Syntheses of dopaminergic 1-cyclohexylmethyl-7,8-dioxygenated tetrahydroisoquinolines by selective heterogeneous tandem hydrogenation

Inmaculada Andreu,a Nuria Cabedo,a Gregorio Torres,b Abdeslam Chagraoui,c M. Carmen Ramírez de Arellano,d Salvador Gil,d Almudena Bermejo,a María Valpuesta,b Philippe Protais,c and Diego Cortesa,*

a Departamento de Farmacología, Facultad de Farmacia, Universidad de Valencia, 46100 Burjassot, Valencia, Spain
b Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain
c Laboratoire de Physiologie, Faculté de Médecine-Pharmacie, Université de Rouen, 76183 Rouen, France
d Departamento de Química Orgánica, Facultad de Química, Universidad de Valencia, 46100 Burjassot, Valencia, Spain

Received 1 August 2002; revised 9 October 2002; accepted 23 October 2002

Abstract—We describe the preparation in a ‘one-pot’ sequence 1-cyclohexylmethyl 7,8-dioxygenated tetrahydroisoquinoline, substituted and unsubstituted in the C ring by application of the Photo–Fries transposition, followed by a tandem reduction–cyclization and further reduction. Indeed, we have accomplished for the first time regioselective hydrogenation of the benzylic ring of the tetrahydroisoquinoline systems. All 1-cyclohexylmethyl THIQ synthesized were able to displace D2 dopamine receptor from its specific binding site in rat striatal membranes, while the N-methylated derivatives showed also affinity for D1 dopamine receptors. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The neurotransmitter dopamine is involved in the regulation of several functions, including locomotor activity, emotion, cognition and neuroendocrine secretion. Previous results suggest that some natural and synthetic benzyltetrahydroisoquinoline (BTHIQ) alkaloids bind to dopamine receptors (D1-like and D2-like) from striatal membranes1 and in some cases inhibit dopamine uptake by striatal synaptosomes.2

D1 and D2 dopaminergic affinities of the 6,7-dioxygenated BTHIQ and their N-methylated homologues have been reported.3 We recently accomplished the synthesis of pairs of enantiomers of 6,7-dioxygenated BTHIQs. The (1S)-enantiomers are 5–15 times more effective at dopamine receptors (D1 and D2) than (1R)-enantiomers.4 The only previous study reported concerning the dopaminergic activity of 7,8-dioxygenated BTHIQs, has been carried out by isocrassifoline, a natural N-methylated-8-hydroxy-BTHIQ.5

The 7,8-dioxygenated BTHIQ are precursors of cularines, a group of isoquinoline alkaloids with a dihydrobenzoxepine system in their skeleton.6,7 This substitution pattern is unusual in the isoquinoline moiety, furthermore the synthesis of this type of compounds is not easy.

