incision was closed with auto-clips. Test compounds were dissolved in a 2.5% Tween 80 solution and were administered intraperitoneally at a dose of 0.5 mL/200 g of body weight. Four hours after drug administration, the animals were killed and the stomachs removed. The contents of the stomach were collected and the volume was recorded. An aliquot was removed and the acid concentration was determined by automatic titration against 0.1 N NaOH to a pH end point of 7.0. The AO was calculated by multiplying the volume of gastric content in liters times the acid concentration in milliequivalents per liter, yielding AO values in milliequivalents/4 h. Six rats were used for each test compound and eight rats for the control. Percent inhibition was calculated as follows: 100 – [100 × (mean test AO/mean control AO)]. Results were statistically analyzed by Student's t test. The mean plus or minus SE acid output in our control studies using this procedure was 0.61 ± 0.04 mequiv/4 h.

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Dopamine Agonist Properties of *N*-Alkyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines

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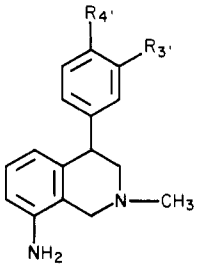
A series of homologous *N*-alkyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines was synthesized and examined for a dopamine-like ability to dilate the renal artery. The *N*-methyl derivative was equipotent to the 3′,4′-dihydroxy derivative of the antidepressant agent nomifensine, indicating that the 8-amino group of the latter is not essential for dopamine-like activity. The *N*-ethyl homologue was reduced in potency when compared to the *N*-methyl, and the *N*-*n*-propyl, surprisingly, was essentially devoid of activity. This was unexpected in view of the fact that in all series of dopamine-like agents reported to date, *N*-alkylation, when one of the alkyls was an *n*-propyl group, either allowed retention or enhancement of potency.

Recently a number of reports have appeared which describe the dopamine agonist properties of the dihydroxy derivative 1 and of nomifensine (2).[1-3] Nomifensine itself

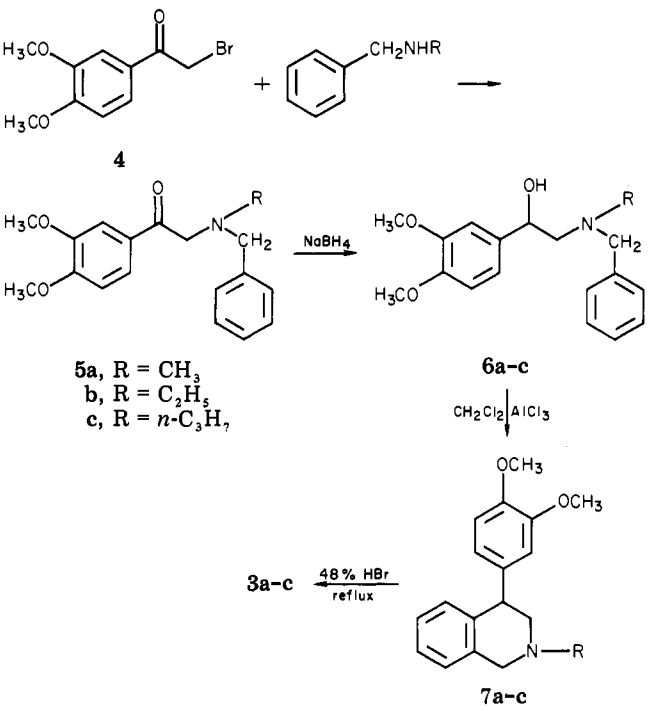


1, $R_{3'} = R_{4'} = OH$
2, $R_{3'} = R_{4'} = H$

possesses clinical utility as an antidepressant.[4] The further modification of adding hydroxy groups was apparently prompted by identification of the 4′-hydroxy metabolite, as well as by the observation that systemic administration of nomifensine produced modifications of motor behavior in rats characteristic of dopamine-like agents.[5,6]

In view of the currently accepted structure–activity relationships for dopamine agonists, it seemed that the presence of the 8-amino group on the isoquinoline nucleus might be superfluous to such an action. It was therefore decided to prepare derivatives of 1 which lacked this functionality. In particular, compounds **3a–c** were of interest. It was also speculated that extension of the *N*-alkyl to an *N*-propyl (**3c**) might result in enhanced activity, in parallel with other series of dopamine agonists.[7-11]

