# 6-Chlorochroman-2-carboxylic Acids. Synthesis and Biological Evaluation as Antagonists for Cholesterol Biosynthesis and Lipolysis *in Vitro*

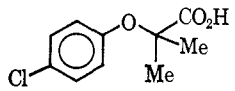
DONALD T. WITIAK,* EUGENE S. STRATFORD,[1a,b] RALPH NAZARETH, GWEN WAGNER,[1c] AND DENNIS R. FELLER

*Divisions of Medicinal Chemistry and Biochemical Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210*

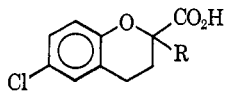
*Received November 23, 1970*

Studies leading to, and the synthesis of, DL-6-chlorochroman-2-carboxylic acid (**2**) and DL-2-methyl-6-chlorochroman-2-carboxylic acid (**3**) are presented. These compounds are cyclic analogs of the hypocholesterolemic and hypolipidemic agent α-(4-chlorophenoxy)-α-methylpropionic acid (**1**). Preliminary results on their ability to antagonize glycerol release from rat epididymal fat pads and inhibit mevalonate-2-$^{14}C$ incorporation into nonsaponifiable material of rat liver homogenate are discussed.

As part of a continuing program designed to prepare asymmetric analogs of the hypocholesterolemic and antilipidemic agent, α-(4-chlorophenoxy-α-methylpropionic acid (**1**),[2-4] we set out to synthesize the cyclic chroman analogs **2** and **3**. Whereas **1** contains



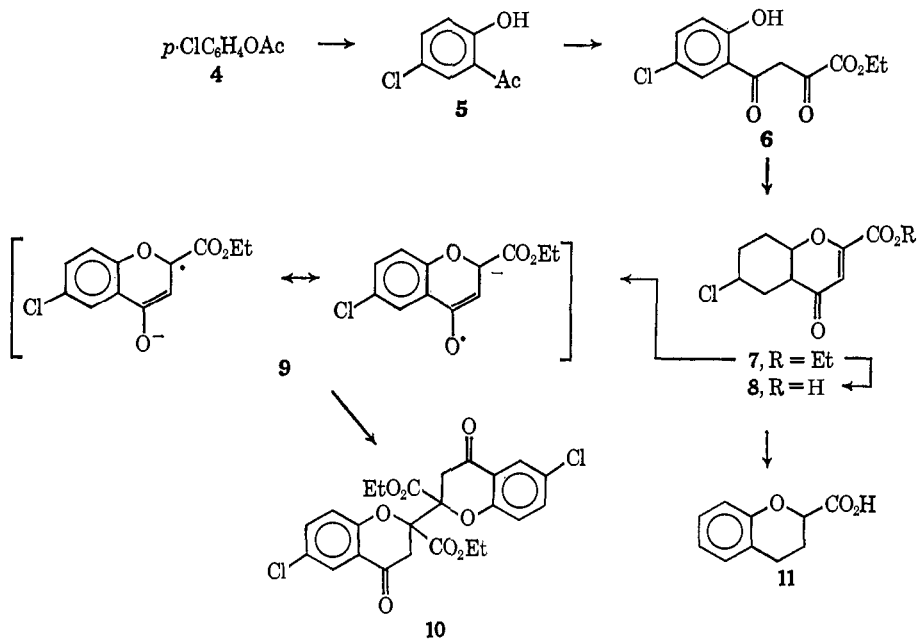
**1**



**2**, R = H
**3**, R = Me

no asymmetric center, chromans **2** and **3** may ultimately be resolved and their respective enantiomorphs employed as stereoselective chemical probes for receptor site studies. In this report we discuss the synthesis of the DL compounds, our preliminary biological studies relating to their ability to block glycerol release from rat epididymal fat pads, and their inhibitory action of mevalonate-2-$^{14}C$ incorporation into nonsaponifiable products in a rat liver homogenate preparation.

**Synthetic Aspects.**—In our initial attempts to synthesize **2** we employed 6-chlorochromone-2-carboxylic acid (**8**) and its Et ester **7**. Standard procedures[5] for the Fries rearrangement reaction were used to convert *p*-chlorophenyl acetate (**4**) to 2-hydroxy-5-chloroacetophenone (**5**). Treatment of acetophenone **5** with diethyl oxalate in the presence of NaOEt afforded intermediate **6** which was not purified; the crude intermediate was cyclized to the known chromone derivatives **7** and **8**. Ester **7** was obtained by heating **6** in HOAc containing HCl.[6] Acid **8** was obtained either from intermediate **6** or from ester **7** by heating crude **6** or pure **7** in concd HCl–HOAc (1:4).[7]



**4** **5** **6** **9** **7**, R = Et; **8**, R = H **10** **11**

Although the nmr spectra of chromones show that the heterocyclic ring is not aromatic in character,[8]

(1) (a) Abstracted in part from a dissertation presented to the Graduate School of The Ohio State University (1970); (b) U. S. Public Health Service Predoctoral Fellow (5-F01-GM-37591); (c) NSF Undergraduate Research Participant, Summer, 1970.

(2) (a) D. T. Witiak, T. C-L. Ho, R. E. Hackney, and W. E. Connor, *J. Med. Chem.*, **11**, 1086 (1968); (b) D. T. Witiak, R. E. Hackney, and M. W. Whitehouse, *ibid.*, **12**, 697 (1969).

(3) (a) D. T. Witiak and M. W. Whitehouse, *Biochem. Pharmacol.*, **18**, 971 (1969); (b) D. T. Witiak, T. D. Sokoloski, M. W. Whitehouse, and F. Hermann, *J. Med. Chem.*, **12**, 754 (1969).

(4) D. T. Witiak, D. R. Feller, E. S. Stratford, R. E. Hackney, R. Nazareth, and G. Wagner, *J. Med. Chem.*, **14**, 754 (1971).

(5) A. H. Blatt, *Org. React.*, **1**, 359 (1942).

(6) V. A. Zagorevskii, D. A. Zykov, and E. K. Orlova, *Zh. Obshch. Khim.*, **30**, 3894 (1960); *cf. Chem. Abstr.*, **55**, 22301*f* (1961).

(7) P. Niviere, P. Tronche, and J. Couquetet, *Bull. Soc. Chim. Fr.*, 3658 (1965).

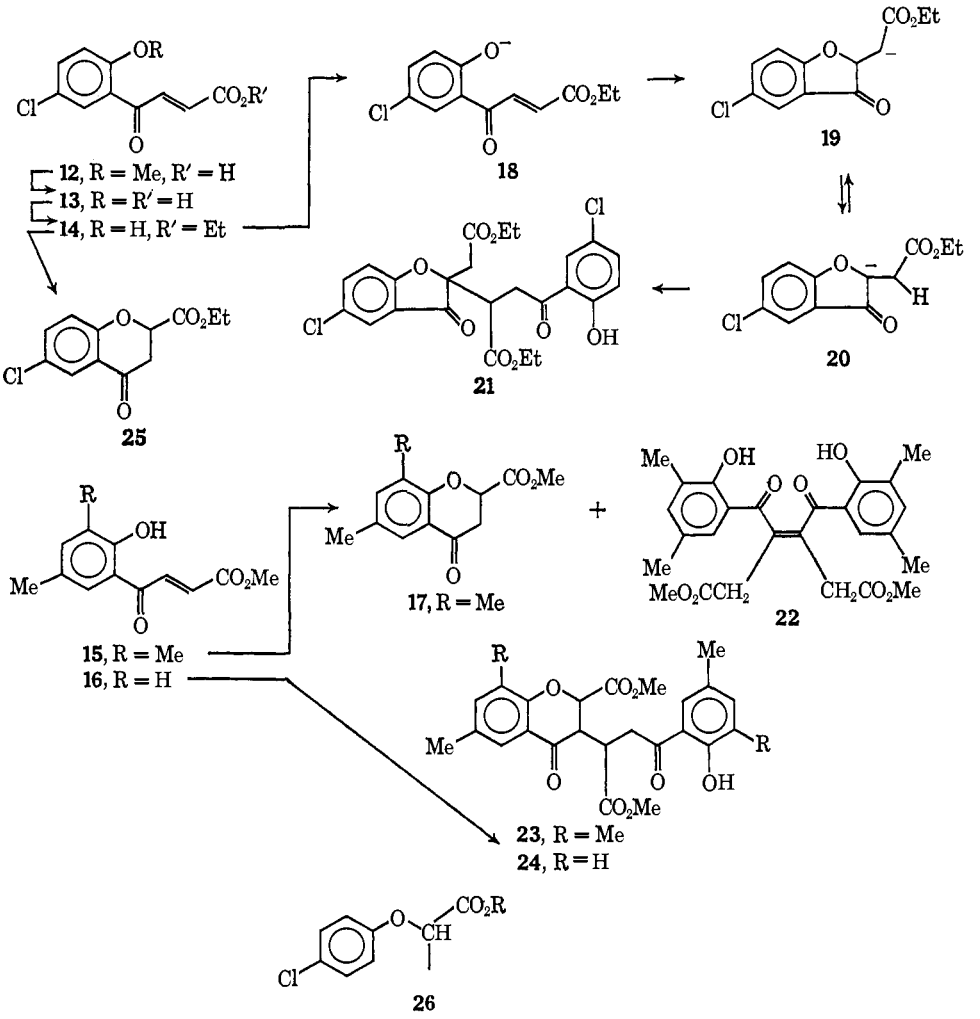
(8) (a) M. M. Badawi and M. B. E. Fayez, *Indian J. Chem.*, **5**, 93 (1967); (b) G. Govil and C. L. Khetrapal, *Curr. Sci.*, **35**, 564 (1966).

attempts to reduce the isolated double bond were unsuccessful. Treatment with Zn dust in HOAc[9] afforded a mixture consisting mainly of starting material and dimer **10**. These compounds were separated by repeated column chromatography on silicic acid–$CHCl_3$ and the structure for dimer **10** was assigned primarily on the basis of its nmr spectrum (see Experimental Section).

