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Potential Antiatherosclerotic Agents. 4.[1] [(Functionalized-alkyl)amino]benzoic Acid Analogues of Cetaben

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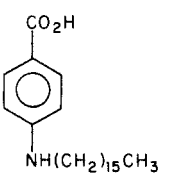
The synthesis of a series of analogues in which the alkyl group of cetaben is substituted with various functional groups or replaced entirely by a functionalized alkanoyl moiety is described. Also reported are the syntheses of branched-chain (alkylamino)benzoic acids in which branching is specifically localized at the terminus of the alkyl chain. Structure–activity relationships of these compounds, both as hypolipidemic agents and as inhibitors of the enzyme fatty acyl-CoA:cholesterol acyltransferase (ACAT), are discussed. Certain compounds were specifically synthesized to test the hypothesis that groups located near the terminus of the alkyl chain of cetaben might retard metabolic degradation of the molecule and, thus, enhance biological activity. Some of these (**48–50**) were found to be the most active analogues synthesized.

This report continues[1] a series of papers describing the synthesis and structure–activity relationships of the series of analogues from which the potential antiatherosclerotic agent cetaben (1) was selected. Compounds in which the



1 (cetaben)

alkylamino moiety of cetaben is substituted with various groups, such as halo, alkoxy, hydroxy, alkylthio, mercapto, amino, keto, trifluoromethyl, trimethylsilyl, cyano, carboxamido, carboalkoxy, and carboxy, are described in this paper. Also discussed are compounds in which the alkylamino moiety bears more complex substituents, such as 4-carboxyphenoxy and 4-carboxyphenylthio, as well as compounds in which the alkylamino group is replaced entirely by a substituted alkanamido group. Finally, a group of branched-chain (alkylamino)benzoic acids, in which branching or substitution is specifically localized at the terminus of the alkyl chain, is reported.

The general biological rationale for the investigation of cetaben and its analogues has been discussed in detail.[2] The scope of analogue synthesis reported in this paper were the specific rationale for the preparation of certain cetaben congeners are described below. The [(substituted-alkyl)amino]benzoic acids, esters, and salts of Table I were synthesized to study the effects of various alkyl substituents on the biological activity of cetaben. Although many of the compounds shown in Table II were prepared as intermediates for the synthesis of analogues of Table I, these amides were of interest in their own right due to the persistently high activity of these and other amide analogues of cetaben as inhibitors of cholesterol esterification.[1]

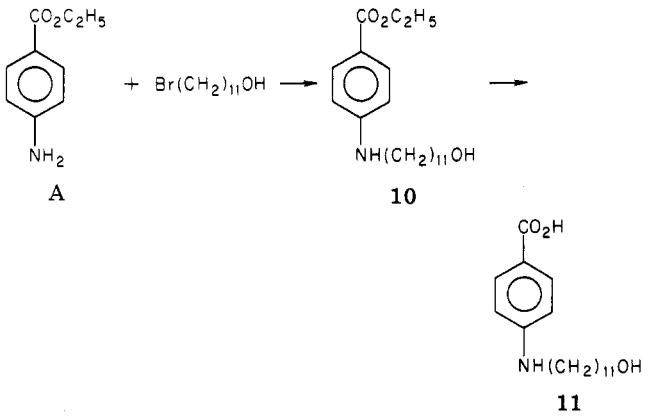
Some of the branched-chain (alkylamino)benzoic acids, esters, and salts of Table III, as well as certain analogues of Table I (e.g., **40–50**), were specifically synthesized to test the hypothesis that groups located near the terminus of the alkyl chain of cetaben might retard or prevent metabolism and, thus, prolong or enhance in vivo activity. Metabolism of cetaben by oxidative functionalization at

(1) Part 3 of this series: J. D. Albright, V. G. DeVries, M. T. Du, E. E. Largis, T. G. Miner, M. F. Reich, and R. G. Shepherd, *J. Med. Chem.*, second paper in a series of three in this issue.

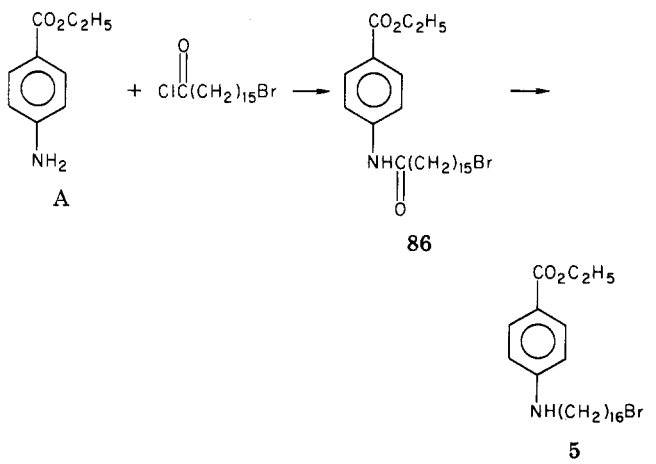
(2) Part 2 of this series: J. D. Albright, V. G. DeVries, E. E. Largis, T. G. Miner, M. F. Reich, S. A. Schaffer, R. G. Shepherd, and J. Upeslacis, *J. Med. Chem.*, first paper in a series of three in this issue.

0022-2623/83/1826-1411$01.50/0

Scheme I



Scheme II



the penultimate carbon of the alkyl chain would be likely, and such a transformation could render the molecule biologically inactive. This well-recognized phenomenon is termed (ω - 1)-hydroxylation and is preferred for alkyl chains of four or more carbons.[3] The opposite hypothesis, namely, that the in vivo activity of cetaben was actually due to a metabolite, was also considered. Dicarboxylic acids such as **60**, **66**, **71**, and **74** represent possible products of oxidative degradation of the alkyl chain of cetaben.

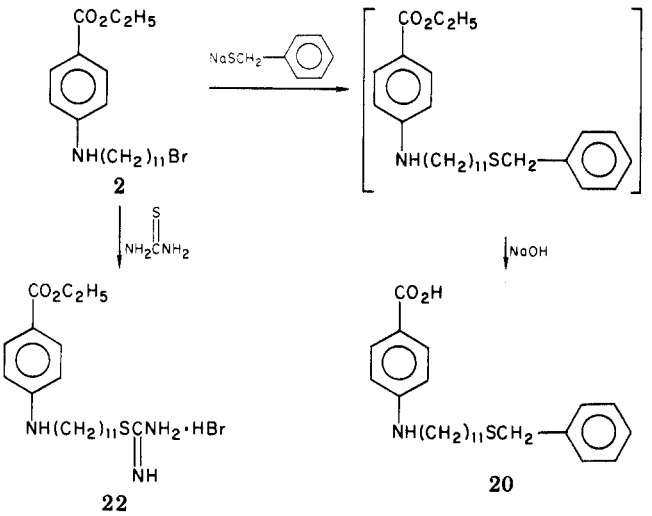
Chemistry. Many of the compounds shown in Tables I–III were prepared by general methods discussed previously.[2] As illustrated in Scheme I, alkylation of ethyl 4-aminobenzoate (A) with 11-bromoundecanol afforded hydroxy ester **10**, and subsequent alkaline hydrolysis yielded hydroxy acid **11**.

Alternatively, certain of the analogues of Tables I and II were obtained by acylation of A with functionalized acyl halides, followed by diborane reduction of the resulting alkanamidobenzoate esters. An illustration of this synthesis (Scheme II) is the preparation of ethyl 4-[(16-bromohexadecyl)amino]benzoate (**5**).

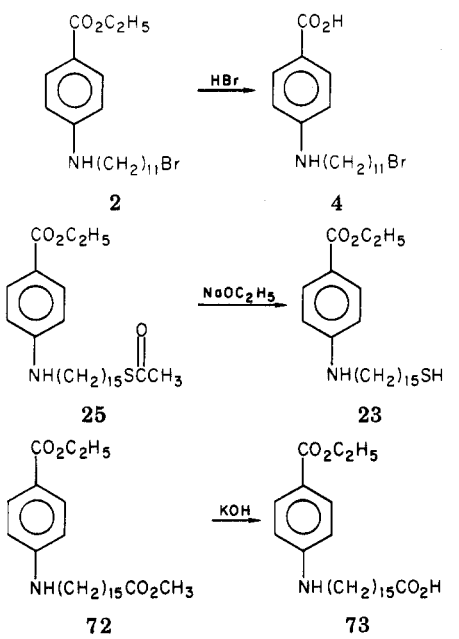
Certain substituents were introduced into the alkylamino and alkanamido moieties of substituted benzoate esters by the nucleophilic displacement of halo or methanesulfonate ester groups. These nucleophilic substitutions (Scheme III) involved reactions of sodium benzyl mercaptide to yield thioether **20** or thiourea to yield thiuronium salt **22**.