Scheme I



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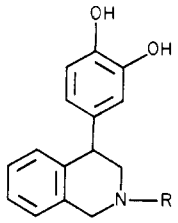

3a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7

Chemistry. Compounds **3a–c** were prepared essentially by a modification of the procedure of Hoffmann et al.[4] This scheme (Scheme I) is outlined and consisted of first reacting the appropriate *N*-alkylbenzylamine with α-bromo-3,4-dimethoxyacetophenone (**4**). The amino ketones **5** were then reduced with sodium borohydride to the amino alcohols **6**. A variety of cyclization conditions were then explored to effect the conversion to the dimethyl ethers **7** of the desired compounds. Of the conditions examined, the procedure which gave the most consistent results involved treating the amino alcohols **6** with anhydrous $AlCl_3$ in methylene chloride solvent. As expected, some O-demethylation was observed in this step. However, modification of the reaction conditions minimized this loss. Further, base extraction removed the phenolic products. Final ether cleavage was accomplished by treating the *O,O*-dimethyl ethers with 48% HBr at reflux.

Pharmacology. Our primary interest in this work was the identification of dopamine agonists which were active at the renal dopamine receptor. Thus, each of the compounds **3a–c** were tested following the methods described by McNay and Goldberg[12] for an effect on renal blood flow.

Results and Discussion

The effects of compounds **3a** and **3b** are shown in Figure 1. Included in the figure is the dose–response curve for dopamine and also for the dihydroxy metabolite of nomifensine, **1** (n = 4). Compound **3a** can be seen to be equipotent with the dihydroxy metabolite of nomifensine (**1**). Thus, as predicted, the 8-amino function contributes little, if anything, to the dopaminergic activity of **1**. However, extension of the *N*-alkyl to ethyl decreased activity rather markedly. More surprisingly, activity was abolished when the *N*-alkyl was *n*-propyl. Even upon injection of 3000 nmol of **3c**, no change in renal blood flow was observed. To our knowledge this is the first series of dopamine congeners where the presence of an *n*-propyl group on the nitrogen has failed to give a compound which either retained activity or possessed enhanced activity.

Although **3a** and **3b** were dopamine-like in action, they were relatively weak, with **3a** being about one-hundredth the potency of dopamine itself. All compounds were antagonized by sulpiride (0.5 mg), and no antagonism was produced by propranolol, indicating that the renal vasodilation is a dopamine receptor-mediated action.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries using a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-33 instrument; frequencies

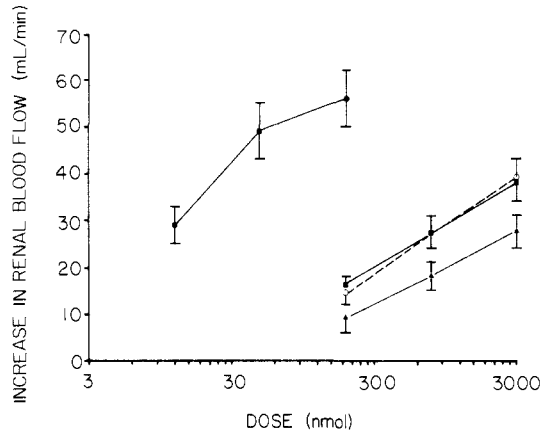

Figure 1. Effect of injection of dopamine, **1**, **3a**, and **3b** (as the HBr salts) on renal blood flow. Dopamine (●) was considerably more potent than either **3a** (○, n = 4) or **3b** (▲, n = 5). The effect of the 8-amino compound **1** is shown for comparison (■). Compound **3c** had no effect, even at the 3000-nmol dose (n = 5). Points plotted with bars represent the mean plus or minus SEM.

are expressed in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 or FT-80 instrument. Chemical shifts are reported in parts per million, with Me_4Si as the internal reference. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br broad. Chemical-ionization (CI) mass spectra were obtained with a DuPont 21-492 spectrometer. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values unless otherwise noted.

