with ether and decapitated, and their brain (forebrain) and heart removed. Brain was homogenized in ice-cold 50 mM sodium phosphate buffer pH 7.4 (32 mL per gram of tissue) in a Polytron (3 × 30 s, 75% maximum), centrifuged at 40000g for 2 min, resuspended in the original volume of buffer and recentrifuged. The resulting pellet was resuspended at a concentration of 3 mg of protein per milliliter and stored in aliquots at −70 °C. Heart tissue was minced, homogenized in 145 mM NaCl, 10 mM Tris-HCl pH 7.4 in a Polytron (3 × 30 s, 75% maximum) and centrifuged at 40000g for 20 min. The resulting pellet was washed three times by resuspension in fresh buffer followed by centrifugation as above. The final pellet was resuspended at 6 mg of protein per milliliter and stored at −70 °C.

Binding of [^{3}H]NMS was performed by incubating 200–300 μg of membrane with 0.5 nM [^{3}H]NMS and the indicated compound in a total volume of 1 mL of phosphate-buffered saline. After 60 min at 37 °C, the mixture was rapidly filtered over glass fiber filters which were washed three times with ice-cold 0.9% NaCl and processed for scintillation counting. Binding of [^{3}H]Oxo-M was performed by incubating membrane with 2.7 nM [^{3}H]Oxo-M and the indicated compound in a total volume of 1 mL of buffer G (50 mM $NaPO_4$, 2 mM $MgCl_2$, pH 7.4) for 20 min at 37 °C. This mixture was then filtered over glass fiber filters that had been presoaked in 0.05% polyethylenimine. The filters were washed with ice-cold 0.9% NaCl, then processed for scintillation counting. Nonspecific binding was determined by coincubation with 1 μM atropine and was routinely subtracted from the total binding. The nonspecific binding amounted to less than 10% of total binding for [^{3}H]NMS and to 20–50% for [^{3}H]Oxo-M binding.

The K_i values were determined by computer analysis of displacement curves obtained by incubating membranes with various concentrations of either **1a** or **6** and with 2.7 nM [^{3}H]Oxo-M as described above. The data represent means ± SEM from three determinations each made in duplicate.

Stimulation of PI Turnover in A9L Cells. Transfected A9L fibroblast cells were obtained from Dr. Mark Brann (NIH) and were grown in DMEM supplemented with 10% newborn calf serum (Advanced Biotechnologies, Columbia, MD). Cells were plated into 24-well plates at 100 000 cells per well. After 24 h, they were labeled overnight with 2 μCi per well of [^{3}H]*myo*-inositol (American Radiolabeled Chemicals, Inc., St. Louis, MO; 15 Ci/mM). The cells were then rinsed twice with 10 mM LiCl in DMEM–Hepes and the cells were incubated in this solution for 5 min at 37 °C. The indicated compound was then added at a final concentration of 100 μM and the cells were incubated for another 30 min at 37 °C. The reaction was stopped by aspirating the solution and adding cold methanol to the cells. After the cells were transferred to a glass tube and sonicated briefly, chloroform and water were added to make a two-phase system. The upper aqueous phase was applied to 0.6-mL anion exchange columns (AG X8, Bio-Rad), and the columns were washed and total inositol phosphates were eluted with 1 M ammonium formate and 0.1 M formic acid.

Inhibition of PGE_1-Stimulated cAMP Levels in NG108-15 Cells. This assay was performed as previously reported.[14]

Isomeric Monomethyl Ether Derivatives of (*RS*)-9,10-Dihydroxyaporphine ("Isoapomorphine") as Possible Products of Metabolism by Catechol-*O*-methyltransferase

