Journal of Medicinal Chemistry, 1974, Vol. 17, No. 4 427

α-Methyldopamine Derivatives. Synthesis and Pharmacology†

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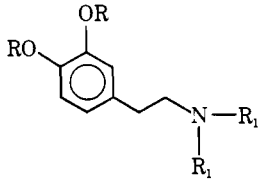
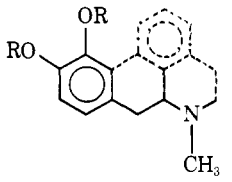
Received October 26, 1973

Several labile, lipophilic analogs of α-methyldopamine were synthesized and evaluated pharmacologically for dopamine-receptor activation and potential anti-Parkinson activity. The compounds were synthesized by selective O-acetylation and N-alkylation procedures. Compound **10** showed dopamine-receptor stimulating properties and was able to antagonize oxotremorine-induced inhibition of motor activity. These findings are consistent with our previous suggestion that O-acetylation and N-alkylation are required to confer activity in some tests which have been proposed for evaluating dopaminergic and/or anti-Parkinson activity.

In a previous report,[1] evidence was presented that certain labile, lipophilic analogs of dopamine are capable of crossing the blood-brain barrier and activating dopamine receptors in the central nervous system (CNS) of the mouse. For central dopaminergic activity, it appears that both O-acetylation and N-alkylation of the dopamine molecule are required to provide entry into the brain. In a continuing effort to develop direct-acting dopaminergic agents, we have undertaken the investigation of α-methyldopamine derivatives and analogs **5–10**. These analogs may be considered to be lipophilic analogs of dopamine (**1**) or partial structural analogs of apomorphine (**3**) and *O,O'*-diacetylapomorphine (**4**).



1, R = R$_1$ = H
2, R = Ac; R$_1$ = CH$_3$



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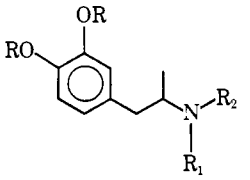


5, R = R$_1$ = R$_2$ = H
6, R = Ac; R$_1$ = R$_2$ = H
7, R = R$_1$ = H; R$_2$ = CH$_3$
8, R = Ac; R$_1$ = H; R$_2$ = CH$_3$
9, R = H; R$_1$ = R$_2$ = CH$_3$
10, R = Ac; R$_1$ = R$_2$ = CH$_3$

The α-methyldopamine analogs appeared worthy of investigation for several reasons. α-Methyldopa has been reported to have antitremorigenic activity in animal models[2,3] and in human Parkinsonism.[4] It also has been reported to reverse reserpine-induced suppression of motor activity in rats[5] and have the same, but lesser effect in mice.[6] α-Methyldopa has also been shown to be a weak activator of central dopamine receptors.[6,7] Furthermore, in addition to providing some protection from monamine oxidase, the introduction of an α-methyl group into the dopamine molecule generates a chiral center which confers structural similarities to apomorphine. At the time this work was initiated, it was felt that these chiral molecules might provide an opportunity to explore the possibility of stereospecificity of the dopamine receptors. Since that time, however, it has been reported that (*S*)-(+)-apomorphine does not possess significant (*R*)-(−)-apomorphine-like activity.[8]

Chemistry. (±)-α-Methyldopamine (**5**) was prepared by modifications of standard procedures starting from the corresponding benzaldehyde and nitroethane. The *O,O'*-diacetyl derivative **6** was prepared from **5** by selective O-acetylation[1] (Scheme I). An attempted methylation of the benzal derivative of (*RS*)-1-(3,4-dimethoxyphenyl)-2-aminopropane (**12**) failed to give the corresponding *N*-methyl derivative **14**. This was unexpected since 3,4-dimethoxy-β-phenethylmethylamine could be prepared in almost quantitative yield from 3,4-dimethoxy-β-phenethylamine by an analogous procedure.[1] Therefore, compound **14** was prepared *via* hydrogenating a mixture of 1-(3,4-dimethoxyphenyl)propan-2-one (**13**) and methylamine. The diether **14** was cleaved to **7** and the diester **8** was prepared by direct acetylation of **7**.

