Benzopyrones. Part 19.[1] Synthesis and some Reactions of Ethyl 3-Bromo-4-oxochromen-2-carboxylate

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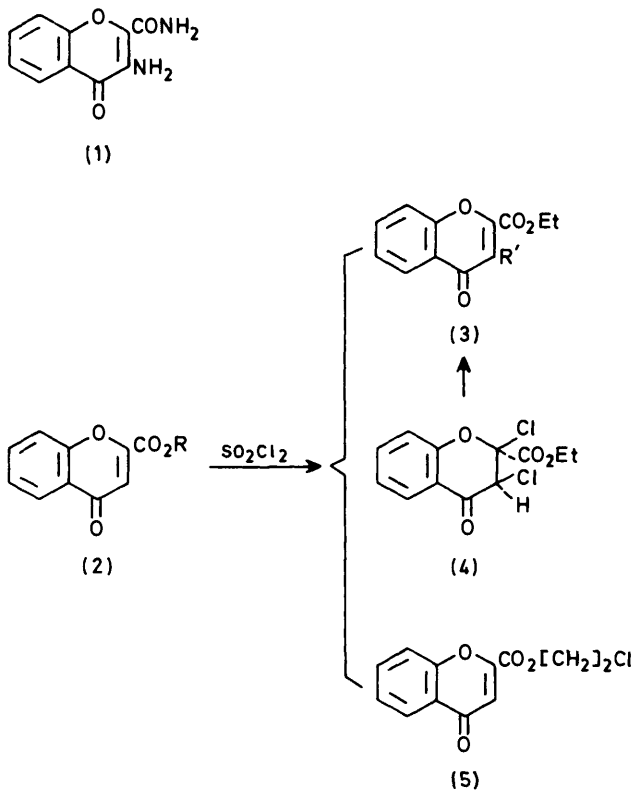
The product of the condensation of *o*-hydroxyacetophenone and diethyl oxalate, ethyl 2-hydroxy-4-oxochroman-2-carboxylate (13), slowly and partially isomerises in solution to the phenolic ketone (16), but in the presence of mineral acid, it is rapidly dehydrated directly to ethyl 4-oxochromen-2-carboxylate (2; R = Et). Bromination of the oxochroman (13) gave a 72 : 28 mixture of epimeric 3-bromo-esters. The major isomer (*trans*-OH, H) was readily dehydrated to give the title compound which contains a reactive bromine atom.

The synthesis of 3-amino-4-oxochromen-2-carboxamide (1) has been described.[2] Its formation from ethyl 3-chloro-4-oxochromen-2-carboxylate (3; R′ = Cl) occurs under mild conditions but this is one of three compounds formed simultaneously when ethyl 4-oxochromen-2-carboxylate (2; R = Et) is treated with sulphuryl chloride (Scheme 1).[2] This route to the amino-carboxamide is therefore not convenient for the preparation of moderately large quantities of the compound. We now describe other approaches to the amino-carboxamide (1).

In the original synthesis,[2] an appreciable amount of ethyl 4-oxochromen-2-carboxylate was lost by its conversion into 2-chloroethyl 3-chloro-4-oxochromen-2-carboxylate (5). This loss is avoided by chlorination of the methyl ester (2; R = Me) which gave, on treatment with hot pyridine [to decompose the 2,3-dichlorochromanone (4)], a good yield of methyl 3-chloro-4-oxochromen-2-carboxylate (6) but a suspension of this ester in methanol reacted with gaseous ammonia to give a poor yield of the amino-carboxamide. The chloro-ester was more soluble in methanol–dichloromethane (1 : 1) but similar treatment of this gave a high yield of 3-chloro-4-oxochromen-2-carboxamide (7). Passage of ammonia through an acetone solution of the chloro-ester gave the Schiff's base (8) (Scheme 2) which resisted acid hydrolysis to the amine (1). Application of the copper-catalysed amination [3] of the chlorine atom of ester (3; R′ = Cl) gave poor results. From these experiments, it appeared that displacement of the chlorine atom was less facile than amination of the alkoxycarbonyl group.

