ibid., 1350 (1969); (d) ibid., 19 (8a), HB 419 (1969).
(6) W. A. Hartung, et al., J. Amer. Chem. Soc., 53, 1875 (1931).
(7) W. R. Brode and M. S. Raasch, J. Amer. Chem. Soc., 64, 1449 (1942).
(8) Y. Sugi and S. Mitsui, Bull. Chem. Soc. Jap., 43, 564 (1970).
(9) G.-A. Hoyer, D. Rosenberg, C. Rufer, and A. Seeger, Tetrahedron Lett., 985 (1972).
(10) A. McCoubrey and D. W. Mathieson, J. Chem. Soc., 696 (1949).
(11) E. Miller, et al., J. Amer. Chem. Soc., 62, 2101 (1940).
(12) K. Petterson, Ark. Kemi, 10, 283 (1956).
(13) A. Huggett and D. A. Nixon, Lancet, 368 (1957).
(14) E. Weber, "Grundriss der biologischen Statistik," Gustav Fischer Verlag, Stuttgart, 1967.

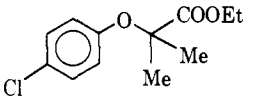
Hypolipidemic Substituted 1,3-Benzodioxole-2-carboxylates

J. Martin Grisar,* George P. Claxton, Roger A. Parker, Frank P. Palopoli, and Takashi Kariya

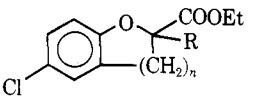
Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. *Received December 10, 1973*

Ethyl 5-(4-fluoro-α,α-dimethylbenzyl)-1,3-benzodioxole-2-carboxylate (11, RMI 14,676) was found to be a potent hypolipidemic agent, while ethyl 5-(1-phenyl-1-cyclopentyl)-1,3-benzodioxole-2-carboxylate (19, RMI 14,654), although less potent, was found to show only minimal hepatomegaly in young rats. The two compounds were selected from a series of substituted 1,3-benzodioxole-2-carboxylates and represent a novel type of cyclic analog of clofibrate with structural relationship also to treloxinate. Particular emphasis was given to attempt separation of hypolipidemic activity from hepatomegaly by minor structural modification.

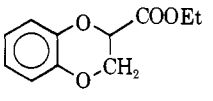
A number of investigations have been concerned with synthesizing and evaluating cyclic analogs of the hypolipidemic agent clofibrate [ethyl 2-methyl-2-(4-chlorophenoxy)propionate, I]. Thus, Witiak and coworkers[1-4] synthesized ethyl 6-chlorochroman-2-carboxylates II and III, 5-chloro-2,3-dihydro-2-benzofurancarboxylate IV, and 1,4-benzodioxane-2-carboxylate V. They found that II, IV, and V reduced serum cholesterol and triglycerides in Triton-induced hyperlipemic rats.[4] From our laboratories[5] we reported evaluation of hypolipidemic activity in rats of compounds VI and VII of which 5-chloroindole-2-carboxylic acid VII was found to be twice as potent as I in lowering serum cholesterol. We now wish to report on a series of substituted 1,3-benzodioxole-2-carboxylates VIII. These compounds, in addition to their structural relationship to clofibrate I, also share with 1-methyl-4-piperidyl 2,2-bis(*p*-chlorophenoxy)acetate (lifibrate, IX)[6] and methyl 2,10-dichloro-12*H*-dibenzo[*d,g*][1,3]dioxocin-6-carboxylate



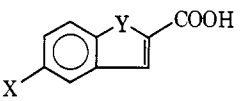
I



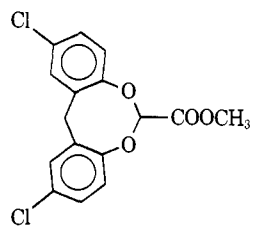
II, R = H; n = 2
III, R = CH_3; n = 2
IV, R = H; n = 1



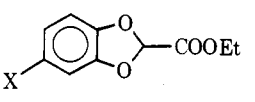
V



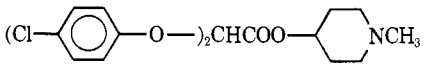
VI, Y = O, S; X = H
VII, Y = NH; X = Cl



X



VIII



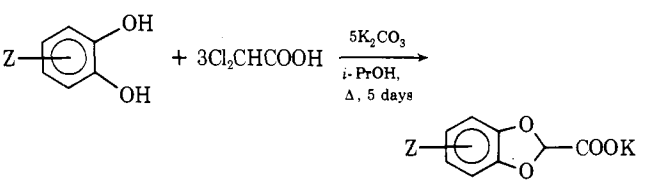
IX

(treloxinate, X)[7] the property of containing an α,α-dioxyacetate moiety, which may be responsible for some of the advantages that these agents possess over clofibrate.[8]

Clofibrate and treloxinate cause liver hypertrophy in young rats. This phenomenon has been studied extensively with hepatotoxins, enzyme inducers and other chemicals in general, and with clofibrate and clofibrate analogs in particular.[9-15] Goldberg[9] advanced the hypothesis that in certain instances, liver enlargement should be considered as an adaptive, functional response of the liver to an increased work load. On the other hand, it is well known that many agents cause liver hypertrophy without affecting serum lipids, while others lower serum cholesterol and triglycerides without causing hepatomegaly.[15] It therefore seemed reasonable to hypothesize that hypolipidemia and hepatomegaly are two separate pharmacological responses to clofibrate-like agents and that it might be possible to separate these two properties by structural modification. Since 1,3-benzodioxole-2-carboxylates showed good hypolipidemic properties, we set out to study this possibility.

