Synthesis of Ethyl 6-Substituted-Chroman- and -Chromone-2-carboxylates. A Comparative Structure–Activity Study Employing the 6-Phenyl and Phenoxy Analogs in the Triton Hyperlipidemic Rat Model†

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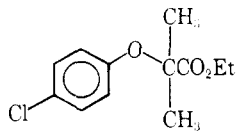
To explore the effect of lipophilicity on antilipidemic activity in the Triton WR-1339 induced hyperlipidemic rat model we synthesized the 6-cyclohexyl, phenyl, and phenoxy analogs of ethyl chroman-2-carboxylate. Results obtained were analyzed in light of the biological activity observed for the 6-chloro-substituted and unsubstituted chromans, the 6-chlorochroman-4-one ester, and the 6-chloro-, phenyl-, and phenoxychromone esters. The suggestion is made that chromones likely exert their antilipidemic effects by a somewhat different set of mechanisms than do the chromans and clofibrate. Whereas the 6-chlorochromanone ester is inactive, the 6-chlorochromone ester is active in both normal and hyperlipidemic Sprague–Dawley rats. The major differential effect was observed for ethyl 6-cyclohexylchroman-2-carboxylate which did not lower cholesterol levels but returned triglyceride levels to normal in hyperlipidemic rats.

We previously reported the synthesis of certain cyclic chroman analogs of the antilipemic agent clofibrate (**1**).[1] Ethyl chroman-2-carboxylate (**2**) exhibited no hypocholesterolemic activity and only marginal hypotriglyceridemic activity in a Triton WR-1339 induced hyperlipidemic rat model.[2] However, the 6-chloro analog of **2**, chroman ester **3**, approached the hypocholesterolemic and hypotriglyceridemic activity observed for **1**.[2]

To further explore the effect of lipophilicity on antilipemic activity we synthesized the 6-cyclohexyl, phenyl, and phenoxy analogs **4**, **5**, and **6**, respectively. In this investigation we compare the biological activity in the Triton WR-1339 rat model of these 6-substituted chromans with the activity previously observed for **1**, **2**, and **3**. During the course of these studies we also noted that the previously synthesized[1] 6-chlorochromanone ester **7** was inactive, whereas the completely unsaturated chlorochrome analog **8** exhibited significant hypocholesterolemic and hypotriglyceridemic activity in normal and Triton-induced hyperlipidemic Sprague–Dawley rats. For these reasons we also evaluated the 6-phenyl- and 6-phenoxy-substituted chromone esters **9** and **10**. Structure–activity relationships for these compounds are discussed in terms of their predicted lipid solubility.



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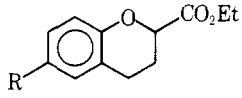
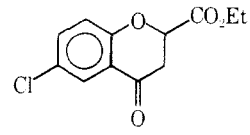


2, R = H
3, R = Cl
4, R = C_6H_{11}
5, R = C_6H_5
6, R = C_6H_5O



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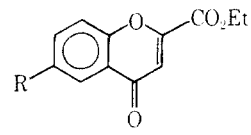
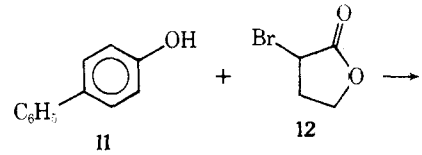
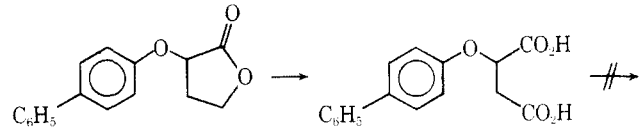


8, R = Cl
9, R = C_6H_5
10, R = C_6H_5O

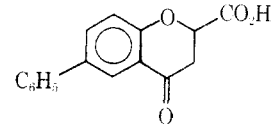
Synthetic Aspects. Phenyl-substituted chroman **5** could not be synthesized by a reaction sequence similar to the one employed for the preparation of chlorochroman **3**.[1] Although intermediate α-(*p*-phenylphenoxy)-γ-butyrolactone (**13**) was prepared from *p*-phenylphenol (**11**) and α-bromo-γ-butyrolactone (**12**) according to the method of *Julia and Baillarge*[3] *in 88% yield, the succinic acid derivative* **14**, obtained by Jones oxidation of **13**, could not be cyclized to chromanone **15** under typical Friedel–Crafts acylation conditions[1,3] (concentrated H_2SO_4 or polyphosphoric acid).



11 **12**



13 **14**



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Alternatively, intermediate chromone ester **9** was prepared in 63% overall yield by condensation of 2-hydroxy-5-phenylacetophenone (**16**) with diethyl oxalate (**18**) followed by cyclization of **19** in HOAc containing a catalytic amount of HCl.[1,4] When a 4:1 ratio of HOAc–HCl was employed chromone acid **21** was isolated in 85% yield based on starting **16**. Similarly, phenoxy analog **10** was prepared from **17** and **18** in 53% overall yield under conditions identical with those employed for the preparation of **9**; when a 4:1 ratio of HOAc–HCl was employed, acid **22** was isolated in 88% yield based on starting acetophenone **17**. This reaction sequence could not be employed for the synthesis of chlorochroman **3** since catalytic reduction (Pd/C) of the α,β-unsaturated ketone of intermediate **8** yielded deschlo-

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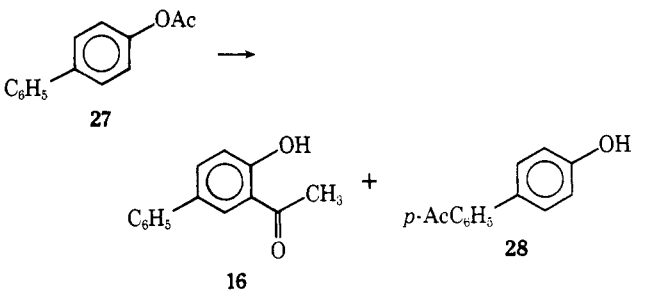
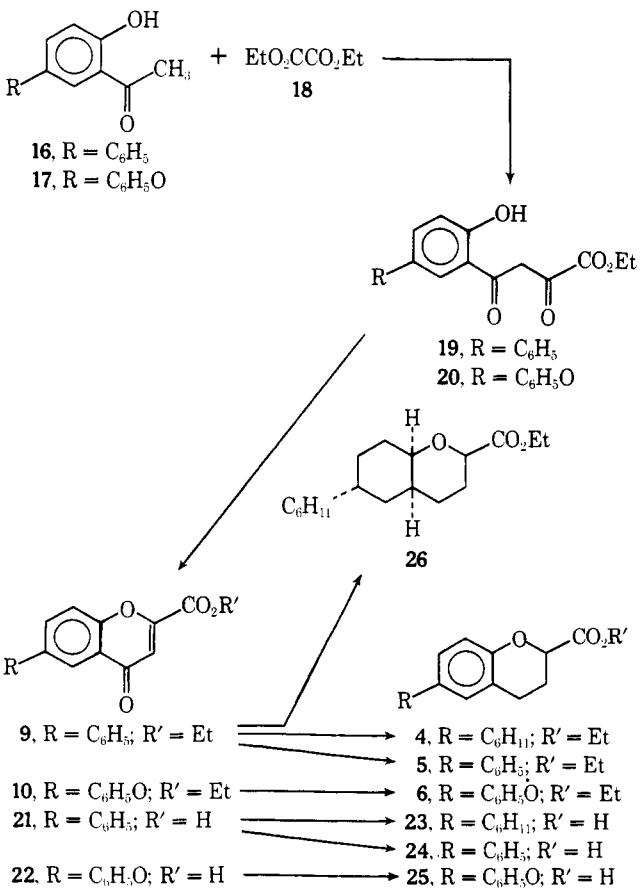
rochroman **2**.[1] However, **9** and **10** served as useful intermediates for the preparation of chromans **5** and **6**, respectively.

Catalytic reduction of chromone ester **9** and acid **21** was studied under a variety of reaction conditions. Hydrogenation of **21** (Pd/C, 70 ± 5°, 40 psi, 2 hr) or **9** (Pd/C, 60 ± 5°, 4 hr) afforded the desired chromans **24** or **5**, respectively, in good yields. Under more rigorous conditions (90 ± 5°, 50 psi), reduction of **9** for 8 hr or **21** for 5 hr yielded the respective cyclohexyl analogs **4** and **23** in yields of 80 and 85%. Chroman esters **4** and **5** were also obtained by standard Fischer esterification of chroman acids **23** and **24**, respectively. When the reaction time, during hydrogenation of **9**, was increased to 15 hr, ethyl 6-cyclohexyloctahydrobenzopyran-2-carboxylate (**26**) of undefined stereochemistry was obtained in 56% yield. Having determined conditions required for selective reduction of the α,β-unsaturated ketone system phenoxychromone ester **10** and acid **22** were easily converted to chromans **6** and **25** in 64 and 69% yields, respectively.

