XI. Synthesis of 9(*S*)-[*N*-[(5-Azido-2-formylphenoxy)acetyl]amino]erythromycin (15). (5-Azido-2-formylphenoxy)acetic acid (14) (11 mg) was mixed with 6 mg of *N*-hydroxysuccinimide and 11 mg of *N*,*N*-dicyclohexylcarbodiimide in 0.5 mL of 1,2-dimethoxyethane, and the solution was left in the dark for 3 h at room temperature and then at 0 °C overnight with continuous agitation. After removal of the precipitated dicyclohexylurea, 40 mg of 9(*S*)-aminoerythromycin in 0.2 mL of 1,2-dimethoxyethane was added and the reaction was allowed to proceed in the dark at 0 °C overnight. The extent of the reaction was followed by TLC using eluant 8 and the final product was purified by preparative TLC using the same eluant. The product gave a single ninhydrin-negative, UV-absorbing, and H_2SO_4-sensitive spot when checked by analytical TLC (R_f 0.36 in eluant 8 and 2). IR (KBr) in cm^{-1}: 3600–3100 (OH st, NH st); 2100 (N=N⁺=N⁻, as. st), 1730 (C=O st, lactone), 715 (C=O st, aldehyde), 1655 (C=O st, amide I), 1280 (ar COC, as. st), 1175–1160 (al COC-al, as. st). UV (ethanol): like **14**.

XII. Reduction of 15 to 9(*S*)-[*N*-[[5-Azido-2-(hydroxymethyl)phenoxy]acetyl]amino]erythromycin (16). Derivative **15** (8.5 mg) in 0.2 mL of ethanol was made to react at 0 °C with 0.085 mL of $NaBH_4$ (2 mg/mL in ethanol), which was added drop by drop with continuous agitation followed by addition of 0.085 mL of ethanol. The solution was left at 0 °C and the reaction was followed by UV spectroscopy until the 320-nm aldehyde-absorbing band disappears. After 3 h, the reaction was over and 0.8 mL of 5% $NaCO_3H$, pH 8.8, was added and the mixture was kept in ice for 10 min. A chromatographically homogeneous product (R_f 0.41; eluant 8) was extracted with chloroform. Its UV spectrum showed the absence of the aldehyde band and the presence of azide absorption. Anal. ($C_{46}H_{77}N_5O_{15}$) C, H, N.

Biological Tests. Ribosomes were prepared from *E. coli* MRE600 following standard methods as previously reported.[3]

Binding and competition studies were carried out by filtration on nitrocellulose filters as described elsewhere.[17]

Basically, the ribosomes (1 mg/mL) in 60 mM NH_4Cl, 8 mM $MgCl_2$, 10 mM Tris-HCl, pH 7.4, and 4 mM β-mercaptoethanol were incubated at 30 °C for 15 min in the presence of 0.1 μM [^{14}C]erythromycin and then the competing antibiotic was added at the concentration indicated; after additional incubation for 20 min, the samples were filtered on nitrocellulose filters that were washed twice with 5 mL of the same buffer, dried, and counted. Growth inhibition was tested in 1 mL of culture growing exponentially at 37 °C, to which the appropriate concentration of antibiotic was added. After incubation for 1 h, growth was stopped by addition of 1 mL of 1 mg/mL sodium azide and the optical density of the culture (A_{600}) was checked.

The "puromycin reaction" and the "fragment reaction" were performed with [^{3}H]-*N*-acetylphenylalanine-tRNA as a substrate under the conditions described previously.[18]

Acknowledgment. We thank M. C. Fernández Moyano for expert technical assistance. The work has been supported by Grant 420 from the Consejo Superior de Investigaciones Científicas and by institutional grants to Centro de Biología Molecular from Fundación Ramón Areces.

Registry No. **2**, 100200-99-5; **3a**, 121329-76-8; **3b**, 121329-82-6; **4a**, 121329-77-9; **4a** (*N*-hydroxysuccinimide ester), 111621-31-9; **4b**, 121329-83-7; **5**, 121329-78-0; **6**, 121329-79-1; **7**, 121329-80-4; **8**, 111621-32-0; **9**, 121329-81-5; **10**, 121329-84-8; **13**, 66761-28-2; **14**, 85819-05-2; **15**, 121329-85-9; **16**, 121329-86-0; Ery-NH_2, 26116-56-3; H-Gly-OH, 56-40-6; H-Tyr-OH, 60-18-4; $Br(CH_2)_{10}OH$, 53463-68-6; ICH_2CONH_2, 144-48-9.

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Synthesis and Biological Activity of 3-Substituted Imidazo[1,2-*a*]pyridines as Antiulcer Agents

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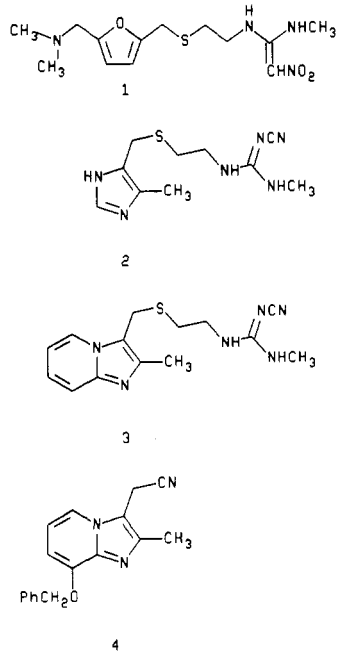
New imidazo[1,2-*a*]pyridines substituted at the 3-position have been synthesized as potential antisecretory and cytoprotective antiulcer agents. The synthetic routes began with cyclization of aminopyridines **5a,b** and chloro ketones **6a,b** to give imidazo[1,2-*a*]pyridines **7–9**. The side chain at the 3-position was elaborated to give primary amines **12a–c**, which were treated with either butoxyaminocyclobutenedione **13** or methoxyaminothiadiazole 1-oxide (**15**) to give **14a,b** and **16a–c**, respectively. Thiadiazole 1-oxides **16a–c** were converted to thiadiazoles **19a–c** in a two-step process which involved extrusion of the sulfoxide in **16a–c** to afford diimidamides **17a–c**, which were subsequently treated with thiobisphthalimide (**18**). None of the compounds displayed significant antisecretory activity in the gastric fistula rat model, but several demonstrated good cytoprotective properties in both the EtOH and HCl models. 8-(Benzyloxy)-3-[1-[[2-[(4-amino-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (**19c**) showed comparable cytoprotective activity to SCH-28080 (**4**).

