Synthesis and Antiallergic Activity of Some Mono- and Disubstituted Xanthone-2-carboxylic Acids[1]

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A series of xanthone-2-carboxylic acids, substituted mainly with electron-withdrawing groups, has been synthesized and assayed for antiallergic activity, using the passive cutaneous anaphylaxis (PCA) reaction in the rat. The effect of substituent type and substitution pattern on PCA neutralizing capacity is presented.

Khellin,[2] a naturally occurring oxygen heterocycle, has served as a basis for the development of the antiasthma drug disodium cromoglycate.[3,4] Recent investigations in this field have focused on the chemistry and pharmacology of a variety of other chromones[5] as well as xanthones[6] and annellated γ-pyrones.[7]

Continuing our work on xanthone-2-carboxylic acids,[8] we have prepared a number of compounds with increased potency in the PCA assay by selecting substituents with mainly -I/-E character and determining the influence of size, shape, and substitution pattern of these groups on antiallergic activity.

7-Methylsulfinylxanthone-2-carboxylic acid (11a; tixanox, USAN) has been shown to be orally active against exercise-induced asthma in man.[9]

Chemistry. Since xanthone-2-carboxylic acid (1) cannot be acylated directly under Friedel–Crafts conditions, it was first converted into xanthene-2-carboxylic acid (2) by a Huang-Minlon reduction and then esterified with Li_2CO_3–MeI in DMF. Reaction of the resulting methyl ester 3 with an acyl halide and $AlCl_3$ in 1,2-dichloroethane, followed by oxidation with Jones reagent in DMF and base hydrolysis, provided the desired 7-acylxanthone-2-carboxylic acids 4a–e (Scheme I).

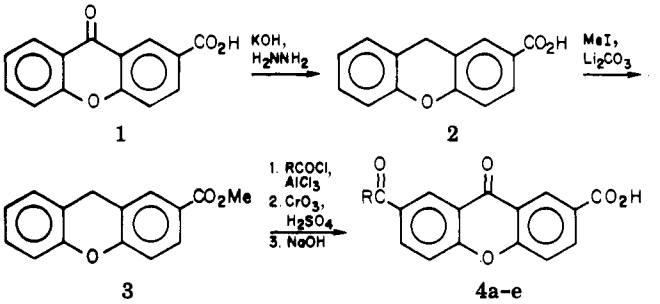
Introduction of a thio function into the 7 position of the xanthone nucleus was achieved through thermal rearrangement[10] of the dimethylthiocarbamate 6 derived from the hydroxy ester 5 (Scheme II). Base hydrolysis of the resulting *S*-aryl derivative 7 provided the mercapto acid 8.

Alkylation of 8 with MeI or *i*-PrBr in the presence of K_2CO_3 gave the alkylthio esters 9a,b, which were converted into the corresponding carboxylic acids 10a,b by saponification with NaOH. Oxidation of 9a and 9b with *m*-chloroperoxybenzoic acid, followed by base hydrolysis, furnished the alkylsulfinyl derivatives 11a,b. The sulfone 12 was obtained by oxidation of 10a with H_2O_2 in refluxing AcOH.

