

(Aryloxy)[*p*-(aryloxy)phenyl]- and (Aryloxy)[*p*-(arylthio)phenyl]acetic Acids and Esters as Hypolipidemic Agents¹

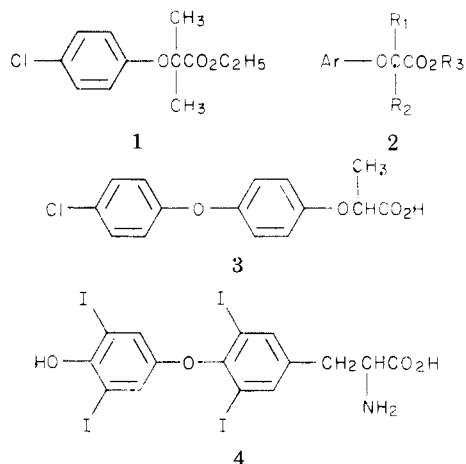
Ronald I. Trust,* Francis J. McEvoy, and J. Donald Albright*

Cardiovascular-CNS Disease Research Section, Medical Research Division, American Cyanamid Company, Lederle Laboratories, Pearl River, New York 10965. Received January 29, 1979

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 hypolipi-

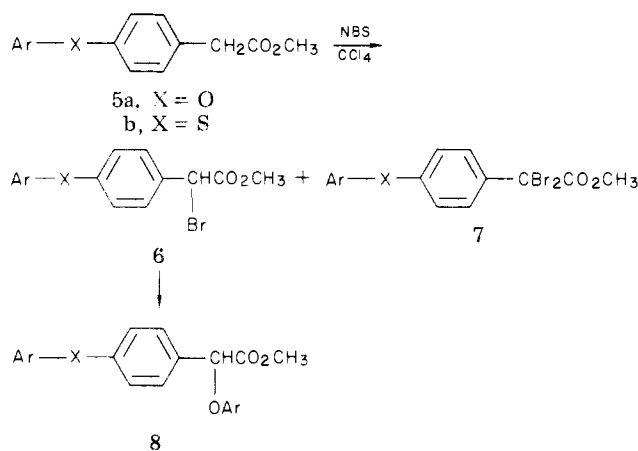


dem agent,³ a number of compounds (2) bearing the aryloxyacetic acid moiety have been studied.⁴ Recently, a new agent, 2-[*p*-(*p*-chlorophenoxy)phenyl]propionic acid (3), with hypolipidemic activity claimed to be 15–20 times that of clofibrate has been reported.⁵ The diphenyl ether moiety is present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

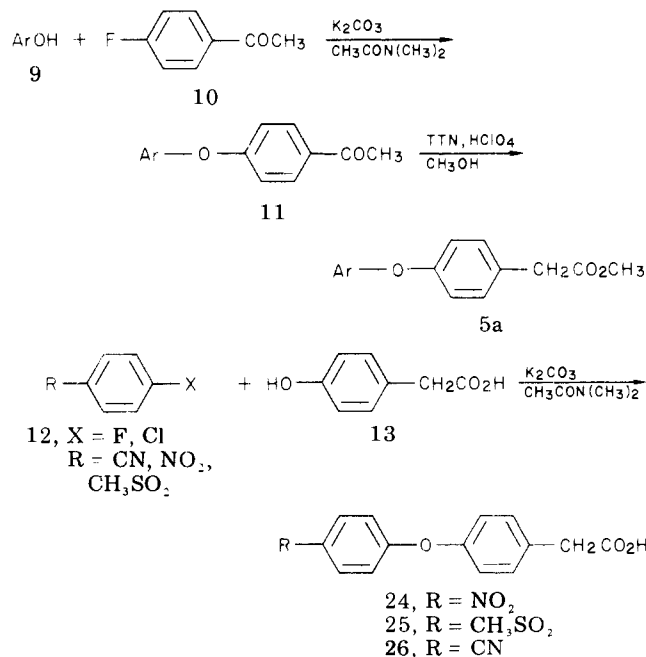
Of general interest, therefore, was the preparation of structures with potential hypolipidemic activity containing a diphenyl ether moiety as a lipophilic group. This paper describes the synthesis of compounds of general structure 8 and their activity as hypolipidemic agents.

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 ¹H 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,

Scheme I



Scheme II



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.

