# Benzopyrones. Part XI.[1] Some 3-Substituted 4-Oxochromen-2-carboxylic Acid Derivatives

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The homolytic chlorination of ethyl 4-oxochromen-2-carboxylate produces three chlorine-containing esters: the known 3-chloro-derivative (1), 2-chloroethyl 3-chloro-4-oxochromen-2-carboxylate (2), and ethyl *cis*-2,3-dichloro-4-oxochroman-2-carboxylate (13). Ammonia converted the ester (1) into 3-amino-4-oxochromen-2-carboxamide, but 3-chloro-4-oxochromen-2-carbonitrile under the same conditions gave 2-amino-3-chlorochromone (15). The preparation and some reactions of ethyl 3-bromomethyl-4-oxochromen-2-carboxylate are described. Conflicting reports of the characteristics of ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate have been resolved and the corresponding methyl ester has been synthesized; aminoethylation of the latter yielded the 3-dimethylaminomethylchromone (11).

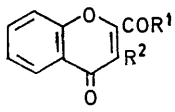
WHEN ethyl 4-oxochromen-2-carboxylate and sulphuryl chloride are heated together under reflux in the presence of benzoyl peroxide, the 3-chloro-derivative (1), m.p. 91—91·5°, is formed in 43% yield.[2] A repetition of this

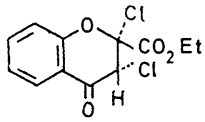
[1] Part X, G. P. Ellis and I. L. Thomas, *J.C.S. Perkin I*, 1973, 2781.

[2] V. A. Zagorevskii, I. D. Tsvetkova, and E. K. Orlova, *Chem. Heterocyclic Compounds*, 1967, 624.

reaction [3,4] on a larger scale gave a product, m.p. 82—85°, which contained an appreciable amount of an impurity which was difficult to remove. Fractional crystallization of the crude product gave three crystalline chlorine-containing compounds in approximately equal proportions which varied slightly with the ratio of reactants and reaction time. In addition to the 3-chloro-ester (1), 2-chloroethyl 3-chloro-4-oxochromen-2-carboxylate (2), and ethyl *cis*-2,3-dichloro-4-oxochroman-2-carboxylate (13) were isolated, and were characterized by elemental analysis, n.m.r. spectra, and chemical reactions. Treatment of the ester (2) with gaseous ammonia under mild conditions gave 3-amino-4-oxochromen-2-carboxamide (4) which was produced in higher yield by similar treatment of ethyl 3-chloro-4-oxochromen-2-carboxylate. The stereochemistry of the chromanone (13) was demonstrated by its ready dehydrochlorination in pyridine to ethyl 3-chloro-4-oxochromen-2-carboxylate. With a knowledge of the structure of the by-products, it was possible to modify the procedure for isolating the desired chloro-ester (1): the crude product was treated with pyridine to dehydrochlorinate the dichlorochromanone to give the 3-chloro-ester, which was hydrolysed to the 3-chloro-acid (3), and the acid (3) was esterified to give the pure ester (1), m.p. 94—95°.

