Synthesis of 2-Aminochromones. Studies on the Nucleophilic Displacement of Sulphinyl and Sulphonyl Groups in the 2-Position of 5,8-Dimethoxychromone

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Received December 23, 1980

The synthesis is described of a number of *N*-substituted 2-amino-5,8-dimethoxychromones (**1**) by replacement of the sulphoxide group in 2-ethylsulphinyl-5,8-dimethoxychromone (**5a**) with the appropriate amine. Analogous substitution of 2-ethylsulphonyl-5,8-dimethoxychromone (**5b**) is also possible but limited by the instability of the sulphone. Replacement reactions of **5a** involving oxygen, sulphur, and phosphorus nucleophiles are also described.

J. Heterocyclic Chem., **18**, 679 (1981).

A number of methods have been described in the literature for the synthesis of 2-amino-4*H*-1-benzopyran-4-ones (2-aminochromones) and their *N*-substituted derivatives (1). Primary aminochromones have been obtained by cyclisation of (2-hydroxybenzoyl)acetonitriles with base or heat (2), or with hydroxylamine (3), or from reduction of a 2-nitrochromone with sodium dithionite (4). An alternative approach involved hydrogenolysis of the benzyl carbamate obtained from the Curtius rearrangement of chromone-2-carboxylic acid (5). Methylation of the intermediate carbamate led to the *N*-methylamino derivative (6). Rearrangement of chromone-3-carboxaldoxime, or treatment of chromone-3-carbonitrile with ethylenediamine, gave 2-amino-3-formylchromone (7).

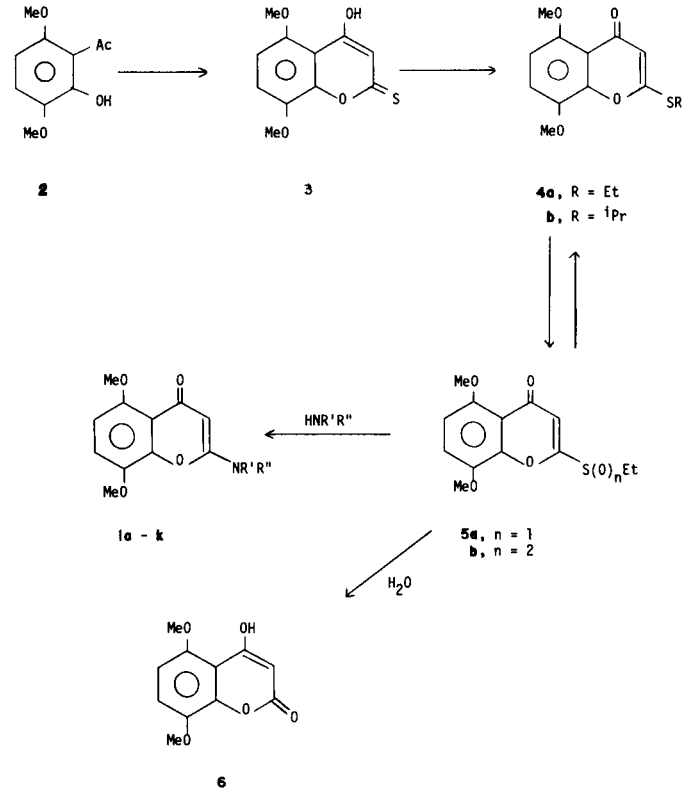
A number of secondary and tertiary amino chromones have been obtained from naphthols and phenols by reaction with an appropriately *N*-substituted ethoxycarbonylacetamide in the presence of phosphorus oxychloride (8). The intermediate phenoxyenamine was cyclised under the reaction conditions to form the γ-pyrone ring.

An alternative approach involves pre-forming the chromone ring with a suitable leaving group in the 2-position, which then by a Michael addition and elimination process is displaced by an amino function. The ready displacement of 2-halochromones (9) (in effect vinylogous acid halides) was utilised in the preparation of a series of *N*-substituted 2-amino-3-hydroxychromones from 2-chloro-3-hydroxychromone (10).

The present paper describes a versatile synthesis of 2-substituted chromones in which sulphinyl acts as the leaving group for nucleophilic displacements. In this way primary, secondary and tertiary amino, alkoxy, phenoxy and alkylthio substituents can be introduced at the 2-position of the chromone nucleus. The corresponding sulphone was also investigated for substitution reactions, but only to a limited extent because of its instability.