Normally, the tetrahydroisoquinolines (THIQ) are prepared by classical methods: Bischler–Napieralski, Pictet–Spengler, or Pomeranz–Fritsh.8 The Bischler–Napieralski cyclization is not a favorable method for preparation of 7,8-dioxygenated BTHIQs, because this procedure requires an electron-donating group at para to the cyclized position, so the position 6 is preferred to 2.1,3 Kametani et al. synthesized petaline, a 7,8-dioxygenated BTHIQ by usual Bischler–Napieralski cyclization with a bromo-substituent at 6 position with a very poor yield.9 The Pomeranz–Fritsh reaction and its modifications10 are more often used to obtain 8-hydroxylated THIQ, through Reissert compounds as an intermediate of the synthesis11 but this procedure involves many steps and low yields. The synthetic applications of the Photo–Fries reaction have been aimed at the preparation of oxygenated heterocycles, especially in those systems with an occupied para-position.12 Photo–Fries rearrangement was applied by Suau et al. for the synthesis of 7,8-dioxygenated THIQ alkaloids from appropriately trisubstituted benzene derivatives with a cyano-methyl group which proved to be inert under the irradiation
conditions. The Photo–Fries step is followed by a cyclization–reduction sequence by heterogeneous catalytic hydrogenation to obtain the corresponding 7,8-dioxygenated BTHIQ. In order to further explore the structural basis of the affinity of the 1,2,3,4 THIQ moiety for dopamine receptors we decided to study for the first time 1-cyclohexylmethyl-7,8-dioxygenated THIQ, substituted and unsubstituted in the C ring, which were prepared in a one-pot sequence by application of the Photo–Fries transposition followed by selective catalytic reduction of the C aromatic ring. Hydrogenation of the benzene ring is a classic method for the preparation of cyclohexane rings. Reaction rate and product stereochemistry depend on the catalyst used and on the nature of the aromatic rings substituents. The reduction of aromatic rings without affecting their substituents is difficult due to the easy hydrogenolysis of the alkoxy groups. Selective hydrogenation of anisol to cyclohexyl methyl ether was carried out by a silica-supported carboxymethyl cellulose–platinum complex at 30°C and 1 atm. All 1-cyclohexylmethyl derivatives synthesized were tested for their ability to displace [3H]-raclopride (a selective ligand of D2 dopamine receptor) and [3H]-SCH 23390 (a selective ligand of D1 dopamine receptor) from their specific binding sites in the rat striatum.

2. Results and discussion

2.1. Chemistry

The synthesis of these compounds was carried out irradiating the appropriate cyanomethyl phenyl ester (I), based on the radical mechanism accepted for the Photo–Fries rearrangement.

Compound 1 was irradiated at 254 nm, for 16 h in t-BuOH/H2O/THF (v/v/v), a solvent mixture combining appropriate polarity, viscosity, and a low hydrogen donor capability and giving rise to the best ortho/para ratio. Under these conditions, the crude reaction provided a mixture of 1a as major product) and low concentrations of the para-isomer (1b) in addition to the phenol (b). Both 1a and 1b, had been generated from the corresponding ortho and para transposition, respectively. The products resulting from decarbonylation of the phenylacetyl radical were not detected due to singlet biradical formation in the primary photoprocess from S1 excluding the triplet biradical formation, from which

\[ 
\text{Scheme 1.} 
\]

\[ 
\text{† Compound 1 has been described in Ref. 13.} 
\]

\[ 
\text{We accomplished the O-deprotection of the cyanomethyl precursor using HCl 50\% aq/EtOH (1:1 v/v) to prevent the solvolysis of the cyanide group.} 
\]
the decarbonylation process occurs.\(^{16}\) I was also irradiated for the first time at 254 nm, 400 w for 3 min and the results were similar.

Heterogeneous catalytic hydrogenation of the photochemical crude (1a, 1b) using PtO\(_2\) in EtOH and some milliliters of CHCl\(_3\), afforded 1-cyclohexylmethyl 7,8-di-oxygenated THIQ (2, 3, 4) obtained directly from 1a, as a majority amount, as well as, 1-cyclohexylmethyl 6,7-di-oxygenated THIQ (5, 6, 7) obtained from 1b. In the reduction step the cyanide group is converted in a primary amine, and an intramolecular cyclization was performed to furnish the corresponding dihydroisoquinoline (DHIQ).

Six compounds were purified from the crude reaction after heterogeneous catalytic hydrogenation. Three of them (2–4) come from ortho-hydroxyketone (1a) and the other three (5–7) from the para-hydroxyketone (1b) in a 7:3 ratio. In both cases, the cis isomers were obtained as majority compounds (3 and 6, respectively).

