of 4 as white plates: mp >300 °C; IR (KBr) identical with authentic 4.[29] Anal. ($C_9H_{15}NO_2\cdot{}^1/_2H_2O$) C, H, N.

3-*exo*-Aminobicyclo[3.2.1]octane-3-carboxylic Acid (5). Spirohydantoin 3 was treated as in 2 to give 5 (53% yield) as white plates: mp >300 °C; IR (KBr) identical with authentic 4.[29] Anal. ($C_9H_{15}NO_2\cdot 1.5H_2O$) H, N; C: calcd, 55.07; found, 55.55.

Transport Methods. Ehrlich ascites tumor cells were propagated in Swiss white mice, separated, and washed in Na^+-free media.[33] We synthesized ^{14}C-labeled BCH[2] and MeAIB[34] from $Na^{14}CN$ and the corresponding ketones at specific activities in the range 3.3 to 50 Ci/mol. These are extensively studied preparations that yield no evidence for radiological impurity under tests with Ehrlich cell suspensions varying widely in density.[35] Their uptake was observed at 37 °C during 0.5 and 1 min, respectively, in 5% cell suspensions, the first in Na^+-free, choline-containing Krebs–Ringer bicarbonate medium and the second in the same medium containing Na^+, in a 5% CO_2–O_2 atmosphere, yielding a pH of 7.4. Uptake was terminated by dilution with ice-cold medium, followed by 2-min centrifugation at 200*g*. Adhering medium was blotted from the cell pellet before weighing.[1] Radioactive disintegrations in the separated suspending medium and in a sulfosalicylic acid extract of the cells were then counted for ^{14}C by liquid scintillation spectrometry.[1,36] Extracellular water was measured by the quantity of sucrose, provided in the medium, that was retained by the cell pellet. The uptake of the two amino acids in Figure 1A and Table II is recorded in millimoles per kilogram of cell water per minute.

Hepatoma cells of an HTC cell line,[37] propagated and extensively studied in our laboratory, were grown in a monolayer under a humidified atmosphere of 5% CO_2/95% air in Medium 199 (from GIBCO) at pH 7.4, containing 26 mM $NaHCO_3$, 62.5 μg/mL of penicillin, 5.8 μg/mL of streptomycin, 31.2 μg/mL of gentamycin, and 5 to 8% fetal bovine serum (Flow Laboratories). Three or four days before the transport test, cells were seeded in 24-well tissue culture cluster trays (Costar).[38] Transport was initiated by simultaneously adding to all test wells 0.25 mL of Krebs–Ringer phosphate medium (pH 7.4 and 37 °C) containing labeled BCH and a range of concentrations of carrier BCH, of BCO (4), of its β-epimer (5), or of 4-amino-1-methylpiperidine-4-carboxylic acid (MPA). After 1 min the medium was quickly decanted, and the cells were washed with 2 mL of ice-cold Na^+-free, choline-containing Krebs–Ringer phosphate medium.[37] The cells were then extracted with 220 μL of 5% trichloroacetic acid for 1 h. Radioactivity was then assayed by placing 200 μL of the extract in 2 mL of the scintillant 3a70B (Research Products International) and counting decompositions in a liquid scintillation spectrometer. The cell residues were dissolved in 200 μL of 1 N NaOH, and protein was assayed by a modified Lowry method[39] in the presence of 1% sodium dodecyl sulfate, with bovine serum albumin as a standard. The uptake rates are expressed in Figure 1B as nanomoles of test amino acid per milligram of protein per minute.

Acknowledgment. The transport work received support from Grant HDO1233 to H.N.C. from the Institute for Child Health and Human Development, National Institutes of Health, United States Public Health Service.

Registry No. 1, 14252-05-2; 2, 86495-71-8; 3, 86495-72-9; 4, 81639-48-7; 5, 81639-49-8; 3-aminobicyclo[3.2.1]octane-3-carboxynitrile hydrochloride, 86456-40-8.

(33) Y. Inui and H. N. Christensen, *J. Gen. Physiol.*, **50**, 203 (1966).
(34) H. N. Christensen, *Adv. Enzymol.*, **49**, 41 (1979).
(35) H. N. Christensen, "Biiological Transport", 2nd ed., W. A. Benjamin, Reading, MA, 1975, pp 446–447.
(36) P. R. Pal and H. N. Christensen, *J. Biol. Chem.*, **236**, 894 (1961).
(37) E. B. Thompson, G. M. Tomkins, and J. F. Curran, *Proc. Natl. Acad. Sci. U.S.A.*, **56**, 296 (1966).
(38) G. C. Gazzola, V. Dall'Asta, R. Franchi-Gazzola, and M. F. White, *Anal. Biochem.*, 115, 368 (1981).
(39) C. S. Wang and R. L. Smith, *Anal. Biochem.*, **63**, 414 (1975).

Potential Antiatherosclerotic Agents. 2.[1] (Aralkylamino)- and (Alkylamino)benzoic Acid Analogues of Cetaben

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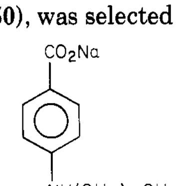
The syntheses of a series of (aralkylamino)- and (alkylamino)benzoic acids, as well as the corresponding esters and sodium salts, are described. The compounds were evaluated in vivo in rats for serum sterol and triglyceride lowering activity and in vitro for activity in inhibiting the principle cholesterol-esterifying enzyme of the arterial wall, fatty acyl-CoA:cholesterol acyltransferase (ACAT). Based on a combination of these two activities, cataben sodium (150) was selected for development as a hypolipidemic and potential antiatherosclerotic agent.

The syntheses of a group of alkoxybenzoic acids, as well as structure–activity relationships for their activity as hypolipidemic agents, have been reported;[2] however, the toxicity of these compounds has precluded their development as pharmaceuticals. As part of a continuing search for hypolipidemic and/or antiatherosclerotic agents of novel structure, a series of (alkylamino)- and (aralkylamino)benzoic acids, which were similar in lipophilicity to the alkoxybenzoic acids, was examined. As a class, these aminobenzoic acids were found to be less toxic than the related alkoxybenzoic acids, and one member of the series, cetaben sodium (150), was selected for further evaluation



150 (cetaben sodium)

as a hypolipidemic and potential antiatherosclerotic agent.[1,3–5] This paper begins a series of reports describing

(1) Part 1 of this series: J. D. Albright, S. A. Schaffer, and R. G. Shepherd, *J. Pharm. Sci.*, **68**, 936 (1979).
(2) V. G. DeVries, D. B. Moran, G. R. Allen, Jr., and S. J. Riggi, *J. Med. Chem.*, **19**, 946 (1976).
(3) W. Hollander, S. Prusty, S. Nagraj, B. Kirkpatrick, J. Paddock, and M. Columbo, *Atherosclerosis*, 31, 307 (1978).
(4) E. E. Largis, A. S, Katocs, Jr., L. W. Will, D. K. McClintock, and S. A. Schaffer, *J. Am. Oil Chem. Soc.*, **53**, 104A (1976).

0022-2623/83/1826-1378$01.50/0

syntheses and structure–activity relationships for the group of analogues from which cetaben was selected.

Approaches to the discovery of new agents for the treatment of atherosclerosis are commonly based on one or more aspects of the multifactorial pathogenesis of the disease. The approach used in this research relied on two well-known correlates of atheromatous lesion development: serum cholesterol concentration and the high level of cholesteryl esters found in atherosclerotic lesions.

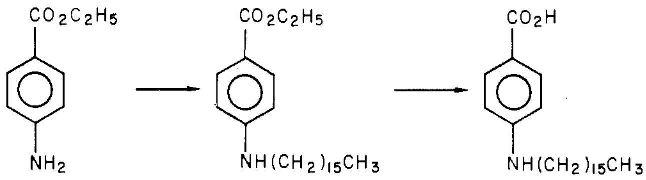
The correlation of elevated serum cholesterol with the development of atheromatous plaque has long been appreciated[6,7] and has prompted extensive research aimed at the discovery of hypocholesteremic agents.[8,9] A variety of compounds that exhibit hypolipidemic activity in rats have also been demonstrated to lower serum cholesterol in humans. The search for more potent and more efficacious agents has continued in the expectation that such compounds will retard or prevent the development of atheromatous lesions and thus be useful in the treatment of atherosclerosis. The compounds whose syntheses are described in this paper were tested in normal rats for serum sterol and triglyceride lowering activity.

A second aspect of the pathogenesis of atherosclerosis that has received more recent attention is the manner in which cholesterol is stored in the atheromatous lesion.[10] It has been demonstrated[11] that atherosclerotic lesions in man contain a greater proportion of esterified as opposed to unesterified cholesterol than the surrounding undiseased arterial wall. The intracellular esterification of cholesterol with fatty acids is catalyzed by the enzyme fatty acyl-CoA:cholesterol acyltransferase (ACAT). Increased activity of this enzyme is associated with the accumulation and storage of cholesteryl esters in the arterial wall.[12] In addition, cholesteryl esters are removed from cells at a slower rate than unesterified cholesterol.[13,14] Thus, compounds that inhibit the ACAT enzyme would be expected to decrease the accumulation of cholesteryl esters in the arterial wall and therefore offer potential as antiatherosclerotic agents. The compounds described in this paper were also evaluated in vitro as ACAT inhibitors.

The scope of analogue syntheses described in this paper includes (aralkylamino)- and (alkylamino)benzoic acids, as well as the corresponding esters and sodium salts. Subsequent papers will describe analogues in which the carboxy group has been replaced or the alkylamino moiety modified. Aralkyl and heteroarylalkyl compounds are shown in Tables I–IV. Based on the persistent activity of analogues containing the 3-(4-chlorophenyl)propylamino moiety, additional compounds containing this group were prepared, and these are shown in Tables V and VI. The homologous series of (alkylamino)benzoic acids and the corresponding esters and sodium salts are shown in Table VII.

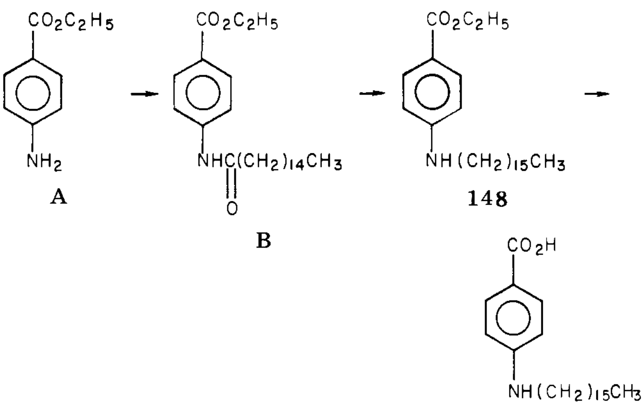
Chemistry. The aminobenzoic acids whose syntheses are described below were obtained by three general

Scheme I



A 148 149

Scheme II

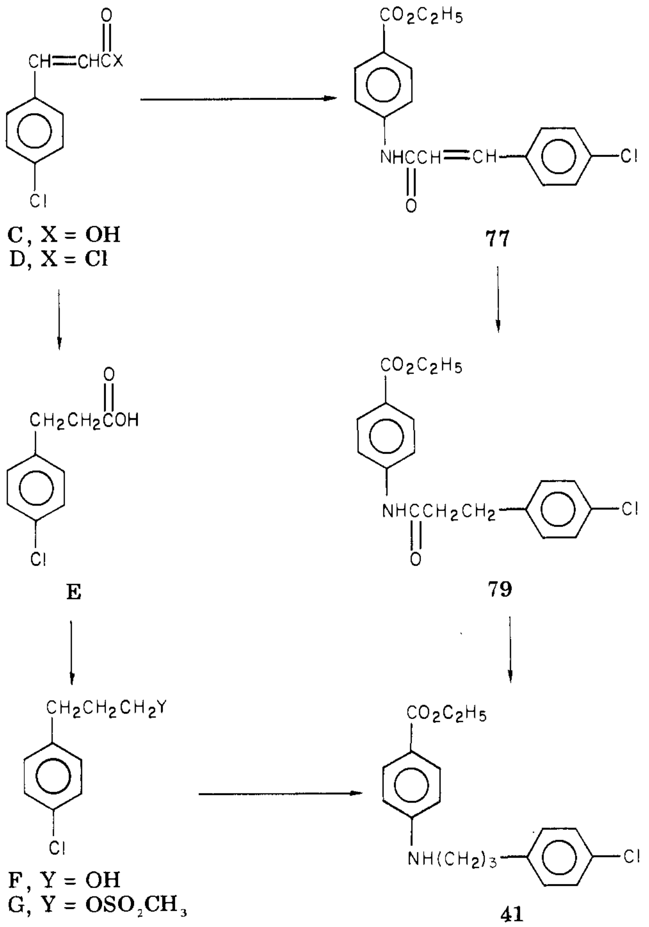


methods: direct alkylation, acylation followed by reduction, and reductive alkylation. In the first method, alkylations of aminobenzoate esters with alkyl or aralkyl halides or alternatively with methanesulfonate esters, followed by alkaline hydrolysis of the resulting benzoate ester, afforded the desired aminobenzoic acids. This method is illustrated in Scheme I for the synthesis of cetaben (**149**) via the corresponding ethyl ester (**148**). Reaction conditions that afforded the fastest rate and fewest byproducts employed temperatures of approximately 125 °C and hexamethylphosphoramide as the solvent. Under these conditions, only a trace amount of dialkylation, i.e., the formation of ethyl 4-(di-*n*-hexadecylamino)benzoate in the case of **148**, was observed. Solvents such as *N,N*-dimethylformamide and *N,N*-dimethylacetamide were useful only at temperatures of less than 100 °C (with slower rates of reaction) due to the formation of additional byproducts, which included ethyl 4-(*N*-formyl-*N*-*n*-hexadecylamino)benzoate and ethyl 4-(*N*-acetyl-*N*-*n*-hexadecylamino)benzoate, respectively, as well as *N,N*-dimethyl-4-(*n*-hexadecylamino)benzamide. Although inorganic bases, such as powdered potassium carbonate, were used in certain reactions as acid acceptors, superior yields were usually obtained with an excess of the aminobenzoate ester serving as the base.

