Synthesis and Pharmacological Evaluation of Aromatic Dihydroxylated Spiro[indan-1,3′-pyrrolidine] and Spiro[indan-2,2′-pyrrolidine] Derivatives

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Abstract □ Aromatic hydroxylated derivatives of the spiro[indan-1,3′-pyrrolidine] and spiro[indan-2,2′-pyrrolidine] ring systems have been synthesized and evaluated for dopaminergic agonist and antagonist activities. None of these conformationally restricted catecholamines possessed any dopaminergic activity, but 5,6-dihydroxy spiro[indan-1,3′-pyrrolidine] hydrobromide exhibited weak dopamine antagonist properties.

As part of a structure–activity study designed to develop new leads in the discovery of novel CNS agents, a series of new aromatic dihydroxylated derivatives of the spiro[indan-1,3′-pyrrolidine] (**1**) and spiro[indan-2,2′-pyrrolidine] (**2**) ring systems have been prepared. These compounds contain the elements of a conformationally restricted catecholamine moiety within their structure, and were evaluated both in vitro and in vivo for dopaminergic agonist and antagonist properties.

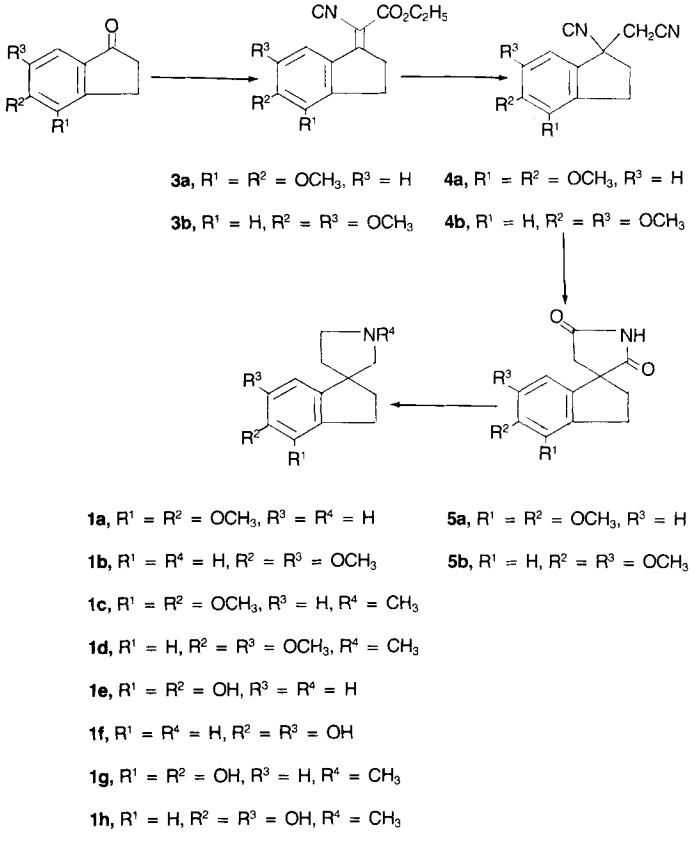
Results

Chemistry—The synthetic route to the dihydroxy spiro[indan-1,3′-pyrrolidines] is outlined in Scheme I. The formation of the indanylidene derivative **3** from the appropriate 1-indanone and ethyl cyanoacetate, was carried out utilizing a modification of a procedure previously described by Cope and Field.[1] Reaction of the resulting 1-indanylidenecyanoacetate derivative **3** with potassium cyanide then afforded the corresponding 1-cyano-1-cyanomethylindane **4**. The intermediate spiro[indan-1,3′-pyrrolidine-2′,5′-dione] **5** could be obtained in good yield by acid hydrolysis of **4**. Lithium aluminum hydride reduction of **5** then afforded the appropriate spiro[indan-1,3′-pyrrolidine].

