troleum ether gave the *l* isomer **24** as colorless crystals: mp 102–104°; yield, 1 g; $[\alpha]^{26}D$ -39.3° (*c* 2.1, EtOH). Anal. ($C_{17}H_{14}O_4$) C, H.

Methyl 2-Bromomethyl-4-iodobenzoate. A mixture of methyl 4-iodo-2-methylbenzoate (0.83 g, 3 mmol), NBS (0.53 g, 3 mmol), and benzoyl peroxide (0.07 g) in CCl_4 (20 ml) was refluxed with stirring for 19 h and filtered. The filtrate was washed with 2% NaOH and water and dried. After removal of the solvent, the residue was purified by silica gel chromatography using C_6H_6 and crystallized from n-C_6H_{14}: yield, 0.85 g (76%); mp 67.5–68.5°. Anal. ($C_9H_8BrIO_2$) C, H.

Methyl 2-Methyl-4-trifluoromethylbenzoate. Methyl 4-iodo-2-methylbenzoate (7.0 g, 25 mmol), active Cu[16] (10 g, dried under vacuum at 100–110° for 5 h), and CF_3I (17 g, 87 mmol) in dry DMF (14 ml) were put into a stainless tube which was chilled at -40 to -50°. The sealed tube was heated at 130–140° for 72 h. After cooling, the reaction mixture was shaken with $CHCl_3$. The washed, dried $CHCl_3$ extract was concentrated and the residue was separated on silica gel chromatography using C_6H_6–petroleum ether (1:1) as an elute. The oily residue was distilled under reduced pressure to yield a colorless oil of 4.3 g (80%): bp 105–107° (30 mm). Anal. ($C_{10}H_9F_3O_2$) C, H.

Methyl 2-Bromomethyl-4-trifluoromethylbenzoate. A mixture of methyl 2-methyl-4-trifluoromethylbenzoate (2.18 g, 10 mmol), NBS (1.78 g, 10 mmol), and benzoyl peroxide (0.5 g) in CCl_4 (40 ml) was refluxed for 8 h and treated in the same manner as described above. The crude colorless oil which showed a methylene proton signal at δ 4.99 (s, 2 H) in the NMR spectrum ($CDCl_3$) was used in the next step without further purification.

Acknowledgment. Gratitude is due to Drs. N. Koga and G. Ohta for continuous support and pertinent discussion, to the personnel of the analytical section of our Institute for the elemental analyses, and to Miss M. Ohara for assistance with the manuscript.

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Hypolipidemic Alkoxybenzoic Acids

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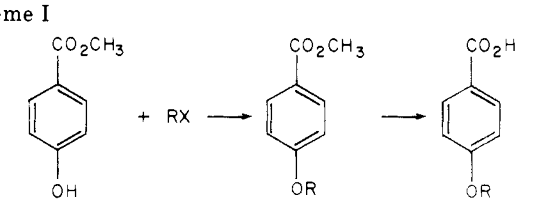
The preparation of a series of *p*-alkoxybenzoic acids bearing aromatic ring substituents or modified alkyl chains is described. The compounds were screened in rats for serum sterol and triglyceride-lowering activity.

The serum sterol and triglyceride-lowering properties of the homologous *p*-(*n*-alkoxy)benzoic acids have been reported.[1] *p*-Hexadecyloxybenzoic acid was selected as the most interesting member of this series; however, administration of this compound to dogs was accompanied by undesirable side effects on the central nervous system. In an effort to find a compound lacking this toxicity, the preparation of a variety of *p*-alkoxybenzoic acid analogues was undertaken. Benzoic acids bearing aromatic ring substituents (**59–63**) or modified alkoxy groups are described here. The latter class includes acids having γ-substituted tetradecyloxy (**64–69**), ω-substituted alkoxy (**70–91**), branched primary alkoxy (**92–94**), *sec*-alkoxy (**95–99**), and *tert*-alkoxy groups (**100–105**). Additionally, olefinic (**106–112**), acetylenic (**113**), polyunsaturated (**114**, **115**), and oxygenated (**116–120**) derivatives are reported.

The procedure of greatest utility for the preparation of these analogues involved the alkylation of a phenoxide with the requisite bromide or methanesulfonate (Scheme I). Methyl *p*-hydroxybenzoate (methylparaben) as well as

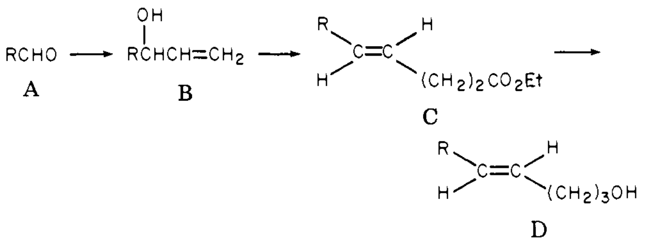
Scheme I



certain ring-substituted methylparabens and *p*-hydroxybenzoic acids[2] were the phenoxides alkylated in this manner. The ester products were saponified to yield the corresponding acids. Esters and acids prepared by these procedures (methods A and B) are among those shown in Tables I–IV. These include acids having ring substituents, γ-substituted tetradecyloxy, ω-substituted alkoxy, branched primary alkoxy, and *sec*-alkoxy groups, as well as olefinic, acetylenic, polyunsaturated, and oxygenated chains.

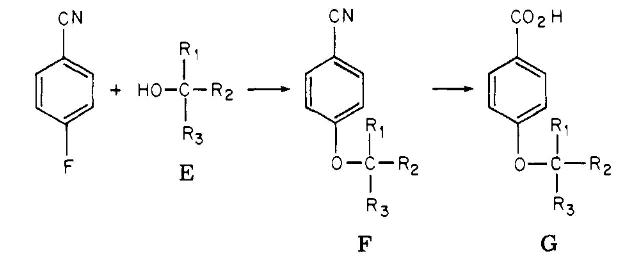
The bromides required for these preparations were obtained by the action of phosphorus tribromide or hy-

Scheme II



R = $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_8CH{=}CH_2$

Scheme III



drogen bromide on the appropriate alcohol (see Experimental Section) or by borane reduction of ω-bromoalkanoic acids (eq 1). The methanesulfonates (Table V) required for the preparation of a series of unsaturated analogues

$$Br(CH_2)_{n-1}CO_2H \rightarrow Br(CH_2)_nOH \quad (1)$$
$$n = 12, 15, 16, 18$$

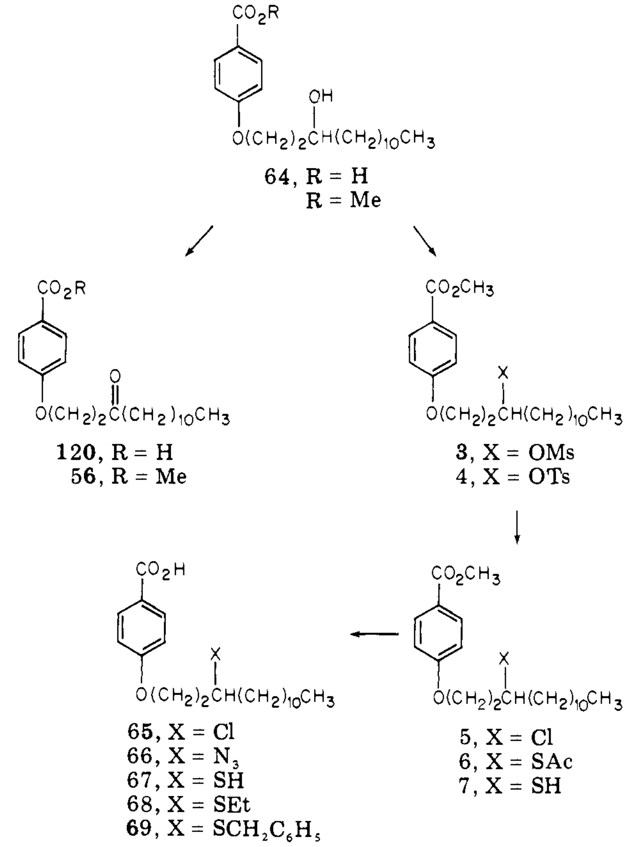
were prepared from the corresponding alcohols in the usual way. Several of these unsaturated alcohols were prepared by the sequence of Scheme II. The Grignard addition of vinylmagnesium bromide to various aldehydes A afforded alcohols B which upon heating with triethyl orthoacetate and propionic acid underwent stereoselective Claisen rearrangement[3] to trans-olefinic esters C. Lithium aluminum hydride reduction of these esters afforded the desired alcohols D.

An alternate synthesis (method H) was developed to prepare *tert*-alkoxybenzoic acids. The method (Scheme III) involved nucleophilic aromatic substitution[4] on *p*-fluorobenzonitrile with the anion derived from a *tert*-alcohol E to yield an intermediate *p*-alkoxybenzonitrile F. The crude nitrile was hydrolyzed to the desired acid G. The required alcohols E were prepared by the addition of Grignard reagents to appropriate ketones. The method of Scheme III was also applied to cyclododecanol and 1- and 2-adamantanol (see Table IV).

