of MeSH, a 30% excess). 4-Chloro-3-cyanobenzyl trifluoride (20.5 g, 0.1 mol) was then added in one portion and the reaction mixture became slightly exothermic. After stirring for a few minutes, a solid started to precipitate from the reaction mixture and stirring was continued for 2 h. After filtration, the filtrate was diluted with H_2O (500 ml) and extracted with Et_2O. This Et_2O extract was washed with H_2O (100 ml), dried over Na_2SO_4, and evaporated in vacuo to give 15.2 g (70%) of crude 4-thiomethyl-3-cyanobenzyl trifluoride as a gummy white solid. This material (15.2 g, 0.07 mol) was dissolved in EtOH (150 ml) and 20% NaOH (200 ml) and heated at 90° for 18 h. At this point the mixture was cooled and acidified with 12 N HCl and the white solids which precipitated were removed by filtration and washed well with H_2O to give 16.4 g (99%) of 171: a white solid; mp 198–200°. A small sample was sublimed (125°, 0.02 mm) to give the analytical sample: mp 198.5–200°. Anal. ($C_9H_7F_3O_2S$) C, H.

5-Chloro-2-methoxynicotinic Acid (172). Chlorine gas was bubbled into a stirred suspension of 2-methoxynicotinic acid (10.0 g, 0.065 mol) in H_2O (750 ml) for 30 min at room temperature. The precipitated crystals were collected and dried to give 10.19 g (84%) of 172: mp 149–150°. Anal. ($C_7H_6ClNO_3$) C, H, N.

Acknowledgment. The competent technical assistance of Messrs. Herman Griffin, Mark A. Guadliana, Thomas E. Johnson, Werner H. Kappeler, Paul R. Kelbaugh, Charles H. Lamphere, Robert M. McIntyre, Stephen S. Massett, Donald L. Riggs, and Frank W. Rusek is greatly appreciated.

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Synthesis and Biological Evaluation of Substituted 2,2'-Oxybis(propionic acid) Derivatives and Related Compounds

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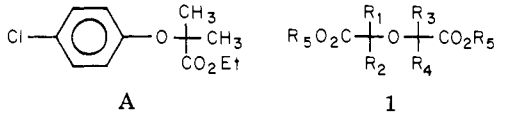
A series of 2,2'-oxybis(propionic acid) derivatives was prepared and their hypolipidemic activity measured. The lipid lowering activity of various 2,2,5,5-tetrasubstituted furan derivatives was also measured. No significant hypolipidemic activity was observed.

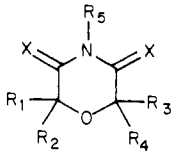
An enormous research effort has been directed at understanding and attacking atherosclerosis and coronary artery disease. Both abnormal serum lipoprotein metabolism[1] and abnormal arterial wall lipid metabolism[2] have been implicated. Whereas it has not been established that lowering serum lipoprotein concentration decreases the rate of deposition of lipid in arterial walls, the elevated serum lipid level associated with abnormal lipoprotein metabolism has been designated as a major risk factor in the atherosclerotic heart disease.[3] That coronary heart disease and cerebral vascular accident are the single largest cause of death in this country has stimulated efforts to discover agents which reduce circulatory lipid levels.

A large number of aryl- and aryloxy-substituted alkylcarboxylic acids have been reported to possess hypolipidemic activity.[4] Among these, clofibrate (A) has been the major drug available for treatment of these hyperlipidemias. The disadvantages of low potency[5] as well as its lack of effectiveness toward type II hyperlipoproteinemia[6] have led to a concentrated search for superior hypolipidemic agents among compounds containing the structural elements of clofibrate.[7]



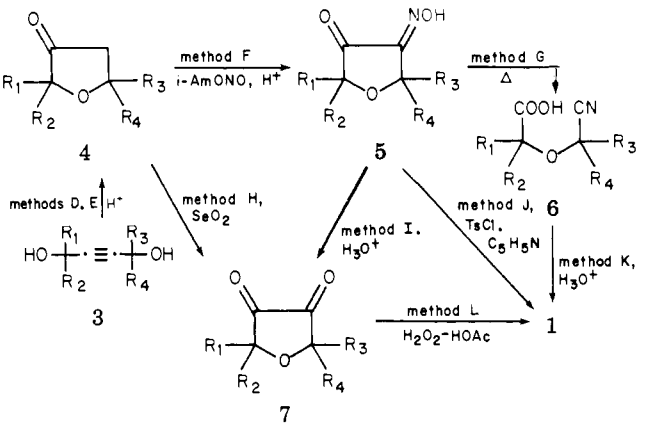
A

1



2

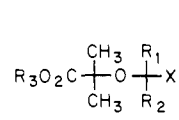
Scheme I



In this regard, a synthetic program directed toward 2,2'-oxybis(propionic acid) derivatives of type **1**, morpholines of structure **2**, and related compounds was initiated.

