Synthesis and Dopaminergic Activity of 3-(3,4-Dihydroxyphenyl)-1-*n*-propylpyrrolidine Hydrobromide

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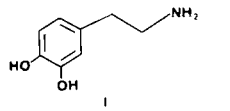
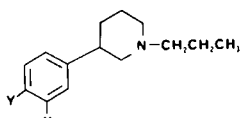
Abstract □ 3-(3,4-Dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide was synthesized by a six-step reaction sequence and was evaluated, and compared with apomorphine, for central dopaminergic agonist activity. The compound produced behavioral and biochemical changes characteristic of central dopaminergic stimulation. Administration of 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide to rats resulted in the reversal of the reserpine syndrome, stereotypic behavior, contralateral turning following 6-hydroxydopamine lesion of the substantia nigra, a decrease in dopamine turnover, and inhibition of prolactin release. These results indicate that 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide is a dopaminergic agonist. However, the compound exhibited a lower potency but a slightly longer duration of action than apomorphine.

Keyphrases □ 3-(3,4-Dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide—synthesis, central dopaminergic activity, compared with apomorphine □ Dopaminergic activity—central, apomorphine, 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide

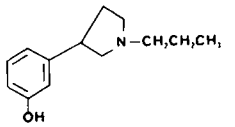
In an attempt (1) to prepare compounds with dopaminergic activity, our efforts were directed toward the synthesis of a compound in which the ethylamine chain of dopamine (I) is embodied in a pyrrolidine ring. Specifically, the purpose of this investigation was to synthesize and evaluate the dopaminergic activity of 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine (XI). The substitution of an *n*-propyl group on nitrogen has been shown to optimize activity in a variety of dopamine agonists (2, 3). Thus, the *n*-propyl substitution on the pyrrolidine ring nitrogen should maximize dopaminergic activity.



I

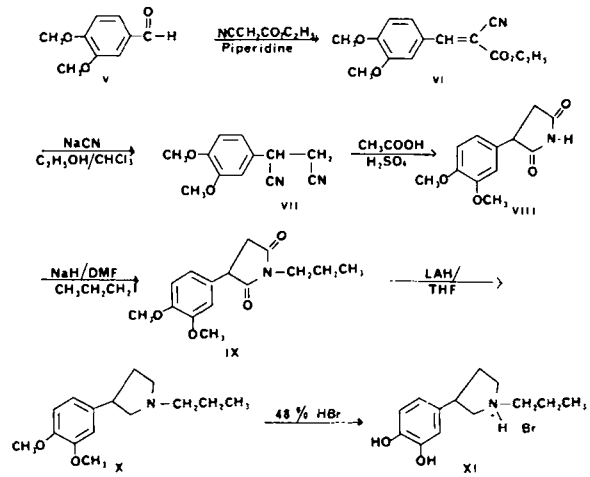


II : X = OH, Y = H
III : X = OH, Y = OH



IV

During the course of this investigation, a preliminary report indicated that II was a selectively acting dopamine autoreceptor agonist (4). Further testing of II has shown that this compound is a centrally acting dopamine autoreceptor agonist (5, 6). Structure-activity studies revealed that the pyrrolidine analogue IV of 3-(3-hydroxyphenyl)-1-*n*-propylpiperidine (II) was very weak as a dopamine autoreceptor agonist (7). These workers did not report the synthesis and biological activity of the target compound of their investigation. However, the (3,4-dihydroxyphenyl)piperidine III was prepared and pharmacologically evaluated. Compound III, unlike II, exhibited potent postsynaptic dopaminergic agonism.



Scheme I

EXPERIMENTAL SECTION[1]

Ethyl α-Cyano-β-(3,4-dimethoxyphenyl)acrylate (VI)—A mixture of 3,4-dimethoxybenzaldehyde (V) (20.0 g, 0.120 mol), ethyl cyanoacetate (12.8 g, 0.120 mol), and piperidine (1.5 mL) in toluene (200 mL) was heated to 110 °C. Water was removed during heating *via* a Dean-Stark trap. The mixture was cooled, and the solvent was removed under reduced pressure to yield 28.4 g (90%) of a light-yellow solid. An analytical sample was prepared by recrystallization from ethanol-chloroform to give VI, mp 156–158 °C [lit. (8) mp 155 °C]; IR (KBr): 2275 (C≡N), 1740 (C=O, ester), and 1610 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3, J = 8 Hz, CH_3), 3.97 (s, 6, OCH_3), 4.33 (q, 2, J = 8 Hz, CH_2), 6.83–7.80 (m, 3, ArH), and 8.17 ppm (s, 1, CH=C).