A large number of the compounds shown in Tables I and II were obtained by transformations of various functional

Scheme III



Scheme IV



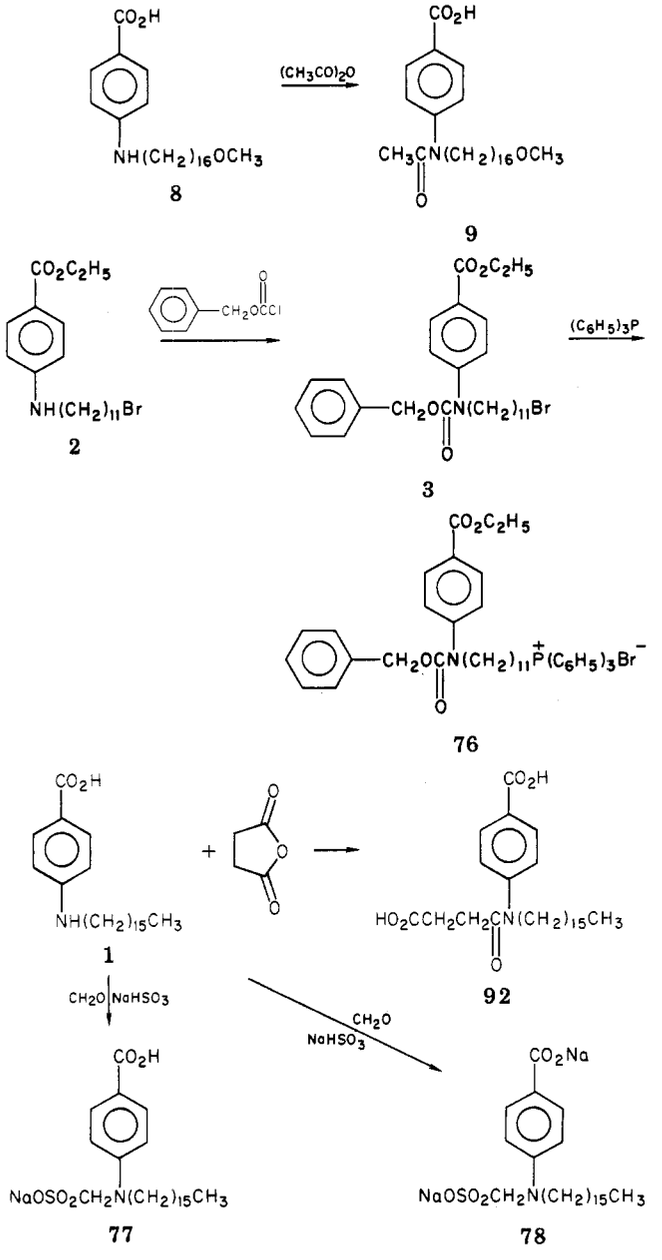
groups located on the alkylamino or alkanamido moieties of other analogues. Since alkaline hydrolysis of the ester group in **2** was accompained by displacement of the bromo group by hydroxide to yield **11**, bromo acid **4** was obtained by treatment of **2** with a mixture of hydrobromic and acetic acids (Scheme IV). Deacetylation of thioester **25** and selective hydrolysis of the methyl ester group in **72** afforded benzoate ester analogues **23** and **73**, respectively.

Acylation and alkylation reactions of (alkylamino)-benzoic acids and esters yielded the analogues whose syntheses are shown in Scheme V. Acylations of **8** and **1** with acetic and succinic anhydrides led to amides **9** and **92**, respectively. Acylation of **2** with benzyl chloroformate afforded **3**, which in turn was converted to **76** by reaction with triphenylphosphine. Attempts to employ **76** in various Wittig reactions were unsuccessful. Sulfomethylation of **1** with 1 equiv of sodium bisulfite and 1 equiv of formaldehyde yielded monosodium salt **77**, while previous conversion of **1** to its sodium salt and the use of an excess of these reagents afforded the disodium salt **78**.

Ketone **30** was employed in the synthesis of a series of analogues as shown in Scheme VI. Selective reduction of the keto carbonyl group using sodium borohydride afforded alcohol **12**, which was converted to the chloro

(3) P. Jenner and B. Testa, "Concepts in Drug Metabolism", Marcel Dekker, New York, 1980, pp 100 and 187.

Scheme V



analogue **6** by treatment with thionyl chloride. Reaction of **12** with methanesulfonyl chloride[4] yielded the corresponding methanesulfonate ester, which was not isolated but reacted directly with sodium cyanide to afford the cyano analogue **53**, or it was reacted with potassium thioacetate to yield **27**. Reductive amination of **30** using sodium cyanoborohydride and ammonium acetate yielded amino analogue **28**, and treatment of **30** with hydroxylamine hydrochloride, followed by alkaline hydrolysis, afforded oxime **34**.

Oxidation and oxymercuration reactions were employed in the synthesis of hydroxy and sulfinyl analogues as shown in Scheme VII. Sodium metaperiodate oxidation of thioether **16** yielded **17**, and treatment of olefin B[2] with mercuric acetate and sodium borohydride afforded tertiary alcohol **14**.

The 4,4′-[poly(methylene)diimino]bis[benzoic acids and esters] shown in Table IV were obtained as byproducts in the synthesis of some of the compounds of Table III.

(4) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

Biology. The cetaben analogues whose syntheses are described above were assayed for two types of biological activity related to their potential use as antiatherosclerotic agents. Compounds were tested in vivo for serum hypolipidemic activity in normal rats. They were also tested in vitro for the ability to inhibit fatty acyl-CoA:cholesterol acyltransferase (ACAT), the enzyme that catalyzes the intracellular esterification of cholesterol. Details of the biological methodology and the relevance of these tests have been reported.[2]

Functionalization of the alkyl group of cetaben (**1**) generally diminished hypocholesteremic activity, and most of the compounds shown in Tables I and II were less active than **1**. Hydroxy analogues **12–15** exhibited excellent hypotriglyceridemic activity but relatively little hypocholesteremic activity. The best ACAT inhibitor of Table I, thiol **26**, showed little hypocholesteremic activity. As had been anticipated, modification of the alkyl group of cetaben near its terminus had the most dramatic effect on in vivo activity.

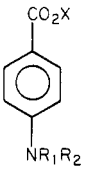
Functionalization of the terminus of the alkyl chain with poly(fluoro)alkyl groups (**35–41**) resulted in excellent hypolipidemic activity. As a group, the trimethylsilyl analogues (**42–50**) were the most active cetaben analogues synthesized. In addition to excellent hypolipidemic activity, **46–50** also had ACAT inhibitory activity comparable to that of cetaben. Other substituents placed at the terminus of the alkyl chain, for example, halo (**5**), methoxy (**8**), ethylthio (**19**), mercapto (**24**), carboxy (**74**), or the aryl groups described previously,[2] resulted in decreased hypolipidemic activity. As expected, based on the persistence of ACAT inhibitory activity for other amide analogues of cetaben,[1] several of the alkanamidobenzoic acids and esters of Table II were ACAT inhibitors; however, none possessed the combination of ACAT and hypocholesteremic activity.

The analogues shown in Table III illustrate the effect that chain branching and cycloalkyl moieties have on biological activity. Direct comparison of the best of the trimethylsilyl compounds (**48–50**) with their carbon isosteres (**107–109**) demonstrates that the presence of a silicon atom is not essential either for hypolipidemic or for ACAT inhibitor activity. In fact, the excellent activity of alkylaminobenzoic acids **102**, **104**, **106**, and **108** relative to **98**, **100**, **110**, **112**, and **116** indicates that branching of the alkyl group at the $(\omega - 1)$-carbon atom is uniquely compatible with biological activity.

It was noted previously[2] that food intake was monitored during evaluation of all compounds for hypolipidemic activity in rats. Since compounds were administered admixed in the diet, decreased food consumption would reduce the dose of compound; moreover, decresed caloric intake per se might account for hypolipidemic activity or might be an indication of drug toxicity. Poly(fluoro)alkyl compounds (**35–41**) generally produced large decreases in food intake, and thus no accurate assessment of their hypolipidemic activity is possible. The branched alkyl compounds (**102–108**) as a class caused smaller decreases in food intake. The highly active trimethylsilyl analogues (**48–50**) had no significant effect on food consumption, implying that these compounds possess intrinsic hypolipidemic activity.

In summary, compounds specifically designed to test the hypothesis that groups located near the terminus of the alkyl chain of cetaben might retard metabolic degradation of the molecule via ω or $\omega - 1$ oxidation and thus enhance biological activity were the most active types of analogues synthesized. Also, the hypothesis that the molecule might be rendered inactive by oxidative degradation of the alkyl