Chemistry. The synthetic pathways used to prepare the 2,2'-oxybis(propionic acid) derivatives **1** are displayed in Scheme I. Of the reported[8-11] conversions of furandiones **7** or furandione monooximes **5** (Table III) into 2,2'-oxybis(propionic acid) derivatives of formula **1** (Table I), oxidative cleavage[8] of α-dione **7** proved the most general pathway. In several cases (**1b,d,f**) purification of the diacid

Table I. 2,2'-Oxybis(propionic acids) 1 and Cyano Acids 6



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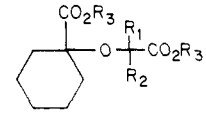
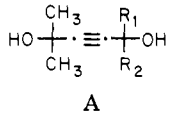


B

Compd	Mp or bp (mm), °C	Yield, %	Method	Structure type	R_1	R_2	R_3	X	Emp formula	Analyses
1a[a]	154-155	78	J	A	CH_3	CH_3	H	CO_2R_3	$C_8H_{14}O_5$	C, H
1b	132-135 (0.6)	16	L	A	CH_3	C_6H_5	CH_3	CO_2R_3	$C_{15}H_{20}O_5$	C, H
1c	136-137	62	L	A	C_6H_5	C_6H_5	H	CO_2R_3	$C_{18}H_{18}O_5$	C, H
1d	140-153 (0.8)	29	L	A	CH_3	p-Cl-C_6H_4	CH_3	CO_2R_3	$C_{15}H_{19}O_5Cl$	C, H, Cl
1e	132-134	69	L	A	C_6H_5	p-Cl-C_6H_4	H	CO_2R_3	$C_{18}H_{17}O_5Cl$	C, H, Cl
6a	131-133	<10	G	A	CH_3	CH_3	H	CN	$C_8H_{13}NO_3$	C, H, N
6b	155-157	30	G	A	C_6H_5	C_6H_5	H	CN	$C_{18}H_{17}NO_3$	C, H, N
1f	96-100 (0.2)	73	L	B	CH_3	CH_3	CH_3	CO_2R_3	$C_{13}H_{22}O_5$	C, H
1g	103-104.5	70	L	B	CH_3	C_6H_5	H	CO_2R_3	$C_{16}H_{20}O_5$	C, N

[a] See ref 9.

Table II. Acetylenic Diols 3



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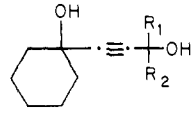

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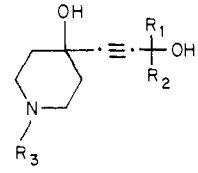


C

Compd	Mp, °C	Yield, %	Method	Structure type	R_1	R_2	R_3	Emp formula	Analyses
3a[a]	92-94	38	A	A	CH_3	CH_3		$C_8H_{14}O_2$	C, H
3b[b]	83-84	57	A	A	CH_3	C_6H_5		$C_{13}H_{16}O_2$	C, H
3c[c]	119-121	58	A	A	C_6H_5	C_6H_5		$C_{18}H_{18}O_2$	C, H
3d	131-132	44	A	A	CH_3	p-Cl-C_6H_4		$C_{13}H_{15}O_2Cl$	C, H, Cl
3e	89.5-95.5	60	A	A	C_6H_5	p-Cl-C_6H_4		$C_{18}H_{17}O_2Cl$	C, H, Cl
3f	168-171	50	A	A	4-Pyridyl	p-Cl-C_6H_4		$C_{17}H_{16}O_2NCl$	C, H, N, Cl
3g[b]	93.5-95	52	A	B	CH_3	CH_3		$C_{11}H_{18}O_2$	C, H
3h[d]	124-125.5	23	A	B	CH_3	C_6H_5		$C_{16}H_{20}O_2$	C, H
3i	110-111.5	16	B	B	C_6H_5	C_6H_5		$C_{21}H_{22}O_2$	C, H
3j	141.5-142	58.5	C	C	CH_3	CH_3	CH_3	$C_{11}H_{19}O_2N$	C, H, N
3k	180-181	43	C	C	$-(CH_2)_2N(CH_3)(CH_2)_2-$		CH_3	$C_{14}H_{24}O_2N_2$	C, H, N
3l	Oil	58	C	C	CH_3	CH_3	COC_6H_5	$C_{17}H_{21}O_3N$	C, H, N
3m	Oil	18	B	C	$-(CH_2)_2N(COC_6H_5)(CH_2)_2-$		COC_6H_5	$C_{20}H_{26}O_3N$	C, H, N

