M borate, pH 10. To this was added 2 mL of toluene/isoamyl alcohol (7:3), and the phases were mixed and centrifuged to facilitate separation. An aliquot (1 mL) was transferred to a counting vial, which contained 5 mL of scintillation cocktail (3a-70; Research Products International Corp.) for counting. Substrate constants were calculated by a hyperbolic curve-fitting program and also by linear regression of the reciprocal plots of the data; numbers calculated by the two different methods were in good agreement. Racemic phenylethanolamine was used as the variable substrate for the determination of inhibitor constants, with at least three different concentrations of inhibitor used to calculate each K_i value.

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Directional Probes of the Hydrophobic Component of the Aromatic Ring Binding Site of Norepinephrine *N*-Methyltransferase[1a]

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We investigated the directional nature of the bulk tolerance and hydrophobic binding in the aromatic ring binding region of the active site of norepinephrine *N*-methyltransferase (NMT) by comparing the substrate and inhibitor activities of *m*- and *p*-phenyl-substituted derivatives of amphetamine, phenylethanolamine, and α-methylbenzylamine. The para isomers of amphetamine and phenylethanolamine displayed significantly greater activities as inhibitor and substrate, respectively, than the meta isomers, which indicated that the bulk tolerance was near the para position. For benzylamines, the greatest inhibitory activity was observed for the meta isomer, demonstrating a significant difference in the binding requirements for phenylethylamines and benzylamines. These findings are consistent with a two-state model for the NMT active site that has been proposed elsewhere to account for its ability to bind both benzylamines and phenylethylamines in a fully extended side-chain conformation.

There now exists a considerable body of evidence that relates the increased activity of certain brainstem and hypothalamic nuclei, which appear to utilize epinephrine as their neurotransmitter, to the development of hypertension.[2-5] As a result, development of a means of selective modulation of epinephrine levels in these regions has become an attractive target for drug design. A possible approach to reduction of epinephrine levels without directly affecting other catecholamine levels is by the inhibition of norepinephrine *N*-methyltransferase (NMT, EC 2.1.1.28; also known as phenylethanolamine *N*-methyltransferase, PNMT), which is the only enzyme unique to the biosynthesis of epinephrine. In order to establish an experimental basis for the rational design of inhibitors of this enzyme, we have been attempting to characterize the active site of NMT by determining the optimum structural requirements for binding of substrates and inhibitors.[6-8] One aspect of this investigation has led to the conclusion that the region of the active site that secures the aromatic ring of substrates such as phenylethanolamine is primarily hydrophobic in character and can accommodate structures much larger than the phenyl ring.[8] The region appears to be roughly rectangular, with dimensions of 2–3 × 6–7 Å. Aromatic substrates and inhibitors are apparently bound to one end of this region, while more hydrophobic nonaromatic analogues tend to be attracted toward the center of the hydrophobic area.[9] Since the ring binding region promises to be an important factor in the design of novel and selective inhibitors for NMT, we have continued our investigation of this binding region.

Directionality in hydrophobic binding by the NMT active site has been suggested by Hansch and Glave as an interpretation of a QSAR correlation of the inhibitory activity of some ring-substituted amphetamines.[10] Their conclusion was that hydrophobic substituents contributed toward affinity only when attached to the ortho and/or the meta position but not the para position, which was taken as evidence of a hydrophobic "cleft" near the ortho and meta positions of the bound phenyl ring. A drawback in this earlier investigation, however, is that the size of the substituents employed, particularly in the meta position, was not large enough to allow unambiguous determination of the directionality of the bulk tolerance of the active site.

The phenyl substituent appeared to be well suited for probing the bulk tolerance and the directional nature of the hydrophobic region, since it is considerably larger and more hydrophobic than the substituents previously examined. In addition, the phenyl ring is planar, and we know from previous studies that the hydrophobic region best accommodates planar structures and has a severely limited "height" tolerance.[7,11] While the phenyl substituent extends the conjugated system and could enhance binding interactions involving the π electrons (π complex, charge transfer), our previous studies[7] have suggested this binding interaction to be minimal within the NMT active site. The phenyl substituent has little σ character, so that any

