5,7-Dihydroxy-2-aminotetralin Derivatives: Synthesis and Assessment of Dopaminergic and Adrenergic Actions

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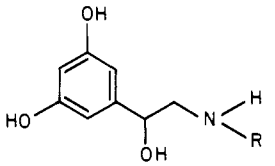
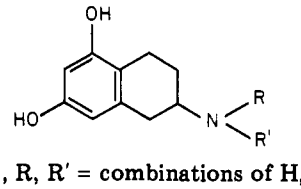
Replacement of the catechol 3,4-dihydroxylation pattern of certain adrenergic β-phenethylamines by a resorcinol 3,5-dihydroxylation pattern has led to a greater selectivity of adrenergic agonist effects in certain molecules. This strategy has been applied to a series of dopaminergic agents derived from 2-aminotetralin, leading to a 5,7-dihydroxylation pattern. Traditional literature approaches to formation of a tetralin ring with this oxygenation pattern failed. A method was used which involved cyclization of 3,5-dimethoxybenzylsuccinic acid derivatives with pyridinium poly(HF) and subsequent modification of the tetralin ring. The resorcinol-derived 2-aminotetralins were less potent and less active dopaminergic agents than their catechol-derived isomers (5,6-dihydroxy and/or 6,7-dihydroxy). Certain of the subject compounds demonstrated α- and β_1-adrenoceptor activating properties.

Biological evidence obtained from a variety of studies[1-3] suggests that there exists in mammals a heterogeneous population of dopamine receptors. It was speculated that it might be possible to prepare synthetic dopamine agonists which would interact appropriately with only certain type(s) of dopamine receptor(s), to elicit a selective response. Selective adrenergic agonists have been prepared (inter alia) by replacing the 3,4-dihydroxyphenyl moiety, characteristic of many adrenergic agonists, with a 3,5-dihydroxy substitution pattern. Examples of this type of molecular modification are metaprotereonol (1) and terbutaline (2), which are selective at β_2 adrenoceptors.[4] The



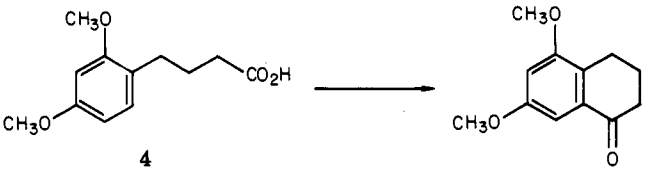
1, R = 2-C_3H_7,
2, R = t-C_4H_9



3, R, R' = combinations of H, Me, Et, n-C_3H_7, 2-C_3H_7

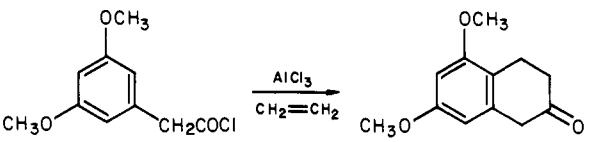
present study was based upon the premise that conformationally restricted analogues of the 3,5-dihydroxy-β-phenethylamine moiety, derived from tetralin system 3, might exhibit dopamine agonist properties selective for certain types of dopamine receptors. A 5-hydroxy group on the 2-aminotetralin molecule seems to be a critical component of agonist activity for certain dopamine receptor populations.[5] This 5-hydroxy group is analogous to the "meta" OH of dopamine itself, which has been suggested[6] to be of unique significance in interaction of different conformers of dopamine with different dopamine receptors. The 5,7-dihydroxytetralin system 3 thus represents a "di-meta-OH" arrangement, lacking the "para" OH of dopamine.

Chemistry. The initial approach to 3 involved intramolecular acylation of 4-(2,4-dimethoxyphenyl)butyric acid (4) to give the α-tetralone 5, which had been reported in



4 5

6% yield by Davies et al.[7] In the present study, all attempts to improve this yield failed. A series of variations of the Burckhalter–Campbell reaction[8] (6 → 7) for the preparation of β-tetralones provided no isolable β-tetralone product. Scheme I illustrates the successful route to



6 7

2-amino-5,7-dimethoxytetralin (15), which includes an extensive modification of a sequence used for the preparation of 11 by Yagi.[9] The use of HF/pyridine for cyclization of 10 reduces the tendency of the 5-methoxy group of 11 (which is peri to a keto group) to undergo O-demethylation, as has been reported[10] to occur in aluminum chloride mediated cyclizations in similar systems. The workup of the HF/pyridine reaction is much less onerous than that for aluminum chloride reactions. Subsequent to completion of the work described in Scheme I, Glatz et al.[11] reported preparation of 8 (Scheme I) and

