Antisecretory screening was performed as described by Cavanagh et al.[13]

Acknowledgment. We are grateful to John C. Reiffenstein for the cytoprotective screening and John Reynolds for the antisecretory testing. Additionally, we appreciate the support of Dr. E. McNiff and the analytical department at Bristol-Myers Syracuse in obtaining IR, NMR, MS, and elemental analysis data.

Introduction of a Putative Dopaminergic Prodrug Moiety into a 6,7-Substitution Pattern Characteristic of Certain 2-Aminotetralin Dopaminergic Agonists

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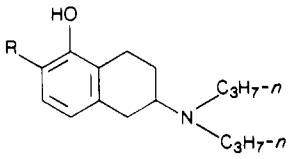
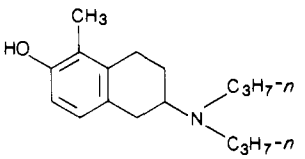
On the basis of the premise that the dopaminergic agonist profile of 2-(di-*n*-propylamino)-5-hydroxy-6-methyltetralin (**1a**) is due to in vivo oxidation of the 6-methyl moiety and that **1a** may represent a novel prodrug strategy, the vicinal methyl–hydroxyl substitution pattern was incorporated into the 6- and 7-positions of 2-(di-*n*-propylamino)tetralin to give the 6-methyl-7-hydroxy and 6-hydroxy-7-methyl isomers **8** and **9**, respectively. A multistep synthetic approach was devised which permitted preparation of target molecules **8** and **9**. Pharmacological data revealed that both target compounds exhibit modest dopamine-like effects in the cardioaccelerator nerve assay in the cat, but neither appeared to be metabolically activated as was the case with **1a**. The effects of **9** (but not of **8**) were antagonized by pretreatment with haloperidol. Thus, the 5-hydroxy-6-methyl substitution pattern in the 2-aminotetralins remains unique as a dopaminergic agonist prodrug structure.

5-Hydroxy-6-methyl-2-(di-*n*-propylamino)tetralin (**1a**) is a dopaminergic agonist prodrug, orally active with a long duration of activity.[1a-f] The 6-methyl group of **1a** is metabolized to higher oxidation states (i.e., hydroxymethyl **1b** and formyl **1c**) which exhibit a high degree of dopaminergic activity.[1a] In these 5,6-disubstituted 2-aminotetralin derivatives, the β-phenethylamine moiety is held in the α-conformation, which has been proposed[2,3] to be significant in the binding of dopaminergic agonists to receptors. In contrast, 5-methyl-6-hydroxy-2-(di-*n*-propylamino)tetralin (**2**) exhibits only a low order of dopaminergic effects,[4] and there is no experimental indication that it is metabolically activated.[5]

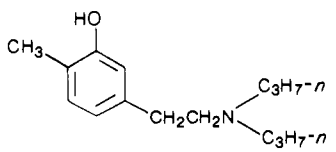


1a: R = CH_3
b: R = CH_2OH
c: R = CH=O



2

The vicinal methyl–hydroxy subsitution pattern has been incorporated into other ring systems **3–6**, whose corresponding catechol derivatives show dopaminergic agonism.[1f,6] These compounds showed diverse, inconsistent, and unpredictable pharmacological activities. None were dopaminergic agonist prodrugs, and some showed no dopaminergic effects of any kind.



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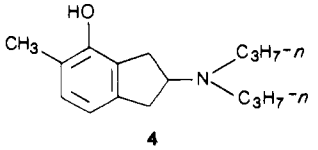

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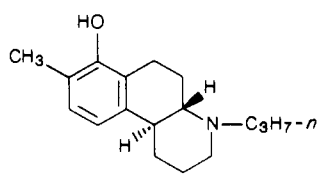

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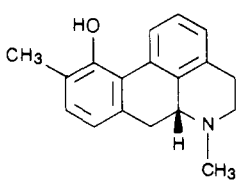

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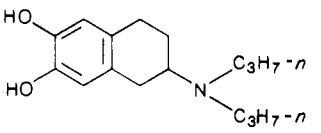
Thus, 5-hydroxy-6-methyl-2-(di-*n*-propylamino)tetralin (**1a**) and, by inference, the tetralin ring system appeared to represent a unique structure for a dopaminergic prodrug. In the present study, the vicinal methyl–hydroxy aromatic substitution pattern replaced the catechol substitution pattern of 6,7-dihydroxy-2-(di-*n*-propylamino)-tetralin (**7**) which is a potent dopaminergic agonist,[7] albeit



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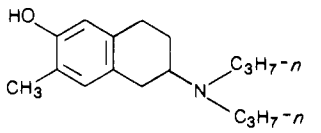

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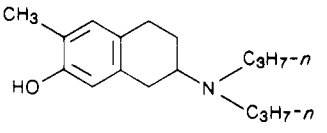

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† Division of Medicinal and Natural Products Chemistry.
‡ Department of Pharmacology.