(1) (a) This paper has been taken, in part, from the Ph.D. Dissertation submitted to the Graduate School of the University of Kansas by M.F.R., 1982. (b) Supported by NIH Predoctoral Training Grant GM 07775.
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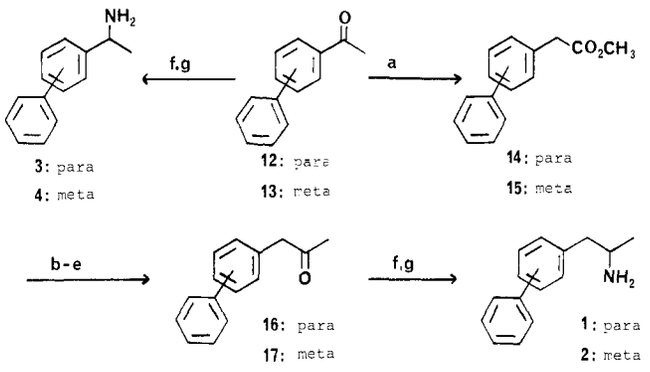
Scheme I. Synthesis of *m*- and *p*-Phenyl-Substituted Amphetamines (1 and 2) and α-Methylbenzylamines (3 and 4)[a]



[a] a = $Tl(NO_3)_3 \cdot H_2O$, $HClO_4$/MeOH; b = NaOH, 60% EtOH; c = $SOCl_2$, benzene; d = ethoxymagnesium diethylmalonate; e = $HOAc/H_2SO_4$, Δ; f = NH_4OCHO, Δ; g = 6 N HCl, Δ.

positive contribution toward binding provided by this substituent would likely be due to hydrophobic interactions.

We have, therefore, prepared the *m*- and *p*-phenyl-substituted analogues of amphetamine for evaluation as inhibitors of NMT. In order to confidently apply the findings of this study to the binding requirements for phenylethanolamine substrates and benzylamine-type inhibitors, we also prepared and evaluated the corresponding analogues of these compounds. The need for including substrate analogues in this investigation is based on the interpretation of the results from an earlier study, in which it was suggested that the binding requirements for substrates were more demanding than for inhibitors;[9] hence, it might be possible for amphetamine derivatives to bind to the active site in a range of orientations, which could cast some ambiguity upon conclusions based on the activity of these compounds alone. In contrast, substrate activity is very sensitive to slight changes in binding orientation, and so results obtained with bulky substrate analogues would complement and refine any conclusions that can be drawn from the activities of the amphetamine analogues. With regard to benzylamines, it was previously found by Fuller et al.[12,13] that the required aromatic substitution pattern of benzylamines for optimum NMT inhibitory activity is different from that for phenylethylamines. The directional nature of hydrophobic binding and bulk tolerance for benzylamine inhibitors must therefore be determined independently. Finally, the 1- and 2-naphthylethanolamines **10** and **9** were also included as planar steric probes with dimensions that are intermediate between the phenyl-substituted compounds employed in this study and the substiuents used by Hansch and Glave, which should allow for a more accurate determination of the extent of the bulk tolerances around the ring binding region. The synthesis and biochemical evaluation of these compounds are presented in this paper.

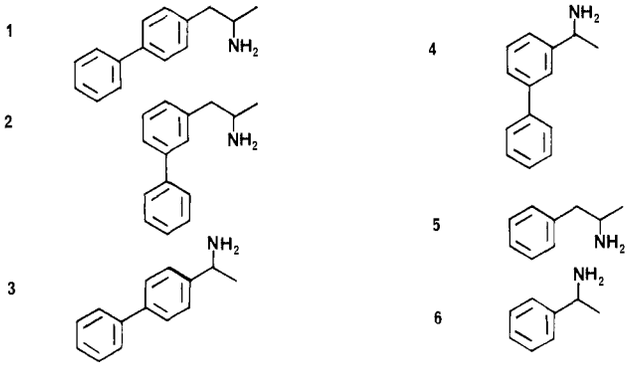
Chemistry. The route followed for the synthesis of amphetamine analogues **1** and **2** is illustrated in Scheme I. In each case, the starting material was the appropriate acetyl-substituted biphenyl (**12** or **13**), which could be directly converted to the benzylamines **3** and **4** by Leuckardt reductive amination. Thallium trinitrate induced rearrangement of the acetyl side chain[14] afforded, in good yields, the methyl esters **14** and **15**. We subsequently converted the esters to the acid chloride and then on to the necessary methyl ketones **16** and **17** by employing the method of Walker and Hauser[15] via the acylmalonates. Again, Leuckardt amination proved convenient for the preparation of the final products **1** and **2**.

