Table III

Compd	Jiggle-cage effect,[a] dose, mg/kg sc	Jiggle-cage effect,[a] dose, mg/kg po	Dosage range effect,[a] dose, mg/kg po
7	−3, 100	T, 200	
	−2, 25	−2, 50	
8	−3, 75	−3, 150	T, 600
	−2, 18.75	−2, 38	+1, 150
9	−3, 75	−3, 150	
	−2, 18.75	0, 60	
10	−2, 75		
11	−3, 50		
	0, 12.5		
12	−3, 150	−2, 300	
	−2, 37.5		
13	−3, 150	T, 300	
	−2, 37.5	−3, 75	
		−2, 38	
19	−3, 75		
	0, 19		
16	T, 62		
	−2, 15		
14	−3, 100	−3, 200	T, 800
	−2, 25	−2, 50	−1, 200
15	T, 75		
	0, 19		
20	−3, 100		
	0, 25		
21	−3, 100	−2, 200	
	−2, 25		

[a] − = depression; 3 = marked; 2 = moderate; 1 = minimal; T = toxic; + = stimulation.

residue (4.2 g) was dissolved in ethanol and neutralized with anhydrous HCl to give 3.65 g of hydrochloride (mp 143°).

Procedure B. A solution of 3.5 g of 3-hydroxy-1-phenyltetrahydroindazole (16.3 mmoles) in 35 ml of DMF was treated for 1 hr with a suspension of 810 mg of NaH (55% washed with ether) in 15 ml of DMF. Then a solution of α-chloro-*N*-methylacetamide (1.2 equiv) was added with stirring, and the solution kept at 60° for 20 hr. After cooling, the mixture was diluted with ether, washed with water, and dried. Residue after evaporation of solvent was 4.2 g of solid amide.

The crude amide was dissolved in 60 ml of THF and added to a cold solution of borane (2.5 equiv) in THF. After refluxing for 3 hr, the solution was cooled, an excess of aqueous 5 *N* HCl was added, and the THF was distilled off at atmospheric pressure. The aqueous acidic layer was made basic, the product extracted into CH_2Cl_2, dried over Na_2SO_4, and evaporated. The residue was taken up in ethanol and neutralized with ethereal HCl to give 3.1 g of crystalline HCl salt (8), mp 197–99°; yield, 63.5% over 2 steps.

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Synthesis and Antiinflammatory Activities of α-Methylfluorene-2-acetic Acid and Related Compounds

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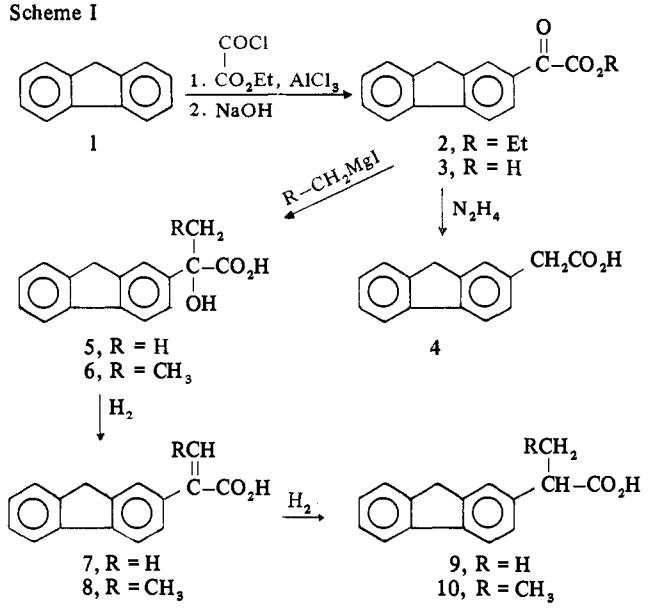
In a search for new nonsteroidal antiinflammatory agents, a series of fluoreneacetic acid derivatives was synthesized and evaluated in the carrageenin-induced edema assay. Fluorene-2-acetic acid (4) and α-methylfluorene-2-acetic acid (9) emerged as compounds with potent antiinflammatory activity. Structure–activity relationships within this series are discussed.

Recently, several reports concerning the synthesis and antiinflammatory activities of non-N-containing aryl acetic acids have appeared in the literature.[1-8] Our own efforts in this area have culminated in the synthesis of several compounds containing a fluorene ring as the aryl portion and possessing antiinflammatory activities. In fact, we first observed antiinflammatory activity in the carrageenin-induced edema assay† with the known fluorene-2-acetic acid (4). This observation led us to prepare a series of monosubstituted fluorene derivatives in which the position of the acid side chain and the nature of the alkyl group on the benzylic side-chain carbon atom were varied. In addition, several

†Modification of the method described by Winters, *et al.*

Scheme I



7-substituted derivatives of **4** and of α-methylfluorene-2-acetic acid (**9**) were synthesized.

