Comparison of Biological Effects of N-Alkylated Congeners of β-Phenethylamine Derived from 2-Aminotetralin, 2-Aminoindan, and 6-Aminobenzocycloheptene

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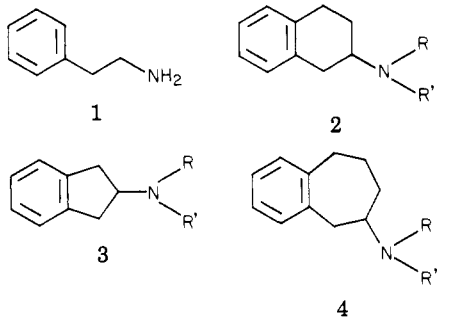
Three series of bicyclic, semirigid congeners of β-phenethylamine have been prepared for evaluation of the effect of ring size (and of concomitant conformational variation) on biological activity in a variety of assays for adrenergic and dopaminergic actions. Pharmacologic activity was associated with 2-aminotetralin and 2-aminoindan derivatives, but was not found with 6-aminobenzocycloheptene derivatives. Noteworthy is the ability of several aminotetralins and aminoindans to increase the hot-plate reaction time without eliciting dopaminergic effects. This action was not blocked by pretreatment with naloxone.

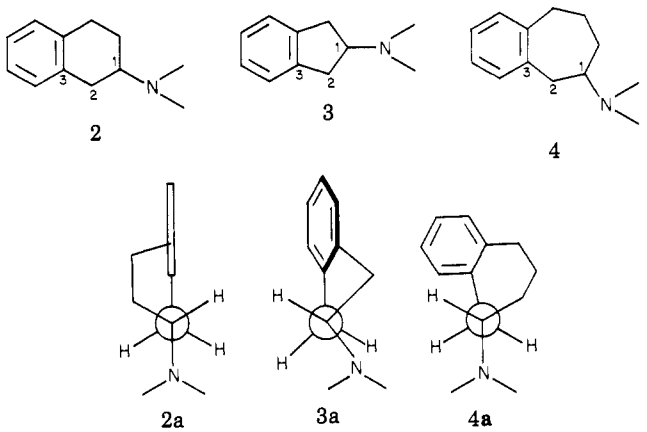
β-Phenethylamine (1) is an endogenous substance and



1 2 3 4

it possibly acts as a "cotransmitter" or as a "neuromodulator" for norepinephrine.[1] A variety of physiological effects have been ascribed to β-phenethylamine, especially involvement in brain function,[1] but these are largely speculative. The literature reveals a number of accounts of biological evaluation of bicyclic systems which are congeners of β-phenethylamine. Members of the 2-aminotetralin series (**2**) have been reported to exhibit pressor or hypotensive effects[2] and dopamine-like effects in several animal models.[3-5] A tertiary amine derivative of **2** (R = R′ = *n*-Pr) decreases heart rate and blood pressure, possibly by stimulation of α-adrenoceptors in the central nervous system.[6] Bovet and Virno[7] found that certain N-alkylated derivatives of **2** by peripheral administration increased motor activity in several animal species and also induced hyperthermia and hypertension or hypotension. However, bilateral injection into the nucleus accumbens of the rat of some symmetrically N,N-disubstituted derivatives of **2** produced neither hyperactivity nor stereotyped behavior.[8] Some derivatives of **2** were found by the Bovet group to be sympathomimetic in small doses and sympatholytic in large doses.[9] Certain N-alkylated derivatives of **2** demonstrated low activity in inhibition of apomorphine-induced behavioral effects in rodents.[10] 2-Aminoindan (**3**, R = R′ = H) has some bronchodilator activity[11,12] and exhibits marked analgesic action not antagonized by nalorphine.[13] Vejdelek et al.[14] described anorectic, antireserpine, and mydriatic effects in mice from high doses of 6-aminobenzocycloheptene (**4**, R = R′ = H). Some secondary and tertiary amine analogues of **4** were less active than the primary amine. Fuller and Molloy[15] compared β-phenethylamine (1) and the primary amine derivatives of **2**–**4** as in vitro inhibitors of norepinephrine *N*-methyltransferase. Activity was maximal with 2-aminotetralin (**2**), and the 2-aminoindan system (**3**) was also potent.

