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STUDIES ON ANTIANAPHYLACTIC AGENTS—I

A FACILE SYNTHESIS OF 4-OXO-4*H*-1-BENZOPYRAN-3-CARBOXALDEHYDES BY VILSMEIER REAGENTS[1]

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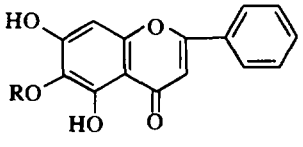
Abstract—By the application of the Vilsmeier-Haack reaction to various *o*-hydroxyacetophenone derivatives, 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes were synthesized in one step. Their IR, NMR and mass spectra were studied. In the mass spectra characteristic fragmentation pathways were observed.

It has been reported[2,3] that baicalein **1a** and its phosphate derivative, baicalein-6-phosphate **1b** depress the release of mediators (Histamine, SRS-A etc.) for tissues involved in the antigen-antibody reaction. Several known compounds (flavones and chromones) were submitted to biological tests and it was observed that 3-acetyl-5,7-dihydroxy-2-methylchromone **2** depresses the mediator release more strongly than 5,7-dihydroxy-2-methylchromone **3**.[4] Therefore, the presence of a CO group at C-3 position of the chromone seemed to be valuable for the compound to display such activity. This fact and paucity of the reports concerning chromone derivatives containing substituents at C-3 position prompted us to explore the synthesis of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes which have a wide range of synthetic utility.

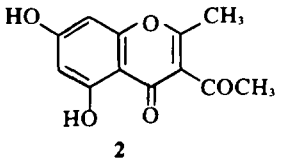
4-Oxo-4*H*-1-benzopyran-3-carboxaldehyde **4** as a parent compound has been prepared for the first time in 30% yield by formylating 2-formyl-2'-hydroxyacetophenone derived from *o*-hydroxyacetophenone **5**, with ethyl orthoformate and acetic anhydride.[5] On the other hand, benzochromone-3-carboxaldehydes have been synthesized from 2, 2-difluoro-4-methylnaphtho-1,3,2-dioxaborin compounds by the Vilsmeier-Haack reaction,[6] and as an another special case, the synthesis of tetrafluorochromone-3-carboxaldehyde from 2,3,4,5,6-pentafluoroacetophenone was reported.[7] Though many methods relating to C-formylation have been known, it is preferred to use milder reaction conditions to prepare the desired compounds containing various functional groups. For this purpose, Vilsmeier-Haack reaction seemed to be suitable.



1

a: R = H

b: R = —P(=O)(OH)$_2$



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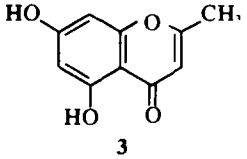

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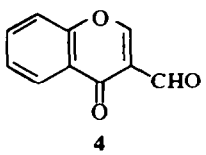

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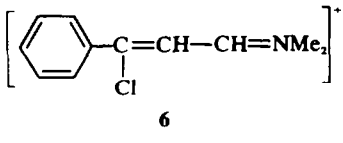

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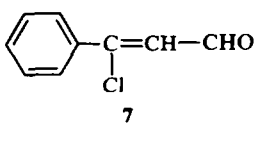

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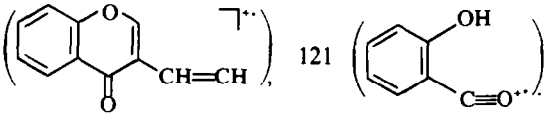
An earlier investigation concerning the Vilsmeier-Haack reaction of $RCOCH_3$ type compounds indicated the following results; if the R group has no H atom (e.g. acetophenone), the intermediate **6** cannot be formylated further, and gives β-chlorovinylaldehyde derivative **7** by treatment with water.[8] In order to add one more formyl group to **6**, more complicated procedure is necessary.[9] But in the case of 2,2-difluoro-4-methylnaphtho-1,3,2-dioxaborin compounds, double formylation of the Me group takes place by Vilsmeier reagent.[6] The difference between these reaction mechanisms can be rationalized as follows; while enolated acetophenones react with the reagent to give monoformyl derivatives, those compounds in which the enolization was prohibited by 1,3,2-dixoaborin ring formation can be doubly formylated.

As *o*-hydroxyacetophenone **5** takes a similar ring form as dioxaborin compounds by the H-bond under the usual conditions, we considered the desired 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **4** would be produced from *o*-hydroxyacetophenone itself by Vilsmeier reagent. Actually Vilsmeier-Haack reaction with *o*-hydroxyacetophenone afforded **4** in 61% yield in one step. The structure of **4** was confirmed by direct comparison with an authentic sample. In this reaction a small amount of by-product **9**[10] was obtained. The mass spectrum exhibited peaks at *m/e* 292 (M^+), 171

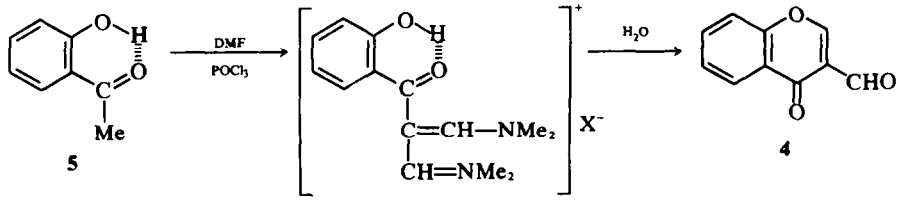


The NMR spectrum (d_6-DMSO) exhibited H-bonded hydroxyl (δ 12·46, 1 H, singlet), trans vinyl protons (δ 8·52, 1 H, doublet and δ 7·56, 1 H, doublet, each J = 16 Hz) and a C-2 proton of pyrone ring (δ 9·01, 1 H, singlet). The structure of **9** was inferred from these data and m.p.[10] This was confirmed by converting **9** to 4-oxo-chroman derivative **10**[10] by heating with 85% H_3PO_4. The NMR spectrum of **10** exhibited ABX pattern signals due to chromanone at δ 5·66, δ *ca* 3·2 and δ *ca* 2·82 (each 1 H) besides the signals of chromone.