We wished to synthesize a number of aminochromones of general structure **1**. As a route to these compounds, nucleophilic displacement of a suitable chromone 2-substituent seemed attractive because it would allow all the compounds to be prepared from a common precursor by reaction with the appropriate amine.

SCHEME I



It was expected that the procedures used to synthesize 2-chlorochromones unsubstituted in the 3-position, which involved either a Fries rearrangement of an aryl β,β-dichloroacrylate (9) or cyclisation of a β-aryloxy-β-chloroacryloyl chloride with aluminium chloride (11), would cause difficulties, including unwanted demethylation, when applied to 2,5-dimethoxyphenol. In the literature

0022-152X/81/040679-06$02.25

there are isolated references to nitro (10), cyano (12), and in the case of an intramolecular displacement, dimethylamino (13), groups in the 2 position of chromones acting as leaving groups to nucleophilic attack. However in nitrogen heterocyclic chemistry displacement of the sulphonyl group by nucleophiles is well documented (14). The sulphinyl group has been used less frequently (15). Since 2-alkylthiochromones are readily prepared from 2-hydroxyacetophenones (16), a route was in principle available to either a 2-alkylsulphinyl or a 2-alkylsulphonyl group, depending on the oxidation conditions. These intermediates were therefore investigated.

Condensation of the acetophenone **2** with carbon disulphide in the presence of potassium *t*-butoxide (17) in benzene gave the thionocoumarin **3** (Scheme 1). The reaction mixture became thick and difficult to stir, which placed a practical limit of about 0.4 mole on the scale of the reaction. Substituting toluene or tetrahydrofuran for the solvent led to lower yields and a less pure product. Alkylation of **3** with iodoethane and potassium carbonate, followed by oxidation of the resulting thio ether **4a** with 2 moles of *m*-chloroperbenzoic acid (MCPBA), yielded the sulphone **5b** as a labile solid which was rapidly hydrolysed by atmospheric moisture to the 4-hydroxycoumarin **6**. If the isolated sulphone was quickly treated with an alkylamine the desired replacement of the sulphonyl group to give the aminochromone took place.

However, it was found that one mole of peracid cleanly gave the sulphoxide **5a**, which was stable for many months in a stoppered bottle at room temperature. Consequently this derivative was used for all subsequent reactions.

The general procedure for the preparation of the 2-aminochromones was to treat the sulphoxide **5a** in acetonitrile at room temperature with an excess of the appropriate amine for 2-24 hours. The arylamino compound (Entry **1k** Table II) required the more forcing conditions of heating at 100° in DMF. In most cases the products, although weak bases (18), could most conveniently be isolated as their hydrochlorides, and then converted to the free base. The results are summarised in Table I.

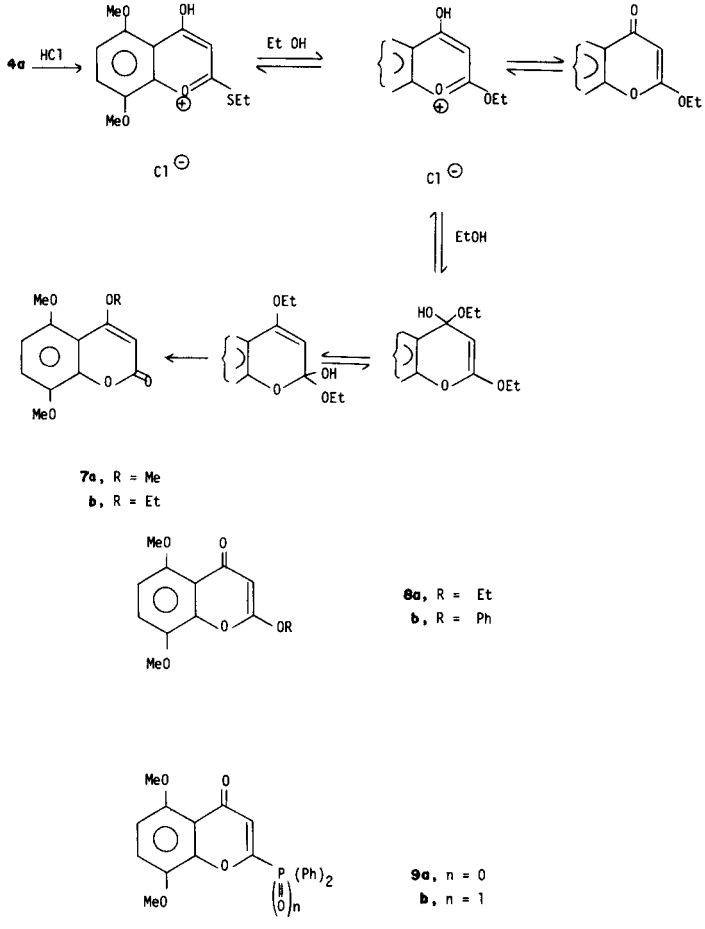
Because of the ease with which the sulphoxide **5a** underwent addition-elimination reactions with amines, its reactions with other nucleophiles were investigated. Reference has already been made to the ready hydrolysis of the sulphone **5b**. The sulphoxide gave the same product **6** after being stirred with 5% sodium hydroxide for 2 days. With propane-2-thiol the sulphoxide gave the sulphide **4b**, identical to that obtained by the alkylation of the thionocoumarin **3** with 2-bromopropane.

