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Studies on Antianaphylactic Agents. II.[1] Oxidation and Reduction of 4-Oxo-4*H*-1-benzopyran-3-carboxaldehydes. Synthesis of 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids and 3-Hydroxymethylchromones[2]

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4-Oxo-4*H*-1-benzopyran-3-carboxylic acids were synthesized by Jones oxidation of 3-carboxaldehyde derivatives. Their infrared spectrum, nuclear magnetic resonance, p*K*a, and mass spectra were studied under comparison with those of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid. In the mass spectra characteristic fragmentation pathways were observed. 3-Hydroxymethylchromones were prepared by the reduction of 3-carboxaldehyde derivatives with sodium borohydride in the presence of anhydrous aluminum chloride.

It has been reported by Koda, *et al.*[4] that baicalein (5,6,7-trihydroxyflavone) and its phosphate derivative, (baicalein-6-phosphate) markedly depress the release of mediators (Histamine, SRS-A *etc.*) from tissues involved in the antigen-antibody reaction. Several known compounds (flavones and chromones) were submitted to the biological test and it was observed that 3-acetyl-5,7-dihydroxy-2-methylchromone depressed the mediator release more strongly than 5,7-dihydroxy-2-methylchromone.[5] Therefore the presence of carbonyl group at the C-3 position of the chromone seemed to be valuable for the compounds to exhibit such activity. On the other hand, it is well known that 4-oxo-4*H*-1-benzopyran-2-carboxylic acid derivatives, *e.g.* disodium cromoglycate [disodium 5,5′-(2-hydroxy-1,3-propanediyldioxy)-bis(4-oxo-4*H*-1-benzopyran-2-carboxylate)][6] inhibit allergic reaction. Despite growing interest in chromone chemistry, limited information is as yet available concerning the biological activities of several 4-oxo-4*H*-1-benzopyran-3-carboxylic acids. These facts prompted us to explore their synthesis.

The synthesis of chromone derivatives carrying carboxyl group at C-3 position has been regarded as difficult one. 6,7-Dimethoxy-2-methylchromone-3-carboxylic acid has been synthesized by decarbonylation of the 3-ketocarboxylic acid ester derivative followed by hydrolysis.[7] Flavone-3-carboxylic acids have been prepared by oxidation of the benzopyrano-[3,2-*c*]coumarins to the chromones whose lactone group was then simultaneously hydrolyzed and methylated.[8] Recently another route to chromeno[4,3-*b*]chromen-6,7-dione from *cis* disalicylide was reported by Dean, *et al.*[9] Chromone-3-carboxylic acid esters containing

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[1] Part I: A. Nohara, T. Umetani, and Y. Sanno, *Tetrahedron*, **30**, 3553 (1974).

[2] A preliminary report of this work has been published: A. Nohara, T. Umetani, and Y. Sanno, *Tetrahedron Letters*, **1973**, 1995.

[3] Location: *Juso, Yodogawa-ku, Osaka.*

[4] A. Koda, H. Nagai, and H. Wada, *Folia Pharmacologica Japonica*, **66**, 194, 273 (1970); A. Koda, H. Nagai, Y. Yoshida, and L.H. Kiat, *ibid.*, **66**, 471 (1970).

[5] Y. Sanno, A. Nohara, H. Kuriki, and A. Koda, *J. Takeda Res. Lad.*, **33**, 225 (1974).

[6] H. Cairns, C. Fitzmaurice, D. Hunter, P.B. Johnson, J. King, T.B. Lee, G.H. Lord, R. Minshull, and J.S.G. Cox, *J. Med. Chem.*, **15**, 583 (1972).

[7] G.G. Badcock, F.M. Dean, A. Robertson, and W.B. Whalley, *J. Chem. Soc.*, **1950**, 903.

[8] E. Ziegler, K. Mayr, and U. Rossmann, *Monatsh, Chem.*, **92**, 296 (1961).