Chemistry. Preparation of the parent compound, ethyl 1,3-benzodioxole-2-carboxylate,[16-18] and its 5-chloro derivative[18,19] has been reported in low yields. We now have developed a preparative method, analogous to that employed for preparation of 12*H*-dibenzo[*d,g*][1,3]-dioxocin-6-carboxylate derivatives,[7] shown in Scheme I. Yields of up to 71% of pure substituted 1,3-benzodioxole-2-carboxylates were obtained, as shown in Table I. Examples are given in the Experimental Section.

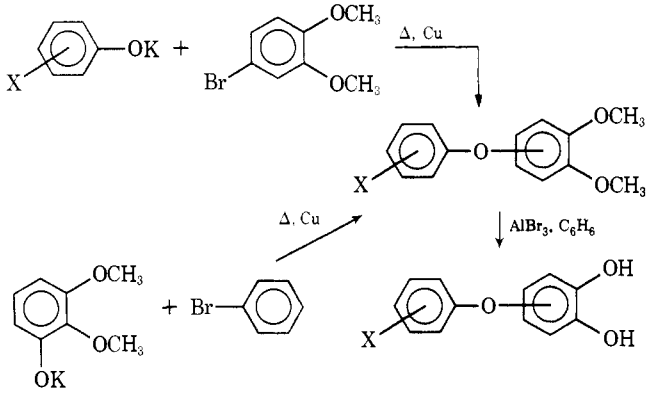
Scheme I



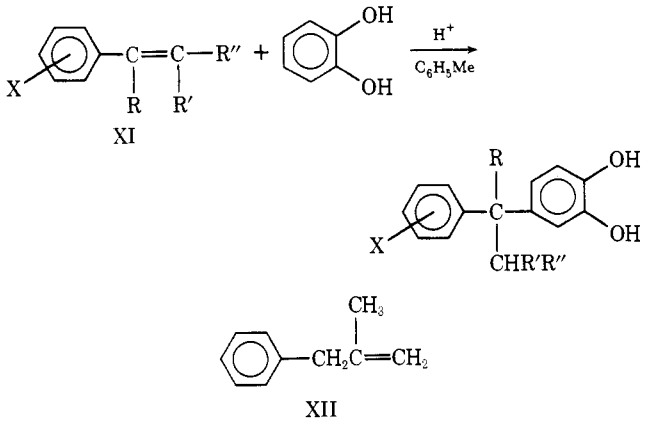
The substituted 1,2-benzenediols required were synthesized by known methods and are listed in Table II. The phenoxy-substituted 1,2-benzenediols **22-27** were prepared by Ullmann reaction, followed by ether cleavage as shown in Scheme II, by a procedure described by Mayer and coworkers.[20] The phenylalkyl-, phenylcycloalkyl-, and in-

danyl-substituted 1,2-benzenediols **28–40** were prepared by H_2SO_4-catalyzed Friedel-Crafts reaction in refluxing toluene (Scheme III) by the procedure described by Buu-Hoi and coworkers.[21] Yields are given in Table II. Reaction of 1,2-benzenediol with either 2-methyl-1-phenyl-1-propene (XI, X, R = H; R′, R″ = Me) or 2-methyl-3-phenyl-1-propene (XII) gave a 1:1 mixture of the two possible addition products **35** and **36** that cocrystallized, as described in the Experimental Section.

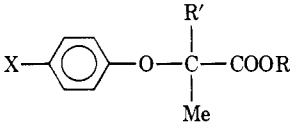
Scheme II



Scheme III



Biological Evaluation. Compounds **1–21** were evaluated for their effects on plasma lipids and liver and body weight changes after four consecutive daily administrations by admixture to the diet of young rats of the Wistar strain. The results, along with data for clofibrate, are listed in the last four columns of Table I. The direct clofibrate analog **1** was inactive. The phenyl-substituted analog **2** was active but the effect did not increase with the dose; the corresponding clofibrate analogs, especially methyl 2-methyl-2-(4-phenylphenoxy)propionate (methyl clofenapate, XIII), are reported to be very potent.[22] Of the



XIII, R, R′ = Me; X = $-C_6H_4$-*p*-Cl
XIV, R, R′ = H; X = $-OC_6H_4$-*p*-Cl
XV, R = H, R′ = Me; X = $-C(Me)_2C_6H_5$

phenoxy-substituted analogs, only **3, 5,** and **8** were active at high doses and the latter two severely affected body weight indicating probable toxicity. The clofibrate analog XIV (HCG 004) corresponding to **5** has been reported to be much more potent than clofibrate.[23]