Chart I. Newman Projections (τ N-C_2-C_2-C_3) of Conformations of Cyclic β-Phenethylamine Congeners



2 3 4

2a 3a 4a

The purpose of the present study was to prepare series of N-alkylated **2**, **3**, and **4** and to observe effects of ring size (and concomitant changes in spatial disposition of the

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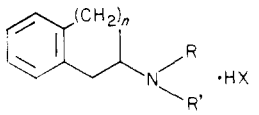
Table I. Cyclic Congeners of β-Phenethylamine



no.	n	R	R'	X	mp, °C	yield, %	method of prepn	formula	anal.
2a	2	H	H	Cl	242–244[a,b]	40	B		
2b	2	H	CH_3	Cl	184–186[c,d]	60	A		
2c	2	H	C_2H_5	Cl	228–230[a,e]	42	A		
2d	2	H	n-C_3H_7	Cl	249–250[a,f]	50	A		
2e	2	H	2-C_3H_7	Cl	235–240 dec[c]	36	A	$C_{13}H_{20}ClN$	w
2f	2	H	n-C_4H_9	Cl	219–220[a,g]	71	A		
2g	2	CH_3	CH_3	Cl	214–215[c,h]	48	A		
2h	2	C_2H_5	C_2H_5	Cl	149–150[i,j]	20	A		
2i	2	n-C_3H_7	n-C_3H_7	Cl	159–160[k,l]	41	C		
2j	2	n-C_4H_9	n-C_4H_9	Br	105–107[m]	52	C	$C_{18}H_{30}BrN$	C, H, N
2k	2	CH_3	2-C_3H_7	Cl	180–182[a]	50	D	$C_{14}H_{22}ClN$	C, H, N
3a	1	H	H	Cl	245 dec[n,o]	44	E		
3b	1	H	CH_3	Cl	230 dec[n,p]	41	H		
3c	1	H	C_2H_5	Cl	190–193[n,q]	69	A		
3d	1	H	n-C_3H_7	Cl	196–199[n]	74	A	$C_{12}H_{18}ClN$	C, H, N
3e	1	H	2-C_3H_7	Cl	252–254 dec[n]	99	F	$C_{12}H_{18}ClN$	C, H, N
3f	1	H	n-C_4H_9	Cl	210 dec[n,r]	69	A		
3g	1	CH_3	CH_3	Cl	212–215[n,s]	41	A		
3h	1	C_2H_5	C_2H_5	Cl	163–165[n]	61	A	$C_{13}H_{20}ClN$	C, H, N
3i	1	n-C_3H_7	n-C_3H_7	Cl	181–182[n]	38	A	$C_{15}H_{24}ClN$	C, H, N
3j	1	n-C_4H_9	n-C_4H_9	Cl	132–134[n]	99	A	$C_{17}H_{28}ClN$	C, H, N
3k	1	CH_3	2-C_3H_7	Cl	210–213 dec[n]	86	G	$C_{13}H_{20}ClN$	C, H, N
4a	3	H	H	Br	237–239[t,u]	68		$C_{11}H_{16}BrN$	C, H, N
4e	3	H	2-C_3H_7	Br	221–223[t]	84	J	$C_{14}H_{22}BrN$	C, H, N
4g	3	CH_3	CH_3	Br	223.5–225[u,v]	75	I	$C_{13}H_{20}BrN$	C, H, N
4i	3	n-C_3H_7	n-C_3H_7	Br	157–159[t]	79	C	$C_{17}H_{28}BrN$	C, H, N

[a] From n-BuOH-heptane. [b] Lit.[26] mp 242–243 °C [c] From 2-PrOH-heptane. [d] Lit.[27] mp 196–204 °C. [e] Lit.[26] mp 223.5 °C. [f] Lit.[28] mp 242–243 °C. [g] Lit.[28] mp 217 °C. [h] Lit.[28] mp 214–215 °C. [i] From MeOH-EtOAc. [j] Lit.[3] mp 145–147 °C. [k] From EtOH-Et_2O. [l] Lit.[3] mp 154–154.5 °C. [m] From n-BuOH-Et_2O. [n] From 2-PrOH-Et_2O. [o] Lit.[29] mp 240–241 °C. [p] Lit.[12] mp 210 °C dec. [q] Lit.[30] mp 187–189 °C. [r] Lit.[30] mp 202–204 °C. [s] Lit.[31] mp 205–206 °C. [t] From n-PrOH-Et_2O. [u] Lit.[14] reported the HCl salt. [v] From n-PrOH. [w] Mass spectrum m/e 189. M_r of free base 189.