As anticipated, acetophenone **16** could not be synthesized in high yield by Fries rearrangement[5,6] of ester **27** to the ortho position. Although reports in the literature[7-10] describe several instances where biphenyl esters undergo para Fries migration, Cheetham and Hey[11] have reported ortho migration in the synthesis of **16** under typical Fries rearrangement conditions. Under conditions identical with those employed by Cheetham and Hey,[11] we only obtained acetophenone **28**; Fieser and Bradsher[8] obtained both **16** and **28** upon treatment of acetate **27** under similar Fries rearrangement conditions. While Cheetham and Hey did not report a yield for their ortho migration product, the physical properties which they report for this compound are identical with those which we observed for **16** synthesized by an alternate route. In an attempt to obtain **16** by this more direct method we altered the temperature, solvent, and catalyst;[12] only under conditions employing 1 equiv of $TiCl_4$ in nitrobenzene for 18 hr at 20° was **27** converted to any product resulting from ortho migration. Under these conditions the desired product **16** and acetophenone **28** were obtained in 6 and 50% yield, respectively. Although the two products could not be easily differentiated by NMR spectroscopy, their structures were easily assigned from their ir spectra; acetophenone **16** exhibits broad H-bonded OH stretching at 3550 cm^{-1} whereas acetophenone **28** exhibits a sharp OH stretching band at 3600 cm^{-1}. Acetophenone **16** was conclusively characterized by alternate synthesis and conversion to chroman **5**.



Initially, we explored the synthesis of acetophenones **16** and **17** from starting phenols **11** and **29**, respectively. Treatment under standard Marasse modified Kolbe–Schmidt conditions[13] afforded salicyclic acids **30** and **31**, in 90 and 97% yields, respectively. Esterification, affording **32** and **33**, respectively, followed by phenolic OH protection through reaction with benzyl chloride (**34** and **35**, respectively) and ester hydrolysis yielded the benzyl-protected salicyclic acids **36** and **37** in 59 and 57% overall yield, respectively, based on **30** and **31**. Reaction of **36** and **37** with 2 equiv of MeLi gave rise to ketones **38** and **39** in 76 and 80%



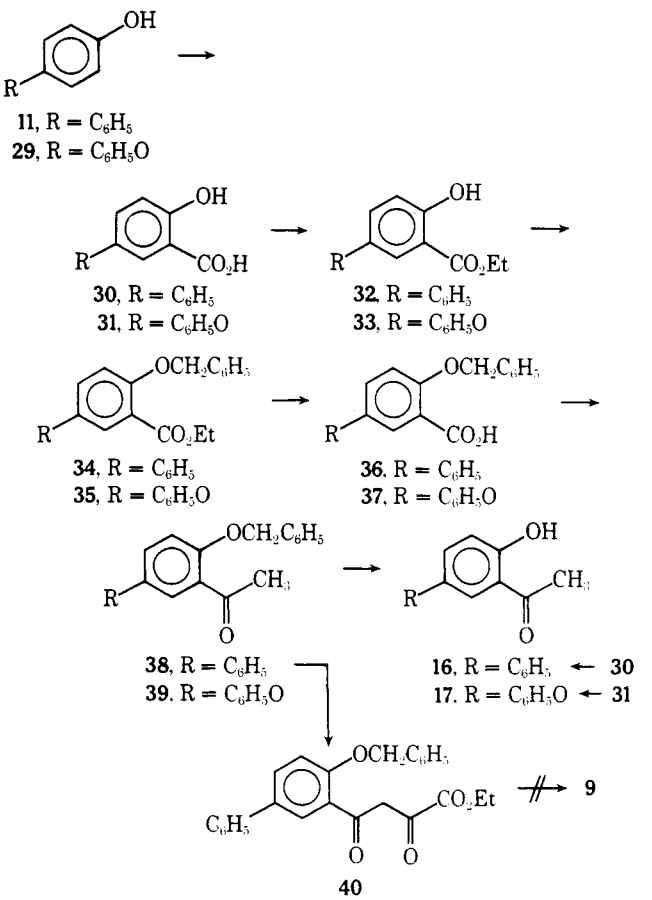


Table I. Effect of Analogs on Serum Cholesterol Levels (mg %) in Male Sprague-Dawley Rats

Compd	Control group (I)	Drug-treated control (II)	Triton hyperlipidemic (III)	Drug-treated Triton hyperlipidemic (IV)
1[a]	60.6 ± 7.2	62.4 ± 8.5	267 ± 85.0	59.3 ± 12.0[b,e,g]
2[a]	69.0 ± 17.0	71.0 ± 19.9	354 ± 45.0	325 ± 66.0[c,f]
3[a]	57.6 ± 5.0	52.0 ± 8.4	249 ± 116	64.0 ± 22.0[b,e,f]
4	75.2 ± 8.4	73.8 ± 13.6	154 ± 79.6	116 ± 35.2[c,f]
5	84.7 ± 9.9	86.8 ± 8.4	226 ± 88.5	94.4 ± 14.3[b,e]
6	81.8 ± 7.9	81.3 ± 10.8	417 ± 261	198 ± 83.3[b,c,f]
7	82.9 ± 10.0	79.0 ± 9.6	176 ± 108	181 ± 105[c,f]
8	82.7 ± 9.2	60.3 ± 10.7[d]	270 ± 124	103 ± 13.0[b,c,e,f]
9	63.4 ± 8.9	67.3 ± 10.8	150 ± 68.6	71.1 ± 13.3[b,e]
10	88.8 ± 8.1	78.9 ± 7.9	234 ± 130	135 ± 30.3[b,c,f]

[a]Data abstracted from ref 2; numbers are the mean ± SD for six rats. For all other compounds numbers represent the mean ± SD for ten rats. [b]Statistically significant, $p < 0.05$; Triton hyperlipidemic vs. drug-treated Triton hyperlipidemic (comparison of groups III and IV). [c]Statistically significant, $p < 0.05$; drug-treated hyperlipidemic vs. control (comparison of groups I and IV). [d]Statistically significant, $p < 0.05$; control group vs. drug-treated control (comparison of groups I and II). [e]Statistically significant, nonparametric rank-sum test, Triton hyperlipidemic vs. drug-treated hyperlipidemic, $p < 0.02$ (comparison of groups III and IV). [f]Statistically significant, nonparametric rank-sum test, Triton hyperlipidemic clofibrate-treated vs. Triton hyperlipidemic drug-treated, $p < 0.002$ (comparison of groups I–IV and *n*–IV). [g]Five rats per group.

Table II. Effect of Analogs on Serum Triglyceride Levels (mg %) in Male Sprague-Dawley Rats

Compd	Control group (I)	Drug-treated control (II)	Triton hyperlipidemic (III)	Drug-treated Triton hyperlipidemic (IV)
1[a]	20.9 ± 6.2	30.5 ± 8.2	774 ± 329	27.6 ± 15.0[b,f,i]
2[a]	34.0 ± 18.0	25.1 ± 13.6	1324 ± 207	659 ± 193[c,f,g]
3[a]	12.5 ± 6.3	22.8 ± 4.7	526 ± 226[i]	40.7 ± 24.0[b,c,f]
4	36.8 ± 5.3	32.4 ± 4.8	122 ± 130	32.9 ± 13.0[b,f]
5	36.4 ± 9.0	29.7 ± 10.7	237 ± 177	28.9 ± 11.4[b,f]
6	30.7 ± 8.4	28.5 ± 4.5	399 ± 224	151 ± 176[b,c,f]
7	21.8 ± 7.5	26.4 ± 4.2	152 ± 110	125 ± 90.8[c,g]
8	40.2 ± 17.5	10.9 ± 6.1[d]	320 ± 207	12.8 ± 7.2[b,e,f,h]
9	25.4 ± 10.3	18.0 ± 7.0	175 ± 144	23.6 ± 5.3[b,f]
10	19.5 ± 8.2	11.8 ± 3.3	166 ± 96.6	30.0 ± 17.4[b,f]

[a]Data abstracted from ref 2; numbers are the mean ± SD for six rats. For all other compounds numbers represent the mean ± SD for ten rats. [b]Statistically significant, $p < 0.05$; Triton hyperlipidemic vs. drug-treated Triton hyperlipidemic (comparison of groups III and IV). [c]Statistically significant, $p < 0.05$; drug-treated hyperlipidemic vs. control (comparison of groups I and IV). [d]Statistically significant, $p < 0.05$; control group vs. drug-treated control (comparison of groups I and II). [e]Statistically significant, $p < 0.05$ (group IV has a value lower than group I). [f]Statistically significant, rank-sum test, Triton hyperlipidemic vs. drug-treated Triton hyperlipidemic, $p < 0.02$ (comparison of groups III and IV). [g]Statistically significant, rank-sum test, clofibrate-treated Triton hyperlipidemic vs. drug-treated Triton hyperlipidemic, $p < 0.02$ (group I–IV has a lower value than group *n*–IV). [h]Statistically significant, rank-sum test, clofibrate-treated Triton hyperlipidemic vs. drug-treated Triton hyperlipidemic, $p < 0.002$ (groups 8–IV has a lower value than 1–IV). [i]Five rats per group.

yields, respectively. The benzyl-protecting groups were removed by catalylic hydrogenation;[14] ketones **16** and **17** were thus obtained from phenols **11** and **29**, respectively, in 30 and 33% overall yield. Although both benzyl group removal[15] and cyclization of 1,3-diketophenols[4] are known to take place in refluxing HOAc–HCl, chromone **9** could not be directly obtained from the benzyl-protected 1,3-diketo ester **40** under such conditions.