(1) Cools, A. R.; Van Rossum, J. M. *Psychopharmacologia* **1976**, *45*, 243.
(2) Kebabian, J. W.; Calne, D. B. *Nature (London)* **1979**, *227*, 93.
(3) Cannon, J. G. *Adv. Neurol.* **1975**, *9*, 177.
(4) Innes, I. R.; Nickerson, M. In "The Pharmacological Basis of Therapeutics", 5th ed.; Goodman, L. S.; Gilman, A., Eds.; Macmillan: New York, 1975; p 482.
(5) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547.
(6) Cannon, J. G. In "Peripheral Dopaminergic Receptors"; Imbs, J.-L.; Schwartz, J., Eds.; Pergamon Press: Oxford, 1979; pp 87–94.
(7) Davies, J. E.; King, F. E.; Roberts, J. C. *J. Chem. Soc.* **1955**, 2782.
(8) Burckhalter, J. H.; Campbell, J. R. *J. Org. Chem.* **1961**, *26*, 4232.
(9) Yagi, K. *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **1955**, *12*, 173; *Chem. Abstr.* **1956**, *50*, 16726.
(10) Hardegger, E.; Steiner, K.; Widmer, E.; Pfluffner, A. *Helv. Chim. Acta.* **1964**, *47*, 2027.
(11) Glatz, B.; Helmchen, G.; Muxfeldt, H.; Porcher, H.; Prewo, R.; Senn, J.; Stezowski, J. J.; Stojda, R. J.; White, D. K. *J. Am. Chem. Soc.* **1979**, *101*, 2171.

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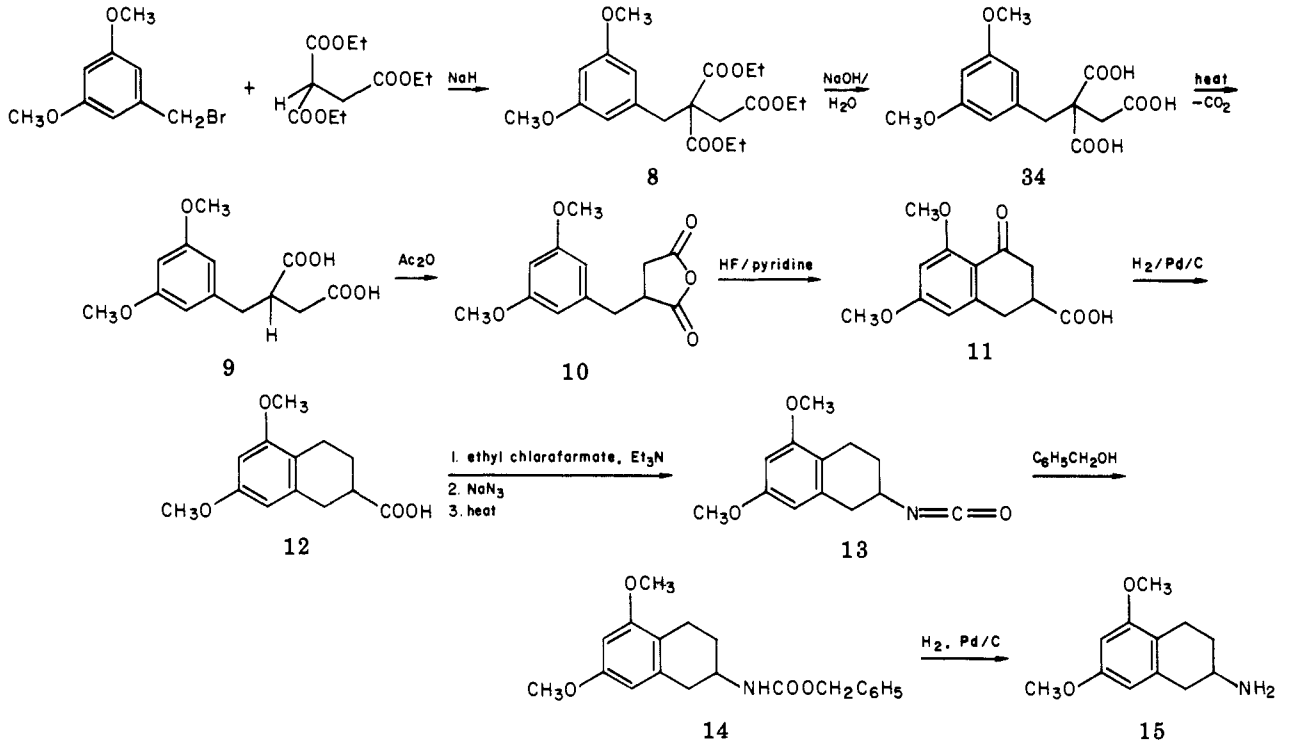
Scheme I. Preparation of 5,7-Dimethoxy-2-aminotetralin



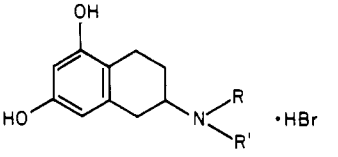
cyclization of the dicarboxylic acid **9** to **11** using polyphosphoric acid. It was convenient to convert the Curtius rearrangement product **13** to the benzyl carbamate **14** and subsequently to liberate the primary amine **15**, similar to the methodology described by Ehrhardt et al.[12] The amino group of **15** was appropriately alkylated by literature procedures, and the ether linkages were cleaved with 48% HBr. The free phenolic product obtained by treatment of the primary amine **15** with HBr was not stable under the conditions required for its isolation. However, the *N*-benzyl group of **15** underwent a successful ether cleavage reaction with 48% HBr, and the resulting free phenol was N-debenzylated by catalytic hydrogenolysis to afford the HBr salt of the primary amine. Ether cleavage products of the *N*-*n*-propyl (**32**) and the *N*-methyl-*N*-2-propyl (**33**) homologues invariably decomposed during attempts to isolate and purify them.