Table I. [(Substituted-alkyl)amino]benzoic Acids, Esters, and Salts



no.	R_1	R_2	X	method	yield, %	crystn solvent
1	$(CH_2)_{15}CH_3$	H	H	B, C	95	EtOH
2	$(CH_2)_{11}Br$	H	C_2H_5	A	72	EtOH
3	$(CH_2)_{11}Br$	CO_2CH_2-C_6H_5	C_2H_5		98	
4	$(CH_2)_{11}Br$	H	H		86	MeCN
5	$(CH_2)_{16}Br$	H	C_2H_5	A	81	EtOH
6	$(CH_2)_5CH(Cl)(CH_2)_9CH_3$	H	C_2H_5		53	CH_2Cl_2
7	$(CH_2)_{11}O(CH_2)_3CH_3$	H	H	D, C	13	EtOH
8	$(CH_2)_{16}OCH_3$	H	H	D, C	78	MeOH
9	$(CH_2)_{16}OCH_3$	$COCH_3$	H		86	hexane-acetone
10	$(CH_2)_{11}OH$	H	C_2H_5	B	47	MeCN
11	$(CH_2)_{11}OH$	H	H	C	81	MeCN
12	$(CH_2)_5CH(OH)(CH_2)_9CH_3$	H	C_2H_5		86	hexane
13	$(CH_2)_5CH(OH)(CH_2)_9CH_3$	H	H	C	51	EtOH
14	$(CH_2)_5C(CH_3)(OH)(CH_2)_9CH_3$	H	C_2H_5		83	hexane
15	$(CH_2)_5C(CH_3)(OH)(CH_2)_9CH_3$	H	H	C	92	hexane-CH_2Cl_2
16	$(CH_2)_{11}S(CH_2)_3CH_3$	H	H	D, C	48	MeOH
17	$(CH_2)_{11}SO(CH_2)_3CH_3$	H	H		83	acetone-CH_2Cl_2
18	$(CH_2)_{16}SC_2H_5$	H	C_2H_5	D	81	hexane-CH_2Cl_2
19	$(CH_2)_{16}SC_2H_5$	H	H	C	96	CH_2Cl_2
20	$(CH_2)_{11}SCH_2$-C_6H_5	H	H	D, C	61	acetone-water
21	$(CH_2)_{11}SH$	H	H	C	66	EtOH
22	$(CH_2)_{11}SC(=NH)NH_2 \cdot HBr$	H	C_2H_5	F	84	EtOH
23	$(CH_2)_{16}SH$	H	C_2H_5		76	hexane
24	$(CH_2)_{16}SH$	H	H	C	82	ether-CH_2Cl_2
25	$(CH_2)_{16}SCOCH_3$	H	C_2H_5	E	72	hexane-CH_2Cl_2
26	$(CH_2)_5CH(SH)(CH_2)_9CH_3$	H	H	C	74	hexane-CH_2Cl_2
27	$(CH_2)_5CH(SCOCH_3)(CH_2)_9CH_3$	H	C_2H_5	E	43	hexane
28	$(CH_2)_5CH(NH_2)(CH_2)_9CH_3$	H	C_2H_5		49	hexane
29	$(CH_2)_5CH(NH_2)(CH_2)_9CH_3$	H	Na	C	52	
30	$(CH_2)_5C(=O)(CH_2)_9CH_3$	H	C_2H_5	B	70	EtOH
31	$(CH_2)_5C(=O)(CH_2)_9CH_3$	H	H	C	75	HOAc
32	$(CH_2)_{10}C(=O)(CH_2)_4CH_3$	H	C_2H_5	B	55	MeCN
33	$(CH_2)_{10}C(=O)(CH_2)_4CH_3$	H	H	C	78	EtOH
34	$(CH_2)_5C(=NOH)(CH_2)_9CH_3$	H	H		71	EtOH-water
35	$(CH_2)_{10}CF_3$	H	C_2H_5	B	85	EtOH
36	$(CH_2)_{10}CF_3$	H	H	C	97	MeCN
37	$(CH_2)_{15}CF_3$	H	C_2H_5	B	91	MeCN
38	$(CH_2)_{15}CF_3$	H	H	C	79	acetone
39	$(CH_2)_{15}CF_3$	H	Na	C	89	EtOH-water
40	$CH_2(CF_2)_6CF_3$	H	C_2H_5	B	45	MeCN
41	$CH_2(CF_2)_6CF_3$	H	H	C	80	MeCN
42	$(CH_2)_3Si(CH_3)_3$	H	C_2H_5	B	70	EtOH-water
43	$(CH_2)_3Si(CH_3)_3$	H	H	C	86	MeCN
44	$(CH_2)_3Si(CH_3)_3$	H	Na	C	70	EtOH
45	$(CH_2)_{11}Si(CH_3)_3$	H	C_2H_5	B	70	EtOH-water
46	$(CH_2)_{11}Si(CH_3)_3$	H	H	C	72	toluene
47	$(CH_2)_{11}Si(CH_3)_3$	H	Na	C	61	EtOH-water
48	$(CH_2)_{14}Si(CH_3)_3$	H	C_2H_5	B	81	EtOH
49	$(CH_2)_{14}Si(CH_3)_3$	H	H	C	91	acetone
50	$(CH_2)_{14}Si(CH_3)_3$	H	Na	C	77	EtOH-water
51	$(CH_2)_3CN$	H	C_2H_5	B	73	C[l]
52	$(CH_2)_3CN$	H	H	C	57	acetone-water
53	$(CH_2)_5CH(CN)(CH_2)_9CH_3$	H	C_2H_5		74	hexane
54	$(CH_2)_5CH(CN)(CH_2)_9CH_3$	H	H	C	87	hexane-acetone
55	CH_2CONH_2	H	H	B, C	44	EtOH
56	$CH_2CO_2C_2H_5$	H	C_2H_5	B	56	C[l]
57	$CH(CH_3)CO_2C_2H_5$	H	C_2H_5	B	48	C[l]
58	$CH(CH_2CH_2CH_3)CO_2C_2H_5$	H	C_2H_5	B	39	C[l]
59	$CH_2CO_2C_2H_5$	$CH_2CO_2C_2H_5$	C_2H_5	B[i]	76	hexane-EtOH
60	CH_2CO_2H	H	H	C	57	hexane-ether
61	$CH(CH_2CH_2CH_3)CO_2H$	H	H	C	78	MeCN, toluene
62	CH_2CO_2H	CH_2CO_2H	H	C	75	acetone
63	$CH_2CO_2C_2H_5$	$(CH_2)_{15}CH_3$	CH_3[j]	B	90	C[l]
64	CH_2CO_2H	$(CH_2)_{15}CH_3$	H	C	71	HOAc
65	$CH_2CH_2CO_2C_2H_5$	H	C_2H_5	B	79	C[l]
66	$CH_2CH_2CO_2H$	H	H	C	81	hexane-ether
67	$CH_2CH_2CO_2Na$	H	Na	C	80	
68	$(CH_2)_3CO_2C_2H_5$	H	C_2H_5	B	46	hexane-ether

