mmol) of THF containing 5% CH_3NH_2 was stirred for 73.5 h at room temperature. After removal of solvent in vacuo the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to give a residue which was chromatographed on silica gel. The residue of fractions eluted with CH_2Cl_2 was collected and washed with isopropyl ether to give 574 mg (83%, mp 248–250 °C) of **9j**. Recrystallization from MeOH gave the pure sample: 387 mg (56%); mp 249–251 °C; IR (Nujol) 3200, 1690, 1665 cm^{-1}; NMR (Me_2SO-d_6) 3.72 (s, 3 H, OMe), 5.72 (s, 1 H, C_5-H), 6.43 (d, 1 H, J = 2.0 Hz, aromatic H-d_6), 7.00–7.83 (m, 7 H, aromatic H), 11.12 (br, 1 H, CONH). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, Cl, N.

The residue of fractions eluted with CH_2Cl_2 containing 2% MeOH was collected and washed with isopropyl ether to give 81 mg (12%) of **8j**.

7-Chloro-1,5-dihydro-3-methylamino-2*H*-1,4-benzodiazepin-2-one (9s). A solution of 100 mg (0.3 mmol) of **8s** in 10 mL (1.6 mmol) of THF containing 5% CH_3NH_2 was stirred for 66 h at room temperature. Analogous work-up gave a residue, which was washed with isopropyl ether to give 31 mg (31%, mp 197–199 °C) and 21 mg (21%, mp 198–199 °C) of **9s**. Recrystallization from a mixture of AcOEt and isopropyl ether gave the pure sample: mp 197.5–199 °C; IR (Nujol) 3470, 3225, 1675, 1647 cm^{-1}; NMR ($CDCl_3$) 2.87 (d, 3 H, J = 4 Hz, NMe), 5.37 (br, 1 H, NHMe), 5.62 (s, 1 H, C_5-H), 6.67 (d, 1 H, J = 1.5 Hz, aromatic C_6-H), 7.00–8.33 (m, 7 H, aromatic H), 11.42 (br, 1 H, CONH). Anal. ($C_{16}H_{14}ClN_3O$) C, H, Cl, N.

1,5-Dihydro-1-methyl-3-methylamino-6-nitro-2*H*-1,4-benzodiazepin-2-one (9t). A solution of 147 mg (0.5 mmol) of **8t** in a mixture of 6 mL of CH_2Cl_2, 96 mL of MeOH, and 1.81 g (4.6 mmol) of CH_2Cl_2 containing 7.8% CH_3NH_2 was stirred for 41 h at room temperature. The reaction mixture was washed with H_2O and dried over Na_2SO_4, filtered, and evaporated to give a residue which was washed with a mixture of AcOEt and isopropyl ether to give 123 mg (84%, mp 208–212.5 °C dec) of **9t**. Recrystallization from AcOEt gave the pure sample: mp 211–212.5 °C dec; IR (Nujol) 3280, 1656 cm^{-1}; NMR ($CDCl_3$) 2.78 (d, 3 H, J = 5.0 Hz, C_3-NMe), 3.17 (s, 3 H, CONMe), 5.65 (s, 1 H, C_5-H), 6.17 (d, 1 H, J = 1.5 Hz, aromatic C_6-H), 6.50–8.33 (m, 7 H, aromatic H). Anal. ($C_{17}H_{16}N_4O_3$) C, H, N.

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5-(Tetradecyloxy)-2-furancarboxylic Acid and Related Hypolipidemic Fatty Acid-Like Alkyloxyarylcarboxylic Acids[1]

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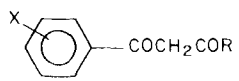
5-(Tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) was found to lower blood lipids and to inhibit fatty acid synthesis with minimal effects on liver weight and liver fat content. This fatty acid-like compound represents a new class of hypolipidemic agent; it is effective in rats and monkeys. The compound resulted from discovery of hypolipidemic activity in certain β-keto esters, postulation and confirmation of the corresponding benzoic acids as active metabolites, and systematic exploration of the structure–activity relationships.

During our continued search for novel hypolipidemic agents, we discovered that methyl *p*-dodecylbenzoylacetate[2] (**3**) effectively lowered serum cholesterol and triglycerides in rats (cf. Table I). We also noted, however, that **3** caused an elevation of liver fat, particularly liver cholesterol, as well as liver weight. Further studies indicated that **3** and the corresponding benzoic acid **34** were incorporated to an appreciable degree into liver lipids of rats (triglycerides and cholesterol esters).[3] We subsequently prepared and evaluated a number of analogues to find an effective compound without these side effects. These compounds and their activities are listed in Tables I–V. (See Experimental Section for methods of evaluation.)

Systematic exploration of the structure–activity relationships of these fatty acid-like alkyloxyarylcarboxylic acids led to the preparation and selection of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) for extended biological studies.[4]

Structure–Activity Relationships. Quite early during our investigation it was postulated[5] and subsequently shown that the β-keto esters are metabolized to the corresponding benzoic acids and that these are also active. Thus the benzoates **33**, **34**, **42**, **45**, and **59** have effects on lipids nearly identical with those of the corresponding β-keto esters **2**, **3**, **4**, **6**, and **13**, respectively. It is known that natural fatty acids are metabolized via β-oxidation to β-keto acids[6] and that this process is interrupted in unnatural fatty acid analogues in which a phenyl group is built into the alkyl chain.[7] It is therefore reasonable to postulate that β-keto esters of Table I are similarly metabolized to the corresponding benzoic acids as their co-

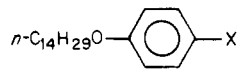
Table I. Hypolipidemic Activity of Benzoylacetates



No.	X	R	Mp, °C[a] (lit. mp)	Recrystn solvent[b]	% yield[c]	Mol formula[d]	Dose, μmol/kg/day[f]	Effects on lipids in rats[e]: Plasma, % redn: Cholesterol	Plasma, % redn: Triglycerides	Liver, % increase: Wt	Liver, % increase: Cholesterol
1	*p*-C_6H_{15}-*n*	OCH_3	44-45	B	58	$C_{16}H_{22}O_3$	606[g]	2[i]	35[i]	2	
2	*p*-$C_{10}H_{21}$-*n*	OCH_3	54-56	A	42	$C_{20}H_{30}O_3$	411[g]	30[j]	69[j]		
3[k,l]	*p*-$C_{12}H_{25}$-*n*	OCH_3	57	B	30	$C_{22}H_{34}O_3$	944[g]	53[j]	84[j]	20	151[j]
							303[g]	37[j]	63[j]	7	97[j]
							89[g]	4[i]	6[i]	8	38[j]
4[k]	*p*-$OC_{12}H_{25}$-*n*	OCH_3	56-59	C		$C_{22}H_{34}O_4$	406[g]	27[j]	71[j]	34	24[j]
							400[h]	35[j]	84[j]	22	32[j]
5	*p*-$OC_{12}H_{25}$-*n*	OCH_3, Cu[m]	115-118 dec	D	41	$C_{44}H_{66}O_8Cu$	420/2[h]	27[j]	50[j]	11	
6[k]	*p*-$OC_{14}H_{29}$-*n*	OCH_3	52-55			$C_{24}H_{38}O_4$	402[g]	40[j]	75[j]	7	9[j]
							179[g]	27[j]	54[j]	3	4[i]
							85[g]	9[i]	44[i]	0	0
7	*p*-$OC_{14}H_{29}$-*n*	OC_2H_5	32-33	E	68	$C_{25}H_{40}O_4$	358[g]	30[j]	59[j]	3	10[i]
							193[g]	20[j]	43[j]	1	11[i]
							96[g]	13[i]	44[j]	1	0
8	*p*-$OC_{14}H_{29}$-*n*	$OCH_2C_6H_5$	49-52	F	64	$C_{30}H_{42}O_4$	332[g]	24[j]	43[j]	5	10[i]
							169[g]	15[i]	70[j]	1	2[i]
							84[g]	16[i]	8[i]	0	0
9	*p*-$OC_{14}H_{29}$-*n*	$O(CH_2)_2NHCOCH_3$	75-83	B	19	$C_{27}H_{43}NO_5$[n]	312[g]	35[j]	60[j]	15	8[i]
10	*p*-$OC_{14}H_{29}$-*n*	NH_2	102-103	B	54	$C_{23}H_{37}NO_3$[n]	439[g]	4[i]	3[i]	8	
11	*p*-$OC_{14}H_{29}$-*n*	OCH_3, Cu[m]	135-137 dec	G	66	$C_{48}H_{74}O_8Cu$	368/2[h]	38[j]	65[j]	11	
12	*p*-$OC_{16}H_{33}$-*n*	OH	95-97 dec	B	18	$C_{25}H_{40}O_4$	311[g]	29[j]	49[j]	0	0
13	*p*-$OC_{16}H_{33}$-*n*	OCH_3	55-60 (60-62[o])	B	93	$C_{26}H_{42}O_4$	339[h]	32[j]	57[j]	18	2[i]
14[k]	*o*-$OC_{16}H_{33}$-*n*	OCH_3	49-51 dec			$C_{26}H_{42}O_4$	456[g]	10[i]	23[i]		
Clofibrate							1693[g]	41[j]	78[j]	50	
							766[g]	36[j]	66[j]	22	
							304[g]	18[i]	48[j]	2	
							119[g]	9[i]	30[i]	0	

[a] Melting points are corrected and were determined on a Hoover capillary melting point apparatus. [b] A = MeOH; B = hexane; C = Et_2O-hexane; D = dioxane; E = absolute EtOH; F = MeCN; G = tetrahydrofuran; H = Me_2CO; I = Me_2CO-MeOH; J = Et_2O; K = C_6H_6-hexane. [c] Yields refer to purified material, unless value given is placed in parentheses. [d] All compounds were analyzed for C and H; analytical results obtained for these elements were within ±0.4% of calculated values unless otherwise indicated. [e] Young male rats of the Wistar strain, obtained from Royalheart Laboratory Animals, Inc., New Hampton, N.Y., of average initial weight of 170-190 g were treated in groups of six animals for 4 or 10 days, as indicated, and compared to an untreated control group. Plasma and liver cholesterol and triglycerides were determined by automated procedures as described in the Experimental Section. Liver wet weight was determined, calculated as g/100 g of final body weight, and compared with values from the control group. [f] Daily dose administered by admixture to food. Actual dose calculated from food consumption. [g] Administered for 10 days. [h] Administered for 4 days. [i] Not statistically significant; $p > 0.05$. [j] Statistically significant at $p \leq 0.05$. [k] Obtained from commercial source. [l] See ref 2. [m] Cu chelate of enolate. [n] Anal. C, H, N. [o] J. Jaeken, A. H. deCat, and R. J. Thiers, Belgian Patent 559 466 (1957); *Chem. Abstr.*, 54, 24054 (1960).