It is apparent from these results that the structural changes that lead to increased potency in the clofibrate series do not have this effect in the present series of 1,3-benzodioxole-2-carboxylates. An exception was compound **9** that is analogous to 2-methyl-2-[(α-phenyl-*p*-cumenyl)-oxy]propionic acid (XV, Su-13,314 or ICI 53,072),[11,24] another highly potent clofibrate analog. Since **9** was found to be very active, a number of structural analogs (**10–21**) were prepared. Three of these (**9, 10,** and **18**), although very potent, showed signs of toxicity. Compound **11** (RMI 14,676) emerged as the most potent compound of this series.

Of the compounds investigated, only three showed hypolipidemic effects without causing liver hypertrophy; these were compounds **2, 12,** and **19**. These compounds, however, were less potent and failed to show increased hypolipidemic effect at higher doses. The desired separation of hypolipidemia and hepatomegaly was therefore achieved only at the expense of efficacy. Compound **19** (RMI 14,654) was selected from this group for extended biological evaluation. We concluded from the findings here reported that neither **11** nor **19** showed sufficiently convincing distinction over clofibrate to warrant clinical evaluation at this time.

Experimental Section

Melting points are corrected and were taken on a Thomas-Hoover capillary melting point apparatus; boiling points are uncorrected. Ir spectra were taken on a Perkin-Elmer 521 instrument. Uv spectra were taken on a Cary 17 instrument. Nmr spectra were taken on a Varian Model A-60 instrument (Me_4Si as internal standard). A Barber-Colman series 5000 gas chromatograph equipped with flame ionization detector was used for gc. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4%.

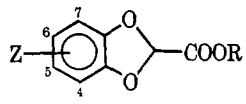
Methyl 5-Phenyl-1,3-benzodioxole-2-carboxylate (2). To a mixture of 100.0 g (0.537 mol) of 4-phenyl-1,2-benzenediol, 298.0 g (2.160 mol) of K_2CO_3, and 1.41 l. of *n*-PrOH was added 69.5 g (0.537 mol) of $Cl_2CHCOOH$ and the mixture was stirred at reflux temperature for 24 hr. An additional 69.5 g (0.537 mol) of $Cl_2CHCOOH$ was added dropwise over 4 hr and stirring at reflux temperature was continued for a total of 4 days. *n*-PrOH was boiled off while 1.5 l. of H_2O was added gradually. The precipitate that resulted on cooling was collected, washed by suspension in 1 l. of 0.2 *N* KOH, and resuspended and heated in 1 l. of H_2O that contained sufficient 2 *N* HCl to obtain a pH of 2. The resulting free acid was extracted with Et_2O–EtOH, the extract was washed (H_2O) and dried (Na_2SO_4), and the residue was recrystallized from toluene to give 92.0 g (71%) of 5-phenyl-1,3-benzodioxole-2-carboxylic acid, mp 162–163° dec. *Anal.* ($C_{14}H_{10}O_4$) C, H.

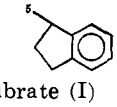
A portion of the acid was treated with MeOH and concentrated H_2SO_4 to give the methyl ester **2** (Table I): uv λ max (MeOH) 284 nm (ε 7900), 259 (11,000); ir (KBr) 1780 cm^{-1}; nmr ($CDCl_3$) δ 3.77 (s, 3), 6.31 (s, 1), 6.7–7.5 (m, 8).

Methyl 4-Phenoxy-1,3-benzodioxole-2-carboxylate (4). To 49.0 g (0.32 mol) of 2,3-dimethoxyphenol was added 22.3 g (0.32 mol) of KOMe and 100 ml of MeOH. After the reaction had subsided, the solvent was evaporated and the residue was dried at 140° and 0.5 mm overnight. The resulting solid was scraped out of the flask and 30 g of copper bronze ("Venus" brand) was added and mixed thoroughly in a mortar. Then 39.3 g (0.25 mol) of BrC_6H_5 was added; the mixture was ground into a paste, transferred to a flask, and heated slowly to 190–200°. After 4 hr at that temperature, the mixture was allowed to cool, 2 *N* KOH was added, the product was extracted into ether, the extract was washed (2 *N* KOH, saturated NaCl solution) and dried (Na_2SO_4), and the solvent was evaporated. The residue was vacuum distilled and 3-phenoxyveratrole, bp 128–138° (0.05 mm), 18.8 g (0.082 mol), was collected. This material was treated with 44.7 g (0.164 mol) of $AlBr_3$ in 200 ml of refluxing C_6H_6 for 4 hr, the mixture was poured into concentrated HCl–ice (1:1), the C_6H_6 layer was separated, washed with saturated NaCl solution, and dried (Na_2SO_4), and 15.1 g (91%) of **23** was obtained. Recrystallization from cyclohexane raised the melting point by 1° (Table II).

