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A stereoselective synthesis of unknown spirobenzodihydropyrancyclohexanes is described starting from arylcyclohexenes alkylated and cyclized *via* a coumarin intermediate and leading to new amino derivatives which are rigid analogs of dopamine.

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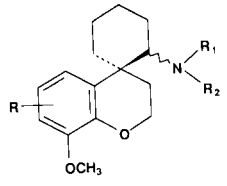
Many reports [1] have shown that dopaminergic agonist and antagonist activity exist in different compounds. Common structural features imply generally a basic nitrogen and a phenolic ring at a distance defined by Cannon [2].

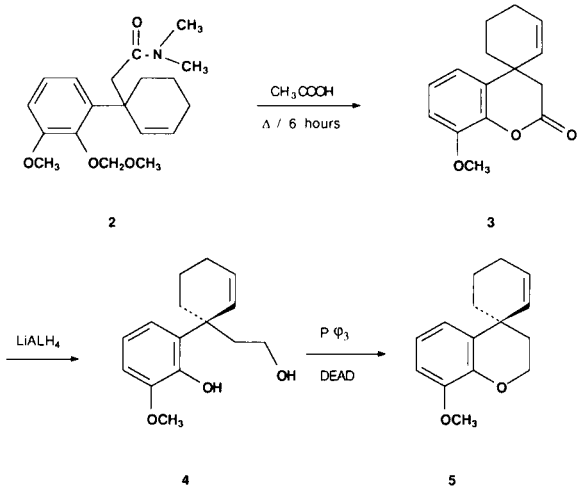
As part of an ongoing program toward the development of dopamine-like derivatives, we synthesized spiroaminobenzodihydropyrancyclohexanes **1**. The structure of these rigid analogs of dopamine was previously unknown:



1

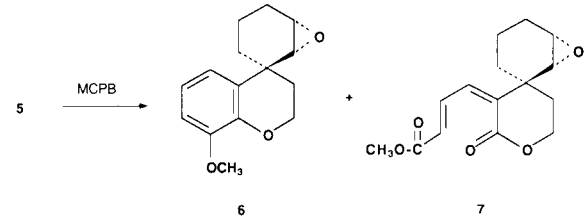
As starting material, we used substituted arylcyclohexenes, as the amide **2** [3], converted into spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohex-2′-ene] as outlined in Scheme 1.

Scheme 1



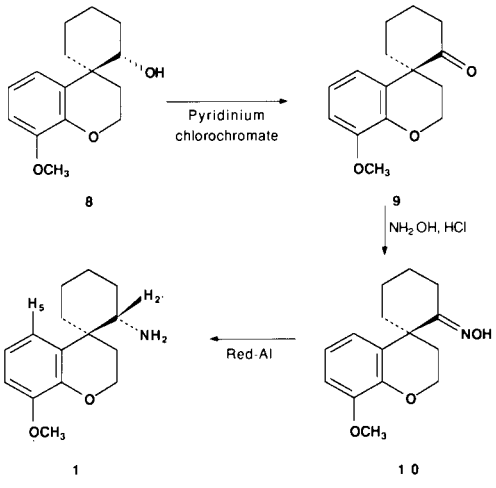
Compound **2** is converted into **3** by heating in acetic acid in 98% yield or by heating with a base followed by acidification the latter in a lower yield (80%). The reduction without opening of the lactonic carbonyl (Dibal, diisobutylaluminum hydride) was unsuccessful and we reduced the lactone **3** into diol **4** by the action of lithium aluminum hydride at room temperature. The diol cyclization into pyran **5** was obtained in an excellent yield by triphenylphosphine with diethyl azodicarboxylate [4].

In order to introduce an amine function on the cyclohexene ring, we prepared the epoxide **6**. The epoxidation of **5** by 3-chloroperbenzoic acid is stereospecific and only one of the two possible diastereoisomers is obtained. The stereochemistry is verified by nmr data (NOE difference) and confirmed by X-ray crystallography [5]. The stereoselectivity of the formation of compound **6** can be explained by the less crowded face attack in **5**. We note that formation of compound **7** (2%) can be formed as the major product if a great excess of 3-chloroperbenzoic acid is used:



The epoxide **6** is unreactive under the usual experimental conditions toward amines or azides, but is regioselectively reduced by lithium aluminum hydride with aluminum chloride [6]. This regioselective opening of the oxirane ring of compound **6** can be explained by an attack on the less crowded oxirane carbon. More bulky nucleophiles such as amines or azides do not react even in the presence of Lewis acid catalysts.

