Chem. Pharm. Bull. **38**(5) 1266—1277 (1990) Vol. 38, No. 5

Studies on Uricosuric Diuretics. I. Syntheses and Activities of Xanthonyloxyacetic Acids and Dihydrofuroxanthone-2-carboxylic Acids

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Received September 20, 1989

A series of substituted xanthonyloxyacetic acids (5 and 6), 1,2-dihydrofuro[2,3-*c*]xanthone-2-carboxylic acids (7) and 2,3-dihydrofuro[3,2-*b*]xanthone-2-carboxylic acids (8) were synthesized and tested for diuretic and uricosuric activities in rats. Most of the xanthon-3-yloxyacetic acids (5) and 7 showed potent diuretic activities, while 8 had lower activities. Uricosuric activities were found in 5c, 5f, 5k, 5m, 5o, 5p, 5r, 7m, 7p and 8q.

Keywords diuretic activity; uricosuric activity; xanthonyloxyacetic acid; 1,2-dihydrofuro[2,3-*c*]xanthone-2-carboxylic acid; 2,3-dihydrofuro[3,2-*b*]xanthone-2-carboxylic acid

Diuretic agents have been widely used as the drugs of first choice in the treatment of hypertension. However, they frequently cause hyperuricemia as a side effect. Furthermore, it is known that hypertension is often complicated by hyperuricemia. Many cases of hyperuricemia are believed to be due to disorders in the renal excretion of uric acid.[1] Under these circumstances, there exists a strong need for the development of diuretics having uricosuric activity.

Tienilic acid (**1**)[1] (Chart 1) is known to be a diuretic having uricosuric activity, but it has been withdrawn from the market in most countries because of the liver toxicity.

Attempts to develop uricosuric diuretics of a similar type led to the discovery of indacrinone (**2**),[1,2] a dihydrobenzofuran homolog (**3**),[1,3] and HP-522 (**4**)[1,4] (Chart 1). We noticed that these compounds had aryloxyacetic acid as a common structure and so aimed at discovering better uricosuric diuretics possessing the aryloxyacetic acid structure.

We selected tienilic acid (**1**) as the prototype. It is highly conceivable that the liver toxicity of **1** might be due to the metabolic change of the thienyl moiety in liver[5] and that the formation of metabolites might be reduced by changing the thienyl group to a phenyl group and constructing more hydrophilic ring systems. Under these conceptions, we designed aryloxyacetic acids having a variety of ring skeletons, but the substituents were generally limited to a halogen atom or methyl group from the reported results of structure–activity relationship studies of the aryloxyacetic acid diuretics.[1]

In this paper we describe the syntheses, and diuretic and uricosuric activities of xanthone derivatives (**5** and **6**) and furoxanthone derivatives (**7** and **8**) (Chart 2).

Chemistry

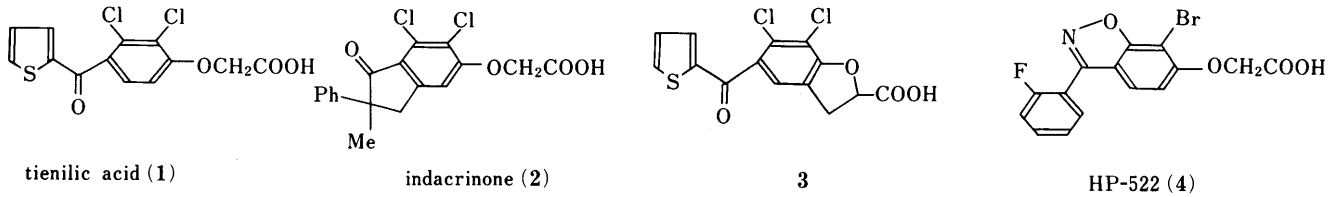
The xanthon-3-yloxyacetic acids (**5**) were synthesized by the route shown in Chart 3.

Resorcinol dimethyl ethers (**10**) were treated with substituted 2-fluoro or 2-chlorobenzoyl chlorides (**9**) (1 eq) and aluminum chloride (1 eq) in 1,2-dichloroethane under the controlled conditions (see Experimental section) to afford 2-hydroxy-4-methoxybenzophenones (**11**), which were consecutively cyclized with ethanolic potassium hydroxide or sodium methoxide to the 3-methoxyxanthones (**12**) in moderate to good overall yields (Table VI). Treatment of **12** with pyridine hydrochloride at 180—200 °C gave the corresponding 3-hydroxyxanthones (**13**) (Table VII). Compounds **13** were converted into ethyl xanthon-3-yloxyacetates (**14**) by the reaction with ethyl bromoacetate in the presence of anhydrous potassium carbonate (Table VIII). The esters **14** were hydrolyzed with aqueous sodium hydroxide to give the desired carboxylic acids (**5**) (Table I). These last 2 steps could be improved by a one-pot procedure where **13** was treated with ethyl bromoacetate as described above, followed by treatment with hot aqueous sodium hydroxide, to give **5** (Table I).

In a similar way, the xanthon-2-yloxyacetic acids (**6**) were synthesized by the route starting from 2-substituted 1,4-dimethoxybenzenes (**16**) as shown in Chart 4 (Tables II, IX and X).

The synthetic pathways to the 1,2-dihydrofuro[2,3-*c*]-xanthone-2-carboxylic acids (**7**) and the 2,3-dihydrofuro-[3,2-*b*]xanthone-2-carboxylic acids (**8**) are illustrated in Chart 5.

The 3-hydroxyxanthones (**13**) were smoothly alkylated with allyl bromide to give the 3-allyloxyxanthones (**20**) (Table XI). Compounds **20** were heated in *N*,*N*-dimethylaniline or in *N*,*N*-diethylaniline to afford the rearrangement of products 4-allyl-3-hydroxyxanthones (**21**) when the 4 position of **20** was not substituted, or 2-allyl isomers (**22**) when **20** had a methyl group at the 4 position, and both **21** and **22** when **20** had chlorine at the 4 position



tienilic acid (**1**) indacrinone (**2**) **3** HP-522 (**4**)

Chart 1

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(Table XII). Oxidation of **21** and **22** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the corresponding epoxide intermediates, which immediately cyclized to the dihydrobenzofurans **23** and **24**, respectively (Tables XIII and XIV). The Jones oxidation of **23** and **24** yielded the desired carboxylic acids **7** and **8**, respectively (Tables III and IV).

Physico-chemical properties of the carboxylic acids **5**—**8** synthesized are shown in Tables I—IV.

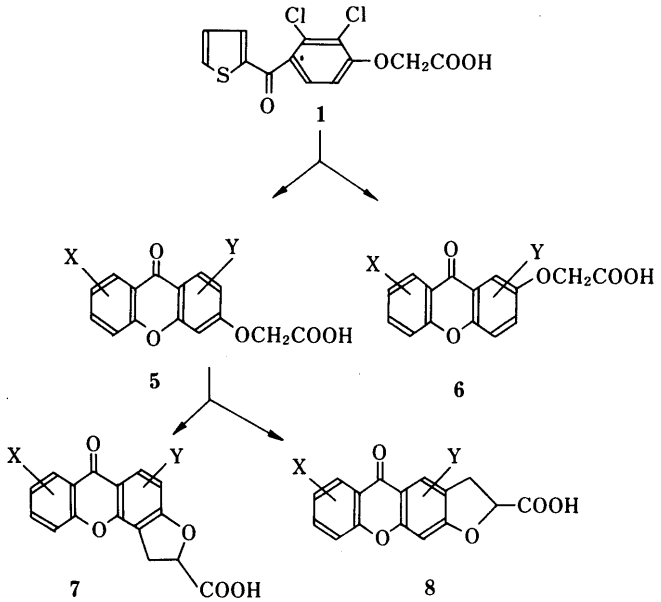


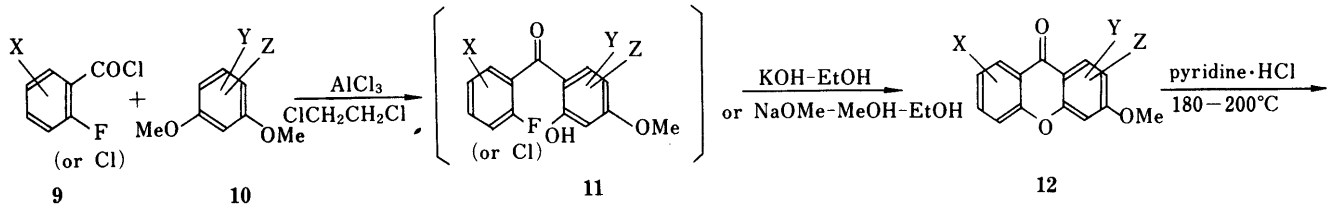
Chart 2

Biological Activities

Diuretic and Uricosuric Activities Diuretic and uricosuric activities in rats of the compounds **5**—**8** are shown in Table V. Tienilic acid and indacrinone were used as the reference agents. Tienilic acid showed moderate diuretic and uricosuric activities, and indacrinone showed potent diuretic and uricosuric activities.