The commercial success of ranitidine (**1**) and cimetidine (**2**) (see Chart I) in the treatment of peptic ulcer disease has resulted in a search for other drugs to combat this commonly occurring malady. As a result of this effect, several new compounds have been identified which act via a number of different mechanisms of action. These mechanisms include inhibition of acid secretion (H_2-receptor antagonists, H^+/K^+ ATPase inhibitors, anticholinergics, and prostaglandins), cytoprotection (prostaglandins), and mucosal coating (sucralfate).[1] Most of these agents are reported to be active from a single mechanism

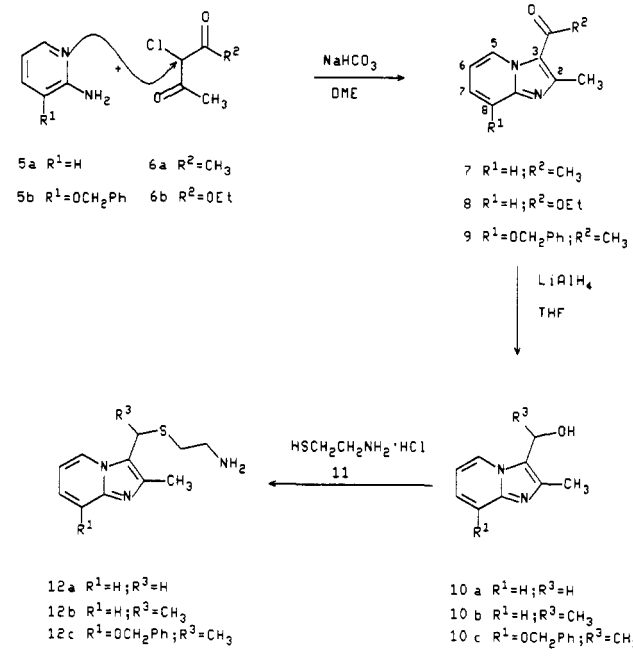
(1) For recent summaries on agents being used in the treatment of peptic ulcer disease, see: Garay, G. L.; Muchowski, J. M. *Annu. Rep. Med. Chem.* **1985**, *20*, 93 and Bauer, R. F.; Collins, P. W.; Jones, P. H. *Annu. Rep. Med. Chem.* **1987**, *22*, 191.

0022-2623/89/1832-2204$01.50/0

Chart I



Scheme I



of action; however, the prostaglandins have exhibited both antisecretory and cytoprotective properties.[2] In addition to the prostaglandins, several imidazo[1,2-*a*]pyridines have also been reported to have both antisecretory and cytoprotective properties.[3,4] Specifically, 3-[[2-[(*N'*-cyano-*N''*-methylguanidino)ethyl]thio]methyl]-2-methylimidazo[1,2-*a*]pyridine (**3**)[4] and 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (SCH-28080, **4**)[3] have been identified as potential antiulcer agents.

Despite the success of approved antiulcer agents in the treatment of peptic ulcer disease, the relapse rate of patients receiving currently available therapy with subsequent recurrence of ulcers continues to be a significant shortcoming. The relapse rates in patients with recently healed duodenal ulcers receiving maintenance doses of either ranitidine or cimetidine for 12 months were reported to be 16 and 43%, respectively.[5] Another study examined the recurrence of duodenal ulcers in patients healed with either cimetidine or the prostaglandin misoprostol. It was found that at 6 months after the termination of therapy that the relapse rates were 42% for patients treated with misoprostol and 46% for those administered cimetidine.[6] Clay recently analyzed published clinical studies to compare the effects of various antiulcer agents on the spontaneous relapse rates of patients with duodenal ulcers 6 months after healing.[7] It was concluded that the rate of recurrence for cimetidine, ranitidine, and misoprostol was 59, 59, and 44%, respectively. In addition to the problems associated with the relapse rate, some reports have questioned the safety and possible long term effects of drugs which act solely on the basis of a major inhibition of acid secretion.[1,6,8]

A compound which has the appropriate balance of antisecretory and cytoprotective properties has several potential advantages over currently available therapy. During the initial phase of treatment, the antisecretory and cytoprotective properties of the drug could be employed to allow the ulcer to heal. Then during maintenance therapy, a lower dose might be employed which, while having adequate cytoprotective properties, lowers acid secretion to a lesser degree.

Imidazo[1,2-*a*]pyridine **3**, reported by Massaroli and co-workers to exhibit antisecretory and cytoprotective properties,[4] can be viewed as an annulation of the imidazole nucleus of cimetidine (**2**). Kaminski et al. have synthesized compound **4**, which does not contain the H_2-receptor antagonist side chain, but is reported to have both cytoprotective and antisecretory properties.[3] The antisecretory activity is believed to arise from inhibition of H^+/K^+ ATPase. This compound was initially entered into clinical trials, but the trials were subsequently suspended due to toxicological problems.[3b] We felt it would be of interest to combine the imidazo[1,2-*a*]pyridine nucleus with some of the H_2-receptor antagonist side chains which are found in compounds which we have previously shown to have antiulcer activity. Specifically, we synthesized derivatives containing the 4-amino-1,2,5-thiadiazole 1-oxide,[9] 4-amino-1,2,5-thiadiazole,[10] and 4-aminocyclobutene-1,2-dione functionalities.[11]

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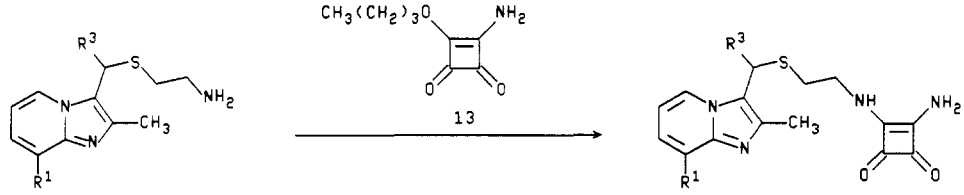
Scheme II



