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Cycloalkanones. 8. Hypocholesterolemic Activity of Long-Chain Ketones Related to Pentadecanone

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Received June 5, 1975

Aliphatic analogs of 2,8-dibenzylcyclooctanone which includes C_{15}–C_{18} ketones have been investigated for hypocholesterolemic activity in rats. The position of the carbonyl group in the chain for maximum activity appears to be the 2 position. 2-Hexadecanone reduced serum cholesterol levels significantly without altering serum triglyceride levels. This drug was not estrogenic at effective doses which is in contrast to the cyclooctanones which possess this activity.

It has recently been demonstrated that aliphatic ketone analogs related to 2,8-dibenzylcyclooctanone are effective hypocholesterolemic agents (i.e., 8-pentadecanone).[2] The aliphatic ketones do not have the estrogenic and antifertility characteristics which are associated with the cyclooctanones.[2] Further expansion of this aliphatic chain to include C_{15}–C_{18} ketones and the importance of position of the ketone in the carbon chain have now been examined. Separation of the hypocholesterolemic effect from the uterotropic effect has been achieved in a C_{16} ketone, while preserving the hypocholesterolemic activity.

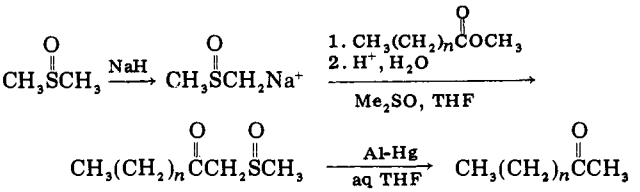
Experimental Section

All melting points were determined on the Thomas-Hoover melting point apparatus and were corrected. Infrared spectra were obtained on the Perkin-Elmer 257 spectrophotometer. All thin-layer chromatography was carried out on silica gel G coated microslides. Column chromatography was performed using 70–230 mesh silica gel 60. Elemental analyses were determined by M-H-W Laboratories, Garden City, Mich., and were correct within 0.4% of the theoretical values.

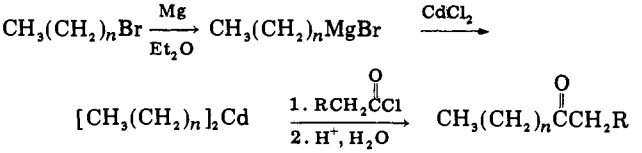
2-Pentadecanone (1). This compound was purchased from Calbiochem and was used in biological studies after proven pure by TLC and infrared spectroscopy. This ketone is a colorless semisolid at 25°.

Synthesis of β-Keto Sulfoxides. General Procedure.[3] A weighed amount of a 50% w/w dispersion of sodium hydride in mineral oil was placed in a three-neck round-bottom flask and washed with petroleum ether. The hydride was allowed to settle and the petroleum ether was decanted off. This washing procedure was repeated three times, and the flask was then evacuated with a water aspirator, and a nitrogen atmosphere was established. Dry dimethyl sulfoxide (about 100 ml/4.0 g of sodium hydride) was then added through a dropping funnel over a 15-min period with stirring. The temperature was then slowly raised to and maintained at 60–63° for 1.0 hr by which time a cloudy gray-green solution of methylsulfinyl carbanion was obtained. The reaction was diluted with an equal volume of dry tetrahydrofuran and cooled to 0° and 0.5 equiv of the appropriate methyl ester (based on 1 equiv of sodium hydride) was added dropwise either neat or as a THF solution. After stirring for 1.0 hr at room temperature, the entire mixture was poured into 600 ml of water and the pH adjusted to 3–4 (pH paper) using concentrated HCl. The resulting suspension was extracted with chloroform, the chloroform extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed in vacuo to leave the crude β-keto sulfoxide as a yellow solid. Recrystallization from ethyl acetate–benzene (10:1) afforded pure β-keto sulfoxide in 35–70% yield (Scheme I, Table I).

