Derivatives of 5-Hydroxy-6-methyl-2-aminotetralin

Joseph G. Cannon,* Dale L. Koble,

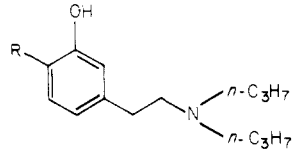
Division of Medicinal Chemistry and Natural Products, College of Pharmacy

John Paul Long, and Turkiz Verimer

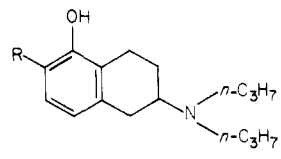
Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242. *Received January 21, 1980*

The title compounds were designed to provide semirigid congeners of *m*-tyramine in which the ring position ortho to the phenolic OH is blocked to metabolic hydroxylation. A sequence leading to a key synthetic intermediate, 5-methoxy-6-methyl-2-tetralone, has been developed. In animal test models for dopamine-like effects, the title compounds demonstrated qualitative and quantitative differences from the isomeric 5-methyl-6-hydroxy-2-aminotetralins and from 5,6-dihydroxy-2-aminotetralins. Two of the compounds were potent in a cat cardioaccelerator nerve assay, which involves dopamine receptors.

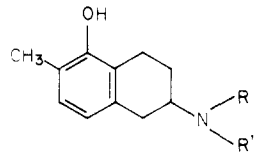
The marked dopamine agonist activity reported for *N*,*N*-di-*n*-propyl-*m*-tyramine (**1a**)[1] and for 2-(di-*n*-propylamino)-5-hydroxytetralin (**2a**)[2] led to speculation that a significant factor in the agonist effects might be a metabolic ring hydroxylation to give a catechol system (**1b**, **2b**) which results in molecules more closely resembling dopamine itself. The purpose of the present study was the preparation of 5-hydroxy-6-methyl-2-aminotetralin systems **3** in which the ring position ortho to the OH is blocked to metabolic hydroxylation. McDermed et al.[3] reported an isomeric 5-methyl-6-hydroxy-2-aminotetralin system **4** and stated that this compound "retained respectable potency" in emetic tests (dog), in stereotypy production (rat), and in blockade of the tonic electromyogram (reserpinized rat). However, **4** was approximately 100 times less potent an emetic than its 5,6-dihydroxy congener, and the relative potencies in stereotypy and in the antitremor assay were of the same order of difference. Compound **4** was likewise decidedly less potent in these assays than was apomorphine. Insofar as comparison may be valid, it is noted that **4** seems to be less potent in the rat stereotypy assay than is 6,7-dihydroxy-2-(di-*n*-propylamino)tetralin (**5**), as reported by our group previously,[4] but only by a factor of approximately 20. It seemed possible that the modest activity displayed by **4** might be a reflection of its in vivo hydroxylation to a system such as **6**. 6,7-Dihydroxy-2-aminotetralin systems (such as **5**) have a variety of dopamine-like effects in a variety of animal models.[4,5]



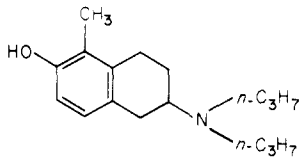
1a, R = H
b, R = OH



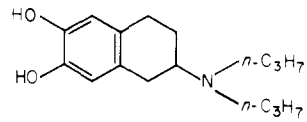
2a, R = H
b, R = OH



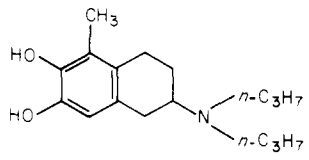
3, R, R' = H; Me; Et; *n*-C_3H_7, 2-C_3H_7



4



5



6

The target compounds **3**, unlike the isomeric system **4**, retain the "meta" OH groups which has been proposed[6] to be instrumental in determining type(s) of dopaminergic effects in synthetic dopamine-like molecules.

A key intermediate in the synthetic work was 5-methoxy-6-methyl-2-tetralone (**15**), the synthesis of which is outlined in Scheme I. Use of a phase-transfer catalysis technique in etherification of 3-methylsalicylic acid (**7** → **8**) resulted in very high yields of product, which were not attainable by more classical etherification procedures. Likewise, the phase-transfer catalysis strategy (based upon a procedure of Lee and Freedman)[7] permitted oxidation of the benzyl alcohol **9** to the aldehyde **10** in excellent yield in a reaction of a few minutes duration. A similar reaction without the phase-transfer catalyst was reported[8] to require overnight shaking at room temperature. The two-step conversion of the ester **8** to the aldehyde **10** resulted in overall much higher yields and in cleaner and more facile reactions than did a variety of one-step reductions of the free carboxylic acid of **8** to the aldehyde state. The Pummerer rearrangement–cyclization of **14** to **14a** (Scheme I) was unsuccessful using trifluoroacetic acid as the catalyst. However, use of trifluoracetic anhydride permitted a successful cyclization, albeit in modest yield. The 2-tetralone **15** was converted into the desired 2-aminotetralins by use of standard methods. Representative reactions are described under Experimental Section. The ether links were cleaved with concentrated HBr–acetic acid to give the free phenolic systems for pharmacologic testing. Spectral (IR, NMR, MS) data on all intermediates and final compounds were consistent with the proposed structures. See Table I.