[9] F.M. Dean, K.B. Hindley, and S. Small, *J. C. S. Perkin* I, **1972**, 2007.

four fluorine atoms on the benzene ring were synthesized from pentafluorobenzoyl chloride and ethyl acetoacetate in the presence of magnesium ethoxide.[10] These methods have the disadvantages such as requiring many steps or giving low yields.

The approach to the preparation of 4-oxo-4*H*-1-benzopyran-3-carboxylic acids by the oxidation of 3-carboxaldehydes[1,2] which can be easily prepared in one step from *o*-hydroxyacetophenones and Vilsmeier reagent, was pursued. Oxidation of 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **1**[1,2,11] with 30% hydrogen peroxide aqueous solution in acetic acid gave salicylic acid, and products oxidized with 30% hydrogen peroxide in acetone showed several spots on silica gel thin-layer chromatography (TLC). Other oxidation with silver oxide, argentic oxide, dilute nitric acid, chromic anhydride-dimethylformamide, or electrolytic oxidation also did not give good results. On the other hand, oxidation reaction of chromic anhydride in acetic acid yielded the desired 4-oxo-4*H*-1-benzopyran-3-carboxylic acid (**2**) in a poor yield. Then the oxidation by Jones reagent[12] anticipating increased yield was examined. Jones oxidation of **1** in acetone at 15—20° gave **2** in 39% yield. Similarly following 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes carrying ethyl, *n*-propyl, methoxy groups and chlorine atom at C-6 position (**3**, **5**, **7** and **9**)[1,2] were oxidized to the 3-carboxylic acid derivatives (**4**, **6**, **8** and **10**). Next, we selected dihydroxy-4-oxo-4*H*-1-benzopyran-3-carboxylic acid derivatives as possible anti-allergic agents on the analogy of the chemical structure of baicalein and some physiologically active chromones. 5,7-Diacetoxy- and 6,7-diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (**11**, **12**)[1,2] were oxidized by Jones reagent similarly to the corresponding diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxylic acids (**13** and **14**) in 18.5% and 9.5% yield, respectively (Table I). As **2** was stable under heating with hydrochloric acid in acetic acid, the desired 5,7-dihydroxy- and 6,7-dihydroxy-3-carboxylic acids (**15** and **16**) were obtained by treating **13** and **14** under the same reaction conditions.

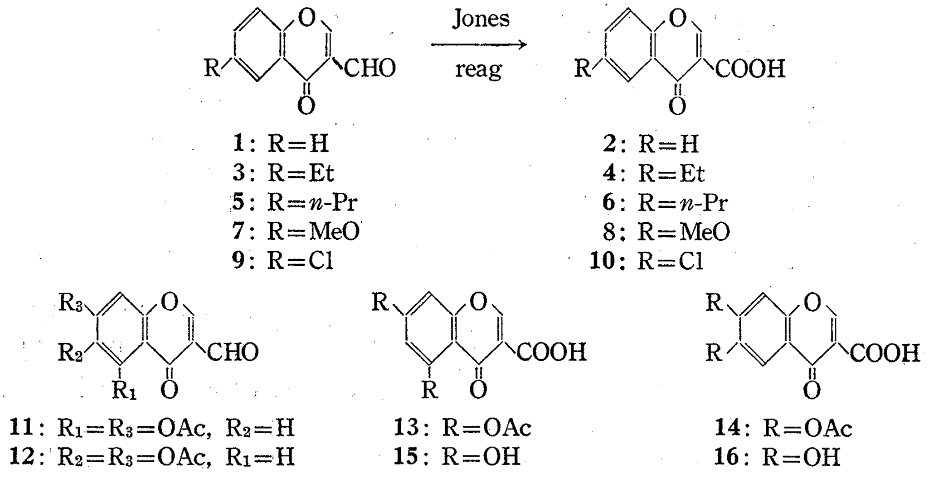

Chart 1

Compound **2** was also prepared by the alternative route. That is to say, heating of 4-oxo-4*H*-1-benzopyran-3-carbonitrile **17**[13] in conc. sulfuric acid yielded 3-carboxamide derivative **18** in 65% yield which was hydrolyzed to **2** with 6N sulfuric acid and acetic acid (1:1), in 20% yield. On the other hand, the preparation of the other carboxamide by the Ritter reaction was tried. The reaction of **17** with *t*-butanol in trifluoroacetic acid containing

