Tetrahedron Letters 52 (2011) 6453–6456

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Questions about the structures of nitraraine and nitraraidine

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ARTICLE INFO

Article history:
Received 3 August 2011
Revised 16 September 2011
Accepted 20 September 2011
Available online 25 September 2011

Keywords:
Alkaloid
Indole
Nitraraine
Tangutorine
Biomimetic synthesis

ABSTRACT

Investigations have been carried out in order to give new insights into the real structure of two alkaloids isolated from the *Nitraria* genus namely nitraraine and nitraraidine. Closely related tangutorine is put forward as a plausible alternative to the structure proposed so far for nitraraine.

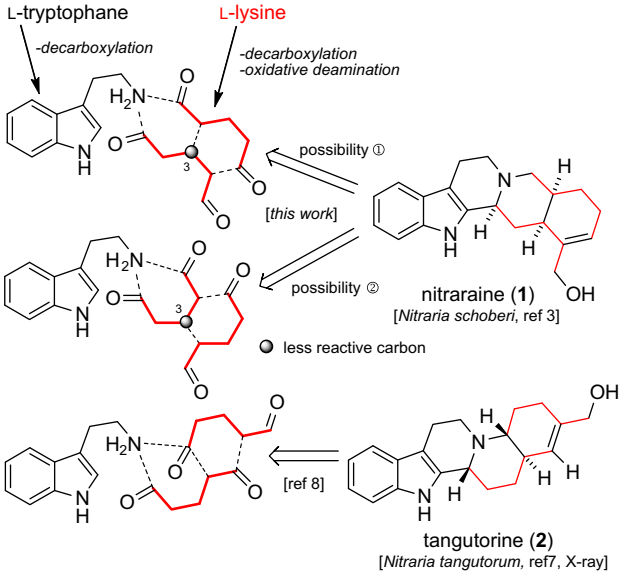
Introduction

The *Nitraria* genus (Nitrariaceae) has provided a wide range of diverse alkaloids isolated during the last 40 years. A particular lysine-derived metabolism is now accepted to account for the biosynthesis of these alkaloids which encompasses various subtypes (e.g., piperidinic alkaloids, indole alkaloids).[1] The different successes in preparing these alkaloids by the means of biomimetic strategies have greatly contributed to a better understanding of this class of alkaloids.[2]

One of these alkaloids, namely nitraraine (**1**) (Scheme 1), has attracted particular interest in our group. Our experiments and the deductive conclusions concerning the doubts that have arisen concerning the 'real' chemical structure of **1** and closely related analogs are presented in this Letter.

Nitraraine was isolated in 1985 from the epigeal part of *Nitraria schoberi* and was assigned as structure **1** (Scheme 1) characterized by a yohimbane skeleton.[3] In itself, this structure merits a few comments concerning its actual existence. Particularly noteworthy are the following points:

- Scarce analytical data are available for **2** (see discussion below).[3]
- The biosynthesis of nitraraine may be explained with the classical lysine metabolism implying the intervention of C_5 units such as equivalent of glutaraldehyde.[2] Nevertheless, despite totally consonant, these proposals (Scheme 1) systematically involve unreactive methylene at C-3 of the dialdehyde.
- Moreover, an indolomonoterpene metabolism is highly questionable in terms of chemotaxonomy as monoterpenoid indole alkaloids are mainly encountered in eight plant families.
- Two total syntheses of **1** have been published by the groups of Takano[4] and Yamaguchi.[5] Synthetic nitraraine was prepared and led to unambiguous conclusions concerning the veracity



Scheme 1. Nitraraine (**1**) versus tangutorine (**2**) structures and biosynthetic considerations.

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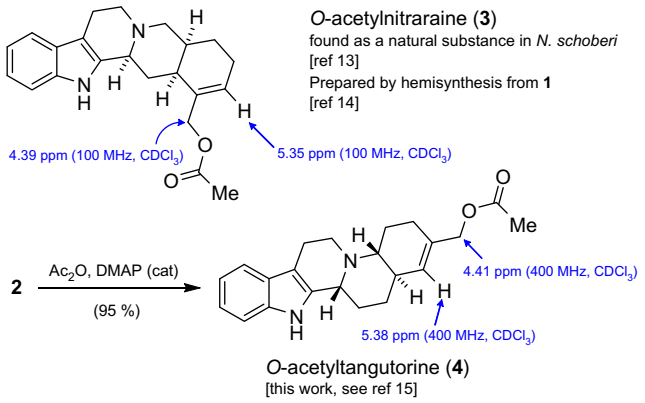
doi:10.1016/j.tetlet.2011.09.101



Scheme 2. *O*-Acetylnitraraine (**1**) versus *O*-acetyltangutorine (**2**) structures and biosynthetic considerations.

of the structure of **1**.[6] Particularly, spectral data were not in agreement with the few ones available for natural nitraraine (see discussion below).

Our own interest in the chemistry of *Nitraria* alkaloids has led us to deeply study a closely related alkaloid named tangutorine (**2**) isolated in 1999 from *Nitraria tangutorum* (Scheme 2).[7] Previous work from our group culminated in the straightforward total synthesis of **2** according to new biosynthetic proposals involving the particular lysine derived metabolism encountered in the *Nitraria* genus[8,9] (Scheme 2) counterbalancing the previously proposed complex rearrangement of yohimbine.[9b] Tangutorine displays a particular benz[*f*]indolo(2,3-*a*)quinolizidine pentacyclic core which is unique in nature.[10] The striking similarity between nitraraine and tangutorine prompted us to hypothesize that the structure of nitraraine should be revised into the structure known for tangutorine. The pros and cons resulting from our experimental investigations are reported in this Letter.