Additional *p*-alkoxybenzoic acid analogues were obtained by structural modification of compounds prepared by methylparaben alkylations (Scheme IV). These include certain γ-substituted tetradecyloxy- and ω-substituted alkoxybenzoic acids. Thus, *p*-(3-hydroxytetradecyloxy)benzoic acid (**64**) and its methyl ester[1] were oxidized to the corresponding ketones **120** and **56**. The methyl ester was also converted to the sulfonates **3** and **4**, displacements on which furnished the chloro- **5**, acetylthio- **6**, and crude azidobenzoates. Treatment of acetylthio ester **6** with sodium methoxide afforded mercapto ester **7**, whereas hydrolysis yielded mercapto acid **67**. Alkylation of **7** with ethyl iodide and benzyl chloride followed by alkaline hydrolysis of the resulting esters afforded ethylthio- and benzylthiotetradecyloxybenzoic acids **68** and **69**, respectively.

The ω-substituted alkoxybenzoic acids were derived from methanesulfonates H of the previously mentioned methyl ω-hydroxybenzoates **8–14** by the methods illustrated in Scheme V. Displacement with potassium thioacetate afforded thioesters I whose alkaline hydrolysis yielded mercapto acids L. Alternatively, methanolysis of I afforded mercapto esters J which were converted to (alkylthio)benzoates K by reaction with alkyl or benzyl halides. Alkaline hydrolysis of K gave the (alkylthio)-

Scheme IV



Scheme V

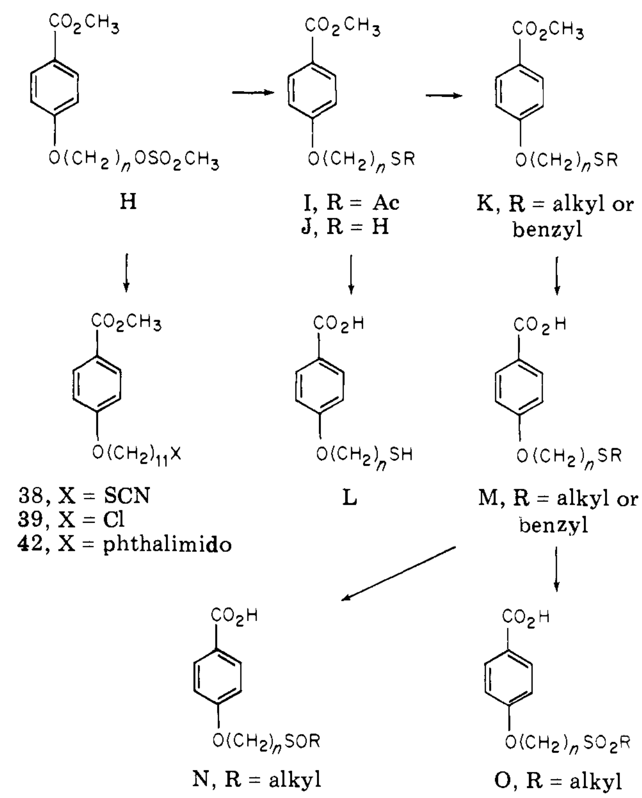
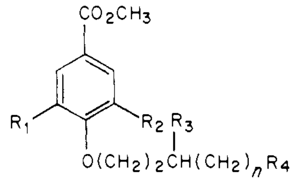
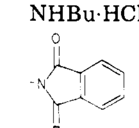


Table I.[a] *p*-Alkoxybenzoates



Compd no.	R_1	R_2	R_3	R_4	*n*	Method	Yield, %	Crystn solvent	Mp, °C
1	NO_2	Br			13	A	43	MeCN	57-59
2	Br	Br			13	A	81	MeCN	52-54
3			OMs		11	C	89	Petr ether	55-57
4			OTs		11	C	38	Petr ether	90-91
5			Cl		11		96	Pentane	45-47
6			SAc		11	D	87	Petr ether	44-47
7			SH		11	E	69	MeCN	40-41
8				OH	8	A	92	Petr ether	81-82
9[b]				OH	8		89	Petr ether-Et_2O	48-50
10[c]				OH	8		86	Petr ether-Et_2O	31-32
11				OH	9	A	77	Petr ether-Et_2O	84-85
12				OH	12	A	81	Petr ether-Et_2O	94-96
13				OH	13	A	62	Petr ether-Me_2CO	93-95
14				OH	15	A	63	Hexane-Me_2CO	99-100
15				OMs	8	C	88	Hexane-Me_2CO	73-75
16[b]				OMs	8	C	88	Petr ether-Et_2O	70-72
17[c]				OMs	8	C	90	Petr ether-Et_2O	60-61
18				OMs	9	C	72	Petr ether-Et_2O	79-80
19				OMs	12	C	81	Petr ether-Et_2O	87-89
20				OMs	13	C	92	Hexane-Me_2CO	86-88
21				OMs	15	C	87	Hexane-Me_2CO	93-95
22				OMs	8		84	Petr ether-Et_2O	51-53
23[b]				OEt	8		82	Petr ether-Et_2O	36-37
24				SAc	8	D	54	Petr ether-Et_2O	45-47
25				SAc	9	D	63	Petr ether-Et_2O	73-74
26				SAc	12	D	62	Petr ether-Et_2O	61-62
27				SAc	13	D	85	Hexane-Me_2CO	84-86
28				SAc	15	D	91	Hexane-Me_2CO	87-88
29				SH	8	E	96	Petr ether-Et_2O	51-53
30				SH	12	E	75	Heptane	71-73
31				SH	13	E	83	Petr ether-Et_2O	80-81
32				SEt	8	G	62	MeOH	34-36
33				SEt	13	G	98	Hexane	67-71
34				SPr	8	G	84	MeOH	42-43
35				SBu	8	G	69	MeOH	41-42
36				SBz	8	G	77	MeOH	58-59
37				SBz	12	G	45	Hexane	66-69
38				SCN	8		78	Petr ether-Et_2O	37-39
39				Cl	8		38	Pentane	41-43
40				NHBu	8		70	Hexane	57-59
41				NHBu·HCl	8		71	MeOH	194-196
42					8		71	MeOH	88-90
				C(=O)NHBu·HCl	7		82	Hexane-Me_2CO	93-95
44[e]					13		62	Petr ether-Et_2O	66-70

[a] Only substituents other than hydrogen are shown under R_1-R_4. [b] The compound is an ethyl ester. [c] The compound is an *n*-butyl ester. [d] C: calcd, 69.43; found, 69.85. [e] The compound is a 1-methyl-4-piperidinyl ester and was prepared by

benzoic acids M. Oxidation of these acids with 1 equiv of sodium metaperiodate afforded sulfoxides N while the use of excess periodate led to sulfones O. The 11-thiocyanato- **38**, 11-chloro- **39**, and 11-phthalimidoundecyloxybenzoates **42** were prepared by appropriate displacements on mesylate **15**.

Acid-catalyzed esterification of **70** afforded the ethyl and *n*-butyl esters P which were then converted to the corresponding methanesulfonates Q. Displacements with the appropriate alkoxide yielded the ethoxyalkyl and butoxyalkyl alkylbenzoates R, hydrolysis of which furnished the corresponding acids (Scheme VI).

A series of nitrogen-containing alkoxybenzoic acids and esters was synthesized (Scheme VII) from half-ester T.[5] Reaction of the mixed anhydride derived from T and isobutyl chloroformate with *n*-butylamine afforded amide **43** which could be selectively hydrolyzed to acid **91**. Reduction of **43** with borane afforded the corresponding amine **40**. Alkaline hydrolysis then yielded the amino acid, isolated as the hydrochloride salt **89**.

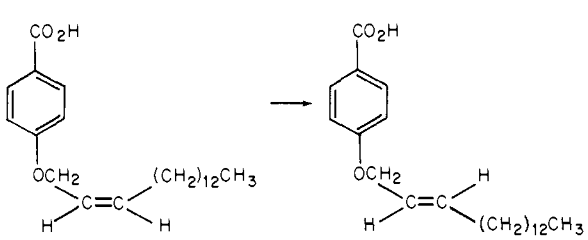
Limited studies (Scheme VIII) with *trans*-alkenyloxybenzoic acid **109** or ester **48** indicated that these derivatives could be converted to the corresponding epoxides **116** and **58** by oxidation with *m*-chloroperbenzoic acid. Hydrolysis of **116** afforded the corresponding diol **117**.