The second general method for the synthesis of (alkylamino)benzoic acids involves acylation of aminobenzoate esters with acyl halides, followed by selective reduction of the amide carbonyl group of the resulting amido ester. Highly selective reductions were accomplished by using diborane.[15] Subsequent alkaline hydrolysis afforded the desired benzoic acids. This method is illustrated for the synthesis of cetaben (**149**) via amido ester B in Scheme II. Acylation generally proceeded readily at ambient temperature or below in ether or methylene chloride with trimethylamine as an acid acceptor (avoiding the use of either hot hexamethylphosphoramide or a 2nd equiv of the aminobenzoate). This three-step procedure was used for the preparation of several compounds shown in Tables

(5) A. S, Katocs, Jr., and S. A. Schaffer, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 36, 1160 (1977); *Artery*, 11(3), 192 (1982).
(6) J. Davignon, *Arch. Surg.*, 113, 28 (1978).
(7) C. J. Glueck and P. O. Kwiterovich, Jr., *Arch. Surg.*, 113, 35 (1978).
(8) R. Paoletti, R. Fumagalli, A. Poli, and C. R. Sirtori, *Atherosclerosis Rev.*, 7, 213 (1980).
(9) W. L. Bencze, *Adv. Exp. Med. Biol.*, 109, 77 (1978).
(10) S. R. Bates, *Circ. Res.*, 45(6), 821 (1979).
(11) C. M. W. Adams, O. B. Bayliss, R. W. R. Baker, Y. H. Abdulla, and C. J. Hunter-Craig, *Atherosclerosis*, 13, 429 (1974).
(12) S. Hashimoto and S. Dayton, *Atherosclerosis*, 28, 447 (1977).
(13) G. Bondjers and S. Bjorkerud, *Atherosclerosis*, 15, 273 (1972).
(14) G. Bondjers and S. Bjorkerud, *Atherosclerosis*, 22, 379 (1975).
(15) H. C. Brown and P. Heim, *J. Org. Chem.*, 38, 912 (1973).

Scheme III



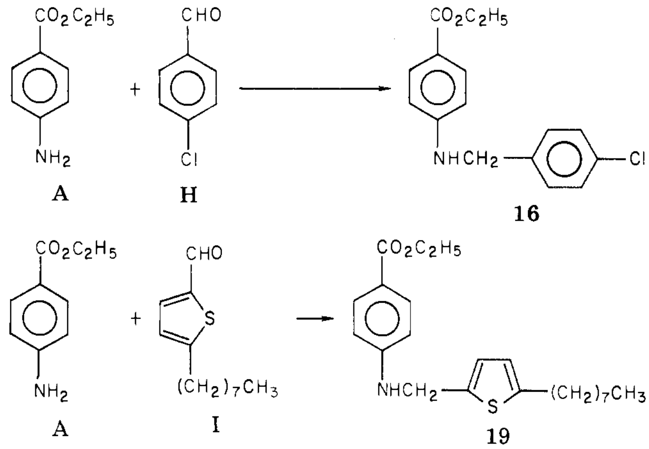
I-VII. The overall yield of ester **148** from ethyl 4-aminobenzoate (A) was 60% by the first method and 79% by the second.

A second comparison of these two methods is provided by the syntheses of ethyl 4-[[3-(4-chlorophenyl)propyl]-amino]benzoate (**41**) shown in Scheme III. Catalytic hydrogenation of cinnamic acid C, followed by diborane reduction of the resulting propionic acid (E), afforded alcohol F in 81% overall yield. Although F could be obtained in a single step by lithium aluminum hydride reduction of C, the yield was only 39%. Conversion of F to the corresponding methanesulfonate ester (G), followed by alkylation of ethyl 4-aminobenzoate, yielded ester **41** in 67% overall yield from C. The alternative sequence of reactions, acylation of ethyl 4-aminobenzoate with acid chloride D, followed by catalytic hydrogenation of **77** and diborane reduction of **79**, afforded ester **41** in 55% overall yield.

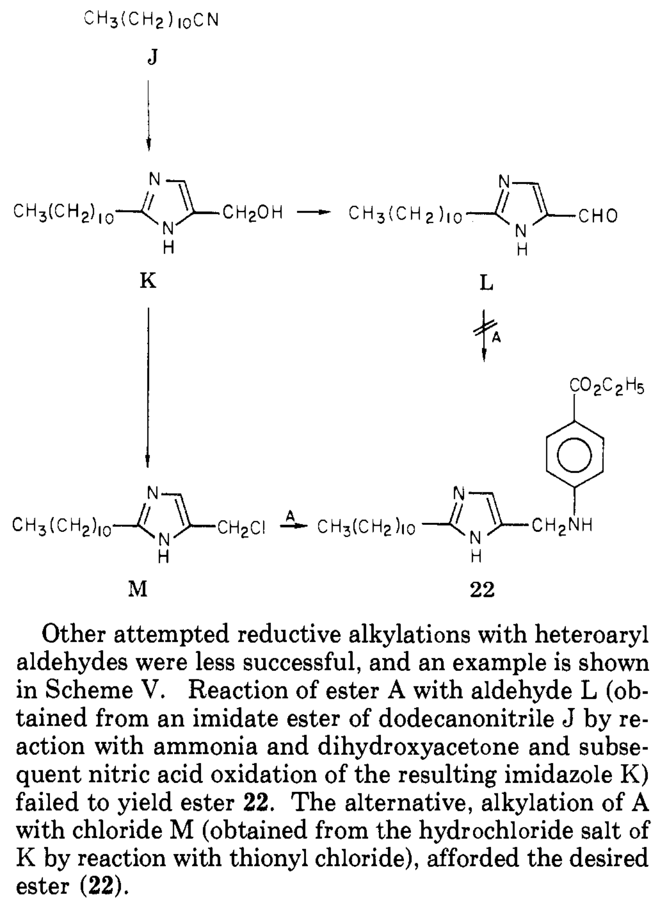
A third method potentially useful for the synthesis of (alkylamino)benzoic acids involves reductive alkylation of aminobenzoate esters with aldehydes[16] or carboxylic acids.[17] Attempts to reductively alkylate ester A either with aliphatic aldehydes or alkanoic acids afforded very low yields. In contrast, reductive alkylation of A either with aryl aldehydes, such as H, or heteroaryl aldehydes, such as I, in the presence of sodium borohydride, afforded excellent yields of esters **16** and **19**, respectively, as shown in Scheme IV. Aldehyde I, required for the latter synthesis, was obtained by formylation of 2-*n*-octylthiophene.[18]

(16) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(17) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).

Scheme IV



Scheme V

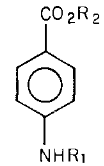


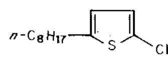
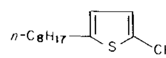
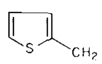
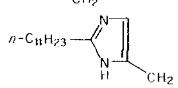
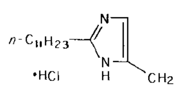
Other attempted reductive alkylations with heteroaryl aldehydes were less successful, and an example is shown in Scheme V. Reaction of ester A with aldehyde L (obtained from an imidate ester of dodecanonitrile J by reaction with ammonia and dihydroxyacetone and subsequent nitric acid oxidation of the resulting imidazole K) failed to yield ester **22**. The alternative, alkylation of A with chloride M (obtained from the hydrochloride salt of K by reaction with thionyl chloride), afforded the desired ester (**22**).

Although certain of the alkyl halide, aralkyl halide, heteroalkyl halide, acyl halide, alcohol, aldehyde, and carboxylic acid intermediates required for these three general synthetic methods were described in the literature or commercially available, many were newly synthesized, and these syntheses are described below. Aralkyl alcohols, such as 11-phenylundecanol, were obtained by diborane reduction of the corresponding carboxylic acids.[19,20] Some arylpropanols were obtained by lithium aluminum hydride reductions[21] of the corresponding cinnamic acids or, al-

(18) V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1667 (1962).
(19) H. C. Brown and B. C. SubbaRao, *J. Am. Chem. Soc.*, **82**, 681 (1960).
(20) H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970).
(21) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

Table I. 4-[(Arylmethyl)amino]benzoic Acids

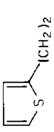
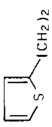
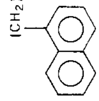
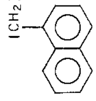


no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet: 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet: 0.10	0.03	0.01	ACAT,[c] inhibn, %
1	$C_6H_5CH_2$ [i]	Et	A	60	EtOH	96-97	$C_{16}H_{17}NO_2$	86*	90*[d]	108[e]	78	88***	97[e]	45***
2	$C_6H_5CH_2$	H	B	90	EtOH	167-169	$C_{14}H_{13}NO_2$	87**	86*[d]	101[e]	65*	62***[d]	92[e]	2
3	4-$(CH_3O)C_6H_4CH_2$	Et	A	68	EtOH	128-130	$C_{17}H_{19}NO_3$	94	92[d]	95[f]	48***	62**[d]	73*[f]	49***
4	4-$(CH_3O)C_6H_4CH_2$ [j]	H	B	88	EtOH	209-210	$C_{15}H_{15}NO_3$	94	95[d]	91[f]	60**	76[d]	69**[f]	5
5	4-$(C_6H_5)C_6H_4CH_2$	Et	A	39	benzene-acetone	164-167	$C_{22}H_{21}NO_2$	94	94*[d]	102[f]	52**	76[d]	74[f]	19*
6	4-$(C_6H_5)C_6H_4CH_2$	H	B	67	EtOH-benzene	234-237	$C_{20}H_{17}NO_2$	90	98[d]	98[f]	42***	70*[d]	61**[f]	7
7	4-$(C_6H_5CH_2O)C_6H_4CH_2$	Et	A	80	EtOH	146-148	$C_{23}H_{23}NO_3$	91*	100[d]	105[e]	92	85*[d]	97[e]	45***
8	4-$(C_6H_5CH_2O)C_6H_4CH_2$	H	B	80	HOAc	206-208	$C_{21}H_{19}NO_3$	97	98[d]	93[f]	89*	85*[d]	91[d]	16
9	4-$(n\text{-}C_{10}H_{21})C_6H_4CH_2$	Et	A	58	EtOH-H_2O	87-90	$C_{26}H_{37}NO_2$	99	95[d]	90[f]	94	69***[d]	82[f]	19*
10	4-$(n\text{-}C_{10}H_{21})C_6H_4CH_2$	H	B	77	EtOH	135-136	$C_{24}H_{33}NO_2$	78*	88*[d]	99[e]	114	113[d]	100[e]	51***
11	4-$(n\text{-}C_{10}H_{21}O)C_6H_4CH_2$	H	A, B	40	EtOH	131-134,[g] 159-161	$C_{24}H_{33}NO_3$	82***	90*[d]	97[f]	37**	51*[d]	54*[f]	35**
12	4-$(n\text{-}C_{13}H_{27}O)C_6H_4CH_2$	Et	A	45	EtOH-benzene	100-105	$C_{29}H_{43}NO_3$ [k]							
13	4-$(n\text{-}C_{13}H_{27}O)C_6H_4CH_2$	H	B	23	acetone	110-112,[g] 155-160	$C_{27}H_{39}NO_3$	81	100[d]	100[e]	56***	65***[d]	62***[e]	36***
14	4-$(n\text{-}C_7H_{15}O)C_6H_4CH_2$	Et	A	47	EtOH	111-113	$C_{23}H_{31}NO_3$	90	86**[d]	100[e]	80*	76*[d]	88[e]	
15	4-$(n\text{-}C_7H_{15}O)C_6H_4CH_2$	H	B	85	EtOH	148-152	$C_{21}H_{27}NO_3$	84***	84***[d]	100[e]	72*	70*[d]	95[e]	24*
16	4-$ClC_6H_4CH_2$	Et	F	86	acetonitrile	147-148	$C_{16}H_{16}ClNO_2$	84*	86	94	50**	53**	78	33*
17	4-$ClC_6H_4CH_2$	H	B	81	HOAc-H_2O, acetonitrile	216-217	$C_{14}H_{12}ClNO_2$	71*	80*	89	52*	72	98	13
18	4-$ClC_6H_4CH_2$	Na	C	98	MeOH	>400	$C_{14}H_{11}ClNO_2Na$	83	90**	91	67*	61*	70	15
19		Et	F	75	EtOH	83-86	$C_{22}H_{31}NO_2S$	82	90	97	61*	59*	100	32*
20		H	B	41	cyclohexane	107-108	$C_{20}H_{27}NO_2S$	72**	76**	85	70	70	82	15
21		Et	*m*	1	cyclohexane	104-107	$C_{14}H_{15}NO_2S$		98	104		78	94	44*
22		Et	*h*	22	MeOH, $CHCl_3$	103-107	$C_{24}H_{37}N_3O_2$	100			83			59***
23		H	B	81	MeOH-H_2O	188-192	$C_{22}H_{34}ClN_3O_2$ [l]	100	93	99	70*	71*	79	19

