volume percent of methanol in the preliminary methanol/water mixture is taken as the volume percent of methanol to be used in the phosphate-buffered mobile phase. Once the volume percent of methanol has been established, the mole fraction (χ) of HPO_4^{2-} required to yield calculation values of μ 0.15 m and pH 7.40 can be accurately determined from eq i, where V is the volume

$$\chi = -4.554 \times 10^{-8}V_3 + 1.673 \times 10^{-6}V_2 - 3.728 \times 10^{-4}V + 0.7971 \quad \text{(i)}$$

$$n = 50,\ r = 0.99996,\ s = 7.265 \times 10^{-5}$$

percent methanol, n is the number of data points, r is the coefficient of correlation, and s is the standard deviation of regression. This expression was obtained for values of V from 1.25 to 62.5%. It has been our experience that precipitation of small amounts of phosphates have been observed in filtered solutions at volume percents greater than 50–55%, and mobile phases with compositions of methanol >55% (v/v) are not recommended.

After substitution of the value of $\chi(HPO_4^{2-})$ calculated from eq i into eq ii and iii, the weights of salts are then

$$[H_2PO_4^-] = \frac{0.15(1-\chi)}{2\chi+1} - \text{molal concn} \quad \text{(ii)}$$

$$[HPO_4^{2-}] = \frac{0.15\chi}{2\chi+1} - \text{molal concn} \quad \text{(iii)}$$

determined by multiplying these concentrations first by the calculated total weight of the solvent in kilograms [$\rho(H_2O)$ = 0.9971 g/mL and ρ(MeOH) = 0.7864 g/mL at 18 °C], and secondly by the appropriate molecular weights. A final recommendation is that the salts be dissolved in the appropriate volume of H_2O prior to the addition of MeOH.

Registry No. Sulfaguanidine, 57-67-0; sulfanilamide, 63-74-1; sulfacetamide, 144-80-9; sulfadiazine, 68-35-9; sulfamethoxazole, 723-46-6; sulfisoxazole, 127-69-5; sulfamerazine, 127-79-7; sulfathiazole, 72-14-0; sulfamethoxypyridazine, 80-35-3; sulfamethazine, 57-68-1; barbital, 57-44-3; allobarbital, 52-43-7; phenobarbital, 50-06-6; metharbital, 50-11-3; aprobarbital, 77-02-1; butabarbital, 125-40-6; cyclobarbital, 52-31-3; butalbital, 77-26-9; hexobarbital, 56-29-1; amobarbital, 57-43-2; pentobarbital, 76-74-4; secobarbital, 76-73-3; thiopental, 76-75-5; thiamylal, 77-27-0; methohexital, 151-83-7.

Phenylenebis(oxy)bis[2,2-dimethylpentanoic acid]s: Agents That Elevate High-Density Lipoproteins

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A series of phenylenebis(oxy)bis[2,2-dimethylpentanoic acid]s have been synthesized and evaluated as potential hypolipidemic agents. Compound 18 (CI-924) was found to be the most potent compound in this series. In rats, compound 18 not only reduced low-density lipoprotein cholesterol but also increased high-density lipoprotein (HDL) cholesterol. Comparative studies in rats indicated 18 produced an equal elevation of HDL cholesterol at one-third of the dose required of gemfibrozil. Structure–activity relationships are discussed.

The recent Framingham and other studies[1,2] have pointed out that high-density lipoprotein (HDL) cholesterol levels are inversely correlated with the incidence of atherosclerosis. Clofibrate or other hypolipidemic drugs do raise HDL cholesterol somewhat in patients, but the effect is not significant.[3] The most recent studies on new drugs affecting lipid and lipoprotein levels have therefore been aimed at the development of agents that decrease atherogenic lipoproteins (particularly LDL)[4] or increase high-density lipoproteins. Several hypolipidemic drugs, such as procetofene,[5] gemfibrozil,[6,7] bezafibrate,[8] and BR-931,[9] were recently shown to increase HDL levels in rats, as well as in humans. During our continued search for agents more potent than gemfibrozil, we discovered that phenylenebis(oxy)bis[alkanoic acid]s and their derivatives (Tables I–IV) effectively increase HDL cholesterol in rats treated with high lipid diets. In this paper we report the synthesis and structure–activity relationships of these compounds.

Chemistry. Phenylenebis(oxy)bis[alkanoic acid]s (IV) were prepared from various bis[phenol]s (I) by alkylation with α,ω-dihaloalkanes[10] (II) to give III (Table V), which were condensed with the dianion of isobutyric acid[11] (Scheme I, method A). Alternatively, the bis[phenol]s (I) were alkylated with methyl ω-bromo-2,2-dimethylalkanoate (V) to give the desired esters (VI), which were saponified to give the acids IV (Scheme I, method B).

Esters **54–56** were prepared by treating the corresponding acid chlorides with the respective alcohols or phenols (method C). Acids **3** and **18** on reduction with lithium aluminum hydride in tetrahydrofuran gave the corresponding alcohols **51** and **52** (method D). Acetate **53**

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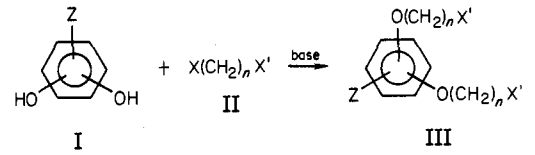
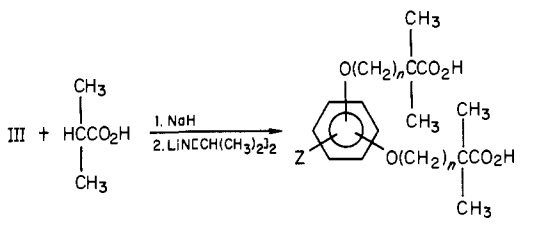
Method A[a]

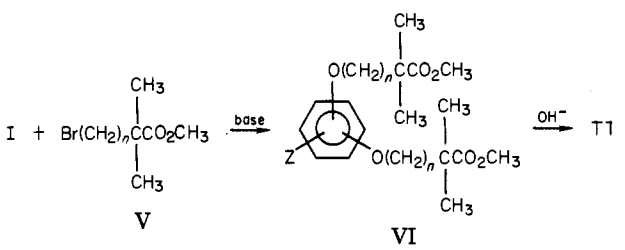


I II III



IV

Method B



V VI

[a] X and X' = Cl, Br.

was prepared by heating **52** with acetic anhydride. Compounds **24–27** were obtained from their precursors **20–23** by sodium borohydride reduction (method E). Alcohol **26** was subsequently dehydrated to the corresponding olefin **28** by heating with *p*-toluenesulfonic acid. Compound **44** was obtained from **43** by reduction with zinc dust and sodium hydroxide (method F), whereas compound **43** on catalytic reduction gave **45** (method G). Sulfoxide and sulfones (**41**, **42**, **47**, and **48**) were prepared from the corresponding sulfides (**40** and **46**) by oxidation either with *m*-chloroperbenzoic acid or with 30% hydrogen peroxide.

