Absolute and Atropisomeric Structure of ES-242s, N-Methyl-D-aspartate Receptor Antagonists

Sir:

ES-242s were isolated from the culture broth of Verticillium sp. in 1992 as N-methyl-D-aspartate (NMDA) antagonists. Structurally, ES-242s belong to bioxanthracene groups corresponding to a dimer of naphthopyran1).

Recently, we have synthesized natural ES-242-4 (1a) and its atropisomer 1b), which are chromatographically less-polar and polar, respectively, from the a,β-unsaturated lactone 3 through dimerization of a monomeric naphthopyran 4 and deprotection of 5a and 5b, respectively, as shown in Fig. 1 and Scheme 1.

Similarly, their trans analogs 2a and its atropisomer 2b have been synthesized from 8a and 8b, respectively, which were prepared from 6 through 73).

However, their absolute structures including atropisomerism remained undetermined.

Herein, we describe the determination of their absolute configurations mainly on the basis of X-ray crystallographic analysis and chemical derivation to more understand the structure-activity relationships.

First of all, many kinds of derivatives were synthesized from previously reported atropisomeric intermediates 5a, 5b, 8a and 8b2,3) (Scheme 2). For examples, 8a was O-benzylated with NaH and BnBr in DMF at 20°C for 1 hour, followed by treatment with AcCl in MeOH-dioxane at 20°C for 1.5 hours to give 9a [FAB-MS m/z 758 (M+)] (Table 1). Similarly, 9b, 12a and 12b were obtained from 8b, 5a and 5b, respectively, which were prepared from 6 through 73).

However, their absolute structures including atropisomerism remained undetermined.

Herein, we describe the determination of their absolute configurations mainly on the basis of X-ray crystallographic analysis and chemical derivation to more understand the structure-activity relationships.

Fig. 1

1a (ES-242-4): R1 = OH, R2 = H
2b: R1 = H, R2 = OH
1b: R1 = OH, R2 = H
2a: R1 = H, R2 = OH

A pale yellow crystal of 9a having approximate dimensions of 0.40 × 0.30 × 0.35 mm was chosen for the analysis. The crystal data are as follows: Orthorhombic, P212121, a = 11.475(2), b = 42.315(4), c = 8.648(2) Å, V = 4199(1) Å³, Z = 4. The structure was solved by direct methods (SIR92). The final cycle of full-matrix least-squares refinement was based on 2825 observed reflections (I > 1.5 σ [I]) and 440 variable parameters and converged with the agreement factor of R = 0.080.

Consequently, 9a was confirmed to exist only as one atropisomer of (aS)-configuration as shown in Fig. 2, although the flipping of its pyran ring and O-benzyl groups was observed in the crystal structure. The dihedral angle between two naphthalene planes is 82.3°.

The absolute structure including the atropisomerism of 9a was determined as depicted in Scheme 2 and, consequently, the atropisomer was as 9b.

Both compounds 9a and 9b were oxidized under Swern’s conditions to give the diketones 10 and 11, respectively, which were also obtained from oxidation of 12b and 12a, respectively. Both products 10 and 11 showed m/z 755 ([M+H]+) in their FAB-MS. These results indicated that 9a and 12b have the same (aS)-configurational atropisomerism, and their diastereomers 9b and 12a have the (aR)-configurational one (Scheme 2).

Hydrogenolysis of 9a, 9b, 12a and 12b afforded quantitatively the corresponding 2a, 2b, 1a (ES-242-4) and 1b, respectively. Therefore, these structural features were defined unambiguously as shown in Fig 1.

Two hydroxy groups at C-4 and C-4′ in 1a and 2a are observed to be far apart, while two hydroxy groups in 1b and 2b are close together. The shorter distance between these two hydroxy groups may be responsible for the stronger inhibitory activities against [3H]MK-801 binding to the NMDA receptor (Table 2)3). Namely, 1b and 2b showed stronger activities than 1a and 2a, suggesting that the appearance of their activities may be attributed to the intramolecular metal chelation formation between their two hydroxy groups3).