Scheme I



Scheme II



Reduction of β-Keto Sulfoxides. General Procedure.[3] A weighed amount of the above β-keto sulfoxide was dissolved in 10% aqueous tetrahydrofuran (about 600 ml/20 g). To this solution was added aluminum amalgam (10:1 molar ratio) prepared as follows. Aluminum foil was cut into 4 × 0.5 in. strips. Each strip was separately dipped into 2% aqueous mercuric chloride for 15 sec, rinsed with absolute ethanol and then anhydrous diethyl ether, and cut into 0.5 in. squares directly into the reaction vessel containing the β-keto sulfoxide solution. The reaction was then mechanically stirred under spontaneous reflux for 1.0 hr. The solid residue was filtered, the filtrate evaporated, and the residue was taken up in diethyl ether and extracted with 50 ml of water. The ether solution was dried over anhydrous Na_2SO_4 and filtered, and the ether was removed in vacuo leaving the crude ketone. Purification by recrystallization or column chromatography afforded the pure ketone in about 50–60% yield (Scheme I, Table I).

Synthesis of Hexadecanone Isomers. General Procedure.[4] To a weighed amount of dry magnesium turnings covered with sufficient dry diethyl ether was added 1 equiv of the appropriate alkyl halide dropwise neat or in ether solution. Addition and reflux were maintained at approximately the same rate. Upon reaction of all the magnesium, the reaction was cooled to 5–10° and 1 equiv of anhydrous cadmium chloride (previously dried to constant weight) was added over a 5–10-min period. The mixture was then stirred under reflux for 1.0 hr. At this time 0.8 equiv of the appropriate acid chloride in dry diethyl ether was added dropwise

Table I

$$CH_3(CH_2)_nC(=O)CH_2S(=O)CH_3 \rightarrow CH_3(CH_2)_nC(=O)CH_3$$

Compd no.	n	Mp, °C	% yield	Recrystn solvent	Formula	Analyses
				β-Keto Sulfoxide		
2	15	97-99	62		$C_{19}H_{38}O_2S$	
3	14	84-87	46		$C_{18}H_{36}O_2S$	
4	13	92-93	39		$C_{17}H_{34}O_2S$	
				Ketone		
5		51-52	46	2-Propanol	$C_{18}H_{36}O$	C, H
6		47-48	60	Benzene, benzene-ether, 95:5, 9:1[a]	$C_{17}H_{34}O$	C, H
7		44-45	63	Benzene, benzene-ether, 95:5, 9:1[a]	$C_{16}H_{32}O$	C, H

[a] Eluting solvent system used for column chromatography.

Table II. Hexadecanone Isomers

$$CH_3(CH_2)_nC(=O)CH_2R$$

Compd no.	R	n	Mp or bp (mm), °C	% yield	Recrystn solvent	Formula	Analyses
8	CH_3	12	39-41	55	Benzene, benzene-ether, 95:5[a]	$C_{16}H_{32}O$	C, H
9	C_2H_5	11	34-36	38	Benzene-ether, 9:1[a]	$C_{16}H_{32}O$	C, H
10	C_3H_7	10	35-37	43	2-Propanol-benzene, 4:1	$C_{16}H_{32}O$	C, H
11	C_4H_9	9	Semisolid	40	Benzene, benzene-ether 95:5[a]	$C_{16}H_{32}O$	C, H
12	C_5H_{11}	8	32-34	17	2-Propanol-petr ether (bp 30-60°), 4:1	$C_{16}H_{32}O$	C, H
13	C_6H_{13}	7	104-106 (0.35)	20	Distilled	$C_{16}H_{32}O$	C, H

[a] Eluting solvent system used for column chromatography.