The diuretic activities of most of the xanthon-3- and xanthon-2-yloxyacetic acids (**5** and **6**) were comparable to, or more potent than, that of tienilic acid. The uricosuric activities of compounds **5** having a substituent at the 2 position were comparatively potent. Among these compounds, **5k**, **5m**, **5p** and **5r** had relatively well-balanced diuretic and uricosuric activities.

The diuretic activities of compounds **7** were generally more potent than those of the corresponding compounds **5**. On the other hand, the diuretic activities of compounds **8**, except for **8q**, were comparable to, or less potent than, those of the corresponding compounds **5**. Compounds **7m**, **7p** and **8q** possessed uricosuric activity. Among compounds



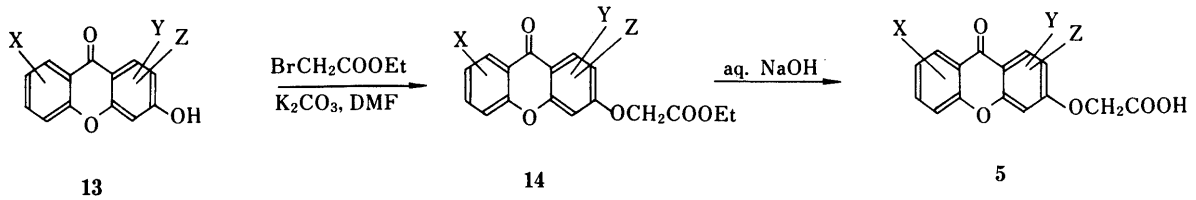
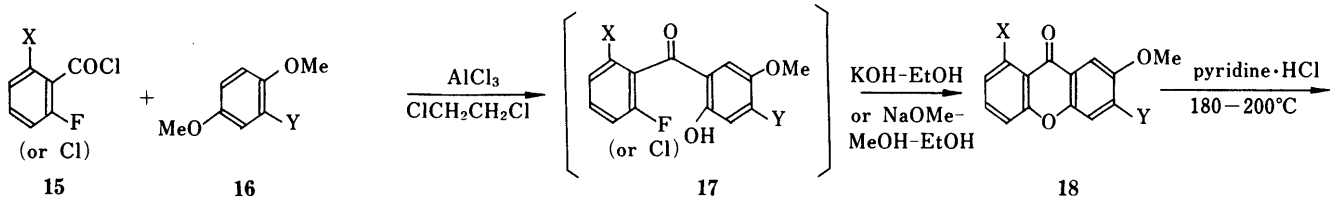


Chart 3



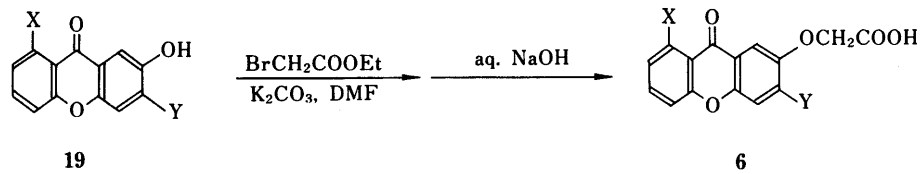


Chart 4

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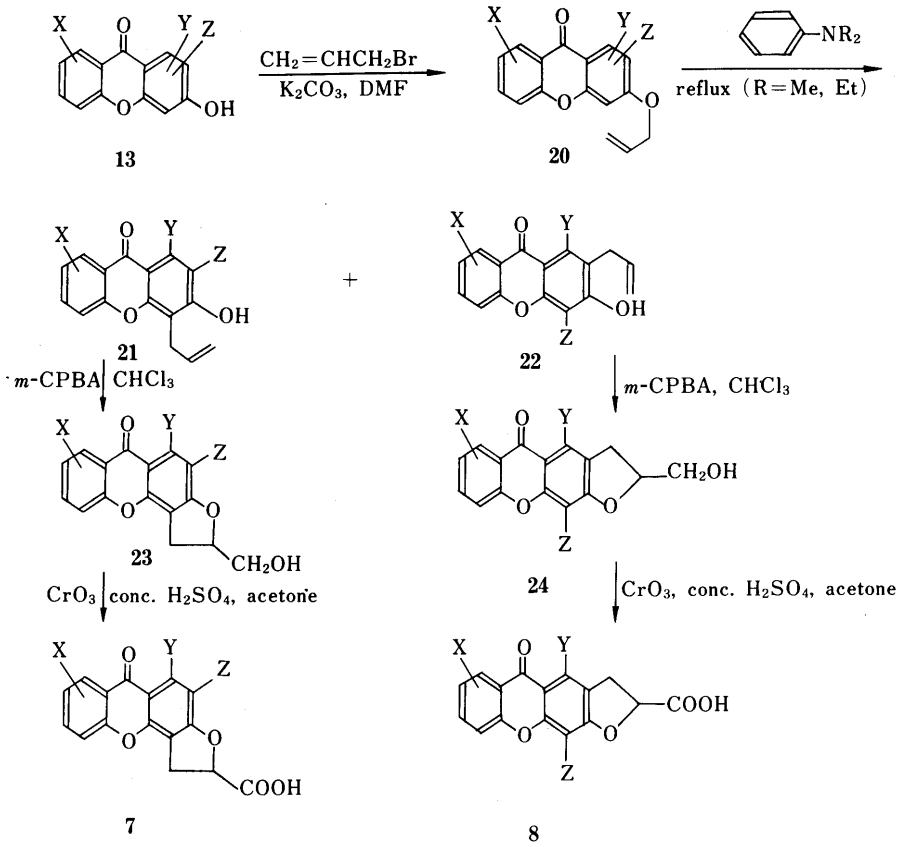
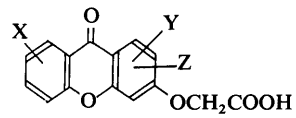


Chart 5

TABLE I. Xanthon-3-yloxyacetic Acids (**5**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
5a	H	H	H	91[a]	203—204 (lit.[6] 204)	DMF–H_2O			
5b	8-F	H	H	Quant.	210—211	DMF–H_2O	$C_{15}H_9FO_5$	62.51 (62.32)	3.15 3.10)
5c	8-F	4-Cl	H	82	301—303	DMF–EtOH	$C_{15}H_8ClFO_5$	55.83 (55.76	2.50 2.45)
5d	8-F	2-Cl	H	85	239—241	DMF–H_2O	$C_{15}H_8ClFO_5$	55.83 (55.87	2.50 2.55)
5e	8-F	4-Me	H	75[a]	266—267	DMF–H_2O	$C_{16}H_{11}FO_5$	63.58 (63.22	3.67 3.95)
5f	8-Cl	4-Cl	H	89	270—271	DMF–EtOH	$C_{15}H_8Cl_2O_5$	53.13 (53.15	2.38 2.34)
5g	7-Cl	4-Cl	H	97	262—263	DMF–EtOH	$C_{15}H_8Cl_2O_5$	53.13 (53.25	2.38 2.37)
5h	6-Cl	4-Cl	H	65	270—271	DMF–EtOH	$C_{15}H_8Cl_2O_5$	53.13 (52.95	2.38 2.31)
5i	5-Cl	4-Cl	H	81	283—286	DMF–EtOH	$C_{15}H_8Cl_2O_5$	53.13 (53.16	2.38 2.46)
5j	H	1-Cl	2-Cl	71[a]	288—290	DMF–EtOH	$C_{15}H_8Cl_2O_5$	53.13 (53.30	2.38 2.36)
5k	H	2-Cl	4-Cl	44	242—244	DMF–H_2O	$C_{15}H_8Cl_2O_5$	53.13 (53.12	2.38 2.18)
5l	H	1-Cl	H	65[a]	231—233	CH_2Cl_2–EtOH	$C_{15}H_9ClO_5$	59.13 (59.02	2.98 3.05)
5m	H	2-Cl	H	81[a]	248—249	DMF–EtOH–H_2O	$C_{15}H_9ClO_5$	59.13 (59.00	2.98 3.00)

