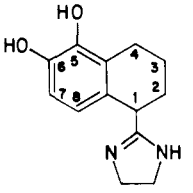
Conformationally Defined Adrenergic Agents. 3. Modifications to the Carbocyclic Ring of 5,6-Dihydroxy-1-(2-imidazolinyl)tetralin: Improved Separation of α_1 and α_2 Adrenergic Activities

John F. DeBernardis,* Martin Winn, David L. Arendsen, Daniel J. Kerkman, and John J. Kyncl

Division of Cardiovascular Research, Abbott Laboratories, Abbott Park, Illinois 60064. *Received October 15, 1985*

A series of modifications to positions 1, 2, and 4 of the tetralin ring of 5,6-dihydroxy-1-(2-imidazolinyl)tetralin (1, A-54741) succeeded in improving the separation of the potent α_1 and α_2 adrenergic agonism observed for the parent compound 1. In particular 5,6-dihydroxy-4,4-dimethyl-1-(2-imidazolinyl)tetralin (7) was found to be a specific α_1 adrenergic agonist, and 7,8-dihydroxy-4-(2-imidazolinyl)chroman (2) was found to have improved α_2 adrenergic agonistic selectivity relative to the parent compound 1.

Renewed interest in the area of adrenergic receptors, in particular α-adrenergic receptors, can be attributed to recent advances in the knowledge and understanding of the various processes involved in adrenergic nervous system transmission.[1] α-Receptors located presynaptically and involved in a negative feedback mechanism have been designated α_2, whereas the α-receptors located postsynaptically on effector cells have been defined as α_1.[2] Investigations aimed at determining differences between these presynaptic and postsynpatic α-receptors resulted in the discovery that receptors resembling the presynaptic α_2 type were encountered postsynaptically.[3,4] The prefixes α_1 and α_2 are presently applied to receptors with different sensitivities to adrenergic agents regardless of location or function.[5,6]



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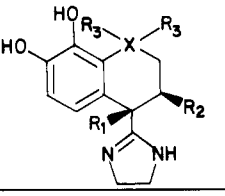
Recently, we reported[7] on the synthesis and biological activity of 5,6-dihydroxy-1-(2-imidazolinyl)tetralin (1, A-54741) a potent α-adrenergic agonist. In view of the extraordinary potency associated with the above compound, we undertook to investigate changes in the carbocyclic ring (i.e., positions 1–4) of 1 and the effects these changes had on the biological activity at α_1 and α_2 adrenergic receptors. Of primary interest was the possibility of separating the α_1/α_2 activities associated with 1. This paper describes the synthesis and pharmacological characterization of a series of derivatives (Table I) of 1 modified by the insertion of a heteroatom in the carbocyclic ring or by addition of substituents to this ring.

Chemistry

Compounds **2**, **3**, and **5–8** were prepared from the corresponding ketones. In Scheme I the method is illustrated using compound **2** as an example.

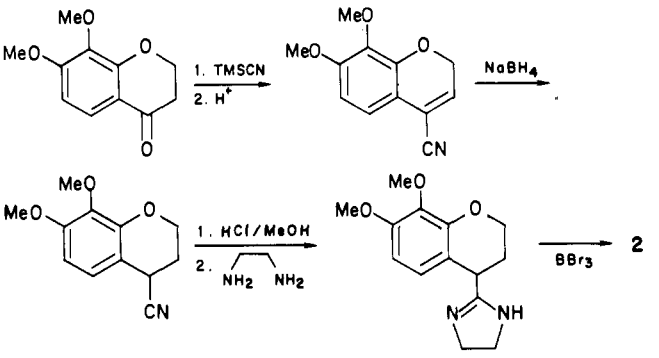
The trimethylsilyl cyanohydrin, formed from the starting ketone with trimethylsilyl cyanide and a Lewis acid catalyst, is desilylated and dehydrated by means of a Brønsted acid catalyst. The resulting unsaturated nitrile is conjugately reduced with sodium borohydride and treated with methanolic HCl followed by ethylenediamine to provide the imidazoline. Finally, the catechol deprotection is accomplished by employing boron tribromide.

Table I. Compounds Prepared To Investigate Modifications of the Carbocyclic Ring of 1

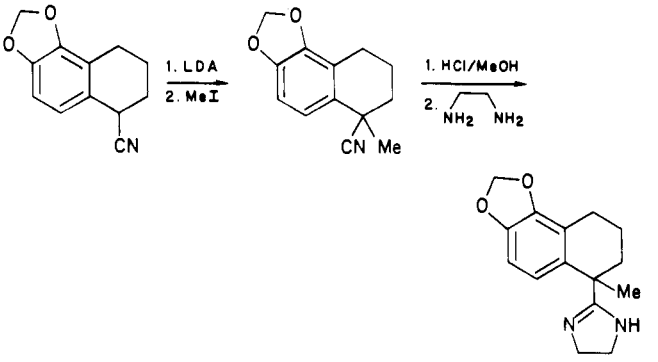


compd	R_1	R_2	R_3	X
2	H	H		O
3	H	H		S
4	Me	H	H	C
5	H	Me	H	C
6	H	Ph	H	C
7	H	H	Me	C
8	H	H	Et	C

Scheme I



Scheme II



(1) Lefkowitz, R. J.; Michel, T. *J. Clin. Invest.* **1983**, *72*, 1185.
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0022-2623/86/1829-1413$01.50/0