Biological Results and Discussion

The compounds were evaluated for hypolipidemic effects in male rats as described under Experimental Section. This modified screening test was developed to emphasize the elevation of HDL cholesterol. The activities of 1,4-phenylenebis(oxy)bis[alkanoic acid]s are shown in Table I. There is an optimal chain length (n), since greater activities were observed with compounds **2** and **3**, where n is 3 and 4, than with compounds **1** and **4**, where n is 2 and 6. In following the structure–activity relationships, the optimum chain length of three carbon units was held constant. The *gem*-dimethyl group (R_1 and R_2) next to the carboxylic acid moiety is required for activity because replacement with the cyclobutyl group in compound **3** led to the inactive compound (**5**). A monohalogen substitution on the phenyl ring generally retained activity (**7–9**), whereas dihalogen substitution decreased activity considerably (**10**). The same was true with alkoxy and alkyl substitution, though the effect was more pronounced with a branched alkyl group. The methyl and dimethyl compounds (**13** and **15**) are more active than the corresponding *tert*-butyl analogues (**14** and **16**). The CF_3 compound **29** was as active as the methyl compound **13**.

Compounds **20–23**, where the phenyl ring was substituted with an acyl group, retained the activity, and the activity increased with the size of the alkyl group. The same relationship holds true in compounds **24–27**, where the acyl group was reduced to the hydroxyalkyl group. Although increasing the size of the alkyl group led to potent compounds (**23** and **27**), no higher homologues were synthesized due to toxicity. Semicarbazone and thiosemicarbazones (**57** and **58**) were inactive. Activity was retained by replacement of one oxygen of compounds **2** and **15** with sulfur (**46** and **49**). In general, the activity decreased from sulfide to sulfoxide to sulfone (**46–48**).

Phenyl substitution seemed to be the most effective in enhancing activity, and with substituted phenyl the optimum chain length was found to be the three carbon unit. Compound **18** elevated HDL cholesterol 1410% at 50 mg/kg, and the ratio HDL/LDL went up 2432%. Several substituted phenyl compounds (**34–39**) were synthesized, but, in general, substitution seemed to have a detrimental effect. The compounds where the two phenyl groups are separated by S, SO, SO_2, CO, CHOH, and CH_2 (**40–45**) were all less active than the parent biphenyl compound **18**.

Table II lists the activities of biphenylbis(oxy)bis[alkanoic acid]s where the two side chains were attached to two phenyl groups instead of one. In general, the compounds were inactive, except **60**, which was only slightly active.

Table III lists the activities of 1,3-phenylenebis(oxy)-bis[alkanoic acid]s. In general, this series was less potent, and the structure–activity relationships seem to be different from that of 1,4-phenylenebis(oxy)bis[alkanoic acid]s (Table I). Compounds (**71–73**) where the chain lengths are two to four carbon units were equally active. Any substitution except methyl (**75**) in position 2 seemed to abolish the activity.

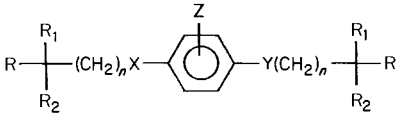
Substitution in position 4 had a similar effect. Substitutions by alkyl, halo, acyl, and formyl (**81–91**) all led to inactive compounds, except the 4-benzoyl compound (**91**) and the thiosemicarbazone (**87**), which retained some activity. Surprisingly, the 4-phenyl analogue (**92**) turned out to be inactive. Similarly, any substitution except methyl (**93**) in position 5 led to inactive compounds (**93–96**).

The activity of the 1,2-phenylenebis(oxy)bis[alkanoic acid]s is included in Table IV. Activity was seen only in compounds with a five carbon unit chain (**99**). This was the least potent of all the series and, hence, not studied thoroughly.

The primary objective of this work was the identification of compounds that produced an elevation of HDL cholesterol superior to that of gemfibrozil. Thus, the most active compounds in this series (**13**, **46**, **7**, **3**, and **18**) were directly compared with gemfibrozil at doses of 12.5, 25, and 50 mg/kg administered orally for 30 days to rats on a high lipid diet. The results are shown in Table VI. Compound **18** was 4–5 times as potent as gemfibrozil (**101**) in elevating HDL cholesterol and also caused a greater reduction in LDL cholesterol.

Gemfibrozil has been shown to have a unique profile of biological activity when compared to other hypolipidemic agents,[20] and compound **18** has a similar profile. Thus, in rats given [1-^{14}C]octanoate, both agents caused a very significant increase of incorporation of labeled precursors into cholesterol, while clofibrate and bezafibrate inhibit this process. However, in rats fed an atherogenic diet, gemfibrozil and **18** reduced liver sterol accumulation by 60–90%, while clofibrate and bezafibrate had no effect. The details of these studies will be reported elsewhere, but apparently both agents are increasing the efflux of cholesterol from the liver by some novel mechanism that to date has not been defined.