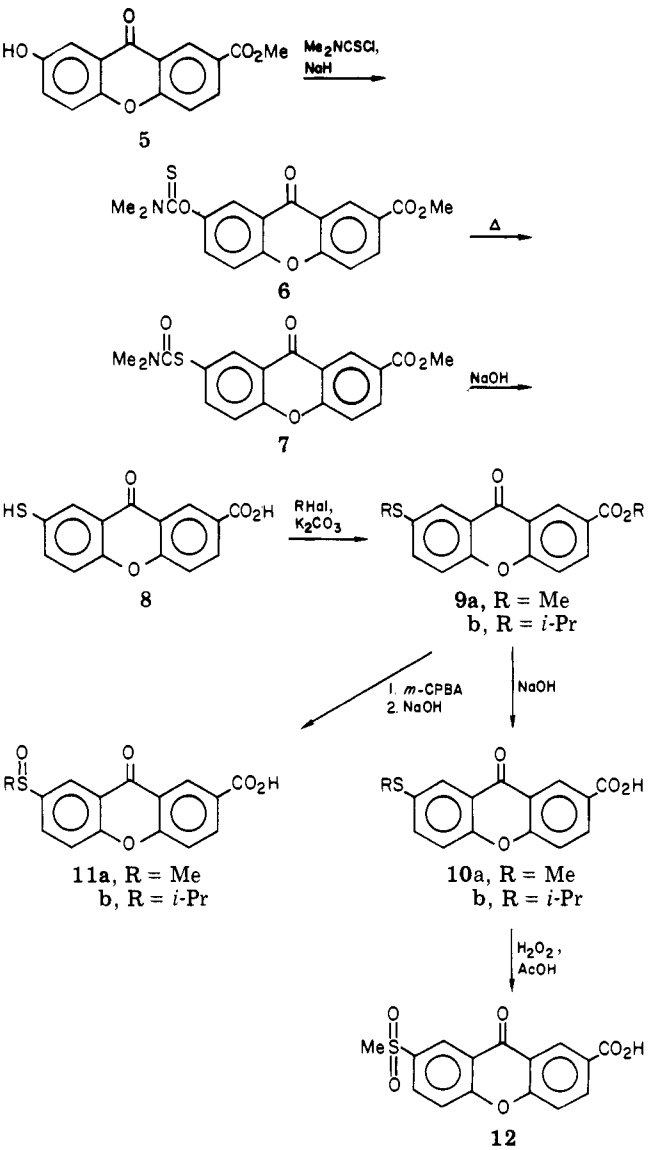
The disubstituted xanthone-2-carboxylic acids 15a–g were prepared by coupling[11] the required phenols with dimethyl 4-bromoisophthalate in the presence of Cu_2O, hydrolyzing the ester groups of the intermediate diphenyl ethers 13a–f, and cyclizing the resulting dicarboxylic acids 14a–f with PPA (Scheme III). Starting from 3,4-dimethylphenol, isomers 15e and 15f were obtained as a mixture which was esterified and separated by column chromatography. Structures were readily assigned on the basis of the ^1H NMR spectra (see the Experimental Section).

O-Demethylation of 15g with HI–AcOH (→16) followed by esterification with Li_2CO_3–MeI in DMF provided the phenolic intermediate 17, which was converted into the desired 5-alkoxy-7-methylsulfinylxanthone-2-carboxylic acids 18a–h by alkylation, oxidation, and saponification (Scheme IV).

Scheme I



Scheme II



Discussion and Conclusions

As has already been noted earlier,[8] introduction of a substitutent only into the 5 or 7 position of the xanthone nucleus leads to compounds with increased PCA activity.

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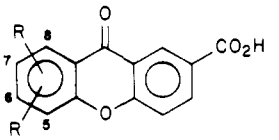
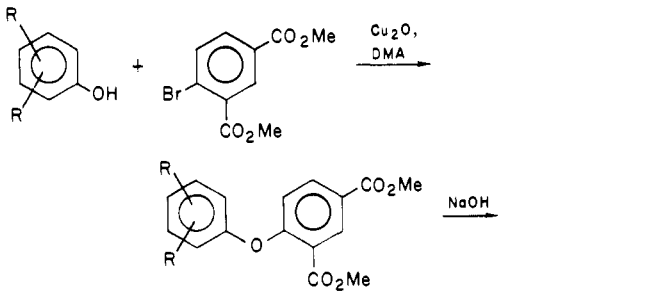
Table I. Rat Passive Cutaneous Anaphylaxis Assay of Xanthone-2-carboxylic Acids[a]