The ethanolamines **7–10** were all prepared by addition of cyanotrimethylsilane to the corresponding aldehydes, followed by reduction with lithium aluminum hydride. 3-Biphenylcarboxaldehyde, which was required for the synthesis of **8**, was synthesized from 3-phenyltoluene by a multistep but overall high-yield procedure requiring NBS bromination, acetate displacement (potassium acetate in DMF), methanolysis, and oxidation with pyridinium chlorochromate.

Table I. NMT Inhibition Constants (K_i) for *m*- and *p*-Phenyl Analogues of Amphetamine and α-Methylbenzylamine

compd	K_i ± SEM, μM
1	262 ± 32
2	>2000
3	737 ± 31
4	89 ± 18
5	740 ± 68
6	460 ± 52

Biochemistry. In vitro evaluation of the compounds prepared in this study was accomplished by a radiochemical assay with partially purified bovine adrenal NMT.[16] Phenylethanolamine was the variable substrate in the determination of the K_i values for the competitive inhibitors **1–6**. The assay employs an extraction step with



organic solvent as a means of separating radiolabeled product from the assay mixture, which is dependent upon the extraction efficiency of the methylated product and would necessarily be corrected for in the calculation of absolute values for K_m and V_{max} of the substrates. However, since this study was concerned with the relative, and not absolute, activities for closely related structural isomers, slight differences in the partitioning of these isomers were not considered to be sufficient to result in significant error, and extraction efficiencies were not measured.

Results and Discussion

The inhibitory constants (K_i values) for the amphetamine derivatives **1** and **2** and the benzylamine analogues **3** and **4** are presented in Table I. In Table II are listed the kinetic constants found for substrates **7–11**. Com-

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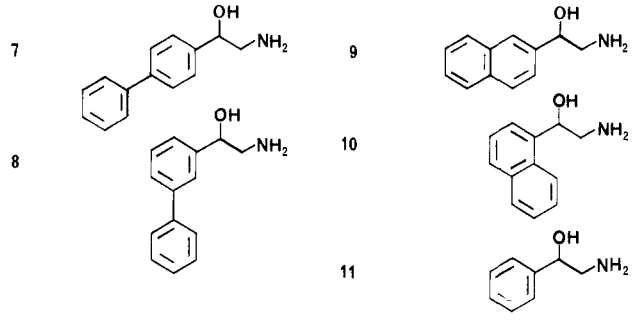

pound 1, with the substituent in the para position, was considerably more active as an inhibitor than the corresponding *m*-phenyl-substituted amphetamine isomer **2**. It was not possible to accurately determine a K_i value for **2** due to the low solubility of the HCl salt in water; however, we observed no significant inhibition at the maximum achievable assay concentration of 400 μM. Compound **1** was also significantly more potent than amphetamine (**5**),[6] suggesting that favorable interactions (presumably hydrophobic in nature) occurred with the added phenyl substituent. These data indicate that the bulk tolerance of the hydrophobic ring binding site is located near the para position of bound phenylethylamines, which is in contrast to the earlier conclusion based on the QSAR correlation.[17] The substrate constants in Table II also indicate the bulk tolerance of the active site to be near the para position, since neither of the ethanolamines that bear substantial bulk on the ortho or meta positions of the aromatic ring (compounds **8** and **10**) was well tolerated as a substrate. This is probably a result of unfavorable steric interactions within the ring binding site, although it is not possible to rule out the inducement of unfavorable conformational bias in the side chain of compound **10** by the naphthyl ring, which could affect the ability of **10** to bind.

With regard to the benzylamines **3** and **4**, in this case the para isomer **3** was found to be the less potent isomer. Compound **4** was found to be approximately 4 times more potent than α-methylbenzylamine (**6**) at inhibiting NMT, indicating that for this class of compounds the heart of the hydrophobic region is situated near the meta position of the aromatic ring. These results correspond to earlier reports in which it was found that, while a meta, para substitution pattern was preferred for NMT inhibitory activity in phenylethylamines (e.g., 3,4-dichloroamphetamine),[12] the optimum substitution pattern for benzylamines was found to be ortho, meta[13] (e.g., 2,3-dichloro-α-methylbenzylamine).