5,6-Dimethoxy spiro[indan-2,2′-pyrrolidine] **2a** was synthesized via a four-step procedure starting from *N*-benzoyl-2-(3,4-dimethoxybenzyl)proline (**6**), which has been reported previously from our laboratory[2] (see Scheme II). *N*-Methylations of **1a**, **1b**, and **2a** were carried out in formic acid:formaldehyde solution, and *O*-demethylations of **1a–d**, **2a**, and **2b** were carried out under nitrogen in refluxing 48% aqueous hydrobromic acid containing 1% orthophosphoric acid.

Pharmacology—No direct effects on turning behavior in striatal-lesioned rats were observed following subcutaneous injection of **1e–h**, **2c**, or **2d** at 1, 10, and 30 mg/kg. Compound **1f** produced a 60% inhibition of apomorphine-induced turning behavior in rats at 30 mg/kg. This blockade was not observed at 10 mg/kg. None of the other dihydroxy spiro derivatives listed in Table I were active in this test.

In the radioligand binding assay (Table I) only **1f** had any significant activity. None of the dihydroxy spiro derivatives was effective in displacing *N*-*n*-[^{3}H]propylnorapomorphine ([^{3}H]NPA) binding from rat striatal membranes. Compound **1f** exhibited an IC_{50} of 1.1×10^{-8} in the 2-[^{3}H]amino-6,7-dihydroxytetralin ([^{3}H]ADTN) binding assay ($IC_{50}^{ADTN} = 1.7 \times 10^{-9}$ M) compared to an IC_{50} of 6.1×10^{-6} M for its positional isomer **1e** and to an IC_{50} value of $>10^{-5}$ M for the isomeric spiro compound **2c**.



Scheme I

In the mouse hypothermia test, no significant temperature changes, compared to saline control, were observed for any of the dihydroxy spiro compounds listed in Table I.

Discussion

Previous studies from our laboratory have shown that both 5,6- and 6,7-dihydroxy spiro[tetralin-1,3′-pyrrolidines] effectively block apomorphine-induced turning in striatal-lesioned rats.[3] However, the dose required (30 mg/kg sc) is relatively high. Our present study was designed to investigate the effect of decreasing the size of the saturated ring in the above compounds on the dopamine blocking activity. This structural modification also restricts considerably the conformational

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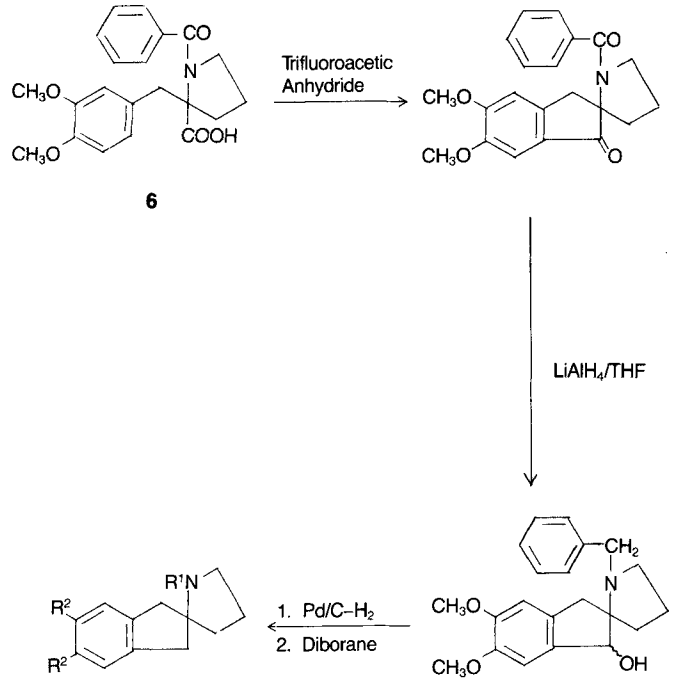
flexibility in the resulting spiro[indan-1,3′-pyrrolidine] system and affords a dopamine analogue in which the phenethylamine moiety is held in a relatively fixed conformation. The isomeric spiro[indan-2,2′-pyrrolidine] system has also been investigated in our study.

