Tetrahedron Letters, Vol. 33, No. 45, pp. 6831-6834, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Geissoschizine Revisited - Definite Proof of Its Stereostructure.

Hiromitsu Takayama,[a] Toshiyuki Watanabe,[a] Hiroko Seki,[b] Norio Aimi,[a] and Shin-ichiro Sakai,[a]*

Faculty of Pharmaceutical Sciences[a] and Chemical Analysis Center,[b] Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba, 263 Japan

Abstract: By re-assignment and detailed analysis of the NMR spectra of geissoschizine (**1**) and its derivatives, the hitherto accepted conformer **1a** was revised to another possibility **1c** that favored the *trans*-quinolizidine form and the *D*-ring adopting twist boat form, in which the intramolecular hydrogen bonding between the enol hydroxyl and N_b function was present.

Geissoschizine, first obtained as an acidic hydrolysis product of a dimeric indole alkaloid geissospermine[1] and subsequently isolated from the *Apocynaceae* plants,[2] plays an important role as a pivotal early biogenetic intermediate[3] of many skeletal type of indole alkaloids, such as *Corynanthe-Yohimbine, Strychnos, Aspidosperma, Iboga, Sarpagine*, and *Picraline* groups, etc. By the spectroscopic analysis[4] as well as the synthetic studies[5] on this biogenetically important alkaloid, the structure was elucidated to be the formula **1** and the stereostructure has been accepted as **1a** that possessed a *cis C/D* ring junction (*cis*-quinolizidine form) and a boat formed *D*-ring. However, our recent spectroscopic re-examination of geissoschizine and its derivatives led to a new conclusion on the stereostructure of **1**, which we would like to propose in this communication.

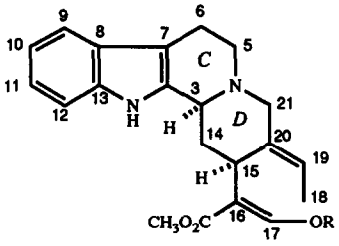
In 1969 during the synthetic study on corynantheine, van Tamelen *et al* supposed that the *D*-ring of geissoschizine (**1**) existed in a boat or twist form and the presence of the hydrogen bonding or twitterionic species between the enol hydroxyl and tertiary amine.[6] Later, Winterfeldt *et al.* proposed a *cis*-quinolizidine conformation **1a**[4c] on the basis of the absence of Bohlmann bands in the IR spectrum and appearance of a low field signal at δ 4.51 as assigned to be the C3-H in the ^{1}H NMR spectrum. Generally, in the *cis*-quinolizidine type indole alkaloids, C3-H, which lies on the syn position to the N_b electron pair, appears at lower than δ 4.0 in the ^{1}H NMR spectra. Furthermore, they claimed that *D*-ring adopted a boat conformation which relieved the nonbonded interactions that would exist between the equatorial C15 side chain and the methyl group in the (19*E*) ethylidene group (an $A^{1,3}$ strain) if geissoschizine existed in a *D*-ring chair form. The conformation **1a** proposed above was supported by Zenk group by using high field (270 MHz) ^{1}H NMR analysis.[4f] They explained that, for example, the coupling constant (*J* 12 Hz) between the C3-Hα and C14-Hβ agreed with the dihedral angle of these protons in the conformer **1a**. Potier *et al.* independently proposed another conformation **1b**[4d] from the ^{13}C-NMR analysis. In this conformer, C15-H approaches to the N_b electron pair so that the chemical shift at C15 moves to upfield (Δ 8.7 ppm) compared with that of **2**. Goutarel and Wenkert group explained the ^{13}C NMR spectrum of **1** by using the conformer **1a**.[4e] Thus, the chemical shift at C3 (δ 53.5) reflected the *cis*-quinolizidine type, on the other hand, that of C6 (δ 20.4) and C21 (δ 59.1), which showed the typical values of

trans-quinolizidine type,[7] could be interpreted by the conformational change of the *D*-ring into the boat form **1a**. The X-Ray data of a dimeric indole alkaloid geissospermine,[8] which contained a geissoschizine unit in the molecule, was also ground for believing that **1** existed in the *cis*-quinolizidine form.