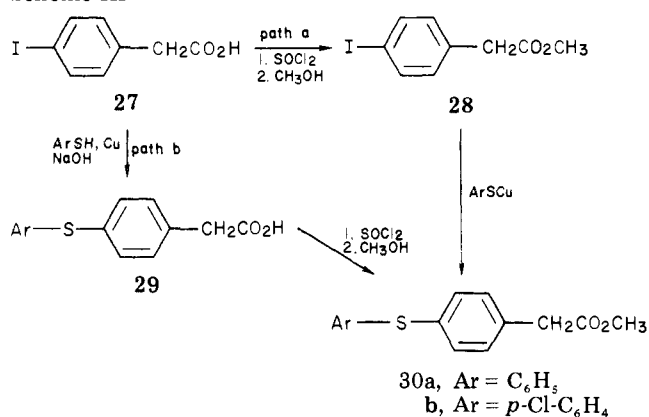
The reactions of the bromo esters 6 with phenols were, in general, straightforward. A solution of the phenol (0.025 mol) and sodium methoxide in methanol was stirred for ca. 30 min, followed by the addition of 0.02 mol of the appropriate bromo ester in 10 mL of benzene and 50 mg

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 ₆ H ₅	COCH ₃	46-49 ^b	58	<i>e</i>	C ₁₄ H ₁₂ O ₂
15	<i>p</i> -ClC ₆ H ₄	COCH ₃	66-68 ^c	89	<i>e</i>	C ₁₄ H ₁₁ ClO ₂
16	<i>m</i> -CF ₃ C ₆ H ₄	COCH ₃	130-142 (0.2)	86		C ₁₅ H ₁₁ F ₃ O ₂
17	4-Cl-1-naphthyl	COCH ₃	100-104	63	<i>f</i>	C ₁₈ H ₁₃ ClO ₂
18	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄	COCH ₃	160-165 (0.1)	97		C ₁₈ H ₂₀ O ₂
19	C ₆ H ₅ ^d	CH ₂ CO ₂ CH ₃	122-131 (0.05)	98		C ₁₅ H ₁₄ O ₃
20	<i>p</i> -Cl-C ₆ H ₄	CH ₂ CO ₂ CH ₃	173-178 (0.5)	94		C ₁₅ H ₁₃ ClO ₃
21	<i>m</i> -CF ₃ -C ₆ H ₄	CH ₂ CO ₂ CH ₃	120-148 (0.07)	92		C ₁₆ H ₁₃ F ₃ O ₃ ^h
22	4-Cl-1-naphthyl	CH ₂ CO ₂ CH ₃	196 (0.1)	83		C ₁₉ H ₁₅ ClO ₃
23	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄	CH ₂ CO ₂ CH ₃	152-163 (0.04)	66		C ₁₉ H ₂₂ O ₃
24	<i>p</i> -NO ₂ -C ₆ H ₄	CH ₂ CO ₂ H	135-137	90	<i>g</i>	C ₁₄ H ₁₁ NO ₅
25	<i>p</i> -CH ₃ SO ₂ -C ₆ H ₄	CH ₂ CO ₂ H	125-126	48	<i>f</i>	C ₁₅ H ₁₄ O ₅ S
26	<i>p</i> -CN-C ₆ H ₄	CH ₂ CO ₂ H	125-127	58	<i>g</i>	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 acid¹⁰ and thionyl chloride, followed by methanolysis. ^e Evaporative distillation in a Büchi Kugelrohrföfen; the product crystallized. ^f CHCl₃-hexane. ^g CH₃OH-H₂O. ^h F: calcd, 18.37; found, 17.73.

Scheme III



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 mercaptide¹³ 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 activity¹⁴ found for [*p*-(*p*-chlorophenoxy)phenyl]acetic acids and esters substituted with diverse α -aryloxy groups.