Table II. Hypolipidemic *p*-Tetradecyloxyphenyl Derivatives



No.	X	Mp, °C[a] (lit. mp) [bp (mm)]	Recrystn solvent[b]	% yield[c]	Mol formula[d]	Dose, μmol/kg/day[f]	Effects on lipids in rats[e]: Plasma, % redn: Cholesterol	Plasma, % redn: Triglycerides	Liver, % increase: Wt	Liver, % increase: Cholesterol
15	$-CH_2COOCH_3$	36-37	B	37	$C_{23}H_{38}O_3$	472[h]	0	23[i]	8	0
16	$-CH_2CH_2COOCH_3$	88-90	B	(97)	$C_{24}H_{40}O_3$	401[h]	41[j]	73[j]	17	15[i]
17	$-HC{=}CHCOOCH_3$	79-80	B	86	$C_{24}H_{38}O_3$	430[h]	28[j]	67[j]	3	18[j]
18[k,l]	$-COCH_2CH_2COOH$	110-111			$C_{26}H_{42}O_4$	374[h]	15[i]	42[j]	0	
19	$-CONH_2$	132-138	A	82	$C_{21}H_{35}NO_2$[m]	459[g]	3[i]	0	0	0
20	$-CON(C_2H_5)_2$	30-31	B	54	$C_{25}H_{43}NO_2$[m]	449[h]	0	0	5	
21	$-CN$	50-53 33-35	B	(91)	$C_{21}H_{33}NO$[m]	482[h]	10[i]	6[i]	4	
22	$-CHO$	[225-235 (7)[n]]	B	34	$C_{21}H_{38}O_2$	499[h]	25[j]	68[j]	18	12[i]
23	$-CH_2OH$	76-78	H	50	$C_{21}H_{36}O_2$	477[h]	35[h]	41[j]	17	33[j]
24	$-CH_2OCOCH_3$	45-46	I	89	$C_{23}H_{38}O_3$	406[h]	22[j]	62[j]	17	11
25	$-CH_2OCO_2C_2H_5$	40-41	B	56	$C_{24}H_{40}O_4$	385[h]	38[j]	70[j]	11	12
26	$-CH_3$	31-33	H	16	$C_{21}H_{36}O$	509[h]	0	30[j]	10	0
27[l]	$-COCH_3$	65-67	B	91	$C_{24}H_{40}O_2$	399[h]	8[i]	40[i]	0	0
28		146-147	H	19	$C_{21}H_{34}N_4O$[m]	480[h]	0	0	1	
29	$-OCH_2CO_2CH_3$	74-77	A	44	$C_{23}H_{38}O_4$	446[h]	10[j]	0	4	0
30	$-SCH_2CO_2H$	81-82	B	42	$C_{22}H_{36}O_3S$	420[g]	16[j]	11[i]	0	3

[a-k] See Table I. [l] n-$C_{16}H_{33}O$ analogue. [m] Anal. C, H, N. [n] R. Nodzu, H. Watanabe, S. Kuwata, C. Nagaishi, and K. Shibuya, *J. Pharm. Soc. Jpn.*, 74, 1248 (1954).

enzyme A derivatives. Direct evidence for this was provided by the observation that methyl *p*-dodecylbenzoylacetate (**3**) was incorporated into liver lipids as a *p*-dodecylbenzoate ester; the extent of incorporation was the same as that observed after administration of **34**.[3] Metabolism by β-oxidation is further substantiated by the finding that the *p*-tetradecyloxyphenylpropionic and -propenoic esters **16** and **17** were active, while the corresponding phenylacetic ester **15** was not. Compounds of a lower oxidation state, **22–25**, were also active, presumably due to metabolic oxidation to **45** (Scheme I; the actual metabolic pathway presumably would proceed through the Co-A derivatives).

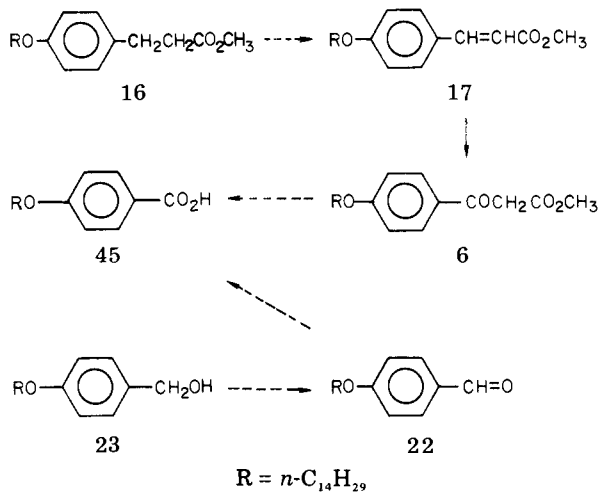
On the other hand, the γ-keto acid **18**, amides **19** and **20**, the nitrile **21**, the acetyl derivative **27**, and the methyl analogue **26**, which might also have been expected to be suitable substrates for metabolic conversion to the free acid **45**, were inactive. Metabolic hydrolysis of methyl, ethyl, and benzyl esters to the corresponding free acids has been demonstrated in many instances.

In analogy to nicotinic acid and several other hypolipidemic acids, when it was shown that a tetrazole moiety can replace a carboxylic acid function,[8-10] compound **28** was prepared but was found to be inactive.

Since a large number of aryloxyalkylcarboxylic acids (e.g., clofibrate) have been reported to have hypolipidemic activity,[11,12] *p*-tetradecyloxyphenoxyacetic acid (**29**) and thio analogue **30** were synthesized. These compounds had only marginal hypolipidemic activity.

Definition of optimal structural parameters was studied in the benzoic acid series because these compounds were more readily synthesized and purified than the benzoylacetates (Table III). Of the *p*-alkyl substituted analogues **31–37**, those with a *p*-alkyl chain of from 10 to 15 carbon atoms showed hypolipidemic activity (**33–36**). As noted earlier with the β-keto ester **3**, however, these compounds caused a pronounced increase in liver cholesterol content; this effect was particularly pronounced with the dodecyl congener **34**. *p*-Alkoxy congeners, on the other hand,

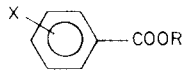
Scheme I



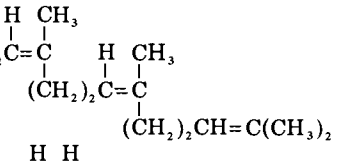
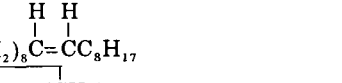
caused no accumulation of liver fat, little increase in liver weight, and no incorporation into liver lipids. Again, a chain length of at least ten carbon atoms was required (**38–42, 44, 45, 58, 59**) and an abrupt drop in activity was observed in compounds with a *p*-alkoxy chain containing more than 17 carbon atoms (**65–67**). Poor absorption of these larger compounds is believed to be the reason for this sudden loss of activity as well as for the inconsistent data obtained with the 16-carbon atom *p*-alkoxy analogues **59–61**. Also consistent with this interpretation is the finding that the unsaturated 18-carbon atom *p*-alkoxy analogue **79** is active, while the saturated congener **66** with the same chain length is not. It is known from natural fatty acids that unsaturation enhances absorption.[13]

The para-substituted alkoxybenzoates **42, 46**, and **60** are more active than the corresponding meta-substituted congeners **43, 48**, and **62**, respectively, while the ortho-substituted congener **49** was inactive (cf. also **14** vs. **13**). Compounds with additional aromatic electron-withdrawing