Table II. Indexes and ED_{50} Values for Compounds **2–8** in the Rabbit Aorta (α_1)

compd	index (ED_{50} NE/ED_{50} CPD)[a,b]	n	E_{max}[a,c]	ED_{50} NE × 10^7[a]	ED_{50} CPD × 10^7[a]
2	1.01 ± 0.58	3	118 ± 3	0.67 ± 0.22	0.35 ± 0.05
3	10.5 ± 2.2	5	129 ± 8	2.19 ± 0.50	0.20 ± 0.10
4	0.003 ± 0.0003	3	69 ± 7	0.41 ± 0.11	166 ± 30
5	0.01 ± 0.001	4	66 ± 4	0.48 ± 0.03	43.9 ± 4.9
6	inactive	2	inactive	0.73 ± 0.26	inactive
7	0.46 ± 0.13	7	100 ± 2	1.25 ± 0.53	2.84 ± 0.42
8	0.002 ± 0.001	2	44 ± 4	0.98 ± 0.60	470 ± 44
1[d]	13 ± 2	31	114 ± 1	1.4 ± 0.2	0.17 ± 0.06

[a] Mean of n experiments ± SEM. [b] See ref 14. [c] Expressed as a percent of the maximum response of the tissue to NE. [d] Included for reference; see ref 7.

Table III. Indexes and ED_{50} Values for Compounds **2–8** in the PBZ-Pretreated Dog Saphenous Vein (α_2)

compd	index (ED_{50} NE/ED_{50} CPD)[a,b]	n	E_{max}[a,c]	ED_{50} NE × 10^7[a]	ED_{50} CPD × 10^7[a]
2	37 ± 11	7	107 ± 2	7.2 ± 0.9	0.35 ± 0.10
3	41 ± 13.5	5	105 ± 3	5.26 ± 0.61	0.19 ± 0.05
4	0.16 ± 0.03	4	76 ± 3	9.24 ± 0.43	61 ± 9
5	0.2 ± 0.08	5	10 ± 3	5.6 ± 0.31	45 ± 13
6	inactive	4	inactive	5.19 ± 1.0	inactive
7	inactive	4	inactive	12.4 ± 0.68	inactive
8	inactive	4	inactive	6.03 ± 1.96	inactive
1[d]	184 ± 25	8	102 ± 2	7.2 ± 0.7	0.05 ± 0.01

[a–d] See footnotes to Table II.

The production of compound 4 required a variation in this basic synthesis (Scheme II).

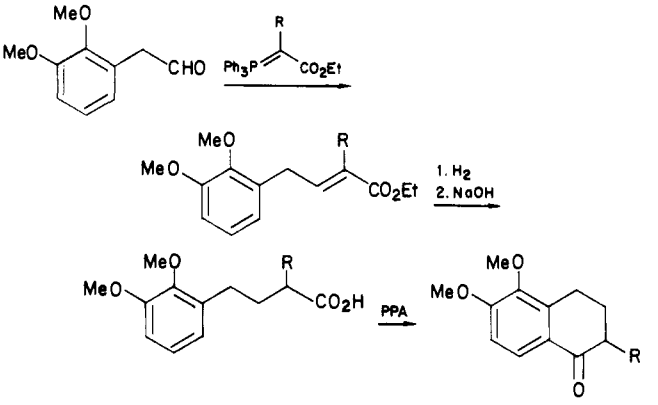
The saturated nitrile was deprotonated with lithium diisopropylamide and alkylated with use of methyl iodide. The resulting tertiary nitrile was then converted to imidazoline as before, although, due to the additional steric hindrance produced by the methyl group, it was necessary to use neat ethylenediamine in order to carry out this transformation.

The starting ketones for compounds **2**,[8] **3**,[9] and **4**[10] were prepared by the published methods. The synthesis of the tetralones (Scheme III) necessary for making compounds **5** and **6** began with the known[11] (2,3-dimethoxyphenyl)-acetaldehyde.

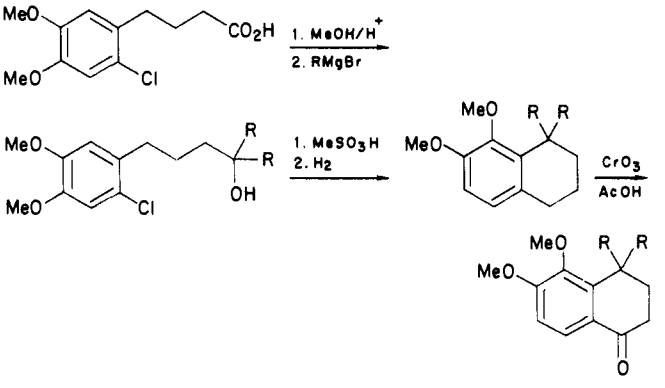
Wittig reaction of this aldehyde using either (carbethoxyethylidene)triphenylphosphorane (Aldrich) or (carbethoxybenzylidene)triphenylphosphorane[12] provided the trisubstituted olefins, which could be hydrogenated and saponified to the substituted phenylbutyric acids prior to cyclization to the 2-methyl- or 2-phenyl-1-tetralones using polyphosphoric acid. Compounds **5** and **6**, which were prepared from these tetralones, were both found to have the substituents at positions 1 and 2 of the tetralin ring disposed in a trans relationship. This determination was based on the 10-Hz coupling constant found in each case for the proton at C-1 (see Experimental Section).