Table I. 1,4-Phenylenebis(oxy)bis[alkanoic acid]s

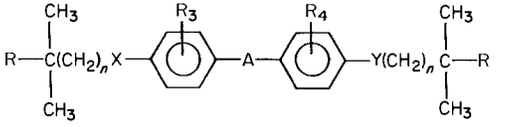


no.	R	R_1	R_2	n	Y	X	Z	prepn method[a]	mp or bp (mm), °C	yield,[b] %	recrystn solvent	formula[c]	plasma CHO	plasma TG	act.,[d] % change[e] HDL CHO	act.,[d] % change[e] LDL CHO	liver wt
1	CO_2H	CH_3	CH_3	2	O	O	H	A	163–165	51	CH_3CN	$C_{18}H_{26}O_6$[f]	−33	0	+370		+40
2	CO_2H	CH_3	CH_3	3	O	O	H	A	167–168	63	THF/PE	$C_{20}H_{30}O_6$	−45	0	+791		+39
3	CO_2H	CH_3	CH_3	4	O	O	H	A	158–159	56	THF/PE	$C_{22}H_{34}O_6$	0	−20	+1477		+36
4	$CO_2C_2H_5$	CH_3	CH_3	6	O	O	H	B		32		$C_{30}H_{50}O_6$[g]	−26	0	0	−29	0
5	CO_2H	$(CH_2)_3$		4	O	O	H	A	132–133	36	THF/PE	$C_{24}H_{34}O_6$	−23	0	+55	−32	0
6	CO_2H	CH_3	CH_3	2	O	O	Cl	A	138–139	27	THF/PE	$C_{18}H_{25}ClO_6$	−62	−32	+348		+13
7	CO_2H	CH_3	CH_3	3	O	O	Cl	A	134–135	78	THF/PE	$C_{20}H_{29}ClO_6$	−53	0	+753		+38
8	CO_2CH_3	CH_3	CH_3	3	O	O	Br	B	200–201 (0.3)	69		$C_{25}H_{33}BrO_6$[h]	−45	−39	+728		+30
9	CO_2CH_3	CH_3	CH_3	3	O	O	F	B	33–35	20	PE	$C_{22}H_{33}FO_6$	−30	0	+347	−65	+41
10	CO_2H	CH_3	CH_3	3	O	O	2,5-Cl_2	A	161–162	10	THF/PE	$C_{20}H_{28}Cl_2O_6$[i]	−55	+35	+384		+41
11	CO_2CH_3	CH_3	CH_3	3	O	O	OCH_3	B	199–200 (0.2)	60		$C_{23}H_{36}O_7$	−26	0	+566	−31	+30
12	CO_2CH_3	CH_3	CH_3	3	O	O	2,5-$(OCH_3)_2$	B	50–51	38	hexane	$C_{24}H_{38}O_8$	−33	0	+39		0
13	CO_2CH_3	CH_3	CH_3	3	O	O	CH_3	B	190–192 (0.15)	30		$C_{23}H_{36}O_6$	−37	+62	+743	−71	+38
14	CO_2CH_3	CH_3	CH_3	3	O	O	$C(CH_3)_3$	B	198–200 (0.5)	48		$C_{26}H_{42}O_6$	−34	0	+171	−41	+11
15	CO_2CH_3	CH_3	CH_3	3	O	O	2,5-$(CH_3)_2$	B	77–78	30	IPE	$C_{24}H_{38}O_6$	−30	+27	+688	−64	+14
16	CO_2CH_3	CH_3	CH_3	3	O	O	2,5-$[C(CH_3)_3]_2$	B	65–66	10	hexane	$C_{30}H_{50}O_6$	0	−15	0		0
17	CO_2H	CH_3	CH_3	3	O	O	2,3,5-$(CH_3)_3$	A	142–143	62	IPE	$C_{23}H_{36}O_6$	−37	+42	+165		+21
18	CO_2H	CH_3	CH_3	3	O	O	Ph	A	139–140	47	E/IPE	$C_{26}H_{34}O_6$	−27	+31	+1410	−85	+34
								B	139–140	86	E/IPE						
19	CO_2H	CH_3	CH_3	4	O	O	Ph	A	125–126	46	THF/PE	$C_{28}H_{38}O_6$	−49	0	+51	−53	+8
20	CO_2CH_3	CH_3	CH_3	3	O	O	CHO	B	218–220	55		$C_{23}H_{34}O_7$	0	0	+217	−20	+9
21	CO_2CH_3	CH_3	CH_3	3	O	O	$COCH_3$	B	210–212	57		$C_{24}H_{36}O_7$	0	+20	+381	−39	+21
22	CO_2CH_3	CH_3	CH_3	3	O	O	$COCH_2CH_3$	B		73		$C_{25}H_{38}O_7$	0	0	+723	−57	+40
23	CO_2CH_3	CH_3	CH_3	3	O	O	$COCH_2CH_3CH_3$	B		45		$C_{26}H_{40}O_7$	+39	0	+1100	−52	+34
24	CO_2H	CH_3	CH_3	3	O	O	CH_2OH	E	128–129	76	THF/PE	$C_{21}H_{32}O_7$	+40	+18	+319	0	+9
25	CO_2H	CH_3	CH_3	3	O	O	$CH(OH)CH_3$	E	141–143	33	THF/PE	$C_{22}H_{34}O_7$	−27	0	+525	−70	+12
26	CO_2H	CH_3	CH_3	3	O	O	$CH(OH)CH_2CH_3$	E	112–113	56	THF/PE	$C_{23}H_{36}O_7$	0	0	+947	−62	+34
27	CO_2H	CH_3	CH_3	3	O	O	$CH(OH)CH_2CH_2CH_3$	E	122–123	62	E/PE	$C_{24}H_{38}O_7$	+61	0	+1292	−45	+37
28	CO_2CH_3	CH_3	CH_3	3	O	O	$CH{=}CHCH_3$			46		$C_{25}H_{38}O_6$	−39	−31	+268	−66	+29
29	CO_2H	CH_3	CH_3	3	O	O	CF_3	B	114–115	46	THF/PE	$C_{21}H_{29}F_3O_6$	0	0	+674	−45	+39
30	CO_2CH_3	CH_3	CH_3	3	O	O		B	220–222 (0.01)	34		$C_{26}H_{36}O_6$	−54	−23	+30		+6
31	CO_2H	CH_3	CH_3	3	O	O		A	163–164	33	THF/PE	$C_{25}H_{36}O_6$	−21	0	+44	−27	+4
32	CO_2CH_3	CH_3	CH_3	3	O	O	2,3-$(CN)_2$	B	65–66	40	E/IPE	$C_{24}H_{32}N_2O_6$	0	0	0	0	0
33	CO_2CH_3	CH_3	CH_3	3	O	O	C_6H_{11}	B	220–222 (0.04)	63		$C_{28}H_{44}O_6$	−49	−24	+35	−54	+6
34	CO_2H	CH_3	CH_3	3	O	O	2-ClPh	B	101–102	28	E/IPE	$C_{26}H_{33}ClO_6$	0	+38	+480	−38	+23
35	CO_2H	CH_3	CH_3	3	O	O	4-ClPh	B	110–111	48	THF/PE	$C_{26}H_{33}ClO_6$	−47	−29	+224	−78	+17
36	CO_2H	CH_3	CH_3	3	O	O	2,4-Cl_2Ph	B	85–86	78	E/IPE	$C_{26}H_{32}Cl_2O_6$	−45	−20	+64	−54	0
37	CO_2H	CH_3	CH_3	3	O	O	2-CH_3Ph	B	65–68	55	E/IPE	$C_{27}H_{36}O_6$	0	+55	+628	−52	+22
38	CO_2H	CH_3	CH_3	3	O	O	4-CH_3Ph	B	87–89	73	E/IPE	$C_{27}H_{36}O_6$	−32	−27	+66	−42	0
39	CO_2H	CH_3	CH_3	3	O	O	4-OCH_3Ph	B	71–73	35	E/PE	$C_{27}H_{36}O_7$	−30	−30	+52	−38	0
40	CO_2H	CH_3	CH_3	3	O	O	SPh	B	117–118	75	THF/PE	$C_{26}H_{34}O_6S$	+32	+44	+428	−30	+14