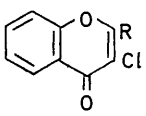
In another approach to the synthesis of 3-amino-4-oxochromen-2-carboxylic acid, an attempt was made to displace the halogen of 3-chloro-4-oxochromen-2-carbonitrile [3] (14) by passing gaseous ammonia through an ice-cooled ethanolic solution. The product, however, contained chlorine and analytical figures indicated the constitution $C_9H_6ClNO_2$, representing a net loss of one carbon and a gain of two hydrogen atoms. The spectral and chemical properties of this product indicated that it was 2-amino-3-chlorochromone (15) or its tautomer, 3-chloro-4-hydroxy-2-iminochromen (18). Acidic hydrolysis of this gave 3-chloro-4-hydroxycoumarin (19). The displacement of a cyano-group attached to the pyrone ring by amino has not been recorded previously. The amino-compound gave a mono- and a di-acetate. Possible structures for the latter are (16) and (20). Zagorevskii, Glozman, and Zhmurenko,[5] on the basis of the presence of a single amide absorption at 1734 $cm^{-1}$ (chloroform), assigned the *NN*-diacetate structure [type (16)] to the corresponding 3-bromo-compound. However, a structure containing the Ac–N–Ac grouping should show evidence of symmetric and dissymmetric stretching vibrations in the 1750—1700 $cm^{-1}$ region.[6] Our diacetate (in chloroform) absorbs strongly at 1737 $cm^{-1}$, and this peak broadens through shoulders at 1731 and 1728 $cm^{-1}$ to give a multiple absorption similar to that observed in *NN*-diacetates.[6] The two methyl groups of the diacetate have identical chemical shifts (δ 2·45 in $CDCl_3$) and this sharp peak shows no sign of broadening when the solvent is changed to carbon disulphide, benzene, or [$^2H_6$]dimethyl sulphoxide. Moreover, the 5-proton of chromones is subject to the paramagnetic effect of the pyrone carbonyl group and consequently its signal usually appears downfield of the remainder of the aromatic proton multiplet. In the diacetate, a quartet (*J* 8·2 and 2·5 Hz) at δ 8·44 is well separated from the multiplet at δ 7·95—7·31. By contrast, all benzenoid protons of coumarin and 4-acetoxycoumarin absorb together at higher field (δ 7·75—7·10). I.r. and n.m.r. evidence thus identifies the diacetate as the chromone (16).



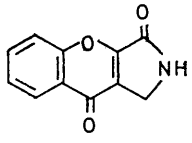


(13)

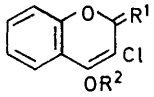
(1) $R^1$ = OEt, $R^2$ = Cl
(2) $R^1$ = $OCH_2 \cdot CH_2Cl$, $R^2$ = Cl
(3) $R^1$ = OH, $R^2$ = Cl
(4) $R^1$ = $R^2$ = $NH_2$
(5) $R^1$ = OEt, $R^2$ = $CH_2Br$
(6) $R^1$ = $NH_2$, $R^2$ = $CH_2 \cdot NH_2$
(7) $R^1$ = OEt, $R^2$ = $CH_2 \cdot OAc$
(8) $R^1$ = OEt, $R^2$ = $CH_2 \cdot CN$
(9) $R^1$ = OEt, $R^2$ = $CH_2 \cdot CO_2Et$
(10) $R^1$ = OH, $R^2$ = H
(11) $R^1$ = OMe, $R^2$ = $CH_2NMe_2$, HCl
(12) $R^1$ = OH, $R^2$ = $CH_2NMe_2$, HCl



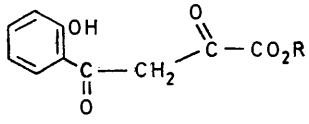
(14) R = CN
(15) R = $NH_2$
(16) R = $NAc_2$
(17) R = NHAc



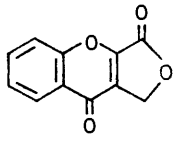
(21)



(18) $R^1$ = NH, $R^2$ = H
(19) $R^1$ = O, $R^2$ = H
(20) $R^1$ = NHAc, $R^2$ = OAc



(22) R = Et
(23) R = Me



(24)

The n.m.r. spectrum of the monoacetate (see Experimental section) is similar to that of the diacetate and its structure is therefore believed to be (17).

Direct hydrolysis of the nitrile (14) by boiling with aqueous sodium hydrogen carbonate yielded 3-chloro-4-hydroxycoumarin. The halogen atom of 3-chloro-4-oxochromen-2-carboxylic acid did not react with ammonia. From this and earlier work,[7] the reactivity of a 3-chloro-atom is seen to decrease as the 2-substituent changes from methyl through ethoxycarbonyl to cyano and carboxy.

[3] G. P. Ellis and D. Shaw, *J. Medicin. Chem.*, 1972, **15**, 865.
[4] D. Shaw, Ph.D. Thesis, University of Wales, 1972.
[5] V. A. Zagorevskii, S. M. Glozman, and L. A. Zhmurenko, *Chem. Heterocyclic Compounds*, 1970, 943.
[6] R. A. Abramovitch, *J. Chem. Soc.*, 1957, 1413.
[7] C. W. Winter and C. S. Hamilton, *J. Amer. Chem. Soc.*, 1952, **74**, 3999.