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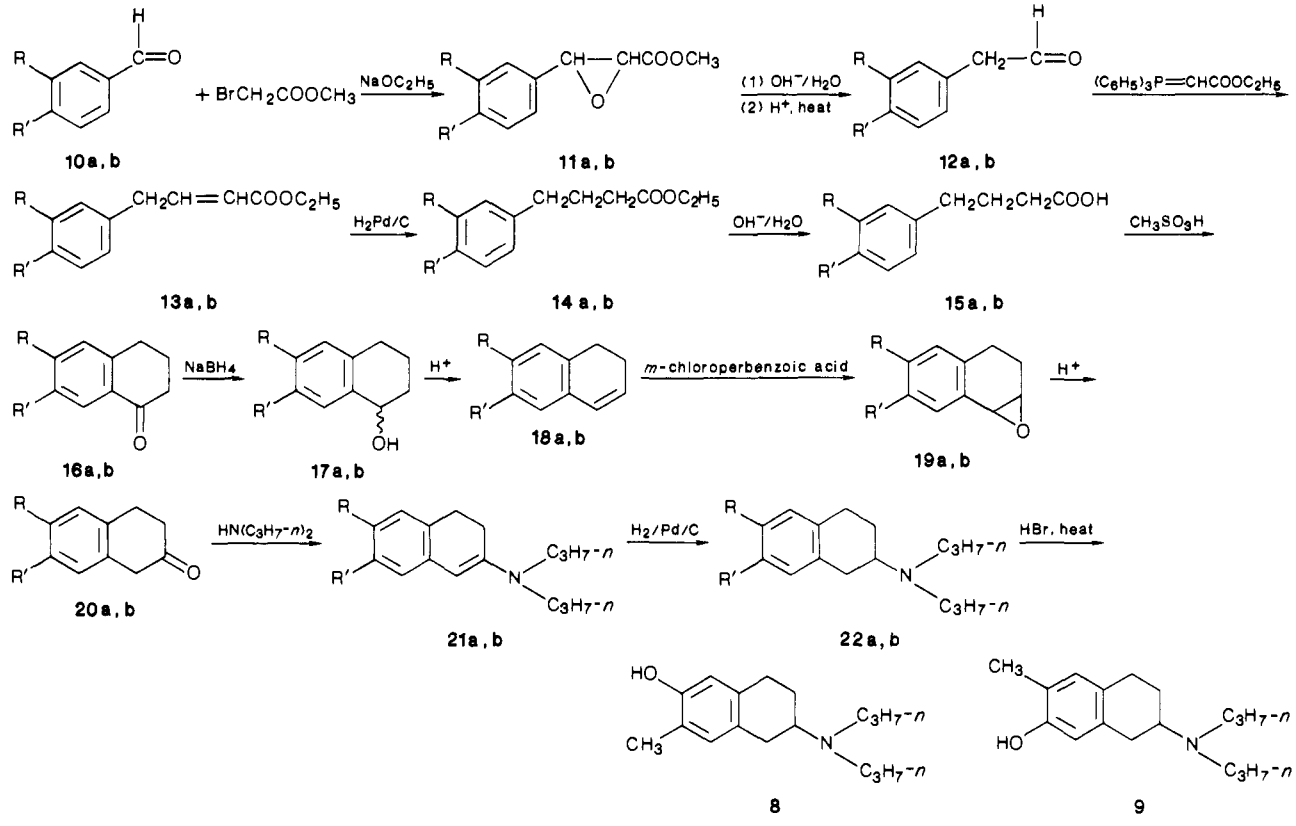
Scheme I. Preparation of 6-Methyl-7-hydroxy- and 6-Hydroxy-7-methyl-2-(di-*n*-propylamino)tetralin (9 and 8)[a]



[a] **a**: R = CH_3; R′ = OCH_3. b: R = OCH_3; R′ = CH_3.

with a different spectrum of effects than its 5,6-dihydroxy isomer. In **7**, the dopamine moiety is held in the β-conformation.[2,3] Compounds **8** and **9** were targeted for preparation and pharmacological study.

