Table VII. Group Contributions as Calculated by the Free-Wilson Model from Structure II

Position	Group	Contribution Run 1	Contribution Run 2
	μ	8.39	8.46
A	H	1.12	1.07
A	Cl	−0.25	−0.09
A	NO_2	−7.52	−7.12
A	Br	0.13	0.53
B	H	0.38	−0.09
B	Cl	1.35	1.13
B	NO_2	−2.87	−3.00
B	Br	−0.62	2.39
n	1	−3.02	−2.78
n	2	0.86	0.88
C	OH	0.45	0.77
C	NH_2	−0.48	−0.83

3-[5-(4-Acetamidophenyl)-2-tetrazolyl]propionic Acid (14). A solution of 5 g (0.022 mole) of 3-[5-(4-aminophenyl)-2-tetrazolyl]-propionic acid 34 in 200 ml of Ac_2O was allowed to stand for 24 hr at room temperature. The reaction was diluted with 2 l. of water and the solid collected and dried. Recrystallization from MeOH gave 2.4 g (40%) of fine white needles, mp 218°.

3-[5-(4-Phenylazophenyl)-2-tetrazolyl]propionic Acid (16). A solution of 10 g (0.043 mole) of 3-[5-(4-aminophenyl)-2-tetrazolyl]-propionic acid (34) and 4.6 g (0.043 mole) of nitrosobenzene in 150 ml of warm glacial acetic acid was allowed to stand for 24 hr. The precipitate was collected, washed with MeOH, and recrystallized from THF–MeOH to give 9 g (65%) of red crystals, mp 234°.

Acknowledgment. I wish to thank Messrs. H. E. Hartzler and W. G. Strycker for some of the preparations, Dr. O. J. Lorenzetti for his screening data, and particularly Mr. Ralph C. Naegele for his many helpful suggestions and assistance.

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Synthesis and Structure–Activity Relationships of Disodium Cromoglycate and Some Related Compounds

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The synthesis of the antiasthmatic substance 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane disodium salt (disodium cromoglycate) and a number of its analogs is described. The homologous passive cutaneous anaphylaxis (PCA) reaction in the rat, based on a reaginic antibody–antigen system, has been used as a routine screen to assess the activity of these compounds as potential antiasthmatic drugs. The structural requirements for biological activity in the PCA reaction are discussed with reference to the type and position of linkage of the two chromone nuclei. There is an indication that in this system coplanarity of the chromone nuclei is one requirement for activity.

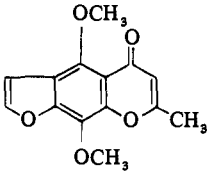
Khellin (I)[1,2] is a naturally occurring oxygen heterocycle with vasodilator and smooth muscle relaxing properties, which has had limited clinical use in the treatment of angina and bronchial asthma. Our investigations led to a series of chromone-2-carboxylic acids which did not possess the biological properties associated with khellin. On administration to an asthmatic volunteer prior to antigen challenge, however, they inhibited in varying degrees the bronchoconstrictor response. The development of this discovery led to the introduction of disodium cromoglycate (II) (cromolyn sodium, USAN)† for the treatment of asthma.

†Intal, Lomudal.

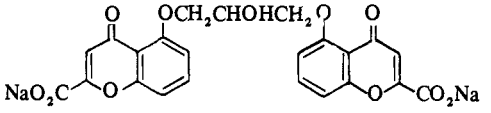
This drug represents a new pharmacological approach to the treatment of allergic bronchial asthma. It has been shown to inhibit the liberation of the mediators of immediate type allergic reactions initiated by reaginic antibody-antigen interactions. It is not an antagonist of histamine, 5-HT, bradykinin, or the slow-reacting substance of anaphylaxis (SRS-A), nor is it antiinflammatory.[3] It does however inhibit the release of histamine and SRS-A from sensitized human lung *in vitro* as well as preventing homologous passive cutaneous anaphylaxis (PCA) reactions in the rat.[4-6] The homologous PCA reaction induced by reaginic antibodies provides not only a very convenient model system for studying the mode of action of disodium cromoglycate, but also acts as a routine screen for this type of biological activity.[7]‡

In this paper we describe the synthesis of a series of bischromone-2-carboxylic acids and, using quantitative results obtained from the PCA reaction in the rat, we indicate some structural requirements for activity.

Chemistry. Several methods for the synthesis of chromone-2-carboxylic acids have been reported. It was convenient to use the condensation of a dialkyl oxalate with an *o*-hydroxyacetophenone[8] and we have adapted this route for the preparation of the bischromone carboxylic acids. The appropriate bis(*o*-hydroxyacetophenone) (III) was condensed with an excess of diethyl oxalate and the resultant bis(2,4-dioxobutyric acid) esters (IV) were cyclized under acid conditions to give the esters of the desired bischromone carboxylic acids (V, R = C_2H_5). The hydrolysis stage to the final acid (V, R = H) was achieved by restricting the alkali metal hydroxide to a stoichiometric amount, as the pyrone



