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Potential Antiatherosclerotic Agents. 3.[1] Substituted Benzoic and Non Benzoic Acid Analogues of Cetaben

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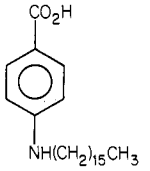
The synthesis of a series of analogues in which the carboxylic acid group of cetaben is replaced by carboxylate ester, carboxamide, or a variety of other substituent groups is described. Also reported are the syntheses of analogues in which the phenyl ring of cetaben is either modified by the presence of additional substituents or replaced entirely by another moiety. Structure–activity relationships of these compounds both as hypolipidemic agents and as inhibitors of the enzyme fatty acyl-CoA:cholesterol acyltransferase (ACAT) are discussed. Analogue syntheses designed to produce compounds that would be better absorbed orally than cetaben failed to yield any congeners of enhanced biological activity. In contrast, analogue syntheses directed toward non carboxylic acids of similar acidity to cetaben produced a very active class of sulfonamides.

This report continues a series of papers describing syntheses and structure–activity relationships of analogues of the potential antiatherosclerotic agent cetaben (1). The focus of this part of the study was modification of the carboxy group and substitution or replacement of the aromatic ring of cetaben.



1

The compounds shown in Tables I and II are non benzoic acid analogues of cetaben. Carboxy group replacements included substituents such as hydroxy, cyano, acetyl, carboxamido, and various heterocyclic moieties, as well as alkanoic acid residues such as those derived from acetic, malonic, or pyruvic acid. Tables III and IV show analogues in which the aromatic ring of cetaben has been substituted with groups such as halo, alkyl, alkoxy, and carboxy or replaced entirely by cyclic moieties derived from cyclohexane, naphthalene, pyrimidine, or thiophene. The remaining tables illustrate a more detailed elaboration of structure–activity relationships for carboxylate (Table V), carboxamide (Table VI), and N,N-disubstituted congeners (Table VII) of cetaben.

The general biological rationale for the investigation of cetaben and its analogues has been discussed in detail.[1] The types of analogue syntheses reported in this paper, and the specific rationale for the preparation of certain congeners of cetaben is described below.

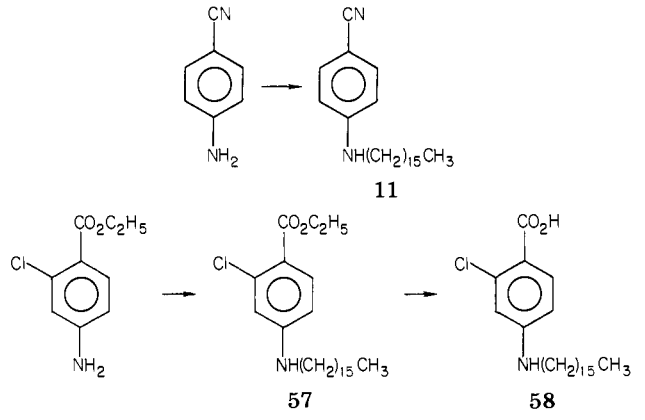
Structural modification of cetaben described in this paper somewhat paralleled an earlier investigation[2] into the antibacterial activity resulting from variations in the structure of 4-aminobenzoic acid. These modifications involved replacement of the carboxylic acid group and substitution or replacement of the phenyl ring. In addition to compounds in which the acidic carboxyl group of cetaben was replaced by nonacidic substituents, compounds that exhibited minor variations in the acidity of the

(1) 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.

(2) R. G. Shepherd in "Medicinal Chemistry", 3rd ed., A. Burger, Ed., Wiley, New York, 1970, Part I, pp 280–286.

0022-2623/83/1826-1393$01.50/0

Scheme I



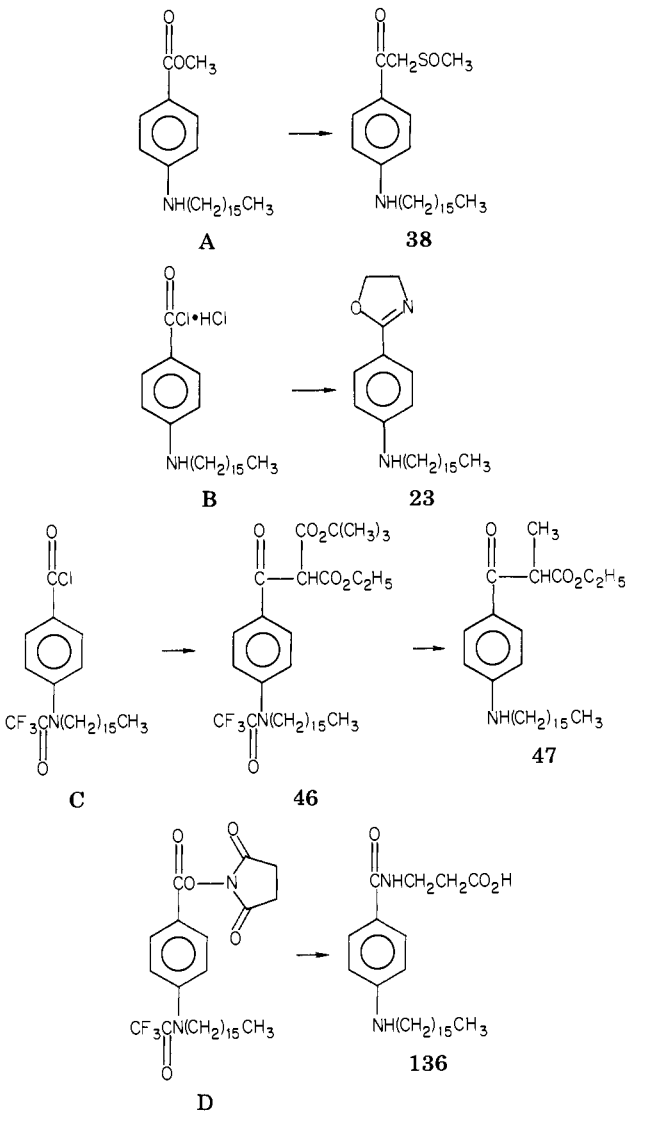
molecule were also synthesized. The antibacterial activity of sulfanilamides has been shown to depend upon their acidity,[3] and this relationship has been interpreted[4] as a mixed phenomenon involving transport as well as intrinsic activity. In the hope of enhancing biological activity, we prepared non carboxylic acid analogues with aciditity similar to that of cetaben, such as tetrazole **22** and a series of sulfonamides (**141–146**). Carboxylic acids structurally similar to cetaben but of lesser acidity (**25**, **29**, **32**, **35**, **41**, **49**, and **52**) were also synthesized; however, strong acids, such as sulfonic or phosphonic acids, were not studied.

The synthesis of certain glycerol esters shown in Table V was prompted by the structural similarity of cetaben to the naturally occurring fatty acids. It is well-known[5] that the intestinal absorption of long-chain (more than 14 carbon atoms) fatty acids occurs both via the free acid and the 1-monoglyceride. Based on the hypothesis that glyceryl esters of cetaben might be better absorbed than cetaben itself and thus show enhanced in vivo activity, esters such as **104–106**, **112**, **113**, **164**, **167**, and **168** were synthesized and evaluated.

Chemistry. Some of the compounds in Tables V–VII were prepared by a general method discussed in detail in the previous paper of this series,[1] namely, alkylation with 1-bromohexadecane. As illustrated in Scheme I, alkylation reactions were used for the synthesis of benzonitrile **11** and benzoate ester **57**. Alkaline hydrolysis of **57** afforded benzoic acid **58**. Almost all of the carboxylic acids shown in the tables were obtained by hydrolysis of the corresponding esters, and this step is generally excluded from discussion in subsequent schemes.

Many of the compounds shown in the tables were prepared by using activated derivatives of cetaben as intermediates. These derivatives included methyl 4-(hexadecylamino)benzoate[1] (A), 4-(hexadecylamino)benzoyl chloride hydrochloride (B), 4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl chloride (C), and *N*-[[4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl]oxy]succinimide (D), and examples of the use of these intermediates are shown in Scheme II. Reaction of A with the anion of dimethyl sulfoxide yielded sulfoxide **38**, and lithium aluminum hydride reduction of A (not shown in the scheme) afforded alcohol **4**. Acylations of bromoalkylamines with B yielded, after cyclization, oxazoline **23** and oxazine **24**. Reaction of B with the anion of diethyl malonate afforded

Scheme II

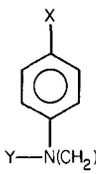


keto ester **45**. Treatment of B with diazomethane led to the corresponding diazo ketone, which was not isolated but reacted with acetic acid to yield the acetate ester of **36**, which in turn was reacted with methanolic potassium hydroxide to yield methoxymethyl ketone **37**. The hydroxymethyl ketone itself, **36**, was obtained from C in a similar series of transformations. Acylation of *tert*-butyl ethyl malonate with C afforded keto ester **46**, which was an intermediate for the synthesis of both **47** and **48**. Thus, methylation of **46** using methyl iodide, selective acidic hydrolysis of the *tert*-butyl ester in the presence of trifluoroacetic acid (accompanied by spontaneous decarboxylation), and removal of the *N*-trifluoroacetyl group with cold aqueous sodium hydroxide yielded ester **47**. The use of this same series of reactions, only in a different order, led to ester **48**. Finally, an example of the use of D as an intermediate is its reaction with β-alanine to yield amido acid **136**.

The majority of compounds shown in Tables I and II were obtained by synthetic transformations of the various functional groups present in cetaben analogues as replacements of the carboxy moiety. Examples of the use of cetaben analogues as intermediates for chemical syntheses are illustrated in Scheme III. Both phenol **2** and benzyl alcohol **4** underwent acetylation, and by varying the acylating agent, we obtained acetates **3**, **6**, **7**, and **8**. Aldehyde **10**, prepared by diisobutylaluminum hydride

(3) P. H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2905 (1942).
(4) P. B. Cowles, *Yale J. Biol. Med.*, 14, 599 (1942).
(5) A. White, P. Handler, E. L. Smith, R. L. Hill, and I. R. Lehman, "Principles of Biochemistry", 6th ed., McGraw-Hill, New York, 1978, p 570.

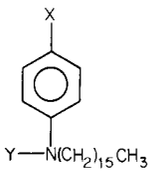
Table I. 1-Substituted 4-(Hexadecylamino)benzenes



no.	X	Y	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
1	CO_2H		A, B	95	ethanol	108–110, 126–128	$C_{23}H_{39}NO_2$	54***	71**	72***	31***	45***	71*	57***
2	OH		A	71	Et_2O–pet ether	89–90	$C_{22}H_{39}NO$	92	99	104	104	124	118	0
3	O_2CCH_3·HBr		E	71	*i*-PrOH	113–114	$C_{24}H_{42}BrNO_2$	91	95	92	117	146	108	12*
4	CH_2OH		*d*	55	hexane	74–75	$C_{23}H_{41}NO$	95	95	98	91	117	110	10
5	CH_2OH·HCl		*g*	97		solid	$C_{23}H_{42}ClNO$	99			100			16
6	CH_2OH	$COCH_3$	*d*	94	hexane	71–72	$C_{25}H_{43}NO_2$	99			105			22*
7	$CH_2O_2CCH_3$·HBr		E	75	Et_2O	80–82	$C_{25}H_{44}BrNO_2$	85*	92	93	114	135	79	
8	$CH_2O_2CCH_3$	$COCH_3$	F	91	hexane	55–56	$C_{27}H_{45}NO_3$	95	93	97	80	71*	70*	
9	$CHOHCH_3$		*d*	86	hexane	55–56	$C_{24}H_{43}NO$	93			93			33***
10	CHO		*d*	58	CH_2Cl_2–hexane	84–85	$C_{23}H_{39}NO$	85**	92	91	53**	64*	66*	30***
11	CN		A	84	hexane–Et_2O	63–64	$C_{23}H_{38}N_2$	96	92	86	75	71	83	8
12	CN·HCl		*h*	99		125–130	$C_{23}H_{39}ClN_2$[i]	100			88			30***
13	CN	$COCF_3$	*d*	99	MeOH–hexane	53–54	$C_{25}H_{37}F_3N_2O$[i]							
14	CN	$COCH_3$	F	99	Et_2O–MeOH	78–80	$C_{25}H_{40}N_2O$[h]							
15	$CH(SC_2H_5)_2$		G	60	hexane	79–80	$C_{27}H_{49}NS_2$	88	101	96	77	106	86	0
16	$CH{=}NNHC(=NH)NHCH_2C_6H_5$		*d*	80	*i*-PrOH	101–102	$C_{31}H_{49}N_5$	94			49***			0
17	$COCH_3$		A	63	ethanol	89–90	$C_{24}H_{41}NO$	98	119[e]	129[f]	78	88[e]	84[f]	14
18	$C(=O)SCH_2CH_2OH$		H	33	MeOH	105–107	$C_{25}H_{43}NO_2S$	84*	86*	87**	59***	74	70	1
19	$C(=O)SCH_2CHOHCH_2OH$		H	59	MeOH	111–113	$C_{26}H_{45}NO_3S$[j]	82**	92	93	64*	83	106	3
20			*d*	81	hexane	67–68	$C_{25}H_{43}NO_2$	71***	77***	85**	47***	82	100	0
21			G	60	hexane	79–80	$C_{26}H_{45}NS_2$	93	92	102	91	114	105	9
22			*d*	30		114–116	$C_{23}H_{39}N_5$	89			91			78***
23			*d*	13	MeCN	129–130	$C_{25}H_{42}N_2O$	86	100	100	76	94	103	0
24			*d*	12	MeCN	95–96	$C_{26}H_{44}N_2O$	87*	100	97	68*	127	99	2

[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. [d] Where no general method is shown, the procedure for preparing the compound is described in the Experimental Section. [e] The testing dose was 0.05% of diet. [f] The testing dose was 0.025% of diet. [g] Prepared from 4 by using anhydrous hydrogen chloride in ether. [h] Prepared from 11 by using anhydrous hydrogen chloride in methanol. [i] These intermediates were not characterized by microanalyses. [j] Calcd: N, 3.10. Found: N, 3.65.