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

Compd	$\bar{x}$ ± SD on day 4	$\bar{x}$ ± SD on day 10	$\bar{x}$ ± SD on day 16
Control	100 ± 8	100 ± 5	100 ± 9
Clofibrate	100 ± 16	98 ± 21	106 ± 9
2-Pentadecanone (1)	114 ± 8	113 ± 9	98 ± 4
2-Hexadecanone (5)	79 ± 8[a]	72 ± 19[b]	58 ± 7[a]
3-Hexadecanone (8)	64 ± 7[a]	83 ± 9[b]	92 ± 5
4-Hexadecanone (9)	65 ± 12[b]	89 ± 5[b]	103 ± 3
5-Hexadecanone (10)	63 ± 3[a]	89 ± 9[c]	94 ± 5
6-Hexadecanone (11)	70 ± 6[a]	92 ± 4[c]	100 ± 7
7-Hexadecanone (12)	89 ± 11	89 ± 8[c]	77 ± 8[a]
8-Hexadecanone (13)	102 ± 12	97 ± 6	72 ± 5[a]
2-Heptadecanone (6)	83 ± 6[b]	75 ± 4[b]	74 ± 12[a]
2-Octadecanone (7)	79 ± 12[a]	86 ± 13	73 ± 8[a]

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

Table IV. Percent of Initial Rat[d] Body Weight after 16 Days of Treatment with 10 mg/kg/day of Test Compound

Compd	% increase in body wt: $\bar{x}$ ± SD (day 10)	% increase in body wt: $\bar{x}$ ± SD (day 16)
1% CMC[a]	160 ± 13	195 ± 16
2-Pentadecanone (1)	156 ± 15	233 ± 22[c]
2-Hexadecanone (5)	145 ± 13	228 ± 19[c]
3-Hexadecanone (8)	167 ± 11	212 ± 12
4-Hexadecanone (9)	175 ± 9	213 ± 13
5-Hexadecanone (10)	165 ± 9	206 ± 15
6-Hexadecanone (11)	168 ± 8	209 ± 10
7-Hexadecanone (12)	169 ± 11	207 ± 19
8-Hexadecanone (13)	167 ± 9	209 ± 19
2-Heptadecanone (6)	165 ± 12	229 ± 14[b]
2-Octadecanone (7)	175 ± 19	242 ± 32[c]

[a] Average animal weight on day 0 was 120 ± 6 g. [b] $p = 0.010$. [c] $p = 0.025$. [d] $N = 8$.

Table V. Percent of Control of Rat[d] Serum Cholesterol after Treatment with 2-Hexadecanone (5)

Compd	$\bar{x}$ ± SD on day 4	$\bar{x}$ ± SD on day 10	$\bar{x}$ ± SD on day 16	% increase body wt, $\bar{x}$ ± SD
Control (1% CMC)	100 ± 5	100 ± 18	100 ± 5	195 ± 16
2-Hexadecanone (5)				
1 mg/kg	82 ± 13	80 ± 8	71 ± 5[a]	229 ± 31
5 mg/kg	74 ± 6[a]	78 ± 10[c]	67 ± 5[a]	244 ± 16[a]
10 mg/kg	79 ± 8[a]	72 ± 19[b]	58 ± 7[a]	228 ± 19[c]
20 mg/kg	74 ± 5[a]	76 ± 5[b]	69 ± 6[a]	225 ± 15[c]
50 mg/kg	75 ± 16[b]	74 ± 12[b]	68 ± 7[a]	226 ± 17[c]

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

Table VI. Average Weekly Food Intake (g/rat[a]/day) after Treatment with 2-Hexadecanone (5)

Compd	$\bar{x}$ ± SD 1st week	$\bar{x}$ ± SD 2nd week
Control (1% CMC)	20.9 ± 4.9	24.8 ± 1.1
2-Hexadecanone (5)		
1 mg/kg	22.3 ± 2.7	26.6 ± 2.2
5 mg/kg	21.8 ± 6.8	26.3 ± 5.3
20 mg/kg	21.4 ± 4.7	24.2 ± 1.5
50 mg/kg	22.5 ± 2.6	25.6 ± 1.0