A mixture of 14.0 g (69 mmol) of **23**, 38.2 g (297 mmol) of K_2CO_3, and 8.9 g (69 mmol) of $Cl_2CHCOOH$ in 200 ml of *n*-PrOH

Table I. Effect of Benzodioxole-2-carboxylates on Plasma Lipids and Liver Weight in Wistar Rats



No.	Z	R	Mp[a] or bp (mm), °C	Yield,[b] %	Formula[c]	Plasma lipids, rats[d] Dose,[e] mg/kg	% redn vs. control: Cholesterol	% redn vs. control: Triglycerides	Rel liver wt,[d] % increase vs. control
1	5-Cl	H	137–139 dec[f]	19	$C_8H_5ClO_4$	252	10[g]	0	0
						170	16[h]	3[g]	0
2	5-C_6H_5	Me	43–47[i]	71[j]	$C_{15}H_{12}O_4$	145	24[h]	11[g]	
						137	18[h]	22[g]	4
						48	20[h]	37[h]	
3	5-OC_6H_5	Me	148–159 (0.02)	(76)[j]	$C_{15}H_{12}O_5$	257	30[h]	54[h]	42
4	4-OC_6H_5	Me	77–79[i]	63	$C_{15}H_{12}O_5$	301	7[g]	59[h]	16
5	5-OC_6H_4-*p*-Cl	Me	183–193 (0.05)	(28)	$C_{15}H_{11}ClO_5$	108[k]	21[h]	73[h]	76
6	5-OC_6H_4-*m*-CF_3	Me	157–164 (0.04)	30	$C_{16}H_{11}F_3O_5$	62[k,l]	0[m]	50[h]	27
						37[k,l]	0[m]	75[h]	28
7	5-OC_6H_4-*p*-Et	Et	194–199 (0.09)	34	$C_{18}H_{18}O_5$	255	6[g]	70[h]	32
8	5-OC_6H_4-*o*-Me	Me	162–165 (0.03)	(63)[j]	$C_{16}H_{14}O_5$[n]	193[k]	28[h]	66[h]	21
9	5-$C(Me)_2C_6H_5$	Na	251–253 dec[o]	(81)[j]	$C_{17}H_{15}NaO_4$	167[k]	37[h]	69[h]	25
						28[k]	43[h]	72[h]	32
10	5-$C(Me)_2C_6H_4$-*p*-Cl	Et	199–203 (0.06)	(83)[j]	$C_{19}H_{19}ClO_4$	69[k,l]	54[h]	91[h]	55
						40[k,l]	41[h]	93[h]	54
11	5-$C(Me)_2C_6H_4$-*p*-F	Et	181–187 (0.30)	45	$C_{19}H_{19}FO_4$	57	41[h]	81[h]	38
						44	41[h]	71[h]	38
						24	30[h]	52[h]	23
						11	13[g]	31[g]	7
						6	0	14[g]	3
12	5-$C(Me)_2C_6H_4$-*p*-Me	Et	189–195 (0.04)	56	$C_{20}H_{22}O_4$	226	19[h]	23[g]	6
13	5-$CH(Me)C_6H_3$-*o*,*p*-Me_2	Et	184–193 (0.02)	(98)[j]	$C_{20}H_{22}O_4$	226	21[h]	56[h]	26
14	5-$CH(Me)C_6H_5$	Et	183–187 (0.28)	50	$C_{18}H_{18}O_4$	148	30[h]	77[h]	51
15	5-$CH(Bu)C_6H_5$	Et	184–199 (0.35)	59	$C_{21}H_{24}O_4$	108	18[h]	72[h]	37
16	5-$CH(i\text{-}Pr)C_6H_5$	Et	178–186 (0.15)	57[p]	$C_{20}H_{22}O_4$	279	28[h]	74[h]	30
17	5-$C(Me)_2CH_2C_6H_5$	Et							
18	5-$C(Et)_2C_6H_5$	Et	186–194 (0.22)	61	$C_{21}H_{24}O_4$	180[k]	23[h]	81[h]	23
19		Et	204–208 (0.16)	(42)	$C_{21}H_{22}O_4$	368	27[h]	59[h]	15
						265	23[h]	55[h]	11
						191	17[h]	48[h]	7
						105	25[h]	27[h]	6
20		Et	211–216 (0.04)	49	$C_{22}H_{24}O_4$	223	21[g]	62[h]	25
21		Et	201–208 (0.25)	61	$C_{19}H_{18}O_4$	262	39[h]	78[h]	40
Clofibrate (I)						29	9[g]	30	0
						74	18[g]	48[h]	2
						186	36[h]	66[h]	22
						411	41[h]	78[h]	50