In a separate investigation employing conformationally defined analogues of phenylethylamine, we were able to conclude that the NMT active site requires substrates to assume a fully extended (trans-antiperiplanar) conformation in order for methyl transfer to occur.[18] To account for the potent inhibitory activity of benzylamine derivatives, which clearly cannot assume a conformation resembling that of a fully extended phenylethylamine, we proposed a two-state conformational model for the NMT active site.[18,19] This proposal can also be employed to rationalize the difference in the direction of bulk tolerance observed for phenylethylamines and benzylamines, as illustrated in Figure 1. In this case we have arbitrarily shown the amino group binding site to be conformationally adaptable, which allows it to "adjust" to accommodate both a benzylamine structure (Figure 1b) and an extended phenylethanolamine (Figure 1c). The transition from a benzylamine binding mode to a conformation that accepts substrates in a catalytically active state apparently requires a minimum of 0.5–1 kcal/mol in added energy, which corresponds to the difference in the observed binding energies of benzylamine and phenylethylamine to NMT.[11] Similar "substrate activation" mechanisms have been proposed for a wide variety of enzymes.[20]

Table II. NMT Substrate Constants for Biphenyl and Naphthyl Analogues of Phenylethanolamine

compd	K_m ± SEM, μM	V_{max}[a]	$V_{max}/K_m \times 100$
7	64 ± 13	3.48	5.44
8	656 ± 112	0.93	1.42
9	20 ± 4	1.12	5.60
10	132 ± 18	0.17	1.29
11	108 ± 23	1.75	1.62

[a] Units of V_{max} are nanomoles of product per milligram of protein per minute.

To summarize, the results presented here lead us to conclude that the hydrophobic component of the ring binding site for NMT substrates is oriented such that the addition of large hydrophobic substituents to the para position of phenylethylamine substrates and inhibitors would result in increased affinity. Benzylamines, in contrast, require that additional hydrophobic bulk be added to the meta position of the aromatic ring for favorable interactions to occur. These findings lend support to our hypothesis that phenylethylamines and benzylamines bind to different conformational states of the enzyme active site. That these results do not completely agree with the interpretations of earlier QSAR studies suggests that investigation of the NMT ring binding site be continued.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus calibrated with known compounds and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as an internal standard. IR spectra were taken on a Beckman IR-33 spectrophotometer. Elemental analyses were obtained at the University of Kansas on a Hewlett Packard 185B CHN analyzer and were within ±0.4% of the calculated values. Mass spectra were obtained on a Varian Atlas CH-5 electron-impact mass spectrometer. The following starting materials were purchased from Aldrich Chemical Co.: 4-acetylbiphenyl, 4-biphenylcarboxaldehyde, 1-naphthaldehyde, cyanotrimethylsilane, and 2-naphthaldehyde. 3-Phenyltoluene was purchased from Parish Chemical Co., and lithium aluminum hydride was purchased from Alfa Products. Silica gel for preparative chromatography (270–400 mesh) was obtained from Merck. 3-Acetylbiphenyl was prepared according to Sam and Shafik.[21]

1-(3-Biphenylyl)ethylamine (4). The procedure of Ingersol et al.[22] was followed. Into a 50-mL flask equipped with stir bar and reflux condenser was placed 6.0 g (95 mmol) of ammonium formate, which was heated at 185 °C for 2 h. After the ammonium

(17) Calculation of the expected inhibitory activities of the 3- and 4-phenylamphetamines 1 and 2 with the equation derived by Hansch and Glave predicted the 3-phenyl isomer 2 to be considerably more potent than 1. Precise comparisons are not possible, since their equation calculates IC_{50} values, whereas our study employed K_i values; nonetheless, the relative order of potency found in our investigation is clearly not as predicted by the equation.

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(22) Ingersol, A. W.; Brown, J. H.; Kim, C. K.; Beauchamp, W. D.; Jennings, G. *J. Am. Chem. Soc.* **1936**, *58*, 1808.