Starting from alcohol **8**, several approaches might lead to desired amines. Direct or indirect substitution reactions of a proper derivative by an amine or an azide were unsuccessful [7]. Direct amino-reduction according to Borch or Johansson [8-9] cannot be used. Only oxidation into a ketone followed by transformation into an oxime followed by reduction afforded amines.



Pyridinium chlorochromate leads to ketone **9** (89%) which was transformed into oxime **10** by hydroxylamine (90% yield). Only one of the two predictable diastereoisomers is formed. Reduction by lithium aluminum hydride gives the amine in a poor yield (25%) and we used sodium bis(2-methoxyethoxy) aluminum hydride [10]. Thus, the isolated amine (60% yield) is solely the diastereoisomer **1**. The equatorial position of the amino group is established by the ^{1}H nmr spectra: H2′ signal is a doublet of doublet (J_1 = 11 Hz; J_2 = 4 Hz) and in this conformation, only the configuration of compound **1** showed in Scheme can be explained by a positive NOE between H2′ and H5. The stereoselective reduction of oxime **10** can hardly be explained by a greater crowding of one face of the double bound; but it is fortunate that this reduction affords the stereoisomer with the more potential biological effect.

EXPERIMENTAL

Thin-layer chromatography was performed on Kieselgel 60 F plates Merck. Column chromatography was performed by using silica gel (63-200 μm, Merck 7734). Flash chromatography was performed by using silica gel (40-63 μm, Merck 9385). Analytical analyses were performed on a Perkin Elmer 240 instrument. Mass spectra were recorded with a V.G. 70-70F mass spectrometer (S.A.M.M. du Centre d'Etudes Pharmaceutiques de Châtenay-Malabry). Infrared spectra were recorded on a Perkin Elmer 177 or 841 instrument (potassium bromide). Proton nmr spectra were recorded on a Varian T 60 (60 MHz) or Bruker AC 200 P (200 MHz) instrument in deuteriochloroform solution and are reported in ppm relative to an internal standard of tetramethylsilane. The ^{13}C nmr spectra were recorded on a Brucker AC 200 P (50 MHz) instrument. Yields were calculated from pure isolated products.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-2-one-4,1′-cyclohex-2′-ene] (**3**).

The amide **2** (3.8 g, 11.4 mmoles) was heated under reflux in 25 ml of glacial acetic acid during six hours. Ice was added to the reaction mixture and the precipitate was collected, washed with sodium bicarbonate solution, then with water and dried. The residue was purified by silica-gel chromatography (petroleum ether/ethyl acetate 1/1) to give 2.73 g (98%) of **3**; ir: ν 1770 cm^{-1} (very broad band); ^{1}H nmr: (60 MHz) δ 7.2-6.8 (m, 3H), 6.2 (dt, 1H), 5.5 (dt, 1H), 3.9 (s, 3H), 2.7 (s, 2H), 2.3-1.4 (m, 6H); ^{13}C nmr: δ 167.0 (s, C2), 147.0 (s, C8 and C8a), 139.8 (s, C4a), 131.1 (d, C2′), 129.5 (d, C3′), 123.8 (d, C6), 118.9 (d. C5), 111.1 (d, C7), 56.0 (q, CH_3), 41.4 (t, C3), 38.0 (s, C4), 33.9 (t, C6′), 24.5 (t, C4′), 17.9 (t, C5′).

Anal. Calcd. for $C_{15}H_{16}O_3$, 244.29: C, 73.75; H, 6.60. Found: C, 73.61; H, 6.49.

2-[1′-(2″-hydroxy-3″-methoxyphenyl)cyclohex-2′-en-1′-yl]-ethanol (**4**).