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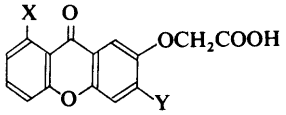
TABLE I. (continued)

Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
5n	H	4-Cl	H	Quant.	279—282	DMF–H_2O	$C_{15}H_9ClO_5$	59.13 (59.23	2.98 2.89)
5o	H	1-Me	H	80[a)]	189—190	EtOH–H_2O	$C_{16}H_{12}O_5$	67.60 (67.60	4.26 4.22)
5p	H	2-Me	H	72[a)]	241—242	DMF–H_2O	$C_{16}H_{12}O_5$	67.60 (67.54	4.26 4.22)
5q	H	4-Me	H	79[a)]	244—247	EtOH	$C_{16}H_{12}O_5$	67.60 (67.80	4.26 4.21)
5r	H	2-Br	H	50[a)]	227—230	EtOH	$C_{15}H_9BrO_5$	51.60 (52.00	2.60 2.58)
5s	H	1-Me	1-Cl	57[a)]	275—278	DMF–EtOH	$C_{16}H_{11}ClO_5$	60.30 (60.09	3.48 3.53)

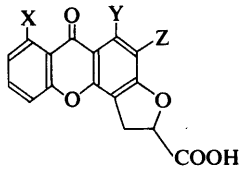
a) From **13** (see Experimental section).

TABLE II. Xanthon-2-yloxyacetic Acids (**6**)



Compd. No.	X	Y	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
6a	F	Cl	75	242—245	EtOH	$C_{15}H_8ClFO_5$	55.83 (55.94	2.50 2.56)
6b	H	Cl	81	237—238	DMF–H_2O	$C_{15}H_9ClO_5$	59.13 (59.18	2.98 2.92)
6c	H	Me	94	225—227	DMF–EtOH	$C_{16}H_{12}O_5$	67.60 (67.77	4.26 4.33)

TABLE III. 1,2-Dihydrofuro[2,3-*c*]xanthone-2-carboxylic Acids (**7**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
7a	H	H	H	86	287—289	DMF–H_2O	$C_{16}H_{10}O_5$	68.08 (67.68	3.57 3.67)
7b	F	H	H	96	262—265	DMF–H_2O	$C_{16}H_9FO_5$	64.01 (63.71	3.02 3.22)
7f	Cl	H	H	85	294—295	DMF–H_2O	$C_{16}H_9ClO_5$	60.68 (60.28	2.86 2.95)
7l	H	Cl	H	77	255—258	DMF–EtOH	$C_{16}H_9ClO_5$	60.68 (60.52	2.86 2.88)
7m	H	H	Cl	67	300—302	DMF–H_2O	$C_{16}H_9ClO_5$	60.68 (60.51	2.86 2.92)
7o	H	Me	H	57	234—235	DMF–H_2O	$C_{17}H_{12}O_5$	68.91 (68.57	4.08 4.26)
7p	H	H	Me	69	292—294	DMF–H_2O	$C_{17}H_{12}O_5$	68.91 (68.87	4.08 4.04)
7r	H	H	Br	55	283—286	EtOH–CH_2Cl_2	$C_{16}H_9BrO_5$	53.21 (53.56	2.51 2.56)
7s	H	Me	Cl	48	284—287	DMF–EtOH	$C_{17}H_{11}ClO_5$	61.74 (61.57	3.35 3.33)

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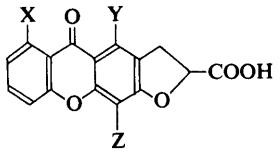
TABLE IV. 2,3-Dihydrofuro[3,2-*b*]xanthone-2-carboxylic Acids (**8**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
8c	F	H	Cl	48	300—302	DMF–EtOH	$C_{16}H_8ClFO_5$	57.42 (57.09	2.41 2.40)
8e	F	H	Me	37	292—294	DMF–H_2O	$C_{17}H_{11}FO_5$	64.97 (64.65	3.53 3.76)
8f	Cl	H	Cl	44	291—294	EtOH–$CHCl_3$	$C_{16}H_8Cl_2O_5$	54.73 (54.58	2.30 2.31)
8n	H	H	Cl	86	301—303	DMF–H_2O	$C_{16}H_9ClO_5$	60.68 (60.48	2.86 2.57)
8q	H	H	Me	66	296—299	DMF–H_2O	$C_{17}H_{12}O_5$	68.91 (68.79	4.08 4.15)

TABLE V. Diuretic and Uricosuric Activities[a]

Compd. No.	No. of animals	Diuretic[b] (0—6 h)	Uricosuric[b] (0—6 h)
5a	5	153[e]	84
5b	5	127	NT[f]
5c	11	150[c]	128[c]
5d	6	166[c]	110
5e	5	119	NT[f]
5f	15	141[d]	126[c]
5g	5	215[d]	105
5h	5	144[c]	105
5i	5	146[c]	78
5j	9	180[e]	109
5k	10	178[e]	134[e]
5l	5	263[e]	108
5m	30	200[e]	149[e]
5n	6	166	109
5o	5	203[d]	125[c]
5p	10	207[e]	129[c]
5q	5	134	NT[f]
5r	5	188[e]	137[d]
5s	5	168	101
6a	5	123	129
6b	10	181[e]	102
6c	5	123	99
7a	5	203[e]	95
7b	5	146	129
7f	6	163[d]	95
7l	5	295[e]	100
7m	15	286[e]	130[e]
7o	5	314[e]	112
7p	10	282[e]	141[d]
7r	5	203[d]	116
7s	5	198[e]	97
8c	5	118	96
8e	5	86	118
8f	5	100	95
8n	10	165[e]	126
8q	15	164[e]	138[c]
Tienilic acid	15	143[e]	118[c]
Indacrinone	19	265[e]	156[e]

a) Test compounds were administered at 100 mg/kg *p.o.* to Wistar-Imamichi rats and the activities are shown as relative activity (%) to the control (100%). Details of the test protocol are described in the experimental section. *b*) Student's *t*-test: *c*) $p<0.05$, *d*) $p<0.01$, *e*) $p<0.001$ *vs.* control; values without marks are not statistically significant. *f*) Not tested.

7 and **8**, **7m**, **7p** and **8q** had both diuretic and uricosuric activities.

As a result, compound **5m** was found to possess diuretic and uricosuric activities more potent than those of tienilic acid and balanced diuretic and uricosuric activities better than those of indacrinone.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-24B spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are given in Hertz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, br=broad. For column chromatography, Wakogel C-200 (Wako, 0.074—0.149 mm) was used.

3-Methoxyxanthones (12) A typical example is given to illustrate the general procedure.

2-Chloro-3-methoxyxanthone (**12m**): 2-Fluorobenzoyl chloride (7.9 g, 0.05 mol) and 4-chlororesorcinol dimethyl ether (8.6 g, 0.05 mol) were dissolved in 1,2-dichloroethane (120 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (6.7 g, 0.05 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 3 h period and then refluxed for 1 h. After cooling, ice-water and conc. HCl were added to the reaction mixture, and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 14 g of 4-chloro-2-(2-fluorobenzoyl)-5-methoxyphenol (**11m**) as crystals (CH_2Cl_2–EtOH), mp 135—136 °C. *Anal.* Calcd for $C_{14}H_{10}ClFO_3$: C, 59.91; H, 3.59. Found: C, 59.87; H, 3.57. MS *m/z*: 280 (M^+), 279. IR (KBr) cm^{-1}: 3460 (OH), 1628 (C=O). NMR ($CDCl_3$) δ: 3.94 (3H, s, O–C<u>H</u>$_3$), 6.53 (1H, s, 6-H), 6.97—7.74 (5H, m, arom. H), 12.46 (1H, s, O<u>H</u>).