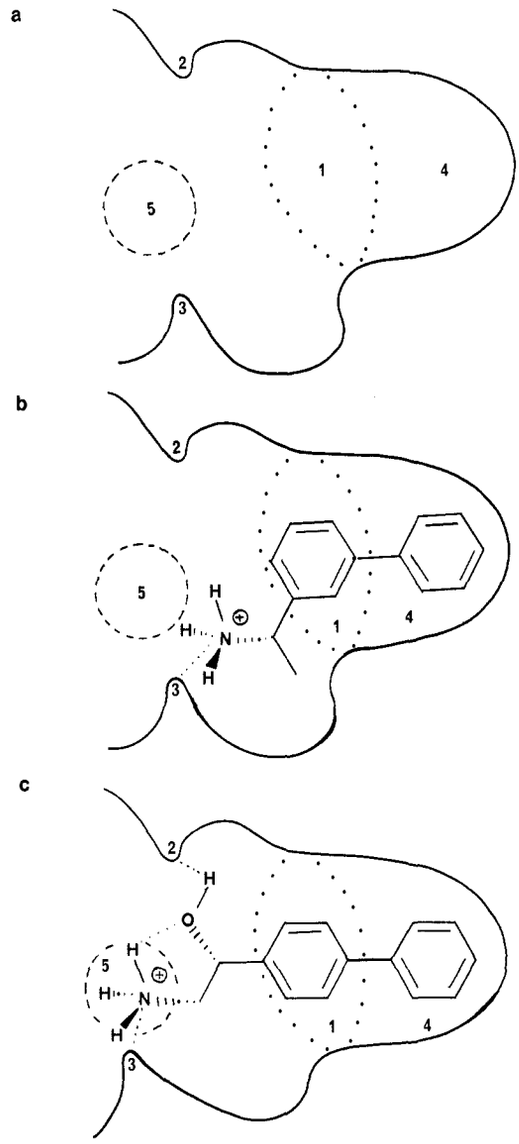

Figure 1. (a) Schematic representation of the NMT–amine binding site. Region 1 represents the binding region for the aromatic ring of benzylamines and phenylethylamine substrates and inhibitors; 2 represents the side-chain hydroxy binding site (defined in this case as a hydrogen bond acceptor), 3 represents the conformationally adaptable amino group binding site, and 4 represents the hydrophobic region near site 1. Area 5 is a hypothetical "reaction zone" in which the amino group must be for methylation to occur. (b) Proposed binding mode for 3-phenyl-α-methylbenzylamine (**4**). In this case, binding site 3 is capable of interacting with the amino group without having to relocate from its ground-state position (Figure 1a). The *S* isomer of **4** is illustrated, since it is known that the *S* isomer of α-methylbenzylamine is the more potent isomer at inhibiting NMT.[13] Compound **4** cannot serve as a substrate for NMT within this hypothetical active-site model because the amino group of **4** cannot reach the "reaction zone" 5. (c) Proposed binding mode of ethanolamine **7** within the NMT active site. The ethanolamine side chain is in a fully extended conformation, which is required for the amino group to reach the "reaction zone" 5. In this illustration, the hydroxy group stabilizes the side-chain conformation via intramolecular hydrogen bonding; further stabilization of the amino group within zone 5 is accomplished by the hydroxy-group interaction with site 2. In order to accept **7** in this conformation, it is necessary for site 3 to relocate slightly to assume an active-site conformation that is slightly higher in energy than the conformation illustrated in Figures 1a and 1b.

formate cooled to room temperature, 2.0 g of 3-acetylbiphenyl (**13**, 10 mmol) was added, and the rapidly stirred mixture was heated to 160 °C, which was maintained for 4 h. After the reaction mixture was cooled, 10.0 mL of 6 N HCl was added, and the solution was brought to reflux for 3 h. After the solution cooled, the contents of the flask were diluted with 25 mL of water and extracted with $CHCl_3$ (2 × 10 mL). The aqueous layer was then made basic by the cautious addition of solid KOH to the ice-cooled mixture, and the oil that separated out was extracted with ether (4 × 20 mL). The pooled ether layers were reextracted with 1 N HCl (3 × 25 mL), and the combined acid layers were concentrated in vacuo to approximately 20 mL, at which point a reddish oil separated out and crystallized. Recrystallization from water yielded 420 mg of **8**·HCl (18%) as clear plates: mp 141 °C; IR (amine base, film) 3390, 3305 (NH_2) cm^{-1}; NMR (amine base, $CDCl_3$) δ 7.12–7.65 (m, 9, arom), 4.12 (q, J = 6.5 Hz, 1, C*H*NH_2), 1.93 (br s, 2, D_2O exchangeable, NH_2), 1.42 (d, J = 6.5 Hz, 3, CH_3); EIMS (70 eV), m/e (relative intensity) 197 (M^+, 9), 183 (14), 182 ($M^+ - CH_3$, 100), 155 (17), 152 (9), 91 (12), 77 (14). Anal. ($C_{14}H_{15}N$·HCl) C, H, N.