Reductive dimerizations in the absence of a protic solvent are well known. A possible explanation for the formation of dimer **10** involves formation of resonance-stabilized anion radical **9** resulting from donation of an electron from the Zn metal surface. The combined influence of the $CO_2Et$ group and the ring O may enhance the stabilization of free radical **9** which ultimately dimerizes and abstracts a proton from the solvent by either a concerted or stepwise process to yield **10**.

Low pressure hydrogenation of **8** (max 2.1 kg/cm$^2$) over Raney Ni catalyst[10] or hydrogenation of the Na salt of **8** over copper chromate catalyst at high pressures and temperatures[11] only afforded starting material. Hydrogenation of **8** in HOAc in the presence of 5% Pd/C afforded the expected deschlorochroman **11**. The use of less polar solvents (*e.g.*, EtOAc) in the presence of Pd/C or with $PtO_2$ catalyst resulted in the formation of a complex mixture of products analyzing for as many as 10 compds by glpc.

A second approach to the synthesis of **2** involves cyclization of a β-(2-hydroxyaroyl)acrylate according to methods reported by Cocker and coworkers.[12] Starting β-(2-hydroxy-5-chlorobenzoyl)acrylic acid (**13**) was prepared from *p*-chloroanisole and maleic anhydride followed by demethylation of **12**.[13] Increasing the temp of the reaction results in formation of **13** directly. Ester **14** was prepared from **13**; the large coupling constant ($J$ = 15.7 Hz) for the vinyl protons substantiates the trans geometry for **12**, **13**, and **14**.[14] However, whereas **15** is reported to cyclize to chromanone **17** in the presence of $N(Pr)_3$ and 5 equiv of diethyl malonate,[12] in our hands monomer **14** only afforded dimer **21**. The structural assignment for **21** is based on ir and nmr analysis and differs from structures proposed by other investigators. For example, Cocker and coworkers reported that if diethyl malonate was omitted from the reaction a mixture of dimer **22** and chromanone **17** is obtained.[12] Barr and coworkers[15] obtained a mixture of **17** and **22** irrespective of con-




(9) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **501**, 247 (1933).

(10) (a) P. Naylor, G. R. Ramage, and F. Schofield, *J. Chem. Soc.*, 1190 (1958); (b) C. J. Jarowski, W. J. Moran, and B. J. Cramer, *J. Amer. Chem. Soc.*, **71**, 944 (1949).

(11) (a) L. F. Fieser and W. H. Daubt, *ibid.*, **63**, 782 (1941); (b) H. O. House and R. J. McCaulley, *J. Org. Chem.*, **24**, 725 (1959).

(12) W. Cocker, D. H. Hayes, and W. R. N. Williamson, *J. Chem. Soc.*, 824 (1955).

(13) G. Baddeley, S. M. Makar, and M. G. Ivinson, *ibid.*, 3969 (1953).

(14) N. Sugiyama, Y. Gasha, H. Kataoka, and C. Kashima, *Bull. Chem. Soc. Jap.*, **41**, 971 (1968).

(15) K. P. Barr, F. M. Dean, and H. D. Locksley, *J. Chem. Soc.*, 2425 (1959).

ditions employed. Based on the uv spectrum for dimer **22** and potentiometric titration of the partial hydrolysis products these investigators[15] assigned structure **23** to dimer **22**. Of particular interest is the observation that **16** afforded only the dimer **24**; the structure of this dimer was assigned on the basis of its similarity to **23**. The uv spectrum[12] and the ir CO absorption frequencies[15] for dimer **23** are similar to the data obtained for our dimer **21** (Experimental Section) and suggest that the structural types of the 2 dimers may be the same. Additional evidence, however, does not support either of the structural types previously proposed. The ir absorption of the chromanone CO in **25** occurs at 1690 $cm^{-1}$. The higher frequency of the nonchelated CO in the dimer suggests a 5-membered ring rather than a 6-membered ring. The C**H** resonance signal in a number of compounds possessing structural unit **26** has been observed, in our studies, to appear in the region 4.5 to 5.5 ppm downfield from TMS (see Table II, Experimental Section). No resonance is observed in this region of the spectrum for the dimer obtained in our laboratories and the nmr spectrum is in agreement with structure **21**.[16]

Further support for the proposed structure was obtained by the use of chromanone **25** prepared under different conditions. Barr and coworkers[15] reported that chromanone **17** could be converted to dimer **23** by treatment with $NEt_3$. In our studies, however, **25** was not affected under similar conditions; only the starting material could be isolated. The reasons for the discrepancy between our observations and those of Barr and coworkers is not known.[17] When equal parts of chromanone **25** and acrylate **14** were stirred with $NEt_3$ in EtOH, the chromanone could be quantitatively recovered from the reaction mixture. This observation indicated that the chromanone was not an intermediate in the formation of the dimer as proposed by the previous investigators.[15]

The formation of **21** can be rationalized as follows: cyclization of the initially formed anion **18** to give carbanion **19** would be kinetically favored over cyclization to the 6-membered ring.[18] A prototropic shift in carbanion **19** to give the more stable carbanion would afford **20**. Reaction of **20** with another molecule of starting material, followed by protonation, would afford the observed dimer. The insolubility of the dimer in the reaction mixture also serves to drive the reaction toward its formation.

Cyclization of **14** to the desired chromanone was accomplished by the method of Annigeri and Siddappa.[19] Refluxing **14** in EtOH in the presence of orthophosphoric acid afforded chromanone **25** in low yields. The low yields obtained in this reaction made it desirable to find an alternative pathway to the synthesis of the chromanone intermediate. We therefore employed the method of Julia and Baillarge[20] in preparing $\alpha$-(*p*-chlorophenoxy)-$\gamma$-butyrolactone (**28**) from **26** and **27**; this product was oxidized with $CrO_3$ affording the succinic acid derivative **29**.[20]

Acylation reactions on aromatic rings involving cyclodehydration have been shown to be accomplished readily by employing polyphosphoric acid (PPA) as the condensing reagent and solvent.[21] Examples of the use of this synthetic method in the preparation of the 4-chromanone system have also appeared in the literature.[22] However, when **29** was heated in PPA, the expected keto acid **31** was not obtained. The major product of the reaction was a neutral compound identified by its physical and spectral characteristics as 6-chlorochromone (**30**). This compound was also obtained when $ZnCl_2$ in $POCl_3$ was employed according to the method of Iyer and Shah.[23]

A phosphorylated derivative of the desired keto acid is probably an intermediate in this conversion which is further dehydrodecarboxylated to the observed product. Evidence in support of this assumption was obtained by conversion of keto acid **31** under similar reaction conditions to chromone **30**. Keto acid **31** was obtained in good yield by cyclization of **29** in warm concd $H_2SO_4$.

Reduction of chromanone **25** was first attempted by the method involving dithioketalization and Raney Ni desulfurization according to the procedure of Sondheimer and Rosenthal.[24] The dithioketal ester **32** was obtained readily in good yield. However, attempted desulfurization in EtOH with Raney Ni W-2 catalyst resulted in dechlorination as well as desulfurization affording ester **33**. This ester was found to be identical with the ester produced by acid-catalyzed esterification of **11**. Conversion of **25** and **31** to **2** was accomplished under Clemmenson reduction conditions according to the method of Bridge and coworkers.[25] Esterification was readily accomplished in the usual manner affording **34**.

It could be argued that the reactions employed in the preparation of the chromanone derivatives discussed might actually result in the production of the isomeric coumaranone compounds (*i.e.*, the 5-membered ring derivatives). Distinction between these two possible alternatives is difficult on the basis of spectral evidence alone. The fact that the chromanone system was actually formed was proved by the demonstration that **33** is identical with the ester obtained from esterification of **11**. For these reasons, keto ester **25** must be a chromanone; it is not likely that a rearrangement occurred during the formation of dithioketal **32**.