Relative configuration of stereomers 3-cis and 4-trans were deduced from NMR data. The \(^{13}\)C chemical shift reveals that in the cis diastereomer (3), the carbon \(\alpha\) to the methoxy group at \(4'\) position appears at \(\delta 76.7\), while in the trans diastereomer (4) this carbon appears at \(\delta 79.8\). In the \(^1H\) NMR spectrum the H-4' chemical shift in the trans diastereomer is 0.28 ppm upfield (\(\delta 3.12\)) with respect to the same proton in the cis isomer (\(\delta 3.40\)). An identical relationship is observed between compounds 6 (cis) and 7 (trans), coming from para Photo–Fries transposition. This assignment of the stereochemistry at C-4' level, is in agreement with the multiplicities observed for the H-4' signals. The H-4' equatorial (compound 3), appears as a septuplet (\(J_{eq,eq}=J_{ax,eq}=2.7\) Hz) due to the similar coupling constants between H-4' and the protons H-3' and H-5', as well as the long distance coupling in cyclohexane ring (W effect) with the protons at H-2' and H-6'.\(^{17}\) In the case of compound 4 the H-4' axial appears as a characteristic \(tt\) signal with two coupling constants \(J_{ax,ax}=11\) Hz, and \(J_{ax,eq}=4\) Hz, due to \(3j\) correlation with the neighbours protons at H-3' and H-5' position.\(^{17}\) X-ray crystal structure determination of compound 3-HCl racemate confirms a cis configuration between the methoxy and methyltetrahydroisoquinoline groups on axial and equatorial positions of the cyclohexyl ring, respectively (see Fig. 1). The cyclohexyl ring is on a chair conformation. The molecular structure shows the N and C3 atoms at 0.45 and 0.30 Å, respectively out of the THIQ main plane on a half-chair conformation. For C(1) atom the methyl cyclohexyl group is on a pseudo-axial position with the cyclohexyl ring pointing outwards of the THIQ moiety. An intramolecular interaction O1–H1···O2 have been found [O1···O2 2.692(2) Å, H1···O2 2.32 Å, O1–H1···O2 108.1°] (see Fig. 2A). In the crystal, N–H···Cl interactions form dimers (N–H0A···Cl#1 and N–H0B···Cl). An intermolecular interaction O1–H1···O3#2 forms infinite linear chains parallel to \(a\) (see Fig. 2B).

Figure 1. Ellipsoid plot of 3-HCl cation with the molecular labelling.
Catalytic hydrogenation of the benzylic ring of precursors 1a and 1b can be selectively achieved by action of catalytic PtO2 when 8-hydroxylated DHIQ were generated. This selective hydrogenation of the aromatic ring without affecting their substituents is consistent under our mild reaction conditions. Indeed only two demethoxylated minor compounds were obtained (2 and 5). These may come from the partially reduced intermediate where the hydrogenolysis process competes with hydrogenation, especially under the acidic medium needed for the cyclization–reduction tandem. In order to slow down hydrogenolysis, a low acidic medium generated in situ from the protic solvents was used. In our case the ring C was regioselectively hydrogenated, but under these conditions the THIQ ring was not affected. Thus, we have prepared an original series of cyclohexylmethyl THIQ, which are not easily obtained with other isoquinolines. When papaverine, a tetramethoxy isoquinoline 6,7-dioxygenated, was catalytically hydrogenated in the same conditions, it afforded only traces of the benzylic reduced compound, along with the expected BTHIQ derivative.

### 2.2. Bioactivities

All 1-cyclohexylmethyl THIQ synthesized were able to displace [3H]-raclopride (a selective ligand of D2 dopamine receptor) from its specific binding site in rat striatal membranes (see Table 1). The compounds 2, 3, 6, 7 show selectivity for D2 dopamine receptors. A dopaminergic affinity difference was found between both cis and trans stereoisomers. Thus, the cis-diastereomer (3), appeared to be about 10 times more potent at D2 dopamine receptors than its trans-diastereomer (4), which is considerably the less potent of the series. Comparative IC50 values between 7,8-dioxygenated THIQ (2–4) and 6,7-dioxygenated THIQ (5–7) indicate that the presence of a hydroxy group in the 8 or 6 positions does not appear to be very important for the improvement of the affinities of 1-cyclohexylmethyl THIQ for D1 and D2 dopamine receptors. The compounds 2a and 3a (N-methyl derivatives of compounds 2 and 3, respectively) are non-selective among dopamine receptors since they showed increased affinities for D1 dopamine receptors labelled with [3H]-SCH 23390 (a selective D1 ligand), both compared to compounds 2 and 3, respectively, without change of affinities for D2 dopamine receptors.

