Conformationally Restricted and Conformationally Defined Tyramine Analogues as Inhibitors of Phenylethanolamine *N*-Methyltransferase[1a]

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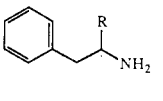
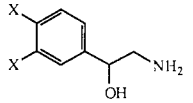
In a search for a selective inhibitor for the epinephrine synthesizing enzyme phenylethanolamine *N*-methyltransferase (PNMT; EC 2.1.1.28), phenolic 2-aminotetralins (**12–15** as conformationally restricted analogues of tyramine) and phenolic benzobicyclo[3.2.1]octylamines (**22–24** as conformationally defined analogues of tyramine) were used to gain information about the binding interactions of the catecholic hydroxyl groups in the natural substrate norepinephrine at the active site of PNMT. In addition, these analogues provided information about the effects of conformational flexibility on active-site interaction of the aminoethyl side chain in phenolic phenylethylamines that may aid in learning the manner in which norepinephrine binds at the active site of PNMT. Analogues **22–24** were synthesized by a nine-step sequence, in which a Friedel–Crafts type intramolecular cyclization was the key step in the construction of the benzobicyclo[3.2.1]octane skeleton. *p*-Tyramine (**10**, K_i = 294 μM) was more potent than phenylethylamine (**1**, K_i = 854 μM) but *m*-tyramine (**9**, K_i = 1250 μM) was less potent than phenylethylamine as an inhibitor of PNMT. Similarly, in the conformationally restricted and conformationally defined tyramine analogues (**12–15** and **22–24**, respectively), the analogues with the *p*-tyramine moiety (**14**, K_i = 4.7 μM; **23**, K_i = 111 μM) bind to PNMT better than do the corresponding unsubstituted compounds (**16**, K_i = 6.8 μM; **25**, K_i = 206 μM) while the analogues with the *m*-tyramine moiety (**13**, **15**, **22**, and **24**) have a lower binding affinity than do **16** and **25**. The greatly enhanced activity of the phenolic 2-aminotetralins (**12–15**) compared with *m*- and *p*-tyramine (**9** and **10**, respectively) is likely due to the restriction of the side-chain conformation. The conformationally defined analogues **22–24** were less active than the comformationally restricted ones, **12–15**, although the low-energy half-chair conformation of 2-aminotetralin is defined in **22–24**. The reduced activity of **22–24** compared with the activity of **12–15** is probably due to the steric hindrance from the extra bridging atoms in binding to PNMT. The interaction of the *p*-hydroxyl group of the tyramine moiety may involve hydrogen bonding since the corrresponding methyl ethers show a greatly reduced affinity for the active site of PNMT (K_i = 34 and 389 μM for methoxy analogues **28** and **35**, compared to K_i = 4.7 and 111 μM for the corresponding phenolic analogues **14** and **23**).

Phenylethanolamine *N*-methyltransferase (PNMT; EC 2.1.1.28) is an enzyme responsible for the methylation of norepinephrine to form epinephrine.[2] Two major classes of PNMT ligands are phenylethylamine analogues [usually competitive inhibitors; e.g. phenylethylamine (**1**) and amphetamine (**2**)] and phenylethanolamine analogues [usually substrates; e.g. phenylethanolamine (**3**) and norepinephrine (**4**)]. Although it is the natural substrate for



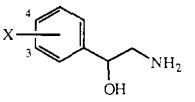
1 R = H
2 R = CH_3



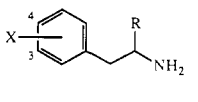
3 X = H
4 X = OH

the enzyme, norepinephrine was an outlier in a quantitative structure–activity relationship (QSAR) study with a series of phenylethanolamine substrates.[3] Whether norepinephrine binds in the same orientation at the active site of PNMT as do other phenylethanolamine substrates remains to be established.

A few compounds containing the catechol moiety have been studied. However, this approach was hindered by the observation that the catechol moiety was not stable under the assay conditions required.[4] Alternatively, the interaction of the hydroxyl groups with the enzyme has been studied with phenolic phenylethanolamines (octopamines; e.g. **5** and **6**)[5] as PNMT substrates and phenolic amphetamines (**7** and **8**)[6] as PNMT inhibitors. In both cases, the *p*-hydroxyl analogues (**6** and **8**) have the better affinity for the enzyme than the *m*-hydroxyl analogues (**5** and **7**).

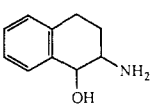


5 X = 3-OH
6 X = 4-OH



7 R = CH_3, X = 3-OH
8 R = CH_3, X = 4-OH
9 R = H, X = 3-OH
10 R = H, X = 4-OH

Previous studies have shown that the conformationally restricted 2-aminotetralin (**16**) was more potent than either phenylethylamine or amphetamine[7] and that the conformationally restricted *cis*- and *trans*-2-amino-1-tetralol (**11**) had higher affinity to PNMT than corresponding flexible molecules (i.e. phenylethanolamine, norephedrine, and norpseudoephedrine).[8] To further study the role of the hydroxyl group of phenolic ligands in the interaction with PNMT and the effects of conformational flexibility, we report here the results for the phenolic 2-aminotetralins **12–15**, in which the conformations for the aminoethyl side chain of the tyramine moiety are restricted.



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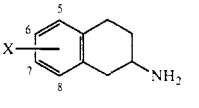

12 X = 8-OH
13 X = 7-OH
14 X = 6-OH
15 X = 5-OH
16 X = H

We recently reported[9] the inhibitory activity for PNMT of four tyramine analogues **17–20** with the benzobicyclo[2.2.1]heptane skeleton, in which a half-boat 2-aminotetralin moiety exists. We now report the results with PNMT for three conformationally defined tyramine ana-

(1) (a) Paper 15 in our series "Conformationally Defined Adrenergic Agents"; for paper 14, see ref 24. (b) Recipient of the 1988 Robert Irsay–Norman Dahle Award in Medicinal Chemistry at the University of Kansas.
(2) Fuller, R. W. *Annu. Rev. Pharmacol. Toxicol.* **1982**, *22*, 31.
(3) Fuller, R. W.; Marsh, M. M. *J. Med. Chem.* **1972**, *15*, 1068.
(4) Grunewald, G. L.; Pleiss, M. A.; Rafferty, M. F. *Life Sci.* **1982**, *31*, 993.
(5) Fuller, R. W.; Hemrick-Luecke, S. K.; Midgley, J. M. *Res. Commun. Chem. Pathol. Pharmacol.* **1981**, *33*, 207.
(6) Fuller, R. W.; Mills, J.; Marsh, M. M. *J. Med. Chem.* **1971**, *14*, 322.
(7) Fuller, R. W.; Molloy, B. B. *Biochem. Pharmacol.* **1977**, *26*, 446.
(8) (a) Grunewald, G. L.; Ye, Q. *J. Med. Chem.* **1988**, *31*, 1984. (b) Grunewald, G. L.; Ye, Q.; Kieffer, L.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 169.
(9) Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* **1986**, *29*, 1972.

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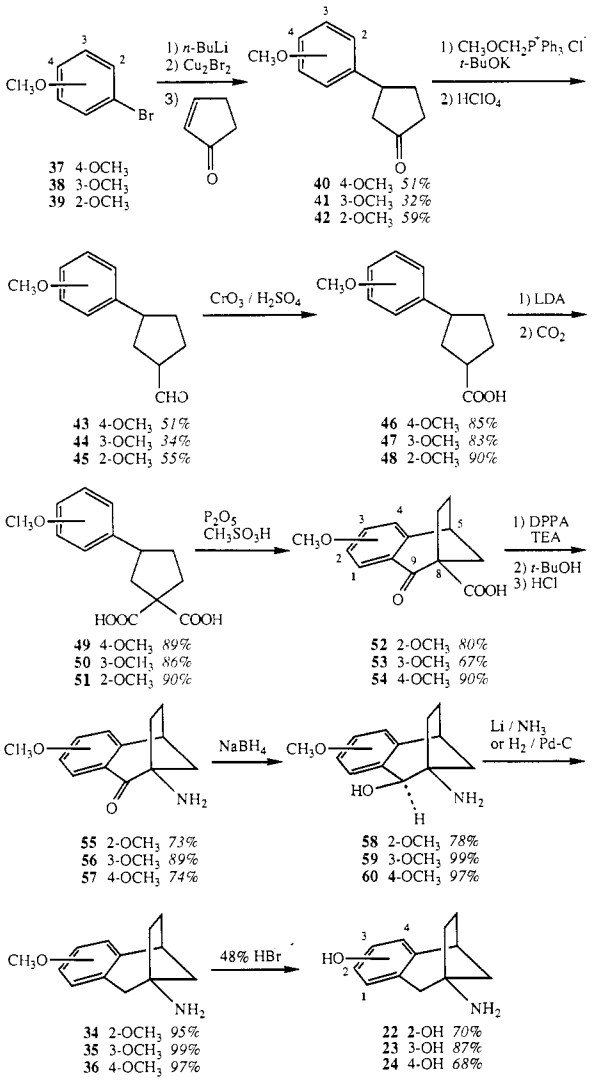
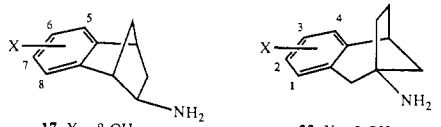
Scheme I

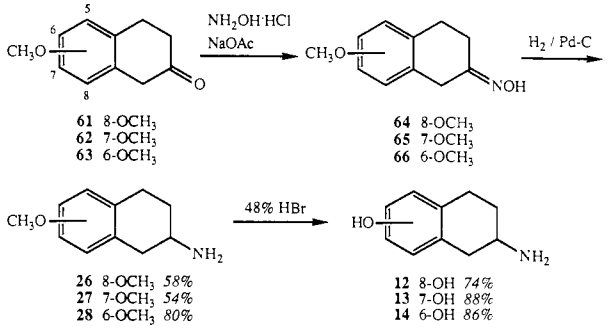


logues **22–24** containing the benzobicyclo[3.2.1]octane skeleton, in which the 2-aminotetralin moiety is defined in a half-chair conformation. The positional preference for the phenolic hydroxyl group and the effects of conformational flexibility for the side chain of tyramine in several series of tyramine analogues in the interaction with PNMT are discussed.



Chemistry. The synthesis of the conformationally defined tyramine analogues **22–24** is shown in Scheme I. The 1,4-addition of the lithium organocuprate prepared from one of the three isomeric bromoanisoles (**37–39**) to 2-cyclopentenone generated the ketones **40–42**. A one-carbon unit was introduced with a Wittig reaction using (methoxymethyl)triphenylphosphonium chloride; after hydrolysis of the vinyl ether intermediate with perchloric acid, the aldehydes **43–45** were obtained. Oxidation with Jones reagent[10] gave the acids **46–48**. With 2 equiv of

Scheme II



lithium diisopropylamide (LDA) and carbon dioxide, the second carboxyl group was introduced into **46–48**. One of the carboxyl groups in the diacids **49–51** is cis to the aromatic ring so that a Friedel–Crafts type intramolecular cyclization was accomplished with phosphorus pentoxide/methanesulfonic acid (prepared according to the method of Eaton et al.[11]), which generated the acids **52–54** with the benzobicyclo[3.2.1]octane skeleton.