Spectral (IR, NMR) data on all intermediates and final compounds were consistent with the proposed structues (see Table I).

Pharmalcology. Results and Discussion. Table II shows the effects of the target compounds in an emesis assay in dogs, the effect on arterial blood flow in dogs, and the inhibition of cardioaccelerator nerves in cats. Table III shows the activity on arterial blood pressure and resting heart rate in cats. In all of these tests the duration of action of the compounds was no more than 30 min. With compounds **25–28**, propranolol (1.0 mg/kg) completely blocked the heart rate increase produced by the test compound. The pressor responses to these compounds were inhibited by phentolamine (2.0 mg/kg). Haloperidol (100 μg/kg) significantly antagonized the inhibition of cardioaccelerator nerve stimulation induced by compounds **21–31**.

Qualitative differences in biological activity seemed to be dependent upon the nature of the substitution on the amino group. The primary amine (**25**) demonstrated α- and β_1-adrenoceptor activation but was inactive in assays for emesis in dogs, in the renal blood flow assay in dogs, and in the ability to inhibit cardioaccelerator nerve stimulation in cats. The *N*-methyl homologue **26** showed a similar pattern of action. The *N*-isopropyl homologue **28** seemed less active at β_1 adrenoceptors than the *N*-methyl system **26**. The monoethyl (**29**) an the tertiary amino (**27**, **30**, and **31**) derivatives inhibited cardioaccelerator nerve stimulation, a dopaminergic effect. The *N*,*N*-diethyl and di-*n*-propyl homologues (**30** and **31**) and decreased heart rate and blood presure in the cat. High activity at peripheral dopamine receptors has been reported for series of 5,6- and 6,7-dihydroxy-2-aminotetralin derivatives.[13-16]

Table I. 5,7-Dihydroxy-2-aminotetralin Derivatives



no.	R	R'	yield, %	mp, °C	formula	anal.
25	H	H	60	224-226[a]	$C_{10}H_{14}BrNO_2$	C, H, N
26	Me	H	53	233-234[b]	$C_{11}H_{16}BrNO_2$	C, H, N
27	Me	Me	69	224.5-226[b]	$C_{12}H_{18}BrNO_2$	C, H, N
28	2-Pr	H	77	237-238[b]	$C_{13}H_{20}BrNO_2$	C, H, N
29	Et	H	62	207-210[c]	$C_{12}H_{18}BrNO_2$	C, H, N
30	Et	Et	67	194-198[c]	$C_{14}H_{22}BrNO_2$	C, H, N
31	*n*-Pr	*n*-Pr	86	199-203[c]	$C_{16}H_{26}BrNO_2$	C, H, N

[a] From *n*-BuOH-Et_2O and then from EtOH-Et_2O. [b] From MeOH-Et_2O. [c] From MeOH-Me_2CO-Et_2O.

(12) Ehrhardt, P. W.; Gorczynski, R. J.; Anderson, W. G. *J. Med. Chem.* **1979**, *22*, 907.

(13) Long, J. P.; Heintz, S.; Cannon, J. G.; Lim, K. *J. Pharmacol. Exp. Ther.* **1975**, *192*, 336.

(14) Sheppard, H.; Burghardt, C. R.; Long, J. P. *Res. Commun. Chem. Pathol. Pharmacol.* **1978**, *19*, 213.

(15) Kitzen, J. M.; Long, J. P.; Cannon, J. G. *J. Pharmacol. Exp. Ther.* **1978**, *206*, 239.

(16) Long, J. P.; Rusterholz, D. B.; Flynn, J. R.; Cannon, J. G. In "Presynaptic Receptors"; Langer, S. Z.; Starke, K.; Dubocovich, M. L., Eds.; Pergamon Press: Oxford, **1979**; p 73.

Table II. Various Biological Actions of the 5,7-Dihydroxy-2-aminotetralin Derivatives

compd	dog emesis: ED_{50}, μmol/kg	increase in renal blood flow	inhibn of cat cardioaccelerator nerve: ED_{50}, μmol/kg	potency rel to apomorphine
apomorphine	0.142 (0.13-0.15)[a]	nt[c]	0.022 (0.01-0.04)[a]	1.0
25	no[b]	no[d]	no[e]	
26	no[b]	no[d]	no[e]	
27	nt[c]	nt[c]	0.021 (0.009-0.05)[a]	1.45
28	no[b]	no[d]	no[e]	
29	0.36 (0.17-0.56)[a]	no[d]	0.04 (0.01-0.1)	1.04
30	nt[c]	no[d]	0.024 (0.01-0.05)	1.40
31	nt[c]	no[d]	0.035 (0.02-0.17)	0.95

[a] 95% confidence limits of the ED_{50} value. [b] No emesis was produced by sc administration of 2 μmol/kg ($N = 5$). [c] NT = not tested. [d] Inactive at doses up to 2 μmol/kg injected into the renal blood flow. [e] Inactive with iv doses up to 2 μmol/kg.