To a solution of the crude **11m** (14 g) in EtOH (200 ml), 28% NaOMe–MeOH (19.3 g, 0.1 mol) was added and the mixture was refluxed for 1 h. The product crystallized upon the addition of H_2O was collected by filtration and washed successively with H_2O and EtOH to give **12m** (11.9 g, overall 92%) as crystals (CH_2Cl_2–EtOH), mp 195—197 °C. *Anal.* Calcd for $C_{14}H_9ClO_3$: C, 64.51; H, 3.48. Found: C, 64.52; H, 3.54. MS *m/z*: 260 (M^+). IR (KBr) cm^{-1}: 1644 (C=O). NMR ($CDCl_3$) δ: 3.93 (3H, s, O–C<u>H</u>$_3$), 6.78 (1H, s, 4-H), 7.11—7.82 (3H, m, arom. H), 8.07—8.32 (1H, m, 8-H), 8.13 (1H, s, 1-H).

Other compounds **12** in Table VI were similarly prepared.

3-Hydroxyxanthones (13) A typical example is given to illustrate the general procedure.

2-Chloro-3-hydroxyxanthone (**13m**): Compound **12m** (10 g, 0.038 mol) was heated with pyridine hydrochloride (60 g) at 180—200 °C for 2 h and

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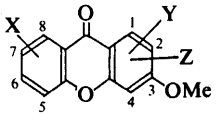
TABLE VI. 3-Methoxyxanthones (12)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
12a	H	H	H	68	127—128 (lit.[7] 129)	EtOH	$C_{14}H_{10}O_3$	74.33 (74.56	4.46 4.46)
12b	8-F	H	H	82	196—198	DMF–EtOH	$C_{14}H_9FO_3$	68.85 (69.01	3.71 3.76)
12c	8-F	4-Cl	H	90	206—208	CH_2Cl_2–EtOH	$C_{14}H_8ClFO_3$	60.34 (60.29	2.89 3.08)
12d	8-F	2-Cl	H	79	288—289	CH_2Cl_2–EtOH	$C_{14}H_8ClFO_3$	60.34 (60.31	2.89 3.01)
12e	8-F	4-Me	H	79	197—199	CH_2Cl_2–EtOH	$C_{15}H_{11}FO_3$	69.76 (69.63	4.29 4.32)
12f	8-Cl	4-Cl	H	93	247—248	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (56.85	2.73 2.72)
12g	7-Cl	4-Cl	H	42	255—256	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (57.09	2.73 2.68)
12h	6-Cl	4-Cl	H	76	257—258	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (56.90	2.73 2.82)
12i	5-Cl	4-Cl	H	86	271—272	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (57.01	2.73 2.70)
12j	H	1-Cl	2-Cl	80	236—237	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (56.93	2.73 2.74)
12k	H	2-Cl	4-Cl	48	205—207	CH_2Cl_2–EtOH	$C_{14}H_8Cl_2O_3$	56.98 (56.96	2.73 2.84)
12l	H	1-Cl	H	53	164—167	CH_2Cl_2–EtOH	$C_{14}H_9ClO_3$	64.51 (64.63	3.48 3.48)
12m	H	2-Cl	H	92	195—197	CH_2Cl_2–EtOH	$C_{14}H_9ClO_3$	64.51 (64.52	3.48 3.54)
12n	H	4-Cl	H	85	215—216	CH_2Cl_2–EtOH	$C_{14}H_9ClO_3$	64.51 (64.66	3.48 3.46)
12o	H	1-Me	H	40	130—131 (lit.[8] 130—132)	CH_2Cl_2–EtOH	$C_{15}H_{12}O_3$	74.99 (74.98	5.03 5.10)
12p	H	2-Me	H	81	156—157 (lit.[9] 160—161)	CH_2Cl_2–EtOH	$C_{15}H_{12}O_3$	74.99 (74.84	5.03 5.11)
12q	H	4-Me	H	81	179—180 (lit.[9,10] 177—178)	CH_2Cl_2–EtOH	$C_{15}H_{12}O_3$	74.99 (74.96	5.03 4.93)
12r	H	2-Br	H	42	190—191	CH_2Cl_2–EtOH	$C_{14}H_9BrO_3$	55.11 (55.00	2.97 2.96)
12s	H	1-Me	2-Cl	50	193—195	CH_2Cl_2–EtOH	$C_{15}H_{11}ClO_3$	65.59 (65.41	4.04 3.90)

then cooled to 70 °C. The product crystallized upon the addition of H_2O was collected by filtration and washed with H_2O to give **13m** (9.3 g, 98%) as crystals (AcOEt–hexane), mp > 310 °C. *Anal.* Calcd for $C_{13}H_7ClO_3$: C, 63.31; H, 2.86. Found: C, 63.31; H, 2.85. MS *m/z*: 246 (M^+). IR (KBr) cm^{-1}: 3160 (OH), 1644 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 7.01 (1H, s, 4-H), 7.15—8.00 (3H, m, arom. H), 8.00—8.34 (1H, m, 8-H), 8.04 (1H, s, 1-H), 11.40 (1H, br s, OH).

Other compounds **13** in Table VII were similarly prepared.

Ethyl Xanthon-3-yloxyacetates (14) A typical example is given to illustrate the general procedure.

Ethyl 4-Chloro-8-fluoroxanthon-3-yloxyacetate (**14c**): A mixture of 4-chloro-8-fluoro-3-hydroxyxanthone (**13c**) (2.6 g, 9.8 mmol), ethyl bromoacetate (3.3 g, 20 mmol) and anhyd. K_2CO_3 (2.8 g, 20 mmol) in dimethylformamide (DMF) (40 ml) was heated at 60—70 °C for 4 h. After cooling, H_2O was added to the mixture and the resulting crystals were collected by filtration, washed with H_2O and dried. Recrystallization gave **14c** (3.4 g, 99%) as crystals (EtOH), mp 188—190 °C. *Anal.* Calcd for $C_{17}H_{12}ClFO_5$: C, 58.22; H, 3.45. Found: C, 58.11; H, 3.41. MS *m/z*: 350 (M^+), 315. IR (KBr) cm^{-1}: 1738 (COOEt), 1668 (C=O). NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz, CH_3), 4.23 (2H, q, J=7.0 Hz, O–CH_2–CH_3), 4.78 (2H, s, O–CH_2), 6.77 (1H, d, J=9.0 Hz, 2-H), 6.76—7.80 (3H, m, arom. H), 8.06 (1H, d, J=9.0 Hz, 1-H).

Other compounds **14** in Table VIII were similarly prepared.

Xanthon-3-yloxyacetic Acids (5) Typical examples are given to illustrate the general procedure.

4-Chloro-8-fluoroxanthon-3-yloxyacetic Acid (**5c**): A mixture of **14c** (3.3 g, 9.4 mmol) and NaOH (1.9 g, 47.5 mmol) in EtOH (10 ml) and H_2O (100 ml) was refluxed for 30 min. After cooling, the mixture was acidified with HCl and the deposited crystals were collected by filtration, washed with H_2O and dried. Recrystallization gave **5c** (2.5 g, 82%) as crystals (DMF–EtOH), mp 301—303 °C. *Anal.* Calcd for $C_{15}H_8ClFO_5$: C, 55.83; H, 2.50. Found: C, 55.76; H, 2.45. MS *m/z*: 322 (M^+). IR (KBr) cm^{-1}: 1736 (COOH), 1666 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 4.85 (2H, s, O–CH_2), 6.98 (1H, d, J=9.0 Hz, 2-H), 6.96—7.85 (3H, m, arom. H), 8.02 (1H, d, J=9.0 Hz, 1-H).