α-Bromo-3,4-dimethoxyacetophenone (4). Following a modification of the method of Mannich and Hahn,[13] 18 g (99 mmol) of 3,4-dimethoxyacetophenone (Aldrich) was dissolved in 90 mL of $CHCl_3$. Bromine (15.6 g, 98 mmol) dissolved in 40 mL of $CHCl_3$ was added slowly to the stirred solution of the ketone at room temperature. After the addition was complete, the mixture was stirred for an additional 1 h. The $CHCl_3$ solution was first washed with 10% $NaHCO_3$ solution and then with brine and was dried ($MgSO_4$). The solution was filtered and concentrated under vacuum to yield the crude product, which was then crystallized from EtOAc to yield 10.53 g (58.5%) of pure material, mp 81 °C (lit.[13] mp 80–81 °C).

α-(*N*-Methyl-*N*-benzylamino)-3,4-dimethoxyacetophenone (5a). To a solution of **4** (10 g, 39 mmol) in 75 mL of benzene was added *N*-methylbenzylamine (9.45 g, 78 mmol). The mixture was heated at reflux overnight. The cooled reaction mixture was filtered to remove 7.15 g (89%) of the hydrobromide salt of the excess *N*-methylbenzylamine. The filtrate was reduced under reduced pressure, and the residual oil was treated with HCl–EtOH. The HCl salt thus formed was recrystallized from EtOH–Et_2O to yield 5.79 g (44%): mp 194–195 °C; NMR (Me_2SO-d_6) δ 7.2–8 (m, 8, ArH), 5.05 (s, 2, $ArCH_2$), 4.5 (s, 2, CH_2CO), 3.8 (2 d, 6, OCH_3), 2.8 (s, 3, NCH_3). Anal. ($C_{18}H_{22}ClNO_3$) C, H, N.

α-(*N*-Ethyl-*N*-benzylamino)-3,4-dimethoxyacetophenone (5b). Using the procedure described above, **4** was treated with *N*-ethylbenzylamine. Following workup the product was isolated as the viscous free amine in 78% yield. A sample could not be purified for elemental analysis but was pure by TLC: mass spectral analysis (CI) gave M + 1 = 314; NMR ($CDCl_3$) δ 7.5 (s, 5, ArH), 6.9 (m, 3, ArH), 4.0 (s, 6, OCH_3), 3.97 (s, 2, $COCH_2$), 3.85 (d, 2, $ArCH_2$), 2.8 (q, 2, CH_2CH_3 J = 7 Hz), 1.15 (t, 3, CH_3 J = 7 Hz).

α-(*N*-*n*-Propyl-*N*-benzylamino)-3,4-dimethoxyacetophenone (5c). Following a procedure analogous to that for **5a** and **5b**, treatment of **4** with *N*-*n*-propylbenzylamine led to isolation of the desired product as the viscous free amine in 71% yield. The product was pure by TLC ($CHCl_3$–MeOH, 10:1; silica gel). As with **5b**, neither the free base nor the hydrochloride salt gave consistent elemental analysis. Mass spectral analysis (CI) gave M + 1 = 328; NMR ($CDCl_3$) δ 7.4–7.8 (m, 8, ArH), 4 (s, 6, OCH_3),

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3.8, 3.9 (2 s, 4, CH_2CO, $ArCH_2$), 2.6 (m, 2, CH_2), 1.55 (m, 2, CH_2CH_3), 0.85 (t, 3, CH_2CH_3 J = 7 Hz).

N-Methyl-N-benzyl-2-(3,4-dimethoxyphenyl)-2-hydroxyethylamine (6a). A mixture of the amino ketone **5a** (8 g, 27 mmol) and 1.6 g of $NaBH_4$ in 25 mL of EtOH was stirred overnight at room temperature and then heated at reflux for 3 h. The mixture was cooled, diluted with 50 mL of water, and extracted 3 times with CH_2Cl_2. The combined organic extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration of the filtrate under vacuum gave 6.53 g (80%) of the amino alcohol: mp 72–73 °C; NMR ($CDCl_3$) δ 7.4 (s, 5, ArH), 6.9 (m, 3, ArH), 4.8 (m, 1, CH), 3.9 (s, 6, OCH_3), 3.7 (d, 2, NCH_2Ar), 2.55 (d, 2, NCH_2), 2.3 (s, 3, NCH_3). The amino alcohol was further characterized as its hydrochloride salt and recrystallized from EtOH–ether, mp 204–205 °C. Anal. ($C_{18}H_{24}ClNO_3$) C, H, N.

