(Aryloxy)[*p*-(aryloxy)phenyl]- and (Aryloxy)[*p*-(arylthio)phenyl]acetic Acids and Esters as Hypolipidemic Agents[1]

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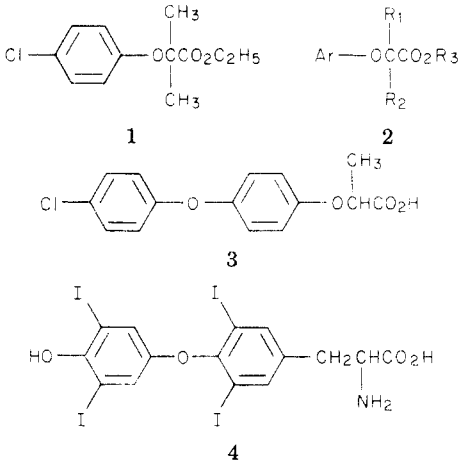
A series of (aryloxy)[*p*-(aryloxy)phenyl]- and (aryloxy)[*p*-(arylthio)phenyl]acetic acids and esters of general structure **8** were prepared and tested for lipid-lowering activity in normal rats. At a dose of 0.1% of the diet (ca. 100 mg/kg), approximately half of the compounds reduced serum sterols in the range of 20–30% and lowered serum triglycerides by 40–60%. Over 35 analogues lowered serum sterols by 15–25% when fed at 0.03% of diet, and 15 of these maintained their activity at 0.01% of the diet (10 mg/kg). Synthetic methodology and structure–activity relationships are discussed.

The field of atherosclerosis therapy may very well be regarded to be in the pioneering stages, for while agents are known which reduce serum lipids,[2] the utility of drugs for inhibiting the progression of atherosclerotic lesions and the prevention of myocardial infarction has yet to be established clinically. Thus, there remains a challenge to discover drugs which reduce serum lipids, induce favorable lipoprotein patterns, and also check the progress of the disease either by inhibiting plaque formation or inducing regression of atherosclerotic lesions.

Since the introduction of clofibrate (**1**) as a hypolipidemic agent,[3] a number of compounds (**2**) bearing the aryloxyacetic acid moiety have been studied.[4] Recently, a new agent, 2-[*p*-(*p*-chlorophenoxy)phenyl]propionic acid (**3**), with hypolipidemic activity claimed to be 15–20 times that of clofibrate has been reported.[5] The diphenyl ether moiety is present in **3**, as well as in D-thyroxine (**4**) and related thyroid analogues which exhibit serum *cholesterol-lowering properties*.[6]



1 **2**

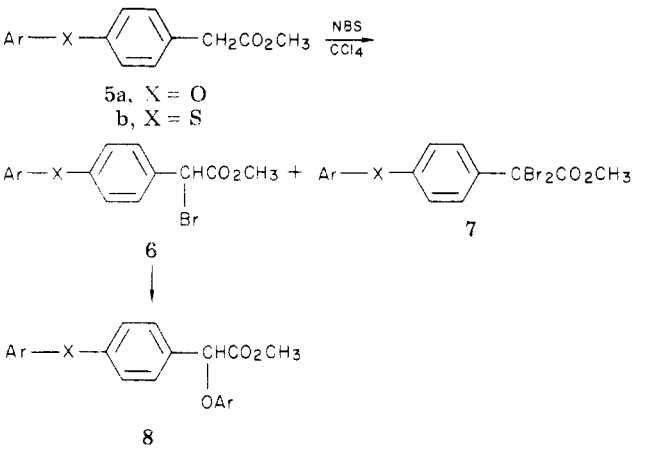
3

4

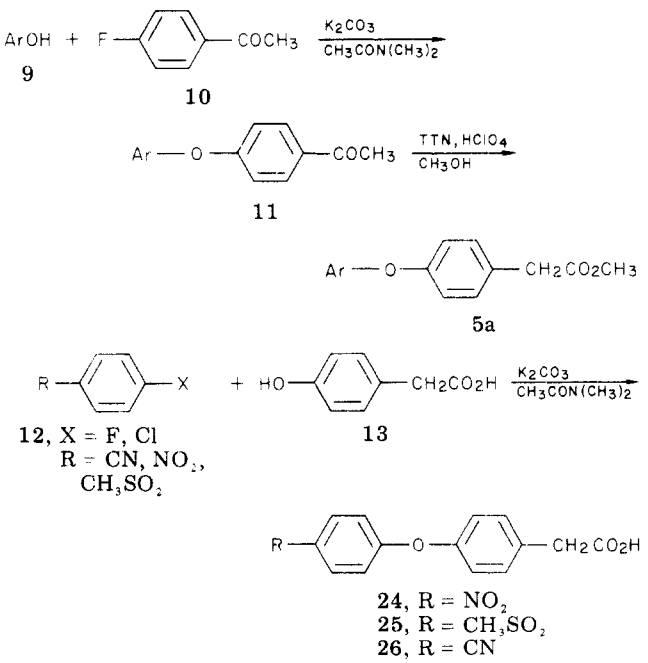
Of general interest, therefore, was the preparation of structures with potential hypolipidemic activity containing a diphenyl ether moiety as a lipophilic group. This paper describes the synthesis of compounds of general structure **8** and their activity as hypolipidemic agents.

Chemistry. The general synthetic route for preparation of compounds **8** is depicted in Scheme I. Bromination of *p*-(aryloxy)phenylacetic acid ester **5a** or the thia analogues **5b** with *N*-bromosuccinimide (NBS)[7] in carbon tetrachloride gave the α-bromo esters **6**. Generally, a 2–3% excess of NBS was used along with HBr as catalyst.[8] The reaction times varied markedly (3–40 h); however, the progress of the reaction could be readily followed by examining the ^{1}H NMR spectrum of an aliquot of the reaction mixture. The methyl signal of the unsubstituted esters **5** appeared at ca. 3.85 ppm, while that of the developing monobromo esters **6** was shifted downfield to ca. 3.90 ppm. When the reaction was about 90% complete, a new signal appeared at 3.95–4.00 ppm, which is attributed to the formation of dibromo ester **7**. Further reaction did not increase the amount of monobromo ester. No attempts were made to purify these intermediates, except for a rapid filtration through silica gel with benzene as eluent.