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10) N.N. Vorozhtsov, V.A. Barkhash, A.T. Prudchenko, and T.I. Khomenko, *Proc. Acad. Sci. U.S.S.R.*, **164**, 962 (1965); *idem*, *Zh. Ohshch. Khim.*, **35**, 1501 (1965); *idem*, *Chem. Abstr.*, **64**, 2045b (1966).

11) F. Eiden and H. Haverland, *Arch. Pharm.*, **300**, 806 (1967).

12) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," 1st ed., John Wiley and Sons, Inc., New York, 1967, pp. 142—143.

13) A. Nohara, *Tetrahedron Letters*, **1974**, 1187.

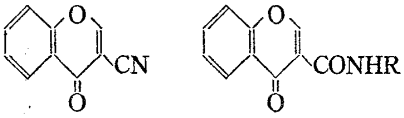
Table I. Synthesis of 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids from Corresponding 3-Carboxaldehydes

Compound	mp (°C)	Yield (%)	Solv.[a]	Formula	Analysis (%)			
					Calcd.		Found	
					C	H	C	H
2	204—205 (decomp.)	39	A	$C_{10}H_6O_4$	63.17	3.18	63.18	3.18
4	151—152	20	B	$C_{12}H_{10}O_4$	66.05	4.62	66.00	4.37
6	135—136	22	B	$C_{13}H_{12}O_4$	67.23	5.21	67.22	5.10
8	173—174	25	A	$C_{11}H_8O_5$	60.00	3.66	59.94	3.54
10	231—232 (decomp.)	15	A	$C_{10}H_5ClO_4$	53.47	2.24	53.34	2.20
13	155—156 (decomp.)	18.5	C	$C_{14}H_{10}O_8 \cdot 1/2H_2O$	53.34	3.52	53.43	3.64
14	189—191 (decomp.)	9.5	A	$C_{14}H_{10}O_8$	54.91	3.29	54.90	3.20
15[b]	[c]	88	D	$C_{10}H_6O_6$	54.06	2.72	54.03	2.75
16[b]	285—287 (decomp.)	83	D	$C_{10}H_6O_6$	54.06	2.72	53.75	2.71

a) solvent for recrystallization: A=$(CH_3)_2CO$, B=C_6H_6, C=EtOH, D=DMF–H_2O
b) Prepared by the hydrolysis of the acetate derivative.
c) Polarized light disappears at about 280° and the substance turns black.

a small amount of conc. sulfuric acid at room temperature afforded N-*t*-butylcarboxamide derivative **19** in 89% yield.

The infrared (IR) spectra of 4-oxo-4*H*-1-benzopyran-2-carboxylic acids and their esters have already been studied[14–17] but those of 4-oxo-4*H*-1-benzopyran-3-carboxylic acids have not been yet examined. We now record the IR spectra between 1800—1600 cm^{-1} region of some 4-oxo-4*H*-1-benzopyran-3-carboxylic acids in the solid state. (Table II). Most of spectra showed a strong carboxylic acid band at 1752±13 cm^{-1} and a strong carbonyl band of the pyrone at 1622±12 cm^{-1}.



