Table X. Effect of 2-Hexadecanone (5) on Rat[a] Liver Cell Membrane in Vitro

	% of unlyzed cells, $\bar{x}$ ± SD					
	0 min	15 min	30 min	1 hr	2 hr	4 hr
1% CMC	100	91 ± 6	93 ± 7	90 ± 4	77 ± 8	17 ± 4
2-Hexadecanone						
5 mg/g of liver	100	95 ± 5	93 ± 6	91 ± 5	83 ± 5	17 ± 8
10 mg/g of liver	100	96 ± 4	95 ± 7	92 ± 4	77 ± 6	19 ± 7
25 mg/g of liver	100	97 ± 7	96 ± 3	92 ± 6	85 ± 9	18 ± 4

[a] $N = 6$.

Table XI. Effect of 2-Hexadecanone (5) on Rat[a] Liver Lysosomal Membranes in Vitro

	% free acid phosphatase act., $\bar{x}$ ± SD	p
1% CMC	100 ± 16	
2-Hexadecanone		
5 mg/g of liver	85 ± 14	NS
10 mg/g of liver	89 ± 3	NS
25 mg/g of liver	116 ± 12	NS

[a] $N = 6$.

Table XII. Uterotropic Activity in Ovariectomized Sprague-Dawley Rats[c] after 3 Days of Treatment

	% uterine wt (mg), $\bar{x}$ ± SD
1% CMC	100 ± 15
2-Hexadecanone (5) (10 mg/kg)	64 ± 23[b]
2-Heptadecanone (6) (10 mg/kg)	76 ± 17
17-Ethinylestradiol (10 μg/kg)	372 ± 12[a]

[a] $p = 0.001$. [b] $p = 0.025$. [c] $N = 7$.

membrane. In vitro studies with compound 5 actually showed lower unbound enzyme concentration (percent free enzyme activity) than the control (Table XI). Although these findings provide only indirect evidence, it appears that compound 5 is not having a major effect on membranes of the cell.

The LD_{50} for compound 5 in CF_1 mice was 1.75 g/kg. Since there was no atrophy of the epididymis, vas deferens, testes, and vesicular glands (Table XII), and the uterotropic test was negative, compound 5 had no estrogenic activity at 10 mg/kg/day.

From this study it was concluded that compound 5 is a good potential hypocholesterolemic agent which does not lower serum triglycerides. It does not possess the estrogenic characteristics of the cyclooctanones and is not toxic at therapeutic doses.

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Hypocholesterolemic Activity of 1,3-Bis(substituted phenoxy)-2-propanones

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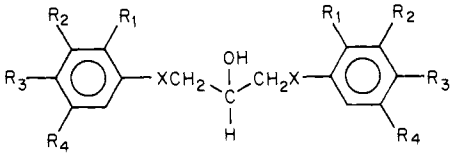
A series of 1,3-bis(substituted phenoxy)-2-propanones was found to be active hypocholesterolemic agents at 10 mg/kg/day. The *p*-chloro- and *p*-methyl-substituted phenoxy compounds possess the highest activity. These compounds did not possess the estrogenic and antifertility activities of the related previously reported derivatives of the bis(β-phenylethyl) ketone series. The 1,3-bis(*p*-methylphenoxy)-2-propanone (7) also lowered serum triglycerides and glycerol which appeared to be due to increased levels of serum lipase and reduced activity of liver lipase. There was reduced incorporation of free fatty acids into complex lipids by the liver. Cholesterol was excreted faster in the treated animals.

It has previously been demonstrated that derivatives of the bis(β-phenylethyl) ketone system, i.e., 1,5-diphenyl-2,4-dimethyl-3-pentanone, exhibit hypocholesterolemic, estrogenic, and antifertility activities.[2] A series of 2-propanone derivatives in which the benzylic carbon has been replaced isosterically with oxygen has now been examined. The 1,3-bis(substituted phenoxy)-2-propanones were synthesized by reacting the appropriate phenols with epichlorohydrin in the presence of sodium hydroxide to generate the 1,3-bis(substituted phenoxy)-2-propanols. Oxidation[3] with dimethyl sulfoxide (Me_2SO) and dicyclohexylcarbodiimide (DCC) gave the corresponding propanones in good yields (Schemes I and II). In addition, the synthesis of 1,1-dibenzyl-1-hydroxy-3-(*p*-methylphenoxy)-2-propanone was accomplished according to Scheme III. Others have reported[4] small amounts (<1%) of 1,3-bis(*p*-tolyloxy)acetone in reactions of 1,3-dichloroacetone with phenols which were not significantly ionized. Hypocholesterolemic activity remains relatively the same in the oxygenated series while antifertility and

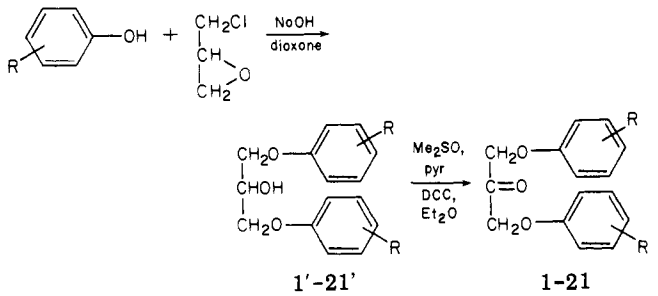
Table I. 1,3-Bis(substituted phenoxy)-2-propanols