β-phenethylamine moiety) and of nitrogen substituents on biological activity in a variety of animal assay models, for neurohormonal effects.

In the most stable conformer of **2** (Chart I), the amino group is attached to the ring by a pseudoequatorial bond, and the amino group and the benzene ring are antiperiplanar.[16] The benzene ring approaches coplanarity with the ethylamine side chain; the torsion angle τ for the train of atoms N–C_1–C_2–C_3 is approximately 170°.[17] NMR studies have led to the conclusion[18,19] that the cyclopentane ring of 2-substituted indan systems is nonplanar and that the substituent group adopts a pseudoequatorial position. Analysis of Dreiding models indicates that τ (N–C_1–C_2–C_3) for the 2-aminoindan system (**3**, Chart I) is 140–150°, as shown in **3a** (Chart I). With respect to the benzocycloheptene system (**4**), analysis of Dreiding models suggests that a stable conformer of **4** presents the seven-membered ring in a chair conformation with the amino group attached to the ring by an equatorial bond, in which case τ (N–C_1–C_2–C_3) is approximately 150° (antiplanar range), and the plane of the benzene ring is almost perpendicular to the plane described by N–C_1–C_2. Other seemingly less stable conformers of **4**, with the seven-membered ring in a boat form, present τ (N–C_1–C_2–C_3) in an antiplanar disposition with the benzene ring perpendicular to or coplanar with the plane N–C_1–C_2. Thus, **2**, **3**, and **4** represent a variety of conformational possibilities for the β-phenethylamine moiety, for evaluation of possible relationships between conformation and biological activity.

The target compounds (several of which are known in the literature) were prepared by standard methods. Spectral (IR, NMR) data on all intermediates and final compounds were consistent with the proposed structures (see Table I). The Experimental Section describes representative types of alkylation procedures employed for the compounds in Table I.

Pharmacology. Results and Discussion. Results obtained from various tests probably involving the central nervous system are presented in Table II and indicate that several of the N-alkylated congeners of β-phenethylamine inhibit exploratory activity in the mouse, induce circling behavior in the rat, and increase reaction time in the mouse in the hot-plate assay for analgesia. This latter effect was not blocked by prior administration of naloxone. Induction of circling behavior probably results from central dopaminergic effects, but a variety of mechanisms can underlie increased hot-plate latency and depressed motor behavior. Compounds with narcotic analgesic properties will increase hot-plate latency, but in analgesic doses morphine does not depress exploratory activity.[20] It seems unlikely that the

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(17) Giesecke, J., Ph.D. Thesis, Department of Medical Physics, Karolinska Institutet, Stockholm, Sweden, 1979, has found by X-ray study that the conformation of (+)-*N*,*N*-di-*n*-propyl-5-hydroxy-2-aminotetralin hydrochloride in the crystalline state is as shown in **2a** (Chart I).

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Table II. Effect of N-Alkylated Congeners of β-Phenethylamine on Hot-Plate Latency, Exploratory Activity, and Rotational Behavior

no.	hot-plate latency,[a] mean (s) ± SEM	exploratory act.,[b] mean % reduction ± SEM	rotational behavior,[c] mean turns/h ± SEM
2a	25.6 ± 2.8*[d]	55.1 ± 4.9*	104 ± 14 (i)
2b	16.0 ± 0.5	70.2 ± 12.8*	263 ± 129 (i + c)
2c	29.6 ± 4.8*	76.4 ± 0.9*	508 ± 48 (c)
2d	18.9 ± 4.8	79.0 ± 5.6*	804 ± 56 (c)
2e	27.0 ± 3.0*	NT[e]	NT
2f	17.6 ± 5.1	20.7 ± 0.8	7 ± 2
2g	24.2 ± 7.1*	88.1 ± 3.5*	53 ± 31
2h	33.5 ± 4.8*	73.4 ± 6.3*	501 ± 72 (c)
2i	29.2 ± 4.3	76.5 ± 13.8*	734 ± 106 (c)
2j	12.0 ± 1.4	0.8 ± 3.6	4 ± 2
2k	20.6 ± 4.7	79.7 ± 5.2*	16 ± 7
3a	35.8 ± 5.5*	76.0 ± 4.3*	27 ± 17
3b	28.6 ± 3.9*	80.3 ± 7.7*	6 ± 4
3c	22.1 ± 2.7	73.6 ± 3.2*	17 ± 10
3d	15.0 ± 1.9	21.9 ± 1.9	6 ± 2
3e	17.8 ± 2.5	2.8 ± 5.6	25 ± 14
3f	17.7 ± 1.8	7.1 ± 3.8	3 ± 1
3g	NT	NT	23 ± 13
3h	33.9 ± 3.6*	50.6 ± 3.4*	304 ± 27 (c)
3i	22.0 ± 1.9*	64.0 ± 6.1*	289 ± 69 (c)
3j	11.7 ± 1.4	8.4 ± 9.7	2 ± 2
3k	29.4 ± 5.6	64.0 ± 8.6*	15 ± 7
4a	NT	NT	inactive
4i	NT	NT	inactive[f]

