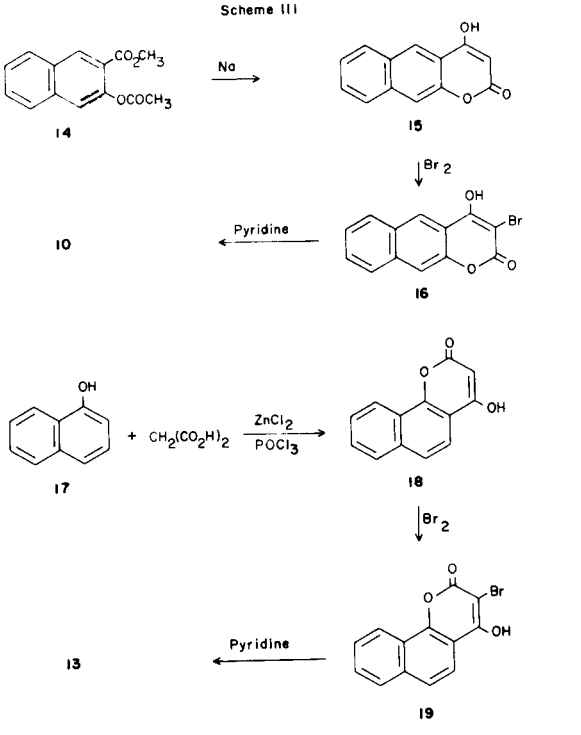


0022-152X/81/030587-04$02.25

Scheme II



Scheme III



spectrum indicated 8 aromatic protons including two at δ 8.9 due to the protons adjacent to the positively charged nitrogen. Protons which would be ascribed to a methyl group attached to a sulfur or sulfinyl group were absent. Thus the inner salt structure **4** was proposed for this compound. The genesis of **4** was probably as shown in Scheme I. Ketosulfoxide **1** was initially converted to the desired 4-hydroxy-3-(methylsulfinyl)coumarin (**2**). The sulfoxide group in **2** then attacked a phosgene molecule to produce Pummerer intermediate **3**. Nucleophilic attack of the pyridine nitrogen at the 3-position of **3**, loss of an electronically neutral sulfur species, followed by loss of hydrogen chloride gave **4**. Compound **7** was identical in all respects (mp, ir, nmr) to 7-methoxy-2-(methylthio)-3-(2*H*)-benzofuranone prepared previously (2) by treating **1** with trifluoroacetic acid in benzene. Compound **7** was formed by intramolecular nucleophilic attack of the phenolic oxygen onto the Pummerer intermediate generated by the reaction of the sulfoxide group with phosgene as shown in Scheme I.

Similarly treatment of ketosulfoxide **8** with phosgene in pyridine gave a mixture of furanone **9** and inner salt **10**. Ketosulfoxide **11** gave a mixture of **12** and **13**.

Inner salts derived from 3-bromo-4-hydroxycoumarin and various substituted pyridines have been described (4), but inner salts **4**, **10**, and **13** are novel compounds. Thus in order to unequivocally establish the inner salt structures assigned to **4**, **10**, and **13**, compounds **10** and **13** were prepared by an unambiguous route. The routes to these compounds are shown in Scheme III. Hydroxycoumarins **15** (5) and **18** (6) were brominated to give bromides **16** and **19**, respectively. The bromides were reacted with pyridine to yield compounds identical in all respects (mp, ir, uv and nmr) to inner salts **10** and **13**. Surprisingly, 4-hydroxy-8-methoxycoumarin is not described in the literature. Attempts to synthesize this compound by several different routes failed to yield any product. Thus the route shown in Scheme I remains the only road to **4** currently available.

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Varian EM 390 or a Bruker WH-90 pulsed Fourier transform instrument at 90 MHz with TMS as internal standard. Infrared spectra were recorded on a Beckman IR-9 or IR-7 prism grating instrument on a Digital FTS-14 interferometer. Ultraviolet spectra were recorded on a Cary Model-118 spectrophotometer.

1-(4-Hydroxy-8-methoxy-2-oxo-2*H*-1-benzopyran-3-yl)pyridinium Hydroxide Inner Salt (**4**) and 7-Methoxy-2-(methylthio)-3-(2*H*)benzofuranone (**7**).

A solution of 12% phosgene in benzene (34 g) was added to a solution of 1-(2-hydroxy-3-methoxyphenyl)-2-(methylsulfinyl)ethanone (11.4 g, 0.05 mole) in pyridine (50 ml). The resulting mixture was heated at 80° for 4 hours. The reaction mixture was cooled and filtered. The residue was recrystallized from *N,N*-dimethylformamide to give 1-(4-hydroxy-8-methoxy-2-oxo-2*H*-1-benzopyran-3-yl)pyridinium hydroxide inner salt (3.1 g, 23%), mp 295-297°; uv (methanol): max 274 (19,200) and 323 (17,600); ir (potassium bromide): 1675 cm^{-1} (CO); nmr (DMSO): δ 8.9 (d, 2, ArH), 8.48 (m, 1, ArH), 8.1 (d, 1, ArH), 8.0 (d, 1, ArH), 7.42 (m, 1, ArH), 7.15 (m, 2, ArH) and 3.85 (s, 3, OMe).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.56; H, 4.20; N, 5.19.