Pharmacology. Results and Discussion. Compounds **17**, **19**, **21**, and **32**, in doses as high as 10 μmol/kg, were inactive in inhibition of transmission in the cat cardioaccelerator nerve. Table II summarizes biological ac-

(1) Geissler, H. E. *Arch. Pharm. (Weinheim)* **1977**, *310*, 749.
(2) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547.
(3) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362.
(4) Cannon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 1111.
(5) Costall, B.; Naylor, R. J.; Cannon, J. G.; Lee, T. *Eur. J. Pharmacol.* **1977**, *41*, 307.
(6) Cannon, J. G. *Adv. Neurol.* **1975**, *9*, 177.
(7) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, 1641.
(8) Meyers, C. Y. *J. Org. Chem.* **1961**, *26*, 1046.

0022-2623/80/1823-0750$01.00/0

Scheme I. Synthesis of 5-Methoxy-6-methyl-2-tetralone

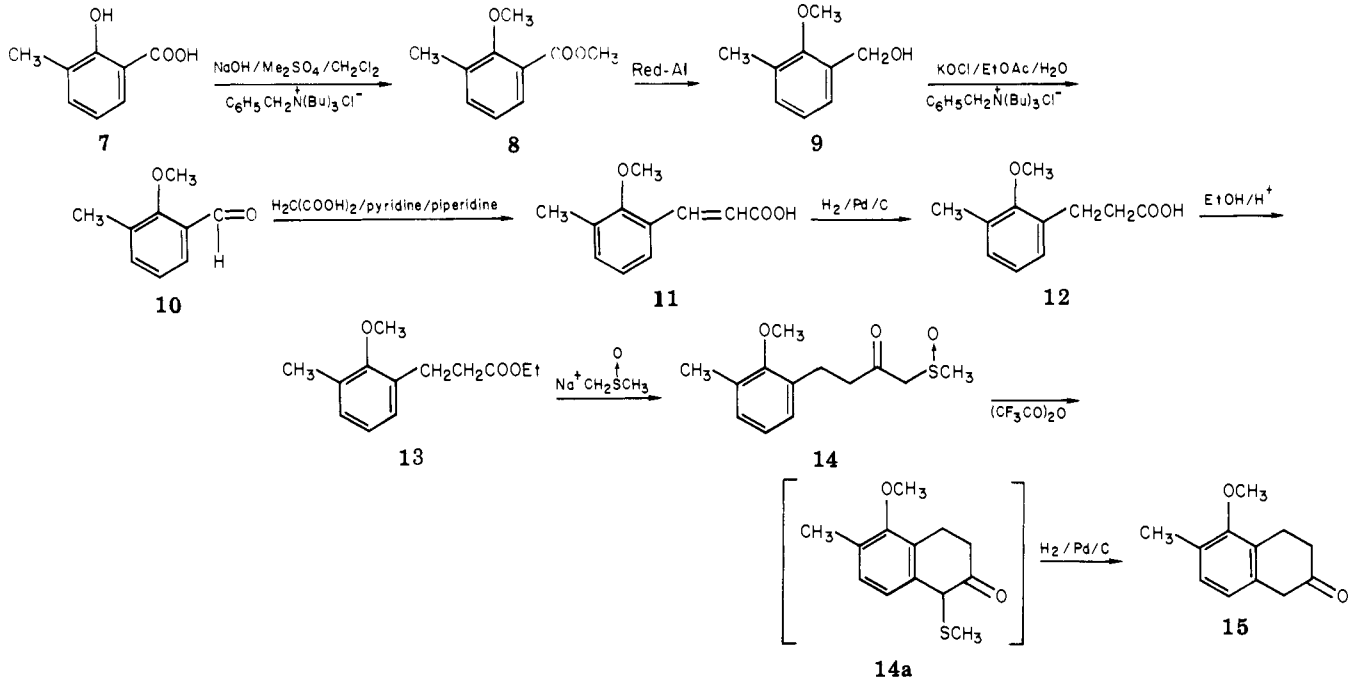
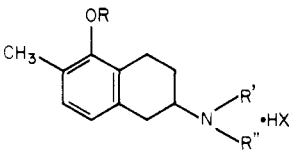


