Experimental Section

Melting points were taken on a Gallenkamp apparatus (Registered Design No. 889339) using capillaries and are uncorrected. All compounds were characterized by ir, uv, nmr, and elemental analyses (C, H, N) which were within ±0.4% of the theoretical values.

Triethyloxonium fluoborate was prepared by the method of Meerwein[9] and successfully stored under anhydrous Et_2O for periods up to 6 months.

2-(4-*N,N*-Di-*n*-butylaminomethylstyryl)-5-nitro-1-vinylimidazole (6). 2-(4-*N,N*-Di-*n*-butylcarbamoylstyryl)-5-nitro-1-vinylimidazole, 18.2 g (0.046 mol), was stirred in CH_2Cl_2 (100 ml) at room temperature. A solution of triethyloxonium fluoborate, 9.8 g (0.051 mol), in CH_2Cl_2 (20 ml) was added rapidly and the clear orange yellow solution stirred for 20 hr. CH_2Cl_2 was removed *in vacuo* (rotary), the resultant viscous oil was stirred with EtOH (100 ml) and cooled to 0°, and $NaBH_4$ (4.5 g) added in small portions over 1 hr. After stirring at room temperature overnight, the hazy solution was poured into H_2O (300 ml) and the resultant yellow oily solid was separated, taken up in EtOH (50 ml), treated with EtOH–HCl, and evaporated to dryness twice in the presence of 2-propanol. The crystalline solid was treated with hot H_2O (100 ml) (small precipitate removed here by filtration), the clear filtrate made alkaline with Na_2CO_3 and extracted with $CHCl_3$, and the $CHCl_3$ removed *in vacuo* (rotary) to give a brownish yellow oil which was crystallized from EtOH: yield 7.8 g (45%); mp 63–64°.

Compounds **2**, **3**, **5**, **7**, and **8** were prepared in a similar manner. Compound **2** was very soluble in EtOH and was isolated as the hydrochloride salt.

2-(4-*N*-*n*-Butylamidinostyryl)-5-nitro-1-vinylimidazole (14). The primary amide **1d**, 28.4 g (0.1 mol), was suspended in dry CH_2Cl_2 (300 ml) and stirred with a solution of $Et_3O^+BF_4^-$, 20 g (0.11 mol), in CH_2Cl_2 (30 ml) for 20 hr at room temperature. The mixture was evaporated (rotary) to low volume and the solid stirred with anhydrous Et_2O, filtered, washed with further Et_2O, and dried *in vacuo*.

This product, 25 g (0.062 mol), was added with stirring to liquid ammonia (100 ml) and the excess ammonia allowed to evaporate overnight. The greenish yellow solid was extracted with hot $CHCl_3$ and the $CHCl_3$ evaporated (rotary) to give the free imino ether: yield 8.0 g (27%). Recrystallization from 2-propanol gave a highly crystalline solid: mp 178–179°.

The recrystallized imino ether, 3 g (*ca.* 0.01 mol), was refluxed in MeOH (150 ml) with *n*-butylamine hydrochloride, 1.5 g (0.014 mol), for 4 hr. The clear solution was cooled and the MeOH evaporated (rotary). The resultant solid was extracted with hot H_2O (2 × 200 ml) (some insoluble removed here) and the filtrate was made alkaline (4 *N* NaOH). After extraction into $CHCl_3$ and concentration, the product was obtained as yellow crystals: yield 1.4 g (40%); mp 143–144°. Compounds **10**, **12**, and **13** were similarly prepared.

2-(4-*N*-Methylamidinostyryl)-5-nitro-1-vinylimidazole Hydrochloride. The imino ether tetrafluoborate, 25 g (0.062 mol), prepared as above, was stirred in EtOH (200 ml) and treated with methylamine in EtOH (12 ml, 33% w/w solution). After stirring for 3 days at room temperature (closed flask), the resultant solid was filtered off, dissolved in warm water, and made alkaline (4 *N* NaOH). The yellow solid which formed was purified twice *via* the sequence: treatment with hot dilute HCl solution, filtration, and reprecipitation with 4 *N* NaOH and finally by crystallization from EtOH–HCl to give the desired compound as the hydrochloride: yield 2.2 g (11%); mp 279–280° dec.