I



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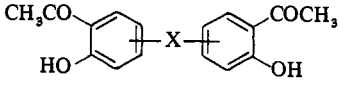
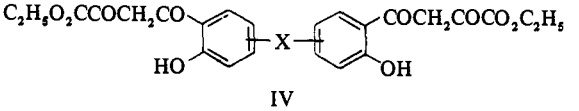
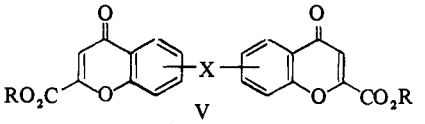


III

a, X = alkylenedioxy chain
b, X = alkylene chain
c, X = covalent bond



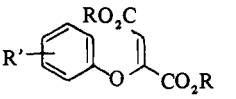
IV



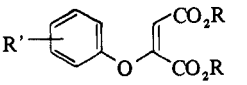
V

a, X = alkylenedioxy chain
b, X = alkylene chain
c, X = covalent bond
d, X = a single atom

‡Absence of PCA activity does not *a priori* preclude compounds showing antiallergic activity in other systems.



VI



VII

ring is unstable to excess of alkali (see also Experimental Section).

An alternative route which has proved useful in cases where the bishydroxyacetophenone was not readily available was a modification of that due to Ruhemann[9] for the preparation of chromone-2-carboxylic acid. Condensation of the appropriate phenols with dimethyl acetylenedicarboxylate or diethyl chlorofumarate led to a mixture of the esters of the fumaric acids (VI, R = CH_3 or C_2H_5) and the isomeric maleic acids (VII, R = CH_3 or C_2H_5). The formation of these mixtures is shown by nmr spectroscopy. We found that for the substituted phenoxyfumaric and phenoxymaleic esters the signals for the ethylenic protons appeared in the region of τ 3.6 and 4.9 (in $CDCl_3$), respectively. These values are in good agreement with those found for the unsubstituted esters prepared by Gudi, *et al.*[10] The ratio of the intensities of these signals also gives an indication of the proportion of the 2 isomers. For convenience the isomeric esters were not isolated, but the mixture was hydrolyzed and the mixed isomeric acids were then treated with a dehydrating agent. Only the fumaric acid cyclized to give a chromone which was readily separated in a pure state from the more soluble uncyclized phenoxymaleic acid. This method has been applied to certain members of the bischromone series.

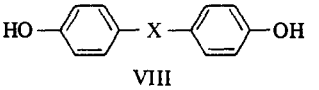
Those bischromones in which the 2 chromone nuclei are joined by a covalent bond (Vc) (Table IX) were in some cases prepared by linking 2 preformed iodochromones (Table III) using the conditions of the Ullmann reaction.[11]

The bisacetophenone derivatives (III) (Table I) were prepared by linking two *o*-hydroxyacetophenones. For the substances in which the linkage was an alkylenedioxy chain (IIIa) the synthesis consisted of the condensation of 2 molecules of a dihydroxyacetophenone with an alkylene dihalide, or in particular cases with epichlorohydrin.

In the case of 2,6-dihydroxyacetophenone condensation can take place with either OH group. Once monoalkylation has occurred it is found that the alkylation of the second OH does not proceed readily. This is due to the strong H bonding of this second OH with the O of the Ac group.

With dihydroxyacetophenones in which only one OH is adjacent to the Ac group (*e. g.*, resacetophenone, quinacetophenone) condensation takes place with the other (non-H-bonded) OH.

In the case of the bischromones joined by an alkylene chain or a single atom (Vb or Vd, Table VII and Table VIII), the diphenols of formula VIII (Table II) were used

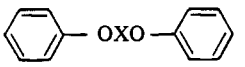


VIII

(X = alkylene chain or a single atom).

as starting materials, thus introducing the linkage X at an early stage of the synthesis. These diphenols were treated with dimethyl acetylenedicarboxylate or diethyl chlorofumarate to give the diphenoxyfumaric esters. An alternative procedure was to treat the diphenols with AcCl under Friedel-Crafts conditions in order to prepare the bis(3-acetyl-4-hydroxyphenyl)alkanes (IIIb). A variant for the preparation of these latter substances was to treat bis(4-methoxyphenyl)alkanes with AcCl which resulted in