The filtrate was evaporated at reduced pressure to give an oil. The oil on trituration with water gave a solid product. Recrystallization from

ethanol gave 7-methoxy-2-(methylthio)-3-(2*H*)benzofuranone (5.1 g, 48%), mp 103-105° [lit. (2) mp 103-105°].

1-(4-Hydroxy-2-oxo-2*H*-naphtho[2,3-*b*]pyran-3-yl)pyridinium Hydroxide Inner Salt (**10**) and 2-(Methylthio)naphtho[2,3-*b*]furan-3-(2*H*)one (**9**).

A solution of 12% phosgene in benzene (34 g) was added to a solution of 1-(3-hydroxy-2-naphthalenyl)-2-(methylthio)ethanone (12.4 g, 0.05 mole) in pyridine (50 ml). The resulting mixture was heated at 80° for 4 hours. The reaction mixture was cooled and filtered. The residue was recrystallized from *N,N*-dimethylformamide to give 1-(4-hydroxy-2-oxo-2*H*-naphtho[2,3-*b*]pyran-3-yl)pyridinium hydroxide inner salt (2.05 g, 14%), mp 295-297°; uv (methanol): max 234 (52,656), 245 (41,600) and 315 (14,537); ir (potassium bromide): 1675 and 1635 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 8.99-8.58 (m, 4, ArH) and 8.36-7.47 (m, 7, ArH).

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.88; H, 4.20; N, 4.84.

The filtrate was evaporated at reduced pressure to give an oil. The oil crystallized on trituration with water. Recrystallization from ethanol gave 2-(methylthio)naphtho[2,3-*b*]furan-3-(2*H*)one (2.8 g, 24%), mp 118-120° [lit. (2) mp 118-120°].

1-(4-Hydroxy-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-yl)pyridinium Hydroxide Inner Salt (**13**) and 2-(Methylthio)naphtho[1,2-*b*]furan-3-(2*H*)one (**12**).

A solution of 12% phosgene in benzene (34 g) was added to a solution of 1-(1-hydroxy-2-naphthalenyl)-2-(methylsulfinyl)ethanone (12.4 g, 0.05 mole) in pyridine (60 ml). The resulting mixture was heated at 80° for 5 hours. The reaction mixture was cooled and filtered. The residue was recrystallized from *N,N*-dimethylformamide to give 1-(4-hydroxy-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-yl)pyridinium hydroxide inner salt (1.4 g, 10%), mp 300-308°; uv (methanol): max 251 (35,900) and 340 (5,780); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 8.98-7.58 (m, 11, ArH).

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.39; H, 3.98; N, 4.87.

The filtrate was poured into water, an oil precipitated out and became granular on scratching. The solid was washed with ethanol, filtered and dried. Recrystallization from ethyl acetate gave 2-(methylthio)naphtho-[1,2-*b*]furan-3-(2*H*)one (1.9 g, 17%), mp 131-132°; ir (potassium bromide): 1720 cm^{-1} (CO); nmr (deuteriochloroform): δ 8.5-7.5 (m, 6, ArH), 5.8 (s, 1, SCH) and 2.13 (s, 3, SCH_3).

Anal. Calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; N, 13.92. Found: C, 67.53; H, 4.51; N, 13.98.

4-Hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (**15**).

Sodium (1.6 g, 0.07 mole) was added to a stirred mixture of methyl 3-(acetyloxy)-2-naphthalenecarboxylate (7) (10 g, 0.04 mole) in light paraffin oil (60 ml) at 200° under nitrogen. The resulting mixture was stirred at 225° for 2 hours. The mixture was allowed to cool and the excess sodium was decomposed by the addition of a small amount of methanol. The solid was filtered, washed with ether and sucked dry. The product was dissolved in water (200 ml), boiled with charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water and dried. Recrystallization from 2-propanol-water (5:1) gave 4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (1.9 g, 22%), mp 263° dec. (lit. (5) mp 225-230°); uv (methanol): max 225 (48,550), 253 (23,090), 263 (24,190), 274 (19,250), 311 (16,380) and 320 (17,760); ir (potassium bromide): 3060 (OH) and 1685 cm^{-1} (CO); nmr (DMSO): δ 8.40 (s, 1, OH), 8.17-7.34 (m, 6, ArH) and 5.63 (s, 1, C_3-H).

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.49; H, 3.84.

3-Bromo-4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (**16**).