Table I. 2-Aminotetralin Derivatives



no.	R	R'	R''	X	method of prepn	mp, °C	yield, %	formula	anal.
16	Me	Me	H	Cl	A	220-221[a]	60	$C_{13}H_{20}ClNO$	C, H, N
17	H	Me	H	Br		237-238[a]	58	$C_{12}H_{18}BrNO$	C, H, N
18	Me	*n*-Pr	H	Cl	A	270-271[b]	75	$C_{15}H_{24}ClNO$	C, H, N
19	H	*n*-Pr	H	Br		183-184[a]	89	$C_{14}H_{22}BrNO$	C, H, N
20	Me	Et	H	Cl	A	204-205[a]	57	$C_{14}H_{22}ClNO$	C, H, N
21	H	Et	H	Br		225-226[a]	77	$C_{13}H_{20}BrNO$	C, H, N
22	Me	2-Pr	H	Cl	A	249-250[a]	25	$C_{15}H_{24}ClNO$	C, H, N
23	H	2-Pr	H	Br		249-250[a]	68	$C_{14}H_{22}BrNO$	C, H, N
24	Me	Me	Me	Cl	B	247-248[a]	85	$C_{14}H_{22}ClNO$	C, H, N
25	H	Me	Me	Br		235-239[c]	75	$C_{13}H_{20}BrNO$	C, H, N
26	Me	Et	Et	Cl	C	163-164[a]	96	$C_{16}H_{26}ClNO$	C, H, N
27	H	Et	Et	Br		188-189[a]	98	$C_{15}H_{24}BrNO$	C, H, N
28	Me	*n*-Pr	*n*-Pr	Cl	D	161-164[a]	48	$C_{18}H_{30}ClNO$	C, H, N
29	H	*n*-Pr	*n*-Pr	Br		180-184[a]	93	$C_{17}H_{28}BrNO$	C, H, N
30	Me	$CH_2C_6H_5$	H	Cl	D[d]	239-240[a]	50	$C_{19}H_{24}ClNO$	C, H, N
31	H	$CH_2C_6H_5$	H	Br		246-247[a]	91	$C_{18}H_{22}BrNO$	C, H, N
32	H	H	H	Br		234-235[a]	60	$C_{11}H_{16}BrNO$	H, N; C[e]

[a] From EtOH-Et_2O. [b] From MeOH-Et_2O. [c] From EtOH. [d] The benzene solution was diluted with an equal volume of AcOH prior to the catalytic hydrogenation. [e] C: calcd, 51.57; found, 49.89.

tivities of the *N,N*-dialkyl compounds. **27** and **29** caused inhibition of cardioacceleration induced by stimulation of postganglionic cardioaccelerator nerves. The potency ratios to apomorphine were 0.046 (0.02–0.08) and 0.765 (0.03–6.2) for **27** and **29**, respectively. The inhibitory effects of these compounds were blocked by haloperidol (0.1 mg/kg), a dopamine receptor blocking agent. These two compounds possess weak emetic activity. The central postsynaptic dopaminergic test, rat rotational behavior, showed a different profile for **27** and **29**. Compound **29** caused contralateral rotation in 6-hydroxydopamine-lesioned rats, but relatively high doses of **27** did not induce rotation. Surprisingly, the *N,N*-dimethyl homologue (**25**) and the primary amine (**32**) demonstrated no dopaminergic receptor agonist properties in any of the assays employed.

These results suggest that in the peripheral sympathetic nervous system the *N,N*-diethyl (**27**) and the *N,N*-di-*n*-propyl (**29**) derivatives possess potent inhibitory effects on transmission and that this inhibitory effect is probably mediated by presynaptic dopamine receptors. Low doses of haloperidol, a known dopamine receptor blocking agent, was an effective antagonist of the inhibition. Doses of **27** up to 400 μg/kg did not induce rotational behavior in rats. Likewise, no gnawing responses were noted with this dose. Thus, **27**, unlike **29**, appeared to be primarily a presynaptic inhibitor.