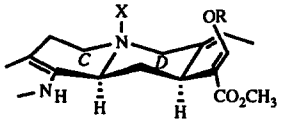
On the other hand, we have isolated geissoschizine methyl ether (**2**) from *Uncaria rhynchophylla* Miq.,[9] one of the original plant of the important Chinese crude drug, Gou teng, and determined the structure by spectroscopic analysis and by chemical studies including the correlation with geissoschizine.[10] The spectroscopic data of **2** (see Table)[11], [4d] demonstrated that **2** took a normal *trans*-quinolizidine form as depicted in the figure. The wonder was that a structural minor difference in the side chain between geissoschizine (**1**) and the methyl ether derivative (**2**) caused a significant conformational change. Then, we made a start on the re-assignment of the protons and carbons in **1** by applying 2D NMR (500 MHz, $CDCl_3$) techniques, *viz*, HH-COSY, CH-COSY, COLOC, and NOESY spectra. As a result, a signal at δ 4.51 (dd, *J* 11.3 and 1.5 Hz), which was previously assigned as C3-H, proved to be C15-H by the observation of the two or three bond heteronuclear connectivities between that proton and ester carbonyl, C16, C17, C20, and C21 in the COLOC spectrum.[12] In place of that proton, a signal at δ 3.85 (dd, *J* 11.6 and 6.2 Hz) was assigned as C3-H, whose δ value was reasonable for the *trans*-quinolizidine type compound. The dihedral angles calculated by the observed coupling constants ($J_{3H\text{-}14H\alpha}$ 6.2 Hz, $J_{3H\text{-}14H\beta}$ 11.6 Hz, $J_{15H\text{-}14H\beta}$ 1.5 Hz, $J_{15H\text{-}14H\alpha}$ 11.3 Hz) as well as the NOEs {21-Hα to 19-H (10.9%), 15H to $18H_3$ (11.5%), 21-Hα to 5-Hα (4.0%), 21-Hα to 3-H (5.0%), and 14Hα to N_a-H (4.2%)} implies that *D* ring adopts a twist boat form **1c**. Furthermore, the absence of Bohlmann band and a relatively stronger contribution from the enolate anion form in the UV spectrum (270 nm) in neutral solution suggest the presence of intramolecular hydrogen bonding of the acidic enol hydroxyl to the basic tertiary nitrogen as supposed by van Tamelen.[6] The extraordinary low field shift of the C15-H (δ 4.51) can be explained by not only in terms of diallylic position but also the anisotropy effect from sp^2 plane of the ester carbonyl function. Thus, the free rotation of the C15-16 single bond is fixed by the hydrogen bonding so that the C15-H lies on the conjugated acrylate plane and closes to the carbonyl oxygen atom. Also by this hydrogen bonding the large side chain on C15 stands up from the *D* ring and the steric interaction between the β-hydroxyacrylate residue and the 18 methyl group might be relieved. In the ^{13}C NMR spectra (Table), the signals due to C3 and C21 of **1** were observed upfield 5.3 and 5.5 ppm, respectively, higher than the corresponding signals of **2**. This phenomena can be interpreted by the elimination of the 1,3-diaxial hydrogen alignment[13] in **2** owing to the conformational change in the *D* ring. The large upfield shift (Δ 8.7 ppm) at C15 from **2** to **1** can be explained by the reason as discussed above and additionally the strong γ-steric interaction between C15-H and C18, as showing by the differential NOE data (11.5%) between C15-H and $C18\text{-}H_3$. The N_b-methyl derivative **3**[14] prepared in 81% yield by treatment of **1** with ethereal CH_2N_2 have the *trans*-quinolizidine type structure.[15] That was confirmed by the NOE between the N_b-methyl group and C14-Hβ and by the comparison the chemical shift at C15 (δ 33.0) and coupling patterns of the protons in **2** and **3**. Since it is not possible to build up the intramolecular hydrogen bonding between the N_b electron pair and the enol hydroxyl in **3**, its conformation would be resemble to that of geissoschizine methyl ether (**2**).

In conclusion, geissoschizine must take a *trans-quinolizidine* configuration **1c** including the *twist boat D-ring* and the *intramolecular hydrogen bonding*, that is settled to the satisfaction of all the puzzling spectroscopic data of geissoschizine in solution.[16]

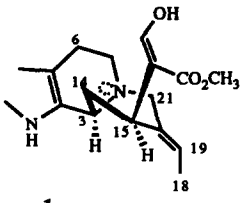
Acknowledgement We thank Professor E. Winterfeldt (Institut für Organische Chemie der Univ. Hannover) for providing the synthetic geissoschizine and for the helpful comments to this manuscript.