Scheme I



Scheme II



The reactions of the bromo esters **6** with phenols were, in general, straightforward. A solution of the phenol (0.025 mol) and sodium methoxide in methanol was stirred for ca. 30 min, followed by the addition of 0.02 mol of the appropriate bromo ester in 10 mL of benzene and 50 mg

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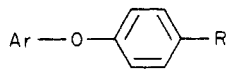
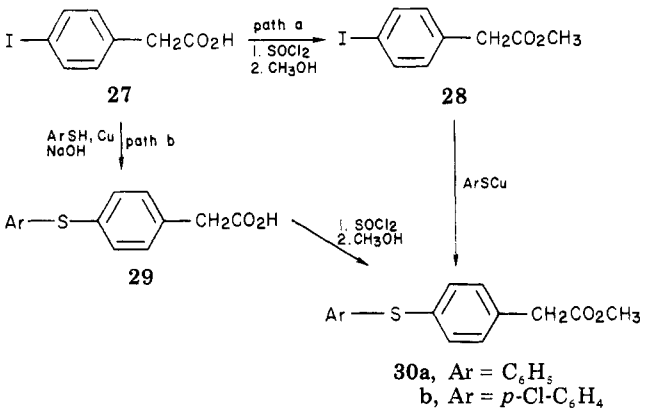
Table I. *p*-(Aryloxy)acetophenones and *p*-(Aryloxy)phenylacetic Acids and Esters



no.	Ar	R	mp or bp (mm), °C	% yield	recrystn solvent	formula[a]
14	C_6H_5	$COCH_3$	46-49[b]	58	*e*	$C_{14}H_{12}O_2$
15	*p*-ClC_6H_4	$COCH_3$	66-68[c]	89	*e*	$C_{14}H_{11}ClO_2$
16	*m*-$CF_3C_6H_4$	$COCH_3$	130-142 (0.2)	86		$C_{15}H_{11}F_3O_2$
17	4-Cl-1-naphthyl	$COCH_3$	100-104	63	*f*	$C_{18}H_{13}ClO_2$
18	*p*-$(CH_3)_3C$-C_6H_4	$COCH_3$	160-165 (0.1)	97		$C_{18}H_{20}O_2$
19	C_6H_5[d]	$CH_2CO_2CH_3$	122-131 (0.05)	98		$C_{15}H_{14}O_3$
20	*p*-Cl-C_6H_4	$CH_2CO_2CH_3$	173-178 (0.5)	94		$C_{15}H_{13}ClO_3$
21	*m*-CF_3-C_6H_4	$CH_2CO_2CH_3$	120-148 (0.07)	92		$C_{16}H_{13}F_3O_3$[h]
22	4-Cl-1-naphthyl	$CH_2CO_2CH_3$	196 (0.1)	83		$C_{19}H_{15}ClO_3$
23	*p*-$(CH_3)_3C$-C_6H_4	$CH_2CO_2CH_3$	152-163 (0.04)	66		$C_{19}H_{22}O_3$
24	*p*-NO_2-C_6H_4	CH_2CO_2H	135-137	90	*g*	$C_{14}H_{11}NO_5$
25	*p*-CH_3SO_2-C_6H_4	CH_2CO_2H	125-126	48	*f*	$C_{15}H_{14}O_5S$
26	*p*-CN-C_6H_4	CH_2CO_2H	125-127	58	*g*	$C_{15}H_{11}NO_3$

[a] Analysis for C, H, N, Cl, F, and S were within ±0.4% of theoretical values. [b] Lit.[11] mp 49 °C. [c] Lit.[10] mp 68 °C. [d] Prepared from acid[10] and thionyl chloride, followed by methanolysis. [e] Evaporative distillation in a Büchi Kugelrohrofen; the product crystallized. [f] $CHCl_3$-hexane. [g] CH_3OH-H_2O. [h] F: calcd, 18.37; found, 17.73.

Scheme III



30a, Ar = C_6H_5
b, Ar = *p*-Cl-C_6H_4

of potassium iodide as catalyst. The preparation of the intermediate methyl *p*-(aryloxy)phenylacetates (**5a**) is illustrated in Scheme II.

Reaction of phenols **9** with *p*-fluoroacetophenone (**10**) gave *p*-(aryloxy)acetophenones **11**, which were subjected to oxidative rearrangement with thallium(III) nitrate[9,10] to afford intermediates **5a**. *p*-Phenoxyacetophenone (**14**) was prepared by Friedel–Crafts acetylation of diphenyl ether.[11] *p*-Phenoxyphenylacetic acids containing a para nitro, cyano or methylsulfonyl group were most conveniently prepared by reacting an activated phenyl halide **12** with *p*-hydroxyphenylacetic acid (**13**) to give derivatives **24–26**. These acids (**24–26**) were reacted with thionyl chloride, brominated (NBS), and treated with methanol to give the corresponding α-bromo methyl esters. Physical data for the ketone intermediates **11** and *p*-(aryloxy)-phenylacetic acids and esters are listed in Table I.

p-(Arylthio)phenylacetic acids and esters **30** were prepared as shown in Scheme III from *p*-iodophenylacetic acid (**27**).[12]

In path a, the acid **27** was esterified to give ester **28**, which was coupled with cuprous phenyl mercaptide[13] or cuprous *p*-chlorophenyl mercaptide. Alternatively, *p*-iodophenylacetic acid (**27**) was coupled directly with sodium thiophenoxide or sodium *p*-chlorothiophenoxide with copper catalysts. The resulting acids **29** were then converted to the methyl esters **30**.

Pharmacology. In Table II is listed the hypolipidemic activity[14] found for [*p*-(*p*-chlorophenoxy)phenyl]acetic acids and esters substituted with diverse α-aryloxy groups. Multiple variations of substituents in the α-phenoxy moiety show that there is no simple correlation of activity with polar or electronic properties of the substituents. Derivatives **33**, **35**, **38**, **52**, and **63** with *p*-*tert*-butyl, *m*-*tert*-butyl, *p*-cyclohexyl, 3,4-dimethyl, and *p*-(1-methylcyclohexyl) groups all exhibited activity (15–25% sterol lowering) at 0.01% of the diet. The introduction of the polar substituents *p*-chloro (**31**), *p*-fluoro (**40**), *p*-(benzyloxy) (**41**), and *p*-phenoxy (**42**) gave derivatives with significant activity at 0.01% of the diet. Inroduction of a trifluoromethyl group (electron withdrawing and lipophilic) in the meta or para position gave active derivatives **34** and **59**, but only **59** (*p*-CF_3) retained activity at 0.01% of the diet.

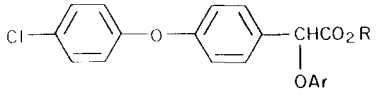
Except for the *tert*-butyl compound **35**, derivatives with meta substituents (**34** and **44**) were less active than the corresponding para-substituted derivatives (**33** and **59**). Mulitple substitutions with one or more meta groups (compounds **39**, **43**, **46**, **47**, and **48**) gave analogues which were inactive at 0.01% of the diet. The *p*-chloro derivative **31** and the 3,4-dimethyl derivative **32** have comparable activities, while a combination of the *p*-chloro and *m*-methyl moieties in compound **55** appears to increase sterol-lowering activity.

Analogues **36** and **51** with a 1-(naphthyloxy) moiety were inactive, while **58** with a 2-(naphthyloxy) group showed moderate activity. Tetrahydronaphthyloxy and indanyloxy analogues (**53**, **54**, **57**, and **60–62**) show that fusing a second ring onto the phenyl group in the 2,3 position (**53**, **54**, **61** and **62**) markedly lowers activity, while fusing the ring onto the 3,4 position (compounds **57** and **60**) leads to highly active derivatives. In comparison with **57** and **60**, it is interesting to note that the 3,4-dimethylphenoxy analogue **52** has comparable activity.