Of the four synthetic spiro[indan-1,3′-pyrrolidine] derivatives evaluated (Table I), only **1f** exhibited any significant pharmacological activity. None of the compounds possessed any dopamine agonist activities. However, **1f** exhibited an IC_{50} of 1.1×10^{-8} M against [^{3}H]ADTN in the radioligand binding assay and was a weak blocker of apomorphine-induced turning behavior in striatal-lesioned rats. Interestingly, the positional isomer **1c** was inactive in both these tests. The two spiro[indan-2,2′-pyrrolidine] derivatives **2c** and **2d** displayed no significant activity in any of the test systems employed.



2a, R^1 = H, R^2 = R^3 = OCH_3

2b, R^1 = CH_3, R^2 = R^3 = OCH_3

2c, R^1 = H, R^2 = R^3 = OH

2d, R^1 = CH_3, R^2 = R^3 = OH

Scheme II

The lack of dopaminergic activity exhibited by the above rigid dopamine analogues could be due to a number of factors. The spiro system increases overall steric bulk, which may not be tolerated by the receptor. In addition, although in **1e** and **1f**, molecular models show that the catechol moiety and the side-chain nitrogen can be superimposed upon the equivalent groupings in the apomorphine molecule, it is also apparent that these spiro systems represent dopamine conformations that are different from the α- and β-conformations thought to be necessary for dopaminergic agonist activity.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. IR spectra were determined as nujol mulls on a Perkin-Elmer 237 spectrophotometer, and NMR spectra were determined on a Perkin-Elmer R12B instrument using Me_4Si as internal standard. Spectral (IR and NMR) data for all compounds were consistent with the proposed structures.

5,6-Dimethoxy-1-indanone was prepared by the method of Levshina et al.,[4] and ethyl 4,5-dimethoxy-1-indanylidenecyanoacetate was prepared by the method of Horning and Walker.[5]

Ethyl 5,6-Dimethoxy-1-indanylidenecyanoacetate (3b)—A mixture of 5,6-dimethoxy-1-indanone (19.2 g, 0.1 mol), ethyl cyanoacetate (12.43 g, 0.11 mol), NH_4OAc (15.4 g, 0.2 mol), and glacial AcOH (48 g, 0.8 mol) in benzene (100 mL) was heated under reflux with a Dean–Stark water trap for 45 h. The cooled mixture was washed with water (3 × 100 mL), the washings were extracted with benzene (2 × 50 mL), and

Table II—Physical Data for 4,5- and 5,6-Dimethoxyindane Derivatives

Compound	Formula[a]	Yield, %	Melting Point, °C
3b	$C_{16}H_{17}NO_4$	54	193–194
4a	$C_{15}H_{14}N_2O_2$	98	83–86
4b	$C_{15}H_{14}N_2O_2$	70	127.5–129.5
5a	$C_{14}H_{15}NO_4$	69	217–219 (subl.)
5b	$C_{14}H_{15}NO_4$	69	160–176
1a	$C_{14}H_{19}NO_2$	58	bp 132–132.5 (0.03 mm Hg) (mp Fumarate salt, 162–167)
1b	$C_{14}H_{19}NO_2$	64	bp 136–137 (0.02 mm Hg) (mp Fumarate salt, 177–181)
1c	$C_{15}H_{21}NO_2$	93	bp 109–111 (0.07 mm Hg) (mp Fumarate salt, 181–185)
1d	$C_{15}H_{21}NO_2$	86	bp 128–129 (0.01 mm Hg) (mp Fumarate salt, 138–145)
2b	$C_{15}H_{21}NO_2$	64	bp 131–134 (0.05 mm Hg)

[a] All compounds were analyzed for C, H, and N; all values were within ±0.4% of the theoretical value.