41	CO_2H	CH_3	CH_3	3	O	O	SOPh		141–143	46	THF/PE	$C_{26}H_{34}O_7S$	−27	−21	+599	−58	+16
42	CO_2H	CH_3	CH_3	3	O	O	SO_2Ph		194–196	71	THF/PE	$C_{26}H_{34}O_8S$	−32	+35	+303	−53	+10
43	CO_2CH_3	CH_3	CH_3	3	O	O	COPh	B		93		$C_{29}H_{38}O_7$	0	+43	+421	−42	+11
44	CO_2H	CH_3	CH_3	3	O	O	CH(OH)Ph	F	125–128	50	E/PE	$C_{27}H_{36}O_7$	−17	+27	+410	−42	+16
45	CO_2H	CH_3	CH_3	3	O	O	CH_2Ph	G	140–141	78	THF/PE	$C_{27}H_{36}O_6$	−44	0	+389	−71	+14
46	CO_2H	CH_3	CH_3	3	O	S	H	A	111–112	73	THF/PE	$C_{20}H_{30}O_5S$	−44	−40	+628		+18
47	CO_2H	CH_3	CH_3	3	O	SO	H		98–100	60	THF/PE	$C_{20}H_{30}O_6S$	−33	+16	+289	−31	+19
48	CO_2H	CH_3	CH_3	3	O	SO_2	H		106–107	83	THF/PE	$C_{20}H_{30}O_7S$	0	0	+93	−20	+9
49	CO_2H	CH_3	CH_3	3	O	S	$2,5\text{-}(CH_3)_2$	B	97–98	33	E/PE	$C_{22}H_{34}O_5S$	−20	0	+220	−35	+14
50	CO_2H	CH_3	CH_3	3	O	O	CO_2H	B	116–117	50	E/PE	$C_{21}H_{30}O_8$	0	0	0	−17	0
51	CH_2OH	CH_3	CH_3	4	O	O	H	D	71–72	67	THF/PE	$C_{22}H_{38}O_4$	0	0	+907	−54	+30
52	CH_2OH	CH_3	CH_3	3	O	O	Ph	D	75–76	56	E/PE	$C_{26}H_{38}O_4$	+37	0	+1105	−36	+30
53	CH_2OCOCH_3	CH_3	CH_3	3	O	O	Ph			87		$C_{30}H_{42}O_6$	0	0	+602	−36	+19
54	CO_2CH_2-3-Py	CH_3	CH_3	3	O	O	Ph	C				$C_{38}H_{44}N_2O_6$	+63	0	+594	0	+19
55	$CO_2C_2H_5$	CH_3	CH_3	3	O	O	Ph	C	240–242 (0.1)	80		$C_{30}H_{42}O_6$	+43	0	+536	−18	+20
56	CO_2Ph-4-*t*-Bu	CH_3	CH_3	3	O	O	H	C	132–133			$C_{40}H_{54}O_6\cdot0.5H_2O$	0	0	0	0	0
57	CO_2CH_3	CH_3	CH_3	3	O	O	$CH{=}NNHCONH_2$		110–111	76	CH_3OH	$C_{24}H_{37}N_3O_7\cdot0.5H_2O$	−28	0	0	−33	+4
58	CO_2CH_3	CH_3	CH_3	3	O	O	$CH{=}NNHCSNH_2$		97–98	54	E/PE	$C_{24}H_{37}N_3O_6S$	0	0	0	0	0
59	CO_2CH_3	CH_3	CH_3	3	O	O		B		40		$C_{24}H_{34}N_2O_7$	−26	0	+31	−33	+11

[a] The letter refers to the general methods described in the text. [b] No efforts were made to optimize yields. PE = petroleum ether (refers to the fraction boiling between 60 and 80 °C); IPE = isopropyl ether; E = ethyl ether. [c] All compounds were obtained with reasonable IR and NMR spectra and analyzed for C, H, N, S, and halogen (Cl, Br) if present within ±0.4% of theory unless otherwise stated. [d] All the compounds were screened orally at 50 mg/kg. [e] Statistically significant, $p < 0.001$. [f] Synthesized by Dr. P. Creger, Chemistry Department. [g] C: calcd, 71.11; found, 70.62. [h] C: calcd, 55.81; found, 55.29. [i] C: calcd, 55.17; found, 55.77.

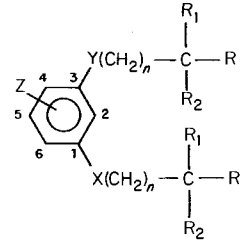
Table II. Biphenylbis(oxy)bis[alkanoic acid]s



no.	R	n	Y	X	R_3	R_4	A	prepn method[a]	mp or bp (mm) °C	yield,[b] %	recrystn solvent	formula[c]	plasma CHO	plasma TG	act.,[d] % change[e] HDL CHO	act.,[d] % change[e] LDL CHO	liver wt
60	CO_2H	3	O	O	H	H		A	200–201	68	THF/PE	$C_{26}H_{34}O_6$	−30	0	+138		+15
61	CO_2H	3	O	O	3-C_3H_7	3′-C_3H_7		A	150–151	50	THF/PE	$C_{32}H_{46}O_6$	0	0	0	0	0
62	CO_2H	2	O	O	H	H	S	A	108–109	57	E/IPE	$C_{24}H_{30}O_6S$	−25	−32	+46		0
63	CO_2H	3	O	O	H	H	S	A	149–150	70	THF/PE	$C_{26}H_{34}O_6S\cdot0.5H_2O$	−35	+20	0		0
64	CO_2H	3	O	O	H	H	SO_2	B	89–89.5	40	E/IPE	$C_{28}H_{38}O_8S$	0	0	+26	0	+10
65	CO_2H	3	O	O	H	H	O	B	133–134	76	THF/PE	$C_{26}H_{34}O_7$	−35	0	0	−36	0
66	CO_2CH_3	3	O	O	H	H	CO	B	86–88	67	E/IPE	$C_{29}H_{38}O_7$	0	0	0	0	0
67	CO_2CH_3	3	O	O	H	H	$C(CH_3)_2$	B	52–53	36	CH_3OH	$C_{31}H_{44}O_6$	0	0	0	0	0
68	CO_2CH_3	3	S	S	H	H		B	46–47	58	E/IPE	$C_{28}H_{38}O_4S_2$	0	+60	+245	−39	+14
69	CO_2CH_3	3	S	S	H	H	O	B		56		$C_{28}H_{38}O_5S_2$	−29	0	0	−31	+4

[a-e] See corresponding footnotes in Table I.