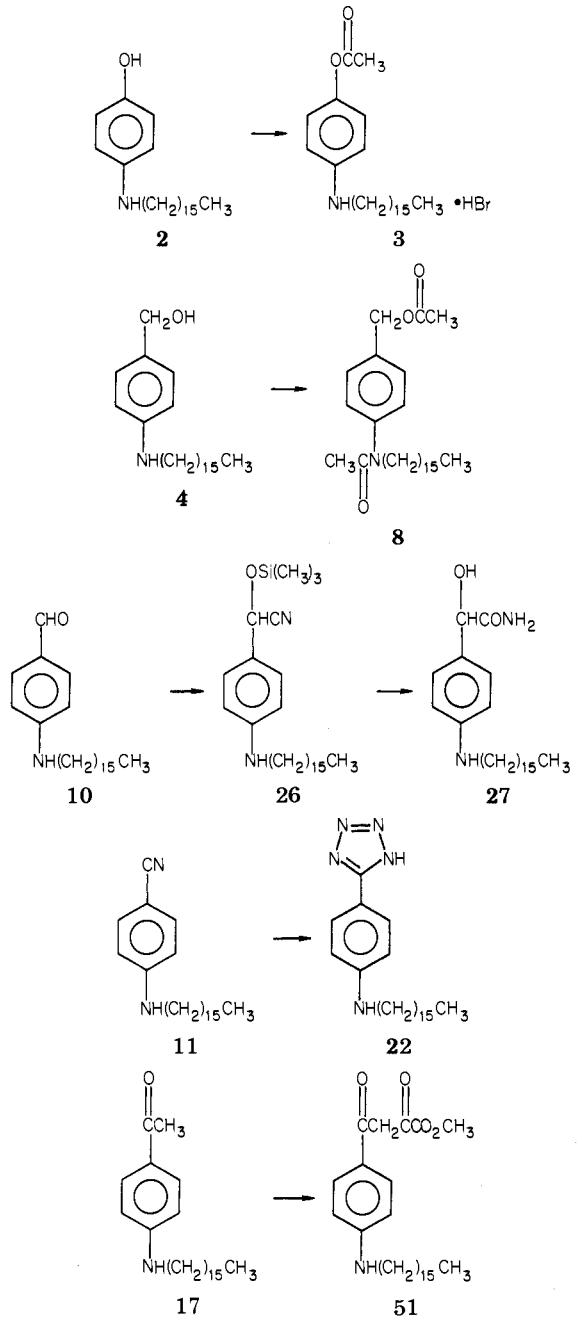
Table II. 4-(Hexadecylamino)phenyl, 4-(Hexadecylamino)benzoyl, and 4-(Hexadecylamino)phenylthio Compounds



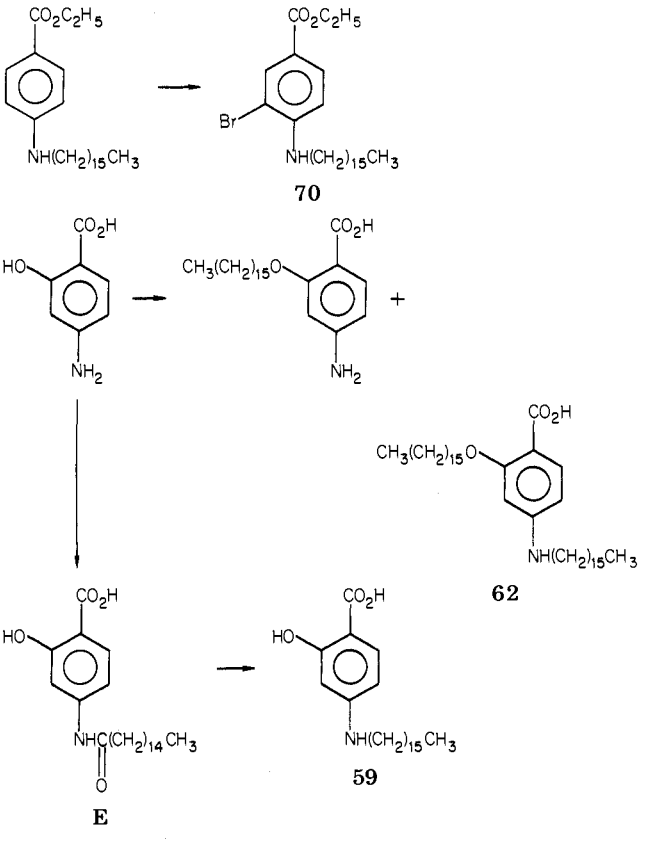
no.	X	Y	meth-od	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
25	CH_2CO_2H		A	24	HOAc	94–96	$C_{24}H_{41}NO_2$	87	87[h]	93[i]	63*	81[h]	76[i]	
26	$CH[OSi(CH_3)_3]CN$		*d*	90		29–30	$C_{27}H_{48}N_2OSi$[k]	82			36*			0
27	$CH(OH)CONH_2$		*d*	51		solid	$C_{24}H_{42}N_2O_2$	94			57			34***
28	$CH(O_2CCH_3)CONH_2$	$COCH_3$	F	88	hexane–CH_2Cl_2	113–114	$C_{28}H_{46}N_2O_4$	110	111	109	89	86	93	40**
29	$CH_2CH_2CO_2H$		B	84	EtOH	95–97	$C_{25}H_{43}NO_2$	92	80*	88	37**	50**	59**	50***
30	$(CH_2)_2CO_2C_2H_5$		A	77	C[g]	42–44	$C_{27}H_{47}NO_2$	84	89	89	45***	88	96	7
31	$(CH_2)_2CO_2C_2H_5$	$(CH_2)_{15}CH_3$	A[h]	9	C[g]	oil	$C_{43}H_{79}NC_2$	94			84			28**
32	$(CH_2)_3CO_2H$		B	77	EtOH	127–130	$C_{26}H_{45}NO_2$	97	95	100	51***	61*	68*	32*
33	$(CH_2)_3CO_2C_2H_5$		A	69	C[g]	56–58	$C_{28}H_{49}NO_2$	99			76			0
34	$(CH_2)_3CO_2C_2H_5$	$(CH_2)_{15}CH_3$	A[i]	9	C[g]	oil	$C_{44}H_{81}NO_2$	103			90			18
35	$C(CH_3)_2CO_2H$		A, B	57	EtOH–H_2O	93–94	$C_{26}H_{45}NO_2$	107	111	93	116	121	109	27*
36	$C(=O)CH_2OH$		*d*	30	CCl_4	solid	$C_{24}H_{41}NO_2$	85*	97	103	71*	75	89	20
37	$C(=O)CH_2OCH_3$		*d*	12	EtOH–H_2O	solid	$C_{25}H_{43}NO_2$	91	88	88	65***	85	77	47***
38	$C(=O)CH_2SOCH_3$		I	41	C[g]	152–154	$C_{25}H_{43}NO_2S$		95	95		55**	64*	6
39	$C(=O)CH_2SO_2CH_3$		I	18	C[g]	134–136	$C_{25}H_{43}NO_3S$	100	97	98	110	112	88	0
40	$C(=O)CH_2CN$		A	78	HOAc	130–132	$C_{25}H_{40}N_2O$	115	104	107	130	140	132	22**
41	$C(=O)CH_2CO_2H$		B	27	MeOH–CH_2Cl_2	91–94	$C_{25}H_{41}NO_3$	104	100	105	100	90	80	28**
42	$C(=O)CH_2CO_2CH_3$		*d*	75	MeOH	89–94	$C_{26}N_{43}NO_3$	84*			47**			43***
43	$C(=O)CH_2CO_2C_2H_5$		J	10	EtOH	82–84	$C_{27}N_{45}NO_3$	85*	83*	105	30***	53**	71	2
44	$C(=O)CH(CN)CO_2C_2H_5$		J	32	hexane	97–99	$C_{28}H_{44}N_2O_3$	100	100	115	105	90	83	40***
45	$C(=O)CH(CO_2C_2H_5)CO_2C_2H_5$		J	20	Et_2O	75–77	$C_{30}H_{49}NO_5$	87*	96	100	59**	66**	68*	9
46	$C(=O)CH[CO_2C(CH_3)_3]CO_2C_2H_5$	$COCF_3$	K	90	K[j]	oil	$C_{34}H_{52}F_3NO_6$	90			64***			49***
47	$C(=O)CH(CH_3)CO_2C_2H_5$		*d*	27	hexane	70–72	$C_{28}H_{47}NO_3$	73***	87	100	66**	88	87	21
48	$C(=O)C[(CH_3)_2]CO_2C_2H_5$		*d*	26	hexane	71–74	$C_{29}H_{49}NO_3$	90	103	94	101	65*	101	0
49	$C(=O)CH_2CH_2CO_2H$		B	91	Et_2O–EtOH	130–133	$C_{26}H_{43}NO_3$	109	100[e]	116[f]	66**	72**[e]	82*[f]	16
50	$C(=O)CH_2CH_2CO_2CH_3$		A	50	hexane–MeOH	91–93	$C_{27}H_{45}NO_3$	84*	81**[e]		86	93[e]		7
51	$C(=O)CH_2C(=O)CO_2CH_3$		*d*	52	MeOH	97–98	$C_{27}H_{43}NO_4$[l]	85	96	92	81	77	101	43***
52	SCH_2CO_2H		B	94	EtOH–H_2O	82–84	$C_{24}H_{41}NO_2S$	93	97	92	100	110	72	22*
53	$SCH_2CO_2C_2H_5$		A	86	EtOH	40–41	$C_{26}H_{45}NO_2S$	99			126			13

[a–f] See footnotes *a* to *f* in Table I. [g] The compound was purified by silica gel chromatography. [h] Isolated as a byproduct from the synthesis of 30. [i] Isolated as a byproduct from the synthesis of 33. [j] The product was purified by evaporative distillation using a Kugelrohr apparatus at reduced pressure. [k] Calcd: C, 72.91. Found: C, 74.04. [l] Calcd: C, 72.77. Found: C, 71.98.

Scheme III



Scheme IV



reduction of nitrile **11**, was converted by reaction with trimethylsilyl cyanide and zinc chloride to **26**, which in turn was hydrolyzed to mandelamide **27**. Aldehyde **10** was also reacted with methyllithium to yield alcohol **9** and derivatized in a variety of ways to yield **15**, **16**, **20**, and **21**. Benzonitrile **11** was reacted with sodium azide to yield tetrazole **22** and also used in the synthesis of *N*-acyl analogues **13** and **14**. Acetophenone **17** was acylated with dimethyl oxalate to yield ester **51**.

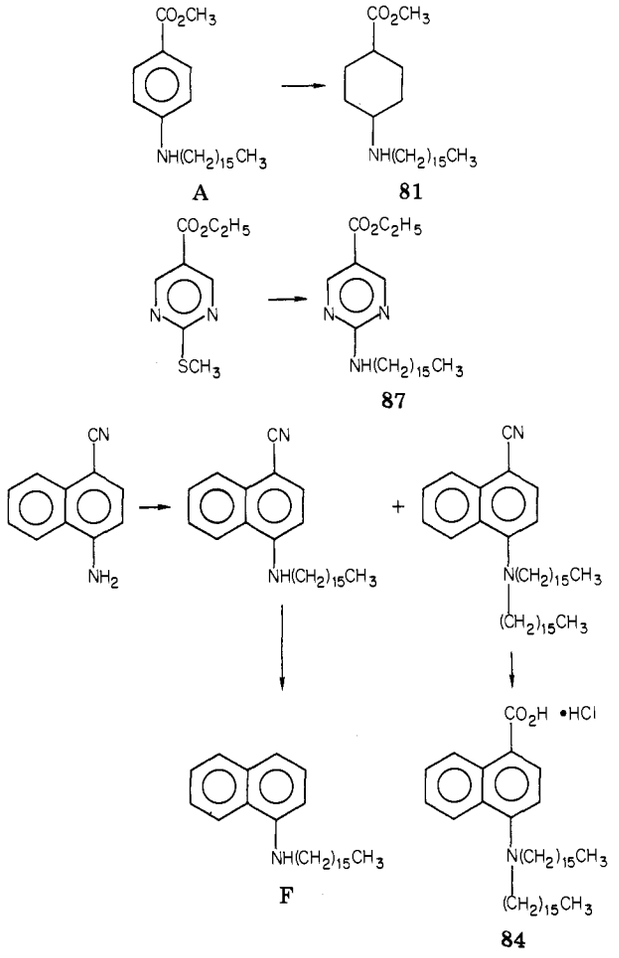
Direct alkylation, as illustrated in Scheme I, was the method of choice for several of the compounds shown in Table III. A second method for the preparation of ring-substituted analogues involved introduction of the substituent after the alkylation reaction (Scheme IV). Typical of this method was the synthesis of ester **70** by bromination of ethyl 4-(hexadecylamino)benzoate. Formation of the hexadecylamino group by reduction is also illustrated in Scheme IV. Selective N-alkylation of 4-aminosalicylic acid with 1-bromohexadecane was unsuccessful due to the formation of a mixture of the *O*-hexadecyl and *N,O*-dihexadecyl (**62**) alkylation products. In order to circumvent this problem, the acid was acylated with hexadecanoyl chloride, and the resulting amido acid E was reduced with diborane in the presence of sodium hydride to yield acid **59**.

Analogues in which the phenyl ring of cetaben was replaced entirely by another moiety (Table IV) were synthesized by a variety of methods, some of which are illustrated in Scheme V. Catalytic hydrogenation of A afforded ester **81**, and nucleophilic substitution of the methylthio group of ethyl 2-(methylthio)pyrimidine-5-carboxylate with *n*-hexadecylamine yielded heterocyclic ester **87**. Other methods used included alkylation reactions (**83** and **85**), nitrile hydrolysis (**90**), and acylation followed by reduction (**92**). Alkylation of 4-amino-1-naphthonitrile yielded both mono- and dialkylation products, as shown in Scheme V, and all attempts to hydrolyze the monoalkylation product or its *N*-acyl derivatives to the desired naphthoic acid analogue were unsuccessful. Invariably, nitrile hydrolysis was accompanied by an unexpected decarboxylation, and the only product isolated was 1-(hexadecylamino)naphthalene (F). In contrast, hydrolysis of the dialkylation product under vigorous conditions afforded a 60% yield of naphthoic acid **84**.

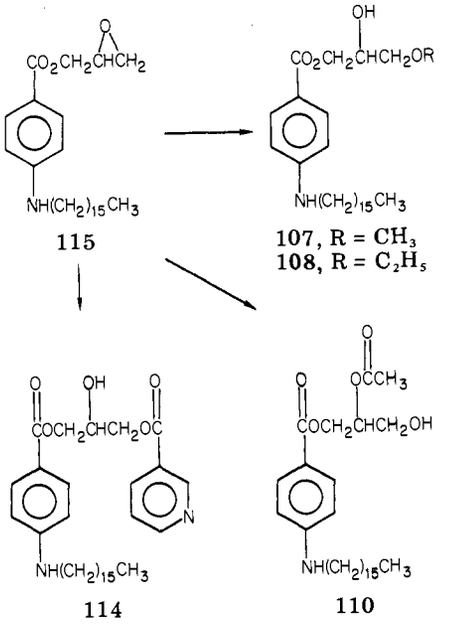
The series of ester analogues of cetaben shown in Table V was synthesized by common esterification procedures. Methods included the alkylation of sodium 4-(hexadecylamino)benzoate with alkyl halides,[6] the boron trifluoride etherate catalyzed reaction of **1** with alcohols,[7] and the reaction of 4-(hexadecylamino)benzoyl chloride hydrochloride (B) with alcohols. The *p*-toluenesulfonic acid catalyzed 2,3-dihydroxypropyl of **1** with 1,3-propanediol and dihydropyran afforded esters **96** and **124**, respectively.