Results and discussion

Indeed, several data collected by us are in accordance with the proposal of revision.

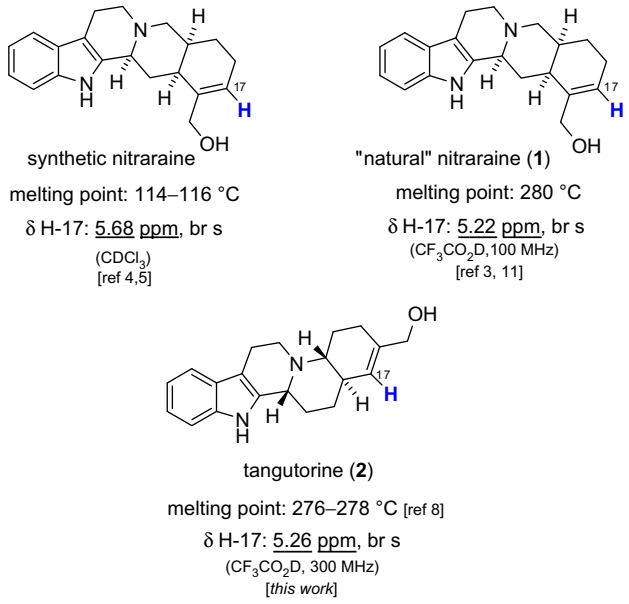


Figure 1. Nitraraine **1** versus tangutorine **2**: analytical data.

Table 1
^{1}H NMR data relative to H-17 of tangutorine given in the literature

δ (ppm)[a]	$CDCl_3$/MeOD	MHz	Ref.
5.26	95:5	500	9e
5.38	95.2:4.8	500	9c
5.39	95:5	400	9f
5.40	93:7	300	8
5.41	95:5	400	7[b]
5.41	100:0	400	9a
5.46	50:50[c]	500	8

[a] Signal appears as a broad singlet.
[b] Natural tangutorine.
[c] $CDCl_3$/DMSO-d_6.

- The comparison of melting points was puzzling and very informative in this case. A melting point of 280 °C was announced for natural nitraraine[3] to be compared to 114–116 °C for synthetic **1**.[4] Strangely, we[8] and others[9] measured a melting point of 276–278 °C for synthetic tangutorine (**2**) (Fig. 1).
- The only characteristic NMR chemical shift available for **1** is for proton H-17 of 'natural' nitraraine[11,12] at 5.26 ppm (100 MHz in trifluoroacetic acid).[3] This signal appears as a singlet. In the case of tangutorine, proton H-17 chemical shift varies from 5.26 to 5.46 ppm depending on the solvent and the concentration (see Table 1). We specifically performed NMR analysis in CF_3CO_2D (400 MHz) and found δ = 5.26 ppm. In view of the wide range of chemical shifts recorded for **2**, no clear conclusion can be drawn at this stage. In addition, a chemical shift of 5.68 ppm ($CDCl_3$) is reported for synthetic nitraraine.[4,5]
- *O*-Acetylnitraraine (**3**) was isolated in 2005 from *N. schoberi*.[13,14] A chemical correlation was established by the authors by acidic hydrolysis of **3** which furnished **1**. The NMR data available of natural *O*-acetylnitraraine are partial.[14] The presence of an olefinic proton at 5.35 ppm as a broad singlet and an acetoxymethyl group at 4.39 ppm (Scheme 2) are given by the authors (^{1}H NMR 100 MHz in $CDCl_3$). We acetylated our synthetic tangutorine (**2**) to afford *O*-acetyltangutorine (**4**)[15] and recorded a 5.38 ppm singlet and a 4.41 ppm singlet, respectively (^{1}H NMR 400 MHz in $CDCl_3$). Based on the close similitude between the spectral data available for **3** and **4**, **1** and **2** could as well be one and the same molecule.
- Dihydronitraraine (**5**) was isolated from *N. schoberi*[16] and was presented as the reduced counterpart of nitraraine (Scheme 3). Given, once again, the lack of complete analytical data concerning **5**, the same doubts logically arise concerning its true structure. In fact, the authors mainly deduced the structure from the chemical correlation by reducing natural **1** into **5**. We performed the reduction of synthetic tangutorine (**2**) under the same conditions, namely catalytic hydrogenation and synthesized dihydrotangutorine (**7**, not known as a natural product).[17] At this stage and given the lack of NMR details, the striking similarities between natural **1** and **2**, **3** and **4,** and **5** and **7** are obviously to be confronted to the important differences between natural and synthetic nitraraine as a clue to the assumption of this Letter.

An intriguing natural product was also isolated from *N. schoberi* and named nitraraidine (**6**).[18] With a tetravalent nitrogen atom and its cage structure, **6** possesses an unprecedented molecular architecture that attracted us. The authors proposed the structure as depicted in Scheme 3 and came to this conclusion by converting dihydronitraraine (**5**) into nitraraidine (**6**) by treatment with tosylchloride in pyridine.[19] We performed the reaction under the same conditions with synthetic **7**. No traces of any compound with the mass of **6** (m/z = 293) could be detected on mass spectra. Obvious