The synthesis of the starting tetralones for compounds **7** and **8** from the known[13] (2-chloro-4,5-dimethoxyphenyl)butyric acid is shown in Scheme IV. Notice that the chlorine atom in position 2 of the aromatic ring blocks the usual route of cyclization and forces the ring to close at carbon 6 of the aromatic ring as desired. Having served its purpose, the chlorine atom is removed hydrogenolytically and the resulting tetralin is oxidized to the target 1-tetralone.

Scheme III



Scheme IV



Biological Results and Discussion

The α_1 adrenergic activity of these catechol imidazolines was measured with use of isolated rabbit aortic tissues. Stimulation of the α-adrenergic receptors in this tissue produces an increase in the force of contraction, which is inhibited by α_1 antagonists such as prazosin. The potency of each test compound was expressed as a molar ED_{50}, and an index number was obtained by calculating the ratio of

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the ED_{50} of norepinephrine (NE) to that of the test compound (CPD).[14] The larger the index number, the more potent the compound (relative to NE).

The α_2 adrenergic activity was measured in the dog saphenous vein, which had been pretreated for 30 min with phenoxybenzamine (PBZ, 100 nM).[15] At the end of the PBZ pretreatment, the tissues were thoroughly washed and a control cumulative dose–response curve was obtained for NE. Following washout of the NE, the tissues were equilibrated and a cumulative dose–response curve was obtained for the test compound. As in the case of the α_1 activities, an index number (ED_{50} NE/ED_{50} CPD)[14] for the α_2 potency of the compounds was calculated.

The biological activities of the compounds that resulted from modifications to the carbocyclic nucleus of 1 are shown in Table II (α_1) and Table III (α_2). Of particular interest was compound **3**, which contained a sulfur atom in position 4 of the carbocyclic nucleus. Insertion of this sulfur atom resulted in a compound that maintained the same α_1 potency as 1: however, the α_2 activity, although considerable, was reduced relative to 1. This was in contrast to the corresponding oxygen analogue **2**, which had decreased α_1 activity, being only equipotent with NE at the α_1 receptor and showing a potency similar to that of **3** at the α_2 site. Thus, the insertion of an oxygen or sulfur atom into the carbocyclic ring of 1 resulted in decreased α_2 activity for both compounds, but this substitution had no effect on the α_1 activity of **3**, while producing reduced α_1 activity for **2**.

Substitution of a methyl group at positions 1 or 2 (**4**, **5**) on the carbocyclic ring of 1 resulted in compounds possessing only modest, at best, biological effects at either the α_1 or α_2 adrenoceptors. We presume this is due to the unfavorable steric interactions of these substituents with the α-adrenergic receptors. Likewise, substitution of a phenyl ring in position 2 (**6**) resulted in complete abolition of adrenergic activity.

Interestingly, dimethyl substitution on position 4 (i.e., **7**) of 1 had a beneficial effect on the compound's selectivity. Although the potency of **7** at the α_1 receptor was reduced relative to 1, unlike the latter, compound **7** possessed no detectable α_2 adrenergic activity. The 4,4-dimethyl compound, therefore, was a selective α_1 agonist. We believe that steric effects at this position play an important role in the interaction of compounds with the α-adrenergic receptors, being favorable for the α_1 site and unfavorable for the α_2 receptor. However, even the α_1 receptor shows very little tolerance for steric bulk at position 4, as compound **8** (the diethyl derivative) was inactive at both the α_1 and α_2 adrenergic receptors.

In summary, modifications on the carbocyclic ring of 1 dramatically affected the biological activity of these compounds at the α_1 and α_2 adrenergic receptors. Incorporation of heteroatoms at position 4 of 1 resulted in compounds that were less potent than the parent molecule but which still possessed significant α-adrenergic activities. In particular compound **2** was found to have improved α_2 selectivity relative to 1. Substitution at position 4 with geminal methyl groups resulted in complete elimination of α_2 effects but maintained α_1 activity about equal to that of NE. Although this produced a less potent compound than 1 at the α_1 site, unlike 1, compound **7** was a specific α_1 agonist when tested in adrenergic receptor containing tissues. Further work on structural analogues of 1 is in progress in our laboratories.

(14) Because the ED_{50} NE and ED_{50} CPD were both determined in the same tissue (see Experimental Section for details) these values are "paired", and the index must be calculated for each experiment and then summed to produce a mean. It is not appropriate to divide the mean ED_{50} NE by the mean ED_{50} CPD since these are not independent observations. For a discussion of paired comparisons see Mainland, D. *Elementary Medical Statistics*; Saunders: Philadelphia, PA, 1963; p 202.

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Experimental Section

α_1 Activities Using Isolated Rabbit Aorta. Female rabbits, weighing 2–5 kg, were sacrificed by cervical dislocation. The thoracic cavity was immediately opened, and the descending aorta was removed and placed in a petri dish containing Krebs buffer aerated with 95% O_2 and 5% CO_2. The Krebs buffer solution was prepared as follows (mM concentrations): NaCl 119, $NaHCO_3$ 25, KCl 4.7, $MgSO_4$ 1.5, KH_2PO_4 1.2, $CaCl_2$ 2.5, glucose 11, NaEDTA 0.03, and ascorbic acid 0.3. The buffer was prepared daily from a concentrated stock solution and was adjusted to a pH of 7.4.