Attention was then turned to the possibility of preparing the bromo analogue of the ester (3) which would be expected to be more reactive. Gammill [4] recently synthesized 3-bromo-2-methylchromen-4-one in good yield from 2-methylchromen-4-one by reaction with pyrrolidine [*via* the enamine (9)] followed by bromine and mineral acid (Scheme 3, $R^1 = R^2 =$ Me). When ethyl 4-oxochromen-2-carboxylate was subjected to similar treatment, a low overall yield of the bromocarboxamide [10; $R^2 = CON(CH_2)_4$] was obtained and its conversion into the carboxylic acid or ester was not considered to be worthwhile.

Ethyl 4-oxochromen-2-carboxylate is usually prepared by the condensation of *o*-hydroxyacetophenone with diethyl oxalate, and the diketone (11a) or its enol is generally regarded as the product of this reaction.[5] Replacement of a hydrogen of the methylene group by alkyl,[6] acyl,[7] hydroxyalkyl,[7] and aminomethyl [2,7] groups has been described but halogenation does not seem to have been recorded. With this aim in mind, we isolated the condensation product by treatment of the sodium salt of (11a) with dilute sulphuric acid at *ca.* −5 °C. The i.r. and n.m.r. spectra of the freshly prepared product showed it to have the isomeric cyclic structure (13) similar to

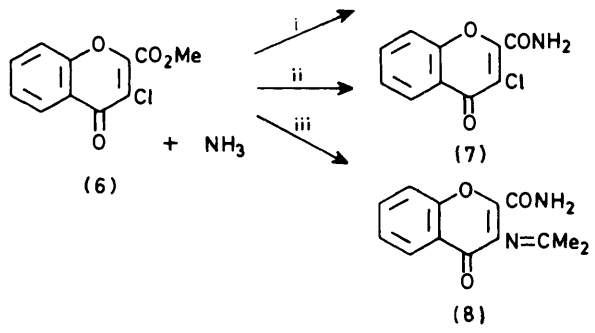


Scheme 1.

that proposed by Trowitzsch.[8] The corresponding trifluoromethyl analogue (15) also exists in the cyclic form.[9] When a solution of the chromanone (13) in deuteriochloroform was allowed to stand at 20 °C, it partially isomerized into the diketone (11a), 18% and 25% of this isomer being present after 24 and 96 h respectively, by which time equilibrium had been attained. The methyl ester (14) isomerized to a greater extent, 12% of the acyclic form being present within the few minutes taken to observe the n.m.r. spectrum and equilibrium (42% of diketone) being reached within 20 h. The presence of the hydrogen bonded diketone (16) was measured by the intensity of the (phenolic OH) signal at δ 11.74 (Table).

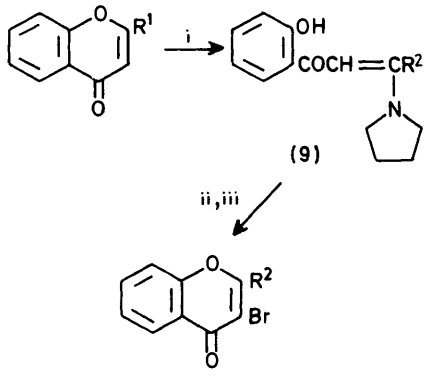
For spectral comparison, the acetate (11b) was synthesized from 2-acetoxyacetophenone. In contrast to the usual procedure, the diketone was formed in good yield in the presence of as little as 0.25 molar equivalent of base. This may be

(1)



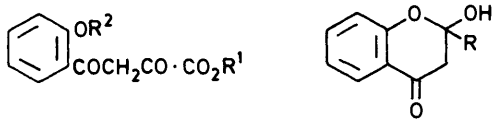
(6) (7) (8)

Scheme 2. *Solvents:* i, MeOH; ii, CH_2Cl_2–MeOH; iii, Me_2CO



(9) (10)