2-Chloroxanthon-3-yloxyacetic Acid (**5m**): A mixture of **13m** (1.5 g, 6.1 mmol), ethyl bromoacetate (3.1 g, 18.6 mmol) and anhyd. K_2CO_3 (2.5 g, 18.3 mmol) in DMF (40 ml) was stirred at 65—75 °C for 2 h. After cooling the mixture, 1 N NaOH (100 ml) was added, and the mixture was stirred at 80—90 °C for 30 min. After cooling, the mixture was acidified with HCl and the deposited crystals were collected by filtration, washed with H_2O and dried to give **5m** (1.5 g, 81%) as crystals (DMF–EtOH–H_2O), mp 248—249 °C. *Anal.* Calcd for $C_{15}H_9ClO_5$: C, 59.13; H, 2.98. Found: C, 59.00; H, 3.00. MS *m/z*: 304 (M^+). IR (KBr) cm^{-1}: 1724

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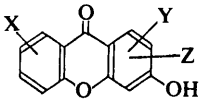
TABLE VII. 3-Hydroxyxanthones (13)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
13a	H	H	H	Quant.	254—255 (lit.[11] 246)	AcOEt–hexane	$C_{13}H_8O_3$	73.58 (73.61)	3.80 3.74)
13b	8-F	H	H	96	294—295	AcOEt–hexane	$C_{13}H_7FO_3$	67.83 (68.01)	3.07 3.32)
13c	8-F	4-Cl	H	93	306—307	AcOEt–hexane	$C_{13}H_6ClFO_3$	59.00 (59.05)	2.29 2.21)
13d	8-F	2-Cl	H	69	>310	AcOEt–hexane	$C_{13}H_6ClFO_3$	59.00 (59.06)	2.29 2.32)
13e	8-F	4-Me	H	95	294—295	AcOEt–hexane	$C_{14}H_9FO_3$	68.85 (68.85)	3.71 3.77)
13f	8-Cl	4-Cl	H	97	282—283	AcOEt–hexane	$C_{13}H_6Cl_2O_3$	55.55 (55.61)	2.15 2.09)
13g	7-Cl	4-Cl	H	Quant.	263—265	EtOH	$C_{13}H_6Cl_2O_3$	55.55 (55.75)	2.15 2.37)
13h	6-Cl	4-Cl	H	92	245—246	EtOH	$C_{13}H_6Cl_2O_3$	55.55 (55.62)	2.15 2.26)
13i	5-Cl	4-Cl	H	Quant.	272—273	AcOEt–hexane	$C_{13}H_6Cl_2O_3$	55.55 (55.68)	2.15 2.11)
13j	H	1-Cl	2-Cl	91	308—310	AcOEt–hexane	$C_{13}H_6Cl_2O_3$	55.55 (55.62)	2.15 2.16)
13k	H	2-Cl	4-Cl	65	191—192	DMF–EtOH	$C_{13}H_6Cl_2O_3$	55.55 (55.73)	2.15 2.10)
13l	H	1-Cl	H	90	>310	AcOEt–hexane	$C_{13}H_7ClO_3$	63.31 (63.31)	2.86 2.94)
13m	H	2-Cl	H	98	>310	AcOEt–hexane	$C_{13}H_7ClO_3$	63.31 (63.31)	2.86 2.85)
13n	H	4-Cl	H	96	250—251	AcOEt–hexane	$C_{13}H_7ClO_3$	63.31 (63.21)	2.86 2.87)
13o	H	1-Me	H	Quant.	298—299 (lit.[12] 285—287)	DMF–EtOH	$C_{14}H_{10}O_3$	74.33 (74.17)	4.46 4.44)
13p	H	2-Me	H	Quant.	283—285	AcOEt–hexane	$C_{14}H_{10}O_3$	74.33 (74.20)	4.46 4.43)
13q	H	4-Me	H	96	278—279 (lit.[10b,13] 271—272)	AcOEt–hexane	$C_{14}H_{10}O_3$	74.33 (73.99)	4.46 4.30)
13r	H	2-Br	H	92	>310 (lit.[14] 310)	AcOEt–hexane	$C_{13}H_7BrO_3$	53.64 (53.83)	2.42 2.58)
13s	H	1-Me	2-Cl	95	260—261	AcOEt–hexane	$C_{14}H_9ClO_3$	64.51 (64.55)	3.48 3.52)

(COOH), 1664 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 4.86 (2H, s, O–C$\underline{H}_2$), 7.02 (1H, s, 4-H), 7.18—7.91 (3H, m, arom. H), 8.00—8.26 (1H, m, 8-H), 8.10 (1H, s, 1-H).

Other compounds **5** in Table I were similarly prepared.

2-Methoxyxanthones (18) A typical example is given to illustrate the general procedure.

3-Chloro-2-methoxyxanthone (**18b**): 2-Fluorobenzoyl chloride (7.9 g, 0.05 mol) and 2-chloro-1,4-dimethoxybenzene (8.6 g, 0.05 mol) were dissolved in 1,2-dichloroethane (120 ml) and cooled to 0—5 °C. $AlCl_3$ (6.7 g, 0.05 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 3 h period and then refluxed for 1 h. Ice-water and conc. HCl were added to the reaction mixture and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O, and the extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 14 g of 3-chloro-6-(2-fluorobenzoyl)-4-methoxyphenol (**17b**). To a solution of crude **17b** (14 g) in EtOH (200 ml), 28% NaOMe–MeOH (19.3 g, 0.1 mol) was added and the mixture was refluxed for 1 h. The product crystallized upon the addition of H_2O was collected by filtration and washed successively with H_2O and EtOH to give **18b** (8.4 g, 65%) as crystals (CH_2Cl_2–EtOH), mp 176—177 °C. *Anal.* Calcd for $C_{14}H_9ClO_3$: C, 64.51; H, 3.48. Found: C, 64.21; H, 3.44. MS *m/z*: 260 (M^+), 245. IR (KBr) cm^{-1}: 1656 (C=O). NMR ($CDCl_3$) δ: 3.93 (3H, s, O–C$\underline{H}_3$), 7.08—7.78 (3H, m, arom. H), 7.41 (1H, s, 4-H), 7.58 (1H, s, 1-H), 8.07—8.33 (1H, m, 8-H).

Other compounds **18** in Table IX were similarly prepared.

2-Hydroxyxanthones (19) A typical example is given to illustrate the general procedure.

3-Chloro-2-hydroxyxanthone (**19b**): Compound **18b** (8.0 g, 0.031 mol) was heated with pyridine hydrochloride (50 g) at 180—190 °C for 2 h and then cooled to 70 °C. The product crystallized upon the addition of H_2O was collected by filtration and washed with H_2O to give **19b** (6.9 g, 91%) as crystals (AcOEt–hexane), mp 285—286 °C. *Anal.* Calcd for $C_{13}H_7ClO_3$: C, 63.31; H, 2.86. Found: C, 63.40; H, 2.85. MS *m/z*: 246 (M^+). IR (KBr) cm^{-1}: 3304 (OH), 1656 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 3.14 (1H, br s, O$\underline{H}$), 7.21—7.85 (3H, m, arom. H), 7.45 (1H, s, 4-H), 7.63 (1H, s, 1-H), 8.00—8.23 (1H, m, 8-H).

Other compounds **19** in Table X were similarly prepared.

Xanthon-2-yloxyacetic Acids (6) A typical example is given to illustrate the general procedure.