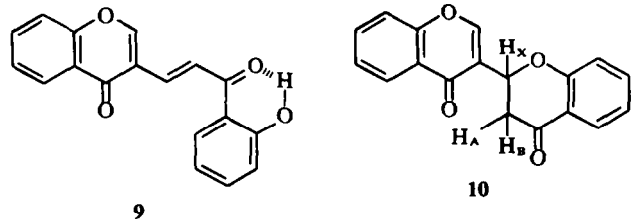
It has become apparent that the synthesis of **4** can be achieved in one step from *o*-hydroxyacetophenone. Accordingly, *o*-hydroxyacetophenone derivatives containing various substituents were submitted to the Vilsmeier-Haack reaction, and the results are shown in Table 1. A typical example is shown for 6-ethyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (**14**) in the Experimental. The starting materials were synthesized mainly by Fries rearrangement of phenyl acetate derivatives (**11–25**, **35–39**). Alkylation of OH groups (**27**, **31**), dealkylation of alkoxy group (**29**), nitration (**43**), or acylation of the OH group (**47**, **49**) were carried out on *o*-hydroxyacetophenones. 5'-Dimethylamino-2'-hydroxyacetophenone **45** was prepared by catalytic hydrogenation of **43** with formalin in the presence of palladium chloride.

Generally speaking, *o*-hydroxyacetophenones containing electron attracting or releasing groups react with Vilsmeier reagent to give the desired products. However, *o*-hydroxyacetophenones carrying a OMe group at C-4' position, e.g. 4'-methoxy-, 4',5'-dimethoxy- and 4',6'-dimethoxy-2'-hydroxyacetophenones, give the desired products in low yield, because of the formylation on the benzene ring and formation of the tarry material. Likewise, *o*-hydroxyacetophenones carrying one more OH group, (e.g. 2',4'-dihydroxyacetophenone) also give the desired hydroxy derivatives in a poor yield.

Meanwhile, good results were obtained by using the material with an OH group protected by an acetyl group at positions other than C-2'.



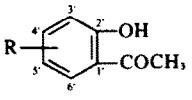
5 4



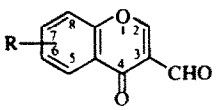
9 10

Table 1. Synthesis of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes from 2'-hydroxyacetophenones with Vilsmeier reagent

Starting materials



Products



Compound and position	R-	Compound and position	Mp(°C)	Yield (%)	Solv[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
11[b] 5'-	Me	12 6-	174–175	65	A	$C_{11}H_8O_3$	70·21	4·29		70·24	4·49	
13[c] 5'-	Et	14 6-	109–111	76	B	$C_{12}H_{10}O_3$	71·28	4·99		71·21	4·88	
15[d] 5'-	n-Pr	16 6-	100–102	53	C	$C_{13}H_{12}O_3$	72·21	5·57		71·89	5·44	
17[e] 5'-	i-Pr	18 6-	98–99·5	42	D	$C_{13}H_{12}O_3$	72·21	5·57		72·43	5·58	
19[g] 5'-	n-Bu	20 6-	86·5–88	32	E	$C_{14}H_{14}O_3$	73·02	6·13		73·08	6·12	
21[g] 5'-	n-Hex	22 6-	oil	60	—	$C_{16}H_{18}O_3$						
23[g] 5'-	cyclo-Hex	24 6-	164–165	42·5	A	$C_{16}H_{16}O_3$	74·98	6·29		74·68	6·03	
25[f] 3',5'-	Me_2	26 6,8-	186–187	24·5	F	$C_{12}H_{10}O_3$	71·28	4·99		71·24	4·79	
27[g] 4'-	OMe	28 7-	188–190	6	A	$C_{11}H_8O_4$	64·70	3·95		64·76	3·98	
29[h] 5'-	OMe	30 6-	164–166	62	A	$C_{11}H_8O_4$	64·70	3·95		64·74	3·93	
31[i] 6'-	OMe	32 5-	115–116	61	A	$C_{11}H_8O_4$	64·70	3·95		64·67	3·99	
33[j] 4',5'-	$(OMe)_2$	34 6,7-	226–226·5	4	B	$C_{12}H_{10}O_5$	61·54	4·30		61·40	4·18	
35[k] 5'-	Cl	36 6-	166–168	73	A	$C_{10}H_5ClO_3$	57·58	2·42		57·63	2·54	
37[l] 3',5'-	Br_2	38 6,8-	177–178	40	A	$C_{10}H_4Br_2O_3$	36·18	1·21		36·26	1·02	
39[m] 5'-	COOH	40 6-	271·5–273·5(d.)	14	A	$C_{11}H_6O_5$	60·56	2·77		60·51	2·91	
41[n] 5'-	CN	42 6-	216–217·5	55	A	$C_{11}H_5NO_3$	66·33	2·58	7·03	66·05	2·43	6·96
43[o] 5'-	NO_2	44 6-	163–164	53·6	A	$C_{10}H_{10}NO_5$	54·80	2·30	6·39	54·56	2·05	6·28
45* 5'-	NMe_2	46 6-*	153·5–154·5	49	F	$C_{12}H_{11}NO_3$	66·35	5·10	6·45	65·99	5·00	6·38
47[p] 4'-	OAc	48 7-	155–156	67	A	$C_{12}H_8O_5$	62·07	3·47		62·12	3·43	
49[q] 6'-	OAc	50 5-	177–179	97	B	$C_{12}H_8O_5$	62·07	3·47		62·13	3·46	
53[r] 4',6'-	$(OAc)_2$	54 5,7-	162–163(d.)	80	A	$C_{14}H_{10}O_7$	57·94	3·47		58·23	3·45	
55* 4',5'-	$(OAc)_2$	56 6,7-*	140–141	66	A	$C_{14}H_{10}O_7$	57·94	3·47		58·15	3·48	