Chemistry. A single synthetic route was adaptable to preparation of both target compounds (**8** and **9**), and it is illustrated in Scheme I. Some improvements were made in preparation of certain of the intermediates which are literature compounds. The present method for preparation of 3-methoxy-4-methylbenzaldehyde (**10b**) seems preferable to the literature[8] procedure which involved reduction of the corresponding acid chloride. 4-(3-Methoxy-4-methylphenyl)butyric acid (**15b**) was first prepared[9] from toluene by a tedious seven-step sequence; the present method is shorter and much less onerous. Reaction time for sodium borohydride reduction of the tetralones (**16** → **17**) was reduced from the literature[10] requirement of 16 h to 1 h by use of a different solvent system, and nearly quantitative yields were achieved. Mumm and Diederichsen[11] reported formation of 3-methyl-4-methoxyphenylacetaldehyde (**12a**) by ozonolysis of an appropriately substituted *n*-pent-2-enylbenzene, but the crude product (described as a bright yellow oil) was not purified, and it was characterized as its semicarbazone. Spectral (IR, NMR, MS) data on all intermediates and final compounds were consistent with the proposed structures.

Results and Discussion. Table I shows test data for the target compounds **8** and **9**. Maximal inhibition by **8** or **9** of cardiac responses to cardioaccelerator nerve stimulation occurred within 3 min of intravenous administration. With the homologue **1a**, no inhibition of transmission was observed for 10–15 min, and approximately 40 min were required for maximal inhibition to occur. Considerable evidence suggests that **1a** is a prodrug.[1d] Thus, the pattern of inhibitory activity for **8** and **9** is different from that of **1a**. Haloperidol (0.1 mg/kg) antagonized biological responses to **9** but not to **8**. Thus, while the behavior of **9** is consistent with its exerting DA_2 agonist effects, the mechanism of action of **8** in the cardioaccelerator nerve assay remains unclear. The duration of inhibition of cardioaccelerator nerve activity by **9** was >2 h and by **8** was >30 min. Neither **8** nor **9** induced observable behavioral alterations in rats, with doses up to 10 mg/kg. This lack of apparent central nervous system properties for **9** was unexpected; peripheral DA_2-receptor agonists usually demonstrate several behavioral responses. The present studies further illustrate the unique dopaminergic prodrug character of the 5-hydoxy-6-methyl-2-aminotetralin system **1a**. The 10-methyl-11-hydroxyaporphine system **6** is a potent/active serotonergic (5-HT_{1A}) agonist.[5] However, neither **8** nor **9** demonstrated the behavioral "serotonin syndrome" (e.g., "piano playing") characteristic of serotonergic agonists.[12]

Table I. Biological Properties of 2-Aminotetralin Derivatives

compd no.	inhibn of cat cardioaccelerator nerve: ID_{50} (95% CL), μmol/kg	behavior responses
1a	0.025 (0.017–0.056)	active (0.2 mg/kg)
8	1.75 (1.1–4.9)	none[a]
9	0.54 (0.2–0.9)	none[a]
apomorphine	0.035 (0.03–0.04)	active (0.25 mg/kg)

[a] Subcutaneous doses (up to 10 mg/kg) in rats did not alter locomotion, nor was there evidence of "serotonin syndrome" behavior.

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Experimental Section

Pharmacology. Methods. Cardioaccelerator Nerve Stimulation. Experiments were performed using cats (2–4 kg) of either sex. Cats were anesthetized by intraperitoneal injection of pentobarbital sodium (30 mg/kg). All animals were artificially respired with a Harvard respirator. Arterial 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. After bilateral vagotomy, the right postganglionic cardioaccelerator nerves were isolated and placed on bipolar electrodes and were stimulated for 30 s with a Grass S48 stimulator with the following parameters: 2 Hz, 5-ms pulse duration, supramaximal voltage usually 20–25 V. All animals were pretreated with atropine sulfate (0.2 mg/kg). Each test compound was administered intravenously to at least three cats. The compounds were administered in sequential doses, but only after the inhibitory effect on tachycardia had stabilized. At least three doses, spaced by 0.48 log intervals, were administered to each cat.

Behavior in Rats. Compounds were administered subcutaneously to rats (n = 3 or more), and the animals were observed every 10 min for 2 h thereafter for alteration of behavior, including locomotion, and for induction of the "serotonin syndrome".[12] Doses ranged from 0.1 to 10 mg/kg.