When ethyl 3-methyl-4-oxochromen-2-carboxylate was treated with *N*-bromosuccinimide, a high yield of the 3-bromomethyl derivative (5) was obtained. This reacted with gaseous ammonia at 0° to give 3-aminomethyl-4-oxochromen-2-carboxamide (6), which was also formed by the action of ammonia on ethyl 3-acetoxymethyl-4-oxochromen-2-carboxylate (7) [the latter was prepared from the bromomethyl ester (5) and silver acetate]. The amino-amide (6) was notable for its lack of reactivity: it could not be acetylated neither could it be cyclized to (21) under a variety of conditions.

Numerous attempts were made to convert the 3-bromomethyl ester (5) into its cyanomethyl analogue (8). Several metal cyanides and a variety of solvents were used but the yield was consistently low, probably because of the occurrence of nucleophilic attack on the pyran ring. Alcoholysis of a small quantity of the nitrile (8) gave the diester (9). When the 3-bromomethyl ester was heated under reflux with a mixture of hydrochloric and acetic acids in an attempt to prepare the bromomethyl acid, the lactone (24) was formed. Similar treatment of the 3-acetoxymethyl ester (7) also gave the lactone.

Chromones undergo the Mannich reaction either in an activated benzene [8] or in the pyrone ring [9] but an electron-withdrawing group at C-2 prevents the reaction. Nivière, Tronche, and Couquelet [10] have shown that the methylene group of the 2,4-dioxobutanoate (22), which is an intermediate in the Kostanecki synthesis [11] of 4-oxochromen-2-carboxylic acids, is readily hydroxymethylated when treated with formaldehyde. In the chromone synthesis, the keto-ester is not normally isolated but it was necessary to do so in this instance in order to treat it with the Mannich reagents.[12] The keto-ester (22) is described by Nivière *et al.*,[10] as a solid, m.p. 107° (sample A), but a repetition of this experiment gave a product, m.p. 123—124°, which was shown to be the methyl ester (23). It is likely that sample A was a mixture of the methyl ester (23) and methyl 4-oxochromen-2-carboxylate. This is supported by the presence in the i.r. spectrum [10] of sample A of an absorption at 1648 $cm^{-1}$ which is absent from that of the ester (23) but is characteristic of methyl 4-oxochromen-2-carboxylate. A transesterification apparently occurred when the solid sodio-derivative of (22) was suspended in methanol and acidified with sulphuric acid. When ethanol was substituted for methanol, the oily ester was isolated: Kostka [13] obtained a similar product by neutralizing the sodio-derivative of (22) with acetic acid in the absence of an alcoholic solvent. The transesterification provides a convenient synthesis of methyl 4-oxochromen-2-carboxylate from the readily available diethyl oxalate.

When kept at room temperature for about 3 weeks, the oil (22) deposited crystals of ethyl 4-oxochromen-2-carboxylate. Similarly, the methyl ester (23) gave methyl 4-oxochromen-2-carboxylate on heating with hydrochloric acid. Methyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (23) reacted with dimethylammonium chloride and formaldehyde to give methyl 3-(dimethylaminomethyl)-4-oxochromen-2-carboxylate hydrochloride (11), which was hydrolysed by refluxing acetic and hydrochloric acids to the amino-carboxylic acid hydrochloride (12).

## EXPERIMENTAL

M.p.s were determined on a Reichert hot-stage apparatus. N.m.r. spectra were obtained with a Perkin-Elmer R10 (60 MHz) instrument (tetramethylsilane as internal reference). U.v. spectra were determined for solutions in ethanol with a Unicam SP 700A spectrophotometer. I.r. data were obtained for potassium bromide discs with a Perkin-Elmer model 521 spectrophotometer unless otherwise stated. Mass spectra were recorded with a Varian CH5D or A.E.I. MS-902 instrument at 70 eV.