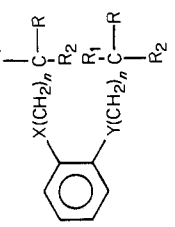
Table III. 1,3-Phenylenebis(oxy)bis[alkanoic acid]s



no.	R	R_1	R_2	n	Y	X	Z	prepn method[a]	mp or bp (mm), °C	yield,[b] %	recrystn solvent	formula[c]	plasma CHO	plasma TG	act.,[d] % change[e] HDL CHO	act.,[d] % change[e] LDL CHO	liver wt
70	CO_2H	CH_3	CH_3	0	O	O	H	B	128–130	10		$C_{16}H_{22}O_6$	0	0	0	0	0
71	CO_2H	CH_3	CH_3	2	O	O	H	A	104–105	53	E/PE	$C_{18}H_{26}O_6$	−28	+240	+383	−46	+17
72	CO_2H	CH_3	CH_3	3	O	O	H	A	135–136	55	E/IPE	$C_{20}H_{30}O_6$	−52	0	+294		+17
73	CO_2H	CH_3	CH_3	4	O	O	H	A	85–86	48	E/IPE	$C_{22}H_{34}O_6$	−37	+41	+317	−52	+18
74	CO_2H	CH_3	CH_3	5	O	O	H	A	84–85	60	THF/IPE	$C_{24}H_{38}O_6$	−22	0	+48	−27	0
75	CO_2CH_3	CH_3	CH_3	3	O	O	2-CH_3	B	200–202 (0.3)	52		$C_{23}H_{36}O_6$	−37	−15	+385		+33
76	CO_2CH_3	CH_3	CH_3	3	O	O	2-CO_2CH_3	B	210–212 (0.5)	44		$C_{24}H_{36}O_8$	0	0	+21	0	0
77	CO_2CH_3	CH_3	CH_3	3	O	O	2-$COCH_3$	B	198–200 (0.05)	40		$C_{24}H_{36}O_7$	−38	0	0	−40	0
78	CO_2CH_3	CH_3	CH_3	3	O	O	2-NO_2	B	228–230 (1.0)	37		$C_{22}H_{33}NO_8$	−33	0	+109	−43	+5
79	CO_2CH_3	CH_3	CH_3	3	O	O	2-NH_2		52–53	79	PE	$C_{22}H_{35}NO_6$	−37	−41	+46	−42	+8
80	CO_2CH_3	CH_3	CH_3	3	O	O	2-$NHCOCH_3$		54–55	50	E/PE	$C_{24}H_{37}NO_7 \cdot 0.2C_2H_4O_2$	0	0	0	0	0
81	CO_2CH_3	CH_3	CH_3	3	O	O	4-Cl	B	31–32	38	PE	$C_{22}H_{33}ClO_6$	−42	0	+37	+80	+8
82	CO_2CH_3	CH_3	CH_3	3	S	S	4-Cl	B	200–202 (0.02)	70		$C_{22}H_{33}ClO_4S_2$	−53	0	+56	−52	0
83	CO_2CH_3	CH_3	CH_3	3	O	O	4-Br	B	40–41 220–222 (0.1)	74		$C_{27}H_{33}BrO_6$	−47	0	+26	−52	+5
84	CO_2CH_3	CH_3	CH_3	3	O	O	4,6-Cl_2	B	57–58	44	hexane	$C_{22}H_{32}Cl_2O_6$	0	0	0	0	0
85	CO_2CH_3	CH_3	CH_3	3	O	O	4-CO_2CH_3	B	32–33	20	E/PE	$C_{24}H_{36}O_8$	0	0	0	0	0
86	CO_2CH_3	CH_3	CH_3	3	O	O	4-CHO	B	209–210 (0.1)	66		$C_{23}H_{34}O_7$	−18	0	+79	−30	+11
87	CO_2CH_3	CH_3	CH_3	3	O	O	4-CH=NN(SH)CNH_2		117–118	70	EtOH	$C_{24}H_{37}N_3O_6S$	−60	−50	+280	−83	+38
88	CO_2CH_3	CH_3	CH_3	3	O	O	4-CH_3	B	198–200 (0.5)	70		$C_{23}H_{36}O_6$	−55	0	+38	-64	+4
89	CO_2CH_3	CH_3	CH_3	3	O	O	4,6-(t-C_4H_9)$_2$	B	208–210 (0.1)	15		$C_{30}H_{50}O_6$	0	0	0	0	0
90	CO_2H	CH_3	CH_3	3	O	O	4-$C_{12}H_{25}$	A	50–51	15		$C_{32}H_{54}O_6$	0	0	0	−12	0
91	CO_2H	CH_3	CH_3	3	O	O	4-COPh	B	125–126	40	THF/PE	$C_{27}H_{34}O_7$	0	+57	+169	−10	+11
92	CO_2CH_3	CH_3	CH_3	3	O	O	4-Ph	B	228–230 (0.1)	60		$C_{28}H_{38}O_6$	0	0	+40	−25	+6
93	CO_2CH_3	CH_3	CH_3	3	O	O	5-CH_3	B	198–200 (0.3)	46		$C_{23}H_{36}O_6$	−62	−53	+262		+18
94	CO_2CH_3	CH_3	CH_3	3	O	O	5-C_5H_{11}	B	218–220 (0.02)	62		$C_{27}H_{44}O_6$	−57	−32	+47	−67	+8
95	CO_2CH_3	CH_3	CH_3	3	O	O	5-Ph	B	238–240 (0.3)	12		$C_{28}H_{38}O_6$	−41	0	0	−42	+13
96	CO_2CH_3	CH_3	CH_3	3	O	O	5-CO_2CH_3	B	218–220 (0.1)	35		$C_{24}H_{36}O_8$	0	0	0	0	0
97	CO_2CH_3	CH_3	CH_3	3	O	O		B	59–60	36	E/PE	$C_{26}H_{36}O_6$	−21	−18	0	−22	0

[a-e] See corresponding footnotes in Table I.