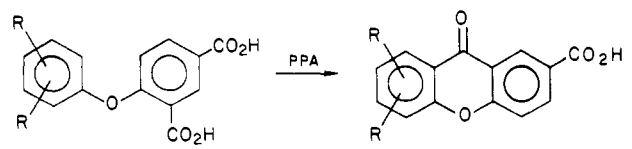
Compd	R[b]	Mp, °C	Formula[c]	Yield, %	No. of rats[d]	RPCA[e]
4a	CH_3CO	324-325	$C_{16}H_{10}O_5$	73[f]	30	6
4b	C_2H_5CO	290-292	$C_{17}H_{12}O_5$	79[f]	15	2
4c	i-C_3H_7CO	263-265	$C_{18}H_{14}O_5$	62[f]	35	3
4d	C_3H_5CO[g]	277-279	$C_{18}H_{12}O_5$	77[f]	30	3
4e	C_5H_9CO[h]	>300	$C_{20}H_{16}O_5$	81[f]	30	2
10a	CH_3S	298-300	$C_{15}H_{10}O_4S$	79[i]	45	5
10b	i-C_3H_7S	278-280	$C_{17}H_{14}O_4S$	74[i]	15	2
11a	CH_3SO	>300	$C_{15}H_{10}O_5S$	68[i]	54	25
11b	i-C_3H_7SO	>350	$C_{17}H_{14}O_5S$	63[i]	15	4
12	CH_3SO_2	>320	$C_{15}H_{10}O_6S$	70[i]	33	7
15a	5,7-$(CH_3O)_2$	>300	$C_{16}H_{12}O_6$	54[j]	15	6
15b	6,7-$(CH_3O)_2$	363-365	$C_{16}H_{12}O_6$	61[j]	15	2
15c	6,8-$(CH_3O)_2$	>300	$C_{16}H_{12}O_6$	57[j]	4	~0.1
15d	5,7-$(CH_3)_2$	306-309	$C_{16}H_{12}O_4$[k]	48[j]	49	1
15e	6,7-$(CH_3)_2$	365	$C_{16}H_{12}O_4$	56[j,l]	39	0.2
15f	7,8-$(CH_3)_2$	335	$C_{16}H_{12}O_4$	56[j,l]	40	0.2
18a	5-C_2H_5O-7-CH_3SO	273-274	$C_{17}H_{14}O_6S$	82[m]	59	80
18b	5-n-C_3H_7O-7-CH_3SO	265-267	$C_{18}H_{16}O_6S$	75[m]	59	50
18c	5-i-C_3H_7O-7-CH_3SO	280-282	$C_{18}H_{16}O_6S$	71[m]	69	190
18d	5-n-C_4H_9O-7-CH_3SO	269-270	$C_{19}H_{18}O_6S$	68[m]	60	260
18e	5-n-$C_5H_{11}O$-7-CH_3SO	263-265	$C_{20}H_{20}O_6S$	71[m]	108	90
18f	5-i-$C_5H_{11}O$-7-CH_3SO	271-273	$C_{20}H_{20}O_6S$	75[m]	94	100
18g	5-C_5H_9O-7-CH_3SO[h]	274-276	$C_{20}H_{18}O_6S$	81[m]	59	100
18h	5-n-$C_8H_{17}O$-7-CH_3SO	258-260	$C_{23}H_{26}O_6S$	74[m]	35	35

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] All single substituents at C-7. [c] All compounds were analyzed for C and H. [d] Total number of rats receiving the test material. [e] Potency of the compounds in the rat passive cutaneous anaphylaxis assay, iv (see Experimental Section); disodium cromoglycate = 1. [f] Yield based on **3**. [g] C_3H_5 is cyclopropyl. [h] C_5H_9 is cyclopentyl. [i] Yield based on **8**. [j] Yield based on dimethyl 4-bromoisophthalate. [k] C: calcd, 71.63; found, 72.08. [l] Yield of mixture of **15e** and **15f**. [m] Yield based on **17**.

Scheme III



13a, 2,4-$(MeO)_2$
b, 3,4-$(MeO)_2$
c, 3,5-$(MeO)_2$
d, 2,4-$(Me)_2$
e, 3,4-$(Me)_2$
f, 2-MeO-4-MeS



14a, 2,4-$(MeO)_2$
b, 3,4-$(MeO)_2$
c, 3,5-$(MeO)_2$
d, 2,4-$(Me)_2$
e, 3,4-$(Me)_2$
f, 2-MeO-4-MeS

15a, 5,7-$(MeO)_2$
b, 6,7-$(MeO)_2$
c, 6,8-$(MeO)_2$
d, 5,7-$(Me)_2$
e, 6,7-$(Me)_2$
f, 7,8-$(Me)_2$
g, 5-MeO-7-MeS