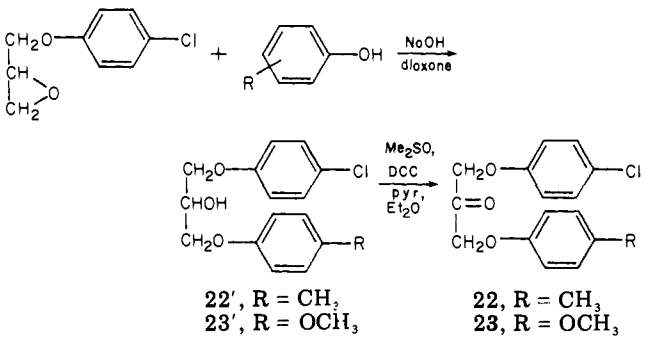
No.	R_1	R_2	R_3	R_4	X	Mp, C°	% yield	Formula	Recrystn solvent
1′	H	H	H	H	O	75-77	73	$C_{15}H_{18}O_3$	2-Propanol
2′	H	H	H	H	S	Oil	84 (crude)	$C_{15}H_{16}OS_2$	
3′	Cl	H	Cl	Cl	O	Gum	99 (crude)	$C_{15}H_{10}Cl_6O_3$	
4′	H	H	Cl	H	O	87-89	95	$C_{15}H_{14}Cl_2O_3$	2-Propanol
5′	H	Cl	H	H	O	Oil	34	$C_{15}H_{14}Cl_2O_3$	CCl_4, CCl_4-ether, 95:5, 9:1[a]
6′	Cl	H	H	H	O	Oil	47	$C_{15}H_{14}Cl_2O_3$	Benzene, benzene-ether, 9:1, 8:2[a]
7′	H	H	CH_3	H	O	80-82	70	$C_{17}H_{20}O_3$	2-Propanol
8′	CH_3	H	H	H	O	Oil	28	$C_{17}H_{20}O_3$	CCl_4, CCl_4-ether, 95:5, 9:1, 8:2[a]
9′	H	CH_3	H	H	O	Oil	58	$C_{17}H_{20}O_3$	Benzene, benzene-ether, 95:5, 9:1, 8:2[a]
10′	H	H	C_2H_5	H	O	84-86	33	$C_{19}H_{24}O_3$	2-Propanol
11′	H	H	OCH_3	H	O	93-95	51	$C_{17}H_{20}O_5$	2-Propanol
12′	OCH_3	H	H	H	O	Oil	76	$C_{17}H_{20}O_5$	$CHCl_3$, $CHCl_3$-ether, 1:1[a]
13′	H	H	OC_2H_5	H	O	50-51	21	$C_{19}H_{24}O_5$	$CHCl_3$, $CHCl_3$-ether, 9:1, 8:2[a]
14′	H	H	n-C_3H_7	H	O	Oil	107 (crude)	$C_{21}H_{28}O_3$	
15′	H	H	t-C_4H_9	H	O	Oil	56	$C_{23}H_{32}O_3$	CCl_4, CCl_4-ether, 9:1, 8:2[a]
16′	H	H	Cl	H	S	Oil	92 (crude)	$C_{15}H_{14}Cl_2OS_2$	
17′	Cl	H	CH_3	CH_3	O	117-119	97 (crude)	$C_{19}H_{22}Cl_2O_3$	
18′	H	CH_3	Cl	CH_3	O	Oil	106 (crude)	$C_{19}H_{22}Cl_2O_3$	
19′	H	H	F	H	O	Oil	71 (crude)	$C_{15}H_{14}F_2O_3$	
20′	H	H	Br	H	O	Oil	94 (crude)	$C_{15}H_{14}Br_2O_3$	
21′	H	H	I	H	O	128-131	16	$C_{15}H_{14}I_2O_3$	Benzene-2-propanol, 8:1

[a] Eluting solvent system used for column chromatography.

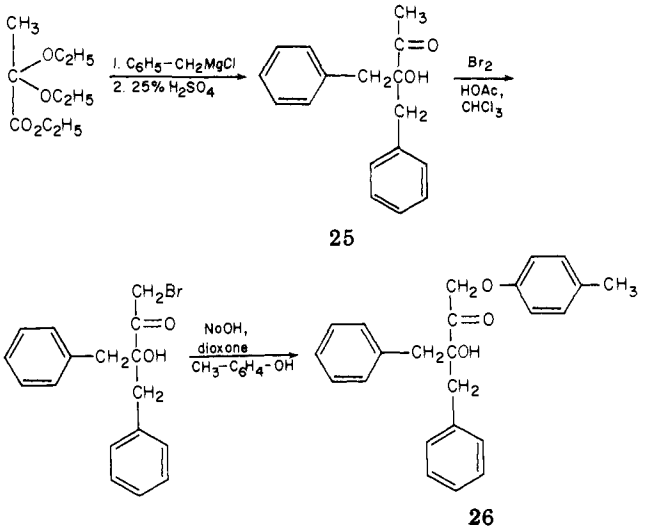
Scheme I



Scheme II



Scheme III



estrogenic activities were lost. Isosteric replacement of the benzyl carbon also removed the requirement for α,α'-disubstitution which exists in the β-phenylethyl ketone series.

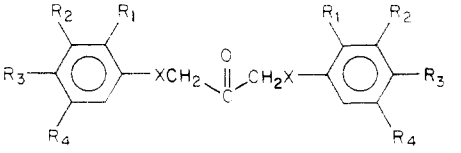
Experimental Section

The designation of the propanol compounds is by prime arabic numerals (Table I), while the ketone analogs of these alcohols are referred to by an arabic number (Table II).

All 1,3-bis(substituted phenoxy)-2-propanols were prepared by utilizing the appropriate substituted phenol with epichlorohydrin in the presence of sodium hydroxide to obtain the 2-propranol derivative which was then oxidized to the propanone using Me_2SO and DCC. All melting points were corrected and were obtained on a Hoover melting point apparatus. Elemental analyses agreed with theoretical values within ±0.4% and were obtained from M-H-W Laboratories, Garden City, Mich., or Atlantic Microlab, Atlanta, Ga. Epichlorohydrin and all substituted phenols were used as received from suppliers.

General Procedure for Preparation of 1,3-Bis(substituted phenoxy)-2-propanols (1′–21′). The synthetic route is illustrated in Scheme I. The appropriate phenol was dissolved in 40–60 ml of 1,4-dioxane at 60–70°. Powdered NaOH (0.5 equiv) was added to this solution. The temperature was raised to 98–100° and stirred until all the NaOH had reacted. Maintaining the temperature at 98–100°, 1.0 equiv of epichlorohydrin was added neat over a 10–15-min period and the reaction was then stirred under reflux for 5–6 hr or until TLC revealed completion of reaction. The dioxane was removed in vacuo, the residue was dissolved in diethyl ether or chloroform, and the solution was extracted with water. The organic phase was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed to yield the crude 2-propanol derivative. In most instances no further purification was needed in order to oxidize the 2-propanol derivative to the propanone. However, when required, the 2-propanols were purified by recrystallization from 2-propanol or 2-propanol–benzene mixture.