[a] Control value for hot-plate reaction time was 12.7 ± 0.4 s (seconds ± SEM) ($N = 10$). [b] Control exploratory activity, which was used as 100% in calculating percent reduction, was 1860 ± 57 (counts/18 min ± SEM). [c] Direction of rotational behavior is indicated by i (ipsilateral) or c (contralateral). [d] Statistical significance is indicated by an asterisk for $p < 0.01$. [e] Not tested. [f] See ref 5.

present compounds produce opioid-like analgesia. Dopamine antagonists can depress exploratory activity, but in depressant doses haloperidol does not increase hot-plate latency.[20] A previous study with 5,8-dimethoxy-2-aminotetralins showed that compounds with central noradrenergic effects will increase hot-plate reaction time and will depress exploratory behavior.[20] In light of evidence that structures of the type investigated in the present study exert effects on noradrenergic processes in the brain,[6,21] the inhibition of exploratory activity and increases in hot-plate latency are probably related to this type of action. This hypothesis is strengthened by the observation that N-alkylated derivatives of **2** and **3** that increase hot-plate latency also tend to be effective as inhibitors of exploratory activity.

Contralateral rotational behavior was found to be associated with the presence of one or two ethyl or *n*-propyl substituents on the amine portion of the 2-aminotetralin structure: **2c**, **2d**, **2h**, and **2i** (Tables I and II). In the 2-aminoindan system, selected N,N-disubstitution appeared to contribute to dopamine-like activity. Monoethyl and mono-*n*-propyl derivatives **3c** and **3d** were inactive, whereas diethyl and di-*n*-propyl derivatives **3h** and **3i** were active. In the 6-aminobenzocycloheptene series, even di-*n*-propyl substitution (**4i**) failed to impart rotational behavior. Turning responses induced by the 2-aminotetralins **2a** and **2b** included ipsilateral circling, suggesting that these agents act, at least in part, indirectly. This contrasts with those agents (Table II) that stimulate only contralateral turning which is the result of direct dopaminergic action.

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Table III. Compounds Active in Inhibition of Reflex Induction of Pressor Responses in Cats and Dogs

no.	ED_{50}, μmol/kg (95% CL): inhibn of pressor response during carotid occlusion[a] in dogs	ED_{50}, μmol/kg (95% CL): inhibn of pressor response during central sciatic nerve stimulation[b] in cats
2c	0.52 (0.29-1.1)	2.3 (1.5-5.2)
2d	3.38 (1.3-14.2)	0.9 (0.4-1.4)
2g	inactive	0.16 (0.07-0.9)
2h	NT[c]	0.35 (0.12-0.65)
2i	0.22 (0.15-0.33)	0.09 (0.03-0.20)
3h	NT[c]	1.14 (0.48-9.8)
3i	NT[c]	0.25 (0.15-2.6)

[a] The values are the calculated amounts needed to produce a 50% inhibition of the pressor responses induced by bilateral carotid occlusion. [b] The right sciatic nerve was sectioned and the central stump stimulated at a frequency of 4 Hz, pulse duration of 5 ms, and supramaximal voltage. The duration of stimulation was 30 s. The values shown are calculated amounts required to inhibit the pressor response by 50%. At least six animals were used for each compound. [c] Not tested.