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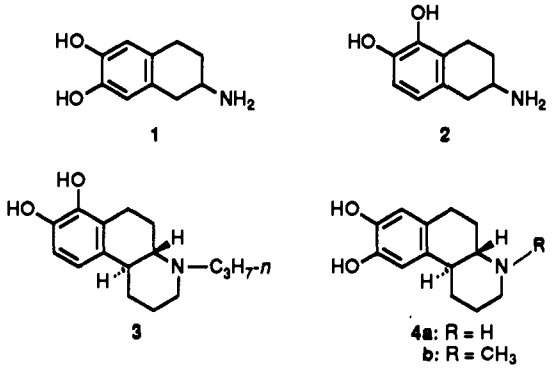
The isomeric monomethyl ether derivatives of (*RS*)-9,10-dihydroxyaporphine ("isoapomorphine") were synthesized unequivocally as possible metabolites in catechol-O-methyltransferase (COMT) mediated O-methylation reactions. In vitro incubation studies revealed that isoapomorphine is not a substrate for the COMT using experimental conditions under which apomorphine (10,11-dihydroxyaporphine) is converted in high yield into its 10-methyl ether, apocodeine. The in vivo dopaminergic inactivity of isoapomorphine (as compared with that of apomorphine) seems to be due to factors other than metabolic inactivation by COMT.

Rollema et al.[1] have reported that incubation of (*RS*)-6,7-dihydroxy-2-aminotetralin (**1**) with crude rat liver



catechol-*O*-methyltransferase (COMT) gave rise to the two isomeric monomethyl ethers in approximately equal amounts. When (*RS*)-5,6-dihydroxy-2-aminotetralin (**2**) was incubated under the same conditions, it was found to be a poor substrate. This difference in susceptibility to COMT has been invoked[2] to explain observed differences in central nervous system (CNS) effects of **1** and **2**.

We recently reported[3] similar studies with (*RS*)-7,8-dihydroxy- and (*RS*)-8,9-dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (**3** and **4a**) using porcine COMT. Only the 8,9-dihydroxy isomer **4a** was a substrate for the enzyme, and the sole detectable product of the reaction was the "meta"-methylated product **4b**. In the 2-aminotetralins (**1**, **2**) and in angularly annulated octahydrobenzoquinolines (**3**, **4b**) it is the β conformer[4] (**1**, **4b** of the dopaminergic moiety which is a substrate for COMT, and the α-conformer[4] (**2**, **3**) is re-

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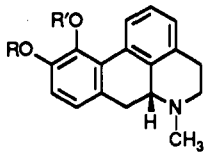
Table I. HPLC Retention Times for Apomorphine and Isoapomorphine and for Their Monomethyl Ethers

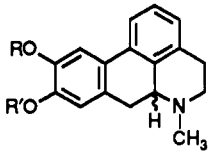
no.	5a	5c	6	7	8
t_R, min	8.4	22.8	6.6	13.4	17.8

fractory to the enzyme. This suggested[3] that the lack of prominent CNS dopaminergic effects of the 8,9-dihydroxy system **4b** as compared with that of the 7,8-dihydroxy system **3** might be a reflection of preferential and facile in vivo metabolism and inactivation of **4b** (which contains the β-conformer of the dopamine moiety) by COMT. This is consistent with the proposals of Horn, et al.,[2] cited previously for 2-aminotetralins (**1**, **2**).

The central[5] and peripheral[6] dopaminergic inactivity of (*RS*)-8,9-dihydroxyaporphine ("isoapomorphine") **6** (in which the dopamine moiety is held in the β-conformation) suggested the possibility of COMT-mediated metabolic inactivation of this compound. The literature has not revealed information about the action of COMT on isoapomorphine.



5a: R = R′ = H
b: R = H; R′ = CH_3
c: R = CH_3; R′ = H



6: R = R′ = H
7: R = H; R′ = CH_3
8: R = CH_3; R′ = H

However, (*R*)-10,11-dihydroxyaporphine (apomorphine) **5a**, a potent and active central and peripheral dopaminergic agonist, is an excellent substrate in vitro for rat liver COMT.[7] Under the incubation conditions used, the ratio of "para"-methylated product (apocodeine) **5c** to "meta"-methylated product ("isoapocodeine") **5b** was on the order of 70:1. The relative amounts of isomeric monomethyl ether products of in vitro COMT metabolism of catechols depend in part upon the biological source of the enzyme.[8,9]

The isomeric monomethyl ethers of isoapomorphine, (*RS*)-**7** and **8** were synthesized as authentic samples of possible metabolic products in our studies in vitro action of COMT on **6**. Racemic isoapomorphine was employed in these studies because pharmacological data have been obtained only for the racemic material.[5,6] As a control, apomorphine **5a**, a known substrate for COMT in vitro,[7] was carried through the same enzyme incubation procedure.

