

istaltic pump, we perfused the synaptosomes at a rate of 0.5 mL/min for 5 min without collecting the superfusate. Serial 1-min samples (0.5 mL) were then collected directly into liquid scintillation vials for the next 5 min. At this point, 25- μ L aliquots of previously prepared solutions of 1-6 were added to produce the desired drug concentrations in the superfusion chambers. One-minute samples (0.5 mL) of superfusate were collected for the remaining 10 min. The filters were aspirated to dryness and collected for counting. Treatment order was randomized, and treatments were randomized across the baths. Four experiments were run for each drug.

To each of the scintillation vials was added 5 mL of 2-ethoxyethanol, followed by 10 mL of 0.5% PPO/toluene. The vials were counted for tritium. Activity for each sample was expressed as a percent of the total radioactivity (total eluted plus residual

activity on the filter). These data are plotted in Figures 2A,B and 4A,B. A plot of the \log_{10} (percent radioactivity unreleased) vs. time gave linear regressions which closely approximated first-order disappearance kinetics (Figures 3A,B and 5A,B). Squared correlation coefficients (r^2) for all regressions were in the range 0.9976-0.9997. Rates for release were taken as the negative slopes of these lines and are expressed in Tables I and II as $K \times 10^4$. These served as convenient measures of relative potency for release, whereas the raw release data were difficult to quantitate. Comparison of these gave relative release rates, with the control release rate defined as 1.00.

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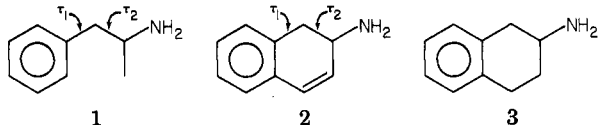
A New, Potent, Conformationally Restricted Analogue of Amphetamine: 2-Amino-1,2-dihydronaphthalene^{1,2}

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A new stimulant compound, 1,2-dihydro-2-naphthalenamine (2-amino-1,2-dihydronaphthalene, 2-ADN), was prepared as an analogue of amphetamine and of 2-aminotetralin. The optical isomers of 2-ADN were obtained by chemical resolution, and the absolute configuration was determined to be *R*-(+) and *S*-(-). Preliminary pharmacological evaluation revealed that racemic 2-ADN is approximately one-fourth as potent as (+)-amphetamine as a stimulant in mice. The *S*-(-) isomer of 2-ADN was found to be solely responsible for the stimulant effects of the racemate. Both reserpine and α -methyl-*p*-tyrosine antagonized the stimulation produced by 2-ADN.

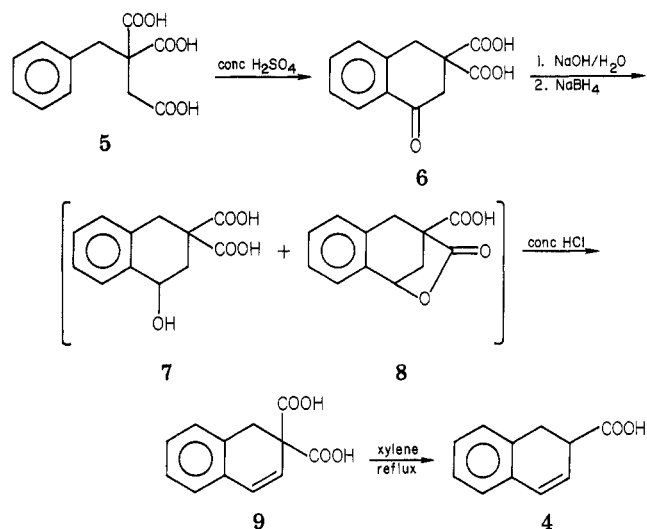
In this paper, we report the synthesis and preliminary pharmacology of a new, potent, conformationally restricted analogue of amphetamine (1), 2-amino-1,2-dihydronaphthalene (2-ADN, 2). This compound is conforma-



tionally restricted in the sense that there is no longer free rotation about the carbon-carbon bonds labeled τ_1 and τ_2 in amphetamine, since these are now part of a ring in 2, as shown above. One can also view 2-ADN as an analogue of 2-aminotetralin (3). The introduction of a double bond into the 3,4 position of 3 should serve to "flatten" the reduced ring, and it was of interest to see how this change would affect biological activity. We previously reported that 3 was inactive as a stimulant in mice at doses up to 8 mg/kg (44 μ mol/kg),^{3,4} although 3 has been reported by other workers to be a stimulant with one-tenth the activity of amphetamine.⁵