Table IV. 1,2-Phenylenebis(oxy)bis[alkanoic acid]s



no.	R	R_1	R_2	n	Y	X	Z	prepn method[a]	mp or bp (mm), °C	formula[c]	plasma CHO	plasma TG	act.,[d] % change[e] HDL CHO	act.,[d] % change[e] LDL CHO	liver wt
98	CO_2CH_3	CH_3	CH_3	3	O	O	H	B	189–190 (0.3)	$C_{22}H_{34}O_6$	−40	−30	0		0
99	CO_2CH_3	CH_3	CH_3	5	O	O	H	A	60–61	$C_{24}H_{38}O_6$	0	+140	+276	−19	+11
100	CO_2CH_3	CH_3	CH_3	3	O	O	3-OCH_3	B	178–180 (0.05)	$C_{23}H_{36}O_7$	0	0	0	0	0

[a–e] See corresponding footnotes in Table I.

Compound 18 has been selected for preclinical toxicology, and additional efficacy evaluations are in progress.

Experimental Section

Biological Methods. Male Charles River CD rats having a 75–85-g initial body weight were used for screening the compounds as antiatherosclerotic agents. The screening test[12] was designed specifically to demonstrate the effect of drugs on plasma cholesterol fractions.

Rats were fed for 7 days a diet containing ground rat chow, 10% fat (5.5% added peanut oil plus 4.5% fat as in chow), 1.5% cholesterol, and 0.1% cholic acid. This diet in this time elevates total plasma cholesterol to 200–250% of normal and reduces plasma high-density lipoprotein (HDL) cholesterol to 20–25% of normal. Groups of 10 rats were used for each compound or variable. On days 4–7, test compounds were dosed by oral gavage. The dosing vehicle is 4% acacia, and the dosing volume was 0.25 mL/100 g of body weight. The initial daily dose level was usually 50 mg/kg. After fasting overnight, on day 8 rats were killed, and blood was taken from the atrium and poured into vacutainer tubes containing 0.048 mL of EDTA to give a final concentration of 0.14%. Plasma was obtained by centrifugation.

Total cholesterol and triglycerides were determined in an aliquot of the plasma by standard Autoanalyzer II methodology. HDL cholesterol was determined by the autoanalyzer in an aliquot of plasma after removal of low-density lipoproteins [very low density lipoproteins (VLDL) plus LDL] by precipitation with 0.05 M $MnCl_2$ plus 0.2% heparin. HDL/LDL (including VLDL) ratios were determined by densitometric measurement of patterns obtained by electrophoresis of plasma in polyacrylamide gel.

Gemfibrozil (101) was used as the reference agent in all studies. The significance of differences between treated groups and control groups was evaluated by student's t test.

Chemistry. Melting points were uncorrected and taken on a Thomas-Hoover capillary melting point apparatus. Boiling points were uncorrected. The spectra of all new compounds were consistent with the proposed structures. Each analytical sample was homogeneous by TLC.

2,5-Dihydroxybenzophenone,[13] phenylthiobenzohydroquinone,[14] fluoro- and trifluorohydroquinones,[15] and the substituted phenylhydroquinones[16] were prepared by the methods described in the literature. The 4- and 5-phenylresorcinols were prepared from the corresponding 1,3-cyclohexanedione by dehydrogenation.[17] 2-(1,3,4-Oxadiazol-2-yl)-1,4-benzenediol (mp 166–167 °C) was prepared from gentisic acid hydrazide[18] by treatment with triethyl orthoformate.

Methyl 5-Bromo-2,2-dimethylpentanoate (V). General Method for the Preparation of Methyl ω-Bromo-2,2-dimethylalkanoate. Hydrogen bromide was bubbled into a stirred solution of 128.6 g (1.0 mol) of 2,2-dimethyl-4-pentenoic acid[19] and 260 mL of petroleum ether containing 1.3 g (0.005 mol) of benzoyl peroxide. When 95 g of hydrogen bromide had been added, the reaction mixture was washed with water and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give 191 g of a colorless oil. This was directly converted to the methyl ester, which was purified by distillation, bp 77–78 °C (1.5 mm). Anal. ($C_7H_{13}BrO_2$) C, H, Br.

Method A. 5,5′-[1,4-Phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid] (2). Isobutyric acid (17.69, 0.2 mol) was added

(12) Maxwell, R. E.; Nawrocki, J. W.; Uhlendorf, P. D. *Artery* **1978**, *4*(4), 303.
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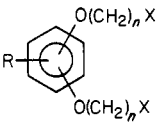
(15) Feiring, A. E.; Sheppard, W. A. *J. Org. Chem.* **1975**, *40*, 2543.
(16) Kvalnes, D. E. *J. Am. Chem. Soc.* **1934**, *56*, 2478.
(17) Nilsson, M.; Norin, T. *Acta. Chem. Scand.* **1963**, *17*(4), 1157.
(18) Libermann, D.; Rist, N.; Grumbach, F.; Moyeux, M.; Ganthier, B.; Ronaix, A.; Maillard, J.; Himbert, J.; Cals, S. *Bull. Soc. Chim. Fr.* **1954**, 1430.
(19) Brown, R. F.; Van Gulick, N. M. *J. Am. Chem. Soc.* **1955**, *77*, 1092.
(20) Maxwell, R. E.; Nawrocki, J. W.; Uhlendorf, P. D. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 350.

Table V. Bis(haloalkoxy)benzene Intermediates



no.	side-chain positions	X	*n*	R	mp or bp (mm), °C	yield %	recrystn solvent	formula[a]
102	1, 4	Br	2	H	145-147 (2.0)	25		$C_{10}H_{12}Br_2O_2$
103	1, 4	Cl	3	H	63-64	66	IPE	$C_{12}H_{16}Cl_2O_2$
104	1, 4	Cl	4	H	77-79	64	IPE	$C_{14}H_{20}Cl_2O_2$
105	1, 4	Cl	3	Cl	170 (0.2)	75		$C_{12}H_{15}Cl_3O_2$
106	1, 4	Cl	2	Cl	164-165 (1.0)	59		$C_{10}H_{11}Cl_3O_2$
107	1, 4	Cl	3	2,3,5-$(CH_3)_3$	155-156 (0.03)	20		$C_{15}H_{22}Cl_2O_2$
108	1, 4	Cl	4	Ph	230-232 (1.0)	62		$C_{20}H_{24}Cl_2O_2$
109	1, 4	Cl	3	Ph	200-202 (0.8)	30		$C_{18}H_{20}Cl_2O_2$
110	1, 4	Cl	3		45-47	27	hexane	$C_{17}H_{22}Cl_2O_2$
111	1, 4	Cl	3	2,5-Cl_2	75	75	acetone/PE	$C_{12}H_{14}Cl_4O_2$
112	1, 3	Cl	2	H	115 (0.1) 45-46	27		$C_{10}H_{12}Cl_2O_2$
113	1, 3	Cl	3	H	157-158 (1.0) 39-41	80		$C_{12}H_{16}Cl_2O_2$
114	1, 3	Cl	4	H	165 (0.15)	48		$C_{14}H_{20}Cl_2O_2$
115	1, 3	Br	5	H	210 (0.3)	46		$C_{16}H_{24}Br_2O_2$
116	1, 2	Br	5	H	184-185 (0.1)	26		$C_{16}H_{24}Br_2O_2$

[a] In general, these compounds did not give a good analysis because of the presence of mixed halogen.