Chemistry. Preparation of (*RS*)-**7** and **8** paralleled our earlier synthesis[10] of (*RS*)-8,9-dimethoxyaporphine. Spectral (NMR, MS) data on all intermediates and final products were consistent with the proposed structures.

High-Performance Liquid Chromatography and Enzyme Experiments. The identification and quantitative determination of O-methylated metabolites arising from the action of COMT upon catecholamines by high-performance liquid chromatography has been described by Rollema et al.[1,11] Chromatography of the catechol standards **5a** and **6** and of the metabolite standards **7**, **8**, and apocodeine (**5c**) (the principal in vivo COMT metabolite of apomorphine) was performed on a Nucleosil column as described by Rollema et al.;[1,11] however, the composition of the mobile phase was changed in the present studies. The retention times are shown in Table I. Rollema and co-workers[1,11] utilized crude rat liver preparations as the source of COMT. In the present study, commercially available partially purified porcine COMT was used.

Sufficient COMT was used in each incubation to produce 10 μmol of product/h. Comparison of the chromatograms and retention times on the incubation sample of **6** with those of COMT and the standard monomethyl ethers **7** and **8** showed that no monomethyl ether product(s) (**7** or **8**) could be detected. Under analogous experimental conditions, and consistent with previous studies,[7] (*R*)-apomorphine (**5a**) was converted in high yield into apocodeine (**5c**). Thus, under the in vitro conditions employed, (*RS*)-isoapomorphine (**6**) is not a substrate for COMT. The dopaminergic inactivity of isoapomorphine in vivo appears to be due to factors other than metabolic inactivation by COMT.

It is not possible to relate substrate preference of COMT to the conformation (α or β) of the dopamine moiety within a complex molecule. No explanation to reconcile differences in COMT substrate selectivity in aporphines as compared with 2-aminotetralins and angularly annulated octahydrobenzoquinolines is apparent.

Experimental Section

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. For enzyme incubation assay, alumina (Al_2O_3, Type E, neutral, Merck), *S*-adenosyl-L-methionine hydriodide (92%, Sigma), catechol-O-methyltransferase (Sigma; from porcine liver; 1480 units/mg of protein), $MgCl_2$ (hexahydrate, Mallinckrodt), Nucleosil 5 C18 (Altech Applied Science), and phosphate buffer (NaH_2PO_4, anhydrous, adjusted to pH 7.6 with H_3PO_4, enzyme grade, Fisher Biotech) were used. MeOH used for the HPLC analyses was Fisher HPLC grade, and the mobile phase of MeOH, H_2O, and formic acid (30:70:1) was degassed prior to use.

(*RS*)-9,10-Dihydroxyaporphine ("Isoapomorphine," 6). This was prepared by the procedure of Cannon et al.[10]

(*R*)-11-Hydroxy-10-methoxyaporphine (Apocodeine, 5c). This was prepared by the procedure of Cannon et al.[7]

4-(Benzyloxy)-3-methoxytoluene (9). To a refluxing, stirred mixture of 13.82 g (0.1 mol) of 2-methoxy-4-methylphenol and 15.19 g (0.126 mol) of K_2CO_3 in 76 mL of absolute EtOH was added dropwise over 0.5 h 15.19 g (0.12 mol) of benzyl chloride. The reaction mixture was then heated under reflux overnight. To the cooled reaction mixture was added 40 mL of H_2O and the resulting mixture was stirred to dissolve all solids. This solution was thoroughly chilled, and a crystalline solid separated which was collected on a filter and washed with a small volume of cold MeOH. To the mother liquor was added a second 40-mL portion of H_2O and upon cooling, a second crop of crystals resulted which was collected on a filter and washed with cold MeOH. The combined solid product was dried at ambient temperature under reduced pressure to afford 20.28 g (89%) of white crystals, mp 47–48 °C (lit.[12] mp 45–46 °C).