N-Ethyl-N-benzyl-2-(3,4-dimethoxyphenyl)-2-hydroxyethylamine (6b). A mixture of the amino ketone **5b** (5.68 g, 18 mmol) and 1.05 g of $NaBH_4$ in 50 mL of EtOH was heated at reflux for 2 h and then was stirred overnight. Isolation as described for **6a** gave a quantitative yield of the viscous amino alcohol. Repeated purification attempts did not give material with a satisfactory elemental analysis. However, the product was pure by TLC, and mass spectral analysis (CI) gave M + 1 = 316: NMR ($CDCl_3$) δ 7.5 (s, 5, ArH), 6.9 (m, 3, ArH), 3.9 (s, 6, OCH_3), 3.7 (m, 2, $ArCH_2$), 2.6–2.8 (m, 4, NCH_2), 1.1 (t, 3, CH_3, J = 7 Hz).

N-n-Propyl-N-benzyl-2-(3,4-dimethoxyphenyl)-2-hydroxyethylamine (6c). Reduction of **5c** with $NaBH_4$ as described above for **6a** and **6b** gave an 86% yield of the desired amino alcohol. Conversion to the HCl salt and recrystallization from EtOH–ether gave mp 160–161 °C; NMR (Me_2SO-d_6) δ 7.80 (br s, 1, NH^+), 7.7 (br s, 5, ArH), 6.90 (br s, 3, ArH), 4.80 (m, 1, CH), 4.5 (br s, 2, $ArCH_2N$), 3.80 (s, 6, OCH_3), 3–3.5 (m, 5, OH, NCH_2), 1.80 (m, 2, CH_2CH_3), 0.85 (t, 3, CH_3, J = 8 Hz). Anal. ($C_{20}H_{28}ClNO_3$) C, H, N.

2-Methyl-4-(3′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7a). To a solution of 2.0 g (6.5 mmol) of amino alcohol **6a** in 25 mL of CH_2Cl_2 was slowly added 1.73 g (13 mmol) of anhydrous $AlCl_3$. This mixture was stirred and heated at reflux overnight. The reaction was cooled in an ice bath and quenched with H_2O. The mixture was basified with 10% NaOH and repeatedly extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration of the filtrate under vacuum yielded 1.2 g (66%) of the cyclized product: NMR ($CDCl_3$) δ 6.7–7.4 (m, 7, ArH), 4.2–4.5 (m, 1, CH), 3.90, 3.93 (2 s, 6, OCH_3), 3.8 (br s, 2, $ArCH_2$), 2.9–3.3 (m, 2, CH_2CH), 2.5 (s, 3, NCH_3). The amine was further characterized as its hydrochloride salt and recrystallized from EtOH–ether, mp 254–256 °C. Anal. ($C_{18}H_{22}ClNO_2$) C, H, N.

2-Ethyl-4-(3′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7b). A solution of 5.5 g (17.5 mmol) of **6b** in 90 mL of CH_2Cl_2 was treated with 5.58 g (41.8 mmol) of $AlCl_3$ as described above for **7a**. Following a similar isolation procedure, the cyclized compound was obtained in 85% yield: NMR (Me_2SO-d_6) δ 7.29–6.83 (m, 7, ArH), 4.46–4.83 (m, 1, CH), 3.75 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 3.63–3.21 (m, 4, NCH_2), 1.36 (t, 3, CH_3, J = 7 Hz). The product was further characterized as the hydrochloride salt, mp 219 °C (EtOH–ether). Anal. ($C_{19}H_{24}ClNO_2$) C, H, N.

2-n-Propyl-4-(3′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7c). A solution of 1.0 g (3 mmol) of **6c** in 15 mL of CH_2Cl_2 was treated with 1.06 g of $AlCl_3$ as described above for **7a** and **7b**. The isolated free amine was converted to the hydrochloride salt and repeatedly recrystallized from EtOH to yield 21% of the salt: mp 204–205 °C; NMR (Me_2SO-d_6) δ 7.25–6.71 (m, 7, ArH), 4.64–4.44 (br s, 3, $ArCH_2$, CH), 3.75 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 3.63–3.03 (m, 2, NCH_2), 1.93–1.35 (m, 2, CH_2CH_3), 0.93 (t, 3, CH_3, J = 7 Hz). Anal. ($C_{20}H_{26}ClNO_2$) C, H, N.