Chemistry. Fluorene-2-acetic acid (**4**) has been previously prepared by a variety of methods: (1) from 2-nitrofluorene, by an eight-step, low-yield process;[10] (2) by the Willgerodt–Kindler reaction on 2-acetylfluorene (57% yield);[11] (3) from fluorene-2-carboxylic acid by Arndt–Eistert homologation (32% yield);[11] (4) *via* chloromethylation of fluorene, followed by cyanide displacement and hydrolysis (7% yield);[12] and (5) by the condensation of fluorene with chloroacetic acid (19% yield).[13]

We have prepared **4** by the method shown in Scheme I. Acylation of fluorene (**1**) with ethyloxalyl chloride‡ and hydrolysis of the 2-glyoxylate ester (**2**), followed by Wolff–Kishner reduction of the resulting acid (**3**), gave **4** in 75% overall yield. An advantage of this method is that the intermediate acid (**3**) can also be converted into α-alkylacetic acid derivatives. Thus, treatment of **3** with methyl- or ethylmagnesium iodide,[15] followed by acidic dehydration of the resulting tertiary carbinol and catalytic hydrogenation, gave the corresponding α-alkyl acids **9** and **10**.

Several 7-substituted-fluorene-2-acetic and α-methylfluorene-2-acetic acids were prepared as outlined in Scheme II. Nitration of the acids (**4** and **9**) gave the corresponding 7-nitro compounds (**11**[13] and **12**), which were esterified and then reduced to the 7-amino derivatives (**15** and **16**). These acids were then diazotized and converted by standard methods into the 7-chloro (**17**), 7-hydroxy (**18** and **19**), and 7-methoxy acids (**24** and **25**). We were also able to prepare the acids **18** and **19** more directly by incubation of either **4** or **9** with *Aspergillus niger* or *Cunninghamella blakesleeana*.

In the final part of our structure–activity studies, we prepared modifications of **1** in which the acid residue was attached at a position other than C-2. Fluorene-4-acetic acid (**26**) and -9-acetic acid (**27**) were prepared by the reported methods,[11] from fluorenone-4-carboxylic acid and 9-bromofluorene, respectively, while Arndt–Eistert homologation of fluorene-1-carboxylic acid gave the corresponding -1-acetic acid (**28**).

The syntheses of α-methylfluorene-1-acetic acid (**29**) and α-methylfluorene-4-acetic acid (**30**) were achieved by homologation of the corresponding carboxylic acids, utilizing diazoethane. Condensation of 9-bromofluorene with the potassium salt of diethyl methylmalonate, followed by hydrolysis and decarboxylation, afforded α-methylfluorene-9-acetic acid (**31**).

‡ A modification of the procedure used in the acenaphthene series was employed.[14]

Table I. Antiinflammatory Activities of Fluorene Derivatives

Compound	Carrageenin-induced edema, ID_{50}, mg/kg,[a] po
2	>150
3	>150
4	67
5	>150
7	85
9	82
10	>150
11	>150
17	150
18	140
19	>150
24	90
25	100
26	>150
27	>150
28	>150
29	>150
30	>150
31	>150
Phenylbutazone	102

[a] Dose required to produce 50% inhibition of edema.

Antiinflammatory Activity. The antiinflammatory activities of the compounds listed in Table I were determined by their ability to inhibit carrageenin-induced edema. The compounds were administered orally as a suspension in 1% CMC to young-adult male Sprague–Dawley rats, 180–200 g, that had been fasted for 16–18 hr but allowed H_2O *ad lib.* Two hours later, the volume of the left hind paw was measured by Hg displacement; then 0.05 ml of a 1% soln of carrageenin in sterile pyrogen-free 0.9% NaCl soln was injected into the paw. Three hours later, the vol of the paw was again measured.

On the basis of the results shown in Table I, it is apparent that, in this series, the greatest antiinflammatory activity was achieved when the acetic or propionic acid residue had been attached to the fluorene nucleus at position 2, as in **4** and **9**. The substitution of small groups (Cl, OH, OCH_3) at the 7 position of **4** and **9** did not lead to enhanced activity. Similarly, increasing the size of the group α to the CO_2H from Me to Et led to decreased activity.