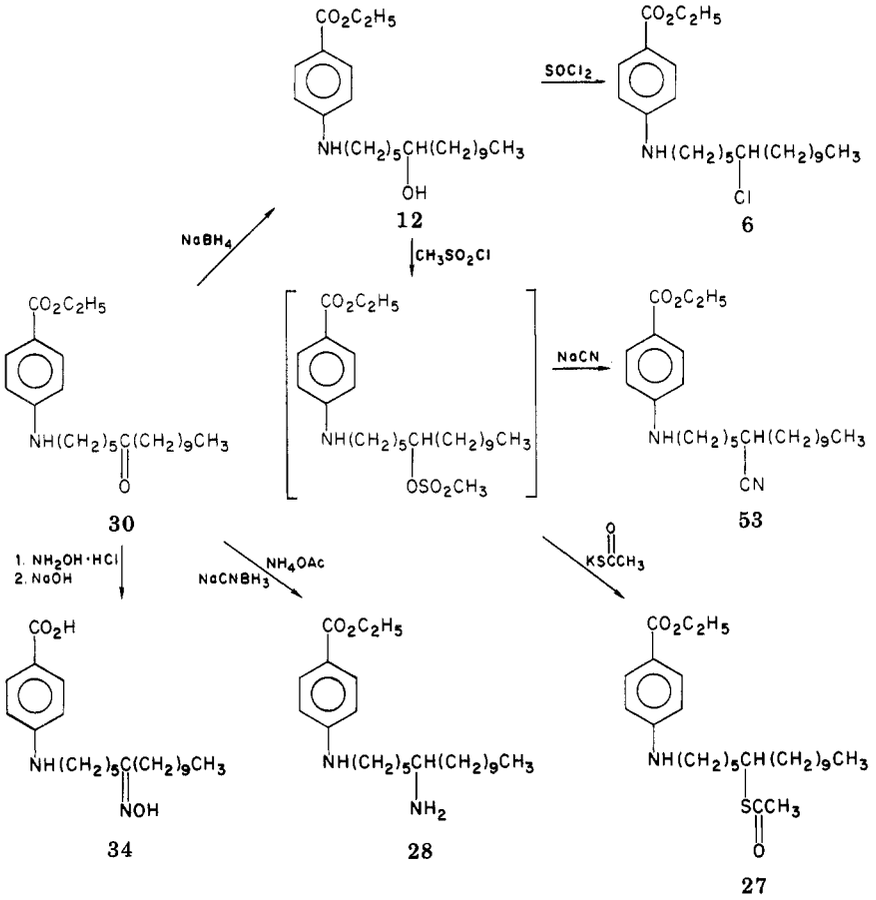
mp, °C	formula[a]	sterol lowering,[b] dose as % of diet			triglyceride lowering,[b] dose as % of diet			ACAT,[c] % inhibn
		0.10	0.03	0.01	0.10	0.03	0.01	
108-110, 126-128	$C_{23}H_{39}NO_2$	54***	71**	72***	31***	45***	71*	57***
85-86	$C_{20}H_{32}BrNO_2$[d]	101	94	108	74	83	83	61***
oil	$C_{28}H_{38}BrNO_4$	100			91			71***
125-128	$C_{18}H_{28}BrNO_2$	100	86**	99	55**	65*	78	8
82-85	$C_{25}H_{42}BrNO_2$	93	98	99	100	84	100	10
62-63	$C_{25}H_{42}ClNO_2$[e]	94	91	98	53***	84	82	13
70-72, 92-93	$C_{22}H_{37}NO_3$[f]	91		86*	44***		74	62***
101-104	$C_{24}H_{41}NO_3$	86*	96	97	52*	73*	76	43**
74-76	$C_{26}H_{43}NO_4$	100			93			22**
77-78	$C_{20}H_{33}NO_3$	94			93			60***
125-126	$C_{18}H_{29}NO_3$	99	95	93	78	101	111	30**
70-71	$C_{25}H_{43}NO_3$	93			39***			51***
112-113	$C_{23}H_{39}NO_3$	86*	96	104	31***	43***	66**	
46-47	$C_{26}H_{45}NO_3$	82*			28***			59***
115-116	$C_{24}H_{41}NO_3$	73*			37*			53***
79-81, 92-93	$C_{22}H_{37}NO_2S$	78***	91	91	62**	71*	79	40**
153-154	$C_{22}H_{37}NO_3S$	91	95	106	66*	94	87	15*
77-78	$C_{27}H_{47}NO_2S$	89*			58***			10
103-104	$C_{25}H_{43}NO_2S$[m]	88	91	91	59*	58*	62	36**
96-99	$C_{25}H_{35}NO_2S$	90	95	99	51**	52*	55*	54***
119-122	$C_{18}H_{29}NO_2S$	84*	89	92	50***	61*	65*	26*
164-166	$C_{21}H_{36}BrN_3O_2S$	98	107	100	59*	69*	85	73***
78-79	$C_{25}H_{43}NO_2S$	90			51***			8
159-160	$C_{23}H_{39}NO_2S$	101	101	96	40*	45*	67	38***
86-87	$C_{27}H_{45}NO_3S$	93	96	98	57*	75	91	0
60-75	$C_{23}H_{39}NO_2S$	84			43*			79***
41-42	$C_{27}H_{45}NO_3S$	94			46*			26**
63-65	$C_{25}H_{44}N_2O_2$	84	99	97	45**	70	68	0
>250	$C_{23}H_{39}N_2O_2Na$[g]	98	117	100	120	107	68	7
92-94	$C_{25}H_{41}NO_3$	107	104	109	81	86	103	19*
133-134	$C_{23}H_{37}NO_3$	84*	90	95	46***	68*	63*	18
80-83	$C_{25}H_{41}NO_3$	89	100	99	42***	58**	64*	44***
131-134	$C_{23}H_{37}NO_3$	81**	89	93	42***	57***	59**	33**
90-95	$C_{23}H_{38}N_2O_3$	75***	84**	86	31***	30***	52**	
102-103	$C_{20}H_{30}F_3NO_2$	87*	88	86*	46**	61**	74*	24*
122-123, 132-133	$C_{18}H_{26}F_3NO_2$	69**	80*	92	56*	57**	57**	22
89-91	$C_{25}H_{40}F_3NO_2$	75**	72**	83*	41***	47***	75*	8
111-112, 130-131	$C_{23}H_{36}F_3NO_2$	61***	72**	75**	42**	41***	46**	14
>250	$C_{23}H_{35}F_3NO_2Na$	34***	62**	75**	21***	39***	63*	55**
113-114	$C_{17}H_{12}F_{15}NO_2$	44***	65**	81*	35***	43***	47***	7
158-160, 183-185	$C_{15}H_8F_{15}NO_2$[h]	59**	66**	87*	31***	40**	51***	42***
64-66	$C_{15}H_{25}NO_2Si$	77*	86	99	54**	63*	60**	59***
164-165	$C_{13}H_{21}NO_2Si$	82**	90	100	47***	58*	69**	12
385-388	$C_{13}H_{20}NO_2SiNa$	64***	82*	87	77**	85	102	23*
66-68	$C_{23}H_{41}NO_2Si$	57***	87	85	78*	111	113	17
121-122	$C_{21}H_{37}NO_2Si$	44***	69*	79**	25***	54**	67**	57***
360 dec	$C_{21}H_{36}NO_2SiNa$	48***	73*	81*	46***	88	122	56***
91-92	$C_{26}H_{47}NO_2Si$	53**	66***	84	62**	66**	77*	50***
105-107	$C_{24}H_{43}NO_2Si$	40***	51***	70**	30**	38*	59*	60***
350-355	$C_{24}H_{42}NO_2SiNa$	39***	56**	75	22**	43*	55*	62***
84-85	$C_{13}H_{16}N_2O_2$	109	118	116	97	113	131	26*
188-190	$C_{11}H_{12}N_2O_2$	94			93			8
54-56	$C_{26}H_{42}N_2O_2$	87	97	100	51**	69*	66*	69***
126-128	$C_{24}H_{38}N_2O_2$	83	85*	96	50**	66*	75	64***
247-249	$C_9H_{10}NO_3$	100			102			17*
63-64	$C_{13}H_{17}NO_4$	100	100	90	121	114	109	24*
52-53	$C_{14}H_{19}NO_4$	107	93	107	82	110	123	23
75-79	$C_{16}H_{23}NO_4$	102	109	103	77	96	93	44***
74-75	$C_{17}H_{23}NO_6$	100	98	93	122	120	77	32**
>270 dec	$C_9H_8NO_4$	98	87	89	106	93	90	18*
175-176	$C_{12}H_{14}NO_4$		87*	95		74	93	0
227-228	$C_{11}H_{11}NO_6$	91	89	95	100	84	92	14
50-51	$C_{28}H_{47}NO_4$	104	100	106	104	97	113	11
201-202	$C_{25}H_{41}NO_4$	93	109	105	99	100	105	15
70-71	$C_{14}H_{19}NO_4$	94	100	97	103	98	109	28*
194-196	$C_{10}H_{11}NO_4$	100	118	101	72**	108	97	6
>250	$C_{10}H_{10}NO_4Na$							0
37-39	$C_{15}H_{21}NO_4$	93			103			11

Table I (*Continued*)

no.	R_1	R_2	X	method	yield, %	crystn solvent
69	$(CH_2)_3CO_2H$	H	H	C	80	HOAc
70	$(CH_2)_5CO_2C_2H_5$	H	C_2H_5	B	57	C[l]
71	$(CH_2)_5CO_2H$	H	H	C	84	HOAc
72	$(CH_2)_{15}CO_2CH_3$	H	C_2H_5	B	74	MeCN
73	$(CH_2)_{15}CO_2H$	H	C_2H_5		90	toluene
74	$(CH_2)_{15}CO_2H$	H	H	C	34	HOAc
75	$(CH_2)_{15}CO_2Na$	H	Na	C	89	EtOH-water
76	$(CH_2)_{11}P(Br)(C_6H_5)_3$	CO_2CH_2-C_6H_5	C_2H_5		86	
77	CH_2SO_3Na	$(CH_2)_{15}CH_3$	H		79	
78	CH_2SO_3Na	$(CH_2)_{15}CH_3$	Na		25	
79	p-$(CH_2)_{11}O$-C_6H_4-CO_2CH_3	H	C_2H_5	D	64	EtOH
80	p-$(CH_2)_{11}O$-C_6H_4-CO_2H	H	H	C	96	EtOH
81	p-$(CH_2)_{11}S$-C_6H_4-$CO_2C_2H_5$	H	C_2H_5	D	75	EtOH
82	p-$(CH_2)_{11}S$-C_6H_4-CO_2H	H	H	C	99	EtOH

[a] Unless otherwise indicated by footnotes, microanalytical values for C, H, N, F, Cl, Br, and S, if present, were within ±0.4% of calculated values. [b] Serum sterol and triglyceride values are expressed as the mean percent of control values. Results marked with asterisks are significantly different from control values: * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. [c] ACAT inhibition values are expressed as the mean percent inhibition of enzyme at a drug concentration of 5.2 μg/mL.

Scheme VI



chain appears reasonable, since the type of metabolites that would be anticipated, dicarboxylic acids such as **60**, **66**, **69**, **71**, and **74**, were all found to be devoid of hypocholesteremic activity. Dicarboxylic acids of this type, as well as lactam **96**, were, indeed, subsequently identified as metabolites by using radiolabeled cetaben.[5]

Experimental Section

Generalizations regarding the syntheses described in this section and details of the biological methods used have been reported.[2] Intermediate alkyl halides, alkyl methanesulfonate esters, and acyl halides required for the synthesis of analogues shown in Tables I–IV, which were not commerically available, were prepared by one of the methods shown immediately below.

16-Bromo-6-hexadecanone. A solution of n-pentylmagnesium bromide [prepared by stirring a mixture of 3.07 g (0.126 g-atom) of magnesium, 22.7 g (0.150 mol) of n-pentyl bromide, and 200 mL of Et_2O at reflux for 30 min] was treated with 15.1 g (82.5 mmol) of freshly dried cadmium chloride,[6] stirred at reflux for 45 min, and then concentrated by distillation while the solvent was replaced by 200 mL of toluene. When the reaction tem-

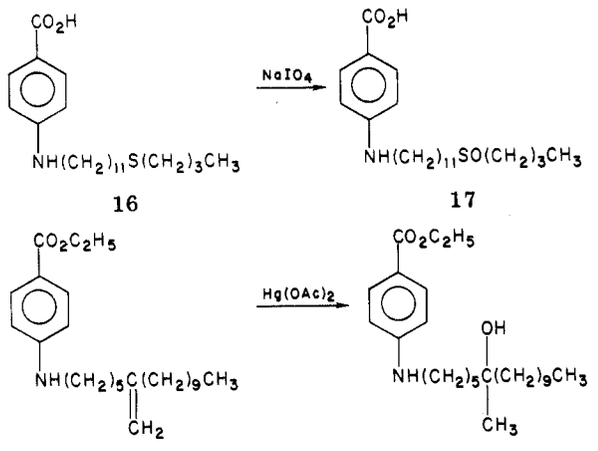
(5) S. I. Heimberger, G. Nicolau, G. E. VanLear, and W. H. Wu, unpublished results.