(6) J. E. Shaw and D. C. Kunerth, *J. Org. Chem.*, **39**, 1968 (1974).
(7) P. K. Kadaba, M. Carr, M. Tribo, J. Triplett, and A. C. Glasser, *J. Pharm. Sci.*, **58**, 1422 (1969).

Scheme V

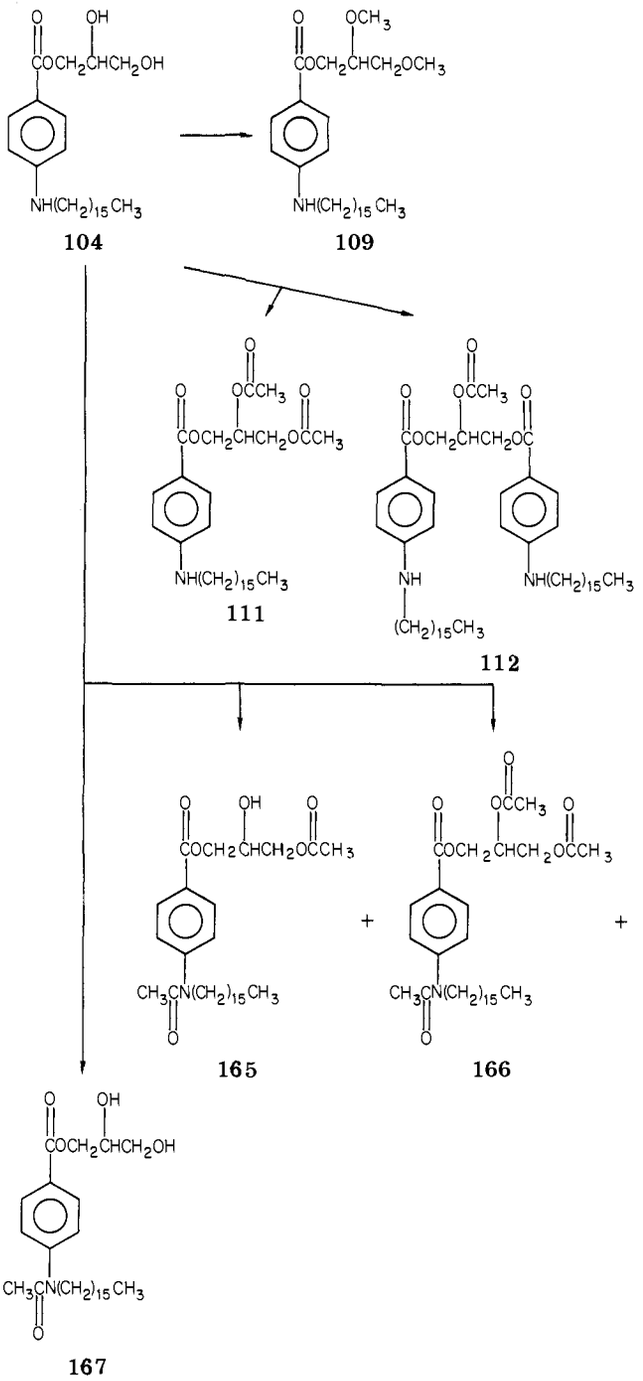


Scheme VI



Two of the esters in Table V, 2,3-epoxypropyl 4-(hexadecylamino)benzoate (**115**) and 2,3-dihydroxypropyl 4-(hexadecylamino)benzoate (**104**), were used as intermediates in the synthesis of additional esters. The epoxy ester **115** was subjected to acid-catalyzed ring opening in the presence of alcohols (Scheme VI). Alkoxypropyl esters **107** and **108** were isolated in low yield from the mixture of products that formed. Epoxy ester **115** was also acylated with glacial acetic acid to yield **110** and with aqueous

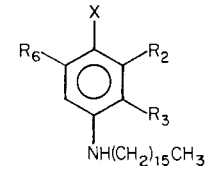
Scheme VII



nicotinic acid to yield **114**. The diol **104**, in addition to being used for the synthesis of ketal **116** and acetal **117**, was alkylated with methyl iodide to yield ether **109**, as shown in Scheme VII. Acylation of **104** with acetic anhydride in the presence of sodium hydride afforded a mixture of products, from which **111** and **112** were isolated. Acylation of **104** with acetic anhydride also afforded a mixture of acetates, and in this instance **165**, **166**, and **167** were isolated and characterized. The assignment of structures of the alkylation and acylation products shown in Schemes VI and VII is based on the NMR data shown in Table VIII.

Many of the amide analogues shown in Table VI were obtained from B or C. Sulfonamides **141–146** were obtained by reactions of alkyl- and arylsulfonamide anions with acid chloride hydrochloride B, and benzamide **140** was prepared by a similar reaction with 4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl chloride (C). Epoxy ester **115**

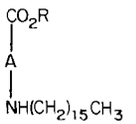
Table III. Ring-Substituted Benzoic Acids and Esters

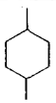
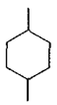
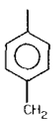
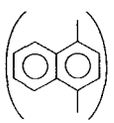
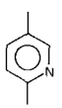
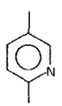
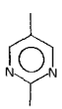
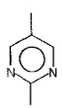


no.	X	R_2	R_3	R_6	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
54	CO_2CH_3	F			A	10	hexane	77-80	$C_{24}H_{40}FNO_2$	99			79			23**
55	$CO_2C_2H_5$	F			A	12	hexane	84-85	$C_{25}H_{42}FNO_2$	90			68*			
56	CO_2H	F			B	83	chloroform	137-138	$C_{23}H_{38}FNO_2$	75*	77*	93	40**	79	77	57***
57	$CO_2C_2H_5$	Cl			A	24	ethanol, benzene	solid[g]	$C_{25}H_{42}ClNO_2$							
58	CO_2H	Cl			B	95	ethanol	110-114	$C_{23}H_{38}ClNO_2$[h]	95	95[e]	100[f]	101	109[e]	113[f]	
59	CO_2H	OH			C	22	acetonitrile	112-114	$C_{23}H_{39}NO_3$	108			57*			49***
60	CO_2CH_3	OCH_3			A	37	ethanol	solid[g]	$C_{25}H_{43}NO_3$							
61	CO_2H	OCH_3			B	82	ethanol	115-117	$C_{24}H_{41}NO_3$	98	105[e]	104[f]	77	66*[e]	75[f]	
62	CO_2H	$O(CH_2)_{15}CH_3$			A	63	acetonitrile	83-84	$C_{39}H_{70}NO_3$	95	99	90	84	82	126	6
63	CO_2CH_3	CH_3			A	84	methanol, ether	70-72	$C_{25}H_{43}NO_2$	99			60*			0
64	CO_2H	CH_3			B	99	acetonitrile	94-96	$C_{24}H_{41}NO_2$	103	100	101	105	121	112	38***
65	$CO_2C_2H_5$	$CO_2C_2H_5$			A	38	methylene chloride, pet ether	59-60	$C_{28}H_{47}NO_4$	90	99	98	72**	93	86	37***
66	CO_2H	CO_2H			B	94	ether, pet ether	134-136	$C_{24}H_{39}NO_4$							
67	CO_2Na	CO_2Na			D	90	water, ethanol	solid[k]	$C_{24}H_{37}NO_4Na_2$	101	105	100	67**	85	110	63***
68	$CO_2C_2H_5$		F		A	34	hexane	58-59	$C_{25}H_{42}FNO_2$[i]	105			74			5
69	CO_2H		F		B	72	chloroform	120-122	$C_{23}H_{38}FNO_2$	79*	98	108	49***	89	91	27*
70	$CO_2C_2H_5$		Br		L	81	ethanol	41-43	$C_{25}H_{42}BrNO_2$[j]							
71	CO_2H		Br		B	97	ethanol	105-107	$C_{23}H_{38}BrNO_2$	97	99[e]	101[f]	100	99[e]	104[f]	
72	$CO_2C_2H_5$		CH_3		A	31	hexane	59-62	$C_{26}H_{45}NO_2$	103	87**[e]	92[f]	95	94[e]	81[f]	
73	CO_2H		CH_3		B	95	ethanol, benzene	107-109	$C_{24}H_{41}NO_2$	91*	92[e]	94[f]	101	96[e]	75[f]	1
74	$CO_2C_6H_5$	$CO_2C_6H_5$		$CO_2C_6H_5$	A	77		oil[g]	$C_{43}H_{51}NO_6$							
75	CO_2H	CO_2H		CO_2H	B	90	ether, hexane	128-129	$C_{25}H_{39}NO_6$							
76	CO_2Na	CO_2Na		CO_2Na	D	86	water, ethanol	solid[k]	$C_{25}H_{36}NO_6Na_3$[l]	97	100	100	93	68*	82	24*
77		CO_2CH_3		CO_2CH_3	A	10	methylene chloride, pet ether	90-91	$C_{26}H_{43}NO_4$	108			86			6
78		CO_2H		CO_2H	B	92	ether, pet ether	solid[k]	$C_{24}H_{39}NO_4$							
79		CO_2Na		CO_2Na	D	93	water, ethanol	solid[k]	$C_{24}H_{37}NO_4Na_2$	90	99	92	103	115	96	0
80	CO_2H[m]		Br		L	84	ethanol	103-105	$C_{21}H_{34}BrNO_2$	93	100[e]	92[f]	91	96[e]	95[f]	

[a-f] See footnotes *a* to *f* in Table I. [g] The crude ester was converted to the corresponding acid without purification. [h] Calcd: C, 69.76. Found: C, 70.72. [i] Calcd: C, 73.64. Found: C, 74.16. [j] Calcd: Br, 17.11. Found: Br, 18.20. [k] The product was isolated by evaporation as an amorphous solid without a distinct melting point. [l] Calcd: C, 56.28. Found: C, 56.94. [m] The compound is 3-bromo-4-(tetradecylamino)benzoic acid.

Table IV. Ring-Replaced Acids and Esters

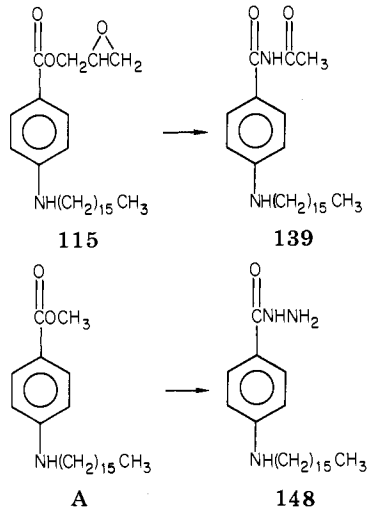


no.	A	R	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
81		CH_3	*d*	16	methanol	35–37	$C_{24}H_{47}NO_2$	71**	92	99	63**	88	78	37***
82		H	B	81	ethanol, acetonitrile	125–145	$C_{23}H_{46}ClNO_2$[g]	75*	86*	97	71	79	75	48***
83		H	*d*	59	water, ethanol	247–251	$C_{24}H_{42}ClNO_2$[g]	88*	89*[e]	97[f]	96	91[e]	86[f]	
84		H	*d*	60	acetone	145–146	$C_{43}H_{74}ClNO_2$[g]	101	109[e]	111[f]	112	99[e]	100[f]	
85		CH_3	A	95		solid[h]	$C_{23}H_{40}N_2O_2$	114	108					
86		H	B	95	ether, acetone	132–135	$C_{22}H_{38}N_2O_2$	90	84*[e]	102[f]	94	88[e]	121[f]	45**
87		C_2H_5	*d*	25	hexane	87–88	$C_{23}H_{41}N_3O_2$							13
88		H	B	50		194–195	$C_{21}H_{37}N_3O_2$[i]	114	108[e]	108[f]	93	94[e]	89[f]	21***
89		C_2H_5	A	49		66–68	$C_{23}H_{41}NO_2S$	112						24**
90		H	B	58		185–189	$C_{21}H_{38}ClNO_2S$[g,j]	98	101	98	79	103	112	70***

91		(CN)[k]	A	41	hexane	65–68	$C_{21}H_{36}N_2S$	92	99	41***
92		C_2H_5	C	63	carbon tetrachloride	solid[h]	$C_{23}H_{42}ClNO_2S$[g]			
93		H	B	80	water, ethanol	97–100	$C_{21}H_{37}NO_2S$			

[a–f] See footnotes a to f in Table I. [g] The product was isolated and characterized as a hydrochloride salt. [h] The crude ester was converted to the corresponding acid without purification. [i] Calcd: C, 69.38. Found: C, 68.31. [j] Calcd: H, 9.48. Found: H, 8.85. [k] The compound is 4-(hexadecylamino)-2-thiophenecarbonitrile. It was converted to 38 by the method used to prepare 32. [l] The compound is 4-(dihexadecylamino)-1-naphthoic acid hydrochloride.

Scheme VIII



was reacted with acetamide in the presence of sodium hydride in the hope of obtaining an acetamidohydroxypropyl ester and ultimately an aminohydroxypropyl ester analogue. Instead of the anticipated epoxide ring opening reaction, displacement of the epoxypropyl group occurred (Scheme VIII), and acetamide **139** was obtained. Similarly, methyl 4-(hexadecylamino)benzoate (A) was treated with hydrazine to yield hydrazide **148**.

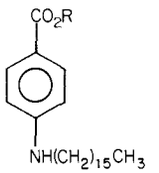
Biology. The cetaben analogues whose syntheses are described above were assayed for two types of biological activity related to their potential use as antiatherosclerotic agents. Compounds were tested in vivo in normal rats, for serum hypolipidemic activity. They were also tested in vitro for the ability 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 assays have been reported.[1]

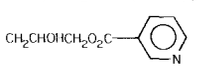
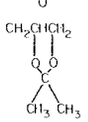
Replacement of the carboxyl group of cetaben with substituents that diminish or eliminate the acidity of the molecule appears to reduce hypocholesteremic activity. All of the compounds shown in Tables I and II were less active than cetaben as hypolipidemic agents. Analogues that could be metabolized in vivo to cetaben (by oxidative and/or hydrolytic reactions), such as **7**, **10**, **18–20**, as well as a series of keto esters (**42**, **43**, **45**, **47**, and **50**), exhibited moderate hypocholesteremic activity. The tetrazole analogue **22**, synthesized as a non carboxylic acid with acidity similar to that of cetaben, although devoid of hypolipidemic activity, showed the highest ACAT-inhibiting activity of this group of compounds.