To a suspension of 1 g (25 mmoles) of lithium aluminum hydride in 30 ml of anhydrous THF under nitrogen was dropwise added 1.2 g (5 mmoles) of the spirocoumarin **3** and the reaction mixture was stirred during four hours at room temperature. The reaction was quenched with a hot aqueous sodium sulfate solution and filtered under reduce pressure; the solid residue was washed with ethyl acetate. The organic layers were dried over sodium sulfate and concentrated under reduced pressure. The product was purified by silica-gel chromatography (ethyl acetate/hexane 2/1) to give 1.24 g (100%) of compound **4**; ir: ν 3390 cm^{-1}; ^{1}H nmr: (60 MHz) δ 6.8 (m, 3H), 6.0 (m, 2H, one proton is deuterium oxide exchanged), 5.85 (dt, 1H), 3.9 (s, 3H), 3.55 (m, 2H), 2.45 (m, 2H), 2.15-1.9 (m, 4H), 1.7-1.3 (m, 3H, one proton is deuterium oxide exchanged); ^{13}C nmr: δ 146.6 (s, C3″), 143.5 (s, C2″), 133.7 (d, C2′), 131.5 (s, C1″), 127.3 (d, C3′), 122.6 (d, C5″), 118.3 (d, C6″), 108.6 (d, C4″), 60.0 (t, C1), 55.9 (q, CH_3), 41.7 (s, C1′), 41.6, 33.1 and 25.3 (3t, C4′, C6′ and C2), 19.3 (t, C5′).

Anal. Calcd. for $C_{15}H_{20}O_3$, 248.32: C, 72.55; H, 8.12. Found: C, 73.01; H, 7.94.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohex-2′-ene] (**5**).

To a solution of 1.24 g (5 mmoles) of compound **4** and 1.57 g (6 mmoles) of triphenylphosphine in 30 ml of anhydrous tetrahydrofuran, was added dropwise 1.2 g (7 mmoles) of diethyl azodicarboxylate (DEAD) at 0°. Its decoloration indicates the evolution of the reaction. The reaction mixture was stirred during the night at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by silica-gel chromatography (ethyl acetate/petroleum ether 1/4) to give 1.15 g (98%) of compound **5**; ^{1}H nmr: (60 MHz) δ 6.9-6.75 (m, 3H), 6.0 (dt, 1H), 5.55 (d broad, 1H), 4.55-4.25 (m, 2H), 3.9 (s, 3H), 2.3-1.7 (m, 8H); ^{13}C nmr: δ 147.8 (s, C8), 143.0 (s, C8a), 134.5 (d, C2′), 130.3 (s, C4a), 127.2 (d, C3′), 120.7 (d, C6), 118.9 (d, C5), 108.6 (d, C7), 62.4 (t, C2), 55.6 (q, CH_3), 36.6 and 33.8 (2t, C3 and C6′), 35.1 (s, C4), 24.6 (t, C4′), 18.2 (t, C5′).

Anal. Calcd. for $C_{15}H_{18}O_2$, 230.29: C, 78.23; H, 7.83. Found: C, 78.44; H, 7.89.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,2′-7′-oxabicyclo-[4.1.0]heptane] (**6**).

To a solution of 0.7 g (3 mmoles) of compound **5** in 20 ml of dichloromethane was dropwise added 1.3 g (7.5 mmoles) of 3-chloroperbenzoic acid in 10 ml of dichloromethane. The mixture was stirred during four hours at 25-30°. The reaction was quenched with a 10% sodium sulfite solution, the 3-chlorobenzoic acid was

extracted with a 5% sodium bicarbonate solution; the organic layer was washed with water and the solvent was evaporated under reduced pressure. The residue was purified by silica-gel chromatography (ethyl acetate/petroleum ether 1/1) to afford 554 mg (98%) of compound **6**. An evaporation of a propanone solution afforded crystals of epoxide **6** submitted to X-ray crystallography [5]; ^{1}H nmr: (200 MHz) δ 6.9-6.75 (m, 3H), 4.4 (dt, 1H, H2), 4.2 (dt, 1H, H2), 3.85 (s, 3H), 3.4 (m, H6'), 3.0 (d, H1'), 2.3-2.0 (m, 2H), 2.0-1.8 (m, 2H), 1.7-1.4 (m, 4H); ^{13}C nmr: δ 148.4 (s, C8), 143.5 (s, C8a), 129.2 (s, C4a), 120.2 (d, C6), 119.9 (d, C5), 109.4 (d, C7), 62.8 (t, C2), 60.0 (d, C1'), 56.0 (q, CH_3), 53.9 (d, C6'), 35.1 (t, C3 or C3'), 33.5 (s, C4), 30.8 (t, C3 or C3'), 24.8 (t, C5'), 15.1 (t, C4').