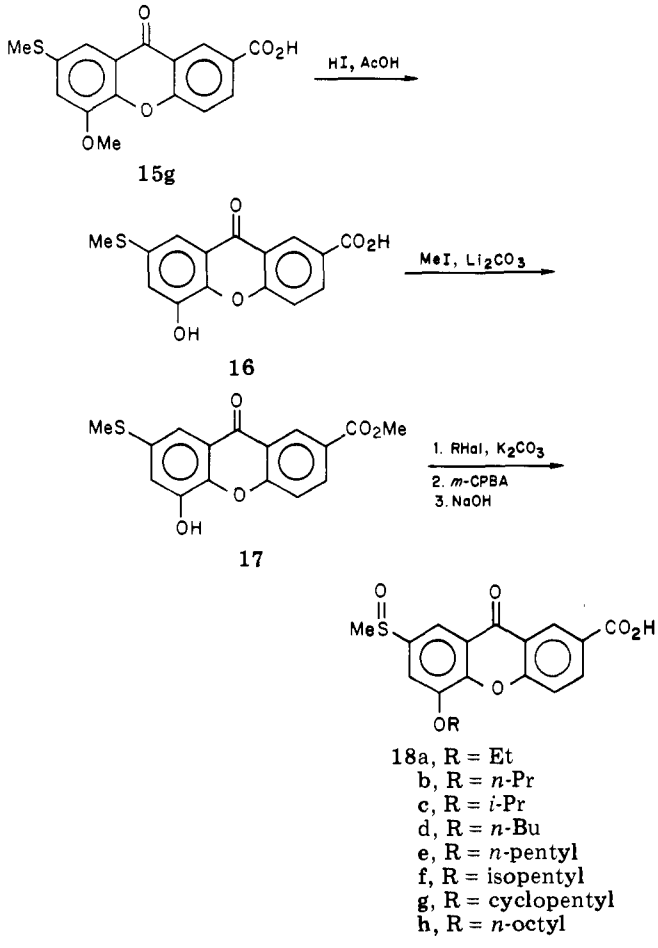
Additionally, a wide range of lipophilic-hydrophilic character is tolerated in the substituent, whereas there seems to exist an optimum regarding its size. In contrast to the compounds containing mostly electron-releasing groups like alkyl and alkoxy, described before,[8] we have now focused our attention on substituents with electron-withdrawing properties as well as combinations of two substituents.

The results of the PCA assay[12] in the 7-acyl series (Table I) show maximum activity for the acetyl compound **4a**. Although increased chain length causes a reduction of activity (see **4b** vs. **4a**), branching of the side chain at the α-carbon is generally consistent with maintaining some PCA activity, an effect which has also been observed in the 7-alkyl and 7-alkoxy series.[8] Therefore, one can find only a limited correlation between potency and parameters characterizing only substituent bulk like molar refraction[13] or the steric substituent constant E_s.[14]

A group of compounds carrying sulfur-containing substituents with widely dissimilar electronic as well as hydrophobic character was examined next (Table I). In contrast to the alkoxy series, the methylthio and methylsulfinyl analogues **10a** and **11a** display higher PCA activity than their isopropyl counterparts **10b** and **11b**, which may be a reflection of the larger bulk of the sulfur atom compared to oxygen. A rather unexpected enhancement of activity is achieved by introduction of the hydrophilic methylsulfinyl and methylsulfonyl groups (compounds **11a** and **12**), which are both characterized by strongly negative π values.[13] Interestingly, MeS, MeSO, and $MeSO_2$ are groups of very similar size (molar refraction MR = 13.28, 13.70, and 13.49, respectively[13]).

In an attempt to further define the structural requirements for increased PCA activity observed so far in this series, we were interested in determining how this activity would be influenced by introduction of two substituents. In particular, we were hoping to find an additive effect with groups occupying both the 5 and 7

Scheme IV



18a, R = Et
b, R = *n*-Pr
c, R = *i*-Pr
d, R = *n*-Bu
e, R = *n*-pentyl
f, R = isopentyl
g, R = cyclopentyl
h, R = *n*-octyl

positions, monosubstitution of which has already been shown to lead to active compounds.

Again, using the methoxy group as a probe,[8] three different dimethoxy analogues were examined (Table I). While the 6,8 isomer **15c** was found to be considerably less active than either of the corresponding monosubstituted compounds, an enhancement of activity was observed on moving one methoxy group from the 8 to the 7 position (**15b**). In the case of the 5,7-substitution pattern, as represented by **15a**, PCA activity increased by a factor of 3 relative to **15b**. A rather similar correlation is evident in the dimethyl series (Table I), where the 5,7 combination (**15d**) is superior to 6,7-Me_2 (**15e**) or 7,8-Me_2 (**15f**).

