HOAc at a flow rate of 25 ml/hr. The peptide material was eluted as a single peak at 87% of the column volume and was recovered by lyophilization: 64 mg. This material was again subjected to partition chromatography as above in the solvent system BuOH–C_6H_6–HOAc–H_2O (8:3:2:8). [Phe^4]oxytocin was eluted as a broad peak at R_f 0.32 and was recovered by lyophilization from dilute HOAc as above: 64 mg (30% overall); $[\alpha]^{25}D$ +1.8° (*c* 0.7, 1 *N* HOAc); homogeneous to TLC (B, 0.55; C, 0.61). Amino acid analysis following 24-hr hydrolysis in 6 *N* HCl at 110° gave the following molar ratios: Asp, 1.00; Pro, 1.01; Gly, 1.00; Cys, 2.08; Ile, 0.91; Leu, 1.05; Tyr, 1.01; Phe, 1.03; NH_3, 1.89. Anal. $C_{47}H_{67}N_{11}O_{11}S_2 \cdot 3H_2O$) C, H, N.

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Cycloalkanones. 7.[1] Hypocholesterolemic Activity of Aliphatic Compounds Related to 2,8-Dibenzylcyclooctanone

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A series of 19 aliphatic analogs of 2,8-dibenzylcyclooctanone and 1,5-diphenyl-2,4-dimethyl-3-pentanone was examined. Separation of hypocholesterolemic activity from the previously observed uterotropic and antifertility activities was achieved by simplification of the parent compound to 2-octanone. There was no loss of hypocholesterolemic activity. Reduction of serum cholesterol levels in male rats to less than 50% of control values was obtained at a dose of 10 mg/kg/day.

2,8-Dibenzylcyclooctanone (1) has been shown to be an effective hypolipidemic agent in rats and mice.[2a] The acyclic analog 1,5-diphenyl-2,4-dimethyl-3-pentanone (2) has also demonstrated hypolipidemic activity.[2b] Both 1 and 2, as well as the most active derivatives of 1, have also shown a positive uterotropic effect.[2] Although the uterotropic effect is relatively small when compared to a standard such as diethylstilbestrol, elimination of this effect has been an objective of the SAR studies completed.[3] Compounds 1 and 2 also possess antifertility activity which has been separated from the hypolipidemic effects in subsequent analogs of the cyclic series.[3]

It has been shown that modifications of the cyclooctane ring and the aromatic moiety of 1 produce large changes in

Table I. Hypocholesterolemic Activities of Aliphatic Analogs of 2,8-Dibenzylcyclooctanone at 10 mg/kg/day in Sprague-Dawley Rats

Compd no.	Name[d]	Serum cholesterol as % of control on day			% body wt increase
		4	10	16	
Control (1% CMC)		100 ± 7	100 ± 12	100 ± 8	100 ± 4
2	1,5-Diphenyl-2,4-dimethyl-3-pentanone	56 ± 23[b]	51 ± 12[c]	54 ± 14[c]	65 ± 4[c]
3	3-Pentanone	104 ± 18	81 ± 12[b]	93 ± 11	93 ± 3[b]
4	2,4-Dimethyl-3-pentanone	108 ± 10	63 ± 8[c]	86 ± 10	106 ± 13
5	3,5-Dimethyl-4-heptanone	113 ± 8[b]	70 ± 20[a]	85 ± 7	100 ± 8
6	2-Octanone	74 ± 11[c]	59 ± 7[c]	34 ± 8[c]	100 ± 5
7	2-*Undecanone*	991 ± 12	87 ± 9	90 ± 9	98 ± 5
8	2-Pentadecanone	114 ± 8	113 ± 9	94 ± 4	104 ± 4
9	8-Pentadecanone	99 ± 7	77 ± 10[c]	59 ± 16[c]	100 ± 7
10	9-Heptacosanone	115 ± 11	104 ± 16	89 ± 13	104 ± 3
11	14-Heptacosanone	86 ± 7[b]	81 ± 8[b]	82 ± 8[b]	101 ± 8
12	1,3-Diphenyl-2-propanone	89 ± 9	104 ± 10	88 ± 7[b]	95 ± 3[a]
13	1,5-Diphenyl-3-pentanone	98 ± 8	89 ± 9	81 ± 13[a]	97 ± 4
14	1,5-Diphenyl-2-methyl-3-pentanone	106 ± 8	76 ± 14[a]	66 ± 15[b]	103 ± 9
15	2,4-Dibenzylidene-3-pentanone	106 ± 8	76 ± 9[b]	91 ± 12	95 ± 5
16	1,2-Dibenzoylethane	91 ± 7	92 ± 7	80 ± 10[c]	102 ± 5
17	Methyl dibenzylacetate	96 ± 18	84 ± 13[b]	103 ± 8	106 ± 6
18	Methyl 3,3-diphenylpropionate	109 ± 14	71 ± 8[c]	80 ± 6[c]	91 ± 7
19	1,3-Dibenzyl-1,3-dimethylurea	91 ± 13	104 ± 10	94 ± 13	102 ± 6
20	1,5-Diphenyl-2,4-dimethyl-3-pentanol	102 ± 17	92 ± 12	85 ± 9[a]	98 ± 6
	Clofibrate	111 ± 16	98 ± 21	106 ± 9	106 ± 6

[a] $p = 0.025$. [b] $p = 0.10$. [c] $p = 0.001$. [d] $N = 8$ for all compounds.

the hypocholesterolemic activity of **1**. A similar SAR study of the aliphatic portion of **2** has now been completed. Separation of the hypocholesterolemic effect from the uterotropic effect has been achieved in a simple aliphatic analog of **2**, while retaining the hypolipidemic activity.

