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Proposed Biogenetic Origin of Secu'amamine A from Allosecurinine: A Model Study To Support the Intermediacy of the Putative Aziridinium Ion

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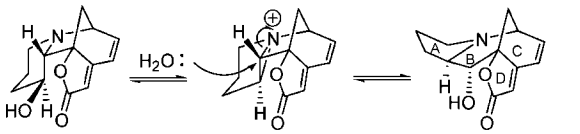
ABSTRACT



5, 3β-Hydroxy **2** **6** **7**, Secu'amamine A

A model study to support the intermediacy of the aziridinium ion in the proposed biogenetic origin of secu'amamine A from allosecurinine is described.

The *Securinega* and *Phyllantus* genera of Euphorbiaceae are a source of the securinine and norsecurinine alkaloids, exemplified by the structures of securinine **1**, and its C-2 epimer allosecurinine **2**, and by norsecurinine **3**, and its C-2 epimer allonorsecurinine **4**, Figure 1.[1] The antitumor, antimalarial, antibacterial, and CNS activity of these compounds has initiated interest in the synthesis of this structurally unique class of alkaloids.[2a−m]

In 2003 Ohsaki and Kobayashi reported the structure of secu'amamine A **7** isolated from *Securinega suffruticosa* var. *amamiensis*, Scheme 1.[3]

We propose that this new securinega skeletal-type is biogenetically derived from 3*β*-hydroxyallosecurinine **5** (not a known securinine alkaloid) by dehydration to the aziridinium ion **6**, and ring opening to give **7**. The stereochemistry at the A/B ring fusion in **7** is determined by the stereochemistry at C-3 in **5**. This is further illustrated by comparison with the C-3 epimer 3α-hydroxysecurinine **8** (also not a known securinine alkaloid), which on ionization leads to the aziridinium ion **9**, opening to **10** (epimeric at the A/B ring fusion and the *sec*-hydroxyl group). Of all of the stereoisomeric 3-hydroxysecurinine and 3-hydroxyallosecurinine alkaloids, only **5** can be converted into **7** via an aziridinium ion intermediate.[4]

(1) For a review of the securinega alkaloids see: Snieckus, V. The Securinega Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 425−506.

(2) (a) Horii, Z.; Hanoaka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Shigematsu, N.; Kotera, K.; Yoshikawa, H.; Sato, Y.; Nakai, H.; Sugimoto, N. *Tetrahedron* **1967**, *23*, 1165−1174. (b) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75−78. (c) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384−5392. (d) Xi, F. D.; Liang, X. T. *Acta Pharm. Sci.* **1992**, *27*, 349−352. (e) Magnus, P.; Rodríguez-López, J.; Mulholland, K.; Matthews, I. *J. Am. Chem. Soc.* **1992**, *114*, 382−383. (f) Magnus, P.; Rodríguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8959−8072. (g) Han, G.; La Porte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293−6306. (h) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703−706. (i) Honda, T.; Namika, H.; Kudoh, M.; Nagase, H.; Mizutani, H. *Heterocycles* **2003**, *59*, 169−187. (j) Kammler, R.; Polborn, K.; Wanner, K. T. *Tetrahedron* **2003**, *59*, 3359−3368. (k) Alibés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813−1816. (l) Honda, T.; Namika, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87−89. (m) Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; García-García, E.; González-Gálvez, D. *Org. Lett.* **2005**, *7*, 5107−5109.

(3) Oshaki, A.; Ishiyama, H.; Yoneda, K.; Kobayashi, J. *Tetrahedron Lett.* **2003**, *44*, 3097−3099.

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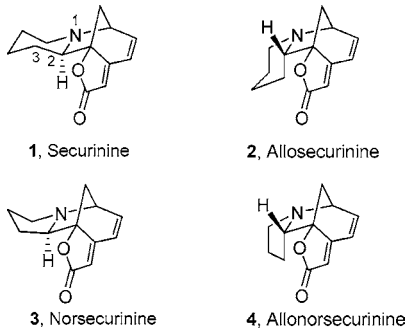
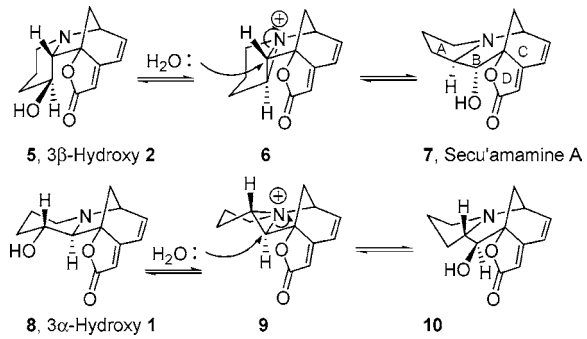


Figure 1. Structures of some securinine alkaloids.

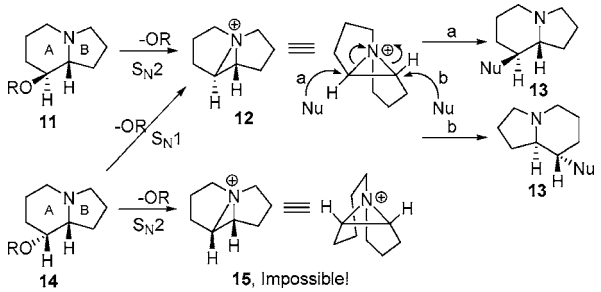
To examine the possible intermediacy of an aziridinium ion in the rearrangement of **5** into **7** we decided to study the

Scheme 1. Proposed Biogenetic Route to Secu'amamine A



model system **11**, which has the A and B rings of the 3-hydroxysecurinine alkaloids, Scheme 2. If **11** forms the