In order to determine whether it would be possible to increase PCA activity by combining a hydrophilic substituent at C-7 with a lipophilic group at C-5, a number of 5-alkoxy-7-methylsulfinyl derivatives were prepared (Table I). Surprisingly high activities were observed in this case, with a maximum potency of 260 times disodium cromoglycate elicited by the butoxy compound **18d**. Even the lipophilic *n*-octyloxy analogue **18h** still surpasses the unsubstituted 7-sulfoxide **11a**. Apparently, the stringent requirements as to bulk and shape of a given substituent, noted previously, do not dominate this particular series and can be discerned only when comparing *n*-propoxy with isopropoxy groups (compounds **18b** and **18c**).

Experimental Section

Melting points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical values. All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. Thin-layer chromatograms were eluted with a benzene–THF–AcOH (30:3:1) mixture. For filtrations, "Woelm" alumina (activity II, neutral) was used.

Xanthene-2-carboxylic Acid (2). Huang-Minlon reduction[15] (hydrazine, KOH, and triethylene glycol) of xanthone-2-carboxylic acid[16] (1) provided the desired compound **2** in 85% yield: mp 257–258 °C (THF–EtOH). Anal. ($C_{14}H_{10}O_3$) C, H.

Methyl Xanthene-2-carboxylate (3). A mixture of 43.5 g (0.192 mol) of **2**, 35 g (0.47 mol) of Li_2CO_3, 30 mL (0.485 mol) of MeI, and 500 mL of DMF was stirred for 16 h at room temperature. AcOH–H_2O (400 mL, 1:1) containing 10 g of $NaHSO_3$ was added in small portions, followed by dilution with 2 L of H_2O. Ester **3** was filtered off, washed with H_2O, and dried: 41.2 g (89.5%); mp 131–133 °C. Anal. ($C_{15}H_{12}O_3$) C, H.

7-Acylxanthone-2-carboxylic Acids 4a–e. A solution of 3.0 g (12.5 mmol) of **3**, 5.0 g (37.5 mmol) of $AlCl_3$, and 15.0 mmol of the corresponding acyl chloride in 60 mL of $ClCH_2CH_2Cl$ was stirred at room temperature for 3 h and then poured on ice–HCl. Extraction with CH_2Cl_2, followed by filtration of the dried ($MgSO_4$) extracts through alumina and crystallization from CH_2Cl_2–MeOH, provided the desired 7-acylxanthene-2-carboxylates, which were dissolved in 100 mL of DMF and treated with excess Jones reagent (8 N CrO_3 in 8 N H_2SO_4) until TLC indicated the absence of starting material. Water (400 mL) was then added, and the resulting precipitate was filtered off and washed thoroughly with warm water. These esters were refluxed for 30 min with 600 mg (15.0 mmol) of NaOH in 100 mL of 80% aqueous EtOH. After acidification with 2 N HCl, the 7-acylxanthone-2-carboxylic acids **4a–e** (Table I) were isolated by suction filtration and recrystallized from DMF–AcOH.

Methyl 7-Hydroxyxanthone-2-carboxylate (5). Esterification of 7-hydroxyxanthone-2-carboxylic acid[8] with Li_2CO_3–MeI in DMF as described for **2** → **3** gave a 91.3% yield of **5**, mp 280–282 °C (AcOH). Anal. ($C_{15}H_{10}O_5$) C, H.

Methyl 7-Dimethylthiocarbamoyloxyxanthone-2-carboxylate (6). Treatment of **5** with dimethylthiocarbamoyl chloride and NaH in DMF as described[10] provided the *O*-arylthiocarbamate **6** in 82% yield: mp 236–238 °C ($CHCl_3$–AcOEt). Anal. ($C_{18}H_{15}NO_5S$) C, H.

Methyl 7-(Dimethylcarbamoylthio)xanthone-2-carboxylate (7). A solution of 8.0 g (22.4 mmol) of **6** in 150 mL of sulfolane was stirred and heated at 230–240 °C under N_2 for 6 h, during which time a single new compound (more polar on TLC) had been formed. After cooling to 80 °C, 600 mL of water was added, and the resulting precipitate was filtered off, washed with water, dried, and recrystallized from $CHCl_3$–EtOH to give 7.5 g (87.5%) of **7**, mp 237–238 °C. Anal. ($C_{18}H_{15}NO_5S$) C, H, S.