Table II. 1,3-Bis(substituted phenoxy)-2-propanones



No.	R_1	R_2	R_3	R_4	X	Mp, C°	% yield	Formula	Recrystn solvent	Analyses
1	H	H	H	H	O	56-58	42	$C_{15}H_{14}O_3$	Diethyl ether	C, H
2	H	H	H	H	S	40-41	14	$C_{15}H_{14}OS_2$	Hexane-benzene, 3:1	C, H, S
3	Cl	H	Cl	Cl	O	138-140	28	$C_{15}H_8Cl_6O_3$	Benzene, benzene-ether, 95:5[a]	C, H, Cl
4	H	H	Cl	H	O	98-99	73	$C_{15}H_{12}Cl_2O_3$	Ligroine	C, H, Cl
5	H	Cl	H	H	O	Oil	26	$C_{15}H_{12}Cl_2O_3$	CCl_4, CCl_4-ether, 95:5, 9:1[a]	C, H, Cl
6	Cl	H	H	H	O	110-112	25	$C_{15}H_{12}Cl_2O_3$	Benzene, benzene-ether, 9:1[a]	C, H, Cl
7	H	H	CH_3	H	O	63-64	69	$C_{17}H_{18}O_3$	Benzene, benzene-ether, 9:1, 8:2[a]	C, H
8	CH_3	H	H	H	O	93-94	37	$C_{17}H_{18}O_3$	2-Propanol	C, H
9	H	CH_3	H	H	O	Oil	38	$C_{17}H_{18}O_3$	CCl_4, CCl_4-ether, 95:5, 9:1, 8:2[a]	C, H
10	H	H	C_2H_5	H	O	67-69	60	$C_{19}H_{22}O_3$	Benzene, benzene-ether, 9:1[a]	C, H
11	H	H	OCH_3	H	O	59-60	66	$C_{17}H_{18}O_5$	Benzene, benzene-ether, 8:2, 7.3[a]	C, H
12	OCH_3	H	H	H	O	61-63	49	$C_{17}H_{18}O_5$	2-Propanol	C, H
13	H	H	OC_2H_5	H	O	85-87	63	$C_{19}H_{22}O_5$	2-Propanol	C, H
14	H	H	n-C_3H_7	H	O	43-45	51	$C_{21}H_{26}O_3$	2-Propanol	C, H
15	H	H	t-C_4H_9	H	O	89-91	56	$C_{23}H_{30}O_3$	Benzene, benzene-ether, 9:1, 8:2	C, H
16	H	H	Cl	H	S	79-81	19	$C_{15}H_{12}Cl_2OS_2$	Benzene, benzene-ether, 9:1[a]	C, H, Cl, S
17	Cl	H	CH_3	CH_3	O	138-139	59	$C_{19}H_{20}Cl_2O_3$	MeOH-benzene, 5:1	C, H, Cl
18	H	CH_3	Cl	CH_3	O	148-149	27	$C_{19}H_{20}Cl_2O_3$	Benzene-hexane, 1:1	C, H, Cl
19	H	H	F	H	O	73-75	31	$C_{15}H_{12}F_2O_3$	2-Propanol	C, H, F
20	H	H	Br	H	O	105-107	13	$C_{15}H_{12}Br_2O_3$	2-Propanol-hexane, 4:1	C, H, Br
21	H	H	I	H	O	145-146	75	$C_{15}H_{12}I_2O_3$	$CHCl_3$, $CHCl_3$-ether, 9:1[a]	C, H, I

[a] Eluting solvent system used for column chromatography.

Repeated chromatography on a column of 70–230 mesh silica gel 60 was also used (Table I).

1-(*p*-Chlorophenoxy)-3-(*p*-methylphenoxy)-2-propanol (22'). The synthetic route is illustrated in Scheme I. *p*-Cresol (9.7 g, 0.081 mol) was dissolved in 40 ml of 1,4-dioxane at 90–100°. To this solution was added 3.2 g (0.081 mol) of powdered NaOH and the reaction was stirred at 98–100° until all NaOH had reacted. *p*-Chlorophenyl 2,3-epoxypropyl ether (15.0 g, 0.081 mol) was added neat over a 10-min period and the reaction was then stirred at 98–100° for another 4 hr. The dioxane was removed in vacuo and the brown solid residue was dissolved in sufficient ether and extracted with water. The ether solution was dried over anhydrous Na_2SO_4 and filtered, and the ether was removed to leave a crude, brown solid which was recrystallized from 2-propanol to give 11.8 g (50%) of the pure hydroxy compound as a light yellow solid: mp 85–87°.

1-(*p*-Chlorophenoxy)-3-(*p*-methoxyphenoxy)-2-propanol (23'). Compound 23' was prepared in an analogous manner as the *p*-methyl derivative above and was obtained as an oil. All attempts at crystallization failed; consequently the crude hydroxy compound was oxidized in this state of purity: yield, 94% crude.

1,3-Bis(*p*-chlorobenzyloxy)-2-propanol (24'). *p*-Chlorobenzyl alcohol (15.0 g, 0.105 mol) was dissolved in 100 ml of dry *p*-xylene and added dropwise over a 30-min period to a suspension of 4.1 g (0.105 mol) of granulated potassium metal in dry *p*-xylene at 90–96° with stirring. After all of the potassium had reacted, 4.8 g (0.052 mol) of epichlorohydrin was added neat over a 10-min period. The reaction was then stirred at 120° overnight. The xylene was removed in vacuo and the dark residual oil was dissolved in 400 ml of diethyl ether and extracted with water. The ether solution was dried over anhydrous Na_2SO_4 and filtered, and the ether was removed to give a dark oil which was chromatographed on silica gel ($CHCl_3$, $CHCl_3$–ether, 8:2) to give 9.9 g (56%) of the 2-propanol derivative as a yellow oil.

General Oxidation Procedure (1–21). The appropriate 2-propanol derivative was dissolved in dry diethyl ether (400 ml of ether/25.0 g of hydroxy compound) along with 15–20 ml of Me_2SO, 3.0 equiv of dicyclohexylcarbodiimide, and 2–4 ml of dry pyridine. If the hydroxy compound was insoluble, dry ethanol-free chloroform was added to achieve solution. To this solution was added 2.0 ml of trifluoroacetic acid to initiate the reaction. Cooling in an ice bath was sometimes necessary during addition of acid. The reaction was then stirred for 3–5 hr, being monitored by TLC. When reaction was complete, 15–20 g of oxalic acid in MeOH was added in small portions and the reaction stirred for another 20 min. The precipitated dicyclohexylurea was then suction filtered and washed with either diethyl ether or chloroform. The filtrate was extracted with 5% $NaHCO_3$ and then with water, dried over anhydrous Na_2SO_4, and filtered, and the solvents were removed. The crude residual ketone was purified by either recrystallization or column chromatography on silica gel (Table II).

1-(*p*-Chlorophenoxy)-3-(*p*-methylphenoxy)-2-propanone (22) was recrystallized from 2-propanol to give 9.1 g (76%) of colorless needles: mp 96–98°. Anal. ($C_{16}H_{15}ClO_3$) C, H, Cl.

1-(*p*-Chlorophenoxy)-3-(*p*-methoxyphenoxy)-2-propanone (23) was chromatographed on silica gel (chloroform) and then crystallized from 2-propanol to give 10.6 g (43%) of light yellow needles: mp 81–82°. Anal. ($C_{16}H_{15}ClO_4$) C, H, Cl.

1,3-Bis(*p*-chlorobenzyloxy)-2-propanone (24) was chromatographed on silica gel (CCl_4, CCl_4–ether, 95:5, 9:1) to give 1.8 g (18%) of a light yellow oil. Anal. ($C_{17}H_{16}Cl_2O_3$) C, H, Cl.