[a] See ref 9. [b] See ref 13b. [c] See ref 17. [d] See ref 16b.

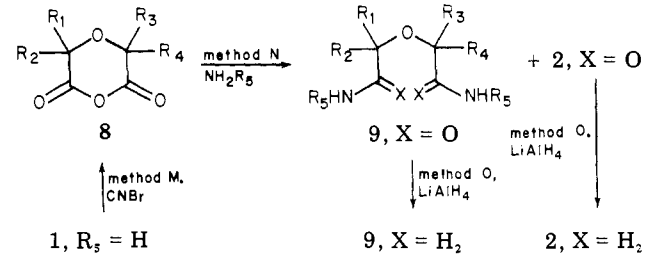
required conversion to the more volatile diester. Diazomethane[12a] was used for this transformation due to the failure of standard exchange methods.[12b] The needed α-diones **7** (Table III) were prepared by either SeO_2 oxidation[13] of furanones **4** or hydrolysis[14] of the corresponding ketoximes **5**. Nitrosation[15] of the furanones **4** provided the ketoximes **5**.

The acetylenic diols **3** (Table II) which were prepared by known procedures[16] could be cyclized[13,17] to the necessary furanone intermediates **4**.

Treatment of the diacids **1** (R = H) with CNBr in pyridine[18] as is depicted in Scheme II gave anhydrides **8** (Table IV) cleanly and in good yields. On exposure of the anhydrides to excess amine at 130°, a mixture of diamides **9** (X = O) (Table V) and imides **2** (X = O) (Table IV) was realized. The interconversion of **9** and **2** (X = O) was effected by treatment under the appropriate conditions. Heating **9** under reduced pressure afforded **2**, whereas reaction of **2** with excess amine gave **9**. Reduction of **2** or **9** (X = O) with $LiAlH_4$ gave morpholine **2** or diamine **9** ($X = H_2$), respectively.

Turning our attention to related furans (Scheme III) reduction of acetylenic diol **3** with 1 equiv of hydrogen,

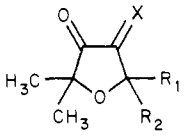
Scheme II



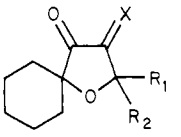
even over 10% Pd/C catalyst, gave cis diol **10** (Table VI) which could be dehydrated to dihydrofuran **12** (Table VII) or reduced with an additional equivalent of hydrogen to the fully saturated diol **11** (Table VI). Diol **11** could be dehydrated to tetrahydrofuran **13** (Table VII). While dihydrofurans **12** could be epoxidized by treatment with peracid (Table VII), they proved relatively inert to other attempts at functionalization.

Pharmacology (See Table VIII). Of the 2,2'-oxybis(propionic acids) (**1**) prepared, only **1a** displayed any hypolipidemic activity. This activity was accompanied by a large weight loss (46%) and the compound was not