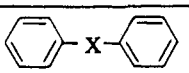
Table I

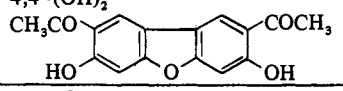


Compd No.	Substituents	Linkage X	Mp, °C	Formula[c]	Method of prepn
1	2,2'-Ac_2 3,3'-$(OH)_2$	$CH_2CHOHCH_2$	165–166	$C_{19}H_{20}O_7$	A
2	3,3'-Ac_2 4,4'-$(OH)_2$	$CH_2CHOHCH_2$	127–129	$C_{19}H_{20}O_7$	A
3	4,4'-Ac_2 3,3'-$(OH)_2$	$CH_2CHOHCH_2$	178–180[a]	$C_{19}H_{20}O_7$	A
4	2,4'-Ac_2 3,3'-$(OH)_2$	$CH_2CHOHCH_2$	182–185	$C_{19}H_{20}O_7$[b]	B
5	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_5$	131–133	$C_{21}H_{24}O_6$	A
6	3,3'-Ac_2 4,4'-$(OH)_2$	$(CH_2)_5$	107–109	$C_{21}H_{24}O_6$	A
7	3,3'-$(OH)_2$ 4,4'-Ac_2	$(CH_2)_5$	119–121	$C_{21}H_{24}O_6$	A
8	3,3'-Ac_2 2,2'-$(OH)_2$	$(CH_2)_5$	103.5–104.5	$C_{21}H_{24}O_6$	A
9	2,4'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_5$	91–91.5	$C_{21}H_{24}O_6$	B
10	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_2$	188–189	$C_{18}H_{18}O_6$	A
11	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_3$	184–185	$C_{19}H_{20}O_6$	A
12	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_4$	219–221	$C_{20}H_{22}O_6$	A
13	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_6$	147.5–148.5	$C_{22}H_{26}O_6$	A
14	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_8$	108–109	$C_{24}H_{30}O_6$	A
15	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_9$	55–59	$C_{25}H_{32}O_6$	A
16	2,2'-Ac_2 3,3'-$(OH)_2$	$(CH_2)_{10}$	102.5–104	$C_{26}H_{34}O_6$	A
17	2,2'-Ac_2 3,3'-$(OH)_2$ 5,5'-$(OCH_3)_2$	$CH_2CHOHCH_2$	108–182	$C_{21}H_{24}O_9$	A
18	2,2'-Ac_2 3,3'-$(OH)_2$ 5,5'-$(OCH_3)_2$	$(CH_2)_5$	146–147	$C_{23}H_{28}O_8$	A
19	5,5'-Ac_2 4,4'-$(OH)_2$ 2,2'-$(OCH_3)_2$	$(CH_2)_5$	145–148	$C_{23}H_{28}O_8$	A

[a]Known, see ref 27. [b]C: found, 62.8; calcd, 63.3. [c]All compds were analyzed for C, H.

Table II



Compd No.	Substituents	X	Mp, °C	Formula[a]	Method of prepn
20	3,3'-Ac_2 4,4'-$(OH)_2$	CH_2	156–157	$C_{17}H_{16}O_4$	C
21	3,3'-Ac_2 4,4'-$(OH)_2$	$(CH_2)_3$	112	$C_{19}H_{20}O_4$	D
22	3,3'-Ac_2 4,4'-$(OH)_2$	$(CH_2)_6$	97–98	$C_{22}H_{26}O_4$	D
23	3,3'-Ac_2 4,4'-$(OH)_2$	CO	174–176	$C_{17}H_{14}O_5$[b]	C
24	3,3'-Ac_2 4,4'-$(OH)_2$	O	181–183	$C_{16}H_{14}O_5$	C
25			306	$C_{16}H_{12}O_5$	C

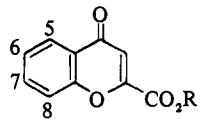
[a]See Table I, footnote *c*. [b]Known; see ref 20.

simultaneous acetylation and demethylation.

The physical properties of these bischromone-2-carboxylic acids are similar to those of disodium cromoglycate.[3] One feature of these compounds is their high acid strength due to the effects of the conjugated carbonyl group and the O atom in the pyrone ring. The pK_a values for all the chromone-2-carboxylic acids so far examined have been found to lie between 1.3 and 2.0. This property has been considered in relation to biological activity but as yet no satisfactory correlations have been found.

Structure-Activity Relationships. We consider the effect on the biological activity of the position of attachment and

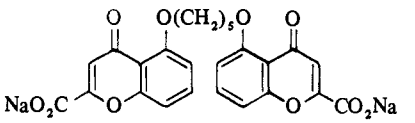
Table III



Compd No.	Substituents	R	Mp, °C	Formula[a]	Method of prepn
26	7-I	H	251-252	$C_{10}H_5IO_4$	E
27	7-I	Et	145-146	$C_{12}H_9IO_4$[b]	
28	8-I	H	277 dec	$C_{10}H_5IO_4$	G
29	8-I	Et	114-115	$C_{12}H_9IO_4$[b]	
30	8-I 7-OH	Et	218-219	$C_{12}H_9IO_5$	H
31	8-I 7-OCH_3	Et	154-155	$C_{13}H_{11}IO_5$	H
32	8-I 5,7-$(OCH_3)_2$	Et	208-209	$C_{14}H_{13}IO_6$	E
33	5-I 6-OH	Et	170-171	$C_{12}H_9IO_5$	H
34	5-I 6-OCH_3	Et	168-169	$C_{13}H_{11}IO_5$	H

[a]See Table I, footnote *c*. [b]Prepared by esterification of the free acid.

length of the connecting link or chain in the bischromone-2-carboxylic acids (V, R = H), and also the effect of the presence of atoms other than C in the linking chain. The biological results obtained are compared with those for 2 selected standard compounds, disodium cromoglycate itself



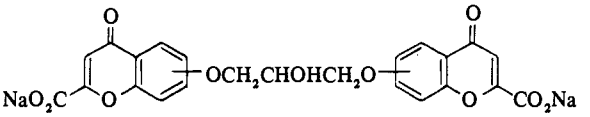
IX

(II) and the pentamethylenedioxy linked analog (IX).