With phenolate ion low yields of the 2-phenoxychromone **8b** were obtained, but as a synthetic route the reaction may have utility by providing an alternative strategy for the synthesis of naturally occurring polyalkoxy-2-aryloxychromones (19), since the chromone nucleus can be constructed under basic conditions. To our knowledge the only other 2-aryloxychromone synthesis so far reported (19b) utilised a 2-chlorochromone to give a Capillarisin constituent.

An attempt to substitute the ethylsulphinyl group by a phosphorus nucleophile met with only limited success. Diphenylphosphine was deprotonated with potassium *t*-butoxide (20) and the resulting anion reacted with the ethylsulphinylchromone **5a**. A mixture was obtained which decomposed during an attempt to separate the components. Mass spectroscopy and nmr implied that the 2 major constituents of the mixture were the expected phosphine **9a** and the corresponding phosphine oxide **9b**.

The reaction of the sulphoxide **5a** and an equivalent of sodium ethoxide gave, not the expected 2-ethoxychromone, but 4-hydroxycoumarin **6** as the major component (tlc evidence) of a mixture. Possibly **6** arose from a competing reaction by hydroxyl ion generated from the water resulting from the subsequent reactions of the displaced sul-

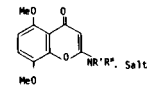
SCHEME II



phenate anion and alkoxide (15). The 2-ethoxy compound **8a** was obtained, however, by reaction of sulphoxide **5a** with ethanol in the presence of potassium cyanide. No reaction took place in the absence of cyanide ion. Possibly under these conditions the 2-cyanochromone is formed as an intermediate and the nitrile group is then replaced by ethoxide ion. Facile nucleophilic displacement of a 2-cyano-3-chlorochromone has been reported (12). In principle therefore, by using the appropriate alcohol it should be possible to introduce other alkoxy groups into the 2-position. Previously, 2-alkoxychromones have been obtained from 4-hydroxycoumarins by alkylation with trimethyl or triethyloxonium tetrafluoroborate (22), or by alkylation with diazomethane and separation of the isomer mixture (23).