While the reaction sequence starting with **27** proved successful for the synthesis of **2**, it failed for the preparation of **3** owing to the necessity of displacing a tertiary halide from starting $\alpha$-methyl-$\alpha$-bromo-$\gamma$-

(16) An apparent 2 $H^+$ singlet appearing at $\delta$ 3.5 suggests the presence of an isolated $CH_2$ group in which both protons are magnetically equiv. A dimeric product corresponding to structures **22** and **23** would not be expected to show such a singlet. The C**H** and C$\mathbf{H_2}$ of the open chain unit of the dimer appear as a closely spaced $A_2B$ (or ABC) system centered at $\delta$ 3.53.

(17) One possibility is that these investigators isolated some of the 5-membered ring cyclized product rather than the chromanone.

(18) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 115–116.

(19) (a) A. C. Annigeri and S. Siddappa, *Monatsh. Chem.*, **96**, 625 (1965); (b) *Indian J. Chem.*, **2**, 413 (1964). Azaflavones were prepared from azachalcones.

(20) M. Julia and M. Baillarge, *Bull. Soc. Chim. Fr.*, 470 (1954).

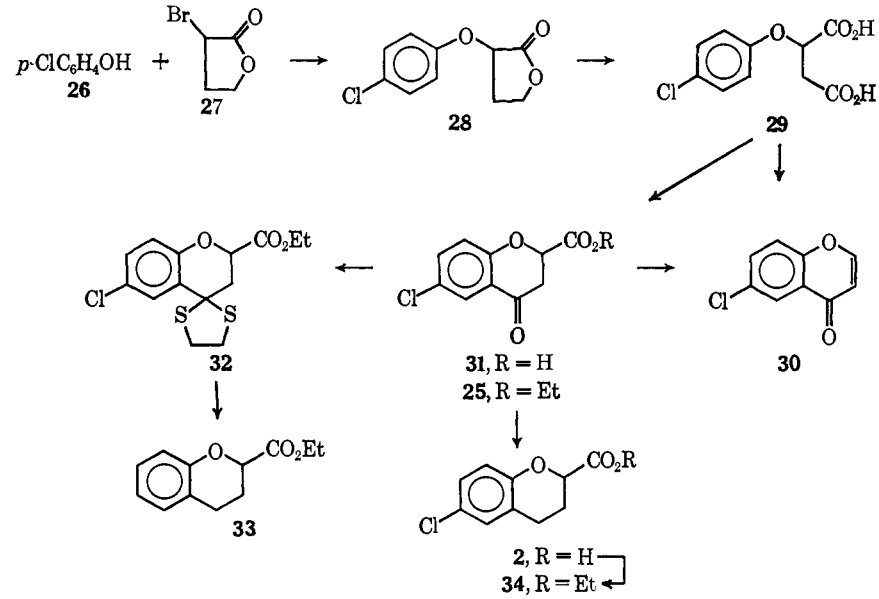
(21) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 894–898.

(22) (a) P. S. Bramwell, A. O. Fitton, and G. R. Ramage, British Patent 1,077,066 (1967), *cf. Chem. Abstr.*, **68**, 78137 (1968); (b) W. E. Parham and L. D. Huestis, *J. Amer. Chem. Soc.*, **84**, 813 (1962).

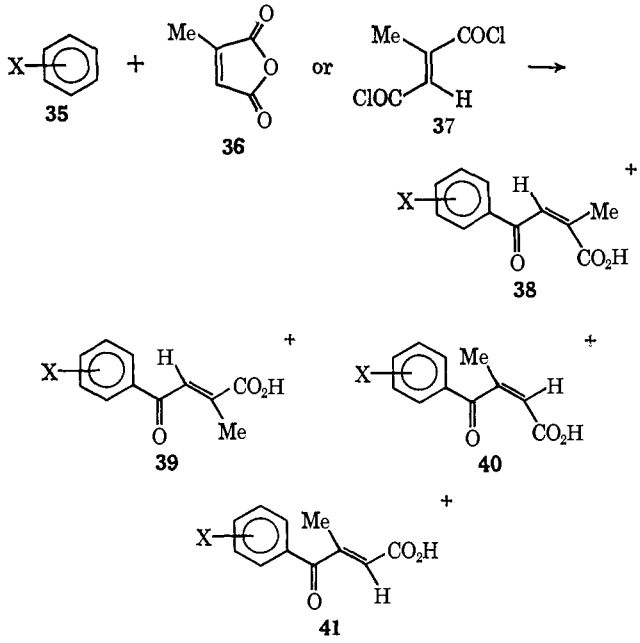
(23) P. R. Iyer and G. D. Shah, *Indian J. Chem.*, **6**, 227 (1968).

(24) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).

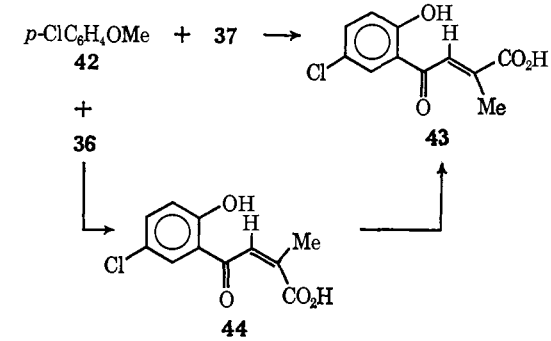
(25) W. Bridge, A. J. Crocker, T. Cubin, and A. Robertson, *J. Chem. Soc.*, 1530 (1937).



butyrolactone.[26] For these reasons we resorted to the acrylate ester sequence originally used to prepare **2**. Acylation of benzenoid derivatives **35** with citraconic anhydride (**36**) or with mesaconyl Cl (**37**) could afford 4 isomeric acids; these compounds, the *cis*-α-Me (**38**), *trans*-α-Me (**39**), *cis*-β-Me (**40**), and *trans*-β-Me (**41**) acrylic acids, could result from electrophilic attack at either of the CO functions.[27,28]



Lutz and Taylor[27] studied the reaction of benzenoid derivatives **35** with **36** and **37**. The major product resulting from the reaction of **35** (X = Br) with **36** was found to be the *cis*-β-methyl compound **40** (X = *p*-Br) with **39** isolated as a minor product. When **35** (X = Br) undergoes reaction with **37** the *trans*-α-methyl compound **39** (X = *p*-Br) was isolated. Arora and Brassard[28] also report the synthesis of a number of *trans*-α-methyl analogs **39** upon reaction of **37** with benzenoid analogs **35**, but in addition observed two examples of reactions which afforded the unexpected *trans*-α-methyl analogs **39** when the Me half-ester of mesaconyl chloride (**37**) was employed. In our experiments, Friedel–Crafts reaction of *p*-chloroanisole (**42**) with **37** afforded the expected *trans*-α-Me isomer **43**. However, when **42** underwent reaction with **36** the unexpected *cis*-α-methyl isomer **44** was isolated rather than the *cis*-β-methyl system (**40**) reported by Lutz and Taylor.[27] In both reactions (*i.e.*, **42** + **37** and **42** + **36**) the MeO group was readily cleaved and only the phenol was obtained. Isolation of *cis*-α-methyl isomer **44** contradicts the suggestion by Lutz and Taylor[27] that such isomers (*i.e.*, **38**) are too labile to exist under the reaction conditions, but further experimental work is necessary to determine the reasons for the differences in results. Differences in reaction conditions, concn of $AlCl_3$,[28] and the steric influence of the *o*-$CH_3O$ (or OH) in the reaction should be studied.



The structures for acids **43** and **44** were deduced from a number of observations. The nmr spectra in $Me_2CO$-$d_6$ of these compounds showed the same number of protons were present and gave similar splitting patterns. The spectrum for the product obtained using **36** as the acylating agent showed the expected quartet for the vinyl proton resonance centered at δ 7.10. The spectrum for the product obtained using **37** as the reactant exhibited a vinyl proton resonance signal at δ 7.91 indicating the compounds were isomeric. Further, **44** could be converted to **43** by heating in aq EtOH in the presence of a mineral acid. This observation,

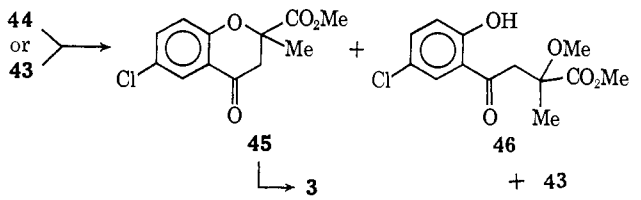
(26) A similar reaction of phenol with α-carbethoxy-α-bromobutylactone has been reported. T. N. Rozanova and I. T. Skrukov, *Khim.-Farm. Zh.*, **1**, 40 (1967). *cf. Chem. Abstr.*, **68**, 48995 (1968).

(27) R. E. Lutz and R. J. Taylor, *J. Amer. Chem. Soc.*, **55**, 1168 (1933).

(28) P. C. Arora and P. Brassard, *J. Chem. Can.*, **45**, 67 (1967).