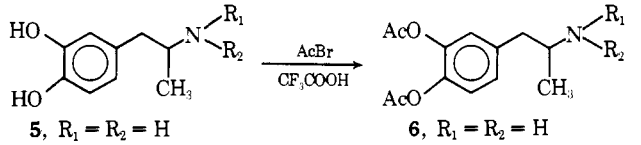
(±)-1-(3,4-Dihydroxyphenyl)-2-(dimethylamino)propane (**9**) and the corresponding diester **10** (Scheme II) were prepared from **15** by a procedure similar to that reported for the preparation of 3,4-dimethoxy-*N,N*-dimethyl-β-phenethylamine.[1] However, a crystalline **9** could not be obtained directly from **15** but was prepared by hydrolysis of the purified diester **10**.

Pharmacology. Preparations. Hydrochloride or hydrobromide salts of all compounds were dissolved in appropriate volumes of physiological saline. The solutions were prepared immediately before use.

Standards. Apomorphine hydrochloride, U.S.P. (S. B. Penick and Co.), dopamine hydrobromide (Aldrich Chemical Co.), and/or levodopa (Nutritional Biochemicals Corp.) were included in the series of compounds examined and served as reference standards.

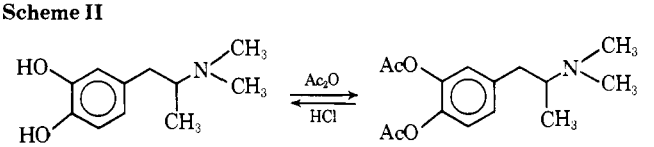
Biological Activities Investigated. Studies evaluating the effects of the α-methyldopamine derivatives and analogs are reported in Tables I–III. The activity of the compounds was examined in each of three animal experimen-

Scheme I



5, R$_1$ = R$_2$ = H
7, R$_1$ = H; R$_2$ = CH$_3$
6, R$_1$ = R$_2$ = H
8, R$_1$ = H; R$_2$ = CH$_3$

Scheme II



9 **10**

† This investigation was supported by grants from the West Virginia University Senate Research Fund.

Table I. Antagonism of Oxotremorine (OT)[a]-Induced Tremor and Decreased Motor Activity in Mice

Compound	Antagonist dose, mg/kg	Motor activity[b]	Tremor severity[c]
Saline		170 ± 15[d]	0
OT		76 ± 12	+++
Apomorphine + OT	50	154 ± 32[d]	++
5 + OT	50	16 ± 6[d]	+++
	100	16 ± 8[d]	+++
	200	24 ± 6[d]	+++
6 + OT	50	8 ± 2[d]	+++
	100	37 ± 7[d]	+++
	200	16 ± 4[d]	++
8 + OT	50	1 ± 1[d]	+++
	100	12 ± 2[d]	+++
	200	7 ± 1[d]	+++
9 + OT	50	28 ± 4[d]	+++
	100	17 ± 10[d]	+++
	200	34 ± 11[d]	+++
10 + OT	50	120 ± 9[d]	+++
	100	69 ± 11	++
	200	51 ± 25	++

[a]Motor activity and tremor rating were determined using at least six animals per group beginning 3 min after the OT administration. Apomorphine was given in a dose of 50 mg/kg ip. [b]Squares crossed per 6 min. [c]0 (none), + (mild), ++ (moderate), +++ (severe). [d]$p < 0.05$ when compared to OT alone.