Table III. Hypolipidemic Activity of Substituted Benzoates



No.	X	R	Mp, °C[a] (lit. mp)	Recrystn solvent[b]	% yield[c]	Mol formula[d]	Dose, μmol/kg/day[f]	Effects on lipids in rats[a]			
								Plasma, % redn		Liver, % increase	
								Cholesterol	Triglycerides	Wt	Cholesterol
31	p-C_6H_{13}-n	H	99-100 (97[l])	B	33	$C_{13}H_{18}O_2$	906[g]	0	28[j]	8	4[i]
32	p-C_8H_{17}-n	H	100-102 (98-99[m])	B	43	$C_{15}H_{22}O_2$	538[g]	6[i]	21[i]	11	11[i]
33	p-$C_{10}H_{21}$-n	H	96-97 (95-97[m])	B	25	$C_{17}H_{26}O_2$	640[g]	32[j]	63[j]	18	43[j]
34	p-$C_{12}H_{25}$-n	H	98-100 (93-95[m])	B	13	$C_{19}H_{30}O_2$	1498[g]	55[j]	74[j]	38	323[j]
							558[g]	48[j]	78[j]	29	215[j]
							179[g]	34[j]	62[j]	14	79[j]
35	p-$C_{13}H_{27}$-n	H	99-100	B	38	$C_{20}H_{32}O_2$	571[g]	54[j]	77[j]	25	61[j]
36	p-$C_{15}H_{31}$-n	H	101-103	B	43	$C_{22}H_{36}O_2$	415[h]	27[j]	58[i]	4	13[j]
37	p-$C_{19}H_{39}$-n	H	103-105	B	17	$C_{26}H_{44}O_2$	425[g]	8[i]	2[i]	10	0
38[k]	p-OC_6H_{13}-n	H	104-105 (105-150[n])			$C_{13}H_{18}O_3$	675[g]	6[i]	16[i]	1	
39[k]	p-OC_6H_{17}-n	H	100-110 (100-145[n])			$C_{15}H_{22}O_3$	591[h]	8[i]	35[i]	0	12
40	p-$OC_{10}H_{21}$-n	CH_3	47-48	B	(89)	$C_{18}H_{28}O_3$	489[g]	36[j]	94[j]	19	43[j]
41	p-$OC_{11}H_{23}$-n	CH_3	58-60	B	40	$C_{19}H_{30}O_3$	444[g]	45[j]	88[j]	23	41[j]
42[k]	p-$OC_{12}H_{25}$-n	H	132-137 (137[o])			$C_{19}H_{30}O_3$	470[h]	33[j]	58[j]	22	22
							428[g]	16[j]	31[j]		
43	m-$OC_{12}H_{25}$-n	CH_3	42-44	B	47	$C_{20}H_{32}O_3$	505[h]	7[i]	55[j]	4	
44	p-$OC_{13}H_{27}$-n	CH_3	66-67 (60-63[p])	B	35	$C_{21}H_{34}O_3$	496[h]	27[i]	31[i]	20	9
							460[g]	25[j]	70[j]	20	6[i]
45	p-$OC_{14}H_{29}$-n	H	98-130 (129-132[p,q])	B	76	$C_{21}H_{34}O_3$	407[h]	31[j]	39[i]	14	1[i]
							511[g]	24[j]	36[j]	19	2[i]
							275[g]	33[j]	46[j]	20	4[i]
							149[g]	16[j]	30[j]	5	7[i]
46	p-$OC_{14}H_{29}$-n	CH_3	65-66 (52-57[p])	J	62	$C_{22}H_{36}O_3$	445[n]	6[i]	49[j]	7	12[j]
							201[h]	23[j]	70[j]	0	12[j]
							98[h]	27[j]	72[j]	0	0
47	p-$OC_{14}H_{29}$-n	C_2H_5	41-42 (80-82[p])	E	45	$C_{23}H_{38}O_3$	461[h]	23[j]	42[j]	16	20[j]
							439[g]	24[j]	54[j]	10	3[i]
							392[g]	33[j]	61[j]	2	0
48	m-$OC_{14}H_{29}$-n	CH_3	47-48 (40-43[p])	B	45	$C_{22}H_{36}O_3$	462[g]	24[j]	59[j]	0	12[i]
							453[h]	0	51[j]	0	
49	o-$OC_{14}H_{29}$-n	CH_3	41-43	B	47	$C_{22}H_{36}O_3$	491[h]	0	0	0	
50	3-Cl-4-$OC_{14}H_{29}$	C_2H_5	51-53	E	55	$C_{23}H_{37}ClO_3$[r]	418[h]	0	0	0	
51	3,5-Cl_2-4-$OC_{14}H_{29}$	CH_3	37-39	A	74	$C_{22}H_{34}Cl_2O_3$[r]	381[h]	1[i]	73[j]	0	
52	2-CH_3-4-$OC_{14}H_{29}$	H	88-90	B	92	$C_{22}H_{36}O_3$	471[h]	6[i]	27[j]	5	
53	2-OH-4-$OC_{14}H_{29}$	C_2H_5	49-50	E	(48)	$C_{23}H_{38}O_4$	439[h]	0	0	1	
54	2-OCH_3-4-$OC_{14}H_{29}$	CH_3	60-62	A	89	$C_{23}H_{38}O_4$	417[h]	7[i]	0	0	
55	2,4-$(OC_{14}H_{29})_2$	H	40-53	B	9	$C_{35}H_{62}O_4$	291[h]	0	0	7	
56	3-CO_2CH_3-4-$OC_{14}H_{29}$-n	CH_3	42-43	A	58	$C_{24}H_{38}O_5$[s]	423[h]	7[i]	10[i]	0	
57	3-CO_2CH_3-5-$OC_{14}H_{29}$-n	CH_3	58-62	A	94	$C_{24}H_{38}O_5$	332[h]	5[i]	39[i]	0	
58	p-$OC_{15}H_{31}$-n	CH_3	72-73 (63-66[p])	B	67	$C_{23}H_{38}O_3$	439[h]	19[j]	46[j]	7	9
							419[g]	20[j]	57[j]	15	2[i]
							417[g]	37[j]	73[j]	0	9[i]

59	p-$OC_{16}H_{33}$-n	H	98-130 (97-131[p])	B	43	$C_{23}H_{38}O_3$	419[g]	15[i]	55[j]	5	17[j]
60	p-$OC_{16}H_{33}$-n	CH_3	70-72 (62-65[p])	B	57	$C_{24}H_{40}O_3$	385[g]	20[j]	63[j]	5	1[i]
							398[g]	14[i]	40[j]	12	2[i]
							204[g]	0	23[i]	10	0
61	p-$OC_{16}H_{33}$-n	C_2H_5	48-49	B	59	$C_{25}H_{42}O_3$	422[h]	8[i]	29[i]	11	9[i]
62	m-$OC_{16}H_{33}$-n	CH_3	52-53	B	69	$C_{24}H_{40}O_3$	430[h]	0	0	3	
							401[h]	0	32[i]	0	
63[k]	3-OCH_3-4-$OC_{16}H_{33}$	H	107-109 (108-110[t])			$C_{24}H_{40}O_4$	415[h]	3[i]	33[i]	0	
64[k]	3-$OC_{16}H_{29}$-4-NH_2	H	111-112			$C_{23}H_{39}NO_3$[u]	384[h]	1[i]	19[i]	0	
65	p-$OC_{17}H_{35}$-n	CH_3	76-78 (68-71[p])	A	88	$C_{25}H_{42}O_3$	420[h]	12[i]	53[j]	2	
66	p-$OC_{18}H_{37}$-n	CH_3	74-76 (69-72[p])	B	93	$C_{26}H_{46}O_3$	348[h]	0	0	5	7
67	p-$OC_{20}H_{41}$-n	CH_3	80-81 (76-78[p])	B	71	$C_{28}H_{50}O_3$	362[h]	0	0	4	0
68	p-$O(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$	H	95-97	B	78	$C_{17}H_{26}O_3$	553[h]	16[j]	18[i]	0	
69	p-$OCH(n\text{-}C_4H_9)C_7H_{15}$-n	H	73-76	A	23	$C_{19}H_{30}O_3$	541[h]	0	52[i]	2	
70	p-$OCH(CH_3)C_{12}H_{25}$-n	H	77-79	B	44	$C_{21}H_{34}O_3$	451[g]	35[j]	78[j]	12	25[i]
71	p-$O(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)$-$(CH_2)_3CH(CH_3)_2H$	H	55-58	B	49	$C_{22}H_{36}O_3$	264[h]	15[i]	80[j]	0	
72	p-$OCH_2CH{=}C(CH_3)_2$	CH_3	45-46	A	44	$C_{13}H_{16}O_3$	717[g]	8[i]	29[i]	9	2[i]
73	p-$O(CH_2)_2CH(CH_3)(CH_2)_2CH{=}C(CH_3)_2$	H	72-84	B	20	$C_{17}H_{24}O_3$	597[h]	15[i]	12[i]	4	
74	p-$OCH_2HC{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$	H	119-121	C	25	$C_{17}H_{22}O_3$[v]	565[h]	10[i]	33[j]	3	
75	p-$O(CH_2)_3C{\equiv}CC_8H_{11}$-n	H	125-126	K	79	$C_{17}H_{22}O_3$	558[g]	7[i]	23[i]	6	0
76	p-$O(CH_2)_9CH{=}CH_2$	H	77-134 (75-82, 119-120[p])	B	60	$C_{18}H_{26}O_3$	740[g]	40[j]	94[j]	28	43[j]
77	p-$O(CH_2)_9CH{=}CH_2$	CH_3	40-41 (35-37[p])	A	16	$C_{19}H_{28}O_3$	509[g]	51[j]	91[j]	33	36[j]
78		H	85-88 (82-85[p])	B	10	$C_{22}H_{30}O_3$	374[h]	13[i]	0	0	
79		CH_3	37-47	A	11	$C_{26}H_{42}O_3$	400[g]	29[j]	79[j]	15	0
80		H	171-173 (176-177[p])	B	6	$C_{19}H_{28}O_3$	539[h]	1[i]	37[j]	2	
81	p-$SC_{14}H_{29}$-n	H	108-110	E	22	$C_{21}H_{34}O_2S$[w]	428[h]	8[i]	6[i]	6	
82	p-$SC_{16}H_{33}$-n	H	106-108 (111[x])	E	31	$C_{23}H_{38}O_2S$[w]	404[h]	14[j]	0	6	
83	p-$NHC_{14}H_{29}$-n	C_2H_5	82-83	E	62	$C_{23}H_{39}NO_2$[u]	418[h]	20[i]	58[j]	6	13
84	p-$NHCOC_{11}H_{23}$-n	C_2H_5	88-90	B	93	$C_{21}H_{33}NO_3$[u]	489[h]	0	0	3	
85	p-$NHCOC_{13}H_{27}$-n	C_2H_5	95-96	B	81	$C_{23}H_{37}NO_3$[u]	474[h]	0	0	6	
86	p-$N(CH_3)COC_{13}H_{27}$-n	H	87-89	B	23	$C_{22}H_{35}NO_3$[u]	412[h]	9[i]	23[i]	0	
87	p-$O(CH_2)_{14}OC_6H_4COOCH_3$	CH_3	125-128	A	55	$C_{30}H_{42}O_6$	327[h]	1[i]	25[j]	9	