Owing to our need for large quantities of ketones **16** and **17** we investigated the direct methylation of salicylic acids **30** and **31**. Under appropriate conditions unpurified acids **30** and **31** (97% pure) can be methylated utilizing 3.9 equiv of MeLi in 1,2-dimethoxyethane to give ketones **16** and **17** directly in 85 and 79% yields, respectively.

Biological Results. The effects of clofibrate (**1**), chromans **2–6**, chromanone **7**, and chromones **8–10** on serum cholesterol (Table I) and triglyceride (Table II) concentrations were tested in starved normal and Triton WR-1339 induced[16] hyperlipidemic Purina chow-fed Sprague–Dawley rats. All compounds were evaluated at the same dosage (mmol/kg; see Experimental Section). In order to define and evaluate the effectiveness of these drugs in lowering cholesterol and triglyceride levels in hyperlipidemic animals, groups III (Triton hyperlipidemic) and IV (drug-treated Triton hyperlipidemic) were compared. Further, to determine whether the drug could lower hyperlipidemic serum levels of cholesterol and triglycerides to those found in normal animals groups, I (control) and IV were compared. Groups I and II (drug-treated control) were contrasted for significant differences to determine whether these new compounds exhibited hypolipidemic activity in normal Sprague–Dawley rats.

Among the chroman analogs **2–6** only the deschlorochroman **2** and 6-cyclohexyl-substituted chroman **4** exhibited no hypocholesterolemic activity in either normal or hyperlipidemic animals. On the other hand, the chloro (**3**) and phenyl (**5**) substituted chromans reduced the hypercholesterolemia to serum levels of the control group (I) and, thus, compared favorably with clofibrate (**1**). The phenoxy analog **6** significantly lowered serum hypercholesterolemia but

did not reduce serum cholesterol concentrations to those levels observed for group I. Insertion of a ketone function at position 4 of chlorochroman 3 afforded chromanone 7 having no hypocholesterolemic activity in either normal or hyperlipidemic rats. Chlorochromone 8 resulting from introduction of additional unsaturation into the molecule (double bond between position 2 and 3 of 7) exhibited hypocholesterolemic activity. Whereas analog 8 did not reduce elevated serum cholesterol levels to those found in group I, this compound did exhibit hypocholesterolemic activity in normal Sprague–Dawley rats. On the other hand, the 6-phenyl analog 9 showed no hypocholesterolemic activity in normal rats, but was found to reduce hypercholesterolemic serum levels back to those found in group I, and in this regard compares favorably with clofibrate (1). Replacement of phenyl with a phenoxy function at position 6 in the chromone series (compare compounds 9 and 10) has the same effect on cholesterol levels as the analogous substitution in the chroman series (compare compounds 5 and 6). Such a change in the substituents renders the compound less active or virtually inactive as a serum cholesterol lowering agent.

The relative order of activity, observed for these compounds as serum cholesterol lowering agents, does not follow the order observed for serum triglyceride lowering activity. In this assay, the deschlorochroman 2 showed some activity, but the significance of the activity is difficult to assess in light of the high values obtained for the Triton hyperlipidemic group (III). As in the cholesterol assay, chlorochromanone 7 exhibited no ability to lower hypertriglyceridemic serum levels. Within the chroman series 2–6, the chloro analog 3, which lowered hypercholesterolemia to normal levels, was as effective in lowering elevated serum triglyceride levels. While chlorochroman 3 did not reduce elevated serum triglyceride levels to those found in group I, this compound was shown to be a relatively effective agent if compared nonparametrically to clofibrate. Most striking, however, is the selective activity observed for the 6-cyclohexyl analog 4. This compound was found to be equally as active as clofibrate (1) when assessed for its ability to lower elevated serum triglyceride levels although it had no effect on elevated serum cholesterol levels. Again, chlorochromone 8 was found to lower serum triglyceride levels in both normal and hyperlipidemic rats; this is the only analog which reduces serum triglyceride levels in hyperlipidemic rats to levels significantly below those of normal rats and below levels found in clofibrate treated Triton hyperlipidemic animals. Replacement of Cl by phenyl in the chromone series (analog 9) affords a compound with serum cholesterol and triglyceride lowering properties similar to clofibrate (1). The phenoxychromone 10 also has excellent hypotriglyceridemic activity but does not compare favorably with clofibrate (1) when assessed for its ability to lower elevated serum cholesterol levels.

Discussion

During the past several years we have been interested in the design and synthesis of antilipidemic drugs which could be employed as biological probes useful in elucidating mechanisms of action and differentiating between biological effects in vivo and in vitro of the parent drug, clofibrate (1).[1,2,17–23] We are particularly interested in differential effects since subsequent parallel studies in vivo and in vitro with hypocholesterolemic, hypotriglyceridemic, and inactive analogs should provide greater insight concerning the relevance of certain assays in vitro as compared to the in vivo situation. Interpretation of such studies must also take into consideration differential effects of absorption, distribution, metabolism, and enzyme induction of the various drugs.[2,21–23] While we plan to carry out such investigations with a limited number of analogs, at this time we have succeeded in accomplishing one primary goal. That is, we have discovered one analog, namely ethyl 6-cyclohexylchroman-2-carboxylate (4), which exhibits selective hypotriglyceridemic activity in hyperlipidemic rats. Further, 2 is virtually inactive, 8 has effects in normal Sprague–Dawley rats, and chroman 5 and chromone 9 compare favorably with clofibrate (1). In connection with these results it is interesting to note that Grisar and coworkers[24] have synthesized a series of clofibrate related hypolipidemic 1,3-benzodioxole-2-carboxylates, some of which also show selective activity. In particular, the 5-Cl analog was observed to have selective hypocholesterolemic effects in normal Wistar rats whereas certain other substitutions resulted in greater hypotriglyceridemic activity. Since clofibrate (1) is not active, when administered under these conditions, in normal 270 ± 10 g Sprague–Dawley rats, but is active in normal Wistar[24] and older Swiss–Webster rats,[18] we anticipate that 8, which significantly reduced normal serum levels, will be found to exert its effects by mechanisms somewhat different than those observed for clofibrate (1). Further efforts with these compounds will be directed toward an attempt to understand the reasons for the differential effects. Further, it should be pointed out that these findings are only valid in the Triton-induced, starved rat model and considerably further work is needed to establish whether or not the findings are valid under more physiological conditions.

We previously observed a deschloro analog of clofibrate (1) to have hypocholesterolemic activity in normal Swiss–Webster rats.[18] However, removal of the Cl group generally affords less active or inactive analogs in biological tests of clofibrate related compounds.[2,25] On the other hand, aromatic substitution (including phenyl and phenoxy functions) generally affords compounds with good to very potent activity.[24,26–28] The results reported in this article for the phenyl and phenoxy analogs are consistent with this general structure–activity relationship. However, it is also instructive to consider the biological results in terms of the calculated log P values for the corresponding free carboxylic acids. The log P values calculated or experimentally determined for each acid corresponding to esters 1–10 are found in Table III. Calculated values were estimated by adding the substituent constants (π) to the experimentally determined[22] log P value for the unsubstituted free acid hydrolysis product of chroman 2 (log P = 1.90). The log P values for the carboxylic acids, rather than for the esters, were calculated and used for correlation purposes since we have previously shown that several clofibrate (1) related drugs undergo rapid hydrolysis by serum esterase preparations,[22] and thus it is assumed that the free acids are the active species as suggested for clofibrate by Thorp.[29]

Whereas the calculated log P values can only be considered as approximations, it seems to us, from analysis of the data, that the chroman series of compounds (2–6) probably work by mechanisms similar to those observed for clofibrate (1) and its analogs; i.e., insertion of Cl, Ph, and PhO groups into both the chroman and phenoxyisobutyrate series results in an increase in lipophilicity and relatively good antilipidemic activity when compared to the unsubstituted compound. The cyclohexyl analog 4 is an exception; the lack of hypocholesterolemic activity observed for this analog either may be due to structural factors or the result of exceeding the log P optimum for hypocholesterolemic activity. Insertion of the 4-keto function into 3 (i.e., 7) renders the compounds inactive; this could be due to decreased lipid solubility (below the log P for inactive 2). On the other hand, insertion of a C=C group into the 2,3 position affords a new series of active compounds; their calcu-