Table II. Antagonism of Reserpine (R)[a]-Induced Motor Depression and Ptosis in Mice

Compound	Dose, mg/kg[b]	Motor activity[c]	Ptosis[d]
O		128 ± 13[e]	−
R	5	0	+
R + apomorphine	50	9 ± 2[e]	−
R + dopamine	200	0	−
R + L-Dopa	200	46 ± 21[e]	−
R + **5**	100	0	−
R + **6**	100	1 ± 1	−
R + **8**	100	2 ± 1	−
R + **9**	100	17 ± 9[e]	−
R + **10**	100	0	−

[a]Groups of six animals were given reserpine (5 mg/kg ip) 24 hr prior to drug testing. [b]The compounds were given at approximately their maximally tolerated dose in reserpine-treated animals. [c]Squares crossed per 6 min. [d]+ (present), − (absent). [e]Indicates statistical significance at least at the $p < 0.05$ level of probability.

tal models identical with those utilized in our previous paper.[1] The models were chosen either because they mimicked some aspect of the clinical symptomatology of Parkinson's disease or because they allowed an estimate of the agent's ability to stimulate central dopamine receptors. These included (a) protection against oxotremorine-induced tremor in mice, (b) antagonism of both reserpine-induced motor depression and ptosis in mice, and (c) production of hypothermia in mice and its antagonism by haloperidol.

Oxotremorine-Induced Tremor in Mice. Leslie and Maxwell[9] have suggested that oxotremorine may be a useful agent in screening compounds for anti-Parkinson activity. Oxotremorine administration to mice (600 μg/kg ip) results in changes in their locomotor activity, including sustained generalized tremor, muscular rigidity, and decreased spontaneous movement. Although oxotremorine is often used in the screening of compounds possessing anticholinergic activity, Everett, *et al.*,[10] have reported that both L-Dopa and apomorphine (a dopamine-mimetic drug) are effective in antagonizing many of the symptoms produced by oxotremorine. It should be noted, however, that Horst, *et al.*,[11] have recently suggested that the antagonism of oxotremorine by L-Dopa may be of peripheral rather than central origin. The oxotremorine model was primarily used for comparative purposes with our earlier studies.

Table III. Hypothermia in Mice

Compound	Dose, mg/kg	Δ*t*, °C ± S.E.M.[a]
Saline		0
Dopamine	25	−1.8 ± 0.6[c]
	50	−2.4 ± 0.6[c]
Apomorphine	0.5	−2.7 ± 0.4[c]
	1.0	−3.3 ± 0.6[c]
5	5	−1.2 ± 0.2[c]
	20	−0.5 ± 0.2[b]
	50	1.9 ± 0.3[c]
6	5	−0.9 ± 0.2[b]
	10	−1.6 ± 0.6
	20	0.7 ± 0.1[c]
8	5	−0.8 ± 0.3
	10	−0.5 ± 0.4
	20	0.6 ± 0.5
9	5	−2.6 ± 0.7[b]
	10	−1.7 ± 0.7
	20	−1.9 ± 0.8[b]
10	5	−0.3 ± 0.1[b]
	10	−0.1 ± 0.1
	20	−4.7 ± 0.5[c]

[a]Rectal temperatures were determined in groups of six mice 30 min postintravenous administration of the test compound. [b]Indicates statistical significance at the $p < 0.05$ level of probability. [c]Indicates statistical significance at the $p < 0.01$ level of probability.

Various doses of the test drugs were given 10 min prior to administration of oxotremorine and then were evaluated for their ability to antagonize both the tremor and the diminished locomotor activity. The latter test involved placing the animals in a 1-ft^2 observation chamber divided into 16 3-in. squares. The number of times the animal crossed from one square to another was then determined. Only compound **10** (50 mg/kg) and apomorphine were able to both antagonize the decreased locomotor activity and partially antagonize the severity of the tremors.

Reserpine-Induced Depression. Reserpine administration to mice results in decreased spontaneous motor activity and ptosis of the eye. Horst, *et al.*,[11] have shown that reserpine-induced ptosis can be reversed by L-Dopa and dopamine. However, reserpine-induced catatonia was reversed only by L-Dopa and was directly correlated with the restoration of brain dopamine levels. The above authors also reported that pretreatment with peripheral decarboxylase inhibitors potentiated L-Dopa reversal of reserpine catatonia but did not result in ptosis reversal. These findings support the assumption that in reserpine-treated animals compounds possessing central, but not peripheral, dopamine-like activity can reverse locomotor inhibition. Test drugs, plus apomorphine, L-Dopa, and dopamine, were examined for their ability to restore motor activity in mice pretreated (24 hr) with reserpine (5 mg/kg ip). All compounds antagonized the ptosis (Table II) while only apomorphine, L-Dopa, and compound **9** had moderate ability to antagonize reserpine-induced motor depression. The rest of the test drugs and dopamine were inactive.