Replacement of the 6-OH of a 5,6-dihydroxy-2-aminotetralin by CH_3 appears to produce a compound with less

Table II. Biological Activities of Certain 5-Hydroxy-6-methyl-2-aminotetralin Derivatives

compd	inhibn of chronotropic response to cardioaccelerator nerve stimulation in the cat: ED_{50}, μmol/kg (95% CL)	blockade by haloperidol, 0.1 mg/kg	dog emesis, potency ratio[b]	rotational behavior in rats,[c] turns/h (dose)
apomorphine	0.022 (0.017–0.031); 8[a]	yes	1	175.21 ± 36.38 (0.41 μmol/kg); 7[a]
32	no inhibn up to 1.55 μmol/kg; 4[a]		NT[d]	inactive up to 15.6 μmol/kg; 3[a]
25	no inhibn up to 2.8 μmol/kg; 5[a]		NT	inactive up to 14.0 μmol/kg; 3[a]
27	0.48 (0.3–0.99); 7[a]	yes	0.046 (0.019–0.077) 3[a]	inactive up to 400 μmol/kg; 2[a]
29	0.025 (0.017–0.056); 5[a]	yes	0.042 (0.012–0.075); 4	131.43 ± 65.56 (5.85 μmol/kg); 7[a] 346.86 ± 166.56 (11.7 μmol/kg); 7[a]

[a] Number of experiments. [b] Apomorphine was administered in 0.08, 0.16, and 0.32 μmol/kg doses. The ED_{50} was 0.17 μmol/kg, and this value was assigned a potency value of 1. [c] Contralateral turning. [d] Not tested.

emetic activity than reported in the literature for the isomeric 5-methyl-6-hydroxy system 4[3] and for the 5,6-dihydroxy system **2b**[3], as well as less emetic activity than was reported[2] for the 5-hydroxy system **2a**. The inactivity of the primary amine **32** (Table I), the *N,N*-dimethyl homologue **25**, and all of the N-monoalkylated derivatives (**17**, **19**, **21**, **23**) in the cardioaccelerator nerve preparation contrasts with results in the 5,6-dihydroxy-2-aminotetralin series where high activity was observed for the primary amine, the secondary amines, and the *N,N*-dimethyl homologue.[9] The *N,N*-dimethyl and *N,N*-di-*n*-propyl homologues (**27** and **29**) are potent inhibitors in the cardioaccelerator nerve assay, and they showed a long duration of action (>3 h). They were effective inhibitors of the cardioaccelerator nerve when they were injected into the ileum of the cat,[9] which suggests that they may be orally effective.

Whether these pharmacological actions shown by 5-hydroxy-6-methyl-2-aminotetralins reflect effect(s) of the 6-methyl group on the metabolic fate of the molecules cannot yet be stated.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 267 instrument. NMR spectra were recorded with a Varian Associates T-60 instrument using tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. Cat Cardioaccelerator Nerve Stimulation. Cats (2–4 kg) were anesthetized ip with pentobarbital sodium (30 mg/kg). The arterial blood pressure was measured from the femoral artery by a Statham P23AA transducer, and heart rate was monitored with a Beckman cardiotachometer. All injections were made via a catheter placed in the femoral vein. A Beckman R511A recorder was used to monitor physiological changes in these experiments. After bilateral vagotomy, the right postganglionic cardioaccelerator nerves were isolated and placed on bipolar electrodes. The nerves were stimulated with a Grass S48 stimulator using the following parameters: 2 Hz, 5-ms pulse duration for 30 s at 20–25 V. All animals were pretreated iv with atropine sulfate (0.2 mg/kg). This preparation is useful to evaluate dopamine receptor interaction on the adrenergic nerve terminal.[10–13]

Emesis Experiments. Five adult mongrel dogs were housed individually and standard laboratory diet was supplied ad libitum. Drug solutions were administered sc and the frequency of vomiting was observed for 1 h. Apomorphine hydrochloride was used as the reference standard. The frequencies of vomiting produced by three doses of apomorphine and three doses of experimental compound were tabulated, and relative potencies and 95% confidence limits were calculated by a 3 × 3 parallel line bioassay.

Rotational Behavior. Male Sprague Dawley rats (Biolabs) received a unilateral stereotaxically placed injection of 6-hydroxydopamine hydrobromide (6 μg in 3 μL) in the region of the substantia nigra (anterior, 24; lateral, 1.8; vertical, 7.0). Drugs were administered sc and the rotational behavior was quantified during the next 1-h period. Circling responses were recorded atuomatically and were expressed as turns/hour. See Table II.