[a] Unless otherwise indicated by footnote, microanalytical values for C, H, N, S, Br, F, and Cl are 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] The testing dose was 0.05% of diet. [e] The testing dose was 0.017% of diet. [f] The testing dose was 0.025% of diet. [g] Some of the 4-aminobenzoic acid derivatives, particularly those with long side chains, are mesomorphic, and double melting points were observed. [h] Where no general method is shown, the preparation of the specific compound is found in the Experimental Section. [i] J. H. Billman, J. W. McDowell, *J. Org. Chem.*, 26, 1437 (1961): mp 96.5-97 °C. [j] B. T. Hayes, T. S. Stevens, *J. Chem. Soc.* C, 1088 (1970): mp 204-205 °C. [k] Calcd: C, 76.78; H, 7.55; N, 3.09. Found: C, 78.82; H, 10.14; N, 2.11. [l] Calcd: Cl, 8.06. Found: Cl, 7.58. [m] The compound was isolated as a byproduct in the synthesis of 115 and 116.

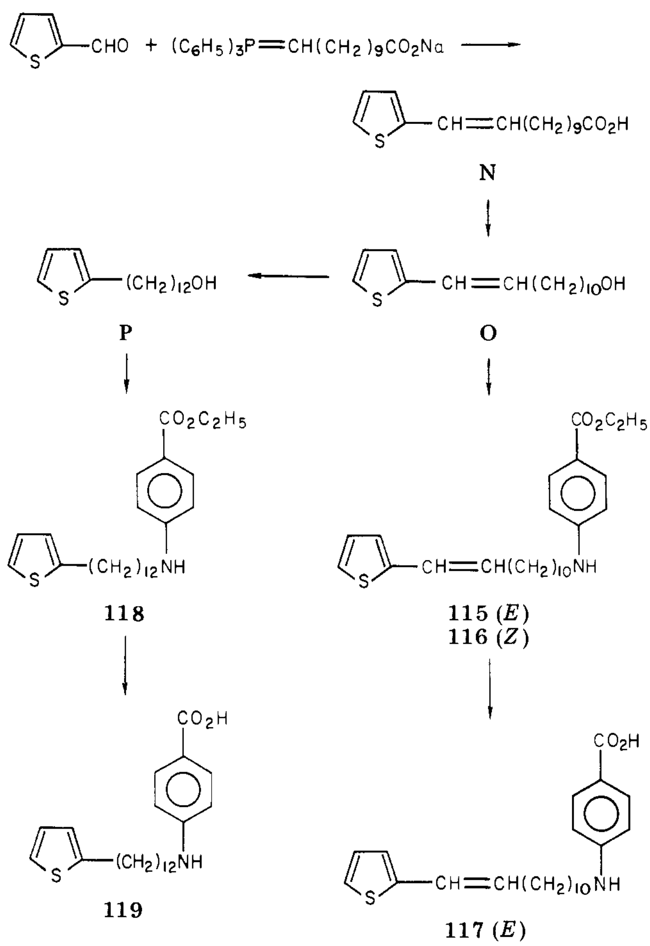
Table II. 4-[(Arylethyl)amino]benzoic Acids

R_1NH–C_6H_4–CO_2R_2

no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet: 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet: 0.10	0.03	0.01	ACAT,[c] % inhibn
24	$C_6H_5(CH_2)_2$	H	A, B	37	hexane-EtOH	124-126	$C_{15}H_{15}NO_2$	88**	87[d]	90[f]	48**	70[d]	64*[f]	9
25	$4\text{-}FC_6H_4(CH_2)_2$	H	A, B	45	EtOH	161-163	$C_{15}H_{14}FNO_2$	91	98[d]	104[f]	54***	50**[d]	72**[f]	0
26	$4\text{-}(C_6H_5CH_2O)C_6H_4(CH_2)_2$	Et	A	36	EtOH	95-97	$C_{24}H_{25}NO_3$							
27	$4\text{-}(C_6H_5CH_2O)C_6H_4(CH_2)_2$	H	B	67	HOAc	187-189	$C_{22}H_{21}NO_3$[i]	98	103[d]	100[f]	84	81[d]	70*[f]	18
28		Et	A	24	hexane-CCl_4	93-95	$C_{15}H_{17}NO_2S$	86***	90[d]	86**[e]	69	94[d]	87[e]	49***
29		H	B	42	EtOH	161-163	$C_{13}H_{13}NO_2S$	88	81[d]	74[e]	103	97[d]	121[e]	5
30		Et	A	63	Et_2O-EtOH	104-105	$C_{21}H_{21}NO_2$[j]	94	103[d]	98[e]	73*	80[d]	112[e]	9
31		H	B		acetone	168-169	$C_{19}H_{17}NO_2$	93	108[d]	108[e]	63*	67**[d]	89[e]	
32	$4\text{-}ClC_6H_4(CH_2)_2$	Et	A	43	methylcyclohexane	74-76	$C_{17}H_{18}ClNO_2$	97	113	115	60***	90	70**	37**
33	$4\text{-}ClC_6H_4(CH_2)_2$	H	B	46	THF-acetonitrile	182-184	$C_{15}H_{14}ClNO_2$	105	90	106	67*	91	114	6

[a-h] See footnotes *a* to *h* in Table I. [i] Calcd: C, 76.06. Found: C, 75.30. [j] Calcd: C, 78.97. Found: C, 78.29.

Scheme VI

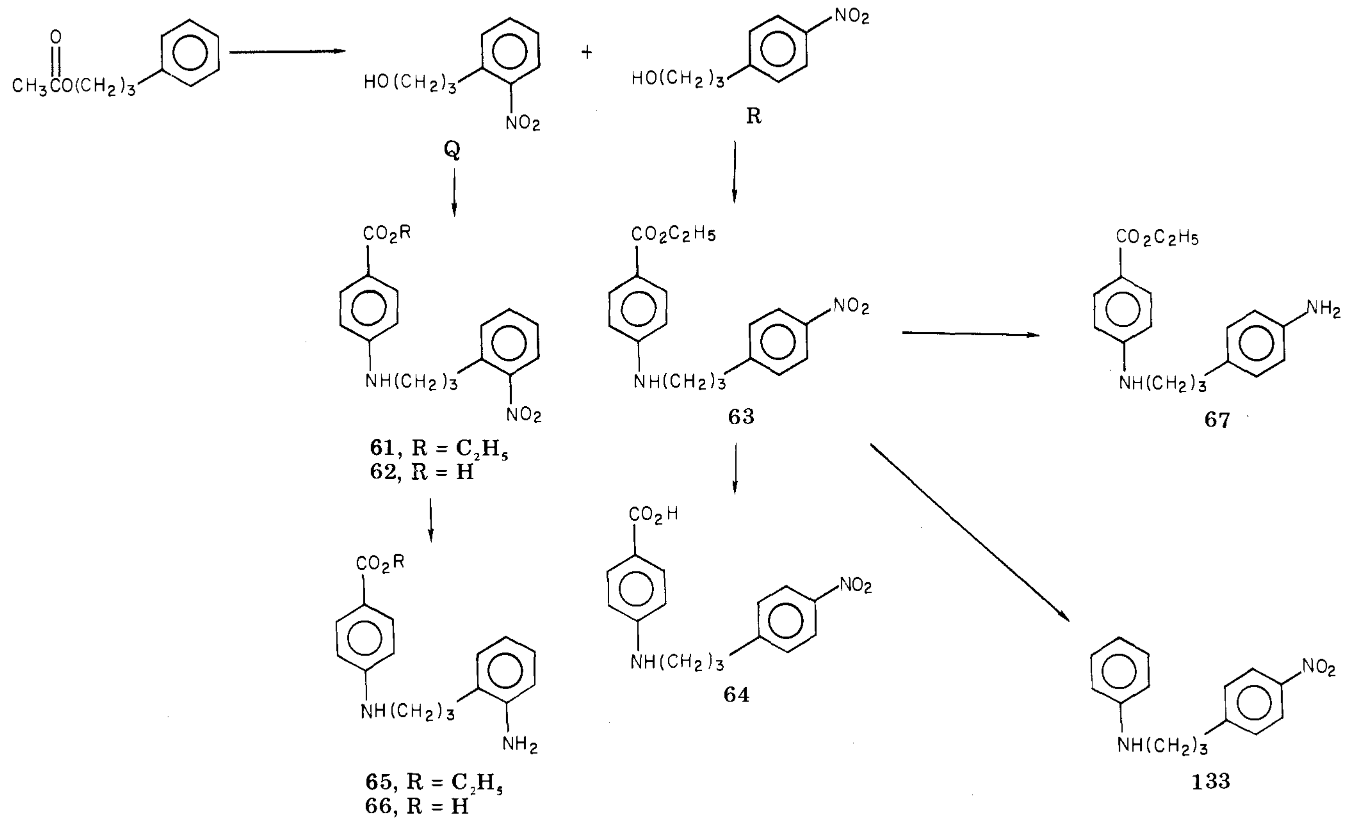


ternatively, in two steps using catalytic hydrogenation, followed by diborane reduction. The latter procedure commonly afforded higher yields. The yield in the preparation of 4-chlorocinnamyl alcohol by reduction of methyl 4-chlorocinnamate[22,23] was substantially improved by conducting the reaction at −10 °C rather than at reflux. The methanesulfonate ester of this alcohol, used to prepare **75**, was too reactive to survive an aqueous workup, so a nonaqueous procedure was developed. 4-*n*-Decylbenzyl alcohol was obtained by Friedel-Crafts acylation[24,25] of *n*-decylbenzene with oxalyl chloride, followed by diborane reduction of the resulting benzoic acid. 4-Alkoxybenzyl alcohols required for the synthesis of **11–15** were prepared by alkylations[26] of 4-hydroxybenzoic acid with alkyl bromides, followed by diborane reductions of the resulting alkoxybenzoic acids.

The synthesis of some of the analogues shown in Tables I–VI required the design of reaction sequences specific for the individual compound desired. Examples of these syntheses are shown in Schemes VI–IX. Lithium aluminum hydride reduction of carboxylic acid N, prepared as shown in Scheme VI by a Wittig reaction of 2-thiophenecarboxaldehyde, yielded alcohol O as a mixture of *E* and *Z* isomers, which were separated by fractional crystallization. The individual isomers were converted via

(22) A. Brossi and O. Schneider, German Patent 1 109 700 (1961); *Chem. Abstr.*, **56**, 12802*f* (1962).
(23) V. M. Micovic and M. L. Mihailoic, *J. Org. Chem.*, **18**, 1190 (1953).
(24) L. Friedman and A. Shami, *J. Am. Chem. Soc.*, **96**, 7101 (1974).
(25) M. Tamura and J. Kochi, *Synthesis*, **2**, 303 (1971).
(26) C. A. Young, R. R. Vogt, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **58**, 1806 (1936).