4-(Benzyloxy)-5-methoxy-2-nitrotoluene (10). Compound **9** (10.0 g, 0.044 mol) in 34 mL of glacial AcOH was added dropwise

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with stirring to a chilled (4–6 °C) mixture of 20 mL of concentrated HNO_3 and 10 mL of glacial AcOH. The reaction mixture was stirred an additional 2 h at this temperature, then it was poured into 400 mL of an ice–H_2O mixture. After 10 min, this mixture was filtered through sintered glass and the solid on the filter was washed with H_2O until the washings were neutral to pH paper. The solid was recrystallized from EtOH to yield 10.82 g (90%) of light yellow crystals, mp 118–119 °C (lit.[12] mp 117–118 °C).

1-[4-(Benzyloxy)-5-methoxy-2-nitrobenzal]-2-methyl-1,2,3,4-tetrahydroisoquinoline (11). A solution of 1.6 g (0.07 g-atom) of Na in 70 mL of 99% EtOH was divided into equal halves. Isoquinoline methiodide (6.1 g, 0.0226 mol) was dissolved in one portion, and 7.0 g (0.0256 mol) of **10** was dissolved in the other half, and this solution was heated to 50 °C. The isoquinoline methiodide solution was added in one portion, and heating was continued with stirring. When the temperature reached 78 °C, the reaction mixture deposited a copious amount of precipitate. After cooling to room temperature, this solid was collected on a filter and was washed with EtOH. It was then heated under reflux for 10 min with 70 mL of 99% EtOH, and the resulting hot suspension was filtered to yield 8.95 g (94%) of a brick-red solid, mp 140–142 °C. Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

(*RS*)-1-[2-Amino-4-(benzoyloxy)-5-methoxybenzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (12). Compound 11 (4.0 g, 0.0096 mol) in 40 mL of 99% EtOH and 3.5 mL of concentrated HCl was hydrogenated in a Parr shaker apparatus over 0.1 g of 10% Pt/C at an initial pressure of 45 psig. When the calculated amount of H_2 was absorbed, the reduction mixture was filtered and the solid on the filter was washed with two small portions of warm H_2O which were pooled with the filtrate. Volatiles were removed from this solution under reduced pressure. The residue was treated with cold 99% EtOH and the off-white crystalline product was collected on a filter (yield 3.09 g, 70%), mp 246–247 °C. Anal. ($C_{25}H_{30}Cl_2N_2O_2$) C, H, N.

(*RS*)-10-(Benzyloxy)-9-methoxyaporphine Hydrochloride (13). To a well-chilled (10 °C) solution of 2.5 g (0.0084 mol) of **12** in 36 mL of glacial AcOH and 1.8 mL of concentrated H_2SO_4 was added dropwise over 10 min 1.0 g (0.0145 mol) of $NaNO_2$ in 4.5 mL of H_2O. The resulting dark green solution was stirred at 2–4 °C for 1.5 h, during which time the reaction mixture turned brown. Sulfamic acid (0.059 g, 0.6 mmol), 0.03 g (0.22 mmol) of CuCl, and 50 mL of Me_2CO were added and this mixture was heated under reflux for 0.75 h. The hot solution was filtered and the filtrate was basified with concentrated NH_4OH to give a red heterogeneous mixture. The upper organic layer was separated and the lower aqueous layer was extracted with Et_2O. The combined organic phases were washed with saturated NaCl, dried (Na_2SO_4), and filtered, and volatiles were removed from the filtrate under reduced pressure. To the residue was added excess 5% ethanolic HCl. The resulting mixture was chilled and the solid which separated was collected on a filter and washed with cold 99% EtOH to yield 0.65 g (24%) of a yellow solid, mp 262 °C dec. Anal. ($C_{25}H_{26}ClNO_2$) C, H, N (Karl Fischer H_2O 1.09%).