2-(4-Hydroxyamidinostyryl)-5-nitro-1-vinylimidazole (15). A mixture of hydroxylamine hydrochloride, 2.45 g (0.035 mol), MeOH (35 ml), and 5 *N* NaOH solution (7 ml) was added to the cyano compound **1e**, 9.3 g (0.035 mol), in EtOH (500 ml) and refluxed for 24 hr. The mixture, containing a lighter yellow solid than at the start, was filtered hot and the resulting solid washed with H_2O (to remove NaCl), then extracted with boiling $CHCl_3$ (to remove unreacted cyano compound), and finally crystallized from DMF: yield 6.9 g (66%); mp 249–250° dec.

Acknowledgments. We thank Dr. M. D. Pittam and Miss J. A. O'Brien for the biological results and Mr. G. Maciak of the Lilly Research Laboratories, Indianapolis, Ind., for the microanalytical data on the compounds described in this paper.

References

(1) W. J. Ross, W. B. Jamieson, and M. C. McCowen, *J. Med. Chem.*, **16**, 347 (1973).
(2) E. M. Lourie and W. Yorke, *Ann. Trop. Med.*, **33**, 280 (1939).
(3) H. King, E. M. Lourie, and W. Yorke, *Lancet*, **2**, 1360 (1937).
(4) W. A. Sexton "Chemical Constitution and Biological Activity," 3rd ed, E & F. N. Spon, London, 1963, p 391.
(5) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(6) H. J. Barber and R. Slack, *J. Amer. Chem. Soc.*, **66**, 1607 (1944).
(7) A. W. Dox, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N.Y., 1941, p 5.
(8) F. Hawking, *Exp. Chemother.*, 1, 129 (1963).
(9) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

Cycloalkanones. 6. Separation of Hypocholesterolemic and Antifertility Activities in Derivatives of 2,8-Dibenzylcyclooctanone

G. L. Carlson,*,† I. H. Hall, and C. Piantadosi

Department of Medicinal Chemistry, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514.
Received October 3, 1974

Fluoro and hydroxy derivatives of 2,8-dibenzylcyclooctanone were prepared. Separation of antifertility activity from hypolipidemic and uterotropic effects was achieved with 2,8-bis(4-acetoxybenzyl)cyclooctanone. Some enhancement of the hypolipidemic effect in relation to the uterotropic and antifertility activities was seen in 2,8-bis(4-fluorobenzyl)cyclooctanone. Synthetic methods for the hydroxy compounds are presented.

The hypocholesterolemic uterotropic, and antifertility activities of compounds related to the parent 2,8-dibenzylcyclooctanone (**1**) have been reported (Figure 1).[1,2] An earlier study has shown that a causal relationship between uterotropic and hypolipidemic activities is unlikely;[3] however, the problem of separating the three activities remained. The changes in the effects of some derivatives [2,8-bis(4-methylbenzyl)cyclooctanone (**2**) and 2,8-bis(2-methylbenzyl)cyclooctanone (**3**)] led to the speculation that further modification of the aromatic nucleus could result in a separation of the antifertility activity from the hypolipidemic activity.

Experimental Section

2,8-Bis(4-fluorobenzyl)cyclooctanone, 2,8-bis(4-methoxybenzyl)cyclooctanone, and 2,8-bis(4-methoxybenzyl)cyclooctanone were prepared from the appropriate aldehydes using methods previously described.[3]

2,8-Bis(4-hydroxybenzyl)cyclooctanone (5). General Method for Aryl Methyl Ether Cleavage.[4] NaH (4 g, 50%) in mineral oil was added to 75 ml of freshly distilled DMF at 5°. Excess ethanethiol (7.5 ml) was added at a rate sufficiently slow to prevent foaming over the top of the flask. 2,8-Bis(4-methoxybenzyl)cy-

†This investigation was supported in part by a R. J. Reynolds Fellowship to Gerald L. Carlson. We wish to express our appreciation to Dr. Claude E. Teague, Jr., for his interest and encouragement.