The bridgehead carboxyl group in **52–54** was converted to an amine by a modified Curtius rearrangement.[12] After treatment of **52–54** with diphenyl phosphorazidate (DPPA) and *tert*-butyl alcohol, the mixture was hydrolyzed to the amines **55–57** with hydrochloric acid without separating the carbamate intermediate.

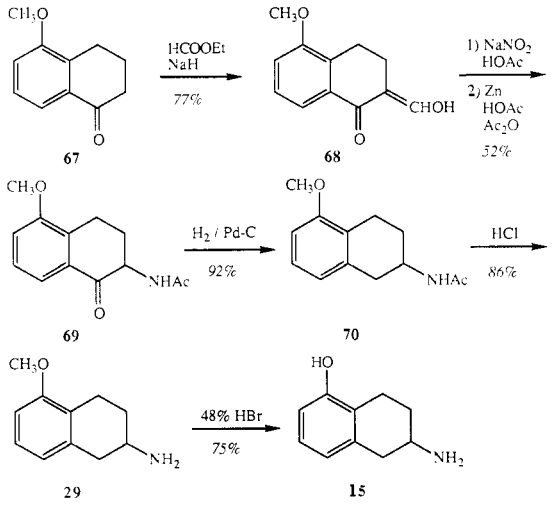
Amines **34–36** were obtained by reductive removal of the carbonyl oxygen in two steps. The reduction with sodium borohydride of the amino ketones **55–57** gave the endo alcohols **58–60** as the major products (>90%). These results from the sodium borohydride reduction indicated that the carbonyl group is much more accessible by hydride from the methano bridge side than from the side of the ethano bridge in this ring system. Similar stereochemical results were observed with other compounds in this ring system.[13] Removal of the benzylic hydroxyl group from **58** and **60** was accomplished by lithium/ammonia reduction according to the procedure of Small et al.[14] However, the 3-methoxy isomer **59** was resistant to this reduction. This is in agreement with previous studies[15] that *m*-methoxybenzaldehyde or *m*-methoxyacetophenone underwent the lithium/ammonia reduction while, presumably because of the electronic effects of the methoxy substituent, the *p*-methoxy isomers were resistant to reduction under these conditions. Reductive removal of the benzylic hydroxyl group from **59** was accomplished by catalytic hydrogenolysis.

Cleavage of the methyl ether in the amines **34–36** was performed with 48% hydrobromic acid. The conformationally defined tyramine analogues **22–24** were obtained as hydrobromide salts.

The conformationally restricted tyramine analogues containing the 2-aminotetralin moiety (**12–15**) were synthesized by modification of literature routes[16,17] as shown

(10) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.
(11) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.
(12) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
(13) Grunewald, G. L.; Ye, Q. *J. Org. Chem.* **1988**, *53*, 4021.
(14) Small, G. H.; Minnella, A. E.; Hall, S. S. *J. Org. Chem.* **1975**, *40*, 3151.
(15) Birch, A. J. *J. Proc. R. Soc. N.S.W.* **1950**, *83*, 245.
(16) Ames, D. E.; Evans, D.; Grey, T. F.; Islip, P. J.; Richards, K. E. *J. Chem. Soc.* **1965**, 2636.
(17) (a) Thrift, R. I. *J. Chem. Soc. C* **1967**, 288. (b) McDermed, J. D.; McKenzie, G. M.; Philips, A. P. *J. Med. Chem.* **1975**, *18*, 362.

Scheme III



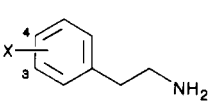
in Schemes II and III. The oximes **64–66** were produced from 2-tetralones **61–63** and reduced to the amines **26–28** by catalytic hydrogenation (Scheme II). Because 5-methoxy-2-tetralone was not commercially available, the 2-amino-5-methoxytetralin (**29**) was made by the sequence shown in Scheme III. Formylation at the 2-position of 5-methoxy-1-tetralone (**67**) introduced the hydroxymethylene group. The oxime intermediate was obtained by treatment of **68** with sodium nitrite and acetic acid.[18] The oxime, without purification, was treated with zinc in acetic acid and acetic anhydride, to give **69**. Hydrogenolysis followed by hydrolysis gave the amine **29**. Methyl ethers **26–29** were cleaved with 48% hydrobromic acid.

Biochemistry. The racemic conformationally restricted tyramine analogues **12–15** and the racemic conformationally defined tyramine analogues **22–24** were evaluated as their hydrobromide salts. The methoxy-substituted intermediates **26–29** and **34–36** were studied as their hydrochloride salts. In vitro activities as both PNMT substrates and PNMT inhibitors were assessed by use of a standard radiochemical assay that has been previously described for substrates[19] and inhibitors.[20] Bovine adrenal PNMT was used,[21] which had been purified according to the method of Connett and Kirshner[22] through the isoelectric precipitation step. Inhibition constants in this investigation were determined by using at least three different concentrations of the inhibitor with phenylethanolamine as the variable substrate. The mode of inhibition was ascertained by inspection of the $1/V$ vs $1/S$ plot of the data.

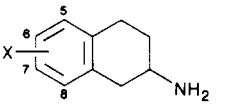
Results and Discussion

The results from in vitro assays for activities as PNMT substrates or inhibitors for the conformationally restricted tyramine analogues **12–15** and the conformationally defined tyramine analogues **22–24**, along with those from corresponding methoxy derivatives **26–29** and **34–36**, are summarized in Tables I and II. For comparison, the

Table I. In Vitro Activity as Inhibitors of PNMT



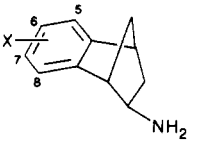
1, 9, 10



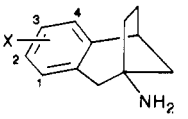
12–16, 26–29

compd	X	K_i, μM
9	3-OH	1250 ± 76
10	4-OH	294 ± 19
1	H	854 ± 55
12	8-OH	39 ± 2
13	7-OH	76 ± 4
14	6-OH	4.7 ± 0.3
15	5-OH	21 ± 3
16	H	6.8 ± 0.2
26	8-OCH_3	144 ± 8
27	7-OCH_3	228 ± 12
28	6-OCH_3	34 ± 1
29	5-OCH_3	157 ± 9

Table II. In Vitro Activity as Inhibitors of PNMT



17–21, 30–33



22–25, 33–36

compd	X	K_i, μM
17	8-OH	>3000[a]
18	7-OH	1114 ± 118[a]
19	6-OH	304 ± 15[a]
20	5-OH	>10000[a]
21	H	479 ± 27[b]
30	8-OCH_3	>2000[c]
31	7-OCH_3	>2000[c]
32	6-OCH_3	1259 ± 123[c]
33	5-OCH_3	>2000[c]
22	2-OH	1270 ± 60
23	3-OH	111 ± 5
24	4-OH	3470 ± 250
25	H	206 ± 10[d]
34	2-OCH_3	1410 ± 51
35	3-OCH_3	389 ± 19
36	4-OCH_3	8420 ± 481

[a] Taken from ref 9. [b] Taken from ref 20. [c] Taken from ref 23. [d] Taken from ref 24.

results from *m*- and *p*-tyramine (**9** and **10**), phenylethylamine (**1**), and 2-aminotetralin (**16**) are included in Table I; the results, which have been reported earlier, for the conformationally defined compounds **17–21** and **30–33**,[9,23] as well as compound **25**,[24] are included in Table II. A value for norepinephrine is not listed; because of the high water solubility of [^{3}H]epinephrine, the radiochemical assay[19,20] with isoamyl alcohol/toluene extraction could not be used for (−)-norepinephrine. A Reineckate salt assay,[4] in which unreacted [^{3}H]-*S*-adenosyl-L-methionine is precipitated and the supernatant is counted, was used to obtain comparison values for (±)-phenylethanolamine and (−)-norepinephrine. It was found that (−)-norepinephrine (K_m = 7.7 ± 3.2 μM, V_{max} = 0.22 ± 0.05, 100 × V_{max}/K_m = 2.9) is a better substrate than (±)-phenylethanolamine (K_m = 239 ± 113 μM, V_{max} = 1.5 ± 0.1, 100 × V_{max}/K_m = 0.63).

Tyramines (**9** and **10**) were not PNMT substrates, nor were the tyramine analogues **12–15**, **17–20**, and **22–24**.

(18) For a similar conversion, see: Itoh, K.; Motohashi, M.; Kuriki, H.; Sugihara, H.; Inatomi, N.; Nishikawa, M.; Oka, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2917.
(19) Grunewald, G. L.; Grindel, J. M.; Vincek, W. C.; Borchardt, R. T. *Mol. Pharmacol.* **1975**, *11*, 694.
(20) Grunewald, G. L.; Borchardt, R. T.; Rafferty, M. F.; Krass, P. *Mol. Pharmacol.* **1981**, *20*, 377.
(21) PNMT in brain has similar properties to that in adrenal gland; see ref 2 and Diaz Borges, J. M.; Urbina, M.; Drujan, B. D. *Neurochem. Res.* **1978**, *3*, 15.
(22) Connett, R. J.; Kirshner, N. *J. Biol. Chem.* **1970**, *245*, 329.
(23) Sall, D. J.; Grunewald, G. L. *J. Med. Chem.* **1987**, *30*, 2208.
(24) Grunewald, G. L.; Ye, Q.; Sall, D. J.; Criscione, K. R.; Wise, B. *Mol. Pharmacol.*, in press.

Weak activity as PNMT substrates for **32** and **33**[23] as well as **21**[25] was reported. However, none of the methoxy compounds **26–29** and **34–36** showed activity as a substrate. The competitive inhibition displayed by all of these compounds of Tables I and II indicates a direct active-site interaction.

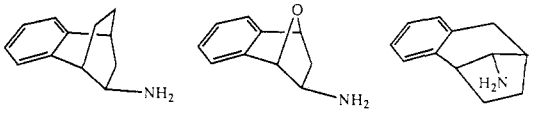
p-Tyramine (K_i = 294 μM) was more potent than phenylethylamine (K_i = 854 μM) as an inhibitor of PNMT, but *m*-tyramine (K_i = 1250 μM) was less potent than phenylethylamine. These results are consistent with the previous study for hydroxyl-substituted amphetamines[6] and octopamines.[26] This potency rank order holds throughout the different series of tyramine analogues (**12–15**, **17–20**, and **22–24**) with different conformational flexibility. In each case, the *p*-hydroxyl analogue (refers to the tyramine moiety) was more potent than the corresponding two *m*-hydroxyl analogues.