Scheme VII



the corresponding methanesulfonate esters to **115** and **116**. Alkaline hydrolysis of the former afforded acid **117**. Catalytic hydrogenation of O using palladium on barium sulfate yielded alcohol P, which was converted in a similar series of reactions to ester **118** and acid **119**.

Nitration of 3-phenylpropyl acetate as shown in Scheme VII yielded an equal mixture of ortho and para isomers, which was hydrolyzed, and the resulting mixture of alcohols[27] was separated by spinning-band distillation. The individual alcohols were converted via methanesulfonate esters to **61** and **63**. Alkaline hydrolysis of **61** afforded **62**; however, a similar hydrolysis of **63** yielded only polymeric material. Hydrolysis of **63** to the benzoic acid **64** was accomplished under acidic conditions; however, the product was contaminated with a significant quantity of the decarboxylated byproduct **133**. Catalytic hydrogenation of ester **61** yielded ester **65**, which was readily saponified to acid **66**. Although ester **67** was obtained in a similar manner from **63**, all attempts to prepare the corresponding benzoic acid yielded inseparable mixtures of products.

A series of analogues was prepared from keto ester S by using the reaction sequences shown in Scheme VIII. The starting keto ester (S), obtained by Friedel–Crafts acylation of chlorobenzene with ethyladipoyl chloride,[28] was hydrolyzed to the corresponding keto acid, which, in turn, was converted to the corresponding keto acid chloride. Acylation of ethyl 4-aminobenzoate with this acid chloride afforded amide **91** and, after alkaline hydrolysis, **92**. Diborane reduction of **91** yielded hydroxy ester V, which was hydrolyzed to yield benzoic acid **93**. Oxidation of V using Collins reagent[29] afforded benzoate **94**. Clemmenson-Martin reduction[30] of keto ester S yielded, in addition to the expected acid U, the unsaturated acid T, which comprised approximately 50% of the reduction product. Catalytic hydrogenation of this mixture was required to obtain pure acid U for the synthesis of **95–98** as shown.

The use of a nucleophilic displacement in the synthesis of ester **113** is illustrated in Scheme IX. Bromo ester X was prepared by diborane reduction of amide W (itself obtained by acylation of ethyl 4-aminobenzoate with 11-bromoundecanoyl chloride) and reacted with the anion of imidazole to yield **113**.

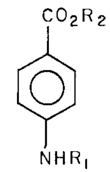
Biology. The analogues whose syntheses are described above were screened for two types of biological activity, and the results are shown in Tables I–VII. The hypolipidemic activity of the compounds, i.e., their ability to lower serum sterols and/or triglycerides, was measured in normal rats. In addition, the compounds were tested in vitro to measure their ability to inhibit the enzyme fatty acyl-CoA:cholesterol acyltransferase (ACAT).

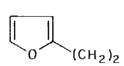
Among the 4-[(arylmethyl)amino]benzoic acid analogues shown in Table I, **17** exhibited the greatest hypocholesteremic activity. Since the propyl analogue (**42**) also showed hypocholesteremic activity, the lack of activity of the ethyl analogue (**33**) is surprising; however, very few of the 4-[(2-arylethyl)amino]benzoic acid analogues of Table II showed significant hypolipedemic activity. In contrast, the next higher homologue (**42**) was active as a hypolipidemic agent, and, in fact, the activity of other derivatives containing the 3-(4-chlorophenyl)propyl moiety (**41** and **43**) prompted the synthesis of additional analogues of this type (Tables V and VI). Although many of these were less active, the phenylacetic acid analogue (**130**) had the highest hypolipidemic activity of all the compounds in Tables I–VI.

Of the various heteroaryl-containing analogues, those containing the thiophene moiety most consistantly ex-

(27) L. L. Serveena, N. N. Shorygina, B. J. Lobatin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2114 (1967).
(28) L. F. Fieser and H. L. Leffer, *J. Am. Chem. Soc.*, **70**, 3197 (1948).
(29) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972).
(30) E. L. Martin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 499.

Table III. 4-[(Arylpropyl)amino]benzoic Acids

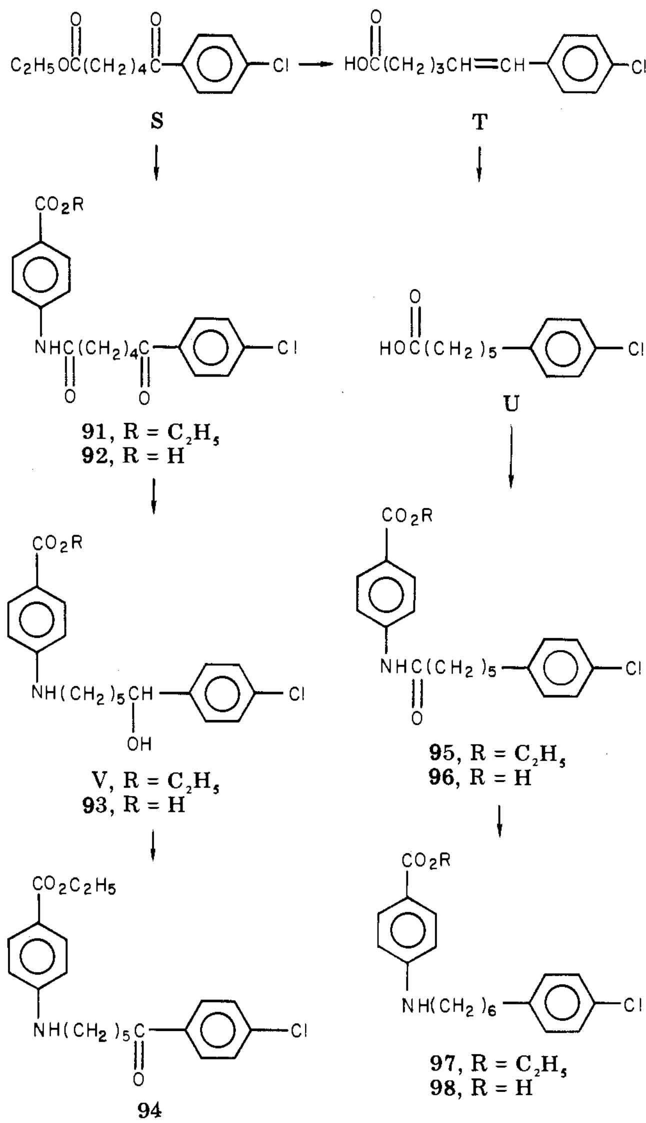


no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
34	$C_6H_5(CH_2)_3$[i]	Et	A	84	EtOH	87-89	$C_{18}H_{21}NO_2$	79**	77***[d]	94[f]	57**	56**[d]	77**[f]	61***
35	$C_6H_5(CH_2)_3$	H	B	78	EtOH	162-163	$C_{16}H_{17}NO_2$	81*	75*[d]	81*[f]	68*	51***[d]	64***[f]	18
36	$C_6H_5(CH_2)_3$	$CH_2CHOHCH_2OH$	*n*	35	CH_2Cl_2-hexane	84-86	$C_{19}H_{23}NO_4$	74*	85	90	49**	92	57*	21**
37	2-$CH_3OC_6H_4(CH_2)_3$	Et	A	80	EtOH	111-113	$C_{19}H_{23}NO_3$	107	107[d]	96[f]	74	66[d]	61*[f]	64***
38	2-$CH_3OC_6H_4(CH_2)_3$	H	B	83	EtOH	156-158	$C_{17}H_{19}NO_3$	110	100[d]	102[f]	72	87[d]	100[f]	0
39	4-$C_6H_5CH_2OC_6H_4(CH_2)_3$	Et	A	82	EtOH	114-116	$C_{25}H_{27}NO_3$	96	86[d]	86[f]	56***	46***[d]	56**[f]	50***
40	4-$C_6H_5CH_2OC_6H_4(CH_2)_3$	H	B	87	EtOH	171-172	$C_{23}H_{23}NO_3$	93	96[d]	90[f]	60***	69**[d]	67**[f]	2
41	4-$ClC_6H_4(CH_2)_3$	Et	D, E	81	acetone	122-124	$C_{18}H_{20}ClNO_2$	76*	89	90	52**	61**	64*	42***
42	4-$ClC_6H_4(CH_2)_3$	H	B	97	CH_2Cl_2	192-193	$C_{16}H_{16}ClNO_2$	72**	94	94	50**	54**	70	19
43	4-$ClC_6H_4(CH_2)_3$	$CH_2CHOHCH_2OH$	*h*	60	benzene, $CHCl_3$	121-123	$C_{19}H_{22}ClNO_4$	81*	88*	97	57**	63	78	17
44	4-$ClC_6H_4(CH_2)_3$	Na	C	88	EtOH-H_2O	360 dec	$C_{16}H_{15}ClNO_2Na$	84*	92	94	52**	60**	72	18*
45	3-$ClC_6H_4(CH_2)_3$	Et	A	78	cyclohexane	92-93	$C_{18}H_{20}ClNO_2$	80**	88	93	56*	65*	65*	79***
46	3-$ClC_6H_4(CH_2)_3$	H	B	86	toluene-EtOH	138-140	$C_{16}H_{16}ClNO_2$	85	90	82**	55*	48**	64*	29**
47	3,4-$Cl_2C_6H_3(CH_2)_3$	Et	A	66	EtOH	114-116	$C_{18}H_{19}Cl_2NO_2$	90	98	86	66*	98	90	43***
48	3,4-$Cl_2C_6H_3(CH_2)_3$	H	B	73	acetone, acetonitrile	174-176	$C_{16}H_{15}Cl_2NO_2$	73*	89	96	63*	70*	79	19**
49	2,6-$Cl_2C_6H_3(CH_2)_3$	Et	A	68	methylcyclohexane	97-99	$C_{18}H_{19}Cl_2NO_2$	92			64**			62***
50	2,6-$Cl_2C_6H_3(CH_2)_3$	H	B	95	acetonitrile, EtOH	180-182	$C_{16}H_{15}Cl_2NO_2$	106			82			21**
51	3-$BrC_6H_4(CH_2)_3$	Et	A	63	methylcyclohexane	95-97	$C_{18}H_{20}BrNO_2$[j]	94	84**	84	63	60*	74	50***
52	3-$BrC_6H_4(CH_2)_3$	H	B	81	toluene	139-141	$C_{16}H_{16}BrNO_2$	80**	91	92	60**	67*	63**	18*
53	4-$CH_3OC_6H_4(CH_2)_3$	Et	A	68	acetonitrile	114-115	$C_{19}H_{23}NO_3$	86*	90	97	60**	59**	82	54***
54	4-$CH_3OC_6H_4(CH_2)_3$	H	B	61	acetonitrile, EtOH	183-184 dec	$C_{17}H_{19}NO_3$	70**	86	89	91	89	82	38*
55	2-$FC_6H_4(CH_2)_3$	Et	A	61	acetonitrile, EtOH	103-105	$C_{18}H_{20}FNO_2$	97	100	104	92	116	106	37***
56	2-$FC_6H_4(CH_2)_3$	H	B	86	acetonitrile	160-162	$C_{16}H_{16}FNO_2$	81	85	87*	52*	55*	58*	58***
57	3-$FC_6H_4(CH_2)_3$	Et	A	61	EtOH	92-94	$C_{18}H_{20}FNO_2$	77*	88	91	37***	55**	78**	50***
58	3-$FC_6H_4(CH_2)_3$	H	B	84	toluene	143-145	$C_{16}H_{16}FNO_2$	90	97	94	35***	61**	53**	18**
59	4-$FC_6H_4(CH_2)_3$	Et	A	68	acetonitrile	118-120	$C_{18}H_{20}FNO_2$	81*	78*	83*	68	71	90	25*
60	4-$FC_6H_4(CH_2)_3$	H	B	85	acetonitrile	171-173 dec	$C_{16}H_{16}FNO_2$	82	82*	83	61*	90	94	16*
61	2-$(NO_2)C_6H_4(CH_2)_3$	Et	A	41	acetonitrile, EtOH	137-139	$C_{18}H_{20}N_2O_4$	89	96	93	68	83	70*	9
62	2-$(NO_2)C_6H_4(CH_2)_3$	H	B	84	acetonitrile	186-188	$C_{16}H_{16}N_2O_4$	83*	83	88	77*	103	84	2
63	4-$(NO_2)C_6H_4(CH_2)_3$	Et	A	65	acetonitrile	155-156	$C_{18}H_{20}N_2O_4$	85*	81*	85	73	84	81	19**
64	4-$(NO_2)C_6H_4(CH_2)_3$	H	*h*	45	THF-acetonitrile	228-230 dec	$C_{16}H_{16}N_2O_4$[k]	96	91	98	83	75	78	18**
65	2-$(NH_2)C_6H_4(CH_2)_3$	Et	*o*	87	*i*-PrOH	99, 104-105[g]	$C_{18}H_{22}N_2O_2$	98	96	103	69**	97	83	43***
66	2-$(NH_2)C_6H_4(CH_2)_3$	H	B	73	*i*-PrOH	160-162	$C_{16}H_{18}N_2O_2$	84	96	121	92	84	99	15*
67	4-$(NH_2)C_6H_4(CH_2)_3$	Et	*h*	70	*i*-PrOH	98-100	$C_{18}H_{22}N_2O_2$	100	97	93	79*	70*	113	28***
68		Et	A	21	methylcyclohexane, EtOH	85-87	$C_{16}H_{19}NO_3$	101	94	96	83	96	90	56***