Table VI. Dose Ranging Studies of Gemfibrozil and Other Compounds[a]

		% change					
no.	dose, mg/kg	plasma CHO	plasma TG	HDL CHO	HDL/LDL electrophoretic	LDL CHO	liver wt
13	50	−37	+62	+743	+1009	−71	+38
101[b]	50	0	+233	+339	+364	−32	+17
13	25	−41	0	+269	+452	−65	+25
101	25	0	+106	+215	+168	−19	+10
13	12.5	−43	0	+102	+142	−54	+13
101	12.5	0	+45	+134	+91	−16	+7
46	50	−44	−40	+628	+785	−51	+18
101							
46	25	−22	+37	+232	+302	−40	+6
101	25	0	+109	+257	+233	−22	+10
46	12.5	−19	0	+74	+101	−25	0
101	12.5	0	+30	+88	+98	0	+7
7	50	−53	0	+753	+1445	−62	+38
101							
7	25	−60	−31	+206	+493	−77	+18
101	25	0	+61	+171	+214	−22	+8
7	12.5	−65	−28	+94	+242	−74	+8
101	12.5	0	+39	+134	+134	−15	+7
3	50	0	−20	+1477	+1722		+36
101	50	−26	+57	+498	+594		+26
3	25	−35	0	+227	+339	−50	+14
101	25	0	+64	+236	+181	−27	+9
3	12.5	−33	−16	+81	+180	−40	+4
101	12.5	0	+72	+116	+83	−12	+4
18	50	−27	+31	+1410	+2432	−85	+34
101	50	−29	+69	+306	+405	−42	+13
18	25	−52	+82	+741	+1798	−72	+22
101	25	−28	+37	+246	+389	−36	+11
18	12.5	−53	+32	+518	+945	−78	+13
101	12.5	−38	0	+133	+221	−44	+4

[a] The drug was administered to rats on a high lipid diet for 30 days. [b] Gemfibrozil (101) was utilized as a reference agent.

dropwise to a stirred suspension of 10.6 g (0.22 mol) of 50% NaH and 20.6 g of (0.2 mol) of diisopropylamine in 170 mL of anhydrous THF at room temperature under nitrogen. The mixture was heated to reflux for 30 min, followed by cooling to 0 °C. At this time, 138 mL (0.2 mol) of a solution of butyllithium in heptane was added slowly. The ice bath was retained for 30min, followed by warming to 30–40 °C for another 30 min. The slightly turbid solution was cooled to 0 °C, and a solution of 26.3 g (0.1 mol) of 1,4-bis(3-chloropropoxy)benzene (**103**) in 50 mL of dry THF was added dropwise while the temperature was maintained below 10 °C. After 30 min the mixture was allowed to warm up to room temperature, and stirring was continued for 16 h. The mixture was cooled and hydrolyzed with 250 mL of water. The aqueous phase was separated, washed with 100 mL of ether, and acidified with 6 N HCl. The acid was filtered and washed with water to give 28 g of the crude product, which was crystallized from THF/*i*-Pr_2O to give 23 g of **2**.

Method B. 5,5′-[[1,1′-Biphenyl]-2,5-diylbis(oxy)]bis[2,2-dimethylpentanoic acid] (**18**). A solution of 60.0 g (0.32 mol) of phenylhydroquinone in 200 mL of DMF was added dropwise

to a suspension of 27.5 g (0.68 mol) of 59% sodium hydride in 100 mL of DMF with stirring under N_2. The mixture was stirred for 1 h at room temperature to complete the reaction. Methyl 5-bromo-2,2-dimethylpentanoate (V; 156 mL, 0.7 mol) was added dropwise at room temperature, followed by heating the mixture at 80–85 °C for 12–14 h. The mixture was cooled, filtered from the inorganic residue, and the DMF was distilled under reduced pressure. The residue was treated with water, and the organic material was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$ and concentrated, leaving behind an oil. The unreacted alkyl bromide was removed by distillation under high vacuum, and the residue was purified by chromatography over silica gel with hexane–$CHCl_3$ (8:1) as the eluent. The crude diester (160 g) thus obtained was saponified by refluxing with 2 N methanolic NaOH (1600 mL) for 3 h. The residue obtained after removal of methanol was treated with water and acidified. The solid thus obtained was filtered and washed with water to give 135 g of the crude product, which was crystallized from THF/*i*-Pr_2O to give 125 g of 18.

Method C. Ethyl 5,5′-[[1,1′-Biphenyl]-2,5-diylbis(oxy)]bis[2,2-dimethylpentanoate] (55). To a solution of 17.68 g (0.04 mol) of the acid 18 in 180 mL of THF was added a solution of 44 mL of $(COCl)_2$ in 220 mL of THF, keeping the temperature around 0 °C. The solution was stirred for 2 h at 0 °C, followed by stirring overnight at room temperature. THF was distilled off under reduced pressure, and the residual oil was dried under high vacuum. The crude acid chloride was dissolved in 200 mL of anhydrous THF and was added slowly to a solution of 10 mL of EtOH in 20 mL of THF containing 12 mL of Et_3N. The mixture was allowed to stir overnight at room temperature. Removal of the solvents give the crude product, which was purified by distillation to give 10.0 g of 55.

Method D. 6,6′-[1,4-Phenylenebis(oxy)]bis[2,2-dimethyl-1-hexanol] (51). A solution of 6.56 g (0.016 mol) of the acid 3 in 25 mL of THF was added to a stirred suspension of 1.1 g (0.03 mol) of $LiAlH_4$ in 75 mL of THF, followed by refluxing for 5–6 h. The mixture was cooled, and the excess hydride was decomposed with saturated Na_2SO_4 solution. The inorganic solids were removed by filtration, and the filtrate was evaporated. The crude product was purified by crystallization from THF/hexane to give 4.0 g of 51.

5,5′-[[1,1′-Biphenyl]-2,5-diylbis(oxy)]bis[2,2-dimethylpentanol diacetate] (53). A mixture of 2.59 g (0.006 mol) of the alcohol 52 and 5.0 mL of Ac_2O was heated on a steam bath for 4 h. Acetic anhydride was decomposed with water and the oil was extracted with ether. The ether extract was washed with $NaHCO_3$ solution followed by water, dried over anhydrous $MgSO_4$, and concentrated to give an oil, which was purified by chromatography over silica gel to give 2.6 g of 53 as a highly viscous oil.