17

18: R=H
19: R=C(CH$_3$)$_3$

Chart 2

Table II. IR Absorption Data (KBr discs) of Some 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids between 1800 and 1600 cm^{-1}

Compound	COOH	CO (pyrone)	AcO
2	1750	1620	
4	1760	1620	
6	1740	1630	
8	1740	1610	
10	1755	1620	
13	1750	1635	1780
14	1765	1625	1785
15	1715	1655, 1620	
16	1730	1635, 1620	

In the IR spectrum of **2**, the carbonyl band of the pyrone at 1620 cm^{-1} is lower than those of chromone **20** (1650 cm^{-1}) and 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (**21**) (1640 cm^{-1}).[14] The carboxylic acid band of **2** (1750 cm^{-1}) is higher than that of **21** (1734 cm^{-1}).[14] The pK_a' of **2** was 8.85, which was obtained by a potentiometric method in dimethyl sulfoxide (DMSO)–

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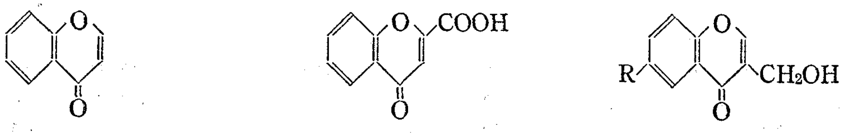
14) P. Niviere, P. Tronche, and J. Couquelet, *Bull. Soc. Chim. France*, **1965**, 3658.
15) G. Barker and G.P. Ellis, *J. Chem. Soc.* (*C*), **1970**, 2609.
16) W. Cocker, T.B.H. McMurray, and P.A. Staniland, *J. Chem. Soc.*, **1965**, 1034.
17) S. Gronowitz and R. Ekman, *Ark. Khemi.*, **17**, 93 (1960).

H_2O system. This value is very high in comparison with that of **21** (pK_a' 4.15: pK_a 2.96[18]). These observations suggest that intramolecular hydrogen bonding between C-3 carboxylic acid and carbonyl group of the pyrone exists in **2** and homologous series. Furthermore, the signals of carboxylic acid around δ 13 in the NMR spectra (Table III) also support the above estimation.



20 **21** **22**: R=H
23: R=Cl

Chart 3

Table III. NMR Spectral Data of Some 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids

Compound	Solv.[a]	H_2[b]	COOH[c]	Other protons
2	A	9.12		[d]
4	B	9.00	13.4	[e]
6	B	8.98	13.4	[f]
8	A	9.05	13.2	[g]
10	A	9.13		[h]
13	A	8.95		[i]
13	B	8.88	13.12	[j]
14	A	9.08		[k]
16	A	9.00		[l]

a) A=d_6-DMSO, B=$CDCl_3$
b) All signals are singlet.
c) These signals are broad.
d) 8.13 (H_5, dd, *J*=7 and 2), 7.4—8.0 ($H_{6,7,8}$, m)
e) 8.20 (H_5, m), 7.67 ($H_{7,8}$, m), 2.85 (CH_2, q, *J*=8), 1.35 (CH_3, t, *J*=8)
f) 8.08 (H_5, br, s), 7.62 ($H_{7,8}$, m), 2.80 (CH_2, t, *J*=7), 1.75 (CH_2, sex, *J*=7), 1.00 (CH_3, t, *J*=7)
g) 7.39—7.82 ($H_{5,7,8}$, m), 3.87 (OMe, s)
h) 8.14 (H_5, m), 7.94 ($H_{7,8}$, m)
i) 7.52 (1H, d, *J*=2), 7.15 (1H, d, *J*=2), 2.33 (OAc, s), 2.30 (OAc, s)
j) 7.43 (1H, d, *J*=2), 7.05 (1H, d, *J*=2), 2.42 (OAc, s), 2.37 (OAc, s)
k) 8.00 (H_5, s), 7.80 (H_8, s), 2.33 (2×OAc, s)
l) 7.38 (H_5, s), 7.02 (H_8, s)

In the nuclear magnetic resonance (NMR) spectra, C-2 protons of 4-oxo-4*H*-1-benzopyran-3-carboxylic acids occur at δ 9.04±0.09 in d_6-DMSO, and at δ 8.94±0.06 in $CDCl_3$. This tendency is demonstrated by the compound **13** whose NMR spectra were measured in both solvents.