In conclusion, we have accomplished for the first time the regioselective hydrogenation of C ring in the BTHIQ systems, by a one-pot procedure including the Photo–Fries rearrangement followed by a tandem reduction–cyclization and further reduction. Moreover, we have noted that the presence of a 1-benzylic or 1-cyclohexylmethyl moiety in the THIQ compounds, do not affect the dopaminergic activity results. Both hydrophobic groups showed similar affinities for dopamine receptors.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC50 (µM) on specific binding of</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[3H]-SCH 23390</td>
<td>[3H]-raclopride</td>
</tr>
<tr>
<td>1</td>
<td>102.4±9.9</td>
<td>9.2±0.3</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100</td>
<td>9.6±0.8</td>
</tr>
<tr>
<td>4</td>
<td>&gt;100</td>
<td>85.9±2.1</td>
</tr>
<tr>
<td>5</td>
<td>10.2±3.1</td>
<td>6.4±0.3</td>
</tr>
<tr>
<td>6+7</td>
<td>62.5±11.5</td>
<td>10.1±0.4</td>
</tr>
<tr>
<td>2a</td>
<td>6.0±0.7</td>
<td>9.6±0.4</td>
</tr>
<tr>
<td>3a</td>
<td>29.2±4.3</td>
<td>12.1±0.9</td>
</tr>
<tr>
<td>Isocrassifoline 5</td>
<td>5.48</td>
<td>9.95</td>
</tr>
</tbody>
</table>

IC50 values and their SEM confidence limits were calculated from concentration-effect curves with 11 concentrations and four determinations for each concentration.

### 3. Experimental

#### 3.1. General instrumentation

Melting points were taken on a Cambridge microscope instruments coupled with a Reichert-Jung. IR spectra (film) were run on a Perkin–Elmer 1750 FTIR Spectrometer. EIMS, LSIMS and HRLSIMS were determined on a VG Auto Spec Fisons instrument. Liquid chromatography with mass spectrometry detection (LC-MSD) with APIES (atmospheric pressure electrospray ionization) in positive or negative mode was determined on a Hewlett Packard (HP-1100). NMR spectra were recorded on Bruker AC-300, Varian Unity-400 or Bruker AC-500 spectrometer at 300, 400 or 500 MHz respectively for 1H, and 100 or 125 MHz for 13C. Multiplicities of 13C NMR signals were assigned by DEPT experiments. COSY 45, HSQC and HMBC correlations were recorded at 400 or 500 MHz. All reactions were monitored by analytical TLC with silica gel 60 F254 (Merck 5554). Compounds employed in the synthesis of 1 were obtained by standard methods� and purified by flash chromatography (230–400 µm, Merck 9385) and Biotage flash 40 system, showed satisfactory physical and spectroscopic properties.

#### 3.2. General procedure for synthesis of cyanomethyl-ester

3.2.1. 1-(4′-Methoxy-phenyl)-acetoxy-2-methoxy-5-cyano- methylphenyl, 1. To a solution of 3-hydroxy-4-methoxy-phenyl acetonitrile,13 (500 mg, 3.06 mmol) in dry CH2Cl2 (7 mL) powered KOH (200 mg, 3.57 mmol) was added, and the mixture stirred for 30 min. Then, commercially available 4-methoxy-phenylacetyl chloride, (0.5 mL, 3.27 mmol) in dry CH2Cl2 was incorporated dropwise to the mixture. After stirring at room temperature for 14 h, 5% aq HCl (5 mL) solution was added and extracted with CH2Cl2. The organic layer was washed with 2% aq K2CO3 solution, brine, and water, dried over anhydrous Na2SO4 and concentrated under reduced pressure. The residue was purified through 60 H silicagel column (hexane/CH2Cl2/MeOH 74:20:6) to afford compound 1 as colorless crystals (700 mg, 76%), mp 94–96°C; C13H17NO4; IR (film) vmax