Table I—Physical Data for Dihydroxy Spiro[indanylpyrrolidines] and Their Ability to Displace [^{3}H]ADTN and [^{3}H]NPA in Radioligand Binding Assays

Compound	Formula[a]	Yield, %	Melting Point, °C	IC_{50}, M[b]	
				[^{3}H]NPA	[^{3}H]ADTN
1e·HBr	$C_{12}H_{16}NO_2Br$	73	256–261 (dec.)	9.0×10^{-6}	6.1×10^{-6}
1f·HBr	$C_{12}H_{16}NO_2Br$	82	253–262 (dec.)	1.0×10^{-7}	1.1×10^{-8}
1g·HBr	$C_{13}H_{18}NO_2Br$	89	265–262 (dec.)	3.1×10^{-6}	9.7×10^{-6}
1h·HBr	$C_{13}H_{18}NO_2Br$	87	229–235 (dec.)	7.8×10^{-6}	$>10^{-5}$
2c·HBr[c]	—	—	—	$>10^{-5}$	$>10^{-5}$
2d·HBr	$C_{13}H_{18}NO_2Br$	69	221–225	$>10^{-5}$	$>10^{-5}$
ADTN	—	—	—	2.8×10^{-9}	1.7×10^{-9}
Apomorphine	—	—	—	1.9×10^{-9}	1.5×10^{-9}
Dopamine	—	—	—	2.0×10^{-9}	2.1×10^{-9}

[a] The hydrobromide salts of **1e–h** and **2d** were analyzed for C, H, and N; all values were within ±0.4% of the theoretical value. [b] IC_{50} values were determined as the concentration of drug causing a half-maximal displacement of 1.0 nM [^{3}H]ADTN and 1.0 nM [^{3}H]NPA specific binding, assessed using 10^{-5} sulpiride and (±)-ADTN, respectively. Each value is the mean value of two experiments performed in quadruplicate. [c] See ref. 3 for physical data.

the combined benzene liquors were dried ($MgSO_4$) and concentrated. Recrystallization from ethanol afforded an analytical sample (Table II).

4,5-Dimethoxy-1-cyano-1-cyanomethylindane (4a)—This compound was prepared by addition of a solution of **3a**[4] (28.7 g, 0.1 mol) in absolute ethanol (200 mL) to a solution of KCN (6.5 g, 0.25 mol) in water (35 mL) and stirring the resulting mixture at 65°C for 16 h. The mixture was then concentrated under reduced pressure, and the residue was suspended in water (200 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic liquors were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give a light-brown solid. Recrystallization from absolute ethanol afforded the purified material (Table II).

5,6-Dimethoxy-1-cyano-1-cyanomethylindane(4b)—Compound **4b** was prepared from ethyl 5,6-dimethoxy-1-indanylidenecyanoacetate[5] by an analogous procedure to that described for the preparation of **4a** (Table II).

4,5-Dimethoxy Spiro[indan-1,3′-pyrrolidine-2′,5′-dione] (5a)—Compound **4a** (25.4 g, 0.1 mol) was suspended in a mixture of glacial AcOH (50 mL) and aqueous H_2SO_4 (78% v/v, 17 mL), which was then heated to 140°C (oil bath) for 1 h. Removal of the acetic acid by vacuum distillation afforded solid material that was suspended in water (50 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic liquors were washed with a saturated solution of $NaHCO_3$ (2 × 200 mL) followed by water (1 × 100 mL), and then dried over $MgSO_4$. Evaporation of the solvent afforded crude **5a**, which was recrystallized from absolute ethanol (Table II).

5,6-Dimethoxy Spiro[indan-1,3′-pyrrolidine-2′,5′-dione] (5b)—This compound was prepared from 5,6-dimethoxy-1-indanylidenecyanoacetate by an analogous procedure to that described for the preparation of **5a**.