(6) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, 1954, p 714.

mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
254-257	$C_{11}H_{13}NO_4$	99			86			0
69-70	$C_{17}H_{25}NO_4$	84	92	96	71	72	68	18
233-234	$C_{13}H_{17}NO_4$	105	100	92	102	91	85	4
88-90	$C_{26}H_{43}NO_4$	104	110	105	129	173	140	0
116-118	$C_{25}H_{41}NO_4$	106	106	100	147	133	99	4
176-178	$C_{23}H_{37}NO_4$[n]	92	92	101	96	90	124	0
>250	$C_{23}H_{35}NO_4Na_2$	106	102	102	132	97	93	9
oil	$C_{46}H_{53}BrNO_4P$[k]							
>170 dec	$C_{24}H_{40}NO_5SNa$	72**	87**	91	49**	57**	79	32*
>230 dec	$C_{24}H_{39}NO_5SNa_2$[o]	75**	91	89	89	95	77	7
95-96	$C_{28}H_{39}NO_5$	100			72**			52***
251-252	$C_{25}H_{33}NO_5$	103	91	103	91	79	90	36***
101-103	$C_{29}H_{41}NO_4S$	102			132			45***
228-230	$C_{25}H_{33}NO_4S$	98	104		78	92		29**

[d] Calcd: Br, 20.06. Found: Br, 19.41. [e] Calcd: Cl, 8.36. Found: Cl, 7.30. [f] Calcd: C, 72.69; H, 10.26. Found: C, 66.73; H, 9.64. [g] Calcd: C, 69.31. Found: C, 68.32. [h] Calcd: C, 34.70; F, 54.89. Found: C, 34.11; F, 53.95. [i] Compound 59 was isolated as a byproduct in the synthesis of compound **56**. [j] Compound **63** was prepared by alkylation of methyl 4-(hexadecylamino)benzoate; see paper 2 of this series.[2] [k] Calcd: C, 69.51; N, 1.76; Br, 10.05. Found: C, 70.96; N, 2.87; Br, 9.22. [l] The compound was purified by silica gel chromatography. [m] Calcd: H, 10.28. Found: H, 10.70. [n] Calcd: N, 3.58. Found: N, 3.15. [o] Calcd: S, 6.40. Found: S, 5.40.

Scheme VII



perature reached 80 °C, 23.0 g (75.4 mmol) of 11-bromoundecanoyl chloride was added dropwise, and heating was continued for 30 min. The mixture was cooled and diluted with 200 mL of 10% H_2SO_4, and the resulting layers were separated. The organic layer was combined with an Et_2O extract of the aqueous layer, washed with saturated $NaHCO_3$, dried, and evaporated. Distillation (Kugelrohr apparatus) afforded 17.0 g (71%) of 16-bromo-6-hexadecanone as a light yellow oil, bp 162–167 °C (0.45 mmHg).

Also prepared by this method was 16-bromo-11-hexadecanone, bp 160–173 °C (1.0 mmHg).

16-Bromo-1,1,1-trifluorohexadecane. A stainless-steel bomb was charged with 300 g (0.895 mol) of 16-bromohexadecanoic acid and 900 g of sulfur tetrafluoride[7] at −78 °C and then shaken at 120 °C for 7 h. The bomb was allowed to cool, and pressure was released slowly. The residue in the bomb was treated with 1 L of H_2O, and the resulting mixture was extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. The residue was distilled (Kugelrohr apparatus), and a solution of the distillate in CH_2Cl_2 was filtered through hydrous magnesium silicate and evaporated. The reside was redistilled to yield 312 g (97%) of 16-bromo-1,1,1-trifluorohexadecane as a light yellow liquid, bp 125–130 °C (0.06 mmHg).

Prepared in this same manner from 11-bromoundecanoic acid was 11-bromo-1,1,1-trifluoroundecane, bp 75–80 °C (0.19 mmHg).

1-[(Trifluoromethanesulfonyl)oxy]-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctane. A mixture of 40.0 g (0.100 mol) of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanol, 11.1 g (0.110 mol) of triethylamine, and 200 mL of CH_2Cl_2 was stirred at −20 °C under argon while a solution of 18.5 g (0.110 mol) of trifluoromethanesulfonyl chloride in 50 mL of CH_2Cl_2 was added dropwise and then stirred at ambient temperature for 1 h. The solution was washed with 150 mL each of ice-cold 10% HCl, saturated $NaHCO_3$, H_2O, and saturated NaCl. The solution was dried and evaporated and the residue was distilled (Kugelrohr apparatus) to yield 45 g (85%) of 1-[(trifluoromethanesulfonyl)oxy]-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctane as a colorless liquid, bp 80–86 °C (15 mmHg).

1-(Methanesulfonyloxy)-14-(trimethylsilyl)tetradecane. A solution of 3-(trimethylsilyl)propylmagnesium bromide [prepared from 4.00 g (0.165 g-atom) of magnesium and 31.6 g (0.162 mol) of 3-(trimethylsilyl)propyl bromide[8,9] in 100 mL of THF at 60 °C under argon] was added dropwise at −20 °C to a solution of dilithium cupric chloride[10,11] (prepared from 82 mg of lithium chloride and 125 mg of cupric chloride in 10 mL of THF) and 33.0 g (0.162 mol) of 11-[(2-tetrahydropyranyl)oxy]undecyl bromide in 250 mL of THF during 20 min under argon. The resulting solution was stirred at ambient temperature for 16 h and diluted with 400 mL of 10% HCl. The organic layer was separated, combined with an Et_2O extract of the aqueous layer, dried, and evaporated. A mixture of the residue, 250 mL of EtOH, and 15 mL of concentrated HCl was stirred at 70 °C for 40 h and evaporated. A solution of the residue in CH_2Cl_2 was filtered through hydrous magnesium silicate and evaporated. Distillation of the residue afforded 14-(trimethylsilyl)tetradecanol as a clear, colorless liquid, bp 131–138 °C (0.06 mmHg). The 14-(trimethylsilyl)tetradecanol was converted to 1-(methanesulfonyloxy)-14-(trimethylsilyl)tetradecane.[4]

Also prepared by this method using 11-bromoundecanoic acid was 14-(trimethylsilyl)tetradecanoic acid, the starting material for the synthesis of **90**.

The 14-methylpentadecyl bromide and 15-methylhexadecyl bromide required for the synthesis of **101** and **103** were prepared by the dilithium cupric chloride catalyzed[10,11] coupling of isopentylmagnesium bromide with 1,11-dibromoundecane and 1,12-dibromododecane, respectively. Similarly, 13,13-dimethyltetradecyl bromide and 15,15-dimethylhexadecyl bromide required for the synthesis of **105** and **107** were prepared by the dilithium cupric chloride catalyzed coupling of (3,3-dimethylbutyl)magnesium bromide[12,13] with 1,10-dibromodecane and 1,12-di-

(7) W. R. Hasek, W. G. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).
(8) D. Seyferth, H. Yamazaki, and Y. Sato, *Inorg. Chem.*, **2**, 734 (1963).
(9) L. H. Sommer, R. E. VanStrien, and F. C. Whitmore, *J. Am. Chem. Soc.*, **71**, 3056 (1949).
(10) L. Friedman and A. Shami, *J. Am. Chem. Soc.*, **96**, 7101 (1974).
(11) M. Tamura and J. Kochi, *Synthesis*, **2**, 303 (1971).
(12) C. A. Young, R. R. Vogt, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **58**, 1806 (1936).

Table II. Substituted Alkanamidobenzoic Acids and Esters

no.	R	X	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
83	$NHC(=O)(CH_2)_{14}CH_3$	C_2H_5	G	86	EtOH	97–98	$C_{25}H_{41}NO_3$	91						
84	$NHC(=O)(CH_2)_{14}CH_3$	H	C			220–222	$C_{23}H_{37}NO_3$	112	118[d]	111[e]	105	94[d]	103[e]	16
85	$NHC(=O)(CH_2)_{10}Br$	C_2H_5	G	88	MeCN	84–86	$C_{20}H_{30}BrNO_3$	115			100			71***
86	$NHC(=O)(CH_2)_{15}Br$	C_2H_5	G	95	MeCN	89–92	$C_{25}H_{40}BrNO_3$	86**	93	96	79	94	84	32**
87	$NHC(=O)(CH_2)_{10}S(CH_2)_3CH_3$	CH_3	D	65	MeOH	88–90	$C_{23}H_{37}NO_3S$	92			81			56***
88	$NHC(=O)(CH_2)_{10}SC(=NH)NH_2 \cdot HBr$	C_2H_5	F	69	EtOH	134–136	$C_{21}H_{34}BrN_3O_3S$	92			96			91***
89	$NHC(=O)(CF_2)_6CF_3$	C_2H_5	G	32	MeCN	126–127	$C_{17}H_{10}F_{15}NO_3$	69**	73*	68***	28***	43***	61**	0
90	$NHC(=O)(CH_2)_{13}Si(CH_3)_3$	C_2H_5	G	74	MeCN	68–70	$C_{26}H_{45}NO_3Si$	101	98	99	97	91	99	21*
91	$NHC(=O)(CH_2)_2CO_2CH_3$	C_2H_5	G	67	hexane–CH_2Cl_2	94–95	$C_{14}H_{17}NO_5$	97	99	86	114	92	99	2
92	$N[(CH_2)_{15}CH_3]C(=O)(CH_2)_2CO_2H$	H		91	MeCN	122–125	$C_{27}H_{43}NO_5$	88	105	111	117	90	84	13
93	p-$NHC(=O)(CH_2)_{10}O$-C_6H_4-CO_2CH_3	CH_3	D	66	EtOH	111–112	$C_{27}H_{35}NO_6$	94			118			63***
94	p-$NHC(=O)(CH_2)_{10}O$-C_6H_4-CO_2H	H	C	79	EtOH	251–253	$C_{25}H_{31}NO_6$[h]	100	93	100	93	106	116	33***
95		C_2H_5	B[f]	19	C[g]	95–96	$C_{13}H_{15}NO_3$	84*			72			6
96		H	C	78	EtOH–H_2O	257–258	$C_{11}H_{11}NO_3$							0