A helical strip of aorta was mounted in a 10-mL tissue bath containing Krebs buffer and was attached to a force transducer (Grass or Statham) so that an initial tension of 2 g was applied. The tissue was allowed to equilibrate for 1 h during which time the tissue was washed four times and the tension reset to 2 g until it had stabilized. A mixture of 95% O_2 and 5% CO_2 was continuously bubbled through the tissue bath and reservoir. Stirring in the bath was provided by vigorous bubbling of the gas mixture. The temperature of the tissue bath was maintained at 37 ± 0.5 °C by means of a constant-temperature bath that circulated approximately 8 L/min of warmed water through the water jacket of the tissue bath. Standard weights were hung on the force transducers to calibrate them. Contractions, measured by the force transducers, were recorded on a Grass Model 7 polygraph, and periodic samples of the data were acquired by an on-line computer system, which included a PDP 11/45 and DEC 10 computer.

A cumulative concentration–effect curve of contraction was produced with the standard agonist, norepinephrine, from 1×10^{-8} to 1×10^{-3} M. Drugs were administered by means of an adjustable microliter pipet in volumes usually from 10 to 100 μL. The response to each concentration of standard or test compound was allowed to plateau before the administration of the next concentration. Following the sequential addition of norepinephrine, the tissue was washed with aliquots of buffer every 10–15 min for 60–90 min until the tension returned to base line or reached a plateau near the base-line level. The tension of the tissues was readjusted until it stabilized at 2 g before the increasing concentrations of the test compound were added and the responses were measured.

α_2 Activities Using PBZ-Pretreated Dog Saphenous Vein. Rings (3–4 mm wide) of lateral saphenous veins excised from beagle dogs of either sex were suspended in 10-mL tissue baths containing bicarbonate buffer of the following composition (mM): NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.5, KH_2PO_4 1.2, $NaHCO_3$ 20, dextrose 11, ascorbic acid 0.3, NaEDTA 0.03, cocaine 0.03, hydrocortisone hemisuccinate 0.04, and propranolol 0.004. The solution was gassed with 95% O_2 and 5% CO_2 at 37 °C, pH 7.45. Isometric contractions of the tissues, preloaded with a tension of 2 g, were measured with Grass FTO3 strain gauges and recorded on a Grass Model 7 polygraph.

Following an equilibration period of 15–20 min and maximal contraction by norepinephrine (1×10^{-4} M), the tissues were washed for 60 min at which time they were exposed to phenoxybenzamine (PBZ) (1×10^{-7} M) for 30 min. At the end of the PBZ treatment a thorough washout followed for 60 min. Tissues were then adjusted to 2-g tension, and a control cumulative concentration–effect curve was obtained for the standard agonist, norepinephrine. After washout of norepinephrine (45–60 min), tissues were again equilibrated and a cumulative concentration–response curve for the test agonist was obtained.

Chemistry. Proton magnetic resonance (^1H NMR) spectra were recorded on a Varian T-60, or Varian XL-100, using Me_4Si as an internal standard. Mass spectra were obtained on a Varian CH7 spectrophotometer. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra

were recorded on a Perkin-Elmer 521 spectrophotometer. Elemental analyses were done in-house, and determined values are within 0.4% of theoretical values.

5,6-Dimethoxy-2-methyl-1-tetralone. To a solution of 21.6 g (60 mmol) of (carbethoxyethylidine)triphenylphosphorane (Aldrich) in 60 mL of benzene was added 10 g (56 mmol) of (2,3-dimethoxyphenyl)acetaldehyde.[11] After the initial exothermic reaction had subsided the solution was heated at reflux for 2 h, then it was cooled and concentrated. Addition of heptane caused the separation of solid triphenylphosphine oxide, which was filtered and washed with heptane. The filtrate was treated with Norite, filtered, and evaporated to give 15 g of an oil (ethyl 4-(2,3-dimethoxyphenyl)-2-methyl-2-butenoate).

All of this ester was dissolved in 85 mL of EtOH and was hydrogenated in a Parr shaker at 50 psi using 3 g (wet) of 20% Pd on carbon as a catalyst. After hydrogen uptake ceased the catalyst was filtered and washed with EtOH. The filtrate was evaporated and distilled (bp 110–115 °C (0.2 mmHg)) to give 13.4 g (91%) of ethyl 4-(2,3-dimethoxyphenyl)-2-methylbutanoate.

The entirety of this substituted ethyl phenylbutanoate was saponified by heating for 30 min at reflux with 50 mL of H_2O, 16 mL of 45% KOH, and 12 mL of EtOH. The EtOH was removed by distillation and the solution was cooled, acidified, and extracted with ether. The evaporated extracts gave 12 g of a colorless oil (4-(2,3-dimethoxyphenyl)-2-methylbutanoic acid).