The mass spectra of **21** and many esters have been described in detail in a recent paper.[19] We examined the fragmentation of some 4-oxo-4*H*-1-benzopyran-3-carboxylic acids. (Table IV). Their fragmentation pattern is exemplified in Chart 4 for the parent compound **2**. The molecular ion loses carbon dioxide to give the base paek at *m/e* 146, which undergoes the expected retro-Diels–Alder reaction (RDA) to give the peak at *m/e* 120 and can also lose carbon monoxide from the pyrone ring to give the peak at *m/e* 118. This feature shows marked difference from **21** whose molecular ion loses in the first step carbon monoxide from the pyrone ring to give the base peak at *m/e* 162 and also undergoes RDA to give *m/e* 120 at the same time.[19] The molecular ion peaks of 3-carboxylic acid derivatives are very weak, whereas that of **21** is very strong.

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18) J. Dauphin, D. Chatonier, J. Couquelet, M. Payard, and M. Picard, *Lab-Pharma-Probl. Tech.*, **18**, 58 (1970).
19) G. Barker and G.P. Ellis, *Org. Mass Spectrometry*, **5**, 857 (1971).

An alternative mode of breakdown of the *m/e* 146 ion produced from **2** occurs through loss of C_2H_2O, and the ion so produced (*m/e* 104)[20] then elides carbon monoxide to afford the benzyne ion-radical (*m/e* 76).[20] The above transitions are substantiated by the observation of appropriate metastable ions (74.1 and 55.5). Though the *m/e* 146 ion produced from **2** appears to be the same as the molecular ion of chromone **20**,[21] their degradation patterns are very different. These characteristic degradation pathways (*m/e* 146→*m/e* 104→*m/e* 76) which markedly differ from those of flavones and chromones,[21] are also observed obviously in a series of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes.[1,2] The fragmentation pattern of **2** at less than *m/e* 146 is almost identical with that of **1**.