In Table III are listed analogues in which the ω-(*p*-chlorophenoxy) group was replaced by *p*-cyanophenoxy (**67–70**), *p*-(methylsulfonyl)phenoxy (**71** and **72**), 4-chloro-1-naphthyloxy (**78** and **79**), *m*-(trifluoromethyl)-phenoxy (**80–83**) and *p*-*tert*-butylphenoxy (**84–87**) groups. Although a number of these derivatives exhibited significant activity at 0.1% of the diet, only compounds **67**, **70**, **75**, **77**, and **79** had activity at 0.01% of the diet, with none showing enhanced activity over the most active derivatives in Table II.

A series of methyl [*p*-(phenylthio)phenyl]acetates were prepared (Table IV). These derivatives, in which sulfur is substituted for oxygen, appear to have diminished

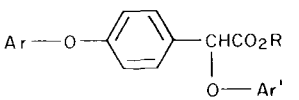
Table II. Aryloxy[*p*-(*p*-chlorophenoxy)phenyl]acetic Acids and Esters

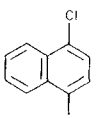
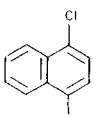
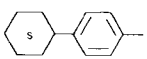
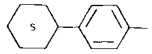


no.	Ar	R	mp or bp (mm), °C	% yield	recrystn solvent	emp form[a]	% serum lipid reduction vs. control[b] sterol, % diet 0.1	sterol, % diet 0.03	sterol, % diet 0.01	triglycerides, % diet[c] 0.1	triglycerides, % diet[c] 0.03	triglycerides, % diet[c] 0.01
31	4-Cl-C_6H_4	CH_3	100–101.5	80	*d*	$C_{21}H_{16}Cl_2O_4$	33 ± 4.2[p]	23 ± 4.9[p]	16 ± 4.2[p]	56 ± 5.5[p]	48 ± 5.8[p]	39 ± 4.5[p]
32	C_6H_5	CH_3	204 (0.075)	84		$C_{21}H_{17}ClO_4$	31 ± 4.7[p]	18 ± 4.8[p]	18 ± 4.3[p]	68 ± 4.9[p]	67 ± 12.5	77 ± 11.2
33	4-*t*-Bu-C_6H_4	CH_3	118–120	62	*d*	$C_{25}H_{25}ClO_4$	20 ± 5.2[p]	20 ± 3.2[p]	27 ± 4.4[p]	57 ± 5.2[p]	53 ± 5.5[p]	41 ± 8.0[p]
34	3-CF_3-C_6H_4	CH_3	178 (0.05)	51		$C_{22}H_{16}ClF_3O_4$	28 ± 6.2[p]	16 ± 5.8[p]	−6 ± 7.9	61 ± 7.6[p]	47 ± 7.3[p]	18 ± 21.7
35	3-*t*-Bu-C_6H_4	CH_3	182 (0.05)	68		$C_{25}H_{25}ClO_4$	41 ± 4.0[p]	20 ± 4.2[p]	23 ± 7.6[p]	63 ± 5.1[p]	49 ± 8.3[p]	41 ± 8.2[p]
36	4-Cl-1-naphthyl	CH_3	94–96	42	*d*	$C_{25}H_{18}Cl_2O_4$	11 ± 4.8	−3 ± 8.5	−18 ± 6.0	32 ± 15.7	−8 ± 13.4	−15 ± 14.8
37	3-biphenylyl	CH_3	glass	34		$C_{27}H_{21}ClO_4$[e]	28 ± 8.4[p]	21 ± 7.1[p]	8 ± 6.9	66 ± 4.9[p]	45 ± 8.8[p]	38 ± 11.0
38	4-cyclohexyl-C_6H_4	CH_3	122–123.5	51	*d*, *f*	$C_{27}H_{27}ClO_4$	51 ± 7.3[p]	21 ± 8.3	20 ± 10.5	66 ± 5.4[p]	47 ± 2.3[p]	37 ± 12.0[p]
39	3,4,5-Cl_3-C_6H_2	CH_3	oil	90		$C_{21}H_{14}Cl_4O_4$[g]	30 ± 6.2[p]	−2 ± 10.4	3 ± 8.8	55 ± 4.8[p]	46 ± 7.3[p]	15 ± 6.4
40	4-F-C_6H_4	H	106–111	78	*d*	$C_{20}H_{13}ClFO_4$	29 ± 10.3[p]	28 ± 7.2[p]	41 ± 12.0[p]	58 ± 3.6[p]	48 ± 7.1[p]	20 ± 10.8
41	4-(benzyloxy)-C_6H_4	CH_3	88–90	61	*h*, *i*	$C_{28}H_{23}ClO_5$[j]	30 ± 4.5[p]	26 ± 4.2[p]	13 ± 4.5	57 ± 5.3[p]	37 ± 8.6[p]	29 ± 10.1
42	4-phenoxy-C_6H_4	H	oil	78		$C_{26}H_{19}ClO_5$[j]	33 ± 3.5[p]	21 ± 8.3[p]	13 ± 11.3	54 ± 5.3[p]	38 ± 8.4[p]	53 ± 6.6[p]
43	4-Cl-3,5-Me_2-C_6H_2	CH_3	92.5–95.5	62	*d*	$C_{23}H_{20}Cl_2O_4$	21 ± 5.8[p]	22 ± 5.9[p]	0 ± 6.2	66 ± 7.1[p]	49 ± 5.6[p]	33 ± 6.3[p]