1-(4-Biphenylyl)ethylamine (7) was prepared by the same procedure used for the preparation of **8**: IR (amine base, film) 3395, 3330 (NH_2) cm^{-1}; NMR (amine base, $CDCl_3$) δ 7.08–7.61 (symmetrical m, 9, arom), 4.04 (q, J = 6.2 Hz, 1, C*H*NH_2), 1.54 (br s, 2, D_2O exchangeable, NH_2), 1.39 (d, J = 6.3 Hz, 3, CH_3); EIMS (70 eV) m/e (relative intensity) 197 (M^+, 10), 196 (M^+ – 1, 5), 183 (17), 182 ($M^+ - CH_3$, 100), 180 (7), 155 (28), 154 (6), 153 (10), 152 (10), 91 (14), 77 (10); mp of the HCl salt, 219–222 °C (lit.[23] mp 221 °C). Anal. ($C_{14}H_{15}N$·HCl) C, H, N.

1-(3-Biphenylyl)acetic Acid. The procedure of McKillop et al.[14] was followed. 3-Acetylbiphenyl (2.0 g, 10.0 mmol) was dissolved in 10 mL of methanol and added dropwise to a stirred solution of 4.55 g (10.2 mmol) $Tl(NO_3)_3$·H_2O in 50 mL of methanol/70% $HClO_4$ (4:1) at room temperature. After 24 h, the reaction mixture was filtered to remove precipitated thallium salts, and the filtrate was concentrated in vacuo to ~30 mL. The remaining solution was diluted 3-fold with water and extracted with ether (4 × 30 mL). The pooled ether layers were dried (Na_2SO_4) and evaporated to leave 2.1 g of methyl 1-(3-biphenylyl)acetate (**15**). The ester was not purified but was taken up directly in 50 mL of 60% ethanol to which 1.0 g of NaOH had been added. After stirring at room temperature overnight, the solution was concentrated to approximately half its original volume, diluted with 25 mL of H_2O, and made acidic by the careful dropwise addition of concentrated HCl. The acid that precipitated from the solution was recovered by filtration and recrystallized from benzene to yield 1.7 g (80%) of clear plates: mp 135 °C (lit.[21] mp 135–136 °C); NMR ($CDCl_3$) δ 8.25 (unresolved m, 1, COOH), 7.16–7.68 (m, 9, arom), 3.65 (s, 2, CH_2).

1-(3-Biphenylyl)-2-propanone (17). The above acid (1.0 g, 4.7 mmol) was heated with 0.662 g (5.6 mmol) of freshly distilled $SOCl_2$ in 5.0 mL of benzene at reflux for 2 h. Evaporation of the solvent and excess reagent in vacuo left 1.04 g (96%) of acid chloride as a light yellow solid: NMR ($CDCl_3$) δ 7.05–7.55 (m, 9, arom), 4.05 (s, 2, CH_2).

This acid chloride (0.76 g, 3.3 mmol) was dissolved in 6.0 mL of dry ether and added dropwise via syringe to a flame-dried, N_2-purged flask containing 5.0 mL of an approximately 1.2 M solution of freshly prepared ethoxymagnesium diethylmalonate in benzene.[15] After stirring for 2 h at room temperature, the solution was treated with 5.0 mL of 20% H_2SO_4. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 10 mL). After drying ($MgSO_4$), the pooled organic layers were evaporated to leave a light brown oil, which was immediately taken up in a mixture of 8 mL of water, 2 mL of concentrated H_2SO_4, and 12 mL of glacial acetic acid. The resulting milky suspension was heated at reflux for 2 h, during which time the solution became clear. After it had cooled to room temperature, the mixture was placed in an ice bath and adjusted to neutral pH with 4 N NaOH. The milky solution was extracted with ether (4 × 25 mL), and the pooled ether layers were dried ($MgSO_4$) and evaporated to yield 0.55 g of brown oil. The oil was applied to a 5 × 15 cm column of silica gel (silica gel 60, Merck, 270–400 mesh) that was equilibrated in hexanes/ether (7:3) and subjected to flash chromatography with the same solvent mixture to yield 0.32 g (46%) ketone **17** as a clear oil. An analytical sample