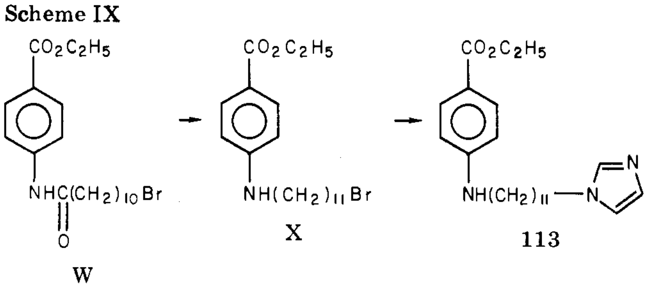
69	4-CH$_3$C$_6$H$_4$(CH$_2$)$_3$	Et	A	65	acetonitrile, EtOH	119-120	C$_{19}$H$_{23}$NO$_2$	122*	103	127	68*	54**	72**	31***
70	4-CH$_3$C$_6$H$_4$(CH$_2$)$_3$	H	B	81	acetonitrile	165-167	C$_{17}$H$_{19}$NO$_2$	110	98	90	50***	54***	63*	49***
71	n-C$_8$H$_{17}$–C$_4$H$_2$S–(CH$_2$)$_3$	Et	A	58	MeOH	84-88	C$_{24}$H$_{35}$NO$_2$S	83*			46***			57***
72	n-C$_8$H$_{17}$–C$_4$H$_2$S–(CH$_2$)$_3$	H	B	94	cyclohexane	117-119	C$_{22}$H$_{31}$NO$_2$S	78*	92*	88	57*	72	76	27**
73	(E)-C$_6$H$_5$CH=CHCH$_2$	Et	A	55	EtOH-benzene	135-137	C$_{18}$H$_{19}$NO$_2$ ^{l}	84*	86^d	92^f	60***	58*^{d}	73*^{f}	
74	(E)-C$_6$H$_5$CH=CHCH$_2$	H	B	66	EtOH	200-202	C$_{16}$H$_{15}$NO$_2$ ^{m}	96	70***	86*	44**	43*	85	0
75	(E)-4-ClC$_6$H$_4$CH=CHCH$_2$	Et	h	57	EtOH, acetonitrile	144-147	C$_{18}$H$_{18}$ClNO$_2$	78	100	93	46***	45***	64**	23**
76	(E)-4-ClC$_6$H$_4$CH=CHCH$_2$	H	B	43	acetone	231-233	C$_{16}$H$_{14}$ClNO$_2$	90	92	83	54***	48***	95	26***
77	(E)-4-ClC$_6$H$_4$CH=CHCO	Et	D	91	EtOH-CHCl$_3$	203-204	C$_{18}$H$_{16}$ClNO$_3$	107	107	98	80	110	104	51***
78	(E)-4-ClC$_6$H$_4$CH=CHCO	H	B	85	methyl-cellosolve	333-336 dec	C$_{16}$H$_{12}$ClNO$_3$	120	100	100	116	109	94	41***
79	4-ClC$_6$H$_4$(CH$_2$)$_2$CO	Et	h	89	EtOH	164-166	C$_{18}$H$_{18}$ClNO$_3$	99	107	101	66**	101	85*	30**
80	4-ClC$_6$H$_4$(CH$_2$)$_2$CO	H	B	83	EtOH	273-275 dec	C$_{16}$H$_{14}$ClNO$_3$	96	104	104	100	115	100	33***
81	4-CH$_3$C$_6$H$_4$(CH$_2$)$_2$CO	Et	D	86	acetonitrile	154-155	C$_{19}$H$_{21}$NO$_3$	88	99	97	69	64	73	25**
82	4-CH$_3$C$_6$H$_4$(CH$_2$)$_2$CO	H	B	85	HOAc	266-267 dec	C$_{17}$H$_{17}$NO$_3$	91	83*	94	70	97	75	0
83	4-CH$_3$OC$_6$H$_4$(CH$_2$)$_2$CO	Et	p	87	toluene	134-136	C$_{19}$H$_{21}$NO$_4$	98	85	80*	105	89	98	26***
84	4-CH$_3$OC$_6$H$_4$(CH$_2$)$_2$CO	H	B	89	HOAc	252-255 dec	C$_{17}$H$_{17}$NO$_4$							0
85	(E)-4-CH$_3$OC$_6$H$_4$CH=CHCO	Et	D	64	EtOH	165-167	C$_{19}$H$_{19}$NO$_4$							52***
86	(E)-4-CH$_3$OC$_6$H$_4$CH=CHCO	H	B	97		289-291 dec	C$_{17}$H$_{15}$NO$_4$							20**

[a-h] See footnotes a to h in Table I. [i] German Patent 716 668 (1941); *Chem. Abstr.*, 38, p2346[2] (1944). [j] Calcd: Br, 22.06. Found: Br, 22.60. [k] Calcd: C, 63.99. Found: C, 64.43. [l] Calcd: C, 76.84. Found: C, 77.25. [m] Calcd: C, 75.87. Found: C, 76.30. [n] The compound was synthesized by the method used to prepare 43. [o] The compound was synthesized by the method used to prepare 67. [p] The compound was synthesized by the method used to prepare 79.

Scheme VIII



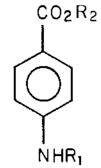
Scheme IX

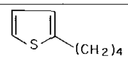
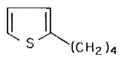
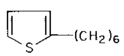
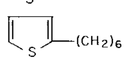
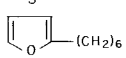
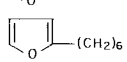
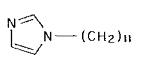
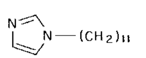


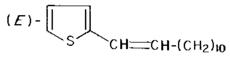
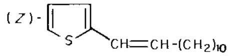
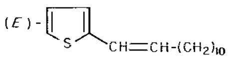
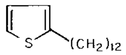
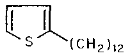
hibited hypolipidemic activity. Good activity was observed whether the heterocyclic moiety was located in the interior (**20** and **72**) or at the terminus (**102**, **117**, and **119**) of the alkyl group.

Very few of the higher homologues (Table IV) of the (aralkylamino)- and [(heteroarylalkyl)amino]benzoic acids showed good hypocholesteremic activity. In marked contrast, both hypocholesteremic and hypotriglyceridemic activities increased as the length of the alkyl chain increased in the homologous series of 4-(alkylamino)benzoic acids (Table VII) and were clearly maximized when the alkyl group was n-hexadecyl, i.e., cetaben (**149**). This result parallels a similar observation for the p-n-alkoxybenzoic acids.[2] Somewhat surprisingly, the meta isomer (**153**) was devoid of activity. Unsaturated analogues (**162–173**) all

Table IV. 4-[[Aryl(C_4-C_{12})alkyl]amino]benzoic Acids

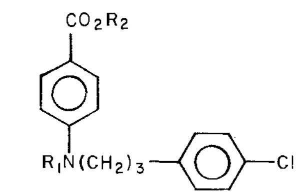


no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose at % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
87		Et	A	50	EtOH	65-67	$C_{17}H_{21}NO_2S$	90	97[d]	94[f]	99	96[d]	89[f]	56***
88		H	B	70	EtOH	139-141	$C_{15}H_{17}NO_2S$	77	98[d]	90[e]	90	89[d]	94[e]	10
89	$C_6H_5(CH_2)_5$	Et	A	66	EtOH	73-75	$C_{20}H_{25}NO_2$	90	85**[d]	92[f]	62**	66**[d]	84[f]	69***
90	$C_6H_5(CH_2)_5$	H	B	92	EtOH	142-144	$C_{18}H_{21}NO_2$	108	84*[d]	95[f]	89	78[d]	96[f]	26**
91	4-$ClC_6H_4CO(CH_2)_4CO$	Et	D	78	acetone	161-163	$C_{21}H_{22}ClNO_4$	90	88	90	96	131	110	37**
92	4-$ClC_6H_4CO(CH_2)_4CO$	H	B	68	HOAc	230-232 dec	$C_{19}H_{18}ClNO_4$	97	94	82*	56**	70	94	40***
93	4-$ClC_6H_4CHOH(CH_2)_5$	H	B	70	acetonitrile	140-142 dec	$C_{19}H_{22}ClNO_3$	86	100	100	72*	90	85	30**
94	4-$ClC_6H_4CO(CH_2)_5$	Et	*h*	51	acetonitrile, EtOH	112-114	$C_{21}H_{24}ClNO_3$	99	92	98	79	56**	76	50***
95	4-$ClC_6H_4(CH_2)_5CO$	Et	D	78	toluene	107-108	$C_{21}H_{24}ClNO_3$	99	101	93	104	95	96	42**
96	4-$ClC_6H_4(CH_2)_5CO$	H	B	79	EtOH	218-220	$C_{19}H_{20}ClNO_3$[i]	99	93	86	90	104	96	18*
97	4-$ClC_6H_4(CH_2)_6$	Et	E	39	methylcyclohexane	95-97	$C_{21}H_{26}ClNO_2$	85	95	99	50**	68*	73*	30**
98	4-$ClC_6H_4(CH_2)_6$	H	B	64	toluene	138-140	$C_{19}H_{22}ClNO_2$	82	78**	81*	43**	65*	61	22*
99	$C_6H_5(CH_2)_6$	Et	A	50	EtOH	69-72, 81-83[g]	$C_{21}H_{27}NO_2$	82**	84**[d]	89*[f]	43***	45***[d]	59[f]	41***
100	$C_6H_5(CH_2)_6$	H	B	98	EtOH	126-129	$C_{19}H_{23}NO_2$	86	85*[d]	83**[f]	40***	46***[d]	52***[f]	17
101		Et	A	33	acetonitrile	64-67	$C_{19}H_{25}NO_3S$[j]							63***
102		H	B	86	acetonitrile	117-120	$C_{17}H_{21}NO_2S$[k]	76***	83**	90	57**	63**	58**	31***
103		Et	A	49	acetonitrile	149-150	$C_{18}H_{25}NO_3$[l]	90	103	95	60*	64*	68*	37***
104		H	B	76	acetonitrile	95-98	$C_{17}H_{21}NO_3$	86*	87	91	51*	61	67	21*
105	$C_6H_5(CH_2)_7$	Et	A	81	EtOH	66-68	$C_{22}H_{29}NO_2$	89	89[d]	90[f]	72*	82*[d]	84**[f]	54***
106	$C_6H_5(CH_2)_7$	H	B	84	EtOH	123-125	$C_{20}H_{25}NO_2$	91	96[d]	94[e]	71*	61**[d]	79[e]	14
107	$C_6H_5(CH_2)_8$	Et	A	77	EtOH	75-76	$C_{23}H_{31}NO_2$	98	96[d]	88[f]	54*	65**[d]	61*[f]	50***
108	$C_6H_5(CH_2)_8$	H	B	83	EtOH	113-115	$C_{21}H_{27}NO_2$	84	78*	90	74*	56**	54*	35**
109	$C_6H_5(CH_2)_9$	H	A, B	8[m]	EtOH	105-107	$C_{22}H_{29}NO_2$[n]	92	96[d]	96[f]	68**	58**[d]	50***[f]	28**
110	$C_6H_5(CH_2)_{10}$	Et	A	70	EtOH	74-76	$C_{25}H_{35}NO_2$	89*	84**	100	77*	58**	77	63***
111	$C_6H_5(CH_2)_{10}$	H	B	63	EtOH	96-98	$C_{23}H_{31}NO_2$	87*	89[d]	87*[f]	81	88[d]	79*[f]	44***
112	$C_6H_5(CH_2)_{11}$	H	A, B	24	ether	53-55	$C_{24}H_{33}NO_2$	83*	76***[d]	83[f]	74**	69**[d]	68**[f]	24*
113		Et	*h*	71	acetonitrile	77-80	$C_{23}H_{35}N_3O_2$	89	100	89	57**	92	78	72***
114	 •HCl	H	B	84	EtOH	181-183	$C_{21}H_{32}ClN_3O_2$	113	99	95	47**	48**	74	22

no.	R	R2	method	yield, %	crystn solvent	mp, °C	formula	sterol 0.10	sterol 0.03	sterol 0.01	triglyceride 0.10	triglyceride 0.03	triglyceride 0.01	ACAT, % inhibn
115		Et	A	14	cyclohexane	62-64	$C_{25}H_{35}NO_2S$							62***
116		Et	A	10	cyclohexane	63-67	$C_{25}H_{35}NO_2S$[o]	82**			72			47*
117		H	B	47	EtOH	86-102	$C_{23}H_{31}NO_2S$[p]	73**	83**	84**	41***	59*	69	53***
118		Et	A	55	cyclohexane	70-71	$C_{25}H_{37}NO_2S$	103			46**			40*
119		H	B	92	EtOH	92-109	$C_{23}H_{33}NO_2S$	70*	81*	85	42**	50**	59*	57***