44	3-Cl-C_6H_4	CH_3	oil	59		$C_{21}H_{16}Cl_2O_4$	19 ± 8.3[p]	11 ± 8.8	−3 ± 7.7	50 ± 6.3[p]	22 ± 13.1	13 ± 15.1
45	2-Cl-4-*t*-Bu-C_6H_3	CH_3	85.5–88	49	*d*	$C_{25}H_{23}Cl_2O_4$[k]	28 ± 3.0[p]	29 ± 6.1[p]	17 ± 4.9[p]	64 ± 5.5[p]	50 ± 4.7[p]	25 ± 9.2
46	3,5-di-*t*-Bu-C_6H_3	CH_3	glass	54		$C_{29}H_{32}ClO_4$[l]	−6 ± 9.7	−12 ± 10.0	−30 ± 11.4[p]	7 ± 4.0	−7 ± 24.6	23 ± 12.4
47	3,4-Cl_2-C_6H_3	CH_3	78.5–82	60	*d*	$C_{21}H_{15}Cl_3O_4$	24 ± 9.6[p]	26 ± 4.6[p]	5 ± 6.7	67 ± 3.3[p]	60 ± 4.0[p]	14 ± 11.7
48	3,5-Cl_2-C_6H_3	CH_3	oil	53		$C_{21}H_{15}Cl_3O_4$	26 ± 6.3[p]	10 ± 6.6	−11 ± 9.5	47 ± 5.4[p]	6 ± 8.9	−44 ± 22.1
49	7-coumarinyl	CH_3	179.5–182.5	34	*h*	$C_{24}H_{17}ClO_6$	−4 ± 5.6	7 ± 5.7	−5 ± 6.0	−16 ± 20.0	−23 ± 29.9	4 ± 11.1
50	5-Cl-8-quinolyl	CH_3	glass	23		$C_{24}H_{17}Cl_2NO_4$	5 ± 9.0	4 ± 9.9	4 ± 8.9	5 ± 27.0	4 ± 24.5	−3 ± 23.5
51	1-naphthyl	CH_3	107–109.5	12	*d*	$C_{25}H_{19}ClO_4$	4 ± 6.2	3 ± 5.9	-	39 ± 6.5[p]	36 ± 6.2[p]	
52	3,4-Me_2-C_6H_3	CH_3	oil	51		$C_{23}H_{21}ClO_4$	46 ± 5.9[p]	28 ± 5.0[p]	18 ± 5.9[p]	63 ± 5.7[p]	45 ± 8.3	23 ± 11.5
53	5,6,7,8-H_4-1-naphthyl	CH_3	oil	37		$C_{25}H_{23}ClO_4$	23 ± 5.2[p]	14 ± 4.9[p]	1 ± 5.8	41 ± 9.7	−1 ± 19.8	−34 ± 26.6
54	4-indanyl	CH_3	oil	38		$C_{23}H_{21}ClO_4$	19 ± 7.4	10 ± 7.2	−7 ± 9.4	17 ± 21.4	−8 ± 19.1	−39 ± 23.1
55	4-Cl-3-Me-C_6H_3	CH_3	77–79	57		$C_{22}H_{18}Cl_2O_4$	39 ± 7.9[p]	34 ± 5.4[p]	34 ± 4.5[p]	54 ± 7.3[p]	39 ± 7.4[p]	28 ± 8.3
56	4-CH_3CONH-C_6H_4	CH_3	157–160	73	*h*, *i*	$C_{23}H_{20}ClNO_5$	−3 ± 6.7	−11 ± 8.1	−4 ± 5.7	13 ± 13.4	−20 ± 11.1	−9 ± 11.2
57	5-indanyl	CH_3	oil	54		$C_{24}H_{21}ClO_4$	25 ± 3.2[p]	30 ± 3.4[p]	26 ± 3.3[p]	52 ± 8.6[p]	51 ± 8.9[p]	37 ± 12.1
58	2-naphthyl	CH_3	glass	58		$C_{25}H_{19}ClO_4$	32 ± 4.3[p]	15 ± 7.7	10 ± 5.2	55 ± 5.5[p]	44 ± 10.3	32 ± 11.5
59	4-CF_3-C_6H_4	CH_3	oil	69		$C_{22}H_{16}F_3O_4$	20 ± 5.8[p]	28 ± 3.5[p]	24 ± 6.3[p]	53 ± 6.0[p]	51 ± 5.7[p]	60 ± 5.7[p]
60	5,6,7,8-H_4-2-naphthyl	CH_3	oil	81		$C_{25}H_{23}ClO_4$	42 ± 5.7[p]	26 ± 7.2[p]	24 ± 4.8[p]	47 ± 13.3	35 ± 12.4	8 ± 16.6
61	8-Cl-4-indanyl	CH_3	94–96	80	*d*	$C_{24}H_{20}Cl_2O_4$	17 ± 5.4[p]	9 ± 4.7	15 ± 5.1[p]	62 ± 4.0	23 ± 10.8	6 ± 9.2
62	4-Cl-5,6,7,8-H_4-1-naphthyl	CH_3	87.5–90	70	*d*	$C_{25}H_{22}Cl_2O_4$	25 ± 4.9[p]	30 ± 4.3[p]	−1 ± 8.2	54 ± 5.2[p]	28 ± 6.8[p]	24 ± 14.4
63	4-(1-methylcyclohexyl)-C_6H_4	CH_3	111–112.5	79	*f*, *m*	$C_{28}H_{29}ClO_4$	18 ± 3.7[p]	13 ± 7.3	26 ± 4.7[p]	65 ± 5.7[p]	70 ± 3.6[p]	64 ± 4.1[p]
64	4-(1-adamantyl)-C_6H_4	CH_3	148.5–150.5	74	*d*, *f*	$C_{31}H_{31}ClO_4$	3 ± 4.8	16 ± 3.9[p]	14 ± 7.4[p]	17 ± 13.1	29 ± 11.6	11 ± 9.0
65	4-Cl-C_6H_4	H	141–142	94	*d*, *f*	$C_{20}H_{14}Cl_2O_4$	31 ± 5.3[p]	23 ± 4.8[p]	12 ± 5.0	60 ± 5.6[p]	50 ± 7.8[p]	34 ± 6.0[p]
66	4-Cl-C_6H_4	C_2H_5	52.5–54	62[n]	*d*	$C_{22}H_{18}Cl_2O_4$	25 ± 5.8[p]	25 ± 3.7[p]	18 ± 3.7	60 ± 3.0[p]	51 ± 8.6[p]	40 ± 7.4[p]
67	clofibrate						0 ± 3.2			30 ± 9.0		
	clofibrate[q]						(19 ± 4.6)					(58 ± 15.3)
68	halofenic acid						26 ± 9.1	14 ± 10.4	25 ± 7.7	49 ± 3.1	10 ± 7.9	14 ± 12.8