The effects of varying the position of attachment of the linking chain on the chromone nuclei are shown in Tables IV and V for the isomers of the 2 compounds.

In Table IV it can be seen that little effect on PCA activity results from changing the position of the linking chain. An exception appears to result from linkage in the 8 and 8′ positions (42, Table V), where even with a dose as high as 10 mg/kg little or no activity was observed. This loss in activity cannot be explained readily but it is consistent with

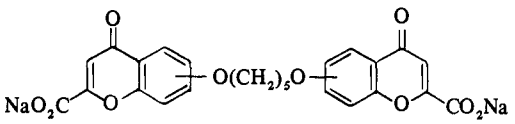
Table IV



Compd No.	Link	Mp, °C ester	Mp, °C acid	Mol formula of free acid[a]	Method of prepn	PCA ID_{50}, mg/kg
35	5,5′	180-182	216-217	$C_{23}H_{16}O_{11}\cdot H_2O$	E	0.7
36	6,6′	187-189	268-270	$C_{23}H_{16}O_{11}\cdot 2H_2O$[b]	E	0.3
37	7,7′	178-180	271-272	$C_{23}H_{16}O_{11}\cdot H_2O$	E	0.5
38	5,7′	193-194.5	194-200	$C_{23}H_{16}O_{11}\cdot 0.5H_2O$	E	0.2

[a]All acids and esters were analyzed for C, H. [b]H: found, 3.3; calcd, 3.9.

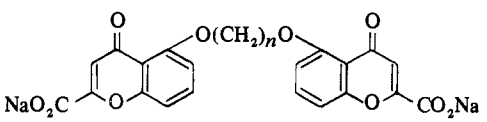
Table V



Compd No.	Link	Mp, °C ester	Mp, °C acid	Mol formula of free acid[a]	Method of prepn	PCA ID_{50}, mg/kg
39	5,5′	150-152	234-235	$C_{25}H_{20}O_{10}\cdot H_2O$	E	2.9
40	6,6′	Indefinite	275-277	$C_{25}H_{20}O_{10}$	E	2.4
41	7,7′	148-150	283-284	$C_{25}H_{20}O_{10}$[b]	E	2.0
42	8,8′	128-130	237-238	$C_{25}H_{20}O_{10}\cdot H_2O$	E	>10.0
43	5,7′	149-152	249-251	$C_{25}H_{20}O_{10}\cdot H_2O$	E	4.5

[a]See Table IV, footnote *a*. [b]C: found, 61.8; calcd, 62.5.

Table VI



Compd No.	*n*	Mp, °C ester	Mp, °C acid	Mol formula of free acid[a]	Method of prepn	PCA ID_{50}, mg/kg
44	2	264-265	262-263	$C_{22}H_{14}O_{10}\cdot 0.5H_2O$	E	1.2
45	3	182-183		$C_{27}H_{24}O_{10}$[b,c]	E	0.7
46	4	195-199	238-240	$C_{24}H_{18}O_{10}\cdot 0.5H_2O$[d]	E	6.4
39	5	150-152	234-235	$C_{25}H_{20}O_{10}\cdot H_2O$	E	2.9
47	6	154.5-155	223-225	$C_{26}H_{22}O_{10}$	E	4.7
48	8	139-141	Indefinite	$C_{28}H_{26}O_{10}\cdot 1.5H_2O$	E	>10.0
49	9	128-129	123-127	$C_{29}H_{28}O_{10}$	E	>10.0
50	10	146.5-148		$C_{34}H_{38}O_{10}$[b,c]	E	>5.0

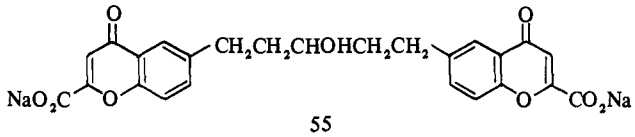
[a]See Table IV, footnote *a*. [b]Formula of ester. [c]Acid not isolated. [d]C: found, 63.9; calcd, 64.4.

the low activity which we had previously found in 8-substituted monochromone-2-carboxylic acids.

The effect of varying the length of the alkylene chain is shown in Table VI. There is a considerable loss of activity when the alkylene group exceeds 6 atoms.

As an extension of the above studies on the length of the connecting chain, a series of compounds was made in which the 2 chromone nuclei were linked by a polymethylene chain which did not have terminal O atoms (Table VII).

These results, with the exception of that for **51**, clearly demonstrate that terminal O atoms in the bridging chain are not essential for activity. This observation received further support when it was found that **55**, which is isosteric with **36**, the 6,6′ isomer of disodium cromoglycate, had high PCA activity (ID_{50} 0.25 mg/kg).