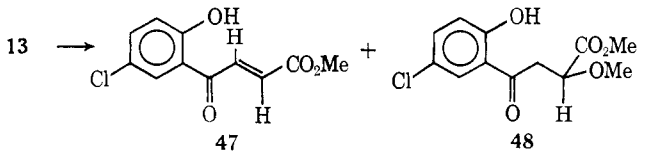
coupled with elemental and nmr analysis, demonstrated that **43** and **44** were geometric rather than structural isomers. When these data are considered in light of the geometry of the acylating agent, acids **43** and **44** must have the trans and cis configurations, respectively.

Assignment of the Me group to the $\alpha$ position was confirmed by esterification and cyclization to **45** in MeOH. When either **43** or **44** was refluxed in MeOH–$H_2SO_4$, the same mixture of products was observed (glpc analysis). The gas chromatogram of the reaction mixture showed the presence of 2 major and 2 minor compounds with relative intensities for peaks a, b, c, and d of 32–35, 7–8, 45–48, and 11–12%, resp (see Experimental Section for retention times). Peak a corresponds to the product of the reaction identified as the cyclized ester **45**. A minor product **46** from the reaction mixture has the same retention time as peak d. Compounds corresponding to peaks b and c have not been conclusively identified. Upon work-up of the reaction mixture, starting with either **43** or **44**, compounds **45**, **46**, and trans acid **43** (recovered in 46% yield), but no cis acids, are obtained. From the intensities of the peaks in the gas chromatogram, it appears that the component giving rise to peak c is rapidly converted to **43** by treatment with dil NaOH during the work-up. Column chromatography (silicic acid–$HCCl_3$) of the mixture not treated with NaOH does not give good band separation. Nmr analysis of a fraction enriched in the component giving rise to peak c, however, indicates that this compound is probably the ester of *trans*-**43** since the quartet for the vinyl proton resonance appears at $\delta$ 7.67. Extraction of an $Et_2O$ soln of this enriched mixture with dil NaOH followed by rapid acidification affords trans acid **43**. We do not know the reason for the facile hydrolysis of this ester.




The products in this reaction apparently represent an equilibrium mixture since the ratio of products is not altered by refluxing the reaction mixture more than 48 hr. Cyclized ester **45** was isolated from the reaction in 32 to 35% yield. Since **45** is the desired intermediate product in the synthesis of **3**, the utility of the reaction is expressed more accurately when the yield of **45** is based upon the amount of starting material consumed. Thus, the 46% recovery of **43** represents a yield of 61–65% of cyclized ester **45**. Reduction of **45** affording **3** was readily accomplished under the same conditions employed for reduction of **25** and **31**. The structure of **45** was readily deduced from its ir and nmr spectra thus establishing the position of the Me group in the isomeric acids employed as starting materials (see Experimental Section).

Finally, it should be mentioned that cyclization of acrylate esters in a MeOH–$H_2SO_4$ solution appears to be facilitated by the presence of the Me group. When **13** is refluxed in MeOH containing $H_2SO_4$, a low yield of the unsaturated ester **47** can be obtained, but the major product is a compound resulting from the addition of MeOH to the double bond. The addition compound is probably **48** which would result from addition of the MeO group to the $\alpha$ position; however, we do not have evidence to eliminate the possibility that **48** is really an isomer resulting from nucleophilic attack at the $\beta$ position.




**Biological Results.**—In the studies on the inhibition of norepinephrine (NE)-induced lipolysis by the 6-chlorochroman-2-carboxylic acid analogs, these compounds ($10^{-2}$–$10^{-3}$ $M$) were incubated with epididymal fat tissue as described previously.[4,29] The antilipolytic activity was measured by assaying the release of glycerol according to the procedures of Lambert and Neish[29b] and Nash.[29c] The results given in Table I demonstrate that chromans **2** and **3** possess the same order of inhibitory activity on the NE-induced release of glycerol as the parent drug **1**. The deschlorochroman **11** and the chromanone **31** are less potent than either **1**, **2**, or **3**, but also show appreciable antagonism at $10^{-2}$ $M$. A comparison of the dose–response curves for chroman derivatives **2** and **3** with the curve for **1** is shown in Figure 1. From this comparison it appears that the chroman derivatives are slightly more effective inhibitors of NE-induced lipolysis *in vitro*. At $10^{-2}$ $M$ **2** and **3** showed greater than 100% inhibition indicating that these compounds not only block NE-induced lipolysis, but also the basal release of glycerol.

TABLE I
EFFECT OF CYCLIC ANALOGS RELATED TO **1** ON THE RELEASE OF GLYCEROL FROM RAT EPIDIDYMAL ADIPOSE TISSUE IN RESPONSE TO NOREPINEPHRINE ($2.4 \times 10^{-6}$ $M$) *in Vitro*

| Compd No. | Concn, $M$ | % Inhibition of glycerol release[a] |
|---|---|---|
| 1 | $5 \times 10^{-3}$ | 57.3 ± 3.0[b,c] |
| | $10^{-2}$ | 100.7 ± 1.1[c] |
| 2 | $10^{-3}$ | 7.3 ± 14.4 |
| | $2 \times 10^{-3}$ | 38.3 ± 2.1[c] |
| | $5 \times 10^{-3}$ | 78.3 ± 5.2[c] |
| | $10^{-2}$ | 112.4 ± 4.5[c,d] |
| 3 | $10^{-3}$ | −4.1 ± 11.3 |
| | $2 \times 10^{-3}$ | 39.5 ± 5.9[c] |
| | $5 \times 10^{-3}$ | 82.9 ± 4.7[c] |
| | $10^{-2}$ | 112.7 ± 2.8[c,d] |
| 11 | $5 \times 10^{-3}$ | 41.6 ± 4.4[c] |
| | $10^{-2}$ | 70.3 ± 4.6[c] |
| 31 | $5 \times 10^{-3}$ | 8.2 ± 1.3 |
| | $10^{-2}$ | 65.4 ± 4.1[c] |

[a] Each value represents the average of at least 3 experiments. [b] Standard error of the mean. [c] Significantly different from the control ($p < 0.05$). [d] Greater than 100% inhibition indicates that the compd is blocking the basal release at the indicated concn in addn to NE-induced lipolysis.

Inhibition of mevalonate-2-$^{14}C$ incorporation into nonsaponifiable products was studied according to the

(29) (a) K. F. Finger, J. G. Page, and D. R. Feller, *Biochem. Pharmacol.*, **15**, 1023 (1966); (b) M. Lambert and A. Neish, *Can. J. Res.*, **28**, 83 (1950); (c) T. Nash, *Biochem. J.*, **55**, 416 (1953).

method described in ref 2b. The results are illustrated in Figure 2. Significant inhibitory activity is observed for the deschlorochroman **11**, chromanone **31**, and the DL-chromans **2** and **3**. In this biological system **2**, **3**, and **31** were equally as active as the parent compound **1**[2b] at a concn range of 1.5 to 9.0 m*M*. The deschlorochroman **11** exhibits considerably less inhibitory action of **1**, **2**, **3**, and **31** at **4** concns; *i.e.*, 1.5, 3.0, 4.5, and 9.0 m*M*.

## Discussion

Thus far our studies with open chain analogs of **1**[4] and the 2,3-dihydrobenzofuran[4] and chroman cyclic analogs **2**, **3**, **11**, and **31** reveal all of these compounds to be effective in inhibiting NE-induced lipolysis from rat epididymal fat pads. Compounds **2** and **3** are slightly more active than **1**, and like **1** also inhibit the basal release of glycerol.[4] Removal of the Cl affords **11** with inhibitory activity nearly equal to **1** in lipolysis, but markedly reduced inhibitory action for incorporation of mevalonate-2-$^{14}C$ into nonsaponifiable products *in vitro* in a rat liver homogenate system. These data, considered in conjunction with the similar results obtained in both *in vitro* systems for the deschlorobenzodioxane analog[4] of **1** indicate that the *p*-Cl group plays a more significant role in the rat liver homogenate preparation.

For **1**, the lipase enzyme(s) has been suggested as the site of action in lipolysis;[4] **1** and an L(*S*)-desmethyl analog of **1** have been shown to inhibit cholesterol biosynthesis between mevalonate and squalene.[2b] However, further studies are indicated to determine the exact site of action of the chroman analogs in both *in vitro* preparations. While the preparation of **2** and **3** has not lead to an appreciable alteration in the antilipolytic activity of the parent drug **1**, the similarity of action for **1**, **2**, and **3** thus far observed suggests the resolved isomers of the chromans may be useful stereoselective chemical probes for a number of enzyme systems which are either stimulated or blocked by **1**.