[a-h]See footnotes a to h in Table I. [i] Calcd: Cl, 10.25. Found: Cl, 9.83. [j] Calcd: H, 6.21. Found: H, 6.91. [k] Calcd: C, 67.29. Found: C, 67.74. [l] Calcd: C, 72.35. Found: C, 71.81. [m] The lower yield was due to the inadvertent use of hydrated sodium iodide as catalyst. [n] Calcd: C, 77.84. Found: C, 78.51. [o] Calcd: C, 72.59. Found: C, 72.12. [p] Calcd: S, 8.32. Found: S, 7.87.

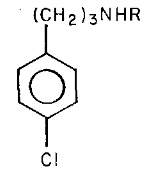
Table V. Amino Disubstituted Analogues

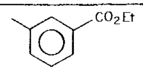
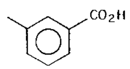
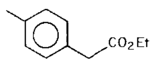
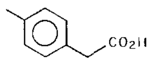
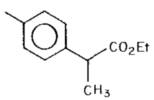
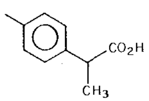
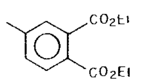
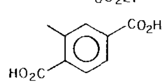
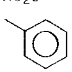


no.	R1	R2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
120	CH_3	Et	*h*	33	hexane	63-65	$C_{19}H_{22}ClNO_2$	99			49***			53***
121	CH_3	H	B	67	benzene, EtOH	145-146	$C_{17}H_{18}ClNO_2$	107			74**			24**
122[k]	CH_3CH_2	Et	*j*	78			$C_{20}H_{24}ClNO_2$	86			67*			48***
123	CH_3CH_2	H	B	74	EtOH, acetonitrile	132-134	$C_{18}H_{20}ClNO_2$[i]	83			68*			52***
124	$4\text{-}ClC_6H_4(CH_2)_3$	H	B	26	acetonitrile	132-134	$C_{25}H_{25}Cl_2NO_2$	98	84	98	85	91	126	33***

[a-h] See footnotes a to h in Table I. [i] Calcd: C, 68.03. Found: C, 68.45. [j] Prepared by the method used for 120. [k] Bp 192-195 °C, 16 mm.

Table VI. Benzoic Acid Variants



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
125		A	61	hexane	84-85	$C_{18}H_{20}ClNO_2$	96	93	96	59**	62**	75*	50***
126		B	70	methylcyclohexane	118-119	$C_{16}H_{16}ClNO_2$	92	89	103	37***	93	80	0
127		A	55	methylcyclohexane	52-54	$C_{19}H_{22}ClNO_2$	91	91	103	67	126*	119	91***
128		B	60	CCl_4	125-127	$C_{17}H_{18}ClNO_2$[i]	82	85	83	61*	95	111	9
129		A	46	methylcyclohexane	60-62	$C_{20}H_{24}ClNO_2$	75	89	86	42***	48**	57**	85***
130		B	73	CCl_4	122-124	$C_{18}H_{20}ClNO_2$[j]	62**	96	94	33***	63*	63*	14
131		A	76	EtOH, *i*-PrOH	77-79	$C_{21}H_{24}ClNO_4$	96	99	95	80	91	93	54***
132		A, B	65	HOAc	266-268 dec	$C_{17}H_{16}ClNO_4$[k]	103	100	102	51**	57***	72	0
133		*l*	29	EtOH	72-74	$C_{15}H_{16}N_2O_2$	87	88	90	49***	61*	90	46***

[a-h] See footnotes *a* to *h* in Table I. [i] Calcd: C, 67.22; Cl, 11.67. Found: C, 66.73; Cl, 12.17. [j] Calcd: C, 68.03; Cl, 11.15. Found: C, 67.52; Cl, 11.96. [k] Calcd: Cl, 10.62. Found: Cl, 10.21. [l] The compound was isolated as a byproduct in the synthesis of 64; the chloro substituent shown in the general formula of the table is replaced by nitro.

showed good hypolipidemic activity regardless of the position or stereochemistry of the double bond; in fact, an analogue that combined both unsaturation and chain branching (**173**) was equal in activity to cetaben (**149**).

Many of the analogues shown in Tables I–VII exceeded cetaben in their ability to inhibit the ACAT enzyme. Where acids and the corresponding ethyl esters are shown in the tables, the ACAT activity of the ester is usually greater; however, this was not the case for cetaben itself (**148** and **149**). Most of the good inhibitors were inactive (**22**, **37**, **49**, **56**, **89**, **127**, and **129**) or less active (**34**, **45**, **71**, **110**, **113**, and **157**) as hypolipidemics. Two compounds that showed good activity both as ACAT inhibitors and as hypolipidemics were a thiophene analogue (**119**), the best of all the aralkyl analogues, and the branched-chain, unsaturated analogue **173**. Based on a combination of the two activities, cetaben (**149**) was selected for development as a hypolipidemic and potential antiatherosclerotic agent.

Experimental Section

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

Solutions were dried with anhydrous magnesium sulfate and clarified if necessary with activated carbon. Evaporations were carried out at reduced pressure with a rotary evaporator. Halide, alcohol, aldehyde, and carboxylic acid intermediates that were commercially available were used without purification. Methanesulfonate esters were prepared by the sulfene procedure.[31]

Ethyl 4-(Hexadecylamino)benzoate (148). Method A. The following experiment illustrates a general procedure used to prepare esters shown in Tables I–VII. A mixture of 6.60 g (40.0 mmol) of ethyl 4-aminobenzoate (A), 6.11 mL (6.10 g, 20.0 mmol) of 1-bromohexadecane, and 25 mL of hexamethylphosphoramide was stirred at 125 °C for 24 h, allowed to cool, and diluted with 4 mL of H_2O and 30 mL of EtOH. (In the preparation of most other analogues, the reaction mixture was diluted with 50% aqueous EtOH to ensure separation of the desired ester from the byproduct amine salts.) The mixture was chilled and filtered, and the crude solid was recrystallized from 9:1 EtOH/benzene to yield 4.66 g (60%) of **148** as a white solid, mp 84–86 °C.

4-(Hexadecylamino)benzoic Acid (149). Method B. The following experiment illustrates a general procedure used to prepare the acids shown in Tables I–VII. A mixture of 28.0 g (71.8 mmol) of **148**, 20.1 g (359 mmol) of KOH, and 400 mL of 95% EtOH was stirred at reflux for 5 h and then diluted with 360 mL of H_2O and acidified to approximately pH 3 with HCl. The mixture was chilled and filtered, and the crude solid was recrystallized from 95% EtOH to yield 24.7 g (95%) of **149** as a white solid, mp 108–110 and 126–128 °C (see footnote *g* of Table I).

Sodium 4-(Hexadecylamino)benzoate (150). Method C. The following experiment illustrates a general method used to prepare sodium salts shown in Tables I–VII. A mixture of 3.62 g (10.0 mmol) of 4-(hexadecylamino)benzoic acid (**149**) and 25 mL of 9:1 EtOH/H_2O containing 0.400 g (10.0 mmol) of NaOH was stirred at ambient temperature for 4 h and then filtered. The solid was dried in vacuo to yield 3.65 g (95%) of **150** as a white, amorphous solid.

Ethyl 4-[(4-Chlorocinnamoyl)amino]benzoate (77). Method D. The following experiment illustrates a general procedure used to prepare amides shown in Tables I–VII. To a solution of 54.8 g (0.273 mol) of 4-chlorocinnamoyl chloride in 250 mL of CH_2Cl_2 was slowly added a solution of 50 g (0.303 mol, 1.11 equiv) of A and 31 g (1.12 equiv) of triethylamine in 250 mL of CH_2Cl_2. A brief exotherm was observed, after which the solution was left to stir at room temperature overnight. The mixture was treated with 250 mL of H_2O and filtered to yield 78.4 g of solid. The CH_2Cl_2 layer of the filtrate was washed with 250 mL of 10% HCl solution, dried, and evaporated to yield an additional 16.5 g of yellow solid. The combined products were crystallized from 600 mL EtOH/$CHCl_3$ (1:1) to yield 81.9 g (91%) of light yellow crystals, mp 199–202 °C. A portion was crystallized again to yield analytically pure **77** as a white solid, mp 203–204 °C.

Ethyl 4-[[3-(4-Chlorophenyl)propyl]amino]benzoate (41). Method E. The following experiment illustrates a general procedure used to prepare esters shown in Tables I–VII. A 500-mL three-neck flask equipped with dropping funnel, stirrer, and gas inlet tubes was thoroughly flushed with nitrogen, cooled in an ice–water bath, and charged with 60 mL (1.5 equiv) of 1 M borane in THF. A solution of 13 g (39.2 mmol) of ethyl 4-[[3-(4-chlorophenyl)propionyl]amino]benzoate (**79**) in 100 mL of THF was added dropwise, and the reaction was stirred at ambient temperature for 1 h and then for 90 min at reflux. The cooled solution was treated with 50 mL of saturated HCl/EtOH and refluxed for 1 h. The solvents were evaporated, and the residue was diluted with 100 mL of H_2O and extracted twice with 100-mL portions of $CHCl_3$. The combined organic layers were washed with 50 mL of H_2O, dried, and evaporated to 21.7 g of a light yellow oil. Crystallization from 100 mL of EtOH yielded 8.4 g (68%) of light yellow crystals, mp 120–122.5 °C. Additional crystallization from acetone afforded analytically pure **41**, mp 122–124 °C.

Ethyl 4-[[(4-Chlorophenyl)methyl]amino]benzoate (16). Method F. The following experiment illustrates a general procedure used to prepare esters shown in Tables I–VII. A solution of 108 g (0.77 mol) of 4-chlorobenzaldehyde and 127 g (0.77 mol) of A in 700 mL of anhydrous EtOH was heated at reflux for 30 min. The solution was cooled and filtered to yield 190 g of the imine. A 144 g (0.50 mol) portion of the imine was dissolved in 1.1 L of warm (65–72 °C) EtOH under argon, and to this was added 21 g (0.57 mol) of sodium borohydride in portions during 1 h. The solution was refluxed for 3 h, cooled, and poured into 500 mL of ice–water to yield 124 g (86%) of **16**. A portion of the sample was recrystallized from acetonitrile and then from methylcyclohexane to yield analytically pure **16**, mp 147–148 °C.

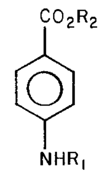
Ethyl 4-[[(5-octyl-2-thienyl)methyl]amino]benzoate (**19**) was prepared by using method F. The aldehyde required for this preparation was prepared as follows.

5-Octyl-2-thiophenecarboxaldehyde. A mixture of 80.0 g (0.387 mol) of 2-octylthiophene and 71.8 mL (67.8 g, 0.930 mol) of DMF was cautiously treated with 42.4 mL (71.0 g, 0.464 mol) of phosphorus oxychloride, and an exothermic reaction and some gas evolution were observed. The mixture was stirred at 100 °C for 1 h and then poured into 600 mL of ice and neutralized with sodium acetate. The mixture was extracted with Et_2O, and the extract was washed with aqueous K_2CO_3 solution, dried, and distilled to yield the aldehyde as a yellow oil, bp 132–140 °C (0.22 mmHg).