Statistics. Relative potency and 95% fiducial limits were calculated with a 3 × 3 parallel line bioassay.[13] The ID_{50} values were determined by nonquantal analysis.[14]

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. NMR spectra were recorded on a Varian Associates EM 360A spectrometer and on a Brucker-IBM NR80 instrument. Mass spectra were recorded with a Ribermag R10-10C mass spectrometer. Flash chromatography was performed with Analtech flash column grade silica, 150-Å pore size, 35–75-μm particle size. Radial thin-layer chromatography was performed on a Harrison Research Chromatotron apparatus, model 7924T, using E.M. Science gipshaltig kieselgel 60PF_{254} silica as the stationary phase on the rotors.

Methyl 3-(3-Methyl-4-methoxyphenyl)glycidate (11a). To a solution of NaOMe prepared in situ from 3.5 g (0.15 g-atom) of Na dissolved in 45 mL of absolute MeOH at −10 °C was slowly added dropwise 15 g (0.10 mol) of 3-methyl-4-methoxybenzaldehyde (**10a**) in 16.2 g (0.15 mol) of methyl chloroacetate. After the addition was complete, stirring was continued for 2 h at −5 °C and then for 3 h at room temperature. The reaction mixture was poured into 200 mL of ice–H_2O containing 1.5 mL of AcOH. The oil which collected on the bottom of the beaker was taken up in benzene. The benzene was evaporated under reduced pressure and the oily residue was flash chromatographed on silica with EtOAc–hexane (1:8) as the eluent. Evaporation of the eluate gave 14.4 g (65%) of a colorless solid, mp 44–45 °C. Anal. ($C_{12}H_{14}O_4$) C, H.

3-Methyl-4-methoxyphenylacetaldehyde (12a). To a solution of 10 g (0.045 mol) of **11a** in 60 mL of Na-dried benzene at 5 °C was added a solution of NaOMe prepared from 1.6 g (0.068 g-atom) of Na and 15 mL of absolute MeOH. The resulting solution was stirred for 5 min while 2 mL of H_2O was added dropwise. The resulting mixture was allowed to stand overnight. The white precipitate which separated was collected on a filter and was used in the next step without further purification. This white precipitate (9.8 g) was added to a mixture of 18 mL of H_2O and 30 mL of benzene. After 2.3 mL of AcOH was added, the stirred mixture was warmed at 80 °C until evolution of CO_2 ceased. The benzene layer was separated from the cooled reaction mixture, and the aqueous layer was extracted with three 40-mL portions of benzene. The pooled benzene extracts were evaporated under reduced pressure, and the oily residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:19) as the eluent. The eluate was evaporated to give 7.0 g (75%) of a clear oil, bp 75 °C (0.0025 mm), MS m/e 164 (M^+).

Ethyl 4-(3-Methyl-4-methoxyphenyl)-2-butenoate (13a). Compound **12a** (5.0 g, 0.030 mol) and 10.7 (0.030 mol) of (carbethoxymethylene)triphenylphosphorane were heated under reflux in 100 mL of anhydrous benzene for 2 h. After the solution cooled, the benzene was evaporated under reduced pressure. The residue was shaken in 200 mL of petroleum ether and the resulting mixture was filtered. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:48) as the eluent. The eluate was evaporated to give 6.8 g (97%) of a clear liquid, bp 95 °C (0.0025 mm). Anal. ($C_{14}H_{18}O_3$) C, H.

Ethyl 4-(3-Methyl-4-methoxyphenyl)butanoate (14a). Compound **13a** (4.0 g, 0.017 mol) in 20 mL of AcOH was hydrogenated in a Parr shaker apparatus over 1 g of 5% Pd/C at room temperature and at an initial pressure of 55 psig. The catalyst was removed by filtration and the AcOH was evaporated from the filtrate under reduced pressure to leave a clear, liquid residue which was taken up in 50 mL of EtOAc. This solution was washed with 5% $NaHCO_3$ and then with H_2O. The EtOAc was evaporated and the clear residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:48) as the eluent. The eluate was evaporated to give 4 g (99%) of a clear oil, bp 90 °C (0.0025 mm). Anal. ($C_{14}H_{20}O_3$) C, H.

4-(3-Methyl-4-methoxyphenyl)butanoic Acid (15a). A suspension of 4 g (0.017 mol) of **14a** in 30 mL of 5% KOH was heated under reflux for 2 h. The resulting solution was cooled and brought to pH 4 (pH paper) with 3 N HCl. The resulting milky suspension was extracted with three 60-mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered, and the $CHCl_3$ was removed from the filtrate under reduced pressure. The solid residue was recrystallized from benzene–petroleum ether (1:3) to give 2.9 g (81%) of white crystals, mp 57–58 °C (lit.[15] mp 59.5–60.5 °C).