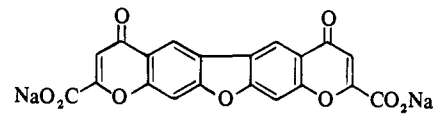


55

Probably the most interesting result from these studies was the unexpected loss in activity which occurred when the 2 chromone nuclei were separated by CH_2. A steric model of **51** showed that the chromone nuclei were unlikely to be coplanar. In the other compounds so far considered the flexible linking chains do not impose this restriction. It therefore seemed possible that for drug-receptor interaction one requirement could be that the molecule as a whole should be able to adopt a planar conformation. A study of other bischromones linked with a single atom (Table VIII) did not entirely support this view. The increase in activity shown by the compounds containing C=O and O linkages was in accord with the fact that a planar conformation is more possible. The activity of the N-linked compound seems surprisingly high however.

For compounds in which the 2 chromone nuclei were directly linked by a covalent bond, the effect on activity of nuclear substituents which would restrict the rotation about this bond and so hinder a coplanar conformation was studied (Table IX). Molecular models show that none of the compounds in this table except **59** and **60** can adopt such a conformation. The introduction of alkoxy substituents ortho to the linkage leads to loss of activity. We believe that this result is due to restriction of rotation about the linking bond since in our experience the introduction of alkoxy groups into bischromones usually results in the activity being either maintained or enhanced.

The facts presented support the suggestion that in this series a planar conformation is necessary for PCA activity. Carrying this suggestion a stage further we decided to synthesize **65** which would be planar and therefore should be active. When the compound was prepared and tested this supposition was borne out; the ID_{50} was 0.5 mg/kg.

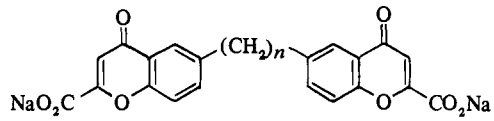


65

The ability of the bischromones to take up a coplanar conformation is clearly not the sole requirement for activity. For example, several of the relatively less active compounds (**42**, **48**, **49**, and **50**) possess a long alkylene chain which by its flexibility should permit coplanarity of the two chromone nuclei. However, it is our view that the results presented here support the hypothesis that the inability of a bischromone to adopt a planar conformation is associated with poor activity.

Biological Test Procedure. The biological screening test, which measures inhibition of passive cutaneous anaphylaxis

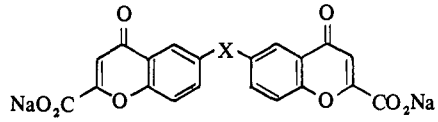
Table VII



Compd No.	*n*	Mp, °C ester	Mp, °C acid	Mol formula of acid[a]	Method of prepn	PCA ID_{50}, mg/kg
51	1	183–185	295–296	$C_{21}H_{12}O_8 \cdot 0.5H_2O$[b]	E	>10.0
52	3	192–194		$C_{27}H_{24}O_8$[c]	E	2.0
53	5	162–164	265–267 dec	$C_{25}H_{20}O_8 \cdot 0.5H_2O$	F	0.7
54	6	160	249–251 dec	$C_{26}H_{22}O_8$	E	7.0
55[e]		172–175	240	$C_{29}H_{28}O_9$[d]	E	0.3

[a] See Table IV, footnote *a*. [b] C: found, 64.5; calcd, 67.0. [c] Formula of ester; acid not isolated. [d] Formula of ester; acid not characterized. [e] Structure given in text.

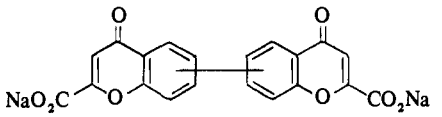
Table VIII

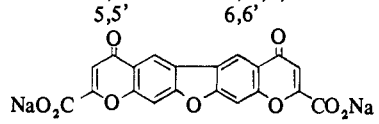


Compd No.	X	Mp, °C ester	Mp, °C acid	Mol formula of acid[a]	Method of prepn	PCA ID_{50}, mg/kg
56	C=O	218–220		$C_{25}H_{18}O_9$[b,c]	E	3.0
57	O	183–184	280–281	$C_{20}H_{10}O_9 \cdot 1.5H_2O$	E	3.7
58	NH		303–305 dec	$C_{20}H_{11}NO_8 \cdot 2H_2O$[d,e]	E	0.5

[a] See Table IV, footnote *a*. [b] Formula of ester, acid not isolated. [c] C: found, 64.4; calcd, 64.9. [d] Ester not isolated. [e] C: found, 55.4; calcd, 55.9.

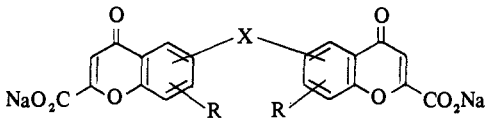
Table IX



Compd No.	Bridge	MeO substituent	Mp, °C ester	Mp, °C acid	Mol formula of free acid[a]	Method of prepn	PCA ID_{50}, mg/kg
59	6,6'			280	$C_{20}H_{10}O_8 \cdot H_2O$[b]	E, F	0.2
60	7,7'		224-226	291-293	$C_{20}H_{10}O_8 \cdot 1.5H_2O$	I	0.3
61	8,8'		231-233	319-320	$C_{20}H_{10}O_8 \cdot 0.5H_2O$	I	>10.0
62	8,8'	7,7'	220-221	296-297	$C_{22}H_{14}O_{10} \cdot 0.5H_2O$	I	10.0
63	8,8'	5,5',7,7'	242-244	258-260	$C_{24}H_{18}O_{12} \cdot H_2O$	I	>10.0
64	5,5'	6,6'	243-244	303	$C_{22}H_{14}O_{10}$	I	>10.0
65			303-304 dec	>300	$C_{20}H_8O_9 \cdot 2H_2O$	E	0.5

[a]See Table IV, footnote *a*. [b]Ester not characterized.