[a] Analyses for C, H, N, Cl, and F were within 0.4% of theoretical values. [b] Eight rats in group; serum sterols and triglycerides in controls ranged from 50–70 to 60–130 mg %, respectively. [c] Plus or minus values are standard deviations; food consumption did not differ significantly from controls; approximate doses for 0.1, 0.03, and 0.01% of diet are 100, 30 and 10 mg/kg, respectively. [d] Hexane. [e] Calcd: C, 72.88; Cl, 7.9. Found: C, 72.16; Cl, 9.29. [f] $CHCl_3$. [g] Calcd: C, 53.4; Cl, 30.0. Found: C, 50.1; Cl, 29.3. [h] Acetone. [i] Petroleum ether. [j] Calcd: C, 69.88; Cl, 7.93. Found: C, 70.56; Cl, 7.13. [k] Calcd: Cl, 15.47. Found: 14.97. [l] Calcd: H, 6.72. Found: 7.23. [m] Methanol. [n] Plus 17% yield of hydrolyzed product **65**. [p] Significant at $p < 0.05$. [q] At 0.3% of diet.

Table III. (Aryloxy)[(*p*-Aryloxy)phenyl]acetic Acids and Esters



no.	Ar	Ar'	R	mp or bp (mm), °C	% yield	recrystn solvent	emp form[a]	% serum lipid reduction vs. control[b] sterol, % diet 0.1	sterol, % diet 0.03	sterol, % diet 0.01	triglycerides, % diet 0.1	triglycerides, % diet 0.03	triglycerides, % diet 0.01
67	*p*-NC-C_6H_4-	*p*-Cl-C_6H_4-	CH_3	oil	60		$C_{22}H_{16}NO_4Cl$[d]	16 ± 7.7	19 ± 5.9	20 ± 7.3	71 ± 4.6[m]	60 ± 6.3[m]	50 ± 6.5[m]
68	*p*-NC-C_6H_4-	*p*-F-C_6H_4-	CH_3	93–95	36	*e, f*	$C_{22}H_{16}FNO_4$	33 ± 4.7[m]	19 ± 5.9[m]	13 ± 4.8	60 ± 6.1[m]	31 ± 14.1	38 ± 7.5[m]
69	*p*-NC-C_6H_4-	*m*-CF_3-C_6H_4-	CH_3	oil	67		$C_{23}H_{16}NO_4F_3$	32 ± 9.7[m]	24 ± 7.0[m]	12 ± 7.9	50 ± 6.2[m]	34 ± 7.3[m]	−37 ± 18.7
70	*p*-NC-C_6H_4-	*p*-$(CH_3)_3$C-C_6H_4-	CH_3	122–124	41	*e, f*	$C_{26}H_{25}NO_4$	13 ± 8.6	13 ± 5.6	16 ± 4.0	59 ± 7.1[m]	63 ± 5.3[m]	69 ± 6.1[m]
71	*p*-CH_3SO_2-C_6H_4-	*p*-Cl-C_6H_4-	CH_3	182–184	44	*f, g*	$C_{22}H_{19}ClO_6S$	15 ± 6.3	−1 ± 5.0	8 ± 5.3	22 ± 7.6	−11 ± 20.9	11 ± 11.8
72	*p*-CH_3SO_2-C_6H_4-	*p*-F-C_6H_4-	CH_3	136–138	50	*e, f*	$C_{22}H_{19}FO_6S$	10 ± 6.3	−1 ± 4.7	−3 ± 6.1	3 ± 22.5	−8 ± 10.5	16 ± 17.1
73	*p*-O_2N-C_6H_4-	*p*-$(CH_3)_3$C-C_6H_4-	CH_3	101–103	43	*h*	$C_{25}H_{25}NO_6$	10 ± 7.7	−4 ± 8.8	−3 ± 9.3	51 ± 4.2[m]	40 ± 7.2[m]	34 ± 9.6[m]
74	*p*-$CH_3C(=O)NH$-C_6H_4-	*p*-$(CH_3)_3$C-C_6H_4-	CH_3	141–143	80	*i*	$C_{27}H_{29}NO_5$	16 ± 4.5[m]	18 ± 4.3[m]	5 ± 9.5	55 ± 3.8[m]	50 ± 5.3[m]	44 ± 5.0
75	C_6H_5-	*p*-Cl-C_6H_4-	CH_3	99–102	87	*e, j*	$C_{21}H_{17}ClO_4$	13 ± 8.1	3 ± 5.5	19 ± 5.2[m]	58 ± 7.3[m]	56 ± 5.3	62 ± 5.6[m]
76	C_6H_5-	C_6H_5-	CH_3	75.5–77.5	90	*j*	$C_{21}H_{18}O_4$	21 ± 8.0[m]	19 ± 4.8[m]	10 ± 6.3	58 ± 7.9[m]	49 ± 5.9[m]	46 ± 8.9[m]
77	C_6H_5-	C_6H_5-	H	144–146	81	*j, k*	$C_{20}H_{16}O_4$[l]	22 ± 4.8[m]	15 ± 6.8	21 ± 6.1[m]	51 ± 7.6[m]	37 ± 6.3[m]	3 ± 13.6
78		*p*-Cl-C_6H_4-	CH_3	glass	74		$C_{25}H_{18}Cl_2O_4$	23 ± 4.7[m]	17 ± 5.6	6 ± 6.0	38 ± 9.4	12 ± 14.5	33 ± 11.1
79		*p*-$(CH_3)_3$C-C_6H_4-	CH_3	glass	69		$C_{29}H_{27}ClO_4$	23 ± 4.8[m]	24 ± 4.5[m]	16 ± 6.4	56 ± 12.2[m]	39 ± 9.3	29 ± 26.1
80	*m*-CF_3-C_6H_4-	*p*-Cl-C_6H_4-	CH_3	79–82	66	*e*	$C_{22}H_{16}ClF_3O_4$	32 ± 6.7[m]	31 ± 3.5[m]	8 ± 9.2	50 ± 7.0[m]	47 ± 8.0[m]	35 ± 7.1[m]
81	*m*-CF_3-C_6H_4-	*p*-F-C_6H_4-	CH_3	70–72	81	*e*	$C_{22}H_{16}F_4O_4$	32 ± 5.2[m]	6 ± 9.3	4 ± 4.5	48 ± 6.9[m]	27 ± 8.4[m]	45 ± 5.6[m]
82	*m*-CF_3-C_6H_4-		CH_3	oil	67		$C_{28}H_{27}F_3O_4$	20 ± 7.8[m]	18 ± 5.4[m]	8 ± 9.8	59 ± 3.4[m]	34 ± 13.4[m]	40 ± 7.5[m]
83	*m*-CF_3-C_6H_4	*p*-$(CH_3)_3$C-C_6H_4-	CH_3	oil	72		$C_{26}H_{23}F_3O_4$	26 ± 11.4[m]	35 ± 4.3[m]	12 ± 8.1	77 ± 5.0[m]	70 ± 2.9[m]	52 ± 10.0[m]
84	*p*-$(CH_3)_3$C-C_6H_4-	*p*-Cl-C_6H_4-	CH_3	glass	87		$C_{25}H_{25}ClO_4$	7 ± 7.4	11 ± 8.3	17 ± 5.8	46 ± 4.5[m]	30 ± 6.8[m]	25 ± 14.7
85	*p*-$(CH_3)_3$C-C_6H_4-	*m*-CF_3-C_6H_4	CH_3	oil	78		$C_{26}H_{25}F_3O_4$	13 ± 5.5	−4 ± 7.2	−5 ± 9.4	19 ± 12.1	−18 ± 20.7	−12 ± 20.6
86	*p*-$(CH_3)_3$C-C_6H_4-	*m*-$(CH_3)_3$C-C_6H_4-	CH_3	glass	83		$C_{29}H_{34}O_4$	4 ± 6.7	6 ± 8.0	−5 ± 6.7	33 ± 10.2	13 ± 8.8	21 ± 13.0
87	*p*-$(CH_3)_3$C-C_6H_4-		CH_3	glass	78		$C_{31}H_{36}O_4$	33 ± 4.4	16 ± 5.3	−5 ± 13.7	52 ± 4.1[m]	49 ± 9.0[m]	29 ± 9.1[m]

[a] Analysis for C, H, N, Cl, and F within 0.4% of theoretical values. [b] Eight rats in group. [c] See Table II, footnote *c*. [d] Calcd: C, 67.1. Found: 66.0. [e] Hexane. [f] Acetone. [g] CH_2Cl_2. [h] Methanol. [i] Ether. [j] Petroleum ether. [k] $CHCl_3$. [l] Calcd: C, 74.99. Found: C, 73.99. [m] Significant at $p < 0.05$.

hypolipidemic activity. The glycerol ester (**95**) and copper salt (**97**) of (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)-phenyl]acetic acid were prepared (Table V). In addition, substitution of the α-hydrogen of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate (**31**) with a methyl, methoxycarbonyl, or a diethoxyphosphinyl group afforded derivatives **93**, **94**, and **98** (Table V), which exhibited good activity at 0.03% of the diet. Oxidation of the sulfide group in compound **89** to a sulfoxide gave analogue **96**, which retained its activity.