Hypothermia in Mice. This model assesses the ability of the test drugs to stimulate central dopamine receptors. Barnett, *et al.*,[12] and Fuxe and Sjögvist[13] have demonstrated that stimulation of brain dopaminergic receptors leads to a lowering of body temperature. This effect is relatively specific since it can be blocked by dopamine-receptor antagonists such as haloperidol and spiroperidol.

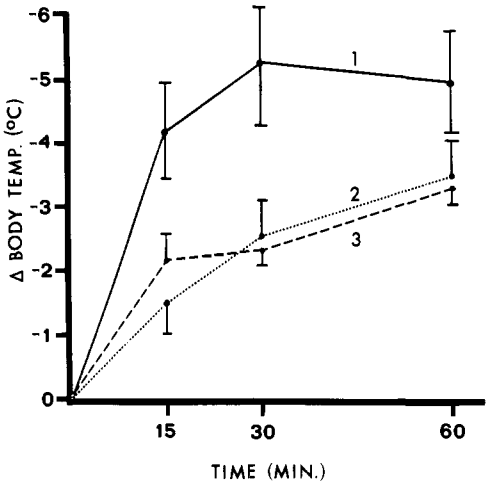


Figure 1. Antagonism of compound **2**-induced hypothermia by haloperidol (5 mg/kg). Curve 1 represents compound **2** (100 mg/kg ip); curve 2, haloperidol; curve 3, compound **2** plus haloperidol. The data are plotted as means ± S.E. obtained from six animals. Curve 3 is significantly different from curve 1 ($p < 0.01$) but not from curve 2.

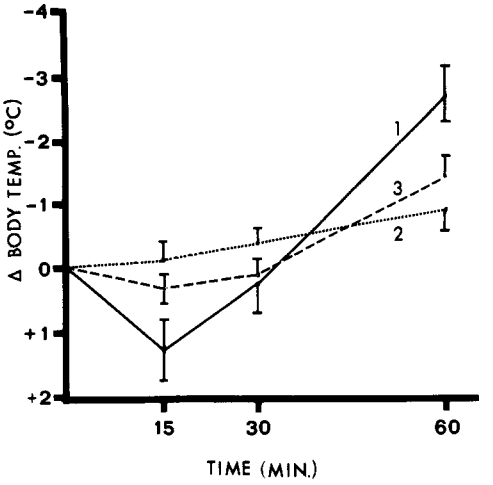


Figure 2. Antagonism of compound **10**-induced hypothermia by haloperidol (5 mg/kg). Curve 1 represents compound **10** (100 mg/kg ip); curve 2, haloperidol; curve 3, compound **10** plus haloperidol. The data are plotted as means ± S.E. obtained from six animals. The compound **10**-induced hypothermia (curve 1, 60-min interval) was significantly ($p < 0.05$) antagonized by haloperidol (curve 3, 60-min interval). Curves 2 and 3 were not statistically different at any time period studied.

but not by phentolamine, phenoxybenzamine, thioridazine, or chlorpromazine.

Rectal temperatures of mice were determined both before and 15, 30, 60, and 90 min after intravenous drug administration. The results of these experiments are given in Table III. Compound **9** (5 mg/kg), compound **10** (20 mg/kg), apomorphine, and high doses of dopamine were quite potent in lowering body temperature. The other compounds exhibited either slight hypothermic activity or were hyperthermic.

Antagonism of Hypothermia in Mice. It was previously reported[1] that 3,4-diacetoxy-*N,N*-dimethyl-β-phenethylamine (compound **2** in this report) was the most potent temperature-lowering agent of the first series of compounds synthesized. In the present series, the α-methyl derivative of compound **2** also possessed the greatest hypothermic activity. Therefore, it was decided to examine the receptor-activating properties of compounds **2** and **10** by assessing the ability of haloperidol to antagonize their temperature-lowering effects.