Chemistry. Although a few aryl-substituted derivatives of 2-ADN had been reported in the literature,⁶ the unsubstituted 2-ADN apparently had not been synthesized. Our initial approach was directed toward the synthesis of 4 (Scheme I). Since a general synthesis for a series of aryl-substituted derivatives of 2-ADN was desired, the published route to 4, utilizing sodium amalgam reduction of 2-naphthalenecarboxylic acid, appeared unsatisfactory.⁷ Therefore, a new synthesis of 4 was developed. Triacid 5⁸ was cyclized to keto diacid 6, which was reduced with NaBH₄ to a mixture of hydroxy diacid 7 and lactone acid 8, as determined by NMR analysis of the crude reaction

Scheme I



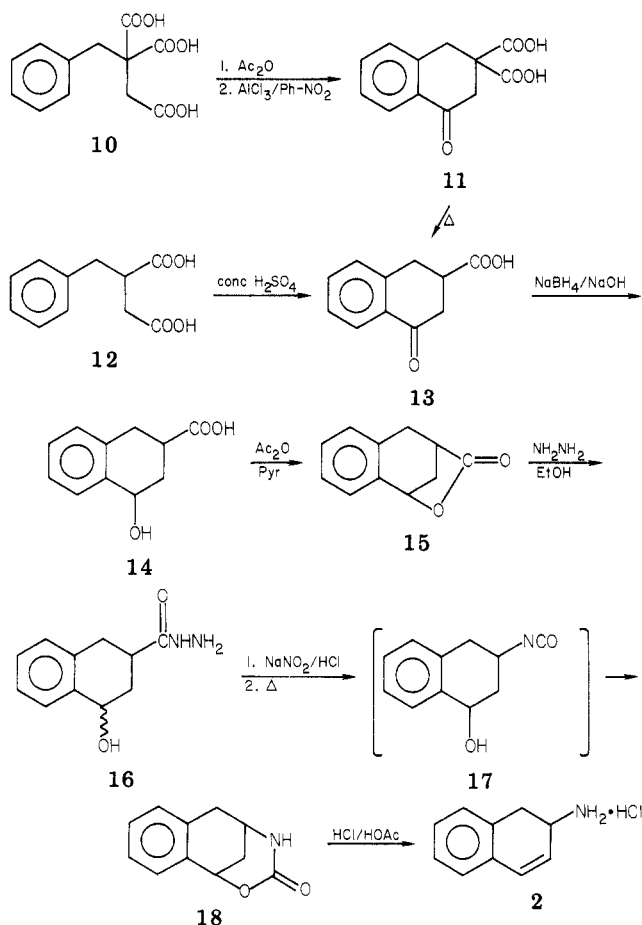
mixture. Treatment of the mixture with concentrated HCl gave diacid 9. Thermal decarboxylation of 9 in refluxing

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- (1) Taken, in part, from the Ph.D. Thesis of B.A.H., Purdue University, 1980.
- (2) A preliminary report of this work was presented at the 10th Annual Meeting of the Society for Neuroscience, Cincinnati, OH, 1980, Abstr 245.15.
- (3) Barfknecht, C. F.; Nichols, D. E.; Rusterholz, D. B.; Long, J. P.; Engelbrecht, J. A.; Beaton, J. M.; Bradley, R. J.; Dyer, D. C. *J. Med. Chem.* **1973**, *16*, 804.
- (4) Nichols, D. E.; Pfister, W. R.; Yim, G. K. W.; Cosgrove, R. J. *Brain Res. Bull.* **1977**, *2*, 169.
- (5) Van der Schott, J. B.; Ariens, E. J.; Van Rossum, J. M.; Hurkmans, J. A. T. M. *Arzneim.-Forsch.* **1962**, *12*, 902.
- (6) Violland, R.; Violland-Duperet, N.; Pacheco, H. *Bull. Soc. Chim. Fr.* **1971**, 307.
- (7) Derick, C. G.; Kamm, O. J. *Am. Chem. Soc.* **1961**, *38*, 400.

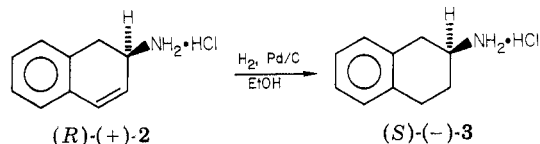
Scheme II



xylene yielded the required acid 4.