This butanoic acid (12 g, 50 mmol) was added with stirring to 214 g of hot (92 °C) polyphosphoric acid. After 20 min at 90 °C the reaction was removed from the steam bath, quenched with ice and H_2O, and extracted with ether. The combined extracts were treated with Norite, dried over $MgSO_4$, filtered, and evaporated, and the residue was crystallized from ether–hexane to give 9.3 g (85%) of 5,6-dimethoxy-2-methyl-1-tetralone: mp 103–105 °C; ^1H NMR ($CDCl_3$) 1.15 (d, 3, J = 6 Hz), 1.50–3.20 (m, 5), 3.80 (s, 3), 3.90 (s, 3), 6.90 (d, 1, J = 9 Hz), 7.87 (d, 1, J = 9 Hz); mass spectrum, m/e 220 (M^+), 205, 191, 178, 163, 150. Anal. ($C_{13}H_{16}O_3$) C, H.

5,6-Dimethoxy-2-phenyl-1-tetralone. Starting with (2,3-dimethoxyphenyl)acetaldehyde[11] and (carbethoxybenzylidine)-triphenylphosphorane[12] and using the procedure described for the synthesis of 5,6-dimethoxy-2-methyl-1-tetralone gave a 66% overall yield of 5,6-dimethoxy-2-phenyl-1-tetralone: mp 145–147 °C (lit.[16] mp 146–148 °C).

5,6-Dimethoxy-4,4-dimethyl-1-tetralone. A mixture of 61.7 g (0.24 mol) of (2-chloro-4,5-dimethoxyphenyl)butyric acid,[13] 80 mL of MeOH, 200 mL of benzene, and 0.2 g of toluenesulfonic acid was heated at reflux for 20 h. The cooled solution was evaporated; to the residue was added heptane, which was then evaporated, and the residue was dissolved in benzene. The organics were washed with aqueous $KHCO_3$, brine, and H_2O. The organic layer was dried with $MgSO_4$, decolorized with activated charcoal, filtered, and evaporated, and the residue was crystallized from a mixture of hexane and pentane to give 60.5 g (93%) of methyl (2-chloro-4,5-dimethoxyphenyl)butyrate: mp 44–46 °C.

The above ester, 60.5 g (0.22 mol) in 230 mL of tetrahydrofuran (THF), was added dropwise at 0 °C to 200 mL of 2.9 M methylmagnesium bromide (0.58 mol) diluted with 230 mL of THF. After the addition was complete the reaction was allowed to stir for 1 h at ambient temperature and was quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ether, dried over K_2CO_3, filtered, and evaporated to give 63.3 g of 5-(2-chloro-4,5-dimethoxyphenyl)-2-methyl-2-pentanol as an oil that was used without further purification.

A slow addition of this alcohol (60 g, 0.22 mol) to 450 mL of methanesulfonic acid at 0 °C resulted in a dark solution, which was stirred at ambient temperature for 1 h before it was quenched with ice and extracted with ether. The combined organic layers were backwashed with NaOH, dried over $MgSO_4$, filtered, and evaporated, and the residue was crystallized from pentane to give 49 g (88%) of 8-chloro-5,6-dimethoxy-4,4-dimethyltetralin: mp 42–45 °C.

Hydrogenation of this tetralin (49 g, 0.19 mol) in a Parr shaker under 3 atm of hydrogen in 500 mL of MeOH with 26.2 g (0.19 mol) of sodium acetate trihydrate and 7.35 g of 5% palladium on carbon at ambient temperature was stopped after hydrogen uptake ceased. The catalyst was filtered and washed with MeOH. The organic layer was evaporated; the residue was dissolved in cyclohexane, evaporated, and partitioned between hexane and aqueous KOH. The pooled hexane extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was distilled to give 38.6 g (91%) of 5,6-dimethoxy-4,4-dimethyltetralin: bp 85–90 °C (0.1 mmHg).

This tetralin (38.6 g, 0.18 mol) was dissolved in a mixture of 100 mL of acetic acid and 20 mL of propionic acid. To this solution with ice cooling was added dropwise over 20 min a solution of 35.1 g (0.35 mol) of chromium trioxide in a mixture of 22 mL of H_2O and 55 mL of acetic acid. After the mixture was stirred for 2 h at ambient temperature there was added 20 mL of 2-propanol and the whole was evaporated. To the residue was added dilute HCl and the resulting mixture was extracted with ether. The combined extracts were backwashed with dilute NaOH, dried over $MgSO_4$, filtered, and evaporated, and the residue was distilled. The fraction with bp 110–140 °C (0.2 mmHg) was collected and crystallized from hexane to give 26.8 g (65%) of 5,6-dimethoxy-4,4-dimethyl-1-tetralone: mp 51–55 °C; ^1H NMR ($CDCl_3$) 1.46 (s, 6), 1.80–2.10 (m, 2), 2.40–2.70 (m, 2), 3.88 (s, 3), 3.93 (s, 3), 6.95 (d, 1, J = 8 Hz), 7.90 (d, 1, J = 8 Hz) Anal. ($C_{14}H_{18}O_3$) C, H.