2-Methyl-4-(3′,4′-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (3a). The dimethyl ether **7a** (1.0 g, 3.7 mmol) was dissolved in 100 mL of 48% HBr and heated to reflux under N_2 for 4 h. The excess HBr was removed under vacuum and the residue was treated with charcoal and recrystallized from EtOH to yield 436 mg (37%): mp 264–265 °C; NMR (Me_2SO-d_6 + D_2O) δ 7.5–6.5 (m, 7, ArH), 4.6 (br s, 3, $ArCH_2N$, CH), 3.7 (m, 2, NCH_2), 3.0 (s, 3, NCH_3). Anal. ($C_{16}H_{18}BrNO_2$) C, H, N.

2-Ethyl-4-(3′,4′-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (3b). A solution of 3.93 g (13 mmol) of **7b** was heated at reflux in 100 mL of 48% HBr for 4 h, and the product was isolated as described above for **3a** to yield 2.05 g (44%) of the HBr salt of **3b**: mp 241–245 °C (EtOH); NMR (Me_2SO-d_6) δ 10.04 (br s, 1, NH^+), 8.96–8.88 (br s, 2, OH), 7.28–6.58 (m, 7, ArH), 4.58–4.52 (m, 3, ArCH, $ArCH_2$), 3.48–3.25 (m, 4, CH_2CH_3, NCH_2), 1.34 (t, 3, CH_3, J = 7 Hz). Anal. ($C_{17}H_{20}BrNO_2$) C, H, N.

2-n-Propyl-4-(3′,4′-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (3c). A solution of 5.59 g (18 mmol) of **7c** in 300 mL of 48% HBr was heated at reflux for 4 h under N_2. The salt was isolated as described above for **3a** and **3b** to yield 3.085 g (47%): mp 192–193 °C (EtOH); NMR (Me_2SO-d_6) δ 10.12 (br s, 1, NH^+), 8.87 (br s, 2, OH), 7.30–7.24 (m, 3, ArH), 6.89–6.53 (m, 4, ArH), 4.57 (br s, 2, $ArCH_2$), 4.49–3.96 (m, 1, CH), 3.86–3.12 (m, 4, NCH_2), 1.87–1.73 (m, 2, CH_2CH_3), 0.95 (t, 3, CH_3). Anal. ($C_{18}H_{22}BrNO_2$) C, H, N.

Pharmacology. Evaluation for renal vasodilatation was carried out essentially by the method of McNay and Goldberg.[12] Experiments were done in pentobarbital-anesthetized adult male mongrel dogs, 20–25 kg. Following a flank incision and retroperitoneal dissection, the right renal artery was isolated and prepared for measurement of renal blood flow using an electromagnetic flow probe. Drug injection was via a 25-gauge needle bent at about an 80° angle and placed into the renal artery proximal to the flow probe.

Phenoxybenzamine, 5–10 mg/kg, was infused intraarterially over a 15 to 20-min period. Complete α-adrenergic blockade was confirmed by abolition or reversal of the vasoconstrictor effect of injection of 12 nmol of norepinephrine. Under these conditions, dopamine (DA) in doses of 12–190 nmol (contained in 0.2-mL injection volume) produced short-lived reversible increases in renal blood flow (see Figure 1). After standard responses to DA had been obtained, the test drugs **3a–c** (again in 0.2-mL injection volumes) were injected in increasing doses into the renal artery. Results in Figure 1 are expressed in milliliter per minute increase in blood flow.

Agonists which exhibited vasodilation were also tested with sulpiride to determine the degree of inhibition. A dose of 0.5 mg of sulpiride in 0.2 mL volume was combined with a dose of 750 nmol of the test drug in 0.2 mL (total injection volume 0.4 mL) and simultaneously injected. In order to determine whether the dilatation was β-adrenergic in origin, propranolol (2.5–5 mg/kg) was infused intraarterially over a 20-min period. β-Adrenergic blockade was established by abolition of the vasodilator effects of isoproterenol (3 nmol).

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