Table III. Influence of the 5,7-Dihydroxy-2-aminotetralin Derivatives on Heart Rate and Mean Arterial Pressure of the Cat[a]

compd	intravenous dose, μmol/kg	% change in arterial pressure	change in heart rate, beats/min
apomorphine	0.008	−9.9 ± 5.0	−4.3 ± 2.2
	0.016	−11.5 ± 4.3	−6.5 ± 3.5
	0.032	−18.2 ± 2.4	−10.3 ± 4.8
25	0.038	19.7 ± 5.3	0.0
	0.115	21.6 ± 10.2	3.6 ± 1.8
	0.38	30.5 ± 4.2	17.6 ± 1.7
26	0.36	49.7 ± 14.6	26.7 ± 15.0
	1.09	84.2 ± 16.7	44.0 ± 12.6
27	0.01	4.1 ± 4.0	0.0
	0.03	8.0 ± 5.1	0.6 ± 0.6
	0.1	23.2 ± 16.1	12.8 ± 1.4
28	0.11	16.9 ± 8.5	3.2 ± 2.0
	0.33	19.7 ± 4.3	7.7 ± 4.2
	0.99	25.2 ± 6.0	14.4 ± 5.0
29	0.01	−6.3 ± 3.3	−6.6 ± 1.9
	0.033	−18.5 ± 4.2	−10.6 ± 5.6
	0.10	−19.6 ± 1.6	−6.0 ± 1.2
30	0.003	−8.7 ± 4.2	−2.1 ± 0.8
	0.009	−23.0 ± 5.9	−23.0 ± 5.9
	0.033	−25.0 ± 3.6	−25.0 ± 3.6
31	0.003	−12.2 ± 0.9	−3.6 ± 1.2
	0.009	−17.2 ± 8.3	−4.8 ± 2.4
	0.033	−27.2 ± 4.5	−5.6 ± 3.2

[a] Three to five cats were used to assay each compound.

The compounds reported herein are decidely less active, and their duration of action is not increased over the other series of aminotetralins. Activation of α and β_1 adrenoceptors was noted with the N-unsubstituted and the smaller monoalkyl derivatives. It has been shown that the 5,6-dihydroxy derivatives are considerably more active than the 6,7-dihydroxy derivatives in activation of β_1 adrenoceptors. Apparently, hydroxy group substitution in the 5 position of the 2-aminotetralin system permits retention of considerable β_1-receptor activation activity.

Peripheral administration of up to 10 g/kg sc of the 2-amino-5,7-dihydroxytetralins failed to cause climbing or stereotyped behavior in normal mice and did not induce circling in mice with unilateral striatal electrolesions.

The bilateral injection of **26–30** directly into the nucleus accumbens of chronically cannulated rats, in doses up to 50 μg, failed to induce locomotor hyperactivity or stereotyped behavior. Compounds **25** and **31** caused a low intensity locomotor response at the maximum dose of 50 μg; this response for both agents was no more than 20 counts/5 min at maximum intensity. Dopamine can induce a response of 70 counts/5 min. The onsets of action for **25** and **31** were delayed for 1 h and the duration of effect was 2–3 h, whereas dopamine is active almost immediately upon administration and is effective for at least 6 h.

The potent abilities of the 2-amino-5,6-dihydroxytetralins to stimulate cerebral dopamine receptors are markedly reduced or abolished by transference of the OH function from the 6 to the 7 position. With respect to the present series of 5,7-dihydroxy compounds, the reduced activity was particularly emphasized by the failure of the *N,N*-diethyl and the *N,N*-di-*n*-propyl compounds (**30** and **31**) to induce stereotypy, circling, or climbing in mice. It is unlikely that the inactivity of the 5,7-dihydroxy compounds reflects an unusual difficulty of the "di-meta-OH" arrangement to cross the blood–brain barrier, since, on direct injection into the nucleus accumbens of the rat brain, the typical locomotor hyperactivity induced by dopamine or the locomotor hyperactivity/stereotyped biting induced by the 5,6-dihydroxytetralin derivatives was not observed for the 5,7-dihydroxy compounds. The low intensity and delayed locomotor response observed following administration of **25** and **31** may reflect an ability to release endogeneous dopamine from transmitter stores.