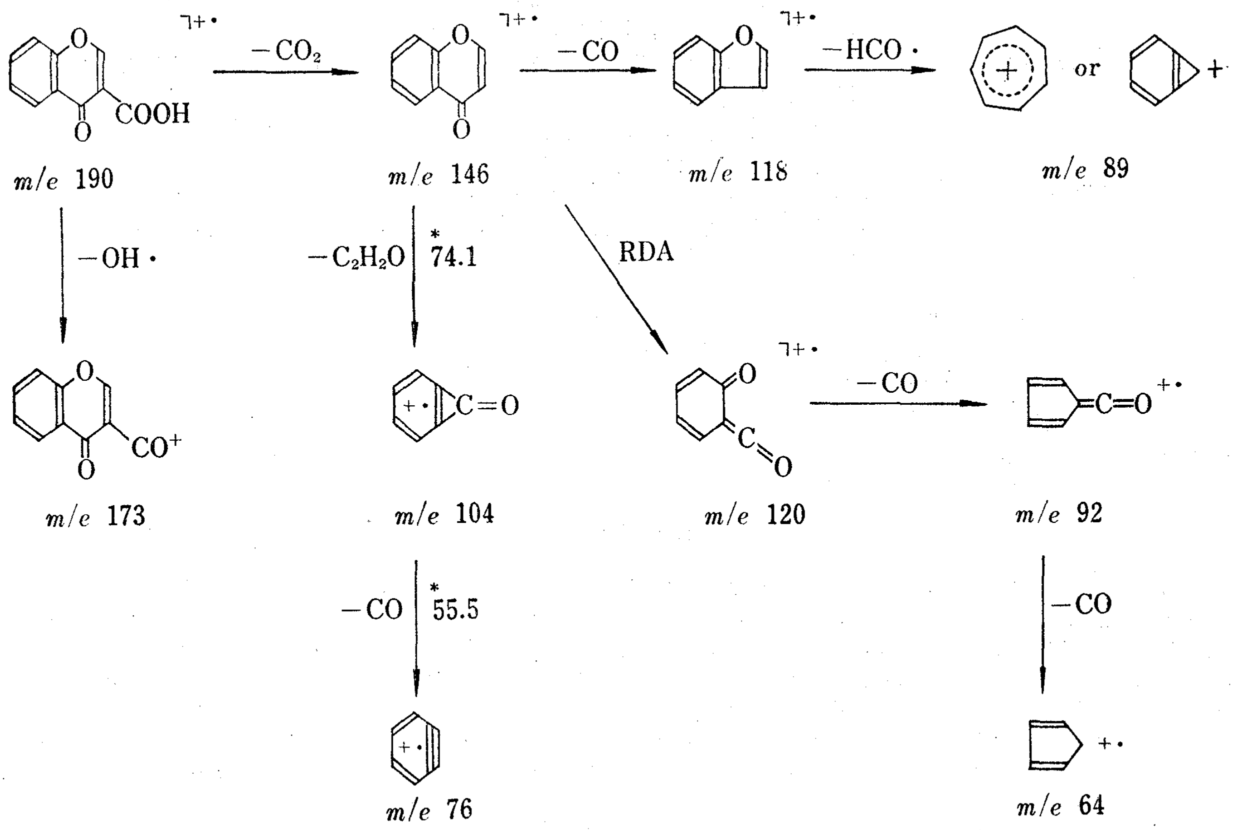

Chart 4

3-Hydroxymethylchromone derivatives have not been synthesized, and their biological activities are also unknown. Therefore, their synthesis was tried by the reduction of 3-carboxaldehyde derivatives. The attempts to hydrogenate **1** with palladium black in methanol or platinum dioxide in acetic acid were not successful. On the other hand, the reduction of **1** with sodium borohydride in the presence of anhydrous aluminum chloride in tetrahydrofuran gave the desired 3-hydroxymethylchromone **22** in 12% yield. Similarly 6-chloro derivative **23** was obtained in 12% yield.

Some of the compounds synthesized herein were tested for the biological activities, but 4-oxo-4*H*-1-benzopyran-3-carboxylic acids (**2**, **13**, **14**, **15**, **16**) and 3-hydroxymethylchromone **22** were found to be almost inactive in the passive cutaneous anaphylaxis test. This result appears to be attributable to weak acidity of C-3 carboxylic acids because of the intramolecular hydrogen bonding, which were evidenced by pK_a, IR and NMR spectral data.

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20) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, (San Francisco) 1964, pp. 274—275.

21) Q.W. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, 1971, pp. 168—174.

Table IV. Mass Spectral Data of Some 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids[a)]

Compound	
2[b)] *m/e* (%)	190(4), 173(3), 147(13), $\underline{146(100)}$[c)], 121(8), 120(19), 118(2), 105(5), $\underline{104(21)}$, 92(11), 90(10), 89(7), $\underline{76(6)}$, 73(6), 64(6), 63(9), 53(12)
13[b)] *m/e* (%)	306(2), 265(14), 264(100), 223(11), 222(94), 220(6), 205(9), 204(46), 179(10), $\underline{178(95)}$, 176(5), 175(7), 152(7), $\underline{136(6)}$, $\underline{108(8)}$, 69(21), 53(39)
14[b)] *m/e* (%)	306(2), 264(22), 223(9), 222(69), 205(8), 204(56), 179(11), $\underline{178(100)}$, 152(15), $\underline{136(6)}$, $\underline{108(6)}$, 69(41)
15[b)] *m/e* (%)	223(11), 222(98), 205(9), 204(40), 179(12), $\underline{178(100)}$, 176(22), 175(6), 153(9), 152(32), $\underline{136(30)}$, 124(23), 122(6), 121(9), 120(11), 111(10), $\underline{108(38)}$, 96(15), 79(13), 78(10), 77(16), 75(9), 74(12), 69(77)
16 *m/e* (%)	222(11), 179(11), $\underline{178(100)}$, 153(9), 152(47), 150(10), $\underline{136(19)}$, 124(9), 122(8), 121(9), $\underline{108(19)}$, 96(12), 95(7), 82(38), 79(13), 78(8), 77(13), 76(9), 75(17), 74(10), 70(10), 69(55)

a) Intensities as percentage of base peak. Values lower than 5% are quoted only if these ions are used for interpreting the fragmentation pathway.