*Chlorination of Ethyl 4-Oxochromen-2-carboxylate.*—A solution of ethyl 4-oxochromen-2-carboxylate [14] (10 g) and benzoyl peroxide (0·06 g) in sulphuryl chloride (60 $cm^3$) was heated under reflux for 10 h. The excess of sulphuryl chloride was distilled off under reduced pressure, and ether (50 $cm^3$) was added to the residue. A sparingly soluble component was filtered off and recrystallized successively from ethanol and benzene–light petroleum (b.p. 60—80°) to give *2-chloroethyl 3-chloro-4-oxochromen-2-carboxylate* (2) (1·3 g), m.p. 149—150° (Found: C, 50·1; H, 2·6; Cl, 24·5. $C_{12}H_8Cl_2O_4$ requires C, 50·2; H, 2·8; Cl, 24·7%), $\nu_{max.}$ 1741 (ester C=O) and 1668 $cm^{-1}$ (pyrone ring C=O); δ ($CDCl_3$) 8·34—7·40 (4H, m, aromatic), 4·72 (2H, t, $OCH_2$), and 3·84 (2H, t, $CH_2Cl$).

Evaporation of the ethereal filtrate and recrystallization of the residue several times from aqueous ethanol gave *ethyl* cis-*2,3-dichloro-4-oxochroman-2-carboxylate* (13) (1·6 g), m.p. 102—103° (Found: C, 49·8; H, 3·7; Cl, 24·5. $C_{12}H_{10}Cl_2O_4$ requires C, 49·8; H, 3·5; Cl, 24·5%), $\nu_{max.}$ 1770 (ester C=O), 1712 (pyrone C=O), and 1608 $cm^{-1}$ (ring breathing); δ ($CDCl_3$) 8·24—7·20 (4H, m, aromatic), 4·88 (1H, s, 3-H), 4·44 (2H, q, $CH_2$), and 1·43 (3H, t, Me), and ethyl 3-chloro-4-oxochromen-2-carboxylate (1) (1·5 g), m.p. 94—95° (lit.,[2] 91—91·5°), $\nu_{max.}$ 1738 (ester C=O) and 1655 $cm^{-1}$ (pyrone C=O); δ ($CDCl_3$) 8·41—7·38 (4H, m, aromatic), 4·54 (2H, q, $CH_2$), and 1·49 (3H, t, Me).

*Hydrolysis of 2-Chloroethyl 3-Chloro-4-oxochromen-2-carboxylate* (2). The ester (2) (1 g) in glacial acetic acid (20 $cm^3$) and concentrated hydrochloric acid (10 $cm^3$) was heated under reflux for 2 h and the solution was poured into water. The precipitate was filtered off and dried to give 3-chloro-4-oxochromen-2-carboxylic acid, m.p. and mixed m.p. with an authentic sample [3] 211—212° (with decarboxylation) (Found: C, 53·5; H, 2·2. Calc. for $C_{10}H_5ClO_4$: C, 53·5; H, 2·2%).

*Dehydrochlorination of Ethyl 2,3-Dichloro-4-oxochroman-2-carboxylate* (13).—A solution of the ester (13) (0·5 g) in dry pyridine (2·5 $cm^3$) was warmed on a steam-bath for

[8] P. Da Re, L. Verlicchi, and I. Setnikar, *Arzneim.-Forsch.*, 1960, **10**, 800; P. Da Re and L. Cimatoribus, *Ann. Chim.* (*Italy*), 1962, **52**, 506.
[9] P. F. Wiley, *J. Amer. Chem. Soc.*, 1952, **74**, 4326.
[10] P. Nivière, P. Tronche, and J. Couquelet, *Bull. Soc. chim. France*, 1965, 3658.
[11] G. P. Ellis and G. Barker, *Progr. Medicin. Chem.*, 1972, **9**, 65.
[12] H. Abu-Shady, *U.A.R. J. Pharm. Sci.*, 1970, **11**, 295.
[13] K. Kostka, *Roczniki Chem.*, 1966, **40**, 1861.
[14] Z. J. Vejdelek, V. Trcka, O. Chyba, and H. Chybova, *Chem. listy*, 1953, **47**, 575.