However, all attempts to convert 4 into 2 were unsuccessful. Failures were traced to base-catalyzed rearrangement of the 3,4 double bond into the 2,3 position. Attempts to prepare the acyl azide in the absence of base were also unsuccessful. Similarly, attempts to prepare the acid hydrazide or amide from the methyl ester of 4 led to double-bond isomerization. A modification of the method of Violland et al.⁶ was therefore employed to obtain 2. This route is shown in Scheme II.

Resolution of 2 into its optical isomers was accomplished by recrystallization of the salt obtained from the amine and either (+)- or (-)-*O,O*-dibenzoyltartaric acid. Catalytic reduction of (+)-2 gave (-)-3, previously shown to have the *S* configuration.⁹ This establishes the absolute configuration of 2 as *R*-(+) and *S*-(-).



Although 2 and its derivatives give stable, crystalline salts at room temperature, several decompose upon drying, especially at elevated temperatures, with the formation of naphthalenes as products.

Pharmacology. The parent amine, 2, and its two enantiomers were tested for their ability to increase spontaneous motor activity (SMA) in mice. The dose required

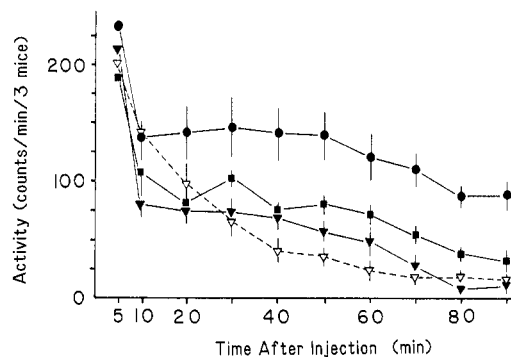


Figure 1. Effects on spontaneous motor activity in mice following intraperitoneal administration of racemic 2-HCl: (▼) 10 $\mu\text{mol/kg}$, (■) 20 $\mu\text{mol/kg}$, (●) 40 $\mu\text{mol/kg}$ (▽ = saline controls). The lowest dose did not significantly increase activity relative to controls at any time. The two higher doses gave significant increases, the highest at all times after 30 min postinjection and the 20 $\mu\text{mol/kg}$ dose at times between 30 and 80 min. ($p < 0.05$).

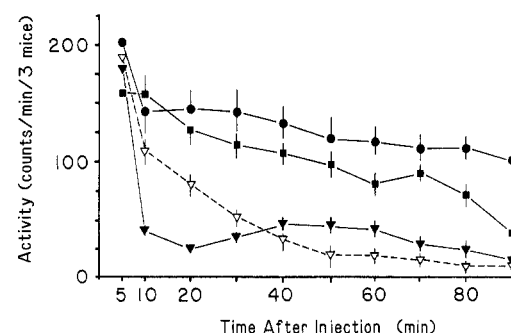


Figure 2. Effects on spontaneous motor activity in mice following intraperitoneal injection of racemic 2-HCl (●), (+)-2-HCl (▼), or (-)-2-HCl (■) (▽ = saline controls). Groups of three mice were used; $N = 6$. Using point by point Student's *t* test, racemic 2 and the (-) isomer gave significant activity increases, compared with controls ($p < 0.05$). Activity following administration of the (+) isomer was not significantly different from control at times from 30 to 90 min postinjection.

to increase SMA to 200% of the saline-treated control levels, called the SD_{200} , was calculated as described by Ogren and Ross,¹⁰ using groups of three mice. What we define as SD_{200} was called ED_{200} by Ogren and Ross. The effects of the catecholamine biosynthesis inhibitor α -methyl-*p*-tyrosine (AMPT, administered as the methyl ester hydrochloride) and the catecholamine-depleting agent reserpine on the increase in SMA elicited by 2 were also evaluated. Racemic 2 was further examined for its ability to produce stereotypic behavior in rats.