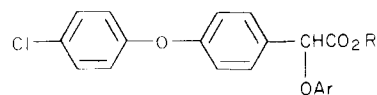
Multiple variations of substituents in the α -phenoxy moiety show that there is no simple correlation of activity with polar or electronic properties of the substituents. Derivatives **33**, **35**, **38**, **52**, and **63** with *p*-*tert*-butyl, *m*-*tert*-butyl, *p*-cyclohexyl, 3,4-dimethyl, and *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. Introduction of a trifluoromethyl group (electron withdrawing and lipophilic) in the meta or para position gave active derivatives **34** and **59**, but only **59** (*p*-CF₃) 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**). Multiple 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-(naphthoxy) moiety were inactive, while **58** with a 2-(naphthoxy) group showed moderate activity. Tetrahydronaphthoxy 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-naphthoxy (**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			triglycerides, % diet ^c		
							0.1	0.03	0.01	0.1	0.03	0.01
31	4-Cl-C ₆ H ₄	CH ₃	100-101.5	80	<i>d</i>	C ₂₁ H ₁₆ Cl ₂ O 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 ₆ H 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- <i>t</i> -Bu-C ₆ H ₄	CH ₃	118-120	62	<i>d</i>	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 ₆ H ₄	CH ₃	178 (0.05)	51		C ₂₇ H ₁₆ ClF ₃ O 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- <i>t</i> -Bu-C ₆ H 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	<i>d</i>	C ₂₅ H ₁₈ Cl ₂ O ₃	11 ± 4.8	-3 ± 8.5	-18 ± 6.0	32 ± 15.7	-8 ± 13.4	-15 ± 14.8
37	3-biphenyl	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 ₆ H ₄	CH ₃	122-123.5	51	<i>d, f</i>	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 ₆ H ₂	CH ₃	oil	90		C ₂₁ H ₁₄ Cl ₃ O 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 ₆ H ₄	H	106-111	78	<i>d</i>	C ₂₆ 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 ₆ H ₄	CH ₃	88-90	61	<i>h, i</i>	C ₂₈ H ₂₃ ClO ₅	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 ₆ H 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 ₆ H ₂	CH ₃	92.5-95.5	62	<i>d</i>	C ₂₃ H ₂₀ Cl ₂ O 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 ₆ H ₄	CH ₃	oil	59		C ₂₁ H ₁₆ Cl ₂ O 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- <i>t</i> -Bu-C ₆ H ₃	CH ₃	85.5-88	49	<i>d</i>	C ₂₅ H ₂₃ Cl ₂ O 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- <i>t</i> -Bu-C ₆ H 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 ₆ H ₃	CH ₃	78.5-82	60	<i>d</i>	C ₂₁ H ₁₅ Cl ₃ O 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 ₆ H ₃	CH ₃	oil	53		C ₂₁ H ₁₅ Cl ₃ O 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	<i>h</i>	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 ₂ NO 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	<i>d</i>	C ₂₃ H ₁₉ ClO ₄	4 ± 6.2	3 ± 5.9	-	39 ± 6.5 ^P	36 ± 6.2 ^P	
52	3,4-Me ₂ -C ₆ H 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 ₂₄ 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 ₆ H ₃	CH ₃	77-79	57		C ₂₃ H ₁₈ Cl ₂ O 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 ₃ CONH-C ₆ H ₄	CH ₃	157-160	73	<i>h, i</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 ₆ H ₄	CH ₃	oil	69		C ₂₇ H ₁₆ F ₃ O 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	<i>d</i>	C ₂₄ H ₂₀ Cl ₂ O 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	<i>d</i>	C ₂₅ H ₂₂ Cl ₂ O 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 ₆ H ₄	CH ₃	111-112.5	79	<i>f, m</i>	C ₂₈ H ₃₀ 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 ₆ H ₄	CH ₃	148.5-150.5	74	<i>d, f</i>	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 ₆ H ₄	H	141-142	94	<i>d, f</i>	C ₂₆ H ₁₄ Cl ₂ O 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 ₆ H ₄	C ₂ H ₅	52.5-54	62 ⁿ	<i>d</i>	C ₂₂ H ₁₈ Cl ₂ O 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 CHCl₃. ^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			triglycerides, % diet		