12 a,b

14 a,b

a R^1=H;R^3=H
b R^1=H;R^3=CH_3

Chemistry

Imidazo[1,2-*a*]pyridines **7–9** were prepared in 65–78% yield by condensing the appropriately substituted 2-aminopyridines **5a** and **5b** with chloro ketones **6a** and **6b** in refluxing DME containing $NaHCO_3$ (see Scheme I). The regiochemistry of the imidazo[1,2-*a*]pyridine nucleus was determined by which nitrogen on aminopyridines **5a** and **5b** initiated the attack on chloro ketones **6a** and **6b**. Elliot et al.[12] have shown that reaction of α-halocarbonyls with 2-aminopyridines occurs with initial displacement of the halogen atom by the pyridine-ring nitrogen as shown in Scheme I. Subsequent ring closure of the intermediates and aromatization gave imidazo[1,2-*a*]pyridines **7–9**.

Reduction of the side chain carbonyl in **7–9** with $LiAlH_4$ proceeded smoothly to give alcohols **10a–c** in 76–93%. Although alcohols **10b,c** contain a chiral center, no attempt was made to separate the pair of enantiomers and the racemic mixture was used in subsequent reactions. All of the alcohols produced were of sufficient purity to be used in the next reaction without further purification beyond an extractive workup. Treatment of alcohols **10a,b** with cysteamine hydrochloride (**11**) in concentrated HCl followed by treatment with excess base afforded sulfides **12a,b** in 73 and 91% yield, respectively. Attempts to synthesize **12c** under the same conditions were unsuccessful because of the instability of **10c** under the strongly acidic conditions used. We found that the substitution of refluxing acetic acid for concentrated HCl gave, after neutralization, sulfide **12c** in good yield (90%). The regiochemistry of the products (**12a–c**) was dictated by which of the potential nucleophilic centers on cysteamine **11** (S or N) reacted with alcohols **10a–c**. Under acidic conditions, the primary amine remained potonated and displacement of the alcohol occurred only with sulfur. The NMR spectra of **12a–c** were consistent with structures containing a primary amine (a broad, 2 H singlet). The coupling pattern at C-1′ was also consistent with the structure as shown. All three sulfides (**12a–c**) were used in the following reactions without any further purification.

Amines **12a,b** were dissolved in dry methanol and treated with 3-butoxy-4-aminocyclobutene-1,2-dione[11] (**13**) as shown in Scheme II to give cyclobutenediones **14a,b** in 84 and 60% yield, respectively. Treatment of a methanolic solution of amines **12a–c** with methoxythiadiazole 1-oxide (**15**)[9] gave thiadiazole 1-oxides **16a–c** (see Scheme III). The reaction of amine **12a** with **15** to give **16a** could not be driven to completion. The poor solubility of **16a** made purification from unreacted starting materials by either recrystallization or column chromatography difficult, resulting in a 28% yield. Thiadiazoles **16b** and **16c** were obtained in 96 and 51% yield, respectively. Although we were working with racemic materials, as mentioned above, compounds **12b,c** contain a chiral carbon on the side chain. As a result of the chirality of the sulfoxide functionality, compounds **16b,c** can occur as a mixture of diastereomers. We could find no evidence of such mixtures upon examination of NMR or TLC data, probably due to the rapid equilibration of the sulfoxides.

Previous studies in our laboratories by Crenshaw and Algieri[10a] and Montzka[10b] have shown the inability to directly reduce thiadiazole 1-oxides to thiadiazoles by conventional methods. Consequently, we employed a two-step process to convert **16a–c** to **19a–c**. Thus, thiadiazole 1-oxides **16a–c** were converted first to ethanediimidamide trihydrochloride **17a–c** by treatment with excess HCl in methanol. Subsequent reaction of diimidamides **17a–c** with *N,N′*-thiobisphthalimide (**18**)[10b] gave the desired thiadiazoles **19a–c** in 30–61% yield over two steps.

Biological Results and Discussion

The imidazo[1,2-*a*]pyridines were tested for cytoprotective activity in the EtOH and HCl models. Details of the testing procedure and the methods used for calculating the percent inhibition of lesion formation are given in the Experimental Section. Testing for antisecretory activity was performed by employing the chronic gastric fistula rat model as described by Cavanagh et al.[13] Activity was measured as percent inhibition of gastric secretion and the dose at which gastric acid secretion was inhibited by 50% (ED_{50}) was calculated by probit analysis as described by Finney.[14]

The best cytoprotective activity was observed with thiadiazoles **19a–c** as can be seen in Table I. Benzyloxy **19c** was the most active compound prepared, exhibiting 84% inhibition at 30 mg/kg in the ethanol model and 62% at 30 mg/kg in the HCl model. In both of these models, the compounds to be tested were orally administered, followed by administration of either 100% ethanol or 0.75 N HCl. The resulting lesions were then measured and the percent inhibition of lesion formation was calculated. The inhibition seen with **19c** was comparable to that of the lead compounds imidazo[1,2-*a*]pyridines **3** and **4**. Thiadiazole 1-oxides **16a–c** were less active than the corresponding thiadiazoles. Cyclobutenediones **14a,b** were virtually inactive in the ethanol model, but showed small levels of activity in the HCl model. The increase in activity in the HCl model as compared with that of the ethanol model was in contrast to the other series of compounds (thiadiazole 1-oxides, thiadiazoles, **3**, and **4**). Substitution of benzyloxy (**19c**) for hydrogen (**19b**) at the C-8 position (R^1) resulted in increased cytoprotective activity, as did sub-