1 h. Dilution with water precipitated ethyl 3-chloro-4-oxochromen-2-carboxylate (1) (0·4 g, 91%), m.p. and mixed m.p. with an authentic sample, 94—95°.

*Improved Preparation of Ethyl 3-Chloro-4-oxochromen-2-carboxylate* (1).—Ethyl 4-oxochromen-2-carboxylate (20 g) was chlorinated as described above and the crude product was successively treated with pyridine and an acetic–hydrochloric acid mixture. The resulting carboxylic acid was re-esterified by heating under reflux for 4 h with ethanol and a little sulphuric acid to give the pure ester (1) (14 g, 60%), m.p. 94—95° (from ethanol).

*3-Amino-4-oxochromen-2-carboxamide* (4).—A stream of gaseous ammonia was passed for 20 min into a solution of ethyl 3-chloro-4-oxochromen-2-carboxylate (3 g) in anhydrous ethanol (40 cm³) kept at 0°. The solution was poured into water, and the precipitate was collected and recrystallized from ethanol to give the *carboxamide* (1·6 g, 66%), m.p. 220—221° (decomp.) (Found: C, 58·6; H, 4·0; N, 13·4. $C_{10}H_8N_2O_3$ requires C, 58·8; H, 4·0; N, 13·7%); $\nu_{max.}$ 3455, 3410, 3300br, 1718, 1640, 1628, 1618, and 1575 cm⁻¹; $\lambda_{max.}$ 224 (log ε 3·87), 262 (3·79), 327 (3·99), 388 (4·23), and 410 nm (4·28); *m/e* 204 (100%, $M^+$), 161 (9, $M$ − 43), 160 (83, $M$ − 46), 105 (5, $M$ − 99), 76 (5, $M$ − 128), and 44 (7).

*Action of Ammonia on 3-Chloro-4-oxochromen-2-carbonitrile* (14).—The nitrile (14) (1 g) was dissolved in dry ethanol (60 cm³) and the solution was cooled in ice. A steady stream of ammonia gas was bubbled in for 15 min and the solvent was then allowed to evaporate off overnight. The residue was recrystallized from benzene–dimethylformamide to give *3-chloro-4-hydroxy-2-iminochromen* (18) (0·6 g, 61%), m.p. 275—276° (decomp.) (Found: C, 55·0; H, 3·0; N, 6·9. $C_9H_6ClNO_2$ requires C, 55·3; H, 3·1; N, 7·2%); $\nu_{max.}$ 3300, 3142br, 1665, 1640, and 1600 cm⁻¹; δ ($CF_3{\cdot}CO_2H$) 8·55—7·62 (m, aromatic); *m/e* 197 (35%) and 195 (100, $M^+$), 169 (9) and 167 (24, $M$ − 28), 132 (20, $M$ − 63), 122 (7, $M$ − 73), 121 (83, $M$ − 74), 120 (23, $M$ − 75), 104 (20, $M$ − 91), 93 (24, $M$ − 102), 92 (35, $M$ − 103), and 84 (23, $M$ − 111).

Hydrolysis of the iminochromen with hot 2N-hydrochloric acid gave 3-chloro-4-hydroxycoumarin, m.p. 220—221° (lit.,[15] 219°) (Found: C, 54·9; H, 2·6. Calc. for $C_9H_5ClO_3$: C, 55·0; H, 2·6%).

*Acetylation of 3-Chloro-4-hydroxy-2-iminochromen.*—The imine (18) (1 g) was dissolved in dry pyridine (20 cm³) and acetic anhydride (2 cm³) was added. The solution was kept at room temperature for 15 h. Water (20 cm³) and chloroform (60 cm³) were added with stirring and the lower layer was washed repeatedly with water, then dried ($Na_2SO_4$). Removal of the solvent and crystallization of the residue from benzene gave *2-acetamido-3-chlorochromone* (17) (0·4 g), m.p. 187—188° (Found: C, 55·7; H, 3·4; N, 5·8. $C_{11}H_8ClNO_3$ requires C, 55·6; H, 3·4; N, 5·9%); δ ($CDCl_3$) 8·24 (1H, q, 5-H, $J$ 8 and 2·5 Hz), 7·75—7·30 (5H, m, aromatic + 1H), and 2·42 (3H, s, Me).