(23) Ingersol, A. W.; White, E. G. *J. Am. Chem. Soc.* **1932**, *54*, 274.

was obtained by bulb to bulb distillation [bp 122–126 °C (0.15 mm)]: IR (film) 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.05–7.60 (m, 9, arom), 3.67 (s, 2, CH_2), 2.11 (s, 3, CH_3). Anal. ($C_{15}H_{14}O$) C, H.

1-(3-Biphenylyl)-2-aminopropane (2). The procedure employed was similar to that described above for **4**. To 6.0 g (95 mmol) of ammonium formate, which had been heated to 185 °C as outlined in the above procedure, was added ketone **17** (1.0 g, 4.7 mmol), and the mixture was heated at 170 °C overnight (17 h). In this case, the intermediate formamide that formed in this step was purified prior to acid hydrolysis by flash chromatography on a 5 × 7 cm column of silica gel [ether, R_f 0.13 on 0.2-mm silica gel TLC plates (Brinkman) eluted with the same solvent]. The purified material was suspended in 40 mL of 6 N HCl and heated at 80 °C with stirring for 36 h. The HCl salt of amine **2** crystallized out of the hydrolysis mixture and was recovered by filtration. Recrystallization from water gave 430 mg (36%) of **2**·HCl as clear, colorless plates: mp 217–220 °C; IR (amine base, film) 3380, 3290 (NH_2) cm^{-1}; NMR (amine base, $CDCl_3$) δ 6.87–7.56 (m, 9, arom), 2.75–3.33 (m, 1, $CHNH_2$), 2.65 (d, J = 2.5 Hz), 2.53 (d, J = 5.8 Hz, 2, CH_2), 1.27 (br s, D_2O exchangeable, 2, NH_2), 1.10 (d, J = 5.9 Hz, 3, CH_3); EIMS (70 eV), m/e (relative intensity) 212 (M^+ + 1, 7), 211 (M^+, 8), 179 (6), 178 (13), 168 (17), 167 (46), 166 (23), 165 (100), 164 (12.5), 163 (9), 153 (14), 152 (55), 151 (12), 139 (12), 128 (10), 127 (5), 115 (15), 102 (5), 98 (7), 91 (8), 89 (14), 82 (6), 77 (14). Anal. ($C_{15}H_{17}N$·HCl) C, H, N.

1-(4-Biphenylyl)-2-aminopropane (1) was prepared from 4-biphenylacetic acid by an identical procedure, mp HCl salt 235–238 °C (lit.[24] 237-238 °C). Anal. ($C_{15}H_{17}N$·HCl) C, H, N.

3-Biphenylcarboxaldehyde. 3-Phenyltoluene (0.228 g, 1.36 mmol) was dissolved in 30 mL of CCl_4 containing 0.254 g (1.42 mmol) of NBS, and the stirred mixture was heated to 80 °C. Approximately 3 mg of benzoyl peroxide (BPO) was then added, and the mixture was heated to reflux. After 2 h, an additional 2 mg of BPO was added, and heating was continued for another 2 h. After cooling, the reaction mixture was washed with water (3 × 10 mL), dried ($MgSO_4$), and evaporated to leave 0.318 mg of clear oil. NMR ($CDCl_3$) revealed that all of the starting material had been consumed (no CH_3 singlet at δ 2.37), and the residue consisted of the monobromo derivative [δ 4.45 (CH_2)] and a trace of the dibromo product [δ 6.59 (CH)]. This material was taken up in 15 mL of DMF, to which 0.255 g (2.6 mmol) of potassium acetate was added. The solution was heated at 80 °C for 7 h. After cooling to room temperature, the reaction mixture was diluted with 50 mL of water and extracted with ether (4 × 30 mL). After drying ($MgSO_4$), the pooled ether extracts were evaporated to yield 0.252 g (82%) of 3-phenylbenzyl acetate: NMR ($CDCl_3$) δ 6.84–7.35 (m, 9, arom), 4.91 (s, 2, CH_2), 2.00 (s, 3, CH_3). Methanolysis of the ester in 25 mL of methanol/1 N HCl (8:1) for 2 h at room temperature left the alcohol after evaporation, which was purified by flash chromatography on a 15 × 2.5 cm column of silica gel (Merck, 270–400 mesh) with $CHCl_3$ as the eluting solvent: yield 0.19 g (93%). The alcohol was treated with 0.39 g (1.8 mmol) of pyridinium chlorochromate in 15 mL of CH_2Cl_2 for 2 h at room temperature, followed by the addition of 1 g of Celite. Ether (40 mL) was then added, and the slurry was filtered through a 1-cm pad of Celite. The colorless filtrate was evaporated to leave 0.151 g of aldehyde (61% yield based on 3-phenyltoluene): IR (film) 2880, 2740, 1700 cm^{-1}; NMR ($CDCl_3$) δ 9.93 (s, 1, HCO), 8.14–7.28 (m, 9, arom). This material was suitable for conversion to the ethanolamine **8** without further purification.