Table III. Calculated Log P (Octanol-Water Partition Coefficients) Values for the Free Acid Hydrolysis Products of the Listed Parent Esters

Free acid of compd	Value of substituents	Calcd log P, 1.90 + π values (exptl determined log P values)[a]
1		(2.57)[a]
2		(1.90)[g]
3	6-Cl = 0.6[b]	2.50 (2.40)[a]
4	6-Cyclohexyl = 2.51[c]	4.41
5	6-C_6H_5 = 1.96[d]	3.86
6	6-C_6H_5O = 2.08[d]	3.98
7	6-Cl = 0.6,[b] 4-keto oxygen = −1.21[e]	1.29
8	6-Cl = 0.6,[b] 4-keto oxygen = −1.21,[e] insertion of C=C = −0.48[f]	0.81
9	6-C_6H_5 = 1.96,[d] 4-keto oxygen = −1.21,[e] insertion of C=C = −0.48[f]	2.17
10	6-C_6H_5O = 2.08,[d] 4-keto oxygen = −1.21,[e] insertion of C=C = −0.48[f]	2.29

[a] Taken from ref 22; experimentally determined at pH two units below the pK_a. [b] π value taken from ref 23. [c] π value for 4-cyclohexyl in the phenoxyacetic acid series; taken from ref 30 and 31. [d] π value taken from ref 31. [e] Estimated from the π-substituent constant for substitution on benzene; CH_3 (0.56), ref 30 or 31; CHO (−0.65), ref 31; i.e., −0.65 − 0.56 = −1.21. [f] Estimated from the π-substituent constant for substitution on benzene; $CH_2CH{=}CH_2$ (1.10), CH_3 (0.56), CH_2CH_3 (1.02); taken from ref 31; i.e., 1.10 − 0.56 = 0.54 for $CH{=}CH_2$; since CH_2CH_3 = 1.02 the CH_2CH_2 to CH=CH transformation = −0.48. However, since $CH{=}CH_2$ has been experimentally determined to be 0.82 (ref 31) this value for the CH_2CH_2 to CH=CH transformation may be between −0.48 to −0.20. The lower value seems more attractive to us for these approximations since the function $O{=}CC{=}CCO_2^-$ is expected to impart greater water solubility than what might be calculated owing to its polar nature and possibilities for H bonding. [g] See ref 2.

lated log P values are considerably lower than those calculated for the corresponding members of the chroman series. Again, the phenyl analog, which has the largest log P value in the chromone series, is the most active of the three compounds studied in hyperlipidemic rats. The chlorochromone **8** having the lowest log P value among the analogs studied is active in normal and hyperlipidemic Sprague–Dawley rats. Differences in mechanism of action between chromans and chromones are to be expected, not only on the basis of log P considerations but also on electronic grounds; unlike chromans, chromones have α,β-unsaturated C=O groups capable of undergoing resonance stabilization through participation of the pyran oxygen electrons. Electronic factors, which influence affinity for enzymes, are considerably different for chromans and chromones.

Experimental Section[&]

Clofibrate (1), ethyl chroman-2-carboxylate (2), ethyl 6-chlorochroman-2-carboxylate (3), ethyl 6-chloro-4-chromanone-2-carboxylate (7), and ethyl 6-chlorochromone-2-carboxylate (8) were synthesized according to methods previously published.[1,18]

Ethyl 6-Cyclohexylchroman-2-carboxylate (4). Acid **23** (2.6 g, 0.01 mol) was dissolved in a mixture of absolute EtOH (50 ml), toluene (10 ml), and concentrated H_2SO_4 (1 ml). The mixture was refluxed for 15 hr with periodic removal of H_2O by use of a Dean-Stark trap. The mixture was cooled, concentrated under reduced pressure, and distilled with Et_2O. The Et_2O solution was separated, washed with saturated NaCl solution and 10% $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized from hexane affording 2.2 g (79%) of white crystals, mp 72–73°.

Chroman ester **4** was also obtained by direct hydrogenation [0.5 g of Pd/C (10%)] of chromone ester **9** (2.94 g, 0.01 M) in 50 ml of HOAc at 90 ± 5° by shaking for 8 hr, maintaining a pressure between 45 and 50 psi. The catalyst was filtered and then filtrate concentrated under reduced pressure. The residue was chromatographed on 45 g of silica gel and eluted with benzene. All fractions homogenous on TLC ($CHCl_3$) were combined and concentrated under reduced pressure affording 2.3 g (80%) of white plates from MeOH: NMR ($CDCl_3$) δ 1.24 (t, 3, J = 7 Hz, ester methyl), 1.24, 2.02 (m, 11, cyclohexyl protons), 2.32 (m, 2, pyran methylene at C-3), 2.80 (m, 2, pyran methylene at C-4), 4.32 (q, 2, J = 7 Hz, ester methylene), 4.78 (m, 1, pyran methine at C-2). Anal. ($C_{18}H_{24}O_3$) C, H.

Ethyl 6-Phenylchroman-2-carboxylate (5). Acid **24** (2.5 g, 0.01 mol) was dissolved in a mixture of absolute EtOH (50 ml), toluene (20 ml), and concentrated H_2SO_4 (1 ml). The mixture was refluxed for 15 hr; H_2O was removed through use of a Dean-Stark trap. The solution was cooled, concentrated under reduced pressure, and diluted with Et_2O. The Et_2O solution was washed with saturated NaCl solution and 10% $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in benzene and treated with decolorizing charcoal. The solvent was removed under reduced pressure affording 2.3 g (85%) of clear yellow oil **5**, bp 220–224 (0.2 mm).

Chroman ester **5** was also obtained by direct hydrogenation of chromone ester **9** under conditions nearly identical with those employed in the reduction of chromone acid **21** to chroman acid **24** except that the reaction was carried out at 60 ± 5° for 4 hr. Crystalline **5** was obtained when the residue was dissolved in benzene and filtered through silica gel 60 (EM Reagents) using a ratio of 25 parts of silica gel to 1 part of residue. All fractions determined by TLC to be homogenous were combined and concentrated under reduced pressure and the residue was recrystallized from a combination of high- and low-boiling petroleum ethers affording 2.0 g (73%) of white plates: mp 49–50°; NMR ($CDCl_3$) δ 1.24 (t, 3, J = 7 Hz, ester methyl), 2.24 (m, 2, methylene at C-3), 2.80 (m, 2, methylene at C-4), 4.26 (q, 2, J = 7 Hz, ester methylene), 4.84 (m, 1, methine), 6.90–7.74 (m, 8, aromatic protons). Anal. ($C_{18}H_{18}O_3$) C, H.

Ethyl 6-phenoxychroman-2-carboxylate (6) was prepared from acid **25** (2.7 g, 0.01 mol) under Fisher esterification conditions identical with those described for the preparation of ester **5** affording 2.6 g (88%) of clear oil, bp 190–195° (0.4 mm).

Chroman ester **6** was also obtained in 64% yield by direct hydrogenation of chromone ester **10** under conditions identical with those employed in the hydrogenation of chromone acid **22** to chroman acid **25**: NMR ($CDCl_3$) δ 1.20 (t, 3, ester methyl), 2.20 (m, 2, methylene at C-3), 2.94 (m, 2, methylene at C-4), 4.24 (q, 2, J = 7 Hz, ester methylene), 4.84 (m, 1, methine), 6.82–7.56 (m, 8, aromatic protons). Anal. ($C_{18}H_{18}O_4$) C, H.

Ethyl 6-Phenylchromone-2-carboxylate (9). The diketo ester **19** (2.1 g, 0.001 mol) was mildly refluxed with 100 ml of AcOH containing 3 ml of concentrated HCl at 80° for 2 hr. The mixture was cooled and diluted with H_2O (200 ml), and the resulting solid was filtered and recrystallized from 95% EtOH affording 2.1 g (72%) of white needles: mp 123–124°; NMR ($CDCl_3$) δ 1.44 (t, 3, J = 7 Hz, $-CH_2CH_3$), 4.40 (q, 2, J = 7 Hz, $-CH_2CH_3$), 6.92 (s, 1, vinyl proton), 7.54 (m, 8, aromatic protons); ir (KBr) 1740 cm^{-1} (α,β-unsaturated ketone). Anal. ($C_{18}H_{14}O_4$) C, H.

Ethyl 6-phenoxychromone-2-carboxylate (10) was prepared from diketo ester **20** (3.3 g, 0.01 mol) according to conditions identical with those employed in the synthesis of **9** from **19** affording 2.0 g (70%) of clear white needles: mp 108–109°; NMR ($CDCl_3$) δ 1.42 (t, 3, J = 7 Hz, ester methyl), 4.54 (q, 2, J = 7 Hz, ester methylene), 7.02–7.98 (m, 9, aromatic protons and vinyl proton). Anal. ($C_{18}H_{14}O_5$) C, H.