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Scheme III

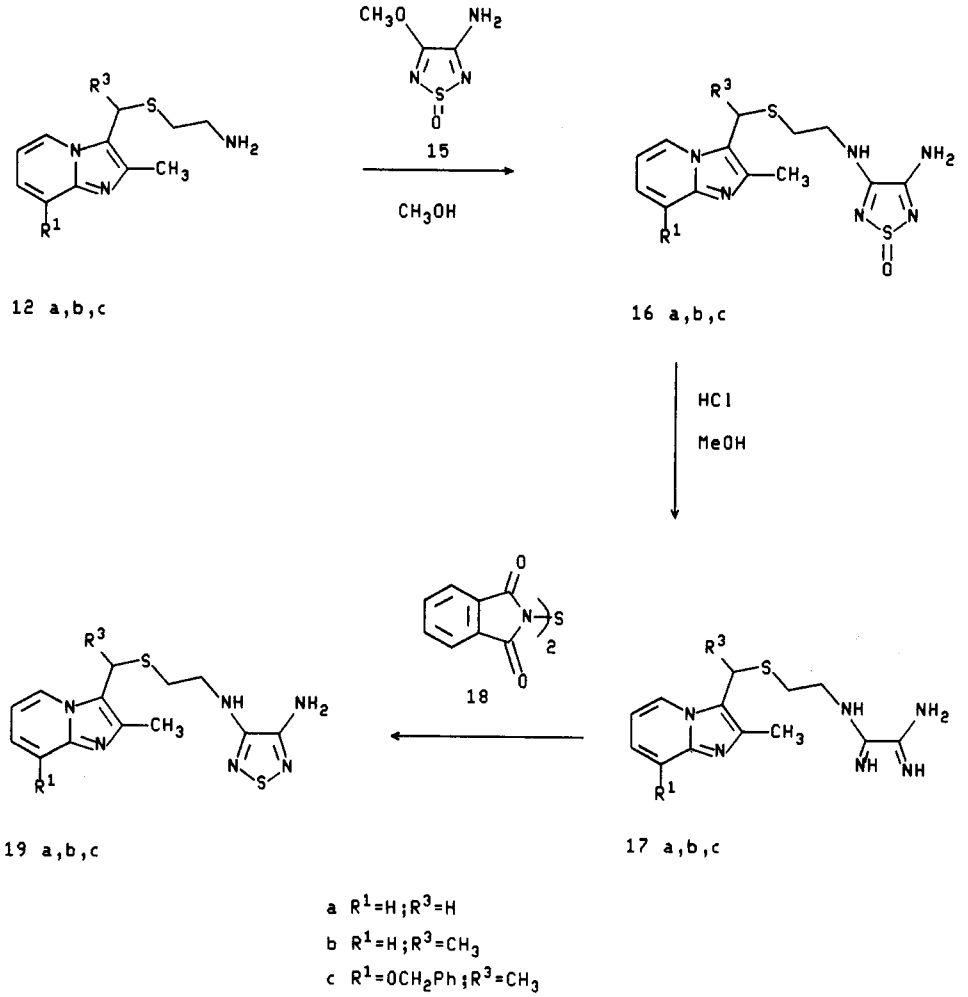
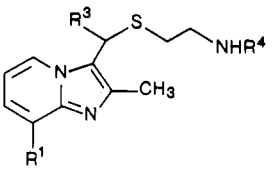
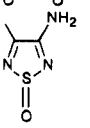


Table I. Pharmacological Activity of 3-Substituted Imidazo[1,2-*a*]pyridine Derivatives



compd	R^1	R^3	R^4	cytoprotective act.: % inhibn/dose,[a] mg/kg po EtOH	cytoprotective act.: % inhibn/dose,[a] mg/kg po HCl	antisecretory act.: ED_{50}, mg/kg po gastric fistula rat
14a	H	H		0/50 (0)	34/50 (5)	≫25
14b	H	CH_3		7/50 (17)	27/50 (9)	≫25
16a	H	H		2/50 (22)	NT	≫25
16b	H	CH_3		47/50 (7)	36/50 (12)	≫25
16c	OCH_2Ph	CH_3		57/50 (8)	57/50 (8)	≫25
19a	H	H		70/50 (5)	24/50 (11)	≫25
19b	H	CH_3		54/50 (2)	51/50 (11)	≫25
19c	OCH_2Ph	CH_3		84/30 (5)	62/30 (10)	≫25
3				97/30 (1)	60/50 (11)	≫25
4				90/30 (5)	68/100 (20)	0.9
PGE_2				89/0.25 (3)	70/0.10 (13)	0.83

[a] Number in parentheses indicates standard error based on five animals per dose. NT = not tested.

stitution of methyl (**16b**) for hydrogen (**16a**) at the R^3 position.

None of the compounds synthesized showed significant antisecretory activity when orally administered in the dose range at which cytoprotective activity was seen; i.e. the observed ED_{50} was much greater than 25 mg/kg. It is of interest to note that in contrast to a published report which stated that cyanoguanidine **3** exhibited good antisecretory activity in the Shay rat model,[3a] we could find no antisecretory activity with **3** in the chronic gastric fistula rat

model at doses up to 50 mg/kg.

In conclusion, a series of imidazo[1,2-*a*]pyridines were synthesized, resulting in a compound (**19c**) which demonstrated significant cytoprotective activity. Although we were able to obtain compounds which exhibited cytoprotection, none of the structures synthesized contained any of the desired antisecretory properties.

Experimental Section

Melting points were determined with either a Fisher-Johns or Thomas Hoover apparatus and are uncorrected. NMR spectra (90 MHz) were recorded on a JEOL FX900 instrument with tetramethylsilane as internal standard. IR spectra were recorded on a Beckman IR-4240 instrument. Mass spectra were recorded on either a HP 5985B or a Kratos MS50TC instrument. IR, NMR, and mass spectral data of all compounds was consistent for reported structures. Flash chromatography was performed as described[15] with 32–63-μm silica gel (ICN). Elemental analyses were carried out by the Elemental Analysis Laboratory, Bristol-Myers Co., Syracuse, NY. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