The overall lipophilic character of the aromatic ring binding region within the active site of PNMT has been suggested by several studies. For example, a QSAR study[6] with amphetamine analogues showed that those possessing an electron-withdrawing, lipophilic substituent have enhanced activity as inhibitors of PNMT with respect to amphetamine. A similar result was obtained in a study of phenylethanolamine substrates.[27] In both phenylethylamine inhibitors[6] and phenylethanolamine substrates,[3] the potency of the analogues with a *p*-hydroxyl group is almost always underestimated. We have offered[9,23] the likely explanation that there exists a compact hydrophilic region at the active site that interacts with the *p*-hydroxyl group, probably via hydrogen-bond interaction. The reduced activity of the corresponding methoxy-substituted compounds **26–36** compared with the hydroxyl compounds **12–15**, **17–20**, and **22–24** is consistent with the existence of a hydrogen-bond acceptor at the active site of PNMT.

The effects of conformational restriction have been demonstrated in both phenylethanolamine substrates[8] and phenylethylamine inhibitors[7] with 2-aminotetralin derivatives. The increased potency of the conformationally restricted phenolic 2-aminotetralins (**12–15**) compared to that of either *m*- or *p*-tyramine (**9** and **10**) with a flexible aminoethyl side chain is consistent with the previous findings with *cis*- and *trans*-2-amino-1-tetralol (**11**)[8] and 2-aminotetralin (**16**).[7]

The conformations of 2-aminotetralin derivatives have been studied by NMR,[28] X-ray crystallography,[29] and theoretical calculations.[30] The half-chair conformation for the cyclohexene portion of 2-aminotetralin derivatives is lower in energy than the half-boat conformation by 3–5 kcal/mol.[30] The conformationally defined tyramine analogues **22–24** with a half-chair 2-aminotetralin moiety were better inhibitors of PNMT than were the conformationally defined half-boat 2-aminotetralin analogues **17–20**. Apparently, the half-chair conformation for the 2-aminotetralin system is preferred by the enzyme.

All of the conformationally defined tyramine analogues **17–20** and **22–24** were less potent than the conformationally restricted tyramine analogues **12–15**. The reduced activity of these conformationally defined tyramine analogues **17–20** and **22–24** could be because (1) the conformation defined for the 2-aminotetralin moiety is not the active conformation, or (2) steric hindrance from the extra bridging atoms inhibits binding to PNMT. Besides the benzobicyclo[2.2.1]hept-2-ylamine (e.g. **17–21** and **30–33**) and the benzobicyclo[3.2.1]octylamine (e.g. **22–25** and **34–36**), we have used other conformationally defined benzobicyclic systems in our studies. These investigations have included compounds incorporating the benzobicyclo[2.2.2]oct-2-ylamine (**71**),[20] the 1,4-epoxy-1,2,3,4-tetrahydro-2-naphthylamine (**72**),[20] and the positional isomer of **25** in the benzobicyclo[3.2.1]octane skeleton (**73**).[31] These ring systems cover a range of conformations



71 72 73

for the 2-aminotetralin moiety, including a number of conformationally defined gauche phenylethylamines. The enhanced activity in both of the benzobicyclo[3.2.1]-octylamine systems **25** and **73**, compared with the others we have studied, suggests that the half-chair conformation with an equatorial amino group for the 2-aminotetralin moiety is the active conformation and a fully extended side chain conformation for the phenylethylamine moiety is required for optimal interaction with the enzyme.[20,23,25,31] It is likely that the reduced activity of **17–20** and **22–24**, compared to that of **12–15**, is due to the steric hindrance from the bridging atoms in binding to PNMT.

The extra methano bridge in the benzobicyclo[2.2.1]-heptane ring system (**17–20**) and the extra ethano bridge in the benzobicyclo[3.2.1]octane ring system (**22–24**) could change the orientation of the molecule at the active site of PNMT by unfavorable steric or lipophilic interactions. However, the same potency rank order in the four series of analogues (**9–10**, **12–15**, **17–20**, and **22–24**) coupled with their competitive inhibition suggests that they bind at the active site of PNMT in the same orientation.

In the flexible *m*- and *p*-tyramine (**9** and **10**), in the conformationally restricted tyramines **12–15**, and in the conformationally defined tyramines **17–20** and **22–24**, those analogues with a *p*-hydroxyl group (**10**, **14**, **19**, and **23**) bind to PNMT better than do the corresponding unsubstituted compounds (**1**, **16**, **21**, and **25**); but the analogues with a *m*-hydroxyl group (**9**, **13**, **15**, **18**, **20**, **22**, and **24**) bind poorer than the corresponding unsubstituted compounds (**1**, **16**, **21**, and **25**). The results from this study with the phenolic compounds suggest a positive interaction for the *p*-hydroxyl group and a negative interaction for the *m*-hydroxyl group. However, the effect of adjacent hydroxyl groups on binding to the active site of PNMT (the catechol moiety in norepinephrine) may not be the sum of the binding contributions of the individual hydroxyl groups and the potency for catechol ligands could be underesti-

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mated. Further studies with catechol ligands are needed to elucidate the contribution of the catechol moiety in the binding of norepinephrine as a substrate for PNMT.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus calibrated with known compounds and are corrected accordingly. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian XL-300 instrument operating at 300 MHz for proton and 75 MHz for carbon-13. All chemical shifts were in parts per million (ppm) relative to tetramethylsilane (Me_4Si, 0.00 ppm) for ^{1}H NMR and deuteriated chloroform ($CDCl_3$, 77.00 ppm) or deuteriated dimethyl sulfoxide (DMSO-d_6, 39.50 ppm) for ^{13}C NMR. Multiplicity abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on an IBM FTIR-32 spectrophotometer. Mass spectra were measured on a Varian CH-5 mass spectrometer. Microanalyses were conducted at the University of Kansas or Midwest Microlab, Ltd., Indianapolis, IN. Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison Model 7924 Chromatotron on Merck silica gel 60 PF254 containing $CaSO_4 \cdot 0.5H_2O$ as binder. Bulb-to-bulb distillations were carried out with a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI) and oven temperatures were recorded.

S-Adenosyl-L-methionine was obtained from Sigma Chemical Co. (St. Louis, MO). For the radiochemical assays, [*methyl*-^{3}H]-*S*-adenosyl-L-methionine was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands, required for the purification of the enzyme used in this study, were obtained from Pel-Freez Biologicals (Rogers, AR). Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium–benzophenone ketyl; dry methylene chloride (CH_2Cl_2) was obtained by distillation over phosphorus pentoxide; dry benzene was obtained by distillation from calcium hydride; anhydrous methanol (MeOH) and ethanol (EtOH) were obtained by distillation from magnesium. Unless otherwise stated, all MeOH and EtOH used was anhydrous. Hexanes refers to a mixture of isomeric hexanes (bp 68–70 °C), petroleum ether refers to low-boiling hydrocarbons (primarily pentanes and hexanes, bp 35–60 °C), and brine refers to saturated aqueous NaCl. All reactions requiring inert conditions were performed in oven-dried or flame-dried glassware under a N_2 or Ar atmosphere.

Amine hydrochloride salts were generally prepared by adding ethereal HCl to an ether or ether/methanol solution of the free amine. All of the HCl salts and HBr salts were recrystallized from ether/ethanol after removal of the solvent.

3-(4-Methoxyphenyl)cyclopentanone (40). The reaction was carried out at 0 °C and under a N_2 atmosphere. To a solution of 4-bromoanisole (**37**, 12.34 g, 66 mmol) in 100 mL of ether was added *n*-BuLi solution (26 mL, 2.3 M in hexanes, 60 mmol) through syringe. After being stirred for 15 min, the cloudy solution was transferred into another flask containing a suspension of Cu_2Br_2 (4.30 g, 15 mmol) in 400 mL of ether. Immediately following the transfer, 2-cyclopentenone (2.46 g, 30 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C and then precooled 1 N HCl (400 mL) was added. The stirring was continued until the mixture became clear. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The product was separated by PCTLC with 8:1 hexanes/AcOEt as eluent. Bulb-to-bulb distillation (125–135 °C, 0.6 mm) gave **40** (2.90 g, 50.9%) as a colorless oil. An analytical sample was obtained by crystallization from petroleum ether: mp 46–48 °C (lit.[32] mp 47–49 °C); IR (KBr) 2963, 2843, 1742 (C=O), 1611, 1514, 1246, 1028, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 9 Hz, 2 H), 6.89 (d, J = 9 Hz, 2 H), 3.80 (s, 3 H, CH_3O), 3.37 (m, 1 H), 2.65 (dd, J = 8, 18 Hz, 1 H), 2.5–2.2 (m, 4 H), 1.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.52 (C=O), 158.30, 135.10, 127.63, 114.00, 55.27 (CH_3O), 45.99, 41.44, 38.87, 31.36; mass spectrum, m/z (relative intensity) 191 (12), 190 (82, M$^+$), 161 (27), 147 (16), 135 (25), 134 (100).

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3-(3-Methoxyphenyl)cyclopentanone (41). By the same procedure as described for **40**, **41** (1.80 g, 31.6% yield) was obtained from 2-cyclopentenone (2.46 g, 30 mmol) and 3-bromoanisole (**38**) as a colorless oil. An analytical sample was obtained by crystallization from petroleum ether: mp 35–36 °C; bp 120–135 °C (bulb-to-bulb distillation, 0.7 mm); IR (KBr) 2961, 1742, 1603, 1584, 1493, 1271, 1152, 1049, 787, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26, (t, J = 8 Hz, 1 H), 6.80 (m, 3 H), 3.82 (s, 3 H, CH_3O), 3.40 (m, 1 H), 2.66 (dd, J = 8, 18 Hz, 1H), 2.5–2.2 (m, 4 H), 1.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.25 (C=O), 159.82, 144.73, 129.68, 119.02, 112.93, 111.57, 55.18 (CH_3O), 45.73, 42.20, 38.82, 31.07; mass spectrum, m/z (relative intensity) 191 (13), 190 (89, M$^+$), 162 (26), 148 (32), 147 (25), 134 (100), 91 (46). Anal. ($C_{12}H_{14}O_2$) C, H.

3-(2-Methoxyphenyl)cyclopentanone (42). By the same procedure as described for **40**, **42** (3.35 g, 58.8% yield) was obtained from 2-cyclopentenone (2.46 g, 30 mmol) and 2-bromoanisole (**39**) as a colorless oil: bp 110–115 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 2961, 2838, 1744, 1601, 1495, 1244, 1028, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 2 H), 6.90 (m, 2 H), 3.82 (s, 3 H, CH_3O), 3.67 (m, 1 H), 2.62 (dd, J = 8, 19 Hz, 1 H), 2.5–2.2 (m, 4 H), 2.05 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 219.12 (C=O), 157.22, 130.97, 127.49, 126.42, 120.36, 110.30, 54.98 (CH_3O), 44.34, 38.48, 36.57, 28.89; mass spectrum, m/z (relative intensity) 191 (19), 190 (100, M$^+$), 161 (15), 159 (14), 147 (19), 134 (51), 119 (67), 91 (88). Anal. ($C_{12}H_{14}O_2$) C, H.