α-(p-Phenylphenoxy)-γ-butyrolactone (13). Sodium (2.8 g, 0.12 g-atom) was dissolved in absolute EtOH (60 ml) in a 250-ml

[&] Elemental analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer. Gas–liquid partition chromatography was performed using the F & M Scientific Model 402 gas chromatograph. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrophotometer. All melting points were taken with a calibrated Thomas-Hoover capillary melting point apparatus.

two-necked round-bottom flask fitted with a dropping funnel and condenser. To this stirring solution was added dropwise 21 g (0.12 mol) of *p*-phenylphenol (11) dissolved in absolute EtOH (50 ml). The resulting solution was cooled to room temperature in an ice bath and 20 g (0.12 mol) of α-bromo-γ-butyrolactone (12) was added dropwise to the stirring solution. The mixture was stirred for 10 hr at ambient temperature and then heated at reflux on a steam bath to neutrality. The solution was cooled, concentrated under reduced pressure, diluted with H_2O (100 ml), and extracted with Et_2O. The Et_2O layer was washed with 5% NaOH solution and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid residue was recrystallized from benzene–Skellysolve B affording 21.4 g (88%) of white crystals: mp 164.5–165°; NMR (Me_2SO-d_6) δ 2.05–2.90 (m, under solvent, $CHCH_2CH$), 4.35 (m, 2, CH_2CH_2O), 5.34 (t, 1, J = 8 Hz, lactone methine), 7.00–7.75 (m, 9, aromatic protons). Anal. ($C_{16}H_{14}O_3$) C, H.

α-(*p*-Phenylphenoxy)succinic Acid (14). To a solution of 5.0 g (0.02 mol) of lactone **13** in acetone (70 ml) was added with stirring and cooling (ice bath) 20 ml of Jones reagent (prepared with 4.0 g of CrO_3, 15 ml of H_2O, and 3 ml of concentrated H_2SO_4). After the addition was complete, the reaction was stirred for 1 hr in an ice bath and then for 24 hr at room temperature. The reaction mixture was diluted with H_2O (70 ml) and extracted with four portions of Et_2O (100 ml). The combined Et_2O extracts were washed with saturated NaCl solution and extracted with four portions of 10% $NaHCO_3$ solution (100 ml). The $NaHCO_3$ extracts were acidified with 10% HCl solution and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from Et_2O–benzene affording 1.8 g (32%) of white plates: mp 177–178°; NMR (Me_2CO-d_6) δ 3.06 (d, 2, J = 6 Hz, acid methylene), 5.20 (t, 1, J = 6 Hz, acid methine), 7.40 (m, 9, aromatic protons), 10.34 (s, 2, $2CO_2H$'s). Anal. ($C_{16}H_{14}O_5$) C, H.

2-Hydroxy-5-phenylacetophenone (16). A mixture of acetophenone **38** (3.0 g, 0.01 mol) and preequilibrated 10% Pd/C (0.5 g) in 40 ml of 95% EtOH was hydrogenated at room temperature under 35 psi for 2 hr. After 2 hr, hydrogen absorption ceased, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O (100 ml) and the Et_2O solution was extracted with 10% NaOH solution. The aqueous portion was reacidified with 10% HCl solution and extracted with two portions of Et_2O (100 ml). The combined Et_2O extracts were concentrated under reduced pressure and the residue was recrystallized from absolute EtOH affording 1.8 g (84%) of white needles, mp 60–61° (lit.[11] mp 61.5–62°). This compound was previously reported prepared by Fries rearrangement of ester **27** in $AlCl_3$ and tetrachloroethane (no yield was reported).[11]

2-Hydroxy-5-phenylacetophenone (16) by Direct Methylation of 30. To a well-stirred solution of crude 6-phenylsalicylic acid (**30**, 2.14 g, 0.01 mol) in 50 ml of 1,2-dimethoxyethane (distilled from $LiAlH_4$) under N_2 and maintained at 10–12° was added dropwise a solution of methyllithium in Et_2O [1.25 g (0.039 mol of MeLi) in 21.6 ml of Et_2O] over a 1-hr period. After the addition the reaction mixture was stirred for an additional 2 hr at ambient temperatures and the milky white suspension was slowly added to a vigorously stirred slurry of 400 g of ice containing 20 ml of concentrated HCl. The aqueous phase was extracted with two 100-ml portions of Et_2O and the combined Et_2O extracts were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oil was filtered through 75 g of silica gel packed in benzene in a 4.0-cm i.d. column and eluted with the same solvent. All fractions determined by TLC to be homogeneous were combined and concentrated affording 1.80 g (85%) of an oil which crystallized on standing (mp 58–60°) Recrystallization from absolute Et_2O afforded white needles, mp 60–61°

2-Hydroxy-5-phenoxyacetophenone (17). A mixture of the benzyloxyacetophenone **39** (3.2 g, 0.01 mol) and preequilibrated 10% Pd/C (0.5 g) in 40 ml of 95% EtOH was hydrogenated at room temperature at 35 psi for 2 hr. The mixture was filtered and concentrated under reduced pressure, and the residue was dissolved in Et_2O. The Et_2O solution was extracted with three portions of 10% NaOH solution. The combined aqueous layers were reacidified with 10% HCl solution and extracted with Et_2O. The Et_2O extract was concentrated under reduced pressure and the resulting residue was recrystallized from absolute isopropyl alcohol affording 2.0 g (85%) of white needles: mp 71–73°; NMR ($CDCl_3$) δ 2.52 (s, 3, methyl), 6.74–7.44 (m, 8, aromatic protons), 12.64 (s, 1, acid proton). Anal. ($C_{14}H_{12}O_3$) C, H.

2-Hydroxy-5-phenoxyacetophenone (17) by Direct Methylation of 31. Ketone **17** was obtained using 5-phenoxysalicylic acid (**31**, 2.30 g, 0.01 mol) under conditions identical with those employed for the synthesis of 2-hydroxy-5-phenylacetophenone by methylation with MeLi. The product (1.81 g, 79%) had mp 70–72°. Recrystallization from absolute isopropyl alcohol afforded white needles, mp 71–73°.

Ethyl 2,4-Dioxo-4-(2′-hydroxy-5′-phenylphenyl)butyrate (19). To a solution of Na (1.0 g, 0.04 g-atom), absolute EtOH (50 ml), and phenone **16** (4.2 g, 0.02 mol) was added diethyl oxalate (**18**, 6.0 g, 0.04 mol). The addition was kept at such a rate that refluxing did not become too vigorous. After the addition was complete, the orange solid residue was heated on a steam bath for 0.5 hr. The mixture was cooled and diluted with 50 ml of Et_2O and the solid precipitate was collected by filtration. The solid was added to 100 ml of 6% AcOH solution and extracted with two portions of Et_2O (50 ml). The combined Et_2O extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized from EtOH–H_2O affording 5.5 g (88%) of pale yellow plates: mp 108–110°; NMR at 10% w/v concentration ($CDCl_3$) δ 1.30 and 1.38 (pair of triplets, 3, J = 7 Hz for each triplet; methyl of ethyl ester appears as two triplets in a 3:1 ratio owing to the presence of three H-bonded keto-enol tautomers), 3.10 and 3.28 (pair of doublets, 1, J = 17 Hz for each doublet; geminally coupled nonequivalent protons at C-3; each doublet represents 0.5 protons found at C-3 in diketone tautomer), 4.30 and 4.38 (pair of quartets, 2, J = 7 Hz for each quartet; methylene group of ethyl ester appears as two quartets in 3:1 ratio owing to the presence of three H-bonded keto-enol tautomers), 5.30 (broad singlet, 0.5, enolic hydroxyl proton), 7.04–8.06 (m, 9, aromatic protons and phenolic proton), 8.08 and 8.13 (two singlets, 0.5, nonequivalent vinylic protons of two enol tautomers); ir ($CHCl_3$) 3500–3100 (broad, weak; intramolecularly hydrogen bonded phenol), 1760 (ester), 1700 (1,3-diketone), 1600 cm^{-1} (enol of 1,3-diketone). Anal. ($C_{18}H_{16}O_5$) C, H.