[a] Solvent for recrystallization: A = Me_2CO, B = EtOAc, C = ligroin-EtOAc, D = petroleum ether-EtOAc, E = ligroin-cyclohexane, F = DMF-Me_2CO.

[b] *Dictionary of Organic Compounds*, p. 1717, Maruzen, (1965).

[c] K. Auwers, W. von Mauss, *Liebigs Ann.* **460**, 240 (1938).

[d] E. N. Marvell, B. Richardson, R. Anderson, J. L. Stephenson, T. Crandall, *J. Org. Chem.* **30**, 1032 (1965).

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[f] K. V. Auwers, M. Lechner, H. Bundesmann, *Chem. Ber.* **58**, 45 (1925)

[g] *Dictionary of Organic Compounds*, p. 1710, Maruzen (1965).

[h] C. T. Chang, M. F. Young, F. C. Chen, *Formosan Sci.* **16**, 29 (1962); *Chem. Abstr.* **59**, 2758h (1963).

[i] A. A. Shamshurin, Y. M. Revenko, *Izu. Akad. Nauk. Moldavsk. S. S. R.* 86, (1962); *Chem. Abstr.* **62**, 16102h (1965).

[j] G. Bergellini, G. B. Marini-Bettolo, *Gazz. Chim. Ital.* **70**, 170 (1940).

[k] K. Kindler, H. Oelschläger, *Chem. Ber.* **87**, 194 (1954).

[l] C. C. Tai, *J. Chin. Chem. Soc.* **4**, 361, 366 (1936); *Beilstein*, **8**, III, 269, (1969).

[m] T. Nagano, K. Matsumura, *J. Am. Chem. Soc.* **75**, 6237 (1953).

[n] G. P. Ellis, D. Shaw, *J. C. S. Perkin I*, 779 (1972).

[o] S. S. Joshi, H. Singh, *J. Am. Chem. Soc.* **76**, 4993 (1954).

[p] L. Jurd, L. A. Rolle, *Ibid.* **80**, 5527 (1958).

[q] P. Moses, R. Dahlbom, *Acta Chem. Scand.* **24**, 312 (1970).

[r] G. Büchi, D. M. Foulkes, M. Kurono, G. F. Mitchell, R. S. Schneider, *J. Am. Chem. Soc.* **89**, 6745 (1967).

*Refer to the experimental.

Thus Vilsmeier reaction of 4'-acetoxy-2'-hydroxyacetophenone **47** gave 7-acetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **48** in 67% yield.

Since it is noticed that the existence of OH groups on the benzene ring is important for baicalein to exert biological activity,[4] 5,7-dihydroxy- and 6,7-dihydroxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (**51** and **52**) selected from the pharmacological point of view, were synthesized. Vilsmeier-Haack reaction of 4',6'-diacetoxy-2'-hydroxyacetophenone **53**[11] afforded 5,7-diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **54** in 80% yield which was hydrolyzed with a mixture of hydrochloric acid and acetic acid to give the intended 5,7-dihydroxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **51**. On the other hand, another starting material, 4',5'-diacetoxy-2'-hydroxyacetophenone **55** has been unknown.

But there is a report that hydroxydiacetoxyacetophenone produced by the reaction of 1,2,4-triacetoxybenzene **57** with zinc chloride in acetic acid was hydrolyzed to 2',4',5'-trihydroxyacetophenone **60** by acid.[12] Although the structure and m.p. of the hydroxydiacetoxyacetophenone was not described, in view of the position to be attacked by acetyl group, we thought the product must be the desired compound (**55**). However, the reaction gave a mixture of **55**, 5'-acetoxy-2',4'-dihydroxy acetophenone **58** and 5-acetoxy-1,3-diacetyl-2,4-dihydroxybenzene **59**, and the yield of **55** was low. Therefore selective acetylation of 2',4',5'-trihydroxyacetophenone **60**[13] was attempted and succeeded by using two moles of acetic anhydride in pyridine. **55** was converted to 6,7 diacetoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **56** by a similar reaction in 66% yield. **56** was hydrolyzed to the desired 6,7-dihydroxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **52** in a similar manner.

7-Methoxy- and 6-nitro-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (**28** and **44**) were also prepared by alternative routes. 7-Hydoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **61** prepared by hydrolysis of **48** was methylated with dimethyl sulfate to give **28**. **44** was obtained in good yield by the nitration of **4**.

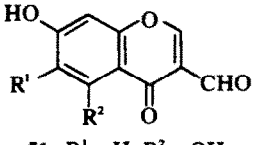
3-Acetylchromone was prepared from 2-hydroxy-ω-acetyl-acetophenone with ethyl orthoformate and acetic anhydride,[5] but its isomer 2-methyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde **62** has not been isolated. Though the yield was low, the reaction of **4** with diazomethane gave **62**.