Furthermore, the information gained by transforming 12a into the 4-deoxy derivative (ES-242-5)1) of 1a was adequate to permit definition of other ES-242s in absolute stereochemical terms as well5).
Scheme 1

\[ R^2 \text{O} \] + \[ \text{MeCO}_2\text{Me} \] → \[ \text{MeO}_2\text{OH} \]

3: \( R^1 = \text{OMOM}, R^2 = \text{H} \)
6: \( R^1 = \text{H}, R^2 = \text{OMOM} \)

4: \( R^1 = \text{OMOM}, R^2 = \text{H} \)
7: \( R^1 = \text{H}, R^2 = \text{OMOM} \)

1a, 1b, 2a or 2b

5a, b: \( R^1 = \text{OMOM}, R^2 = \text{H} \)
8a, b: \( R^1 = \text{H}, R^2 = \text{OMOM} \)

Scheme 2

8a → 9a
9a → 10
10 → 12b
12b → 1b

8b → 9b
9b → 11
11 → 12a
12a → 1a

a) 1) BnBr, NaH/DMF, rt, 1 hour. 2) AcCl/MeOH, rt, 1.5 hours.
b) \((\text{COCl})_2, \text{DMSO}, \text{Et}_3\text{N/CH}_2\text{Cl}_2, -78^\circ \text{C} - \text{rt}, 30 \text{ minutes}\)
c) \( \text{H}_2, \text{Pd-C/EtOH-THF, rt} \).
### Table 1. Physico-chemical properties of compounds.

<table>
<thead>
<tr>
<th>No.</th>
<th>Rf</th>
<th>Solvents</th>
<th>MP (°C)</th>
<th>δ, XHNMR (270, 300 or 500 MHz; CDCl₃; δ ppm; J Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.55</td>
<td>(A)</td>
<td>185-186</td>
<td>+58°</td>
</tr>
<tr>
<td>1b</td>
<td>0.29</td>
<td>(A)</td>
<td>280-281</td>
<td>+86°</td>
</tr>
<tr>
<td>2a</td>
<td>0.48</td>
<td>(A)</td>
<td>268-269</td>
<td>+129°</td>
</tr>
<tr>
<td>2b</td>
<td>0.16</td>
<td>(A)</td>
<td>208-209</td>
<td>+171°</td>
</tr>
<tr>
<td>5a</td>
<td>0.33</td>
<td>(B)</td>
<td>105-106</td>
<td>-38°</td>
</tr>
<tr>
<td>5b</td>
<td>0.24</td>
<td>(B)</td>
<td>115-116</td>
<td>-64°</td>
</tr>
<tr>
<td>8a</td>
<td>0.32</td>
<td>(B)</td>
<td>202-303</td>
<td>-46°</td>
</tr>
<tr>
<td>8b</td>
<td>0.18</td>
<td>(B)</td>
<td>115-116</td>
<td>+26°</td>
</tr>
<tr>
<td>9a</td>
<td>0.48</td>
<td>(C)</td>
<td>160-161</td>
<td>+81°</td>
</tr>
<tr>
<td>9b</td>
<td>0.17</td>
<td>(C)</td>
<td>120-121</td>
<td>+146°</td>
</tr>
<tr>
<td>10</td>
<td>0.48</td>
<td>(D)</td>
<td>Syrup</td>
<td>+60°</td>
</tr>
<tr>
<td>11</td>
<td>0.56</td>
<td>(D)</td>
<td>Syrup</td>
<td>+2.4°</td>
</tr>
<tr>
<td>12a</td>
<td>0.57</td>
<td>(C)</td>
<td>129-130</td>
<td>-49°</td>
</tr>
<tr>
<td>12b</td>
<td>0.31</td>
<td>(C)</td>
<td>158-159</td>
<td>-132°</td>
</tr>
</tbody>
</table>

* Solvents: (A) PhH: MeCN = 2:1 (B) PhMe: MeCN = 3:1 (C) PhH: MeCN = 4:1 (D) PhH: MeCN = 10:1.

These ¹H NMR spectra have been already reported in our previous papers²,³).

δ 1.13 (3H, d, J = 6), 3.05 (3H, s), 3.12 (1H, d, J = 7), 3.39 (3H, s), 3.49 (1H, d, J = 7), 3.75 (1H, dq, J = 6 and 16), 3.82 (1H, q, J = 16), 4.05 (3H, s), 4.89 (1H, d, J = 16), 5.27 (1H, d, J = 16), 6.01 (1H, d, J = 2), 6.43 (1H, d, J = 2), 9.51 (1H, s).

δ 1.25 (3H, d, J = 6), 3.21 (3H, s), 3.22 (1H, d, J = 7), 3.46 (3H, s), 3.63 (1H, dq, J = 6 and 16), 3.89 (1H, d, J = 16), 4.07 (3H, s), 4.28 (1H, d, J = 16), 4.90 (1H, d, J = 16), 5.25 (1H, d, J = 16), 6.01 (1H, d, J = 2), 6.45 (1H, d, J = 2), 9.53 (1H, s).