3-Chloroxanthon-2-yloxyacetic Acid (**6b**): A mixture of **19b** (1.5 g, 6.1 mmol), ethyl bromoacetate (3.1 g, 18.6 mmol) and anhyd. K_2CO_3 (2.5 g, 18.3 mmol) in DMF (40 ml) was stirred at 65—75 °C for 2 h. After cooling, 1 N NaOH (100 ml) was added to the reaction mixture, and the

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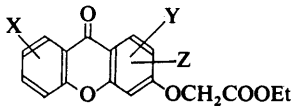
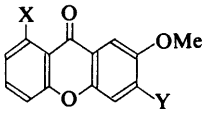
TABLE VIII. Ethyl Xanthon-3-yloxyacetates (**14**)



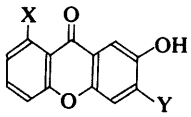
Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
14b	8-F	H	H	98	166—167	EtOH	$C_{17}H_{13}FO_5$	64.56 (64.43	4.14 4.20)
14c	8-F	4-Cl	H	99	188—190	EtOH	$C_{17}H_{12}ClFO_5$	58.22 (58.11	3.45 3.41)
14d	8-F	2-Cl	H	71	199—201	EtOH	$C_{17}H_{12}ClFO_5$	58.22 (58.35	3.45 3.34)
14f	8-Cl	4-Cl	H	77	184—186	EtOH	$C_{17}H_{12}Cl_2O_5$	55.61 (55.39	3.29 3.21)
14g	7-Cl	4-Cl	H	98	178—180	EtOH	$C_{17}H_{12}Cl_2O_5$	55.61 (55.88	3.29 3.27)
14h	6-Cl	4-Cl	H	65	193—194	EtOH	$C_{17}H_{12}Cl_2O_5$	55.61 (55.82	3.29 3.26)
14i	5-Cl	4-Cl	H	97	155—157	EtOH	$C_{17}H_{12}Cl_2O_5$	55.61 (55.69	3.29 3.43)
14k	H	2-Cl	4-Cl	63	155—157	EtOH	$C_{17}H_{12}Cl_2O_5$	55.61 (55.73	3.29 3.24)
14n	H	4-Cl	H	68	183—185	EtOH	$C_{17}H_{13}ClO_5$	61.37 (61.35	3.94 3.85)

TABLE IX. 2-Methoxyxanthones (**18**)



Compd. No.	X	Y	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
							C	H
18a	F	Cl	62	224—225	CH_2Cl_2–EtOH	$C_{14}H_8ClFO_3$	60.34 (60.42	2.89 3.00)
18b	H	Cl	65	176—177	CH_2Cl_2–EtOH	$C_{14}H_9ClO_3$	64.51 (64.21	3.48 3.44)
18c	H	Me	53	147—148	CH_2Cl_2–EtOH	$C_{15}H_{12}O_3$	74.99 (74.79	5.03 4.94)

TABLE X. 2-Hydroxyxanthones (**19**)



Compd. No.	X	Y	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
							C	H
19a	F	Cl	95	307—308	AcOEt–hexane	$C_{13}H_6ClFO_3$	59.00 (59.05	2.29 2.25)
19b	H	Cl	91	285—286	AcOEt–hexane	$C_{13}H_7ClO_3$	63.31 (63.40	2.86 2.85)
19c	H	Me	89	275—276	AcOEt–hexane	$C_{14}H_{10}O_3$	74.33 (74.24	4.46 4.48)

whole mixture was stirred at 80—90 °C for 30 min and then cooled. The mixture was acidified with HCl and the deposited crystals were collected by filtration, washed with H_2O and dried to give **6b** (1.5 g, 81%) as crystals (DMF–H_2O), mp 237—238 °C. *Anal.* Calcd for $C_{15}H_9ClO_5$: C, 59.13; H, 2.98. Found: C, 59.18; H, 2.92. MS *m/z*: 304 (M^+), 259. IR (KBr) cm^{-1}: 1744 (COOH), 1660 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 4.76 (2H, s,

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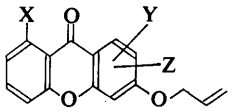
TABLE XI. 3-Allyloxyxanthones (**20**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
20a	H	H	H	95	131—132 (lit.[15] 137)	EtOH			
20b	F	H	H	63	143—145	CH_2Cl_2–EtOH	$C_{16}H_{11}FO_3$	71.11 (70.95	4.10 4.04)
20c	F	4-Cl	H	57	167—168	EtOH	$C_{16}H_{10}ClFO_3$	63.07 (63.15	3.31 3.26)
20e	F	4-Me	H	77	164—166	EtOH	$C_{17}H_{13}FO_3$	71.82 (71.99	4.61 4.57)
20f	Cl	4-Cl	H	96	176—177	CH_2Cl_2–EtOH	$C_{16}H_{10}Cl_2O_3$	59.84 (59.86	3.14 3.16)
20l	H	1-Cl	H	98	124—125	EtOH	$C_{16}H_{11}ClO_3$	67.03 (66.87	3.87 3.70)
20m	H	2-Cl	H	Quant.	160—161	EtOH	$C_{16}H_{11}ClO_3$	67.03 (67.19	3.87 3.84)
20n	H	4-Cl	H	98	142—143	EtOH–H_2O	$C_{16}H_{11}ClO_3$	67.03 (67.09	3.87 3.80)
20o	H	1-Me	H	98	116—118	CH_2Cl_2–EtOH	$C_{17}H_{14}O_3$	76.67 (76.35	5.30 5.34)
20p	H	2-Me	H	87	126—127	EtOH	$C_{17}H_{14}O_3$	76.67 (76.38	5.30 5.23)
20q	H	4-Me	H	94	149—150 (lit.[10b] 144)	EtOH	$C_{17}H_{14}O_3$	76.67 (76.63	5.30 5.28)
20r	H	2-Br	H	99	143—144	CH_2Cl_2–EtOH	$C_{16}H_{11}BrO_3$	58.03 (58.10	3.35 3.47)
20s	H	1-Me	2-Cl	89	178—180	CH_2Cl_2–EtOH	$C_{17}H_{13}ClO_3$	67.89 (67.73	4.36 4.30)

O–C$\underline{H}_2$), 5.75 (1H, br s, COO$\underline{H}$), 7.12—7.92 (3H, m, arom. H), 7.56 (1H, 1H, s, s, 1-H, 4-H), 8.01—8.27 (1H, m, 8-H).

Other compounds **6** in Table II were similarly prepared.

3-Allyloxyxanthones (20) A typical example is given to illustrate the general procedure.

3-Allyloxy-2-chloroxanthone (**20m**): A mixture of **13m** (6.2 g, 0.025 mol), allyl bromide (9.1 g, 0.075 mol) and anhyd. K_2CO_3 (10.4 g, 0.075 mol) in DMF (60 ml) was stirred at 55—65 °C for 1 h. The product crystallized upon the addition of H_2O was collected by filtration and washed with H_2O to give **20m** (7.2 g, quant.) as crystals (EtOH), mp 160—161 °C. *Anal.* Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87. Found: C, 67.19; H, 3.84. MS *m/z*: 286 (M^+), 251. IR (KBr) cm^{-1}: 1648 (C=O). NMR ($CDCl_3$) δ: 4.50—4.83 (2H, m, O–C$\underline{H}_2$), 5.08—5.73 (2H, m, –CH=C$\underline{H}_2$), 5.73—6.43 (1H, m, –C$\underline{H}$=CH_2), 6.81 (1H, s, 4-H), 7.11—7.83 (3H, m, arom. H), 8.09—8.36 (1H, m, 8-H), 8.19 (1H, s, 1-H).

Other compounds **20** in Table XI were similarly prepared.

2(or 4)-Allyl-3-hydroxyxanthones (21 or 22) Typical examples are given to illustrate the general procedure.

4-Allyl-2-chloro-3-hydroxyxanthone (**21m**): A solution of **20m** (7.0 g, 0.024 mol) in *N,N*-diethylaniline (100 ml) was stirred at 185—195 °C for 4 h, then cooled. The reaction mixture was acidified with conc. HCl and the deposited crystals were collected by filtration, washed with H_2O, dried and chromatographed on silica gel with CH_2Cl_2 to give **21m** (3.6 g, 51%) as crystals (EtOH), mp 198—200 °C. *Anal.* Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87. Found: C, 67.04; H, 3.85. MS *m/z*: 286 (M^+). IR (KBr) cm^{-1}: 1638 (C=O). NMR ($CDCl_3$–DMSO-d_6) δ: 3.70 (2H, dt, J=6.0, 1.0 Hz, Ph–C$\underline{H}_2$), 4.80—5.31 (2H, m, –CH=C$\underline{H}_2$), 5.65—6.40 (1H, m, –C$\underline{H}$=CH_2), 7.12—7.90 (3H, m, arom. H), 7.50 (1H, br s, O$\underline{H}$), 8.05 (1H, s, 1-H), 8.10—8.31 (1H, m, 8-H).