Table I

Physical Properties of the Salts of Amines **1a-k**



Compound No.	R'	R''	Yield	M.p.°	Formula of Salt	Analysis (%) Calcd./(Found) C	H	N	Cl	IR cm^{-1} (C=O)	UV λ max (log ε)	^{1}H-NMR (δ) H-3 (DMSO) (a)
1a	H	H	64 (b)	209-211	$C_{11}H_{11}NO_4 \cdot H_2SO_4 \cdot 0.5\ H_2O$	40.2 (40.1)	4.0 (4.25)	4.3 (4.4)	9.8 (c) (10.2)	1655	233 (4.29) 292 (3.94)	6.05
1b	H	Me	76	178-180	$C_{12}H_{13}NO_4 \cdot HCl \cdot 0.5\ H_2O$	51.3 (51.4)	5.05 (5.3)	5.0 (4.8)		1650	234 (4.30) 300 (4.00)	6.37
1c	H	Et	70	178-179	$C_{13}H_{15}NO_4 \cdot HCl \cdot 0.5\ H_2O$	53.0 (52.8)	5.5 (5.7)	4.7 (4.6)	12.05 (12.3)	1650	236 (4.34) 305 (4.03)	6.46
1d	H	*n*-Pr	68	175-176	$C_{14}H_{17}NO_4 \cdot HCl$	56.1 (56.5)	6.05 (6.2)	4.7 (4.7)	11.8 (11.7)	1655	236 (4.34) 360 (4.07)	6.5
1e	H	*n*-Bu	78	166.5-168	$C_{15}H_{19}NO_4 \cdot HCl$	57.4 (57.8)	6.4 (6.5)	4.45 (4.2)	11.35 (11.3)	1655	236 (4.33) 301 (4.02	6.9
1f	H	$-CH_2CHMe_2$	74	183-184	$C_{15}H_{19}NO_4 \cdot HCl$	57.4 (57.8)	6.4 (6.6)	4.45 (4.55)	11.3 (11.2)	1660	236 (4.34) 305 (4.06)	6.54
1g	H	$-CH_2Ph$	28 (d)	140-141	$C_{16}H_{17}NO_4 \cdot HCl \cdot 1.5\ H_2O$	57.6 (57.7)	5.6 (5.5)	3.7 (3.6)	9.5 (10.3)	1650	237 (4.33) 300 (4.06)	6.40
1h	Me	Me	84 (e)	196 dec.	$C_{13}H_{15}NO_4 \cdot HCl \cdot 0.25\ H_2O$	58.8 (53.85)	5.4 (5.75)	4.8 (5.1)	12.2 (12.2)	1645	237 (4.38) 310 (4.07)	6.25
1i	$-(CH_2)_4-$		81	209-210 dec.	$C_{15}H_{17}NO_4 \cdot HCl$	57.8 (58.1)	5.8 (6.0)	4.5 (4.85)	11.4 (11.35)	1645	238 (4.37)	6.02
1j	$-(CH_2)_2N(Me)(CH_2)_2-$		69 (d)									
1k	H	$-C_6H_4OMe$ (*p*)	45 (d)	206	$C_{18}H_{17}NO_5 \cdot HCl \cdot 0.5\ H_2O$	57.8 (58.0)	5.1 (5.3)	3.7 (3.6)	9.5 (9.2)	1655	330 (4.23)	6.35

(a) All H-3 protons exchanged on addition of deuterium oxide. (b) Isolated as bisulphate salt. Yield, m.p., and analytical data refer to this salt. (c) Analysis figure for sulphur. (d) Yield of free base. (e) Recrystallized from ethanol.

Table II

Physical Properties of Amines **1a-k**

Compound No.	M.p.°	Recrystallization Solvent	Analysis (%) Calcd./(Found) C	H	N	IR (cm^{-1}) (C=O)	UV λ max (log ε)	^{1}H NMR (δ) H-3 (deuteriochloroform)
1c	155-156.5	toluene	62.6 (62.3)	6.1 (6.2)	5.6 (5.4)	1640	245 (4.40) 300 (4.09)	5.3
1e	110-111		63.9 (a) (63.9)	7.0 (a) (6.9)	5.0 (a) (5.3)	1640	235 (4.32) 300 (4.02)	5.3
1g	136-137	toluene	69.4 (69.4)	5.5 (5.6)	4.5 (4.6)	1640	236 (4.33) 300 (4.06)	5.33
1h	127-130	benzene	59.4 (b) (59.7)	6.3 (b) (6.1)	5.3 (b) (5.0)	1630	239 (4.25) 315 (3.96)	5.32
1i	173-175		65.4 (65.1)	6.2 (6.4)	5.1 (5.4)	1640	240 (4.37) 315 (4.12)	5.20
1j	123	benzene-petroleum ether	61.4 (c) (61.55)	6.7 (c) (6.9)	8.95 (c) (8.6)	1635	238 (4.38) 303 (4.11)	5.43
1k	252-253	ethanol-water	66.05 (66.1)	5.2 (5.4)	4.3 (4.6)	1645	329 (4.26)	5.26

(a) Calcd. for 0.25 H_2O. (b) Calcd. for 0.75 H_2O. (c) Calcd. for 0.5 H_2O.

The isomeric 4-ethoxy coumarin **7b** was unexpectedly obtained from the thio ether **4a** and ethanolic hydrogen chloride, presumably via a series reversible reactions involving pyrilium salts eventually leading to **7b** (Scheme II). Since in contrast to 2-alkoxy chromones, 4-alkoxycoumarins are reported to be insufficiently basic to form pyrilium salts (21), the last step would be expected to be irreversible, and the reaction would therefore proceed to give entirely coumarin **7b**.