Scheme 3. *Reagents:* i, pyrrolidine; ii, Br_2–$CHCl_3$; iii, dil. HCl



(11a) R^1 = Et, R^2 = H
(11b) R^1 = Et, R^2 = Ac
(12) R^1 = Me R^2 = H

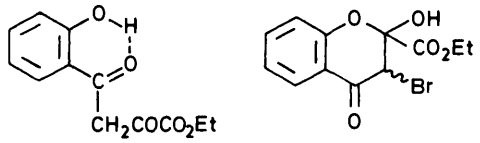
(13) R = CO_2Et
(14) R = CO_2Me
(15) R = CF_3

explained by the formation of more ethoxide ion by attack of the anion derived from 2-acetoxyacetophenone on the diester. When an excess of base was present, there was a tendency for the acetate group to be removed. The diketone (11b) in deuteriochloroform existed entirely in the enol form (δ 12.2, chelated OH) and gave a deep violet colour with methanolic iron(III) chloride. The acetate (11b) was stable to boiling ethanolic hydrochloric acid but when heated with an excess of sodium ethoxide and then acidified at low temperature, it gave the chroman ester (13).

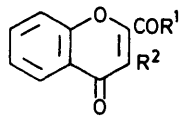
Dehydration of the chroman ester (13) with hot mineral acid gave the chromone (2; R = Et). It is possible for this conversion to proceed directly or by isomerization through the diketone (11a) or its enol. We have followed this conversion by n.m.r. spectroscopy. The intensities of the AB quartet (3-CH_2) of the substrate and the deshielded enolic hydroxy and vinylic hydrogen of the enol of (11a) were monitored. Firstly, we followed the reaction in deuteriated acetone containing hydrogen chloride, but dehydration was so rapid that the spectrum obtained was that of the chromone ester (2; R = Et). Secondly, reaction of the chroman ester (13) in the same solvent containing a few drops of hydrochloric acid at 34 °C proceeded more slowly, dehydration being complete in 50 min. During this time, the AB quartet steadily decreased in intensity and there was no evidence of the formation of the diketone or its enol. As mentioned earlier, equilibration of the chromanone with the diketone is a much slower reaction. It is therefore apparent that the intermediate in the formation of a chromone by this method is normally the 2-hydroxychromanone (13) and not the diketone (11a) or its enol.

Table. Ring-chain isomerization of chromanone esters (13) and (14)

Time (h)	Integrator (mm) (13) (δ 4.75)	(11a) (δ 11.74)	% of (11a)	Integrator (mm) (14) (δ 4.59)	(12) (δ 11.72)	% of (12)
0	10	0	0	11	1.5	12
20	—	—	—	7	9.50	42
24	9	2	18	—	—	
96	9	3	25	—	—	



(16) (17)



(18) R^1 = R^2 = $NH(CH_2)_2OH$
(19) R^1 = OEt, R^2 = NHPh. HBr

Although chromanones are readily halogenated,[10] no report could be found of the halogenation of 2-hydroxy-4-oxochroman-2-carboxylic acids or esters. Treatment of the ester (13) with bromine–chloroform or bromine–acetic acid gave unsatisfactory or negative results. Bromine–dioxan yielded a mixture of three products including ethyl 3-bromo-2-hydroxy-4-oxochroman-2-carboxylate (17) and the chromone (3; R′ = Br). When the chromanone (13) in chloroform and pyridine at −3 °C was treated with bromine, a high yield of the 3-bromochromanone (17) was obtained. Its n.m.r. spectrum showed this to be a 72 : 28 mixture of *cis* and *trans* isomers; this ratio varied slightly from one experiment to another. Except for the C-2 atom, the pyran-4-one ring of chromanone is coplanar with the benzene ring;[11] the most favoured approach by bromine would be from the less hindered side, that is, the same side as the hydroxy group to give mainly the *trans*-OH,H isomer. This is the major isomer obtained experimentally as demonstrated by the formation in 49% yield of the chromone ester (3; R′ = Br) by treatment of the mixed isomers with ethanolic hydrobromic acid through elimination of the *trans*-placed elements of water. Hence, the corrected yield of chromone (3; R′ = Br) from the *trans*-OH,H isomer present is 68%, assuming no epimerization had occurred. The hydrogen at C-3 of the chromanone (17) is very labile as was shown by stirring the compound in pyridine for

a short time; the ratio of isomers produced on acidification rose to 85 : 15. This ratio is based on integrator measurements; there was no spectral evidence of the formation of other products.