Ethyl 4-[[(2-Undecyl-4-imidazolyl)methyl]amino]benzoate (22). A solution of 100 g (0.550 mol) of *n*-undecyl cyanide in 100 mL of EtOH and 400 mL of Et_2O was treated with 60 g of anhydrous HCl at 0 °C, stirred at that temperature for 16 h, and evaporated. The residual oil was triturated with 1.0 L of Et_2O in the cold, and the resulting precipitate was collected by filtration. A mixture of the solid, 46.9 g (0.520 mol) of dihydroxyacetone, and 500 mL of liquid ammonia was heated at 60 °C in a sealed bomb for 5 h, evaporated, and treated with 200 mL of saturated K_2CO_3 solution. The solid was collected by filtration and crystallized from acetonitrile–MeOH and then from EtOH to yield 44 g (32%) of 2-undecyl-4-imidazolemethanol (K) as a white solid, mp 97–99 °C. A solution of 2.50 g (10.0 mol) of the 2-undecyl-4-imidazolemethanol in 25 mL of EtOH was saturated with anhydrous HCl, stirred at ambient temperature for 30 min, and then evaporated. A solution of the residual oil in 25 mL of toluene was treated with 2.0 mL of thionyl chloride, stirred at reflux for 2 h, and then evaporated. A solution of the residual oil in 25 mL of EtOH was treated with 1.60 g (10.0 mmol) of A and 3.0 g of

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

Table VII. 4-(Alkylamino)benzoate Acids, Esters, and Salts



no.	R_1	R_2	method	yield, %	crystn solvent	mp, °C	formula[a]	sterol lowering,[b] dose as % of diet 0.10	0.03	0.01	triglyceride lowering,[b] dose as % of diet 0.10	0.03	0.01	ACAT,[c] % inhibn
134	$CH_3(CH_2)_5$	Et	A	53	benzene, heptane	91-94	$C_{15}H_{23}NO_2$	87	80***[d]	79*[f]	86	76*[d]	73*[d]	
135	$CH_3(CH_2)_5$	H	B	87	ethanol	122-124, 127-128[g]	$C_{13}H_{19}NO_2$	94						
136	$CH_3(CH_2)_7$	Et	A	65	benzene, ethanol	79-80	$C_{17}H_{27}NO_2$							
137	$CH_3(CH_2)_7$	H	B	78	ethanol	117-118	$C_{15}H_{23}NO_2$	90	97[d]	101[f]	67**	88[d]	91[f]	24*
138	$CH_3(CH_2)_{11}$	Et	A	20	ethanol	77-78	$C_{21}H_{35}NO_2$							
139	$CH_3(CH_2)_{11}$	H	B	27	ethanol	112-113, 125-126[g]	$C_{19}H_{31}NO_2$	89*	80**[d]	86**[f]	32**	40***[d]	51***[f]	21*
140	$CH_3(CH_2)_{11}$	Na	C	96		solid[i]	$C_{19}H_{30}NO_2Na$[j]	88	92	89	34***	56***	72**	17
141	$CH_3(CH_2)_{12}$	Et	A	13	acetonitrile	78-79	$C_{22}H_{37}NO_2$	91			70*			22**
142	$CH_3(CH_2)_{12}$	H	B	65	ethanol	106-109, 112-113[g]	$C_{20}H_{33}NO_2$	84**	87*[d]	95[f]	60**	36***[d]	54*[f]	29*
143	$CH_3(CH_2)_{12}$	Na	C	80		352-360	$C_{20}H_{32}NO_2Na$	76*	90	110	62**	70	66*	38***
144	$CH_3(CH_2)_{13}$	Et	A	24	ethanol	81-82	$C_{23}H_{39}NO_2$							
145	$CH_3(CH_2)_{13}$	H	B	56	ethanol	108-111	$C_{21}H_{35}NO_2$	89	90[d]	93[f]	53**	50***[d]	65***[f]	
146	$CH_3(CH_2)_{14}$	Et	A	46	benzene, ethanol	73-75	$C_{24}H_{41}NO_2$	86	84***[d]	91*[f]	62**	76*[d]	88[f]	
147	$CH_3(CH_2)_{14}$	H	B	95	ethanol	107-108, 126-127[g]	$C_{22}H_{37}NO_2$	79**	86[d]	90[f]	60*	80[d]	72[f]	56***
148	$CH_3(CH_2)_{15}$	Et	A D, E	60 79	benzene, ethanol	84-86	$C_{25}H_{43}NO_2$	98	103[d]	109[f]	69*	54**[d]	70*[f]	8
149	$CH_3(CH_2)_{15}$	H	B	95	ethanol	108-110, 126-128[g]	$C_{23}H_{39}NO_2$	54***	71**	72***	31***	45***	71*	57**
150	$CH_3(CH_2)_{15}$	Na	C	95		solid[i]	$C_{23}H_{38}NO_2Na$[l]	60***	76**	90	41***	60**	75*	53***
151	$CH_3(CH_2)_{15}$	Me	*k*	90	hexane, methylene chloride	92-93	$C_{24}H_{41}NO_2$	97			85			0
152	$CH_3(CH_2)_{15}$	Et[m]	A	85	hexane, methylene chloride	solid[n]	$C_{25}H_{43}NO_2$							
153	$CH_3(CH_2)_{15}$	H[o]	B	62	ethanol	108-110	$C_{23}H_{39}NO_2$	93	100[d]	100[f]	81	92[d]	98[f]	34*
154	$CH_3(CH_2)_{16}$	Et	A	12	benzene	87-88	$C_{26}H_{45}NO_2$	111						
155	$CH_3(CH_2)_{16}$	H	B	83	ethanol	105-106, 127-128[g]	$C_{24}H_{41}NO_2$	87	86**[d]	87**[f]	57**	77[d]	80[f]	58***
156	$CH_3(CH_2)_{17}$	Et	A	40	benzene, ethanol	88-89	$C_{27}H_{47}NO_2$[p]							
157	$CH_3(CH_2)_{17}$	H	B	55	ethanol	103-106, 123-126[g]	$C_{25}H_{43}NO_2$	82**	94[d]	86**[e]	60***	71*[d]	70*[f]	61***
158	$CH_3(CH_2)_{17}$	Na	C	84		solid[i]	$C_{25}H_{42}NO_2Na$[q]	79*	86	84*	52***	76*	90	60***
159	$CH_3(CH_2)_{18}$	Et	A	75	ethanol	solid[n]	$C_{28}H_{49}NO_2$							

160	$CH_3(CH_2)_{18}$	H	B	91	ethanol	104–106, 120–124[g]	$C_{26}H_{45}NO_2$	100	96[d]	90*[f]	46***	46***[d]	52***[f]	36**
161	$CH_3(CH_2)_{18}$	Na	C	85		357–365 dec	$C_{26}H_{44}NO_2Na$	98	98	93	70*	99	102	51**
162	(E)-$CH_3(CH_2)_8CH{=}CH(CH_2)_3$	Et	A	59	ethanol	76–78	$C_{23}H_{37}NO_2$	83***	85**[d]	88*[f]	79	75[d]	78[f]	40*
163	(E)-$CH_3(CH_2)_8CH{=}CH(CH_2)_3$	H	B	89	ethanol	109–111	$C_{21}H_{33}NO_2$	79***	83*[d]	86**[f]	75	97[d]	85[f]	
164	(E)-$CH_3(CH_2)_9CH{=}CH(CH_2)_3$	Et	A	70	ethanol	76–78	$C_{24}H_{39}NO_2$	86**	94[d]	86**[f]	83	77[d]	90[f]	40***
165	(E)-$CH_3(CH_2)_9CH{=}CH(CH_2)_3$	H	B	97	ethanol	106–108	$C_{22}H_{35}NO_2$	79**	82*[d]	84*[f]	83	83*[d]	86[f]	48***
166	(E)-$CH_3(CH_2)_9CH{=}CH(CH_2)_3$	Na	C	92		solid[i]	$C_{22}H_{34}NO_2Na$	82*	93	86	63*	117	112	46***
167	(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_8$	Et	A	50	ethanol	53–59	$C_{27}H_{45}NO_2$	96*	99[d]	95*[f]	77	57**[d]	68*[f]	
168	(Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_8$	H	B	90	ethanol	66–67, 92–103[g]	$C_{25}H_{41}NO_2$	75***	85[d]	88*[f]	63**	58**[d]	72*[f]	
169	(E)-$CH_2{=}CH(CH_2)_8CH{=}CH(CH_2)_3$	Et	A	46	ethanol	70–72	$C_{24}H_{37}NO_2$	85**	85*[d]	87*[f]	64	76[d]	90[f]	50***
170	(E)-$CH_2{=}CH(CH_2)_8CH{=}CH(CH_2)_3$	H	B	68	ethanol	99–100	$C_{22}H_{33}NO_2$	80***	81*[d]	86**[f]	88	79[d]	71*[f]	47***
171	(E)-$CH_2{=}CH(CH_2)_8CH{=}CH(CH_2)_3$	Na	C	69		solid[i]	$C_{22}H_{32}NO_2Na$[r]	86	92	88	87	90	106	44***
172	$CH_3(CH_2)_9C({=}CH_2)(CH_2)_5$	Et	h	58	hexane	74–75	$C_{26}H_{43}NO_2$	88*			56*			9
173	$CH_3(CH_2)_9C({=}CH_2)(CH_2)_5$	H	B	85	hexane, methylene chloride	69–70	$C_{24}H_{39}NO_2$	53***	85*	81***	30***	64*	65*	71***

[a–h] See footnotes a to h in Table I. [i] Many of the sodium salts were obtained as amorphous solids lacking characteristic melting points. [j] Calcd: C, 69.50; H, 9.85. Found: C, 68.66; H, 8.77. [k] The compound was obtained by boron trifluoride catalyzed esterification of 149; P. K. Kadaba, M. Carr, M. Tribo, J. Triplett, and A. C. Glassner, *J. Pharm. Sci.*, 58, 1422 (1969). [l] The compound contains 0.25 mol of H_2O. Calcd: KF, 1.16. Found: KF, 1.10. [m] The meta isomer: ethyl 3-(hexadecylamino)benzoate. [n] The crude ester was converted to the corresponding acid without purification. [o] The meta isomer: 3-(hexadecylamino)benzoic acid. [p] Calcd: C, 77.64. Found: C, 77.14. [q] Calcd: C, 72.95. Found: C, 71.18. [r] Calcd: C, 72.29. Found: C, 71.67.

Na_2CO_3, stirred at ambient temperature for 16 h and then at reflux for 2 h, diluted with 150 mL of H_2O, and then filtered. The solid was crystallized twice from MeOH and once from $CHCl_3$ to yield 1.2 g (22%) of **22** as a white solid, mp 103–107 °C.

1-*O*-Glyceryl 4-[[3-(4-Chlorophenyl)propyl]amino]benzoate (43). A solution of 32.0 g (0.103 mol) of sodium 4-[[3-(4-chlorophenyl)propyl]amino]benzoate (**44**), 37.8 g (0.341 mol) of 3-chloro-1,2-propanediol, and 200 mL of hexamethylphosphoramide was stirred for 6 h at 100 °C. The cooled solution was poured into 600 mL of H_2O, whereupon a precipitate formed. This was collected, dried in vacuo, and crystallized once from 1 L of benzene and once from 500 mL of $CHCl_3$ to afford 22.5 g (60%) of **43**, mp 121–123 °C.

4-[[3-(4-Nitrophenyl)propyl]amino]benzoic Acid (64) and *N*-[3-(4-Nitrophenyl)propyl]aniline (133). A solution of 4.0 g (12.2 mmol) of ethyl 4-[[3-(4-nitrophenyl)propyl]amino]benzoate (**63**), 100 mL of 15% H_2SO_4, and 50 mL of EtOH was heated at reflux for 72 h. A small amount of remaining starting material was hydrolyzed by distilling the EtOH at this point. The solution was diluted with 100 mL of H_2O and cooled to room temperature, whereupon a light yellow precipitate (2.7 g) of the desired acid crystallized from solution. The filtrate was adjusted to pH 7 with 5 N NaOH solution, which caused another product (0.78 g) to precipitate. Both products were stirred in hot CH_2Cl_2, and the insoluble materials of both (corresponding to the desired acid) were combined. The filtrate was chromatographed on 200 g of activity grade III silica gel by using gradient elution of CH_2Cl_2 to EtOAc. The appropriate fractions were combined to yield 2.09 g of acid **64** and 1.26 g of **133**. The acid was crystallized twice from 50 mL of THF/acetonitrile to yield 1.63 g (45%) of yellow-green crystals, mp 224–227 °C dec. A portion of the product was crystallized twice more from THF/acetonitrile to yield the analytical sample, mp 228–230 °C dec. The decarboxylated product (**133**) was crystallized three times from 20 mL of EtOH to yield 0.92 g (29%) of bright yellow crystals, mp 72–74 °C.