β_2-Adrenoceptor agonist acitivity was observed for compounds **25**, **26**, and **28**. The most active compound was **26**. The ED_{50} to relax helical cut strips of guinea pig trachea which was contracted with methacholine chloride was 47.3 μM (24–221 μM). The ED_{50} values for **25** and **28** were >100 μM. The relaxant properties of all three compounds were significantly antagonized by propranolol (0.5 μg/mL). The ED_{50} for epinephrine was 0.24 μM (0.17–0.30 μM). Thus, these compounds were not highly potent at β_2 receptors.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded with a Varian Associates T-60 instrument using tetramethylsilane as the internal standard. IR spectra were recorded with a Perkin-Elmer 267 instrument. Mass spectra were recorded on a Finnigan 1015 S/L spectrometer. Elemental analyses were perfomed 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. Climbing, Circling, and Stereotyped Behavior in the Mouse. Hyperactivity and Stereotyped Behavior following Intracerebral Injection into the Nucleus Accumbens of the Rat. These methods are identical with those described previously.[17]

Emesis in Dogs. Five mongrel dogs of either sex weighing 14–26 kg were housed individually and were maintained on a standard laboratory diet. On drug trial days, drug solutions were administered subcutaneously and the number of vomiting episodes that occurred in the following 60 min were counted and recorded.

(17) Cannon, J. G.; Perez, Z.; Long, J. P.; Rusterholz, D. B.; Flynn, J. R.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1973**, *22*, 901.

Emesis was defined as the active expulsion of fluid or solid matter. At least two nondrug days were allowed between drug trial days.

Renal Blood Flow Assay. Dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and systemic blood pressure and heart rate were recorded. The left renal artery was exposed through the retroperitoneal incision, and an electromagnetic flow probe (Carolina) was placed around the artery. Blood flow was recorded with a Carolina Flowmeter (Model 420R) and was displayed on a Beckman recorder. Test drugs were injected directly into the renal artery. This preparation is essentially the same as described by McNay and Goldberg.[18]

Blood Pressure, Heart Rate, and Right Cardioaccelerator Nerve Stimulation in Cats. Cats weighing 2–4 kg were anesthetized by injection into the thoracic cavity of sodium pentobarbital (30 mg/kg). After endotracheal intubation, artificial respiration was maintained with a Harvard ventilator. Bilateral vagal section was performed. The arterial blood pressure was measured from the femoral artery and injections were made through a catheter placed into the femoral vein. Blood pressure was monitored using a Statham arterial transducer and was recorded with a Beckman RS recorder. The heart rate was monitored by a Beckman Model 9873 cardiotachometer. The ability of propranolol (1 mg/kg) to antagonize the positive chronotropic response induced by some of the experimental compounds was evaluated.

In another series of experiments, cats were prepared as described above and the right postganglionic cardioaccelerator nerve was exposed following a midline incision. The postganglionic nerve was placed on a bipolar silver electrode. Parameters of stimulation were constant for a given experiment: 20-s stimulation periods were used and the parameters were 2 Hz, 5-ms duration with a maximal voltage of 15–20 V. A Grass stimulator (Model S-48) was used. The test compound was administered iv to three to five animals. Doses were varied by 0.48 log intervals. Positive chronotropic responses following nerve stimulation were allowed to return to control levels before a subsequent dose was given. The effectiveness of haloperidol (100 μg/kg) and phentolamine (2 mg/kg) to antagonize the inhibitory activity of the compounds was evaluated.

β_2 Adrenoceptor Assay. Helically cut guinea pig tracheae were used to assay for β_2-receptor agonist activity. Strips were mounted in a 10-mL bath containing Krebs bicarbonate solution. One end of the strip was tied to a firm mount and the other end was attached to a Statham FT-03 force transducer. A Beckman RS recorder was used to record responses. Methacholine chloride (0.3 μg/mL) was added to the bath in induce contracture; solutions of the test compounds were then added to the bath, and the amount of relaxation occurring within 5 min was recorded. The doses for each compound were increased by 0.48 log intervals.

Statistics. The potencies of the test compounds relative to apomorphine were calculated using a 3 × 3 parallel line bioassay as described by Finney.[19] ED_{50} values were determined using a weighed least-squares analysis.

3-(3,5-Dimethoxyphenyl)-1,2,2-propanetricarboxylic Acid (34). A mineral oil dispersion containing 16.4 g (0.683 mol) of NaH was washed with several portions of pentane. Benzene (1 L) was added to the NaH, and 160 g (0.65 mol) of triethyl 1,1,2-ethanetricarboxylate was added dropwise with stirring at 25 °C. The mixture was stirred for 6 h, then it was heated under reflux, and 149.5 g (0.683 mol) of 3,5-dimethoxybenzyl bromide in 200 mL of benzene was added dropwise. The reaction mixture was then stirred for an additional 24 h. The benzene layer was washed several times with saturated NaCl and then it was dried ($MgSO_4$). Volatiles were removed under reduced pressure to yield 275 g (107%) of crude intermediate: NMR ($CDCl_3$) δ 1.23 (t, 9 H, J = 7 Hz, OCH_2CH_3), 2.75 (s, 2 H, CH_2), 3.22 (s, 2 H, CH_2), 3.70 (s, 6 H, OCH_3), 4.09 and 4.14 (3 q, 6 H, J = 7 Hz, OCH_2CH_3), 6.17 (s, 3 H, Ar H). The NMR showed the major impurity present to be benzene. The crude oil was saponified by heating under reflux with 86 g (2.15 mol) of NaOH in 1 L of H_2O for 3 days. The aqueous layer was washed with Et_2O and then was heated under reflux for an additional 24 h. The volatiles were removed under reduced pressure, and the residual sludge was taken up in a minimum amount of H_2O. This solution was acidified with concentrated HCl. The white solid which formed was collected on a filter, washed several times with H_2O, and dried in a vacuum desiccator to yield 174.8 g (86%) of **34**, mp 167–168 °C (lit.[9] mp 173 °C).