[a-k] See corresponding footnotes in Table I. [l] A. Zaki and H. Fahim, *J. Chem. Soc.*, 307 (1942). [m] F. K. Kirchner, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, 71, 1210 (1949). [n] B. Jones, *J. Chem. Soc.*, 1874 (1935). [o] B. Jones, *J. Chem. Soc.*, 420 (1939). [p] During our studies on fatty acid-like hypolipidemic compounds U.S. Patent 3 716 644 (1973) [*Chem. Abstr.*, 78, 110935b (1973)], issued to H. J. Albers, S. J. Riggi, F. L. Bach, and E. Cohen, appeared describing hypolipidemic use of several alkyloxybenzoates of Table III. Also see V. G. De Vries, D. B. Moran, G. R. Allen, and S. J. Riggi, *J. Med. Chem.*, 19, 946 (1976). [q] A. J. Herbert, *Trans. Faraday Soc.*, 63, 555 (1967). [r] Anal. C, H, Cl. [s] Calcd: C, 70.90; H, 9.42. Found: C, 71.59; H, 9.56. [t] See footnote *o* in Table I. [u] Anal. C, H, N. [v] Anal. Calcd: C, 74.42; H, 8.08. Found: C, 73.88; H, 8.18. [w] Anal. C, H, S. [x] Gevaert-Agfa N. V., Belgian Patent 667 370 (1965); *Chem. Abstr.*, 64, 16038 (1965).

Table IV. Hypolipidemic Activity of Substituted Furan- and Thiophenecarboxylic Acids

No.	X	Y	Mp, °C[a]	Recrystn solvent[b]	% yield[c]	Mol formula[d]	Dose, μmol/kg/day[f]	Effects on lipids in rats[e]			
								Plasma, % redn		Liver, % increase	
								Cholesterol	Triglycerides	Wt	Cholesterol
88	*n*-$OC_{10}H_{21}$	O	124–126 dec	A	27	$C_{15}H_{24}O_4$	540[h]	5[i]	46[i]	1	17
89	*n*-$OC_{12}H_{25}$	O	122–123 dec	A	11	$C_{17}H_{28}O_4$	533[h]	38[j]	79[j]	22	0
90	*n*-$OC_{13}H_{27}$	O	116–117 dec	H	10	$C_{18}H_{30}O_4$	319[h]	31[j]	6[j]	15	3
91	*n*-$OC_{14}H_{29}$	O	117–120 dec	B	46	$C_{19}H_{32}O_4$	154[g]	12[i]	27[i]	1	5
							314[g]	38[j]	61[j]	15	0
							410[h]	40[j]	75[j]	6	12
							583[g]	64[j]	92[j]	33	0
92	*n*-$SC_{14}H_{29}$	O	84–86	A	46	$C_{19}H_{32}O_3S^m$	443[h]	18[i]	62[j]		
93	*n*-$OC_{14}H_{29}$	S	95–96	B	10	$C_{19}H_{32}O_3S^{m,n}$	441[h]	54[j]	83[j]	21	1
94	*n*-$SC_{14}H_{29}$	S	106–108	B	39	$C_{19}H_{32}O_2S_2{}^m$	463[h]	15[j]	61[i]	4	
95	*n*-$OC_{16}H_{33}$	O	118–119 dec	A	18	$C_{21}H_{36}O_4$	437[h]	24[j]	25[i]	4	5
96	*n*-$OC_{18}H_{37}$	O	117–118 dec	A	10	$C_{23}H_{40}O_4$	420[h]	18[j]	53[j]	0	18
97	$-O(CH_2)_8HC{=}CHC_8H_{17}$	O	93–96	A	7	$C_{23}H_{38}O_4$	351[h]	4[i]	26[i]	0	11

[a–k] See corresponding footnotes in Table I. [l] Anal. Calcd: C, 69.64; H, 9.74. Found: C, 69.19; H, 9.68. [m] Anal. C, H, S. [n] Anal. Calcd: C, 67.03; H, 9.47; S, 9.40. Found: C, 67.13; H, 9.89; S, 9.43.

or -donating substituents (**50–57**, **63**, **64**) were found to be inactive. It appears that changes in electron density of the benzene ring do not enhance activity. Alternatively, drug–receptor interaction may be diminished by additional steric bulk on the aromatic ring or the loss of activity may be due to poor absorption of these polysubstituted derivatives.

Compounds with a branched *p*-alkoxy side chain **68–71** and a cyclic alkoxy analogue **80** generally had inferior biologic properties. Of several unsaturated and polyunsaturated analogues, **72–79**, all but two had activities similar to those of the corresponding saturated analogues. The exceptions were **75**, which was inactive while the corresponding saturated analogue **40** had hypolipidemic activity, and **79**, which has already been discussed. Thus, features making the compound less like natural fatty acids result in decreased activity.

Replacement of the oxygen heteroatom in compound **47** with an amino function retains biologic activity as seen by alkylaminobenzoate **83**. However, the alkylthio analogues **81** and **82** had only marginal activity. Alkylamidobenzoates **84–86** and the "bis" analogue **87** were inactive.

It was concluded from this study that the *p*-tetradecyloxy side chain provided the optimal hypolipidemic activity in the benzoates and benzoylacetate series (Table III).

Replacement of the benzene ring in **45** with a furan or thiophene heterocycle (**91** and **93**) enhanced the potency of the fatty acid-like hypolipidemic compounds. The optimal structural parameters were studied in the 5-alkoxy-2-furancarboxylic acid series (Table IV) and structure–activity relationships appeared to parallel those of the alkyloxybenzoates (Table III). A chain length of at least 12 carbon atoms was required for hypocholesterolemic activity in the furoic acid series. Biologic potency decreased with an alkyloxy chain of 18 carbon atoms (**96**). The corresponding benzoate **66** had little or no activity. The tetradecyloxy chain represents the optimal structure in this heterocyclic carboxylic acid series. Thiophenecarboxylic acid **93** was found to be equivalent to furan **91** in hypolipidemic potency.

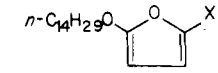
As predicted from our previous studies, ester derivatives **98** and **99** as well as imidazolide **100** retain biologic activity. The amide **101**, the decarboxylated product **102**, and the acetyl derivatives **103–105** had little or no hypolipidemic activity (Table V).

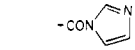
5-(Tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) was selected for extended biologic evaluation, as discussed in the last section (vide infra).

Chemistry. The β-keto esters (Table I) were prepared by a modification of the method of Stiles[14] from methyl ketones and magnesium methyl carbonate. It was found that the magnesium chelates derived from *p*-alkoxyacetophenones could not be converted directly to the β-keto esters by treatment with alcohols due to extensive hydrolysis to β-keto acids. The latter, however, could readily be obtained in good yields under appropriate conditions and were converted to the esters via the mixed anhydrides with trifluoroacetic acid. This method also permitted preparation of the ethyl, benzyl, and acetylaminoethyl esters (**7–9**) as well as the amide **10**. The copper chelates **5** and **11** were obtained by reaction with cupric acetate, as described in the Experimental Section.

The cinnamic acid ester analogue **17** (Table II) was obtained from *p*-hydroxycinnamic acid ester, tetradecyl bromide, and base as described in the Experimental Section. In analogous fashion were compounds **15**, **16**, **21**, **22**, **26**, **27**, and **29** prepared. The synthesis of the phe-

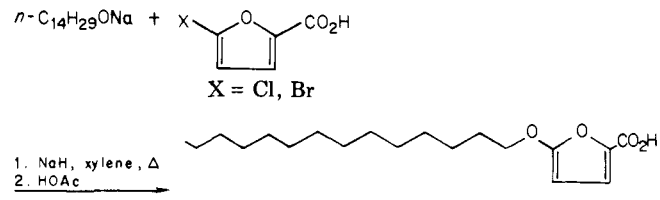
Table V. Hypolipidemic Tetradecyloxyfuran Derivatives



No.	X	Mp, °C[a]	Recrystn solvent[b]	% yield[c]	Mol formula[d]	Effects on lipids in rats[e]				
						Dose, μmol/kg/day[f]	Plasma, % redn		Liver, % increase	
							Cholesterol	Triglycerides	Wt	Cholesterol
98	$-CO_2CH_3$	56-58	A	25	$C_{20}H_{34}O_4$	430[h]	32[j]	67[j]	8	0
99	$-CO_2C_2H_5$	39-40	E	94	$C_{21}H_{36}O_4$	443[h]	30[j]	64[j]	6	0
100		74-76	H	67	$C_{22}H_{34}N_2O_3$[l]	403[h]	22[j]	39[j]	14	1
101	$-CONH_2$	132-134	H	75	$C_{19}H_{33}NO_3$[m]	482[h]	0	14[i]	7	
102	-H	(Oil)[n]		77	$C_{18}H_{32}O_2$	524[h]	0	0	1	
103	$-COCH_3$	70-72	B	43	$C_{20}H_{34}O_3$	499[h]	0	21[i]	0	
104	$-COCF_3$	55-57	B	82	$C_{20}H_{31}F_3O_3$	420[h]	2[i]	30[j]	0	
105	$-COCCl_3$	52-53	A	58	$C_{20}H_{31}Cl_3O_3$[o]	369[h]	9[j]	33[j]	6	

[a-k] See corresponding footnotes in Table I. [l] Anal. Calcd: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.68; H, 9.66; N, 7.02. [m] Anal. C, H, N. [n] Purified by chromatography on alumina. [o] Anal. Calcd: C, 56.41; H, 7.34; Cl, 24.93. Found: C, 57.23; H, 7.68; Cl, 24.35.