Derivatives that showed activity as inducers of rotational behavior also appeared to be effective in the hot-plate and exploratory activity tests. This may result because these agents also affect noradrenergic systems in the brain or because of an involvement of dopaminergic systems in these latter two tests. *N*-Ethyl and *N*-*n*-propyl secondary amine derivatives of the 2-aminotetralin system were active. However, a number of N-alkylated congeners (**2g**, **2k**, **3a**, **3b**, **3c**, **3k**) were able to increase hot-plate reaction time and to inhibit exploratory activity without eliciting dopaminergic effects. These compounds may have a greater selectivity for central noradrenergic mechanisms.

The active compounds' ability to inhibit reflex activation of the sympathetic nervous system is shown in Table III. In general, activity was found, in selected derivatives of aminotetralins and aminoindans, with the dialkyl derivatives. None of the present compounds inhibited postganglionic cardioaccelerator nerve stimulation in the cat. In the 6-aminobenzocycloheptene series, the *N*-isopropyl and *N*,*N*-dimethyl derivatives (**4e** and **4g**) were inactive as inhibitors in the dog carotid occlusion assay at 0.5 mg/kg.

While it does not seem possible to draw extensive or detailed structure–activity conclusions on the basis of these biological data, it may be stated that, in general, substitution on the amino nitrogen of the five- or six-membered ring systems by an ethyl or *n*-propyl group(s) results in enhancement of dopamine-like and/or adrenergic effects, consistent with previous observations[4,16] in an analogous series of compounds. In addition, the inactivity of all of the benzocycloheptene compounds tested leads to the conclusion that the β-phenethylamine conformations permitted in the benzocycloheptene ring system are not appropriate for triggering the biological responses (direct or indirect) represented by the assays listed in Tables II and III. Thus, it may be concluded that β-phenethylamine conformers approaching the antiperiplanar disposition represented by **2a** and **3a** (Chart I) represent optimal stereochemical situations for the biological activities described. Other factors such as metabolism, distribution, and excretion may modify the biological activity of various analogues. Lipophilicity may enhance activity as the size of *N*-alkyl substituents increases, but some other factor(s) must be invoked to explain the decreased activities of the *N*,*N*-dibutylindan (**3j**) and *N*,*N*-dibutyltetralin (**2j**) systems (Table II).

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Hot-Plate Test. Male Swiss-Webster mice (Biolabs) weighing 20–30 g were tested using the hot-plate method of Eddy et al.[22] Plate temperature was 55 ± 0.5 °C; jumping or licking of paws was used as the end point. Test compounds were administered ip 10 min prior to testing. Compounds were screened at a single dose of 10 mg/kg, and 10 animals were used for each drug. Control animals received saline solution. Animals were exposed only once to the hot plate. On each day of testing, 10 control animals were included in the test procedure. The assay was also performed on animals which had been administered naloxone (5 mg/kg ip) prior to administration of the test compounds. The significance of the drug effect relative to the control response was determined using a grouped Student's t test.

Inhibition of Exploratory Activity. Male Swiss-Webster mice (Biolabs) weighing 20–30 g were housed in groups of nine and were allowed to become accustomed to their surroundings for several days before being used. The activity of groups of three mice was monitored and recorded using a Columbus Instruments Model S selective activity meter as previously described.[20] The test compounds (10 mg/kg) were given ip immediately prior to time zero when the mice were introduced into the cage. Control animals received H_2O in place of the experimental compound, and activity for control animals was determined on each test day. Each compound was screened in three groups of three mice (N = 3). Counts of activity were recorded in 5-min blocks for 1 h. Responses during the 18-min period beginning 6 min after time zero were summed for statistical analysis. The significance of the drug-induced inhibition of exploratory behavior was determined using a one-way analysis of variance by Scheffe's method of comparison.[23]

Rat Rotational Behavior. Male Sprague–Dawley rats (Biolabs) weighing 200–300 g were lesioned unilaterally in the substantia nigra by application of 6-hydroxydopamine as previously described.[5] Each compound was given sc in a single dose of 10 mg/kg to four animals at the start of the 1-h recording period. Turning responses were recorded automatically and expressed as turns/hour. Mean total turns/hour greater than 100 were regarded as a substantial circling response.

Carotid Occlusion in Dogs. Dogs weighing 8–15 kg were anesthetized iv with thiopental sodium (15 mg/kg), followed by barbital sodium (200 mg/kg). The femoral arterial pressure was monitored using a Statham P23AA transducer and a Beckman R-511 recorder. The pressor responses were induced by bilateral occlusion of the common carotid arteries for 45 s. At least 15 min elapsed before repeating the occlusion. The compounds were administered iv into the femoral vein. The responses were monitored for at least 1 h, and after returning to control levels the dose of the compound was altered by 0.48 log interval and administered to the animal. At least five dogs were used to evaluate the activity of each compound.