Results

Upon pharmacological screening, racemic 2-HCl was found to increase SMA in mice in a dose-dependent manner, as shown in Figure 1. The SD_{200} dose for racemic 2 was calculated to be 22 $\mu\text{mol/kg}$, while the SD_{200} dose for (+)-amphetamine was determined to be 5 $\mu\text{mol/kg}$. When the enantiomers of 2 were compared, the *S*-(-) isomer was found to be responsible for the increase in SMA; the increase in SMA by a 20 $\mu\text{mol/kg}$ dose of (*S*)-(-)-2 was not statistically different from that produced by a 40 $\mu\text{mol/kg}$ dose of racemic 2 for the first 70 min. By comparison, a 44 $\mu\text{mol/kg}$ dose of (*R*)-(+)-3 [which has the same absolute configuration as (*S*)-(-)-2] produced only

(8) Horii, Z.; Sakai, T.; Tamura, Y.; Tanaka, K. *Chem. Pharm. Bull.* 1961, 9, 442.

(9) Zymalkowski, F.; Dornhege, E. *Tetrahedron Lett.* 1968, 55, 5743.

(10) Ogren, S.-V.; Ross, S. B. *Acta Pharmacol. Toxicol.* 1977, 41, 353.

Table I. Effects of α -Methyl-*p*-tyrosine Pretreatment on the Spontaneous Motor Activity Increase in Mice Induced by (+)-Amphetamine or (-)-2·HCl

treatment	mean total act. counts per 90 min per 3 mice \pm SEM	% block of act.
saline	4 764 \pm 1048	
(+)-amphetamine ^a	14 356 \pm 1254	
(+)-amphetamine + AMPT ^b	5 144 \pm 1217 ^d	64.2
(-)-2 ^c	8 566 \pm 549	
(-)-2 + AMPT ^b	3 491 \pm 898 ^d	59.3

^a (+)-Amphetamine sulfate, 10 μ mol/kg. ^b α -Methyl-*p*-tyrosine methyl ester hydrochloride, 250 mg/kg ip, 4 h prior to testing. ^c (-)-2·HCl, 20 μ mol/kg. ^d $p < 0.05$.

a slight, but not significant, increase in SMA.⁴ In contrast to (S)-(-)-2, (R)-(+)-2 decreased SMA relative to saline controls for the first 30 min and was not significantly different from saline after that time. This is similar to the effects of (S)-(-)-3, which produced a significant decrease in SMA for 40 min.⁴ The results for 2 and its isomers are shown in Figure 2.

Pretreatment of mice with AMPT (250 mg/kg) produced a significant block of the SMA increase induced by 2, indicating that ongoing synthesis of catecholamines is necessary for the stimulant effect (Table I). As shown in Table II, marked stereotypy was produced in rats by a dose of 110 μ mol/kg of racemic 2. A similar level of stereotypy was produced by a dose of 27 μ mol/kg of (+)-amphetamine. Unlike amphetamine, 2-induced stereotypy was partially antagonized by pretreatment with reserpine, indicating that vesicular stores of catecholamines may also be involved in 2-induced stereotypy.

Conclusion

Based on these results, 2-ADN (2) represents a new conformationally restricted analogue of amphetamine. It produces stimulation of spontaneous motor activity in mice, and the racemate is approximately one-fourth as potent as (+)-amphetamine on a molar basis. The stimulant effects appear to be due primarily to the S-(-) isomer of 2-ADN. Studies with α -methyl-*p*-tyrosine and reserpine indicate that both intact vesicular stores and ongoing synthesis of catecholamines are important components of the stimulation produced by 2. Further pharmacological studies of 2 and its isomers are in progress to investigate more thoroughly the mechanism of action of 2 and its isomers.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries, using a Mel-Temp or a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-33 instrument, and absorbances are recorded in reciprocal centimeters. NMR spectra were recorded on a Varian EM 360 60-MHz or FT-80 spectrometer or on an NTC-FT superconducting 360-MHz instrument; the spectra were recorded at 60 MHz unless otherwise indicated. Chemical shifts are reported in δ units (parts per million) relative to Me₄Si as an internal standard. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a CEC 110 or on a Dupont 21-492 spectrometer. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within $\pm 0.4\%$ of the calculated values unless otherwise noted.

3,4-Dihydro-4-oxo-2,2(1*H*)-naphthalenedicarboxylic Acid (6). Triacid 5⁸ (15.3 g, 0.061 mol) was dissolved in 300 g of

concentrated H₂SO₄ and stirred for 3 h at 25 °C. The solution was poured over 400 g of ice, allowed to cool to room temperature, and stored at 5 °C. The resulting crystals were filtered and dried in vacuo to yield 11.22 g (79.0%) of 6: mp 176–178 °C dec (lit.¹¹ mp 170 °C); IR (KBr) 3400–2400 (OH), 1730 (acid C=O), 1690 (C=O) cm⁻¹; NMR (CDCl₃-Me₂SO-*d*₆) δ 3.10 (s, 2 H, C₃ H₂), 3.55 (s, 2 H, C₁ H₂), 7.50 (m, 3 H, Ar₆₋₈ H₃), 8.10 (m, 1 H, Ar₅ H).