Scheme II



91 (RMI 14 514)

nylthioacetic acid **30** is described in the Experimental Section. The amides **19** and **20** were obtained via the acid chloride, and the hydroxymethyl analogue **23** was obtained by sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) reduction of the acid **45**. Benzyl alcohol **23** was acetylated to **24** or converted to **25** by treatment with ethyl chloroformate. Preparation of the tetrazole analogue **28** is described in the Experimental Section. The benzoic acids and esters (Table III) were prepared by known methods and as examples the preparation of **45**, **47**, **71**, and **79** is described in the Experimental Section.

Alkylthiobenzoates **81** and **82** were synthesized by the reaction of *p*-bromobenzoate with the corresponding thio alcohol. The tetradecylaminobenzoate **83** was prepared by N-alkylation of ethyl *p*-aminobenzoate with tetradecyl bromide. Amides **84-86** were synthesized from ethyl *p*-aminobenzoate by known methods. Representative examples are described in the Experimental Section. No efforts were made to obtain optimal yields, except for compounds **8** and **45**, and in many instances the waxy nature of the compounds caused considerable losses during purification.

The substituted furan- and thiophenecarboxylic acids (Table IV) were prepared by nucleophilic displacement of the halogen of haloheterocyclic acids with alkoxide or thioalkoxide ion as shown in Scheme II for **91**. Manly and Amstutz[15] studied the reaction of 5-bromo-2-furancarboxylic acid esters with short-chain alkoxide ions. We found that long-chain esters (tetradecyl 5-bromo-2-furancarboxylate) gave little or no reaction with sodium tetradecylate; the free acid gave reasonable yields (30-60%) of the alkyloxy- and alkylthiofurancarboxylic acids.

The following observations were made during this study. (A) The chloro-substituted heterocyclic acids were more reactive than the bromo acids. Alkyloxythiophene **93** could only be obtained from 5-chloro-2-thiophenecarboxylic acid. (B) Sodium or sodium hydride was found to be more effective than other bases; KNH_2, KO-*t*-Bu, or LiH gave no reaction. (C) A number of solvents can be used in this synthesis. Xylene gave higher yields and cleaner products than solvents such as DMF, DMA, or HMPA. The synthesis of furan **91** and thiophene **94** is described in the Experimental Section.

The alkyloxyfurancarboxylic acids were found to be unstable to strong acid. Compound **91** in methanolic HCl decomposed rapidly at room temperature to give tetradecanol and products of ring opening. Esters **98** and **99** were prepared by reaction of **91** potassium salt with dimethyl sulfate and ethyl iodide, respectively. The imidazolide **100** was also used for preparation of **99** as well as for conversion to amide **101**.

The furancarboxylic acids are also heat labile. The compounds of Table IV underwent rapid decarboxylation at their melting points. This process was used for the preparation of **102**. The thiophene derivatives **93** and **94** were more stable to acid and heat. Attempted Friedel-Crafts acylation of **102** with Ac_2O or AcCl resulted in decomposition. The desired product **103** was obtained by the reaction of acid **91** with methyllithium. Mixed anhydrides of acetic acid with either trichloro- or trifluoroacetic acid did not give **103** but the trihaloacetyl compounds **104** and **105**. These derivatives were also obtained by use of trichloro- or trifluoroacetic anhydride under mild conditions without catalyst. Hydrolysis of **105** afforded the carboxylic acid **91**. This procedure was recommended for the preparation of radiolabeled **91**.

Biologic Evaluation of 5-(Tetradecyloxy)-2-furancarboxylic Acid (91, RMI 14514).[4] The hypolipidemic activity of **91** (RMI 14514) was compared with that of clofibrate [ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate] in rats. Rats were fed diets containing varying concentrations of **91** or clofibrate for 4-10 days. Plasma cholesterol and triglyceride levels were determined and compared with those obtained from untreated control rats. **91** produced a dose-related reduction of plasma cholesterol levels, ranging up to 64% reduction at 583 μmol/kg/day. Under identical conditions, the greatest reduction produced by clofibrate was approximately 40% in a dose range of 766-1693 μmol/kg/day. Thus, the maximum hypocholesterolemic effect attainable with **91** was found to be greater than that attainable with clofibrate. Comparable

Table VI. Effect of RMI 14 514 and Clofibrate on Incorporation of Label from [1-^{14}C]Acetate into Cholesterol and Fatty Acids in Vivo

Group	Daily dose mg/kg/day	Daily dose μmol/kg/day	Liver fatty acids,[a] dpm × 10^{-3}	Liver cholesterol,[a,b] dpm × 10^{-3}
Ad Lib Fed Rats				
Control			27.2 ± 4.8	12.7 ± 2.6
91 (RMI 14514)	154	475	22.8 ± 2.1	14.9 ± 2.9
Clofibrate	261	1075	50.0 ± 12.2	4.1 ± 0.6[c]
Meal-Fed Rats				
Control			182 ± 22	41.3 ± 3.2
91 (RMI 14514)	95	293	60 ± 32[c]	40.8 ± 3.2
Clofibrate	188	775	205 ± 18	43.3 ± 7.0

[a] All rats injected intraperitoneally with 5.8 μ Ci of sodium [1-^{14}C]acetate. [b] Measured as digitonin precipitable sterols. [c] Indicates $p < 0.01$.

effects on reduction of plasma triglyceride levels were obtained with both drugs, although **91** appeared to be slightly more potent than clofibrate.

In vivo experiments indicated that, in contrast to clofibrate,[16] **91** does not inhibit cholesterol biosyntheses from acetate. On the other hand, de novo biosynthesis of fatty acids was found to be inhibited in meal-fed rats pretreated with **91**, while no inhibition was found in clofibrate-treated rats. Rats were fed diets containing no drug, 0.15% **91**, or 0.25% clofibrate. One-half of each diet group was fed ad lib, and the other half was fed its food in meals lasting 2 h each day. After 7 days of treatment, each rat was injected intraveneously with sodium [1-^{14}C]acetate. The rats were sacrificed exactly 1 h after injection of labeled acetate, and the livers were removed for isolation of cholesterol and total fatty acids. Radioactivity in the lipid fractions was determined in a liquid scintillation spectrometer. The data are shown in Table VI. The results indicate that the mechanism by which **91** exerts hypolipidemic effects is different from that of clofibrate. Gas chromatographic analysis of various lipid fractions isolated from livers of rats treated with RMI 14 514 for 2 weeks indicated that the drug was not incorporated into liver triglycerides or cholesterol esters. A trace amount of drug was found in the liver phospholipid fraction.

Compound **91** was also evaluated in rhesus monkeys at 92 and 308 μmol/kg/day (30 and 100 mg/kg/day, two animals per dose level) and gave 10–16% and 24–28% reduction of plasma cholesterol, respectively, after 28 days of treatment. Furan **91** has been selected for pathologic–toxicologic evaluation and extended biological studies.

Experimental Section

Melting points are corrected and were taken on a Thomas-Hoover capillary melting point apparatus; boiling points are uncorrected. IR spectra were taken on a Perkin-Elmer 521 instrument. UV spectra were taken on a Cary 17 instrument. NMR spectra were taken on a Varian Model A-60 instrument (Me_4Si as internal standard). Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4%.

Biological Methods. Young male rats of the Wistar strain, obtained from Royalhart Laboratory Animals, Inc., New Hampton, N.Y., of average initial weight of 170–190 g were used in these tests. The compounds to be tested were mixed thoroughly with Purina Lab Chow (Ralston Purina Co., St. Louis, Mo.), and the diet was fed ad libitum to groups of six animals for 4 or 10 days. An untreated control group was included in each experiment. Food consumption and body weights were routinely recorded and these data were used to calculate the average daily dose of the test compounds. For example, compound **91** (Table IV) was administered in food at levels of 0.05, 0.1, 0.15, and 0.2%. Daily dosage calculated from food consumption was 154, 314, 410, and 583 μmol/kg (50, 102, 133, and 189 mg/kg), respectively. At the end of the treatment period, the rats were bled by cardiac puncture. Plasma cholesterol[17] and triglyceride[18] levels were determined on the Technicon Auto Analizer (Technicon Instrument Corp., Tarrytown, N.Y.).

Livers were rapidly excised, blotted, and weighed at the end of the treatment period. Total lipids were extracted and washed by the Folch[19] procedure and aliquots were evaporated to dryness and redissolved in *i*-PrOH for automated cholesterol determination.

Values for plasma cholesterol and triglyceride concentration in the treated animals were compared with the values obtained for untreated control rats run simultaneously. Significance of the difference between the values was calculated by the Student's *t* test. The data are expressed as percent reduction from control levels. Liver weight is expressed in g/100 g of final body weight, and liver cholesterol concentration is expressed as mg/g of wet tissue.