3,4-Dihydro-6-methyl-7-methoxy-1(2*H*)-naphthalenone (16a). A solution of 2.5 g (0.012 mol) of **15a** in 40 mL of methanesulfonic acid was stirred under N_2 for 12 h at room temperature. The reaction mixture was poured into 50 mL of ice–H_2O. The resulting cloudy mixture was extracted with three 75-mL portions of CH_2Cl_2. The pooled extracts were dried (Na_2SO_4) and filtered, and the CH_2Cl_2 was removed under reduced pressure. The solid residue was recrystallized from cyclohexane to yield 2.1 g (90%) of white crystals, mp 47–48 °C (lit.[15] 44–45 °C).

1,2,3,4-Tetrahydro-6-methyl-7-methoxy-1-naphthalenol (17a). To a cooled (ice bath), stirred solution of 2 g (0.011 mol) of **16a** in 6 mL of MeOH and 3 mL of CH_2Cl_2 was added 0.2 g (0.0053 mol) of $NaBH_4$ in one portion. The resulting mixture was stirred for 3 h at room temperature, and then the solvents were evaporated, and the solid residue was partitioned between 30 mL of H_2O and 30 mL of Et_2O. The aqueous layer was extracted with two 20-mL portions of Et_2O, and the combined ether layers were washed with 1 N HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl. The ethereal solution was dried (Na_2SO_4) and filtered. Et_2O was evaporated under reduced pressure and the residue was chromatographed with a Chromatotron apparatus using a 4-mm silica rotor and EtOAc–hexane (1:8) as the eluent. Evaporation of the eluate gave 2 g (99%) of a solid, mp 68–69 °C. Anal. ($C_{12}H_{16}O_2$) C, H.

3,4-Dihydro-6-methyl-7-methoxynaphthalene (18a). Compound **17a** (1 g, 0.0052 mol) was heated with one crystal of $KHSO_4$ and then was distilled immediately under reduced pressure with a Kugelrohr distillation apparatus (pot temperature 95 °C, 0.025 mm) to give 0.770 g (85%) of distillate which immediately crystallized to a white solid, mp 45–45 °C. Anal. ($C_{12}H_{14}O$) C, H.

3,4-Dihydro-6-methyl-7-methoxy-2(1*H*)-naphthalenone (20a). To a cooled (ice bath), stirred mixture of 0.5 g (0.003 mol)

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of **17a**, 20 mL of CH_2Cl_2, and 8 mL of saturated $NaHCO_3$ was added 0.65 g (80%, 0.003 mol) of 3-chloroperoxybenzoic acid over 5 min. The cooled mixture was stirred for an additional 10 min and then for 2.5 h at room temperature. The liquid layers were separated, and the CH_2Cl_2 layer was washed with saturated $NaHCO_3$ and H_2O. CH_2Cl_2 was removed under reduced pressure to afford a white solid residue which was dissolved in 10 mL of EtOH and 5 mL of 2 N HCl and heated under reflux for 1.5 h. The resulting orange solution was cooled and extracted with three 50-mL portions of benzene. The pooled extracts were dried (Na_2SO_4) and filtered, and the benzene was evaporated from the filtrate to give a reddish solid which was recrystallized from cyclohexane to give 0.371 g (65%) of white crystals, mp 49–50 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

2-(Di-*n*-propylamino)-6-methyl-7-methoxytetralin Hydrochloride (22a). To a stirred solution of 0.4 g (0.0021 mol) of **20a** and 0.04 g (0.00021 mol) of *p*-toluenesulfonic acid in 30 mL of benzene was added 0.850 g (0.0084 mol) of di-*n*-propylamine. This solution was heated under reflux for 72 h in a Dean–Stark apparatus, which provided for removal of H_2O. The cooled, purple reaction mixture was placed immediately in a Parr hydrogenation vessel containing 30 mL of absolute EtOH and 0.3 g of PtO_2, and this mixture was hydrogenated at room temperature overnight at an initial pressure of 55 psig. The catalyst was removed by filtration, and volatiles were removed from the filtrate under reduced pressure. The residue was treated with ethereal HCl and the resulting solid was recrystallized from EtOH–Et_2O to give 0.350 g (61%) of a light tan powder, mp 184–185 °c. Anal. ($C_{18}H_{31}ClNO$) C, H, N.

2-(Di-*n*-propylamino)-6-methyl-7-hydroxytetralin Hydrobromide (9). Compound **22a** (0.2 g, 0.00073 mol) in 11 mL of 48% HBr and 3 mL of AcOH was heated under reflux for 1.5 h. The solvents were evaporated under reduced pressure to give a reddish solid which was recrystallized from EtOH–Et_2O to give 0.180 g (80%) of a light tan powder, mp 213–214 °C. Anal. ($C_{17}H_{29}BrNO$) C, H, N.