Dilution of the benzene mother liquor with light petroleum (b.p. 60—80°) precipitated *3-chloro-2-(diacetylamino)chromone* (16) (0·4 g), m.p. 131° (Found: C, 55·6; H, 3·6; N, 5·0. $C_{13}H_{10}ClNO_4$ requires C, 55·8; H, 3·6; N, 5·0%); $\nu_{max.}$ ($CHCl_3$) 1737, 1731sh, 1728sh ($NAc_2$), 1662 (pyrone C=O), 1624, and 1607 cm⁻¹; δ ($CDCl_3$) 8·44 (1H, q, 5-H, $J$ 8·2 and 2·5 Hz), 7·95—7·31 (3H, m, 6-, 7-, and 8-H), and 2·45 (6H, s, 2Me). In other solvents, a singlet (2Me) appeared at 1·96 ($C_6H_6$), 2·35 ($CS_2$), or 2·44 [$(CD_3)_2SO$].

*Hydrolysis of 3-Chloro-4-oxochromen-2-carbonitrile* (14).—The nitrile (0·25 g) was heated under reflux for 20 min with saturated aqueous sodium hydrogen carbonate. The solution was cooled, filtered, and acidified with dilute hydrochloric acid. The precipitate yielded, after decolourization in aqueous ethanol, 3-chloro-4-hydroxycoumarin (0·1 g), m.p. and mixed m.p. with the sample from (18) 221—223° (lit.,[15] 219°).

*Ethyl 3-Bromomethyl-4-oxochromen-2-carboxylate* (5).—Ethyl 3-methyl-4-oxochromen-2-carboxylate [3] (4 g) was dissolved in dry carbon tetrachloride (80 cm³). *N*-Bromosuccinimide (3·2 g) was added together with a few crystals of benzoyl peroxide and the solution was heated under reflux until the reaction was complete (4—5 h) as shown by the disappearance of *N*-bromosuccinimide from the bottom of the vessel. The solution was cooled, succinimide was removed by filtration and the solvent was distilled off to leave the *3-bromomethylchromone* (4·4 g, 82%), m.p. 112—113° (from aqueous ethanol) (Found: C, 50·5; H, 3·4. $C_{13}H_{11}BrO_4$ requires C, 50·2; H, 3·6%); δ ($CDCl_3$) 8·25—7·3 (4H, m, aromatic), 4·80 (2H, s, $CH_2Br$), 4·50 (2H, q, $OCH_2$), and 1·50 (3H, t, Me).

*Ethyl 3-Cyanomethyl-4-oxochromen-2-carboxylate* (8).—Ethyl 3-bromomethyl-4-oxochromen-2-carboxylate (1 g) and potassium cyanide (0·22 g) in ethanol (20 cm³) and water (5 cm³) were heated under reflux for 11 h. Most of the solvent was distilled off, the residue was diluted with water (30 cm³), and the solution was extracted with ether (2 × 30 cm³). The extracts were washed with water, dried ($Na_2SO_4$), and evaporated, to leave the *3-cyanomethylchromone* (0·2 g, 24%), m.p. 123—125° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 65·8; H, 4·6; N, 5·0. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%); $\nu_{max.}$ 2248 (CN), 1717 (ester C=O), 1650 (pyrone C=O), 1620, and 1605 cm⁻¹.

*Ethyl 2-Ethoxycarbonyl-4-oxochromen-3-ylacetate* (9).—The nitrile (8) (0·8 g), dissolved in dry ethanol (60 cm³), was treated with a stream of hydrogen chloride gas for 10 min and the solution was heated under reflux for 6 h. The solution was concentrated to about one third its bulk and diluted with water (100 cm³). Extraction with ether gave the *diester* (0·4 g, 42%), m.p. 80—81° [from light petroleum (b.p. 60—80°) after decolourization] (Found: C, 63·4; H, 5·3. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%); δ ($CDCl_3$) 8·26 (1H, q, 5-H, $J$ 8·0 and 2·5 Hz), 7·93—7·35 (3H, m, aromatic), 4·48 (2H, q, 2-$OCH_2$), 4·21 (2H, q, 3-$OCH_2$), 4·08 (2H, s, $CH_2$), and 1·35 (6H, q, 2Me).