As the IR, NMR and mass spectra of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes have not been examined, we describe their characteristic spectra. IR spectra between 1800–1600 cm^{-1} in the solid

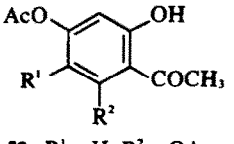
Table 2. IR absorption data (cm^{-1}) of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes between 1800–1600 cm^{-1}

Compound	CHO	CO and C=C		
4	1695	1650	1620	
12	1695	1655	1615	1600
14	1695	1645	1615	1600
16	1700	1650	1615	1605
18	1700	1660	1615	1600
20	1695	1660	1615	1600
22	1695	1655	1610	1600
24	1700	1655	1645	
26	1690	1650		1605
28	1690	1660	1615	
30	1685	1645	1620	
32	1695	1655	1610	
34	1690	1640	1615	
36	1695	1660	1610	
38	1695	1670		1595
40[a]	1700	1670	1610	1600
42	1700	1660	1615	1600
44	1690	1660	1625	1605
46	1695	1645	1620	1595
48[b]	1695	1640	1615	
50[c]	1695	1650	1615	
54[d]	1690	1660	1625	1605
56[e]	1695	1665	1625	1605
61	1700	1630		
62	1695	1645	1615	

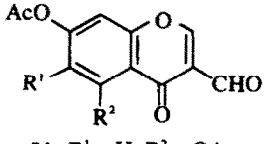
Other Absorptions: [a]COOH: 1720, [b]AcO: 1765, [c]AcO: 1760, [d]AcO: 1790, 1780 [e]AcO: 1785, 1775.



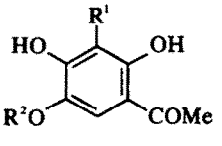
51: $R^1 = H$, $R^2 = OH$
52: $R^1 = OH$, $R^2 = H$



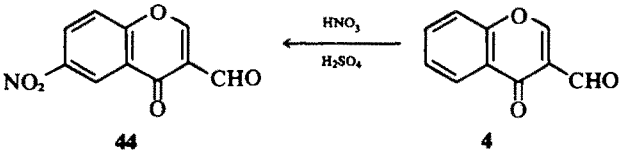
53: $R^1 = H$, $R^2 = OAc$
55: $R^1 = OAc$, $R^2 = H$



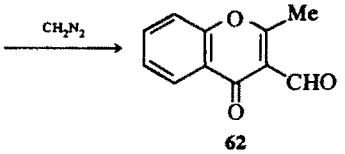
54: $R^1 = H$, $R^2 = OAc$
56: $R^1 = OAc$, $R^2 = H$



58: $R^1 = H$, $R^2 = Ac$
59: $R^1 = R^2 = Ac$
60: $R^1 = H$, $R^2 = H$



44 **4**



62

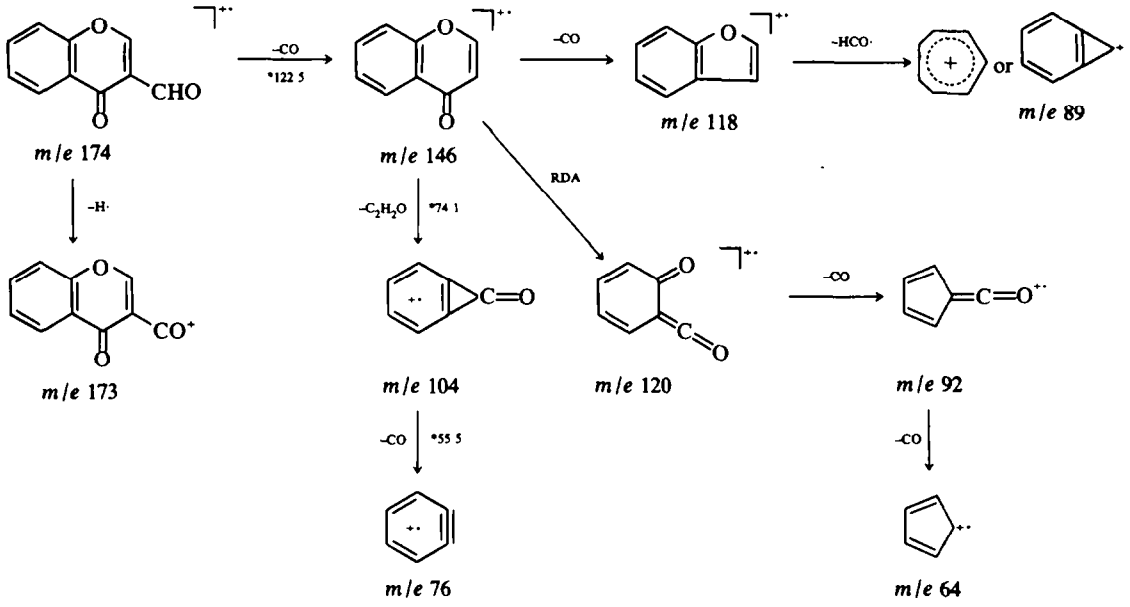
state are recorded in Table 2. They show an aldehyde band at $1692 \pm 8\ cm^{-1}$, a strong CO band of the pyrone at 1645–1665 cm^{-1}, and other peaks in 1600–1625 cm^{-1} region. In the NMR spectra (Table 3) the carboxaldehyde signals occur at δ 10·35 ± 0·10 in $CDCl_3$, while they are generally observed in the higher field at δ 10·05 ± 0·12 in d_6-DMSO. On the other hand the signals of H_2 occur at δ 8·47 ± 0·12 in $CDCl_3$, while they appear in the lower field at δ 8·85 ± 0·15 in d_6-DMSO. This tendency is demonstrated by the compound **14** whose NMR spectra were measured in both solvents.