Anal.—Calc. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 64.16; H, 5.95; N, 5.24.

(3,4-Dimethoxyphenyl)succinonitrile (VII)—Ethyl α-cyano-β-(3,4-dimethoxyphenyl)acrylate (35.0 g, 0.134 mol) was dissolved in a mixture of chloroform (400 mL) and ethanol (300 mL) and treated dropwise with a solution of sodium cyanide (6.90 g, 0.141 mol) in water (100 mL). The mixture was refluxed for 15 h, cooled, and acidified with concentrated hydrochloric acid. Evaporation of the solvents under reduced pressure gave a light-pink solid that was partitioned between water (300 mL) and chloroform (200 mL). The aqueous phase was extracted with chloroform (2 × 200 mL), and the combined chloroform extracts were dried (sodium sulfate), filtered, and evaporated to afford a light-pink solid. Recrystallization from ethanol afforded 24.4 g (84%) of VII, mp 108–110°C; IR (KBr): 2300 (C≡N), 1620 (ArH), and 1280 cm^{-1} (C—O, ether); ^{1}H-NMR (Me_2SO-d_6): δ 3.33 (d, 2, J = 7 Hz, CH_2CN), 3.80 (s, 6, OCH_3), 4.67 (t, 1, J = 6 Hz, CHCN), and 7.03 ppm (m, 3, ArH).

Anal.—Calc. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.60; N, 12.96. Found: C, 66.24; H, 5.67; N, 12.78.

2-(3,4-Dimethoxyphenyl)succinimide (VIII)—Compound VIII was prepared according to the procedure of Crooks (9) for the preparation of spirosuccini-

[1] Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets with a Perkin-Elmer 137 Spectrophotometer. NMR spectra were recorded on a Varian EM360A spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) or, in the case of D_2O (1%), sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Analytical data were obtained from Micro-Analysis Inc., Wilmington, DE. Male Sprague-Dawley rats weighing 175–225 g were given free access to food and water and exposed to a 14:10 h light-dark cycle. Drugs were administered by intraperitoneal injections. Drugs and analytical-grade chemicals were purchased from commercial sources. Spiperone was a gift from Janssen Pharmaceutical Company, Inc. (New Brunswick, NJ). The vehicle for XI and apomorphine was 0.01 M sodium bisulfite solution.

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Table I—Behavioral Changes Effected by Apomorphine and XI [a,b]

Treatment	Catalepsy	Stereotypy	Locomotor Activity	Number of Rotations
Control	3	0	250 ± 35	0
Apomorphine	0	3	1825 ± 225	650 ± 125
XI	0	3	1798 ± 206	635 ± 140

[a] Catalepsy, stereotypy, and locomotor activity were assessed in rats ($n = 6$) pretreated with reserpine (5 mg/kg). Catalepsy and stereotypy were scored (see text) before the administration, and at the time of peak effect, of the dopamine agonists. Rotating rats ($n = 9$) were treated with dopamine agonists or vehicle. Results are expressed as mean ± *SEM*. All changes were statistically significant ($p < 0.05$). [b] Apomorphine and compound XI were administered at dosages of 2 and 100 mg/kg ip, respectively.

Table II—Biochemical Effects of Apomorphine and XI [a,b]

Treatment	Dopamine	Dihydroxyphenylacetic Acid	Homovanillic Acid	Prolactin
Control	7.2 ± 0.4	0.75 ± 0.3	0.44 ± 0.4	20.0 ± 4.0
Apomorphine	9.0 ± 0.5	0.50 ± 0.3	0.28 ± 0.4	2.0 ± 1.0
XI	10.1 ± 0.4	0.46 ± 0.5	0.24 ± 0.3	4.5 ± 2.5

[a] Dopamine, dihydroxyphenylacetic acid, and homovanillic acid are expressed as nanogram per milligram of striatal tissue, and prolactin as nanogram per milliliter of serum. The results represent the mean ± *SEM* of $n = 5$. All changes were statistically significant ($p < 0.05$). [b] Apomorphine and XI were administered at doses of 2 and 100 mg/kg ip, respectively.