Ethyl 4-[[3-(4-Aminophenyl)propyl]amino]benzoate (67). A suspension of 8.3 g (25.3 mmol) of ethyl 4-[[3-(4-nitrophenyl)propyl]amino]benzoate (**63**) and 730 mg of 10% Pd/C in 125 mL of EtOAc was hydrogenated in a Parr hydrogenator at an initial pressure of 35 psi. After 90 min the catalyst was filtered, the filtrate was washed with EtOAc, and the solvent was evaporated to yield 10.2 g of white solid. The product was crystallized three times from 100 mL of isopropyl alcohol to yield 5.28 g (70%) of **67** as tan crystals, mp 98–100 °C.

Ethyl 4-[(4-Chlorocinnamyl)amino]benzoate (75). A solution of 11.9 g (70.2 mmol) of 4-chlorocinnamyl alcohol[22,23] and 14.6 mL (105 mmol) of triethylamine in 300 mL of Et_2O was cooled to −20 °C and then 7.1 mL (77.2 mmol) of methanesulfonyl chloride in 5 mL of ether was added dropwise with stirring at a rate such that the temperature did not exceed −10 °C. After the addition was complete, the reaction was stirred at room temperature for 30 min and then filtered directly into a solution of 23.3 g (140 mmol) of A in 100 mL of Et_2O. The reaction was stirred at ambient temperature for 18 h and then filtered. The solid was washed with several portions of CH_2Cl_2. The filtrate was washed twice with water, dried, and evaporated to 26.9 g of tan solid. Crystallization of this solid from 250 mL of EtOH and then from 150 mL of acetonitrile afforded 11.6 g (57%) of glistening white crystals, mp 143–146 °C. Recrystallization from EtOH and then from acetonitrile yielded **75**, mp 144–147 °C.

Ethyl 4-[[3-(4-Chlorophenyl)propionyl]amino]benzoate (79). A solution of 30 g (91 mmol) of ethyl 4-[[3-(4-chlorophenyl)acryloyl]amino]benzoate (**77**) containing 500 mg of 10% Pd/C in 150 mL of THF was hydrogenated by using a Parr hydrogenator at an initial pressure of 35 psi. After 2 h the catalyst was separated by filtration and washed with several portions of THF. The filtrate was evaporated to yield 29.7 g of white solid. Crystallization from 175 mL of EtOH yielded 26.8 g (89%) of white crystals, mp 163–165 °C. A portion of the product was recrystallized from EtOH to yield **79**, mp 164–166 °C.

Ethyl 4-[[5-(4-Chlorobenzoyl)pentyl]amino]benzoate (94). A dry 2-L flask was thoroughly flushed with nitrogen and then charged with 70.9 g (0.274 mol, 5.9 equiv) of Collins reagent[29] and 1 L of dry CH_2Cl_2. To the resultant dark red solution was added 17.6 (48.8 mmol) of crude ethyl 4-[[6-(4-chlorophenyl)-6-hydroxyhexyl]amino]benzoate (**93**) in 100 mL of dry CH_2Cl_2. The mixture was stirred for 2 h at ambient temperature and filtered through a pad of hydrous magnesium silicate, and the filtrate was evaporated to 13.9 g of an orange residue. The product was crystallized three times from acetonitrile to yield 8.98 g (51%) of light yellow crystals, mp 109–112 °C. A portion of the product was recrystallized from EtOH to yield **94**, mp 112–114 °C.

Ethyl 4-[[11-(1-Imidazolyl)undecyl]amino]benzoate (113). A solution of 7.23 g (0.100 mol) of imidazole in 20 mL of hexamethylphosphoramide was added to a stirred suspension of 4.84 g (0.100 mol) of petroleum ether washed sodium hydride (50% in mineral oil) in 70 mL of hexamethylphosphoramide under argon, and the mixture was stirred for 2 h at ambient temperature. A solution of 20.0 g (0.050 mol) of ethyl 4-[(11-bromoundecyl)amino]benzoate[32] in 20 mL of hexamethylphosphoramide was then added, and the resulting mixture was stirred at ambient temperature for 64 h, poured into 1.5 L of H_2O, and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated. The residue was crystallized from acetonitrile to yield 13.4 g (71%) of **113** as a cream-colored solid, mp 77–80 °C.

The *E* (**115**) and *Z* (**116**) isomers of ethyl 4-[(2-thienyl-11-dodecenyl)amino]benzoate were prepared from (*E*)- and (*Z*)-12-(2-thienyl)-11-dodecenol (O), respectively, by method A. Ethyl 4-[(2-thienylmethyl)amino]benzoate (**21**) was isolated in trace amounts from the preparation of **115** and presumably results from unreacted 2-thiophenecarboxaldehyde, which was carried through the reaction sequence. The mixture of (*E*)- and (*Z*)-12-(2-thienyl)-11-dodecenol (O) was obtained by lithium aluminum hydride reduction of 12-(2-thienyl)-11-dodecenoic acid (N) and the individual isomers were separated by crystallization from cyclohexane; *E* isomer, glass; *Z* isomer, mp 44–46 °C.

12-(2-Thienyl)-11-dodecanoic Acid (N). A 31.2 g (0.65 mol) sample of 50% sodium hydride was washed free of oil with petroleum ether and suspended in 375 mL of dry dimethyl sulfoxide under nitrogen. The mixture was warmed at 55 °C for 2 h and cooled in an ice bath, and to this was added 165 g (0.307 mol) of (10-carboxydecyl)triphenylphosphonium bromide in 170 mL of dimethyl sulfoxide. The reaction was stirred for 1 h, and then 60.7 mL (0.65 mol) of thiophene-2-carboxaldehyde was added. The reaction was heated on a steam bath for 2 h, poured into 1.5 L of H_2O, and extracted twice with EtOAc and once with Et_2O. The aqueous phase was rendered acidic with HCl and a black oil separated. The oil was dissolved in Et_2O, washed with H_2O, dried, and passed through hydrous magnesium silicate. Evaporation of the solvent yielded 111 g of the crude product as a black oil, which partially crystallized on standing. Also prepared by this procedure[33] were 6-(2-thienyl)-4-hexenoic acid, 6-(2-furyl)-4-hexenoic acid, and 3-(5-octyl-2-thienyl)acrylic acid, intermediates for the syntheses of **101**, **103**, and **71**, respectively.

Ethyl *N*-Methyl-4-[[3-(4-chlorophenyl)propyl]amino]benzoate (120). A solution of 14 g (44.1 mmol) of ethyl 4-[[3-(4-chlorophenyl)propyl]amino]benzoate (**41**), 14.0 mL of methyl fluorosulfonate, and 250 mL of CH_2Cl_2 was stirred at ambient temperature overnight. The solution was poured into 400 mL of H_2O and adjusted to pH 11 with 10 N NaOH. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted twice with 250-mL portions of CH_2Cl_2. The combined organic layers were washed once with 250 mL of H_2O, dried, and evaporated to 18.4 g of light yellow, very viscous oil. The oil was triturated three times with 200-mL portions of boiling hexane, and then the hexane fractions were combined and evaporated to a volume of 100 mL. Filtration yielded 4.8 g (33%) of **120** as colorless platelets, mp 60–64 °C. Additional purification was achieved by distilling the product (Kugelrohr): bp 165 °C (16 μm); mp 63–65 °C.

Ethyl 4-[(6-Decyl-6-heptenyl)amino]benzoate (172). A solution of 18.0 g (50.3 mmol) of methyltriphenylphosphonium bromide in 50 mL of warm dimethyl sulfoxide was added to a stirred solution of sodium methylsulfinylmethide [prepared by heating 4.80 g (100 mmol) of hexane-washed sodium hydride (50% in mineral oil) and 25 mL of dimethyl sulfoxide at 60–65 °C for 1 h]. After 10 min the mixture was treated with a solution of 8.80 g (21.8 mmol) of ethyl 4-[(6-oxohexadecyl)amino]benzoate[32] in 50 mL of THF, stirred for 20 h at ambient temperature, and treated successively with 300 mL of H_2O, 5 mL of HOAc, and saturated $NaHCO_3$ solution. Extraction with CH_2Cl_2, followed by chromatography using 600 g of silica gel and eluting with CH_2Cl_2–hexane, afforded 5.08 g (58%) of **172**, mp 75–75 °C.

Biological Methods. The compounds were tested for serum hypolipidemic activity as follows. Male CFE (Carworth Farms) or CD-1 Sprague–Dawley (Charles River) rats weighing 140–150 g were allocated to experimental groups, eight animals per control group and four animals per test group. The compounds to be tested were added to ground commercial rat chow at levels of 0.10, 0.03, and 0.01% (w/w) by dissolving the compound in MeOH–$CHCl_3$ (1:3, v/v), adding this solution to the feed, mixing, and allowing the solvents to evaporate. Control groups were given food treated with the solvents alone. Food intake was monitored for both control and test groups, and unless noted in the structure–activity discussion, compounds that exhibited hypolipidemic activity had no effect on food consumption. Animals were allowed food and water ad libitum for 5 days, after which they were killed in a fed state and bled. Methods for the determination of sterols[34,35] and triglycerides[36] were adapted for use with a Technicon autoanalyzer. The serum sterol and triglyceride values in Tables I–VII are shown as the mean percent of control values. The significance level (p) was determined by the Student's t test. Control groups averaged 75 ± 3 mg/dL of serum sterol and 85 ± 6 mg/dL of serum triglyceride. Lowering of serum sterol to 85% of control values or serum triglyceride to 75% of control values were the minimum criteria for selection of compounds for further study.

The compounds were tested for inhibition of fatty acyl-CoA:cholesterol acyltransferase (ACAT)[37] as follows. Rat adrenals were homogenized in 0.2 M monobasic potassium phosphate buffer (pH 7.4) and centrifuged at 1000*g* for 15 min at 5 °C. The supernatant, containing the microsomal fraction, served as the source of the ACAT enzyme. A mixture comprising 50 parts of adrenal supernatant, 10 parts of bovine serum albumin (50 mg/mL), 3 parts of test compound (final concentration 5.2 μg/mL), and 500 parts of buffer was preincubated at 37 °C for 10 min. After treatment with 20 parts of oleoyl-CoA (^{14}C, 0.4 μCi) the mixture was incubated at 37 °C for 30 min. A control mixture, omitting the test compound, was prepared and treated in the same manner. The lipids from the incubation mixture were extracted into an organic solvent and separated by thin-layer chromatography. The cholesteryl ester zone was scraped off the plate and counted in a scintillation counter. The values shown in Tables I–VII are expressed as the mean percent inhibition of the enzyme. The significance level (p) was determined by the Student's t test. A 50% inhibition of the ACAT enzyme was the criterion for the selection of compounds for further study.

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Registry No. 1, 61439-53-0; **2**, 61439-54-1; **3**, 61439-58-5; 4, 27126-29-0; **5**, 61439-48-3; **6**, 61439-49-4; **7**, 61439-55-2; **8**, 61439-56-3; **9**, 61440-57-1; **10**, 61440-58-2; 11, 64518-60-1; **12**, 61439-65-4; **13**, 61439-66-5; 14, 61440-54-8; **15**, 61440-55-9; **16**, 64288-19-3; **17**, 63759-94-4; 18, 70442-18-1; **19**, 86373-14-0; **20**, 86373-15-1; 21, 18168-49-5; **22**, 86373-16-2; **23**, 86373-17-3; **24**, 61439-45-0; **25**, 61440-42-4; **26**, 61439-61-0; **27**, 61439-62-1; **28**, 61440-50-4; **29**, 61440-51-5; **30**, 61440-59-3; 31, 86373-18-4; **32**,

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

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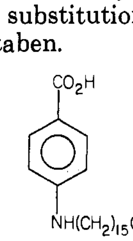
The synthesis of a series of analogues in which the carboxylic acid group of cetaben is replaced by carboxylate ester, carboxamide, or a variety of other substituent groups is described. Also reported are the syntheses of analogues in which the phenyl ring of cetaben is either modified by the presence 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.



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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

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