The fragmentation patterns in their mass spectra (Table 4) are exemplified in Scheme 1 for the parent compound **4**. The molecular ion loses CO to give the base peak at *m/e* 146. The *m/e* 146 ion

Table 3. NMR spectral data of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes

Compound	Solv[a]	CHO[b]	H_2[b]	H_5	H_6	H_7	H_8
4	A	10·16	8·90	7·4–8·3			
12	B	10·42	8·55	8·17 (m)	—	7·62 (dd, J = 2, 8)	7·45 (d, J = 8)
14	B	10·40	8·53	8·12 (m)	—	7·67 (dd, J = 2,9)	7·45 (d, J = 9)
14	A	10·10	8·80	7·90 (m)	—	7·73	7·60 (d, J = 8)
16	B	10·36	8·49	8·07 (d, J = 2)	—	7·59 (dd, J = 2, 9)	7·41 (d, J = 8)
18	B	10·39	8·52	8·13 (d,J = 2)	—	7·64 (dd, J = 2, 8)	7·44 (d, J = 8)
20	B	10·45	8·58	8·15 (d, J = 2)	—	7·63 (dd, J = 2, 9)	7·45 (d, J = 9)
22	C	10·18	8·35	7·90 (d, J = 2)	—	7·2–7·6	
24	B	10·40	8·52	8·05 (d, J = 2)	—	7·3–7·8	
26	A	10·03	8·75	7·70 (m)	—	7·48 (m)	—
28	D	*	9·33	8·40 (d, J = 10)	7·43 (dd, J = 2, 10)	—	7·38 (d, J = 2)
30	B	10·27	8·57	7·58 (d, J = 2)	—	7·1–7·4	
32	B	10·35	8·35	—	7·05 (dd, J = 1, 8)	7·63 (t, J = 8)	6·90 (dd, J = 8, 1)
34	A	10·17	8·83	7·43 (s)	—	—	7·27 (s)
36	B	10·25	8·58	8·27 (d, J = 2)	—	7·73 (dd, J = 2, 9)	7·53 (d, J = 9)
38	A	10·07	9·00	8·33 (d, J = 2)	—	8·12 (d, J = 2)	—
40	A	10·17	8·93	8·63 (d, J = 2)	—	8·33 (dd, J = 2, 9)	7·83 (d, J = 9)
42	A	9·93	8·83	8·42 (d, J = 2)	—	8·20 (dd, J = 2, 9)	7·83 (d, J = 9)
44	A	10·10	9·00	8·73 (d, J = 3)	—	8·63 (dd, J = 3, 9)	8·02 (d, J = 9)
46	A	10·13	8·70	—	—	6·9–7·7	
48	A	10·10	8·87	8·17 (d, J = 8)	7·37 (dd, J = 2, 8)	—	7·95 (d, J = 2)
50	A	10·10	8·85	—	†	7·92 (dd, J = 7, 9)	†
54	B	10·26	8·36	—	‡	—	‡
56	B	10·32	8·48	8·08 (s)	—	—	7·50 (s)

[a] A = d_6-DMSO, B = $CDCl_3$, C = CCl_4, D = CF_3COOH.
[b] All signals are singlet.
*Overlapped with the signal of CF_3COOH.
†7·63 (dd, J = 2, 9) or 7·23 (dd, J = 2, 7).
‡7·26 (d, J = 2·5) or 6·90 (d, J = 2·5).



SCHEME 1

Table 4. Mass spectral data of some 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes[a]

Compound	*m/e* %
4[b]	174(4), 147(10), 146(100)[c], 121(8), 120(24), 118(3), 105(6), 104(34)[c], 92(17), 90(13), 89(11), 76(13)[c], 64(12), 63(18), 53(24)
36	210(2), 208(6), 182(33)[c], 180(100)[c], 156(10), 154(30), 140(8)[c], 138(22)[c], 128(4), 126(13), 112(3)[c], 110(10)[c], 89(11), 75(10), 74(9), 73(8), 63(25)
51[b]	206(30), 179(11), 178(100)[c], 153(6), 152(14), 149(8), 136(23)[c], 124(8), 108(10)[c], 103(6), 78(18), 69(30), 66(8), 63(21)
52[b]	206(9), 179(11), 178(100)[c], 153(7), 152(29), (136(13)[c], 108(11)[c], 82(9), 69(12)
56[b]	290(5), 263(7), 262(47), 221(4), 220(31), 207(6), 206(54), 205(6), 179(11), 178(100)[c], 177(6), 152(11), 132(2), 69(23)
61[b]	190(5), 163(10), 162(100)[c], 137(9), 136(15), 134(8), 121(6), 120(35)[c], 108(13), 106(6), 105(6), 92(10)[c]
62[b]	188(3), 187(2), 161(11), 160(100)[c], 131(9), 121(19), 120(96), 92(23), 77(7), 67(22)

[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:

4, 51, 52, 56, 61, 62

4, *m/e* 174 → 146[M-CO], 146 → 120[146-C_2H_2], 146 → 104[146-C_2H_2O], 104 → 76[104-CO].

51: *m/e* 206 → 178[M-CO], 178 → 152[178-C_2H_2], 178 → 136[178-C_2H_2O].

52: *m/e* 206 → 178[M-CO], 178 → 152[178-C_2H_2], 178 → 136[178-C_2H_2O], 136 → 108[136-CO].

56: *m/e* 290 → 262[M-CO], 262 → 220[262-CH_2CO], 220 → 178[220-CH_2CO], 206 → 178[206-CO].

