Synthesis of Peptide Alkaloid, Amphibine-I and Related Compounds

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Synthesis of amphibine-I (IA-a) and its diastereoisomeric compounds (IA-b), (IB-a), and (IB-b) was completed by condensation of four diastereoisomeric l-(A-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (V_A-a,b and V_B-a,b) with benzyloxycarbonyl-L-valylglycine followed by removal of the protecting group.

Amphibine-I (IA-a) is one of the peptide alkaloids isolated from Zizyphus amphibia A. Cheval (Rhamnaceae) and its structure elucidation and synthesis were accomplished by Tschesche and his co-laborators1, 2, suggesting that the naturally occurring alkaloid is a mixture of the diastereoisomers having (S,R) and (R,S) configuration at C-1 and C-9, respectively.

We report here the synthesis of amphibine-I and its dia-
stereoisomers in optically active form using four diastereoisomeric 1-(a-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (VA-a,b and VB-a,b).

Condensation of the aldehyde (II) (racemic) with dopamine hydrochloride in methanol under argon for 7 days gave a mixture of the diastereoisomeric tetrahydroisoquinolines (III A and III B) revealed by thin layer chromatography in 37% yield. The mixture was, without further purification, subjected to the methylation with diazomethane followed by Eschweiler-Clarke condition to give a mixture of the non-phenolic isoquinolines. Separation of the mixture was carried out at this stage by preparative thin layer chromatography, furnishing a pair of diastereoisomers (IVA) and (IVB). The faster running one (IVA), m.p. 126-127°, showed the following spectroscopic properties: IR (CHCl₃), 1760 and 1700cm⁻¹ (CO); NMR (CDCl₃), δ, 1.47 (3H, d, J=7Hz, CH-CH₃), 2.52 (3H, s, N-CH₃), 3.11 and 3.82 (3H each, s, OCH₃), 6.24 and 6.61 (1H each, s, aromatic H), and 7.77 (4H, m, protons of the phthaloyl moiety). The slower running one (IVB), m.p. 163-165°, showed the same carbonyl bands in its IR spectrum and NMR spectrum (δ) revealed 1.52 (3H, d, J=7Hz, CH-CH₃), 2.27 (3H, s, N-CH₃), 3.90 and 3.92 (3H each, s, OCH₃), 6.67 and 6.81 (1H each, s, aromatic H), and 7.83 (4H, m, protons of the phthaloyl moiety).

Removal of the phthaloyl moiety from (IVA) and (IVB) with hydrazine hydrate in the usual manner gave the corresponding amino-isoquinolines (VA) and (VB) in 85% yield, respectively.

The amino-isoquinolines (VA) and (VB) were resolved.
into four diastereoisomeric amino-isoquinolines \( \text{V}_{A-a}, \text{V}_{A-b}, \text{V}_{B-a}, \text{and V}_{B-b} \) using di-(p-toluoyl)-l- and d-tartaric acids in acetonitrile and l- and d-tartaric acids in methanol, respectively. \([\alpha]_D\) values of four diastereoisomeric amino-isoquinolines obtained by the above resolution were listed in Table II and CD curves of the corresponding benzoates \( \text{VI}_{A-a,b} \text{and VI}_{B-a,b} \) were depicted in Fig. I. Based on the sign of the Cotton effect around 285 nm, it was, at least, indicated that \( \text{VI}_{A-a} \) and \( \text{VI}_{B-a} \) have the S-configuration and \( \text{VI}_{A-b} \) and \( \text{VI}_{B-b} \) have the R-configuration at C-1 position\(^4\). The R-configuration at C-9 of \( \text{V}_{A-a} \) was proposed from the fact that NMR spectrum of amphibine-I synthesised from \( \text{V}_{A-a} \) was identical in the NMR spectrum with that of naturally occurring amphibine-I which had been confirmed to have the S- and R-configuration at C-1 and C-9, respectively, though it was reported that amphibine-I is contaminated with a small amount of the compound enantiomeric at both of the carbons. And configurations at C-9 position of the other diastereoisomers were culminated as indicated in the Chart.

Coupling reaction of each of the amino-isoquinolines \( \text{V}_{A-a,b} \text{and V}_{B-a,b} \) and benzylxycarbonyl-valylglycine\(^5\) with DCC in the presence of N-hydroxybenztriazone \(^6\) gave the diastereoisomeric isoquinolines \( \text{VII}_{A-a}, \text{VII}_{A-b}, \text{VII}_{B-a}, \text{and VII}_{B-b} \), which were hydrogenated with palladium as a catalyst in methanol to give the respective four diastereoisomers \( \text{I}_{A-a}, \text{I}_{A-b}, \text{I}_{B-a}, \text{and I}_{B-b} \). CD curves of these compounds were shown in Fig. II. Of
A: C1 = S, R, Cg = R, S
B: C1 = S, R, Cg = S, R
A-a: C1 = S, Cg = R
A-b: C1 = R, Cg = S
B-a: C1 = S, Cg = S
B-b: C1 = R, Cg = R

(I) R1=R2 = Me
R3 = CO-CH2-NH-CO-CH-NH2 ( = H-Val-Gly ), H
CH-Me2

(III) R1=R2 = H, R3 = phthaloyl
(IV) R1=R2 = Me, R3 = phthaloyl
(V) R1=R2 = Me, R3 = H2
(VI) R1=R2 = Me, R3 = CO-ph, H
(VII) R1=R2 = Me
R3 = ph-CH2-O-CO-NH-CH-CO-NH-CH2-CO, H
CH-Me2

Table I

<table>
<thead>
<tr>
<th>Amphibine-I ( I^1 )</th>
<th>naturally occurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>([ \alpha ] D)</td>
<td>(I)</td>
</tr>
<tr>
<td>- 20.6°</td>
<td>+ 17°</td>
</tr>
</tbody>
</table>

( benzene )
Table II

<table>
<thead>
<tr>
<th></th>
<th>[α] D free base</th>
<th>[α] D salt</th>
<th>[α] D benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-a</td>
<td>+ 21°</td>
<td>+ 106° (methanol)</td>
<td>VI A-a - 78°</td>
</tr>
<tr>
<td>VA-b</td>
<td>- 19.8°</td>
<td>- 100° (methanol)</td>
<td>VI A-b + 70°</td>
</tr>
<tr>
<td>VB-a</td>
<td>+ 10°</td>
<td>- 24° (water)</td>
<td>VI B-a - 8.5°</td>
</tr>
<tr>
<td>VB-b</td>
<td>- 10° (pyridine)</td>
<td>+ 24° (water)</td>
<td>VI B-b + 9.0°</td>
</tr>
</tbody>
</table>

Fig. I

Fig. II
these compounds, \((I_{A-a})\) was identical with amphibine-I in spectroscopic comparison and TLC behaviour, though certain discrepancy of \([\alpha]_D\) values between our compound and that of literature is noted (see Table I).

REFERENCES


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