Among the substituents placed on the phenyl ring of cetaben (Table III), fluoro substitution was unique in preserving hypocholesteremic activity; however, both **56** and **69** were somewhat less active than **1**. The importance of an unsubstituted aromatic ring for biological activity had been observed in two related series of hypolipidemic agents.[8,9] Ring substituents compatible with ACAT inhibition activity were 2-fluoro (**56**), 2-hydroxy (**59**), and 2-carboxy (**67**); however, none of these compounds significantly exceeded **1** in activity. Analogues in which the phenyl ring has been replaced (Table IV) were generally weakly active as hypolipidemics. The most active compounds contained nonpolar moieties, such as benzyl or

(8) V. G. DeVries, D. B. Moran, G. R. Allen, Jr., and S. J. Riggi, *J. Med. Chem.*, **19**, 946 (1976).
(9) R. A. Parker, T. Kariya, J. M. Grisar, and V. Petrow, *J. Med. Chem.*, **20**, 781 (1977).

Table V. 4-(Hexadecylamino)benzoates



no.	R	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
94	$CH_2CH{=}CH_2$	M	43	C[g]	74–77	$C_{26}H_{43}NO_2$	81**	103	94	70*	60**	89	40***
95	CH_2CH_2OH	M	85	hexane, CH_2Cl_2	115–117	$C_{25}H_{43}NO_3$	83*	92	106	52***	65**	75*	17
96	$CH_2CH_2CH_2OH$	*d*	28	C[g]	86–87	$C_{26}H_{45}NO_3$	68***	82*	94	46***	74*	67*	14
97	$CH_2C(CH_3)_2CH_2OH$	N	76	MeCN	99–101	$C_{28}H_{49}NO_3$	101	93	97	101	92	103	13
98	$CH_2CHOHCH_3$	N	48	CH_2Cl_2	89–91	$C_{26}H_{45}NO_3$	89*	82*	96	59**	61*	67*	19*
99	*p*-$CH_2CH{=}CHCH_2O_2C$-C_6H_4-$NH(CH_2)_{15}CH_3$	O	23	MeCN, CCl_4	118–120	$C_{50}H_{82}N_2O_4$	91			96			10
100	$CH_2CO_2CH_3$	M	60	hexane	98–99	$C_{26}H_{43}NO_4$	71**	76*	84	74	72	79	24**
101	$CH_2CO_2C_2H_5$	M	76	MeCN	79–80	$C_{27}H_{45}NO_4$	66**	81*	80*	72	76	92	15
102	CH_2CO_2H	B[k]	73		166–167	$C_{25}H_{41}NO_4$	83*	88	87	65*	91	76	45***
103	$CH_2CH_2N(CH_3)_2$·HCl	O	18	EtOH	162–165	$C_{27}H_{48}N_2O_2$·HCl	92	92*[e]	99[f]	59**	73*[e]	77[f]	
104	$CH_2CHOHCH_2OH$	M	64	MeCN, CCl_4	112–113	$C_{26}H_{45}NO_4$	71***	82**	85*	45***	67**	73*	0
105	$CH_2CHOHCH_2OH$·HCl	*d*	99[h]		126–130	$C_{26}H_{45}NO_4$·HCl	69**	92	88*	30***	49*	98	0
106	$CH_2CHOHCH_2OH$[i]	M	29	EtOH	105–107	$C_{23}N_{39}NO_4$	80**			47**			27
107	$CH_2CHOHCH_2OCH_3$	P	19	cyclohexane, MeCN	77–79	$C_{27}H_{47}NO_4$	77***			65*			0
108	$CH_2CHOHCH_2OC_2H_5$	P	22	hexane	68–70	$C_{28}H_{49}NO_4$	68**			47***			9
109	$CH_2CH(OCH_3)CH_2OCH_3$	*d*	10	MeOH	75–78	$C_{28}H_{49}NO_4$	82	83		70	62		24**
110	$CH_2CH(O_2CCH_3)CH_2OH$	*d*	73	hexane, CH_2Cl_2	64–67	$C_{28}H_{47}NO_5$	86	85	118	47*	71**	90	28
111	$CH_2CH(O_2CCH_3)CH_2OH$	*d*	34	MeOH, CH_2Cl_2	65–67	$C_{30}H_{49}NO_6$[l]	66***			40**			22
112	*p*-$CH_2CH(O_2CCH_3)CH_2O_2C$-C_6H_4-$NH(CH_2)_{15}CH_3$	*d*	17	CH_2Cl_2	82–84	$C_{51}H_{84}N_2O_6$	89			63**			2
113	$CH_2CH[O_2C(CH_2)_{14}CH_3]CH_2O_2C(CH_2)_{14}CH_3$	M	50	hexane	67–68	$C_{58}H_{105}NO_6$	80***			75			4
114		*d*	62	CH_2Cl_2	220 dec	$C_{32}H_{48}N_2O_5$[j]	84	108	103	63**	83	93	0
115		M	75	hexane, CCl_4	85–87	$C_{26}H_{43}NO_3$	75*	75*	92	53**	60*	74*	13
116		Q	75	*i*-PrOH	87–89	$C_{29}H_{49}NO_4$	86			68*			0
117		Q	23	hexane, CH_2Cl_2	74–76	$C_{33}H_{49}NO_4$	84			50**			
118		O	18	hexane	73–74	$C_{30}H_{51}NO_2$	87*			84			0

119	C_6H_5	O	53	hexane	118–119	$C_{29}H_{43}NO_2$	84**	85	89	76*	76	105	0
120	p-C_6H_4-Cl	O	49	Et_2O	116–117	$C_{29}H_{42}ClNO_2$	91	86*	94	83	85	91	0
121	p-C_6H_4-$CO_2C(CH_3)_3$	O	52	Et_2O	115–116	$C_{34}H_{51}NO_4$	103			67**			20*
122	p-C_6H_4-CO_2H	d	95	dimethoxy-ethane	229–230	$C_{30}H_{43}NO_4$	93	95	105	109	81	98	18*
123		O	9	petr ether	94–95	$C_{28}H_{42}N_2O_2$	93			76			22*
124		d	73	acetone	77–78	$C_{28}H_{47}NO_3$	74***	76*	91	54***	86	108	0
125		O	29	C[g]	119–120	$C_{33}H_{49}NO_4$	99	91	95	78	89	103	0

[a–f] See footnotes a to f in Table I. [g] The compound was isolated and purified by chromatography on silica gel. [h] The hydrochloride salt 13 was obtained by treatment of 12 with anhydrous hydrogen chloride. [i] The compound is 2,3-dihydroxypropyl 4-(tetradecylamino)benzoate. [j] Calcd: N, 5.24. Found: N, 4.69. [k] Ester 102 was prepared from ester 101 by selective hydrolysis. [l] Calcd: C, 76.20; H, 10.40. Found: C, 69.44; H, 9.42.

cyclohexyl (81 and 83). Of the analogues in this table, only the thienyl congener (90) exhibited significantly more activity than 1 as an ACAT inhibitor.

As was the case with the simple ethyl ester,[1] the functionalized esters of Table V generally exhibited less hypolipidemic activity than cetaben (1). Glyceryl esters 104 and 106, specifically synthesized in the hope of enhancing absorption, were among the most active of the esters; however, they failed to equal 1 in hypocholesteremic activity. Alkyl esters bearing certain functional groups (96, 101, 108, 111, and 124) were active as hypocholesteremics, while aryl esters (119–123) were much less active. Amide 131, related structurally to glycerol esters 104 and 106, was one of the most active hypocholesteremics of Table VI. As a class, sulfonamides 141–146, which were designed to mimic cetaben in acidity, were among the best hypolipidemics synthesized, and the toluenesulfonyl analogue (143) also had excellent ACAT activity. Very few of the N,N-disubstituted analogues of Table VII showed hypocholesteremic activity, although several were good ACAT inhibitors. The most striking feature of Table VI is the persistence of ACAT inhibitory activity for the amide analogues, many of which exceeded cetaben in activity. This stands in sharp contrast to the relative lack of ACAT activity for the ester analogues (Table V).

In summary, analogue syntheses designed to produce compounds that would be better absorbed orally than cetaben failed to yield any congeners of enhanced biological activity. In contrast, analogue syntheses directed toward non carboxylic acids of similar acidity to cetaben produced one of the most active classes of analogues, sulfonamides 141–146. The excellent activity of amide congeners in inhibiting the ACAT enzyme has prompted further synthetic efforts. Structure–activity relationships for additional structural types of amides as ACAT inhibitors will be reported in subsequent publications.

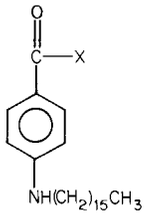
Experimental Section

Generalizations regarding the syntheses described in this section and details of the biological methods used have been reported.[1] The three intermediates (B–D) whose preparation is shown immediately below were all obtained in approximately quantitative yield and used without purification. Several experiments (methods A–X) illustrate general procedures used to synthesize analogues of Tables I–VII.

The aminobenzoate esters required for the synthesis of 54, 55, 57, 68, and 72 were prepared by boron trifluoride etherate catalyzed esterifications[7] of the corresponding acids. 4-Amino-2-fluorobenzoic acid[10] was obtained by oxidation of the N-acetyl derivative of 4-amino-2-fluorotoluene. 4-Hexadecanamidosalicyclic acid, for the synthesis of 59, was prepared by base-catalyzed acylation[1] of 4-aminosalicylic acid. Methyl 4-amino-2-methoxybenzoate, for the preparation of 60, was obtained by methylation of 4-aminosalicyclic acid with dimethyl sulfate.[11] Friedel–Crafts acylation of 3-acetamidotoluene with oxalyl chloride[12] afforded 4-acetamido-2-methylbenzoic acid,[13] which was deacetylated and then esterified[7] to yield ethyl 4-amino-2-methylbenzoate, the starting material for the synthesis of 63. Ethyl 2-(methylthio)-pyrimidine-5-carboxylate was obtained by reduction of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate[14] in the presence of zinc and then used to prepare 87. Ethyl 5-aminothiophene-

(10) F. C. Schmelkes and M. Rubin, J. Am. Chem. Soc., 66, 1631 (1944).
(11) M. Murahami, Chem. Pharm. Bull., 19, 1696 (1971).
(12) P. E. Sokol, In "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 706.
(13) J. Kunckell, Chem. Zentralbl., 136 (1912).
(14) E. Ballard and T. B. Johnson, J. Am. Chem. Soc., 64, 794 (1942).

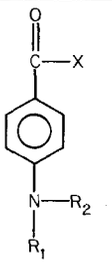
Table VI. 4-(Hexadecylamino)benzamides

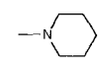
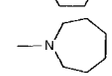


no.	X	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
126	NH_2	R	78	EtOH	129–132	$C_{23}H_{40}N_2O$	86*	102[e]	100[f]	114	115[e]	103[f]	19
127	$N(CH_3)_2$	R	92	cyclohexane	70–72	$C_{25}H_{44}N_2O$	93			89			48***
128		S	80	ether	82–83	$C_{27}H_{46}N_2O$	101	98	113	95	103	75	59***
129		R	74	ether	85–86	$C_{28}H_{48}N_2O$	83			61**			55***
130		S	75	EtOH	74–77	$C_{29}H_{50}N_2O$	106	105	110	68*	90	72	61***
131	$NHCH_2CHOHCH_2OH$	R	70	acetone, MeCN	122–125	$C_{26}H_{46}N_2O_3$[g]	72**	88	99	48**	73*	114	61***
132	$NHCH_2CO_2C_2H_5$	R	20	MeCN	97–99	$C_{27}H_{46}N_2O_3$	92	96	92	69*	74	78	16
133	$NHCH_2CO_2H$	B	15	acetone, H_2O	138–139		77**	87	77***	48***	70*	76	64***
134	$NHCH(CH_3)CO_2H$	S, B	58	ether	99 dec	$C_{26}H_{44}N_2O_3$[i]	102			132			45***
135	$NHC(CH_3)_2CO_2H$	S, B	20	EtOAc	80 dec	$C_{27}H_{46}N_2O_3$	88	95	89	83	90	84	13
136	$NHCH_2CH_2CO_2H$	T	50	EtOAc	136–140	$C_{26}H_{44}N_2O_3$[j]	86*	93	90*	55**	78	99	49***
137	$NHCH_2CH_2SO_3H$	T	45	EtOH, H_2O	190 dec	$C_{25}H_{44}N_2O_4S$	80*	90	91	56**	71	67*	45**
138	p-NH-C_6H_4-CO_2H	B	96	EtOH, H_2O	214 dec	$C_{30}H_{44}N_2O_3$	100	87*	95	103	121	85	12
139	$NHCOCH_3$	d	49	MeCN	130–132	$C_{25}H_{42}N_2O_2$	91	87**	93	74	73	86	35**
140	NHCO-C_6H_5	d	50	MeCN	81–84	$C_{30}H_{44}N_2O_2$	75**	80***	91	58**	66*	76	0
141	$NHSO_2CH_3$	U	27	dioxane	174–175	$C_{24}H_{42}N_2O_3S$	87*	84*	94	54***	73*	77	11
142	$NHSO_2$-C_6H_5	U	22	toluene	136–138	$C_{29}H_{44}N_2O_3S$	67***	84*	88*	36***	55**	86	22*
143	p-$NHSO_2$-C_6H_4-CH_3	U	12	hexane, toluene	123–125	$C_{30}H_{46}N_2O_3S$	61***	56***	89	40***	35***	86*	87***
144	p-$NNaSO_2$-C_6H_4-CH_3	d	93		solid	$C_{30}H_{45}N_2O_3SNa$	48***	52**	64***	32***	37***	52**	77***
145	p-$NHSO_2$-C_6H_4-NH_2	k	73	EtOAc	193–196	$C_{29}H_{45}N_3O_3S$	105	89	93	111	87	78	14
146	p-$NHSO_2$-C_6H_4-NO_2	U	34	EtOH	128–131	$C_{29}H_{43}N_3O_5S$	82*	94	105	108	79**	92	43**
147	NHOH	S	40	EtOH	139–140	$C_{23}H_{40}N_2O_2$	104	106	106	82	76	70	9
148	$NHNH_2$	d	90	EtOH	154–156	$C_{23}H_{41}N_3O$	116	105	110	84	84	108	24**
149	$NHNHCOCH_3$	S	85	EtOH	165–167	$C_{25}H_{43}N_3O_2$[l]	91	83*	93	66**	74**	75	21

[a–f] See footnotes a to f in Table I. [g] Calcd: H, 10.67. Found: H, 10.22. [h] Calcd: N, 6.68. Found: N, 7.22. [i] Calcd: H, 10.33. Found: H, 9.88. [j] Calcd: N, 6.47. Found: N, 7.08. [k] The sodium salt 144 was obtained by treatment of 143 with sodium hydroxide in aqueous ethanol. [l] Calcd: C, 71.91; H, 10.40. Found: C, 70.69; H, 9.99.