---

1 These results are similar to those previously observed with isocrassifoline, a natural N-methylated-BTHIQ 8-hydroxylated derivative and they are in accordance with the results obtained for the 6,7-dioxygenated-BTHIQ and its N-methylated homologue.5

---
A degassed (Ar) solution of compound 1 (500 mg, 1.61 mmol) in a mixture of t-BuOH/H2O/THF (7:2 v/v/v) (190 mL), was distributed among four Vycor tubes that were placed at the center of a cylindrical photochemical reactor equipped with six low pressure Hg lamps (Sylvania G8T5). The solution was irradiated at 254 nm for 16 h, and the reaction was monitored by analytical TLC and HPLC. The reaction solution was made up to 2.5% with HCl (200 mL) and extracted with CHCl3 (3x300 mL). The combined organic layers were washed with H2O, dried over anhydrous MgSO4, and the solvent removed under reduced pressure to give the photochemical crude. In a flask of a hydrogenation apparatus, this photochemical crude was dissolved in EtOH (60 mL) and CHCl3 (2 mL). The stirred solution was degassed and a slow stream of nitrogen was passed through the solution. After addition of PtO2, hydrogenation was carried out with a vigorous stirring at room temperature for 72 h at low pressure (58 psi). The mixture was broken to a boil under vacuum, the catalyst filtered off, and the filtrate was evaporated. The residue obtained was dissolved with CH2Cl2, and extracted with CHCl3. The organic layer was washed with H2O and brine, dried over anhydrous Na2SO4, and concentrated, yielded 350 mg of a residue which was purified through 60 H silicagel column (toluene/AcOEt/DEA 66:32:2) to afford the compounds 2 (75 mg, 17%), 3 (76 mg, 15.5%), 4 (46 mg, 9.5%), 5 (37 mg, 8.4%), 6 and 7 (56 mg, 11.4%), corresponding to the yields from compound 1, with an 62% overall yield of the reaction.

3.3.3. cis-1-(4′-Methoxycyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 3. C18H20NO3; mp 275–276; IR (film) \( \nu_{\text{max}} \) 3350, 2926, 2874, 1615, 1589, 1496, 1440, 1282, 1088, 794 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 500 MHz) \( \delta \) 1.40–1.90 (8H, m, CH2-2, 3, 5′, 6); 1.70 (1H, m, H-1′); 1.50, 1.80 (2H, 2m, CH2-α), 2.61, 2.70 (2H, 2m, CH2-δ), 3.01, 3.10 (2H, 2m, CH2-β), 3.31 (3H, s, OCH3-4′), 3.40 (1H, sept, \( J = 7.2 \) Hz, CH-4′), 3.84 (3H, s, OCH3-7), 4.30 (1H, dd, \( J = 10.7, 2.3 \) Hz, H-1), 5.15 (1H, brs, OH, exchange with D2O), 6.57 (1H, d, \( J = 8.2 \) Hz, H-5) 6.69 (1H, d, \( J = 8.2 \) Hz, H-5); \(^1\)C NMR (CDCl3, 125 MHz) \( \delta \) 26.2 (C-2′), 29.0 (C-2′), 29.5 (C-4′), 29.5 (C-4′), 33.5 (C-1′), 33.8 (C-3′), 39.4 (C-α), 48.9, (C-1′), 55.9 (OCH3-4′), 56.5 (OCH3-7), 76.7 (C-4′), 109.0 (C-6), 119.5 (C-5), 127.7 (C-8′), 128.5 (C-4′a), 142.1 (C-8), 144.5 (C-7′); LC-MS (APIES negative mode) \( m/z \) 304 [M–1]\(^+\); \( \text{EIMS } m/z(\% ) \) 178 (100), 163 (15); HRRLSIMS \( m/z \) 306.20577 [MH]+ (306.20692 calcd for C18H20NO3).