Ethyl 2,4-dioxo-4-(2′-hydroxy-5′-phenoxyphenyl)butyrate (20) was prepared from acetophenone **17** (4.6 g, 0.02 mol) according to the method used for the preparation of **19** from **16** affording 5.0 g (76%) of pale yellow needles from hexane–benzene: mp 92–93°; NMR at 10% w/v concentration ($CDCl_3$) δ 1.32 and 1.36 (pair of triplets, 3, J = 7 Hz for each triplet; methyl ester appears as two triplets in a 3:1 ratio owing to the presence of three H-bonded keto-enol tautomers), 3.05 and 3.23 (pair of doublets, 1, J = 17 Hz for each doublet, geminally coupled, nonequivalent protons found at C-3 in diketone tautomer), 4.33 and 4.37 (pair of quartets, 2, J = 7 Hz for each quartet, methylene of ethyl ester appears as two quartets in 3:1 ratio owing to the presence of three H-bonded keto-enol tautomers), 5.33 (very broad singlet, 0.5, enolic hydroxyl proton), 6.88–7.58 (m, 9.5 aromatic protons and phenolic proton), 8.10 and 8.14 (two singlets, 0.5, nonequivalent vinylic protons of two enol tautomers); ir ($CHCl_3$) 3500–3100 (broad, weak; intramolecularly hydrogen bonded phenol), 1760 (ester), 1700 (ketone), 1600 cm^{-1} (enol of 1,3-diketone). Anal. ($C_{18}H_{16}O_6$) C, H.

6-Phenylchromone-2-carboxylic Acid (21). This acid was prepared by the same procedure used for the preparation of ester **9** except that in the cyclization step a 4:1 ratio of AcOH to concentrated HCl was employed. The white solid obtained was recrystallized from AcOH affording acid **21**, mp 242–243° dec, in 85% yield based on starting **16**: NMR (DMF-d_6) δ 6.90 (s, 1, vinyl protons), 7.30–8.24 (m, 8, aromatic protons), 11.80 (broad singlet, 1, acid proton); ir (KBr) 1760 cm^{-1} (carboxylic acid). Anal. ($C_{16}H_{10}O_4$) C, H.

6-Phenoxychromone-2-carboxylic Acid (22). This acid was prepared by a procedure identical with the one used for the preparation of ester **10** except that in the cyclization step a 4:1 ratio of AcOH to concentrated HCl was used. The white needles obtained were recrystallized from AcOH affording 2.5 g (88%) based on starting **17** of pure white needles: mp 253–254° dec; NMR (Me_2SO-d_6) δ 7.02 (s, 1, vinyl proton), 7.30–8.02 (m, 8, aromatic protons), 11.92 (broad singlet, 1, acid proton). Anal. ($C_{16}H_{10}O_5$) C, H.

6-Cyclohexylchroman-2-carboxylic Acid (23). A mixture of chromone acid **21** (2.6 g, 0.01 mol) and preequilibrated 10% Pd/C (0.5 g) in 50 ml of AcOH was hydrogenated at 50 psi and 90 ± 5° for 5 hr. The pressure was reapplied whenever it dropped below 45 psi. The mixture was cooled, filtered, and concentrated under reduced pressure. The residue was dissolved in Et_2O and extracted with two portions of 10% Na HCO_3 solution. The aqueous layer was acidified with 10% HCl solution and extracted with two portions of Et_2O (50 ml). The combined Et_2O layers were dried

($MgSO_4$), filtered, and concentrated under reduced pressure. The crude acid was recrystallized from absolute EtOH–hexane affording 2.2 g (85%) of white needles: mp 168–169°; NMR ($CDCl_3$) δ 1.02–2.10 (m, 11, cyclohexyl protons), 2.34 (m, 2, methylene at C-3), 2.84 (m, 2, methylene at C-4), 4.72 (m, 1, methine at C-2), 12.00 (s, 1, acid proton). Anal. ($C_{16}H_{20}O_3$) C, H.

6-Phenylchroman-2-carboxylic Acid (24). A solution of chromone acid **21** (2.6 g, 0.01 mol) and preequilibrated 10% Pd/C (0.5 g) in 50 ml of AcOH was hydrogenated at 40 psi and 70 ± 5° for 2 hr. Pressure was reapplied whenever it dropped below 35 psi. The solution was cooled, filtered, and concentrated under reduced pressure. The residue was purified and crystallized according to the method described for compound **23** affording 2.0 g (80%) of white crystals: mp 198–199°; NMR ($CDCl_3$–Me_2SO-d_6) δ 2.22 (m, 2, methylene at C-3), 2.80 (m, 2, methylene at C-4), 4.78 (m, 1, methine), 6.90–7.72 (m, 8, aromatic protons), 12.00 (broad singlet, 1, acid proton). Anal. ($C_{16}H_{14}O_3$) C, H.

6-Phenoxychroman-2-carboxylic Acid (25). A solution of chromone acid **22** (1.4 g, 0.005 mol) and preequilibrated 10% Pd/C (0.5 g) in 50 ml of AcOH was hydrogenated at 70 ± 5° for 2 hr under a pressure of 40 psi. Pressure was reapplied whenever it dropped below 35 psi. The solution was cooled, filtered, and concentrated under reduced pressure. The residue was purified and crystallized according to the method described for compound **23** affording 0.9 g (69%) of white plates: mp 111–112°; NMR ($CDCl_3$) δ 2.24 (m, 2, methylene at C-3), 2.72 (m, 2, methylene at C-4), 4.80 (m, 1, methine), 6.64–7.58 (m, 8, aromatic protons), 11.00 (s, 1, acid proton). Anal. ($C_{16}H_{14}O_4$) C, H.

Ethyl 6-Cyclohexyloctahydrobenzopyran-2-carboxylate (26). A mixture of chromone ester **9** (1.5 g, 0.005 mol) and preequilibrated 10% Pd/C (0.2 g) in 50 ml of AcOH was hydrogenated at 50 psi and 90 ± 5° for 16 hr. Pressure was reapplied whenever it dropped below 35 psi. The mixture was filtered, concentrated under reduced pressure, and diluted with Et_2O. The Et_2O solution was washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was distilled affording 0.7 g (56%) of clear oil: bp 175–179° (0.2 mm); NMR ($CDCl_3$) δ 0.50–2.54 (m, 27, cyclohexyl methylenes and ester CH_3), 4.04 (m, 1, methine at C-2), 4.36 (q, 2, ester methylene); ir ($CHCl_3$) 1735 cm^{-1} (ester). Anal. ($C_{18}H_{30}O_3$) C, H.

4-Acetoxybiphenyl (27). Ester **27** was prepared in 94% yield by the method of Kaiser:[32] mp 87–88° (lit.[32] mp 87°).

4′-Acetyl-4-phenylphenol (28) and 2-Hydroxy-5-phenylacetophenone (16). To a solution of 10.5 g (0.05 mol) of **27** in 75 ml of nitrobenzene contained in a 250-ml round-bottom flask equipped with a drying tube was added, under N_2 atmosphere, 15 g (0.075 mol) of $TiCl_4$. After stirring for 18 hr at 20°, cold 2 *N* HCl solution (200 ml) and Et_2O (200 ml) were added and the layers separated. The Et_2O layer was reextracted with four portions of 5% NaOH solution (100 ml). The combined aqueous layers were acidified with 10% HCl solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. GLC analysis on 2.8% silicone gum rubber on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 200°, injection port temperature 280°, detector temperature 270°, inlet pressure 40 psi, and carrier gas (He) flow rate of 40 ml/min shows three peaks (5:50:45 ratio) with retention times for A = 3.5 min, B = 5.0 min, and C = 6.5 min. Peak A corresponds to acetophenone **16**, B to acetophenone **28**, and C to *p*-phenylphenol (**11**).

The Fries rearrangement products (**16** and **28**) were isolated from the mixture by adding 8.0 g (0.05 mol) of Girard reagent T in 10 ml of AcOH and 40 ml of 95% EtOH to 4.0 g of the reaction mixture. The solution was refluxed for 30 min, cooled, diluted with 100 ml of H_2O, and extracted with two portions of Et_2O (50 ml). The aqueous layer was treated with 8.0 ml of concentrated HCl and heated on a steam bath for 15 min. The solution was cooled, diluted with H_2O (50 ml), and extracted with three portions of Et_2O (50 ml). The combined Et_2O layers were concentrated under reduced pressure and the residue was analyzed by GLC under conditions identical with those reported above. The mixture was identified as known **28** and **16**. Fractional recrystallization utilizing benzene–Skellysolve B afforded 5.5 g (50%) of 4′-acetyl-4-phenylphenol (**28**), mp 205–206° (lit.[8] mp 205°), and 0.6 g (6%) of 2-hydroxy-5-phenylacetophenone (**16**), mp 60–62° (lit.[11] mp 61–62°).

4′-Acetyl-4-phenylphenol (28). A solution of 4-acetoxybiphenyl (**27**, 10.5 g, 0.05 mol) in dry tetrachloroethane (75 ml) was heated at 140° for 2 hr with finely powdered $AlCl_3$ (7.5 g, 0.05 mol) in a 250-ml round-bottom flask equipped with a condenser containing a drying tube. After cooling, 50 g of ice and 100 ml of 10% HCl solution were added and the solvent was removed under reduced pressure. The resulting residue was dissolved in $CHCl_3$ and extracted with 10% NaOH solution. The aqueous layer was acidified with 10% HCl solution and extracted with three portions of Et_2O (100 ml). The combined Et_2O extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording 6.4 g (61%) of transparent pale yellow crystals identified as **28**.