## Experimental Section[30]

**6-Chlorochroman-2-carboxylic Acid (2).**—A mixt of 100 g of mossy Zn and 10 g of $HgCl_2$ was used to prep the Zn(Hg) according to the method described by Martin.[31] To the freshly prepd Zn(Hg) was added concd HCl (100 ml), $H_2O$ (100 ml), AcOH (20 ml), and 18.1 g (0.08 mole) of **31**. The resulting mixt was stirred at room temp for 24 hr and 18% HCl (100 ml) was added and stirring continued at room temp.[25] After an addnl 22 hr, 18% HCl (100 ml) was added and the mixt was heated on a steam bath for 1 hr, and finally at reflux for 1.5 hr. After cooling to room temp, the liq was decanted from the Zn(Hg). The Zn(Hg) was washed with $Et_2O$ and the aq mixture was extd ($Et_2O$). The combined $Et_2O$ soln was extd with satd $NaHCO_3$ soln. The aq layer was acidified with dil HCl and extd ($Et_2O$). The $Et_2O$ soln was washed with satd NaCl soln and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. Recrystn from $Bu_2O$–petr ether (80–100°) afforded 14.0 g (83%) of the crude acid, mp 140–150°. Column chromatography on silicic acid–$CHCl_3$ and recrystn from petr ether (80–100°) afforded **2**, mp 152–155°, which showed only one peak by glpc; nmr ($Me_2CO$-$d_6$), δ 2.19 (t, 2, $CH_2CN$), 2.78 (m, 2, $ArCH_2$), 6.95 (m, 3, aromatic protons), 10.42 (s, 1, $CO_2H$). See Table II for CH resonances. *Anal.* ($C_{10}H_9ClO_3$) C, H, Cl.

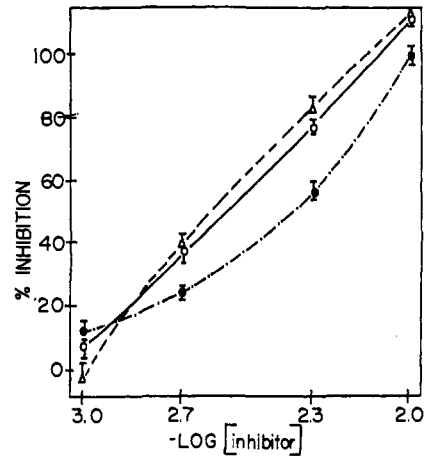



Figure 1.—Inhibition of the release of glycerol from rat epididymal fat pads in response to $2.4 \times 10^{-6}$ *M* NE in the presence of varying concentrations of inhibitors: O—O = α-(4-chlorophenoxy)-α-methylpropionic acid (**1**); O—O = DL-6-chlorochroman-2-carboxylic acid (**2**); Δ—Δ = DL-2-methyl-6-chlorochroman-2-carboxylic acid (**3**).

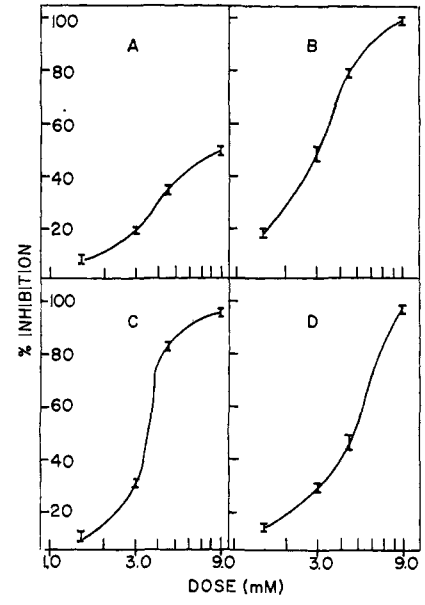



Figure 2.—Dose–response curves for the per cent inhibition of incorporation of mevalonate-2-$^{14}C$ into nonsaponifiable material in fortified rat liver homogenate: (a) DL-chroman-2-carboxylic acid (**11**); (b) DL-6-chlorochroman-2-carboxylic acid (**2**); (c) DL-2-methyl-6-chlorochroman-2-carboxylic acid (**3**); (d) DL-6-chloro-4-chromanone-2-carboxylic acid (**31**).

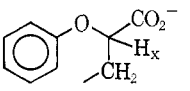
**2-Methyl-6-chlorochroman-2-carboxylic Acid (3).**—To the Zn(Hg) freshly prepd from 20 g of Zn[31] were added concd HCl (40 ml), $H_2O$ (40 ml), AcOH (15 ml), and 6.0 g (0.023 mole) of ester **45**. The mixt was stirred at room temp overnight and heated on a steam bath for 3 hr.[25] After cooling, the resulting mixt was extd ($Et_2O$), and the $Et_2O$ layer was washed (cold $H_2O$) and extd with satd $NaHCO_3$ soln. The acidified aq ext was cooled and the near white solid was collected and dried affording 4.1 g (77%) of the crude acid, mp 144–149°. This was recrystd from petr ether (80–100°) after charcoal treatment to give the pure acid: mp 150–152°; ir, $cm^{-1}$, 2900 (broad, OH), 1720 ($CO_2H$); nmr ($D_2O$ + $K_2CO_3$), δ 1.61 (s, 3, $CH_3$), 1.91 and 2.27 (m, 2, $ArCH_2CH_2$), 2.67 (m, 2, $ArCH_2CH_2$), 7.03 (m, 3, arom protons). *Anal.* ($C_{11}H_{11}ClO_3$) C, H; Cl: calcd 15.65; found, 15.15.

(30) Elemental anal. were performed by Clark Microanalytical Labs., Urbana, Ill. Ir spectra were recorded on a Perkin-Elmer Model 257 grating ir spectrophotometer. Nmr spectra were recorded on a Varian A-60A spectrophotometer. Uv absorption spectra were obtained on a Cary Model 15 spectrophotometer. Glc was performed using the F and M scientific Model 402 high efficiency gas chromatograph. Mp were taken on a calibrated Thomas-Hoover mp apparatus. $^{14}C$ counting was carried out with a Packard scintillation counter.

(31) E. L. Martin, *Org. React.*, **1**, 163 (1942).

TABLE II

THE NMR SIGNAL FOR THE METHINE PROTON IN COMPOUNDS WITH THE STRUCTURAL UNIT



| Compd No. | Solvent | No. of peaks observed | $\delta_X$ in ppm[a] | $J_{AX}$,[b] Hz | $J_{BX}$, Hz |
|---|---|---|---|---|---|
| 2 | $Me_2CO$-$d_6$ | 3 | 4.81 | 5.5 | |
| 11 | $CDCl_3$ | 4 | 4.74 | 6.5 | 4.5 |
| 25 | $CDCl_3$ | 4 | 5.10 | 7.5 | 6.5 |
| 28 | $CDCl_3$ | 3 | 4.93 | 7.5 | |
| 29 | $Me_2CO$-$d_6$ | 4 | 5.17 | 7.1 | 5.5 |
| 31 | $Me_2CO$-$d_6$ | 4 | 5.38 | 7.1 | 5.9 |
| 32 | $CDCl_3$ | 4 | 4.83 | 7.5 | 5.5 |
| 34 | $CCl_4$ | 3 | 4.61 | 5.5 | |

[a] TMS was used as an internal standard for all measurements. [b] The constants listed represent first-order approximations of ABX systems in which $\Delta\nu_{AB} \pm 1/2\ (J_{AX} - J_{BX})$ is small compared to $J_{AB}$ and the outer peaks are lost in the noise.

**2-Hydroxy-5-chloroacetophenone** (**5**) was prepd in 93% yield[5] from 4-chlorophenyl acetate (**4**) by reaction with $AlCl_3$, mp 52–53.5°, lit.[7] mp 52.5°.

**Ethyl-6-chlorochromone-2-carboxylate** (**7**).—The method of Jacobson and coworkers[32] was employed for the prepn of **7**. To a soln of 30 g (1.2 g-atoms) of Na in abs EtOH (500 ml) was added a soln of 51 g (0.3 mole) of **5** in $(CO_2)_2(Et)_2$ (90 ml). The addn was kept at such a rate that refluxing did not become too vigorous. After the addn was complete, the solid yellow mass was heated on a steam bath for 0.5 hr. The mixt was allowed to cool to room temp and $Et_2O$ (500 ml) was added. The solid material **6** was collected by filtration and stirred in 6% AcOH (1.2 l.). The solid was filtered and stirred in AcOH (450 ml) contg concd HCl (15 ml) while heating at 80° for 2 hr. The mixt was allowed to cool to room temp and $H_2O$ (450 ml) was added. The ppt was filtered and recrystd from 95% EtOH affording 45.5 g (60%) of **7**, mp 135–137°. A further recrystn from EtOH, after treatment with charcoal, afforded white needles, mp 137.5–138.5° (lit.[6] mp 136–136.5°).

**6-Chlorochromone-2-carboxylic Acid** (**8**).—This compd was prepd by the same procedure used for the prepn of the ester except that in the cyclization stage a 4:1 ratio of AcOH to concd HCl was employed. The white solid obtained was then recrystd from AcOH affording **8**, mp 267–269° dec, lit.[6,7] mp 262° and 275°. Hydrolysis of ester **7** in AcOH–concd HCl afforded the same acid.