3-Methoxy-4-methylbenzaldehyde (10b). A mixture of 10 g (0.066 mol) of 3-methoxy-4-methylbenzyl alcohol,[16] 1.3 g (0.0033 mol) of benzyltributylammonium chloride, 165 mL of EtOAc, and 264 mL of a KOCl solution (prepared from Olin Chemical Co. "HTH" granular dry chlorine for swimming pools by the method of Meyers[17]) was stirred for 30 min, while cooling the reaction mixture by immersion in running tap H_2O. The two liquid layers were separated, and the aqueous layer was extracted several times with Et_2O. The pooled organic phases were evaporated to leave a liquid residue which was taken up in Et_2O and washed with 5% $NaHCO_3$. Et_2O was removed under reduced pressure and the residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:19) as the eluent. The eluate was evaporated to give 7.9 g (80%) of a colorless solid, mp 39–40 °C (lit.[8] mp 40–41 °C).

Methyl 3-(3-Methoxy-4-methylphenyl)glycidate (11b). To a vigorously stirred solution of NaOMe prepared in situ from 1.4 g (0.069 g-atom) of Na and 20 mL of MeOH at −10 °C was slowly added dropwise 6 g (0.04 mol) of **10b** in 7.5 g (0.069) of methyl chloroacetate. After addition was complete, stirring was continued for 2 h at −5 °C and then for 3 h at room temperature. The reaction mixture was poured into 175 mL of ice–H_2O containing 1 mL of AcOH. The oil which collected on the bottom of the beaker was taken up in benzene. Benzene was evaporated from this solution under reduced pressure and the oily residue was flash chromatographed on silica using EtOAc–hexane (1:8) as the eluent. Evaporation of the eluate gave 7.1 g (80%) of an oil which immediately changed to a colorless solid, mp 45–46 °C. Anal. ($C_{12}H_{14}O_4$) C, H.

3-Methoxy-4-methylphenylacetaldehyde (12b). To a solution of 7.1 g (0.032 mol) of **11b** in Na-dried benzene was added at 5 °C a solution of NaOMe prepared from 0.74 g (0.032 g-atom) of Na and 11 mL of absolute MeOH. The solution was stirred for 5 min while 1.0 mL of H_2O was added. The resulting mixture was allowed to stand overnight, then the white precipitate which separated was collected on a filter and was used in the next step without further purification. This material (6.5 g) was added to a mixture of 12 mL of H_2O and 20 mL of benzene. AcOH (1.5 mL) was added, and the stirred mixture was warmed at 80 °C until evolution of CO_2 ceased. The benzene layer was separated from the cooled reaction mixture, and the aqueous layer was extracted with three 30-mL portions of benzene. The pooled benzene extracts were evaporated under reduced pressure, and the oily residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:18) as the eluent. The eluate was evaporated to give a clear oil: bp 85 °C (0.025 mm); yield, 4.0 g (76%). Anal. ($C_{10}H_{12}O_2$) C, H.

Ethyl 4-(3-Methoxy-4-methylphenyl)-2-butenoate (13b). Compound **12b** (4.0 g, 0.024 mol) and 8.4 g (0.024 mol) of (carbethoxymethylene)triphenylphosphorane were heated under reflux in 50 mL of anhydrous benzene for 2 h. Benzene was evaporated from the cooled reaction mixture under reduced pressure. The residue was shaken with 100 mL of petroleum ether and the resulting mixture was passed through a sintered-glass filter. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:48) as the eluent. The eluate was evaporated to give 5.3 g (95%) of a clear liquid, bp 100 °C (0.005 mm). Anal. ($C_{14}H_{18}O_3$) C, H.

Ethyl 4-(3-Methoxy-4-methylphenyl)butanoate (14b). A solution of 4.0 g (0.017 mol) of **13b** in 20 mL of AcOH was hydrogenated in a Parr shaker apparatus over 1 g of 5% Pd/C at room temperature and at an initial pressure of 55 psig. The catalyst was removed by filtration and AcOH was evaporated from the filtrate under reduced pressure. The clear liquid residue was taken up in 50 mL of EtOAc and was washed with 5% $NaHCO_3$ and H_2O. The EtOAc was evaporated and the clear residue was flash chromatographed on silica using EtOAc–$CHCl_3$–hexane (1:1:48) as the eluent. The eluate was evaporated to give 4 g (99%) of a clear oil, bp 171 °C (11 mm) [lit.[18] bp 171–173 °C (11 mm)].