δ 1.26 (3H, d, J = 6), 3.06 (1H, d, J = 7), 3.12 (3H, s), 3.42 (3H, s), 3.55 (1H, d, J = 7), 3.67 (1H, d, J = 3), 4.05 (3H, s), 4.26 (1H, dq, J = 6 and 3), 4.86 (1H, d, J = 16), 5.09 (1H, d, J = 16), 6.01 (1H, d, J = 2), 6.42 (1H, d, J = 2), 9.50 (1H, s).

δ 1.13 (3H, d, J = 6), 3.23 (3H, s), 3.47 (3H, s), 3.47 (1H, d, J = 7), 3.72 (1H, d, J = 7), 4.07 (3H, s), 4.18 (1H, dq, J = 6 and 2), 4.31 (1H, q, J = 7), 4.89 (1H, d, J = 16), 5.08 (1H, d, J = 16), 6.03 (1H, d, J = 2), 6.45 (1H, d, J = 2), 9.53 (1H, s).

δ 1.15 (3H, d, J = 6), 1.69 (1H, d, J = 3), 3.44 (3H, s), 3.91 (3H, s), 3.97 (2H, m), 4.90 (1H, d, J = 16), 5.02 (1H, d, J = 10), 5.03 (1H, d, J = 16), 5.13 (1H, d, J = 10), 6.01 (1H, d, J = 3), 6.54 (1H, d, J = 3), 7.32 – 7.50 (5H, m).

δ 1.05 (3H, d, J = 7), 3.41 (3H, s), 3.91 (3H, s), 3.97 (1H, d, J = 3), 4.09 (1H, dq, J = 7 and 3), 5.02 (1H, d, J = 10.5), 5.05 (2H, s), 5.17 (1H, d, J = 10.5), 5.90 (1H, d, J = 3), 6.52 (1H, d, J = 3), 7.34 – 7.60 (5H, m).

δ 1.28 (3H, d, J = 7), 3.37 (3H, s), 3.91 (3H, s), 4.04 (1H, q, J = 7), 4.82 (1H, d, J = 15), 5.09 (1H, d, J = 11), 5.18 (1H, d, J = 11), 5.25 (1H, d, J = 15), 5.94 (1H, d, J = 2), 6.59 (1H, d, J = 2), 7.35 – 7.55 (5H, m).

δ 1.23 (3H, d, J = 7), 3.40 (3H, s), 3.90 (3H, s), 4.10 (1H, q, J = 7), 4.76 (1H, d, J = 15), 4.98 (1H, d, J = 11), 5.21 (1H, d, J = 11), 5.44 (1H, d, J = 15), 5.98 (1H, d, J = 2), 6.58 (1H, d, J = 2), 7.35 – 7.55 (5H, m).

δ 1.28 (3H, d, J = 6), 1.54 (1H, d, J = 5), 3.42 (3H, s), 3.63 (1H, dq, J = 6 and 2), 3.84 (1H, dd, J = 5 and 2), 3.89 (3H, s), 4.78 (1H, d, J = 17), 5.01 (1H, d, J = 11), 5.14 (1H, d, J = 11), 5.38 (1H, d, J = 17), 5.97 (1H, d, J = 2), 6.52 (1H, d, J = 2), 7.33 – 7.52 (5H, m).

δ 1.23 (3H, d, J = 6), 3.41 (3H, s), 3.60 (1H, q, J = 6 and 0), 3.90 (3H, s), 3.94 (1H, s, J = 0), 4.96 (1H, d, J = 16), 5.03 (1H, d, J = 12), 5.16 (1H, d, J = 12), 5.30 (1H, d, J = 16), 5.84 (1H, d, J = 3), 6.52 (1H, d, J = 3), 7.34 – 7.56 (5H, m).

Solvents: (A) PhH: MeCN = 2:1 (B) PhMe: MeCN = 3:1 (C) PhH: MeCN = 4:1 (D) PhH: MeCN = 10:1.

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1. The Journal of Antibiotics Vol. 52 No. 4, pp. 425-435
2. Previous papers in our research series
3. These NMR spectra have been already reported.
Fig. 2. ORTEP drawing of compound 9a.

Table 2. Inhibitory activities in the binding of [3H]MK-801 [IC50 (μM)].

<table>
<thead>
<tr>
<th>Compounds</th>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>40</td>
<td>14</td>
<td>&gt;200</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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References