Experimental Section

Biological Activity.[14] Male COBBS-CD rats (Charles River Farms, Cambridge, Mass.) were allocated into experimental groups (four animals) and control groups (eight animals). The compounds to be tested were added to ground commerical rat chow at levels of 0.1, 0.03, and 0.01% (w/w). Control groups were given food treated with the mixing solvents (methanol–chloroform, 1:3, v/v) alone. Animals were allowed food and water ad libitum for 5 days and then killed by decapitation, and the blood was collected. Serum sterols[15] and triglycerides[16] were measured using a Technicon Autoanalyser.

Chemistry. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. IR spectra were determined on a Perkin-Elmer Model 14 spectrophotometer. All IR and NMR spectra were consistant with assigned structures.

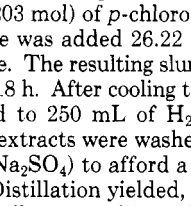
General Procedure for the Preparation of *p*-(Aryloxy)acetophenones. Preparation of *p*-(*p*-Chlorophenoxy)acetophenone (15). To a solution of 20 g (0.145 mol) of *p*-fluoroacetophenone and 26.07 g (0.203 mol) of *p*-chlorophenol in 200 mL of *N*,*N*-dimethylacetamide was added 26.22 g (0.19 mol) of anhydrous potassium carbonate. The resulting slurry was heated under argon at 150–155 °C for 18 h. After cooling to room temperature, the mixture was added to 250 mL of H_2O and extracted with benzene. The organic extracts were washed with dilute sodium hydroxide and dried (Na_2SO_4) to afford a brown liquid which solidified on standing. Distillation yielded, after a small forerun, 31.8 g (89%) of a light-yellow crystalline solid, mp 66–68 °C (lit.[10] 68 °C).

General Procedure for the Preparation of Methyl *p*-(Aryloxy)phenylacetates.[9] Preparation of Methyl *p*-(*p*-Chlorophenoxy)phenylacetate (20). A solution of 62.25 g (0.14 mol) of thallium(III) nitrate trihydrate and 62 mL of 70% $HClO_4$ in 311 mL of MeOH was cooled in an ice bath and 31.4 g (0.127 mol) of **15** was added. The mixture was allowed to warm to room temperature with stirring overnight, after which it was filtered and the filtrate diluted to three times its volume with water. The mixture was extracted with chloroform, and the extracts were washed with saturated $NaHCO_3$, saturated brine, and dried ($MgSO_4$). The solvent was evaporated at reduced pressure, and the residue was diluted with benzene and filtered through a short silica gel column. Evaporation of the solvent and distillation of the residue yielded 33 g (94%) of product as a yellow liquid, bp 173–178 °C (0.5 mm).

General Procedure for the Preparation of *p*-(Aryloxy)phenylacetic Acids. Preparation of *p*-[*p*-(Methylsulfonyl)phenoxy]phenylacetic Acid (25). A mixture of 48.4 g (0.255 mol) of *p*-chlorophenyl methyl sulfone, 38.8 g (0.225 mol) of *p*-hydroxyphenylacetic acid, and 86 g of K_2CO_3 in 500 mL of *N*,*N*-dimethylacetamide was stirred and heated at 155 °C for 72 h and then cooled to room temperature and poured onto 1500 g of ice and water. The solution was extracted with benzene and then carefully acidified with concentrated HCl. The mixture was chilled and filtered to give 45 g (58%) of white crystals, mp 121–124 °C. Recrystallization (with charcoal treatment) from $CHCl_3$–hexane gave 37.3 g (48%) of white crystals, mp 125–126 °C.

Methyl *p*-[(*p*-Chlorophenyl)thio]phenylacetate (30b). (A) From *p*-Iodophenylacetic Acid (27).[12] To a solution of 50.5 g (0.9 mol) of KOH in 505 mL of H_2O was added 37.9 g (0.26 mol) of *p*-chlorothiophenol. The resulting solution was heated to 50 °C and 5.05 g of copper powder and 65.5 g (0.25 mol) of *p*-iodophenylacetic acid[12] were added. The mixture was refluxed

Table IV. (Aryloxy)[*p*-(arylthio)phenyl]acetic Acid Esters



no.	Ar	Ar′	mp or bp (mm), °C	% yield	recrystn solvent	emp formula[a]	% lipid reduction vs. control[b] sterol, % diet[c] 0.1	sterol, % diet[c] 0.03	sterol, % diet[c] 0.01	triglycerides, % diet[c] 0.1	triglycerides, % diet[c] 0.03	triglycerides, % diet[c] 0.01
88	C_6H_5–	*p*-Cl-C_6H_4–	173 (0.01)	26		$C_{21}H_{17}ClO_3S$	−6 ± 4.8	6 ± 8.3	6 ± 7.4	30 ± 8.7	47 ± 9.8	41 ± 7.4[h]
89	*p*-Cl-C_6H_4–	*p*-Cl-C_6H_4–	90–94.5	62	*d*, *e*	$C_{21}H_{16}Cl_2O_3S$	25 ± 4.2[h]	25 ± 5.1[h]	17 ± 5.5[h]	64 ± 4.3[h]	62 ± 4.5[h]	66 ± 6.1[h]
90	*p*-Cl-C_6H_4–	*p*-F-C_6H_4–	84.5–87	74	*d*	$C_{21}H_{16}ClFO_3S$[g]	22 ± 16.7	23 ± 7.3[h]	21 ± 5.2[h]	36 ± 8.7	18 ± 11.6	1 ± 16.8
91	*p*-Cl-C_6H_4–		123–124.5	58	*e*, *f*	$C_{27}H_{27}ClO_3S$	19 ± 6.7[h]	15 ± 8.0	14 ± 5.7[h]	45 ± 6.0	44 ± 7.2[h]	33 ± 13.6[h]
92	*p*-Cl-C_6H_4–	*p*-$(CH_3)_3C$-C_6H_4–	106.5–108	64	*d*, *e*	$C_{27}H_{25}ClO_3S$	12 ± 3.2[h]	27 ± 6.3[h]	10 ± 8.2	59 ± 9.7[h]	56 ± 5.7[h]	45 ± 5.5[h]

[a] Analyses for C, H, Cl, S, and F within 0.4% of theoretical values. [b] Eight rats per group. [c] See Table II, footnote *c*. [d] Hexane. [e] $CHCl_3$. [f] Methanol. [g] Calcd: C, 62.61. Found: 62.15. [h] Significant at $p < 0.05$.