Further extensive testing of **4** and **9** in a variety of assays designed to evaluate their complete antiinflammatory profile led us to conclude that **9** has potential clinical use as a systemic antiinflammatory agent.§

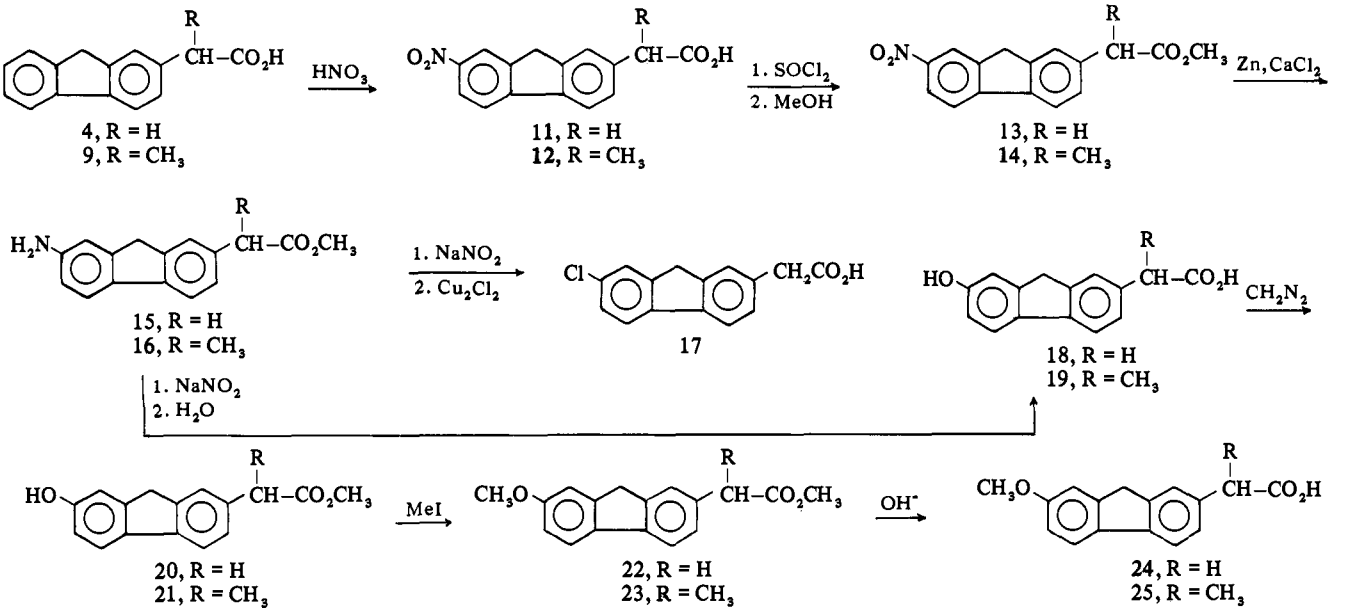
Experimental Section

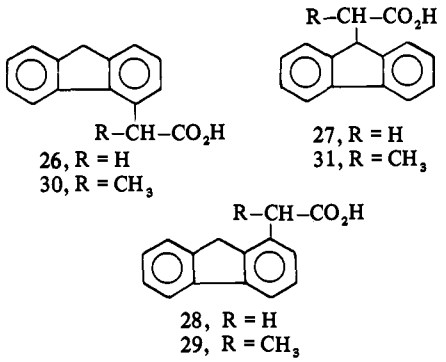
Melting points were determined on a Thomas-Hoover capillary mp apparatus and are uncorrected. All organic solns were dried ($MgSO_4$ or Na_2SO_4), and all evapns were carried out *in vacuo*. The ir and nmr spectra of all new compounds were consistent with their structures. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Ethyl Fluorene-2-glyoxylate (2). A soln of **1** (214 g, 1.29 moles) and ethyloxalyl chloride (200 g, 1.47 moles) in CH_2Cl_2 (800 ml) was added dropwise over a 1-hr period to a stirred susp of

§ The antiinflammatory profile of these compounds was determined in our Immunology Section and will be the subject of a future communication.

Scheme II





$AlCl_3$ (300 g) in CH_2Cl_2 (800 ml) while the temp was maintained below 5°. The reaction mixt was then stirred at room temp for 2 hr, poured onto ice (4 l.), and acidified to pH 3 with 6 *N* HCl. The CH_2Cl_2 was sepd and the aqueous portion was extd (CH_2Cl_2). The exts were washed (H_2O and satd aqueous NaCl), dried, and evapd to give 2 (340 g, mp 73–75°, 99%). The analytical sample was prepared by crystn from MeOH: mp 81–82°. *Anal.* ($C_{17}H_{14}O_3$) C, H.