3-(1-Oxoethyl)-2-methylimidazo[1,2-*a*]pyridine (7). To a stirred solution of 5.00 g (0.0532 mol) of 2-aminopyridine (**5a**) in 50 mL of DME was added 4.56 g (0.0542 mol) of $NaHCO_3$ and 9.50 g (0.0722 mol) of 3-chloro-2,4-pentanedione (**6a**). The heterogeneous mixture was heated to reflux for 16 h and cooled, and the solvents were removed in vacuo. The residue was taken up in water (100 mL) and extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layer was dried over $MgSO_4$ and evaporated to dryness in vacuo. The crude brown oil was purified on a 50-mm flash-chromatography column, eluting with hexane/ethyl acetate 1/2, obtaining 7.20 g (78%) of a white solid: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) 2.60 (3 H, s, CH_3) 6.9–7.8 (3 H, m, ArH), 9.81 (1 H, m, ArH); IR (KBr) 1625, 1495, 1440, 1340, 775 cm^{-1}; EIMS (relative intensity) *m/z* 174 (M^+, 56.5), 159 (100), 131 (13.8), 90 (16.1). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

3-(Ethoxycarbonyl)-2-methylimidazo[1,2-*a*]pyridine (8). This compound was prepared in a manner similar to that for **7**, starting with 2-aminopyridine (**5a**) and ethyl 2-chloroacetoacetate (**6b**). The crude oil was purified on a 50-mm flash-chromatography column, eluting with hexane/ethyl acetate 1/1, obtaining a 74% yield of ester **8** as a light yellow solid; mp 66–68 °C; ^{1}H NMR ($CDCl_3$) 1.45 (3 H, t, *J* = 7.2 Hz, CH_3), 2.66 (3 H, s, $ArCH_3$), 4.23 (2 H, q, *J* = 7.2 Hz, OCH_2) 6.9–7.8 (3 H, m, ArH), 9.39 (1 H, m, ArH); IR (KBr) 2990, 1690, 1400, 1225, 760 cm^{-1}; EIMS (relative intensity) *m/z* 204 (M^+, 100), 176 (29.2), 159 (80.0), 132 (85.4), 90 (154). Anal ($C_{11}H_{12}N_2O_2$) C, H, N.

3-(1-Oxoethyl)-2-methyl-8-(benzyloxy)imidazo[1,2-*a*]pyridine (9). This compound was prepared in a manner similar to that for **7** starting with 3-(benzyloxy)-2-aminopyridine (**5b**) and 3-chloro-2,4-pentanedione (**6a**). The crude product was recrystallized from absolute ethanol to give a 65% yield of ketone **9** as a white, crystalline solid: mp 160–161 °C; H^1 NMR ($CDCl_3$) 1.60 (3 H, s, CH_3), 1.85 (3 H, S, CH_3), 5.38 (2 H, s, OCH_2), 6.8 (2 H, m, H), 7.4 (5 H, m, ArH), 9.4 (1 H, m, ArH); IR (KBr) 1625, 1545, 1400, 1270 cm^{-1}; EIMS (relative intensity) *m/z* 280 (M^+, 100), 237 (8.5), 203 (26.1), 174 (30.8), 91 (74.6). Anal ($C_{17}H_{16}N_2O_2$) C, H, N.

3-(Hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine (10a). Under a nitrogen atmosphere, 1.01 g (0.0266 mol) of lithium aluminum hydride was suspended in 100 mL of THF. The suspension was externally cooled with an ice bath at 0 °C and 5.44 g (0.0267 mol) of ethyl ester **8** was added in small portions (as a solid) over 1 h. The reaction was allowed to warm to 22 °C, was stirred for 1 h, and was quenched with saturated Na_2SO_4, and the resulting salts were collected and washed with THF. The filtrate was dried over $MgSO_4$ and evaporated to dryness in vacuo to give 3.0 g of a fluffy, yellow solid. The salts from above were dissolved in 100 mL of 5% HCl and 20 mL of saturated sodium potassium tartrate. The solution was treated with concentrated NH_4OH until the pH > 8. The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and evaporated to give 0.34 g, which was combined with the previously obtained product to give 3.3 g (76%) of alcohol **10a**, which was used without further purification in the subsequent reaction: ^{1}H NMR ($CDCl_3$) 2.30 (3 H, s, $ArCH_3$), 4.82 (2 H, s, CH_2O), 6.8–7.6 (3 H, m, ArH), 8.4 (1 H, d, *J* = 6.1 Hz, ArH).

3-(1-Hydroxyethyl)-2-methylimidazo[1,2-*a*]pyridine (10b). Under a nitrogen atmosphere, 6.26 g (0.0360 mol) of ketone **7**, dissolved in 50 mL of THF, was added dropwise to a stirred suspension of 1.35 g (0.0355 mol) of lithium aluminum hydride in 100 mL of THF. The reaction was stirred for 1 h after the addition was completed and quenched by the dropwise addition of 5 mL of saturated Na_2SO_4. The resulting salt precipitate was filtered and washed with THF. The filtrate was concentrated to dryness in vacuo to give 5.87 g (93%) of a yellow oil of sufficient purity to use in the subsequent reaction: ^{1}H NMR ($CDCl_3$) 1.65 (3 H, d, *J* = 6.9 Hz, CH_3), 2.12 (3 H, s, $ArCH_3$), 4.25 (1 H, q, *J* = 6.9 Hz, CHOH), 6.7–7.6 (3 H, m, ArH), 8.5 (1 H, m, ArH).

8-(Benzyloxy)-3-(1-hydroxyethyl)-2-methylimidazo[1,2-*a*]pyridine (10c). This compound was prepared in a manner similar to that for **10b**. Ketone **9** was added to the suspension of lithium aluminum hydride (in THF) as a slurry in THF via a wide-bore addition funnel. The workup was similar to that of **10b**, giving alcohol **10c** in 80% yield: ^{1}H NMR ($CDCl_3$) 1.58 (3 H, d, *J* = 7.2 Hz, CH_3), 2.15 (3 H, s, $ArCH_3$), 3.3 (1 H, br s, OH), 5.20 (1 H, d, *J* = 7.2 Hz, OCH), 5.35 (2 H, s, CH_2) 6.6 (2 H, m, ArH), 7.5 (5 H, m, Ar H), 8.1 (1 H, d, *J* = 6.8 Hz, ArH).