1,2-Dihydro-2-naphthalenecarboxylic Acid (4). To a stirred solution of 1.60 g of NaOH (0.04 mol) in 50 mL of H₂O was added 6 (4.68 g, 0.02 mol). NaBH₄ (1.52 g, 0.04 mol) was added all at once, and the reaction was allowed to stir at 25 °C for 6 h. The solution was acidified to pH 1 with 6 N HCl and extracted with 2 \times 100 mL of Et₂O. The Et₂O extracts were combined and dried (MgSO₄), and the solvent was removed to yield a white solid. This was suspended in 30 mL of concentrated HCl and stirred at 25 °C for 60 h. The suspension was poured into 50 mL of H₂O and extracted with 3 \times 100 mL of Et₂O. The ether extracts were combined and dried (MgSO₄), and the solvent was removed to yield 2.61 g (59.9%) of crude diacid 9, mp 142–144 °C (with loss of CO₂).

This crude material (2.40 g, 0.011 mol) was suspended in 50 mL of xylene and heated at reflux, under N₂, for 2 h. The solution was cooled and extracted with 3 \times 50 mL of 10% Na₂CO₃ solution. The aqueous layer was acidified to pH 1 with concentrated HCl to precipitate the product. The acid was collected by suction filtration and air-dried. The crude acid was crystallized from acetone-hexane to yield 1.50 g (78.5%) of 4: mp 103–104 °C (lit.¹² mp 101 °C); IR (KBr) 2900–2400 (OH), 1690 (C=O) cm⁻¹; NMR (CDCl₃-Me₂SO-*d*₆) δ 3.45 (s, 2 H, C₁ H₂), 6.30 (d, *J* = 10 Hz, 1 H, C₃ H), 6.70 (d, *J* = 10 Hz, 1 H, C₄ H), 7.20 (m, 4 H, Ar H), 9.55 (br s, 2 H, COOH); CIMS, *m/e* (relative intensity) 192 (84), 190 (70), 175 (93), 173 (100), 143 (72).

1,2,3,4-Tetrahydro-4-oxo-2-naphthalenecarboxylic Acid (13). The benzy succinic acid (12) was dissolved in concentrated H₂SO₄ (20 g of H₂SO₄/g of benzy succinic acid) and was allowed to stir at 25 °C for 3–6 h. The dark-red reaction mixture was carefully poured over two times its weight of crushed ice while stirring. Upon cooling the reaction mixture to room temperature, the product began to crystallize. Crystallization was completed by cooling overnight at 5 °C. The resulting crystals were collected by suction filtration, washed with water, and dried in vacuo: yield 73.1%; mp 152–154 °C (lit.¹³ mp 146–149 °C); IR (KBr) 2900–2400 (OH), 1690 (C=O) cm⁻¹; NMR (acetone-*d*₆) δ 3.40–2.70 (m, 5 H, CH), 7.50 (m, 3 H, Ar₆₋₈ H₃), 8.10 (m, 1 H, Ar₅ H).