**2-(2-Carbethoxy-6-chloro-4-chromanon-2-yl)-2-carbethoxy-6-chloro-4-chromanone** (**10**).—A soln of 5.0 g (0.02 mole) of **7** in AcOH (100 ml) was stirred at 20° and 2.5 g (0.04 g-atom) of Zn dust added in small portions.[9] The mixt was allowed to stir at room temp for 0.5 hr and heated at 50° for 1 hr. The solvent was concd under reduced pressure to near dryness, and the residue was dissolved in $CHCl_3$ and extd to neutrality with satd $NaHCO_3$ soln. The org layer was dried ($Na_2SO_4$), and the solvent was removed. The amorphous solid obtained was dissolved in $CHCl_3$ and chromatographed on silicic acid–$CHCl_3$. Clear band sepn was not obtained, but the product was eluted in the early portions of the eluant. Early fractions were pooled until the proportion of starting material began to rise as evidenced by glpc analysis. The solvent was evapd under reduced pressure, and the residue was chromatographed as before. The residue obtained was recrystd twice from abs EtOH affording colorless plates, mp 167–169°. A $CHCl_3$ soln of the reaction product obtained before column chromatography was subjected to glpc analysis on 3.8% silicone gum rubber (UC-W98) on chromosorb W (80–100 mesh) with a 1.32 m × 6 mm glass column at a column temp of 200° and a carrier gas (He) flow rate of 26 ml/min. Retention times of 2.0 min for **10** and 3.3 min for **7** were obtained: nmr ($CDCl_3$), $\delta$ 1.16 (t, 3, $J$ = 7 Hz, $CH_3$), 4.19 (q, 2, $J$ = 7 Hz, ester $CH_2$), 3.38 (AB pattern, 2, $J$ = 17 Hz, ring $CH_2$) 7.07 ($H_A$), 7.50 ($H_B$), 7.81 ($H_C$) (3, $J_{AB}$ = 8.8, $J_{AC}$ = 0.5, $J_{BC}$ = 2.6, first-order approx aromatic protons).

(32) C. R. Jacobson, K. R. Brewer, and E. D. Anstutz, *J. Org. Chem.*, **18**, 1117 (1953).

**Chroman-2-carboxylic Acid** (**11**).—To a soln of 22.4 g (0.1 mole) of **8** in AcOH (250 ml) was added 2.0 g of 5% Pd/C.[33] The mixt was shaken at 70° under $H_2$ at 3.5 kg/cm². The pressure was reapplied whenever it dropped below 2.45 kg/cm². A total of 2.25 kg of $H_2$/cm² was absorbed in 4–6 hr (the theoretical amount was calcd to be 23.61 kg/cm². The cooled soln was filtered, and the solvent was removed under reduced pressure. The residue was dissolved in $Et_2O$ and extd ($NaHCO_3$ soln). The aq soln was acidified and extd ($Et_2O$), and the solvent was removed under reduced pressure affording 13.4 g (75%) of crude **11**. Recrystn from petr ether (80–100°) afforded colorless needles, mp 93–96°, lit.[34] mp 98.5–100°. See Table II for CH resonances.

**β-(2-Hydroxy-5-chlorobenzoyl)acrylic Acid** (**13**).—To a stirred mixt of s-$C_2H_2Cl_4$ (30 ml), 20 g (0.15 mole) of $AlCl_3$, and 4.8 g (0.05 mole) of maleic anhydride,[35] was added 7.1 g (0.05 mole) of *p*-chloroanisole during 15 min. After the addn was complete, the flask was heated in a $H_2O$ bath at 50 to 60° for 3 hr. The resulting mixt was extd ($Et_2O$). (The low soly of the product in $Et_2O$ required the use of a continuous extn procedure when larger amts were prepd.) The $Et_2O$ soln was extd with $NaHCO_3$ soln, and the aq layer was acidified with dil HCl. The yellow solid was filtered and dried ($Na_2SO_4$) affording 4.3 g (38%) of material which was recrystd from 95% EtOH affording **13**, mp 207–211°, lit.[33] mp 196–198°. *Anal.* ($C_{10}H_4ClO_4$) C, H, Cl.

**Ethyl β-(2-Hydroxy-5-chlorobenzoyl)acrylate** (**14**).—A soln of 9.7 g (0.043 mole) of **13** in a mixt of abs EtOH (200 ml), $PhCH_3$ (100 ml), and concd $H_2SO_4$ (1 ml) was heated in an oil bath at 115°.[36] As soon as refluxing commenced, the bath temp was lowered to 100°. A total of 100 ml of dist was collected in a Dean–Stark trap and discarded. The remaining soln was allowed to cool and poured into 200 ml of cold $H_2O$ and extd ($Et_2O$). The org layer was washed with cold $H_2O$, followed by $NaHCO_3$ soln and satd NaCl soln. The $Et_2O$ soln was dried ($Na_2SO_4$), and the solvent was removed under reduced pressure affording 10.3 g (94%) of an orange oil which crystd upon standing. Two recrystns from petr ether (30–60°) afforded yellow needles, mp 49.5–51.5°. *Anal.* ($C_{12}H_{11}ClO_4$) C, H, Cl.

**2-Carbethoxymethyl-2-[1-carbethoxy-3-oxo-3-(2-hydroxy-5-chlorophenyl)propyl]-5-chlorobenzofuran-3-one** (**21**) **Formation during Attempted Cyclization[12,15] of Ester 14.**—A mixt of 2.0 g (0.008 mole) of acrylate **14**, 8.0 g (0.05 mole) of diethyl malonate, and $NEt_3$ (0.4 ml) in abs EtOH (50 ml) was allowed to stand at 0–5° overnight. To the cold soln, AcOH (2 ml) was added, and the soln was concd under reduced pressure to approx 30 ml. Distd $H_2O$ was added to the point of incipient crystn, and the soln was cooled to 0–5°. Crystals which sepd were collected and dried affording 1.3 g (65%) of dimer **21**, mp 104–107°. Recrystn from PhH–petr ether (60–80°) afforded white needles, mp 112–114.5°. In a modification of the procedure, 8.0 g ($3.0 \times 10^{-2}$ mole) of **14** was dissolved in abs EtOH (100 ml) and $NEt_3$ (0.4 ml) was added. The soln was stirred at room temp for 0.5 hr while the initial red color changed to a light yellow color; 5% $H_2SO_4$ (10 ml) was added. The ppt was filtered affording 6.7 g (84%) of white crystals **21**. An addnl 0.4 g of **21** was obtained after cooling the filtrate to 0–5° affording a total of 7.1 g (89%) of dimer **21**: uv (MeOH), $\lambda_{max}$, mμ (log ε), 220 (4.66), 251 (4.22), 337 (3.91); ir, $cm^{-1}$, 3440 (OH), 1740–1715 (C=O and $CO_2Et$), 1643 (chelated C=O); nmr ($CDCl_3$), $\delta$ 1.07 (t, 3, $J$ = 7.2 Hz, $CH_3$), 1.15 (t, 3, $J$ = 7.2 Hz, $CH_3$), 3.25 (s, 2, $CH_2CO_2Et$), 3.53 (m, 3, $CHCH_2$), 4.01 (q, 2, $J$ = 7.2 Hz, ester $CH_2$), 4.13 (q, 2, $J$ = 7.2 Hz, ester $CH_2$), 7.30 (m, 6, arom protons), 10.87 (s, 1, OH). *Anal.* ($C_{24}H_{22}Cl_2O_8$) C, H, Cl.

**Ethyl 6-Chloro-4-chromanone-2-carboxylate** (**25**).—A soln of 4.5 g (0.018 mole) of **14** and 10 g of orthophosphoric acid in abs EtOH (200 ml) was heated at reflux.[19] After 3 days the soln was concd to approx 0.5 the original vol and dild with $H_2O$ (200 ml). The mixt was extd ($Et_2O$) and dried ($Na_2SO_4$); the solvent was removed under reduced pressure. The residue was distd under reduced pressure and crystd from petr ether (60–80°) affording 0.9 g (20%) of crude product, mp 61–71°. Two recrystns from petr ether afforded colorless needles, mp 78–79.5°.

(33) S. Mitsui, M. Sudzuki, and H. Yashinaga, *J. Chem. Soc. Jap.*, **64**, 1337 (1943).

(34) J. Augstein, A. M. Monro, G. W. H. Potter, and P. Scholfield, *J. Med. Chem.*, **11**, 844 (1968).

(35) G. Baddeley and J. R. Cooke, *J. Chem. Soc.*, 2797 (1958).

(36) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 385.

Ester **25** was also prepd from acid **31**. Thus, a soln of 5.7 g (0.025 mole) of **31** in abs EtOH (100 ml) and $PhCH_3$ (50 ml) with concd $H_2SO_4$ (0.5 ml) was refluxed for 2 hr and 75 ml of dist was removed in a Dean–Stark trap. The cooled soln was dild with cold $H_2O$ and extd ($Et_2O$). The $Et_2O$ layer was washed with $H_2O$ and satd $NaHCO_3$ soln and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The residue was crystd from petr ether (60–80°) affording 5.3 g (84%) of **25**, mp 80–82°. This compound was identical with the ester obtained by cyclization of **14**: uv, $\lambda_{max}$ mμ (log ε), 219 (4.54), 248 (3.90), 329 (3.53); ir, $cm^{-1}$, 1758 ($CO_2Et$), 1690 (C=O); nmr ($CDCl_3$), δ 1.28 (t, 3, $J$ = 7 Hz, $CH_3$), 3.07 (t, 2, unresolved AB portion of an ABX pattern, ring $CH_2$), 4.27 (q, 2, $J$ = 7 Hz, ester $CH_2$). See Table II for CH resonances. *Anal.* ($C_{12}H_{11}ClO_4$) C, H, Cl.