Typical control groups had plasma cholesterol and triglyceride concentrations of 58 and 66 mg/100 mL, respectively, and liver cholesterol concentrations of 2.63 mg/g.

To determine the effects on cholesterol and fatty acid synthesis, male rats of the same strain and from the same source as described above were fed diets containing no drug: 0.15% **91** or 0.25% clofibrate. One-half of each dietary group was given their diet ad lib while the other half was fed their diets in a single meal lasting 2 h each day (8:30 to 10:30). The meal-fed group had been trained to the feeding schedule for 1 week prior to the start of the experiment. After 7 days of dietary treatment, each rat was injected intraveneously with 5.8 μCi of sodium [1-^{14}C]acetate, about 4.5 h after the meal-fed group was given their food. Each rat was sacrificed exactly 1 h after injection of the labeled precursor, and livers were removed. The livers were homogenized in chloroform–methanol (2:1). Aliquots of the homogenates were taken for isolation of neutral sterols and fatty acids by conventional methods. Cholesterol was isolated from the neutral sterol fraction as its digitonide. Incorporation of label into these lipids was determined by liquid scintillation spectrometry, using an external standard to correct for quenching.

2-[4-(Tetradecyloxy)benzoyl]acetic Acid Benzyl Ester (8). A mixture of 83.0 g (0.61 mol) of 4′-hydroxyacetophenone, 169.0 g (0.61 mol) of 1-bromotetradecane, and 33.0 g (0.61 mol) of $NaOCH_3$ in 1.5 L of dry dimethylformamide was refluxed for 2 h. After the mixture cooled, it was poured into ice–water, the product was extracted with Et_2O, the extract was washed (1 N NaOH, H_2O) and dried (Na_2SO_4), and the solvent was evaporated. The residue was crystallized and recrystallized from hexane and gave 162.0 g (80%) of 4′-(tetradecyloxy)acetophenone. A sample was further recrystallized, mp 58–59 °C. Anal. ($C_{22}H_{36}O_2$) C, H.

A mixture of 100.0 g (0.30 mol) of 4′-tetradecyloxyacetophenone and 900.0 g (1.8 mol) of 2 N magnesium methyl carbonate reagent in dimethylformamide,[14,20] saturated with CO_2, was heated to 120 °C under a stream of N_2 for 4 h while the MeOH that is formed was allowed to escape. The mixture was allowed to cool under CO_2 and was poured slowly into 4 L of concentrated HCl–ice (1:1). The resulting precipitate of 2-[4-(tetradecyloxy)benzoyl]acetic acid was collected, washed with H_2O (about 6 L), and dried at room temperature over P_2O_5 in a desiccator at 0.1 mm overnight: 110.0 g (97%); IR (KBr) 1680, 1600 cm^{-1}; mp 86–89 °C dec [remelts at 57–59 °C, i.e., as 4′-(tetradecyloxy)acetophenone].

To a stirred, ice-cooled solution of 15.0 g (0.04 mol) of the above β-keto acid in 300 mL of anhydrous Et_2O was added 15.0 g (0.072 mol) of $(CF_3CO)_2O$, and, after it was stirred for 30 min at room temperature to allow formation of the mixed anhydride, 15.0 g (0.139 mol) of $C_6H_5CH_2OH$ was added. The mixture was stirred at room temperature for 2 h. More Et_2O was added, the extract was washed (H_2O, saturated $NaHCO_3$ solution) and dried (Na_2SO_4), and the solvent was evaporated. The residue was crystallized and recrystallized twice from MeCN: 11.8 g (64%) of **8** (Table I); IR (KBr) 1730, 1680 cm^{-1}; UV (dioxane) 275 nm (ε 17 600). This procedure was also used to prepare compounds **7**, **9**, and **10**.

The copper chelate **11** was prepared by adding a hot, filtered solution of 0.9 g (4.5 mmol) of cupric acetate in 100 mL of MeOH

to a refluxing solution of 3.0 g (7.7 mmol) of **6** in 200 mL of MeOH. The solution was concentrated to about 200 mL and the precipitate that formed on cooling was collected, washed with MeOH–hexane, and recrystallized from tetrahydrofuran to give 2.1 g (66%) of **11** (Table I): UV (dioxane) 309 nm (ϵ 40600). The Cu chelate **5** was similarly prepared.

(*E*)-3-[4-(Tetradecyloxy)phenyl]-2-propenoic Acid Methyl Ester (17). A mixture of 20.7 g (0.116 mol) of *p*-hydroxycinnamic acid methyl ester and 6.3 g (0.116 mol) of NaOMe in 200 mL of dry dimethylformamide was allowed to stand for 15 min and then 32.3 g (0.116 mol) of 1-bromotetradecane was added. The mixture was stirred at reflux temperature for 1.5 h, was allowed to cool, was poured into H_2O, and was extracted with Et_2O. The extract was washed (1 N NaOH, H_2O) and dried (Na_2SO_4), and the solvent was evaporated. The semicrystalline residue was recrystallized from hexane to give 37.5 g (86%) of **17** (Table II): UV (dioxane) 309 nm (ϵ 24800).

5-[4-(Tetradecyloxy)phenyl]-1*H*-tetrazole (28). A mixture of 100.3 g (0.37 mol) of *n*-$BrC_{14}H_{29}$, 44.0 g (0.37 mol) of 4-cyanophenol, and 51.0 g (0.37 mol) of anhydrous K_2CO_3 in 500 mL of dry dimethylformamide was stirred at reflux temperature for 18 h. The mixture was allowed to cool, was poured into H_2O, and was extracted with Et_2O. The extract was washed (1 N KOH, H_2O) and dried (Na_2SO_4) and the solvent was evaporated to give 105 g (91%) of **21**: mp 50–55 °C; IR (KBr) 2220 cm^{-1}. A sample was recrystallized to give the material listed in Table II.

A mixture of 20.0 g (0.064 mol) of **21**, 4.2 g (0.065 mol) of NaN_3, and 3.5 g (0.065 mol) of NH_4Cl in 200 mL of dry dimethylformamide was refluxed for 4 h; about one-half of the solvent was removed under reduced pressure and the residue was poured into H_2O. The precipitate resulting after acidification with 2 N HCl was crystallized and recrystallized from Me_2CO to give **28** (Table II): UV (dioxane) 257 nm (ϵ 20400).

2-[4-(Tetradecyloxy)phenylmercapto]acetic Acid (30). A mixture of 25.0 g (0.199 mol) of 4-mercaptophenol and 10.7 g (0.199 mol) of $NaOCH_3$ in 500 mL of dry dimethylformamide was stirred for 15 min, and then 33.2 g (0.199 mol) of ethyl bromoacetate was added. The mixture was heated on a steam bath for 4 h, allowed to stand at room temperature overnight, then diluted with H_2O, and extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated to give 39.9 g (95%) of 4-hydroxyphenylthioacetic acid ethyl ester. This ester was combined with 10.2 g (0.188 mol) of $NaOCH_3$ and 300 mL of dry dimethylformamide. The mixture was heated on a steam bath for 1 h, 52.0 g (0.188 mol) of 1-bromotetradecane was added, and the mixture was refluxed for 2 h. The cooled mixture was diluted with H_2O and extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated to give 74.7 g (97%) of crude 2-[4-(tetradecyloxy)phenylmercapto]acetic acid ethyl ester. The ester was hydrolyzed with refluxing 1 N methanolic KOH (1 L); H_2O was added and MeOH was distilled off. The resulting aqueous suspension was acidified with 2 N HCl, and the yellow precipitate was collected, dried, and recrystallized twice from hexane to give 31.8 g (42%) of **30** (Table II); UV (dioxane) 234 nm (ϵ 10000); IR (KBr) 1700 cm^{-1}.

4-(Tetradecyloxy)benzoic Acid (45). A mixture of 13.1 g (0.086 mol) of methyl *p*-hydroxybenzoate and 4.65 g (0.086 mol) of NaOMe in 200 mL of dry dimethylformamide was allowed to stand for 30 min, 20.0 g (0.086 mol) of *n*-$C_{14}H_{29}Cl$ was added, and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure, the residue was taken up in Et_2O, the extract was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized from Et_2O to give 18.2 g (62%) of **46** (Table III).

The ester was hydrolyzed by refluxing 10.5 g (0.03 mol) of **47** in 300 mL of MeOH and 100 mL of 2 N KOH for 1 h. More H_2O was added and the MeOH was allowed to distill off. The residual aqueous suspension was acidified with 2 N HCl and extracted with CH_2Cl_2. The extract was washed (H_2O) and dried ($MgSO_4$) and the solvent was evaporated. The resulting waxy solid was recrystallized from hexane to give 7.6 g (76%) of **45** (Table III).