7-Mercaptoxanthone-2-carboxylic Acid (8). **7** (7.5 g, 21.0 mmol) was refluxed under N_2 with 10 g (0.18 mol) of KOH in 250 mL of 80% aqueous EtOH for 4 h. Water (250 mL) and charcoal (2.0 g) were added, and refluxing was continued for 15 min. After filtration through Celite, the filtrate was acidified with excess 2 N HCl to give 5.3 g (93%) of the thiol acid **8**, mp >400 °C. Anal. ($C_{14}H_8O_4S$) C, H, S.

Alkyl 7-(Alkylthio)xanthone-2-carboxylates 9a,b. Treatment of 1.36 g (5.0 mmol) of **8** with 3.45 g (25.0 mmol) of K_2CO_3 and 25.0 mmol of MeI (or *i*-PrBr) in 40 mL of DMF for 20 h at room temperature, followed by dilution with 2 N HCl, extraction with CH_2Cl_2, and filtration of the dried extracts through a short column of alumina, provided the esters **9a** and **9b** in nearly quantitative yields.

7-(Alkylthio)xanthone-2-carboxylic Acids 10a,b (Table I). Refluxing 10.0 mmol of **9a** or **9b** with 600 mg (15.0 mmol) of NaOH in 75 mL of 80% aqueous EtOH for 30 min, followed by acidification with 2 N HCl, gave the acids **10a** and **10b**, which were recrystallized from DMF–AcOH.

7-Alkylsulfinylxanthone-2-carboxylic Acids 11a,b (Table I). To a solution of 5.0 mmol of **9a** or **9b** in 50 mL of CH_2Cl_2, cooled to 0 °C, a solution of 1.06 g (5.25 mmol) of 85% *m*-chloroperoxybenzoic acid in 50 mL of CH_2Cl_2 was added dropwise with stirring. The reaction mixture was washed with 2 N $NaHCO_3$ and water. Evaporation of the dried CH_2Cl_2 solution gave a crude ester which was directly saponified with NaOH as described for **9** → **10** to provide acids **11a** and **11b**. In this case, aqueous DMF was used to recrystallize the crude products.

7-Methylsulfonylxanthone-2-carboxylic Acid (12) (Table I). A mixture of 1.62 g (5.66 mmol) of **10a**, 6.42 mL (56.6 mmol) of 30% H_2O_2, and 65 mL of AcOH was refluxed for 90 min. The

hot solution was diluted with 75 mL of H_2O and cooled and the resulting precipitate isolated by suction filtration. An analytical sample was prepared by recrystallization from AcOH.

Dimethyl 4-Phenoxyisophthalates 13a–f. A mixture of 12.0 g (44.0 mmol) of dimethyl 4-bromoisophthalate,[17] 50.0 mmol of the desired disubstituted phenol, 3.46 g (24.2 mmol) of Cu_2O, and 200 mL of DMA was refluxed under N_2 for 16 h. The cooled reaction mixture was poured into 1.5 L of H_2O containing 100 mL of 2 N HCl and extracted with ether. The organic phase was washed five times with H_2O, twice with 2 N NaOH, and again with H_2O. The dried ether solution was evaporated and the residue dissolved in CH_2Cl_2 and filtered through alumina. The crude, oily esters obtained in this manner contained dimethyl isophthalate (GLC; formed by reductive debromination) as the only major impurity. They were not purified or characterized further.

4-Phenoxyisophthalic Acids 14a–f. A mixture of 30.0 mmol of one of the foregoing diesters (**13a–f**), 3.6 g (90.0 mmol) of NaOH, and 300 mL of 80% aqueous EtOH was refluxed for 30 min. The resulting clear solution was acidified with 2 N HCl, diluted with 200 mL of H_2O, and concentrated on a rotary evaporator. In some instances, crystalline diacids, contaminated with isophthalic acid (TLC), were obtained. Oily reaction products were extracted with AcOEt. To avoid any loss of material at this stage, no further attempt to purify these compounds was made.

Xanthone-2-carboxylic Acids 15a–g (Table I). The desired dicarboxylic acid **14a–f** (25.0 mmol) was dissolved in 150 mL of sulfolane with overhead stirring at 90 °C on a steam bath. After adding 100 g of PPA, the reaction mixture was stirred at 90 °C for 1 h and then slowly diluted with 450 mL of H_2O. The resulting precipitate was filtered off and washed with 50% aqueous EtOH. The dried, crude products were recrystallized from DMF–AcOH.