3-(4-Methoxyphenyl)cyclopentanecarboxaldehyde (43). To a suspension of *t*-BuOK (2.34 g, 20.9 mmol) in 100 mL of THF at −20 °C was added $CH_3OCH_2P^+(C_6H_5)_3Cl^-$ (7.20 g, 21.0 mmol). After 15 min, the mixture became a red solution. Ketone **40** (1.93 g, 10.1 mmol) in 10 mL of THF was added dropwise. The whole was stirred at −20 °C for 1 h and then allowed to warm to room temperature and stirred for an additional 3 h. The reaction mixture was poured into water (200 mL) and extracted with ether. The combined ether extracts were washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was filtered through a silica gel plug with 4:1 hexanes/AcOEt as eluent, giving the crude vinyl ether as a light yellow oil. A solution of the crude product in 100 mL of ether was cooled at 0 °C and $HClO_4$ (70%, 5 mL) was added dropwise. The mixture was stirred for an addition 15 min at 0 °C and then was poured into 100 mL of ice/water. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of solvent, the product was purified by PCTLC with 8:1 hexanes/AcOEt as eluent. After bulb-to-bulb distillation (115–125 °C, 0.7 mm), **43** (1.06 g, 51.3% yield; a 1:1 mixture of cis and trans isomers) was obtained as a colorless oil: IR (neat) 2955, 2869, 2836, 2716, 1721 (C=O), 1613, 1514, 1248, 1181, 1036, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1 H, aldehyde), 7.16 (2d, J = 9 Hz, 2 H), 6.84 (d, J = 9 Hz, 2 H), 3.79 (3 H, s, CH_3O), 2.96 (m, 2 H), 1.5–2.5 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 203.39 and 203.31 (C=O), 158.04, 157.96, 136.32, 136.04, 127.86, 127.82, 113.80, 55.26 (CH_3O), 51.28 and 50.85 (*C*HCHO), 45.30 and 44.18 (benzylic), 34.66, 34.31, 33.93, 25.90, 25.66; mass spectrum, m/z (relative intensity) 205 (16), 204 (99, M$^+$), 186 (12), 173 (36), 148 (100), 134 (83), 121 (83). Anal. ($C_{13}H_{16}O_2$) H; C: calcd, 76.44; found, 75.91.

3-(3-Methoxyphenyl)cyclopentanecarboxaldehyde (44). By the same procedure as described for **43**, **44** (0.71 g, 34.2% yield; a mixture of cis and trans isomers with one isomer predominant) was obtained from **41** (1.93 g, 10.1 mmol) as a colorless oil: bp 120–130 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 2948, 2869, 2836, 2714, 1719 (C=O), 1601, 1489, 1437, 1264, 1157, 1048, 781, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1 H, aldehyde), 7.21 (t, J = 8 Hz, 1 H), 6.77 (m, 3 H), 3.78 (s, 3 H, CH_3O), 2.97 (m, 2 H), 1.5–2.5 (m, 6 H); ^{13}C NMR ($CDCl_3$) 203.16 (C=O), 159.58, 146.00, 129.25, 119.24, 112.97, 111.09, 55.03 (CH_3O), 50.77, 44.86, 33.97, 33.93, 25.59; mass spectrum, m/z (relative intensity) 205 (16), 204 (95, M$^+$), 186 (9), 173 (36), 148 (100), 135 (52), 121 (36), 91 (48). Anal. ($C_{13}H_{16}O_2$) H; C: calcd, 76.44; found, 75.82.

3-(2-Methoxyphenyl)cyclopentanecarboxaldehyde (45). By the same procedure as described for **43**, **45** (1.13 g, 54.7% yield; a 1:1 mixture of cis and trans isomers) was obtained from **42** (1.93 g, 10.1 mmol) as a colorless oil: bp 110–120 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 2948, 2870, 2836, 2714, 1719, 1601, 1493, 1464, 1240, 1030, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.69 (br s,

1 H, aldehyde), 7.19 (m, 2 H), 6.88 (m, 2 H), 3.81 (s, 3 H, CH_3O), 3.40 (m, 1 H), 2.95 (m, 1 H), 1.6–2.4 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 203.86 and 203.77 (C=O), 157.37, 132.40, 132.04, 127.14, 126.76, 126.62, 120.51, 120.40, 110.36, 55.22 (CH_3O), 51.35, 51.03, 39.81, 38.85, 33.03, 32.61, 32.40, 31.96, 25.94; mass spectrum, *m/z* (relative intensity) 205 (2), 204 (8, M^+), 174 (22), 147 (13), 133 (19), 75 (100). Anal. ($C_{13}H_{16}O_2$) H; C: calcd, 76.44; found, 75.98.

3-(4-Methoxyphenyl)cyclopentanecarboxylic Acid (46). Jones reagent[10] (CrO_3/H_2SO_4; ca. 1.4 mL) was added dropwise to a solution of **43** (0.86 g, 4.2 mmol) in 20 mL of acetone until a yellow color persisted. The mixture was diluted with 100 mL of 1 N HCl and extracted with ether. The ether extracts were combined and extracted with 1 N NaOH. The combined basic, aqueous extracts were acidified with concentrated HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated. After bulb-to-bulb distillation (155–170 °C, 0.7 mm), **46** (0.79 g, 85.2% yield; a 1:1 mixture of cis and trans isomers) was obtained as a yellowish solid: mp 50–57 °C; IR (KBr) 2963 (br), 1703 (C=O), 1514, 1246, 1183, 1034, 810 cm^{-1}; ^1H NMR ($CDCl_3$) 11.0 (br s, 1 H, COOH), 7.17 (2 d, *J* = 8 Hz, 2 H), 6.84 (d, *J* = 8 Hz, 2 H), 3.79 (s, 3 H, CH_3O), 3.05 (m, 2 H), 1.6–2.5 (m, 6 H); ^{13}C NMR ($CDCl_3$) 183.11 and 182.87 (COOH), 157.95, 157.90, 136.68, 136.28, 127.90, 127.84, 113.75, 55.23 (CH_3O), 45.41, 44.16, 43.40, 42.91, 38.26, 37.55, 34.67, 34.02, 29.74, 29.11; mass spectrum, *m/z* (relative intensity) 221 (14), 220 (93, M^+), 174 (50), 148 (100), 134 (36), 121 (47), 91 (63). Anal. ($C_{13}H_{16}O_3$) C, H.

3-(3-Methoxyphenyl)cyclopentanecarboxylic Acid (47). By the same procedure as described for **46**, **47** [0.92 g, 83.3% yield, a mixture of cis and trans isomers with one isomer predominant (ca. 10:1)] was obtained from **44** (1.02 g, 5.0 mmol) as a yellowish oil: bp 150–160 °C (bulb-to-bulb distillation, 0.4 mm); IR (neat) 2942 (br), 1698 (C=O), 1584, 1453, 1233, 1157, 1046, 779, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.6 (br s, 1 H, COOH), 7.21 (t, *J* = 8 Hz, 1 H), 6.78 (m, 3 H), 3.78 (s, 3 H, CH_3O), 3.20 (m, 1 H), 3.05 (m, 1 H), 2.2 (m, 1 H), 2.18 (m, 2 H), 1.95 (m, 2 H), 1.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.23 (COOH), 159.54, 146.34, 129.28, 119.29, 113.00, 111.05, 55.03 (CH_3O), 44.90, 42.92, 37.23, 34.39, 29.74; mass spectrum, *m/z* (relative intensity) 221 (16), 220 (100, M^+), 175 (38), 148 (86), 135 (60), 121 (35), 91 (56). Anal. ($C_{13}H_{16}O_3$) C, H.

3-(2-Methoxyphenyl)cyclopentanecarboxylic Acid (48). By the same procedure as described for **46**, **48** (1.10 g, 90.3% yield; a 1:1 mixture of the cis and trans isomers) was obtained from **45** (1.13 g, 5.5 mmol) as a yellowish oil: bp 140–145 °C (bulb-to-bulb distillation, 0.3 mm); IR (neat) 2953 (br), 1707 (C=O), 1464, 1246, 1032, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.6 (br s, 1 H, COOH), 7.18 (m, 2 H), 6.92 (m, 2 H), 3.81 (s, 3 H, CH_3O), 3.6 and 3.0 (2 m, 1 H), 3.0 (m, 1 H), 2.37 (m, 1 H), 1.9–2.1 (m, 4 H), 1.76 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.36 and 183.23 (COOH), 157.39, 157.32, 132.88, 132.24, 127.04, 126.68, 120.52, 120.37, 110.38, 110.32, 55.23 (CH_3O), 43.50, 43.18, 39.44, 38.96, 36.55, 35.71, 32.80, 32.05, 29.94, 28.97; mass spectrum, *m/z* (relative intensity) 221 (15), 220 (100, M^+), 174 (89), 159 (34), 147 (43), 143 (52), 91 (88). Anal. ($C_{13}H_{16}O_3$) C, H.

3-(4-Methoxyphenyl)cyclopentane-1,1-dicarboxylic Acid (49). To a solution of diisopropylamine (1.6 mL, 11.0 mmol) in 100 mL of THF cooled at 0 °C was added *n*-BuLi (4.6 mL, 2.4 M in hexanes, 11.0 mmol). After 15 min, a solution of **46** (1.10 g, 5.0 mmol) in 5 mL of THF was added. The mixture was heated at 50 °C for 2 h and then cooled at 0 °C. Anhydrous CO_2 gas was bubbled through the yellow solution for 30 min and then 1 N NaOH (150 mL) was added. The mixture was washed with ether, acidified with concentrated HCl while cooled at 0 °C, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated. Acid **49** (1.17 g, 88.7%) was crystallized from CH_2Cl_2/hexanes as a white solid: mp 134–136 °C dec; IR (KBr) 3000 (br), 1703, 1516, 1248, 1181, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.70 (br s, 2 H, COOH), 7.17 (d, *J* = 7 Hz, 2 H), 6.85 (d, *J* = 7 Hz, 2 H), 3.72 (s, 3 H, CH_3O), 3.02 (m, 1 H), 2.51 (m, 1 H), 2.32 (m, 1 H), 1.9–2.2 (m, 3 H), 1.58 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 173.69 and 173.65 (COOH), 157.64, 135.71, 127.81, 113.75, 59.36 (*C*(COOH)$_2$) 54.98 (CH_3O), 43.79 (benzylic), 41.72, 33.88, 33.51; mass spectrum, *m/z* (relative intensity) 265 (2), 264 (12, M^+), 220 (16), 218 (4), 173 (34), 148 (38), 134 (24), 91 (23), 44 (100). Anal. ($C_{14}H_{16}O_5$) C, H.