Hence from two closely related 2-substituted intermediates, a sulphide and a sulphoxide, it is possible to direct alkoxylation of a benzopyrone ring at will to give either a 2- or 4-alkoxy derivative.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer Model 457 grating specctrophotometer using potassium bromide discs, and uv spectra were measured in ethanol. Proton magnetic resonance spectra were determined on a Perkin Elmer R12 spectrometer using TMS as internal standard and deuteriochloroform as solvent, except where stated. Mass spectra were recorded on a Hitachi Perkin Elmer RMU-6 spectrometer. Thin layer chromatography was carried out on Merck silica gel GF 254 precoated plates.

4-Hydroxy-5,8-dimethoxy-2-thio-2*H*-1-benzopyran (**3**).

To a stirred suspension of potassium *t*-butoxide (134 g., 1.2 moles) at 15° in dry benzene (1 l.) under dry nitrogen was slowly added a solution of 3,6-dimethoxy-2-hydroxyacetophenone (78.6 g., 0.4 mole) and carbon disulphide (30.4 g., 0.4 mole) in benzene (700 ml.) with cooling to maintain the reaction temperature between 15-22°. The yellow viscous mixture was stirred at room temperature overnight, and then poured into water (10 l.). The aqueous phase was separated, washed with ether, cooled to below 5°, acidified slowly with 10% ice-cold sulphuric acid and stirred overnight in a fume hood to remove hydrogen sulphide. The precipitate was filtered off and washed well with hot petroleum ether (b.p. 60-80°) to give **3** (83 g., 86%) as a pale yellow solid, m.p. 220-221°, running on tlc (chloroform) as a single spot (Rf, 0.3). A suitable solvent for recrystallization was not found, possibly because of disulphide formation on heating, nor was a satisfactory C and H elemental analysis obtained. Spectral details were consistent with the structure; pmr: δ 3.82 (3H, s), 3.85 (3H, s), 6.60 (1H, s), 6.9 (1H, d, J = 9 Hz), 7.35 (1H, d, J = 9 Hz); ms: m/e 238 (M^+); ir: max 1635 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}O_4S$: S, 13.4. Found: S, 13.1.

2-Ethylthio-5,8-dimethoxy-4*H*-1-benzopyran-4-one (**4a**).

To a stirred suspension of sodium hydride (0.48 g. of a 50% dispersion, washed free from oil, 0.01 mole) in dry DMF (20 ml.) under nitrogen was added **3** (2.45 g., 0.01 mole). After 5 minutes, iodoethane (2 ml.) was added and the mixture was heated at 95° for 2 hours. The mixture was evaporated, treated with dilute hydrochloric acid and extracted with ethyl acetate, which was dried and evaporated to a solid. The solid was crystallized from toluene-petroleum ether (b.p. 60-80°) to afford **4a** (1.4 g., 53%) as needles, m.p. 125-126°; pmr: δ 1.41 (3H, t, J = 7 Hz), 3.04 (2H, q, J = 7 Hz), 3.87 (6H, s), 6.16 (1H, s), 6.68 (1H, d, J = 9 Hz), 7.04 (1H, d, J = 9 Hz); ir: max 1655 cm^{-1}; ms: m/e 266 (M^+); uv: λ max (log ε) 254 (4.17), 278 (4.10), 330 (3.77).

Anal. Calcd. for $C_{13}H_{14}O_4S$: C, 58.6; H, 5.3; S, 12.0. Found: C, 58.4; H, 5.3; S, 12.3.

On a larger scale the following procedure was more convenient.

A stirred mixture of **3** (11.8 g., 0.05 mole), potassium carbonate (7.0 g., 0.051 mole), and iodoethane (10 ml.) in acetone (100 ml.) was refluxed for 3 hours, and then filtered while hot. The filtrate was evaporated and the residue was partitioned between water and chloroform. Evaporation of the organic layer and recrystallization as before gave **4a** (8.8 g., 66%), m.p. 124-126°.

5,8-Dimethoxy-2-(1-methylethyl)thio-4*H*-1-benzopyran-4-one (**4b**).