Three groups of mice were injected intraperitoneally either with haloperidol (as a suspension in 5% sodium carboxymethylcellulose), the experimental compound, or haloperidol plus the experimental compound (Figures 1 and 2). In the latter case the haloperidol was given 30 min before the test drug. Rectal temperatures were determined initially and then 15, 30, and 60 min after the administration of the test compound or beginning 45 min after haloperidol alone. The hypothermic effect of compounds **2** and **10** was significantly antagonized by haloperidol; however, a larger dose of haloperidol was required to antagonize the effects of compound **2**.

Discussion

Compound **10** appears to be the most active compound in this series; it showed significant activity in both the oxotremorine and hypothermia model systems. However, its inactivity in the reserpine model is somewhat disconcerting. Except for **9**, which showed activity in the reserpine model, the other compounds were inactive. Compound **7** was not evaluated because a suitable crystalline salt could not be obtained.

A comparison of **10** in the hypothermia model with 3,4-diacetoxy-*N,N*-dimethyl-β-phenethylamine (**2**) (the most active compound in the first series[1]) shows that **10** is about one-fourth as active in its temperature-lowering effects. Correspondingly, only one-half the dose of haloperidol was required to antagonize the effects of **10** compared to **2**. This decrease in activity is also reflected in the respective ip LD_{50} values for **10** and **2**: 215 mg/kg (195–236) and 175 mg/kg (147–208). It is possible that the lower activity of **10** is due to the use of a racemic modification for the investigation.

Although the introduction of the α-methyl group decreases activity, both O-acetylation and N-alkylation again appear to be necessary for a compound to possess activity in the models investigated. Of the compounds investigated only compounds **9** and **10** exert positive effects in some, but not all, of the tests which have been proposed for screening drugs for dopaminergic and anti-Parkinson activity.

Experimental Section‡

trans-**1-(3,4-Dimethoxyphenyl)-2-nitropropene (11).** To a solution of 3,4-dimethoxybenzaldehyde (21.25 g, 0.128 mol, Aldrich Chemical Co.) in glacial acetic acid (100 g) was added 8.4 g (0.108 mol) of NH_4OAc and 13.2 g (0.044 mol) of nitroethane. The resulting mixture was refluxed for 2 hr and then the hot solution was poured over 1000 g of crushed ice to give a yellow solid. Recrystallization from EtOH gave 17 g (60%) of product, mp 72–73° (lit.[14] mp 73°).

(*RS*)-**1-(3,4-Dimethoxyphenyl)-2-aminopropane Hydrochloride (12).** $LiAlH_4$ (19 g, 0.5 mol) and 800 ml of anhydrous Et_2O were placed in a 2-l. flask equipped with a stirrer, condensor, and a dropping funnel. Compound **11** (40 g, 0.179 mol) in 800 ml of anhydrous Et_2O was added dropwise and the resulting solution was refluxed for 3.5 hr. The remaining $LiAlH_4$ was decomposed according to the method of Steinhardt.[15] In succession, 19 ml of H_2O, 19 ml of 15% NaOH, and 77 ml of H_2O were added. The Et_2O layer was decanted and 300 ml of benzene was then added and the resulting mixture was refluxed with stirring for 0.25 hr. The solids were then removed by filtration and the benzene solution was combined with the Et_2O and dried (Na_2SO_4). The volatiles were removed under reduced pressure to afford an oil. Two additional runs were made and the combined product was distilled through a short-path apparatus to afford 60 g (55%), bp

‡ All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. Ir absorption spectra were recorded on a Beckmann Model 18A spectrophotometer. The nmr spectra were recorded on a Varian T60 spectrometer using TMS or DSS as internal standards.

104° (0.3 mm) [lit.[16] bp 166–168° (20 mm)]. A portion of the product was dissolved in EtOH–Et_2O (20/80) and cooled and stirred. Concentrated HCl was added dropwise until the solution was slightly acidic. The solid which separated was recrystallized from EtOH–EtOAc to give the HCl salt, mp 149–150° (lit.[17] 147.5–148°).