Methyl 2-Methoxy-3-methylbenzoate (8). 3-Methylsalicylic acid (10 g, 0.066 mol) was stirred at room temperature with 4 g (0.013 mol) of benzyltributylammonium chloride,[14] 8 g (0.2 mol) of NaOH, and 25 mL (0.26 mol) of dimethyl sulfate in 325 mL of H_2O and 325 mL of methylene chloride for 24 h. The organic layer was separated and the aqueous phase was extracted with three 150-mL portions of methylene chloride. The pooled organic phases were stirred with 100 mL of 15% NH_4OH for 2 h, and then the organic layer was separated and evaporated. The residue was taken up in 200 mL of Et_2O and stirred with 50 mL of 15% NH_4OH for 2 h. The ethereal phase was separated, the aqueous layer was washed with two 50-mL portions of Et_2O, and the combined ether solutions were dried ($MgSO_4$), filtered, and evaporated to give a yellow liquid which was distilled, bp 88–93 °C (1.2 mm), to afford 11.0 g (94%) of a colorless liquid, lit.[15] bp 120 °C (12 mm).

2-Methoxy-3-methylbenzyl Alchol (9). A solution of 30 g (0.167 mol) of 8 in 150 mL of benzene was added dropwise to 95 mL of 3.5 M sodium bis(2-methoxyethoxy)aluminum hydride in benzene (0.33 mol). After the addition was complete, the reaction mixture was heated under reflux for 2 h. The cooled mixture was then treated with excess 20% H_2SO_4. The white precipitate which formed was removed by filtration, and the organic layer was separated from the filtrate and dried ($MgSO_4$). Evaporation and distillation of the residue gave 24.9 g (98%) of a colorless liquid, bp 98 °C (0.7 mm). Anal. ($C_9H_{12}O_2$) C, H.

2-Methoxy-3-methylbenzaldehyde (10). A mixture of 30 g (0.2 mol) of **9**, 3.9 g (0.01 mol) of benzyltributylammonium chloride,[7] 500 mL of EtOAc, and 717 mL of KOCl solution (0.8

(9) Long, J. P., unpublished data.
(10) Ilhan, M.; Long, J. P.; Cannon, J. G. *Arch. Int. Pharmacodyn. Ther.* **1974**, *212*, 247.
(11) Long, J. P.; Heintz, S.; Cannon, J. G.; Lim, K. *J. Pharmacol. Exp. Ther.* **1975**, *192*, 336.
(12) Ilhan, M.; Long, J. P. *Arch. Int. Pharmacodyn. Ther.* **1975**, *216*, 4.
(13) Ilhan, M.; Long, J. P.; Cannon, J. G. *Arch. Int. Pharmacodyn. Ther.* **1976**, *219*, 193.
(14) McKillop, A.; Fiaud, J. C.; Hug, R. P. *Tetrahedron.* **1974**, *30*, 1379.
(15) Hill, P.; Short, W. F. *J. Chem. Soc.* **1937**, 260.

mol of KOCl, prepared from Olin Chemical Co. "HTH" granular dry chlorine for swimming pools by the method of Meyers[8]) was stirred for 24 min, cooling the reaction mixture by immersion in running tap H_2O. The aqueous layer was extracted several times with Et_2O, and the pooled organic phases were evaporated to leave a liquid, which was taken up in Et_2O and washed with H_2O and then with 5% $NaHCO_3$. The ethereal solution was dried ($MgSO_4$) and filtered, and the Et_2O was evaporated to leave a liquid, which was distilled, bp 69 °C (0.5 mm), to yield 26.2 g (89%) of a colorless liquid which soon crystallized: mp 44–46 °C; lit.[15] bp 115–120 °C (12 mm). Anal. ($C_9H_{10}O_2$) C, H.

2-Methoxy-3-methylcinnamic Acid (11). Malonic acid (35 g, 0.34 mol) and 25 g (0.17 mol) of **10** were heated in 2.5 mL of piperidine and 80 mL of pyridine for 2 h at 85 °C and then for 2 h at 115 °C. The solution was cooled and poured into a 20% excess of cold dilute HCl. The white precipitate which formed was collected on a filter, washed with cold H_2O, and dried in a vacuum desiccator to give 30 g (94%) of product, mp 176 °C. Anal. ($C_{11}H_{12}O_3$) C, H.

3-(2-Methoxy-3-methylphenyl)propionic Acid (12). Compound 11 (25 g, 0.13 mol) in 500 mL of EtOH was hydrogenated over 1 g of 10% Pd/C in a Parr shaker apparatus at an initial pressure of 55 psig. Uptake of H_2 was complete in 1 h. The reduction mixture was filtered and the solvent was evaporated to afford 25 g (99%) of product, mp 77–78 °C. Anal. ($C_{11}H_{14}O_3$) C, H.

Ethyl 3-(2-Methoxy-3-methylphenyl)propionate (13). Compound **12** (31.8 g, 0.16 mol), 66 mL of EtOH, 1.5 mL of concentrated H_2SO_4, and 195 mL of benzene were refluxed in a Dean–Stark apparatus for 36 h. The cooled reaction mixture was washed with 5% $NaHCO_3$, H_2O, and saturated NaCl and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue, bp 139–140 °C (0.3 mm), gave 34.1 g (99%) of product. Anal. ($C_{13}H_{18}O_3$) C, H.