3-(3-Methoxyphenyl)cyclopentane-1,1-dicarboxylic Acid (50). By the same procedure as described for **49**, **50** (1.95 g, 86.0%) was obtained from **47** (1.89 g, 8.6 mmol) as a white solid: mp 139–141 °C dec; IR (KBr) 3438, 3027, 2923, 1700, 1603, 1493, 1453, 756, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.72 (br s, 2 H, COOH), 7.20 (m, 1 H), 6.81 (m, 3 H), 3.74 (s, 3 H, CH_3O), 3.06 (m, 1 H), 2.56 (m, 1 H), 2.32 (m, 1 H), 1.9–2.2 (m, 3 H), 1.62 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 173.64 and 173.60 (COOH), 159.32, 145.59, 129.36, 119.03, 112.68, 111.53, 59.42 (*C*(COOH)$_2$), 54.91 (CH_3O), 44.52, 41.36, 33.67, 33.49; mass spectrum, *m/z* (relative intensity) 265 (6), 264 (34, M^+), 218 (16), 173 (52), 148 (79), 44 (100). Anal. ($C_{14}H_{16}O_5$) C, H.

3-(2-Methoxyphenyl)cyclopentane-1,1-dicarboxylic Acid (51). By the same procedure as described for **49**, **51** (1.19 g, 90.2%) was obtained from **48** (1.10 g, 5.0 mmol) as a white solid: mp 149–150 °C dec; IR (KBr) 3000 (br), 1705 (C=O), 1495, 1293, 1240, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.66 (br s, 2 H, COOH), 7.19 (m, 2 H), 6.93 (m, 2 H), 3.77 (s, 3 H, CH_3O), 3.35 (m, 1 H), 2.51 (m, 1 H), 2.31 (m, 1 H), 1.9–2.2 (m, 3 H), 1.62 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 173.73 and 173.66 (COOH), 156.98, 131.39, 127.19, 126.41, 120.42, 110.77, 59.36 (*C*(COOH)$_2$), 55.28 (CH_3O), 39.98, 38.01, 33.41, 32.04; mass spectrum, *m/z* (relative intensity) 265 (9), 264 (53, M^+), 218 (32), 173 (80), 148 (30), 133 (83), 91 (86), 44 (100). Anal. ($C_{14}H_{16}O_5$) C, H.

2-Methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-8-carboxylic Acid (52). A mixture of **49** (1.17 g, 4.4 mmol) and 1:10 P_2O_5/CH_3SO_3H[11] (117 g) was stirred at room temperature for 3 h. The dark-red reaction mixture was poured into 200 mL of ice/water. The water was extracted with ether. The combined ether extracts were washed once with 1 N HCl and then extracted with 1 N NaOH. After the basic, aqueous extract was acidified, crystals (platelets) were formed. The crystals were filtered, washed with water, and dried under vacuum, giving **52** (0.87 g, 79.8%): mp 190–192 °C; IR (KBr) 3000 (br), 1711 (COOH), 1684 (ArC=O), 1495, 1287 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.61 (br s, 1 H, COOH), 7.1–7.4 (m, 3 H), 3.79 (s, 3 H, CH_3O), 3.44 (m, 1 H, benzylic), 2.47 (m, 1 H), 2.0–2.3 (m, 3 H), 1.56 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 196.44 (ArC=O), 172.81 (COOH), 158.20, 142.92, 129.72, 128.35, 121.48, 109.77, 63.55, 55.31 (CH_3O), 42.41, 40.72, 31.41, 26.87; mass spectrum, *m/z* (relative intensity) 247 (7), 246 (41, M^+), 228 (8), 202 (100), 187 (32), 184 (26), 174 (64), 161 (49), 131 (32), 115 (46). Anal. ($C_{14}H_{14}O_4$) C, H.

3-Methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-8-carboxylic Acid (53). By the same procedure as described for **52**, **53** (0.76 g, 67.4%) was obtained from **50** (1.21 g, 4.6 mmol) as needles: mp 154–156 °C; IR (KBr) 3000 (br), 1740, 1709, 1674, 1646, 1599, 1347, 1281 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.54 (br s, 1 H, COOH), 7.82 (d, *J* = 8 Hz, 1 H), 6.94 (m, 2 H), 3.85 (s, 3 H, CH_3O), 3.44 (m, 1 H, benzylic), 2.43 (m, 1 H), 2.0–2.3 (m, 3 H), 1.59 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 195.36 (ArC=O), 172.92 (COOH), 163.75, 152.95, 129.42, 121.95, 113.51, 110.98, 63.51, 55.61 (CH_3O), 41.92, 41.81, 31.34, 27.47; mass spectrum, *m/z* (relative intensity) 247 (5), 246 (10, M^+), 228 (6), 202 (92), 183 (13), 174 (71), 161 (100), 133 (28), 115 (28). Anal. ($C_{14}H_{14}O_4$) C, H.

4-Methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-8-carboxylic Acid (54). A similar procedure as described for **52** was followed. As the product (**54**) did not crystallize from water, CH_2Cl_2 was used to extract **54** from the aqueous mixture. Acid **54** (2.38 g, 90.2% yield) was obtained from **51** (2.20 g, 10.0 mmol) as a yellowish solid. An analytical sample was obtained by recrystallization from ether: mp 150–152 °C; IR (KBr) 3000 (br), 1715, 1687, 1477, 1267, 957, 751, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.60 (br s, 1 H, COOH), 7.47 (d, *J* = 8 Hz, 1 H), 7.35 (t, *J* = 8 Hz, 1 H), 7.26 (d, *J* = 9 Hz, 1 H), 3.86 (s, 3 H, CH_3O), 3.83 (m, 1 H, benzylic), 2.47 (m, 1 H), 2.23 (m, 1 H), 2.13 (m, 2 H), 1.62 (m, 1 H), 1.48 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 196.54 (ArC=O), 172.74 (COOH), 154.69, 138.17, 129.81, 127.51, 118.49, 115.98, 63.47, 55.94, 41.69, 33.87, 30.35, 27.07; mass spectrum, *m/z* (relative intensity) 247 (6), 246 (37, M^+), 228 (13), 202 (73), 187 (34), 183 (37), 174 (57), 161 (100), 131 (43), 115 (63). Anal. ($C_{14}H_{14}O_4$) C, H.

8-Amino-2-methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (55). A procedure of Ninomiya et al.[12] was followed. Acid **52** (1.52 g, 6.2 mmol) was mixed with toluene (15 mL), triethylamine (0.9 mL, 6.2 mmol), and diphenyl phos-

phorazidate (1.6 mL, 7.4 mmol). After the mixture was heated at 80 °C for 2 h, *t*-BuOH (2.9 mL, 31 mmol) was added. Heating was continued for 20 h and then solvent was removed at room temperature under vacuum. The oily residue was mixed with 3 N HCl (50 mL) and heated under reflux for 3 h. The mixture was diluted with 100 mL of water, washed with ether, basified, and extracted with ether. The combined ether extracts were dried over Na_2SO_4. After removal of solvent, bulb-to-bulb distillation (140 °C, 0.4 mm) gave **55** (0.98 g, 73.1% yield) as a colorless oil: IR (neat) 3359, 3299, 2936, 2865, 2834, 1674, 1605, 1489, 1426, 1267, 1032, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 2 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 7.06 (dd, J = 2, 8 Hz, 1 H), 3.83 (s, 3 H, CH_3O), 3.39 (m, 1 H, benzylic), 2.39 (m, 1 H), 1.7–2.2 (m, 6 H, NH_2 and aliphatic protons), 1.59 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.10 (C=O), 158.26, 143.69, 130.45, 127.61, 121.56, 109.70, 67.19 (CNH_2), 55.31 (CH_3O), 47.25, 42.16 (benzylic), 33.77, 31.89; mass spectrum, m/z (relative intensity) 218 (18), 217 (100, M^+), 199 (19), 188 (61), 174 (33), 161 (42), 145 (12), 82 (29). **55**·HCl was made in ether and recrystallized from ethanol/ether: mp >270 °C; ^1H NMR (DMSO-d_6) δ 9.09 (br s, 3 H, NH_3^+), 7.39 (m, 2 H), 7.27 (m, 1 H), 3.81 (s, 3 H, CH_3O), 3.56 (m, 1 H, benzylic), 2.37 (m, 3 H), 2.20 (m, 1 H), 1.78 (m, 1 H), 1.54 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 194.65 (C=O), 158.31, 143.16, 128.97, 128.58, 122.33, 109.79, 66.23 (CNH_3^+), 55.46 (CH_3O), 42.57, 40.45 (benzylic), 30.81, 28.35. Anal. ($C_{13}H_{15}NO_2$·HCl) C, H, N.

8-Amino-3-methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (56). By the same procedure as described for **55**, **56** (1.88 g, 88.9% yield) was obtained from **53** (2.40 g, 9.9 mmol) as a colorless oil: bp 140–150 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 3360, 3303, 2948, 2870, 1684, 1601, 1493, 1252, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (d, J = 8 Hz, 1 H), 6.84 (dd, J = 8, 2 Hz, 1 H), 6.71 (d, J = 2 Hz, 1 H), 3.87 (s, 3 H, CH_3O), 3.38 (m, 1 H), 2.41 (m, 1 H), 1.7–2.3 (m, 6 H, NH_2 and aliphatic protons), 1.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 200.99 (C=O), 163.85, 153.52, 130.03, 122.92, 112.79, 110.64, 66.98 (CNH_2), 55.37 (CH_3O), 46.77, 43.34 (benzylic), 34.32, 31.88; mass spectrum, m/z (relative intensity) 218 (17), 217 (100, M^+), 199 (23), 188 (49), 82 (40). **56**·HCl was made in ether and recrystallized from ethanol/ether: mp 248–249 °C dec; ^1H NMR (DMSO-d_6) δ 8.96 (br s, 3 H, NH_3^+), 7.90 (d, J = 9 Hz, 1 H), 7.00 (m, 2 H), 3.87 (s, 3 H, CH_3O), 3.57 (m, 1 H, benzylic), 2.35 (m, 3 H), 2.16 (m, 1 H), 1.79 (m, 1 H), 1.58 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 193.45 (C=O), 164.42, 153.23, 129.69, 121.04, 113.89, 111.24, 65.94 (CNH_3^+), 55.77 (CH_3O), 42.06, 41.45, 30.67, 28.98. Anal. ($C_{13}H_{15}NO_2$·HCl) C, H, N.