Table III. Furanones 4, Ketoximes 5, and Diketones 7



A

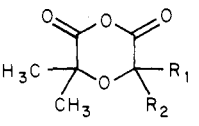


B

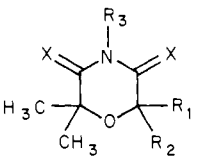
Compd	Mp or bp (mm), °C	Yield, %	Method	Structure type	R_1	R_2	X	Emp formula	Analyses
4a[c]	40-42 (10)	87	E	A	CH_3	CH_3	H_2	$C_8H_{14}O_2$	C, H
4b[d]	126-131 (12)[b]	70	E	A	CH_3	C_6H_5	H_2	$C_{13}H_{16}O_2$	C, H
4c[e]	60-65	75	D	A	C_6H_5	C_6H_5	H_2	$C_{18}H_{18}O_2$	C, H
4d	Oil	70	E	A	CH_3	p-Cl-C_6H_4	H_2	$C_{13}H_{15}O_2Cl$	C, H, Cl
4e	67.5-69	93	D	A	C_6H_5	p-Cl-C_6H_4	H_2	$C_{18}H_{17}O_2Cl$	C, H, Cl
5a[c]	152-154	30	F	A	CH_3	CH_3	NOH	$C_8H_{13}NO_3$	C, H, N
5a'[a]	151-153	32	J	A	CH_3	CH_3	NOH	$C_8H_{13}NO_3$	C, H, N
5b	150-151	89	F	A	C_6H_5	C_6H_5	NOH	$C_{18}H_{17}NO_3$	C, H, N
5b'[a]	151.5-153	84	J	A	C_6H_5	C_6H_5	NOH	$C_{18}H_{17}NO_3$	C, H, N
5c	138-139	50	F	A	CH_3	p-Cl-C_6H_4	NOH	$C_{13}H_{14}NO_3Cl$	C, H, N, Cl
5d	126-127	45	F	A	C_6H_5	p-Cl-C_6H_4	NOH	$C_{18}H_{16}NO_3Cl$	C, H, N, Cl
5e	Oil	40	F	A		$-(CH_2)_5-$	NOH	$C_{11}H_{17}NO_3$	C, H, N
7a[f]	60-85 (20)	28	H	A	CH_3	CH_3	O	$C_8H_{12}O_3$	C, H
7b[f]	83-87 (0.2)	86	H	A	CH_3	C_6H_5	O	$C_{13}H_{14}O_3$	C, H
7c	150-158 (0.2)	86	H	A	C_6H_5	C_6H_5	O	$C_{18}H_{16}O_3$	C, H
7d	122-127 (0.2)	78	H	A	CH_3	p-Cl-C_6H_4	O	$C_{13}H_{13}O_3Cl$	C, H, Cl
7e	185-191 (1.75)	77	H	A	C_6H_5	p-Cl-C_6H_4	O	$C_{18}H_{15}O_3Cl$	C, H, Cl
4f[g]	100-120 (10)[b]	70	E	B	CH_3	CH_3	H_2	$C_{11}H_{18}O_2$	C, H
4g	Oil[b]	53	E	B	CH_3	C_6H_5	H_2	$C_{16}H_{20}O_2$	C, H
4h	Oil	68	E	B	C_6H_5	C_6H_5	H_2	$C_{21}H_{22}O_2$	C, H
7f	60-100 (0.2)	65	H	B	CH_3	CH_3	O	$C_{11}H_{16}O_3$	C, H
7g	135-141 (0.1)	70	H	B	CH_3	C_6H_5	O	$C_{16}H_{18}O_3$	C, H

[a] Stereoisomers. [b] A mixture of both possible ketones. [c] See ref 9. [d] See ref 13. [e] See ref 17. [f] See ref 13a. [g] See ref 13b.

Table IV. Anhydrides 8 and Morpholines 2



8



2

Compd	Mp or bp (mm), °C	Yield, %	Method	R_1	R_2	R_3	X	Emp formula	Analyses
8a	Oil	40	M	CH_3	CH_3			$C_8H_{12}O_4$	C, H
8b	80-82	87	M	C_6H_5	C_6H_5			$C_{18}H_{16}O_4$	C, H
8c	109-111 (0.1)	65	M	CH_3	p-Cl-C_6H_4			$C_{13}H_{13}O_4Cl$	C, H, Cl
8d	110-112	75	M	C_6H_5	p-Cl-C_6H_4			$C_{18}H_{15}O_4Cl$	C, H, Cl
2a	52.5-53.5	44	N	CH_3	CH_3	$C_6H_5CH_2$	O	$C_{15}H_{19}NO_3$	C, H, N
2b	85-90 (0.1)	85	O	CH_3	CH_3	$C_6H_5CH_2$	H_2	$C_{15}H_{23}NO$	C, H, N
2c	54-56	56	N	CH_3	CH_3	p-Cl-$C_6H_4CH_2$	O	$C_{15}H_{18}NO_3Cl$	C, H, N, Cl
2d	51.5-53	58	O	CH_3	CH_3	p-Cl-$C_6H_4CH_2$	H_2	$C_{15}H_{22}NOCl$	C, H, N, Cl
2e	Oil	4	N	C_6H_5	C_6H_5	H	O	$C_{18}H_{17}NO_3$	C, H, N
2f	169-170	8	N	C_6H_5	C_6H_5	C_6H_5	O	$C_{24}H_{21}NO_3$	C, H, N
2g	112-113	56	N	C_6H_5	C_6H_5	$C_6H_5CH_2$	O	$C_{25}H_{23}NO_3$	C, H, N
2h	224-225.5[a]	98	O	C_6H_5	C_6H_5	$C_6H_5CH_2$	H_2	$C_{25}H_{28}NOCl$	C, H, N, Cl
2i	114.5-115	60	N	C_6H_5	C_6H_5	p-Cl-$C_6H_4CH_2$	O	$C_{25}H_{22}NO_3Cl$	C, H, N, Cl
2j	102.5-104.5	48	O	C_6H_5	C_6H_5	p-Cl-$C_6H_4CH_2$	H_2	$C_{25}H_{26}NOCl$	C, H, N, Cl
2k	215-217 (0.2)	40	N	C_6H_5	p-Cl-C_6H_4	$C_6H_5CH_2$	O	$C_{25}H_{22}NO_3Cl$	C, H, N, Cl