The ID NOE difference experiments were obtained using 1 second saturation delays. The irradiation of H1' involved a positive effect on H6' and H5. The irradiation of H5 involved a positive effect on H1'.

Anal. Calcd. for $C_{15}H_{18}O_3$, 246.3: C, 73.14; H, 7.36. Found: C, 73.24; H, 7.55.

Methyl 4-Spiro[7'-oxabicyclo[4.1.0]heptane-2',4''-2'',3'',5'',6''-tetrahydro-2''-oxo-4*H*-1-pyrany-1-idenylbuta-2-enoate (**7**).

This compound had ir: ν 1729 and 1630 cm^{-1}; ^{1}H nmr: (200 MHz) δ 8.0 (d, J = 11 Hz, H2), 7.6 (t, J = 11 Hz, H3), 5.95 (d, J = 11 Hz, H4), 4.35 (m, CH_2-6''), 3.75 (s, CH_3), 3.45 (m, H6'), 3.1 (d, H1'), 2.3 (dxdxd, H5''), 2.1-1.7 (m, 3H), 1.7-1.3 (m, 4H); ^{13}C nmr: δ 166.2 (CO), 165.0 (CO), 139.3 (d, C3), 137.4 (s, C3''), 135.4 (d, C4), 122.9 (d, C2), 65.1 (t, C6''), 57.7 (q, CH_3), 54.3 (d, C1'), 51.4 (d, C6'), 39.3 (s, C4''), 34.0 and 31.6 (2t, C5'' and C3'), 22.5 (t, C5'), 14.9 (t, C4'); ms: m/z 278, 247, 219.

Anal. Calcd. for $C_{15}H_{18}O_5$, 278.3: C, 64.74; H, 6.52. Found: C, 64.56; H, 6.61.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1'-cyclohexan-2'-ol] (**8**).

To a stirred solution of 1.14 g (30 mmoles) of lithium aluminum hydride in 50 ml of anhydrous tetrahydrofuran at 0°, was added 1.33 g (10 mmoles) of aluminum chloride. The mixture was stirred during ten minutes, 1.2 g (5 mmoles) of epoxide **6** in 20 ml of anhydrous tetrahydrofuran was added dropwise and the solution was stirred during four hours at room temperature. The reaction was quenched by the addition of an hot aqueous sodium sulfate solution and filtered under reduced pressure. The precipitate was washed with ethyl acetate, the organic layers dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (ethyl acetate/petroleum ether 1/1) to give 1.21 g (98%) of viscous oil; ir: ν 3350 cm^{-1}; ^{1}H nmr: (200 MHz) δ 6.9 (m, 2H), 6.7 (d, 1H), 4.45 (dt, 1H, H2), 4.2-4.0 (m, 2H, H2 and H2'), 3.85 (s, CH_3), 2.35 (m, 1H, H3'), 1.9-1.75 (m, 3H), 1.7-1.4 (m, 7H, one proton is deuterium oxide exchanged); ^{13}C nmr: δ 148.6 (s, C8), 146.0 (s, C8a), 128.6 (s, C4a), 120.3 (d, C6), 117.6 (d, C5), 109.0 (d, C7), 75.7 (d, C2'), 63.6 (t, C2), 55.7 (q, CH_3), 40.2 (s, C4), 38.0 (t, C3'), 28.6 (t, C3), 24.7 (t, C6'), 23.7 (t, C4'), 20.5 (t, C5').

Anal. Calcd. for $C_{15}H_{20}O_3$, 248.32: C, 72.55; H, 8.12. Found: C, 71.99; H, 8.01.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1'-cyclohexan-2'-one] (**9**).