Finally, the cis-olefinic acid **110**, prepared by catalytic hydrogenation of acetylenic acid **113**, was isomerized (eq 2) to trans-olefinic acid **111** with sodium nitrite[6] in dilute

Formula	Sterol,^{f} dose, % of diet			Triglyceride,^{f} dose, % of diet		
	0.1	0.05	0.025	0.1	0.05	0.025
$C_{24}H_{38}BrNO_5$	97 ± 3	93 ± 3	93 ± 3	95 ± 6	101 ± 5	113 ± 2
$C_{24}H_{38}BrO_3$	82 ± 3^h	94 ± 4	94 ± 5	88 ± 13	103 ± 5	96 ± 5
$C_{23}H_{38}O_6S$						
$C_{29}H_{42}O_6S$	98 ± 3	103 ± 3	102 ± 7	86 ± 12	91 ± 7	91 ± 9
$C_{22}H_{35}ClO_3$	84 ± 9	87 ± 5	100 ± 4	45 ± 5^i	53 ± 3^h	80 ± 3
$C_{24}H_{38}O_4S$	81 ± 6^h	89 ± 3^g	94 ± 2	59 ± 4^i	70 ± 8^h	83 ± 7
$C_{22}H_{36}O_3S$						
$C_{19}H_{30}O_4$	92 ± 3^h	94 ± 1^h	94 ± 3^g	72 ± 13^i	86 ± 8^h	140 ± 10
$C_{20}H_{32}O_4$						
$C_{22}H_{36}O_4$						
$C_{20}H_{32}O_4$						
$C_{23}H_{38}O_4$	93 ± 3	98 ± 4	96 ± 6	89 ± 8	104 ± 8	98 ± 7
$C_{24}H_{40}O_4$						
$C_{26}H_{44}O_4$						
$C_{20}H_{32}O_6S$	91 ± 7	105 ± 6	105 ± 2	72 ± 5^i	81 ± 12	79 ± 8^h
$C_{21}H_{34}O_6S$						
$C_{23}H_{38}O_6S$						
$C_{21}H_{34}O_6S$						
$C_{24}H_{40}O_6S$						
$C_{25}H_{42}O_6S$						
$C_{27}H_{46}O_6S$						
$C_{20}H_{32}O_4$	104 ± 3	96 ± 4	93 ± 3	36 ± 8^i	69 ± 5^i	77 ± 6^h
$C_{22}H_{36}O_4$						
$C_{21}H_{32}O_4S$	113 ± 7	98 ± 6	106 ± 4	63 ± 12^h	88 ± 13	66 ± 13^h
$C_{22}H_{34}O_4S$						
$C_{25}H_{40}O_4S$						
$C_{26}H_{42}O_4S$						
$C_{28}H_{46}O_4S$						
$C_{19}H_{30}O_3S$						
$C_{23}H_{38}O_3S$						
$C_{25}H_{40}O_3S$						
$C_{21}H_{34}O_3S$	100 ± 3	100 ± 3	110 ± 4	65 ± 7^h	74 ± 11	71 ± 4^g
$C_{26}H_{44}O_3S$						
$C_{22}H_{36}O_3S$^{d}						
$C_{23}H_{38}O_3S$	96 ± 3	92 ± 2^g	100 ± 3	69 ± 9^g	62 ± 5^h	87 ± 9
$C_{26}H_{36}O_3S$	87 ± 3^i	85 ± 3^i	91 ± 6^g	58 ± 9^i	49 ± 16^i	64 ± 9^i
$C_{30}H_{44}O_3S$						
$C_{20}H_{29}NO_3S$	160 ± 27	102 ± 2	102 ± 7	145 ± 39	94 ± 16	80 ± 14
$C_{19}H_{29}ClO_3$	102 ± 1	108 ± 4^g	110 ± 4^h	41 ± 30^h	81 ± 17	94 ± 13
$C_{23}H_{39}NO_3$	96 ± 5	95 ± 4	102 ± 7	114 ± 8	88 ± 8	104 ± 11
$C_{23}H_{39}NO_3 \cdot HCl$	89 ± 1^h	96 ± 6	100 ± 2	66 ± 12^h	71 ± 11^h	87 ± 11
$C_{27}H_{33}NO_5$						
$C_{23}H_{37}NO_4$	96 ± 5	100 ± 4	99 ± 5	81 ± 7^h	97 ± 19	95 ± 9
$C_{29}H_{49}NO_3$	96 ± 3	87 ± 1^h	85 ± 3^h	117 ± 8	110 ± 6	100 ± 4

transesterification of ethyl 4-(hexadecyloxy)benzoate (J. D. Albright). ^{f} Sterol and triglyceride values shown as percent of control. ^{g} Statistically significant, $p < 0.10$. ^{h} Statistically significant, $p < 0.05$. ^{i} Statistically significant, $p < 0.01$.

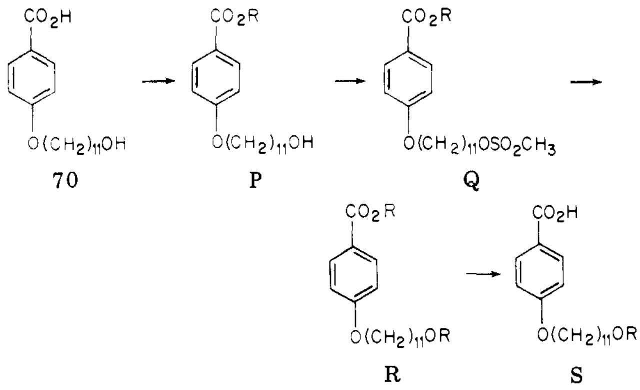
nitric acid.



110 **111** (2)

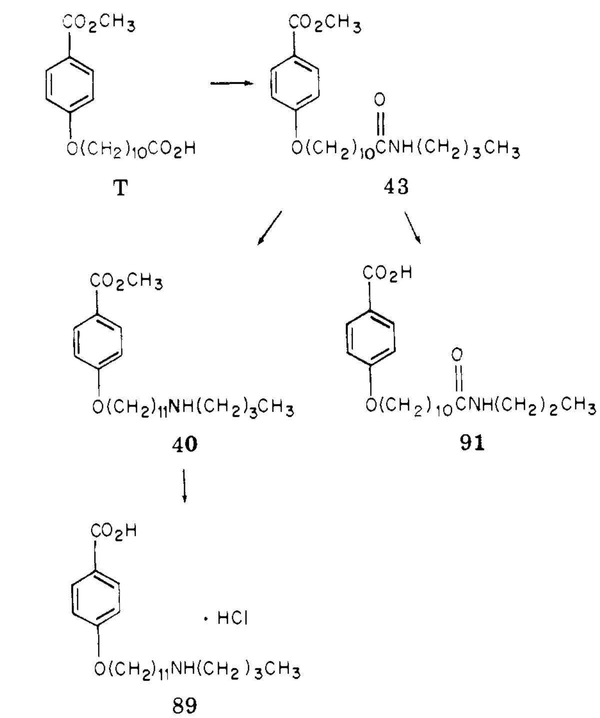
In the homologous series of p-(n-alkoxy)benzoic acids from which p-hexadecyloxybenzoic acid was selected,[1] maximum sterol-lowering activity was observed when the alkyl chain contained 12–20 carbons. In the present series of compounds, alkyl chain substituents such as chloro (**65**) and oximino (**57**) clearly enhance activity. Alkyl chain substituents such as azido (**66**), thiol (**6, 67, 74–77**), and some alkylthio (**68, 79, 82, 83**) retain activity while other alkylthio (**32, 35, 36, 69, 80, 81, 84**) substituents diminish activity. Other substituents on the alkyl chain and those substituents in the aryl ring that were examined abolished sterol-lowering activity. Although the effect of alkyl chain branching is variable (**92–105**) the presence of unsaturation (**48, 107–109, 114**) apparently has no adverse effect on activity, except when located near either end of the chain (**45, 106, 110**).

Scheme VI

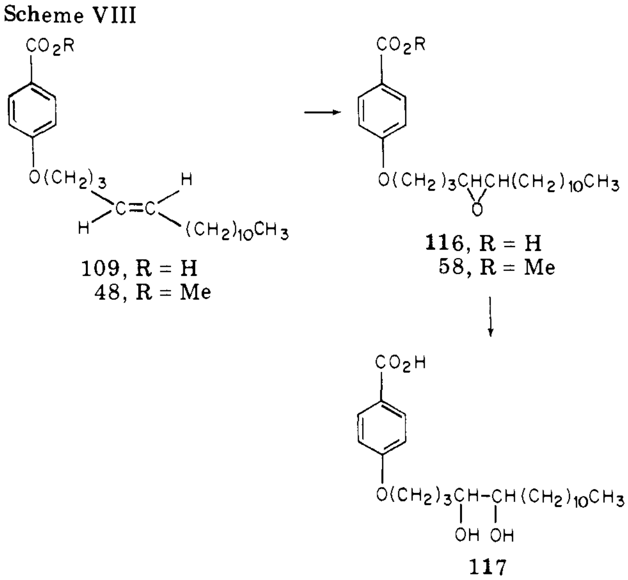


R = Et and *n*-Bu

Scheme VII



Scheme VIII



Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks or as smears between sodium chloride plates with a Perkin-Elmer spectrophotometer. Proton magnetic resonance spectra were determined with a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Where details are not reported, the spectra of the compounds were compatible with the structure assigned. Unless otherwise noted (see footnotes to tables), all compounds gave analytical results for C, H, N, S, Cl, Br, and I, if present, within ±0.4% of theoretical values.

Solutions were dried over anhydrous $MgSO_4$ and where necessary clarified using activated carbon. Evaporations were carried out under reduced pressure.

Farnesyl bromide[9] and 11-bromo-1-undecane[10] were prepared by the action of phosphorus tribromide on the corresponding alcohol. This procedure was adapted to the preparation of 2-bromohexadecane, 3-bromohexadecane, and 4-bromohexadecane which were used without purification. The action of hydrogen bromide on the corresponding alcohol[11] afforded cyclododecylmethyl bromide, 1-bromo-3,7,11-trimethyldodecane, and 1-bromo-3,7,11,15-tetramethylhexadecane which were also used without characterization.