General Procedure for the Synthesis of Ethanolamines 7–11. The procedure followed is described by Evans et al.[25] Into a flame-dried, N_2-purged flask was placed the aldehyde and a small amount of ZnI_2 (approximately 10 mg/mmol of aldehyde). Cyanotrimethylsilane (1.05 equiv) was then added dropwise to the stirred mixture. The reaction commenced immediately and was monitored by the disappearance of the carbonyl stretching frequency in the IR spectrum of the starting aldehyde. After the reaction had been judged complete, the contents of the flask were dissolved in 5 mL of dry ether and added dropwise to a slurry of $LiAlH_4$ (4–5 equiv) in ether at a rate which maintained a gentle reflux. Stirring overnight at room temperature was sufficient to achieve complete reduction. After quenching the excess reagent with water, followed by 1 N NaOH, the reaction mixture was filtered, and the ethereal solution was dried (K_2CO_3) and evaporated. The crude ethanolamines were converted to their HCl salts and characterized.

α-(Aminomethyl)-3-phenylbenzyl Alcohol (8). Amine base: IR (KBr pellet) 3370, 3310 (NH_2) cm^{-1}; NMR ($CDCl_3$) δ 7.12–7.65 (m, 9, arom) 4.48–4.73 (m, 1, CHOC), 2.94 and 2.85 (pair of doublets, J = 3 and 4.8 Hz, respectively, 2, $CHNH_2$), 1.96 (br s, 3, OH and NH_2); EIMS (70 eV), m/e (relative intensity) 213 (M^+, 19.5), 185 (11), 184 (66), 183 (44), 182 (100), 181 (14), 156 (10), 155 (66), 154 (11), 153 (23), 152 (22), 77 (22). HCl salt (recrystallized from ether): mp 158–161 °C (lit.[21] mp 223–225 °C). Anal. ($C_{14}H_{15}NO$·HCl) C, H, N.

α-(Aminomethyl)-4-phenylbenzyl Alcohol (7). **7**·HCl was crystallized from methanol/ether: mp 208 °C (lit.[26] mp 211–214 °C). Anal. ($C_{14}H_{15}NO$·HCl) C, H, N.

α-(Aminomethyl)-1-naphthylmethanol (10). Free amine: mp 127–129 °C (lit.[27] mp 125–126 °C). Anal. ($C_{12}H_{13}NO$) C, H, N.

α-(Aminomethyl)-2-naphthylmethanol (9). IR (amine base, film) 3380, 3310 (NH_2) cm^{-1}; NMR (amine base, $CDCl_3$) δ 8.33–7.12 (m, 7, arom), 5.36 (dd, J = 4 and 7.2 Hz, 1, C*H*OH), 3.0 (d, J = 4 Hz, 1) and 2.82 (d, J = 7 Hz, 1, C$H_2$$NH_2$), 2.81 (m, 3, exchangeable); EIMS (70 eV), m/e (relative intensity) 187 (20, M^+), 159 (7), 158 (54), 157 (67), 156 (50), 155 (16), 130 (10), 129 (100), 128 (51), 127 (34), 77 (6), 69 (6), 57 (10). HCl salt recrystallized from ethanol/ethyl acetate, mp 183–185 °C. Anal. ($C_{12}H_{14}N$-O·HCl) C, H, N.

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