4-(3-Methoxy-4-methylphenyl)butanoic Acid (15b). A suspension of 4 g (0.013 mol) of **14b** in 23 mL of 5% KOH was heated under reflux for 1.5 h. The resulting solution was cooled and brought to pH 4 (pH paper) with 3 N HCl. The resulting milky mixture was extracted with three 50-mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered. $CHCl_3$ was removed from the filtrate under reduced pressure. The solid residue was recrystallized from benzene–petroleum ether (1:3) to give 2.3 g (85%) of a white platelets, mp 69–70 °C (lit.[9] mp 70–71 °C).

3,4-Dihydro-6-methoxy-7-methyl-1(2*H*)-naphthalenone (16b). A solution of 2.5 g (0.012 mol) of **15b** in 40 mL of methanesulfonic acid was stirred under N_2 for 12 h at room temperature. The reaction mixture was poured into 50 mL of ice–H_2O. The resulting suspension was extracted with three 75-mL portions of CH_2Cl_2. The pooled extracts were dried (Na_2SO_4) and filtered, and CH_2Cl_2 was removed from the filtrate under reduced pressure. The solid residue was recrystallized from cyclohexane to yield 2.2 g (95%) of colorless crystals, mp 109–110 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

1,2,3,4-Tetrahydro-6-methoxy-7-methyl-1-naphthalenol (17b). To a cooled (ice bath), stirred solution of 2 g (0.011 mol) of **16b** in 6 mL of MeOH and 3 mL of CH_2Cl_2 was added 0.2 g (0.0053 mol) of $NaBH_4$ in one portion. The mixture was stirred for 3 h at room temperature, and then the solvents were evaporated under reduced pressure. The solid residue was partitioned between 30 mL of Et_2O and 30 mL of H_2O. The aqueous layer was extracted with two 20-mL portions of Et_2O, and the combined extracts were washed with 1 N HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic solution was dried (Na_2SO_4) and filtered, and the volatiles were removed under reduced pressure. The residue was chromatographed with a Chromatotron apparatus using a 4-mm silica rotor and eluting with EtOAc–hexane (1:8). Evaporation of the eluate gave 2 g (99%) of a solid, mp 114–115 °C. Anal. ($C_{12}H_{16}O_2$) C, H.

3,4-Dihydro-6-methoxy-7-methylnaphthalene (18b). Compound **17b** (1.0 g, 0.0052 mol) was heated with one crystal of

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$NaHSO_4$ and was immediately distilled under reduced pressure with a Kugelrohr distillation apparatus (pot temperature 95 °C, 0.050 mm) to give 0.63 g (70%) of distillate that solidified at once, mp 45–46 °C. Anal. ($C_{12}H_{14}O$) C, H.

3,4-Dihydro-6-methoxy-7-methyl-2(1*H*)-naphthalenone (20b). To a cooled (ice bath), stirred solution of 0.5 g (0.003 mol) of **18b** in 20 mL of CH_2Cl_2 and 8 mL of saturated aqueous $NaHCO_3$ was added 0.65 g (80%, 0.003 mol) of 3-chloroperoxybenzoic acid over 5 min. The resulting mixture was stirred for an additional 10 min with cooling and then for 2.5 h at room temperature. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ and H_2O. Volatiles were removed under reduced pressure to give a white solid which was dissolved in 10 mL of EtOH and 5 mL of 2 N HCl and heated under reflux for 1.5 h. The resulting orange solution was cooled and extracted with three 50-mL portions of benzene. The pooled benzene extracts were dried (Na_2SO_4) and filtered, and the benzene was evaporated under reduced pressure to leave a reddish solid which was recrystallized from cyclohexane to give 0.4 g (70%) of white crystals, mp 84–85 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

2-(Di-*n*-propylamino)-6-methoxy-7-methyltetralin Hydrochloride (22b). To a stirred solution of 0.3 g (0.0016 mol) of **20b** and 0.03 g (0.00016 mol) of *p*-toluenesulfonic acid in 20 mL of benzene was added 0.637 g (0.0063 mol) of di-*n*-propylamine. This solution was heated under reflux in a Dean–Stark apparatus to provide removal of H_2O. The cooled purple reaction mixture was immediately placed in a Parr hydrogenation vessel with 20 mL of absolute EtOH and 0.2 g of PtO_2, and this mixture was hydrogenated overnight at an initial pressure of 55 psig. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was treated with ethereal HCl and the resulting solid was recrystallized from EtOH–Et_2O to yield 0.3 g (68%) of a light tan powder, mp 195–196 °C. Anal. ($C_{18}H_{30}ClNO$) C, H, N.