Table X



Compd No.	Position, X	R substituent	Mp, °C acid	Mol formula of free acid[a]	Method of prepn	PCA ID_{50}, mg/kg
35	5,5', $OCH_2CHOHCH_2O$	H				0.7
66	5,5', $OCH_2CHOHCH_2O$	7,7'-MeO	245 dec	$C_{25}H_{20}O_{13}$	E	1.0
39	5,5', $O(CH_2)_5O$	H				2.9
67	5,5', $O(CH_2)_5O$	7,7'-MeO	238	$C_{27}H_{24}O_{12} \cdot H_2O$	E	1.0
40	6,6', $O(CH_2)_5O$	H				2.4
68	6,6', $O(CH_2)_5O$	7,7'-MeO	258-260	$C_{27}H_{24}O_{12} \cdot 2H_2O$	E	1.0

[a]See Table I, footnote *c*.

reaction in rats,[12] was used as a guide to the effectiveness of the compounds in inhibiting the release of the pharmacological mediators of anaphylaxis.

Experimental Section

Melting points are uncorrected. Where analyses are indicated only by symbols of the elements the analytical results obtained for these elements were within ±0.4% of the theoretical value. Nmr spectra were recorded in either DMSO-d_6 or $CDCl_3$, with TMS as an internal standard, on a Perkin-Elmer R10 spectrometer. Ir spectra were measured as Nujol mulls on a Perkin-Elmer 237 spectrophotometer and mass spectra were recorded on an AEI MS902 spectrometer. All spectra were consistent with the assigned structures.

The compds in Table I, with the exception of 17, 18, and 19, were prepd from commercially available dihydroxyacetophenones using the method stated. Compds 17 and 18 were prepd from 2,6-dihydroxy-4-methoxyacetophenone[13] and 19 from 2,5-dihydroxy-4-methoxyacetophenone.[14]

Method A. 1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (1). (i) A mixt of 2,6-dihydroxyacetophenone (10 g), K_2CO_3 (4.6 g), and 1,3-dibromo-2-hydroxypropane (7.15 g) in Me_2CO (100 ml) was heated under reflux for 48 hr. After standing and cooling, the Me_2CO soln was filtered and evapd to yield a yellowish brown oil which solidified. This solid was boiled with Et_2O (100 ml) and the soln was filtered and concd to give colorless crystals, mp 160-162°. The residue was extd in a Soxhlet thimble with Et_2O for 20 hr and the ext on evapn gave a further crop of crystals (3.3 g). The combined products were recrystd from EtOH (50 ml) to give 2.5 g of 1.

(ii) 2,6-Dihydroxyacetophenone (9.7 g) and epichlorohydrin (3.25 g) were dissolved in hot *i*-PrOH (250 ml) with stirring under reflux. A soln of KOH (2.33 g of 85% pellets) in *i*-PrOH (25 ml) and sufficient H_2O (approximately 1 ml) to dissolve was added to the dihydroxyacetophenone soln. The mixt was heated under reflux with stirring for 48 hr. Half the solvent was removed by distn and H_2O (50 ml) was then added. After cooling, the ppt was filtered off and washed with *i*-PrOH and Et_2O. Recrystn from *i*-PrOH (125 ml) gave a first crop (3.8 g) and a second crop (3.0 g) of 1 identical with the material obtained above.

Method B. (i) 1-(2-Acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (4). A mixt of 2,6-dihydroxyacetophenone (10 g), epichlorohydrin (7 g), and benzyltrimethylammonium hydroxide (0.5 ml) in dioxan (18 ml) was heated at 100° in a sealed vessel for 72 hr. The mixt was evapd under reduced pressure and the residue was extd with Et_2O (3 × 20 ml). The Et_2O ext was washed with 2 *N* aqueous Na_2CO_3 (3 × 25 ml) and then with H_2O. After drying (Na_2SO_4) the Et_2O was removed to leave an oil (13 g). This was chromatographed on a column of alumina (200 g) using Et_2O as eluent. Fractions of 100 ml were collected and the first 10 were shown by tlc to be identical. These fractions were combined and the solvent was evapd to leave 2-(3-chloro-2-hydroxypropoxy)-6-hydroxyacetophenone (6 g) as an oil. To the oil was added resacetophenone (3.8 g), anhyd K_2CO_3 (3.65 g), and anhyd Me_2CO (50 ml). This mixt was then refluxed for 48 hr and then the Me_2CO was removed by evapn. H_2O (300 ml) was added to the residue, and the resulting insoluble solid was isolated by filtration and crystd from EtOH–dioxan to yield 2.7 g of 4.