To a solution of 0.64 g (3 mmoles) of pyridinium chlorochromate in 20 ml of dichloromethane was added 0.5 g (2 mmoles) of alcohol **8** and the solution was stirred during six hours at room temperature. To the reaction mixture was then added 20 ml of diethyl ether. The residue was filtered off, washed with ether, the combined organic layers washed with a 5% sodium hydroxide, 20 ml of 5% hydrochloric acid and 20 ml of water. The organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (ethyl acetate/petroleum ether 1/2) to give 438 mg (89%) of **9**; ir: ν 1710 cm^{-1}; ^{1}H nmr: (200 MHz) δ 6.9-6.6 (m, 3H), 4.3 (m, 1H), 4.1 (m, 1H), 3.85 (s, 3H), 2.7-1.7 (m, 10H); ^{13}C nmr: δ 212.1 (s, C2'), 148.3 (s, C8), 144.5 (s, C8a), 125.4 (s, C4a), 120.8 and 119.6 (2d, C5 and C6), 109.4 (d, C7), 62.2 (t, C2), 55.7 (q, CH_3), 50.4 (s, C4), 39.9 and 38.2 (2t, C3 and C3'), 31.9 (t, C6'), 26.5 (t, C4'), 20.8 (t, C5').

Anal. Calcd. for $C_{15}H_{18}O_3$, 246.30: C, 73.14; H, 7.36. Found: C, 73.42; H, 7.66.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1'-2'-hydroxyiminocyclohexane (**10**).

A mixture of 0.6 g (2.5 mmoles) of ketone **9**, 0.4 g (6 mmoles) of hydroxylamine hydrochloride and 0.8 g (9.6 mmoles) of sodium acetate in 15 ml of anhydrous ethyl alcohol was heated under reflux during two hours. The solvent was evaporated under reduced pressure and the residue was taken up in water and extracted with dichloromethane. The residue of the organic layer after drying and concentration under reduced pressure was purified by silica-gel chromatography (ethyl acetate/hexane 1/3) to give 587 mg (90%) of crystals; ir: ν 3410 and 1600 cm^{-1}; ^{1}H nmr: (200 MHz) δ 8.2 (1H, deuterium oxide exchanged), 6.9-6.6 (m, 3H), 4.25 (dt, 1H), 4.05 (dt, 1H), 3.85 (s, 3H), 3.25 (m, 1H), 2.4-2.1 (m, 2H), 2.0-1.4 (m, 7H); ^{13}C nmr: δ 163.1 (s, C2'), 148.1 (s, C8), 144.1 (s, C8a), 126.5 (s, C4a), 120.3 (d, C6), 119.2 (d, C5), 108.8 (d, C7), 62.2 (t, C2), 55.6 (q, CH_3), 41.5 (s, C4), 39.9 (t, C3), 32.5 (t, C3'), 24.9 (t, C6'), 21.2 (t, C4'), 20.0 (t, C5').

Anal. Calcd. for $C_{15}H_{19}NO_3$, 261.32: C, 68.94; H, 7.32; N, 5.36. Found: C, 69.21; H, 7.56; N, 5.31.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1'-2'-aminocyclohexane] (**1**).

To 0.1 g (0.5 mmoles) of oxime **10** was added 3 ml of a 70% sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) solution in toluene. After warming two hours at 80°, toluene was evaporated and the residue was purified by silica-gel chromatography (ethyl acetate/methyl alcohol 9/1) to give 74 mg (60%) of an oil; ms: (NH_3) m/z 248 (MH^+); ^{1}H nmr: (200 MHz) δ 7.0-6.7 (m, 3H), 4.4 (dt, 1H), 4.1 (dt, 1H), 3.85 (s, 3H), 3.25 (dd, 1H), 2.2 (m, 1H), 2.0-1.3 (m, 9H), 1.2 (m, 2H); ^{13}C nmr: δ 148.5 (s, C8), 145.6 (s, C8a), 129.9 (s, C4a), 120.2 (d, C6), 117.9 (d, C5), 108.7 (d, C7), 63.5 (t, C2), 56.7 (d, C2'), 55.8 (q, CH_3), 39.6 (s, C4), 38.5 (t, C3'), 29.8 (t, C3), 25.5 (t, C6'), 23.2 (t, C4'), 20.8 (t, C5').

The ID NOE difference experiments obtained using 1 second saturation delays showed a positive effect between H2' and H5.

Anal. Calcd. for $C_{15}H_{21}NO_2$, 247.34: C, 72.84; H, 8.56; N, 6.04. Found: C, 72.61; H, 8.71; N, 5.89.

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