18-Bromo-1-octadecanol (129). To a stirred solution of 8.77 g (24.2 mmol) of 18-bromooctadecanoic acid (see below) in 70 ml of THF was added dropwise 35 ml of 1 M borane in THF. The solution was stirred for 1 h at ambient temperature, diluted with 1 N NaOH solution, and extracted with Et_2O. The extract was washed with 1 N HCl, dried, and evaporated. The residue was crystallized from hexane to yield 6.47 g (77%) of **129**, mp 60–62°. Recrystallization from hexane afforded the analytical sample, mp 60–62°. Anal. ($C_{18}H_{37}$**Br**O) C, H, Br.

Other alcohols prepared by this procedure were 12-bromo-1-dodecanol (78%), mp 29–31° (lit.[12] mp 28°), 15-bromo-1-pentadecanol (90%), mp 64–66° (lit.[13] mp 59–60°), and 16-bromo-1-hexadecanol (92%), mp 54–56° (lit.[14] mp 53–54°). The required 18-bromooctadecanoic acid[15] was obtained by the peroxide-catalyzed addition[16] of hydrogen bromide to 17-octadecenoic acid.[17] 15-Bromopentadecanoic acid[15] and 16-bromopentadecanoic acid[15] were prepared by the action of 30% HBr in AcOH on the corresponding hydroxyalkanoic acids.[17]

1-Tetradecen-3-ol (130). A mixture of 4.80 g (0.200 g-atom) of magnesium and 100 ml of THF was stirred while 14.2 ml (22.0 g, 0.200 mol) of vinyl bromide was added at a rate such that moderate reflux (dry ice cooled condenser) was maintained. The mixture was stirred an additional 30 min and then a solution of 36.8 g (0.200 mol) of dodecanal in 20 ml of Et_2O was added dropwise. The mixture was stirred under reflux (water-cooled condenser) for 3 h and allowed to cool. After treatment with 30 ml of saturated NH_4Cl solution, the mixture was filtered and the filtrate dried and evaporated. Distillation of the residual oil afforded 15.7 g (37%) of **130**, bp 120–126° (2 mm) [lit.[18] bp 144–146° (11 mm)].

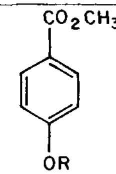
Also prepared by this procedure were 1-dodecen-3-ol (**131**) [54%; bp 105–125° (0.3 mm) [lit.[18] bp 122–122.5° (?)]. Anal. ($C_{12}H_{24}O$) C, H], 1-tridecen-3-ol (**132**) [48%; bp 105–107° (1 mm). Anal. ($C_{13}H_{26}O$) C, H], and 1,12-tridecadien-3-ol (**133**) [45%; bp 100–103° (0.3 mm). Anal. ($C_{13}H_{24}O$) C, H].

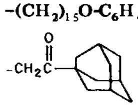
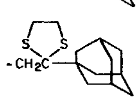
Ethyl *trans*-4-Hexadecenoate (134). A mixture of 19.8 g (93.5 mmol) of **130**, 107 g (659 mmol) of triethyl orthoacetate, and 1.0 ml of propionic acid was stirred at 140° (bath) for 1 h while 30 ml of distillate was collected.[3] After removal of volatile material in vacuo, the residue was distilled to yield 23.1 g (88%) of **134**, bp 149–153° (1 mm). Anal. ($C_{18}H_{34}O_2$) C, H.

Also prepared by this procedure were ethyl *trans*-4-tetradecenoate (**135**) [86%; bp 150° (2 mm). Anal. ($C_{16}H_{30}O_2$) C, H], ethyl *trans*-4-pentadecenoate (**136**) [80%; bp 130° (1 mm). Anal. ($C_{17}H_{32}O_2$) C, H], and ethyl *trans*-4,14-pentadecadienoate (**137**) [86%; bp 160° (5 mm). Anal. ($C_{17}H_{30}O_2$) C, H].

***trans*-4-Hexadecen-1-ol (138).** A solution of 21.9 g (77.8 mmol) of **134** in 80 ml of THF was added dropwise to a stirred suspension of 10.0 g (260 mmol) of $LiAlH_4$ in 80 ml of THF and the resulting mixture was stirred for 3 h under reflux. Excess hydride was decomposed by the dropwise addition of saturated sodium potassium tartarate solution and the mixture was filtered. The filtrate was dried and evaporated and the residual oil crystallized

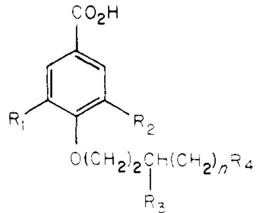
Table II. *p*-Alkoxybenzoates



Compd no.	R	Meth-od	Yield, %	Crystn solvent	Mp, °C	Formula	Sterol,[b] dose, % of diet 0.1	Sterol,[b] dose, % of diet 0.05	Sterol,[b] dose, % of diet 0.025	Triglyceride,[b] dose, % of diet 0.1	Triglyceride,[b] dose, % of diet 0.05	Triglyceride,[b] dose, % of diet 0.025
45	$-(CH_2)_9CH{=}CH_2$	A	48	Petr ether	35–37	$C_{19}H_{38}O_3$	90 ± 3	94 ± 5	97 ± 4	58 ± 4[c]	52 ± 4[c]	65 ± 4[d]
46	$-(CH_2)_3(H)C{=}C(H)(CH_2)_8CH_3$	A	35	MeOH	33–34	$C_{22}H_{34}O_3$						
47	$-(CH_2)_3(H)C{=}C(H)(CH_2)_9CH_3$	A	56	MeOH	52–54	$C_{23}H_{36}O_3$						
48	$-(CH_2)_3(H)C{=}C(H)(CH_2)_{10}CH_3$	A	80	Petr ether	48–50	$C_{24}H_{38}O_3$	75 ± 3[e]	73 ± 4[e]	68 ± 9[d]	68 ± 9[d]	57 ± 6[e]	72 ± 8[d]
49	$-CH_2(H)C{=}C(H)(CH_2)_{12}CH_3$	A	46	MeOH	42–43	$C_{24}H_{38}O_3$	82 ± 3[e]	83 ± 12[d]	89 ± 5[d]	89 ± 4[c]	83 ± 8[d]	96 ± 8
50	$-(CH_2)_8(H)C{=}C(H)(CH_2)_7CH_3$	A	85	MeOH	37–40	$C_{26}H_{42}O_3$	104 ± 4	102 ± 3	102 ± 3	46 ± 21	86 ± 10	73 ± 8[d]
51	$-CH_2C{\equiv}C(CH_2)_{12}CH_3$	A	66	MeOH	43–45	$C_{24}H_{36}O_3$	89 ± 4[d]	83 ± 1[e]	89 ± 1[e]	57 ± 11[e]	66 ± 5[e]	78 ± 6[d]
52	$-(CH_2)_3(H)C{=}C(H)(CH_2)_8CH{=}CH_2$	A	37	MeOH	34–35	$C_{23}H_{34}O_3$						
53	$-(CH_2)_{15}O$-C_6H_4-*p*-CO_2CH_3	A	57	MeOH	88–90	$C_{31}H_{44}O_6$						
54		A	71	MeOH	131–133	$C_{20}H_{24}O_4$	89 ± 1[c]	96 ± 4	97 ± 7	100 ± 7	82 ± 8[c]	88 ± 11
55[a]			81	Petr ether-CH_2Cl_2	168–170	$C_{22}H_{28}O_3S_2$	93 ± 4	93 ± 6	100 ± 2	112 ± 17	83 ± 6[c]	94 ± 15
56	$-(CH_2)_2C({=}O)(CH_2)_{10}CH_3$		84	Petr ether-Et_2O	69–70	$C_{24}H_{34}O_4$	81 ± 7[d]	89 ± 6	94 ± 5	61 ± 6[e]	61 ± 11[d]	78 ± 11
57	$-(CH_2)_2C({=}NOH)(CH_2)_{10}CH_3$		27	Petr ether	72–73	$C_{22}H_{35}NO_4$	64 ± 3[e]	67 ± 7[e]	74 ± 5[e]	32 ± 9[e]	43 ± 17[e]	53 ± 12[e]
58	$-(CH_2)_3CH(O)CH(CH_2)_{10}CH_3$ (epoxide)		82	Petr ether-Et_2O	74–77	$C_{24}H_{38}O_4$	84 ± 5[e]	89 ± 5[d]	103 ± 7	65 ± 12[e]	64 ± 14[e]	74 ± 8[e]

[a] Prepared from **54** by treatment with BF_3-Et_2O and 1,2-ethanedithiol in the usual manner. [b] Sterol and triglyceride values are shown as percent of control. [c] Statistically significant, $p < 0.10$. [d] Statistically significant, $p < 0.05$. [e] Statistically significant, $p < 0.01$.