(ii) 1-(2-Acetyl-3-hydroxyphenoxy)-5-(4-acetyl-3-hydroxyphenoxy)pentane (9). A mixt of 2,6-dihydroxyacetophenone (5.1 g), 1,5-dibromopentane (7.7 g), anhyd K_2CO_3 (2.3 g), and anhyd Me_2CO (100 ml) was refluxed for 20 hr. Approximately half the Me_2CO was removed by evapn and H_2O (400 ml) was added. After stirring, the insoluble 1,5-bis(2-acetyl-3-hydroxyphenoxy)pentane (1.9 g) was removed by filtration. The filtrate was evapd to dryness to leave a crude oil which was purifled by chromatog on alumina (300 g) using Et_2O as eluent. The first nine 20-ml fractions were shown by tlc to be identical. They were combined and evapd to leave 2-(5-bromopentyloxy)-6-hydroxyacetophenone (5 g) as an oil. To this crude product was added resacetophenone (2.45 g), anhyd K_2CO_3 (1 g), and anhyd Me_2CO (40 ml), and this mixt was refluxed for 18 hr. After cooling, the Me_2CO was removed by evapn, H_2O (200 ml) was added to the residue, and the remaining solid was filtered off and crystd from MeOH to yield 3.7 g of 9.

Method C. 4,4'-Diacetoxydiphenyl ether[15] and 3,7-diacetoxydibenzofuran[16] were prepd by known procedures.

Bis(3-acetyl-4-hydroxyphenyl)methane (20). An intimate mixt

of bis(4-acetoxyphenyl)methane[17] (14.2 g), anhyd $AlCl_3$ (21.7 g), and NaCl (9.0 g) was heated at 140–150° for 4 hr. The mixt was then cooled and hydrolyzed with crushed ice acidified with HCl. The reaction products were extd with EtOAc, and the exts were in turn extd with 10% NaOH soln. The alk soln was acidified with dil HCl and extd with EtOAc. The exts were washed with H_2O, dried, and evapd to give a solid which was recrystd first from EtOH and then from dioxan to give 4.0 g of 20.

Method D. 1,3-Bis(4-methoxyphenyl)propane[18] was prepd by a known procedure.

1,6-Bis(3-acetyl-4-hydroxyphenyl)hexane (22). 1,6-Bis(4-methoxyphenyl)hexane[19] (29.8 g) and AcCl (23.5 g) in $(Cl_2CH)_2$ (800 ml) was stirred at 0–5° and $AlCl_3$ (83 g) was gradually added maintaining the temp below 15°. The mixt was stirred overnight and after decompn of the $AlCl_3$ with ice–H_2O the solvent was removed by steam distn. The residue was extd with Et_2O, the exts were dried and the solvent was evapd. The product was crystd from petr ether (bp 80–100°) to give 15.5 g of 22. A further quantity (1 g) was obtained on concn of the mother liquors.

Method E. 3,3'-Diacetyl-4,4'-dihydroxybenzophenone,[20] 3,3'-diacetyl-4,4'-dihydroxybiphenyl,[21] 2-hydroxy-4-iodoacetophenone,[22] and 2-hydroxy-3-iodo-4,6-dimethoxyacetophenone[23] were prepd by known procedures.

1,3-Bis(2-carboxychromon-5-yloxy)-2-hydroxypropane Disodium Salt (35). (i) Na (2.0 g) was dissolved in EtOH (25 ml) with stirring and heating under reflux. After cooling, Et_2O (50 ml) was added followed by a hot soln of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane (7.2 g) in diethyl oxalate (12.5 ml), EtOH (25 ml), and C_6H_6 (25 ml). The mixt was stirred and heated under reflux overnight. Et_2O (100 ml) was added after cooling and the Na salt of the bis(ethyl 2,4-dioxophenylbutyrate) was filtered off, washed with Et_2O (50 ml), and dried. The salt was added to H_2O (120 ml) with stirring and acidified. The syrupy ppt was sepd and dissolved in EtOH (25 ml) and C_6H_6 (25 ml). After azeotroping to remove the H_2O concd HCl (0.25 ml) was added and heating was contd for 5 min. On cooling, a solid sepd which was filtered off, dried, and crystd from EtOH–C_6H_6 (1:1) to give 5.4 g of the diethyl ester of 35. A further quantity (1 g) was obtd from the mother liquors.

(ii) 1,3-Bis(2-ethoxycarbonylchromon-5-yloxy)-2-hydroxypropane (5.24 g) was suspended in EtOH (25 ml) and treated dropwise with a 2 *N* NaOH soln (10.0 ml). The soln was refluxed for 1 hr and, after cooling, a further quantity of EtOH (50 ml) was added to ppt the Na salt. The solid was filtered off and dissolved in the minimum amt of hot H_2O, treated with charcoal, filtered, and reheated to boiling. The hot soln was added slowly to boiling EtOH (75 ml) and, after cooling, the pptd disodium salt (35) was filtered off and dried at 100°, yield 4.3 g.