4-Allyl-8-fluoro-3-hydroxyxanthone (**21c**), 2-Allyl-4-chloro-8-fluoro-3-hydroxyxanthone (**22c**): A solution of 3-allyloxy-4-chloro-8-fluoroxanthone (**20c**) (5.3 g, 0.017 mol) in *N,N*-dimethylaniline (100 ml) was refluxed for 6.5 h. After cooling, the mixture was acidified with conc. HCl and the deposited crystals were collected by filtration, washed with H_2O, dried and chromatographed on silica gel with CH_2Cl_2 to give **21c** (1.5 g, 32%) and **22c** (1.8 g, 34%). Product **21c**: crystals (EtOH), mp 259—261 °C. *Anal.* Calcd for $C_{16}H_{11}FO_3$: C, 71.11; H, 4.10. Found: C, 71.03; H, 4.21. MS *m/z*: 270 (M^+), 255. IR (KBr) cm^{-1}: 3216 (OH), 1628, 1606. NMR ($CDCl_3$–DMSO-d_6) δ: 3.60 (2H, dt, J=6.0, 1.0 Hz, Ph–C$\underline{H}_2$), 4.76—5.30 (2H, m, –CH=C$\underline{H}_2$), 5.61—6.34 (1H, m, –C$\underline{H}$=CH_2), 6.73—7.77 (3H, m, arom. H), 6.88 (1H, d, J=8.4 Hz, 2-H), 7.87 (1H, d, J=8.4 Hz, 1-H). Product **22c**: crystals (EtOH), mp 192—193 °C. *Anal.* Calcd for $C_{16}H_{10}ClFO_3$: C, 63.07; H, 3.31. Found: C, 62.77; H, 3.40. MS *m/z*: 304 (M^+), 303, 289. IR (KBr) cm^{-1}: 3340 (OH), 1656, 1606. NMR ($CDCl_3$) δ: 3.48 (2H, br d, J=6.6 Hz, Ph–C$\underline{H}_2$), 4.90—5.40 (2H, m, –CH=C$\underline{H}_2$), 5.61—6.43 (1H, m, –C$\underline{H}$=CH_2), 6.82—7.86 (3H, m, arom. H), 7.21 (1H, br s, O$\underline{H}$), 8.00 (1H, s, 1-H).

2-Allyl-3-hydroxy-4-methylxanthone (**22q**): A solution of 3-allyloxy-4-methylxanthone (**20q**) (8.0 g, 0.03 mol) in *N,N*-dimethylaniline (100 ml) was refluxed for 29 h. After cooling, the mixture was acidified with conc. HCl and the deposited crystals were collected by filtration, washed with H_2O and dried. Recrystallization gave **22q** (5.6 g, 70%) as crystals (EtOH), mp 199—201 °C. *Anal.* Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.89; H, 5.34. MS *m/z*: 266 (M^+), 265, 251. IR (KBr) cm^{-1}: 3388 (OH), 1640, 1606. NMR ($CDCl_3$–DMSO-d_6) δ: 2.41 (3H, s, C$\underline{H}_3$), 3.48 (2H, br d, J=6.0 Hz, Ph–C$\underline{H}_2$), 4.85—5.35 (2H, m, –CH=C$\underline{H}_2$), 5.70—6.42 (1H, m, –C$\underline{H}$=CH_2), 7.10—7.80 (3H, m, arom. H), 7.50 (1H, br s, O$\underline{H}$), 7.82 (1H, s, 1-H), 8.08—8.32 (1H, m, 8-H).

Other compounds **21**, **22** in Table XII were similarly prepared.

1,2-Dihydro-2-hydroxymethylfuro[2,3-*c*]xanthones (23) A typical example is given to illustrate the general procedure.

4-Chloro-1,2-dihydro-2-hydroxymethylfuro[2,3-*c*]xanthone (**23m**): To a stirred solution of **21m** (2.87 g, 0.01 mol) in $CHCl_3$ (300 ml), *m*-CPBA (3.45 g, 0.02 mol) was added in small portions at room temperature. The solution was stirred for 8 h and left to stand overnight. After addition of an aq. solution of NaOH to the solution, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to give **23m** (2.5 g, 83%) as crystals (EtOH), mp 184—185 °C. *Anal.* Calcd for $C_{16}H_{11}ClO_4$: C, 63.48; H, 3.66. Found: C, 63.50; H, 3.76. MS *m/z*: 302 (M^+). IR (KBr) cm^{-1}: 3420 (OH), 1642 (C=O). NMR ($CDCl_3$–DMSO-

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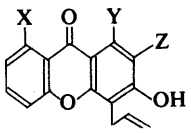
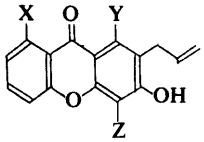
TABLE XII. 4-Allyl-3-hydroxyxanthones (**21**), 2-Allyl-3-hydroxyxanthones (**22**)



21



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Starting comp.	Product No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
20a	**21a**	H	H	H	68	248—251 (lit.[15] 253)	EtOH			
20b	**21b**	F	H	H	57	259—261	EtOH	$C_{16}H_{11}FO_3$	71.11 (71.03	4.10 4.21)
20c	**22c**	F	H	Cl	34	192—193	EtOH	$C_{16}H_{10}ClFO_3$	63.07 (62.77	3.31 3.40)
	21b	F	H	H	32					
20e	**22e**	F	H	Me	36	191—192	EtOH	$C_{17}H_{13}FO_3$	71.82 (71.82	4.61 4.65)
20f	**22f**	Cl	H	Cl	36	180—181	EtOH	$C_{16}H_{10}Cl_2O_3$	59.84 (59.82	3.14 3.08)
	21f	Cl	H	H	44	233—234	EtOH	$C_{16}H_{11}ClO_3$	67.03 (66.87	3.87 3.84)
20l	**21l**	H	Cl	H	70	260—262	EtOH	$C_{16}H_{11}ClO_3$	67.03 (67.06	3.87 4.07)
20m	**21m**	H	H	Cl	51	198—200	EtOH	$C_{16}H_{11}ClO_3$	67.03 (67.04	3.87 3.85)
20n	**22n**	H	H	Cl	24	185—187	EtOH	$C_{16}H_{11}ClO_3$	67.03 (66.81	3.87 4.00)
	21a	H	H	H	13					
20o	**21o**	H	Me	H	55	242—244	EtOH	$C_{17}H_{14}O_3$	76.68 (76.57	5.30 5.29)
20p	**21p**	H	H	Me	97	185—187	EtOH	$C_{17}H_{14}O_3$	76.68 (76.57	5.30 5.25)
20q	**22q**	H	H	Me	70	199—201 (lit.[10b] 165)	EtOH	$C_{17}H_{14}O_3$	76.67 (76.89	5.30 5.34)
20r	**21r**	H	H	Br	49	198—200 (lit.[14] 197)	EtOH	$C_{16}H_{11}BrO_3$	58.03 (58.36	3.35 3.44)
20s	**21s**	H	Me	Cl	76	225—226	EtOH	$C_{17}H_{13}ClO_3$	67.90 (67.86	4.36 4.38)

d_6) δ: 2.80 (1H, br s, OH), 3.47 (2H, d, J=9.0 Hz, Ph-CH$_2$), 3.72—3.98 (2H, m, CH$_2$OH), 4.93—5.47 (1H, m, Ph-CH$_2$-CH), 7.11—7.90 (3H, m, arom. H), 8.00 (1H, s, 5-H), 8.07—8.30 (1H, m, 7-H).

Other compounds **23** in Table XIII were similarly prepared.

2,3-Dihydro-2-hydroxymethylfuro[3,2-*b*]xanthones (24) A typical example is given to illustrate the general procedure.