Table III.[a] *p*-Alkoxybenzoic Acids



Compd no.	R_1	R_2	R_3	R_4	*n*	Method	Yield, %	Crystn solvent	Mp, °C[b]
59	Cl				13	A	76	AcOH	105-107[c]
60	NO_2				13	B	84	Petr ether-Et_2O	100-101[d]
61	Cl	Cl			13	A	73	Petr ether-Et_2O	73, 81-82[e]
62	I	I			13	A	98	Petr ether-Et_2O	107-108
63	Me	Me			13	A	70	AcOH	89-90
64			OH		11	B	77	Petr ether-Me_2CO	118-119
65			Cl		11	B	94	Me_2CO	130-134
66			N_3		11	B	91	Petr ether-Et_2O	99-100
67			SH		11	F	85	Petr ether-Me_2CO	113-116
68			SEt		11	B	96	Petr ether-Et_2O	71-79
69			SBz		11	B	50	Petr ether-Et_2O	68-70
70				OH	8	B	60	Et_2O	111-113
71				OMe	8	B	94	Petr ether-Et_2O	103-105
72				OEt	8	B	45	Petr ether-Et_2O	93-94, 106-108
73				OBu	8	B	95	Petr ether-Et_2O	78-80, 107-108
74				SH	8	F	92	MeCN	108-110
75				SH	9	F	65	MeOH	103-105, 133
76				SH	12	F	95	Hexane-Me_2CO	118-120, 129-130
77				SH	13	F	30	Me_2CO	116-119, 129
78				SH	15	F	53	Me_2CO	116-118, 124-125
79				SEt	8	B	43	Petr ether-Et_2O	83-85, 117-119
80				SEt	13	B	87	Petr ether	102-104, 109-110
81				SPr	8	B	99	MeOH	80-82, 117-118
82				SBu	8	B	76	MeOH	83-85, 117-118
83				SBz	8	B	96	MeOH	62-63, 106-107
84				SBz	12	B	56	Petr ether	75-77, 108-109
85				S(O)Bu	8		80	MeOH	125-127
86				S(O)Et	13		73	MeOH	106-107
87				SO_2Bu	8		68	MeOH	143-145
88				SO_2Et	13		79	MeOH	129-130
89				NHBu·HCl	8	B	75	AcOH	190-192
90				CO_2H	7	B	87	AcOH	169-170
91				C(=O)NHBu	7	B	72	MeCN	141-143

[a] Only substituents other than hydrogen are shown under R_1-R_4. [b] Many *p*-alkoxybenzoic acids are mesomorphic and double melting points were observed. [c] G. W. Gray and B. Jones, *J. Chem. Soc.*, 2556 (1954), report mesomorphic transition temperatures for this compound. [d] J. Jaeken and M. A. de Ramaix, German Patent 1 146 751 (April 4, 1963),

from petroleum ether to yield 14.3 g (77%) of **138**. Anal. ($C_{16}H_{32}O$) C, H.

Also prepared by this procedure were *trans*-4-tetradecen-1-ol (**139**) [71%, bp 106–111° (0.05 mm). Anal. ($C_{14}H_{28}O$) C: calcd, 79.18; found, 78.69. H: calcd, 13.29; found, 12.85], *trans*-4-pentadecen-1-ol (**140**) [80%; bp 110–120° (0.1 mm); NMR ($CDCl_3$) δ 5.46 (2, m, CH_a=CH_b, $J_{a,b}$ = 16 Hz) [$CDCl_3$-Eu(fod)$_3$ added]. Anal. ($C_{15}H_{30}O$) C, H], and *trans*-4,14-pentadecadien-1-ol (**141**) [73%; bp 115° (0.5 mm). Anal. ($C_{15}H_{28}O$) C, H].

Methyl *p*-(11-Hydroxyundecyloxy)benzoate (8) (Method A). The following experiment illustrates a general procedure used to prepare esters and acids of Tables I–III.

A solution of 2.51 g (10.0 mmol) of 11-bromoundecan-1-ol, 1.52 g (10.0 mmol) of methylparaben, and 540 mg (10.0 mmol) of sodium methoxide in 35 ml of MeOH was protected from moisture by a tube filled with anhydrous calcium sulfate and stirred under reflux for 3 days. The mixture was partitioned between H_2O and Et_2O (or an alternate organic solvent) and the organic layer was separated, washed with 1 N HCl, dried, and evaporated. Crystallization afforded 2.97 g (92%) of **8** (Table I).

***p*-(10-Undecenyloxy)benzoic Acid (106) (Method B).** The following experiment illustrates a general method used to prepare carboxylic acids of Tables III and IV.

A solution of 22.0 g (72.2 mmol) of **45** (esters required as starting materials for method B but not shown in Tables I and II were prepared by method A and used without characterization) in 200 ml of EtOH was treated with 10 ml of 10 N NaOH solution and stirred under reflux for 1 h. The mixture was partitioned between CH_2Cl_2 (or an alternate organic solvent) and H_2O and the organic layer was separated, dried, and concentrated. Crystallization afforded 11.0 g (53%) of **106** (Table IV).

Methyl *p*-[11-(Methanesulfonyloxy)undecyloxy]benzoate (15) (Method C). The following experiment illustrates a general procedure used to prepare esters of Table I.

A solution of 53.8 g (0.167 mol) of **8** and 25.5 ml (37.8 g, 0.332 mol) of methanesulfonyl chloride in 500 ml of pyridine was stirred for 1 h at ambient temperature and poured into ice–water. The resulting solid was collected and partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried, and evaporated. Crystallization yielded 58.5 g (88%) of **15** (Table I).

Methyl *p*-[16-(Acetylthio)hexadecyloxy]benzoate (27) (Method D). The following experiment illustrates a general procedure used to prepare esters of Table I.

A mixture of 18.0 g (38.2 mmol) of **20**, 13.0 g (114 mmol) of potassium thioacetate, and 500 ml of Me_2CO was protected from moisture and stirred under reflux for 16 h. The solvent was evaporated and the residual solid was partitioned between Et_2O (mixtures of alternate organic solvents were used in some reactions) and H_2O. The organic layer was separated, dried, and evaporated. Crystallization afforded 14.7 g (85%) of **27** (Table I).

Methyl *p*-(11-Mercaptoundecyloxy)benzoate (29) (Method E). The following experiment illustrates a general method used to prepare esters of Table I.

A solution of 1.00 g (2.62 mmol) of **24** in 30 ml of MeOH was treated with 3.0 ml of 1 M sodium methoxide in MeOH. The