Central Sciatic Nerve Stimulation in Cats. Cats were anesthetized by injecting pentobarbital sodium (30 mg/kg) into the thorax. The left femoral arterial blood pressure was measured as described above. The right sciatic nerve was sectioned and the central portion was stimulated using a Grass (S-5) stimulator with isolation unit. The stimulus was applied for 30 s. The frequency was 4 Hz, pulse duration of 5 ms and supramaximal voltage. These parameters will produce an arterial response (pressor) of 30–60 mmHg. The experimental compounds were administered iv, and responses, if any, were followed for 1 h or until control values were reestablished. The next dosage of the compound was varied by 0.48 log unit. At least six animals were used to assay each compound.

(22) Eddy, N. B.; Touchberry, C. F.; Lieberman, J. E. *J. Pharmacol. Exp. Ther.* **1950**, *98*, 121.

(23) Afifi, A. A.; Azen, S. D. "Statistical Analysis, A Computer Oriented Approach"; Academic Press: New York, 1972; p 74.

Method A. Reductive Amination of a Cyclic Ketone with $NaCNBH_3$. 2-(Methylamino)tetralin Hydrochloride (2b). A mixture of 2.68 g (0.04 mol) of methylamine hydrochloride, 0.992 g (0.0068 mol) of 2-tetralone, and 0.5 g (0.068 mol) of $NaCNBH_3$ in 20 mL of anhydrous MeOH was stirred at room temperature for 20 h. The reaction mixture was treated with 10 mL of concentrated HCl, and then volatiles were removed under reduced pressure. The light orange solid residue was taken up in a convenient volume of H_2O, and this solution was extracted thrice with Et_2O. Excess NaOH was added to the aqueous solution, and the resulting two-phase liquid was extracted repeatedly with Et_2O. The pooled extracts were dried (Na_2SO_4), filtered, and treated with ethereal HCl to afford a heavy, bright orange solid. This was recrystallized several times from 2-PrOH–heptane (charcoal). See Table I.

Method B. Reductive Amination of a Cyclic Ketone with Ammonium Acetate and $NaCNBH_3$. 2-Aminotetralin Hydrochloride (2a). A mixture of 3.1 g (0.04 mol) of ammonium acetate (dried by refluxing over benzene in a Dean–Stark apparatus), 0.992 g (0.0068 mol) of 2-tetralone, and 0.5 g (0.008 mol) of $NaCNBH_3$ in 30 mL of anhydrous MeOH was stirred at room temperature for 72 h. The deep brown reaction mixture was treated with 10 mL of concentrated HCl, and then volatiles were removed under reduced pressure. The brown solid residue was extracted with H_2O; a significant portion of this material did not dissolve. The aqueous extract was filtered and extracted thrice with Et_2O. The aqueous solution was treated with excess NaOH, and the resulting emulsion was extracted repeatedly with Et_2O. The pooled ethereal extracts were dried (Na_2SO_4) and treated with ethereal HCl to afford a dirty brown solid, which was recrystallized. See Table I.

Method C. Reductive Alkylation of a Primary Amine with a Carboxylic Acid and $NaBH_4$. 2-(Di-*n*-propylamino)tetralin Hydrochloride (2i). $NaBH_4$ (0.95 g, 0.025 mol) was added in small portions to a stirred solution of 6.1 g (0.083 mol) of propionic acid in 15 mL of Na-dried benzene, such that the temperature of the reaction mixture did not exceed 15 °C. When all of the $NaBH_4$ was added, the clear, water-white solution was stirred at room temperature for 45 min. A solution of 0.74 g (0.005 mol) of 2-aminotetralin in 20 mL of dry benzene was added in one portion, and the resulting mixture was heated under reflux for 5.5 h. The cooled reaction mixture was shaken with 500 mL of 2 N KOH in divided portions. The pooled KOH washings were extracted with benzene. The combined benzene solutions were dried (Na_2SO_4) and filtered, and volatiles were removed under reduced pressure. The amber syrupy residue was treated with 1 mL of phenyl isocyanate, and this mixture was warmed on a steam bath for 5 min. MeOH (10 mL) was then added, the resulting mixture was warmed on a steam bath for 10 min, and then volatiles were removed under reduced pressure. The residue was taken up in Et_2O, and this solution was extracted several times with 2 N HCl. The pooled HCl extracts were washed twice with Et_2O, and then the aqueous phase was basified with KOH. The resulting emulsion was extracted repeatedly with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and filtered, and the filtrate was treated with ethereal HCl to afford a heavy syrup, which was decolorized with charcoal and crystallized. See Table I.