3,5-Dimethoxybenzylsuccinic Acid (9). Compound **34** (208.2 g, 0.667 mol) was heated at 180–185 °C until no more gas was evolved from the molten mixture. The crude decarboxylated product was taken up in 550 mL of 10% NaOH, then this solution was acidified with conc HCl and was stirred vigorously until a precipitate formed. This solid was collected on a filter and was dried in a vacuum desiccator to yield 163.4 g (92%) of a white powder: mp 128–135 °C (lit.[9] mp 126–128 °C); NMR (CCl_4) δ 2.33–3.33 [m, 5 H, $-(CH_2)CHCH_2$], 3.77 (s, 6 H, OCH_3), 6.33 (s, 3 H, ArH).

5,7-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (11). A mixture of 64.8 g (0.242 mol) of **9** and 300 mL of Ac_2O was heated at 70 °C with stirring for 4 h. The volatiles were removed under reduced pressure, and the last traces of Ac_2O were azeotroped with benzene. The oily residue was transferred to a stoppered polypropylene flask with 300 g of HF/pyridine, and the reaction mixture was stirred overnight. The reaction was quenched with 400 mL of ice–H_2O, and the resulting precipitate was collected on a filter and washed with dilute HCl and H_2O. Recrystallization from Me_2CO yielded 46 g (76%) of thick white needles, mp 201–203 °C (lit.[9] mp 196–198 °C).

5,7-Dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (12). Compound **11** (40 g, 0.16 mol) in 700 mL of AcOH and 20 mL of H_2O was hydrogenated over 4 g of 5% Pd/C at an initial pressure of 50 psig until 2 equiv of H_2 was consumed. The reduction mixture was warmed on a steam bath and was then filtered through Celite. Removal of volatiles from the filtrate under reduced pressure and recrystallization of the solid residue from EtOAc yielded 36.3 g (96%) of thick gray plates: mp 165.5–167 °C; MS, m/e 236 (M^+). Anal. ($C_{13}H_{16}O_4$) C, H.

2-[(Carbobenzyloxy)amino]-5,7-dimethoxytetralin (14). To a chilled (−5 °C) solution of 4.55 g (0.045 mol) of triethylamine and 10.5 g (0.0445 mol) of **12** in 110 mL of Me_2CO was added dropwise with stirring 5.37 g (0.0495 mol) of ethyl chloroformate in 30 mL of Me_2CO. The reaction mixture was stirred for an additional 2 h at −5 °C, then 4.39 g (0.0675 mol) of NaN_3 in 18 mL of H_2O was added dropwise, and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with ice–H_2O, and the aqueous solution was extracted with several portions of benzene. The pooled benzene extracts were dried ($MgSO_4$), and the volatiles were removed under reduced pressure to yield an oil, which was taken up in 200 mL of dry benzene. This solution was heated under reflux until the effervescence ceased. Benzyl alcohol (9.7 g, 0.09 mol) was added, and the resulting mixture was heated overnight under reflux. The volatiles were removed under reduced pressure, and the residual oil was crystallized from cyclohexane to yield 8.3 g (55%) of long white needles: mp 109–110 °C; MS, m/e 341 (M^+). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

2-Amino-5,7-dimethoxytetralin Hydrochloride (15). A mixture of 10.7 g (0.0314 mol) of **14**, 100 mL of glacial AcOH, 5 mL of H_2O, and 0.5 g of 5% Pd/C was hydrogenated at an initial pressure of 50 psig for 12 h, during which time 80% of the theoretical amount of H_2 was consumed. The reduction mixture was filtered through Celite, volatiles were removed from the filtrate under reduced pressure, and the residual oil was extracted with dilute HCl. The aqueous extract was washed with Et_2O and then it was basified with KOH, and the resulting mixture was extracted with Et_2O. The volatiles were removed from the extract under reduced pressure to yield an oil, which was distilled to afford 6 g (92%) of a clear liquid, bp 125–130 °C (0.1 mm). The HCl salt was prepared and recrystallized from EtOH–Et_2O: mp 231–233 °C; MS m/e 207 (M^+ − HCl). Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

2-(Methylamino)-5,7-dimethoxytetralin Hydrochloride (16). Compound **14** (1.3 g, 0.0038 mol) in 20 mL of benzene was added dropwise with stirring to 4.3 mL of "Red-Al" solution (3.5 M, 0.015 mol) in 20 mL of benzene at 25 °C, and the reaction mixture was heated under reflux for an additional 10 h. The benzene layer was diluted with an equal volume of benzene, and

(18) McNay, J. L.; Goldberg, L. I. *J. Pharmacol. Exp. Ther.* **1966**, *151*, 23.