4,4-Diethyl-5,6-dimethoxy-1-tetralone. By using the methods described for the synthesis of 4,4-dimethyl-5,6-dimethoxy-1-tetralone and starting with 25.6 g (0.085 mol) of methyl (2-chloro-4,5-dimethoxyphenyl)butyrate, there was obtained 24.2 g (95%) of 6-(2-chloro-4,5-dimethoxyphenyl)-3-ethyl-3-hexanol: mp 60–61 °C, which was converted to 14.3 g (63%) of 8-chloro-4,4-diethyl-5,6-dimethoxytetralin: mp 50–51 °C. All of this chlorotetralin was converted to 10.4 g (83%) of 4,4-diethyl-5,6-dimethoxytetralin, which was oxidized to 7.8 g (71%) of 4,4-diethyl-5,6-dimethoxy-1-tetralone: IR ($CDCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) 0.68 (t, 6, J = 8 Hz), 1.20–2.67 (m, 8), 3.85 (s, 3), 3.90 (s, 3), 6.92 (d, 1, J = 8 Hz), 7.90 (d, 1, J = 8 Hz).

4-Cyano-3,4-dehydro-7,8-dimethoxychroman. A mixture of 8 g (39 mmol) of 7,8-dimethoxychroman-4-one,[8] 7.65 g (77 mmol) of trimethylsilyl cyanide, 30 mg of aluminum chloride catalyst, and 8 mL of toluene was heated at 65 °C for 2 h. The cooled solution was evaporated, then the residue was twice dissolved in toluene and evaporated. The resulting residue was taken up in benzene and heated at reflux for 0.75 h with 1.1 g of p-toluenesulfonic acid monohydrate. The cooled solution was washed with H_2O, dried over $MgSO_4$, treated with Norite, filtered, and evaporated, and the residue was crystallized from ether to give 7.5 g (90%) of 4-cyano-3,4-dehydro-7,8-dimethoxychroman: mp 102–104 °C; ^1H NMR ($CDCl_3$) 3.85 (s, 3), 3.89 (s, 3), 4.95 (d, 2, J = 4 Hz), 6.47 (t, 1, J = 4 Hz), 6.59 (d, 1, J = 9 Hz), 7.08 (d, 1, J = 9 Hz). Anal. ($C_{12}H_{11}NO_3$) C, H, N.

4-Cyano-7,8-dimethoxychroman. To a solution of 7.42 g (34 mmol) of 4-cyano-3,4-dehydro-7,8-dimethoxychroman in 60 mL of EtOH was added 4.85 g (128 mmol) of $NaBH_4$. After heating at reflux for 30 min, the reaction was evaporated and water was added. The aqueous layer was extracted in $CHCl_3$, and the pooled extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was crystallized from ether to give 6.02 g (80%) of 4-cyano-7,8-dimethoxychroman: mp 88–91 °C; ^1H NMR ($CDCl_3$) 2.10–2.50 (m, 2), 3.87 (s, 6), 4.00 (t, 1, J = 6 Hz), 4.24–4.42 (m, 2), 6.60 (d, 1, J = 9 Hz), 7.03 (d, 1, J = 9 Hz).

7,8-Dimethoxy-4-(2-imidazolinyl)chroman Hydrochloride. Into a solution of 1.5 g (6.8 mmol) of 4-cyano-7,8-dimethoxychroman in 10 mL of MeOH and 20 mL of ether at 0 °C was passed a stream of dry HCl gas until the solution was saturated (ca. 1 h). The solution was stoppered and allowed to stir overnight at ambient temperature. After ca. 18 h the solution was evaporated, benzene was added, and the mixture was reevaporated. Acetonitrile and ether were added to obtain a solid (mp 112–115 °C). To this solid dissolved in 15 mL of MeOH was added dropwise at 0 °C a solution of 1.05 g (17.5 mmol) of ethylenediamine in 5 mL of MeOH. The solution was heated at reflux for 20 min, cooled, and evaporated before quenching with ice water and extracting with $CHCl_3$. The pooled organic extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was dissolved in methanolic HCl and evaporated, and the resulting hydrochloride was crystallized from 2-propanol to give 1.4 g (69%)

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of 7,8-dimethoxy-4-(2-imidazolinyl)chroman hydrochloride: mp 253–255 °C; ^{1}H NMR (Me_2SO-d_6) 2.00–2.50 (m, 2), 3.70 (s, 4), 3.80 (s, 3), 3.89 (s, 3), 4.05–4.55 (m, 3), 6.70 (d, 1, J = 8 Hz), 6.87 (d, 1, J = 8 Hz), 10.50 (bs, 2); mass spectrum, m/e 262 (M^+), 247, 234, 219. Anal. ($C_{14}H_{19}ClN_2O_3$) C, H, N.

7,8-Dihydroxy-4-(2-imidazolinyl)chroman Hydrobromide (2). To a solution of 1.40 g (4.7 mmol) of 7,8-dimethoxy-4-(2-imidazolinyl)chroman hydrochloride in 12 mL of CH_2Cl_2 at −78 °C was added 2.80 g (11.2 mmol) of boron tribromide. The resulting mixture was stirred at 0 °C for 30 min before it was cooled to −78 °C and quenched with 50 mL of MeOH. After evaporation, the residue was dissolved in MeOH and evaporated; it was then dissolved in benzene and evaporated, and crystallized from 2-propanol to give 0.81 g (59%) of **2**: mp 239–241 °C; ^{1}H NMR (Me_2SO-d_6) 2.00–2.40 (m, 2), 3.88 (s, 4), 4.00–4.40 (m, 3), 6.46 (s, 2), 10.00 (s, 2); mass spectrum, m/e 234 (M^+), 217, 205. Anal. ($C_{12}H_{15}BrN_2O_3 \cdot 1/2(H_2O)$) C, H, N.