(*RS*)-10-Hydroxy-9-methoxyaporphine Hydrochloride (7). Compound 13 (0.54 g, 0.145 mmol) in 30 mL of 99% EtOH was treated with sufficient 10% NaOH to bring the pH to 8 (pH paper). The resulting suspension was filtered and the filtrate was hydrogenated over 0.1 g of 10% Pd/C at an initial pressure of 45 psig. When absorption of H_2 ceased, the reduction mixture was filtered and the solid on the filter was washed with a small volume of 99% EtOH. Volatiles were removed from the combined filtrate and washings, and the residue was chromatographed on silica (150 Å) and eluted with 99% EtOH. The eluate solution was taken to pH 1 (pH paper) with ethanolic HCl and was concentrated under reduced pressure to afford 0.284 g (69%) of off-white crystals, mp 271–272 °C dec. Anal. ($C_{18}H_{20}ClNO_2$) C, H, N.

3-Hydroxy-4-methoxytoluene (14). A solution of 15.2 g (0.1 mol) of 3-hydroxy-4-methoxybenzaldehyde in 20 g (0.4 mol) of hydrazine hydrate was heated under reflux for 1 h. The reaction solution was transferred to a 1-L beaker and, with stirring, 3.5 g (0.063 mol) of powdered KOH was added gradually to the solution to maintain the temperature at 120–140°C, until evolution of N_2 ceased. The cooled reaction mixture was taken to pH 1 (pH paper) with 10% HCl, then it was extracted several times with Et_2O. Volatiles were removed from the pooled extracts to afford 13.8 g (99%) of brownish yellow crystals, mp 35–36 °C (lit.[13] mp 35–36 °C).

3-(Benzyloxy)-4-methoxytoluene (15). This was prepared from 13 g (0.094 mol) of **15**, 16.37 g (0.118 mol) of K_2CO_3, 75 mL of 99% EtOH, and 14.75 g (0.117 mol) of benzyl chloride as was described for **10** to yield 20.25 g (95%) of light yellow needles, mp 51–52 °C (EtOH) (lit.[14] mp 54–55 °C).

5-(Benzyloxy)-4-methoxy-2-nitrotoluene (16). This was prepared from 10 g (0.0438 mol) of **15** and 20 mL of concentrated HNO_3 in 44 mL of glacial AcOH, as described for **11** to yield 10.35 g (87%) of light yellow crystals, mp 130–131 °C (EtOH) (lit.[14] mp 131–133 °C).

1-[5-(Benzyloxy)-4-methoxy-2-nitrobenzal]-2-methyl-1,2,3,4-tetrahydroisoquinoline (17). This was prepared from 1.56 g (0.068 g-atom) of Na, 64 mL of 99% EtOH, 5.46 g (0.02 mol) of **16**, and 5.42 g (0.02 mol) of isoquinoline methiodide as described for **12** to yield 6.15 g (75%) of orange needles, mp 111–112 °C (absolute EtOH). Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

(*RS*)-1-[2-Amino-5-(benzyloxy)-4-methoxybenzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (18). Compound 17 (3.0 g, 7.2 mmol) in 30 mL of AcOH and 3.5 mL of concentrated HCl was hydrogenated in a Parr shaker apparatus over 0.1 g of 10% Pd/C at an initial pressure of 45 psig as described for **13** to yield 1.87 g (56%) of light yellow crystals, mp 222–223 °C dec (EtOH). Anal. ($C_{25}H_{30}Cl_2N_2O_2$) C, H, N.

(*RS*)-9-(Benzyloxy)-10-methoxyaporphine Hydrochloride (19). Compound 18 (2.5 g, 0.054 mol) was added in small portions to 80 mL of 10% H_2SO_4. After all of the compound had dissolved, the solution was cooled in an ice/salt bath and 0.38 g (5.5 mmol) of $NaNO_2$ in 7.7 mL of H_2O was added dropwise, to maintain the reaction mixture temperature at −5 °C. After all of the $NaNO_2$ was added, the reaction mixture was stirred for 15 min, then 0.61 of freshly prepared[15] Cu was added, and the reaction mixture was allowed to come to ambient temperature and was stirred for 18 h. The reaction mixture was worked up as described for **14**, to afford 1.0 g (45%) of off-white crystals, mp 241–242 °C (EtOH). Anal. ($C_{25}H_{26}ClNO_2$) C, H, N.