When the bromo-ester (3; R′ = Br) was treated with gaseous ammonia, the desired aminocarboxamide (1) was obtained in 74% yield. The overall yield from *o*-hydroxyacetophenone by this route is considerably better than that through the chloro-ester. The bromoester reacted with 2-aminoethanol to give the bis(hydroxyethylamino) compound (18) but with aniline, ethyl 3-phenylamino-4-oxochromen-2-carboxylate hydrobromide (19) was isolated.

Experimental

Methods of determining m.p.s, spectra, and chromatographic characteristics are described in earlier papers.[12] Dry acetone was obtained by refluxing with, and distilling from, potassium permanganate and storage over molecular sieve. Silica gel (60—120 mesh) was used for column chromatography. The condensation of 2-hydroxyacetophenone with diethyl oxalate was effected by the published method.[2,8]

Methyl 3-Chloro-4-oxochromen-2-carboxylate (6).—Methyl 4-oxochromen-2-carboxylate [2] (26.5 g, 0.13 mol), benzoyl peroxide (60 mg), and sulphuryl chloride (160 ml, 2.0 mol) were heated under reflux for 10 h. The excess of sulphuryl chloride was removed under reduced pressure and the remaining solid was washed with methanol (2 × 15 ml). The solid (31.1 g) consisted of the ester (6) and methyl *cis*-2,3-dichloro-4-oxochroman-2-carboxylate in the ratio (^{1}H n.m.r.) of 77 : 23. Dehydrochlorination and isolation as described for the ethyl ester [2] gave the *methyl ester* (21.4 g, 69%), m.p. 126 °C (from methanol) (Found: C, 55.7; H, 3.0. $C_{11}H_7ClO_4$ requires C, 55.3; H, 2.9%), $\nu_{max.}$ 1 735 (ester CO) and 1 659 cm^{-1} (pyran CO); δ 8.19 (1 H, dd, *J* 8 and 2 Hz, 5-H), 7.85—7.30 (3 H, m, 6-, 7-, 8-H), and 4.02 (3 H, s, Me).

Reaction of the Methyl Ester (6) *with Ammonia*.—(a) *In methanol*. When the methyl ester was subjected to the action of ammonia as described for the ethyl ester,[2] the aminocarboxamide (1) (m.p. and mixed m.p. with authentic sample,[2] 219 °C) was obtained in 17.5% yield.

(b) *In dichloromethane–methanol*. Anhydrous ammonia was passed into a solution of the ester (6.0 g) in the dry solvents (1 : 1; 80 ml) for 20 min at 0 °C. Removal of the solvents under reduced pressure gave *3-chloro-4-oxochromen-2-carboxamide* (4.86 g, 90%) m.p. 263—264 °C (from ethanol) (Found: C, 53.7; H, 2.7; N, 6.2. $C_{10}H_6ClNO_3$ requires C, 53.7; H, 2.7; N, 6.3%); $\nu_{max.}$ 3 400 and 3 340 (NH), 1 725 (amide CO), 1 655 (pyran CO), and 1 630 (amide CO); δ[$(CD_3)_2SO$] 8.70—7.40 (6 H, m, ArH and NH_2).

(c) *In acetone*. Anhydrous ammonia was passed into an acetone solution of the methyl ester (3.0 g) in dry acetone (80 ml) for 30 min at 0 °C. The solution was poured into water (300 ml) and the precipitated solid was collected to give the *anil* (8) (1.55 g, 48%), m.p. 255 °C (Found: C, 63.6; H, 5.1; N, 11.3. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.9; N, 11.5%); $\nu_{max.}$ 3 110, 1 690, and 1 605 cm^{-1}; δ[$(CD_3)_2SO$] 8.00—7.20 (6 H, m, ArH and NH_2) and 1.64 (6 H, s, Me_2).