Table V

no.	X	R_1	R_2	mp, °C	% yield	recrystn solvent	formula[a]	% lipid reduction vs. control: sterol, % diet[c] 0.1	sterol, % diet[c] 0.03	sterol, % diet[c] 0.01	triglyceride, % diet[c] 0.1	triglyceride, % diet[c] 0.03	triglyceride, % diet[c] 0.01
93	O	CH_3	CH_3	oil	69		$C_{22}H_{18}Cl_2O_4$[b]	39 ± 16.2	14 ± 5.6	9 ± 5.0	63 ± 6.8[d]	44 ± 11.6	39 ± 11.4
94	O	CO_2CH_3	CH_3	glass	70		$C_{23}H_{18}Cl_2O_6$	32 ± 4.6[d]	25 ± 22.6	9 ± 14.7	63 ± 7.6[d]	48 ± 6.3[d]	−2 ± 17.7
95	O	H	$-CH_2C(OH)HCH_2OH$	glass	58		$C_{23}H_{20}Cl_2O_6$	39 ± 6.4[d]	27 ± 4.3[d]	13 ± 5.3	63 ± 5.7[d]	53 ± 5.5[d]	24 ± 7.6
96	S(=O)	H	CH_3	138–148	51	CH_3OH	$C_{21}H_{16}Cl_2O_4S$	31 ± 4.5[d]	11 ± 9.9	15 ± 6.6	55 ± 9.2[d]	35 ± 8.3[d]	12 ± 11.2
97	O	H	0.5Cu	>300 dec	95	H_2O	$C_{20}H_{13}Cl_2O_4{\cdot}0.5Cu$	42 ± 5.1[d]	30 ± 6.9[d]	26 ± 6.0[d]	67 ± 6.5[d]	56 ± 6.9[d]	19 ± 9.1
98	O	$(EtO)_2P(=O)-$	CH_3	oil	18		$C_{25}H_{25}Cl_2O_7P$	43 ± 10.6	27 ± 5.9[d]	23 ± 3.8[d]	60 ± 5.4[d]	44 ± 6.3[d]	18 ± 13.4

[a] Analyses for C, H, P, and S within 0.4% of theoretical values. [b] Calcd: C, 59.87. Found: 60.75. [c] See Table II, footnote c. [d] Values are significant at $p < 0.05$.

overnight, during which time most of the copper metal turned to a yellow solid (CuI). The mixture was cooled and filtered through diatomaceous earth and the brown filtrate was acidified to pH 2 (HCl). Filtration gave an off-white solid, which was dissolved in chloroform and washed with aqueous $NaHCO_3$. The aqueous washes were acidified with HCl to give 32.7 g (47%) of white crystals, mp 146–149 °C.

A mixture of 21 g (0.075 mol) of the above acid and 11.9 g of thionyl chloride was stirred overnight at room temperature. The excess thionyl chloride was removed at reduced pressure and the residue was added to 300 mL of MeOH at 0 °C. After stirring briefly, the solvent was evaporated, and the residue was dissolved in ether, washed with $NaHCO_3$, and brine, and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue yielded 21.3 g (97%) of yellow liquid, bp 158 °C (0.1 mm).

(B) From Methyl *p*-Iodophenylacetate (28). A mixture of 69 g (0.25 mol) of methyl *p*-iodophenylacetate (from the acid and $SOCl_2$ and MeOH, as above) and 56.9 g (0.275 mol) of cuprous *p*-chlorophenyl mercaptide[13] in 2500 mL of dry pyridine (4Å sieves) was refluxed under argon for 18 h. After cooling to room temperature, the resulting brown solution was poured into 3 L of H_2O, made slightly acidic with HCl, and extracted with 3 L of ether. The extracts were washed with 10% HCl until the washings were acidic and then with water, $NaHCO_3$, and brine, and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue yielded 57.4 g (78%) of a colorless liquid, bp 170–180 °C (0.2 mm), identical with the product prepared above.

General Procedure for the Substitution of Methyl (Aryloxy)[*p*-(aryloxy)phenyl]acetates and their Thia Analogues. Preparation of Methyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate (31). To a solution of 33.07 g (0.12 mol) of methyl *p*-(*p*-chlorophenoxy)phenylacetate in 350 mL of CCl_4 was added 21.84 g (0.122 mol) of *N*-bromosuccinimide and 1 mL of CCl_4 saturated with HBr. The mixture was refluxed for 3 h, after which the NMR spectrum of an aliquot indicated essentially complete reaction. After cooling, the succinimide was filtered off and the filtrate was concentrated at reduced pressure. The residue was dissolved in benzene and filtered through a short silica gel column. The solvent was removed to afford 25.5 g (60%) of a yellow brown oil (unstable to distillation).

To a solution of 1.19 g (0.022 mol) of sodium methoxide in 40 mL of MeOH was added 3.21 g (0.025 mol) of *p*-chlorophenol and 50 mg of potassium iodide. After ca. 30 min at room temperature, 7.11 g (0.02 mol) of the crude bromo ester in 10 mL of benzene was added, and the mixture was refluxed overnight. After cooling to room temperature, the mixture was poured into 100 mL of water and extracted with benzene. The combined extracts were washed with 5% NaOH, water, and saturated brine, and dried. Evaporation of the solvent yielded an oil, which was induced to crystallize[17] by trituration with hexane to give 6.45 g (80%) of a white solid, mp 100-101.5 °C.

General Procedure for Transesterification of Methyl to Ethyl Esters.[18] Preparation of Ethyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate (61). A solution of 250 mL of ethanol in 3 L of benzene was refluxed under a soxhlet extractor containing 454 g of 3Å molecular sieves for 36 h. The sieves were replaced with a fresh charge, and 1.5 g of sodium was added to the liquid and stirred until the metal dissolved. To this was added 146 g (0.36 mol) of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate (**31**), and the mixture was heated at reflux for 72 h. The mixture was then cooled and filtered to remove an insoluble material (later identified as the sodium salt of the free acid). The filtrate was concentrated to a brown oil, which was filtered through a short silica gel column with benzene eluent and treated with hexane to give 112.5 g (75%) of white solid, mp 52.5–54 °C.

Methyl (*p*-Chlorophenoxy)[*p*-[(*p*-chlorophenyl)sulfinyl]phenyl]acetate (96). To a solution of 1.8 g (4.3 mmol) of methyl (*p*-chlorophenoxy)[*p*-[(*p*-chlorophenyl)thio]phenyl]acetate in 10 mL of dichloromethane was added dropwise 0.891 g (4.7 mmol) of *m*-chloroperbenzoic acid in 10 mL of dichloromethane (exotherm, 24–32 °C). The mixture was chilled overnight and filtered, and the filtrate was washed with 10% sodium sulfite, saturated sodium bicarbonate, and saline solutions. The organic layer was dried ($MgSO_4$) and the solvent removed. The residue

was crystallized from CH_2Cl_2–hexane to give 1.65 g of white crystals, mp 134–144 °C. Recrystallization (three times) from methanol gave 0.96 g of white crystals, mp 138–148 °C. Anal. ($C_{21}H_{16}O_4SCl_2$) C, H, Cl, S.