1,2,3,4-Tetrahydro-4-hydroxy-2-naphthalenecarboxylic Acid Hydrazide (16). A solution of the keto acid 13 (9.5 g, 0.05 mol), in 50 mL of 1.0 N NaOH was prepared and stirred at 25 °C. NaBH₄ (2.10 g, 0.055 mol) was added, portionwise, over a 3-min period, and the solution was allowed to stir for 6 h at 25 °C. The solution was acidified to pH 1 with 5 N HCl and extracted with 2 \times 300 mL of Et₂O. The Et₂O layers were combined and dried (MgSO₄), and the solvent was removed. Traces of H₂O were removed from the residual oil by azeotropic distillation of 150 mL of benzene-EtOH (1:1) to yield the crude hydroxy acid 14 as a white solid. This was dissolved in 100 mL of pyridine, and acetic anhydride (10.74 g, 0.105 mol) was added. The mixture was heated at reflux under N₂ for 3 h. The solvent was removed under reduced pressure, and the resulting oil was dissolved in 100 mL of Et₂O. The Et₂O solution was washed with 2 \times 50 mL of 3 N HCl, 3 \times 50 mL of 10% Na₂CO₃, and then with 50 mL of H₂O. After drying the ether solution over MgSO₄, we removed the solvent to yield lactone 15 as a brown oil. The IR spectra showed a C=O absorption at 1770 cm⁻¹. The lactone was dissolved in 50 mL of absolute ethanol, and 16 mL of 99% hydrazine hydrate was added. The solution was then heated at reflux under N₂ for 16 h. The solvent was removed, and traces of solvent and H₂O were removed from the solid by several azeotropic distillations with benzene and ethanol: yield 6.36 g (61.8%); mp 172–173 °C (MeOH); IR (KBr) 3270 (NH), 1650 and 1620 (C=O) cm⁻¹; NMR (Me₂SO-*d*₆) δ 2.50–1.70 (m, 3 H, C₂ H and C₃ H₂), 2.90 (br s, 2 H, C₁ H₂), 4.30 (br s, 4 H, NH, OH), 4.80 (m, 1 H, C₄ H), 7.20 (m, 3 H, Ar H₃), 7.60 (m, 1 H, Ar₅ H); MS, *m/e* (relative intensity)

(11) Attwood, A. J.; Stevenson, A.; Thorpe, J. C. *J. Chem. Soc.* 1923, 123, 1755.

(12) Pickard, R. H.; Yates, J. J. *J. Chem. Soc.* 1909, 1011.

(13) Haworth, R. D.; Jones, B.; Way, Y. M. *J. Chem. Soc.* 1943, 10.

Table II. Production of Stereotypy in Rats by (+)-Amphetamine and 2·HCl with and without Pretreatment with Reserpine^a

treatment	dose, μmol/kg ip	no. of rats	no. of rats falling within each stereotypy classification ^b				
			0	1	2	3	4
(+)-amphetamine	27	4					4
(+)-amphetamine + reserpine	27	4					4
(±)-2·HCl	110	4					4
(±)-2·HCl + reserpine	110	4			3	1	
saline + reserpine		2	2				

^a Reserpine, 5 mg/kg sc, 24 h prior to testing. ^b Stereotypy score: 0 = none, sleeping; 1 = continuous sniffing, some arousal; 2 = continuous sniffing, some head bobbing and weaving; 3 = continuous sniffing, continuous head bobbing and weaving; 4 = continuous sniffing, with repetitive sequences of head and limb movements, as well as some licking and rearing.

180 (43), 129 (100), 128 (39), 91 (16). Anal. (C₁₁H₁₄N₂O₂) C, H, N.

1,4,5,6-Tetrahydro-1,5-methano-2,4-benzoxazecin-3-one (18). Hydrazide 16 (2.27 g, 0.011 mol) was suspended in 25 mL of H₂O, and sufficient 3 N HCl was added to effect solution. Toluene (50 mL) was added, and the two-phase mixture was cooled to 0 °C. The reaction was stirred slowly while a solution of 0.83 g of NaNO₂ (0.012 mol) in 10 mL of H₂O was added dropwise. The reaction was stirred slowly until both layers were clear (about 10 min). The layers were separated, and the H₂O layer was extracted with 2 × 50 mL of Et₂O. The organic extracts were combined, dried (MgSO₄), filtered, and heated at reflux on a steam bath for 3 h, at which time the product had begun to precipitate. The solution was cooled, and the product was obtained by filtration: yield 1.62 g (78.8%); mp 276 °C dec; IR (KBr) 3150 (NH), 1690 and 1640 (carbamate C=O); NMR (Me₂SO-*d*₆) δ 2.70–2.20 (m, 2 H, methano bridge CH₂), 3.00 (d, 2 H, C₆ H₂), 4.00 (m, 1 H, C₅ H), 5.35 (m, 1 H, C₁ H), 7.45 (m, 5 H, Ar H and NH); CIMS, *m/e* (relative intensity) 190 (100), 174 (27), 129 (11). Anal. (C₁₁H₁₁N₂O₂) C, H, N.

