

Absolute Configuration of Sanjoinine-A (Frangufoline) and Its Heat Induced Artifact; Sanjoinine-Ah₁(2)

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Abstract □ Frangufoline (sanjoinine-A)¹⁾ (**1**) was transformed into its epimer, sanjoinine-Ah₁(**2**), on heat treatment. Absolute configuration of (**1**) and (**2**) was determined.

“Sanjoin”, the seeds of *Zizyphus jujuba* Miller (Rhamnaceae), has been used as an important sedative herbal medicine in the Orient. We isolated sanjoinine-A, one of the active sedative principles from sanjoin. However, the compound was identified as frangufoline, a known 14-membered cyclopeptide alkaloid. Referring to the folkloric heat treatment of sanjoin²⁾, heat treatment of (**1**) was carried out to afford an epimeric artifact named sanjoinine-Ah₁ (**2**) which showed enhanced sedative activity. Although (**1**) is a known compound, its absolute stereochemistry was not firmly established yet. This letter is concerned with the absolute configurations of (**1**) and its heat induced artifact (**2**).

When (**1**) was heated at 220 °C for 15 min, an artifact (**2**) was produced³⁾. The same treatment of (**2**) afforded to (**1**), suggesting reversible isomerization of (**1**) and (**2**) at high temperature. Mass spectra of (**1**) and (**2**) were super-imposable and ¹H- and ¹³C-NMR spectral patterns were also similar except minor differences in chemical shifts, but their physical properties were quite different (mp 247-249 °C for (**1**), 218-220 °C for (**2**), [α]_D²² = -183° for (**1**), -203° for (**2**), c = 0.13 in MeOH).

Structural relationship of (**1**) and (**2**) was studied by deuterium exchange method. Deuterium labeled (**2**)-*d* was prepared by heating (**1**) in CD₃OD 1 D₂O⁴⁾. In a mass spectrum of (**2**)-*d*, the molecular ion peak appeared at *m/z* 535, shifted one mass unit upward, and a⁺ and b⁺ fragments in Fig. 1 were also shifted one mass unit upward, suggesting α-proton of the N,N-dimethylphenyl-alanine (DMPhe) moiety was exchanged with deuterium by a mechanism including carbanion intermediate⁵⁾. In the ¹H-NMR spectrum of (**2**)-*d* it was clearly recognized that the peak due to α-proton of

DMPhe disappeared and the peaks due to two β-protons of DMPhe appeared as a AB quartet instead of a multiplet. The results are consistent with those of mass spectral analysis and suggest that (**2**) is produced through the inversion of the chiral center in DMPhe of (**1**).

Configurations of DMPhe and leucine moieties in (**1**) and (**2**) were determined by gas chromatographic analyses of diastereomeric derivatives of individual amino acid units in the hydrolysates. Configurations of DMPhe and leucine moieties in (**1**) were proven to be (S)-L-forms, and those in (**2**) were proven to be (R)-D-form for DMPhe and (S)-L-form for leucine. This method was not applicable for the analysis of β-oxyleucine, since it was decomposed and/or racemized during acid hydrolysis procedure.

NMR techniques were employed for the elucidation

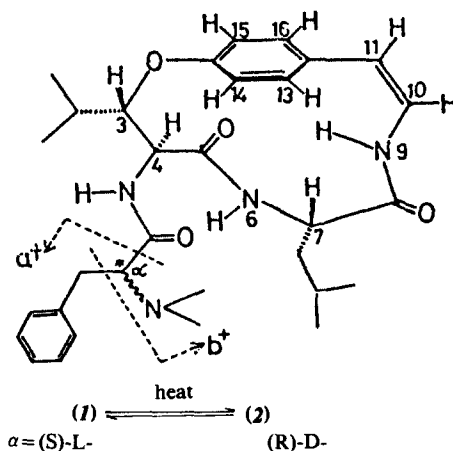


Fig. 1. Structure of (**1**) and (**2**)

tion of the configuration of β -oxyleucine moiety. Coupling constant of 7.6Hz between C_6 -H and C_7 -H in (*I*) suggested dihedral angle (θ) of ca. 20° or 150°. Small NOE (3.7%) preferred 150° of dihedral angle. Large NOE (14.4%) between N_6 -H and C_4 -H suggested that these protons are spatially close. The coupling between C_3 -H and C_4 -H with coupling constant of 7.2Hz suggests the dihedral angle of ca. 20° or 150°. Small NOE (2.7-2.9%) for these protons is more agreeable with the dihedral angle of 150°. On irradiation of N-H of β -oxyleucine, 9.9% NOE was observed at C_7 -H of β -oxyleucine unit, suggesting these protons are spatially close. In the molecular model study, considering L-configuration for leucine moiety (C_7), only L-erythro configuration for β -oxyleucine unit (i.e. 3S,4S) can satisfy these conditions because of rigid character of 14-membered ring.

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LITERATURE CITED AND NOTES

1. Tschesche, R. and Last, H.: *Tetrahedron Lett.* **25**, 2993 (1968).
2. Oriental medicinal literatures describe that roasting of sanjoin potentiates its sedative activity.
3. Heated in sanjoin oil (sanjoin contains much oil), Rf of (1) = 0.5, (2) = 0.4, $CHCl_3$: MeOH = 20:1
4. An artifact produced by heating (*I*) in CD_3OD/D_2O was identical on TLC with the compound obtained by heating (*I*) in sanjoin oil.
5. Vitt, S.V., Saporovskaya, M.B., Gudkova I.P. and Belikov, V.M.: *Tetrahedron Lett.* 2575 (1965).