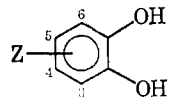
[a]Melting points are corrected and were taken on a Hoover capillary melting point apparatus. Boiling points are uncorrected. [b]Yields refer to purified compound unless otherwise indicated by parentheses. [c]All compounds were analyzed for C, H, and Cl when present. Analytical results obtained for these elements were within ±0.4% of calculated values unless otherwise indicated. [d]Young male rats of the Wistar strain obtained from Royalheart Laboratory Animals, Inc., New Hampton, N. Y., of average initial weight of 170–190 g, treated in groups of six animals for 4 days and compared to an untreated control group. Plasma cholesterol and triglycerides were determined by automated procedures as described in the Experimental Section. Liver wet weight was determined, calculated as g/100 g of final body weight, and compared with values from the control group. [e]Daily dose administered by admixture to food. Actual dose calculated from food consumption. [f]Reference 19 gives mp 132–133°. [g]Statistically nonsignificant at $p > 0.05$. [h]Statistically significant at $p < 0.05$. [i]Recrystallized from MeOH. [j]Yield of acid. [k]Compound caused severe decrease of body weight gain. [l]Bilirubin was determined in plasma of treated animals. [m]Hypercholesterolemic. [n]*Anal.* Calcd: C, 67.12; H, 4.93. Found: C, 67.73; H, 5.06. [o]Recrystallized from EtOH–H_2O. [p]A mixture of *ca.* 1:1 of compounds **16** and **17**.

was stirred at reflux temperature for 24 hr, an additional 8.9 g (69 mmol) of $Cl_2CHCOOH$ was added, and stirring at reflux temperature was continued for a total of 4 days. PrOH was removed by distillation while H_2O was added and the mixture was allowed to cool. The resulting precipitate of K salt was collected and dried at 60° overnight: 20.5 g; mp 138–142° dec; ir (KBr) 1630 cm^{-1}. The salt was treated with 10.9 g of MeI in 200 ml of dry DMF for 16 hr at room temperature, the mixture was poured into H_2O, and the product was extracted into Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4) and the residue after evaporation of solvent was recrystallized twice from MeOH to give 11.9 g (63%) of 4 (Table I): uv (95% EtOH) 275 nm (ε 2500), 269 (2590); ir (KBr) 1770 cm^{-1}; nmr ($CDCl_3$) δ 3.82 (s, 3), 6.36 (s, 1), 6.5–7.5 (m, 8).

Methyl 5-(4-Chlorophenoxy)-1,3-benzodioxole-2-carboxylate (5). A solution of 90.0 g (0.70 mol) of *p*-chlorophenol and 49.0 g (0.70 mol) of KOMe in MeOH was evaporated to dryness and the residue was dried at 120–140° at 0.5 mm overnight. The residue was scraped out of the flask and was mixed with 20.0 g of copper bronze ("Venus" brand) and 102.2 g (0.47 mol) of 4-bromoveratrole in a mortar. The resulting paste was transferred to a flask and was heated to 170–185° for 3 hr. The mixture was allowed to cool, 2 *N* KOH was added, and the product was extracted into Et_2O. The extract was washed (2 *N* KOH, saturated NaCl solution) and dried (Na_2SO_4) and the residue after evaporation of solvent was distilled to give 72.4 g (58%) of 4-(4-chlorophenoxy)-veratrole: bp 166–175° (0.05 mm); nmr ($CDCl_3$) δ 3.80 (s, 3), 3.83 (s, 3), 6.4–7.3 (m, 7).

To this material (0.273 mol) in 500 ml of C_6H_6 was added a so-

Table II. Substituted 1,2-Benzenediols



No.	Z	Mp[a] or bp (mm), °C	Yield,[b] %	Formula	Analyses[c]	Recrystn solvent
22	4-OC_6H_5	100–104[d]	64	$C_{12}H_{10}O_3$	C, H	C_6H_6
23	3-OC_6H_5	68–70	(91)	$C_{12}H_{10}O_3$	C, H	C_6H_{12}
24	4-OC_6H_4-*p*-Cl	114–116	(99)	$C_{12}H_9ClO_3$	Cl[c]	C_6H_6–C_6H_{12}
25	4-OC_6H_4-*m*-CF_3	75–77	(68)	$C_{13}H_9F_3O_3$	C, H	C_6H_{12}
26	4-OC_6H_4-*p*-Et	185–187 (0.02)[f]	(37)	$C_{14}H_{14}O_3$		
27	4-OC_6H_4-*o*-Me	95–97	(48)	$C_{13}H_{12}O_3$	C, H	C_6H_{12}
28	4-$C(Me)_2C_6H_5$	99–100	62	$C_{15}H_{16}O_2$	C, H	C_6H_{12}
29	4-$C(Me)_2C_6H_4$-*p*-Cl	117.5–118	(47)	$C_{15}H_{15}ClO_2$	C, H, Cl	C_6H_{12}
30	4-$C(Me)_2C_6H_4$-*p*-F	59–62	77	$C_{15}H_{15}FO_2$	C, H	(Distilled)
31	4-$C(Me)_2C_6H_4$-*p*-Me	79–83 dec[g]	33	$C_{16}H_{18}O_2$		C_6H_{12}
32	4-$CH(Me)C_6H_3$-*o*,*p*-Me_2	(Oil)[f]	32	$C_{16}H_{18}O_2$		
33	4-$CH(Me)C_6H_5$	77–78[h]	(58)	$C_{14}H_{14}O_2$	C, H	C_6H_{12}
34	4-$CH(Bu)C_6H_5$	99–101	45	$C_{17}H_{20}O_2$	C, H	Et_2O–C_6H_{12}
35	4-$CH(i\text{-}Pr)C_6H_5$	76–77 dec[i]	49	$C_{16}H_{18}O_2$	C, H	Et_2O–C_6H_{12}
36	4-$C(Me)_2CH_2C_6H_5$					
37	4-$C(Et)_2C_6H_5$	90–92	(54)	$C_{17}H_{20}O_2$	C, H	Et_2O–C_6H_{12}
38		88–94[f]	(25)	$C_{17}H_{18}O_2$		Et_2O–C_6H_{12}
39		77–80 dec[f,i]	(24)	$C_{18}H_{20}O_2$		Et_2O–C_6H_{12}
40		111–113 dec	(39)	$C_{15}H_{14}O_2$	C, H	Et_2O–C_6H_{12}