X-Ray crystal structure determination of 3HCl: colourless prism of 0.30×0.20×0.13 mm\(^3\) size, monoclinic, space group P2\(_1\)/c, a=12.122(4), b=11.460(4), c=13.653(5) Å, \( \beta=104.082(7) \)°, \( V=1839.6(10) \) Å\(^3\), \( Z=4, \rho_{\text{calc}}=1.234 \) g cm\(^{-3}\), \( \delta_{\text{max}}=61.1, \) diffractometer Bruker Smart CCD 1000, Mo K\(_\alpha\) (λ=0.71073 Å), \( \omega\)-scan, \( \theta=293(2) \) K, 36452 reflections collected of which 5615 (\( R_{\text{int}}=0.1002) \) were independent, direct primary solution and refinement on F\(^2\) using SHELX97 program, 21121 refined parameters, rigid hydroxyl and methyl groups hydrogen atoms, others riding, \( R_1(>2\sigma(I))=0.0551, \) w\( F_2 \) (all data)=0.1491, residual electron density 0.189 (–0.244) e Å\(^{-3}\).

3.3.3. trans-1-(4′-Methoxycyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 4. C18H20NO3; IR (film) \( \nu_{\text{max}} \) 3350, 2920, 2850, 1610, 1457, 1115, 1028, 668 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 400 MHz) \( \delta \) 1.11–1.20 (8H, m, CH2-2, 3, 5′, 6′), 1.65 (3H, m, H-1′ and CH2-α), 2.62, 2.75 (2H, 2m, CH2-δ), 2.98, 3.13 (2H, 2m, CH2-β), 3.12 (1H, xx, \( J_{\text{ax-xx}}=11 \) Hz and \( J_{\text{ax-ee}}=4 \) Hz, H-4′) 3.35 (3H, s, OCH3-7), 3.84 (3H, s, OCH3-7), 4.24 (1H, dd, \( J=8.2, 4.8 \) Hz, H-1), 6.57 (1H, d, \( J=8.2 \) Hz, H-5); \(^1\)C NMR (CDCl3, 100 MHz) \( \delta \) 28.8 (C-4′), 29.7 (C-2′), 31.6 (C-6′), 31.8 (C-5′), 32.5 (C-3′), 34.0 (C-1′), 37.9 (C-3′), 39.9 (C-α), 48.5 (C-1′), 55.6 (OCH3-4′), 56.1 (OCH3-7), 79.8 (C-4′), 108.6 (C-6), 119.7 (C-5), 127.1, 128.0 (C-4a and C-8a), 141.6 (C-8), 144.1 (C-7′); LC-MS (APIES negative mode) \( m/z \) 304 [M–1]\(^+\); \( \text{EIMS } m/z(\% ) \) 178 (100), 163 (10); HRRLSIMS \( m/z \) 306.21350 [MH]+ (306.20692 calcd for C18H20NO3).