Formula	Sterol,[f] dose, % of diet			Triglyceride,[f] dose, % of diet		
	0.1	0.05	0.025	0.1	0.05	0.025
$C_{23}H_{37}ClO_3$	103 ± 3	97 ± 4	108 ± 10	75 ± 14	87 ± 8	69 ± 8^{h}
$C_{23}H_{37}NO_5$	103 ± 6	101 ± 3	95 ± 3	122 ± 19	120 ± 8	93 ± 10
$C_{23}H_{36}Cl_2O_3$	103 ± 4	105 ± 3	98 ± 2	103 ± 20	89 ± 14	100 ± 5
$C_{23}H_{36}I_2O_3$	93 ± 3	85 ± 5^{h}	94 ± 2	105 ± 5	86 ± 9	96 ± 6
$C_{25}H_{42}O_3$	97 ± 9	89 ± 4^{g}	78 ± 2^{i}	82 ± 7	79 ± 4^{g}	68 ± 16^{h}
$C_{21}H_{34}O_4$	116 ± 3	112 ± 3	105 ± 5	53 ± 8^{i}	60 ± 6^{i}	69 ± 10^{i}
$C_{21}H_{33}ClO_3$	60 ± 2^{i}	69 ± 4^{i}	72 ± 4^{i}	47 ± 6^{i}	53 ± 6^{i}	59 ± 6^{i}
$C_{21}H_{33}N_3O_3$	76 ± 4^{h}	89 ± 10	105 ± 5	55 ± 17^{h}	60 ± 7^{h}	98 ± 13
$C_{21}H_{34}O_3S$	83 ± 9^{g}	89 ± 6	94 ± 3	47 ± 19	53 ± 5^{i}	76 ± 6
$C_{23}H_{38}O_3S$	83 ± 3^{i}	93 ± 4^{g}	95 ± 6	44 ± 17^{i}	74 ± 8^{h}	68 ± 7^{i}
$C_{28}H_{40}O_3S$	92 ± 3	100 ± 5	109 ± 3	69 ± 8^{g}	79 ± 8	92 ± 6
$C_{18}H_{28}O_4$	113 ± 8	106 ± 6	91 ± 3	81 ± 16	93 ± 13	83 ± 10^{h}
$C_{19}H_{30}O_4$	97 ± 7	90 ± 1	79 ± 19	64 ± 13^{h}	53 ± 13^{i}	80 ± 6^{g}
$C_{20}H_{32}O_4$	95 ± 1	109 ± 5	103 ± 3	63 ± 7^{i}	73 ± 10^{i}	66 ± 10^{i}
$C_{22}H_{36}O_4$	97 ± 3	81 ± 4^{i}	75 ± 7^{i}	55 ± 6^{i}	67 ± 12^{i}	74 ± 7^{h}
$C_{18}H_{28}O_3S$	80 ± 6^{h}	74 ± 6^{h}	44 ± 16^{i}	44 ± 16^{i}	47 ± 13^{i}	61 ± 14^{h}
$C_{19}H_{30}O_3S$	79 ± 5^{i}	81 ± 7^{i}	88 ± 3^{i}	26 ± 7^{i}	46 ± 18^{i}	61 ± 15^{i}
$C_{22}H_{36}O_3S$	82 ± 2^{i}	81 ± 5^{i}	100 ± 3	40 ± 5^{i}	42 ± 3^{i}	56 ± 10^{i}
$C_{23}H_{38}O_3S$	83 ± 4^{i}	82 ± 4^{i}	82 ± 3^{i}	37 ± 4^{i}	35 ± 4^{i}	51 ± 7^{i}
$C_{25}H_{42}O_3S$						
$C_{20}H_{32}O_3S$	76 ± 2^{i}	70 ± 6^{i}	74 ± 1^{i}	48 ± 11^{i}	56 ± 3^{i}	60 ± 7^{i}
$C_{25}H_{42}O_3S$	90 ± 2^{h}	88 ± 3^{i}	89 ± 2^{i}	45 ± 1^{i}	48 ± 3^{i}	59 ± 7^{i}
$C_{21}H_{34}O_3S$	86 ± 7^{h}	94 ± 2^{g}	96 ± 5	42 ± 8^{i}	43 ± 4^{i}	61 ± 21^{g}
$C_{22}H_{36}O_3S$	76 ± 1^{i}	76 ± 3^{i}	70 ± 6^{i}	60 ± 17^{i}	53 ± 17^{i}	60 ± 9^{i}
$C_{25}H_{34}O_3S$	77 ± 2^{i}	75 ± 6^{i}	88 ± 8^{g}	41 ± 10^{i}	55 ± 9^{i}	71 ± 7^{h}
$C_{29}H_{42}O_3S$	82 ± 3^{i}	101 ± 4	109 ± 1	37 ± 5^{i}	50 ± 4^{i}	70 ± 2^{i}
$C_{22}H_{36}O_4S$	102 ± 4	97 ± 4	102 ± 2	44 ± 7^{i}	54 ± 8^{i}	83 ± 22
$C_{25}H_{42}O_4S$	94 ± 2	81 ± 3^{i}	89 ± 3^{h}	55 ± 7^{i}	80 ± 1^{i}	87 ± 7^{g}
$C_{22}H_{36}O_5S$	94 ± 2	95 ± 4	91 ± 9	57 ± 23^{h}	69 ± 10^{i}	81 ± 10^{g}
$C_{25}H_{42}O_5S$	89 ± 5^{h}	83 ± 2^{i}	90 ± 5	60 ± 6^{i}	61 ± 10^{i}	70 ± 11^{i}
$C_{22}H_{37}NO_3 \cdot HCl$	100 ± 6	104 ± 2	98 ± 4	100 ± 6	103 ± 4	119 ± 5
$C_{18}H_{26}O_5$	94 ± 2	100 ± 3	96 ± 6	100 ± 6	135 ± 7	118 ± 10
$C_{22}H_{35}NO_4$	88 ± 2^{h}	96 ± 2	99 ± 3	85 ± 5^{g}	87 ± 10	93 ± 8

report mp 98°. [e] Footnote *c* reports mp 60.5° for this compound. [f] Sterol and triglyceride values are shown as percent of control. [g] Statistically significant, $p < 0.10$. [h] Statistically significant, $p < 0.05$. [i] Statistically significant, $p < 0.01$.

mixture was stirred for 30 min at ambient temperature, acidified with 1.0 ml of AcOH, and poured on ice. The solid was collected and dried to yield 0.85 g (96%) of **29** (Table I).

p-**(15-Mercaptopentadecyloxy)benzoic Acid (76) (Method F).** The following experiment illustrates a general procedure used to prepare carboxylic acids of Table III.

A mixture of 3.56 g (8.15 mmol) of **26**, 25 ml of 10 N NaOH, and 100 ml of EtOH was stirred under reflux for 1 h and then acidified with 6 N HCl. An Et_2O extract of the mixture was dried and evaporated to yield 2.95 g (95%) of **76** (Table III).

Methyl *p*-**[11-(Ethylthio)undecyloxy]benzoate (32) (Method G).** The following experiment illustrates a general procedure used to prepare esters of Table I.

A solution of 0.34 g (1.0 mmol) of **29** and 60 mg (1.1 mmol) of sodium methoxide in 20 ml of MeOH was stirred under reflux of 1 h and allowed to cool. After the addition of 0.10 ml (0.19 g, 1.2 mmol) of iodoethane, stirring under reflux was resumed and continued for 18 h. The mixture was concentrated and partitioned between Et_2O and ice–water. The organic layer was separated, dried, and evaporated. Crystallization of the residual oil afforded 0.23 g (62%) of **32** (Table I).

p-**(1,1-Dimethyldodecyloxy)benzoic Acid (100) (Method H).** The following experiment illustrates a general procedure used to prepare acids of Table IV.

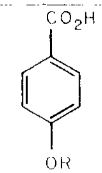
A suspension of 1.24 g (31.8 mg-atoms) of freshly cut potassium metal in 95 ml of THF was stirred under an argon atmosphere while 6.82 g (31.8 mmol) of 2-methyl-2-tridecanol[19] was added. The mixture was protected from moisture by a tube filled with anhydrous calcium sulfate and stirred under reflux for 18 h. A solution of 3.86 g (31.8 mmol) of *p*-fluorobenzonitrile in 16 ml of THF was added dropwise and reflux was continued for 24 h. The mixture was cautiously diluted with H_2O and Et_2O and the organic layer was separated, washed with 1 N NaOH solution and 1 N HCl, dried, and evaporated to yield the intermediate *p*-(1,1-dimethyldodecyloxy)benzonitrile as a yellow oil.

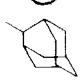
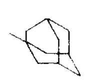
A mixture of the oil, 6.00 g (92.8 mmol) of KOH, and 100 ml of ethylene glycol was stirred under reflux for 18 h, allowed to cool, and partitioned between Et_2O, MeOH, and H_2O. The aqueous layer was separated and acidified with concentrated HCl. The mixture was extracted with Et_2O and the combined extracts were dried and evaporated. Crystallization yielded 3.13 g (30%) of **100** (Table IV).

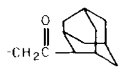
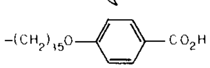
Methyl *p*-**(3-Oxotetradecyloxy)benzoate (56).** The red solution prepared by the addition of 3.00 g (30.0 mmol) of CrO_3 to a stirred solution of 5 ml of pyridine in 150 ml of CH_2Cl_2 was stirred for 15 min at ambient temperature and then treated with a solution of 1.82 g (5.00 mmol) of methyl *p*-(3-hydroxytetradecyloxy)benzoate[1] in 10 ml of CH_2Cl_2. After 15 min, the supernatant liquid was decanted, washed with 1 N NaOH solution and 1 N HCl, dried, and evaporated. Crystallization afforded 1.52 g (84%) of **56** (Table II). Carboxylic acid **120** (Table IV) was also prepared by this procedure. Oxime **57** (Table II) was prepared from **56** in the usual manner.

Methyl *p*-**(11-Chloroundecyloxy)benzoate (39).** A mixture of 1.0 g (2.5 mmol) of **15**, 0.53 g (13 mmol) of LiCl, and 5 ml of DMF was stirred under reflux for 17 h, poured into ice–water,