2-(2-Methoxy-3-methylphenyl)ethyl Methylsulfinylmethyl Ketone (14). A mineral oil dispersion of 15.9 g of 50% NaH (0.33 mol) was washed twice under N_2 with pentane. Dimethyl sulfoxide (210 mL) was added, and the resulting mixture was heated between 55 and 70 °C for 2.5 h. To the resulting cooled solution was added dropwise, with stirring, 31.1 g (0.14 mol) of **13** in 180 mL of tetrahydrofuran (purified by distillation from $LiAlH_4$), maintaining the temperature of the reaction mixture lower than 10 °C. After addition was complete, the reaction mixture was stirred at room temperature for 3 h. It was then poured into ice–H_2O, the resulting mixture was brought to pH 2 with HCl, and this mixture was extracted with several portions of $CHCl_3$. The combined extracts were washed with H_2O and dried ($MgSO_4$). Filtration and evaporation of the solvent gave 34.5 g (92%) of crude product which was used in the next step without purification. An analytical sample of 14 was obtained by recrystallization from Et_2O–petroleum ether, mp 49–50 °C. Anal. ($C_{13}H_{18}O_3S$) C, H, S.

1,2,3,4-Tetrahydro-5-methoxy-6-methyl-2(1*H*)-naphthalenone (15). Trifluoroacetic anhydride (38.5 mL, 0.272 mol) and 34.5 g (0.136 mol) of **14** were refluxed in 1.4 L of MeCN for 1 h. The solvent was evaporated under reduced pressure, the residue was taken up in $CHCl_3$, and this solution was washed with 5% $NaHCO_3$ and H_2O and dried ($MgSO_4$). Filtration and evaporation of the filtrate left a red oil, which was taken up in 400 mL of glacial AcOH and hydrogenated over 19 g of 5% Pd/C at an initial pressure of 55 psig. Uptake of H_2 ceased after 20 h. The reduction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a red oil, which was shaken on a rotary shaker overnight with 31.3 g of $NaHSO_3$, 62 mL of H_2O, and 20.5 mL of EtOH. The bisulfite addition product of **15** was collected on a filter and washed with 99% EtOH and Et_2O. The free ketone was obtained by bringing a suspension of the bisulfite addition product in H_2O to pH 8 with Na_2CO_3 and extracting the resulting aqueous mixture with several portions of $CHCl_3$. The pooled extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 9.44 g (37% based upon the amount of 14 used) of **15**. Recrystallization from Et_2O–petroleum ether gave an analytical sample, mp 56–57 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

Method A. 2-(Methylamino)-5-methoxy-6-methyltetralin Hydrochloride (16). This was a procedure of Weichet et al.[16] Compound **15** (0.95 g, 0.005 mol) and 2 mL of 36% aqueous methylamine solution (0.025 mol) in 8 mL of MeOH were treated with 0.19 g (0.005 mol) of $NaBH_4$, added in portions over 45 min, maintaining the temperature of the reaction mixture below 10 °C. The resulting mixture was stirred at room temperature for 5 h, then 0.66 g (0.005 mol) of K_2CO_3 was added, and MeOH and excess methylamine were removed under reduced pressure. H_2O was added to the oily residue, and the resulting mixture was extracted thrice with Et_2O. The pooled ethereal extracts were extracted with dilute HCl, and the aqueous extract was washed twice with Et_2O. It was then brought to pH 10 with KOH and extracted several times with Et_2O. The pooled extracts were dried ($MgSO_4$) and filtered, and the filtrate was treated with ethereal HCl. The resulting light purple solid was recrystallized. See Table I.

Method B. 2-(Dimethylamino)-5-methoxy-6-methyltetralin Hydrochloride (24). This was a procedure of Sondengam et al.[17] Compound **16** (0.86 g, 0.004 mol) was heated under reflux with 2.63 mL of 37% aqueous formaldehyde and 15 mL of MeOH for 45 min. After the solution cooled, 0.263 g (0.007 mol) of $NaBH_4$ was added in small portions, with stirring, over 30 min. The reaction mixture was then evaporated under reduced pressure. The residue was taken up in 50 mL of H_2O and the solution was brought to pH 10 with NaOH. It was extracted with three 50-mL portions of Et_2O, and the pooled extracts were dried ($MgSO_4$), filtered, and treated with ethereal HCl. The resulting solid was recrystallized. See Table I.