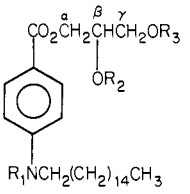
Table VII. N,N-Disubstituted 4-Aminobenzoic Acids, Esters, and Amides



no.	R_1	R_2	X	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering, dose as % of diet: 0.10	0.03	0.01	triglyceride lowering, dose as % of diet: 0.10	0.03	0.01	ACAT, % inhibn
150	$CH_3(CH_2)_{13}$	CH_3	OH	V	42	EtOH	106-108	$C_{22}H_{37}NO_2$	97	94[e]	97[f]	103	92[e]	82[f]	
151	$CH_3(CH_2)_{13}$	C_2H_5	OH	W	36	C_6H_6, EtOH	92-93	$C_{23}H_{39}NO_2$	88	98[e]	93[f]	80	92[e]	90[f]	38*
152	$CH_3(CH_2)_{13}$	CH_3CO	OH	X	84	EtOH	98-99	$C_{23}H_{37}NO_3$	91	80***[e]	95[f]	96	80[e]	98[f]	
153	$CH_3(CH_2)_{15}$	CH_3	OH	B	70	EtOH	105-108	$C_{24}H_{41}NO_2$	85	92[e]	85[f]	56	66**[e]	81**[f]	
154	$CH_3(CH_2)_{15}$	C_2H_5	OH	B		EtOH	95-96	$C_{25}H_{43}NO_2$	86*	60***[e]	74***[f]	98	63**[e]	78*[f]	
155	$CH_3(CH_2)_{15}$	C_2H_5	ONa	g	84		solid	$C_{25}H_{42}NO_2Na$[h]	116	116	114				72***
156	$CH_3(CH_2)_{15}$	HCO	OH	X	85	MeCN	137-138	$C_{24}H_{39}NO_3$	105	96	89*	78	100	77	12
157	$CH_3(CH_2)_{15}$	CH_3CO	OH	X	78	EtOH	100-102	$C_{25}H_{41}NO_3$	103	105[e]	105[f]	121	107[e]	109[f]	
158	$CH_3(CH_2)_{15}$	CH_2CO_2H	OH	B	71	HOAc, H_2O	201-202	$C_{25}H_{41}NO_4$	93	109	105	99	100	105	15
159	$CH_3(CH_2)_{15}$	CH_3	OC_2H_5	V	43	EtOH	49-51	$C_{26}H_{45}NO_2$	74***	84[e]	70***[f]	78	73*[e]	64**[f]	
160	$CH_3(CH_2)_{15}$	C_2H_5	OC_2H_5	d	85	EtOH	29-30	$C_{27}H_{47}NO_2$							
161	$CH_3(CH_2)_{15}$	HCO	OC_2H_5	X	94	hexane	52-53	$C_{26}H_{43}NO_3$	96	117	101	75	90	102	9
162	$CH_3(CH_2)_{15}$	CH_3CO	OC_2H_5	X	99		38-40[i]	$C_{27}H_{45}NO_3$							
163	$CH_3(CH_2)_{15}$	$CH_2CO_2C_2H_5$	OCH_3	d	26	hexane	48-50	$C_{28}H_{47}NO_4$	104	100	106	104	97	113	12
164	$CH_3(CH_2)_{15}$	CH_3	$OCH_2CHOHCH_2OH$	V	50	CH_2Cl_2	64-66	$C_{27}H_{47}NO_4$	99			93			0
165	$CH_3(CH_2)_{15}$	CH_3CO	$OCH_2CHOHCH_2O_2CCH_3$	d	78	C[j]	oil	$C_{30}H_{49}NO_6$[k]	97			113			4
166	$CH_3(CH_2)_{15}$	CH_3CO	$OCH_2CH(O_2CCH_3)CH_2O$-CCH_3	d	13	C[j]	oil	$C_{32}H_{51}NO_7$	101			111			12
167	$CH_3(CH_2)_{15}$	CH_3CO	$OCH_2CHOHCH_2OH$	d	1	C[j]	37-38	$C_{28}H_{47}NO_5$	106			110			0
168	$CH_3(CH_2)_{15}$	$CH_3(CH_2)_{14}CO$	$OCH_2CHOHCH_2OH$	d	22	C[j]	56-60	$C_{42}H_{75}NO_5$	99			72			14
169	$CH_3(CH_2)_{15}$	CF_3CO		S	90		oil[k]	$C_{29}H_{45}F_3N_2O_2$	92			68*			68***
170	$CH_3(CH_2)_{15}$	CF_3CO		S	90		oil[k]	$C_{31}H_{49}F_3N_2O_2$	95			66*			75***
171	$CH_3(CH_2)_{15}$	CF_3CO	p-NH-C_6H_4-$CO_2C_2H_5$	S	74	hexane, Et_2O	91-93	$C_{34}H_{47}F_3N_2O_4$	95			69**			25*
172	$CH_3(CH_2)_{15}$	CF_3CO	$NHNHCOCH_3$	S	90	Et_2O	solid	$C_{27}H_{42}F_3N_3O_3$	81*			61**			50***
173	$CH_3(CH_2)_{15}$	CF_3CO	NHOH	S	80		oil[l]	$C_{25}H_{39}F_3N_2O_3$	96			91			0
174	$CH_3(CH_2)_{16}$	CH_3	OH	V	45	EtOH	113-115	$C_{25}H_{43}NO_2$	98	98[e]	97[f]	109	134[e]	98[f]	
175	$CH_3(CH_2)_{16}$	C_2H_5	OH	W	72	EtOH, HOAc	100-101	$C_{26}H_{45}NO_2$	95	98[e]	98[f]	106	108[e]	126[f]	
176	$CH_3(CH_2)_{17}$	CH_3	OH	V	66	EtOH	111-112	$C_{26}H_{45}NO_2$	91	92[e]	101[f]	75*	61**[e]	86[f]	
177	$CH_3(CH_2)_{17}$	C_2H_5	OH	W	70	EtOH	96-98	$C_{27}H_{47}NO_2$	108	102[e]	102[f]	103	102[e]	85[f]	

[a-f] See footnotes *a* to *f* in Table I. [g] The sodium salt was obtained by treatment of 154 with sodium hydride in tetrahydrofuran solution. [h] Calcd: H, 9.44. Found: H, 9.90. [i] The crude product was not recrystallized but converted to 157. [j] The compound was purified by chromatography on silica gel. [k] Calcd: C, 69.40. Found: C, 68.77. [l] The compound was not purified but converted directly to 147.

Table VIII. Proton Magnetic Resonance Data[a] for Glyceryl Esters



no.	R_1	R_2	R_3	chem shift, δ NCH₂	α	β	γ
104	H	H	H	3.15 (t)	4.36 (d)	4.03 (m)	3.70 (d)
104[b]	H	H	H	3.63 (t)	4.70 (d)	4.55 (m)	4.13 (m)
107	H	H	Me	3.17 (t)	4.36 (d)	4.14 (m)	3.53 (d)
108	H	H	Et	3.16 (t)	4.35 (d)	4.13 (m)	3.55 (d)
109	H	Me	Me	3.15 (t)	4.36 (dd)	3.65 (m)	3.54 (d)
110	H	Ac	H	3.16 (t)	4.37 (d)	5.25 (m)	3.83 (m)
111	H	Ac	Ac	3.16 (t)	4.34 (m)	5.50 (m)	4.34 (m)
112	H	Ac	*c*	3.14 (t)	4.50 (dd)	5.51 (m)	4.50 (dd)
114[b]	H	H	*d*	3.63 (t)	4.83 (s)	~4.7 (m)	~5.1 (m)
165	Ac	H	Ac	3.71 (t)	4.43 (d)	4.26 (m)	4.26 (s)
166	Ac	Ac	Ac	3.70 (t)	4.49 (dd)	5.40 (m)	4.31 (dd)
167	Ac	H	H	3.70 (t)	4.44 (d)	4.08 (m)	3.73 (d)

[a] ^1H NMR spectra were recorded on a Varian HA-100 instrument with $CDCl_3$ as solvent (except where noted), and chemical shifts are presented relative to Me_4Si. [b] Spectrum recorded in trifluoroacetic acid as solvent. [c] R_3 is 4-($C_{16}H_{33}NH$)C_6H_4CO. [d] R_3 is nicotinoyl.

2-carboxylate required for the preparation of **92** was prepared by nitration of thiophene-2-carboxylic acid, followed by esterification and reduction with tin and HCl. Acylation with hexadecanoyl chloride then afforded the required ethyl 5-hexadecanamidothiophene-2-carboxylate.

4-(Hexadecylamino)benzoyl Chloride Hydrochloride (B). A cold solution of 25.0 g (69.1 mmol) of 4-(hexadecylamino)benzoic acid[1] in 500 mL of 4:1 dimethoxyethane–CH_2Cl_2 was treated with anhydrous HCl until no more precipitate formed. The mixture was stirred while 25 mL of thionyl chloride was added, and the solution was then stirred at reflux until all of the precipitate had dissolved. Evaporation of the solution afforded B as an orange glass.

4-(2,2,2-Trifluoro-*N*-hexadecylacetamido)benzoyl Chloride (C). A total of 32.6 g (90.1 mmol) of 4-(hexadecylamino)benzoic acid[1] was added portionwise with vigorous mechanical stirring to 60.0 mL (89.4 g, 0.426 mol) of trifluoroacetic anhydride during 4 min while the temperature was maintained at 20–25 °C with ice-bath cooling. The resulting clear, light-yellow solution was poured with very vigorous stirring (blender) into 250 mL of ice–water. A while solid formed immediately, and the mixture was stirred very vigorously for 5 min and then filtered. The solid was washed with H_2O and dried in vacuo at 35 °C to yield 4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoic acid as a white solid.

A solution of 77.0 g (0.168 mol) of this acid in 800 mL of CH_2Cl_2 was treated with 80.0 mL (131 g, 1.10 mol) of thionyl chloride, and the light yellow solution was stirred at reflux for 4 h. Evaporation afforded C as a yellow oil.

***N*-[[4-(2,2,2-Trifluoro-*N*-hexadecylacetamido)benzoyl]oxy]succinimide (D).** To a stirred, ice-cold solution of 18.3 g (0.040 mol) of 4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoic acid in 80 mL of dioxane were added successively 4.84 g (0.053 mol) of *N*-hydroxysuccinimide and 9.16 g (0.044 mol) of dicyclohexylcarbodiimide. The mixture was stirred for 18 h at 0–5 °C and then partitioned between H_2O and hexane. The organic layer was separated, dried, and evaporated to yield D as a light yellow oil.

4-(Hexadecylamino)benzonitrile (11). Method A. A mixture of 11.8 g (0.100 mol) of 4-aminobenzonitrile, 15.3 g (0.050 mol) of 1-bromohexadecane, and 200 mL of hexamethylphosphoramide was stirred at 120 °C for 22 h, allowed to cool, diluted with H_2O, and filtered. The solid was washed with H_2O and hexane and then recrystallized from Et_2O–hexane to yield 14.4 g (84%) of **11** as a white solid, mp 63–64 °C.

2-Chloro-4-(hexadecylamino)benzoic Acid (58). Method B. A mixture of 2.70 g (6.37 mmol) of ethyl 2-chloro-4-(hexadecylamino)benzoate (**57**), 3.54 g (63.7 mmol) of KOH, and 25 mL of 95% EtOH was stirred at reflux for 6 h, diluted with 100 mL of H_2O, and acidified with 5.30 mL of concentrated HCl. The mixture was chilled and filtered, and the crude solid was recrystallized from 95% EtOH to yield 2.40 g (95%) of **58** as a white solid, mp 110–114 °C.

4-(Hexadecylamino)-2-hydroxybenzoic Acid (59). Method C. A mixture of 1.05 g (20.9 mmol) of hexane-washed sodium hydride (50% in mineral oil), 8.40 g (21.5 mmol) of 4-hexadecanamidosalicylic acid, and 500 mL of 1,2-dimethoxyethane was stirred for 1 h at ambient temperature and then treated with 85 mL of 1 M borane in THF. The mixture was stirred at reflux for 2 h and then poured into 550 mL of ice–water, acidified with concentrated HCl, and extracted with Et_2O. The dried extract was evaporated, and the residual solid was purified by chromatography on silica gel, eluting with Et_2O and CH_2Cl_2. Recrystallization from acetonitrile yielded 1.70 g (22%) of **59** as a white solid, mp 112–114 °C.

Trisodium 5-(Hexadecylamino)-1,2,3-benzenetricarboxylate (76). Method D. A mixture of 5.28 g (11.8 mmol) of 5-(hexadecylamino)-1,2,3-benzenetricarboxylic acid (**75**), 1.42 g (35.5 mmol) of NaOH, and 60 mL of 9:1 EtOH/H_2O was stirred for 3 h at ambient temperature. Filtering, washing with H_2O, EtOH, and Et_2O, and drying in vacuo afforded 5.23 g (86%) of **76** as an amorphous white solid.

4-(Hexadecylamino)benzyl Acetate Hydrobromide (7). Method E. A solution of 1.00 g (2.88 mmol) of 4-(hexadecylamino)benzyl alcohol (**4**) in 5.0 mL of trifluoracetic acid was treated with 0.33 mL (0.55 g, 4.5 mmol) of acetyl bromide, stirred at ambient temperature for 30 min, treated with 2 drops of H_2O, and evaporated. Trituration of the residue with Et_2O afforded 1.01 g (75%) of **7** as a white solid, mp 80–82 °C.

4-(*N*-Acetyl-*N*-hexadecylamino)benzyl Acetate (8). Method F. A solution of 150 mg (0.432 mmol) off 4-(hexadecylamino)benzyl alcohol (**4**) and 0.5 mL of acetic anhydride in 1.0 mL of pyridine was stirred at ambient temperature for 3 h, poured into ice–water, and then filtered. Recrystallization of the solid from hexane yielded 170 mg (91%) of **8** as a white solid, mp 55–56 °C.