mides. A mixture of (3,4-dimethoxyphenyl)succinonitrile (25.6 g, 0.118 mol), glacial acetic acid (150 mL), and 78% sulfuric acid (25 mL) was refluxed for 1 h, cooled, and evaporated under reduced pressure. The resulting mass was triturated with water (300 mL), and the solid material was removed by filtration. Recrystallization from ethanol gave 12.9 g (46%) of white crystals, mp 181–183°C; IR (KBr): 1785 (C=O, imide), 1725 (C=O, imide), and 1280 cm^{-1} (C—O, ether); ^{1}H-NMR (Me_2SO-d_6): δ 2.90 (m, 2, ring CH_2), 3.70 (s, 6, OCH_3), 4.03 (m, 1, ring CH), and 6.87 ppm (m, 3, ArH).

Anal.—Calc. for $C_{12}H_{13}NO_4$: C, 61.26; H, 5.58; N, 5.96. Found: C, 61.15; H, 5.60; N, 5.97.

2-(3,4-Dimethoxyphenyl)-*N*-(*n*-propyl)succinimide (IX)—A 50% mineral oil dispersion of sodium hydride (5.28 g, 0.11 mol) was washed with hexane (3 × 30 mL) and suspended in dimethylformamide (100 mL). A solution of 2-(3,4-dimethoxyphenyl)succinimide (25.8 g, 0.11 mol) in dimethylformamide (100 mL) was added to the sodium hydride suspension in a dropwise manner while maintaining a nitrogen atmosphere. After the addition had been completed, the mixture was heated at 80°C for 2 h and cooled to room temperature. A solution of *n*-propyl iodide (18.7 g, 0.11 mol) in dimethylformamide (30 mL) was added dropwise and the mixture was heated at 80°C for 15 h. The mixture was cooled, treated with a few drops of absolute ethanol, filtered, and the solvent was evaporated to give a light-tan solid. Recrystallization from isopropyl alcohol yielded 18.7 g (61%) of a white solid, mp 76–77°C; IR (KBr): 1785 (C=O, imide) and 1725 cm^{-1} (C=O, imide); ^{1}H-NMR ($CDCl_3$): δ 0.90 (t, 3, $J = 6$ Hz, CH_3), 1.33–4.07 (m, 13, including singlet 3.90, OCH_3), and 6.80 ppm (m, 3, ArH).

Anal.—Calc. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.92; N, 5.05. Found: C, 64.79; H, 7.01; N, 4.93.

3-(3,4-Dimethoxyphenyl)-1-*n*-propylpyrrolidine (X)—A solution of IX (18.0 g, 0.065 mol) in anhydrous tetrahydrofuran (100 mL) was added to a suspension of lithium aluminum hydride (14.8 g, 0.389 mol) in tetrahydrofuran (100 mL). The mixture was refluxed for 19 h, cooled, and the excess lithium aluminum hydride was decomposed by the dropwise addition of water. The resulting sludge was filtered and the inorganic residue was washed with tetrahydrofuran (2 × 50 mL). The combined solvents were evaporated, and the residue was partitioned between chloroform (300 mL) and water (100 mL). The chloroform phase was dried (sodium sulfate), filtered, and the solvent was evaporated to afford a dark-brown oil. Vacuum distillation gave 12.0 g (74%) of a colorless oil, bp 136–138°C (0.7 mm). The hydrochloride of X was prepared and recrystallized from ethanol–ether to yield a white solid, mp 131–133°C; ^{1}H-NMR (D_2O): δ 1.13 (t, 3, $J = 6$ Hz, CH_3), 1.57–3.97 (m, 17, including singlets at 3.93 and 3.97, OCH_3), and 7.03 ppm (m, 3, ArH).

Anal.—Calc. for $C_{15}H_{24}ClNO_2$: C, 63.02; H, 8.48; N, 4.90. Found: C, 63.34; H, 8.35; N, 4.82.

3-(3,4-Dihydroxyphenyl)-1-*n*-propylpyrrolidine Hydrobromide (XI)—A solution of X (3.0 g, 0.012 mol) in 48% aqueous hydrobromic acid (30 mL) was refluxed for 3 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure, and water was removed from the resulting oil by azeotropic distillation with absolute ethanol several times. Trituration of the oil with ether gave a light-yellow solid. Recrystallization from absolute ethanol ether afforded 2.2 g (60%) of a tan solid, mp 152–154°C; IR (KBr): 3450 cm^{-1} (OH, phenol); ^{1}H-NMR (D_2O): δ 1.03 (t, 3, $J = 6$ Hz, CH_3), 1.30–4.47 (m, 11, aliphatic CH_2, ring CH_2, and ring CH), and 6.90 ppm (m, 3, ArH).