(19) Finney, D. J. "Statistical Methods in Biological Assay"; Hafner: New York, 1964.

this was washed with 80 mL of 50% NaOH and saturated NaCl and was dried ($MgSO_4$). The volatiles were removed under reduced pressure to give an oily residue, which was converted to its HCl salt and recrystallized from EtOH–Et_2O to give 0.65 g (66%) of colorless needles: mp 237–239 °C; MS m/e 221 (M^+ – HCl). Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

2-(Dimethylamino)-5,7-dimethoxytetralin Hydrochloride (17). Compound **15** (1.0 g, 0.0041 mol) was added to 10 mL of MeOH which contained 2.2 mL (0.021 mol) of 37% aqueous formaldehyde and 0.775 g (0.0123 mol) of $NaCNBH_3$. This mixture was stirred at 25 °C and was brought to pH 6 (pH paper) by addition of glacial AcOH. After the mixture stirred overnight, the volatiles were removed under reduced pressure, and the residue was basified with 2 N NaOH. The aqueous solution was extracted with $CHCl_3$, and the volatiles were removed from the extract to yield the crude amine as an oil. This was converted to its HCl salt, which was recrystallized from 2-PrOH–Et_2O to give 1.05 g (94%) of needles: mp 243–245 °C; MS m/e 235 (M^+ – HCl). Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

2-(2-Propylamino)-5,7-dimethoxytetralin Hydrochloride (18). The procedure of Sugihara et al.[20] was used. A mixture of 1.0 g (0.0041 mol) of **15**, 0.322 g (0.0051 mol) of $NaCNBH_3$, 0.88 g (0.0102 mol) of dioxane, 40 mL of Me_2CO, and 50 mL of EtOH was stirred overnight at 25 °C. The volatiles were removed under reduced pressure, the residual solid was treated with excess 2 N NaOH, and this solution was extracted repeatedly with $CHCl_3$. Volatiles were removed from the pooled extracts under reduced pressure to give the crude liquid amine. This was converted to its HCl salt, which was recrystallized from 2-PrOH–Et_2O to give 1.1 g (94%) of plates: mp 230–233 °C; MS m/e 249 (M^+ – HCl). Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

2-(Acetylamino)-5,7-dimethoxytetralin (19). The free base (1.82, 0.0088 mol) of **15** was stirred for 12 h with a mixture of 0.97 g (0.0097 mol) of Ac_2O, 0.982 g (0.0097 mol) of triethylamine, and 25 mL of EtOAc. The reaction mixture was diluted with 125 mL of EtOAc and this mixture was washed with saturated $NaHCO_3$, dilute HCl, and saturated NaCl. The organic layer was dried ($MgSO_4$), volatiles were removed under reduced pressure, and the residual solid was recrystallized from EtOAc to give 1.85 g (84%) of small white needles: mp 133–134 °C; MS m/e 249 (M^+). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2-(Ethylamino)-5,7-dimethoxytetralin Hydrochloride (20). A solution of 1.8 g (0.00723 mol) of **19** in 50 mL of dry THF was added dropwise with stirring to 0.5 g (0.0375 mol) of $LiAlH_4$ in 25 mL of dry THF. After the addition was complete, the reaction mixture was heated under reflux for 4 h and then the following were added in order: 0.5 mL of H_2O, 0.5 mL of 15% NaOH, and 1.5 mL of H_2O. The resulting solid was removed by filtration, and volatiles were removed from the filtrate under reduced pressure. The residual free amine was converted to its HBr salt, and this was recrystallized from EtOH–Et_2O to give 1.2 g (53%) of small white needles: mp 226–228.5 °C; MS m/e 235 (M^+ – HBr). Anal. ($C_{16}H_{26}BrNO_2$) C, H, N.

2-(Diethylamino)-5,7-dimethoxytetralin Hydrobromide (21). To a complex formed from 2.4 g (0.063 mol) of $NaBH_4$ and 2.8 g (0.047 mol) of AcOH in 50 mL of benzene, generated according to a procedure of Marchini et al.,[21] was added dropwise, with stirring, 1.3 g (0.0063 mol) of the free base of **15** in 25 mL of benzene. The reaction mixture was heated under reflux overnight, and then volatiles were removed under reduced pressure. The solid residue was treated with excess dilute NaOH, and the resulting mixture was extracted with $CHCl_3$. Volatiles were removed from the extract under reduced pressure, and the crude amine product was distilled, bp 135–137 °C (0.1 mm), to give 0.547 g (35%) of a clear liquid. This material was converted to its HBr salt, which was recrystallized from EtOH–Et_2O: mp 188–191 °C; MS, m/e 263 (M^+ – HBr). Anal. ($C_{16}H_{26}BrNO_2$) C, H, N.