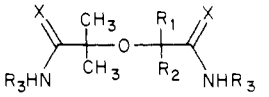
[a] Hydrochloride salt.

pursued further. Both ketoximes **5b** and **5d** exhibited weak–moderate serum triglyceride lowering. Imides **2g**, **2i**, and **2k** displayed weak lipid lowering activity, suggesting that the *p*-chloro substituent may enhance activity. This activity was lost on reduction to the corresponding morpholines **2h** and **2j**.

Diamine **9c**, while producing marked triglyceride lowering activity at doses as low as 30 mg/kg, produced a significant and proportional weight loss at all dose levels and was dropped from further consideration.

Unsaturated diols **10c** and **10d**, prepared by reducing the corresponding acetylenic diols **3j** and **3k**, showed weak and weak–moderate triglyceride lowering activity. Dihydrofuran **12b** produced a weak–moderate reduction in

Table V. Diamines and Diamides 9

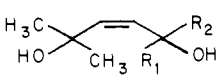


9

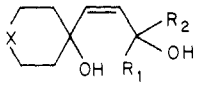
Compd	Mp or bp (mm), °C	Yield, %	Method	R_1	R_2	R_3	X	Emp formula	Analyses
9a	Semisolid	56	N	CH_3	CH_3	$C_6H_5CH_2$	O	$C_{22}H_{28}N_2O_3$	C, H, N
9b	120.5-121.5	24	N	CH_3	CH_3	p-Cl-$C_6H_4CH_2$	O	$C_{22}H_{26}N_2O_3Cl_2$	C, H, N, Cl
9c	227-228[a]	97	O	CH_3	CH_3	p-Cl-$C_6H_4CH_2$	H_2	$C_{22}H_{32}N_2OCl_4$	C, H, N, Cl
9d	Oil	39	N	C_6H_5	C_6H_5	C_6H_5	O	$C_{30}H_{28}N_2O_3$	C, H, N
9e	Oil	33	N	C_6H_5	p-Cl-C_6H_4	$C_6H_5CH_2$	O	$C_{32}H_{31}N_2O_3Cl$	C, H, N, Cl

[a] Dihydrochloride salt.

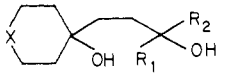
Table VI. Unsaturated Diols 10 and Diols 11



A



B

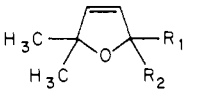


11

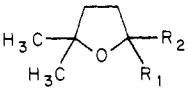
Compd	Mp or bp (mm), °C	Yield, %	Method	Structure type	R_1	R_2	X	Emp formula	Analyses
10a	Oil	44	P	A	C_6H_5	p-Cl-C_6H_4		$C_{18}H_{19}O_2Cl$	C, H, Cl
10b	186-188	95	P	A	4-Pyridyl	p-Cl-C_6H_4		$C_{17}H_{18}NO_2Cl$	C, H, N, Cl
10c	275-278[a]	18	P	B	CH_3	CH_3	NCH_3	$C_{10}H_{20}NO_2Cl$	C, H, N, Cl
10d	103-107	74	P	B	$-(CH_2)_2N(CH_3)(CH_2)_2-$		NCH_3	$C_{14}H_{24}N_2O_2$	C, H, N
10e	248-250	95	P	B	$-(CH_2)_2N(COC_6H_5)(CH_2)_2-$		$NCOC_6H_5$	$C_{26}H_{30}N_2O_4$	C, H, N
10f	140-150 (0.3)	90	P	B	CH_3	CH_3	$NCOC_6H_5$	$C_{12}H_{21}NO_3$	C, H, N
11a	93-94	45	P		C_6H_5	C_6H_5	CH_2	$C_{21}H_{26}O_2$	C, H
11b	194-195	100	P		$-(CH_2)_2N(CH_3)(CH_2)_2-$		NCH_3	$C_{14}H_{28}N_2O_3$	C, H, N
11c	130-135 (0.3)	100	P		CH_3	CH_3	$NCOCH_3$	$C_{12}H_{23}NO_3$	C, H, N