8-Amino-4-methoxy-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (57). By the same procedure as described for **55**, **57** (0.74 g, 73.6% yield) was obtained from **54** (1.14 g, 4.6 mmol) as a yellowish solid: mp 62–65 °C; bp 135–145 °C (bulb-to-bulb distillation, 0.3 mm); IR (KBr) 3376, 2955, 1686, 1584, 1476, 1266, 961, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (d, J = 8 Hz, 1 H), 7.28 (t, J = 8 Hz, 1 H), 7.04 (d, J = 8 Hz, 1 H), 3.93 (m, 1 H), 3.87 (s, 3 H, CH_3O), 2.41 (m, 1 H), 1.7–2.1 (m, 6 H, NH_2 and aliphatic protons), 1.58 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.60 (C=O), 154.96, 139.61, 131.00, 127.09, 119.29, 114.90, 67.35 (CNH_2), 55.81 (CH_3O), 46.75, 35.07 (benzylic), 34.08, 30.97; mass spectrum, m/z (relative intensity) 218 (17), 217 (100, M^+), 199 (21), 188 (49), 158 (41), 82 (40). **57**·HCl was made in ether and recrystallized from ethanol/ether: mp 270 °C dec; ^1H NMR (DMSO-d_6) δ 8.99 (br s, 3 H, NH_3^+), 7.54 (d, J = 8 Hz, 1 H), 7.41 (t, J = 8 Hz, 1 H), 7.34 (d, J = 8 Hz, 1 H), 3.92 (m, 1 H, benzylic), 3.87 (s, 3 H, CH_3O), 2.34 (m, 3 H), 2.12 (m, 1 H), 1.80 (m, 1 H), 1.51 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 194.92 (C=O), 154.82, 138.29, 129.06, 128.14, 118.59, 116.83, 66.14 (CNH_3^+), 56.02, (CH_3O), 41.92, 33.85, 29.78, 28.55. Anal. ($C_{13}H_{15}NO_2$·HCl) C, H, N.

8-Amino-2-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (58). Amine **55** (406 mg, 1.9 mmol) was dissolved in 20 mL of absolute ethanol and the solution cooled at 0 °C. $NaBH_4$ (0.25 g, 6.6 mmol) was added. The mixture was stirred at room temperature for 1.5 h and then solvent was removed under reduced pressure. The residue was dissolved 1 N NaOH (100 mL) and the aqueous mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated. Amine **58** (321 mg, 78.3% yield) was obtained as a white solid: mp 140–141 °C; IR (KBr) 3413, 3326, 2965, 2942, 2869, 1609, 1497, 1244, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (d, J = 2 Hz, 1 H), 6.89 (d, J = 8 Hz, 1 H), 6.69 (dd, J = 2, 8 Hz, 1 H), 4.76 (s, 1 H, C*H*OH), 3.75 (s, 3 H, CH_3O), 3.03 (m, 1 H, benzylic), 2.60 (br s, 3 H, NH_2 and OH), 2.24 (m, 1 H), 2.08 (m, 1 H), 1.88 (m, 2 H), 1.54 (m, 1 H), 1.33 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.28, 137.97, 135.80, 126.88, 113.46, 112.27, 78.82 (CHOH), 62.12 (CNH_2), 55.15 (CH_3O), 45.15, 41.74 (benzylic), 34.18, 29.28; mass spectrum, m/z (relative intensity) 220 (13), 219 (73, M^+), 201 (33), 200 (27), 188 (25), 173 (34), 159 (12), 134 (11), 82 (24), 57 (100). **58**·HCl was made in ether/methanol and recrystallized from ethanol/ether: mp 254–255 °C dec; ^1H NMR (DMSO-d_6) δ 8.52 (s, 3 H, NH_3^+), 7.07 (d, J = 2 Hz, 1 H), 6.96 (d, J = 8 Hz, 1 H), 6.74 (dd, J = 2, 8 Hz, 1 H), 6.29 (d, J = 6 Hz, 1 H, OH), 4.98 (d, J = 6 Hz, 1 H, C*H*OH), 3.72 (s, 3 H, CH_3O), 3.09 (m, 1 H, benzylic), 2.3–1.9 (m, 4 H), 1.64 (m, 1 H), 1.43 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.03, 137.78, 134.60, 126.83, 113.29, 112.86, 73.59, 62.87, 55.04 (CH_3O), 39.98, 39.67, 33.93, 24.85. Anal. ($C_{13}H_{17}NO_2$·HCl) C, H, N.

8-Amino-3-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (59). By the same procedure as described for **58**, **59** (0.89 g, 98.6%) was obtained from **56** (0.91 g, 4.2 mmol) as a white solid: mp 154–156 °C; IR (KBr) 3430 (br), 2938, 2865, 1611, 1495, 1453, 1248, 1036, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 8 Hz, 1 H), 6.76 (dd, J = 8, 2 Hz, 1 H), 6.54 (d, J = 2 Hz, 1 H), 4.74 (m, 1 H, C*H*OH), 3.78 (s, 3 H, CH_3O), 3.03 (m, 1 H, benzylic), 2.77 (m, 1 H, OH), 2.17 (m, 2 H), 1.90 (m, 2 H), 1.60 (m, 1 H), 1.50 (s, 2 H, NH_2), 1.33 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.92, 145.20, 128.80, 123.26, 111.94, 111.28, 79.05, 62.32, 55.22, 45.38, 43.05, 33.96, 29.04; mass spectrum, m/z (relative intensity) 220 (8), 219 (58, M^+), 201 (23), 200 (16), 186 (8), 173 (14), 82 (19), 57 (100). **59**·HCl was made in ether/methanol and recrystallized from ethanol/ether: mp 218–219 °C. Anal. ($C_{13}H_{17}NO_2$·HCl) C, H, N.

8-Amino-4-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (60). By the same procedure as described for **58**, **60** (0.48, 96.8%) was obtained from **57** (0.50 g, 2.3 mmol) as a white solid: mp 119–121 °C; IR (KBr) 3424 (br), 2944, 2865, 1584, 1472, 1266, 1048, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10 (m, 2 H), 6.69 (d, J = 8 Hz, 1 H), 4.78 (s, 1 H, C*H*OH), 3.77 (s, 3 H, CH_3O), 3.55 (m, 1 H, benzylic), 2.80 (br s, 3 H, OH and NH_2), 2.26 (m, 1 H), 2.09 (m, 1 H), 1.82 (m, 2 H), 1.52 (m, 1 H), 1.33 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.42, 138.45, 131.90, 126.76, 119.70, 108.87, 78.79, 61.92, 55.38, 44.32, 34.48, 32.87, 29.69; mass spectrum, m/z (relative intensity) 220 (16), 216 (100, M^+), 200 (12), 173 (47), 82 (36), 57 (71). **60**·HCl was made in ether/methanol and recrystallized from ethanol/ether: mp 245–246 °C. Anal. ($C_{13}H_{17}NO_2$·HCl) C, H, N.

8-Amino-2-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (34). A procedure of Small et al.[14] was followed. Into a flask containing 20 mL of THF was distilled about 100 mL of NH_3. Lithium wire (0.32 g, 9 pieces) was added to the mixture by pieces and a blue solution was obtained. To the solution was added dropwise a solution of **58** (1.00 g, 4.6 mmol) in 20 mL of THF. After 5 min, NH_4Cl (ca. 3 g) was added to the mixture in small portions until the blue color disappeared. The NH_3 was allowed to evaporate and 1 N NaOH (100 mL) was added. The mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over K_2CO_3 and evaporated. The crude product was distilled bulb-to-bulb (115–120 °C, 0.3 mm), giving **34** (0.88 g, 94.9% yield) as a colorless oil: IR (neat) 3355, 3279, 3179, 2996, 2934, 2910, 2832, 1609, 1580, 1499, 1266, 1148, 1038, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (d, J = 8 Hz, 1 H), 6.62 (m, 2 H), 3.73 (s, 3 H, CH_3O), 3.06 (m, 1 H, benzylic), 2.95 (d, J = 16 Hz, 1 H, benzylic), 2.83 (d, J = 16 Hz, 1 H, benzylic), 2.09 (m, 1 H), 1.9–1.5 (m, 7 H, NH_2 and aliphatic protons); ^{13}C NMR ($CDCl_3$) δ 157.54, 136.25, 135.35, 127.05, 113.58, 111.27, 57.57, 54.83 (CH_3O), 47.80, 44.91, 41.95 (benzylic CH), 37.30, 35.47; mass spectrum, m/z (relative intensity) 204 (15), 203 (63, M^+), 202 (20), 188 (19), 174 (100), 159 (23), 144 (20), 130 (18), 115 (24). **34**·HCl was made in ether and recrystallized from ethanol/ether: mp >280 °C; ^1H NMR (DMSO-d_6) δ 8.68 (br s, 3 H, NH_3^+), 6.97 (d, J = 8 Hz, 1 H), 6.71 (m, 2 H), 3.70 (s, 3 H, CH_3O), 3.23 (d, J = 17 Hz, 1 H, benzylic), 3.13 (m, 1 H, benzylic), 2.96 (d, J = 16 Hz, benzylic), 2.03 (m, 3 H), 1.82 (m, 1 H), 1.73 (m, 1 H), 1.56 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 157.77, 134.94, 132.87, 127.47, 113.72, 112.24, 58.40 (CNH_3^+), 54.99 (CH_3O), 42.32, 40.06, 39.01, 34.97,

32.78. Anal. ($C_{13}H_{17}NO$·HCl) C, H, N.

8-Amino-4-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (36). By the same procedure as described for 34, 36 (0.46 g, 97.3%) was obtained from **60** (0.50 g, 2.3 mmol) as a colorless oil: bp 120 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 3357, 3276, 2940, 1584, 1472, 1264, 1084, 776, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (t, J = 7 Hz, 1 H), 6.54 (d, J = 7 Hz, 1 H), 6.49 (d, J = 8 Hz, 1 H), 3.61 (s, 3 H, CH_3O), 3.51 (m, 1 H, benzylic), 2.83 (d, J = 16 Hz, 1 H, benzylic), 2.68 (d, J = 16 Hz, 1 H, benzylic), 1.94 (m, 1 H), 1.7–1.3 (m, 7 H, NH_2 and aliphatic protons); ^{13}C NMR ($CDCl_3$) δ 154.65, 135.44, 131.95, 125.71, 120.64, 106.89, 57.13 (CNH_2), 54.69 (CH_3O), 47.54, 44.10, 37.37, 34.28 (benzylic CH), 34.08; mass spectrum, m/z (relative intensity) 204 (9), 203 (57, M^+), 188 (7), 174 (100), 159 (13), 144 (10), 130 (6), 115 (9). **36**·HCl was made in ether and recrystallized from ethanol/ether: mp >280 °C. Anal. ($C_{13}H_{17}NO$·HCl·0.5H_2O) C, H, N.