Method C. 2-(Diethylamino)-5-methoxy-6-methyltetralin Hydrochloride (26). This was a procedure of Marchini et al.[18] $NaBH_4$ (0.720 g, 0.02 mol) was added, under N_2, to 3.7 mL of glacial AcOH in 25 mL of benzene, maintaining the temperature below 25 °C. The resulting solution was stirred for 1 h, then the free base of **20** (1.08 g, 0.0038 mol) in 25 mL of benzene was added in one portion. The resulting mixture was heated under N_2 under reflux overnight. Volatiles were removed under reduced pressure. The residue was treated with 50 mL of H_2O and 70 mL of benzene, and this mixture was brought to pH 10 with NaOH. The benzene layer was separated and the aqueous layer was extracted with 30 mL of benzene. The combined benzene solutions were evaporated under reduced pressure, and the residue was treated with 50 mL of Et_2O and 50 mL of H_2O. The pH of this mixture was brought to 2 with HCl and the layers were separated. The Et_2O layer was extracted with 50 mL of H_2O. The combined aqueous solutions were brought to pH 10 with NaOH and were extracted with four 50-mL portions of Et_2O. The pooled extracts were dried ($MgSO_4$) and filtered, and the filtrate was treated with ethereal HCl. The resulting solid was recrystallized. See Table I.

Method D. 2-(Di-*n*-propylamino)-5-methoxy-6-methyltetralin Hydrochloride (28). Compound **15** (1.0 g, 0.005 mol), 2.9 mL (0.21 mol) of di-*n*-propylamine, and 0.1 g of *p*-toluenesulfonic acid monohydrate were heated under reflux with 60 mL of benzene in a Dean–Stark apparatus for 3 days. The resulting solution was cooled and an equal volume of anhydrous EtOH was added. This solution was hydrogenated over 0.075 g of PtO_2 in a Parr shaker apparatus at an initial pressure of 45 psig. After 3 h, uptake of H_2 ceased. The reduction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in 150 mL of Et_2O and 50 mL of H_2O. This mixture was brought to pH 10 with KOH. The aqueous phase was separated and the Et_2O layer was washed once with H_2O. A fresh portion of H_2O was added to the Et_2O phase and this mixture was brought to pH 4 with HCl. The aqueous layer was separated, brought to pH 10 with KOH, and extracted with three 50-mL portions of Et_2O. The combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was treated with ethereal HCl. The resulting solid was recrystallized. See Table I.

Method E. 2-Amino-5-hydroxy-6-methyltetralin Hydrobromide (32). Compound **31** (Table I) (0.9 g, 0.0025 mol) in 150

(16) Weichet, J.; Hodrova, J.; Bla'ha, L. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2040.
(17) Sondengam, B. L.; Hentchoya-Hemo, J.; Charles, G. *Tetrahedron Lett.* **1973**, 261.
(18) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 3453.

mL of EtOH was hydrogenated over 0.9 g of 5% Pd/C at an initial pressure of 45 psig. H_2 uptake was complete in 5 h. The reduction mixture was filtered and the filtrate was evaporated under reduced pressure to give a solid residue, which was recrystallized. See Table I.

Ether Cleavage Reactions. The HCl salt of the methyl ether (0.001 mol) was heated under reflux under N_2 (pot temperature 135 °C) in 11 mL of 48% HBr and 3 mL of AcOH for 2 h. Volatiles were removed under reduced pressure and the residue was recrystallized. See Table I.

Acknowledgment. This work was supported by Grant GM-22365 from the National Institute of General Medical Sciences.

Conformationally Defined Aromatic Amino Acids. Synthesis and Stereochemistry of 2-*endo*- and 2-*exo*-Amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic Acids (2-*endo*- and 2-*exo*-Aminobenzobicyclo[2.2.2]octene-2-carboxylic Acids)