1,2-Dihydro-2-naphthalenamine Hydrochloride (2). To a mixture of 38 mL of concentrated HCl and 152 mL of glacial AcOH was added 7.18 g (38 mmol) of 18. The solution was heated at reflux for 6 h. The solvent was removed under reduced pressure. The residue was dissolved in excess 1.0 N NaOH and extracted with 3 × 50 mL of Et₂O. The ether layers were dried (MgSO₄), and the solvent was removed under reduced pressure. The hydrochloride salt was prepared using ethanolic HCl, and the salt was crystallized: yield 4.81 g (69.8%); mp 209 °C (EtOH–Et₂O); IR (HCl salt, KBr) 3200–2400 (NH₃⁺) cm⁻¹; NMR (free base, CDCl₃) δ 2.50 (s, 2 H, NH₂), 2.85 (m, 2 H, C₁ H₂), 3.70 (m, 1 H, C₂ H), 6.0 (d of d, *J* = 10 Hz, *J'* = 4 Hz, 1 H, C₃ H), 6.5 (d of d, *J* = 10 Hz, *J'* = 1 Hz, 1 H, C₄ H), 7.20 (m, 4 H, Ar H); MS, *m/e* (relative intensity) 145 (68), 144 (100), 128 (24). Anal. (C₁₀H₁₂ClN) C, H, N.

Resolution of 2. To a solution of 2 (1.00 g, 5.51 mmol) in 20 mL of water was added NaOH (0.24 g, 6.00 mmol). The solution was extracted with 3 × 20 mL of Et₂O. The ether layers were combined, dried (MgSO₄), and filtered. A solution of (–)-*O,O*-dibenzoyl-L-tartaric acid monohydrate (Aldrich Chemical Co.; 2.07 g, 5.51 mmol) in absolute ethanol (50 mL) was added to the ether solution of 2. The crude salt was collected and recrystallized from 75% EtOH. Since the dibenzoyl tartrate was only sparingly soluble in all solvents tested, the progress of the resolution was checked by conversion of a small portion to the hydrochloride salt. This procedure yielded material of constant specific rotation after three recrystallizations of the dibenzoyl tartrate. The salt

was treated with 10% NaOH solution and extracted with Et₂O. The Et₂O solution was dried (MgSO₄) and filtered, and the solvent was removed. The free base was dissolved in EtOH, ethanolic HCl was added, and the solvent was removed. Crystallization from EtOH–Et₂O yielded 210 mg (42%) of the pure enantiomer, mp 218–220 °C dec; [α]_D²⁰ +194.1° (c 0.71, H₂O).

The combined mother liquors were worked up to obtain the free base enriched in the other isomer. This was treated with (+)-dibenzoyl-D-tartaric acid monohydrate (Aldrich Chemical Co.). The crude salt was collected by filtration and then crystallized three times and converted to the HCl salt as described above to yield 195 mg (39%) of the pure enantiomer: mp 218–220 °C dec; [α]_D²⁰ –191.0° (c 0.92, H₂O).

Pharmacology. Spontaneous Motor Activity in Mice. Male Swiss-Webster mice weighing 20–30 g were maintained on a diet of Wayne Lab Blox and tap water, ad libitum. Experiments were carried out in a well-lighted, quiet laboratory area between 1400 and 1600 hours. All drugs were administered intraperitoneally in a volume of saline equal to 1.0 mL per 10 g of body weight. Spontaneous motor activity (SMA) was measured using circular Woodard actophotometers. The mice were divided into groups of three per actophotometer and remained in the actophotometer for the duration of the experiment. Treatments were completely randomized. Data were analyzed by Student's *t* test. The SD₂₀₀ dose is the dose which produces twice (200%) the activity of the control. The SD₂₀₀'s for the test compounds were determined after the method of Ogren and Ross,¹⁰ except that mice were used in groups of three rather than individually; SD₂₀₀ is equivalent to what Ogren and Ross call ED₂₀₀. In the experiments with α-methyl-*p*-tyrosine (AMPT), AMPT, as the methyl ester hydrochloride (250 mg/kg), was injected intraperitoneally 4 h prior to injection of the test compounds.

Production of Stereotypy in Rats. Male Sprague–Dawley rats, 200–400 g, were maintained on a diet of Wayne Lab Blox and tap water, ad libitum. Experiments were carried out in a well-lighted, quiet laboratory area between 1300 and 1600 hours. Both (+)-amphetamine sulfate and 2·HCl were injected intraperitoneally in saline vehicle, and the level of stereotypy was recorded by a trained observer. The rats were housed individually in cages and only used once. In the experiments with reserpine, reserpine (5 mg/kg) was dissolved in peanut oil and injected subcutaneously 24 h prior to injection of the test compounds.

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