**α-(*p*-Chlorophenoxy)-α-butyrolactone (28).**—The method of Julia and Baillarge was employed for the prepn of this compd.[20] Improved yields of the purified material were obtained by column chromatography of the crude product on silicic acid–$CHCl_3$ which removed most of the resinous material. The solid obtained on removal of the $CHCl_3$ under reduced pressure was recrystd from PhH–petr ether (60–80°) affording a 55–57% yield of **28**, mp 81–83°, lit.[18] mp 75°. See Table II for CH resonances. *Anal.* ($C_{10}H_9ClO_3$) C, H, Cl.

**α-(*p*-Chlorophenoxy)succinic Acid (29).**—This compd was prepd according to Julia and Baillarge from lactone **28** by oxidn with $CrO_3$ in $Me_2CO$ affording white crystals, mp 156–158°, lit.[20] mp 156°. See Table II for CH resonances. *Anal.* ($C_{10}H_9ClO_5$) H, Cl, C: calcd 49.18; found, 49.85.

**6-Chlorochromone (30).**—A mixt of 2.4 g (0.01 mole) of **29** and PPA (*ca.* 60 g) was heated on a steam bath while stirring for 2 hr.[22] After cooling, the mixt was treated with ice $H_2O$. After the PPA had completely decompd, the product was extd ($Et_2O$), the $Et_2O$ soln was washed with successive portions of $H_2O$, satd $NaHCO_3$ soln, and satd NaCl soln and dried ($Na_2SO_4$) and the solvent was removed under reduced pressure affording 1.8 g of the crude product. This was recrystd from petr ether (80–100°) affording 0.85 g (59%) of colorless needles, mp 137–137.5°, lit.[37] mp 139–140°. Treatment of 2.5 g (0.011 mole) of 6-chloro-4-chromanone-2-carboxylic acid (**31**) under analogous condns afforded 1.4 g (70%) of the same chromone. *Anal.* ($C_9H_5ClO_2$) C, H, Cl.

**6-Chloro-4-chromanone-2-carboxylic Acid (31).**—A soln of 12.2 g (0.05 mole) of **29** in concd $H_2SO_4$ (75 ml) was stirred while heating in a $H_2O$ bath at 40–50° for a period of 4 hr.[25] The soln was allowed to cool, poured onto ice (350 g), and extd ($Et_2O$). The $Et_2O$ soln was extd with satd $NaHCO_3$ soln. After acidification of the aq layer with dil HCl, the liberated acid was extd ($Et_2O$), the $Et_2O$ soln was washed with satd NaCl soln and dried ($Na_2SO_4$), and the solvent was removed under reduced pres affording 7.5 g (66%) of the crude acid. Recrystn of the crude product from AcOEt–petr ether (60–80°) afforded 6.3 g (56%) of purified **31**: mp 176–178°; nmr ($Me_2CO$-$d_6$), δ 3.16 (q, 2, $CH_2$), 7.37 (m, 3, arom protons), 10.90 (broad s, 1, $CO_2H$). See Table II for CH resonances. *Anal.* ($C_{10}H_7ClO_4$) C, H, Cl.

**Ethyl 6-Chloro-4-chromanone-2-carboxylate Ethylene Dithioketal (32).**—A mixt of 130 mg (0.5 mmole) of **25**, ethanedithiol (0.4 ml), and $BF_3$–$OEt_2$ (5 drops) was swirled until a soln was obtained and was allowed to stand at room temp for 15 min. MeOH (5 ml) was added, and the soln was cooled in an ice bath; the crystals were collected, washed (MeOH), and dried affording 103 mg (62%) of colorless crystals, mp 110–112°. Two recrystns from petr ether (60–80°) afforded the anal. sample, mp 111.5–113°. See Table II for CH resonances. *Anal.* ($C_{14}H_{15}ClS_2O_3$) C, H, Cl, S.

**Ethyl 4-Chroman-2-carboxylate (33) from Raney Ni Desulfurization of 32.**—A mixt of 1.7 g (0.005 mole) of **32**, 2 teaspoonfuls of Raney Ni catalyst (W-2),[38] and 60 ml of abs EtOH was heated at reflux on a steam bath for 40 min.[24] The mixt was filtered to remove the catalyst and the ppt washed with $Me_2CO$. The combined filtrate and washings were evapd under reduced pressure, and the residue was distd. Ethyl chroman-2-carboxylate (**33**) was collected as a colorless liq, bp 116–117° (0.5 mm), lit.[39] bp 156–159° (6 mm). Ir and nmr spectra of this ester were identical with the spectra obtained from the product prepared by acid-catalyzed esterification of the known acid **11**.

**Ethyl 6-Chlorochroman-2-carboxylate (34).**—A soln of 5.0 g (0.024 mole) of 6-chlorochroman-2-carboxylic acid (**2**) in a mixt of abs EtOH (100 ml) and PhMe (50 ml) contg $H_2SO_4$ (0.5 ml) was heated in an oil bath for 3 hr.[38] During this time 60 ml of dist was removed in a Dean–Stark trap. The cooled soln was dild with $Et_2O$ and washed with satd NaCl soln, satd $NaHCO_3$ soln, and again with satd NaCl soln. The resulting org layer was dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The residue was distd, and ester **34** was collected at 111° (0.04 mm): ir, 1755 $cm^{-1}$ ($CO_2Et$); nmr ($CCl_4$), δ 1.23 (t, 3, $J$ = 7.2 Hz, $CH_3$), 2.13 (m, 2, $CH_2CH$) 2.66 (m, 2, $ArCH_2$), 4.16 (q, 2, $J$ = 7.2 Hz, ester $CH_2$), 6.87 (m, 3, arom protons). See Table II for CH resonances.

***trans*-β-(2-Hydroxy-5-chlorobenzoyl)-α-methylacrylic Acid (43).**—To a suspension of 54 g (0.4 mole) of $AlCl_3$ in *s*-$C_2H_2Cl_4$ (50 ml) cooled in an ice bath was added 25 g (0.175 mole) of *p*-chloroanisole (**42**). Stirring was contd, and the ice bath was removed while 25 g (0.117 mole) of mesaconyl chloride (**37**) was added during 30 min.[14] The mixt was stirred an addl 1.5 hr and poured into ice (700 g)–concd HCl (100 ml). The resulting mixt was extd ($Et_2O$), and the $Et_2O$ layer was washed (1 *N* NaOH soln). The aq layer was acidified and extd ($Et_2O$). The resulting $Et_2O$ soln was washed with $H_2O$ and satd NaCl soln and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure affording 27.0 g of a yellow solid. This was recrystd from PhH–EtOH affording 16.2 g (58%) of the crude acid **43**. A further recrystn from the same solvent afforded yellow needles: mp 168–171°; ir, $cm^{-1}$, 3410 (broad, OH), 1990 (broad, $CO_2H$), 1698 ($CO_2H$), 1640 (chelated C=O); nmr ($Me_2CO$-$d_6$), δ 2.19 (d, 3, $J$ = 1.6 Hz, $CH_3$), 7.91 (q, 1, $J$ = 1.6 Hz, $H_{vinyl}$), 7.40 (m, 3, arom protons), approx 8.4–12.0 (broad, d, 2, OH and $CO_2H$). Recrystn of **43** from PhH afforded orange needles having the same spectral and physical properties. *Anal.* ($C_{11}H_9ClO_4$) C, H, Cl.

***cis*-β-(2-Hydroxy-5-chlorobenzoyl)-α-methylacrylic Acid (44).**—A mixt of 20 g (0.15 mole) of $AlCl_3$, 5.5 g (0.5 mole) of citraconic anhydride (**36**), and *s*-$C_2H_2Cl_4$ (30 ml) was stirred at room temp during the addn of 7.1 g (0.05 mole) of *p*-chloroanisole (**42**) over a 20-min period.[14] The mixt was allowed to stir at room temp for 1 hr followed by heating at 50° for 2 hr. After cooling to room temp the mixt was poured into ice (300 g)–concd HCl (50 ml) and extd ($Et_2O$). The $Et_2O$ soln was extd with satd $NaHCO_3$ soln, and the aq layer was acidified and extd ($Et_2O$). The $Et_2O$ soln was washed (satd NaCl soln) and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The residue remaining was recrystd from PhH–petr ether (60–80°) affording 1.44 g (12%) of acid **44** as yellow plates: mp 174–176°; ir, $cm^{-1}$, 3400 (broad, OH), 2950 (broad, $CO_2H$), 1708 ($CO_2H$), 1650 (C=O), 1615 (weak, C=C); nmr ($Me_2CO$-$d_6$), δ 2.11 (d, 3, $J$ = 1.7 Hz, $CH_3$), 7.10 (q, 1, $J$ = 1.7 Hz, $H_{vinyl}$), 7.30 (m, 3, arom protons), about 9.0–12.0 (broad, s, 2, OH and $CO_2H$). *Anal.* ($C_{11}H_9ClO_4$) C, H, Cl.