1,1-Dibenzyl-1-hydroxy-2-propanone[5] (25). Magnesium turnings (15.6 g, 0.64 mol) were covered with sufficient dry diethyl ether and a few iodine crystals were added to catalyze the formation of benzylmagnesium chloride. Benzyl chloride (88.6 g, 0.7 mol) was added to the magnesium turnings neat dropwise over a 2-hr period. The thick, gray suspension that formed was diluted with another 150 ml of ether and stirred an additional 1.5 hr under reflux. The Grignard suspension was cooled to room temperature, and 38.5 g (0.2 mol) of ethyl pyruvate diethyl ketal in 50 ml of ether was added dropwise over a 30-min period. The thick suspension turned white and another 100 ml of ether was added and the reaction was stirred for 2.0 hr under reflux. At this time, 400 ml of 25% H_2SO_4 was added slowly while cooling the reaction in an ice bath. The resulting two-phase solution was stirred for another 1.5 hr at room temperature. The aqueous layer was drawn off in a separatory funnel. The organic phase was extracted with 5% $NaHCO_3$, dried over anhydrous Na_2SO_4, and filtered and the ether was removed to give 63.4 g of yellow oil which solidified upon standing. Recrystallization from 2-propanol–hexane (4:1) gave 43.7 g (86%) of the hydroxy ketone: mp 80–82°. Anal. ($C_{17}H_{18}O_2$) C, H.

1,1-Dibenzyl-1-hydroxy-3-bromo-2-propanone. Glacial acetic acid (6–7 drops) was added to a solution of 32.5 g (0.127 mol) of **25** in 300 ml of chloroform. Ten drops of a solution of 20.3 g (0.127 mol) of bromine in 120 ml of chloroform was added and stirred with warming until the yellow color disappeared. The remainder of the bromine solution was then added at such a rate as to maintain a deep yellow color in the reaction solution (1.5 hr). The reaction was then stirred another 15 min, the chloroform solution extracted with 5% NaOH and water, dried over anhydrous Na_2SO_4, and filtered, and the chloroform removed to leave 33.5 g of crude yellow solid. Chromatography of this solid on silica gel (benzene, benzene–chloroform, 95:5) gave 13.9 g (33%) of the brominated product as a white solid: mp 103–105°.

1,1-Dibenzyl-1-hydroxy-3-(*p*-methylphenoxy)-2-propanone (26). *p*-Cresol (15.0 g, 0.138 mol) and powdered NaOH (5.2 g, 0.130 mol) were stirred in 40 ml of 1,4-dioxane at 98–100° until solution was obtained. To this solution was added 21.3 g (0.064 mol) of 1,1-dibenzyl-1-hydroxy-3-bromo-2-propanone in 35 ml of 1,4-dioxane, dropwise over a 15-min period. The reaction was stirred 2.5 hr at 98–100°. The dioxane was removed in vacuo and the residue taken up in 350 ml of chloroform and extracted with water. The chloroform phase was dried over anhydrous Na_2SO_4 and filtered and the chloroform removed to leave a crude, viscous oil. Chromatography of this oil on silica gel (benzene, benzene–chloroform, 95:5, 9:1) gave 7.2 g (31%) of product as a white solid: mp 81–83°. Anal. ($C_{24}H_{24}O_3$) C, H.

1,5-Bis(*p*-methylphenyl)-1,4-pentadien-3-one (27). The procedure of Conard and Dolliver was followed.[6] In a 1.0-l. Erlenmeyer flask equipped with mechanical stirrer, a solution of 50.0 g of NaOH in 500 ml of water and 420 ml of 95% EtOH was cooled to 20–22° in a water bath. To this solution was added half of a mixture of 60.1 g (0.5 mol) of *p*-tolualdehyde and 14.5 g (0.25 mol) of acetone, maintaining the temperature at 20–22°. After stirring for 2 min, a heavy yellow precipitate formed. After 15 min the remainder of the above mixture was added and the reaction was stirred for another 30 min. The yellow solid was filtered and washed on the filter with 1.0 l. of distilled water. The product was dried to a constant weight of 59.8 g in an 80° oven. Recrystallization from 600 ml of 2-propanol–chloroform (2:1) at 25° gave 37.1 g (57%) of pure product as light yellow needles: mp 174–176°. Anal. ($C_{19}H_{18}O$) C, H.

1,5-Bis(*p*-methylphenyl)-3-pentanone (28). Due to limited solubility, 3.0 g (0.011 mol) of compound **27** was dissolved in 150 ml of absolute EtOH and 50 ml of chloroform and hydrogenated with 300 mg of 5% palladium on charcoal until the theoretical amount of hydrogen had been consumed. The reaction was filtered and the solvents were removed. The procedure was repeated until 19.0 g (0.072 mol) of **27** had been reduced to give 20.1 g of crude solid. Chromatography on silica gel (chloroform) and subsequent recrystallization from 70 ml of 2-propanol–hexane (6:1) gave 6.3 g (33%) of pure product as colorless crystals: mp 52–54°. Anal. ($C_{19}H_{22}O$) C, H.

1,3-Bis(*p*-chlorobenzenesulfonyl)-2-propanone (29). Glacial acetic acid (400 ml) was used to dissolve 29.8 g (0.087 mol) of **16** with warming. To this solution was added dropwise 100 ml of 30% H_2O_2 and the reaction was allowed to stand at room temperature overnight. The acetic acid was removed on the evaporator to leave a white solid residue. Two recrystallizations from 2-propanol–chloroform (2:1) gave 5.3 g (15%) of pure product as colorless crystals: mp 163–165°. Anal. ($C_{15}H_{12}Cl_2O_5S_2$) C, H, Cl, S.

1,3-Bis(*O*-hexadecyl)-2-propanol (30'). Potassium (4.8 g, 0.123 mol) was stirred until granulated in dry *p*-xylene at 120°. To this suspension was added a solution of 30 g (0.123 mol) of 1-hexadecanol in dry *p*-xylene dropwise over a 15-min period. When all potassium had reacted, 5.3 g (0.056 mol) of epichlorohydrin was added dropwise over a 20-min period and the reaction was then stirred for 48 hr. The *p*-xylene was removed on the evaporator, the residue taken up in 200 ml of chloroform and suction filtered, and the chloroform removed to leave 32.2 g of crude product as a brown gum. Chromatography on silica gel (benzene, benzene–ether, 9:1, 8:2) gave 19.7 g (65%) of pure product as light yellow crystals: mp 57–59°.

1,3-Bis(*O*-hexadecyl)-2-propanone (30). The general oxidation procedure above was employed. Chromatography on silica gel (chloroform) and subsequent recrystallization from 2-propanol–petroleum ether (bp 30–60°, 1:1) gave 0.6 g (20%) of pure product as colorless crystals: mp 61–63°. Anal. ($C_{35}H_{70}O_3$) C, H.

1-(*p*-Propionylphenoxy)-3-chloro-2-propanol (31'). Reaction of 21.0 g (0.14 mol) of *p*-hydroxypropiophenone with 6.5 g (0.09 mol) of epichlorohydrin in the presence of 5.0 g (0.125 mol) of NaOH according to the general procedure for preparation of propanols above gave 6.8 g (40%) of pure product as a light yellow oil after chromatography on silica gel (chloroform, chloroform–ether, 9:1, 8:2, 7:3).