[a] Hydrochloride salt.

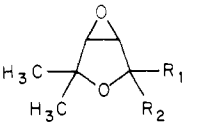
Table VII. Dihydrofurans 12, Tetrahydrofurans 13, and Epoxides 14



12



13



14

Compd	Mp or bp (mm), °C	Yield, %	Method	R_1	R_2	Emp formula	Analyses
12a	98-100 (15)	84	Q	CH_3	C_6H_5	$C_{13}H_{16}O$	C, H
12b	128-131 (0.1)	57	Q	C_6H_5	p-Cl-C_6H_4	$C_{18}H_{17}OCl$	C, H, Cl
12c	147-149 (0.2)	70	Q	4-Pyridyl	p-Cl-C_6H_4	$C_{17}H_{16}NOCl$	C, H, N, Cl
13a	100-110 (0.2)	70	Q	$-(CH_2)_2N(COCH_3)(CH_2)_2-$		$C_{12}H_{21}NO_2$	C, H, N
14a	69-70 (0.1)		R	CH_3	C_6H_5	$C_{13}H_{16}O_2$	C, H
14b[a]	112-113.5	42	R	4-Pyridyl	p-Cl-C_6H_4	$C_{17}H_{16}NO_2Cl$	C, H, N, Cl
14b'[a]	111-113	33	R	4-Pyridyl	p-Cl-C_6H_4	$C_{17}H_{16}NO_2Cl$	C, H, N, Cl
14c[a]	132-135	38	R	C_6H_5	p-Cl-C_6H_4	$C_{18}H_{17}O_2Cl$	C, H, Cl
14c'[a]	157-158	29.5	R	C_6H_5	p-Cl-C_6H_4	$C_{18}H_{17}O_2Cl$	C, H, Cl

[a] Diastereomers.

both serum cholesterol and triglyceride levels. The level of hypolipidemic activity displayed by diol **11c** was increased on dehydration to the corresponding tetrahydrofuran **13a**. Similarly, in going from dihydrofurans **12** to 3,6-dioxabicyclo[3.1.0] hexanes **14**, the level of hypolipidemic activity in all cases increased significantly.

Conclusions

The structural similarities between the 2,2'-oxybis(propionic acid) derivatives described in this publication and clofibrate were not sufficient enough to have provided them with hypolipidemic activity. The corresponding imides and furan derivatives, potential prodrugs, i.e., biological precursors to the 2,2'-oxybis(propionic acids), were similarly devoid of a desirable level of hypolipidemic activity. The phenoxy moiety appears to be a necessary component of clofibrate analogues if hypolipidemic activity is to be maintained or improved.

Scheme III

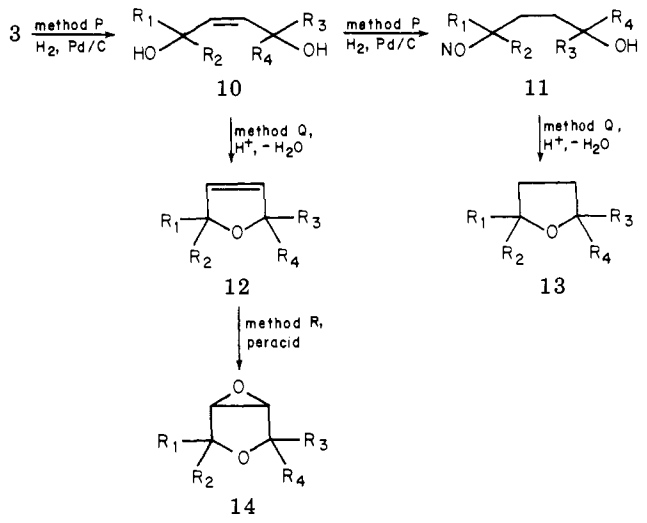


Table VIII. Hypolipidemic Activity[a]

