Pergamon

Tetrahedron Letters 40 (1999) 2593–2596

TETRAHEDRON
LETTERS

Tangutorine: A Novel β-Carboline Alkaloid from *Nitraria tangutorum*

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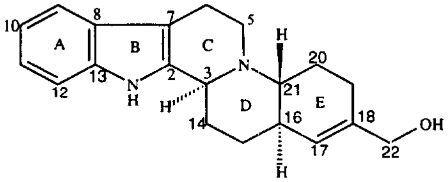
Received 20 November 1998; accepted 9 February 1999

Abstract: Tangutorine (**1**) was isolated from the leaves of *Nitraria tangutorum* and shown to possess a novel β-carboline skeleton. The structure and stereochemistry were determined on the basis of spectral and X-ray crystallographic data.

The genus *Nitraria* (*Zygophyllaceae*), comprising *ca.* 15 species, is widely distributed in the Middle East, central Asia, and the northwest region of China. Among them, *N. tangutorum* L. grows in China, and its leaves are used in folklore medicine as an antispasmodic, antineuropathic, and anti-arrhythmic agent.[1] Prior studies have shown that several members of the genus *Nitraria* contain β-carbolines, quinolizidines, spiropiperidines and quinazolines,[2] yet there is no record on the chemical composition of the Chinese species *N. tangutorum*. We now report the isolation and structural determination of tangutorine (**1**), a novel β-carboline alkaloid, from the leaves of *N. tangutorum*.



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An EtOH extract of the air-dried leaves was partitioned between petroleum ether and water. The water layer was adjusted to *p*H 10 with NH_4OH and extracted by $CHCl_3$. The $CHCl_3$-soluble portion was subjected to repeated chromatographic separation on silica gel using $CHCl_3$-MeOH mixtures of increasing polarity as eluant. The fractions obtained from $CHCl_3$-MeOH (92:8) elution were purified on Sephadex LH-20 eluted with MeOH to afford tangutorine (0.072% yield).

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00306-8

Tangutorine (**1**) was obtained as colorless crystals from a CH_2Cl_2-MeOH mixture, m.p. 276 - 278 °C, $[\alpha]_D$ 0° (*c* = 0.5, MeOH). The molecular formula $C_{20}H_{24}N_2O$ was derived from HR-LSIMS ($[M + 1]^+$ *m/z* 309.1975, calcd. 309.1961). In the EIMS spectrum, an M^+ signal (*m/z* 308) was abundant, and fragment ions at *m/z* 291 and 277 were present, corresponding to the loss of OH and CH_2OH, respectively. Cleavage between the C/D ring and subsequent loss of the ring C fragments gave rise to a series of signals at *m/z* 170 (100%), 169 (60), and 144 (15), typical for β-carboline structures such as the yohimbine alkaloids.[3] The UV spectrum showed absorptions at 225, 281, and 292 (sh) nm, which are characteristic for β-carbolines. The IR absorption bands at 730 (o-disubstituted benzene ring), 1020 (C-O in primary alcohol), 1444, 1470, 1626 (substituted indole nucleus), and 3240 (OH, NH) cm^{-1} further supported the presence of a β-carboline structure.

The ^{13}C NMR spectrum (Table 1) displayed twenty carbon signals. Among the ten carbons resonating at low field, eight were readily identified as carbons of the indole moiety (C-2 and C-7 to C-13). The corresponding aromatic protons (H-9 to H-12) were also assigned through their COSY relationship with these carbons. The remaining two carbon signals in the low-field region belong to an olefinic group; the compound is hence pentacyclic. The HMBC spectrum revealed cross peaks between 5-CH_2 (and 6-CH_2) and C-7, establishing the spectral assignments for the β-carboline part. On the other hand, the H-3 signal (δ 3.54, d, *J* = 11.3 Hz), in addition to an HMBC correlation with C-7, showed long-ranged couplings with a CH signal at δ 65.8 (C-21) and a CH_2 signal at δ 31.5 (C-15). Such an observation led to the suggestion that the compound possessed a D-E ring structure as depicted in **1** instead of a yohimbine-type skeleton. The spectral data for the carbons and protons on rings D and E could be assigned from the COSY, HMQC, and HMBC results (Table 1). The location of a double bond at C-17 was inferred by the results obtained from a selective INEPT (SINEPT) experiment [4] (Fig. 1) in which the olefinic proton (H-17) as well as the oxymethylene protons (22-CH_2) were selectively irradiated. Thus, irradiation of H-17 led to the enhancement of signals for C-15, C-19, C-21, and C-22; while an irradiation of 22-CH_2 resulted in the enhancement of signals for C-17, C-18, and C-19. These long-range correlation results are consistent with the proposed structure **1**.

The structure and relative stereochemistry of **1** were subsequently confirmed by crystallographic analysis,[5] and a thermal ellipsoid plot of the molecular structure is shown in Fig. 2. The space group is centrosymmetric $P2_1/n$ which contains inversion centers of symmetry. Tangutorine (**1**) is thus a racemic mixture of a β-carboline alkaloid with a novel skeleton.