7,8-Dihydroxy-4-(2-imidazolinyl)thiochroman Hydrobromide (3). Starting with 7,8-dimethoxythiochroman-4-one[9] and using the above procedures described for the synthesis of **2** gave compound **3** with a yield of 0.7 g (59%) for the BBr_3 ether cleavage reaction: mp 248–249 °C; IR (KBr) 3460, 1595, 1580 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) 2.15–2.40 (m, 2), 2.80–3.05 (m, 2), 3.85 (s, 4), 4.14 (t, 1, J = 4.5 Hz), 6.45 (d, 1, J = 9 Hz), 6.56 (d, 1, J = 9 Hz), 8.85 (bs, 1), 9.52 (bs, 1), 9.75 (bs, 1); mass spectrum, m/e 250 (M^+), 235. Anal. ($C_{12}H_{15}BrN_2O_2S \cdot {}^1/_2(H_2O)$ C, H, N.

1-Cyano-1-methyl-5,6-(methylenedioxy)tetralin. To a 40-mL solution of lithium diisopropylamide (17.6 mmol, from 1.95 g (19.3 mmol) of diisopropylamine in 30 mL of THF and 11 mL (17.6 mmol) of butyllithium (1.6 M in hexane) at −40 °C for 10 min) at −40 °C under nitrogen was added a solution of 3.0 g (14 mmol) of 1-cyano-5,6-(methylenedioxy)tetralin (prepared from 5,6-(methylenedioxy)-1-tetralone[10] in 89% yield by the method described for the synthesis of **2**) in 6 mL of THF. After the solution was stirred at −20 °C for 10 min, it was cooled to −40 °C, then 2.75 g (19.4 mmol) of methyl iodide was added, and the resulting solution was stirred at ambient temperature for 1 h before it was evaporated. The residue was partitioned between ether and dilute HCl. The organic layer was dried over $MgSO_4$, treated with Darco, filtered, and evaporated, and the residue was crystallized from ether/hexane to give 2.73 g (85%) of 1-cyano-1-methyl-5,6-(methylenedioxy)tetralin: mp 79–81 °C; ^{1}H NMR ($CDCl_3$) 1.63 (s, 3), 1.66–2.33 (m, 4), 2.50–2.80 (m, 2), 6.00 (s, 2), 6.87 (d, 1, J = 8 Hz), 7.05 (d, 1, J = 8 Hz); mass spectrum, m/e 215 (M^+), 200. Anal. ($C_{13}H_{13}NO_2$) C, H, N.

5,6-Dihydroxy-1-(2-imidazolinyl)-1-methyltetralin Hydrobromide (4). The 1-cyano-1-methyl-5,6-(methylenedioxy)-tetralin was carried on using the synthetic sequence described for compound **2** and gave 4 with a yield of 0.84 g (95%) from the BBr_3 cleavage reaction: mp 239–241 °C; ^{1}H NMR (Me_2SO-d_6) 1.54 (s, 3), 1.50–2.10 (m, 4), 2.50–2.70 (m, 2), 3.80 (s, 4), 6.49 (d, 1, J = 9 Hz), 6.65 (d, 1, J = 9 Hz), 9.40 (s, 2); mass spectrum, m/e 246 (M^+), 231, 217, 203, 177. Anal. ($C_{14}H_{19}BrN_2O_2$) C, H, N.

***trans*-5,6-Dihydroxy-1-(2-imidazolinyl)-2-methyltetralin Hydrobromide (5).** Starting with 5,6-dimethoxy-2-methyl-1-tetralone (described above) and following the synthetic sequence described for compound **2** gave **5** with a yield of 0.95 g (95%) for the BBr_3 cleavage reaction: mp 265–268 °C; ^{1}H NMR (Me_2SO-d_6) 1.00 (d, 3, J = 6 Hz), 1.10–1.60 (m, 1), 1.80–2.10 (m, 2), 2.50–2.80 (m, 2), 3.20–3.70 (bs, 2, absent with D_2O), 3.58 (d, 1, J = 10 Hz), 3.88 (s, 4), 6.35 (d, 1, J = 8 Hz), 6.70 (d, 1, J = 8 Hz), 10.05 (s, 2, absent with D_2O); mass spectrum, m/e 246 (M^+), 231, 217, 203, 187, 176. Anal. ($C_{14}H_{19}BrN_2O_2$) C, H, N.

***trans*-5,6-Dihydroxy-1-(2-imidazolinyl)-2-phenyltetralin Hydrobromide (6).** Following the synthetic sequence for compound **2** and starting with 5,6-dimethoxy-2-phenyl-1-tetralone (described above) gave **6** with a yield of 1.96 g (94%) for the BBr_3 cleavage reaction: mp 302–304 °C; ^{1}H NMR (Me_2SO-d_6) 1.80–2.10 (m, 2), 2.50–2.90 (m, 2), 3.10–3.40 (m, 1), 3.66 (s, 4), 4.20 (d, 1, J = 10 Hz), 6.35 (d, 1, J = 8 Hz), 6.70 (d, 1, J = 8 Hz), 7.10–7.40 (m, 5), 10.05 (s, 2); mass spectrum, m/e 308 (M^+), 293, 279, 263, 247, 231, 217, 203. Anal. ($C_{19}H_{21}BrN_2O_2$) C, H, N.