Cheetham and Hey[11] reported that under apparently identical conditions acetophenone **16** was obtained (no yield reported). GLC analysis of our reaction mixture showed only phenol **28** to be present.

5-Phenylsalicylic Acid (30). The method of Erlenmeyer and coworkers[13] was utilized in the preparation of **30**. *p*-Phenylphenol (**11**, 17.0 g, 0.1 mol) was finely ground with 50 g of anhydrous K_2CO_3. The mixture was added to a 300-ml stainless steel reaction bomb. The mixture was heated to 250° in the presence of CO_2 at 30 atm for 3 hr with periodical shaking. The bomb was cooled, flushed with CO_2, and reheated at 30 atm. After 5 hr, the bomb was cooled, the pressure released, and the contents dissolved in cold H_2O (500 ml). The H_2O solution was washed with Et_2O and acidified with 50% HCl solution. Upon acidification, the desired product precipitated and was removed from the aqueous layer by extraction into Et_2O. The Et_2O layer was washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized from AcOEt–Skellysolve B affording 19 g (90%) of the desired acid, mp 213–214° (lit. mp 215–216°,[33] mp 217–218°,[34] lit. mp 212.5–213.5°[35]).

5-Phenoxysalicylic Acid (31). *p*-Phenoxyphenol (**29**, 20.0 g, 0.11 mol) and 50 g of anhydrous K_2CO_3 were triturated and placed in a 300-ml stainless steel bomb. The bomb was pressurized with CO_2 gas to 450 psi prior to being heated for 24 hr and maintained at 130 ± 5°. After this time the contents of the cooled bomb was dissolved in 300 ml of H_2O and extracted with two 100-ml portions of Et_2O. The aqueous phase was acidified with concentrated HCl solution precipitating the desired acid which was collected by filtration affording 23.8 g (97%) of crude acid, mp 127–129°. Recrystallization from ethyl acetate–hexane afforded white crystals, mp 128–129° (lit.[36] mp 134°). Anal. ($C_{13}H_{10}O_4$) C, H.

Ethyl 5-Phenylsalicylate (32). Acid **30** (5.35 g, 0.025 mol) dissolved in absolute EtOH (100 ml) containing toluene (30 ml) and concentrated H_2SO_4 (2 ml) was refluxed for 6 hr while H_2O was periodically removed through the use of a Dean-Stark trap. After 6 hr, the solvent was removed under reduced pressure and the resultant residue was dissolved in Et_2O. The Et_2O layer was washed with 10% $NaHCO_3$ solution and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from absolute EtOH affording 4.8 g (80%) of pale yellow transparent needles: mp 50–51° (lit.[34] mp 49°); NMR ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, CH_2CH_3), 4.34 (q, 2, J = 7 Hz, $-CH_2CH_3$), 7.36 (m, 8, aromatic protons), 10.80 (s, 1, -OH). Anal. ($C_{15}H_{14}O_3$) C, H.

Ethyl 5-Phenoxysalicylate (33). Acid **31** (23.0 g, 0.1 mol) was dissolved in a mixture of absolute EtOH (200 ml), toluene (60 ml), and concentrated H_2SO_4 (5 ml). The mixture was refluxed for 24 hr with periodic removal of H_2O by use of a Dean-Stark trap. The mixture was cooled, concentrated under reduced pressure, and diluted with Et_2O. The Et_2O solution was washed with 10% $NaHCO_3$ solution and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized from AcOEt–petroleum ether to yield 21 g (90%) of white plates: mp 53–54°; NMR ($CDCl_3$) δ 1.42 (t, 3, J = 7 Hz, ester methyl), 4.44 (q, 2, J = 7 Hz, ester methylene), 6.90–7.70 (m, 8, aromatic protons), 10.44 (broad singlet, 1, phenolic proton); ir (Nujol) 1690 (ester), 3200 cm^{-1} (phenol). Anal. ($C_{15}H_{14}O_4$) C, H.

Ethyl 2-Benzyloxy-5-phenylbenzoate (34). Salicylate **32** (25.0 g, 0.1 mol) was dissolved in 500 ml of acetone (previously purified by refluxing in $KMnO_4$, followed by distillation and filtration through anhydrous $MgSO_4$). K_2CO_3 (20.0 g, 0.15 mol) was added in small portions to the stirring mixture which subsequently was refluxed during dropwise addition of benzyl chloride (16.0 g, 0.11 mol). After the addition, the solution was refluxed for 15 hr, cooled, diluted with H_2O (500 ml), and extracted with three portions of Et_2O (100 ml). The combined Et_2O extracts were washed with 10% NaOH solution, dried ($MgSO_4$), and filtered. The solvent was concentrated under reduced pressure and the excess benzyl chloride was removed by distillation [55° (0.1 mm)]. The resultant residue was crystallized from absolute EtOH affording 26 g (81%) of white crystals: mp 81–82°; NMR ($CDCl_3$) δ 1.32 (t, 3, J = 7 Hz, CH_2CH_3), 4.34 (q, 2, J = 7 Hz, CH_2CH_3), 4.94 (s, 2, OCH_2Ph), 7.20 (m, 13, aromatic protons). Anal. ($C_{22}H_{20}O_3$) C, H.

Ethyl 2-benzyloxy-5-phenoxybenzoate (35) was prepared

from salicylate **33** (5.0 g, 0.02 mol) in 100 ml of acetone and K_2CO_3 (5.0 g, 0.03 mol) according to the preparation of **34**. The mixture was gently refluxed while benzyl chloride (4.0 g, 0.03 mol) was added dropwise. After the addition, the solution was refluxed for 5 hr and the compound was isolated by methods identical with those used in the preparation of **34** affording 4.9 g (70%) of white plates from AcOEt–hexane: mp 61–62°; NMR ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, ester methyl), 4.34 (q, 2, J = 7 Hz, ester methylene), 5.10 (s, 2, benzylic protons), 6.88–7.64 (m, 13, aromatic protons). Anal. ($C_{22}H_{20}O_4$) C, H.

2-Benzyloxy-5-phenylbenzoic Acid (36). Ester **34** (9.97 g, 0.03 mol) was added to 200 ml of 10% alcoholic KOH solution and refluxed for 3 hr. H_2O (50 ml) was added and the mixture was refluxed for an additional 2 hr, cooled, and washed with Et_2O (50 ml). The aqueous layer was acidified with 10% aqueous HCl solution and extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from absolute EtOH affording 6.8 g (75%) of white crystalline powder: mp 138–138.5°; NMR ($CDCl_3$) δ 4.90 (s, 2, OCH_2Ph), 6.94–8.50 (m, 13, aromatic protons), 11.54 (s, 1, acid proton). Anal. ($C_{20}H_{12}O_3$) C, H.

2-Benzyloxy-5-phenoxybenzoic Acid (37). Ester **35** (3.5 g, 0.01 mol) was added to 50 ml of 10% alcoholic KOH solution and mildly refluxed for 2 hr. H_2O (50 ml) was added and the solution was refluxed for an additional 2 hr. The mixture was cooled, diluted with 50 ml of H_2O, and washed with Et_2O. The aqueous layer was acidified with 10% aqueous HCl solution and extracted with two portions of Et_2O (50 ml). The combined Et_2O extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from Et_2O–AcOEt affording 2.9 g (90%) of white crystals: mp 108–109°; NMR ($CDCl_3$) δ 5.24 (s, 2 benzylic protons), 6.80–7.84 (m, 13, aromatic protons), 10.84 (broad singlet, 1, acid proton). Anal. ($C_{20}H_{16}O_4$) C, H.

2-Benzyloxy-5-phenylacetophenone (38). Acid **36** (6.0 g, 0.02 mol) was dissolved in 50 ml of anhydrous Et_2O (previously dried and purified by refluxing with $LiAlH_4$ followed by distillation) and 27.2 ml of 2.2 M MeLi–Et_2O solution (0.06 mol) was added dropwise to the stirred solution under N_2 atmosphere. After CH_4 evolution, the reaction mixture was refluxed for 2 hr, cooled, poured over ice (100 g) containing 20 ml of 5% HCl solution, washed with saturated NaCl solution and 10% $NaHCO_3$ solution, and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure and the residue was crystallized from absolute EtOH affording 4.8 g (76%) of white plates: mp 80–81° (lit.[37] mp 136–137.5°**); NMR ($CDCl_3$) δ 2.60 (s, 3, CH_3), 5.04 (s, 2, $-OCH_2Ph$), 7.46 (m, 13, aromatic protons); ir (KBr) 1675 cm^{-1} (benzylic ketone). Anal. ($C_{21}H_{18}O_2$) C, H.