3.3.4. 1-(Cyclohexylmethyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 5. C18H20NO3; IR (film) \( \nu_{\text{max}} \) 3345, 2922, 2849, 1585, 1446, 1108, 790 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 400 MHz) \( \delta \) 1.20–1.71 (10H, 2m, CH2-2′ to 6′), 1.55 (2H, m, CH2-α′), 1.95 (H-1′), 2.65 (2H, m, CH2-δ), 2.95, 3.10 (2H, 2m, CH2-β), 3.86 (3H, s, OCH3-7), 3.95 (1H, m, H-1), 6.54 (1H, s, H-8), 6.60 (1H, s, H-5); \(^1\)C NMR (CDCl3, 100 MHz) \( \delta \) 26.2 (C-4′), 26.4 (C-2′), 26.4 (C-5′), 26.7 (C-3′), 29.2 (C-1′), 32.3 (C-6′), 34.3 (C-1′), 34.8 (C-2′), 40.6 (C-3′), 44.9 (C-α), 52.4 (C-1′), 56.0 (OCH3-7), 108.5 (C-8), 114.7 (C-5), 127.8, 131.7 (C-4a and C-8a), 143.7 (C-6), 144.9 (C-7′); HRREIMS \( m/z \) 276.19740 [MH]+ (276.19655 calcd for C18H20NO3).
3.3.5. *cis* (Compound 6) and *trans* (compound 7)-1-(4'-methoxyethyl)methyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline. C$_{19}$H$_{29}$NO$_3$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.01–1.70, and 1.95 (m, CH$_2$-2, 3, 5, 6), 1.60, (m, CH$_2$-6), 2.61–3.30 (m, CH$_2$-4 and CH$_2$-3), 3.15 (1H, m, H-ax of 4), 3.33 (3H, s, OCH$_3$-4 of 6), 3.34 (3H, s, OCH$_3$-4 of 7), 3.45 (1H, m, Heq-4 of 6), 3.83 (s, OCH$_3$-7), 4.30 (m, H-1), 6.52 (1H, s, H-8 of 6), 6.58 (1H, s, H-5 of 6), 6.68 (1H, s, H-8 of 7), 6.71 (1H, s, H-5 of 7); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 26.2, 29.0, 29.3, 29.4 (CH$_2$-2, 3, 5, 6) 29.5 (C-4), 33.5 (C-1), 38.4 (C-3), 44.3 (C-α of 6), 44.5 (C-α of 7), 52.7 (C-1), 56.9 (OCH$_3$-4 of 6), 56.1 (OCH$_3$-4 of 7), 56.4 (OCH$_3$-7 of 6), 56.5 (OCH$_3$-7 of 7), 76.0 (C-4' of 6), 80.2 (C-4' of 7), 108.9 (C-8 of 6), 109.1 (C-8 of 7), 115.2 (C-5), 128.0, 131.7 (C-4a and C-8a of 6), 128.3, 131.8 (C-4a and C-8a of 7), 142.1 (C-6), 144.2 (C-7 of 6), 145.5 (C-7 of 7); EIMS m/z (%) 178 (95); LSIMS m/z 306 [MH]$^+$.

3.4. Preparation of *N*-methyl derivatives

3.4.1. *N*-Methyl-1-(cyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 2a. A solution of 2 (10 mg, 0.036 mmol) in MeOH (2 mL) was refluxed with HCHO 35 % (2 mL) and some drops of HCOOH for 1 h; after this, sodium borohydride (2 mg, 0.05 mmol) was added in small portions and the solution was refluxed for an additional 45 min. After the solvent was removed under reduced pressure, the crude of reaction was dissolved in CH$_2$Cl$_2$, and washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified by preparative TLC using CH$_2$Cl$_2$/AcOH/DEA 38:60:2 to give 2a (8 mg, 77%).

4. Preparation of analogues

4.1. *N*-Methyl-1-(cyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 3a. Using similar conditions as for 2a, compound 3 (10 mg, 0.032 mmol) was converted into 3a (7.5 mg, 73%).

4.2. *N*-Methyl-1-(4'-methoxyethyl)methyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 3a. Using similar conditions as for 2a, compound 3 (10 mg, 0.032 mmol) was converted into 3a (7.5 mg, 73%).

Acknowledgements

This research has been supported by the Spanish ‘Proyectos I+D Generalitat Valenciana’ (grant GV01-282), and ‘Dirección General de Investigación del Ministerio de Ciencia y Tecnología’ (grant SAF 2001-3142). We wish to thank of the Fundacion Ana y José Royo’ for the award of a postdoctoral fellowship ‘Primo Yuferra’ to N. Cabedo.

References