Reaction of Ethyl 4-Oxochromen-2-carboxylate with Pyrrolidine.—The chromone ester (2; R = Et) (10.9 g, 50 mmol) and pyrrolidine (17.0 g, 240 mmol) in dry ethanol (100 ml) were heated together under reflux for 10 h. The yellow crystals which separated on cooling were combined with a second crop which precipitated after removal of most of the solvent to give N-[3-(2-*hydroxybenzoyl*)-2-*pyrrolidin*-1-*ylacryloyl*]*pyrrolidine* [9; R^2 = $CON(CH_2)_4$] (9.55 g, 60%), m.p. 182 °C (Found: C, 68.8; H, 7.0; N, 8.6. $C_{17}H_{22}N_2O_3$ requires C, 68.8; H, 7.1; N, 8.9%); $\nu_{max.}$ 3 070 (arom. CH), 2 970 and 2 880 (aliphatic CH), 1 726 (amide CO), 1 640 cm^{-1} (pyran CO); δ 13.61 (1 H, s, OH, exchangeable with D_2O), 7.68 (1 H, dd, *J* 8 and 2 Hz, 6′-H), 7.42—6.65 (3 H, m, 3′-, 4′-, 5′-H), 5.64 (1 H, s, CH=), 3.90—2.90 [8 H, m, $2(CH_2NCH_2)$], and 2.11—1.70 [8 H, m, $2(CH_2CH_2)$].

Bromine (1.76 g, 11 mmol) in chloroform (32 ml) was added dropwise to a solution of the enamine [9; R^2 = $CON(CH_2)_4$] in chloroform (180 ml) at 0 °C. When the temperature had reached that of the surroundings, dilute hydrochloric acid (162 ml) was added and stirring was continued for 30 min. The organic layer was separated, the aqueous layer was extracted with chloroform and the combined and dried extracts gave an oil which crystallized on trituration with ethyl acetate to give 1-[(3-*bromo*-4-*oxochromen*-2-*yl*)-*carbonyl*]*pyrrolidine* [10; R^2 = $CON(CH_2)_4$] (1.66 g, 44%), m.p. 130 °C (from ethyl acetate) (Found: C, 52.4; H, 3.8; N, 4.3. $C_{14}H_{12}BrNO_3$ requires C, 52.2; H, 3.8; N, 4.4%); $\nu_{max.}$ 2 970 and 2 880 (aliphatic CH), 1 652 (pyran CO), 1 645 cm^{-1} (t-amide); δ[$(CD_3)_2SO$–$(CD_3)_2CO$] 8.12 (1 H, dd, *J* 8 and 2 Hz, 5-H), 7.95—7.38 (3 H, m, 6-, 7-, and 8-H), 3.80—3.35 (4 H, m, CH_2NCH_2), and 2.19—1.81 (4 H, m, 3,4-CH_2CH_2).

Methyl 2-Hydroxy-4-oxochroman-2-carboxylate (14).—The yellow sodium salt [2] (24 g) obtained in the condensation of *o*-hydroxyacetophenone and diethyl oxalate in the presence of sodium ethoxide was suspended in methanol (120 ml). Ice-cold 10% sulphuric acid was added slowly to the stirred suspension at 0 °C until a pH of 1—2 was reached. After 1 h at 0 °C, water (120 ml) was added to precipitate the *methyl ester* (7.9 g), m.p. 122—124 °C (from methanol) (Found: C, 59.2; H, 4.5. $C_{11}H_{10}O_5$ requires C, 59.5; H, 4.5%); $\nu_{max.}$ 3 300br (OH), 1 748 (ester CO), and 1 671 cm^{-1} (pyran CO); n.m.r. spectrum is given in the next paragraph.

Isomerization of Ethyl and Methyl 2-Hydroxy-4-oxochroman-2-carboxylates.—Freshly prepared solutions of these esters in deuteriated chloroform were kept at 20 °C and placed in the n.m.r. spectrometer periodically. For the ethyl ester, the signals obtained immediately were as follows: δ 7.85 (1 H, dd, *J* 8 and 2 Hz, 5-H), 7.60—6.84 (3 H, m, 6-, 7-, and 8-H), 4.75 (1 H, s, OH), 4.30 (2 H, q, *J* 7 Hz, OCH_2), 3.33 and 2.94 (calculated values of AB quartet,[13] 2 H, *J* 17.1 Hz, 3-CH_2), and 1.30 (3 H, t, *J* 7 Hz, Me). A singlet at δ 11.74 [due to the phenolic group of (16)] slowly appeared (Table 1).