8-Amino-3-methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (35). A mixture of **59** (0.40 g, 1.8 mmol), 5% palladium on carbon (0.20 g), concentrated H_2SO_4 (2 mL), and AcOH (30 mL) was hydrogenated on a Parr shaker with an initial pressure of 50 psi for 1 day. The mixture was filtered and evaporated to near dryness under reduced pressure. The residue was diluted with 100 mL of 0.1 N HCl. The aqueous solution was washed with ether, basified, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over K_2CO_3 and evaporated, to give **35** (0.37 g, 98.9%) as a yellow oil. Bulb-to-bulb distillation (115–120 °C, 0.3 mm) gave a colorless oil (0.32 g, 85.5%): IR (neat) 3357, 3279, 2938, 2863, 2834, 1611, 1503, 1254, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (d, J = 8 Hz, 1 H), 6.66 (dd, J = 8, 2 Hz, 1 H), 6.57 (d, J = 2 Hz, 1 H), 3.75 (s, 3 H, CH_3O), 3.05 (m, 1 H, benzylic), 2.91 (d, J = 16 Hz, 1 H, benzylic), 2.79 (d, J = 16 Hz, 1 H, benzylic), 2.10 (m, 1 H), 1.8–1.5 (m, 7 H, NH_2 and aliphatic protons); ^{13}C NMR ($CDCl_3$) δ 157.43, 145.16, 129.49, 126.13, 111.47, 111.37, 57.80 (CNH_2), 54.93 (CH_3O), 46.95, 44.68, 43.12 (benzylic CH), 37.41, 35.27; mass spectrum, m/z (relative intensity) 204 (18), 203 (100, M^+), 188 (31), 174 (87), 159 (16), 143 (14), 130 (13), 115 (20), 82 (70). **35**·HCl was made in ether and recrystallized from ethanol/ether: mp >280 °C. Anal. ($C_{13}H_{17}NO$·HCl) C, H, N.

8-Amino-2-hydroxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene Hydrobromide (22·HBr). A mixture of **34** (329 mg, 1.62 mmol) and 48% hydrobromic acid (6.5 mL) was heated under reflux for 2 h. The mixture was evaporated under reduced pressure to dryness and **22**·HBr (174 mg, 70.3%) was recrystallized from ethanol/ether as yellowish crystals: mp >270 °C; IR (KBr) 3414 (br), 3029, 2923, 1619, 1506, 1449, 1188 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.17 (s, 1 H, ArOH), 8.30 (s, 3 H, NH_3^+), 6.85 (d, J = 8 Hz, 1 H), 6.51 (m, 2 H), 3.35 (m, 1 H, benzylic), 3.11 (d, J = 16 Hz, 1 H, benzylic), 2.87 (d, J = 16 Hz, 1 H, benzylic), 1.5–2.1 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 155.76, 133.10, 132.45, 127.47, 115.19, 113.39, 58.57 (CNH_3^+), 42.31, 40.12, 39.29, 35.07, 32.82; mass spectrum, m/z, (relative intensity) 190 (7), 189 (44, free amine M^+), 188 (15), 174 (14), 160 (100), 144 (20), 115 (13). Anal. ($C_{12}H_{15}NO$·HBr) C, H, N.

8-Amino-3-hydroxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene Hydrobromide (23·HBr). By the same procedure as described for **22**·HBr, **23**·HBr (0.65 g, 87.3%) was obtained from **35** (0.56 g, 2.8 mmol) as a yellowish solid: mp >270 °C; IR (KBr) 3436 (br), 3027, 2921, 1603, 1495, 1452, 1213, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.18 (br s, 1 H, phenolic), 8.39 (br s, 3 H, NH_3^+), 6.91 (d, J = 8 Hz, 1 H), 6.56 (d, J = 7 Hz, 1 H), 6.48 (s, 1 H), 3.11 (d, J = 16 Hz, 1 H, benzylic), 3.07 (m, 1 H), 2.87 (d, J = 16 Hz, 1 H, benzylic), 1.5–2.1 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 155.64, 143.68, 129.76, 121.22, 113.51, 113.08, 58.76, 41.49, 41.02, 38.79, 34.73, 32.82; mass spectrum, m/z, (relative intensity) 190 (12), 189 (72, free amine M^+), 188 (11), 174 (15), 160 (87), 144 (14), 115 (18), 82 (100). Anal. ($C_{12}H_{15}NO$·HBr) C, H, N.

8-Amino-4-hydroxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene Hydrobromide (24·HBr). By the same procedure as described for **22**·HBr, **24**·HBr (0.39 g, 68.2%) was obtained from **36** (0.43 g, 2.1 mmol) as a white solid: mp 140 °C dec; IR (KBr) 3347, 3027, 2923, 1588, 1495, 1466, 1279, 758, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.33 (br s, 1 H, phenolic), 8.37 (br s, 3 H, NH_3^+), 6.92 (t, J = 8 Hz, 1 H), 6.64 (d, J = 8 Hz, 1 H), 6.56 (d, J = 8 Hz, 1 H), 3.55 (m, 1 H, benzylic), 3.18 (d, J = 16 Hz, 1 H, benzylic), 2.91 (d, J = 17 Hz, 1 H, benzylic), 2.00 (m, 3 H), 1.76 (m, 2 H), 1.55 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 152.91, 132.88, 129.16, 126.66, 119.41, 112.50, 58.58 (CNH_3^+), 42.37, 38.73, 33.92, 33.33, 33.06; mass spectrum, m/z, (relative intensity) 190 (9), 189 (51, free amine M^+), 174 (7), 160 (100), 144 (17), 132 (15), 115 (23), 82 (65). Anal. ($C_{12}H_{15}NO$·HBr) C, H, N.

2-(Hydroxymethylene)-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (68). In a flask equipped with water bath and condenser, a mixture of 5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**67**, 5.00 g, 28.4 mmol), ethyl formate (7 mL, 87 mmol), sodium hydride (50% oil dispersion, 2.73 g, 56.8 mmol), and ether (100 mL) was stirred at room temperature for 12 h. To the mixture was added 100 mL of 1 N NaOH. The aqueous layer was separated, washed with ether, acidified, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated, giving **68** as a light yellow oil (4.46 g, 77.0% yield).

2-Acetamido-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (69).[18] **68** (4.09 g, 20.0 mmol) was dissolved in a mixture of AcOH (50 mL) and CH_2Cl_2 (10 mL) and the solution was cooled at 0 °C. A solution of $NaNO_2$ (2.76 g, 40.0 mmol) in water (10 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min, and then water (200 mL) and CH_2Cl_2 (200 mL) were added to the mixture. The CH_2Cl_2 layer was separated, washed with water, and dried over Na_2SO_4. After removal of solvent, a yellow solid was obtained. The crude oxime was dissolved in a mixture of AcOH (100 mL) and Ac_2O (50 mL). Zinc (dust, 6.54 g, 100 mg-atom) was added in small portions over a 1-h period. The mixture was stirred for 2 h and filtered. The filtrate was evaporated, giving a dark-brown solid. The crude acetamide was mixed with 400 mL of water and 6 g of decolorizing carbon and boiled for a few minutes and filtered. The filtrate was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated, giving **69** as an orange solid (2.44 g, 52.2% yield): mp 155–158 °C (lit.[33] mp 187–190 °C); IR (KBr) 3384, 1690, 1663, 1512, 1323, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (d, J = 8 Hz, 1 H), 7.30 (t, J = 8 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.66 (br s, 1 H, NH), 4.64 (m, 1 H), 3.87 (s, 3 H, CH_3O), 3.14 (m, 1 H), 2.84 (m, 2 H), 2.09 (s, 3 H, CH_3), 1.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 196.27, 170.14, 156.80, 132.75, 132.44, 127.20, 118.89, 114.78, 56.22 (CHNH), 55.63 (CH_3O), 29.74, 23.37 (CH_3), 22.08. Anal. ($C_{13}H_{15}NO_3$) C, H, N.

2-Acetamido-5-methoxy-1,2,3,4-tetrahydronaphthalene (70). A mixture of **69** (2.00 g), 5% palladium on carbon (1.00 g), AcOH (50 mL) and concentrated H_2SO_4 was hydrogenated on a Parr shaker at an initial pressure of 50 psi. The hydrogenation was completed in 4 h. The reaction mixture was filtered and the filtrate was diluted with CH_2Cl_2 (250 mL). The CH_2Cl_2 mixture was washed with water, 5% $NaHCO_3$, and brine and dried over Na_2SO_4. After removal of solvent, **70** (1.73 g, 92.0%) was obtained as a yellowish solid: mp 156–157 °C; IR (KBr) 3299, 1636, 1551, 1472, 1262, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (t, J = 8 Hz, 1 H), 6.68 (d, J = 8 Hz, 2 H), 5.58 (br s, 1 H, NH), 4.29 (m, 1 H), 3.82 (s, 3 H, CH_3O), 3.09 (dd, J = 16, 5 Hz, 1 H), 2.75 (m, 2 H), 2.64 (dd, J = 16, 7 Hz, 1 H), 2.00 (m, 1 H), 1.96 (s, 3 H, CH_3), 1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.54, 157.20, 135.27, 126.41, 124.39, 121.61, 107.29, 55.19 (CH_3O), 44.58 (CHNH), 35.58, 27.82, 23.55 (CH_3), 20.76; mass spectrum, m/z (relative intensity) 220 (1), 219 (2, M^+), 160 (100), 145 (26), 129 (22), 115 (19), 91 (21). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

2-Amino-5-methoxy-1,2,3,4-tetrahydronaphthalene (29). A mixture of **70** (0.80 g, 3.6 mmol) and 3 N HCl (150 mL) was heated under reflux for 18 h. The mixture was washed with ether, basified, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over K_2CO_3 and evaporated. The residue (0.65 g) was distilled bulb-to-bulb (95–105 °C, 0.5 mm; lit.[16] bp 126–128 °C, 2.0 mm), to give **29** (0.56 g, 86.0%) as a colorless oil: IR (neat) 3359, 3283, 2924, 2838, 1586, 1470, 1258, 1100, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (t, J = 8 Hz, 1 H), 6.69 (d, J = 8 Hz, 1 H), 6.65 (d, J = 8 Hz, 1 H), 3.80 (s, 3 H, CH_3O), 3.13 (m, 1 H), 2.93 (m, 2 H), 2.58 (m, 2 H), 1.98 (m, 1 H), 1.50 (m, 1 H), 1.36 (br s, 2 H,

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NH_2); ^{13}C NMR ($CDCl_3$) δ 157.12, 136.64, 126.09, 124.69, 121.37, 106.97, 55.11 (CH_3O), 46.85 ($CHNH_2$), 39.49, 32.41, 22.09 **29**·HCl was made in ether and recrystallized from ethanol/ether: mp 259–262 °C (lit.[16] mp 258–260 °C dec); IR (KBr) 3440, 2926, 1590, 1472, 1260, 1100, 768, 698 cm^{-1}; mass spectrum, *m/z* (relative intensity) 178 (9), 177 (51, free amine M^+), 160 (98), 145 (34), 134 (56), 104 (100), 91 (58). Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