Experimental Section

Ketones **3**–**12** were obtained from commercial sources and were used as received after ir spectra and TLC confirmed identity and showed no contamination.

1,5-Diphenyl-2-methyl-3-pentanone (14) was prepared from benzaldehyde and 2-butanone by Massara's procedure.[4] A mixture of isomers was tested.

1,2-Dibenzoylethane (16) was prepared according to the method of Conant and Lutz.[5]

Methyl dibenzylacetate (17) was prepared according to the method of Hill.[6]

Methyl 3,3-diphenylpropionate (18) was prepared according to the method of Dippy and Young.[7]

1,3-Dimethyl-1,3-dibenzylurea (19) was prepared from benzylmethylamine[8] and phosgene by the method of Papesch and Schroeder.[9] The product was obtained in 38% yield as an oil [bp 190–200° (0.15 mm)] which later crystallized (mp 48–50°). Anal. C, H.

1,5-Diphenyl-2,4-dimethylpentan-3-ol (20) was prepared by $LiAlH_4$ reduction of the ketone **16** using standard procedures.[10] A 0.055-mol run gave 8 g (57%) of product after chromatography on silica gel (benzene). Anal. C, H.

Biological Methods. Sprague–Dawley rats (Zivic Miller, Allison Park, Pa.) and CF_1 mice (Carworth Farms) were fed Purina lab chow with water ad libitium 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 and daily weights of the mice.

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. After the last dose (24 hr), blood was collected by tail vein bleeding and analyzed for serum cholesterol content as previously described[2a] (Table I).

Antifertility Activity. All drugs (50 mg/kg/day) were administered to female CF_1 mice ip daily. The fertility screen has previously been described.[3,13] The percent pregnant, the number of viable fetuses per litter, and the number of reabsorption sites and dead in utero per litter were noted and expressed as a percent of the control value. 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 the percent of control values for the test compounds. A change greater than 25% is considered to be significant at the level of $p = 0.05$[13] (Table II).

Uterotropic Activity. Weaned rats were ovariectomized by the procedure outlined by Emmens et al.[12] Three days were allowed to pass before treatment was commenced with hypocholesterolemic agents. The rats were then treated for 3 days with 10 μg/kg/day of 17-ethinylestradiol or 10 mg/kg/day of compound **2** or **6** and sacrificed. The uterus was removed, trimmed, and weighed (Table III).

Statistical Analysis. In Tables I–III the number of animals in a group, expressed as N, the mean of the percent of control, and standard deviation, expressed as $\bar{x} \pm$ S.D., are noted. The probable significant level (p) was determined by the Student's t test according to the procedure of Snedecor.[11]

Results and Discussion

Aliphatic analogs of **2** in general had only minor lowering effects on serum cholesterol levels of rats. It can be seen that the loss of even one of the α-methyl groups of **2** (e.g., **14**) caused a loss of hypocholesterolemic activity. Loss of

Table II. Antifertility Activities of Aliphatic Analogs of 2,8-Dibenzylcyclooctanone in CF_1 Mice

Compd	N	% pregnant	% av no. of fetuses per litter[a]	% av no. of reabsorption sites per litter[a]
Control	62	100	100 ± 25	100 ± 25
2	8	0	0	0
3	7	87	86	540
4	8	100	96	115
5	8	75	93	519
6	8	75	87	0
7	8	50	60	0
8	8	100	78	0
9	6	67	81	0
10	6	33	68	0
11	8	62	68	0
12	8	75	94	291
13	7	86	92	62
14	8	75	78	267
15	8	75	22	290
17	8	100	91	200
18	8	86	93	327
19	8	100	82	150
20	8	38	49	400
Diethyl stilbestrol (10 μg/kg)	8	0	0	0

[a] Average number of fetuses for CF_1 mice = 12 ± 3 and average number of reabsorption = 0.48 ± 0.12 per litter. These values are considered to be 100%.

both α-methyl groups caused an even greater drop in activity (**13**). Shortening the alkyl chain (**12**), isosteric replacement of the α carbon (**19**), and modification of the ketone (**17, 18, 20**) were in general ineffective in producing a substantial level of hypocholesterolemic activity.

Removal of the aromatic ring (e.g., **3, 4**) produced a transient hypolipidemic state. A series of *n*-alkyl ketones, whose molecular weight and structure were similar to part or all of the lead compound, was examined (**6–11**). Compounds **6** and **9** were found to reduce serum cholesterol to 34% of control and 59% of control, respectively. An extreme example (**11**) was also slightly active.

Compounds **6** and **14** lowered pregnancy levels to 75% of control. Further, **7, 9, 10,** and **20** showed significant antifertility activity. Compound **6** exhibited no uterotropic effect in female rats, whereas compound **2** was estrogenic.

None of the interesting compounds caused any significant changes in body weight during the course of the experiment. None of the compounds caused observable toxic effects during the experiment.

Table III. Uterotropic Activity in Ovariectomized Sprague–Dawley Rats

	N	% control of uterine wt	p
Control (1% CMC)	21	100 ± 23	
2	8	148 ± 17	0.005
6	8	96 ± 15	N.S.
17-Ethinylestradiol (10 μg/kg)	13	259 ± 9	0.001

Compound **6** appears to be a potentially useful hypocholesterolemic agent since it reduced serum cholesterol levels but had no antifertility or uterotropic activities at an effective dose level. Since it is a simple ketone and has few of the structural features associated with hypolipidemic activity in the bis(β-phenethyl) ketone series, **6** may be exerting its effect by a different mechanism than that of **2**. This hypothesis is further supported by the slower onset of hypocholesterolemia produced by **6** compared to that produced by **2**.[2b] Studies are now underway to further elucidate the mechanism by which **6** lowers cholesterol levels.

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