2-(Di-*n*-propylamino)-5,7-dimethoxytetralin Hydrochloride (22). The method described for **21** was followed, using 1.0 g (0.0041 mol) of **15**, 1.55 g (0.041 mol) of $NaBH_4$, 9.1 g (0.123 mol) of propionic acid, and 75 mL of benzene. The crude amine product was coverted to its HCl salt, and this was recrystallized from 2-PrOH–Et_2O to give 1.1 g (82%) of product: mp 146–148.5 °C; MS m/e 291 (M^+ – HCl). Anal. ($C_{18}H_{30}ClNO_2$) C, H, N.

2-(*n*-Propylamino)-5,7-dimethoxytetralin Hydrochloride (32). The method described for **21** was followed, using 1.3 g (0.0053 mol) of **15**, 2.0 g (0.053 mol) of $NaBH_4$, and 50 mL of propionic acid, which was used as the solvent as well as a reagent. The reaction mixture was heated in an oil bath at 80 °C for 3 h. Volatiles were removed under reduced pressure, and the solid residue was basified with 2 N NaOH. This mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and filtered, and volatiles were removed under reduced pressure. The residue was converted to its HCl salt, which was recrystallized from MeOH to give 0.35 g (23%) of product: mp 240–241 °C; MS m/e 249 (M^+ – HCl). Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

2-(*N*-Methyl-*N*-2-propylamino)-5,7-dimethoxytetralin Hydrochloride (33). Compound **18** (1.2 g, 0.0041 mol) was treated with a mixture of 0.775 g (0.0123 mol) of $NaCNBH_3$ and 2.2 mL (0.021 mol) of 37% aqueous formaldehyde in 15 mL of MeOH. Glacial AcOH was added every 30 min for 1.5 h to bring the pH to 6 (pH paper). The reaction mixture was stirred overnight, then the volatiles were removed under reduced pressure, and the residual solid was treated with excess 10% NaOH. The resulting solution was extracted with $CHCl_3$, and volatiles were removed from the extract under reduced pressure to yield the amine free base, which was converted to its HCl salt. This was crystallized from 2-PrOH-Et_2O to give 1.05 g (85%) of white needles: mp 166–169 °C; MS m/e 263 (M^+ – HCl). Anal. ($C_{16}H_{26}ClNO_2$) C, H, N.

2-(Benzylamino)-5,7-dimethoxytetralin Hydrochloride (23). The free base of **15** (1.0 g, 0.0049 mol) was heated under reflux with 0.571 g (0.0054 mol) of benzaldehyde and a catalytic amount of *p*-toluenesulfonic acid in 50 mL of benzene in a Dean-Stark apparatus. After 12 h, volatiles were removed under reduced pressure, and the residue was treated with 0.5 g (0.0079 mol) of $NaCNBH_3$ in 40 mL of MeOH. Glacial AcOH was added every 30 min for 1.5 h to adjust the pH to 6 (pH paper). The reaction mixture was stirred overnight, then the volatiles were removed under reduced pressure, and the residual solid was treated with excess dilute KOH. The resulting mixture was extracted with $CHCl_3$, the volatiles were removed from the extract, and the crude liquid amine was distilled, bp 195–200 °C (0.1 mm), to give 1.3 g (89%) of a clear liquid. This material was converted to its HCl salt, which was recyrstallized from H_2O to give small needles: mp 227–228 °C; MS m/e 297 (M^+ – HCl). Anal. ($C_{19}H_{24}ClNO_2$) C, H, N.

2-(Benzylamino)-5,7-dihydroxytetralin Hydrobromide (24). To 0.25 g (0.00075 mol) of **23** in 10 mL of hot AcOH was added 30 mL of 48% HBr. This mixture was heated at 115–120 °C under N_2 for 2.5 h. The volatiles were removed under reduced pressure, and the residual solid was recrystallized from EtOH–Et_2O to give 0.26 g (99%) of small orange rosettes: mp 251.5–253 °C; MS m/e 269 (M^+ – HBr). Anal. ($C_{17}H_{20}BrNO_2$) C, H, N.

2-Amino-5,7-dihydroxytetralin Hydrobromide (25). Compound **24** (0.32 g, 0.00091 mol) in 49 mL of MeOH and 1 mL of glacial AcOH was hydrogenated over 0.3 g of 5% Pd/C at an initial pressure of 50 psig. After 24 h, the reduction mixture was filtered through Celite, and the volatiles were removed from the filtrate under reduced pressure. The amorphous residue was crystallized (see Table I).

Ether Cleavage Reactions. The amine hydrohalide (0.001 mol) in 10 mL of 48% HBr was heated under N_2 at 125 °C for 2 h. The reaction mixture was diluted with 30 mL of H_2O, and the volatiles were removed under reduced pressure. The solid residue was recrystallized (see Table I).

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(20) Sugihara, H.; Motohashi, M.; Watanae, M.; Nishikawa, M.; Sanno, Y. German Offen. 2 362 535, 1974.
(21) Marchini, P.; Liso, G.;Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 1747.