2-Amino-7-methoxy-1,2,3,4-tetrahydronaphthalene (27). To a solution of NH_2OH·HCl (0.64 g, 9.2 mmol) and NaOAc (1.00 g, 12.2 mmol) in 4 mL of water was added a solution of 7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one (**62**, 1.32 g, 7.5 mmol) in 8 mL of ethanol. The mixture was stirred at room temperature for 30 min and then diluted with water and extracted with ether. The ether extract was washed with water and brine and dried over Na_2SO_4. After removal of solvent, a yellow solid was obtained (1.46 g). The crude oxime **65** was mixed with 5% palladium on carbon (0.25 g), methanol (60 mL), and concentrated HCl (2 mL) and hydrogenated on a Parr shaker at an initial pressure of 50 psi for 1.5 days. The mixture was filtered and evaporated. The residue was dissolved in 0.5 N HCl (150 mL). The aqueous solution was washed with ether, basified, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over K_2CO_3 and evaporated, giving a dark oil (1.14 g, 71.2%). After bulb-to-bulb distillation (110–120 °C, 0.5 mm; lit.[16] bp 109–113 °C, 0.6 mm), **27** (0.87 g, 54.3%) was obtained as a colorless oil: IR (neat) 3364, 3287, 2998, 2919, 2836, 1611, 1505, 1262, 1038, 827 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (d, *J* = 8 Hz, 1 H), 6.67 (dd, *J* = 3, 8 Hz, 1 H), 6.59 (s, 1 H), 3.73 (s, 3 H, CH_3O), 3.12 (m, 1 H), 2.92 (dd, *J* = 5, 16 Hz, 1 H), 2.78 (m, 2 H), 2.50 (dd, *J* = 16, 9 Hz, 1 H), 1.93 (m, 1 H), 1.54 (m, 1 H), 1.28 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 157.29, 136.16, 129.19, 127.62, 113.48, 111.81, 54.86 (CH_3O), 46.97 ($CHNH_2$), 39.49, 32.92, 26.92. **27**·HCl was made in ether and recrystallized from ethanol/ether: mp 216–218 °C (lit.[16] mp 213–214 °C); IR (KBr) 3436, 2924, 1613, 1493, 1453, 1266, 698 cm^{-1}; mass spectrum, *m/z* (relative intensity) 178 (9), 177 (36, free amine M^+), 160 (100), 145 (23), 134 (29), 91 (13). Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

2-Amino-6-methoxy-1,2,3,4-tetrahydronaphthalene (28). By the same procedure as for **27**, **28** (0.64 g, 80.3%) was obtained from **63** (1.20 g, 6.8 mmol) as a colorless oil: bp 110 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 3364, 3281, 2998, 2919, 2836, 1611, 1503, 1266, 1237, 1157, 1038, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (d, *J* = 8 Hz, 1 H), 6.64 (dd, *J* = 2, 8 Hz, 1 H), 6.61 (d, *J* = 2 Hz, 1 H), 3.72 (s, 3 H, CH_3O), 3.10 (m, 1 H), 2.75–2.95 (m, 3 H), 2.43 (dd, *J* = 9, 16 Hz, 1 H), 1.92 (m, 1 H), 1.53 (m, 1 H), 1.34 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 157.31, 136.54, 129.69, 126.98, 112.85, 111.64, 54.75 (CH_3O), 47.13 ($CHNH_2$), 38.35, 32.52, 28.03. **28**·HCl was made in ether and recrystallized from ethanol/ether: mp 250–253 °C (lit.[16] mp 243–246 °C); IR (KBr) 3440, 3023, 2928, 1609, 1505, 1246, 1161, 1044, 824, 698 cm^{-1}; mass spectrum, *m/z* (relative intensity) 178 (7), 177 (41, free amine M^+), 160 (60), 145 (12), 134 (100), 91 (50). Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

2-Amino-8-methoxy-1,2,3,4-tetrahydronaphthalene (26). By the same procedure as for **27**, **26** (0.64 g, 57.8%) was obtained from **61** (1.10 g, 6.2 mmol) as a white solid: mp 58–60 °C; bp 105 °C (bulb-to-bulb distillation, 0.25 mm; lit.[16] bp 110–112 °C, 0.8 mm); IR (KBr) 3030, 3024, 2910, 2830, 1575, 1460, 1245, 1100, 1065, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (t, *J* = 8 Hz, 1 H), 6.71 (d, *J* = 8 Hz, 1 H), 6.65 (d, *J* = 8 Hz, 1 H), 3.80 (s, 3 H, CH_3O), 3.09 (m, 2 H), 2.86 (m, 2 H), 2.26 (dd, *J* = 17, 9 Hz, 1 H), 1.94 (m, 1 H), 1.55 (m, 1 H), 1.33 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 157.35, 137.26, 126.03, 124.24, 120.85, 106.89, 55.19 (CH_3O), 47.19, 33.40, 32.44, 28.33. **26**·HCl was made in ether and recrystallized from ethanol/ether: mp 275–277 °C (lit.[16] mp 273–275 °C); IR (KBr) 3418, 2917, 1586, 1470, 1256, 1098, 1038, 764, 696 cm^{-1}; mass spectrum, *m/z* (relative intensity) 178 (11), 177 (63, free amine M^+), 160 (87), 145 (26), 134 (100), 104 (72), 91 (50). Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

2-Amino-8-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (12·HBr). A mixture of **26** (0.44 g, 2.5 mmol) and 48% HBr (10 mL) was heated at 120–130 °C for 2 h. After removal of solvent, the solid residue was recrystallized from ethanol/ether, giving **12**·HBr as yellow crystals (0.45 g, 74.3%): mp 241–242 °C; IR (KBr) 3332, 3013, 2928, 1588, 1493, 1468, 1316, 1275, 766, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.46 (br s, 1 H, phenolic), 8.13 (br s, 3 H, NH_3^+), 6.93 (t, *J* = 8 Hz, 1 H), 6.65 (d, *J* = 8 Hz, 1 H), 6.54 (d, *J* = 7 Hz, 1 H), 3.42 (m, 1 H), 3.08 (m, 1 H), 2.78 (m, 2 H) 2.46 (m, 2 H), 1.70 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 154.86, 136.02, 126.46, 119.77, 119.05, 111.74, 46.87, 27.55, 27.03, 26.57; mass spectrum, *m/z* (relative intensity) 164 (10), 163 (53, free amine M^+), 146 (82), 145 (50), 131 (36), 120 (91), 91 (100), 80 (58). Anal. ($C_{10}H_{13}NO$·HBr) C, H, N.

2-Amino-7-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (13·HBr). By the same procedure as for **12**·HBr, the **13**·HBr (1.28 g, 87.7%) was obtained from **27** (1.06 g, 6.0 mmol) as needles: mp 180–182 °C; IR (KBr) 3353, 3027, 2923, 1620, 1592, 1503, 1273, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.2 (s, 1 H, phenolic), 8.06 (br s, 3 H, NH_3^+), 6.89 (d, *J* = 8 Hz, 1 H), 6.57 (d, *J* = 8 Hz, 1 H), 6.50 (s, 1 H), 3.42 (m, 1 H), 3.01 (m, 1 H), 2.73 (m, 3 H), 2.08 (m, 1 H), 1.71 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 155.37, 133.51, 129.41, 124.83, 114.92, 113.88, 46.74, 33.10, 27.08, 25.91; mass spectrum, *m/z* (relative intensity) 164 (5), 163 (25, free amine M^+), 146 (100), 145 (46), 131 (26), 120 (94), 91 (63). Anal. ($C_{10}H_{13}NO$·HBr·0.5H_2O) C, H, N.

2-Amino-6-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (14·HBr). By the same procedure as for **12**·HBr, **14**·HBr (0.76 g, 86.2%) was obtained from **28** (0.64 g, 3.6 mmol) as a gray solid: mp >280 °C; IR (KBr) 3324, 3027, 2926, 1613, 1501, 1449, 1285, 1215, 1154, 972, 826, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.2 (br s, 1 H, phenolic), 8.10 (br s, 3 H, NH_3^+), 6.90 (d, *J* = 9 Hz, 1 H), 6.56 (d, *J* = 7 Hz, 1 H), 6.50 (s, 1 H), 3.41 (m, 1 H), 2.95 (m, 1 H), 2.73 (m, 3 H), 2.08 (m, 1 H), 1.71 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 155.62, 135.70, 129.82, 122.69, 114.63, 113.59, 47.01, 32.28, 26.92, 26.76; mass spectrum, *m/z* (relative intensity) 164 (4), 163 (28, free amine M^+), 146 (57), 131 (13), 120 (100), 91 (44). Anal. ($C_{10}H_{13}NO$·HBr) C, H, N.

2-Amino-5-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (15·HBr). By the same procedure as for **12**·HBr, **15**·HBr (0.77 g, 74.5%) was obtained from **29** (0.75 g, 4.2 mmol) as a yellowish solid: mp 249–251 °C (lit.[34] mp 252–253 °C); IR (KBr) 3330, 3025, 2926, 1588, 1495, 1464, 1267, 770, 698 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.36 (br s, 1 H, phenolic), 8.10 (br s, 3 H, NH_3^+), 6.94 (t, *J* = 8 Hz, 1 H), 6.66 (d, *J* = 8 Hz, 1 H), 6.55 (d, *J* = 8 Hz, 1 H), 3.41 (m, 1 H), 3.01 (m, 1 H), 2.78 (m, 2 H), 2.51 (m, 1 H), 2.13 (m, 1 H), 1.72 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 154.83, 133.86, 126.41, 121.73, 119.42, 112.14, 46.54 ($CHNH_3^+$), 33.09, 26.40, 21.23. Anal. ($C_{10}H_{13}NO$·HBr) C, H, N.

Radiochemical PNMT Assay. The assay employed in this investigation has been described elsewhere.[19,20] Briefly, a typical assay mixture consisted of 50 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of a 10 mM solution of unlabeled AdoMet, 5 μL of [*methyl*-^{3}H]AdoMet, containing approximately 2 × 10^6 dpm (specific activity ca. 15 Ci/mmol), 25 μL of substrate solution, 25 μL of inhibitor solution (if added), 25 μL of the enzyme preparation, and sufficient water to achieve a final volume of 250 μL. After incubation for 30 min at 37 °C, the reaction was terminated by the addition of 250 μL of 0.5 M borate buffer (pH 10) and extracted with 2 mL of toluene/isoamyl alcohol (7:3). The organic layer was removed and transferred to a scintillation vial and diluted with cocktail for counting. The mode of inhibition was ascertained by inspection of the $1/V$ vs. $1/S$ plot of the data.

Acknowledgment. This work was supported by National Institutes of Health research grants HL 34193 and GM 22988 and by the University of Kansas General Research Fund. We thank Kevin R. Criscione for doing the PNMT assays and Bart Wise for his assistance in the preparation of some intermediates. Helpful discussions with Dr. Daniel J. Sall during the preparation of this manuscript are very much appreciated.

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