[a–c] See footnotes *a–c* to Table I. [d] Reference 20 gives mp 104–106°; see also D. E. Janssen, J. Van Allan, and C. V. Wilson, *J. Org. Chem.*, **20,** 1326 (1955). [e] *Anal.* Calcd: C, 60.90; H, 3.37; Cl, 15.06. Found: C, 61.11; H, 3.87; Cl, 14.83. [f] Crude product was used for conversion to corresponding benzodioxole-2-carboxylate, listed in Table I. [g] W. L. Bencze, Belgian Patent 627,224 (1963) [*Chem. Abstr.*, **60,** 15780 (1964)] gives mp 84–85°. [h] Reference 21 gives mp 75°. [i] 1:1 mixture of **35** and **36**; see Experimental Section. [j] R. P. Perkins and F. Bryner, U. S. Patent 2,262,249 (1941) [*Chem. Abstr.*, **36,** 1708 (1942)] give mp 99°

lution of 146 g (0.546 mol) of $AlBr_3$ in 500 ml of C_6H_6 and the resulting mixture was stirred at reflux temperature for 5 hr. The mixture was allowed to cool and 1 l. of 6 *N* HCl was added dropwise. The C_6H_6 phase was separated, washed with saturated NaCl solution, and dried over Na_2SO_4 to give after evaporation of solvent 68.2 g (99%) of **24**. A sample was recrystallized from C_6H_6–cyclohexane (Table II).

A mixture of 63.2 g (0.267 mol) of **24**, 148.0 g (1.07 mol) of K_2CO_3, and 34.4 g (0.267 mol) of $Cl_2CHCOOH$ in 1 l. of *n*-PrOH was stirred at reflux temperature for 4 days. After 24 hr an additional 34.4 g (0.267 mol) of $Cl_2CHCOOH$ was added dropwise. PrOH was boiled off and 1 l. of H_2O was added. The resulting precipitate was collected, dried, and converted to the Me ester **5**, as described in the preceding example. Compounds **3**, **6**, **7**, and **8** were similarly prepared *via* **22**, **25**, **26**, and **27**.

Sodium 5-(α,α-Dimethylbenzyl)-1,3-benzodioxole-2-carboxylate (9). To a refluxing mixture of 220.2 g (2 mol) of 1,2-benzenediol in toluene containing 20 ml of concentrated H_2SO_4 was added dropwise over 70 min a solution of 118.2 g (1 mol) of α-methylstyrene in 125 ml of toluene. The mixture was refluxed for 1 hr. The mixture was allowed to cool, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from cyclohexane and gave 150.4 g (66%) of **28**, mp 96–99°. A sample was recrystallized to give the material listed in Table II.

A mixture of 130.0 g (0.57 mol) of **28**, 316.0 g (2.28 mol) of K_2CO_3, and 73.5 g (0.57 mol) of $Cl_2CHCOOH$ in 2.2 l. of PrOH was stirred at reflux temperature for 6 days. Additional 73.5-g portions of $Cl_2CHCOOH$ were added after 24 and 48 hr, respectively. PrOH was boiled off while an equal volume of H_2O was added and the mixture was allowed to cool. The resulting precipitate was collected, washed with 0.2 *N* KOH, and converted to the acid with HCl. The acid was extracted with CH_2Cl_2–Me_2CO (3:1); the extract was dried (Na_2SO_4) and evaporated to dryness to give 142.0 g (81%) of oil. Since the acid could not be induced to crystallize, a sample was converted to the Na salt (Table I): uv (H_2O) 285 nm (ε 4240); ir (KBr) 1630, 1650 cm^{-1}; nmr (DMSO-d_6) δ 1.61 (s, 6), 5.97 (s, 1), 6.5–7.3 (m, 8).