61: *m/e* 190 → 162[M-CO], 162 → 120[162-C_2H_2O].

62: *m/e* 188 → 160[M-CO].

[c] They show the characteristic fragments of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes.

undergoes the expected retro-Diels-Alder reaction (RDA) to give the peak at *m/e* 120 and can also lose CO from the pyrone ring to give the peak at *m/e* 118. Furthermore an alternative mode of breakdown of the *m/e* 146 ion occurs through loss of C_2H_2O, and the ion so produced (*m/e* 104)[14] then elide CO to afford the benzyne ion radical (*m/e* 76).[14] The above transitions are substantiated by the observation of appropriate metastable ions (74·1 and 55·5). The *m/e* 146 ion produced from 4 appears to be the same as the molecular ion of chromone itself, but the degradations (*m/e* 146 → *m/e* 104 → *m/e* 76) are not important pathways in the latter.[15] These degradation pathways which markedly differ from those of flavones and chromones seem to be characteristic to 4 - oxo - 4*H* - 1 - benzopyran - 3 - carboxaldehydes and also - 3 - carboxylic acids.[1,16]

Some of the compounds synthesized herein were tested for the biological activities. They show a relatively strong anti-anaphylactic reaction but have low LD_{50} generally.

Some reactions using 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde derivatives are in progress.

EXPERIMENTAL

M.Ps were taken with micro melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a Hitachi EPI-S2 or a Hitachi 215 Grating Infrared Spectro-photometers. NMR spectra were measured on Varian Associates T-60 or A-100 instruments, and are given parts per million (δ) downfield from an internal TMS standard. Mass spectra were recorded with Hitachi RMU-6D or Hitachi RMS-4 instruments. TLC-sheets Woelm pre-coated Silica gel F 254/366 were used for TLC.

4-Oxo-4H-1-benzopyran-3-carboxaldehyde (**4**) *and trans 1-(2-hydroxybenzoyl)-2-(4-oxo-4H-1-benzopyran-3)-ethylene* (**9**). To a stirred soln of *o*-hydroxyacetophenone (25 g; 0·184 mole) in 80 ml DMF 80 ml of tetrachloropyrophosphate was added dropwise at −20–20° during about 10 min. The mixture was stirred at room temp for 13 hr, and decomposed by ice-water. The resulting ppt was collected by filtration, washed with H_2O and then EtOH, and recrystallized from acetone to afford **4** (19·6 g; 61%) as colorless crystals, m.p. 152–153° (lit.[5] m.p. 152°). This material was identical with an authentic sample prepared by the method of Eiden.[5] EtOH washings were evaporated *in vacuo* and the residual syrup was kept at room temp for about 10 days. The resulting crystals were collected by filtration and washed with MeOH. Two crystallizations from acetone gave **9** (430 mg) as yellow needles, m.p. 177–179°. (lit.[10] m.p. 178–179°). IR (KBr) cm^{-1}: 1655, 1615, 1570, 1460, 1310, 1260, 770, 760. UV λ_{max}^{MeOH} nm: 224 (sh), 231, 281, 312. NMR (d_6-DMSO) (100 MHz): 12·46 (1H, s, hydrogen bonded OH), 9·01 (1H, s, chromone-H_2), 8·52 (1H, d, J = 16 Hz, ethylene-H_2), *ca* 8·14 (1H, dd, J = 8 and 2 Hz, chromone-H_5), *ca* 7·95 (1 H, dd, J = 8 and 2 Hz, benzene-H_6), 7·56 (1 H, d, J = 16 Hz, ethylene-H_1), 6·9–7·1 (2 H, benzene-H_3 and H_5), 7·4–7·85 (4H, m). Mass spectrum: *m/e* 292 (M^+), 172, 171, 121, 120, 115, 93, 92, (Found: C, 73·88; H, 4·23. Calcd. for $C_{18}H_{12}O_4$: C, 73·97; H, 4·14%).

2-(4-Oxo-4H-1-benzopyran-3) chroman-4-one (**10**). A mixture of **9** (290 mg) and 15 ml 85% H_3PO_4 was heated at 120° for 5·5 hr. A small amount of starting material was filtered off. The filtrate was diluted with ice-water and extracted with EtOAc. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on the column of silica gel in $CHCl_3$. The eluate was evaporated *in vacuo* and the residue was recrystallized from acetone to give 68 mg (23%) of orange microcrystals, m.p. 152–153°. (lit.[10] m.p. 154–155°). Mass spectrum: *m/e* 292 (M^+).

6-Ethyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**14**). To a soln of **13** (163 g; 1 mole) in 1 liter (13 mole) DMF, $POCl_3$ (367 ml; 4 mole) was added at −20 − 15° during 30 min and then the dryice-acetone bath was removed. The temp of the mixture rose to 55° after 1 hr by an exothermic reaction. The mixture was kept at 50–52° for 40 min, then cooled to 10°, and added to 3 liter of ice water to afford crystals which were recrystallized from EtOAc (charcoal), yielding 136·2 g (67%) of light yellow crystals.

2'-Hydroxy-5'-butylacetophenone (**19**). To a stirred soln of *p*-butylphenyl acetate (b.p. 92-3°/9 mm) (44·7 g; 0·232 mole) powdered anhydr $AlCl_3$ (70 g; 0·524 mole) was added little by little. The mixture was heated at 130° for 3·5 hr, decomposed by ice-water containing HCl, and EtOAc was added. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent gave oil which was distilled under reduced pressure. 36·0 g (80·5%), b.p. 105–109°/1·5 mm.

p-n-Hexylphenyl acetate. Prepared from *p*-n-hexylphenol and Ac_2O, b.p. 113°/0·9 mm, colorless oil (90%).