By a procedure analogous to the prepartion of **4a**, the thioether **4b** was obtained from **3**, 2-bromopropane, and sodium hydride in DMF, as an amorphous solid (41%), m.p. 75°; pmr: δ 1.44 (6H, d, J = 7 Hz), 3.7 (1H, mult.), 3.87 (6H, s), 6.24 (1H, s), 6.46 (1H, d, J = 9 Hz), 7.07 (1H, d, J = 9 Hz); ir: max 1640 cm^{-1}; ms: m/e 280 (M^+); uv: λ max (log ε) 255 (4.15), 280 (4.10), 335 (3.77).

Anal. Calcd. for $C_{14}H_{16}O_4S$: C, 60.0; H, 5.75; S, 11.4. Found: C, 59.6; H, 5.5; S, 11.4.

2-Ethylsulphonyl-5,8-dimethoxy-4*H*-1-benzopyran-4-one (**5b**).

Thioether **4b** (0.5 g., 1.88 mmoles) in 1,2-dichloroethane (10 ml.) at 0° was treated with *m*-chloroperbenzoic acid (MCPBA) (0.84 g., 85% pure, 4.14 mmoles) with stirring. The mixture was allowed to warm to room temperature and stirring was continued for 20 hours with the addition of a further quantity of MCPBA (0.5 g., 2.46 mmoles) after 1 hour. The mixture was poured into a mixture of ice-cold water and chloroform. The organic layer was separated and washed with cold dilute aqueous sodium bicarbonate solution, dilute aqueous sodium metabisulphite solution, and water. Drying (sodium sulphate) and evaporation yielded an orange oil which was triturated with ether and cooled. The resulting orange solid (70 mg., 12.5%) was filtered off and shown to be pure sulphone **5b**, but substantial decomposition occurred within 24 hours. Consequently, only C and H analyses were obtained; pmr: δ 7.18 (1H, d, J = 9 Hz), 6.77 (1H, d, J = 9 Hz), 6.92 (1H, s), 3.9 (6H, s), 3.34 (2H, q, J = 8 Hz), 1.40 (3H, t, J = 8 Hz); ms: m/e 298 (M^+).

Anal. Calcd. for $C_{13}H_{14}O_6S$: C, 52.4; H, 4.7. Found: C, 52.8; H, 4.7.

2-Ethylamino-5,8-dimethoxy-4*H*-1-benzopyran-4-one Hydrochloride (**1c**).

The sulphone **5b** (20 mg., 0.067 mole) was stirred at room temperature overnight with dry acetonitrile (2 ml.) and ethylamine (5 drops: excess) in a stoppered flask. The solution was evaporated under reduced pressure and the residue was dissolved in ether (5 ml.). Saturated ethanolic hydrogen chloride was added and the mixture was diluted to 100 ml. total volume with ether, and cooled to -20° to afford the hydrochloride of the amine **1c** (12 mg., 63%), m.p. 175-177°. The material was identical (spectra and tlc evidence) to that obtained from the sulphoxide **5a**.

2-Ethylsulphinyl-5,8-dimethoxy-4*H*-1-benzopyran-4-one (**5a**).

A suspension of *m*-chloroperbenzoic acid (10.0 g., 85% pure, 0.049 mole) in dry 1,2-dichloroethane was slowly added to a stirred solution of **4a** (12.6 g., 0.047 mole) in 1,2-dichloroethane (220 ml.) at 0°. After 1.5 hours the mixture was filtered, and the filtrate was washed successively with cold 5% sodium carbonate solution, saturated sodium bisulphite solution, and water, dried, and evaporated. The residue was crystallized from dry benzene-petroleum ether (b.p. 60-80°) to afford **5a** (9.8 g., 74%), m.p. 158-159°; pmr: δ 1.35 (3H, t, J = 8 Hz), 3.2 (2H, m), 3.90 (6H, s), 6.77 (1H, d, J = 9 Hz), 6.82 (1H, s), 7.18 (1H, d, J = 9 Hz); ir: max 1655 cm^{-1}; ms: m/e 282 (M^+); uv: λ max (log ε) 260 (4.24), 345 (3.66).

Anal. Calcd. for $C_{13}H_{14}O_5S$: C, 55.3; H, 5.00; S, 11.3. Found: C, 55.4; H, 5.1; S, 11.1.

Reaction of Sulphoxide **5a** with Amines: Representative Procedure.