Method D. Reductive Methylation of a Secondary Amine with Formaldehyde and $NaCNBH_3$. 2-(*N*-Methyl-*N*-isopropylamino)tetralin Hydrochloride (2k). A mixture of 0.25 g (0.0011 mol) of 2-(isopropylamino)tetralin hydrochloride (**2e**), 1.5 mL of 37% aqueous formaldehyde solution, 0.095 g (0.0015 mol) of $NaCNBH_3$, and 10 mL of MeOH was stirred at room temperature for 36 h. From time to time, 5 M methanolic HCl was added to bring the reaction mixture to pH 5–6 (pH paper). Then, 10 mL of MeOH, 2 mL of 37% aqueous formaldehyde, and 0.1 g of $NaBH_3$ were added, stirring at room temperature was continued for an additional 3 h, and 5 M methanolic HCl was added from time to time to maintain the pH at 5–6. Concentrated HCl (5 mL) was added to quench the reaction. Volatiles were removed from the reaction mixture under reduced pressure. The white solid residue was taken up in H_2O, and this solution was washed with Et_2O. It was then treated with excess KOH, and the resulting emulsion was extracted repeatedly with Et_2O. The pooled ethereal extracts were washed with H_2O and the Et_2O was

removed. The white solid residue was treated with phenyl isocyanate and then with MeOH as described under method C. The tertiary amine product, freed from secondary amine starting material, was converted to its HCl salt, and this was recrystallized. See Table I.

2-Indanone Oxime (5). The procedure of Levin et al.[12] was used. To a solution of 1.3 g (0.01 mol) of 2-indanone in 6 mL of pyridine was added, with cooling and agitation, 0.7 g (0.01 mol) of hydroxylamine hydrochloride in 2 mL of 95% EtOH. The resulting mixture was stirred at room temperature for 36 h, and then it was poured into 40 mL of cold H_2O. The oxime separated as a solid, which was collected on a filter and washed with cold H_2O to give 1.2 g (82%) of colorless crystals, mp 150–153 °C dec, lit.[24] mp 155 °C. This material was used without further purification.

Method E. Catalytic Reduction of an Oxime. 2-Aminoindan Hydrochloride (3a). A mixture of 1.2 g (0.008 mol) of **5**, 0.120 g of 10% Pd/C, and 0.012 g of $PdCl_2$ in 70 mL of 99% EtOH containing 2.7 g (0.07 mol) of HCl was hydrogenated in a Parr shaker apparatus at an initial pressure of 50 psig. H_2 uptake was complete in 8 h. The reduction mixture was filtered, and volatiles were removed from the filtrate under reduced pressure to leave 1.35 g of a light brown solid, which was recrystallized several times. See Table I.

Method F. Reductive Alkylation of a Primary Amine with a Ketone. 2-(Isopropylamino)indan Hydrochloride (3e). A mixture of 1.0 g (0.0075 mol) of 2-aminioindan, 1.8 g (0.032 mol) of acetone, and 0.15 g of PtO_2 in 80 mL of absolute EtOH was hydrogenated in a Parr shaker apparatus at an initial pressure of 50 psig for 2 h. The reduction mixture was filtered and volatiles were removed from the filtrate under reduced pressure. The clear oily residue was converted to its HCl salt, which was recrystallized. See Table I.

Method G. Reductive Methylation of a Secondary Amine with Formaldehyde under Catalytic Reduction Conditions. 2-(*N*-Methyl-*N*-isopropylamino)indan Hydrochloride (3k). A mixture of 1.3 g (0.0074 mol) of 2-(isopropylamino)indan (**3e**, free base), 3 mL of 37% aqueous formaldehyde, and 0.13 g of 10% Pd/C in 85 mL of anhydrous EtOH was hydrogenated in a Parr shaker apparatus at an initial pressure of 50 psig. The reduction was complete in 2 h. The reduction mixture was filtered and volatiles were removed from the filtrate under reduced pressure to leave a yellow oil, which was converted to its HCl salt and crystallized. See Table I.