3-[[(2-Aminoethyl)thio]methyl]-2-methylimidazo[1,2-*a*]pyridine (12a). To a solution of 1.83 g (0.0162 mol) of cysteamine hydrochloride (**11**) in 5 mL of concentrated HCl was added 2.63 g (0.0162 mol) of alcohol **10a**. The solution was stirred at 22 °C for 7 h, cooled to 0 °C and treated with 40% NaOH until the pH = 14. The mixture was extracted 4× with an equal volume of CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and evaporated to dryness in vacuo to give 2.61 g (73% of a greenish-yellow oil of sufficient purity to be used in subsequent reactions: ^{1}H NMR 1.5 (2 H, br s, NH_2), 2.45 (3 H, s, $ArCH_3$), 2.5–3.0 (4 H, m, CH_2CH_2), 4.10 (2 H, s, $ArCH_2S$), 6.7–7.8 (3 H, m, ArH), 8.10 (1 H, d, *J* = 7.1 Hz, ArH).

3-[1-[(2-Aminoethyl)thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (12b). This compound was prepared in a manner similar to that for **12a**, starting with alcohol **10b** and obtaining a 91% yield of amine **12b** as a viscous, yellow-orange oil: ^{1}H NMR ($CDCl_3$) 1.3 (2 H, br s, NH_2), 1.80 (3 H, d, *J* = 6.8 Hz, CH_3), 2.2–2.9 (4 H, m, CH_2CH_2), 2.45 (3 H, s, $ArCH_3$), 4.60 (1 H, q, *J* = 6.8 Hz, CHS), 6.7–7.7 (3 H, m, ArH), 8.40 (1 H, d, *J* = 6.5 Hz, ArH).

8-(Benzyloxy)-3-[1-[(2-aminoethyl)thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (12c). To a solution of 0.64 g (5.6 mmol) of cysteamine hydrochloride (**11**) in 10 mL of glacial acetic acid was added 1.00 g (3.54 mmol) of alcohol **10c**. The mixture was refluxed for 4 h, cooled, diluted with 25 mL of 5% HCl, and washed with CH_2Cl_2 (1 × 30 mL). The organic layer was discarded and the aqueous layer was basified by the careful addition of saturated $NaHCO_3$. The aqueous layer was then washed with CH_2Cl_2 (2 × 40 mL). The combined organic layer from the basic wash was dried over $MgSO_4$ and evaporated to dryness in vacuo to give 1.08 g (90%) of amine **12c** as a viscous, yellow oil: ^{1}H NMR ($CDCl_3$) 1.6 (2 H, br s, NH_2), 1.70 (3 H, d, *J* = 6.9 Hz, CH_3), 2.2–2.9 (4 H, m, CH_2CH_2), 2.45 (3 H, s, $ArCH_3$), 4.55 (1 H, q, *J* = 6.9 Hz, CHS), 6.3–6.8 (2 H, m, Ar H), 7.2–7.8 (5 H, m, Ar H), 8.00 (1 H, d, *J* = 7.0 Hz, ArH).

3-[[[2-[(4-Amino-1,2-dioxycyclobut-3-en-3-yl)amino]ethyl]thio]methyl]-2-methylimidazo[1,2-*a*]pyridine (14a). Under an atmosphere of nitrogen, 1.15 g (5.20 mmol) of amine **12a** was dissolved with stirring in 20 mL of dry methanol. To this solution was added 0.88 g (5.20 mmol) of the cyclobutenedione **13**. After stirring at 22 °C for 3 h, the flask was cooled to −20 °C for 1 h. The precipitate was filtered and washed with cold (0 °C) methanol. The residue was recrystallized from CH_3CN/H_2O to give 1.37 g (84%) of aminobutene **14a** as a white solid: mp 216–218 °C dec.; ^{1}H NMR (DMSO) 2.38 (3 H, s, $ArCH_3$), 2.6 (2 H, m, CH_2), 3.7 (2 H, m, CH_2), 4.30 (2 H, s, $ArCH_2S$), 6.8–7.8 (6 H, m, ArH, NH, NH_2), 8.40 (1 H, d, *J* = 7.0 Hz, ArH); IR (KBr) 3300, 3140, 1640, 1580, 1530, 1500 cm^{-1}; EIMS (relative intensity) *m/z* 316 (M^+, 3.8), 221 (1.9), 177 (6.7), 145 (100), 112 (2.5). Anal. ($C_{15}H_{16}N_4O_2S\cdot0.5H_2O$) C, H, N.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. chem.* **1978**, *43*, 2923.

3-[1-[[2-[(4-Amino-1,2-dioxycyclobut-3-en-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (14b). Starting with amine **12b**, cyclobutene **14b** was obtained according to the procedure used to prepare **14a**, giving a white solid in 60% yield: mp 209–212 °C dec; ^{1}H NMR (DMSO) 1.64 (3 H, d, J = 7.2 Hz, CH_3), 2.40 (3 H, s, Ar CH_3), 2.5 (2 H, m, CH_2), 3.6 (2 H, m, CH_2), 4.80 (1 H, d, J = 7.2 Hz, CHS), 7.0–7.8 (6 H, m, ArH, NH, NH_2), 8.46 (1 H, d, J = 7.0 Hz, ArH); IR (KBr) 3170, 1630, 1570, 1525, 1500 cm^{-1}; EIMS (relative intensity) m/z 331 (M^+, 4.2), 173 (19.2), 158 (100). Anal. ($C_{16}H_{18}N_4O_2S$) C, H, N.

3-[[[2-[(4-Amino-1-oxo-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]methyl]-2-methylimidazo[1,2-*a*]pyridine (16a). To a stirred solution of 2.60 g (0.0117 mol) of amine **12a** in 10 mL of dry methanol under a nitrogen atmosphere was added 1.73 g (0.0117 mol) of thiadiazole 1-oxide **15**. The reaction was stirred at 22 °C for 24 h, cooled to −20 °C for 2 h, filtered, and washed with cold (−20 °C) methanol. The crude solid was dissolved in 20 mL of warm DMF and purified on a 50-mm flash-chromatography column, eluting with CH_2Cl_2/MeOH/NH_4OH 90/10/1, obtaining 1.11 g (28%) of thiadiazole 1-oxide **16a**, mp 208–211 °C dec; ^{1}H NMR (DMSO) 2.30 (3 H, s, Ar CH_3), 2.6 (2 H, m, CH_2), 3.5 (2 H, m, CH_2), 4.24 (2 H, s, $ArCH_2S$), 6.8–8.4 (7 H, m, ArH, NH, NH_2); IR (KBr) 3220, 1615, 1580, 1040 cm^{-1}; EIMS (relative intensity) m/z 320 ($M^+ - NH_2$, 7.3) 276 (11.5), 217 (120), 175 (34.5), 145 (96.0), 132 (100). Anal. ($C_{13}H_{16}N_6OS_2$) C, H, S; N: calcd, 24.98; found, 24.44.