Ethyl 5-(4-Fluoro-α,α-dimethylbenzyl)-1,3-benzodioxole-2-carboxylate (11). A mixture of 91.9 g (0.373 mol) of 4-(4-fluoro-α,α-dimethylbenzyl)-1,2-benzenediol (**30**) (prepared from *p*-fluoro-α-methylstyrene as described for **28**), 257.0 g (1.86 mol) of K_2CO_3, and 47.8 g (0.373 mol) of $Cl_2CHCOOH$ in 2.5 l. of *i*-PrOH was stirred at reflux temperature for 5 days. After 24 and 48 hr, respectively, an additional 47.8 g (0.373 mol) of $Cl_2CHCOOH$ was added dropwise to the mixture. *i*-PrOH was boiled off while an equal volume of H_2O was added. An oil formed that was separated by decantation, acidified with dilute HCl, and extracted into Et_2O. The extract was dried (Na_2SO_4) and the solvent was evaporated to give 102.9 g of oil. It was dissolved in absolute EtOH and treated with gaseous HCl, and the solution was refluxed overnight. The solvent was evaporated and the residue was distilled. The fraction of bp 181–191° (0.30 mm) was collected: 56.3 g (45%) of **11** (Table I); uv (95% EtOH) 286 nm (ε 4000); ir (KBr) 1760 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (t, 3, *J* = 7 Hz), 1.60 (s, 6), 4.26 (q, 2, *J* = 7 Hz), 6.25 (s, 1), 6.7–7.4 (m, 7). Compounds **10** and **12–18** were similarly prepared *via* **29** and **31–37**.

Ethyl 5-(1-Phenyl-1-cyclopentyl)-1,3-benzodioxole-2-carboxylate (19). A mixture of 32.7 g (0.129 mol) of 4-(1-phenyl-1-cyclopentyl)-1,2-benzenediol (**38**) (prepared from 1-phenyl-1-cyclopentene as described for **28**), 88.5 g (0.64 mol) of K_2CO_3, and 16.6 g (0.129 mol) of $Cl_2CHCOOH$ in 1 l. of dry *i*-PrOH was stirred at reflux temperature for 5 days. Additional 16.6-g portions of $Cl_2CHCOOH$ were added after 24 and 48 hr, respectively. The product was isolated and converted to the Et ester as described for **11** to give **19** (Table I): uv (95% EtOH) 286 nm (ε 4230); ir (KBr) 1760 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (t, 3, *J* = 7 Hz), 1.66 (m, 4), 2.21 (m, 4), 4.21 (q, 2, *J* = 7 Hz), 6.20 (s, 1), 6.6–7.3 (m, 8). Compounds **20** and **21** were similarly prepared from **39** and **40** that were synthesized from 1-phenyl-1-cyclohexene and indene, respectively, as described for **28**.

4-(α,α-Dimethylphenethyl)-1,2-benzenediol–4-(α-Isopropylbenzyl)-1,2-benzenediol Mixture (35 and 36). To a refluxing mixture of 93.3 g (0.847 mol) of 1,2-benzenediol in 100 ml of toluene containing 10 ml of concentrated H_2SO_4 was added dropwise

over 60 min 50.0 g (0.424 mol) of 2-methyl-1-phenyl-1-propene in 115 ml of toluene. The mixture was refluxed for 1 hr, allowed to cool, and poured into 800 ml of H_2O. The organic phase was separated, washed with H_2O (3 × 300 ml), dried (Na_2SO_4), and evaporated to dryness. From the residue of 96.1 g crystallized 74.6 g, mp 67–73°, on trituration with hexane. Two recrystallizations from Et_2O–C_6H_{12} gave 53.9 g (56%) of material, mp 73–75° dec. A sample was recrystallized to give the material listed in Table II. The identity of the mixture was determined from the nmr (D_3CCOCD_3) of **35** [δ 0.81 (d, 3, J = 6 Hz), 0.88 (d, 3, J = 6 Hz), 2.03 (m, 1), 3.31 (d, 1, J = 11 Hz), 6.7–7.5 (m, 10)] and **36** [δ 1.23 (s, 6), 2.83 (s, 2), 6.7–7.5 (m, 10)]. Glc on a 2% Apiezon L on 80–100 mesh Chromosorb W/HP column at 200° showed two peaks of approximately equal height. Similarly, the mixture of **16** and **17** that was obtained from **35** and **36** showed two peaks of approximately equal height on glc (same column, 220°) and the nmr was consistent with the two assigned structures, present in approximately equal amounts.

Reaction of 2-methyl-3-phenyl-1-propene (XII) with 1,2-benzenediol in refluxing toluene in the presence of H_2SO_4 gave the same 1:1 mixture of **35** and **36** in 62% yield: the identity was established by mixture melting point (no depression) and comparison of ir and nmr spectra.

Biological Methods. Young male rats of the Wistar strain, obtained from Royalhart Laboratory Animals, Inc., New Hampton, N. Y., of average initial weight of 170–190 g were used in these tests. The compounds to be tested were mixed thoroughly with Purina Lab Chow (Ralston Purina Co., St. Louis, Mo.), and the diet was fed *ad libitum* to groups of six animals for 4 days. An untreated control group was included in each experiment. Food consumption and body weights were routinely recorded and these data were used to calculate the average daily dose of the test compounds. At the end of the treatment period, the rats were bled by cardiac puncture. Plasma cholesterol[25] and triglyceride[26] levels were determined by automated procedures. Livers were rapidly excised, blotted, and weighed at the end of the treatment period and the weight was calculated as g/100 g of final body weight.