For the methyl ester, the spectrum of the freshly made solution was as follows: δ 11.72 (s, phenolic OH), 7.98—6.88 (m, ArH and $COCH_2CO$), 4.59 [s, OH of (14)], 3.94 [s, Me of (12) and (14)], 3.35 and 2.96 [calculated values of AB quartet,[13] *J* 17.1 Hz, 3-CH_2 of (14)] (see text and Table 1).

Ethyl 4-(2′-Acetoxyphenyl)-2,4-dioxobutanoate (11b; Enol form).—(*a*) A mixture of 2-acetoxyacetophenone (7 g, 39 mmol) and diethyl oxalate (5.1 g, 35 mmol) was added rapidly to a solution of sodium ethoxide [from sodium (0.67 g, 29 mmol) and dry ethanol (50 ml)]. After being heated and stirred for 2 h, the solution was cooled and acidified at −5 °C with dilute sulphuric acid. Stirring was continued for 10 min, after which water (200 ml) was added and the oil produced was isolated with ether to give the butanoate (8.25 g, 76%), b.p. 77 °C/6 mmHg with decomposition. A pure sample of the *ester* (11b) was obtained by chromatography on silica gel with ethyl acetate–cyclohexane (40 : 60) (Found: C, 60.5; H, 5.1. $C_{14}H_{14}O_5$ requires C, 60.4; H, 5.0%); $\nu_{max.}$ (liquid film) 3 400—2 700br (OH), 2 985 (aliphatic CH), 1 760 (ester CO), 1 740 and 1 640 cm^{-1} (keto-enol); δ 12.20 (1 H, s, OH), 7.70

(1 H, dd, *J* 8 and 3 Hz, 6'-H), 7.56—6.75 (4 H, m, 3'-, 4'-, 5'-H, and enol CH), 4.31 (2 H, q, *J* 7 Hz, OCH_2), 2.60 (3 H, s, OAc), and 1.35 (3 H, t, *J* 7 Hz, CH_2Me).

(*b*) When the above reaction was repeated using 7 mg-atom of sodium, and the reaction time extended to 5 h, the same product was obtained in 56% yield.

(*c*) On increasing the amount of base in (*a*) to 39 mmol, a low yield (25%) of ethyl 2-hydroxy-4-oxochroman-2-carboxylate (13) was isolated on careful acidification at 0 °C.

Ethyl 4-Oxochromen-2-carboxylate (2).—The above acetoxy-butanoate (11b) (5.0 g, 18 mmol) was added slowly to a solution of sodium (1.02 g, 44 mg-atom) in dry ethanol (25 ml) and the mixture was heated under reflux for 1 h during which time a yellow solid separated. This was collected, washed with a little ether, dried on the filter, and suspended in ethanol (50 ml). Acidification to pH 1—2 with dilute sulphuric acid at −5 °C and stirring for 25 min was followed by adding the solution to water (150 ml). Extraction with ether and isolation in the usual way gave ethyl 2-hydroxy-4-oxochroman-2-carboxylate (13) (3.4 g), m.p. 77 °C (lit.,[8] 77 °C); i.r. and n.m.r. spectra were identical with those given by Trowitzsch.[8] This was refluxed with ethanol (5 ml) and hydrochloric acid (3 ml) for 30 min. Pouring into water and isolation in the usual way gave the chromone ester (2) (1.22 g, 31%), m.p. and mixed m.p. with an authentic sample, 71 °C (lit.,[14] 71—72 °C).

N.M.R. Study of the Dehydration of the Chromanone Ester (13).—When a 10% solution of this ester in deuteriated acetone saturated with hydrogen chloride was immediately examined in the spectrometer, dehydration to the chromone (2) was already complete. In another experiment, the chromanone (13) was dissolved in deuteriated acetone containing a few drops of 6M-hydrochloric acid and the progress of the reaction was followed by observing the intensity of the AB quartet at δ 3.45—2.85. After 50 min at 34 °C, this signal had disappeared and during this time no evidence of the intermediate formation of the diketone form (11a) or its enol was observed. At the end of this period, only signals representing the chromone ester (2) were present.