To the sulphoxide **5a** (1.41 g., 5 mmoles) dissolved in warm acetonitrile (35 ml.) was added an excess of *n*-butylamine (3 ml.). After 16 hours at room temperature the solution was evaporated to yield a solid, which was washed with petroleum ether (b.p. 40-60°). The solid was dissolved in a minimum of 2-propanol and treated with an excess of ethereal hydrogen chloride. On cooling a precipitate was obtained which was collected and washed well with dry ether to yield the hydrochloride of the amine **1e** (1.23 g.).

The salts (Table I), with the exception of **1h**, were analytically pure from this procedure. In the case of **1j** only one equivalent of *N*-methylpiperazine was used, and at the end of the reaction the mixture was treated with dilute hydrochloric acid, washed with ether, and then basified with 5% sodium hydroxide. Extraction with chloroform and evaporation afforded the free base **1j** as a solid, which was recrystallized from ethanol.

For compounds **1a** and **1b**, an excess of a solution of isopropyl alcohol saturated with ammonia and an excess of a 33% solution of methylamine in ethanol, respectively, were used as the amine reagents.

The free bases **1c,e,g-i** (Table II) were obtained from their salts by treatment with aqueous sodium hydrogen carbonate and extraction, followed by crystallization where appropriate.

2-(4-Methoxyphenylamino)-5,8-dimethoxy-4*H*-1-benzopyran-4-one (**1k**).

A mixture of **5a** (1.41 g., 0.005 mole), *p*-methoxyaniline (0.62 g., 0.005 mole) and dry DMF was heated at 100° for 2 days, and then poured into water to give a solid. The solid was chromatographed on silica gel with chloroform-methanol (12:1) to give, after crystallization from aqueous ethanol, the arylamine **1k** (0.73 g., 45%); ms: m/e 327 (M^+).

Hydrolysis of **5a**.

Sulphoxide **5a** (0.050 g.) was stirred with 5% sodium hydroxide (2 ml.) for 2 days at room temperature. The solution was acidified and extracted with ethylacetate, which was washed with water, dried and evaporated to give a solid (0.020 g., 51%), m.p. 191-192° undepressed on admixture of **6**, and possessing identical tlc and spectral characteristics to **6**.

Reaction of Sulphoxide **5a** with 2-Methylethylthiol.

The sulphoxide **5a** (0.56 g., 2 mmoles), 2-methylethylthiol (0.40 g., 0.5 ml., 5.4 mmoles) and Triton B (2 drops) in dry acetonitrile (10 ml.) were stirred at room temperature for 18 hours. The product was poured into water and extracted with chloroform, which was washed with dilute aqueous sodium bicarbonate solution (to remove some **6** formed as by-product) and water, dried, and evaporated to yield a yellow oil. Recrystallization from petroleum ether (b.p. 40-60°) gave the isopropylthiochromone as a pale yellow solid (0.38 g., 68%), m.p. 76-77°, identical (spectral and tlc properties) to **4b** prepared from thiocoumarin **3**.

5,8-Dimethoxy-2-phenoxy-4*H*-1-benzopyran-4-one (**8b**).

To a stirred suspension of sodium hydride (0.17 g. of a 50% suspension, 3.5 mmoles), washed free from oil, in dry dioxan (10 ml.) was added dropwise a solution of phenol (0.33 g., 3.5 mmoles) in dry dioxan (5 ml.). The resulting solution was added dropwise with stirring to a solution of the sulphoxide **5a** (1.0 g., 3.5 mmoles) in dioxan (10 ml.) at 10-15°. The mixture was stirred at room temperature for 1 hour and then poured into dilute aqueous hydrochloric acid and extracted into ethyl acetate. The organic extracts were combined and washed with water, dilute aqueous sodium bicarbonate solution, water and then dried (anhydrous sodium sulphate) to yield a solid which was recrystallized from ethanol to give **8b** (0.20 g., 19%), m.p. 115-117°; pmr: δ 3.95 (6H, s), 5.34 (1H, s), 6.75 (1H, d, J = 9 Hz), 7.12 (1H, d, J = 9 Hz), 7.1 to 7.6 (5H, m); ms: m/e 298 (M^+); uv: λ max (log ε) 235 (4.407), 330 (3.762).

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.7. Found: C, 68.1; H, 5.0.

4-Hydroxy-5,8-dimethoxy-2*H*-1-benzopyran-4-one (**6**).