Table I. Substituted 2,8-Dibenzylcyclooctanones

Compd no.	Name	Formula[a]	Mp, °C	Recrystn[b] solvent	Yield, %
4	2,8-Bis(4-fluorobenzyl)cyclooctanone	$C_{22}H_{24}F_2O$	112–114		48
5	2,8-Bis(4-hydroxybenzyl)cyclooctanone	$C_{22}H_{26}O_3$	117–179	EtOH–H_2O	97
6	2,8-Bis(4-acetoxybenzyl)cyclooctanone	$C_{26}H_{30}O_5$	89–92		93
7	2,8-Bis(4-propionoxybenzyl)cyclooctanone	$C_{28}H_{34}O_5$	54–57		78
8	2,8-Bis(2-hydroxybenzyl)cyclooctanone	$C_{22}H_{26}O_3$	176–178		50[c]
9	2-(2-Hydroxybenzyl)-8-(2-methoxybenzyl)cyclooctanone	$C_{23}H_{28}O_3$	134–136		45[c]

[a] All compounds analyzed within ±0.4% of theory. [b] Where no recrystallization solvent is listed, the compound was isolated by flash evaporation of chromatographic fractions and solidified upon standing. [c] Both were isolated from one run using 2,8-bis(2-methoxybenzyl)-cyclooctanone, refluxed for 8 hr.

Table II. % of Control of Serum Cholesterol and Body Weight after Administration of 10 mg/kg/day of Test Compound ($N = 8$)

Compd	Serum cholesterol, no. of days dosed 4th	10th	16th	Body wt (% of control on day 16)
Control (1% CMC)	100 ± 16	100 ± 10	100 ± 13	
1	48 ± 13[a]	50 ± 12[a]	42 ± 18[a]	75[a]
2	83 ± 19	79 ± 10[a]	79 ± 9[b]	95
3	77 ± 19[c]	82 ± 7[b]	56 ± 14[b]	100
4	78 ± 17[b]	58 ± 18[b]	41 ± 24[b]	93
5	103 ± 18	105 ± 14	110 ± 16	100
6	94 ± 10	94 ± 17	98 ± 8	100
7	80 ± 11[b]	103 ± 20	83 ± 11[b]	100
8	93 ± 16	70 ± 11[b]	85 ± 22	100
9	93 ± 10	75 ± 18[b]	73 ± 8[b]	100

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

clooctanone (8 g, 0.022 *M*) was added and the reaction refluxed for 24 hr. After cooling, the reaction was poured into 400 ml of H_2O and extracted with 300 ml of Et_2O. The aqueous layer was acidified, extracted with 300 ml of Et_2O, dried, and flash-evaporated to give a nearly quantitative yield of yellow oil, which after chromatography on silica gel ($CHCl_3$–acetone, 85:15) and recrystallization (ethanol–water) gave 7.2 g (97%) of pure 2,8-bis(4-hydroxybenzyl)cyclooctanone, mp 178–179°.

The same procedure was used to prepare compounds **8** and **9** from 2,8-bis(2-methoxybenzyl)cyclooctanone. Compound **9** was isolated from compound **8** by the same chromatographic procedure used for **5** (Table I).

2,8-Bis(4-acetoxybenzyl)cyclooctanone (6). General Method for Ester Preparation. 2,8-Bis(4-hydroxybenzyl)cyclooctanone (3.38 g, 0.01 *M*) was dissolved in 30 ml of acetic anhydride containing 1 drop of sulfuric acid. The reaction was heated to 60° for 90 min, cooled, and poured into 200 ml of H_2O. After stirring 30 min, the solution was extracted with 300 ml of ether. The ether solution was washed with 10% sodium hydroxide solution and dried.

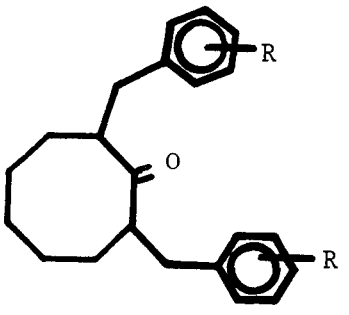

Figure 1. General structure of substituted 2,8-dibenzylcyclooctanone.