1-(*p*-Propionylphenoxy)-3-chloro-2-propanone (31). The

Table III. Percent of Control of Serum Cholesterol after Administration of 10 mg/kg/day of Test Compound Orally to Sprague-Dawley Rats[a]

Compd	$\bar{x}$ ± SD on day 4	$\bar{x}$ ± SD on day 10	$\bar{x}$ ± SD on day 16
Control (1% CMC)	100 ± 13	100 ± 11	100 ± 10
Clofibrate	111 ± 16	98 ± 21	106 ± 9
1	104 ± 16	87 ± 13	90 ± 17
2	96 ± 8	101 ± 11	79 ± 17[c]
3	94 ± 12	82 ± 6[b]	97 ± 10
4	81 ± 14	64 ± 6[a]	62 ± 14[a]
5	97 ± 11	91 ± 14	84 ± 7[b]
6	69 ± 11[a]	69 ± 10[a]	70 ± 6[a]
7	77 ± 22[c]	51 ± 13[a]	59 ± 15[a]
8	90 ± 13	92 ± 13	90 ± 17
9	115 ± 12	119 ± 20	97 ± 13
10	70 ± 7[a]	60 ± 15[a]	64 ± 6[a]
11	76 ± 18[b]	51 ± 11[b]	60 ± 7[a]
12	102 ± 13	83 ± 7	79 ± 6[a]
13	77 ± 11[a]	96 ± 17	85 ± 10
14	94 ± 10	88 ± 8	78 ± 7[b]
15	87 ± 15	95 ± 14	83 ± 9[b]
16	70 ± 11[a]	73 ± 6[a]	66 ± 8[a]
17	79 ± 10[b]	65 ± 8[a]	58 ± 11[a]
18	78 ± 22[c]	70 ± 8[a]	61 ± 9[a]
19	88 ± 9	87 ± 11	82 ± 15[b]
20	74 ± 7[a]	85 ± 21	85 ± 8
21	100 ± 9	103 ± 13	93 ± 12
22	108 ± 16	84 ± 12	75 ± 16[b]
23	102 ± 8	88 ± 13	84 ± 18
24	106 ± 5	88 ± 6	92 ± 15
25	88 ± 13	77 ± 13[a]	84 ± 12
26	80 ± 7[a]	72 ± 9[a]	70 ± 14[a]
27	94 ± 4	83 ± 6	96 ± 5
28	91 ± 7	86 ± 11	96 ± 7
29	82 ± 10	86 ± 11	91 ± 8
30	88 ± 12	89 ± 6	91 ± 7
31	79 ± 11[c]	89 ± 7	90 ± 8
32	106 ± 5	88 ± 6	92 ± 15

[a] $p = 0.001$. [b] $p = 0.010$. [c] $p = 0.025$. [d] $N = 8$.

Table IV. Uterotropic Activity in Sprague-Dawley Female Rats[b]

Compd	% control uterine wt, $\bar{x}$ ± SD
Control (1% CMC)	100 ± 27
17β-Ethinylestradiol	231 ± 51[a]
4	48 ± 12[a]
7	82 ± 25
10	62 ± 15
11	70 ± 16
16	86 ± 21
17	56 ± 12[a]
18	83 ± 34

[a] $p = 0.001$. [b] $N = 8$.

Table V. LD_{50} in Male CF_1 Mice[a]

Compd	g/kg	Compd	g/kg
4	>2[b]	**16**	>3[b]
7	1.5	**17**	>2[b]
10	>3[b]	**18**	>6[b]
11	**6**		

[a] $N = 6$. [b] Insoluble in 1% CMC at higher doses.

Table VI. Percent of Total Rat[a] Body Weight (g) 24 hr after 16 Doses of Test Compound

	$\bar{x}$ ± SD					
Compd	Liver	Kidney	Heart	Epididymis and vas deferens	Testes	Vesicular glands
Control (1% CMC)	4.54 ± 0.29	0.96 ± 0.08	0.43 ± 0.10	0.24 ± 0.07	1.10 ± 0.17	0.11 ± 0.04
4	4.51 ± 0.19	0.86 ± 0.08	0.39 ± 0.06	0.26 ± 0.09	1.23 ± 0.12	0.14 ± 0.05
6	4.66 ± 0.33	1.02 ± 0.05		0.27 ± 0.05	1.21 ± 0.19	0.23 ± 0.06
7	4.74 ± 0.32	0.95 ± 0.05	0.38 ± 0.05	0.34 ± 0.07	1.20 ± 0.16	0.11 ± 0.03
10	4.28 ± 0.27	0.87 ± 0.09		0.27 ± 0.06	1.14 ± 0.15	0.15 ± 0.07
11	4.73 ± 0.65	1.04 ± 0.27	0.54 ± 0.07	0.22 ± 0.06	1.22 ± 0.13	0.11 ± 0.02
16	4.53 ± 0.44	0.94 ± 0.22		0.25 ± 0.05	1.13 ± 0.10	0.12 ± 0.05
17	4.80 ± 0.64	1.06 ± 0.18	0.52 ± 0.16	0.27 ± 0.08	1.24 ± 0.09	0.16 ± 0.02
18	4.66 ± 0.54	1.02 ± 0.09		0.27 ± 0.11	0.91 ± 0.21	0.10 ± 0.13

[a] $N = 8$.

general oxidation procedure above was used. Recrystallization from 2-propanol at 4° gave 3.3 g (49%) of pure product as colorless crystals: mp 103–104°. Anal. ($C_{12}H_{13}ClO_3$) C, H, Cl.

Biological Studies, Procedures, Animals, and Diet. Male Sprague–Dawley rats (Zivic Miller, Allison Park, Pa.) were fed Purina rodent lab chow with water ad libitum for the duration of the experiment. Each test compound was suspended in 1% CMC (carboxymethylcellulose)–H_2O and homogenized. Doses (10 mg/kg/day) were calculated on weekly weights of the rats. All drugs were administered to the animal by oral intubation needle (0.2 cc) at 11:00 a.m. After dosing (22–24 hr) blood was collected by tail-vein bleeding. The blood was collected in nonheparinized microcapillary tubes which were centrifuged for 3 min in an International microcapillary tube centrifuge to obtain the serum. Duplicate 30-μl samples of nonhemolyzed serum were used to determine the mg % serum cholesterol levels by a modification of the Liebermann–Burchard reaction.[7]

Periodic animal weights were obtained and expressed as a percentage of the animal's weight on day 0 of the experiment. After dosing the animals for 16 days, the animals were sacrificed by cervical dislocation, and a number of organs were excised and weighed. The organs were expressed as a percentage of the body weight of that animal on the day of sacrifice. Tissues were examined for gross malformations, atrophy, pathological changes, infection, etc.[8]