[a–c] See footnotes *a* to *c* in Table I. [d] The testing dose was 0.05% of diet. [e] The testing dose was 0.025% of diet. [f] The initially formed product of alkylation with ethyl 4-bromobutyrate, namely, ethyl 4-[(3-carboethoxypropyl)amino]benzoate (**65**), partially cyclizes under the reaction conditions to yield compound **95**. [g] The compound was purified by silica gel chromatography. [h] Calcd: H, 7.08. Found: H, 7.76.

bromododecane, respectively. 11-Cyclohexylundecanol required for the synthesis of **113** was obtained by diborane reduction of 11-phenylundecanoic acid, followed by rhodium on alumina catalyzed hydrogenation of the resulting 11-phenylundecanol.

The following experiments (methods A–G) illustrate general procedures used to prepared the analogues of Tables I–IV.

Ethyl 4-[(16-Bromohexadecyl)amino]benzoate (5). Method A. A solution of 5.00 g (10.4 mmol) of ethyl 4-(16-bromohexadecanamido)benzoate (**86**) in 50 mL of THF was aded dropwise with stirring to 13.0 mL (13.0 mmol) of 1 M borane in THF at 0 °C. The resulting mixture was stirred at reflux for 2 h, allowed to cool, and poured into 50 mL of 10% HCl. The precipitate was collected by filtration, washed with H_2O, and recrystallized from acetonitrile and then from EtOH to yield 3.94 g (81%) of **5**, mp 82–85 °C.

Ethyl 4-[(11-Hydroxyundecyl)amino]benzoate (10). Method B. A solution of 15.0 g (59.7 mmol) of 11-bromo-1-undecanol, 9.86 g (59.7 mmol) of ethyl 4-aminobenzoate, and 8.40 mL (6.04 g, 59.7 mmol) of triethylamine in 50 mL of hexamethylphosphoramide was stirred at 65–70 °C for 18 h, allowed to cool, diluted with 45 mL of H_2O, and filtered. The solid was recrystallized from acetonitrile to yield 9.33 g (47%) of **10**, mp 77–78 °C.

4-[(11-Hydroxyundecyl)amino]benzoic Acid (11). Method C. A solution of 3.00 g (8.94 mmol) of ethyl 4-[(11-hydroxyundecyl)amino]benzoate (**10**) and 3.00 g (53.6 mmol) of KOH in 75 mL of 90% EtOH was stirred at reflux for 3 h, allowed to cool, acidified with concentrated HCl, diluted with 40 mL of H_2O, and filtered. Recrystallization of the solid from acetonitrile afforded 2.21 g (81%) of **11** as a white solid, mp 125–126 °C.

4-[[11-(Benzylthio)undecyl]amino]benzoic Acid (20). Method D. A solution of 8.00 g (20.0 mmol) of ethyl 4-[(11-bromoundecyl)amino]benzoate, 4.00 g (74.1 mmol) of sodium methoxide, 5.30 g (42.7 mmol) of benzyl mercaptan, and 100 mL of MeOH was stirred at reflux for 16 h, allowed to cool, acidified with 150 mL of 5% HCl, and filtered.

The solid was hydrolyzed by the procedure of method C to yield 5.03 g (61%) of **20** as a white solid, mp 96–99 °C.

Ethyl 4-[[6-(Acetylthio)hexadecyl]amino]benzoate (27). Method E. A mixture of 7.60 g (15.8 mmol) of ethyl 4-[(6-hydroxyhexadecyl)amino]benzoate *O*-methanesulfonate,[4] 5.50 g (48.2 mmol) of potassium thioacetate, and 200 mL of acetone was stirred at ambient temperature for 2 days and then at reflux for 3 h. The mixture was evaporated, and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, and filtered through hydrous magnesium silicate, and the filtrate was evaporated. The residue was purified by column chromatography using 500 g of silica gel (eluent 1:1 hexane–CH_2Cl_2). Recrystallization from hexane afforded 3.15 g (43%) of **27** as a tan solid, mp 41–43 °C.

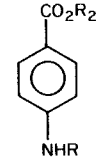
Ethyl 4-[[11-(Amidinothio)undecyl]amino]benzoate Hydrobromide (22). Method F. A solution of 17.0 g (42.7 mmol) of ethyl 4-[(11-bromoundecyl)amino]benzoate (**2**) and 3.40 g (44.7 mmol) of thiourea in 80 mL of 95% EtOH was stirred at reflux under argon for 3 h and cooled. The precipitate was collected and dried to yield 17.0 g (84%) of **22** as a white solid, mp 164–166 °C.

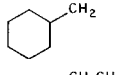
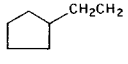
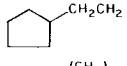
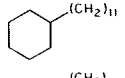
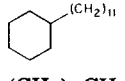
Ethyl 4-(16-Bromohexadecanamido)benzoate (86). Method G. A solution of 20.0 g (0.121 mol) of ethyl 4-aminobenzoate in 100 mL of CH_2Cl_2 was added dropwise to a stirred solution of 21.1 g (0.060 mol) of 16-bromohexadecanoyl chloride in 100 mL of CH_2Cl_2, and the resulting mixture was stirred for 17 h at ambient temperature and then filtered. The filtrate was washed with 10% HCl and H_2O, dried, and evaporated. The residue was crystallized from acetonitrile to yield 27.5 g (95%) of **86** as a white solid, mp 89–92 °C.

Ethyl 4-[*N*-(11-bromoundecyl)-*N*-(11-bromoundecyl)amino]benzoate (3). A mixture of 7.25 g (18.2 mmol) of ethyl 4-[(11-bromoundecyl)amino]benzoate (**2**), 40 mL of $CHCl_3$, 3.20 g of Na_2CO_3, and 30 mL of H_2O was stirred at ambient temperature while 3.76 g (22.0 mmol) of benzyl chloroformate was added dropwise. After 18 h, the organic layer was separated,

(13) M. S. Kharasch, C. Hannum, and H. Gladstone, *J. Am. Chem. Soc.*, **56**, 244 (1934).

Table III. 4-(Alkylamino)benzoic Acids, Esters, and Salts



no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
97	$CH_3(CH_2)_9CH(CH_3)$	Et	B	15	ethanol	solid[d]	$C_{21}H_{35}NO_2$							
98	$CH_3(CH_2)_9CH(CH_3)$	H	C	56	ethanol	77-79	$C_{19}H_{31}NO_2$[f]	92	90*	94	58***	49***	42***	51**
99	$CH_3(CH_2)_{13}CH(CH_3)$	Et	B	26	ethanol	69-70	$C_{25}H_{43}NO_2$[f]	93	100	107	55**	55*	81	18*
100	$CH_3(CH_2)_{13}CH(CH_3)$	H	C	86	acetonitrile	86-90	$C_{23}H_{39}NO_2$	79*	95	114	49**	68	79	51***
101	$CH_3CH(CH_3)(CH_2)_{13}$	Et	B	36	ethanol	82-84	$C_{25}H_{43}NO_2$	80*	89*	92	61*	84	84	9
102	$CH_3CH(CH_3)(CH_2)_{13}$	H	C	68	acetone	109-111, 121-123[e]	$C_{23}H_{39}NO_2$	64***	76***	89*	29***	68*	77	63***
103	$CH_3CH(CH_3)(CH_2)_{14}$	Et	B	42	ethanol	84-86	$C_{26}H_{45}NO_2$	80*	85*	87	58**	54**	66*	0
104	$CH_3CH(CH_3)(CH_2)_{14}$	H	C	87	acetone	106-109, 123-125[e]	$C_{24}H_{41}NO_2$	44***	67***	79**	29***	50***	76	51***
105	$CH_3C[(CH_3)_2](CH_2)_{12}$	Et	B	42	acetone	83-85	$C_{25}H_{43}NO_2$	83**	84*	89*	81	83	99	7
106	$CH_3C[(CH_3)_2](CH_2)_{12}$	H	C	83	acetone	103-105, 109-112[e]	$C_{23}H_{39}NO_2$	75**	77**	94	26***	53***	75*	59***
107	$CH_3C[(CH_3)_2](CH_2)_{14}$	Et	B	47	acetone	85-87	$C_{27}H_{47}NO_2$	68***	78*	69***	44**	71*	79	5
108	$CH_3C[(CH_3)_2](CH_2)_{14}$	H	C	91	acetone	115-116, 121-122[e]	$C_{25}H_{43}NO_2$	48***	53***	69**	20***	42***	59**	74***
109	$CH_3C[(CH_3)_2](CH_2)_{14}$	Na		77		solid[g]	$C_{25}H_{42}NO_2Na$	44***	53***	72***	30***	55**	66*	79***
110		H	C	74	hexane, ethanol	184-186	$C_{14}H_{19}NO_2$	83**	84*	95	62*	71*	73*	1
111		Et	B	66	ethanol	73-75	$C_{16}H_{23}NO_2$	96			69**			60***
112		H	C	85	hexane, ethanol	128-129	$C_{14}H_{19}NO_2$	88	94	92	64*	83	78	
113		Et	B	30	acetonitrile	72-74	$C_{26}H_{43}NO_2$	80			50***			12
114		H	C	65	hexane, ethanol	88-91	$C_{24}H_{39}NO_2$	83	91	95	48**	51**	73	56***
115	$(CH_2)_{14}CH$	Et	B	13	ethanol	90-91	$C_{24}H_{39}NO_2$							
116	$(CH_2)_{14}CH$	H	C	99	acetonitrile	149-150	$C_{22}H_{35}NO_2$	101	114	110	244	173	125	18*

[a-c] See footnotes *a* to *c* in Table I. [d] The crude ester was converted to the corresponding acid without purification. [e] Many 4-(alkylamino)benzoic acids are mesomorphic and double melting points were observed. [f] Calcd: H, 11.13. Found: H, 10.59. [g] Salts were isolated as amorphous solids lacking characteristic melting points.