To a stirred suspension of sodium hydride (4.5 g. of a 50% dispersion, freed from oil, 0.094 mole) and diethyl carbonate (35 g., 0.3 mole) in dry toluene (80 ml.) was slowly added the acetophenone **2** (5.9 g., 0.03 mole) in toluene (50 ml.). The mixture was refluxed for 2 hours, and then distilled to about half volume over 3 hours. After cooling, water was added cautiously and the layers were separated. From the toluene layer, unchanged **2** was recovered. The aqueous layer was acidified to give an oily solid, which was extracted with ethyl acetate. Evaporation and recrystallization from ethanol gave **6** (2.4 g., 74% based on recovered acetophenone), m.p. 193.5-194.5°; pmr: δ 3.85 (3H, s), 3.98 (3H, s), 5.62 (1H, s), 6.65 (1H, d, J = 9 Hz), 7.00 (1H, d, J = 9 Hz); ms: m/e 222 (M^+); ir: max 3220, 1705 cm^{-1}; uv: λ max (log ε) 232 (4.20), 252 (3.91), 300 (4.00).

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.5. Found: C, 59.3; H, 4.3.

4,5,8-Trimethoxy-2*H*-1-benzopyran-2-one (**7a**).

To a stirred refluxing mixture of **6** (1.98 g., 0.01 mole) and anhydrous potassium carbonate (1.5 g., 0.011 mole) in dry acetone (50 ml.) was added dimethylsulphate (1.35 g., 0.011 mole) over 0.5 hour. The mixture was heated for a further hour, and then filtered. The filtrate was evaporated, and the residue was crystallized from ethanol to give **7a** as a pale yellow solid (1.5 g., 73%), m.p. 176-177°; pmr: δ 3.30 (3H, s), 3.8 (3H, s), 3.93 (3H, s), 5.60 (1H, s), 6.62 (1H, d, J = 9 Hz), 7.10 (1H, d, J = 9 Hz); ms: m/e 236 (M^+); ir: max 1695 cm^{-1}; ms: m/e 236 (M^+); uv: λ max (log ε) 258 (3.96), 293 (3.98), 330 (3.51).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 60.9; H, 5.2.

Reaction of **4a** with Methanolic Hydrogen Chloride.

A solution of methanol saturated with hydrogen chloride (3 ml.) was added to a solution of **4a** (0.2 g.) in methanol (3 ml.). After 20 hours at room temperature the solution was evaporated to a solid, which was washed with dilute sodium bicarbonate solution, and then water, to leave needles (0.14 g.), m.p. 173-174°, undepressed on admixture of **7a**. Tlc and spectral characteristics were identical to those of **7a**.

Reaction of **4a** with Ethanolic Hydrogen Chloride.

In a similar manner to the 4-methoxy compound, **4a** and ethanolic hydrogen chloride gave the 4-ethoxy derivative **7b** (35%), m.p. 157-158°; pmr: δ 1.49 (3H, t, J = 7 Hz), 3.78 (3H, s), 3.85 (3H, s), 4.10 (2H, q, J = 7 Hz), 5.55 (1H, s), 6.6 (1H, d, J = 9 Hz); 7.0 (1H, d, J = 9 Hz); ir: max 1710 cm^{-1}; ms: m/e 250 (M^+); uv: λ max (log ε) 258 (3.95), 290 (3.95).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.6; H, 5.8.

2-Ethoxy-5,8-dimethoxy-4*H*-1-benzopyran-4-one (**8a**).

A mixture of **5a** (0.282 g., 1 mmole), potassium cyanide (0.080 g., 1.2 mmoles), ethanol (2 ml.), and acetonitrile (7 ml.) was stirred for 16 hours, then diluted with water and extracted with ethyl acetate. Evaporation gave a solid which was crystallized from toluene to give **8a** (0.070 g., 28%), m.p. 158-159°; pmr: δ 1.46 (3H, t, J = 7 Hz), 3.90 (6H, s), 4.19 (2H, q, J = 7 Hz), 5.50 (1H, s), 6.70 (1H, d, J = 9 Hz), 7.05(1H, d, J = 9 Hz); ir: max 1650 cm^{-1}; ms: m/e 250 (M^+); λ max (log ε) 235 (4.39), 330 (3.77).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.7; H, 5.8.

Acknowledgement.

The authors wish to thank Mr. J. Fuher and Mr. J. Shipman for excellent technical assistance, Dr. J. Dixon for helpful discussions, and Mr. N. Gensmantel for p*K*a measurements.

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