Uterotropic activity was determined in weaned 40-g rats that were ovariectomized by the method of Emmens.[9] Three days afterwards, treatment was commenced with drugs and continued for 3 days. 17-Ethinylestradiol was used as an internal control. The uterus was removed, trimmed, and weighed. Antifertility was determined in CF_1 female mice on compound 4 at 50 mg/kg/day ip.[10] The number of pregnancies, viable fetuses per litter, dead in uterine per litter, and reabsorption per litter were recorded.[10] In our animal quarters, the average gestation time for rodents was 19.4 days with some seasonal variation. The average number of fetuses and reabsorption sites including uterine death for CF_1 mice was 12 ± 3 and 0.48 ± 0.12 per litter, respectively. These values were used to calculate percent of control values for test compounds. An attempt was made to determine the LD_{50} of active hypocholesterolemic propanone derivatives in CF_1 male mice. These drugs were administered ip from 10 mg to 6 g/kg provided the agent was soluble. The number of deaths was recorded.[11]

A dose–response curve for hypocholesterolemic activity of 1,3-bis(*p*-methylphenoxy)-2-propanone (7) was determined in male rats at 1, 5, 10, and 50 mg/kg/day. The average food intake in grams per rat per week was determined over a 2-week period. Calbiochem stat packs were used to measure rat serum triglycerides and glycerol levels[12] after 8 and 14 days of dosing, respectively. Rat serum and liver lipase were determined[12] using the Sigma No. 800 serum lipase kit after 16 days of dosing. The rat liver RNA, DNA, glycogen, protein, and lipid were determined after 16 days of dosing by the method of Shibko et al.[13]

[^{14}C]Palmitic acid and [^{14}C]cholesterol distribution studies[8] were carried out after dosing male rats for 1 week with 1,3-bis(*p*-methylphenoxy)-2-propanone (7) (10 mg/kg/day) or 1% CMC. On day 7, 5 μCi of cholesterol (4-^{14}C) or palmitic acid (1-^{14}C) was administered orally. After 22 hr, the animals were sacrificed, the organs were removed, and a 10% homogenate in water was prepared. An aliquot of 0.1 cc of each homogenate, urine, blood, or feces was digested with Protosol and was placed in scintillation fluid containing two parts of toluene and one part of Triton X-100 with 0.4% PPO and 0.01% POPOP. Liver lipids were extracted by methods previously reported.[8]

In Tables III–XVII the number of animals in the group, ex-

Table VII. Antifertility Activity in CF_1 Female Mice at 50 mg/kg/day of Test Compound

	N	% pregnant	% of no. of fetus/litter[a]	% of no. reabsorption, litter[a]
Control (1% CMC)	62	100	100 ± 25	100 ± 25
1,5-Diphenyl-2,4-dimethyl-3-pentanone	8	0	0	0
1,3-Bis(*p*-chlorophenoxy)-2-propanone		100	84 ± 17	30 ± 29
1,9-Diethylstilbestrol (10 μg)	8	0	0	0

[a] Average number of fetuses for CF_1 mice = 12 ± 3 per litter and average number reabsorption = 0.48 ± 0.12 per litter. These values are considered to be 100%. A change greater than 25% is considered to be significant at the level of $p = 0.05$.[10]

Table VIII. Rat[a] Body Weight in Grams after Treatment with Compound 7

	$\bar{x}$ ± SD on day		
Compd	0	7	16
Control (1% CMC)	119 ± 7	173 ± 12	233 ± 16
Compd 7			
1 mg/kg	117 ± 5	166 ± 8	234 ± 12
5 mg/kg	115 ± 8	168 ± 12	241 ± 18
10 mg/kg	116 ± 9	164 ± 13	234 ± 24
50 mg/kg	114 ± 9	171 ± 15	232 ± 33

[a] $N = 8$.

Table IX. Percent of Control of Rat[a] Serum Cholesterol after Treatment with Compound 7

	$\bar{x}$ ± SD on day		
Compd	4	10	16
Control (1% CMC)	100 ± 7	100 ± 7	100 ± 8
Compd 7			
1 mg/kg	75 ± 14[b]	71 ± 11[b]	46 ± 20[b]
5 mg/kg	74 ± 13[b]	58 ± 12[b]	56 ± 10[b]
10 mg/kg	78 ± 10[b]	50 ± 11[b]	58 ± 9[b]
50 mg/kg	86 ± 10[c]	46 ± 12[b]	44 ± 11[b]
mg % for control	78 ± 8	74 ± 6	78 ± 8

[a] $N = 8$. [b] $p = 0.001$. [c] $p = 0.025$.

Table X. Percent of Control of Rat[b] Serum Triglycerides after 8 Days of Dosing with Compounds 4 and 7

Compd	$\bar{x}$ ± SD
Control (1% CMC)	100 ± 15
7, 10 mg/kg	70 ± 3[a]
4, 10 mg/kg	108 ± 4

[a] $p = 0.001$. [b] $N = 8$.

Table XI. Percent of Control of Rat[b] Serum Glycerol after 14 Days of Dosing with Compound 7

Compd	$\bar{x}$ ± SD
Control (1% CMC)	100 ± 39
7, 10 mg/kg	24 ± 15[a]

[a] $p = 0.001$. [b] $N = 8$.

Table XII. Percent of Control of Rat[b] Serum and Liver Lipase after 16 Days of Dosing with Compound 7

	$\bar{x}$ ± SD	
Compd	Serum	Liver
Control (1% CMC)	100 ± 39	100 ± 39
7, 10 mg/kg	222 ± 36[a]	68 ± 20

[a] $p = 0.001$. [b] $N = 8$.

Table XIII. Average Weekly Food Intake in Grams per Rat[b] after Dosing with Compound 7

	$\bar{x}$ ± SD	
Compd	1st week	2nd week
Control (1% CMC)	19.1 ± 1.7	23.4 ± 1.8
Compd 7	19.2 ± 2.6	29.2 ± 4.7[a]
1 mg/kg	19.2 ± 2.6	29.2 ± 4.7[a]
5 mg/kg	18.8 ± 2.8	28.8 ± 4.7[a]
10 mg/kg	18.2 ± 3.6	28.6 ± 3.6[a]
50 mg/kg	18.9 ± 3.4	28.2 ± 3.8[a]

[a] $p = 0.025$. [b] $N = 8$.

pressed as N, and the mean of the percent of control and standard deviation, expressed as $\bar{x}$ ± SD, are noted. The probable significant level (p) between each test group and control group was determined by the Student's t test according to Snedecor.[14]

Results

The effects of these propanone derivatives on serum cholesterol of Sprague–Dawley rats are presented in Table III. Compounds **4**, **6**, **7**, **10**, **11**, **16–18**, and **26** lowered the mg % serum cholesterol significantly. These hypocholesterolemic compounds demonstrated no uterotropic activity in female rats as noted in Table IV nor were they toxic (Table V) at therapeutic doses. There was no change in body weights of these animals throughout the experiment at 10 mg/kg/day nor was there any change in the organ weights expressed as percentage of body weight (Table VI). Compound **4** caused no change in the percent pregnant and reduced the average number of fetuses per litter by 16% which was not significant (Table VII).