Table IV. *p*-Alkoxybenzoic Acids



Compd no.	R	Method	Yield, %	Crystn solvent	Mp, °C[a]	Formula	Sterol,[b] dose, % of diet 0.1	0.05	0.025	Triglyceride,[b] dose, % of diet 0.1	0.05	0.025
92	$-(CH_2)_2CH(CH_3)(CH_2CH_2CH_2CH(CH_3))_2CH_3$	B	26	MeCN	55–57	$C_{22}H_{36}O_3$	87 ± 12	73 ± 6[e]	81 ± 3[c]	26 ± 21[e]	72 ± 19[d]	72 ± 4[c]
93	$-(CH_2)_2CH(CH_3)(CH_2CH_2CH_2CH(CH_3))_3CH_3$	B	22	Et_2O–MeCN	39–41	$C_{27}H_{46}O_3$	71 ± 6[e]	84 ± 2[e]	87 ± 5[e]	72 ± 10[e]	104 ± 13	110 ± 8
94	$-CH_2\overset{\frown}{CH(CH_2)_{13}}$	B	30	Et_2O	176–177	$C_{20}H_{30}O_3$	101 ± 3	105 ± 3	104 ± 5	160 ± 6	130 ± 5	123 ± 7
95	$-CH(CH_3)(CH_2)_{13}CH_3$	B	33	EtOH	79–81	$C_{23}H_{38}O_3$	84 ± 5[d]	85 ± 5[d]	90 ± 7	70 ± 6[e]	72 ± 6[e]	92 ± 11
96	$-CH(CH_2CH_3)(CH_2)_{12}CH_3$	B	19	Petr ether	48–50	$C_{23}H_{38}O_3$	85 ± 3[c]	86 ± 3[c]	82 ± 5[d]	75 ± 23	78 ± 23	83 ± 6[c]
97	$-CH(CH_2CH_2CH_3)(CH_2)_{11}CH_3$	B	25	Petr ether	37–38	$C_{23}H_{38}O_3$	74 ± 3[e]	76 ± 7[d]	78 ± 3[d]	53 ± 6[e]	62 ± 11[e]	70 ± 10[c]
98	$-\overset{\frown}{CH(CH_2)_{11}}$	H	10	MeOH	165–169	$C_{19}H_{28}O_3$	86 ± 3[d]	94 ± 4	87 ± 4[d]	87 ± 9	81 ± 13	97 ± 4
99		H	6	MeOH	257–260	$C_{17}H_{20}O_3$	96 ± 2	92 ± 3	88 ± 2[c]	88 ± 8	82 ± 14	79 ± 5[d]
100	$-C(CH_3)_2(CH_2)_{10}CH_3$	H	30	MeOH	80–82	$C_{21}H_{34}O_3$	83 ± 2[e]	88 ± 6[e]	90 ± 8[c]	63 ± 14[e]	80 ± 21	74 ± 9[c]
101	$-C(CH_3)_2(CH_2)_{11}CH_3$	H	19	MeOH	76–77	$C_{22}H_{36}O_3$	97 ± 4	90 ± 8	100 ± 1	87 ± 11	79 ± 7	77 ± 7
102	$-C(CH_3)_2(CH_2)_{12}CH_3$	H	20	MeOH	87–88	$C_{23}H_{38}O_3$	100 ± 3	120 ± 8	92 ± 6	83 ± 9	105 ± 16	127 ± 16
103	$-C(CH_3)_2(CH_2)_{14}CH_3$	H	17	MeOH	71–72	$C_{25}H_{42}O_3$	96 ± 4	112 ± 3	101 ± 5	100 ± 8	111 ± 5	103 ± 5
104	$-C(CH_3)(CH_2CH_3)(CH_2)_{13}CH_3$	H	7	MeOH	44–45	$C_{25}H_{42}O_3$	102 ± 4		100 ± 3	94 ± 6		94 ± 12
105		H	25	MeOH	228–230	$C_{17}H_{20}O_3$	88 ± 5[c]	87 ± 2[d]	90 ± 8	85 ± 17	89 ± 8	85 ± 8

106	$-(CH_2)_9CH{=}CH_2$	B	53	Hexane-Me_2CO	75-82, 119-120	$C_{18}H_{36}O_3$	86 ± 8[d]	99 ± 3	100 ± 6	60 ± 11[e]	81 ± 6[e]	82 ± 4[e]
107	$-(CH_2)_3(H)C{=}C(H)(CH_2)_8CH_3$	B	78	Hexane	92-93, 133-134	$C_{21}H_{32}O_3$	77 ± 3[e]	73 ± 1[e]	87 ± 6[d]	87 ± 6	89 ± 11	89 ± 6
108	$-(CH_2)_3(H)C{=}C(H)(CH_2)_9CH_3$	B	87	Hexane	84-86, 131-132	$C_{22}H_{34}O_3$	79 ± 2[e]	92 ± 4[c]	92 ± 6[c]	92 ± 10	76 ± 6[e]	72 ± 6[d]
109	$-(CH_2)_3(H)C{=}C(H)(CH_2)_{10}CH_3$	B	44	Petr ether	94-95, 131-132	$C_{23}H_{36}O_3$	69 ± 7[e]	67 ± 8[e]	75 ± 7[e]	59 ± 4[e]	76 ± 8[c]	76 ± 9[c]
110	$-CH_2(H)C{=}C(H)(CH_2)_{12}CH_3$		78	Hexane	97-99	$C_{23}H_{36}O_3$	90 ± 5[d]	87 ± 2[e]	95 ± 3	60 ± 12[e]	79 ± 8[c]	88 ± 7
111	$-CH_2(H)C{=}C(H)(CH_2)_{12}CH_3$		33	Hexane	104-106, 126-127	$C_{23}H_{36}O_3$	81 ± 4[e]	85 ± 5[e]	106 ± 2	46 ± 36[e]	57 ± 18[e]	45 ± 10[e]
112	$-(CH_2)_8(H)C{=}C(H)(CH_2)_7CH_3$	B	35	Hexane-Me_2CO	84-86, 105-106	$C_{25}H_{40}O_3$						
113	$-CH_2C{\equiv}C(CH_2)_{12}CH_3$	B	74	Hexane	112-113	$C_{23}H_{34}O_3$	82 ± 2[e]	88 ± 3[e]	98 ± 4	75 ± 10[d]	65 ± 7[e]	96 ± 4
114	$-(CH_2)_3(H)C{=}C(H)(CH_2)_8CH{=}CH_2$	B	87	Hexane	73-74, 127-128	$C_{22}H_{32}O_3$	74 ± 3[e]	87 ± 6[e]	92 ± 7	83 ± 11	96 ± 6	83 ± 4[c]
115	$-CH_2CH{=}C(CH_3)(CH_2CH_2CH{=}C(CH_3))_2CH_3$	B	39	Petr ether	82-85	$C_{22}H_{30}O_3$	87 ± 10	102 ± 7	108 ± 3	133 ± 8	111 ± 10	131 ± 9
116	$-(CH_2)_3CH\overset{O}{—}CH(CH_2)_{10}CH_3$		84	Petr ether-Et_2O	99-100, 131-132	$C_{23}H_{36}O_4$	85 ± 3[e]	85 ± 4[e]	90 ± 3[d]	55 ± 9	52 ± 8[e]	74 ± 13[d]
117	$-(CH_2)_3CH(OH)CH(OH)(CH_2)_{10}CH_3$		49	Hexane-EtOAc	144-145	$C_{23}H_{38}O_5$	83 ± 7[d]	86 ± 2[d]		55 ± 10[e]	60 ± 4[d]	
118		B	57	Me_2CO	196-199	$C_{19}H_{22}O_4$	92 ± 4	99 ± 4	93 ± 2	113 ± 2	101 ± 4	90 ± 2
119		B	45	AcOH	222-225	$C_{29}H_{40}O_6$	94 ± 2	103 ± 4	97 ± 1	51 ± 1[d]	77 ± 10[c]	64 ± 11[e]
120	$-(CH_2)_2C({=}O)(CH_2)_{10}CH_3$		45	Et_2O-Me_2CO	122-124	$C_{21}H_{32}O_4$	92 ± 7	89 ± 7	89 ± 3	74 ± 10[d]	75 ± 6[d]	84 ± 12

[a] Many *p*-alkoxybenzoic acids are mesomorphic and double melting points were observed. [b] Sterol and triglyceride values are shown as percent of control. [c] Statistically significant, $p < 0.10$. [d] Statistically significant, $p < 0.05$. [e] Statistically significant, $p < 0.01$.

Table V.[a] Methanesulfonates

			$ROSO_2CH_3$			
Compd no.	R	Yield, %	Crystn solvent	Mp, °C[b]	Formula	Analyses
121	$-(CH_2)_3CH=CH(CH_2)_8CH_3$	99	Hexane	Oil	$C_{15}H_{30}O_3S$	C, H, S
122	$-(CH_2)_3CH=CH(CH_2)_9CH_3$	96	Pentane	Oil	$C_{16}H_{32}O_3S$	H, S; C[c]
123	$-(CH_2)_3CH=CH(CH_2)_{10}CH_3$	53	Petr ether	Oil	$C_{17}H_{34}O_3S$	C, H, S
124	$-(CH_2)_{14}CH=CH_2$	80	Petr ether	46-48	$C_{17}H_{34}O_3S$	C, H, S
125	$-(CH_2)_8CH=CH(CH_2)_7CH_3$	57	Petr ether	36-37	$C_{19}H_{38}O_3S$	C, H, S
126	$-CH_2C{\equiv}C(CH_2)_{12}CH_3$	66	Petr ether	32-34	$C_{17}H_{32}O_3S$	C, H, S
127	$-(CH_2)_3CH=CH(CH_2)_8CH=CH_2$	99	Pentane	Oil	$C_{16}H_{30}O_3S$	H, S; C[d]
128	$-(CH_2)_{15}OSO_2CH_3$	67	Hexane	76-77	$C_{17}H_{34}O_6S_2$	C, H, S

[a] The methanesulfonates of Table V were prepared by method C or the procedure of R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 35, 3195 (1970). [b] Compounds described as oils were crystallized but subsequently melted at or below room temperature. [c] C: calcd, 63.11; found, 62.48. [d] C: calcd, 63.53; found. 64.00.

and filtered. An Et_2O solution of the crude product was filtered to remove insolubles and evaporated. Crystallization from pentane afforded 0.32 g (38%) of **39**, mp 41–43° (Table I). Similarly prepared was methyl *p*-(3-chlorotetradecyloxy)benzoate (**5**), mp 45–47° (Table I).

Methyl *p*-(11-Thiocyanatoundecyloxy)benzoate (38). A mixture of 1.0 g (2.5 mmol) of **15**, 1.22 g (12.5 mmol) of KSCN, and 5.0 ml of DMF was stirred for 17 h under reflux, poured on crushed ice, and filtered. Crystallization afforded 0.70 g (78%) of **38**, mp 35–37° (Table I).