5,6-Dihydroxy-4,4-dimethyl-1-(2-imidazolinyl)tetralin Hydrobromide (7). Starting with 5,6-dimethyoxy-4,4-dimethyl-1-tetralone (described above) and following the synthetic sequence for compound **2** gave **7** with a yield of 1.22 g (83%) for the BBr_3 cleavage reaction: mp 236–238 °C; ^{1}H NMR (Me_2SO-d_6) 1.28 (s, 3), 1.35 (s, 3), 1.40–2.10 (m, 4), 3.82 (s, 4), 3.97 (t, 1, J = 6 Hz), 6.25 (d, 1, J = 8 Hz), 6.70 (d, 1, J = 8 Hz), 9.80 (s, 2); mass spectrum, m/e 260 (M^+), 245, 214, 203. Anal. ($C_{15}H_{21}BrN_2O_2$) C, H, N.

4,4-Diethyl-5,6-dihydroxy-1-(2-imidazolinyl)tetralin Hydrobromide (8). Starting with 4,4-diethyl-5,6-dimethoxy-1-tetralone (described above) and following the synthetic sequence for compound **2** gave 8 with a yield of 0.35 g (85%) for the BBr_3 cleavage reaction: mp 201–202 °C; IR (KBr) 3500, 1600 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) 0.50 (t, 3, J = 7 Hz), 0.63 (t, 3, J = 8 Hz), 1.00–2.60 (m, 4), 3.83 (s, 4), 4.00 (bs, 1), 6.30 (d, 1, J = 8 Hz), 7.07 (d, 1, J = 8 Hz), 8.00 (bs, 1, absent with D_2O), 9.67 (bs, 2 absent with D_2O); mass spectrum, m/e 288 (M^+), 273. Anal. ($C_{17}H_{25}BrN_2O_2$) C, H, N.

Acknowledgment. We thank Steven Buckner, Robert Warner, Karen Oheim, and Dusanka Stanisic for technical assistance and Cyndy Davis for typing the manuscript.

Registry No. **2**, 102535-60-4; **2** (free base), 102745-02-8; **3**, 102573-56-8; **3** (free base), 102745-03-9; **4**, 102535-62-6; **4** (free base), 102745-04-0; **5**, 102535-63-7; **5** (free base), 102745-05-1; **6**, 102535-64-8; **6** (free base), 102745-06-2; **7**, 102535-65-9; **7** (free base), 102745-07-3; **8**, 102535-66-0; **8** (free base), 102745-08-4; (carbethoxyethylidene)triphenylphosphorane, 5717-37-3; (2,3-dimethoxyphenyl)acetaldehyde, 5707-56-2; ethyl 4-(2,3-dimethoxyphenyl)-2-methyl-2-butenoate, 102535-44-4; ethyl 4-(2,3-dimethoxyphenyl)-2-methylbutanoate, 102535-45-5; 4-(2,3-dimethoxyphenyl)-2-methylbutanoic acid, 102535-46-6; 5,6-dimethoxy-2-methyl-1-tetralone, 102535-47-7; 5,6-dimethoxy-2-phenyl-1-tetralone, 65144-89-0; (2-chloro-4,5-dimethoxyphenyl)butyric acid, 56242-82-1; methyl (2-chloro-4,5-dimethoxyphenyl)butyrate, 102535-48-8; 5-(2-chloro-4,5-dimethoxyphenyl-2-methyl-2-pentanol, 102535-49-9; 8-chloro-5,6-dimethoxy-4,4-dimethyltetralin, 102535-50-2; 5,6-dimethoxy-4,4-dimethyltetralin, 102535-51-3; 5,6-dimethoxy-4,4-dimethyltetralone, 102535-52-4; 6-(2-chloro-4,5-dimethoxyphenyl)-3-ethyl-3-hexanol, 102535-53-5; 8-chloro-4,4-diethyl-5,6-dimethoxytetralin, 102535-54-6; 4,4-diethyl-5,6-dimethoxytetralin, 102535-55-7; 4,4-diethyl-5,6-dimethoxytetralone, 102535-56-8; 7,8-dimethoxychroman-4-one, 19149-07-6; 4-cyano-3,4-dehydro-7,8-dimethoxychroman, 102535-57-9; 4-cyano-7,8-dimethoxychroman, 102535-58-0; ethylenediamine, 107-15-3; 7,8-dimethoxy-4-(2-imidazolinyl)chroman hydrochloride, 102535-59-1; 1-cyano-5,6-(methylenedioxy)tetralin, 102035-30-3; 1-cyano-1-methyl-5,6-(methylenedioxy)tetralin, 102535-61-5; 1-(2-imidazolinyl)-1-methyl-5,6-(methylenedioxy)tetralin hydrochloride, 102535-67-1; *trans*-5,6-dimethoxy-1-(2-imidazolinyl)-2-methyltetralin hydrochloride, 102535-68-2; *trans*-5,6-dimethoxy-1-(2-imidazolinyl)-2-phenyltetralin hydrochloride, 102535-69-3; 5,6-dimethoxy-4,4-dimethyl-1-(2-imidazolinyl)tetralin hydrochloride, 102535-70-6; 4,4-diethyl-5,6-dimethoxy-1-(2-imidazolinyl)tetralin hydrochloride, 102535-71-7.