(*RS*)-9-Hydroxy-10-methoxyaporphine Hydrochloride (8). A solution of 0.92 g (2.2 mmol) of **20** in 15 mL of 99% EtOH was treated with 1.5 mL of 10% aqueous NaOH. The resulting mixture was filtered and the filtrate was hydrogenated in a Parr shaker apparatus over 0.5 g of 10% Pd/C at an initial pressure of 45 psig for 12 h. The reduction mixture was treated as described for **7** to afford 0.53 g (74%) of light gray white crystals, mp 277–278 °C dec (EtOH). Anal. ($C_{18}H_{20}ClNO_2$) C, H, N.

High-Performance Liquid Chromatography. Samples of standards **5a**, **5c**, and **6–8** (1 mg) were dissolved in separate 1-mL portions of MeOH/H_2O/HCOOH (20:80:3). Aliquots (5 μL) of these solutions were injected with a Waters U6K valve (2.0-mL loop) onto a 150 × 4.6 mm Nucleosil 5 C_{18} column. The mobile phase (MeOH/H_2O/HCOOH, 20:80:3) was delivered at a flow rate of 1.0 mL/min by a Waters Model 60000A pump, equipped with a Beckman Model 153 UV detector set at 280 nm with a range of 0.2 absorbance units. Chromatograms were recorded on a Houston Instruments Omniscribe recorder and data were collected with an Apple IIe computer equipped with an Interactive Microwave Chromatochart computer board and software for 32 min for each sample.

Identification of O-Methylated Products from Incubation of (*RS*)-9,10-Dihydroxyaporphine ("Isoapomorphine") 6 and (R)-10,11-Dihydroxyaporphine (Apomorphine) 5a with Catechol-*O*-methyltransferase. Compounds **6** and **5a** were incubated separately at 37 °C with catechol-*O*-methyltransferase (COMT), *S*-adenosyl-L-methionine (SAM), and $MgCl_2$. Final concentrations were 1 mg (0.0017 mmol) of **6** or **5a**, 13 mg (0.025 mmol) of SAM, 0.07 mg of COMT (activity rated 1480 units/mg; 100 units produce 0.10 μmol of product/h), 0.5 mL of 0.05 M $MgCl_2$, 0.5 mL of 0.1 M phosphate buffer (pH 7.8), and doubly distilled H_2O to make a total volume of 4 mL. As controls, incubations were run in which COMT, SAM, or substrate (**6** or

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5a) was omitted. After 3 h, the reaction was stopped by addition of 0.08 mL of $HClO_4$. Alumina (0.3 g) was added; the suspensions were sonicated for 5 min, filtered through 0.2-μm Arco disk filters, and injected into the HPL column in 10.0-μL aliquots as described for the standards.

Registry No. **5a**, 58-00-4; **5c**, 641-36-1; (*RS*)-**6**, 99755-62-1; (*RS*)-**7**·HCl, 131792-44-4; (*RS*)-**8**·HCl, 131792-45-5; **9**, 78136-55-7; **10**, 121086-26-8; **11**, 131792-46-6; (*RS*)-**12**·2HCl, 131792-47-7; (*RS*)-**13**·HCl, 131792-48-8; **14**, 1195-09-1; **15**, 4790-01-6; **16**, 2495-83-2; **17**, 131792-49-9; (*RS*)-**18**·HCl, 131792-50-2; (*RS*)-**19**·HCl, 131792-51-3; COMT, 9012-25-3; 2-methoxy-4-methylphenol, 93-51-6; isoquinoline methiodide, 3947-77-1; 3-hydroxy-4-methoxybenzaldehyde, 621-59-0.