5'-n-Hexyl- 2' -hydroxyacetophenone (**21**). Prepared by Fries reaction of *p*-n-hexylphenyl acetate, yellow oil, b.p. 110°/0·7 mm (15%). Mass spectrum: *m/e* 220 (M^-).

5'-Cyclohexyl-2'-hydroxyacetophenone (**23**). A soln of *p*-cyclohexylphenol (10 g) in 10 ml Ac_2O, 8 ml dry pyridine and 10 ml benzene was heated for 10 min on the water bath, washed with H_2O after the cooling and then HCl, dried with Na_2SO_4 and evaporated to dryness. (12 g, 97%). To the residue was added $AlCl_3$ (8 g), heated at 140° for 1·3 hr, and the mixture was decomposed by ice water. EtOAc extract was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness to give an oil which was applied to a silica gel column and eluted with benzene. The eluate was evaporated to give 5·6 g of colorless oil. NMR ($CDCl_3$); 7·48 (1 H, d, J = 2 Hz), 7·30 (1 H, dd, J = 9 and 2 Hz), 6·87 (1 H, d, J = 9 Hz), 2·63 (3 H, s), 1·2–2·2 (11 H).

7-Methoxy-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**28**). To a stirred soln of **61** (0·75 g; 4·0 mmole) in 30 ml DMSO Me_2SO_4 (0·5 ml; 5·3 mmole) and anhyd K_2CO_3 (1·0 g; 7·2 mmole) were added. The mixture was stirred at room temp for 1 hr. More $MeSO_4$ (0·25 ml; 2·7 mmole, total 8·0 mmole) and anhydr K_2CO_3 (0·5 g; 3·6 mmole, total 10·8 mmole) were added to the mixture, and the stirring was continued for 1 hr. The mixture was poured into 300 ml H_2O, and the soln was acidified with 2 N HCl and extracted with EtOAc. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. Benzene was added to the residue and the insoluble material was collected and recrystallized from acetone to afford 0·18 g (23%) of light yellow needles.

6-Nitro- 4 -oxo-4H- 1 -benzopyran- 3 -carboxaldehyde (**44**). Compound **4** (8·70 g; 50 mmole) was added to 20 ml conc H_2SO_4 and the resulting reddish-orange soln was cooled with ice water. To this stirred soln was added 20 ml of fuming HNO_3 dropwise over the course of about 10 min. The mixture was poured over ice water (1 liter)

and the ppt was collected by filtration and recrystallized from acetone to afford 9·02 g (83%) of pale yellow prisms. This material was identical with an authentic sample prepared by the method of Table 1.

5'-Dimethylamino-2'-hydroxyacetophenone (**45**). To a soln of **43** (10 g) in 200 ml MeOH were added 22 ml 37% formalin, 4 g of NaOAc, 4 g of active carbon and the suspension of 2 g of $PdCl_2$ in 5 ml of 2 N HCl. The mixture was hydrogenated under atmospheric pressure. About 5·5 liter of hydrogen was absorbed. The mixture was filtered, and the filtrate was concentrated *in vacuo* and cooled. The yellow needles were collected by filtration. 8·08 g (81·7%), m.p. 76·5–77·5. IR (KBr) cm^{-1}: 1640, 1615, 1495, 1205, 820, 765, 760. NMR ($CDCl_3$): 11·71 (1 H, s, OH), 6·8–7·1 (3 H, m), 2·88 (6 H, s, NMe_2), 2·61 (3 H, s, Ac). (Found: C, 66·72; H, 7·41; N, 7·60. Calcd. for $C_{10}H_{13}NO_2$: C, 67·02; H, 7·31; N, 7·82%).

6-Dimethylamino-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**46**). To a soln of **45** (5·38 g; 30 mmole) in 30 ml DMF $POCl_3$ (11 ml; 120 mmole) was added under cooling with an ice-salt bath. The mixture was kept at room temp over night, then poured over ice. The resulting yellow soln was adjusted to pH 6 with K_2CO_3 and the ppt was removed by filtration. The filtrate was adjusted to pH 9 by the addition of K_2CO_3 aq and extracted with EtOAc. The EtOAc soln was dried (Na_2SO_4) and concentrated *in vacuo*. The ppt was collected by filtration. The combined crystals were recrystallized from acetone-DMF (charcoal) to afford 3·2 g (49·1%) of yellow needles.

4',5'-Diacetoxy-2'-hydroxyacetophenone (**55**)