Values for plasma cholesterol and triglyceride concentration and liver weight in the treated animals were compared with the values obtained for untreated control rats run simultaneously. Significance of the difference between the values was calculated by Student's t test. The data are expressed as per cent reduction from control levels for plasma lipids and as per cent increase for liver weights. Plasma cholesterol and triglyceride concentrations for typical control groups were 58 and 66 mg/100 ml, respectively, by this method.

Acknowledgment. We thank Mr. M. J. Gordon and associates and Dr. D. H. Gustafson for microanalysis, spectra, and glc data. We are indebted to Professor Fred Kaplan of the Chemistry Department of the University of Cincinnati for suggesting the identity of the mixtures of **16**, **17** and **35**, **36**. We thank Mr. W. J. Magner for help in the biological evaluations.

References

(1) D. T. Witiak, D. R. Feller, E. S. Stratford, R. E. Hackney, R. Nazareth, and G. Wagner, *J. Med. Chem.*, 14, 754 (1971).
(2) D. T. Witiak, E. S. Stratford, R. Nazareth, G. Wagner, and D. R. Feller, *J. Med. Chem.*, 14, 758 (1971).
(3) T. F. Whayne, Jr., and D. T. Witiak, *J. Med. Chem.*, **16**, 228 (1973).
(4) H. A. I. Newman, W. P. Heilman, and D. T. Witiak, *Lipids*, **8**, 378 (1973).
(5) T. Kariya, J. M. Grisar, N. L. Wiech, and T. R. Blohm, *J. Med. Chem.*, **15**, 659 (1972).
(6) A. R. Timms, R. G. Griot, and J. A. Spirito, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 242 (1968).
(7) J. M. Grisar, R. A. Parker, T. Kariya, T. R. Blohm, R. W. Fleming, V. Petrow, D. L. Wenstrup, and R. G. Johnson, *J. Med. Chem.*, **15**, 1273 (1972).
(8) T. Kariya, T. R. Blohm, J. M. Grisar, R. A. Parker, and J. R. Martin, *Advan. Exp. Med. Biol.*, **26**, 302 (1972).
(9) L. Golberg, *Proc. Eur. Soc. Study Drug Toxicity*, **7**, 171 (1966).
(10) D. S. Platt and J. M. Thorp, *Biochem. Pharmacol.*, **15**, 915 (1966).
(11) D. S. Platt and B. L. Cockrill, *Biochem. Pharmacol.*, **16**, 2257 (1967).
(12) D. S. Platt and B. L. Cockrill, *Biochem. Pharmacol.*, **18**, 429, 445, 459 (1969).
(13) N. J. Lewis, D. R. Feller, G. K. Poochikian, and D. T. Witiak, *J. Med. Chem.*, **17**, 41 (1974).
(14) J. Reddy, D. Svoboda, and D. Azarnoff, *Biochem. Biophys. Res. Commun.*, **52**, 537 (1973).
(15) J. L. Schmidt and D. L. Martin, *Toxicol. Appl. Pharmacol.*, **7**, 257 (1965).
(16) W. G. Christiansen and M. A. Dolliver, *J. Amer. Chem. Soc.*, **66**, 312 (1944).
(17) A. Burger, D. A. Markees, W. R. Nes, and W. L. Yost, *J. Amer. Chem. Soc.*, **71**, 3307 (1949).
(18) H. A. Hartzfeld, R. G. Johnson, and H. Gilman, *J. Org. Chem.*, **22**, 1717 (1957).
(19) G. W. K. Cavill and D. L. Ford, *J. Chem. Soc.*, 1388 (1954).
(20) W. Mayer, R. Fikentscher, J. Schmidt, and O. T. Schmidt, *Chem. Ber.*, **93**, 2761 (1960).
(21) Ng. Ph. Buu-Hoi, H. Le Bihan, and F. Binon, *J. Org. Chem.*, **17**, 243 (1952).
(22) J. M. Thorp in "Atherosclerosis, Proceedings of the Second International Symposium," R. J. Jones, Ed., Springer-Verlag, New York, N. Y., 1970, pp 541–544.
(23) E. Granzer and H. Nahm, *Arzneim.-Forsch.*, **23**, 1353 (1973).
(24) W. L. Bencze, U. S. Patent 3,332,842 (1966); *Chem. Abstr.*, **68**, 49289 (1968).
(25) W. D. Block, K. C. Jarrett, Jr., and J. B. Levine, *Clin. Chem.*, **12**, 681 (1966).
(26) G. Kessler and H. Lederer in "Automation in Analytical Chemistry," L. T. Skeggs, Ed., Mediad, New York, N. Y., 1965, p 341.