***N*-[4-(1,3-Dithian-2-yl)phenyl]hexadecylamine (21). Method G.** A solution of 5.00 g (14.5 mmol) of 4-(hexadecylamino)benzaldehyde (**10**) in 30 mL of CH_2Cl_2 was treated with 5.00 mL of 1,3-propanedithiol, 5.00 g of magnesium sulfate, and 5.00 g of zinc chloride. The mixture was stirred at ambient temperature for 18 h and then partitioned between Et_2O and H_2O. The organic layer was separated, washed with H_2O and 2 N NaOH solution, dried, and evaporated. Recrystallization from hexane yielded 3.79 g (60%) of **21** as a white solid, mp 79–80 °C.

***S*-(2-Hydroxyethyl) 4-(Hexadecylamino)thiobenzoate (18). Method H.** A mixture of 10.8 g (30.0 mmol) of 4-(hexadecyl-

amino)benzoic acid,[1] 6.70 g (37.5 mmol) of 1,1'-carbonyldiimidazole, and 80 mL of THF was stirred for 2 h at ambient temperature and then treated with 2.81 mL (3.13 g, 40.0 mmol) of 2-mercaptoethanol and 5 mg of sodium hydride (57% in mineral oil). The mixture was stirred for 16 h at ambient temperature and filtered, and the filtrate was evaporated. The solid was crystallized from MeOH to yield 4.17 g (33%) of **18** as a white solid, mp 105–107 °C.

4-(Hexadecylamino)-α-(methylsulfinyl)acetophenone (38). Method I. To a solution of 5.80 g (74.0 mmol) of dimethyl sulfoxide in 50 mL of THF was slowly added 28.0 mL (68.0 mmol) of *n*-butyllithium (2.42 M in hexane), and the resulting mixture was treated with a solution of 10.0 g (26.0 mmol) of methyl 4-(hexadecylamino)benzoate[1] in 200 mL of THF. The mixture was stirred for 2 h at ambient temperature, poured onto ice, acidified with dilute HCl, and extracted with $CHCl_3$. The dried extract was evaporated, and the residue was purified by chromatography on a silica gel column eluting with CH_2Cl_2 to yield 4.50 g (41%) of **38** as a white solid, mp 152–154 °C.

Diethyl [4-(Hexadecylamino)benzoyl]malonate (45). Method J. A solution of 13.3 g (83.1 mmol) of diethyl malonate in 10 mL of 1,2-dimethoxyethane was added dropwise to a stirred suspension of 4.00 g (83.3 mmol) of sodium hydride (50% in mineral oil) in 250 mL of 1,2-dimethoxyethane under an argon atmosphere. When gas evolution ceased, a solution of 17.3 g (40.0 mmol) of 4-(hexadecylamino)benzoyl chloride hydrochloride in 20 mL of 1,2-dimethoxyethane was added, and the mixture was stirred at reflux for 5 h, allowed to cool, and poured onto ice. The mixture was extracted with Et_2O, and the extract was dried and evaporated. Crystallization from Et_2O yielded 4.03 g (20%) of **45** as a white solid, mp 75–77 °C.

***tert*-Butyl Ethyl [4-(2,2,2-Trifluoro-*N*-hexadecylacetamido)benzoyl]malonate (46). Method K.** A mixture of 926 mg (22.0 mmol) of sodium hydride (57% in mineral oil, washed previously with hexane) and 125 mL of 1,2-dimethoxyethane was stirred under argon while a solution of 4.00 g (21.3 mmol) of *tert*-butyl ethyl malonate in 5 mL of 1,2-dimethoxyethane was added dropwise and then stirred for 15 min after hydrogen evolution ceased. A solution of 5.00 g (10.5 mmol) of C in 15 mL of 1,2-dimethoxyethane was then added, and the mixture was stirred at ambient temperature for 3 h, poured onto ice, acidified with HCl, and extracted with Et_2O. The dried extract was evaporated, and the residue was distilled (Kugelrohr apparatus) in vacuo to yield 5.93 g (90%) of **46** as a viscous, yellow oil.

Ethyl 3-Bromo-4-(hexadecylamino)benzoate (70). Method L. A solution of 1.63 mL (5.08 g, 31.7 mmol) of bromine in 50 mL of CCl_4 was added dropwise during 10 min to a stirred mixture of 11.7 g (30.0 mmol) of ethyl 4-(hexadecylamino)benzoate[1] and 150 mL of CCl_4. After 2 h at ambient temperature, the resulting solution was washed with dilute NaOH, dried, and evaporated. The residual solid was crystallized from EtOH to yield 11.5 g (81%) of **18** as a white solid, mp 41–43 °C.

2,3-Dihydroxypropyl 4-(Hexadecylamino)benzoate (104). Method M. A mixture of 6.70 g (0.223 mol) of sodium hydride (50% in mineral oil), 54.2 g (0.150 mol) of 4-(hexadecylamino)-benzoic acid,[1] 55.0 g (0.500 mol) of 1-chloro-2,3-dihydroxypropane, and 350 mL of hexamethylphosphoramide was stirred at ambient temperature for 1 h and then at 140 °C, for 7 h. The mixture was allowed to cool, diluted with 100 mL of H_2O, and filtered. The solid was washed with EtOH, dried in vacuo, and recrystallized from acetonitrile and then from CCl_4 to yield 42.1 g (64%) of **104** as a white solid, mp 112–113 °C.

3-Hydroxy-2,2-dimethylpropyl 4-(Hexadecylamino)-benzoate (97). Method N. A mixture of 7.20 g (18.9 mmol) of 4-(hexadecylamino)benzoic acid,[1] 20.8 g (200 mmol) of 2,2-dimethyl-1,3-propanediol, and 3.90 mL (4.25 g, 9.24 mmol) of freshly distilled boron trifluoride etherate was heated at 100 °C for 16 h. The resulting solution was allowed to cool and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried, and evaporated, and the residual solid was recrystallized from acetonitrile to yield 6.74 g (76%) of **97** as a white solid, mp 99–101 °C.

4-Chlorophenyl 4-(Hexadecylamino)benzoate (120). Method O. A solution of 9.53 g (0.025 mol) of B in 250 mL of CH_2Cl_2 was added to a solution of 6.43 g (0.050 mol) of 4-chlorophenol and 7.58 g (0.075 mol) of triethylamine in 500 mL of CH_2Cl_2, and the solution was stirred at reflux for 4 h, allowed to cool, washed with H_2O and dilute phosphoric acid, dried, and evaporated. The resulting solid was crystallized from Et_2O to yield 5.78 g (49%) of **120** as a cream-colored solid, mp 116–117 °C.

3-Methoxy-2-hydroxypropyl 4-(Hexadecylamino)benzoate (107). Method P. A solution of 8.30 g (19.9 mmol) of 2,3-epoxypropyl 4-(hexadecylamino)benzoate (**115**) and 0.60 mL of concentrated sulfuric acid in 400 mL of MeOH was stirred at reflux for 2 h, allowed to cool, and partitioned between Et_2O and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried, and evaporated to yield a white solid. Chromatography on silica gel (eluted with 1:1 Et_2O/hexane) afforded 1.40 g of solid which was crystallized, first from cyclohexane and then from acetonitrile, to yield 1.70 g (19%) of **107** as a white solid, mp 77–79 °C.

2,3-(Isopropylidenedioxy)propyl 4-(Hexadecylamino)-benzoate (116). Method Q. A solution of 8.71 g (20.0 mmol) of 2,3-dihydroxypropyl 4-(hexadecylamino)benzoate (**104**), 1.10 g (30.1 mmol) of anhydrous HCl, and 3.92 g (24.5 mmol) of anhydrous Na_2SO_4 in 550 mL of acetone was stirred at reflux for 2 h and filtered while hot. The precipitate that formed upon cooling the filtrate was collected and dissolved in a mixture of 200 mL of $CHCl_3$ and 8 mL of MeOH. The solution was washed with saturated aqueous Na_2CO_3 solution, dried, and evaporated. The residue was crystallized from isopropyl alcohol to yield 6.60 g (75%) of **116** as a white solid, mp 87–89 °C.

1-[4-(Hexadecylamino)benzoyl]piperidine (129). Method R. A solution of 7.35 g (17.5 mmol) of B in 50 mL of Et_2O was added with stirring to a solution of 3.50 mL (3.01 g, 35.0 mmol) of piperidine, 2.50 mL (17.5 mmol) of triethylamine, and 600 mg (4.90 mmol) of 4-(dimethylamino)pyridine in 100 mL of Et_2O at −5 °C. The solution was stirred at ambient temperature for 2 h and then at reflux for 2 h, allowed to cool, washed with H_2O, dried, and evaporated. Recrystallization of the residue from Et_2O afforded 5.56 g (74%) of **129** as a white solid, mp 85–86 °C.

1-[4-(Hexadecylamino)benzoyl]pyrrolidine (128). Method S. A solution of 6.24 g (13.1 mmol) of C in 10 mL of CH_2Cl_2 was added during 20 min to a stirred solution of 8.00 mL (6.82 g, 95.8 mmol) of pyrrolidine and 1.0 mL of pyridine in 5 mL of CH_2Cl_2. The resulting yellow solution was stirred at ambient temperature for 1 h, poured into H_2O, and extracted with Et_2O. The extract was washed with 5% HCl and H_2O, dried, and evaporated to yield 6.00 g (90%) of **169** as a light yellow oil.

A stirred solution of **169** in 55 mL of EtOH was treated with 7.0 mL of 2 N aqueous NaOH solution, and the mixture was stirred at ambient temperature for 1 h, diluted with H_2O, and filtered. The solid was crystallized from Et_2O to yield 3.91 g (80%) of **128** as a white solid, mp 82–83 °C.

3-[4-(Hexadecylamino)benzamido]propionic Acid (136). Method T. A mixture of 11.0 g (20.0 mmol) of D, 3.56 g (40.0 mmol) of β-alanine, 11.2 mL of triethylamine, 90 mL of EtOH, and 45 mL of H_2O was stirred at ambient temperature for 5 days. The solution was then treated with 40 mL of 2 N aqueous NaOH, stirred at ambient temperature for 30 min, acidified with 40 mL of 4 N HCl, stirred at ambient temperature for 1 h, diluted with H_2O, and filtered. The solid was crystallized from EtOAc to yield 4.37 g (50%) of **136** as a white solid, mp 136–140 °C.

***N*-(Phenylsulfonyl)-4-(hexadecylamino)benzamide (142). Method U.** A solution of 31.4 g (0.200 mol) of benzenesulfonamide in 250 mL of *N,N*-dimethylacetamide was added dropwise, with stirring and cooling, to a suspension of 11.0 g (0.240 mol) of sodium hydride (50% in mineral oil) in 100 mL of *N,N*-dimethylacetamide during 30 min. The mixture was stirred at ambient temperature for 30 min and then added in one portion to 43.2 g (0.100 mol) of B. The mixture was stirred at ambient temperature for 30 min and filtered. The filtrate was poured into 2.0 L of H_2O, and 250 mL of saturated aqueous NaCl was added. The mixture was extracted with CH_2Cl_2, and the extract was dried and then filtered through hydrous magnesium silicate and evaporated. Crystallization of the resulting solid from toluene yielded 11.0 g (22%) of **142** as a white solid, mp 136–138 °C.

4-(*N*-Methyl-*N*-tetradecylamino)benzoic Acid (150). Method V. A mixture of 25.3 g (70.0 mmol) of ethyl 4-(tetradecylamino)benzoate,[1] 17.5 mL of methyl fluorosulfonate, and 500 mL of CH_2Cl_2 was stirred at ambient temperature for 21 h, poured into ice–water, and rendered alkaline with 10 N KOH.

The organic layer was separated, combined with a $CHCl_3$ extract of the aqueous layer, washed with dilute KOH, dried, and evaporated. The residual oil was treated with a solution of 25 g of KOH in 250 mL of 9:1 EtOH/H_2O, stirred at reflux for 4 h, acidified with 50 mL of concentrated HCl, diluted with 200 mL of H_2O, cooled, and filtered. Crystallization of the solid from EtOH afforded 10.2 g (42%) of **150** as a pale yellow solid, mp 106–108 °C.

4-(*N*-Ethyl-*N*-tetradecylamino)benzoic Acid (151). Method W. A mixture 25.3 g (70.0 mmol) of ethyl 4-(tetradecylamino)benzoate[1] and 39.2 mL (300 mmol) of diethyl sulfate was stirred at 130 °C for 3 h, chilled, diluted with 250 mL of 9:1 EtOH/H_2O, and treated with 30 g of KOH. The mixture was then stirred at reflux for 3 h, acidified with concentrated HCl, diluted with 500 mL of H_2O, and filtered. The solid was recrystallized from EtOH and then from benzene–EtOH to yield 9.15 g (36%) of **151** as a white crystalline solid, mp 92–93 °C.

4-(*N*-Tetradecylacetamido)benzoic Acid (152). Method X. A mixture of 6.67 g (20.0 mmol) of 4-(tetradecylamino)benzoic acid,[1] 50 mL of pyridine, and 25 mL of acetic anhydride was heated on a steam bath for 16 h, poured onto ice, acidified to pH 6 with concentrated HCl, and filtered. Recrystallization of the solid from EtOH yielded 6.3 g (84%) of **152** as a light tan solid, mp 98–99 °C.

4-(Hexadecylamino)benzyl Alcohol (4). A mixture of 1.00 g (2.67 mmol) of methyl 4-(hexadecylamino)benzoate[1] and 10 mL of THF was treated with 500 mg of lithium aluminum hydride and stirred at room temperature for 2 h. The mixture was treated with 10% aqueous NH_4Cl and then filtered. The filtrate was evaporated, and the residue was crystallized from hexane to yield 510 mg (55%) of 4 as a white solid, mp 74–75 °C.

4-(*N*-Acetyl-*N*-hexadecylamino)benzyl Alcohol (6). A mixture of 2.00 g (4.64 mmol) of 4-(*N*-acetyl-*N*-hexadecylamino)benzyl acetate (8) and 25 mL of MeOH was treated with 3 mL of 2 N methanolic KOH and stirred at reflux for 2 h. The mixture was evaporated, the residue was triturated with H_2O, and the resulting solid was collected by filtration. A CH_2Cl_2 solution of the product was dried, the solvent was evaporated, and the residue was crystallized from hexane to yield 1.65 g (94%) of **6** as a white solid, mp 71–72 °C.

1-[4-(Hexadecylamino)phenyl]ethanol (9). A solution of 5.00 g (14.5 mmol) of 4-(hexadecylamino)benzaldehyde (**10**) in 100 mL of 1,2-dimethoxyethane was stirred under nitrogen while 30 mL of methyllithium (1.5 M solution in ether) was added during 10 min. After 15 min, the mixture was cautiously diluted with 30 mL of H_2O and 250 mL of CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, and evaporated. Crystallization of the residual solid from hexane yielded 4.51 g (86%) of **9** as a pale yellow solid, mp 55–56 °C.