Method H. Reductive Amination of a Cyclic Ketone with $NaBH_4$. 2-(Methylamino)indan Hydrochloride (3b). To 1.3 g (0.01 mol) of 2-indanone in 10 mL of MeOH was added, with stirring, 3.8 mL of 40% aqueous methylamine solution (0.05 mol). To the resulting dark brown solution, 0.37 g (0.01 mol) of $NaBH_4$ was added slowly, and stirring was continued for 1 h. K_2CO_3 (5 g) was added, and volatiles were removed under reduced pressure. The residue was treated with H_2O and the resulting mixture was extracted with Et_2O. The ethereal extract was dried ($MgSO_4$), filtered, and treated with ethereal HCl. The resulting HCl salt was taken up in H_2O, and this solution was decolorized with charcoal. H_2O was then removed and the residue was recrystallized. See Table I.

6-Oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (6). To a solution of 1.02 g (0.0443 g-atom) of Na in 20 mL of anhydrous EtOH, cooled to 0 °C under N_2, was added dropwise and with stirring a solution of 5.91 g (0.0369 mol) of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (Aldrich) and 4.18 g (0.0406 mol) of freshly prepared *n*-butyl nitrite[25] in 25 mL of anhydrous Et_2O. The dark reaction mixture was stirred and allowed to come to room temperature overnight, and then 20 mL of Et_2O and 50 mL of H_2O were added. The aqueous layer was separated and was made acidic with 1 M HCl. A dark brown oil separated which, upon scratching with a stirring rod, was induced to crystallize to a tan solid: yield 5.42 g (78%). This material could not be recrystallized without extensive decomposition, and it was employed in the subsequent step without purification.

6-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (4a). A mixture of 2.0 g (0.0105 mol) of **6** and 0.2 g of 10% Pd/C in 150 mL of glacial AcOH was hydrogenated at room temperature at an initial pressure of 50 psig. After 2 equiv of H_2 was absorbed, 2 mL of concentrated $HClO_4$ (70%) was added and hydrogenation was continued at 70 °C at an initial pressure of 52 psig. When an additional 2 equiv of H_2 was absorbed, the reduction mixture was cooled and 2.8 g of potassium acetate in 15 mL of glacial AcOH was added. The resulting mixture was filtered. To the pale red filtrate was added 4 mL of concentrated HCl, and volatiles were removed under reduced pressure. The oily residue was taken up in H_2O, this solution was washed with Et_2O and then basified with 1 M NaOH, and the resulting emulsion was extracted several times with Et_2O. The pooled extracts were treated with 1.5 mL of concentrated HBr, and the volatiles were removed from this mixture under reduced pressure. The semisolid residue was recrystallized. See Table I.

Method I. Reductive Methylation of a Primary Amine with Formaldehyde under Catalytic Hydrogenation Conditions. 6-(Dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (4g). A mixture of 0.25 g (0.001 mol) of **4a**, 10 mL of 37% aqueous formaldehyde, and 0.03 g of 10% Pd/C in 25 mL of EtOH was hydrogenated at room temperature at an initial pressure of 50 psig. When H_2 uptake ceased, the reduction mixture was filtered, volatiles were removed from the filtrate under reduced pressure, and the residue was recrystallized. See Table I.

Method J. Reductive Alkylation of a Primary Amine with a Ketone and $NaCNBH_3$. 6-(Isopropylamino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (4e). To a stirred solution of 0.3 g (0.00122 mol) of **4a** in 12 mL of dry acetone and 10 mL of anhydrous EtOH was added dropwise a solution of 0.096 g (0.00152 mol) of $NaCNBH_3$ in 0.3 mL of dioxane and 10 mL of absolute EtOH. The reaction mixture was stirred at 0–10 °C for 4 h and then at 25 °C for 2 h. The reaction mixture was brought to pH 2 (pH paper) with 1 M HCl, and then volatiles were removed under reduced pressure. The residue was made basic with 1 M NaOH, and the resulting mixture was extracted repeatedly with Et_2O. The pooled ethereal extracts were treated with 0.3 mL of 48% HBr in 0.7 mL of EtOH. The resulting precipitate was recrystallized. See Table I.

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