2-(Di-*n*-propylamino)-6-hydroxy-7-methyltetralin Hydrobromide (8). Compound **22b** (0.2 g, 0.00073 mol) in 11 mL of 48% HBr and 3 mL of AcOH was heated under reflux for 1.5 h. The volatiles were evaporated under reduced pressure to give a reddish solid which was recrystallized from EtOH–Et_2O to give 0.150 g (67%) of a light tan powder, mp 229–230 °C. Anal. ($C_{17}H_{28}BrNO$) C, H, N.

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Quinones. 4.† Novel Eicosanoid Antagonists: Synthesis and Pharmacological Evaluation

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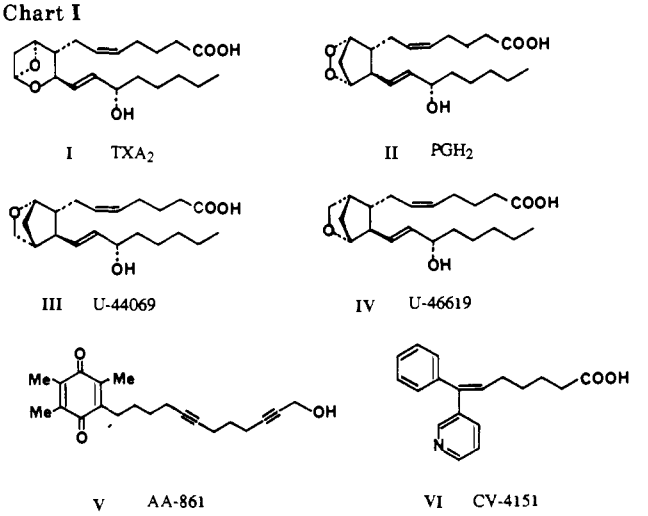
A new series of ω-phenyl-ω-quinonylalkanoic acids and related compounds was synthesized. The compounds were tested for their inhibitory effects on U-44069-induced contraction of the rabbit aorta. (±)-7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**4d**) (AA-2414) with pA_2 value of 8.28 was one of the most potent compounds. Compound **4d** inhibited U-46619-induced contraction of the guinea pig lung (pA_2 = 8.29) and U-44069-induced aggregation of the guinea pig platelet ($IC_{50} = 3.5 \times 10^{-7}$ M). Compound **4d** displaced the binding of [^{3}H]U-46619 to guinea pig platelets ($IC_{50} = 7.4 \times 10^{-9}$ M). Compound **4d** also showed very potent inhibitory effects with an MED of 0.3 mg/kg (po) on U-46619-, LTD_4-, PAF-, or IgG_1-induced bronchoconstriction in guinea pigs. The enantiomers of **4d** were prepared. The *R*-(+) isomer **8a** was active in both in vitro and in vivo tests, but the *S*-(−) isomer **8b** was much less active. We concluded that the antiasthmatic effects of **4d** were based mainly on the TXA_2 receptor antagonistic action. In addition, compound **4d** showed potent inhibitory effects on PGD_2-, $PGF_{2\alpha}$-, and 11-*epi*-$PGF_{2\alpha}$-induced contraction of the guinea pig tracheal strips. The diverse inhibitory effects might be expressed in terms of eicosanoid-antagonistic activity.

Since the discoveries of thromboxane A_2 (TXA_2), prostaglandin I_2(PGI_2), and leukotrienes (LTs) during the period from 1975 to 1979, studies have clarified the physiological and pathological roles of the arachidonate cascade metabolites. Based on these discoveries, novel concepts for designing new drugs that specifically control and manipulate these metabolites have been developed. Our approach to the synthesis of target compounds that affect metabolites of the arachidonate cascade has focused on the synthesis of non-eicosanoid compounds (Chart I). We have found a potent and selective 5-lipoxygenase inhibitor, 2-(12-hydroxy-5,10-dodecadiynyl-3,5,6-trimethyl-1,4-benzoquinone (V, AA-861),[1] from studies on quinone derivatives with alkenyl and alkynyl groups in the side chain, and a potent and long-acting thromboxane synthetase inhibitor, (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenic acid (VI, CV-4151),[2] from the design of a series of ω-(3-pyridyl)alkenoic acids. Both compounds are in clinical trials.

Chart I



† Part 3 is ref 1b.
‡ Chemistry Laboratories.
§ Biology Laboratories.

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