								0.1	0.03	0.01	0.1	0.03	0.01
67	<i>p</i> -NC-C ₆ H ₄ -	<i>p</i> -Cl-C ₆ H ₄ -	CH ₃	oil	60		C ₂₂ H ₁₆ NO ₄ Cl ^d	16 ± 7.7	19 ± 5.9	20 ± 7.3	71 ± 4.6 ^m	60 ± 6.3 ^m	50 ± 6.5 ^m
68	<i>p</i> -NC-C ₆ H ₄ -	<i>p</i> -F-C ₆ H ₄ -	CH ₃	93-95	36	<i>e, f</i>	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	<i>p</i> -NC-C ₆ H ₄ -	<i>m</i> -CF ₃ -C ₆ H ₄ -	CH ₃	oil	67		C ₂₃ H ₁₆ NO ₄ F ₃	32 ± 9.7 ^m	24 ± 7.0 ^m	12 ± 7.9	50 ± 6.2 ^m	34 ± 7.3 ^m	-37 ± 18.7
70	<i>p</i> -NC-C ₆ H ₄ -	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	CH ₃	122-124	41	<i>e, f</i>	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	<i>p</i> -CH ₃ SO ₂ -C ₆ H ₄ -	<i>p</i> -Cl-C ₆ H ₄ -	CH ₃	182-184	44	<i>f, g</i>	C ₂₂ H ₁₉ ClO ₆ S	15 ± 6.3	-1 ± 5.0	8 ± 5.3	22 ± 7.6	-11 ± 20.9	11 ± 11.8
72	<i>p</i> -CH ₃ SO ₂ -C ₆ H ₄ -	<i>p</i> -F-C ₆ H ₄ -	CH ₃	136-138	50	<i>e, f</i>	C ₂₂ H ₁₉ FO ₆ S	10 ± 6.3	-1 ± 4.7	-3 ± 6.1	3 ± 22.5	-8 ± 10.5	16 ± 17.1
73	<i>p</i> -O ₂ N-C ₆ H ₄ -	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	CH ₃	101-103	43	<i>h</i>	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	<i>p</i> -CH ₃ C(=O)NH-C ₆ H ₄ -	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	CH ₃	141-143	80	<i>i</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 ₆ H ₅ -	<i>p</i> -Cl-C ₆ H ₄ -	CH ₃	99-102	87	<i>e, j</i>	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 ₆ H ₅ -	C ₆ H ₅ -	CH ₃	75.5-77.5	90	<i>j</i>	C ₂₁ H ₁₈ O ₄ ^l	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 ₆ H ₅ -	C ₆ H ₅ -	H	144-146	81	<i>j, k</i>	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		<i>p</i> -Cl-C ₆ H ₄ -	CH ₃	glass	74		C ₂₅ H ₁₈ Cl ₂ O ₄	23 ± 4.7 ^m	17 ± 5.6	6 ± 6.0	38 ± 9.4	12 ± 14.5	33 ± 11.1
79		<i>p</i> -(CH ₃) ₃ C-C ₆ H 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	<i>m</i> -CF ₃ -C ₆ H ₄ -	<i>p</i> -Cl-C ₆ H ₄ -	CH ₃	79-82	66	<i>e</i>	C ₂₂ H ₁₆ ClF ₃ O 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	<i>m</i> -CF ₃ -C ₆ H ₄ -	<i>p</i> -F-C ₆ H ₄ -	CH ₃	70-72	81	<i>e</i>	C ₂₂ H ₁₆ F ₄ O ₄	32 ± 5.2 ^m	6 ± 9.3	4 ± 4.5	48 ± 6.9 ^m	27 ± 8.4 ^m	45 ± 5.6 ^m
82	<i>m</i> -CF ₃ -C ₆ H ₄ -		CH ₃	oil	67		C ₂₈ H ₂₇ F ₃ O 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	<i>m</i> -CF ₃ -C ₆ H ₄ -	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	CH ₃	oil	72		C ₂₆ H ₂₃ F ₃ O 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	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	<i>p</i> -Cl-C ₆ H 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	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	<i>m</i> -CF ₃ -C ₆ H ₄ -	CH ₃	oil	78		C ₂₆ H ₂₅ F ₃ O ₄	13 ± 5.5	-4 ± 7.2	-5 ± 9.4	19 ± 12.1	-18 ± 20.7	-12 ± 20.6
86	<i>p</i> -(CH ₃) ₃ C-C ₆ H ₄ -	<i>m</i> -(CH ₃) ₃ C-C ₆ H 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	<i>p</i> -(CH ₃) ₃ C-C ₆ H 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 CH₂Cl₂. ^h Methanol. ⁱ Ether. ^j Petroleum ether. ^k CHCl₃. ^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 commercial 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 sterols¹⁵ and triglycerides¹⁶ were measured using a Technicon Autoanalyser.