[a] $N = 8$.

to the reaction mixture over a 10–20-min period. Stirring was continued under reflux for 1.0 hr. The reaction was cooled to 5–10° and sufficient 20% H_2SO_4 was added to achieve a two-phase solution. The organic layer was drawn off and the aqueous layer extracted once with diethyl ether. The combined ether extracts were washed with 5% $NaHCO_3$ and water, dried over anhydrous

Table VII. Percent Total Rat[a] Body Weight after Treatment with 2-Hexadecanone (5) at 10 mg/kg/day for 16 Days

	$\bar{x}$ ± SD					
	Liver	Kidney	Heart	Epididymis and vas deferens	Testes	Vesicular glands
1% CMC	4.35 ± 0.39	0.91 ± 0.10	0.39 ± 0.04	0.22 ± 0.04	1.09 ± 0.01	0.118 ± 0.062
2-Hexadecanone	4.39 ± 0.35	0.86 ± 0.11	0.39 ± 0.02	0.24 ± 0.06	1.13 ± 0.08	0.121 ± 0.031

[a] $N = 8$.

Na_2SO_4, and filtered, and the ether was removed in vacuo to leave the crude ketone. Purification of this product was achieved by either column chromatography, recrystallization, or vacuum distillation (Scheme II, Table II).

Biological Methods. Sprague–Dawley rats (Zivic Miller, Allison Park, Pa.) were fed Purina lab chow with water ad libitum for the duration of the experiment. Each test compound was suspended in 1% carboxymethylcellulose–H_2O (1% CMC) and homogenized. Doses (mg/kg) were calculated on weekly weights of the rats.

Serum Cholesterol Levels. All drugs (10 mg/kg/day) were administered to male rats by oral intubation needle (0.2 cc) daily at 11:00 a.m. Twenty-four hours after the last dose, blood was collected by tail-vein bleeding. Nonhemolyzed samples (30 μ) were analyzed for serum cholesterol by a modification of the Liebermann–Burchard method. A dose–response study was determined for 2-hexadecanone (5) as described previously.[5]

Animal Weight and Autopsy. Periodic animal weights were obtained and expressed as a percentage of the animal's weight on day 0 of the experiment. On day 16, animals were sacrificed by cervical dislocation and a number of organs excised and weighed. These 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 change, infection, etc., as described previously.[5]

Food Intake. The average food intake in grams per rat per week was determined over a 2-week period of dosing with compound 5 at 10 mg/kg/day.

Toxicity Study. An LD_{50} was determined on compound 5 in CF_1 male mice according to the Litchfield and Wilcoxon method.[6]

Uterotropic Activity. Weaned rats were ovariectomized by the procedure outlined by Emmens et al.[7] Three days were allowed to pass before treatment was commenced with drugs. The rats were then treated for 3 days with 10 μg/kg/day of 17-ethinylestradiol or 10 mg/kg/day of test compound and sacrificed. The uterus was removed, trimmed, and weighed.

Liver Lipid, Glycogen, Protein, and Nucleic Acid Levels. These levels were determined after 16 days of dosing at 10 mg/kg/day with compound 5 by the method of Shibko et al.[8]

Serum triglycerides were measured by the Calbiochem Fast Pack[9] on rats treated with compound 5 on days 14 and 16.

Detergent Effect of Ketone. The possibility exists that a ketone could disrupt the integrity of subcellular membranes and bring about its pharmacological action by this mechanism. In order to determine whether the cellular membrane remains intact two studies were performed. A 10% homogenate (1 ml) of rat liver prepared in 0.25 M sucrose + 0.001 M EDTA, pH 7.2, was incubated at 37°C with 15 ml of Hanke's buffer solution, pH 7.2, and 1 ml of compound 5 in 1% CMC calculated on the basis of milligrams of drug per gram of wet liver. The turbidity of the incubation was measured on a Spectronic 70 as absorption at 660 nm. As lysis occurred the absorbance decreased. Secondly, 2 ml of 10% liver homogenate was incubated with 5 ml of Hanke's buffer solution, pH 7.2, and 1 ml of drug suspension in 1% CMC in a Dubnoff shaker at 37°C. This mixture (1 ml) was removed after 1 hr and the percent free acid phosphatase activity was determined as previously described.[9]