Gary L. Grunewald,* Simon H. Kuttab,[1] Michael A. Pleiss, James B. Mangold,

Department of Medicinal Chemistry

and Phyllis Soine

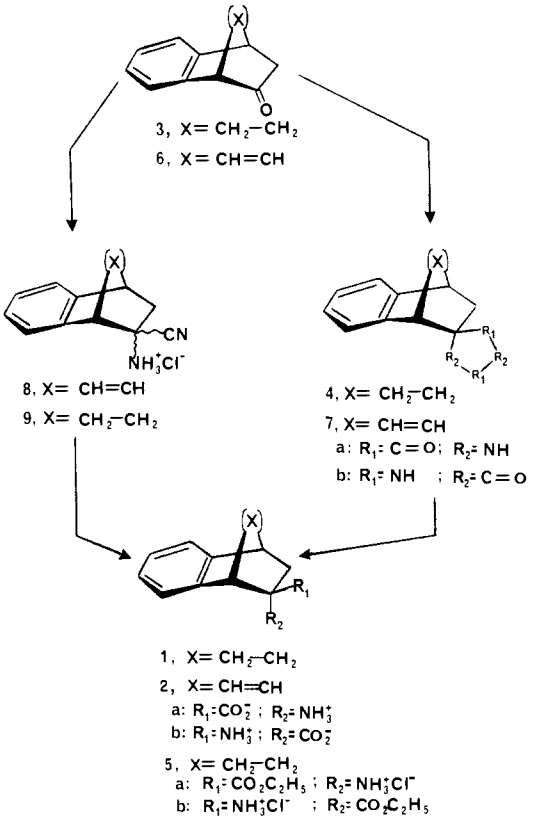
Enzyme Laboratory, University of Kansas, Lawrence, Kansas 66045. *Received November 5, 1979*

The synthesis of the title compounds **1a** and **1b** has been accomplished in good yield by conversion of ketone **3** to the corresponding hydantoins **4a** and **4b** via a Bucherer–Bergs reaction, followed by barium hydroxide hydrolysis. The stereochemical assignments of the intermediate hydantoins **4a** and **4b** and the ethyl ester hydrochlorides **5a** and **5b** were determined by ^1H NMR analysis. Attempts toward the synthesis of 2-amino-1,4-dihydro-1,4-ethanonaphthalene-2-carboxylic acid isomers **2a** and **2b** utilizing the pathway discussed for **1a** and **1b** led only to products arising from a retro-Diels–Alder reaction. Preliminary screening of **1a** and **1b** as inhibitors of phenylalanine hydroxylase (PH) and phenylalanine decarboxylase (PAD) is also discussed. The use of the benzobicyclo[2.2.2]octene nucleus for the construction of conformationally defined analogues of important medicinal agents is rationalized, and the title compounds are compared to several other conformationally defined systems. The title compounds represent conformationally defined models of the lower energy conformations of α-methylphenylalanine.

As part of a current project dealing with the synthesis of conformationally defined analogues of aromatic amino acids and adrenergic amines[2] using the benzobicyclo-[2.2.2]octene and -octadiene ring systems, we wish to report the versatile, high-yielding synthesis of 2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid isomers **1a** and **1b**.[3] The attempted synthesis of 2-amino-1,4-dihydro-1,4-ethanonaphthalene-2-carboxylic acid isomers **2a** and **2b** and preliminary biochemical screening of the title compounds are also discussed. These compounds represent conformationally defined analogues of the lower energy conformations of α-methylphenylalanine.

Chemistry. Synthesis of the two isomeric amino acids **1a** and **1b** in the benzobicyclo[2.2.2]octene series was achieved starting with ketone **3**[4] (Scheme I). Treatment of **3** with potassium cyanide and ammonium carbonate in a Bucherer–Bergs synthesis[5] afforded a mixture of isomeric hydantoins **4a** and **4b** in 92% yield. The nearly equal mixture of isomers has been separated by two methods,

Scheme I



either fractional crystallization or column chromatography as described under Experimental Section. The preferred approach involved fractional crystallization to remove **4b**, followed by column chromatography of the mother liquor.

(1) Taken in part from the dissertation presented by S. H. Kuttab, June 1974, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(2) Grunewald, G. L.; Ruth, J. A.; Kroboth, T. R.; Kamdar, B. V.; Patil, P. N.; Salman, K. N. *J. Pharm. Sci.* **1976**, *65*, 920. Bartholow, R. M.; Eiden, L. E.; Ruth, J. A.; Grunewald, G. L.; Siebert, J.; Rutledge, C. O. *J. Pharmacol. Exp. Ther.* **1977**, *202*, 532. Ruth, J. A.; Grunewald, G. L.; Rutledge, C. O. *Ibid.* **1978**, *204*, 615. Grunewald, G. L.; Walters, D. E.; Kroboth, T. R. *J. Org. Chem.* **1978**, *43*, 3478.
(3) The **a** stands for compounds with the endo-NH and the **b** for those with the exo-NH.
(4) Kitahonoki, K.; Takano, Y. *Tetrahedron Lett.* **1963**, 1597.
(5) Henze, H. R.; Speer, R. J. *J. Am. Chem. Soc.* **1942**, *64*, 522. Counsell, R. E.; Desai, P.; Smith, T. D.; Chan, P. S.; Weinhold, P. A.; Rethy, V. B.; Burke, D. *J. Med. Chem.* **1970**, *13*, 1040.

0022-2623/80/1823-0754$01.00/0