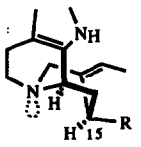
1 R=H Geissoschizine
2 R=Me



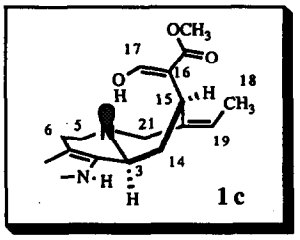
2 X=electron pair, R=Me
3 X=Me, R=electron pair



1a



1b



1c

Table ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data (δ) for **1** and **2** in $CDCl_3$

atom	1		2	
	^{1}H (mult, J(Hz))	^{13}C	^{1}H (mult, J(Hz))	^{13}C
1	7.97 (br s)		7.79 (br s)	
2		132.8		134.8
3	3.85 (dd like, 11.6, 6.2)	53.5	3.52 (dd like, 11.3, 2.0)	58.8
5	α: 2.72 (ddd, 11.7, 11.7, 4.1)	50.5	α: 2.65 (ddd, 11.1, 9.6, 4.6)	51.6
	β: 3.21 (dd, 11.7, 5.4)		β: 3.07 (ddd, 11.1, 5.4, 3.2)	
6	α: 3.07 (dddd, 15.6, 11.7, 5.4, 2.2)	20.4	α: 2.73 (br d like, 15.0)	21.5
	β: 2.82 (dd like, 15.6, 4.1)		β: 2.98 (dddd, 15.0, 9.6, 5.4, 2.0)	
7		107.7		108.3
8		126.5		127.3
9	7.48 (d, 8.0)	118.3	7.46 (dd, 7.8, 1.2)	118.1
10	7.11 (td, 8.0, 1.1)	119.7	7.07 (td, 7.8, 1.2)	119.3
11	7.16 (td, 8.0, 1.1)	122.1	7.11 (td, 7.8, 1.2)	121.2
12	7.31 (d, 8.0)	110.9	7.26 (dd, 7.8, 1.2)	110.7
13		136.5		136.0
14	α: 2.65 (ddd, 13.7, 11.3, 6.2)	33.8	α: 1.89 (ddd, 12.5, 5.0, 2.0)	34.3
	β: 2.10 (ddd, 13.7, 11.6, 1.5)		β: 2.33 (ddd, 12.5, 12.5, 11.3)	
15	4.51 (dd, 11.3, 1.5)	27.7	3.70 (d like, 12.5)	36.4
16		108.2		112.5
17	7.85 (s)	161.2	7.35 (s)	159.6
18	1.82 (dd, 6.9, 1.7)	13.1	1.55 (dt, 7.2, 1.4)	13.1
19	5.41 (br q, 6.9)	121.8	5.42 (br q, 7.2)	120.4
20		133.2		134.0
21	α: 3.18 (d, 13.4)	59.1	α: 3.16 (dd, 12.5, 1.0)	64.6
	β: 3.96 (dt, 13.4, 2.4)		β: 3.44 (d, 12.5)	
CO		170.4		168.7
OCH_3	3.69 (s, 3H)	51.2	3.72 (s, 3H)	51.4
OCH_3			3.82 (s, 3H)	61.7