(a) *5'-Acetoxy-2',4'-dihydroxyacetophenone* (**58**) and *5-acetoxy-1,3-diacetyl-2,4-dihydroxybenzene* (**59**). A mixture of 1,2,4-triacetoxybenzene (30 g; 119 mmole), $ZnCl_2$ (45 g) and AcOH (45 g) was heated with occasionally shaking in an oil bath at 140° for 30 min. The mixture was evaporated *in vacuo* and H_2O and benzene were added into the residue. The insoluble material was collected by filtration, and recrystallized from EtOAc and then acetone-light petroleum (charcoal) to afford **58** (1·87 g; 7%) as colorless needles, m.p. 169–170°. IR (KBr) cm^{-1}: 3400, 1745, 1645. NMR (d_6-DMSO): 12·42 (1 H, s, C_2–OH), 10·88 (1 H, s, C_4–OH), 7·53 (1 H, s, H_6), 6·38 (1 H, s, H_3), 2·50 (3 H, s, Ac), 2·23 (3 H, s, OAc). (Found: C, 57·09; H, 4·86. Calcd. for $C_{10}H_{10}O_5$: C, 57·14; H, 4·80%). The organic layer of the filtrate was washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo*. EtOH was added to the residual syrup and the soln was cooled. The resulting ppt was collected by filtration and recrystallized from EtOH (charcoal) to afford **59** (1·99 g) as colorless needles, m.p. 142–143°. IR (KBr) cm^{-1}: 1765, 1635. NMR ($CDCl_3$): 14·65 (1 H, s, OH), 14·58 (1 H, s, OH), 7·53 (1 H, s, H_6), 2·77 (3 H, s, C_3–Ac), 2·52 (3 H, s, C_1–Ac), 2·32 (3 H, s, C_5–OAc). (Found: C, 57·14; H, 4·76. Calcd. for $C_{12}H_{12}O_6$: C, 57·14; H, 4·80%). The EtOH mother liquor yielded second ppt by cooling which was collected and recrystallized from EtOH to afford **55** (1·22 g) as colorless tablets, m.p. 100–101°. IR (KBr) cm^{-1}: 1785, 1775, 1655. NMR ($CDCl_3$): 12·23 (1 H, s, OH), 7·52 (1 H, s, H_6), 6·82 (1 H, s, H_3), 2·56 (3 H, s, C_1–Ac), 2·25 (6 H, s, 2 × OAc). (Found: C, 57·13; H, 4·81. Calcd. for $C_{12}H_{12}O_6$: C, 57·14; H, 4·80%). The combined EtOH mother liquor was evaporated *in vacuo*. The residue was chromatographed on 350 g of silica gel and elution with $CHCl_3$-acetone-MeOH (50:0·5:0·05) gave additional 1·10 g of **55** and 740 mg of **59**. Total **55**: 2·32 g (7·7%), **59**: 2·73 g (9%).

(b) *4',5'-Diacetoxy-2'-hydroxyacetophenone* (**55**). To a stirred soln of **60**[13] (13·0 g; 77 mmole) in 40 ml pyridine Ac_2O (15·8 g; 155 mmole) was added dropwise. The temp was controlled below 35° during the addition. The mixture was stirred for 2 hr and poured into 200 ml ice water. The ppt was recrystallized from EtOH to afford 10·1 g (52%) of colorless tablets, m.p. 100–102°.

6, 7-Diacetoxy-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**56**). To a stirred soln of **58** (25·2 g; 100 mmole) in 100 ml DMF $POCl_3$ (37 ml) was added dropwise over the course of about 15 min, under cooling with a dryice-acetone bath. The bath was removed and the mixture was cooled for 30 min with an ice water bath. Then the stirring was continued for 3·5 hr at room temp. The mixture was poured into 1·2 liter of ice water and the ppt was collected by filtration, washed with H_2O and dried. Recrystallization from acetone gave 19·2 g (66%) of colorless scales.

5, 7-Dihydroxy-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**51**). A soln of **54** (100 mg) in 2 ml AcOH and 1 ml HCl was heated for 1·5 hr at 80°. The mixture was evaporated *in vacuo* and AcOH was added. The resulting solid was collected by filtration and dissolved in 3 ml warm DMSO. The DMSO soln was diluted with 15 ml H_2O to afford yellowish orange noncrystalline material which was purified by reprecipitation from DMSO-H_2O, yield 18 mg, m.p. 273–275° (dec) (The determination of m.p. was uninteligible). (Found: C, 57·87; H, 2·84. Calcd. for $C_{10}H_6O_5$: C, 58·26; H, 2·93%).

6, 7-Dihydroxy-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**52**). A mixture of **56** (150 mg; 0·5 mmole) in 1·5 ml AcOH and 1·5 ml of conc HCl was heated with an open flame for 1 min and allowed to cool, and the separated solid was collected by filtration and dissolved in 5 ml DMSO. The soln was treated with charcoal. H_2O was added to the filtrate to give 77 mg (72%) of pale purple scales, m.p. >300°. (Found: C, 56·96; H, 3·28. Calcd. for $C_{10}H_6O_5 \cdot 1/4H_2O$: C, 57·01; H, 3·11%).

7-Hydroxy-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**61**). A mixture of **48** (2·0 g; 8·62 mmole) in 30 ml AcOH and 20 ml conc HCl was heated under reflux for 10 min and allowed to cool. 20 ml of H_2O was added to the mixture and the resulting red ppt was collected by filtration, washed with H_2O and acetone. Recrystallization from DMF-acetone-H_2O gave 1·17 g (68·2%) of yellow prisms, m.p. 268–271° (dec) (Found: C, 63·17; H, 3·29. Calcd. for $C_{10}H_6O_4$: C, 63·16; H, 3·18%).

2-Methyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde (**62**). To the soln of **4** (870 mg; 5 mmole) in 20 ml dioxane 10 ml of an ethereal soln of diazomethane was added at room temp over the period of 1 hr, and the soln kept at room temp for 1 week. After the evaporation of the solvent EtOH was added to the resulting residue to crystallize. The crystals were collected by filtration and recrystallized from EtOAc (charcoal) to afford 18 mg (2%) of light yellow prisms, m.p. 134–136° (dec). NMR ($CDCl_3$): 10·57 (1 H, s, CHO), 8·27 (1 H, dd, J = 8 and 2 Hz, H_5), 7·3–7·8 (3 H, m, $H_{6,7,8}$), 2·82 (3 H, s, Me). (Found: C, 70·08; H, 3·99. Calcd. for $C_{11}H_8O_3$: C, 70·21; H, 4·28%).

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