Compd	Plasma levels, % redn: Cholesterol	Plasma levels, % redn: Triglyceride	Compd	Plasma levels, % redn: Cholesterol	Plasma levels, % redn: Triglyceride
1a	+4	−32	2j	+12	−45
1b	0	−3	2k	−7[c]	−4[c]
1c	−11	+8	9c	−7[c]	−77[c]
1d	+29	+9	9c	−15[d]	−64[d]
1e	+6	+33	9c	−25[e]	−9[e]
1f	−8	+8	10c	−4	−10
1g	+28	−2	10d	−17[f]	−28[f]
3d	+1	+6	10e	−3	+27
3e	+48	+3	10f	+21	+92
3f	+30	+34	11a	−5	+74
3j	+20	+86	11b	−4	+29
3k	+19	+43	11c	−7	−22
5b	−6	−19	12a	−7	+27
5d	−6	−29	12b	−11[b]	−17[b]
2a	+35	+51	12c	+32	−65
2b	−14	+9	13a	−11[c]	−39[c]
2c	−3	+50	14a	−11[c]	−6[c]
2d	−3	−10	14b	−8[b]	−15[b]
2f	−6	+8	14b'	−6[b]	−78[b]
2g	−9[b]	−7[b]	14c	−11	−12
2h	0	−15	14c'	−12	+38
2i	−9	−16	Clofibrate (A)	−34[g]	−49[g]
			Lifibrate	−30[h]	−50[h]

[a] Except where noted a dose of 120 mg/kg per diem for 3 days was administered. See the Experimental Section for details. [b] A dose of 60 mg/kg per diem for 3 days. [c] A dose of 250 mg/kg per diem for 6 days. [d] A dose of 120 mg/kg per diem for 6 days. [e] A dose of 60 mg/kg per diem for 6 days. [f] A dose of 250 mg/kg per diem for 3 days. [g] A dose of 300 mg/kg per diem for 6 days. [h] A dose of 30 mg/kg per diem for 6 days.

Experimental Section

Biological Methods. Male albino Wistar Royal Hart rats weighing 160–180 g initially were maintained on a drug-free ground Purina Lab Chow diet for 7 days and then divided into groups of six animals. Each group, with the exception of control, was then given orally 120 mg/kg of body weight per diem of compound for 3 or 6 days. At the end of this period, the animals were anesthetized with sodium hexobarbital and bled from the carotid artery. Serum or plasma samples were collected and 1.0-ml samples of the serum were added to 9.0 ml of redistilled 2-propanol. Two autoanalyzer cupsful of a mixture of zeolite–copper hydroxide and Lloydds reagent[19] were added and the mixture was shaken for 1 h. Cholesterol and triglyceride levels were determined simultaneously on the same sample by Technicon N24A[20] (cholesterol) and N-78[19] (triglyceride) methodology. The mean total serum cholesterol levels were then computed, and the hypocholesterolemic activity was expressed as the fall in cholesterol levels as a percentage of the control level. The change in triglyceride levels induced by the drug was computed as a percentage of the control triglyceride levels.

General Comments. Chemistry. The ir spectra were recorded on a Perkin-Elmer Model 257 or 457 spectrometer and ^{1}H NMR spectra were recorded using either a Varian T-60 or A-60A spectrometer. Chemical shifts (δ) are reported relative to Me_4Si; coupling constants (J) are given in hertz. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Silica gel (0.063–0.2 mm) was used in preparing column chromatograms and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plasic sheets of silica gel G with fluorescent indicator. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation.

All new structures were assigned on the basis of spectral data and combustion analysis. The analyses are within 0.4%. No yields were optimized, and all are reported as isolated yields.

Compounds of type 1, 3, 4, 5, 6, and 7 were prepared according to literature methods A[16b,c], B[16d], C[16a], D[17], E[13], F[15], G[9], H[13], I[14], J[9], K[9], and L[8]. The pertinent data are summarized in Tables I–III.

Method M. 3,3-Dimethyl-5,5-R$_1$,R$_2$-1,4-dioxane-2,6-dione (8). To a solution of diacid 1c (1.99 g, 6.3 mmol) and CNBr (0.88 g, 8.4 mmol) in C_6H_6 (20 ml) at room temperature, pyridine (1.00 g, 12.6 mmol) was slowly added. After an additional 3 h, the solution was filtered and the filtrate washed with brine and 2 N HCl, dried, and evaporated to give a colorless oil. Crystallization from Et_2O–petroleum ether gave 1.57 g (87%) of **8a** as white crystals: mp 80–82°.