3-[1-[[2-[(4-Amino-1-oxo-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (16b). Under a nitrogen atmosphere, to a stirred solution of 0.63 g (2.7 mmol) of amine **12a** in 150 mL of MeOH was added 0.41 g (2.8 mmol) of thiadiazole oxide **15**. The solution was stirred at 22 °C for 16 h and then evaporated to dryness in vacuo. The residue was dissolved in methanol (3 mL) and purified on a 30-mm flash-chromatography column, eluting with CH_2Cl_2/MeOH/NH_4OH 90/10/1, obtaining 0.90 g (96%) of thiadiazole oxide **16b**: mp 142–145 °C dec; ^{1}H NMR (DMSO) 1.70 (3 H, d, J = 6.8 Hz, CH_3), 2.45 (3 H, s, $ArCH_3$), 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2), 4.83 (1 H, q, J = 6.8 Hz, ArCHS), 6.8–8.4 (6 H, m, ArH, NH, NH_2), 8.50 (1 H, d, J = 7.0 Hz, ArH); IR (KBr) 3225, 3065, 1595, 1090, 725 cm^{-1}; CIMS (relative intensity) m/z 317 ($M^+ - 33$, 4.5), 172 (18.5), 159 (100), 133 (29.2). Anal. ($C_{14}H_{18}N_6OS_2$) C, H, S; N: calcd, 23.98; found, 23.21.

8-(Benzyloxy)-3-[1-[[2-[(4-amino-1-oxo-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (16c). Under a nitrogen atmosphere, to a stirred solution of 3.33 g (9.88 mmol) of amine **12c** in 100 mL of dry methanol was added 1.45 g (9.88 mmol) of thiadiazole oxide **15**. The mixture was stirred at 22 °C for 15 h and approximately one-half of the solvent was removed in vacuo. The residue was cooled to 5 °C and the precipitate was removed by filtration. The filtrate was concentrated and purified on a 50-mm flash-chromatography columnnm, eluting with CH_2Cl_2/MeOH/NH_4OH 90/10/1, obtaining 2.27 g (51%) of thiadiazole oxide **16c** as a white solid: mp 166–169 °C dec; ^{1}H NMR (DMSO) 1.70 (3 H, d, J = 7.0 Hz, CH_3), 2.45 (3 H, s, $ArCH_3$), 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2), 4.75 (1 H, q, J = 7.0 Hz, ArCHS), 5.35 (2 H, s, OCH_2), 6.6–8.4 (11 H, m, ArH, NH, NH_2); IR (KBr) 3200, 1580, 1550, 1275, 1085, 1065, 725 cm^{-1}. Anal. ($C_{21}H_{24}N_6O_2S_2$) C, H, N.

3-[[[2-[(4-Amino-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]methyl]-2-methylimidazo[1,2-*a*]pyridine (19a). To a stirred suspension of 1.11 g (3.29 mmol) of thiadiazole oxide **16a** in 50 mL of methanol was added 2 mL of concentrated HCl. The solution became homogeneous within 1 min. After stirring for 3 h at 22 °C, the solvent was removed in vacuo and the residue was suspended in refluxing acetone, cooled, filtered, and washed with acetone to give 1.27 g of diimidamide **17a**, which was used without further purification.

To a stirred suspension of 1.27 g (3.18 mmol) of diimidamide **17a** in 100 mL of CH_2Cl_2 was added 2 mL of triethylamine and 1.26 g (3.18 mmol) of thiobisphthalimide (**18**). After stirring for 16 h, the solution was washed with 10% KOH, dried over $MgSO_4$, and evaporated to dryness in vacuo. The crude dark green oil was purified on a 30-mm flash-chromatography column, eluting with CH_2Cl_2/MeOH 95/5 to give 0.62 g (61%) of thiadiazole **19a**: mp 197–199 °C dec; ^{1}H NMR (DMSO) 2.40 (3 H, s, Ar CH_3), 2.6 (2 H, m, CH_2), 3.3 (1.5 H, s, CH_3OH), 3.4 (2 H, m, CH_2), 4.24 (2 H, s, $ArCH_2S$), 6.35 (2 H, br s, NH_2), 6.6–7.6 (4 H, m, ArH, NH), 8.35 (1 H, d, J = 6.0 Hz, Ar H); IR (KBr) 3425, 3325, 3230, 1625, 1560, 1500 cm^{-1}; EIMS (relative intensity) m/z 320 (M^+, 5.1), 1.77 (3.8), 145 (100). Anal. ($C_{13}H_{16}N_6S_2 \cdot 0.5CH_3OH$) C, H, N.

3-[1-[[2-[(4-Amino-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (19b). To a solution of 3.00 g (8.53 mmol) of thiadiazole oxide **16b** in 30 mL of methanol was added 5 mL of concentrated HCl. The reaction was stirred at 22 °C for 3 h and the solvent was stripped to give 3.50 g of crude diimidamide **17b**, which was used without further purification. To a suspension of **17b** in 100 mL of CH_2Cl_2 was added 6 mL of triethylamine and 4.93 g (12.4 mmol) of thiobisphthalimide (**18**). After stirring at 22 °C for 21 h, the reaction was washed with 10% KOH, dried over $MgSO_4$, and evaporated to dryness in vacuo. The gummy, black tar was purified on a 50-mm flash-chromatography column, eluting with EtOAc/MeOH/NH_4OH 90/10/1. The resulting solid was recrystallized from hexane/EtOAc to give 0.94 g (33%) of thiadiazole **19b**: mp 165–168 °C; ^{1}H NMR (DMSO) 1.70 (3 H, d, J = 7.1 Hz, CH_3), 2.44 (3 H, s, Ar CH_3), 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2), 4.2–5.2 (4 H, m, ArCHS, NH, NH_2), 6.7–7.8 (3 H, m, Ar H), 8.50 (1 H, d, J = 6.8 Hz, ArH); IR (KBr) 3345, 3325, 1520, 1500, 730 cm^{-1}; EIMS (relative intensity) m/z 334 (M^+, 7.9), 159 (100). Anal. ($C_{14}H_{18}N_6S_2$) C, H, N.