Cyclization of **14e** in this manner gave a 1:1 mixture of the two isomers **15e** and **15f**, which was esterified (MeI–Li_2CO_3) and then separated by chromatography on silica gel (benzene). The methyl ester of **15e** showed mp 202–204 °C (THF–EtOH): NMR ($CDCl_3$; δ, ppm) 2.32 (s, 3 H, Me-7), 2.35 (s, 3 H, Me-6), 7.18 (s, 1 H, H-5), 7.95 (s, 1 H, H-8). The Me ester of isomer **15f** had mp 164–166 °C (THF–EtOH): NMR ($CDCl_3$) 2.32 (s, 3 H, Me-7), 2.78 (s, 3 H, Me-8), 7.15 (d, J = 9 Hz, 1 H, H-5), 7.43 (d, J = 9 Hz, 1 H, H-6). Both esters were converted back into the corresponding acids by hydrolysis with NaOH (80% aqueous EtOH, 30 min of reflux). Starting with 2-methoxy-4-(methylthio)phenol,[18] **15g** was obtained in 46% yield based on dimethyl 4-bromoisophthalate: mp 304–305 °C (DMF–AcOH). Anal. ($C_{16}H_{12}O_5S$) C, H, S.

5-Hydroxy-7-(methylthio)xanthone-2-carboxylic Acid (16). HI (116 mL, 47%) was added dropwise to 380 mL of ice-cooled Ac_2O with vigorous stirring. After adding 17.0 g (53.8 mmol) of **15g**, the resulting suspension was refluxed for 20 h. The hot reaction mixture was diluted with 400 mL of H_2O and cooled and the product (**16**) isolated by suction filtration: 14.3 g (88%); mp 364–366 °C dec. Anal. ($C_{15}H_{10}O_5S$) C, H, S.

Methyl 5-Hydroxy-7-(methylthio)xanthone-2-carboxylate (17). Esterification of 13.8 g (45.7 mmol) of **16** with MeI–Li_2CO_3 in DMF as for **2** → **3** gave 12.6 g (87%) of **17**, mp 272–274 °C (AcOH). Anal. ($C_{16}H_{12}O_5S$) C, H, S.

5-Alkoxy-7-methylsulfinylxanthone-2-carboxylic Acids 18a–h (Table I). Alkylation of **17** with an alkyl halide, followed by oxidation of the MeS group with *m*-chloroperoxybenzoic acid and base-catalyzed hydrolysis of the ester moiety (cf. **8** → **9** → **11**) furnished the desired compounds, which were recrystallized from THF–EtOH.

Biological Assay. Female Sprague–Dawley derived albino rats (Simonsen Labs., Gilroy, Calif.) weighing 140–160 g were used. Rat reaginic antibody was produced using the method of Mota.[19] The rats were immunized with 1.25 mg of egg albumin (General Biochemicals, twice crystallized and salt-free) sc and 1.0 mL of *Hemophilus pertussis* vaccine (Eli Lilly and Co.) ip. Eleven days later the rats were bled and the serum obtained was pooled and frozen. This serum met the requirements for reaginic antiserum; namely, it was heat labile (1 h at 56 °C) and could elicit a passive cutaneous anaphylaxis (PCA) reaction 75 h after intradermal injection. The PCA test was based on the method of Goose and Blair.[12] The rats were passively sensitized with two dilutions (right and left flanks) of the antiserum given intradermally in 0.1 mL of normal saline. These rats were challenged 24 h later iv with 1.0 mL of buffered saline (pH 7.2) containing 1.0 mg of albumin, 0.5% Evans blue dye, and the compound to be evaluated. The rats were sacrificed 15–25 min after challenge, at which time the abdominal skin was reflected and the diameter of the dermal bluing (mean of two perpendicular axes) was determined. The relative potencies of the test materials were determined graphically, using dose–response curves obtained from semilog plots of the data, expressed as percent inhibition of the PCA response relative to challenge animals not receiving drug. One or more tests were performed, comparing each test agent simultaneously with cromolyn sodium. Usually three doses of each compound were used (fivefold increments) in each test, each dosage group usually having at least five rats.

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References and Notes

(1) (a) Presented in part before the Division of Medicinal Chemistry at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 2, 1974; (b) Publication No. 438 from the Institute of Organic Chemistry, Syntex Research.
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