References and Notes

1. Rapoport, H.; Onak, T. P.; Hughes, H. A.; Reinecke, M. G. *J. Am. Chem. Soc.*, **1958**, *80*, 1601.
2. Chatterjee, A.; Banerji, A.; Majumder, P.; Majumder, R. *Bull. Chem. Soc. Jpn.*, **1976**, *49*, 2000.
3. (a) Scott, A. I. *Acc. Chem. Res.*, **1970**, *3*, 151. (b) Rueffer, M.; Kan-Fan, C.; Husson, H. P.; Stöckigt , J.; Zenk, M. H. *J. Chem. Soc., Chem. Commun.*, **1979**, 1016. (c) Herbert, R. B. in *Indoles. The Monoterpene Indole Alkaloids*, ed. Saxton, J. E. Wiley, New York, **1983**, Chapter 1.
4. (a) Rapoport, H.; Windgassen, Jr. R. J.; Hughes, N. A.; Onak, T. P. *J. Am. Chem. Soc.*, **1960**, *82*, 4404. (b) Janot, M. M. *Tetrahedron*, **1961**, *14*, 114. (c) Rackur, G.; Winterfeldt, E, *Chem. Ber.*, **1976**, *109*, 3837. (d) Damak, M.; Ahond, A.; Potier, P.; Janot, M. M. *Tetrahedron Lett.*, **1976**, 4731. (e) Goutarel, R.; Pais, M.; Gottlieb, H. E.; Wenkert, E. *Tetrahedron Lett.*, **1978**, 1235. (f) Höfle, G.; Heinstein, P.; Stöckigt, J.; Zenk, M. H. *Planta Medica*, **1980**, *40*, 120.
5. (a) Yamada, K.; Aoki, K.; Kato, T.; Uemura, D. *J. Chem. Soc., Chem. Commun.*, **1974**, 908. (b) Hachmeister, B.; Thielke, D.; Winterfeldt, E. *Chem. Ber.*, **1976**, *109*, 3825. (c) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.*, **1980**, *102*, 7971. (d) Banks, B. J.; Calverley, M. J.; Edwards, P. D.; Harley-Mason, J. *Tetrahedron Lett.*, **1981**, *22*, 1631. (e) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.*, **1985**, 1752. (f) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.*, **1988**, *110*, 5925. (g) Overman, L. E.; Robichaud, A. J. *ibid.*, **1989**, *111*, 300.
6. van Tamelen, E. E.; Wright, I. G. *J. Am. Chem. Soc.*, **1969**, *91*, 7349.
7. Wenkert, E.; Chang, C. J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.*, **1976**, *98*, 3645.
8. Chiaroni, A.; Riche, C.; Pais. M.; Goutarel, R. *Tetrahedron Lett.*, **1976**, 4729.
9. Aimi, N.; Yamanaka, E.;Shinma, N.; Fujiu, M.; Kurita, J.; Sakai, S.; Haginiwa, J. *Chem. Pharm. Bull.*, **1977**, *25*, 2067.
10. Geissoschizine obtained by desmethylation of the enol ether in **2** with aq. hydrochloric acid in 1,2-dimethoxyethane was identical with the synthetic sample provided by Prof. E. Winterfeldt.
11. The IR spectrum (2730, 2800 cm^{-1} ;Bohlmann band), the selected chemical shifts in the ^{1}H- and ^{13}C-NMR spectra at C3-Hα (δ 3.52, dd, *J* 11.3 and 2.0 Hz), C3 (δ 58.8), C6 (δ 21.5), and C21 (δ 64.6), as well as the observed NOEs between C3-Hα and C5-Hα, C3-Hα and C21-Hα, C3-Hα and C15-Hα, and C19-H and C21-Hβ elucidate the stereostructure of **2**.
12. Kessler, H.; Griesinger, C.; Zarbock, J.; Looshi, H. R. *J. Magn. Reson.*, **1984**, *57*, 331.
13. Beierbeck, H; Saunders, J. K. *Can. J. Chem.*, **1976**, *54*, 2985.
14. Compound **3**: amorphous powder, mp 224-228°C (decomp), FABMS; m/z 367 {$(M+H)^+$, 100%}, High resolution FABMS; calcd for MH^+, C22H27NO3 367.2022, found 367.2021, ^{1}H NMR (CD3OD) δ; 8.66 (s, 17-H), 5.62 (br q, *J* 7.2 Hz, 19-H), 4.94 (br d, *J* 13.2 Hz, 3-H), 4.12 (br d, *J* 13.2 Hz, 21-Hα), 3.92 (d, *J* 13.2 Hz, 21-Hβ), 4.05 (m, 15-H), 3.54 (3H, s, OCH3), 2.97 (3H, s, *N*-CH3), 2.47 (ddd, *J* 13.2, 13.2, 13.2, 14-Hβ), 2.28 (ddd, *J* 13.2, 5.2, 2.0, 14-Hα), ^{13}C NMR (CD3OD) δ; 126.8 (C2), 66.8 (C3), 61.6 (C5), 17.3 (C6), 104.0 (7), 125.7 (8), 117.8 (C9), 119.4 (C10), 122.2 (C11), 111.2 (C12), 137.1 (C13), 27.1 (C14), 33.0 (C15), 107.5 (C16), 159.1 (C17), 12.0 (C18), 129.0 (C19), 126.4 (C20), 71.2 (C21), 37.1 (N-CH3), 50.1 (OCH3), 169.2 (CO). By the methylation with diazomethane of desmethyldihydrocorynantheine, van Tamelen obtained a similar betaine compound. van Tamelen, E. E.; Hester, Jr. J. B. *J. Am. Chem. Soc.*, **1969**, *91*, 7342.
15. Sawa, Y. K.; Matsumura, H. *Tetrahedron*, **1969**, *25*, 5319 and 5329.
16. In the crystal state *trans*-quinolizidine form is preferred. Chiaroni, A.; Damak, M.; Ahond, A.; Riche, C. *Journees de Chimie Organique*, Orsay, 7-9 September **1977**, Abstract No. 64 cited in ref. 4e.

(Received in Japan 15 July 1992)