Extensive studies in rats with compound **7** demonstrated no body weight change using doses of 1, 5, 10, and 50 mg/kg/day for 16 days (Table VIII). Furthermore, the hypocholesterolemic activity did not follow a strict dose–response curve. All four dose levels lowered the serum cholesterol to below 60% of control after 16 days of dosing (Table IX). After 8 days of dosing the rat serum triglycerides level was depressed by 30% (Table X) and after 14 days the serum glycerol level was depressed by 76% (Table XI). Serum lipase was elevated twofold after 16 days whereas liver lipase was decreased 32% (Table XII). The average weekly food intake (Table XIII) demonstrated no change the first week. During the second week there was an increase of 5–6 g/day which was not reflected in the total body weight.

The entire propanone caused no lipid infiltration of the major organs resulting in an increase in organ weight (Tables VI and XIV). Compound **7** at 10 mg/kg/day resulted in only marginal changes in liver content of RNA, DNA, protein, glycogen, and lipids (Table XV). Furthermore, there was no atrophy of the vas deferens, epididymis, vesicular glands, and testes as would be expected with hypocholesterolemic agents which also possessed

Table XIV. Percent of Total Rat Body Weight (g) 24 hr after 16 Doses of Compound 7

		$\bar{x}$ ± SD								
	N	Liver	Heart	Kidney	Spleen	Brain	Vas deferens and epididymis	Testes	Vesicular gland	Adrenal glands
Control (1% CMC)	8	4.22 ± 0.29	0.37 ± 0.04	0.92 ± 0.04	0.55 ± 0.12	0.67 ± 0.05	0.22 ± 0.04	1.08 ± 0.08	0.10 ± 0.04	0.015 ± 0.003
Compd 7										
1 mg/kg	6	4.00 ± 0.26	0.38 ± 0.04	0.79 ± 0.06[a]	0.43 ± 0.08	0.74 ± 0.12	0.23 ± 0.05	1.12 ± 0.10	0.19 ± 0.05[b]	
5 mg/kg	6	4.31 ± 0.36	0.43 ± 0.10	0.88 ± 0.03	0.44 ± 0.11	0.73 ± 0.05	0.21 ± 0.05	1.03 ± 0.10	0.13 ± 0.04	
10 mg/kg	8	4.65 ± 0.25[c]	0.41 ± 0.05	0.93 ± 0.08	0.60 ± 0.16	0.71 ± 0.08	0.24 ± 0.03	1.13 ± 0.12	0.12 ± 0.04	0.016 ± 0.003
50 mg/kg	6	4.57 ± 0.28	0.40 ± 0.07	0.88 ± 0.06	0.40 ± 0.11	0.83 ± 0.10[b]	0.25 ± 0.02	1.19 ± 0.12	0.15 ± 0.04	

[a] $p = 0.001$. [b] $p = 0.010$. [c] $p = 0.025$.

Table XV. Percent Control Value of Rat[b] RNA, DNA, Protein, Glycogen, and Lipid Content after 16 Doses with Compound 7

	$\bar{x}$ ± SD				
	RNA	DNA	Protein	Glycogen	Lipid
Control (1% CMC)	100 ± 8	100 ± 25	100 ± 6	100 ± 24	100 ± 16
7, 10 mg/kg	104 ± 6	81 ± 25	102 ± 5	118 ± 23	88 ± 10
4, 10 mg/kg	99 ± 11	78 ± 1[a]	91 ± 4	105 ± 48	101 ± 25

[a] $p = 0.025$. [b] $N = 8$.

Table XVI. [^{14}C]Palmitic Acid Distribution in Rats[a] after 1 Week of Treatment with Compound 7 at 10 mg/kg/day

	% radioactive uptake after 22 hr, $\bar{x}$ ± SD	
Tissue	Control	Treated
Liver	8.06 ± 1.33	9.26 ± 2.53
Kidney	0.68 ± 0.16	0.94 ± 0.63
Heart	0.23 ± 0.10	0.26 ± 0.05
Lung	0.53 ± 0.15	0.50 ± 0.12
Brain	0.07 ± 0.04	0.08 ± 0.03
Spleen	0.46 ± 0.24	0.37 ± 0.11
Testes	0.22 ± 0.10	0.25 ± 0.12
Vas deferens	0.23 ± 0.05	0.50 ± 0.37
Stomach	0.65 ± 0.46	0.48 ± 0.15
Small intestine	4.43 ± 1.43	6.05 ± 1.63
Chyme	0.41 ± 0.17	2.00 ± 1.21[c]
Large intestine	3.46 ± 1.25	9.91 ± 4.62[b]
Feces	75.52 ± 6.21	63.52 ± 10.43[d]
Urine	3.31 ± 1.37	1.82 ± 1.07
Blood	0.11 ± 0.06	0.03 ± 0.02[c]
% recovery	98.00	96.75

[a] $N = 6$. [b] $p = 0.010$. [c] $p = 0.025$. [d] $p = 0.050$.

Table XVII. [^{14}C]Cholesterol Distribution in Rats[a] after 1 Week of Treatment with Compound 7 at 10 mg/kg/day

	% radioactive uptake after 22 hr, $\bar{x}$ ± SD	
Tissue	Control	Treated
Liver	19.80 ± 2.93	22.19 ± 0.62
Kidney	0.69 ± 0.27	1.29 ± 0.29[b]
Heart	0.39 ± 0.13	0.58 ± 0.41
Lung	1.99 ± 1.18	2.45 ± 0.37
Brain	0.12 ± 0.04	0.16 ± 0.06
Spleen	1.41 ± 1.01	1.86 ± 0.45
Testes	0.24 ± 0.17	0.33 ± 0.11
Vas deferens	0.03 ± 0.02	0.07 ± 0.02[c]
Stomach	8.87 ± 4.00	3.36 ± 1.35[c]
Small intestine	22.09 ± 5.68	22.56 ± 3.92
Chyme	8.72 ± 4.95	9.21 ± 3.52
Large intestine	19.12 ± 5.62	12.84 ± 1.53[d]
Feces	15.50 ± 5.24	22.10 ± 6.43
Urine	0.14 ± 0.06	0.94 ± 0.63[c]
Blood	0.01 ± 0.01	0.01 ± 0.01
% recovery	99.11	99.94

[a] $N = 5$. [b] $p = 0.010$. [c] $p = 0.025$. [d] $p = 0.050$.

estrogenic characteristics and there was no hypertrophy of the adrenal gland as seen with many hypocholesterolemic agents.[6]

Treatment with compound 7 for 16 days resulted in little effect on [^{14}C]palmitic acid distribution in the various organs of the rat. However, a larger amount of ^{14}C was found after treatment in the small intestine, chyme, and large intestine with less ^{14}C in the feces, urine, and blood (Table XVI). The [^{14}C]cholesterol distribution resulted in only slight increases in ^{14}C after treatment with compound 7 in the kidney, urine, and feces, while there was a reduction in ^{14}C in the stomach and large intestine (Table XVII). Lipids extracted from the livers of animals treated with [^{14}C]palmitic acid showed that the ^{14}C fatty acid taken up in the cholesterol ester fraction was reduced 46%, that taken up in the triglyceride fraction was reduced 53%, and that taken up in the phospholipid fraction was reduced 16% by compound 7. Furthermore, there was a 10% increase in free fatty acid accumulation in the liver.