Anal.—Calc. for $C_{13}H_{20}BrNO_2$: C, 51.66; H, 6.68; Br, 26.44; N, 4.46. Found: C, 51.53; H, 6.55; Br, 26.34; N, 4.60.

Locomotor Activity—Rats treated 12–18 h previously with reserpine (5 mg/kg) were given vehicle, apomorphine (0.12–2.0 mg/kg), or XI (10–100 mg/kg) and tested for increases in locomotor activity. Locomotor activity[2] was monitored by the minute in single rats by electronic activity meters[3] with an input to a multichannel recorder. Testing was done every 5–7 d to allow recovery from the drugs.

Catalepsy—This was assessed, using the method of Kolbe *et al.* (10), by the length of time a reserpinized rat maintained an abnormal posture with its front paws over a bar (2 cm diameter) 7 cm from bench level. Catalepsy was scored in control reserpinized rats, and in experimental animals, just prior to drug administration and at the peak of effect of apomorphine or XI as follows: 0–9 s = 0; 10 s–2.5 min = 1; 2.6–5.0 min = 2; 5.1–10 min = 3; 10.1–20 min = 4; >20 min = 5.

Stereotypy—This was scored by the method of Kolbe *et al.* (10) at the peak effect of apomorphine or XI as follows: animals indistinguishable from vehicle-treated controls = 0; discontinuous sniffing and continuous locomotor activity = 1; continuous sniffing and discontinuous locomotor activity = 2; continuous sniffing and discontinuous biting, licking, or gnawing = 3; continuous compulsive biting, licking, or gnawing with no locomotor activity = 4.

Rotational Behavior—The left substantia nigra was lesioned according to the method of Reches *et al.* (11). Coordinates were AP −3.7 mm, L +1.9 mm, and DV −7.3 mm. Two weeks after lesioning, apomorphine (0.12–2.0 mg/kg) or XI (10–100 mg/kg) was administered and the resulting total number of rotations recorded. Rats were allowed 4–5 d between test doses. There was no rotation either spontaneously or in response to vehicle administration.

Effects of Apomorphine and XI on Dopamine Turnover—Rats were treated with vehicle, a single maximal dose of apomorphine (2 mg/kg), or XI (100 mg/kg), and the time courses of changes in striatal dopamine were determined. Dose-dependent changes in striatal dopamine were also obtained with apomorphine (0.12–2.0 mg/kg) and XI (10–100 mg/kg). In this study, rats were sacrificed at the times of peak effect of the dopamine agonists as determined from the time-response studies.

In the above studies, the animals were sacrificed by decapitation and the brains rapidly removed. The corpora striata were dissected on an ice-cold glass plate and immediately frozen on dry ice. Dopamine, dihydroxyphenylacetic acid, and homovanillic acid were measured by HPLC with electrochemical detection as previously described (12).

Effects of Apomorphine and XI on Serum Prolactin—Time and dose-dependent changes in serum prolactin induced by the dopamine agonists were investigated simultaneously with dopamine turnover. Following decapitation, trunk blood was collected and allowed to clot, samples were centrifuged at 5000×*g* for 5 min, and serum was stored at −70°C until assayed. Serum prolactin levels were determined by the double-antibody radioimmunoassay method using the reagents supplied by the NIAMDD rat pituitary hormones program. Results are expressed as nanograms per milliliter.

[^{3}H]Spiperone Binding—Competitive inhibition of [^{3}H]spiperone binding by the dopamine agonists was performed by the method of Seeman *et al.* (13) using fresh striatal membrane preparations. Protein concentrations, as measured by Lowry assay (14), were 250–400 ng/mL. Binding assays were performed in triplicate twice.

RESULTS AND DISCUSSION

Neuroleptic-induced hypomotility and catalepsy in rodents are dependent on the inhibition of dopaminergic function (15). The neuroleptic-induced state is antagonized by levodopa (16), apomorphine, or bromocriptine (17). Reserpine induces experimental parkinsonism because it depletes presynaptic dopamine by inhibiting the ATP-Mg^{2+} facilitated transport mechanism at the membrane of the intracellular storage granules (18). Apomorphine or XI reverses the reserpine syndrome and produces stereotypic behavior in a manner similar to other known dopamine agonists. The behavioral effects of XI and apomorphine in rats are summarized in Table I.