4-(Hexadecylamino)benzaldehyde (10). A solution of 11.4 g (33.3 mmol) of 4-(hexadecylamino)benzonitrile (**11**) in 150 mL of toluene was stirred under nitrogen while 54.0 mL of diisobutylaluminum hydride (25% solution in toluene) was added during 30 min. The reaction temperature rose to 40 °C, and the mixture was stirred at ambient temperature for 1 h, treated cautiously during 30 min with 50 mL of 1:1 MeOH/toluene, and poured into 500 mL of vigorously stirred 5% H_2SO_4. The resulting mixture was filtered, and the organic layer of the filtrate was separated, combined with a 100-mL toluene extract of the aqueous layer, washed with saturated aqueous $NaHCO_3$, dried, and evaporated. The residual solid was recrystallized from CH_2Cl_2–hexane to yield 6.67 g (58%) of **10** as a white solid, mp 84–85 °C.

4-(2,2,2-Trifluoro-*N*-hexadecylacetamido)benzonitrile (13). A suspension of 10.0 g (29.2 mmol) of 4-(hexadecylamino)-benzonitrile (**11**) in 21 mL of pyridine and 150 mL of 1,2-dimethoxyethane was stirred at 0 °C while 21.0 mL (31.3 g, 149 mmol) of trifluoroacetic anhydride was added during 5 min and then stirred at ambient temperature for 1 h thereafter. The resulting solution was diluted with Et_2O, cooled to 10 °C, and treated with 50 g of ice. The organic layer was separated, dried, and evaporated. Recrystallization from MeOH–hexane afforded 12.7 g (99%) of **13**, mp 53–54 °C.

1-Benzyl-3-[[4-(hexadecylamino)benzylidene]amino]-guanidine (16). A mixture of 5.00 g (14.5 mmol) of 4-(hexadecylamino)benzaldehyde (**10**), 4.50 g of 1-amino-3-benzylguanidine hydriodide, 10 drops of concentrated HCl, and 150 mL of EtOH was stirred at reflux for 6 h, allowed to cool, and rendered alkaline by the addition of 150 mL of 0.3 N NaOH solution. The precipitate was collected by filtration, washed with H_2O, dried, and recrystallized from EtOH to yield 5.70 g (80%) of **16** as a white solid, mp 101–102 °C.

***N*-[4-(1,3-Dioxolan-2-yl)phenyl]hexadecylamine (20).** A solution of 1.70 g (4.93 mmol) of 4-(hexadecylamino)benzaldehyde (**10**) in 20 mL of toluene and 2.5 mL of ethylene glycol was treated with 10 mg of *p*-toluenesulfonic acid and stirred at reflux for 16 h using a Dean–Stark trap. The reaction mixture was cooled and diluted with 70 mL of toluene. The solution was washed with saturated aqueous $NaHCO_3$ and H_2O, dried, and evaporated. Recrystallization of the residual yellow solid from hexane afforded 1.56 g (81%) of **20** as a pale yellow crystalline solid, mp 67–68 °C.

5-[4-(Hexadecylamino)phenyl]tetrazole (22). A solution of 5.13 g (15.0 mmol) of 4-(hexadecylamino)benzonitrile (**11**) in DMF was treated with 0.98 g (15.0 mmol) of sodium azide and 0.83 g (15.0 mmol) of NH_4Cl, and the mixture was stirred for 42 h at 120 °C, allowed to cool, and poured into ice–water with vigorous stirring. The precipitate was collected by filtration, washed first with H_2O and then with Et_2O, and dried to yield 1.75 g (30%) of **22** as a light brown solid, mp 114–116 °C dec.

2-[4-(Hexadecylamino)phenyl]oxazoline (23). A mixture of 15.0 g (78.1 mmol) of 2-bromoethylamine hydrobromide and 150 mL of 1,2-dimethoxyethane was stirred at 5 °C while a solution of 29.0 g (72.8 mmol) of 4-(hexadecylamino)benzoyl chloride hydrochloride, 50 mL of triethylamine, and 0.5 g of 4-(dimethylamino)pyridine in 60 mL of 1,2-dimethoxyethane was added. The mixture was stirred at ambient temperature for 16 h and then at reflux for 1 h. Filtration afforded a solid, which was partitioned between 350 mL of CH_2Cl_2 and 100 mL of H_2O. The organic layer was separated, dried, and evaporated, and the residue was purified by chromatography on silica gel (eluent CH_2Cl_2). Recrystallization from cyclohexane and then from acetonitrile afforded 3.80 g (13%) of **23**, mp 129–130 °C.

2-[4-(Hexadecylamino)phenyl]-5,6-dihydro-4*H*-1,3-oxazine (24). A mixture of 21.9 g (0.100 mol) of 3-bromopropylamine hydrobromide and 200 mL of 1,2-dimethoxyethane was stirred at 5 °C while a solution of 24.0 g (57.6 mmol) of 4-(hexadecylamino)benzoyl chloride hydrochloride, 26 mL of triethylamine, and 0.2 g of 4-(dimethylamino)pyridine in 100 mL of 1,2-dimethoxyethane was added during 1 h. The mixture was stirred at reflux for 4 h, allowed to cool, and filtered. The filtrate was diluted with 200 mL of H_2O, and the resulting precipitate was collected, purified by chromatography on silica gel (eluent $CHCl_3$), and recrystallized from acetonitrile to yield 3.52 g (13%) of *N*-(3-bromopropyl)-4-(hexadecylamino)benzamide, mp 113–114 °C.

A solution of 2.14 g (4.44 mmol) of this amide in 100 mL of 1,2-dimethoxyethane was stirred at ambient temperature while 400 mg (9.50 mmol) of sodium hydride (57% in mineral oil) was added, followed by 12 mL of triethylamine. The mixture was stirred at reflux for 20 h, diluted with 100 mL of H_2O, and filtered. Crystallization from acetonitrile afforded 1.58 g (89%) of **24** as a white solid, mp 95–96 °C.

4-(Hexadecylamino)-α-[(trimethylsilyl)oxy]benzeneacetonitrile (26). A mixture of 5.00 g (14.5 mmol) of 4-(hexadecylamino)benzaldehyde (**10**), 4.40 mL of trimethylsilyl cyanide, and a small crystal of zinc chloride was stirred at 90 °C for 4 h and then evaporated. The residue slowly solidified to yield 5.80 g (90%) of **26** as an off-white solid, mp 29–30 °C.

4-(Hexadecylamino)mandelamide (27). A mixture of 5.60 g (12.7 mmol) of 4-(hexadecylamino)-α-[(trimethylsilyl)oxy]-benzeneacetonitrile (**26**) and 35 mL of concentrated HCl was heated on a steam bath for 1 h and then cooled in an ice bath, diluted with H_2O, and neutralized (pH 7) with 5 N aqueous NaOH. The mixture was extracted three times with CH_2Cl_2, and the combined extracts were washed with H_2O, dried, and evaporated to yield 2.52 g (51%) of **27** as an off-white solid.

4-(Hexadecylamino)-α-methoxyacetophenone (37). A solution of 13.0 g (32.6 mmol) of B in 50 mL of THF was added dropwise to a stirred solution of 6.0 g (143 mmol) of diazomethane in approximately 600 mL of Et_2O at 0 °C. The solution was stirred for 3 h at 0 °C and then diluted with 50 mL of HOAc. The

solvents were evaporated, and the residue was heated at 50 °C for 30 min and then partitioned between Et_2O and H_2O. The organic layer was separated, washed with saturated $NaHCO_3$, dried, and evaporated. The residue was chromatographed on a silica gel column eluting with $CHCl_3$. The resulting solid was treated with 35 mL of MeOH, 35 mL of dioxane, and a solution of 5 g of KOH in 3.5 mL of H_2O, and the resulting mixture was stirred at reflux for 2 h, evaporated, and extracted with Et_2O. The extract was evaporated, and the residue was chromatographed on silica gel (eluent 2:3 $CCl_4/CHCl_3$). Crystallization from EtOH–H_2O afforded 1.52 g (12%) of **37** as a white solid.

4-(Hexadecylamino)-α-hydroxyacetophenone (36). A solution of 22.6 g (47.7 mmol) of 4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl chloride in 50 mL of Et_2O was added dropwise to a stirred solution of 6.00 g (143 mmol) of diazomethane in 600 mL ether at 0 °C. The mixture was stirred for 1 h, treated with 14 mL of trifluoroacetic acid, stirred at ambient temperature for 2 h, treated with an additional 14 mL of trifluoroacetic acid, and heated at 50 °C for 15 min. The mixture was poured into H_2O and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, dried, and evaporated. A mixture of the residue, 75 mL of 2 N NaOH solution, and 300 mL of 1,2-dimethoxyethane was stirred for 1 h at ambient temperature and partitioned between Et_2O and saturated NaCl solution. The organic layer was separated, dried, and evaporated. The residue was chromatographed on a silica gel column eluting with 2:1 CCl_4–Et_2O and then crystallized from CCl_4 to yield 5.37 g (30%) of **36** as a white solid.

Methyl [4-(Hexadecylamino)benzoyl]acetate (42). A mixture of 4.00 g (6.40 mmol) of *tert*-butyl ethyl [4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl]malonate (**46**) and 20 mL of trifluoroacetic acid was stirred at reflux for 1 h and then evaporated. The residue was partitioned between H_2O and CH_2Cl_2, and the organic layer was separated, dried, and evaporated. A solution of the residue in 25 mL of MeOH and a few drops of CH_2Cl_2 was treated with 7 mL of 1 N NaOH and stirred for 24 h at ambient temperature. The precipitate was collected by filtration and recrystallized from MeOH to yield 2.00 g (75%) of **42** as an off-white solid, mp 89–94 °C.

Ethyl 2-[4-(Hexadecylamino)benzoyl]propionate (47). A suspension of 630 mg (15.0 mmol) of hexane-washed sodium hydride (57% in mineral oil) in 50 mL of DMF was stirred under argon while a solution of 6.25 g (10.0 mmol) of *tert*-butyl ethyl [4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl]malonate (**46**) in 10 mL of DMF was added dropwise and for 30 min thereafter and then treated with a solution of 2.84 g (20.0 mmol of methyl iodide in 5 mL of DMF, stirred for 3 h at ambient temperature, and poured into ice–water. The mixture was extracted with Et_2O, dried, and evaporated. A solution of the residual yellow oil in 30 mL of trifluoroacetic acid was stirred at reflux for 1 h and evaporated. The residue was partitioned between H_2O and CH_2Cl_2, and the organic layer was separated, dried, and evaporated. A mixture of the residue, 10 mL of 1 N NaOH, and 100 mL of EtOH was stirred at ambient temperature for 1 h and filtered. Recrystallization of the solid from hexane yielded 1.20 g (27%) of **47** as a yellow solid, mp 70–72 °C.

Ethyl 2-[4-(Hexadecylamino)benzoyl]-2-methylpropionate (48). A mixture of 6.27 g (10.0 mmol) of *tert*-butyl ethyl [4-(2,2,2-trifluoro-*N*-hexadecylacetamido)benzoyl]malonate (**46**) and 30 mL of trifluoroacetic acid was stirred at reflux for 1 h, evaporated, and partitioned between H_2O and CH_2Cl_2. The organic layer was separated, dried, and evaporated. A solution of the residue in 10 mL of DMF was added under argon to a stirred suspension of 1.26 g (30.0 mmol) of hexane-washed sodium hydride (57% in mineral oil) in 50 mL of DMF. A solution of 4.26 g (30.0 mmol) of methyl iodide in 15 mL of DMF was then added, and the mixture was stirred for 2 h ambient temperature, poured into ice–water, and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. A mixture of the residual yellow oil, 10 mL of 1 N NaOH, and 80 mL of EtOH was stirred at ambient temperature for 1 h, chilled overnight, and filtered. The resulting solid was recrystallized from hexane to yield 1.20 g (26%) of **48** as a white solid, mp 71–74 °C.

Methyl 3-[4-(Hexadecylamino)benzoyl]-2-oxopropionate (51). A mixture of 1.26 g (30.0 mmol) of sodium hydride (50% in mineral oil), 3.60 g (10.0 mmol) of 4-(hexadecylamino)acetophenone (**17**), 2.30 g (20.0 mmol) of dimethyl oxalate, 2 mL of MeOH, and 50 mL of Et_2O was stirred at reflux for 5 h, allowed to cool, and poured into 25 mL of 50% aqueous HOAc. The mixture was extracted with Et_2O, and the dried extract was evaporated. The residue was crystallized from MeOH to yield 2.30 g (52%) of **51** as a yellow solid, mp 97–98 °C.

Methyl 4-(Hexadecylamino)cyclohexanecarboxylate (81). A mixture of 14.1 g (37.6 mmol) of methyl 4-(hexadecylamino)-benzoate,[1] 2.80 g of 5% rhodium on carbon, 5.00 mL of HOAc, and 300 mL of EtOH was shaken in a Parr hydrogenator at an initial pressure of 20 psi of hydrogen at 50 °C for 7 h and then filtered. The filtrate was evaporated, and the residue was crystallized from MeOH to yield 2.30 g (16%) of **81** as a white solid, mp 35–37 °C.

4-[(Hexadecylamino)methyl]benzoic Acid Hydrochloride (83). A mixture of 6.45 g (30.0 mmol) of 4-(bromomethyl)benzoic acid, 24.1 g (100 mmol) of *n*-hexadecylamine, and 200 mL of THF was stirred for 2 h at ambient temperature and then for 2 h at reflux. The mixture was chilled and filtered, and the resulting solid was partitioned between $CHCl_3$ and dilute aqueous NaOH. The aqueous layer was separated, acidified with concentrated HCl, and filtered. The solid was crystallized from 95% EtOH to yield 7.34 g (59%) of **83** as a white solid, mp 247–251 °C.

4-(Dihexadecylamino)-1-naphthoic Acid Hydrochloride (84). A mixture of 3.80 g (90.0 mmol) of sodium hydride (57% in mineral oil), 15.1 g (90.0 mmol) of 4-amino-1-naphthonitrile, 31.5 mL (31.5 g, 90.0 mmol) of 1-bromohexadecane, and 150 mL of DMF was stirred and heated on a steam bath for 6 h, diluted with 250 mL of H_2O, chilled, and filtered. The resulting solid was chromatographed on silica gel eluting with 1:1 benzene/hexane to yield first 2.90 g (10%) of 4-(dihexadecylamino)-1-naphthonitrile as a yellow oil, which was converted to **84** without further purification. Eluted second was a yellow solid, which was recrystalized from 1:19 benzene/EtOH to yield 11.0 g (52%) of 4-(hexadecylamino)-1-naphthonitrile (**F**), mp 91–93 °C.