Discussion

The structure–activity relationship for hypocholesterolemic activity of the 2-propanone series demonstrated that the 2-propanol series was not active. The aromatic ring in position 1 and 3 appeared necessary for hypocholesterolemic activity since substitution with an aliphatic chain [1,3-bis(*o*-hexadecyl)-2-propanone (**30**)] resulted in loss of activity. The distance between the propanone and the phenyl ring must not exceed an ether (**1**) or thioether moiety (**2**) since the benzyloxy derivative 1,3-bis(*p*-chlorobenzyloxy)-2-propanone (**24**) was inactive. The propanone–phenyl bridge must include a heteroatom such as O (**1**) or S (**2**) since the methylene isostere is sterically similar but less active [1,5-bis(*p*-methylphenyl)-3-pentanone (**28**)].

The para substitutions of the phenyl ring with chloro (**4**) or methyl (**7**) groups resulted in the maximum hypocholesterolemic activity. Ortho (**6** and **8**) and meta (**4** and **9**) substitutions resulted in less activity. Para substitution of ethyl (**10**) and methoxy (**11**) maintained approximately the same activity as the chloro and methyl groups. Substitution of the phenyl ring with a mixture of methyl and chloro groups maintained the activity but did not improve it (**17** and **18**). Other halide substitutions (**19–21**) resulted in loss of activity. Substituents smaller than the Cl, i.e., H (**1**) or F (**19**), in the para position were inactive. Since H is less and F is more electronegative than Cl, the electronic influence appears to have no effect on activity. Nevertheless, the hypocholesterolemic activity was inversely related to the halogen size in the para position for Cl, Br, and I. In the alkyl series, hypocholesterolemic activity is inversely related to size in that *p*-CH_3 > C_2H_5 > C_3H_7 > *tert*-butyl and *p*-OCH_3 > *p*-OC_2H_5. Substitution of sulfur (**2**) for oxygen in the ether linkage resulted in improvement of activity; furthermore, when the compound was further substituted with a chloro group in the para position of the phenyl ring (**16**) significant improvement of the activity was observed. With 1-hydroxy, 1,1-dibenzyl-3-propanone (**25**) substitution of a *p*-methylphenoxy group on carbon 3 (**26**) improved activity.

Studies with compound 7 demonstrated that not only was the serum cholesterol levels lowered but also the serum triglycerides and glycerol. A dose–response curve for hypocholesterolemic activity was not obtained with compound 7. Serum triglycerides may be lowered due to increased levels of serum lipase and reduced triglycerides released from the liver to the blood due to decrease liver lipase activity. The loss of serum triglycerides and cholesterol resulted in no drastic change in body weight. The reduction of serum lipids could not be attributed to a reduction in food intake due to suppression of appetite by the drug. However, cholesterol or its metabolites may be excreted faster in the feces and urine after treatment with 7. There was a slight increase in the liver weight at 10 mg/kg/day. This did not appear to be due to lipid de-

position, since liver lipids and DNA were reduced 12 and 18%, respectively, whereas liver glycogen was elevated 18%. Incorporation of fatty acids into complex lipids appears to be blocked by 7. A similar phenomenon was observed with the bis(β-phenethyl) ketone derivatives.[8]

The fact that the vas deferens, epididymis, vesicular glands, and testes had not undergone atrophy after administration of compound 7 along with a negative uterotropic activity indicated that this compound was not estrogenic at this dose. Furthermore at 50 mg/kg compound 4 possesses no antifertility activity in mice. These characteristics differ from the bis(β-phenethyl) ketone derivatives. Furthermore, the propanone series was not toxic. Small doses (10 mg/kg/day) are adequate to reduce the serum cholesterol in rats significantly compared to clofibrate. The maximum pharmacological effects of these agents require a longer length of time to appear, i.e., 10–14 days compared to the bis(β-phenylethyl ketone) series which requires only 48 hr.[8]

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Novel Pyrazolo, Isoxazolo, and Thiazolo Steroidal Systems and Model Analogs Containing Dimethoxylaryl (or Dihydroxylaryl) Groups and Derivatives. Synthesis, Spectral Properties, and Biological Activity

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The total syntheses of a series of vicinal-substituted dimethoxy and dihydroxy heterosteroids of the equilenin type and model analogs are described. A novel class of pyrazolo steroidal *N*-glucosides has also been synthesized. Compounds prepared were screened in vitro for growth inhibition of different microorganisms. Of these, 1-α-D-glucopyranosyl-4,5-dihydro-7-methoxy-1*H*-benz[*g*]indazole tetraacetate (**13**) was quite active. For example, *N*-glucoside **13** inhibited the growth of *Bacillus subtilis*, *Pseudomonas fluorescens*, *Staphylococcus aureus*, and KB cells at moderate concentrations.

The biological activity of heterosteroids[1] with methoxyarene functions as ring A has been evaluated[2] in only a relatively small number of cases.[3] Preliminary results from our laboratory indicated that equilenin-type azasteroids may have bactericidal or bacteriostatic properties as well as ability to potentiate the action of certain drugs.[4] For example, in combination (1:1 molar ratio) with actinomycin D, one of the azasteroids exhibited enhanced antibacterial activity.[5] A working hypothesis was set forth that the observed potentiation may have arisen as a result of formation of a molecular complex between the azasteroid and the anticancer agent.[5,6] NMR (in D_2O), uv, and fluorescence spectroscopic studies supported the idea of such complexation.[5,6]

In continuation of our work in this area, a series of selected heterosteroids,[2] and related model systems, has been synthesized and is described in this paper. An equilenin-type skeleton in the newly synthesized heterosteroids was maintained, with the modification of ring A being substituted with two methoxyl and/or two hydroxyl functionalities. One objective of this work was to determine the biological activity dependence upon the polar nature of end groups in A ring and the small heterocyclic ring. Thus, it was proposed to construct several heterocyclic systems with variations in the five-membered ring (or D ring).

Decreased cell permeability of some heterosteroids and, hence, lack of physiological activity have been attributed to the basic nature of such molecules.[7] Conceivably, heterosteroids with improved water solubility could alter the biological response of a system. This has been partially achieved by addition of a sugar residue to N(1) of the pyrazole ring in a steroidal system. This type of "nucleoside analog" is unknown in literature. Considerable effort has been devoted to the synthesis of nucleosides[8] (and analogs[9]) and application[10,11] thereof in chemotherapy.

Chemistry. A key precursor, 3,4-dihydro-6,7-di-