Table III. Antifertility Activity in CF_1 Female Mice at 50 mg/kg/day

	N	% pregnant	% of no. of fetus/ litter	% of no. reabsorb/ litter
Control (1% CMC)	8	100	100	100
1	8	0	0	0
2	8	100	80	142
3	8	0	0	0
4	8	75	56	250
5	8	88	82	260
6	8	0	0	0
7	8	87	110	114
8	6	100	103	30
9	8	63	65	0
10[a]	8	0	0	0

[a] 10 μg of diethylstilbesterol.

The oil obtained after solvent removal was chromatographed on silica gel (benzene–acetone 9:1) and yielded 3.9 g (93%) of colorless solid, mp 89–92°.

Compound **7** was prepared by the same procedure using propionic anhydride in place of acetic anhydride, followed by chromatographic isolation of the ester.

Biological Studies. 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. Initial weight of the rats used was approximately 140 g.

Administration of Drugs. Each test compound was suspended in 1% carboxymethylcellulose–H_2O and homogenized. Doses were calculated on weekly weights of the rats. All drugs (10 mg/kg/day) were administered to the animals by an oral intubation needle (0.2 cc) daily at 11:00 A.M. for 16 days.

Serum Cholesterol and Triglyceride, Animal Weight, Autopsy, and Uterotropic Activity. These methods have been outlined previously[3] (Table II).

Antifertility activity was determined in CF_1 female mice by the method of Baggett[1,5] (Table III).

Liver, RNA, DNA, glycogen, protein and lipid were determined by the Shibko, *et al.*, method[6] (Table IV).

Discussion

It has been shown that the intact bis(β-phenylethyl) ketone system is the minimal structural requirement for biological activity in the 2,8-dibenzylcyclooctanone series. The various effects may be modulated by substitution of the phenyl moiety. For example, ortho methylation reduced the uterotropic activity to 50% of that of the parent without significant effect upon the antifertility or hypocholesterolemic effects. Para methylation, however, eliminates the uterotropic and antifertility properties of the molecule and drastically lowers the hypocholesterolemic activity (Table V).

Table IV. % of Total Body Weight 24 Hr after the 16th Dose

	Liver	Testes	Vesicular glands	Vas Deferens and epididymis
Control	4.35 ± 0.19	1.09 ± 0.05	0.12 ± 0.02	0.22 ± 0.02
2	4.46 ± 0.11	1.06 ± 0.02	0.13 ± 0.01	0.24 ± 0.01
3	4.19 ± 0.41	1.13 ± 0.10	0.12 ± 0.06	0.31 ± 0.10
4	4.22 ± 0.38	1.05 ± 0.09	0.06 ± 0.02	0.20 ± 0.11
6	4.51 ± 0.15	1.23 ± 0.12	0.11 ± 0.04	0.23 ± 0.05

Table V. Estrogenic Activity in Ovariectomized Sprague-Dawley Rats

	N	% control of uterine wt	p
Control (1% CMC)	21	100 ± 23	
1	13	260 ± 22	0.001
2	8	72 ± 16	n.s.
3	8	131 ± 20	0.050
4	8	195 ± 19	0.001
6	8	74 ± 17	n.s.
Ethinylestradiol	8	259 ± 9	0.001

The propensity of the benzene ring to undergo bioactivation *via* hydroxylation[7] and the effect some hydroxylated aromatic compounds (*e.g.*, diethylstilbestrol) have upon the reproductive cycle led to the speculation that the uterotropic or antifertility activities might be the result of *in vivo* hydroxylation. Conversely, a substituent (*e.g.*, fluorine) which forms a more stable bond with the ring than does hydrogen would be expected to interfere with bioactivation and lower the antifertility activity of the compound.[8,9]

The *p*-fluoro derivative **4** retained both hypocholesterolemic and uterotropic activities and showed a marked drop in antifertility effect compared to the parent compound. The *o*-fluoro analog has an antifertility effect as great as dibenzylcyclooctanone. These compounds support the concept that para hydroxylation may be responsible for the antifertility effect of dibenzylcyclooctanone at the tissue level.