Methyl *p*-(11-Phthalimidoundecyloxy)benzoate (42). A mixture of 1.0 g (2.5 mmol) of **15**, 2.32 g (12.5 mmol) of potassium phthalimide, and 30 ml of DMF was heated on a steam bath for 24 h, poured on ice, and filtered. The solid was collected and crystallized from petroleum ether–Et_2O to yield 0.80 g (71%) of **42**, mp 82–86° (Table I).

***p*-[11-(*n*-Butylsulfinyl)undecyloxy]benzoic Acid (85).** A mixture of 0.22 g (1.1 mmol) of $NaIO_4$, 0.38 g (1.0 mmol) of **82**, 1.0 ml of H_2O, and 20 ml of MeOH was stirred under reflux for 20 min and filtered while hot. The filtrate was allowed to cool and the resulting precipitate was collected to yield 0.32 g (80%) of **85**, mp 125–127° (Table III). Similarly prepared from **80** was *p*-[16-(ethylsulfinyl)hexadecyloxy]benzoic acid (**86**), mp 106–107° (Table III).

***p*-[11-(*n*-Butylsulfonyl)undecyloxy]benzoic Acid (87).** A mixture of 0.38 g (1.0 mmol) of **82**, 1.1 g (5.0 mmol) of $NaIO_4$, 5 ml of H_2O, and 20 ml of MeOH was stirred under reflux for 18 h and filtered while hot. The filtrate was allowed to cool and the precipitate collected to yield 0.28 g (68%) of **87**, mp 140–143° (Table III). Similarly prepared from **80** was *p*-[16-(ethylsulfonyl)hexadecyloxy]benzoic acid (**88**), mp 129–130° (Table III).

Ethyl *p*-(11-Hydroxyundecyloxy)benzoate (9). A mixture of 2.7 g (8.7 mmol) of **70**, 0.5 ml of concentrated H_2SO_4, and 400 ml of EtOH was stirred for 3 days under reflux and then evaporated. The residue was partitioned between ice–water and Et_2O and the organic layer was separated, washed with 1 N NaOH solution, dried, and evaporated to yield 2.59 g (89%) of **9**, mp 48–50° (Table I).

Similarly prepared was *n*-butyl *p*-(11-hydroxyundecyloxy)benzoate (**10**), mp 31–32° (Table I).

Ethyl *p*-(11-Ethoxyundecyloxy)benzoate (23). To the solution formed by adding 3.44 g (0.145 g-atom) of sodium metal to 280 ml of EtOH was added 15.6 g (37.6 mmol) of **16**. The mixture was stirred for 6 days under reflux and evaporated. The residue was triturated with ice–water and collected by filtration. An Et_2O solution of the product was dried and evaporated to yield 11.2 g (82%) of **23**, mp 35–37° (Table I).

Similarly prepared from **17** was *n*-butyl *p*-(*n*-butoxyundecyloxy)benzoate which was used without characterization to prepare **73**. Also prepared by this procedure from **15** was methyl *p*-(methoxyundecyloxy)benzoate (**22**), mp 51–53° (Table I).

Methyl *p*-[10-(*n*-Butylcarbamoyl)decyloxy]benzoate (43). A solution of 33.6 g (0.100 mol) of 11-(*p*-carboxyphenoxy)undecenoic acid[5] and 14.0 ml (10.2 g, 0.101 mol) of triethylamine in 300 ml of THF was stirred at 0° while 13.2 ml (13.7 g, 0.100 mol) of isobutyl chloroformate was added during 5 min. The mixture was stirred for 45 min and then treated with a solution of 10.0 ml (7.64 g, 0.105 mol) of *n*-butylamine in 200 ml of THF while a temperature of 0° was maintained. The mixture was stirred for 2 h at ambient temperature and filtered. The solid was washed with Et_2O and the filtrate and washings were evaporated. Crystallization of the residue afforded 32.1 g (82%) of **43**, mp 92–94° (Table I).

Methyl *p*-[11-(*n*-Butylamino)undecyloxy]benzoate (40). A solution of 20.0 g (51.1 mmol) of **43** in 400 ml of THF was treated with 184 ml of 0.5 M borane in THF at ambient temperature. The solution was stirred for 16 h under reflux, allowed to cool, and acidified with 15 ml of saturated methanolic HCl solution. The mixture was stirred for 1 h under reflux and then partitioned between 500 ml of CH_2Cl_2, 200 ml of H_2O, and 20 ml of MeOH. The lower layer was separated, combined with a 100-ml CH_2Cl_2 extract of the upper layer, dried, and evaporated. Crystallization afforded 15.1 g (71%) of **41**, mp 192–196° (Table I).

A mixture of 5.00 g (12.2 mmol) of **41**, 125 ml of CH_2Cl_2, and 125 ml of 0.1 N NaOH was shaken and the lower layer was separated, dried, and evaporated. Crystallization afforded 3.20 g (70%) of **40**, mp 57–59° (Table I).

***p*-(4,5-Epoxyhexadecyloxy)benzoic Acid (116).** A solution of 2.46 g (12.1 mmol) of 85% *m*-chloroperbenzoic acid in 50 ml of CH_2Cl_2 was added dropwise to a refluxing solution of 3.60 g (10.0 mmol) of **109** in 100 ml of CH_2Cl_2 and reflux was continued for 18 h. The solution was washed with 10% Na_2S solution and 1 N HCl, dried, and evaporated. Crystallization afforded 3.16 g (84%) of **116**, mp 99–100° and 131–132° (Table IV).

Similarly prepared from **48** was methyl *p*-(4,5-epoxyhexadecyloxy)benzoate (**58**), mp 74–77° (Table II).

***p*-(4,5-Dihydroxyhexadecyloxy)benzoic Acid (117).** A solution of 1.50 g (4.00 mmol) of **116**, 1.0 ml of concentrated H_2SO_4, and 40 ml of H_2O in 30 ml of EtOH was stirred for 18 h under reflux. The mixture was diluted with water and extracted with Et_2O. The dried extract was evaporated and the residue crystallized to yield 770 mg (49%) of **117**, mp 144–145° (Table

Table VI

	% of diet	Sterol	Triglyceride
Clofibrate	0.3	81 ± 5	42 ± 8
Boxidine	0.005	60 ± 3	55 ± 6
p-Hexadecyloxybenzoic acid	0.1	74 ± 4	46 ± 7
p-Hexadecyloxybenzoic acid	0.05	83 ± 3	62 ± 6
p-Hexadecyloxybenzoic acid	0.025	89 ± 4	58 ± 8

IV).

***p*-(*cis*-2-Hexadecenyloxy)benzoic Acid** (110). A mixture of 1.80 g (5.03 mmol) of **113**, 200 mg of 5% Pd–$BaSO_4$, and 50 ml of pyridine was shaken under 40 psi of hydrogen for 10 min. The mixture was diluted with CH_2Cl_2 and filtered. The filtrate was evaporated and an Et_2O solution of the residue was washed with 1 N HCl, dried, and evaporated. Crystallization afforded 1.42 g (78%) of **110**: mp 97–99° (Table IV); NMR ($CDCl_3$–Me_2SO) δ 5.70 (2, m, CH=CH).

***p*-(*trans*-2-Hexadecenyloxy)benzoic Acid** (111). To 3.00 g (8.33 mmol) of molten **110** was added 0.11 ml of 6 M HNO_3 and 0.17 ml of 2 M $NaNO_2$ solution.[6] The mixture was stirred at 110° under an argon atmosphere for 36 h, allowed to cool, and partitioned between H_2O and CH_2Cl_2. The organic layer was dried and evaporated and the residue was crystallized to yield 1.00 g (33%) of 111: mp 104–106 and 126–127° (Table IV); NMR ($CDCl_3$–Me_2SO) δ 5.70 (1, s, $=CH_a$), 5.83 (1, s, $=CH_b$) (J_{ab} = 16 Hz).

Biological Methods. Male CFE rats (Carworth Farms) weighing 140–150 g were allocated to experimental groups, eight animals per control group and four animals per test group. The compounds to be tested were added to ground commercial rat chow at levels of 0.1, 0.05, and 0.025% (w/w) by dissolving the compound in methanol–chloroform (1:3 v/v), adding this solution to the feed, mixing, and allowing the solvents to evaporate. Control groups were given food treated with the solvents alone. Animals were allowed food and water ad libitum for 6 days after which they were killed in a fed state and bled. Serum sterols[7] and triglycerides[8] were measured using a Technicon autoanalyzer.

The serum sterol and triglyceride values in Table VI and in Tables I–IV are shown as percent of control values and are expressed as the mean for the test group plus or minus the standard error for the group, $\bar{X} \pm$ SE. The significance level (p) was determined using Student's t test. The mean and standard error for the test groups and those for the control groups, respectively, were used to calculate t. Control groups averaged 75 ± 3 mg % serum sterol and 85 ± 6 mg % serum triglyceride. Clofibrate (ethyl *p*-chlorophenylisobutyrate) and boxidine [1-[2-[4′-(trifluoromethyl)-4-biphenylyloxy]ethyl]pyrrolidine] were used as positive controls. Values for *p*-hexadecyloxybenzoic acid[1] are shown for reference. Compounds which lowered serum sterol to 85% of control values or serum triglyceride to 75% of control values were selected for further study.

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