2-Benzyloxy-5-phenoxyacetophenone (39). Acid **37** (3.2 g, 0.01 mol) was dissolved in 50 ml of Et_2O (previously dried by refluxing with $LiAlH_4$ followed by distillation) and 27.2 ml of 2.2 M MeLi–Et_2O solution (0.06 mol) was added dropwise to the stirred solution under N_2 atmosphere. After evolution of CH_4, the reaction mixture was gently refluxed for 3 hr, cooled, poured over ice (50 g) containing 20 ml of 5% HCl solution, washed with saturated NaCl solution and 10% $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was distilled affording 2.6 g (80%) of colorless oil: bp 164–166° (0.1 mm); NMR ($CDCl_3$) δ 2.54 (s, 3, methyl), 5.02 (s, 2, benzylic methylene), 6.74–7.58 (m, 13, aromatic protons). Anal. ($C_{21}H_{18}O_3$) C, H.

Ethyl 2,4-Dioxo-4-(2′-benzyloxy-5′-phenylphenyl)butyrate (40). To a solution of Na (1.0 g, 0.04 g-atom) in absolute EtOH (20 ml) was added 3.0 g (0.02 mol) of diethyl oxalate (**18**) and 3.0 g (0.01 mol) of benzyl ether **38**. Refluxing was controlled by slow addition. After refluxing for 0.5 hr, the mixture was cooled, diluted with H_2O (50 ml), and extracted with three portions of $CHCl_3$ (50 ml). The combined $CHCl_3$ extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from $CHCl_3$–Skellysolve B affording 5.8 g (90%) of yellow plates: mp 110–111°; NMR (CCl_4) δ 1.24 (t, 3, J = 7 Hz, CH_2CH_3), 4.22 (q, 2, J = 7 Hz, $-CH_2CH_3$), 5.10 (s, 2, OCH_2Ph), 7.48 (m, 15, aromatic and $-COCH_2$ protons); ir (KBr) 1738 cm^{-1} (ketone). Anal. ($C_{25}H_{22}O_5$) C, H.

Biological Aspects. Compounds were tested in a hyperlipidemic rat model[16] in which the hyperlipidemia was induced by ip injection of Triton WR-1339 (oxyethylated *tert*-octylphenol formaldehyde polymer, Ruger Chemical Co., Philadelphia, Pa.). Male albino rats (Sprague–Dawley) were housed in groups of five and fed Purina laboratory chow and water ad libitum for a 2-week stabilizing period. After this period, the rats were redistributed by weight into four experimental groups of ten rats each. Two hyperlipidemic groups (III and IV) were fasted for 24 hr and then injected with 225 mg of Triton per kilogram of body weight dissolved in 0.15 M NaCl solution to give a concentration of 62.5 mg/ml. The two normal groups (I and II) of comparable weight were also fasted and received only 2 ml of saline vehicle. Groups II and IV received test compounds in vehicle (0.25% aqueous methyl cellulose) while groups I and III received vehicle only. Compounds were dispersed in vehicle to obtain a concentration of 8.33×10^{-3} mmol/ml. A total screening dose of 0.124 mmol/kg was administered to 270 ± 10 g rats.[§] Each rat received two 2-ml doses by gastric intubation, the first immediately after the Triton injection and the second 20 hr later. Fasting was continued during the post-Triton period.

At 43 hr after Triton administration, the rats were anesthetized with ethyl ether; blood was drawn from the abdominal aorta and serum was obtained after centrifugation of the clotted blood at 500g for 10 min. Plasma triglyceride was determined by the method of Eggstein;[38] plasma cholesterol was previously analyzed[2] by the method of Parekh and Jung,[39] but for new analogs reported in this article, the method of Holub and Galli[40] was employed. Significant differences in plasma cholesterol and triglyceride concentrations between drug-treated and control groups were determined by Student's t tests on logarithms of individual data to allow the pooling of variances or were determined by the nonparametric rank–sum test.

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** In the patent literature (ref 36) compound **38** was reported prepared from **16** and benzyl chloride. Compound **16** was reported[36] to have been prepared by Fries rearrangement of **27**. Owing to the differences in melting point which we observed for **38** (80–81° vs. 136–137.5°) we speculate the authors of ref 36 really synthesized a mixture of benzyl ethers. We have observed that the melting point for the benzyl ether of **28** is 166–168°

§ This dosage in millimoles per kilogram for all analogs is equivalent to a clofibrate dosage of 30 mg/kg. The number 0.30 mg/kg found in ref 2 should read 30 mg/kg.

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Notes

1-[[(5-Nitrofuranyl)methylene]amino]-4- and/or -5-substituted 2-Imidazolidinones[1]

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A series of 1-[[(5-nitrofuranyl)methylene]amino]-4- and/or -5-substituted 2-imidazolidinones was prepared utilizing three different reaction sequences. The structure of **4**, the product derived from 4-methyl-2-imidazolidinone (**2a**), was verified by synthesis using an alternate, unequivocal route. The levo isomer *l*-**4** was prepared by a series of reactions starting with L(+)-2-amino-1-propanol (*l*-**10**). All of the nitrofurans were examined for potential use as chemotherapeutic agents for urinary tract infections. Based on the high level of activity in the urine and the in vitro antibacterial activity (MIC), **4**, *l*-**4**, and **16** are considered to be the most active as urinary tract agents.

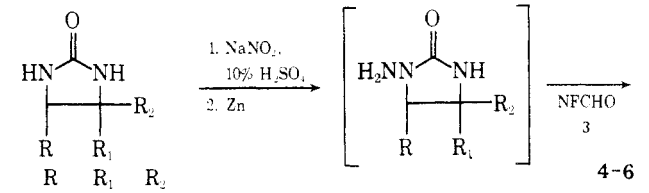
The activity of nifuradene (**1**)[2] (see Table I) as a possible chemotherapeutic agent for urinary tract infections[3] led to the synthesis of a series of N-substituted homologs of **1**.[4] The preparation of homologs of **1** has been expanded to include compounds having substitution on the 2-imidazolidinone ring carbons, e.g., positions 4 and/or 5 of **1**. This paper describes the synthesis, structure determination, and biologic activity of these compounds.

Chemistry. The appropriately substituted 2-imidazolidinones **2** (**a**,[5] **b**,[6] **c**[7]) were nitrosated, reduced, and condensed with 5-nitro-2-furaldehyde (**3**) as previously described[4] to yield **4**, **5**, and **6**, respectively (see Scheme I and Table I). The use of hexahydro-2-benzimidazolinone (**7**)[8] in the place of **2** produced hexahydro-1-[[(5-nitrofuranyl)-methylene]amino]-2-benzimidazolinone (**8**).

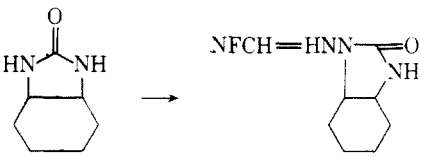
Although the reactions proceeded smoothly, the position of the methyl group(s) in **4** and **5** was questionable. This uncertainty arises from the choice of two nitrogens for the position of nitrosation. Thus, for example, when **2a** was nitrosated, attack at the 1 position would ultimately yield **4** and attack at position 3 would lead to **15**. Therefore, it was necessary to establish unequivocally the position of the methyl group in **4**. The unambiguous synthesis of **4** was carried out as shown in Scheme II. Benzaldehyde semicarbazone (**9**) was heated with 2-amino-1-propanol (**10a**) in 2-ethoxyethanol to yield benzaldehyde 4-(2-hydroxypropyl)semicarbazone (**11a**). The treatment of **11a** with $SOCl_2$ resulted in a water-soluble hydrochloride which was assigned the structure **12a** on the basis of previous work involving the chlorination of 5-nitro-2-furaldehyde 2-(2-hydroxyalkyl)semicarbazones with $SOCl_2$.[9] When **12a** was heated in an inert solvent, rearrangement occurred to yield benzaldehyde 4-(2-chloropropyl)semicarbazone (**13a**). Cyclization of **13a** was achieved in DMF using NaH as the condensing agent to give 1-benzylideneamino-4-methyl-2-imidazolidinone (**14a**). The acid hydrolysis of **14a** in the presence of **3** produced **4**. The two compounds were identical in all respects, e.g., mixture melting point and ir and NMR spectra.

In a similar manner the use of L(+)-2-amino-1-propanol (*l*-**10**) resulted in the synthesis of *l*-**4**, the L(−) isomer of **4**. That the integrity of the asymmetric center was maintained was evidenced by the optical activity of the intermediates *l*-**11**–*l*-**14**. By the utilization of **10b,c**, compounds **15**

Scheme I



	R	R_1	R_2
2a	H	CH_3	H
2b	H	CH_3	CH_3
2c	CH_3	CH_3	H



7 8

NF = O_2N–