Reserpine-induced catalepsy (mean score = 3) was antagonized by both apomorphine and XI in a dose-related manner. The minimum doses of apomorphine and XI which produced a score of zero were 1.0 and 25 mg/kg, re-

[2] All behavioral observations were made between 08:00 and 14:00 hr.
[3] Columbus Instruments, Columbus, Ohio.

spectively. Apomorphine and XI also produced complete clearing of the reserpine-induced ptosis and hunched posture.

Both apomorphine and XI induced dose-dependent stereotyped behavior. A peak score of three (continuous sniffing with discontinuous licking or gnawing) was seen with apomorphine and XI at doses of 2.0 and 100 mg/kg, respectively. Maximal stereotypy was seen at 15 min following the administration of apomorphine and at 30 min after XI had been administered.

6-Hydroxydopamine destroys the presynaptic nerve terminals of the nigro-striatal pathway, causing postsynaptic denervation supersensitivity on the side of the lesion. Contralateral rotation in this model is indicative of direct stimulation of dopaminergic receptors in the denervated caudate nucleus (19). Apomorphine and XI (Table I) were both effective in producing this type of turning behavior. The minimal effective dose with XI was 10 mg/kg while a dose of 40–50 mg/kg produced 50% of maximal rotation. The time of peak effect was 20 min with a duration of 75–90 min. With apomorphine, the minimal effective dose was 0.25 mg/kg and the dose that produced 50% of maximal rotation was 1.0 mg/kg. Apomorphine exhibited its peak effect at 20 min and caused rotation for a period of 50–60 min. Rotation was apparent by 2–3 min for both XI and apomorphine.

The results of the biochemical studies on 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide (XI) and apomorphine are summarized in Table II. Apomorphine (2.0 mg/kg) and XI (100 mg/kg) induced rapid increases in dopamine accumulation. Maximal effect of ~30–35% increases was obtained with both compounds at 15–20 min with a return to the control value at ~90 min. Both apomorphine and XI produced striatal dopamine accumulation in a dose-dependent manner with EC_{50} values of ~0.75 and 40 mg/kg, respectively. Apomorphine and XI also induced dose-related decreases in dihydroxyphenylacetic acid and homovanillic acid.

The administration of XI (100 mg/kg) or apomorphine (2 mg/kg) resulted in rapid decreases in serum prolactin levels. Maximal decreases were obtained 20–45 min after administration of the test compound. In the dose-response study, apomorphine and XI produced dose-dependent decreases in serum prolactin levels with IC_{50} values of 0.5 and 15 mg/kg, respectively.

Compound XI inhibited [^{3}H]spiperone binding to striatal membrane preparations with an IC_{50} of ~10 μM. The IC_{50} value for apomorphine was 200 nM. The time courses of the behavioral and biochemical effects of both apomorphine and XI are generally in close agreement. Compound XI exhibited a much lower affinity for the butyrophenone binding site in the competition binding studies with [^{3}H]spiperone than apomorphine or other known dopamine agonists. However, this low affinity correlates with the potency observed in behavioral and biochemical studies, as apomorphine and XI have similar molecular weights.

3-Phenylpiperidines may exist in a stable conformation in which the β-phenethylamine system assumes a *trans* (antiperiplanar) conformation (20). This conformation is preferred by most dopamine agonists (7). The lack of dopamine autoreceptor activity by the pyrrolidine analogue IV has been attributed to an inability to attain this conformation (7, 20). Thus, XI may not be optimally binding at its receptor sites.

In vivo, apomorphine or bromocriptine produce behavioral and biochemical changes characteristic of central dopaminergic stimulation; these include reversal of the reserpine syndrome, stereotypic behavior, contralateral rotation following unilateral 6-hydroxydopamine lesion of the substantia nigra, reduction in the rate of dopamine turnover, and inhibition of prolactin release. We have compared 3-(3,4-dihydroxyphenyl)-1-*n*-propylpyrrolidine hydrobromide (XI) with apomorphine for these behavioral and biochemical actions. The results reported here show that XI induced typical changes, and it may, therefore, be tentatively concluded that it acts as an effective dopaminergic agonist, with a much lower potency but a slightly longer duration of action, than apomorphine.

Further work is in progress to compare the dopaminergic activity of XI with other known dopamine agonists. Additionally, structure-activity studies are currently being performed with the 3-phenylpyrrolidine series.

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