*Ethyl 3-Acetoxymethyl-4-oxochromen-2-carboxylate* (7).—Ethyl 3-bromomethyl-4-oxochromen-2-carboxylate (0·5 g) and silver acetate (0·28 g) were heated under reflux in acetic acid (15 cm³) for 2 h. The cooled and filtered solution was poured into water and the product was extracted with chloroform (2 × 40 cm³). The washed and dried extracts yielded the *acetoxymethyl compound* (0·32 g, 69%), m.p. 93° [from light petroleum (b.p. 60—80°)] (Found: C, 61·8; H, 4·9. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·9%); $\nu_{max.}$ 1734sh, 1725 (ester C=O), 1654 (pyrone C=O), 1622, and 1604 cm⁻¹.

*3-Aminomethyl-4-oxochromen-2-carboxamide* (6).—Ethyl 3-bromomethyl-4-oxochromen-2-carboxylate (1 g) or ethyl 3-acetoxymethyl-4-oxochromen-2-carboxylate (0·95 g) was suspended in ethanol (30 cm³) and then cooled in ice. Gaseous ammonia was passed for 10 min into the stirred suspension which was kept for a further 10 min at 0° before

[15] B. Puetzer, C. H. Nield, and R. H. Barry, *J. Amer. Chem. Soc.*, 1945, **67**, 832.

being poured into water. The precipitate was recrystallized from acetic acid to give the *amide* (6) (0·5 g, 75%), m.p. 233° (Found: C, 60·7; H, 4·9; N, 12·5. $C_{11}H_{10}N_2O_3$ requires C, 60·5; H, 4·9; N, 12·8%); $\nu_{max.}$ 3461, 3318, 3184, 3082, 1726—1700br, 1647sh, and 1630 $cm^{-1}$.

1H-*Furo*[3,4-b]*chromen*-3,9-*dione* (24).—When either ethyl 3-bromomethyl-4-oxochromen-2-carboxylate (1 g) or ethyl 3-acetoxymethyl-4-oxochromen-2-carboxylate (0·95 g) was heated under reflux with glacial acetic acid (15 $cm^3$) and concentrated hydrochloric acid (10 $cm^3$) for 4 h, dilution with water then gave the lactone (24) (0·5 g, 72%), m.p. 242—243° (lit.,[15] 242°) (Found: C, 64·9; H, 3·1. Calc. for $C_{11}H_6O_4$: C, 65·3; H, 3·0%); δ [$(CD_3)_2SO$] 8·2—7·3 (4H, m, aromatic) and 5·36 (2H, s, $CH_2$).

*Methyl* 4-(2-*Hydroxyphenyl*)-2,4-*dioxobutanoate* (23) *and its Cyclization*.—2′-Hydroxyacetophenone (20 g) and diethyl oxalate (25 g) were added dropwise during 30 min to hot ethanolic sodium ethoxide [from sodium (8·1 g) in dry ethanol (180 $cm^3$)] and the solution was heated under reflux for a further 4 h and cooled. The yellow sodium salt was filtered off, washed thoroughly with dry ether, and dried on the filter. A sample of the salt (10 g) suspended in methanol (50 $cm^3$) was cooled in ice and acidified with ice-cold 10% sulphuric acid. After 1 h at 0°, water (50 $cm^3$) was added to precipitate the *methyl ester* (23) (5 g), m.p. 123—124° (Found: C, 59·8; H, 4·3. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%); $\nu_{max.}$ 3280br (OH), 2961, 2935, (C–H), 1748 (ester C=O), 1671 (ketone C=O), and 1601 $cm^{-1}$ (aromatic ring); δ ($CDCl_3$) 11·8 (1H, s, OH), 8·00—6·96 (6H, m, aromatic and $CH_2$), and 3·98 (3H, s, Me).