Fluorene-2-glyoxylic Acid (3). A soln of 2 (204.4 g, 0.77 mole) in EtOH (1 l.) was treated with a soln of NaOH (32.4 g) in H_2O (1 l.) and refluxed for 1 hr. The mixt was cooled, dild with H_2O (500 ml), and adjusted to pH 2.0 with 10% HCl. The mixt was extd (CH_2Cl_2), and the exts were washed (satd aqueous NaCl and H_2O), dried, and evapd to give 3 (168 g, mp 135–140°, 92%). The analytical sample was prepared by crystn from MeOH: mp 139–140°. *Anal.* ($C_{15}H_{10}O_3$) C, H.

Fluorene-2-acetic Acid (4).[10-13] A mixt of 3 (33.7 g, 0.142 mole) and $N_2H_4 \cdot H_2O$ (50 ml) was refluxed until soln had been achieved. The mixt was cooled below 100°, and treated with KOH (33.7 g) slowly to control excess foaming. The mixt was refluxed for 1 hr, and excess N_2H_4 was removed by distn. The residue was dissolved in H_2O and extd ($CHCl_3$). The aqueous soln was acidified with concd HCl and extd (Et_2O). The exts were washed (H_2O), dried, and evapd to give 4 (29.7 g, mp 184–186°, 94%). Crystn from MeOH (Darco) gave the analytical sample: mp 185–186° *Anal.* ($C_{15}H_{12}O_2$) C, H.

α-Hydroxy-α-methylfluorene-2-acetic Acid (5). The Grignard reagent prepared from Mg (22.7 g, 0.93 g-atom) in Et_2O (50 ml) and MeI (70 ml) in Et_2O (130 ml) was added dropwise under N_2 to a cooled (3–5°), stirred soln of 3 (47.0 g, 0.199 mole) in Et_2O (600 ml) over a 1-hr period. The mixt was stirred for 2 more hr at room temp and poured onto ice. The mixt was acidified with 8.5% HCl and extd (EtOAc). The exts were washed (H_2O, 5% aqueous $NaHSO_3$, and H_2O), dried, and evapd. The residue was crystd from EtOAc to give 5 (44.0 g, mp 176–178°, 88%). Sublimation gave the analytical sample: mp 183–185°. *Anal.* ($C_{16}H_{14}O_3$) C, H.

α-Methylenefluorene-2-acetic Acid (7). A soln of 5 (41.0 g, 0.161 mole) in dioxane (1.65 l.) and concd H_2SO_4 (82 ml) was refluxed for 2 hr, cooled, poured onto ice, and extd (Et_2O). The exts were washed (H_2O), dried, and evapd to give 7 (36.1 g, mp 189–190°, 95%). Crystn from EtOH gave the analytical sample: mp 190–192°. *Anal.* ($C_{16}H_{12}O_2$) C, H.

α-Methylfluorene-2-acetic Acid (9). A soln of 7 (52.2 g, 0.22 mole) in dioxane (625 ml) containing 5% Pd/C (3.5 g) was hydrogenated at 50 psi (Parr) for 4 hr. The catalyst was removed by filtn, and the filtrate was evapd to give 9 (52 g, mp 181–183°, 99%). Crystn from MeCN or sublimation gave the analytical sample: mp 183–184°. *Anal.* ($C_{16}H_{14}O_2$) C, H.

α-Ethylfluorene-2-acetic Acid (10). Compd 10 was prepared in the same manner as described for 9. The reaction of 3 with EtMgI gave 6 (89%), which was dehydrated to form 8 (92%) and hydrogenated to give 10 (94%). Sublimation, followed by crystn from MeCN, gave the analytical sample: mp 100–102°. *Anal.* ($C_{17}H_{16}O_2$) H; calcd: C, 80.92; found: C, 80.37.

7-Nitro-α-methylfluorene-2-acetic Acid (12), Methyl 7-Nitro-α-methylfluorene-2-acetate (14). A suspension of 9 (11.9 g, 0.05 mole) in AcOH (10 ml) was stirred and heated to 60°, and then treated dropwise with concd HNO_3 (12.7 ml) over a 0.5-hr period, while the temp was maintained at 80° by cooling. The mixt was heated at 80° for 15 min, then cooled, and the crysts were collected by filtn to give 12 (7.5 g, mp 206–209°, 53%). Crystn from AcOH gave the analytical sample: mp 215–216°. *Anal.* ($C_{16}H_{13}NO_4$) C, H, N.