Statistical Analysis. In Tables III–IX the number of animals in a group expressed as N, the mean of the percent of control, and standard deviation expressed as $\bar{x}$ ± SD are noted. The probable significant level (p) was determined by Student's t test according to Snedecor.[10]

Results and Discussion

Aliphatic ketones of C_{15}–C_{18} chain length in general possessed only moderate (25%) hypochloesterolemic activity (Table III). 2-Hexadecanone (5) had the maximum effect (42%) on lowering serum cholesterol levels after 16 days of treatment. For long-term effects the most desirable location of the ketone group on the carbon chain was in the 2 position. It is interesting to note that the ketone group in positions 3, 4, and 5 lowered serum cholesterol 36, 35, and 37%, respectively, on the 4th day of dosing but this effect was lost on the 10th and 16th day, whereas the ketone group in position 7 and 8 lowered serum cholesterol 23 and 28%, respectively, over 16 days. One could postulate that these long-chain ketones are being hydrolyzed slowly in vivo which would result in the ketone group being closer to the end of the aliphatic chain particularly if the hydrolytic products were similar to 2-octanone which is a very potent hypocholesterolemic agent, reducing serum cholesterol by 66%.[1] Compound 1, 5, 6, and 7 caused a significant increase in weight at 10 mg/kg (Table IV).

The hypocholesterolemic activity increased with increased dose of 5 up to 10 mg/kg but no further increases were obtained with higher doses (Table V). The average weekly food intake was not significantly altered over 2 weeks (Table VI) after treatment with compound 5; however, there was an increase in total body weight over the same period (Table V). Thus the suppression of appetite could not be the cause of the hypocholesterolemic activity of these drugs. Lipids being removed from the blood were not deposited in the major organs of the body since there was no significant increase in organ weights (Table VII). The liver lipid content was not altered by compound 5 treatment nor was the DNA, RNA, glycogen, and protein content (Table VIII). The serum lipid lowering effects were specific for cholesterol since compound 5 had no effect on serum triglycerides levels (Table IX).

In vitro studies demonstrated that compound 5 did not produce any more cell lysis than 1% CMC (Table X). Since acid phosphatase is an acid hydrolytic enzyme bound to the inner lysosomal membrane, any rise in percent free acid phosphatase would reflect ruptured lysosomal

Table VIII. Effects of 2-Hexadecanone (5) of Rat[a] Liver, DNA, RNA, Lipid, Protein, and Glycogen Levels Expressed as Percentages of Control after 16 Days of Treatment

	$\bar{x}$ ± SD				
	DNA	RNA	Lipid	Glycogen	Protein
Control (1% CMC)	100 ± 2	100 ± 6	100 ± 13	100 ± 26	100 ± 5
2-Hexadecanone, 10 mg/kg	114 ± 2[b]	111 ± 7[c]	101 ± 25	105 ± 48	107 ± 5

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

Table IX. Serum Triglyceride Levels of Sprague-Dawley Rats[a] after Treatment with 2-Hexadecanone (5)

	% control, $\bar{x}$ ± SD	p
1% CMC	100 ± 21	
2-Hexadecanone		
10 mg/kg on day 16	120 ± 29	NS
20 mg/kg on day 14	101 ± 27	NS

[a] $N = 8$.

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.

Acknowledgment. We express our sincere thanks to Bonnie Whitehead for her technical assistance. This investigation was supported by Research Grant HL16464-02 from the Division of Heart and Vascular Disease, National Heart and Lung Institute, National Institutes of Health.

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

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Received June 2, 1975

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