Methyl 2-(*p*-Chlorophenoxy)-2-[*p*-(*p*-chlorophenoxy)-phenyl]propionate (93). The general procedure of Brocksom et al.[19] and Schlessinger et al.[20] was followed. A solution of 2.02 g (0.02 mol) of dry *N,N*-diisopropylamine and 15 mL of dry THF (distilled from lithium aluminum hydride) was cooled to 0 °C, and 8.5 mL of 2.0 M *n*-butytllithium in hexane was added dropwise, keeping the tempature 0–5 °C. The mixture was then cooled to −70 °C, and 6.51 g (0.015 mol) of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate in 10 mL of THF was added over 15 min. After 15 min, 3.58 g (0.02 mol) of dry HMPA was added. After 0.5 h, 4.26 g (0.03 mol) of methyl iodide was added. The color lightened slowly over 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was then poured into 100 mL of water and extracted with 2 × 75 mL of ether. The combined extracts were washed with 4 × 50 mL of 10% HCl, H_2O, and saturated brine, and then dried. Evaporation of the solvent gave a brown oil, which was filtered through a short silica gel column (benzene) to give 4.3 g (69%) of a light yellow oil.

Dimethyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)-phenyl]malonate (94). The ester enolate of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate was prepared identically as in the previous example. To this solution at −70 °C was added 2.82 g (0.03 mol) of methyl chloroformate. The color of the mixture lightened and the temperature rose to −40 °C. The mixture was stirred overnight at room temperature and worked up as in the previous example to afford a yellow oil containing the desired product and methyl *N,N*-diisopropylcarbamate. The latter was removed by trituration with petroleum ether. The residue was chromatographed on 100 g of silica gel (petroleum ether–benzene, 1:1) to give 4.86 g (70%) of a yellow glass.

Methyl (*p*-Chlorophenoxy)[*p*-(*p*-chlorophenoxy)-phenyl](diethoxyphosphinyl)acetate (98). The ester enolate of methyl (*p*-chlorophenoxy)[*p*-(*p*-chlorophenoxy)phenyl]acetate was prepared as in the preceding two examples, and 5.17 g (0.03 mol) of diethyl chlorophosphonate was added. The reaction mixture was stirred at room temperature for 3 days. Workup as before afforded a brown oil, which was chromatographed on 250 g of silica gel (3:2 benzene–chloroform) to afford an unidentified side product. Further elution with chloroform gave the desired product, which was purified further by preparative TLC to give 1.46 g (18%) of product as a yellow oil.

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References and Notes

(1) Presented, in part, at the Joint Conference, CIC/ACS, Montreal, Quebec, Canada, May 29–June 2, 1977.
(2) (a) D. Steinberg, *Adv. Pharmacol.*, **1**, 59 (1962); (b) R. E. Howe, *Adv. Drug Res.*, **9**, 7 (1974); (c) W. L. Bencze, R. Hess, and G. deStevens, *Prog. Drug. Res.*, **13**, 217 (1969); (d) A. C. Sullivan, L. Cheng, and J. G. Hamilton, *Annu. Rep. Med. Chem.*, **12**, 191 (1977); (e) C. E. Day, *ibid.*, **13**, 184 (1978).
(3) J. M. Thorpe and W. S. Waring, *Nature (London)*, **194**, 948 (1962); D. S. Platt and J. M. Thorpe, *Biochem. Pharmacol.*, **15**, 915 (1966). For a recent review, see D. T. Witiak, H. A. I. Newman, and D. R. Feller, "Clofibrate and Related Analogs", Marcel Dekker, New York and Basel, 1977.
(4) For a graphic summation of aryloxyacetic acids in hypolipidemic research, see L. J. Chinn and K. W. Salamon, *J. Med. Chem.*, **20**, 229 (1977).
(5) (a) E. Granzer and H. Nahm, *Arzneim.-Forsch.*, **23**, 1353 (1973); (b) H. Nahm and E. Granzer, Ger. Offen., 2136828.
(6) E.-C. Witte, *Prog. Med. Chem.*, **11**, 119–192 (1975).
(7) (a) I. Felner and K. Schenker, *Helv. Chim. Acta*, **53**, 754 (1970); (b) C. A. Dornfield, U.S. Patent 2893993, July 7, 1959.
(8) Anhydrous HBr gas was found to be preferable to 48% HBr.
(9) A. McKillop; B. P. Swann, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3340 (1973).
(10) Aryloxyacetophenones have been previously prepared by Ullman-type coupling of phenols to *p*-bromoacetophenone using copper catalysts. Acids and esters related to **5a** were also prepared from ketones **11** via a Willgerodt reaction. M. Julia and H. Baillarge, *Bull. Soc. Chim. Fr.*, 644 (1953). The present procedure offers marked improvements over the literature method in both yield and ease of preparation.
(11) D. T. Mowry, M. Renoll, and N. F. Huber, *J. Am. Chem. Soc.*, **60**, 1105 (1946).
(12) M. Giannini and M. Fedi, *Boll. Chim. Farm.*, **97**, 602 (1958).
(13) (a) R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4923 (1959); (b) G. H. Posner, D. J. Brunelle, and L. Sinoway, *Synthesis*, 662 (1974); (c) G. H. Posner and J. S. Ting, *Synth. Commun.*, **4**, 355 (1974).
(14) Biological tests were carried out by Dr. S. A. Schaffer and co-workers.
(15) Serum sterol concentrations were determined by an automated method based on the procedure of J. Levine and B. Zak, *Clin. Chem.*, **10**, 381 (1964).
(16) Serum triglycerides were determined by an automated method based on the procedure of R. P. Noble and F. M. Campbell, *Clin. Chem.*, **16**, 166 (1970).
(17) Not all final ester products were crystalline. Purification of these was accomplished by chromatography on silica gel with benzene as eluent.
(18) D. P. Roelofsen, J. A. Hagendorn, and H. Van Bekken, *Chem. Ind. (London)*, 1622 (1966).
(19) T. J. Brocksom, N. Petragnani, and R. Rodrigues, *J. Org. Chem.*, **39**, 2114 (1974).
(20) R. J. Cregge, J. L. Hermann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).

Antiinflammatory Agents. 1. Synthesis and Antiinflammatory Activity of 2-Amino-3-benzoylphenylacetic Acid

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The synthesis and antiinflammatory activity of 2-amino-3-benzoylphenylacetic acid are described. This compound was postulated to be an active metabolite of 7-benzoylindoline in order to explain the unexpected antiinflammatory activity of the latter compound. Metabolism studies on ^{14}C-labeled 7-benzoylindoline did not confirm this hypothesis. Nevertheless, 2-amino-3-benzoylphenylacetic acid, its ethyl ester, and the sodium salt show potent antiinflammatory activity in pharmacological models.

During the course of synthetic work on a series of tricyclic benzodiazepines, a number of bicyclic amino benzophenones were prepared as intermediates. One compound, 7-benzoylindoline (1),[1] demonstrated unexpected antiinflammatory activity comparable to phenylbutazone in the Evans blue carrageenan pleural effusion model in

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