(iii) Salt 35 (1.0 g) was dissolved in H_2O (20 ml) and acidified with dil HCl. The pptd solid was filtered off and dried at 100° to give 0.5 g of the acid of 35.

Method F. 1,5-Bis(2-carboxychromon-6-yl)pentane Disodium Salt (53). 1,5-Bis(4-hydroxyphenyl)pentane[24] (25.6 g) was added to a soln of Na (4.6 g) in EtOH and the soln was evapd to dryness. The residue was suspended in dioxan and the suspension was refluxed while ethyl chlorofumarate (41.3 g) was added over 1 hr. The mixt was then treated with 10% NaOH soln (200 ml) and refluxing was contd for a further 2 hr. The clear soln was evapd to remove the dioxan and the residue was dild with H_2O. The mixt was filtered and the filtrate was extd with Et_2O. The aqueous soln was acidified and the resulting yellow emulsion was extd with Et_2O. Evapn of the exts gave a yellow oil (36.5 g) which was triturated with cold concd H_2SO_4 (200 ml) for 0.5 hr and then poured onto crushed ice. The oily solid was filtered off and recrystd from aqueous AcOH and then EtOH to give 0.6 g of the free acid of 53. This compd was refluxed in ethanolic HCl for 2 hr. It dissolved slowly and on cooling gave 0.45 g of 53 diethyl ester. This ester (0.45 g) was dissolved in EtOH and refluxed for 2 hr with 0.93 *N* NaOH soln (1.92 ml). The solvent was then evapd, and the residue was taken up in H_2O and freeze-dried to give 0.41 g of 53.

Method G. 8-Iodochromone-2-carboxylic Acid (28). To a soln of *o*-iodophenol (11.0 g) and dimethyl acetylenedicarboxylate (7.6 g) in dry dioxan (100 ml) was added 0.5 ml of a soln of benzyltrimethylammonium hydroxide (40% w/w in H_2O). The soln was heated at 100° for 40 min. After cooling, 25% NaOH soln (35 ml) was added and heating was contd for a further 2 hr. The mixt was cooled and extd with Et_2O. The aqueous soln was then acidified with concd HCl and extd with Et_2O. Evapn of these ethereal exts gave a yellow solid which was crystd from H_2O to give 13.5 g of *o*-iodophenoxyfumaric acid, mp 184–187°. *Anal.* ($C_{10}H_7IO_5$) C, H; I: calcd, 38.02; found 38.9.

o-Iodophenoxyfumaric acid (8 g) was added slowly to concd H_2SO_4 at room temp. After 15 min at room temp the soln was poured into ice–H_2O and the resulting solid was filtered off and crystd from EtOH to yield 3.3 g of 28. This was esterified with EtOH–H_2SO_4 in the usual manner to give the Et ester 29.

Method H. Ethyl 7-hydroxychromone-2-carboxylate[25] and ethyl 6-hydroxychromone-2-carboxylate[26] were prepd by known methods.

Ethyl 6-Hydroxy-5-iodochromone-2-carboxylate (33). (i) To a warm soln of ethyl 6-hydroxychromone-2-carboxylate (17 g) in EtOH, I_2 (7.3 g) and a soln of HIO_3 (2.56 g) in H_2O (5 ml) were added. After stirring at room temp for 4 hr the resulting ppt was filtered off and crystd from EtOH to yield 9.0 g of 33.

(ii) Ethyl 5-Iodo-6-methoxychromone-2-carboxylate (34). A mixt of 33 (7.2 g), Me_2SO_4 (2.6 g), anhyd K_2CO_3 (2.8 g), and Me_2CO (50 ml) was refluxed for 4 hr. The mixt was cooled and poured into a large vol of H_2O. The resulting solid was filtered off and crystd from EtOH to yield 5.5 g of 34.

Method I. 2,2'-Dicarboxy-7,7'-bichromonyl Disodium Salt (60). A mixt of 27 (3.44 g) and Cu bronze (8 g) in DMF (30 ml) was heated at 155–160° for 6 hr. The mixt was then filtered while still hot and the solid was washed with hot DMF (10 ml). The filtrate was poured into H_2O to give a buff-colored ppt which was crystd from EtOAc to give 0.3 g of the diethyl ester of 60 as buff-colored microneedles.

A soln of 2,2'-diethoxycarbonyl-7,7'-bichromonyl (0.5 g) and $NaHCO_3$ (0.5 g) in EtOH and H_2O (1:1) was refluxed until hydrolysis was complete, as shown by tlc. The soln was then treated with charcoal, cooled, filtered, and acidified with concd HCl to give a gelatinous ppt. The mixt was centrifuged and the supernatant liquid was poured off. The gelatinous solid was washed thoroughly with hot EtOH then filtered to give 0.3 g of the free acid of 60 as a colorless solid.

A soln of 2,2'-dicarboxy-7,7'-bichromonyl (0.24 g) and $NaHCO_3$ (0.1 g) in H_2O (40 ml) was freeze-dried to give 60 (0.24 g) as a pale yellow solid.

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