4-(Tetradecyloxy)benzoic Acid Ethyl Ester (47). A mixture of 42.5 g (0.127 mol) of 4-(tetradecyloxy)benzoic acid (**45**) and 300 mL of $SOCl_2$ was refluxed for 3 h. The $SOCl_2$ was removed under reduced pressure to give 43.8 g of the corresponding acid chloride. A mixture of 32.8 g (0.093 mol) of the acid chloride and 500 mL of EtOH was refluxed for 1 h and cooled and the product was collected. Recrystallization from EtOH gave 15.2 g (45%) of **47**, mp 41–42 °C. The melting point does not agree with lit. mp 80–82 °C (Table III): UV (dioxane) 256 nm (ϵ 19000); IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$) δ 8.02 (d, 2, J = 9 Hz, phenyl 2 position), 6.92 (d, 2, J = 9 Hz, phenyl 3 position), 4.37 (q, 2, J = 7 Hz, OCH_2CH_3), 4.00 (t, 2, J = 6 Hz, *n*-$OCH_2C_{13}H_{27}$), 1.37 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

3-Chloro-4-(tetradecyloxy)benzoic Acid Ethyl Ester (50). To 10.0 g (0.0276 mol) of 4-(tetradecyloxy)benzoic acid ester (**47**) and 200 mL of HOAc was added 4.1 g (0.0290 mol) of SO_2Cl_2. The mixture was heated on a steam bath for 1 h, the solvent was removed under reduced pressure, and the residue was crystallized from EtOH to give 6.0 g (55%) of **50** (Table III): UV (dioxane) 256 nm (ϵ 16200).

3,5-Dichloro-4-(tetradecyloxy)benzoic Acid Methyl Ester (51). A mixture of 9.1 g (0.0262 mol) of 4-(tetradecyloxy)benzoic and methyl ester (**46**) and 20 mL of SO_2Cl_2 in 200 mL of HOAc was refluxed for 4 h. The solvent was removed under reduced pressure and the residue crystallized from MeOH to give 7.8 g (74%) of **51** (Table III): UV (dioxane) 248 nm (ϵ 10500).

4-(3,7,11-Trimethyldodecyloxy)benzoic Acid (71). To 25.0 g (0.11 mol) of 3,7,11-trimethyl-1-dodecanol, cooling in an ice bath, was added 50 mL of $SOCl_2$; the mixture was allowed to warm to room temperature and was refluxed for 15 min. The excess $SOCl_2$ was removed under reduced pressure by repeated azeotroping with benzene and toluene and finally by heating to 150 °C at 0.1 mm for 1 h. To the resulting dark oil (27.1 g, 100%) was added 16.7 g (0.11 mol) of *p*-hydroxybenzoic acid methyl ester, 5.9 g (0.11 mol) of NaOMe, 2.0 g of NaI, and 250 mL of dry dimethylformamide, and the mixture was stirred at reflux temperature for 2 h. The mixture was allowed to cool, was poured into H_2O, and was extracted with Et_2O. The extract was washed (cold 1 N NaOH, H_2O) and dried (Na_2SO_4) and the solvent was evaporated. Since the residue failed to crystallize, it was hydrolyzed with refluxing 1 N methanolic KOH (300 mL); H_2O was added and MeOH was distilled off. The resulting aqueous suspension was acidified with 2 N HCl, the product was extracted into Et_2O, the extract was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized twice from hexane to give 18.6 g (49%) of **71** (Table III).

4-(9-Octadecenyloxy)benzoic Acid Methyl Ester (79). To an ice-cold solution of 26.1 g (0.097 mol) of oleyl alcohol in 100 mL of dry pyridine was added 34.2 g (0.30 mol) of CH_3SO_2Cl. The mixture was stirred at 0 °C for 1 h and poured into H_2O, and the mesylate was extracted into Et_2O. The extract was washed (H_2O, saturated $NaHCO_3$ solution, H_2O) and dried (Na_2SO_4) and the solvent was evaporated. To the residue (34.2 g, 97%) was added a solution of 14.3 g (0.095 mol) of *p*-hydroxybenzoic acid methyl ester and 5.1 g (0.095 mol) of NaOMe in 300 mL of dimethylformamide. The mixture was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was taken up in Et_2O. The extract was washed (H_2O, 1 N KOH) and dried (Na_2SO_4) and Et_2O was evaporated. The residue was a waxy solid, 34.6 g, that after one recrystallization from hexane and two from MeOH gave 4.2 g (11%) of **79** (Table III).

4-(Tetradecylthio)benzoic Acid (81). To a mixture of 21.5 g (0.107 mol) of *p*-bromobenzoic acid and 11.6 g (0.214 mol) of NaOMe in 400 mL of *N*,*N*-dimethylacetamide was added 24.7 g (0.107 mol) of 1-tetradecanethiol, and the mixture was stirred at reflux temperature overnight. The mixture was allowed to cool, was poured into ice–water, acidified with 2 N HCl, and extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4) and the solvent was evaporated. The residue crystallized from hexane and was recrystallized from EtOH to give 8.5 g (22%) of 81 (Table III): UV (dioxane) 293 nm (ϵ 19200).

4-(Tetradecylamino)benzoic Acid Ethyl Ester (83). A mixture of 23.0 g (0.139 mol) of *p*-aminobenzoic acid ethyl ester and 19.2 g (0.139 mol) of K_2CO_3 in 500 mL of dry dimethylformamide was stirred at room temperature for 15 min. To this mixture 38.5 g (0.139 mol) of 1-bromotetradecane in 100 mL of dry dimethylformamide was added over a 45-min period. The mixture was refluxed for 5 h and the cooled mixture was diluted with H_2O and extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4), and solvent was evaporated to give a waxy solid residue. Crystallization from hexane and recrystallization

from EtOH gave 31 g (62%) of **83** (Table III): UV (dioxane) 299 nm (ε 25 800); IR (KBr) 3380, 1680 cm^{-1}.

4-[(1-Oxododecyl)amino]benzoic Acid Ethyl Ester (84). A mixture of 28.4 g (0.172 mol) of *p*-aminobenzoic acid ethyl ester and 17.7 g (0.175 mol) of Et_3N in 500 mL of Et_2O was cooled on an ice bath. To this mixture 37.6 g (0.172 mol) of lauroyl chloride in 200 mL of Et_2O was added over a 30-min period and stirred for an additional 30 min. The mixture was filtered, the Et_2O filtrate was washed with H_2O and dried (Na_2SO_4), and the Et_2O was evaporated to give a waxy residue. Crystallization from hexane gave 55.6 g (93%) of **84** (Table III): UV (dioxane) 273 nm (ε 24 500); IR (KBr) 3325, 1710, 1660 cm^{-1}.

4,4'-(Tetradecylenedioxy)dibenzoic Acid Dimethyl Ester (87). To an ice-cooled solution of 12.2 g (0.053 mol) of 1,14-tetradecanediol in 250 mL of dry pyridine was added 27 mL (40.0 g, 0.350 mol) of CH_3SO_2Cl and the mixture was allowed to stand at room temperature for 3 h. The mixture was poured into 6 N HCl–ice, and the dimesylate was extracted into CH_2Cl_2. The extract was washed (H_2O) and dried (Na_2SO_4) and the solvent was evaporated. The residue was combined with 24.4 g (0.160 mol) of *p*-hydroxybenzoic acid methyl ester, 8.6 g (0.160 mol) of NaOMe, and 500 mL of dry dimethylformamide, and the resulting mixture was heated on a steam bath overnight. The mixture was poured into ice–water and the resulting precipitate was collected, washed with water, and dissolved in CH_2Cl_2. The solution was dried (Na_2SO_4) and the solvent was evaporated. The residue was recrystallized twice from MeOH and gave 14.6 g (55%) of **87** (Table III): UV (dioxane) 256 nm (ε 36 800).

5-(Tetradecyloxy)-2-furancarboxylic Acid (91). A mixture of 659 g (3.0 mol) of 1-tetradecanol, 203 g (5.0 mol) of sodium hydride (59% in oil), and 6 L of dry xylene was refluxed with stirring for 2 h and allowed to cool to 70 °C. To this mixture 382 g (2.0 mol) of 5-bromo-2-furancarboxylic acid was added and the reaction refluxed with stirring for 42 h. The cooled mixture was diluted with 9 L of Et_2O and treated with 5 L of 10% aqueous HOAc. The organic layer was separated, washed with H_2O, and dried (Na_2SO_4). The Et_2O was removed under reduced pressure at 30–40 °C, the xylene solution was cooled, and the precipitate was collected. Recrystallization from 2-butanone gave 298 g (46%) of **91** (Table IV): UV (dioxane) 277 nm (ε 16 500); IR (KBr) 1650, 1515 cm^{-1}; NMR (Me_2SO-d_6) 7.10 (d, 1, J = 4 Hz, furan 3 position), 5.52 (d, 1, J = 4 Hz, furan 4 position), 4.10 ppm (t, 2, CH_2O).

5-(Tetradecylthio)-2-thiophenecarboxylic Acid (94). To a mixture of 18.6 g (0.090 mol) of 5-bromo-2-thiophenecarboxylic acid and 25.0 g (0.109 mol) of 1-tetradecanethiol in 500 mL of dry dimethylacetamide was added 10.8 g (0.20 mol) of $NaOCH_3$. The mixture was heated and the MeOH that is formed was allowed to escape. The mixture was refluxed for 24 h. The cooled mixture was acidified with 1 N HCl and the precipitate was collected and dried. The residue was crystallized from MeOH and recrystallized from hexane to give 12.0 g (39%) of **94** (Table IV): UV (dioxane) 314 nm (ε 10 100); IR (KBr) 1690, 1525 cm^{-1}; NMR ($CDCl_3$) δ 7.70 (d, 1, J = 4 Hz, thiophene 3 position), 6.97 (d, 1, J = 4 Hz, thiophene 4 position), 2.97 ppm (t, 2, CH_2S).

5-(Tetradecyloxy)-2-furancarboxylic Acid Ethyl Ester (99). To a mixture of 10.0 g (0.0308 mol) of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**) and 4.3 g (0.0340 mol) of K_2CO_3 in 100 mL of dry dimethylformamide was added 15.6 g (0.1 mol) of EtI. The mixture was refluxed overnight, then diluted with H_2O and extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4) and the solvent evaporated to give a residue. Crystallization from EtOH gave 10.3 g (94%) of **99** (Table V): UV (dioxane) 277 nm (ε 17 500); IR (KBr) 1700 cm^{-1}.