The Enantiomeric Specificity of the Antihypertensive Activity of 1-(Phenylthio)-2-aminopropane, a Synthetic Substrate Analogue for Dopamine β-Monooxygenase

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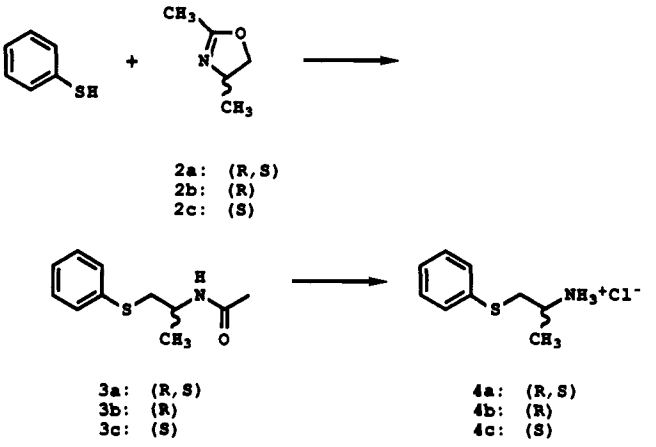
We have found that (*R,S*)-1-(phenylthio)-2-aminopropane (**4a**), a synthetic alternate substrate for the terminal enzyme of norepinephrine biosynthesis, dopamine β-monooxygenase (DBM), is both an indirect sympathomimetic and a potent antihypertensive agent in spontaneously hypertensive rats. We demonstrate herein that there is a distinct enantiospecific difference in the activities of (*R*)-1-(phenylthio)-2-aminopropane (**4b**) and (*S*)-1-(phenylthio)-2-aminopropane (**4c**). We find that **4c**, the more potent DBM substrate analogue, exhibits both the indirect sympathomimetic activity and the antihypertensive activity previously observed for the racemate and inhibits the active transport of catecholamines at the nerve terminal. In contrast, **4b**, which is less potent as a DBM substrate or as an inhibitor of catecholamine uptake, does not exhibit an indirect sympathomimetic effect and is not an effective antihypertensive agent. These results suggest that the greater selectivity of the *S* enantiomer for both the catecholamine reuptake transporter and the target enzyme DBM accounts for its greater potency as an indirect-acting sympathomimetic agent as well as its activity as an antihypertensive agent. These results are also consistent with the hypothesized mechanism of action of this class of sulfur-containing DBM substrate analogues.

(*R,S*)-1-(Phenylthio)-2-aminopropane (**4a**, Scheme I) was synthesized and characterized in our laboratories as one derivative of a class of sulfur-containing substrate analogues for dopamine β-monooxygenase (EC 1.14.17.1, DBM), the terminal enzyme in the biosynthetic pathway to norepinephrine. As we have previously reported, **4a** is both an appreciable substrate for DBM and the most potent antihypertensive derivative of this class when administered in either acute or subchronic dosing protocols to spontaneously hypertensive rats (SHR).[1,2] In addition, **4a** is the most potent indirect sympathomimetic of all of the derivatives of this class, a characteristic which we have demonstrated is directly related to its ability to gain entrance to adrenergic neurons via the catecholamine reuptake mechanism.[2,3]

Although the exact in vivo mechanism of action is yet to be established, we have hypothesized that compounds of this class undergo adrenergic neuronal uptake, subsequent uptake into neurotransmitter vesicular stores, enzymatic oxygenation therein by DBM, and release of DBM-generated "false transmitter" sulfoxide products.[3] While **4a** was originally synthesized in order to assess the effects of monoamine oxidase catabolism on the biological half-life of compounds of this class, its potent antihypertensive activity suggested that the racemate be resolved and the enantiospecificity of the biological effects of **4b** and **4c** be examined. This was particularly important since it is known that α-methylation of monoamine analogues of catecholamines imparts adrenergic receptor specificity.[4]

In the present study, we have separately synthesized and characterized the *R* and *S* enantiomers of 1-(phenylthio)-2-aminopropane (**4b,c**) in order to determine which aspects of the enzymological and cardiovascular activities of these compounds are enantiospecific. We demonstrate herein that **4c** is both an indirect sympathomimetic and a potent antihypertensive agent in SHR. In contrast, **4b** is virtually inert in the cardiovascular assays employed. We also report herein that **4c** is ca. twice as potent as the *R* enantiomer, **4b**, in inhibiting dopamine uptake into rat brain striatal synaptosomes. Finally, we have found that

Scheme I. Synthetic Route to (*R*)- and (*S*)-1-(Phenylthio)-2-aminopropane (**4b,c**)



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