b) Meta stable peaks support the following transitions in compounds **2**, **13**, **14**, **15**:
2: *m/e* 146→104[146-C_2H_2O], 104→76[104-CO]
13, **14**: *m/e* 306→264[M−CH_2CO], 264→222[264−CH_2CO], 222→178[222−CO_2]
14: *m/e* 178→152[178−C_2H_2]
15: *m/e* 222→178[M−CO_2]

c) The underlines show the characteristic fragments of 4-oxo-4*H*-1-benzopyran-3-carboxylic acids.

Experimental

Melting points were determined with a Micro Melting Point Apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a Hitachi Infrared Spectrophotometer EPI-S2. NMR spectra were measured on a Varian Associates T-60 instrument, and are given in parts per million (δ) downfield from an internal tetramethylsilane standard. Mass spectra were recorded with a Hitachi RMU-6D or a Hitachi RMS-4 instrument. TLC-sheets Woelm pre-coated Silica gel F 254/366 were used for thin-layer chromatography.

Oxidation of 1 with Hydrogen Peroxide in AcOH——To a solution of 870 mg (5 mmoles) of 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **1**[1,2,11)] in 20 ml of AcOH was added 3 ml of 30% H_2O_2 aqueous solution. The solution was stood at room temperature overnight, and treated with Pd black to decompose the peracid. The mixture was evaporated *in vacuo*, and the residue was taken up in acetone. The acetone solution was filtered, and evaporated to dryness *in vacuo*. The residue was crystallized from $CHCl_3$ to afford 280 mg of salicylic acid, mp 158—160°. This material was identified with the authentic sample.

4-Oxo-4*H*-1-benzopyran-3-carboxylic Acid (2)——To a solution of 8.90 g (51 mmoles) of **1** in 700 ml of acetone was added during 1 hr at 10—15° under stirring 25 ml of Jones reagent which was prepared from 7.0 g of chromic anhydride in 8 ml of concentrated H_2SO_4 and 40 ml of H_2O. The acetone solution was separated from the dark green resinous substance by decantation, and diluted with 1.5 liters of H_2O. The separated crystals were recrystallized from acetone to give 3.82 g of colorless prisms.

5,7-Diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxylic Acid (13)——To a solution of 7.9 g (27.2 mmoles) of 5,7-diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **11**[1,2)] in 340 ml of acetone was added during 1 hr at 10—15° under stirring 19 ml of Jones reagent which was prepared from 6.0 g of chromic anhydride in 3.6 ml of 97% H_2SO_4 and 18 ml of H_2O. The acetone solution was separated from the dark green resinous substance by decantation, concentrated to a half volume *in vacuo* at room temperature, and diluted with H_2O. The separated crystals were collected by filtration and recrystallized from EtOH to give 1.54 g of colorless needles.

6,7-Dihydroxy-4-oxo-4*H*-1-benzopyran-3-carboxylic Acid (16)——To a solution of 3.76 g of 6,7-diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxylic acid **14** in 75 ml of AcOH was added 25 ml of concentrated HCl and the mixture was heated at 70° for 20 min. The precipitate was collected by filtration, washed with H_2O, and dissolved in 23 ml of dimethyl formamide (DMF). After treating with active carbon, the DMF solution was diluted with H_2O to give 2.27 g (83%) of needles.