Table 1. ^{1}H and ^{13}C NMR Spectral Data of Tangutorine (1) [a]

Position	Carbon	Proton
1	---	---
2	135.8 (s)	---
3	61.6 (d)	3.54 (1H, d, 11.3)
4	---	---
5	46.1 (t)	2.45 (m); 3.61 (m)
6	22.2 (t)	2.84 (m); 2.94 (m)
7	107.4 (s)	---
8	127.4 (s)	---
9	118.2 (d)	7.14 (1H, d, 7.8)
10	119.2 (d)	7.03 (1H, t, 7.3)
11	121.4 (d)	7.10 (1H, t, 7.3)
12	111.5 (d)	7.33 (1H, t, 8.3)
13	137.1 (s)	---
14	29.5 (t)	1.77 (m); 2.29 (m)
15	31.5 (t)	1.39 (m); 1.97 (m)
16	39.6 (d)	2.23 (m)
17	125.9 (d)	5.41 (1H, br s)
18	137.2 (s)	---
19	26.6 (t)	2.21 (m); 2.91 (m)
20	26.4 (t)	1.55 (m); 2.37 (m)
21	65.8 (d)	2.32 (m)
22	66.1 (t)	3.97 (2H, br s)

[a] Recorded on a JEOL JNM-EX-400 FT-NMR spectrometer as a solution in $CDCl_3$-CD_3OD. TMS was used as int. std., and chemical shifts are reported in ppm on the δ scale. Multiplicities and *J* values (in Hz) are given in parenthesis. Spectral assignments were made by the aid of COSY, HMQC, and HMBC spectra.

Figure 1. Results of a Selective INEPT experiment
(a) ^{13}C NMR spectrum (b) Selective irradiation of H-17
(c) Selective irradiation of 22-CH_2

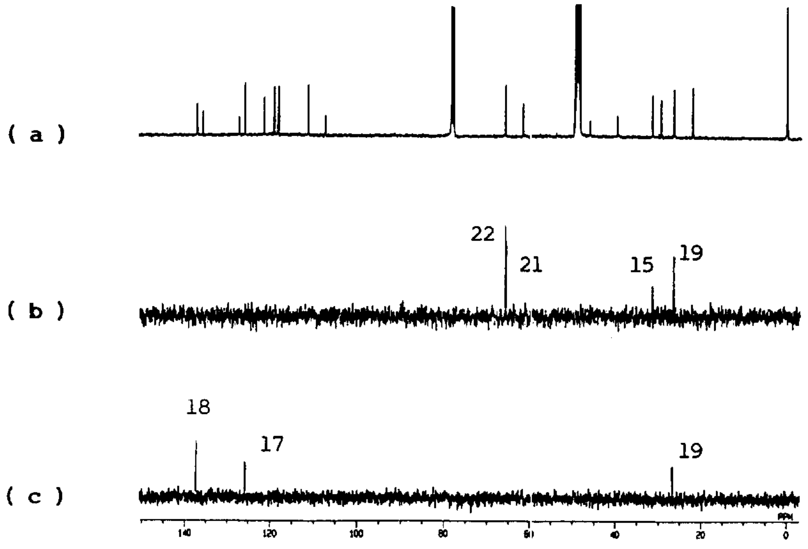
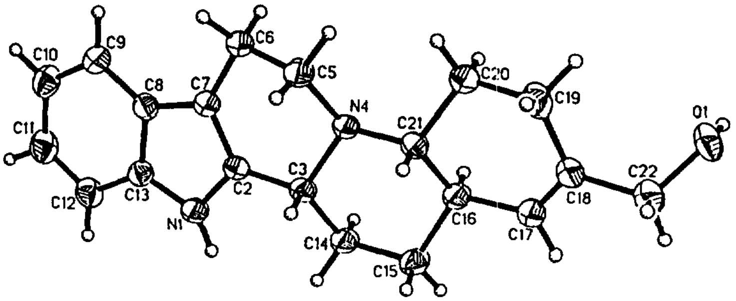


Figure 2. Crystal Structure of 1



Acknowledgments. This study was partially supported by a grant from the Hong Kong Research Grants Council and an Infrastructure Research Grant awarded from the Hong Kong University of Science and Technology. Prof. Dominic Chan (Department of Chemistry, The Chinese University of Hong Kong) is thanked for providing the high-resolution LSIMS results. Dr. Timothy Tam, Dr. Laura Cao, Ms. Y.L. Wong, and Mr. Alvin Siu are acknowledged for their skillful assistance in obtaining spectral and X-ray data.

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5. Tangutorine, $C_{20}H_{24}N_2O$, was crystallized from CH_2Cl_2-MeOH to afford colorless square crystals. A specimen of 1.2 ×1.0 ×1.0 mm was selected for single crystal structure determination. Compound **1** is monoclinic ($P2_1/n$) with lattice parameters a = 8.968 (1) Å, b = 12.445 (1) Å , c = 14.719 (2) Å , β = 92.97 (2)°, V = 1640.5 (5) Å, Z = 4, and Dc =1.249 Mg/m^3. All reflections with 2 θmax < 53° were collected at 23°C in the ω-2 θ scan mode with a Siemens P4-RA diffractometer [λ (MoKα) = 0.71073 Å] operating at 10 kW. Of the 3594 reflections collected, 2620 were unique and observed, and were used for refinement. The structure was determined by direct methods, and refined using full matrix least-squares to R = 0.044, wR = 0.056 with a GOF of 1.78. Residual electron density after location of all atoms including hydrogens was ± 0.2 $e^- Å^{-3}$. Based on a search of the Cambridge Structural Database (April 1998 release) the compound is the first example possessing this carbonide skeleton to be crystallographically characterized.