A mixture of 2.70 g (4.38 mmol) of the crude 4-(dihexadecylamino)-1-naphthonitrile, 5.00 g (98.2 mmol) of KOH, and 25 mL of ethylene glycol was stirred at reflux for 2 days and then diluted with H_2O, acidified with 7.40 mL of concentrated HCl, chilled, and filtered. A solution of the resulting solid in CH_2Cl_2 was treated with anhydrous HCl and then evaporated. The residue was crystallized from acetone to yield 1.75 g (60%) of **84** as a white solid, mp 145–146 °C.

Ethyl 2-(Hexadecylamino)pyrimidine-5-carboxylate (87). A solution of 2.00 g (10.1 mmol) of ethyl 2-(methylthio)pyrimidine-5-carboxylate and 3.00 g (12.4 mmol) of *n*-hexadecylamine in 25 mL of hexamethylphosphoramide was stirred at 110 °C for 10 h under nitrogen, cooled, diluted with 50 mL of H_2O, and filtered. Recrystallization from hexane yielded 1.00 g (25%) of **87** as a white solid, mp 87–88 °C.

3-Hydroxypropyl 4-(Hexadecylamino)benzoate (96). A mixture of 7.22 g (20.0 mmol) of 4-(hexadecylamino)benzoid acid,[1] 6.40 g (90.1 mmol) of 1,3-propanediol, 5.34 g (28.0 mmol) of *p*-toluenesulfonic acid hydrate, and 200 mL of 1,2-dimethoxyethane was stirred at reflux for 18 h, allowed to cool, and diluted with 180 mL of H_2O. The precipitate that formed was collected by filtration and purified by chromatography on alumina (activity grade III) eluting with Et_2O to yield 2.30 g (28%) of **96** as a white solid, mp 86–87 °C.

2,3-Dimethoxypropyl 4-(Hexadecylamino)benzoate (109). A solution of 8.70 g (20.0 mmol) of 2,3-dihydropropyl 4-(hexadecylamino)benzoate (**104**) in 50 mL of hexamethylphosphoramide was added to a slurry of 1.80 g (40.0 mmol) of sodium hydride (53% in mineral oil, previously washed with hexane). The resulting green solution was treated with 5.70 g (40.0 mmol) of methyl iodide, stirred at ambient temperature for 2 h, diluted with H_2O, and extracted with EtOAc. The dried extract was evaporated, and the residue was recrystallized from MeOH to yield 0.95 g (10%) of **109** as a white solid, mp 75–78 °C.

2-Acetoxy-3-hydroxypropyl 4-(Hexadecylamino)benzoate (110). A solution of 8.35 g (20.0 mmol) of 2,3-epoxypropyl 4-(hexadecylamino)benzoate (**115**) in 7.0 mL of HOAc was heated under nitrogen at 110 °C for 1 h, allowed to cool, diluted with H_2O, and filtered. The solid was recrystallized from hexane–CH_2Cl_2 to yield 7.00 g (73%) of **110** as a white solid, mp 64–67 °C.

2-Acetoxy-3-[4-(hexadecylamino)benzoyl]propyl 4-(Hexadecylamino)benzoate (112) and 2,3-Diacetoxypropyl 4-(Hexadecylamino)benzoate (111). A solution of 10.9 g (25.0 mmol) of 2,3-dihydroxypropyl 4-(hexadecylamino)benzoate (**104**) in 75 mL of hexamethylphosphoramide was added to a mixture of 2.32 g (55.0 mmol) of sodium hydride (57% in mineral oil, washed previously with hexane) in 5 mL of hexamethylphosphoramide, and the mixture was stirred for 1 h at ambient temperature and then treated with 4.75 mL (50.0 mmol) of acetic anhydride. The mixture was stirred for 2 h at ambient temperature, diluted with H_2O, and extracted with EtOAc. The dried extracted was evaporated, and the residual solid was chromatographed on silica gel eluting with hexane–EtOAc. The first component eluted was recrystallized from CH_2Cl_2 to yield 1.78 g (17%) of **112** as a white solid, mp 82–84 °C. Recrystallization of the second component from MeOH–CH_2Cl_2 yielded 4.45 g (34%) of **111** as a white solid, mp 65–67 °C.

3-(Nicotinoyloxy)-2-hydroxypropyl 4-(Hexadecylamino)benzoate (114). A mixture of 6.25 g (15.0 mmol) of 2,3-epoxypropyl 4-(hexadecylamino)benzoate (**115**) and 2.21 g (90.0 mmol) of nicotinic acid in 180 mL of H_2O was stirred at reflux for 2 h and then filtered while hot. The solid was stirred with boiling CH_2Cl_2 and filtered to yield 5.10 g (62%) of **114** as a white solid, mp 220 °C dec.

4-Carboxyphenyl 4-(Hexadecylamino)benzoate (122). A solution of 10.0 g (18.6 mmol) of *tert*-butyl 4-[[4-(hexadecylamino)benzoyl]oxybenzoate (**121**) in 50 mL of trifluoroacetic acid was stirred at ambient temperature for 6 h, poured into H_2O, brought to pH 7 with dilute aqueous KOH, and filtered. The solid was recrystallized from 1,2-dimethoxyethane to yield 8.50 g (95%) of **122** as a white solid, mp 229–230 °C.

Tetrahydro-2*H*-pyran-2-yl 4-(Hexadecylamino)benzoate (124). To a stirred solution of 10 mg of *p*-toluenesulfonic acid monohydrate in 45 mL of dihydropyran was added 4.00 g (11.1 mmol) of 4-(hexadecylamino)benzoic acid[1] during 10 min. The mixture was stirred for 30 min at ambient temperature, treated with an additional 10 mg of *p*-toluenesulfonic acid, and then stirred for an additional 20 h at ambient temperature. The resulting solution was treated with 10 mL of saturated aqueous K_2CO_3, stirred for 15 min, and extracted with Et_2O. The ether extract was dried and evaporated to yield 7.5 g of an oil. The oil was chromatographed with 300 g of alumina and eluted with 1:19 EtOAc–hexane. Recrystallization from acetone afforded 3.61 g (73%) of **124** as a white solid, mp 77–78 °C.

***N*-[4-(Hexadecylamino)benzoyl]acetamide (139).** A mixture of 3.00 g (71.2 mmol) of sodium hydride (57% in mineral oil, washed previously with hexane), 2.40 g (40.1 mmol) of acetamide, and 60 mL of THF was stirred at ambient temperature while a solution of 12.5 g (30.0 mmol) of 2,3-epoxypropyl 4-(hexadecylamino)benzoate (**115**) in 100 mL of THF was added. The mixture was stirred at reflux for 5 h, allowed to cool, diluted with 100 mL of H_2O, and filtered. The solid was recrystallized from acetonitrile to yield 5.92 g (49%) of **139** as a white solid, mp 130–132 °C.

***N*-Benzoyl-4-(hexadecylamino)benzamide (140).** A solution of 2.42 g (22.6 mmol) of benzamide in 5.0 mL of THF was added to a stirred suspension of 1.00 g (22.6 mmol) of sodium hydride (54% in mineral oil) in 5.0 mL of THF. The mixture was stirred for 30 min and then a solution of 0.90 g (1.89 mmol) of C in 3 mL of THF was added during 5 min. The mixture was stirred at ambient temperature for 1 h, poured into H_2O, and extracted with Et_2O. The extract was washed with saturated NaCl solution, dried, and evaporated. The residue was recrystallized from Et_2O and then from acetonitrile to yield 5.25 g (50%) of **140** as a pale yellow solid, mp 81–84 °C.

4-(Hexadecylamino)benzoic Acid Hydrazide (148). A mixture of 6.59 g (17.6 mmol) of methyl 4-(hexadecylamino)-benzoate,[1] 45 mL of 95% hydrazine, and 100 mL of diethylene glycol was stirred at 125 °C under nitrogen for 3 h and then allowed to cool. The precipitate was collected, washed with EtOH, dried, and recrystallized from EtOH to yield 5.95 g (90%) of **148** as a white solid, mp 154–156 °C.

Ethyl 4-[*N*-Ethyl-*N*-(hexadecyl)amino]benzoate (160). A solution of 2.34 g (6.00 mmol) of ethyl 4-(hexadecylamino)-benzoate[1] in 50 mL of CH_2Cl_2 was treated with 4.00 g (21.1 mmol) of triethyloxonium tetrafluoroborate, maintained at ambient temperature for 24 h, stirred at reflux for 4 h, and evaporated. The residue was treated with ice–water, rendered alkaline with 10 N NaOH, and extracted with Et_2O. The dried extract was evaporated, and the residual oil was purified by chromatography on silica gel (eluent benzene). Crystallization from EtOH yielded 2.15 g (85%) of **160** as a white solid, mp 29–30 °C.

Methyl 4-[*N*-(Carbethoxymethyl)-*N*-hexadecylamino]-benzoate (163). A mixture of 9.40 g (26.0 mmol) of methyl 4-(hexadecylamino)benzoate,[1] 8.40 g (50.0 mmol) of ethyl bromoacetate, 10.6 g (100 mmol) of powdered Na_2CO_3, and 50 mL of hexamethylphosphoramide was stirred at 130 °C for 18 h, allowed to cool, diluted with H_2O, and filtered. The solid was crystallized from acetonitrile and purified by chromatography on silica gel eluting with hexane–Et_2O. Recrystallization from hexane afforded 3.18 g (26%) of **163** as a white solid, mp 48–50 °C.

3-Acetoxy-2-hydroxypropyl 4-(*N*-Acetyl-*N*-hexadecylamino)benzoate (165), 2,3-Diacetoxypropyl 4-(*N*-Acetyl-*N*-hexadecylamino)benzoate (166), and 2,3-Dihydroxypropyl 4-(*N*-Acetyl-*N*-hexadecylamino)benzoate (167). A solution of 6.50 g (14.9 mmol) of 2,3-dihydroxypropyl 4-(hexadecylamino)benzoate (**104**) and 21.0 mL of acetic anhydride in 100 mL of $CHCl_3$ was heated at reflux for 4 h, allowed to cool, washed with H_2O, dried, and evaporated. The residual oil was chromatographed on silica gel eluting with hexane–EtOAc to yield 6.10 g (78%) of **165** as an oil, 1.09 g (13%) of **166** as an oil, and 0.55 mg (1%) of **167** as a white solid, mp 37–38 °C.

2,3-Dihydroxypropyl 4-(*N*-Hexadecanoyl-*N*-hexadecylamino)benzoate (168). A solution of 13.1 g (30.1 mmol) of 2,3-dihydroxypropyl 4-(hexadecylamino)benzoate (**104**) in 500 mL of 1,2-dimethoxyethane was added to a stirred mixture of 1.40 g (30.0 mmol) of sodium hydride (50% in mineral oil) and 100 mL of 1,2-dimethoxyethane. The resulting mixture was stirred for 30 min and then treatred with a solution of 8.30 g (30.1 mmol) of hexadecanoyl chloride in 100 mL of CH_2Cl_2. The mixture was stirred at reflux for 16 h, allowed to cool, and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and evaporated to yield an oil, which was purified by chromatography on silica gel eluting with CH_2Cl_2 to yield 2.10 g (22%) of **168** as a white solid, mp 56–60 °C.

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Registry No. **1**, 55986-43-1; **2**, 86410-10-8; **3**, 70517-53-2; **4**, 70517-53-2; **5**, 70517-54-3; **6**, 70517-56-5; **7**, 70517-57-6; **8**, 70517-55-4; **9**, 70517-60-1; **10**, 70517-59-8; **11**, 69001-50-9; **12**, 69001-54-3; **13**, 86410-12-0; **14**, 69001-53-2; **15**, 70517-78-1; **16**, 86410-13-1; **17**, 70517-63-4; **18**, 86410-14-2; **19**, 86410-15-3; **20**, 70517-73-6; **21**, 70517-77-0; **22**, 69001-52-1; **23**, 70517-52-1; **24**, 69876-87-5; **25**, 70523-60-3; **26**, 86410-16-4; **27**, 86410-17-5; **28**, 86410-18-6; **29**, 83752-83-4; **30**, 70523-61-4; **31**, 86410-19-7; **32**, 70523-66-9; **33**, 83753-10-0; **34**, 86410-20-0; **35**, 86410-21-1; **36**, 70517-64-5; **37**, 86410-22-2; **38**, 70517-91-8; **39**, 70517-90-7; **40**, 70517-84-9; **41**, 70517-89-4; **42**, 86410-23-3; **43**, 70517-99-6; **44**, 70517-87-2; **45**, 70517-85-0; **46**, 70518-03-5; **47**, 86410-24-4; **48**, 86410-25-5; **49**, 70517-96-3; **50**, 70517-98-5; **51**, 86410-26-6; **52**, 86410-27-7; **53**, 86410-28-8; **54**, 73792-09-3; **55**, 73792-07-1; **56**, 73792-10-6; **57**, 86410-29-9; **58**, 86410-30-2; **59**, 86410-31-3; **60**, 86410-32-4; **61**, 86410-33-5; **62**, 86410-34-6; **63**, 86410-35-7; **64**, 86410-36-8; **65**, 78319-24-1; **66**, 78319-26-3; **67**, 78319-27-4; **68**, 73792-13-9; **69**, 73792-14-0; **70**, 86410-37-9; **71**, 86410-38-0; **72**, 86410-39-1; **73**, 86410-40-4; **74**, 78319-18-3; **75**, 78319-19-4; **76**, 78319-20-7; **77**, 78319-21-8; **78**, 78319-22-9; **79**, 78319-23-0; **80**, 86410-41-5; **81**, 86410-42-6; **82**, 86410-43-7; **83**, 86410-44-8; **84**, 86410-45-9; **85**, 73781-92-7; **86**, 86410-46-0; **87**, 73781-89-2; **88**, 86410-47-1; **89**, 73782-01-1; **90**, 86410-48-2; **91**, 73781-75-6; **92**, 86410-49-3; **93**, 73781-81-4; **94**, 65536-37-0; **95**, 86410-50-6; **96**, 65536-18-7; **97**, 86410-51-7; **98**, 65536-22-3; **99**, 86410-52-8; **100**,

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

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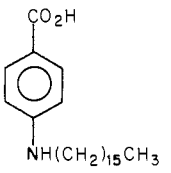
The synthesis of a series of analogues in which the alkyl group of cetaben is substituted with various functional groups or replaced entirely by a functionalized alkanoyl moiety is described. Also reported are the syntheses of branched-chain (alkylamino)benzoic acids in which branching is specifically 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.

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