Bromine (1.5 ml) was added to an ice-cold suspension of 4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (0.5 g, 0.0024 mole) in chloroform (20 ml). After stirring for 2 hours, the product was filtered off, washed with chloroform and sucked dry. Recrystallization from acetonitrile gave 3-bromo-4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (0.6 g, 87%), mp 246-247°; uv (methanol): max 230 (50,739), 258 (18,718), 267 (6,214), 279 (13,507) and 327 (17,874); ir (potassium bromide): 3205 (OH) and 1710 cm^{-1} (CO); nmr (DMSO): δ 9.73 (bs, 1, HO), 8.47 (s, 1, ArH), 8.08-7.72 (m, 3, ArH) and 7.63-7.30 (m, 2, ArH).

Anal. Calcd. for $C_{13}H_7BrO_3$: C, 53.64; H, 2.42; Br, 27.45. Found: C, 53,42; H, 2.60; Br, 27.26.

1-(4-Hydroxy-2-oxo-2*H*-naphtho[2,3-*b*]pyran-3-yl)pyridinium Hydroxide Inner Salt (**10**) from **16**.

A solution of 3-bromo-4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-2-one (0.25 g, 0.0009 mole) in pyridine (2.5 ml) was heated under nitrogen at 95-100° for 5 hours. The reaction mixture was cooled. The precipitate was filtered, washed with cold methanol and dried to give 1-(4-hydroxy-2-oxo-2*H*-naphtho[2,3-*b*]pyran-3-yl)pyridinium hydroxide inner salt (0.19 g, 76%), mp 295-297°; uv (methanol): max 233 (52,587), 245 (41,600) and 315 (14,575); ir (potassium bromide): 1675 and 1635 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 8.99-8.58 (m, 4, ArH) and 8.36-7.47 (m, 7, ArH).

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.33; H, 3.88; N, 4.75.

4-Hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**18**).

Phosphoryl chloride (19 ml, 0.2 mole) was added to a mixture of 1-naphthalenol (10 g, 0.069 mole), propanedioic acid (7.2 g, 0.069 mole) and pulverized, freshly fused zinc chloride (23.5 g, 0.172 mole). The mixture was heated at 75° for 38 hours and then allowed to cool. The black residue was shaken with ice-water. The solid was filtered, washed with water and dissolved in sufficient hot saturated aqueous sodium bicarbonate solution to give a basic indication with test paper. The solution was filtered and the filtrate was carefully acidified with dilute sulfuric acid. The precipitate was filtered off, washed with water and dried to give 4-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (7.2 g, 49%). Recrystallization several times from ethanol gave an analytical sample, mp 287° dec. [lit. (6) mp 287-288° dec.]; uv (methanol): max 252 (20,810), 262 (30,260), 272 (38,860), 300 (6200), 312 (6,220), 336 (4,840) and 350 (4,000); ir (potassium bromide): 3060 (OH) and 1675 cm^{-1} (CO); nmr (DMSO): δ 13.48 (bs, 1, OH), 8.29 (m, 1, ArH), 8.08-7.50 (m, 5, ArH) and 5.67 (s, 1, C_3-H).

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.42; H, 3.77.

3-Bromo-4-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**19**).

Bromine (0.5 ml) was added to an ice-cold suspension of 4-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (2 g, 0.009 mole) in chloroform (20 ml). After stirring for 1 hour, the product was filtered off, washed with chloroform and sucked dry. Recrystallization from 2-propanol gave 3-bromo-4-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (1.3 g, 47%), mp 229-230°; uv (methanol): max 221 (49,330), 255 (18,230), 260 (25,270), 276 (31,710), 306 (7,940), 318 (9,180), 339 (6,880) and 353 (4,510); ir (potassium bromide): 3160 (OH) and 1690 cm^{-1} (CO); nmr (DMSO): δ 10.97 (bs, 1, OH), 8.28 (m, 1, ArH) and 8.07-7.50 (m, 5, ArH).

Anal. Calcd. for $C_{13}H_7BrO_3$: C, 53.64; H, 2.42; Br, 27.45. Found: C, 53.58; H, 2.42; Br, 27.27.

1-(4-Hydroxy-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-yl)pyridinium Hydroxide Inner Salt (**13**) from **19**.

A solution of 3-bromo-4-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (2.85 g, 0.01 mole) in pyridine (25 ml) was heated under nitrogen at 95-100° for 5 hours. The reaction mixture was cooled. The precipitate was filtered, washed with cold methanol and dried to give 1-(4-hydroxy-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-yl)pyridinium hydroxide inner salt (2.1 g, 74%). Recrystallization from methanol and then from pyridine gave an analytical sample, mp 300-308° dec.; uv (methanol): max 252 (33,620) and 341 (5,395); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 8.98-7.58 (m, 11, ArH).

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.48; H, 3.90; N, 4.82.

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