1-[5-(Tetradecyloxy)-2-furanylcarbonyl]-1*H*-imidazole (100). A mixture of 6.5 g (0.020 mol) of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**) and 4.1 g (0.025 mol) of 1,1'-carbonyldiimidazole in 100 mL of tetrahydrofuran was refluxed for 1 h and the solvent was evaporated to 40 mL. The mixture was allowed to cool, was diluted with H_2O, and was extracted with Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated to give 7.2 g of a white solid. Crystallization from acetone gave 5.0 g (67%) of **100** (Table V): IR (KBr) 1680, 1580, 1530 cm^{-1}.

5-(Tetradecyloxy)-2-furancarboxamide (101). A mixture of 10.0 g (0.031 mol) of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**) and 5.2 g (0.032 mol) of 1,1'-carbonyldiimidazole in 150 mL of tetrahydrofuran was refluxed for 30 min and then allowed to cool. To the stirred, ice-cooled mixture of the above imidazolide was added 500 mL of strong ammonia solution. The reaction was stirred for 30 min and then filtered. The precipitate was washed with H_2O, dried, and crystallized from acetone to give 7.5 g (75%) of **101** (Table V): IR (KBr) 3425, 1640, 1580, 1530 cm^{-1}.

2-(Tetradecyloxy)furan (102). A mixture of 10.0 g (0.0308 mol) of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**) in 100 mL of γ-picoline was refluxed for 48 h and the solvent evaporated under reduced pressure to give 9.0 g of an oil. The oil was chromatographed on alumina with Et_2O as the eluent to give 6.6 g (77%) of **102** (Table V): UV (dioxane) 223 nm (ε 7091); NMR ($CDCl_3$) δ 6.90 (m, 1, furan 4 position), 6.29 (m, 1, furan 5 position), 5.18 (m, 1 furan 3 position), 4.05 ppm (t, 2, CH_2O).

1-[5-(Tetradecyloxy)-2-furanyl]ethanone (103). To an ice-cooled mixture of 25.0 g (0.077 mol) of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**) in 600 mL of Et_2O was added 5.5 g (0.25 mol) of methyllithium in Et_2O. The mixture was stirred at room temperature for 1.5 h, cooled in an ice bath, and decomposed by slow addition of 14.0 g (0.262 mol) of NH_4Cl in 60 mL of H_2O. The Et_2O layer was separated, washed (H_2O, 5% aqueous $NaHCO_3$), and dried (Na_2SO_4), and the solvent was evaporated to give 22.5 g of a low-melting solid. Crystallization from hexane gave 10.7 g (43%) of **103** (Table V): IR 1650, 1580, 1530 cm^{-1}.

2,2,2-Trifluoro-1-[5-(tetradecyloxy)-2-furanyl]ethanone (104). To an ice-cooled mixture of 0.43 g (7.15 mmol) of HOAc and 2.0 mL of trifluoroacetic anhydride in 20 mL of Et_2O was added 2.0 g (7.15 mmol) of 2-(tetradecyloxy)furan (**102**) in 20 mL of Et_2O. The mixture was allowed to stand at room temperature for 2 h and was diluted with 50 mL of ice-cold saturated aqueous $NaHCO_3$. The Et_2O layer was separated, washed (H_2O), and dried (Na_2SO_4), and the solvent was evaporated to give 2.8 g of a waxy solid. Crystallization from hexane gave 2.2 g (82%) of **104** (Table V): IR (KBr) 1665, 1580, 1520 cm^{-1}.

2,2,2-Trichloro-1-[5-(tetradecyloxy)-2-furanyl]ethanone (105) and Hydrolysis to 5-(Tetradecyloxy)-2-furancarboxylic Acid (91). To an ice-cooled mixture of 8.0 g (0.0286 mol) of 2-(tetradecyloxy)furan (**102**) in 100 mL of Et_2O was added 9.1 g (0.03 mol) of trichloroacetic anhydride. The mixture was allowed to stand at room temperature for 2 h and was then diluted with ice-cold saturated aqueous $NaHCO_3$. The Et_2O layer was separated, washed (H_2O), and dried (Na_2SO_4), and the solvent was evaporated to give 9.5 g of a low-melting solid. Two recrystallizations from MeOH gave 7.0 g (58%) of **105** (Table V): IR (KBr) 1670, 1580, 1520 cm^{-1}.

A mixture of 1.0 g (2.35 mmol) of 2,2,2-trichloro-1-[5-(tetradecyloxy)-2-furanyl]ethanone (**105**) and 1.0 g of NaOH in 25 mL of MeOH was refluxed for 15 min and was then gradually diluted with 200 mL of H_2O. The ice-cooled mixture was acidified to pH 2 with 1 N HCl and the precipitate was collected and dried. Crystallization from 2-butanone gave 0.5 g (66%) of **91**.

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Studies on Quinoline Derivatives and Related Compounds. 5.[1] Synthesis and Antimicrobial Activity of Novel 1-Alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

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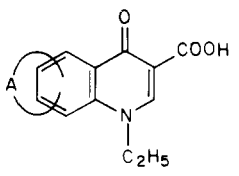
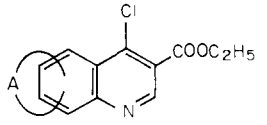
A series of novel 1-alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids was synthesized and screened as antimicrobial agents. The most active compounds in vitro against gram-negative microorganisms and *Staphylococcus aureus* were 1,4-dihydro-1-methoxy-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**22**), 1,2,6,9-tetrahydro-6-methoxy-9-oxofuro[3,2-*f*]quinoline-8-carboxylic acid (**30**), and 2,3,6,9-tetrahydro-6-methoxy-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic acid (**34**). These compounds had antigram-negative activity comparable to that of the corresponding *N*-ethyl derivatives **1**, **2**, and **4**. Their serum levels and urinary recovery rates in rats, however, were significantly improved relative to the latter compounds (**1**, **2**, and **4**).

Since the finding that oxolinic acid (1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid, **1**)[2] exhibited potent in vitro antimicrobial activity against gram-negative microorganisms and *Staphylococci*, many related quinoline derivatives have been synthesized for examination of their antibacterial activity against gram-negative microorganisms.[3] These compounds, however, are poorly absorbed from the gastrointestinal tract and as a result their usefulness as chemotherapeutic agent is limited.

The purpose of this investigation is to obtain new quinoline derivatives, which possess improved pharmacokinetic properties and retain the antibacterial activity of the parent compounds, by structural modification. All the previously synthesized derivatives of this type of compounds have an alkyl group at the nitrogen atom. In view of the structure–activity relationship that the alkyl group at the nitrogen atom seemed to play an important role in enhancing the activity, we became interested in the preparation of compounds having an alkoxy group at the nitrogen atom, in order to examine whether the substituent consisting of a highly polar oxygen atom would confer physiochemical and biological properties on the quinoline molecule different from those conferred by the alkyl group.

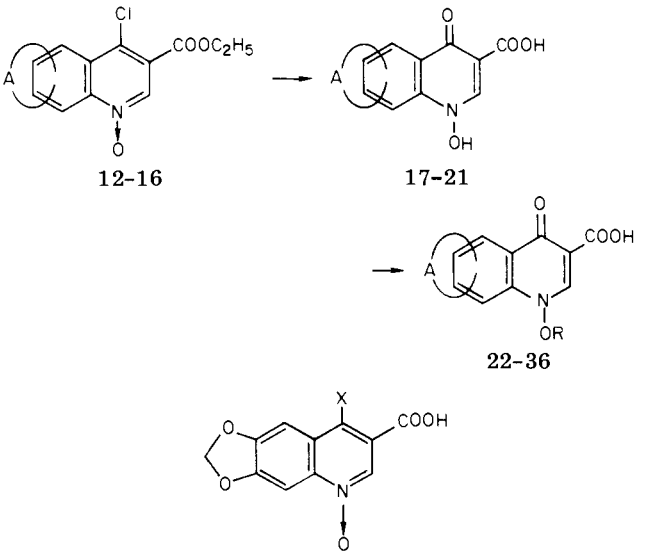


1, A = 6,7-OCH_2O-
2, A = 6,7-OCH_2CH_2-
3, A = 5,6-CH_2OCH_2O-
4, A = 5,6-$SC(=O)N(CH_3)$-
5, A = 7,8-$CH_2CH_2CH_2$-



6, A = 6,7-OCH_2O-
7, A = 6,7-OCH_2CH_2-
8, A = 5,6-CH_2CH_2O-
9, A = 5,6-CH_2OCH_2O-
10, A = 5,6-SC(Cl)=N-
11, A = 7,8-$CH_2CH_2CH_2$-

Scheme I



12-16 17-21 22-36

37, X = Cl
38, X = OCH_3

Chemistry. Ethyl 4-chloro-3-quinolinecarboxylates (**6–11**) employed as starting materials were prepared by the method described in the literature[4] and converted to 3-carboethoxy-4-chloroquinoline 1-oxides (**12–16**) by oxidation with *m*-chloroperbenzoic acid in chloroform. In order to synthesize 1,4-dihydro-1-hydroxy-4-oxo-3-quinolinecarboxylic acids (**17–21**), hydrolysis of **12** under a variety of conditions was attempted and the best results were obtained when sodium hydroxide and aqueous methanol were used.

In this conversion of **12** to **17**, the formation of the intermediates **37** and **38** was observed by NMR study.