4-Oxo-4*H*-1-benzopyran-3-carboxamide (18)——A solution of 855 mg (5 mmoles) of 4-oxo-4*H*-1-benzopyran-3-carbonitrile **17**[13)] in 5 ml of concentrated H_2SO_4 was heated at 100° for 50 min. The solution was poured into 70 ml of ice-water and the precipitate was collected by filtration. Recrystallization from EtOH afforded 620 mg (65.6%) of pale yellow crystals, mp 236—238° (decomp.). *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.73; H, 3.58; N, 7.45. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH_2), 1685 ($CONH_2$), 1665 (pyrone CO). NMR (CF_3COOD): 9.28 (1H, s, H_2), 8.35 (1H, dd, $J=2$ and 8 Hz, H_5), 7.5—8.2 (3H, m, $H_{6,7,8}$).

2 from **18**: A solution of 38 mg (0.2 mmole) of **18** in 1 ml of AcOH and 1 ml of 6 N H_2SO_4 was heated at 120° for 4 hr. The solution was diluted with H_2O and extracted with EtOAc. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting solid was recrystallized from acetone to afford 8 mg (20%) of crystals, mp 204—205° (decomp.). This material was identical with the sample prepared above.

N-*t*-Butyl-4-oxo-4*H*-1-benzopyran-3-carboxamide (19)——A solution of 855 mg (5 mmoles) of **17** in 1.0 ml of *t*-BuOH, 2 ml of trifluoroacetic acid and 4 drops of concentrated H_2SO_4 was stirred at room temperature for 18 hr. The reaction mixture was evaporated *in vacuo* and EtOAc was added to the residue. The solution was washed with 1 N Na_2CO_3 solution until it was neutral, and then H_2O, dried (Na_2SO_4) and evaporated *in vacuo*. Petroleum benzine was added to the residual crystal which was collected. 1.13 g (89%) of colorless crystals, mp 132—134°. *Anal.* Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.46; H, 6.03; N, 5.78. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1680 (CONH), 1620. NMR ($CDCl_3$): 9.25 (1H, br. NH), 8.90 (1H, s, H_2), 8.23 (1H, m, H_5), 7.2—7.9 (3H, m, $H_{6,7,8}$), 1.47 (9H, s, *t*-Bu).

3-Hydroxymethylchromone (22)——To a cooled 100 ml of tetrahydrofuran (THF) were added in turn 8.0 g (60 mmoles) of finely powdered anhydrous $AlCl_3$, 3.48 g (20 mmoles) of **1** and then 760 mg (40 mmoles) of $NaBH_4$. The mixture was refluxed for 1.5 hr, cooled, acidified with 1 N HCl and extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4 and evaporated to dryness. The residue was taken up in $CHCl_3$ and chromatographed on silica gel. Elution with a mixture of $CHCl_3$, acetone and HCO_2H (9:1:0.1) gave a solid which on recrystallization from EtOAc–petroleum ether gave 435 mg (12%) of pale yellow crystals, mp 109—111°. *Anal.* Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.18; H, 4.45. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1640 (CO). NMR ($CDCl_3$): 8.20 (1H, dd, $J=8$ and 2 Hz, H_5), 8.00 (1H, s, H_2), 7.2—7.8 (3H, m, $H_{6,7,8}$), 4.78 (2H, s, CH_2), 3.47 (1H, br, OH). Mass Spectrum *m/e*: 176 (M^+, base peak).

6-Chloro-3-hydroxymethylchromone (23)——Similarly, **23** was prepared from **9**.[1,2] mp 165—167° (EtOH). Yield, 12%. *Anal.* Calcd. for $C_{10}H_7O_3Cl$: C, 57.03; H, 3.35. Found: C, 56.88; H, 3.30. IR ν_{max}^{KBr} cm^{-1}: 3425 (OH), 1635 (CO). NMR (d_6-DMSO): 8.20 (1H, m, H_5), 7.93 (1H, m, H_2), 7.71 (center) (2H, m, $H_{7,8}$), 5.10 (1H, br, OH), 4.40 (2H, s, CH_2).

Determination of the p*K*a′——Using a potentiometric method, the p*K*a′ in DMSO–H_2O (11:5) was determined at 27—28°.

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