2,3-Dihydro-2-hydroxymethyl-11-methylfuro[3,2-*b*]xanthone (**24q**): To a stirred solution of **22q** (1.1 g, 4.1 mmol) in CH_2Cl_2 (150 ml), *m*-CPBA (0.95 g, 5.5 mmol) was added in small portions at room temperature. The solution was stirred for 13 h and then refluxed for 7 h. After addition of an aq. solution of NaOH to the solution, the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated to give **24q** (1.0 g, 85%) as crystals (EtOH), mp 242—243 °C (EtOH). *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.47; H, 5.10. MS *m/z*: 282 (M^+), 251. IR (KBr) cm^{-1}: 3392 (OH), 1640 (C=O), 1614. NMR ($CDCl_3$–DMSO-d_6) δ: 2.31 (3H, s, CH$_3$), 3.20 (2H, br d, J=8.0 Hz, Ph-CH$_2$), 3.53—3.85 (2H, m, CH$_2$OH), 4.67—5.17 (1H, m, Ph-CH$_2$-CH), 4.81 (1H, br s, OH), 7.07—7.93 (3H, m, arom. H), 7.77 (1H, s, 4-H), 8.00—8.22 (1H, m, 6-H).

Other compounds **24** in Table XIV were similarly prepared.

1,2-Dihydrofuro[2,3-*c*]xanthone-2-carboxylic Acids (7) A typical example is given to illustrate the general procedure.

4-Chloro-1,2-dihydrofuro[2,3-*c*]xanthone-2-carboxylic Acid (**7m**): To a stirred solution of **23m** (2.0 g, 6.6 mmol) in acetone (250 ml), a mixture of CrO_3 (3.3 g, 33 mmol), H_2O (17 ml) and conc. H_2SO_4 (5.0 g) was added at room temperature. The resulting mixture was stirred for 10 h and left to stand overnight. Iso-PrOH (20 ml) was added and the mixture was stirred for 1 h, and then filtered. The filtrate was evaporated to dryness *in vacuo*. After addition of H_2O to the residue, the crystals formed were collected by filtration, washed with H_2O and dried. Recrystallization from DMF–EtOH gave **7m** (1.4 g, 67%) as crystals (DMF–H_2O), mp 300—302 °C. *Anal.* Calcd for $C_{16}H_9ClO_5$: C, 60.68; H, 2.86. Found: C, 60.51; H, 2.92. MS *m/z*: 316 (M^+). IR (KBr) cm^{-1}: 3460 (OH), 1756 (COOH). NMR ($CDCl_3$–DMSO-d_6) δ: 3.75 (1H, d, J=7.8 Hz, Ph-CH$_2$), 3.80 (1H, d, J=9.6 Hz, Ph-CH$_2$), 4.80 (1H, br s, COOH), 5.50 (1H, dd, J=9.6, 7.8 Hz, Ph-CH$_2$-CH), 7.16—7.88 (3H, m, arom. H), 8.04 (1H, s, 5-H), 8.08—8.38 (1H, m, 7-H).

Other compounds **7** in Table III were similarly prepared.

2,3-Dihydrofuro[3,2-*b*]xanthone-2-carboxylic Acids (8) A typical example is given to illustrate the general procedure.

2,3-Dihydro-11-methylfuro[3,2-*b*]xanthone-2-carboxylic Acid (**8q**): To a stirred solution of **24q** (4.45 g, 15.8 mmol) in acetone (1.5 l), a mixture of CrO_3 (7.9 g, 79 mmol), H_2O (40 ml) and conc. H_2SO_4 (12.0 g) was added at room temperature. The resulting mixture was stirred for 9 h and left to stand overnight. Iso-PrOH (20 ml) was added and the mixture was stirred for 1 h, and then filtered. The filtrate was evaporated to dryness *in vacuo*. After addition of H_2O to the residue, the crystals formed were collected by filtration, washed with H_2O and dried. Recrystallization gave **8q** (3.1 g, 66%) as crystals (DMF–H_2O), mp 296—299 °C. *Anal.* Calcd for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 68.79; H, 4.15. MS *m/z*: 296 (M^+). IR (KBr) cm^{-1}: 3460 (OH), 1730 (COOH), 1614. NMR ($CDCl_3$–DMSO-d_6) δ: 2.36 (3H, s, CH$_3$), 3.45 (1H, d, J=7.8 Hz, Ph-CH$_2$), 3.53 (1H, d, J=9.6 Hz, Ph-CH$_2$), 5.23 (1H, dd, J=9.6, 7.8 Hz, Ph-CH$_2$-CH), 7.01—7.90 (3H, m, arom. H), 7.44 (1H, br s, COOH), 7.79 (1H, s, 4-H), 8.00—8.22 (1H, m, 6-H).

Other compounds **8** in Table IV were similarly prepared.

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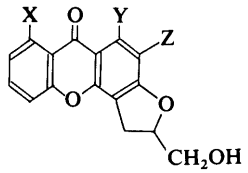
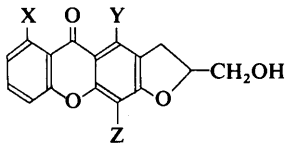
TABLE XIII. 1,2-Dihydro-2-hydroxymethylfuro[2,3-*c*]xanthones (**23**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
23a	H	H	H	56	193—194	EtOH	$C_{16}H_{12}O_4$	71.64 (71.50	4.51 4.60)
23b	F	H	H	79	220—221	EtOH	$C_{16}H_{11}FO_4$	67.13 (66.93	3.87 3.85)
23f	Cl	H	H	63	190—192	EtOH	$C_{16}H_{11}ClO_4$	63.48 (63.08	3.66 3.65)
23l	H	Cl	H	70	233—234	EtOH	$C_{16}H_{11}ClO_4$	63.48 (63.32	3.66 3.68)
23m	H	H	Cl	83	184—185	EtOH	$C_{16}H_{11}ClO_4$	63.48 (63.50	3.66 3.76)
23o	H	Me	H	63	179—180	EtOH	$C_{17}H_{14}O_4$	72.33 (72.12	5.00 4.80)
23p	H	H	Me	94	204—206	EtOH	$C_{17}H_{14}O_4$	72.33 (72.05	5.00 5.08)
23r	H	H	Br	48	196—198	EtOH	$C_{16}H_{11}BrO_4$	55.36 (55.32	3.19 3.44)
23s	H	Me	Cl	54	232—234	EtOH	$C_{17}H_{13}ClO_4$	64.47 (64.28	4.14 4.35)

TABLE XIV. 2,3-Dihydro-2-hydroxymethylfuro[3,2-*b*]xanthones (**24**)



Compd. No.	X	Y	Z	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)	
								C	H
24c	F	H	Cl	31	238—240	EtOH	$C_{16}H_{10}ClFO_4$	59.92 (59.94	3.14 3.17)
24e	F	H	Me	74	261—262	EtOH	$C_{17}H_{13}FO_4$	68.00 (67.96	4.36 4.76)
24f	Cl	H	Cl	82	200—203	EtOH	$C_{16}H_{10}Cl_2O_4$	57.00 (56.73	2.99 3.15)
24n	H	H	Cl	52	231—232	EtOH	$C_{16}H_{11}ClO_4$	63.48 (63.31	3.66 3.72)
24q	H	H	Me	85	242—243	EtOH	$C_{17}H_{14}O_4$	72.33 (72.47	5.00 5.10)

Diuretic and Uricosuric Effects on Rats[16] Seven-week-old Wistar-Imamichi rats that had been fasted for 24 h were divided in groups of five heads so that the animals in each group would excrete almost the same amount of urine. After forced urination, the rats were orally administered the test compounds that were suspended in physiological saline containing 3% gum arabic in a dose volume of 25 ml per kg of body weight. The suspensions were administered typically in an amount of 100 mg/kg. The control rats were given only physiological saline containing 3% gum arabic. The animals were housed in separate metabolic cages and the urine excreted from each animal was collected over a period of 6 h following the administration of the test compounds or physiological saline after complete starvation. The urine volume was directly read on a measuring cylinder after forced urination thereinto, and the amount of urine per kg of body weight was calculated. The amount of uric acid excreted in the urine was determined by the uricase–catalase method.

Acknowledgement The authors are indebted to Drs. S. Hata, B. Aoki, I. Matsunaga, T. Mori, and M. Akima for valuable suggestions throughout this work. We are also grateful to Dr. M. Hamana, Professor emeritus of Kyushu University, for helpful discussions.

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