Chemistry. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ¹H 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 consistent 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 H₂O and extracted with benzene. The organic extracts were washed with dilute sodium hydroxide and dried (Na₂SO₄) 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% HClO₄ 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 NaHCO₃, saturated brine, and dried (MgSO₄). 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*-(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 K₂CO₃ 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 into 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 CHCl₃-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 H₂O 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 acid¹² were added. The mixture was refluxed

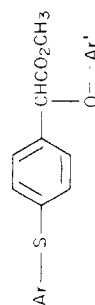
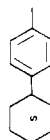


Table IV. (Aryloxy)[*p*-(arythio)phenyl]acetic Acid Esters

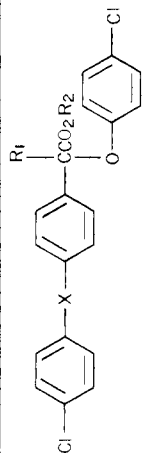
no.	Ar	Ar'	mp or bp (mm), °C	% yield	recrystn solvent	emp formula ^a	% lipid reduction vs. control ^b						
							sterol, % diet ^c		triglycerides, % diet ^c		sterol, % diet ^c		triglycerides, % diet ^c
88	C ₆ H ₅ -	<i>p</i> -Cl-C ₆ H ₄ -	173 (0.01)	26		C ₂₁ H ₁₇ ClO ₃ S	0.1	0.03	0.01	0.1	0.03	0.01	0.01
89	<i>p</i> -Cl-C ₆ H ₄ -	<i>p</i> -Cl-C ₆ H ₄ -	90-94.5	62	<i>d, e</i>	C ₂₁ H ₁₆ Cl ₂ O ₃ S	0.1	0.03	0.01	0.1	0.03	0.01	0.01
90	<i>p</i> -Cl-C ₆ H ₄ -	<i>p</i> -F-C ₆ H ₄ -	84.5-87	74	<i>d</i>	C ₂₁ H ₁₆ ClFO ₃ S ^f	0.1	0.03	0.01	0.1	0.03	0.01	0.01
91	<i>p</i> -Cl-C ₆ H ₄ -		123-124.5	58	<i>e, f</i>	C ₂₇ H ₂₇ ClO ₃ S	0.1	0.03	0.01	0.1	0.03	0.01	0.01
92	<i>p</i> -Cl-C ₆ H ₄ -	<i>p</i> -(CH ₂) ₄ -C ₆ H ₄ -	106.5-108	64	<i>d, e</i>	C ₂₃ H ₁₅ ClO ₃ S	0.1	0.03	0.01	0.1	0.03	0.01	0.01

^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 CHCl₃. ^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	% recrystn yield	solvent	formula ^a	% lipid reduction vs. control				
								sterol, % diet ^c	triglyceride, % diet ^c	0.1	0.03	
93	O	CH ₃	CH ₃	oil	69		C ₂₂ H ₁₈ Cl ₇ O ₄	14 ± 5.6	9 ± 5.0	63 ± 6.8 ^d	44 ± 11.6	39 ± 11.4
94	O	CO ₂ CH ₃	CH ₃	glass	70		C ₂₃ H ₁₉ Cl ₇ O ₆ ^b	25 ± 22.6	9 ± 14.7	63 ± 7.6 ^d	48 ± 6.3 ^d	-2 ± 17.7
95	O	H	-CH ₂ C(OH)HCH ₂ OH	glass	58		C ₂₃ H ₂₀ Cl ₇ O ₆	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 ₃ OH	C ₂₁ H ₁₆ Cl ₇ O ₅ S	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 ₂ O	C ₂₀ H ₁₃ Cl ₇ O ₄ -0.5Cu	30 ± 6.9 ^d	26 ± 6.0 ^d	67 ± 6.5 ^d	56 ± 6.9 ^d	19 ± 9.1
98	O	(EtO) ₂ P(=O)-	CH ₃	oil	18		C ₂₅ H ₂₅ Cl ₂ O ₇ P	43 ± 10.6	27 ± 5.9 ^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 NaHCO₃. 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 NaHCO₃ and brine, and dried (MgSO₄). 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 SOCl₂ and MeOH, as above) and 56.9 g (0.275 mol) of cuprous *p*-chlorophenyl mercaptide¹³ 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 H₂O, 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, NaHCO₃ and brine, and dried (MgSO₄). 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 CCl₄ was added 21.84 g (0.122 mol) of *N*-bromosuccinimide and 1 mL of CCl₄ 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 crystallize¹⁷ 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 (MgSO₄) 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. ($\text{C}_{21}\text{H}_{16}\text{O}_4\text{S}\text{Cl}_2$) 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*-butyllithium in hexane was added dropwise, keeping the temperature 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.

Acknowledgment. We thank Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectra data, and Dr. S. Schaffer and staff for biological testing.

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 2 893 993, 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. Petragrani, 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

William J. Welstead, Jr.,* H. Wayne Moran, Harold F. Stauffer, Lennox B. Turnbull, and Lawrence F. Sancilio
A. H. Robins Company, Richmond, Virginia 23220. Received October 23, 1978

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 com-

pound, 7-benzoylindoline (1),¹ demonstrated unexpected antiinflammatory activity comparable to phenylbutazone in the Evans blue carrageenan pleural effusion model in