4,5- and 5,6-Dimethoxy Spiro[indanylpyrrolidine] Derivatives—Compounds **1a** and **1b** were prepared from **5a** and **5b**, respectively, by $LiAlH_4$ reduction using the following general procedure. The appropriate pyrrolidine-2′,5′-dione (2.61 g, 0.01 mol) was added in portions to a suspension of $LiAlH_4$ (1.12 g, 0.03 mol) in anhydrous tetrahydrofuran (100 mL), and the mixture was refluxed for 16 h. On cooling, the excess hydride was decomposed by the addition of water in a dropwise manner, and anhydrous $MgSO_4$ was then added. The resulting mixture was filtered through fluted filter paper, and the filtrate was evaporated on a rotary evaporator to afford a pale-yellow oil. The oil was taken up in ether (15 mL) and extracted with 5% v/v aqueous hydrochloric acid (3 × 10 mL). The aqueous phase was separated, basified with concentrated aqueous ammonium hydroxide, and extracted with ether (3 × 20 mL). The combined organic liquors were dried over $MgSO_4$, the solvent was evaporated, and the resulting oil was distilled under reduced pressure (Table II).

Compound **2a** was prepared from *N*-benzoyl-5,6-dimethoxy spiro[indan-2,2′-pyrrolidine-1-one] via $LiAlH_4$ reduction, catalytic *N*-debenzylation, followed by reductive dehydroxylation with B_2H_6 as described previously.[2]

***N*-Methylated 4,5- and 5,6-Dimethoxy Spiro[indanylpyrrolidine] Derivatives**—Compounds **1c**, **1d**, and **2b** were prepared from **1a**, **1b**, and **2a**, respectively, by reaction of the appropriate pyrrolidine compound (0.01 mol) with HCO_2H (2.3 g, 0.05 mol) and 40% aqueous HCHO (2 mL, 0.02 mol) at 90°C for 20 h, followed by dilution of the cooled mixture with aqueous HCl (5% v/v, 5 mL) and extraction with ether (2 × 10 mL). Basification of the aqueous phase with concentrated ammonium hydroxide, extraction with ether (3 × 20 mL), followed by evaporation of the dried ($MgSO_4$) organic liquors, afforded an oil, which was distilled under reduced pressure to afford purified material (Table II).

4,5- and 5,6-Dihydroxy Spiro[indanylpyrrolidine] Derivatives—Compounds **1e–h**, **2c**, and **2d** were all prepared by *O*-demethylation of the parent dimethoxy compound with HBr. In a typical procedure, a solution of the appropriate dimethoxy derivative (0.01 mol) in 48% aqueous HBr (25 mL) containing 1% orthophosphoric acid was heated at reflux and under an atmosphere of nitrogen for 2–3 h. The resulting yellow-brown solution was evaporated to dryness under nitrogen, and the residue was taken up in absolute ethanol. Crystallization of the product from ethanol:ether afforded the dihydroxy compound as an off-white powder (Table I).

Pharmacology—Compounds **1e–h**, **2c**, and **2d** were evaluated in vivo for dopaminergic properties by two methods: (*a*) for their direct effect on turning behavior in striatal-lesioned rats, following the procedure of Ungerstedt,[6] and (*b*) for their ability to block apomorphine-induced turning behavior in rats. In the latter study, apomorphine (1 mg/kg) was administered intraperitoneally, and inhibition of turning behavior in drug-treated animals was expressed as a percentage of control values at three concentrations of drug.

Compounds were also evaluated for their ability to cause a dose-related fall in the core temperature of albino mice. Mouse esophageal temperatures were measured as described previously.[7,8] In some experiments, animals were also pretreated with pimozide (0.5 mg/kg). Compounds were evaluated in vitro for their ability to displace [^{3}H]ADTN and [^{3}H]NPA binding from rat striatal membranes as described previously[9] (see Table I).

References and Notes

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