8-(Benzyloxy)-3-[1-[[2-[(4-amino-1,2,5-thiadiazol-3-yl)amino]ethyl]thio]ethyl]-2-methylimidazo[1,2-*a*]pyridine (19c). To a stirred solution of 1.60 g (3.50 mmol) of thiadiazole oxide **16c** in 10 mL of methanol was added 3 mL of concentrated HCl. The reaction was stirred for 3 h, and the solvents were removed in vacuo to give crude diimidamide **17c**. Amide **17c** was suspended in 30 mL of CH_2Cl_2 and to this mixture was added 1.40 g (3.50 mmol) of thiobisphthalimide (**18**) and 1.5 mL of triethylamine. The reaction was stirred for 2 h, washed with 10% NaOH, and dried over $MgSO_4$. After trituration with ethyl acetate, the resulting precipitate was collected and washed with ethyl acetate to give 1.10 g of crude product. Purification was performed on a 20-mm flash-chromatography column, eluting with CH_2Cl_2/MeOH 95/5 to obtain 0.47 g (30%) of thiadiazole **19c**: mp 191–193 °C; ^{1}H NMR (DMSO) 1.70 (3 H, d, J = 7.0 Hz, CH_3), 2.45 (3 H, s, $ArCH_3$), 2.5 (2 H, m, CH_2), 3.4 (2 H, m, CH_2), 4.75 (1 H, q, J = 7.0 Hz, ArCHS), 5.35 (2 H, s, OCH_2), 6.24 (2 H, br s, NH_2), 6.8 (3 H, m, ArH, NH), 7.5 (5 H, m, Ar H), 8.2 (1 H, m, ArH); IR (KBr) 3350, 3210, 1545, 1275, 730 cm^{-1}; EIMS (relative intensity) m/z 441 (M^+, 3.9), 297 (28.3), 265 (100), 129 (34.0), 91 (71.7). Anal ($C_{21}H_{24}N_6OS_2$) C, H, N.

Cytoprotection Screening. A modification of the method described by Robert et al.[16] was used to produce gastric lesions in rats. The present method employed 3.0 mL/kg ethyl alcohol (100%) of 3.0 mL/kg 0.75 N HCl as the necrotizing agent.

Food and water were removed 24 and $1^1/_2$ − 18 h, respectively, prior to receiving EtOH or HCl. Animals received the test compounds po (3–12 mL of an appropriate vehicle/kg) 60 min before administration of 100% ethanol or 0.75 N HCl (3.0 mL/kg by gavage). Sixty minutes after insult, the animals were sacrificed by administration of T-61 (Hoechst), 0.2 mL i.p.

An abdominal incision was made, and the stomach was removed and opened along either the lesser curvature (EtOH) or the greater curvature (HCl).

The stomach was rinsed in water and placed flat in a standard position. The tissue was photographed with a Polaroid close-up camera and scoring of the lesions was done from thie permanent record. Each photograph included a reference scale in mm. Individual ulcers were measured by total lesion area (mm^2) and these scores were added together to determine total ulcer area for stomach.

Standard photographs were about 2× actual size. An estimate of real ulcer area (mm^2) was obtained after dividing the area score by four. For each treatment group, the mean area was calculated. From this, the percent inhibition of lesion formation, I, was calculated as

$$I = [\text{lesion score (controls)} - \text{lesion score (treated)}]/[\text{lesion score (controls)}] \times 100$$

(16) Robert, A.; Nezamis, J. E.; Lancaster, C.; Hanchar, A. J. *Gastroenterology* **1979**, *77*, 433.

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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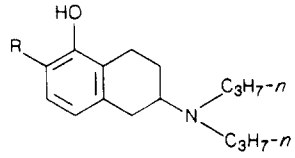
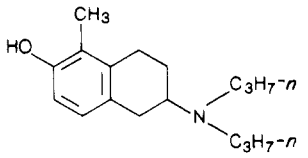
On the basis of the premise that the dopaminergic agonist profile of 2-(di-*n*-propylamino)-5-hydroxy-6-methyltetralin (**1a**) is due to in vivo oxidation of the 6-methyl moiety and that **1a** may represent a novel prodrug strategy, the vicinal methyl–hydroxyl substitution pattern was incorporated 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]

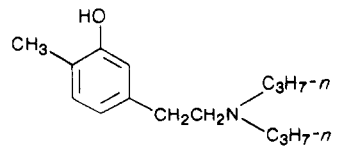


1a: R = CH_3
b: R = CH_2OH
c: R = CH=O



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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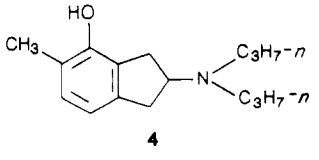

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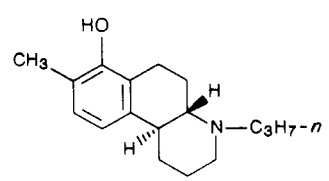

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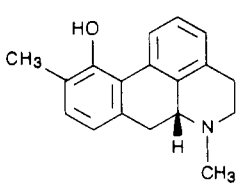
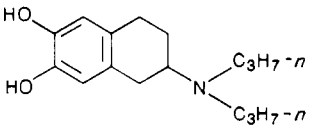
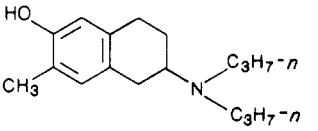


6

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



7



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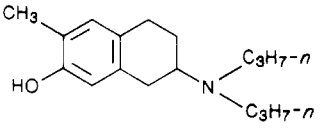

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