(*RS*)-1-(3,4-Dihydroxyphenyl)-2-aminopropane Hydrobromide (5). Compound **12** (12.8 g, 0.055 mol) was dissolved in 50 ml of 48% HBr. The system was flushed with N_2 for 0.25 hr and then heated at 125° for 2 hr. The excess acid was removed under reduced pressure and the residue crystallized in the cold. The solid was recrystallized from *i*-PrOH–Et_2O to give 11.6 g (86%) of the product, mp 180–182° (ref 14 did not report a melting point for this product).

(*RS*)-1-(3,4-Diacetoxyphenyl)-2-aminopropane Hydrobromide (6). Compound **5** (2.48 g, 0.01 mol) was dissolved in 20 ml of anhydrous CF_3COOH and 3.69 g (0.03 mol) of purified acetyl bromide was added dropwise. The resulting solution was stirred for 0.25 hr and then the volatiles were removed under reduced pressure. Then 5 ml of *i*-PrOH was added and the volatiles were again removed under reduced pressure. The residue was taken up in *i*-PrOH and sufficient Et_2O was added to cause crystallization. Recrystallization from *i*-PrOH–Et_2O afforded 2.4 g (72%) of product: mp 144–145°; ir (KBr) 1770 cm^{-1} (ester C=O); nmr (D_2O) δ 1.36 (d, 3, α-CH_3), 2.37 (s, 6, CH_3COOAr), 3.01 (d, 2, $ArCH_2$–), 3.75 (m, 1, –CH–), 7.30 (m, 3, Ar H). *Anal.* ($C_{13}H_{18}BrNO_4$) C, H, N.

1-(3,4-Dimethoxyphenyl)propan-2-one (13). This substituted phenylacetone was prepared by Fe–HCl reduction of compound **11** by the method of Pearl and Beyer:[18] yield 70%; bp 120° (0.7 mm).

(*RS*)-1-(3,4-Dimethoxyphenyl)-2-(methylamino)propane Hydrochloride (14). Compound **13** (12 g, 0.061 mol) and 50 ml of 40% CH_3NH_2–H_2O were added to 3.8 g of 10% Pd/C in 200 ml of anhydrous EtOH. The mixture was hydrogenated at room temperature in a Parr apparatus (24 hr) with an H_2 pressure of 4 kg/cm^2. The catalyst was removed by filtration and the volatiles were removed under reduced pressure. The residual oil was taken up in Et_2O and the base was extracted with 10% HCl. The free base was liberated (K_2CO_3) and extracted with Et_2O and dried (Na_2SO_4). The volatiles were removed under reduced pressure and the remaining oil was distilled through a short-path apparatus: bp 120–122° (1.5 mm); yield 7 g (55%). The compound was made into a hydrochloride salt and recrystallized from EtOH–Et_2O to afford the product, mp 123–124° (lit.[19] 114–119°).

(*RS*)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)propane Hydrobromide (7). Compound **14** (5 g, 0.02 mol) was added to 48% HBr (25 ml). The system was flushed with N_2 for 0.5 hr and then heated at 125° for 2 hr. The excess acid was removed under reduced pressure. All efforts made to obtain the compound as a crystalline salt were unsuccessful; however, a sulfate salt (mp 270° dec) is reported in the literature.[20]

(*RS*)-1-(3,4-Diacetoxyphenyl)-2-(methylamino)propane Hydrobromide (8). Compound **7** was dried at 80° (0.5 mm) for 24 hr. A portion, 2.3 g (8.85 mmol), was dissolved in 20 ml of anhydrous CF_3COOH and treated with 2.77 g (0.027 mol) of purified acetyl bromide. The resulting solution was stirred for 0.25 hr and then the volatiles were removed under reduced pressure. Then 5 ml of *i*-PrOH was added and the volatiles were again removed under reduced pressure. The residue was taken up in *i*-PrOH and sufficient Et_2O was added to cause crystallization. Recrystallization from EtOH–Et_2O afforded 2.4 g (78%) of product, mp 166–167°. Recrystallization from EtOH afforded a product melting at 150°. Both compounds gave identical absorption spectra: ir (KBr) 1770 cm^{-1} (ester C=O); nmr (D_2O) δ 1.33 (d, 3, α-CH_3), 2.40 (s, 6, CH_3COOAr), 2.77 (s, 3, NCH_3), 3.07 (m, 2, $ArCH_2$–), 3.50 (m, 1, –CH–), 7.29 (m, 3, Ar H). *Anal.* ($C_{14}H_{20}BrNO_4$) C, H, N.