(*a*) The ester (0·9 g) in methanol (5 $cm^3$) and concentrated hydrochloric acid (1 $cm^3$) was heated under reflux for 10 min and poured into water. The solid obtained was methyl 4-oxochromen-2-carboxylate, m.p. 119—120° (lit.,[16] 120·5—122°), $\nu_{max.}$ 1740, 1658—1648, 1626, and 1605 $cm^{-1}$.

(*b*) Cyclization of (23) with boiling acetic and hydrochloric acids gave 4-oxochromen-2-carboxylic acid, m.p. and mixed m.p. with an authentic sample 265° (decomp.).

*Ethyl* 4-(2-*Hydroxyphenyl*)-2,4-*dioxobutanoate* (22) *and its Cyclization*.—The dried yellow sodium salt was prepared as described in the preceding paragraph and suspended in ethanol. Acidification at 0° with 10% sulphuric acid gave an oil which was extracted with ether. The extract was washed with water, dried, and evaporated under vacuum to leave the ester (22) as a yellow oil which, when kept at room temperature for about 3 weeks, afforded ethyl 4-oxochromen-2-carboxylate, m.p. 70—71° (lit.,[17] 70—71°). When the yellow oil was heated under reflux with a mixture of acetic and hydrochloric acids, 4-oxochromen-2-carboxylic acid, m.p. 265°, was formed.

3-*Dimethylaminomethyl*-4-*oxochromen*-2-*carboxylic Acid Hydrochloride* (12) *and its Methyl Ester* (11).—A mixture of methyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (20) (3·2 g), dimethylammonium chloride (1·8 g), and formaldehyde solution (40%; 1·1 $cm^3$) was heated under reflux in ethanol (15 $cm^3$) for 4 h. During this period more formaldehyde (3 × 0·5 $cm^3$) was added intermittently. A little suspended solid was filtered off and most of the solvent was removed. The oily residue crystallized on adding hot acetone–ethanol (9 : 1) to give *methyl* 3-*dimethylaminomethyl*-4-*oxochromen*-2-*carboxylate hydrochloride monohydrate* (2·6 g, 57%), m.p. 139—140° (decomp.) (Found: C, 53·3; H, 5·6; N, 4·3. $C_{14}H_{15}NO_4,HCl,H_2O$ requires C, 53·3; H, 5·7; N, 4·4%); $\nu_{max.}$ 3500, 3430, 2962, 2694br, 1745, 1642, 1615, and 1572 $cm^{-1}$; δ [$(CD_3)_2SO$] 10·57 (1H, s, NH), 8·2—7·4 (4H, m, aromatic), 4·60 (2H, s, $CH_2$), 4·06 (3H, s, $OCH_3$), 3·72 ($H_2O$, s), and 2·85 (6H, s, $Me_2N$). On heating the ester under reflux in acetic acid (25 $cm^3$) and hydrochloric acid (5 $cm^3$) for 3 h, the *acid hydrochloride monohydrate*, m.p. 220° (decomp.) (after losing water at about 100°), was formed in 80% yield (Found: C, 51·3; H, 5·5; N, 4·6. $C_{13}H_{13}NO_4,HCl,H_2O$ requires C, 51·7; H, 5·3; N, 4·6%); $\nu_{max.}$ 3280br, 2700br, 1709, 1641, 1635, 1618, and 1465 $cm^{-1}$; δ ($D_2O$) 8·05—7·50 (4H, m, aromatic), 4·9 ($H_2O$, HDO, s), 4·50 (2H, s, $CH_2$), and 3·00 (6H, s, $Me_2N$). Drying this compound at 100° under vacuum gave the *anhydrous salt*, m.p. 220° (decomp.) (Found: C, 54·7; H, 4·9; N, 4·9. $C_{13}H_{13}NO_4,HCl$ requires C, 55·0; H, 5·0; N, 4·9%); $\nu_{max.}$ 2600br, 1710, 1642, 1636, 1618, and 1465 $cm^{-1}$.

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[16] V. A. Zagnorevskii, *J. Gen. Chem.* (*U.S.S.R.*), 1962, **32**, 3698.

[17] P. J. F. Griffiths and G. P. Ellis, *Spectrochim. Acta* 1972, **28A**, 707.