Table IV. 4,4′-[Poly(methylene)diimino]bis[benzoic acids and esters]

no.	R	*n*	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
117	C_2H_5	10	B	25	ethanol	170–172	$C_{28}H_{40}N_2O_4$	140			98			7
118	H	10	C	87	ethanol	261–262	$C_{24}H_{32}N_2O_4$	93			100			8
119	C_2H_5	11	B	81	ethanol	119–120	$C_{29}H_{42}N_2O_4$	92			67			68***
120	H	11	C	69	ethanol	187–188	$C_{25}H_{34}N_2O_4$	87	94	99	84	85	68*	30***
121	C_2H_5	12	B	32	ethanol	165–167	$C_{30}H_{44}N_2O_4$	103			68*			2
122	H	12	C	76	ethanol	256–259	$C_{26}H_{36}N_2O_4$[d]	103			89			60***

[a–c] See footnotes *a* to *c* in Table I. [d] Calcd: C, 70.88. Found: C, 70.46.

washed with 0.6 N HCl and saturated $NaHCO_3$, dried, and evaporated to yield 9.49 g (98%) of **3** as a thick oil.

4-[(11-Bromoundecyl)amino]benzoic Acid (4). A solution of 5.00 g (12.6 mmol) of ethyl 4-[(11-bromoundecyl)amino]-benzoate (**2**) and 20 mL of 48% HBr in 20 mL of H_2O and 20 mL of HOAc was stirred at reflux for 3 h, allowed to cool, and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. The residue was crystallized from acetonitrile to yield 3.62 g (86%) of **4** as a white solid, mp 125–128 °C.

4-[*N*-(16-Methoxyhexadecyl)acetamido]benzoic Acid (9). A solution of 2.00 g (5.11 mmol) of 4-[(16-methoxyhexadecyl)-amino]benzoic acid (**8**) in 10 mL of pyridine was treated with 5 mL of acetic anhydride and stirred at ambient temperature for 3 days, poured into H_2O, and filtered. A solution of the solid in CH_2Cl_2 was dried and evaporated. Crystallization of the residue from hexane–acetone afforded 1.90 g (86%) of **9** as a white solid, mp 74–76 °C.

Ethyl 4-[(6-Chlorohexadecyl)amino]benzoate (6). A solution of 10.2 g (25.0 mmol) of ethyl 4-[(6-hydroxyhexadecyl)-amino]benzoate (**12**) and 2.40 mL (30.0 mmol) of pyridine in 50 mL of $CHCl_3$ was treated with 2.00 mL (27.5 mmol) of thionyl chloride and stirred at reflux for 1 h. The dark solution was washed with H_2O, 1 N HCl, and saturated $NaHCO_3$. The solution was then dried and evaporated. A CH_2Cl_2 solution of the residue was filtered through hydrous magnesium silicate and evaporated. The residue was crystallized from 9:1 EtOH–H_2O to yield 5.61 g (53%) of **6** as a pale yellow solid, mp 62–63 °C.

Ethyl 4-[(6-Hydroxyhexadecyl)amino]benzoate (12). A suspension of 10.0 g (25.0 mmol) of ethyl 4-[(6-oxohexadecyl)-amino]benzoate (**30**) and 2.80 g (74.0 mmol) of sodium borohydride in 250 mL of absolute EtOH was stirred at ambient temperature for 3 h, acidified with HOAc, poured into H_2O, and filtered. The solid was dried and recrystallized from hexane to yield 8.71 g (86%) of **12** as a white solid, mp 70–71 °C.

Ethyl 4-[(6-Hydroxy-6-methylhexadecyl)amino]benzoate (14). A mixture of 2.50 g (6.23 mmol) of ethyl 4-(6-decyl-6-heptenyl)amino)benzoate,[2] 2.40 g (7.62 mmol) of mercuric acetate, 15 mL of THF, and 15 mL of H_2O was stirred at ambient temperature for 8 h. The mixture was then treated with 10 mL of 3 N NaOH, followed quickly by a solution of 190 mg (5.00 mmol) of sodium borohydride in 10 mL of 3 N NaOH, stirred for an additional 20 min at ambient temperature, and then extracted with Et_2O. The extract was dried and evaporated. The residue was purified by chromatography on 200 g of silica gel (eluent 9:1 CH_2Cl_2–Et_2O). Crystallization of the product from hexane yielded 2.17 g (83%) of **14** as a white solid, mp 46–47 °C.

4-[[11-(*n*-Butylsulfinyl)undecyl]amino]benzoic Acid (17). A solution of 5.20 g (14.0 mmol) of 4-[[11-(*n*-butylthio)undecyl]amino]benzoic acid (**16**) in 70 mL of acetone and 65 mL of THF was added dropwise to a stirred solution of 3.70 g (17.3 mmol) of sodium metaperiodate in 3.5 mL of water and 20 mL of THF at 0 °C. The solution was stirred for 3 days at ambient temperature and then for 90 min at reflux. The mixture was cooled and filtered, and the filtrate was treated with 20 mL of saturated NaCl and extracted with $CHCl_3$. The extract was dried and evaporated. The residue was crystallized from $CHCl_3$–acetone to yield 4.59 g (83%) of **17** as a white solid, mp 153–154 °C.

Ethyl 4-[(16-Mercaptohexadecyl)amino]benzoate (23). A suspension of 8.00 g (17.3 mmol) of ethyl 4-[[16-(acetylthio)-hexadecyl]amino]benzoate (**25**) and 24 mL of 1 M ethanolic sodium ethoxide solution in 250 mL of EtOH was stirred vigorously for 1 h, acidified with 8 mL of HOAc, poured into ice–water, and filtered. A solution of the solid in CH_2Cl_2 was dried and evaporated. The residue was crystallized from hexane to yield 5.54 g (76%) of **23** as a white solid, mp 78–79 °C.

Ethyl 4-[(6-Aminohexadecyl)amino]benzoate (28). A suspension of 6.00 g (14.9 mmol) of ethyl 4-[(6-oxohexadecyl)-amino]benzoate (**30**), 12.3 g (160 mmol) of ammonium acetate, 700 mg (11.0 mmol) of sodium cyanoborohydride, and 25 mL of THF in 50 mL of MeOH was stirred at ambient temperature for 2 days, acidified with dilute HCl, concentrated, and then extracted with Et_2O. The extract was washed with H_2O and saturated NaCl, dried, and evaporated. A suspension of the residual oil in H_2O and 5 N NaOH was extracted with Et_2O, and the extract was dried and evaporated. Purification of the residue by silica gel column chromatography, followed by recrystallization from hexane, af-

forded 2.95 g (49%) of **28** as a white solid, mp 63–65 °C.

4-[(6-Oximidohexadecyl)amino]benzoic Acid (34). A mixture of 1.00 g (2.48 mmol) of ethyl 4-[(6-oxohexadecyl)-amino]benzoate (**30**), 207 mg (2.98 mmol) of hydroxylamine hydrochloride, 244 mg (2.98 mmol) of sodium acetate, and 20 mL of 95% EtOH was stirred at reflux and filtered while hot, and the filtrate was then evaporated. A solution of the residue in CH_2Cl_2 was washed with H_2O, dried, and evaporated to yield ethyl 4-[(6-oximidohexadecyl)amino]benzoate as an oil. Alkaline hydrolysis of this ester by method C afforded 0.687 g (71%) of **34** as a white solid, mp 90–95 °C.

Ethyl 4-[(6-Cyanohexadecyl)amino]benzoate (53). A mixture of 5.40 g (11.2 mmol) of ethyl 4-[(6-hydroxyhexadecyl)amino]benzoate *O*-methanesulfonate,[4] 1.60 g (32.7 mmol) of sodium cyanide, and 40 mL DMF was stirred at 75–80 °C for 18 h, cooled, and poured into ice–water. The white solid was collected by filtration, washed with H_2O, and dissolved in CH_2Cl_2. The solution was dried and evaporated. The residual gum was crystallized from hexane to yield 3.43 g (74%) of **53** as a white solid, mp 54–56 °C.