Both *o*- and *p*-hydroxy derivatives were inactive when tested, even if administered ip rather than by the usual oral route. Since the compounds are phenols, it is conceivable that either the lipid solubility had been severely altered or that nonspecific binding to protein or other macromolecules was preventing delivery to the active site. Esterification of the para derivative with acetic acid **6** led to the recovery of antifertility activity without uterotropic or hypolipidemic (serum cholesterol and triglyceride) effect. Furthermore, there was no change in lipid, protein, or glycogen content of the liver with **6** which is contrary to the effects of the parent.[2] Esterification of the *o*-hydroxy derivative led to a compound too unstable to characterize or test reliably, although spectral evidence indicated that the product initially obtained was an ester. Preliminary screening showed activities similar to **6**. Those compounds which demonstrated hypocholesterolemic activity (**2**, **3**, and **4**) caused no deposition of lipids in the liver and **2**, **3**, and **6** caused no atrophy of the vesicular gland or vas deferens and epididymis contrary to the parent compound (Table IV).

Thus with compound **6** we feel that the antifertility activity has successfully been separated from the uterotropic and hypocholesterolemic activities. Furthermore, since compound **6** has no uterotropic activity then this compound cannot be inhibiting pregnancy at this dose due to its estrogenic characteristics and, thus, its mechanism of action must be elsewhere, a theory that we have previously advanced with regard to the antifertility activity of the 2,8-dibenzylcyclooctanone series.[1]

References

(1) I. H. Hall, G. L. Carlson, G. S. Abernethy, and C. Piantadosi, *J. Med. Chem.*, 17, 1253 (1974).
(2) C. Piantadosi, I. H. Hall, J. L. Irvine, and G. L. Carlson, *J. Med. Chem.*, 16, 770 (1973).
(3) G. L. Carlson, I. H. Hall, G. S. Abernethy, and C. Piantadosi, *J. Med. Chem.*, 17, 154 (1974).
(4) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970).
(5) B. Baggett, I. H. Hall, R. G. Boegli, K. H. Palmer, and M. E. Wall, *Fert. Steril.*, 21, 68 (1970).
(6) S. Shibko, P. Koivistoninen, C. A. Tratnyek, A. C. Newhall, and L. Friedman, *Anal. Biochem.*, 19, 514 (1967).
(7) D. M. Jerina and J. W. Daly, *Science*, 185, 573 (1974).
(8) M. B. Chenoweth and L. P. McCarty, *Pharmacol. Rev.*, 15, 673 (1973).
(9) N. P. Buu-Hoi, *Progr. Drug Res.*, 3, 9 (1961).

Homologs of Dopa, α-Methyldopa, and Dopamine as Potential Cardiovascular Drugs

M. Winn,* R. Rasmussen, F. Minard, J. Kyncl, and N. Plotnikoff

Division of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064. *Received September 23, 1974*

Starting from 3,4-dimethoxyphenacyl bromide, 2-amino-4-(3,4-dihydroxyphenyl)butyric acid (homodopa) was synthesized in six steps. 5-Hydroxyhomodopa was similarly prepared. α-Methylhomodopa was synthesized in four steps from zingerone [4-(4-hydroxy-3-methoxyphenyl)-2-butanone]. α-Methylhomodopa showed no antihypertensive activity in the genetic hypertensive rat. Homodopa did not potentiate the behavioral effect of Dopa or inhibit Dopa decarboxylase. Homodopamine, unlike dopamine, did not increase renal blood flow in the dog.

Recent interest in biogenic amines and amino acids has been highlighted by the introduction of Dopa and α-methyldopa as anti-Parkinson and antihypertensive agents, respectively. Many substituted Dopa and tyrosine analogs have been made, the most recent being tetralin and indan analogs.[1] However, no one has reported on homologs of Dopa or α-methyldopa. The closest example is the homolog of tyrosine reported by Evans and Walker.[2] The homolog of dopamine has only been mentioned once[3] in the literature with no method of preparation given, and it was stated that it had "⅔ of the pressor action of dopamine."

A mechanism of action of α-methyldopa was proposed by