Ethyl 3-Bromo-2-hydroxy-4-oxochroman-2-carboxylate (17) *and its Dehydration.*—(a) Ethyl 2-hydroxy-4-oxochroman-2-carboxylate (13) (48.0 g, 0.2 mol) and pyridine (16 ml, 0.2 mol) were dissolved in dry chloroform (300 ml) and stirred at −5 °C while bromine (32.5 g, 0.2 mol) in chloroform (15 ml) was added dropwise. When addition was complete, the solution was allowed to reach room temperature and water (300 ml) was added to the vigorously stirred solution. The organic layer was separated and the aqueous layer was extracted with chloroform. Removal of the solvent from the dried ($MgSO_4$) chloroform extracts gave a yellow oil which crystallized after 2 days in a refrigerator to give the diastereoisomeric product (17) (59.9 g, 94%), m.p. 81—89 °C. Column chromatography of a sample on silica gel using ethyl acetate–cyclohexane (40 : 60) as eluant gave a pure sample of the *bromo-ester* (61% recovery), m.p. 82—89 °C (Found: C, 45.3; H, 3.5. $C_{12}H_{11}BrO_5$ requires C, 45.7; H, 3.5%); $\nu_{max.}$ 3 440 (OH), 2 990 and 2 945 (aliphatic CH), 1 760 and 1 739 (ester CO), 1 690 cm^{-1} (pyran CO); δ 7.92 (1 H, dd, *J* 8 and 2 Hz, 5-H), 7.65—6.90 (3 H, m, 6-, 7-, and 8-H), 5.34 and 4.86 (1 H, s, 3-H), 5.09 (1 H, s, OH, exchangeable with D_2O), 4.60—4.05 (2 H, m, OCH_2), and 1.52—1.10 (3 H, m, Me).

The bromo-ester (4.0 g) was hydrolysed by boiling with acetic acid (20 ml) and hydrobromic acid (20 ml) for 3.5 h to give *3-bromo-4-oxochromen-2-carboxylic acid* (2.3 g, 63%), m.p. 216 °C (from ethyl acetate) (Found: C, 45.0; H, 2.0. $C_{10}H_5BrO_4$ requires C, 44.7; H, 1.9%); $\nu_{max.}$ 3 300—2 400 (OH), 1 710 (carboxy CO), 1 650 cm^{-1} (pyran CO); δ [$(CD_3)_2CO$–$(CD_3)_2SO$] 8.6 (1 H, s, CO_2H), 8.15 (1 H, dd, *J* 9 and 2 Hz, 5-H), and 8.0—7.4 (3 H, m, 6-, 7-, and 8-H).

The mixed bromides (41.7 g) were dissolved in ethanol (200 ml) and hydrobromic acid (40 ml) and heated under reflux for 30 min. Pouring the cooled reaction mixture into water (600 ml) gave the *bromo-ester* (3; R′ = Br) (19.5 g, 49%), m.p. 92 °C (Found: C, 48.1; H, 3.1. $C_{12}H_9BrO_4$ requires C, 48.5; H, 3.0%); $\nu_{max.}$ 3 080 (arom. CH), 2 980 (aliphatic CH), 1 730 (ester CO), and 1 650 cm^{-1} (pyran CO); δ 8.2 (1 H, dd, *J* 8 and 2 Hz, 5-H), 8.0—7.1 (3 H, m, 6-, 7-, and 8-H), 4.47 (2 H, q, *J* 8 Hz, OCH_2), and 1.44 (3 H, t, *J* 8 Hz, Me).

(b) The ester (13) (4.7 g, 0.02 mol) in dioxan (60 ml) was treated with bromine (3.1 g, 0.02 mol).[15] Stirring was continued for 1 h during which the temperature of the mixture rose and the colour of bromine disappeared. Water (500 ml) was added and stirring was maintained for a further hour. A dense colourless oil separated but failed to crystallize after isolation. T.l.c. showed the presence of three compounds which were shown by n.m.r. to be the chromone (3; R′ = Br), the bromochromanone (17), and the chromanone (13).