Ethyl 4-[(15-Carboxypentadecyl)amino]benzoate (73). A solution of 5.00 g (11.5 mmol) of ethyl 4-[(15-carbomethoxypentadecyl)amino]benzoate (**72**) and 0.800 g (14.3 mmol) of KOH in 50 mL of 95% EtOH was stirred at 50 °C for 10 h, allowed to cool, diluted with 100 mL of H_2O, acidified to pH 6 with concentrated HCl, and filtered. The solid was crystallized from toluene to yield 4.34 g (90%) of **73** as a white solid, mp 116–118 °C.

[11-[*N*-(Benzyloxycarbonyl)-*N*-(4-carbethoxyphenyl)-amino]undecyl]triphenylphosphonium Bromide (76). A mixture of 8.00 g (15.0 mmol) of ethyl 4-[*N*-(benzyloxycarbonyl)-*N*-(11-bromoundecyl)amino]benzoate (**3**), 4.22 g (15.1 mmol) of triphenylphosphine, and 40 mL of benzonitrile was stirred for 3 h at 140–150 °C and then concentrated in vacuo at 50 °C. The residue was triturated with 300 mL of Et_2O, and the resulting mixture evaporated to yield 10.2 g (86%) of **76** as a green glass.

4-[*N*-[(Sodiosulfo)methyl]-*N*-hexadecylamino]benzoic Acid (77). A solution of 4.20 g (40.0 mmol) of sodium bisulfite and 3.00 mL (40.0 mmol) of formaldehyde (37.6% aqueous solution) in 10 mL of H_2O was added to a stirred solution of 14.4 g (40.0 mmol) of **1** at 65 °C, and the solution was allowed to cool. The solid was collected by filtration and dried to yield 15.1 g (79%) of **77** as a white solid, mp >170 °C dec.

Sodium 4-[*N*-[(Sodiosulfo)methyl]-*N*-hexadecylamino]-benzoate (78). A solution of 13.0 g (125 mmol) of sodium bisulfite and 9.20 mL (125 mmol) of formaldehyde (37.8% aqueous solution) in 50 mL of H_2O was added to a stirred solution of 9.60 g (25.0 mmol) of sodium 4-(hexadecylamino)benzoate[2] in 900 mL of 1,2-dimethoxyethane and 200 mL of H_2O at 18 °C. The solution was stirred at reflux for 3 days and then concentrated by evaporation to a volume of 500 mL. The precipitate that formed was collected and dried to yield 3.12 g (25%) of **78** as a white solid, mp >230 °C dec.

4-(*N*-Hexadecyl-3-carboxypropionamido)benzoic Acid (92). A solution of 18.5 g (51.1 mmol) of 4-(hexadecylamino)-benzoic acid (**1**), 10.0 g (100 mmol) of succinic anhydride, 10.1 g (100 mmol) of triethylamine, and 0.25 g (2.05 mmol) of 4-(dimethylamino)pyridine in 250 mL of 1,2-dimethoxyethane was stirred at reflux for 3 h, allowed to cool, acidified with concentrated HCl, and diluted with H_2O. The mixture was filtered, and the solid was recrystallized from acetonitrile to yield 21.4 g (91%) of **92** as a white solid, mp 122–125 °C.

Acknowledgment. F. M. Callahan, M. T. Du, W. A. Hallett, L. A. Jacob, J. P. Joseph, J. A. Poletto, R. E. Schaub, Dr. G. J. Siuta, and J. Skotnicki assisted in the synthesis of compounds and D. L. Bull in the biological testing. Large-scale preparations of intermediates were performed by Dr. V. G. Grosso and his associates. Microanalysis and spectral data were obtained by L. M. Brancone, W. Fulmor, and Dr. W. E. Gore and their staffs.

Registry No. **1**, 55986-43-1; **2**, 73780-29-7; **3**, 86364-07-0; **4**, 73780-76-4; **5**, 86364-08-1; **6**, 73780-65-1; **7**, 86372-55-6; **8**, 86364-09-2; **9**, 86364-10-5; **10**, 73780-20-8; **11**, 73780-26-4; **12**, 73780-70-8; **13**, 86364-11-6; **14**, 86364-12-7; **15**, 86364-13-8; **16**, 73780-66-2; **17**, 73780-67-3; **18**, 86364-14-9; **19**, 86364-15-0; **20**, 86364-16-1; **21**, 73780-61-7; **22**, 86364-17-2; **23**, 86364-18-3; **24**, 86364-19-4; **25**, 86364-20-7; **26**, 86364-21-8; **27**, 73780-62-8; **28**, 86364-22-9; **29**, 86364-23-0; **30**, 73780-22-0; **31**, 86364-24-1; **32**, 86364-25-2; **33**, 86364-26-3; **34**, 73780-72-0; **35**, 86364-27-4; **36**, 86364-28-5; **37**, 73782-56-6; **38**, 73782-57-7; **39**, 73782-72-6; **40**, 73792-57-1; **41**, 73782-58-8; **42**, 86372-56-7; **43**, 86364-29-6; **44**, 86364-30-9; **45**, 86364-31-0; **46**, 86364-32-1; **47**, 86364-33-2; **48**, 86364-34-3; **49**, 86372-57-8; **50**, 86364-35-4; **51**, 86364-36-5; **52**, 86364-37-6; **53**, 86364-38-7; **54**, 86364-39-8; **55**, 86364-40-1; **56**, 26815-64-5; **57**, 86364-41-2; **58**, 86364-42-3; **59**, 86364-43-4; **60**, 5698-54-4; **61**, 86364-44-5; **62**, 86364-45-6; **63**, 86364-46-7; **64**, 86364-47-8; **65**, 79421-49-1; **66**, 51552-86-4; **67**, 86364-48-9; **68**, 86364-49-0; **69**, 86364-50-3; **70**, 86364-51-4; **71**, 86364-52-5; **72**, 73782-19-1; **73**, 73782-22-6; **74**, 73782-20-4; **75**, 73782-21-5; **76**, 86372-58-9; **77**, 86364-53-6; **78**, 86364-54-7; **79**, 79181-36-5; **80**, 79181-37-6; **81**, 86364-55-8; **82**, 86364-56-9; **83**, 71134-93-5; **84**, 58725-48-7; **85**, 73780-28-6; **86**, 86364-57-0; **87**, 86364-58-1; **88**, 86364-59-2; **89**, 32429-04-2; **90**, 86364-60-5; **91**, 86364-61-6; **92**, 86364-62-7; **93**, 86364-63-8; **94**, 86364-64-9; **95**, 86364-65-0; **96**, 36151-44-7; **97**, 55791-70-3; **98**, 55791-71-4; **99**, 86372-59-0; **100**, 86364-66-1; **101**, 69876-96-6; **102**, 69876-97-7; **103**, 69876-95-5; **104**, 69877-04-9; **105**, 69876-99-9; **106**, 69877-00-5; **107**, 70518-06-8; **108**, 70518-09-1; **109**, 86364-67-2; **110**, 73779-37-0; **111**, 73779-39-2; **112**, 73779-40-5; **113**, 86364-68-3; **114**, 86364-69-4; **115**, 86364-70-7; **116**, 86364-71-8; **117**, 86364-72-9; **118**, 86364-73-0; **119**, 86364-74-1; **120**, 86364-75-2; **121**, 86364-76-3; **122**, 86364-77-4; *n*-pentyl bromide, 110-53-2; 11-bromoundecanoyl chloride, 15949-84-5; 16-bromo-6-hexadecanone, 73780-19-5; 16-bromo-11-hexadecanone, 86364-78-5; 16-bromohexadecanoic acid, 2536-35-8; 16-bromo-1,1,1-trifluorohexadecane, 73782-53-3; 11-bromoundecanoic acid, 2834-05-1; 11-bromo-1,1,1-trifluoroundecane, 86364-79-6; 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanol, 307-30-2; 1-[(trifluoromethanesulfonyl)oxy]-2,2,3,3,4,4,5,5,6,6,7,7,8,8-pentadecafluorooctane, 17352-09-9; 3-(trimethylsilyl)propyl bromide, 10545-34-3; 11-[(2-tetrahydropyranyl)oxy]undecyl bromide, 52056-69-6; 14-(trimethylsilyl)tetradecanol, 86364-80-9; 1-(methanesulfonyloxy)-14-(trimethylsilyl)tetradecane, 86364-81-0; 14-(trimethylsilyl)tetradecanoic acid, 86364-82-1; 14-methylpentadecyl, 69001-51-0; 15-methylhexadecyl bromide, 69876-94-4; isopentyl bromide, 107-82-4; 13,13-dimethyltetradecyl bromide, 16696-65-4; 15,15-dimethylhexadecyl bromide, 3344-70-5; 3,3-dimethylbutyl bromide, 1647-23-0; 1,10-dibromodecane, 4101-68-2; 1,12-dibromododecane, 3344-70-5; 1,11-dibromoundecane, 69876-98-8; 1,12-dibromododecane, 86364-83-2; 11-bromo-1-undecanol, 1611-56-9; ethyl 4-aminobenzoate, 94-09-7; ethyl 4-[(6-hydroxyhexadecyl)amino]benzoate *o*-methanesulfonate, 86364-84-3; potassium thioacetate, 10387-40-3; thiourea, 62-56-6; 16-bromohexadecanoyl chloride, 73782-15-7; benzyl chloroformate, 501-53-1; ethyl 4-(*N*-decyl-*N*-heptenylamino)benzoate, 86364-85-4; sodium 4-(hexadecylamino)benzoate, 64059-66-1; succinic anhydride, 108-30-5; triphenylphosphine, 603-35-0; ACAT, 9027-63-8.