Method E. 5,5′-[2-(1-Hydroxyethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid] (25). A solution of 4.0 g (0.009 mol) of the ketone 21 in 40 mL of methanol was treated with 0.4 g (0.011 mol) of $NaBH_4$ at room temperature. After the usual workup, the residue was hydrolyzed with 2 N methanolic NaOH solution, yielding the product, which was purified by crystallization from THF/*i*-Pr_2O to give 1.2 g of 25.

Methyl 5,5′-[2-(1-Propenyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoate] (28). A solution of 2.5 g (0.0058 mol) of the hydroxy compound (26) in 25 mL of benzene was heated to reflux for 8 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. After the usual workup, the oil was purified by chromatography to yield 1.1 g of 28.

Method F. 5,5′-[2-(Hydroxyphenylmethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid] (44). A solution of 2.09 g (0.004 mol) of 43 in 20 mL of 95% alcohol was heated to reflux for 18 h with 2.0 g of Zn dust and 2.0 g of NaOH. The suspension was filtered and acidified, and the product obtained was purified by crystallization from Et_2O/hexane to give 1.0 g of 44.

Method G. 5,5′-[[2-(Phenylmethyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid] (45). A solution of 3.0 g (0.006 mol) of 43 was reduced catalytically, and the crude ester was saponified. The product thus obtained was purified by crystallization from THF–petroleum ether to give 2.1 g of 45.

5,5′-[[2-(Phenylsulfinyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid] (41). A solution of 2.8 g (0.006 mol) of 40 in 25 mL of CH_2Cl_2 was stirred overnight with 1.0 g (0.006 mol) of *m*-chloroperbenzoic acid at room temperature. The solid was filtered off, washed with CH_2Cl_2, and dried. The product obtained was crystallized from THF/*i*-Pr_2O to give 1.3 g of 41.

5,5′-[[2-(Phenylsulfonyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid] (42). A solution of 2.4 g (0.005 mol) of 40 in 45 mL of CH_2Cl_2 was treated with 1.8 g (0.01 mol) of *m*-chloroperbenzoic acid. After the usual workup, the product was crystallized from THF/*i*-Pr_2O to give 1.8 g of the sulfone 42.

5-[[4-[(4-Carboxy-4-methylpentyl)oxy]phenyl]sulfinyl]-2,2-dimethylpentanoic acid (47). A solution of 3.05 g (0.008 mol) of 46 in 10 mL of glacial acetic acid containing 0.9 mL (0.005 mol) of 30% hydrogen peroxide was stirred at room temperature for 6 h. The solution was poured into water and extracted with ether. The ether extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give an oil, which solidified on trituration with isopropyl ether and finally crystallized from THF/*i*-Pr_2O to give 1.9 g of 47.

5-[[4-[(4-Carboxy-4-methylpentyl)oxy]phenyl]sulfonyl]-2,2-dimethylpentanoic Acid (48). A solution of 4.77 g (0.0125 mol) of 46 in 20 mL of glacial acetic acid was treated with 4.9 mL (0.043 mol) of 30% hydrogen peroxide at 50 °C in three portions, followed by refluxing for 2 h. After the usual workup, the product obtained was crystallized from THF/*i*-Pr_2O to give 4.3 g of the sulfoxide 48.

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Registry No. 1, 85629-68-1; 2, 79520-79-9; 3, 79520-81-3; 4, 85629-69-2; 5, 79520-82-4; 6, 79520-88-0; 7, 79520-90-4; 8, 79520-73-3; 9, 79520-54-0; 10, 79520-86-8; 11, 79520-71-1; 12, 85629-70-5; 13, 79520-72-2; 14, 79520-53-9; 15, 79520-69-7; 16, 85629-71-6; 17, 79520-84-6; 18, 79520-77-7; 18 dimethyl ester, 79520-76-6; 19, 85629-72-7; 20, 79520-65-3; 21, 79520-55-1; 22, 79521-17-8; 23, 79521-12-3; 24, 79521-11-2; 25, 79521-05-4; 26, 79521-18-9; 27, 79521-13-4; 28, 79521-07-6; 29, 79520-66-4; 32, 85629-73-8; 33, 85629-74-9; 34, 79520-59-5; 35, 79520-61-9; 36, 79520-68-6; 37, 79520-64-2; 38, 79520-62-0; 39, 79520-60-8; 40, 79520-70-0; 41, 79521-14-5; 42, 79521-15-6; 43, 79521-08-7; 44, 79521-10-1; 45, 79521-09-8; 46, 79521-02-1; 47, 79521-03-2; 48, 79521-16-7; 49, 85629-75-0; 50, 85629-76-1; 51, 79521-04-3; 52, 85629-77-2; 53, 85629-78-3; 54, 85629-79-4; 55, 85629-80-7; 56, 85629-81-8; 57, 85629-82-9; 58, 85629-83-0; 60, 79520-91-5; 61, 85629-84-1; 62, 85629-85-2; 63, 85629-86-3; 64, 85629-87-4; 65, 85629-88-5; 66, 85629-89-6; 67, 85629-90-9; 68, 79520-75-5; 69, 85629-91-0; 70, 85629-92-1; 71, 79520-96-0; 72, 79520-95-9; 73, 79520-98-2; 74, 85629-93-2; 75, 79520-56-2; 76, 85629-94-3; 77, 85629-95-4; 78, 85650-27-7; 79, 85629-96-5; 80, 85629-97-6; 81, 85629-98-7; 82, 79520-58-4; 83, 85629-99-8; 84, 85630-00-8; 85, 85630-01-9; 86, 79520-74-4; 87, 85630-02-0; 88, 85630-03-1; 89, 85630-04-2; 90, 85630-05-3; 91, 79534-95-5; 92, 85630-06-4; 93, 79520-57-3; 94, 85630-07-5; 95, 85630-08-6; 96, 85630-09-7; 98, 85630-10-0; 99, 85630-11-1; 100, 85630-12-2; 102, 5471-84-1; 103, 79520-78-8; 104, 79520-80-2; 105, 79520-89-1; 106, 79520-87-9; 107, 79520-83-5; 108, 85630-13-3; 109, 85630-14-4; 111, 79520-85-7; 112, 63807-84-1; 113, 79520-94-8; 114, 79520-97-1; 115, 85630-15-5; 116, 85630-16-6; V (n = 3), 79520-52-8; 2,2-dimethyl-4-pentenoic acid, 16386-93-9; isobutyric acid, 79-31-2; phenylhydroquinone, 1079-21-6.