(c) An oily mixture of several compounds was obtained when the chromanone (13) was similarly treated with either bromine–acetic acid–sodium acetate [16] or bromine–chloroform.[17]

Epimerization of the Bromo-ester (17).—A solution of the bromo-ester (0.1 g, 0.3 mmol) in deuteriochloroform (1 ml) containing pyridine (0.06 g, 0.74 mmol) was stirred for 15 min at 18 °C. The solution was cooled to 0 °C, stirred and acidified with dilute hydrochloric acid (1 ml). The organic layer was separated and dried ($MgSO_4$). Measurement of the intensities of the 3-H signals before and after this treatment showed a change in the signals at δ 5.34 and 4.87 from 15 : 5 mm (which is 75 : 25) to 16.8 : 33 mm (that is, 85 : 15).

3-Amino-4-oxochromen-2-carboxamide (1).—Anhydrous ammonia was passed for 15 min into the bromo-ester (3; R′ = Br) suspended in dry ethanol (120 ml) and kept at −3 °C. During this period, the bromo-ester dissolved and a new yellow solid precipitated. To facilitate the latter process, water (600 ml) was added and the mixture was stirred for *ca.* 15 min. The solid was isolated to give the yellow carboxamide (4.6 g, 74%), m.p. 218 °C (decomp.) (lit.,[2] 220—221 °C) (Found: C, 59.0; H, 4.0; N, 13.6. Calc. for $C_{10}H_8N_2O_3$: C, 58.8; H, 4.0; N, 13.7%); δ [$(CD_3)_2SO$] 11.50 (2 H, s, amide NH_2), 8.50—7.10 (6 H, m, ArH and 3-NH_2).

N-(2-Hydroxyethyl)-3-(2-hydroxyethylamino)-4-oxochromen-2-carboxamide (18).—2-Aminoethanol (0.33 g, 13.6 mmol) was added dropwise to a vigorously stirred suspension of ethyl 3-bromo-4-oxochromen-2-carboxylate (2.0 g, 6.7 mmol) in aqueous ethanol (40 ml; 50% v/v). A clear yellow solution formed and after 24 h this was shown by t.l.c. to contain unchanged ester. More 2-aminoethanol (0.83 g, 13.6 mmol) was added and within an hour, no ester remained. Removal of the solvent and addition of water (50 ml) gave after several hours, yellow crystals of the *amino amide* (18) (0.36 g, 18%), m.p. 149 °C (Found: C, 57.8; H, 5.6; N, 9.5. $C_{14}H_{16}N_2O_5$ requires C, 57.5; H, 5.5; N, 9.6%); $\nu_{max.}$ 3 700—3 000br (OH, NH), 1 680 (amide), and 1 660 cm^{-1} (pyran CO).

Ethyl 3-Phenylamino-4-oxochromen-2-carboxylate Hydrobromide (19).—Ethyl 3-bromo-4-oxochromen-2-carboxylate (3.0 g, 10 mmol) and aniline (1.12 g, 12 mmol) were heated under reflux in dry ethanol (15 ml) for 4 h. Removal of the solvent gave a solid consisting of unchanged ester (0.83 g) and the more soluble *phenylamino ester hydrobromide* (0.36 g, 11%), m.p. 154 °C (Found: C, 55.7; H, 4.2; N, 3.7; $C_{18}H_{16}$-

$BrNO_4$ requires C, 55.4; H, 4.1; N, 3.6%); R_F 0.49 (cyclohexane–ethyl acetate, 60 : 40); $\nu_{max.}$ 3 320 (NH), 1 730 (ester CO), 1 690 (pyran CO); δ[$(CD_3)_2SO$–$(CD_3)_2CO$] 7.91 (1 H, dd, *J* 7 and 2 Hz, 5-H), 7.75—6.70 (10 H, m, ArH and HBr), 4.90 (1 H, s, NH), 4.19 (2 H, q, *J* 7 Hz, CH_2), 1.12 (3 H, t, *J* 7 Hz, Me); M^+, 391.0254, 389.0269 (required: 391.0243, 389.0263) (M − Br − CO_2Et), 237.0728 (237.0787, 27%), (M − Br − CO_2Et − H), 236.0728 (236.0709, 21%).

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