**Isomerization of 44 to 43.**—A soln of 0.5 g (0.0021 mole) of **43** in a mixt of $H_2O$ (25 ml), 95% EtOH (25 ml), and concd HCl (5 ml) was heated at reflux for 1.5 hr. The resulting soln was dild with $H_2O$ and extd ($Et_2O$). The $Et_2O$ soln was washed (cold $H_2O$) and extd with 1 *N* NaOH soln. The aq layer was acidified and extd ($Et_2O$). The resulting $Et_2O$ soln was washed with satd NaCl soln and dried ($MgSO_4$), and the solvent was removed under reduced pressure affording 0.45 g (90%) of a yellow solid. The solid was recrystd from PhH affording the trans acid **43**, mp 166–169°. A mmp with the product obtained from acylation of **42** and **37** was not depressed. Ir and nmr spectra of these acids were identical.

**Methyl 2-Methyl-6-chloro-4-chromanone-2-carboxylate (45).**—A soln of 10 g (0.042 mole) of **44** in MeOH (200 ml) contg concd $H_2SO_4$ (2 ml) was heated at reflux for 48 hr. After cooling, the soln was dild (cold $H_2O$) and extd with $Et_2O$. The $Et_2O$ soln was extd (cold 1 *N* NaOH soln), washed with satd NaCl soln, and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The residue was dissolved in petr ether (30–60°), dried ($Na_2SO_4$), and cooled in a freezer affording 3.5 g (33%) of **45** as nearly colorless crystals, mp 58–64°. A further recrystn from petr ether afforded rectangular rods: mp 64–66°; ir, $cm^{-1}$, 1735 ($CO_2Me$) 1695 (C=O, characteristic of a 6-membered ring); nmr ($CDCl_3$), δ 1.72 (s, 3, $CCH_3$), 2.88 (d, 1, $J$ = 17 Hz, $CH_AH_B$), 3.18 (d, 1, $J$ = 17 Hz, $CH_AH_B$), 3.67 (s, 3, $OCH_3$), 7.00, 7.44, 7.77 (3, $J_{AB}$ = 7.77, $J_{AC}$ = 0.6, $J_{BC}$ = 2.6,

(37) S. Ruhemann, *Ber.*, **54**, 919 (1921).

(38) R. Mozingo, "Organic Synthesis," Collect. Vol. 3, Wiley, New York, N. Y., 1955, p 181.

(39) S. Mitsui, A. Kasahara, T. Oike, and K. Hanaya, *Nippon Kagaku Zasshi*, **83**, 58 (1962). *cf. Chem. Abstr.*, **59**, 3727*f* (1963).

arom protons, first-order approx). Assignment of the chemical shifts to each proton of the methylene AB system cannot be made from the available evidence. It has been shown that the axial proton in α-bromocyclohexanones resonates at lower field than the equatorial proton.[40] However, the $CO_2Me$ group also appears to exert a strong influence on the chemical shift since the $\Delta\nu$ for the $CH_2$ resonances in **3** is still 0.36 ppm. Although it could be assumed from the relative conformational free energies of the $CO_2Me$ and Me groups[41] that the $CO_2Me$ group would occupy the axial position, it is not certain how this would affect the chemical shift for the $CH_2$ protons in the presence of the electronic influence of the β-$CO_2Me$ group. *Anal.* ($C_{12}H_{11}ClO_4$) C, H, Cl.

The basic ext obtained during the work-up of **45** was acidified and extd ($Et_2O$). The $Et_2O$ soln was washed (satd NaCl soln) and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The residue was recrystd from PhH affording orange needles, 4.6 g (46%), mp 166–169°. A mmp of this acid with acid **43** was not depressed. Ir and nmr spectra of these two acids were also identical.

Glpc analysis of a petr ether soln of the reaction mixt (after washing with satd NaCl soln and drying with $Na_2SO_4$) on 3.8% silicone gum rubber (UC-W98) on chromosorb W with a 4 ft × 0.25 in. glass column at a column temp of 160° and a carrier gas (He) flow rate of 32 $cm^3$/min gave 4 peaks with the following retention times (min); (a) 5.6, (b) 6.4, (d) 8.3, (d) 10.5. The retention time of chromanone **45** under the same conditions was 5.6 min.

**Methyl 2-Methyl-2-methoxy-4-oxo-4-(2-hydroxy-5-chlorophenyl)butanoate (46).**—Evapn of the petr ether soln used above in the glpc analysis afforded a yellow-orange oil. This oil was dissolved in $CHCl_3$ and chromatographed on silicic acid–$CHCl_3$. Clear band sepn was not obtained and it was not possible to sep all of the components in the mixt. Removal of the solvent from the trailing fraction after complete elution of the colored components afforded a colorless oil which was crystd from petr ether affording colorless needles, mp 109–111°. The retention time for this compd under the same conditions as described above was 10.5 min; ir, $cm^{-1}$, 3460 (broad, OH), 1750 ($CO_2Me$), 1652 (C=O); nmr ($CDCl_3$), δ 1.58 (s, 3, $CCH_3$), 3.33 (s, 3, $OCH_3$), 3.49 (AB pattern, 2, $J$ = 17 Hz, $CH_2$), 3.78 (s, 3, $CO_2CH_3$), 7.31 (m, 3, arom protons), 11.90 (s, 1, OH). *Anal.* ($C_{13}H_{15}ClO_5$) C, H, Cl.

The compds giving rise to peaks b and c have not been conclusively identified. Column chromatography on silicic acid–$CHCl_3$ afforded an enriched fraction of the component giving rise to peak c. Nmr analysis ($CDCl_3$) indicated that this compd was probably the Me ester of **43**; δ 2.23 (d, 3, $J$ = 1.4 Hz, $CCH_3$), 3.88 (s, 3, $OCH_3$), 7.32 (m, 3, arom protons), 7.67 (q, 1, $J$ = 1.4 Hz, $H_{vinyl}$), 12.10 (s, 1, OH).

Treatment of trans acid **43** with $H_2SO_4$ in MeOH afforded the same product mixt as described for the analogous treatment of the cis acid **44**, affording the same retention times on glpc analysis and the same products on work-up. Thus, 3.6 g ($1.5 \times 10^{-2}$ mole) of **43** afforded 1.2 g (32%) of **45**.

**Methyl *trans*-β-(2-Hydroxy-5-chlorobenzoyl)acrylate (47) and Methyl 2-Methoxy-4-oxo-4-(2-hydroxy-5-chlorophenyl)butanoate (48).**—A soln of 2.3 g (0.01 mole) of **13** in MeOH (50 ml) contg $H_2SO_4$ (0.5 ml) was heated at reflux overnight on a steam bath. The cooled soln was dild ($Et_2O$), washed successively with $H_2O$, satd NaCl soln, satd $NaHCO_2$ soln, $H_2O$, and satd NaCl soln and dried ($Na_2SO_4$) and the solvent was removed under reduced pressure affording 2.0 g of a yellow solid. The material was analyzed by glpc showing the presence of 1 major and 2 minor peaks. Two compds were sepd by column chromatography on silicic acid–$CHCl_3$. The first band eluted was recrystd from petr ether (after removal of the $CHCl_3$) affording **47** as yellow needles, mp 81–84°. *Anal.* ($C_{11}H_9ClO_4$) C, H, Cl.

The trailing portion of the chromatogram afforded **48** as colorless crystals from petr ether (60–80°), mp 72–74°; nmr ($CDCl_3$), δ 3.43 (partially hidden d, 2, $CH_2$), 3.49 (s, 3, $OCH_3$), 3.82 (s, 3, $CO_2CH_3$), 4.40 (t, 1, CH), 7.30 (m, 3, arom protons), 11.90 (s, 1, OH). *Anal.* ($C_{12}H_{13}ClO_5$) C, H, Cl.

**Biological Methods.**—The exptl methods for studying inhibition of lipolysis and inhibition of mevalonate-2-$^{14}C$ incorporation into nonsaponifiable products *in vitro* have been previously described in ref 4 and 2b, respectively.

**Acknowledgment.**—We are grateful to the National Institutes of Health for support of this work through Grant HE 12740. This investigation was supported (in part) by National Institutes of Health Research Grant No. FR-00328 from the Division of Research Facilities and Resources.

(40) (a) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **86**, 1780 (1964); (b) K. M. Wellman and F. G. Bordwell, *Tetrahedron Lett.*, 1703 (1963).

(41) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1967, pp 439–441.