The ester (14) was prepd in 75% yield from 12 by treatment of the acid chloride ($SOCl_2$) with MeOH. Crystn from MeOH gave the analytical sample: mp 108–110°. *Anal.* ($C_{17}H_{15}NO_4$) C, H, N.

Methyl 7-Nitrofluorene-2-acetate (13). Conversion of 11[13] into its acid chloride ($SOCl_2$), followed by treatment with MeOH, gave 13 (95%). Crystn from MeOH–$CHCl_3$ gave the analytical sample: mp 171–172°. *Anal.* ($C_{16}H_{13}NO_4$) C, H, N.

7-Chlorofluorene-2-acetic acid (17) was prepared by reduction of 13 with Zn and $CaCl_2$[16] to give the amino ester 15 (86%), which was converted by a Sandmeyer reaction (Cu_2Cl_2) to 17 (mp 174–175°, 13%) (lit.[13] 167–169°). *Anal.* ($C_{15}H_{11}ClO_2$) C, H, Cl. Attempts to reduce the free acid (11) to 7-aminofluorene-2-acetic acid with Sn and HCl by the reported method[13] were unsuccessful in our hands; we utilized the ester (13) instead.

7-Hydroxyfluorene-2-acetic Acid (18). (a) A soln of 15 (14.5 g, 0.057 mole) in H_2O (380 ml) containing concd HCl (14 ml) was cooled to 2° and treated dropwise over a 1-hr period with a soln of $NaNO_2$ (3.63 g) in H_2O (15 ml). This diazonium soln was then added over a 1-hr period to a refluxing soln of concd H_2SO_4 (18 ml) in H_2O (1.1 l.). The mixt was cooled, and the solids were collected by filtn and heated on a steam bath in 10% aqueous KOH for 0.5 hr. The soln was cooled, then acidified with 4 *N* HCl, and 18 was collected by filtration (12.8 g, mp 236–238° dec, 95%). Crystn from MeCN gave the analytical sample: mp 241–242° dec. *Anal.* ($C_{15}H_{12}O_3$) C, H.

(b) Surface growth from a 2-week-old agar slant of *A. niger*

(ATCC-9142) [the slant containing as a nutrient medium: glucose (10 g)–yeast extract (2.5 g)–K_2HPO_4 (1 g)–agar (20 g) in distd H_2O (*q.s.* to 1 l.)] was suspd in 0.01% aqueous sodium lauryl sulfate. One-milliliter portions of this suspension were used to inoculate three 250-ml erlenmeyer flasks, each containing 50 ml of the following sterilized medium: glucose (30 g)–soy bean meal (20 g)–soy bean oil (2.0 g)–$CaCO_3$ (2.5 g) in distd H_2O (*q.s.* to 1 l.). After a 96-hr incubation at 25° with continuous rotary agitation (280 cpm; 2-in. stroke), 5% (v/v) transfers were made to 20 250-ml erlenmeyer flasks, each containing 50 ml of the following sterilized medium: corn steep liquor (6 g)–$NH_4H_2PO_4$ (3 g)–yeast extract (2.5 g)–dextrose (10 g)–$CaCO_3$ (2.5 g) in distd H_2O (*q.s.* to 1 l.). After 24 hr of further incubation, as described above, 0.25 ml of a sterile soln of 4 in DMF (40 mg/ml) was added. A total of 200 mg (0.00089 mole) was fermented. After 6 days of further incubation as described above, the contents of the flasks were combined, and the broth was adjusted to pH 2.5 with 12 *N* H_2SO_4. The broth was filtd through a Seltz clarifying pad, and the flasks, mycelium, and pad were washed with warm H_2O. The filtrate and washings (1.5 l.) obtained in this way were extd (EtOAc), and the exts were washed (8% aq NaCl), dried, and evapd. Crystn from EtOAc gave 18 (42 mg, mp 235.5–237.5°, mmp, 20%).

7-Hydroxy-α-methylfluorene-2-acetic acid (19) was prepared by reduction of 14 with Zn and $CaCl_2$ to form 16 (93%), which was diazotized and hydrolyzed as described for the preparation of 18 to give 19 (31%). The analytical sample was prepared by sublimation: mp 218–219°. *Anal.* ($C_{16}H_{14}O_3$) C, H. Fermentation of 9 (300 mg, 0.00126 mole) with *C. blakesleeana* (ATCC 8688a), as described above, gave 19 (98 mg, mp 218–220°, mmp, 30%).