(*RS*)-1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)propane Hydrochloride (15). Method A. The compound was prepared from **12** *via* an Eschweiler–Clark modification by the method of Baltzly[21] for the preparation of *N,N*-dimethyl-3,4-dimethoxy-β-phenethylamine.

Method B. Compound **12** (10 g, 0.051 mol) in 200 ml of anhydrous CH_3OH was added to 3 g of Pd/C (10%) in a pressure bottle. Then 50 ml of H_2CO (37%) was added and the mixture was hydrogenated at room temperature in a Parr apparatus (24 hr) with a H_2 pressure of 4 kg/cm^2. The catalyst was removed by filtration and washed with CH_3OH. The filtrate and washings were combined and the volatiles removed under reduced pressure. Then H_2O (100 ml) and concentrated HCl (20 ml) were added and the volatiles again removed under reduced pressure. An additional 100 ml of H_2O was added and the procedure repeated. The residue was made basic with 50% aqueous NaOH and the amine was extracted (Et_2O), dried (Na_2SO_4), and distilled through a short-path apparatus: bp 116–117° (0.80 mm); yield 8.5 g (74%). The product was made into a hydrochloride salt and recrystallized from *i*-PrOH to afford the product, mp 155–157°.

(*RS*)-1-(3,4-Dihydroxyphenyl)-2-(dimethylamino)propane Hydrochloride (9). Compound **10** (3 g, 0.0095 mol) was dissolved in 5 ml of concentrated HCl. The system was flushed with N_2 and then heated on a steam bath for 2 hr. The excess acid was removed under reduced pressure and the residue was triturated with acetone. Cooling produced crystals melting at 131–134°. Recrystallization from *i*-PrOH gave 2 g (90%) of the product: mp 156–157°; ir (KBr) 3250 cm^{-1} (broad, OH); nmr (D_2O) δ 1.25 (d, 3, α-CH_3), 2.89 [s, 6, $N(CH_3)_2$], 6.88 (m, 3, Ar H). *Anal.* ($C_{11}H_{18}ClNO_2$) C, H, N.

(*RS*)-1-(3,4-Diacetoxyphenyl)-2-(dimethylamino)propane Hydrochloride (10). Compound **15** (4 g, 0.019 mol) was dissolved in 48% HBr (20 ml). The system was flushed with N_2 for 0.25 hr and then heated at 125° for 2 hr. The excess acid was removed under reduced pressure to give an oil (**9**). All attempts to obtain the compound as a crystalline salt at this stage were unsuccessful. Excess Ac_2O was added and the resulting solution was warmed on a steam bath for 2 hr. The volatiles were removed under reduced pressure and the residue was taken up in 5% HCl and washed with Et_2O. The free base was liberated ($NaHCO_3$), extracted (Et_2O), dried (Na_2SO_4), and treated with Et_2O·HCl. The salt was recrystallized from *i*-PrOH to afford 3.5 g (60%) of product: mp 168–170°; ir (KBr) 1770 cm^{-1} (ester C=O); nmr (D_2O) δ 1.27 (d, 3, α-CH_3), 2.39 (s, 6, CH_3COOAr), 2.90 [s, 6, $N(CH_3)_2$], 7.33 (m, 3, Ar H). *Anal.* ($C_{15}H_{22}ClNO_4$) C, H, N.

Acknowledgments. The authors wish to express their appreciation to Mrs. Jaqueline Horvath for her assistance in the biological evaluation of these compounds and to Philip Maxwell, Mike Maruish, Peter Vladimery, and John Walker for their assistance in preparing the compounds.

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