Using the above procedure anhydrides **8b** and **8c** were similarly prepared.

Method N. 4-(*p*-Chlorobenzyl)-2,2,6,6-tetramethyl-3,5-morpholinedione (2c) and *N*-(*p*-Chlorobenzyl)-2,2'-oxybis(2-methyl)propionamide (9b). The following experiment is representative of the general technique used to synthesize the 3,5-morpholinediones **2**, (X = O) and diamides **9** (X = O).

A mixture of anhydride **8a** (9.00 g, 52 mmol) and 4-chlorobenzylamine (50 ml) was heated at 130–140° under N_2 for 18 h. The cooled mixture was partitioned between 2 N HCl and Et_2O, and the organic layer was washed with brine, dried, and evaporated to give a yellow oil consisting of two components by TLC analysis. Chromatography over silica gel (30:1) with $CHCl_3$–MeOH (99:1) as elutent gave in fraction 1 8.65 g (56%) of 3,5-morpholinedione **2c**. Recrystallization from Et_2O–CH_2Cl_2 gave **2c**: mp 54–56°. Fraction 2 gave 5.48 g (24%) of diamide **9b**: mp 120.5–121.5°.

Method O. 4-(*p*-Chlorobenzyl)-2,2,6,6-tetramethylmorpholine (2d). The following experiment is described as a general technique for the conversion of 3,5-morpholinediones **2** (X = O) into morpholines **2** (X = H_2) and of diamides **9** (X = O) into diamines **9** (X = H_2).

A solution of 3,5-morpholinedione **2c** (1.92 g, 6.5 mmol) in anhydrous Et_2O (35 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.760 g, 20 mmol) in anhydrous Et_2O (50 ml). The mixture was refluxed for 3 h and stirred for an additional 18 h at room temperature. The excess hydride was decomposed with saturated Na_2SO_4 and evaporation gave 1.01 g (58%) of a colorless oil, homogeneous by TLC. Crystallization from a minimum of petroleum ether at −5° gave morpholine **2d** as a white solid: mp 51.5–53°.

Method P. Preparation of Unsaturated Diols 10 and Saturated Diols 11. In the typical experiment a 2–5% solution of acetylenic diol **3** in absolute EtOH was stirred with 5% Pd/C (10% by weight) under an atmosphere of H_2. By monitoring H_2 uptake, preparation of unsaturated diol **10** or saturated diol **13** was affected. Removal of the catalyst by filtration through Celite and evaporation of the filtrate gave the crude diol which was purified by crystallization or distillation (see Table VI for the pertinent data).

Method Q. 2,5-Dihydro-2,2-dimethyl-5-(*p*-chlorophenyl)-5-phenylfuran (12b). The following experiment is

described as a general procedure for the synthesis of dihydrofurans **12** from the unsaturated diols **10**.

A solution of **10a** (17.5 g, 58 mmol) in toluene (150 ml) was stirred and refluxed with *p*-TsOH (0.1 g) in a flask equipped with a Dean-Stark tube until the water level remained constant (5 h). The cooled solution was washed with 2 N NaOH and brine, dried, and evaporated to give an oil, which on distillation provided 9.4 g (57%) of **12b**: mp 98–100° (15 mm).

Method R. Epoxidation of Dihydrofuran 12c. General Epoxidation Procedure. A solution of dihydrofuran **12c** (11.4 g, 40 mmol) and *m*-chloroperbenzoic acid (85%, 60 g, 0.3 mol) in $CHCl_3$ (350 ml) was refluxed under N_2 for 48 h. Upon evaporation to dryness, the residue was partitioned between Et_2O and H_2O and the two-phased system treated with $NaHSO_3$ until no more oxidant could be detected. The aqueous layer was saturated with NaCl and extracted thoroughly with Et_2O. The combined Et_2O extracts were dried and evaporated to give three components as indicated by the TLC. Chromatography over silica gel (50:1) eluting with MeOH–$CHCl_3$ (1:99) sequentially provided 1.85 g (16%) of starting olefin **12c** (R_f 0.35), 5.05 g (42%) of epoxide **14b** (R_f 0.20), and 3.95 g (33%) of epoxide **14b'** (R_f, 0.15). The epoxides were recrystallized from CH_2Cl_2–Et_2O.

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