Methyl 7-Hydroxyfluorene-2-acetate (20). Esterification of 18 with CH_2N_2 and crystn from C_6H_6 gave 20 (mp 139–140°, 71%). *Anal.* ($C_{16}H_{14}O_3$) C, H.

Methyl 7-Methoxyfluorene-2-acetate (22). Treatment of 20 with MeI–K_2CO_3 in Me_2CO and crystn from EtOAc–*i*-Pr_2O gave 22 (mp 114.5–115.5°, 65%). *Anal.* ($C_{17}H_{16}O_3$) C, H.

Methyl 7-Methoxy-α-methylfluorene-2-acetate (23). Esterification of 19 with CH_2N_2 and treatment of the ester 21 with MeI–K_2CO_3 in Me_2CO, followed by crystn from Me_2CO-*i*-Pr_2O, gave 23 (mp 101–103°, 44%). *Anal.* ($C_{18}H_{18}O_3$) C, H.

7-Methoxyfluorene-2-acetic Acid (24). Hydrolysis of 22 with EtOH–45% aqueous KOH and crystn from EtOH gave 24 (mp 204–205°, 97%). *Anal.* ($C_{16}H_{14}O_3$) C, H.

7-Methoxy-α-methylfluorene-2-acetic Acid (25). Hydrolysis of 23 with EtOH–40% aqueous KOH and crystn from EtOAc gave 25 (mp 183–184°, 80%). *Anal.* ($C_{17}H_{16}O_3$) C, H.

Fluorene-1-acetic Acid (28). Fluorene-1-carboxylic acid was homologated under the Arndt–Eistert conditions employed in the synthesis of 26 and 27,[11] and gave 28 after crystn from EtOH (mp 172–174°, 15%). *Anal.* ($C_{15}H_{12}O_2$) C, H.

α-Methylfluorene-1-acetic acid (29) was prepared from fluorene-1-carboxylic acid (3.0 g, 0.014 mole) by Arndt–Eistert homologation[17] with diazoethane.[18] Crystn from MeOH gave 29 (1.4 g, mp 189–191°, 41%). *Anal.* ($C_{16}H_{14}O_2$) C, H.

α-Methylfluorene-4-acetic acid (30) was prepared, as described for 29, from fluorene-4-carboxylic acid and gave, after sublimation and crystn from MeCN, 30 (mp 176–178°, 62%). *Anal.* ($C_{16}H_{14}O_2$) C, H.

α-Methylfluorene-9-acetic Acid (31). A mixt of 9-bromofluorene (24.5 g, 0.1 mole) and potassium methylmalonic ester [prepared from diethyl methylmalonate (17.2 g) and *tert*-BuOK (11.2 g) in *tert*-BuOH (80 ml)] was refluxed for 4 hr. The mixt was evapd and the residue was dissolved in H_2O and extd (Et_2O). The exts were washed (H_2O), dried, and evaporated. The residue was hydrolyzed with EtOH–40% aqueous KOH to the diacid (2-hr reflux). The diacid was heated at 170–180° until the evolution of CO_2 had ceased. Sublimation of the product gave 31 (3.0 g, mp 103–104°, 13%). *Anal.* ($C_{16}H_{14}O_2$) C, H.

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Xanthone-2-carboxylic Acids, a New Series of Antiallergic Substances†

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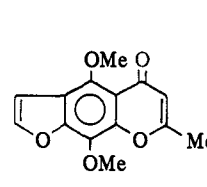
Substituted xanthone-2-carboxylic acids are shown to be highly active in antiallergic bioassays and are, therefore, of possible value in the treatment of asthma.

We wish to report a new series of antiallergic substances based on xanthone-2-carboxylic acid. It has long been known that khellin (1), a chromone isolated from the fruit and seeds of the plant *Ammi visnaga*, exhibits antiasthma properties of clinical value.[1] Starting from this observation, the Fisons group was able to develop disodium cromoglycate (2), which has become an exceptionally important agent in the prophylactic treatment of the allergic condition underlying bronchial asthma.[2,3] Our work



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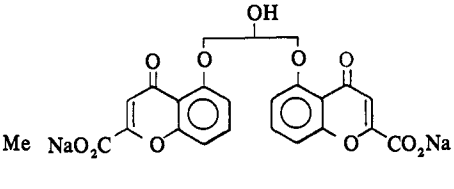

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