Scheme 2. Analysis of Aziridinium Ion Intermediate



aziridinium ion **12**, it can open by nucleophilic attack at either carbon atom (paths a and b) to give the same product **13**. If **11** were a single enantiomer, **13** would have the same absolute configuration, and the displacement of −OR by a nucleophile would occur with retention of stereochemistry

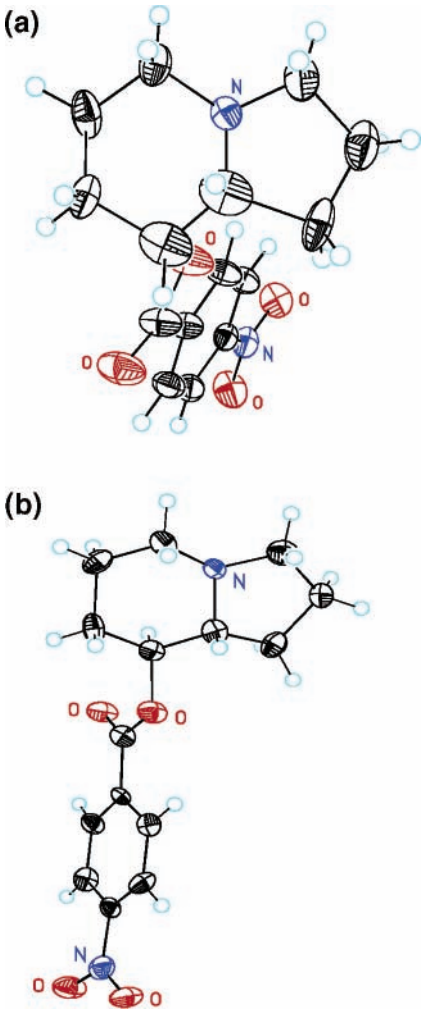


Figure 2. ORTEP representation of the **19** X-ray structure of **19** (a) and **20** (b).

via the double inversion pathway, thus strongly implicating the intermediacy of the aziridinium ion **12**.

The epimeric alcohol derivative **14** cannot form **15** since the three-carbon link between the tetrahedral quaternized nitrogen atom and the aziridinium carbon atoms is too short to allow a trans-ring fusion. Consequently, **14** can only react by ionization (S_N1) and this would lead to **12**.

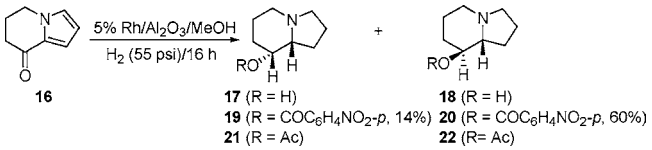
The known ketone **16**[5] was hydrogenated over Rh/Al_2O_3 to give **17** and **18** as an inseparable mixture, Scheme 3. Treatment of the mixture with *p*-nitrobenzoyl chloride/Et_3N/DMAP/CH_2Cl_2 gave **19** (14%) and **20** (60%), which were separated and their structures determined by X-ray crystallography, Figure 2.

When **20** was treated with sodium acetate in acetic acid heated at reflux it was converted into **22** (77%). The stereochemistry of **22** was confirmed by hydrolysis (aq NaOH/reflux) of **20** to give pure **18** followed by acetylation

(4) (a) Setoi, H.; Takeno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261−1264. (b) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartly, O.; Winchester, B. G. *Tetrahedron* **1995**, *51*, 12611−12630.

(5) (a) Bond, T.; Jenkins, R.; Ridley, A.; Taylor, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, *19*, 2241−2242. (b) Amos, R.; Gourlay, B.; Molesworth, P.; Smith, J.; Sprod, O. *Tetrahedron* **2005**, *61*, 8226−8230.

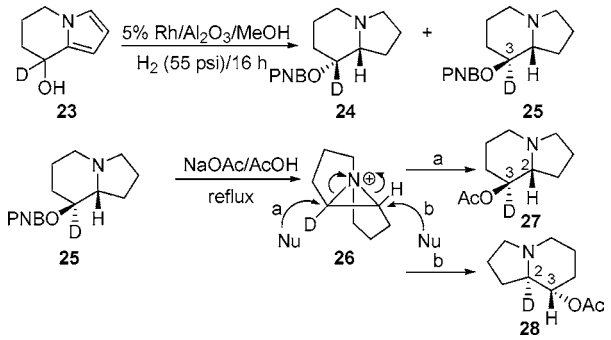
Scheme 3. Solvolysis Experiments



(Ac_2O/py/DMAP), thus providing an unambiguous authentic sample of **22**. By way of contrast, treatment of **19** with sodium acetate in acetic acid at reflux did not give **21**, only unreacted **19** was recovered. Conducting the solvolysis at 160 °C in a sealed tube resulted in decomposition of **19** to a complex mixture.

While the stereochemical outcome of the conversion of **20** into **22** is consistent with the intermediacy of the aziridinium ion **12**, we felt that a simple deuterium labeling experiment would provide even more compelling evidence. Reduction of **16** with $LiAlD_4$/THF gave **23** (84%), Scheme 4.

Scheme 4. Deuterium Labeling Experiment



Hydrogenation of **23** followed by conversion of the mixture of alcohols into their *p*-nitrobenzoate derivatives provided the C-3 deuterated compounds **24** and **25**, respectively. When **25** was treated with sodium acetate in acetic acid heated at reflux it was converted in **27** and **28** [^{2}H NMR (46.03 MHz, C_6H_6) δ_D 4.79 (1D, br s) and 1.76 (1D, br s)], respectively, Figure 3. The scrambling of the deuterium atom

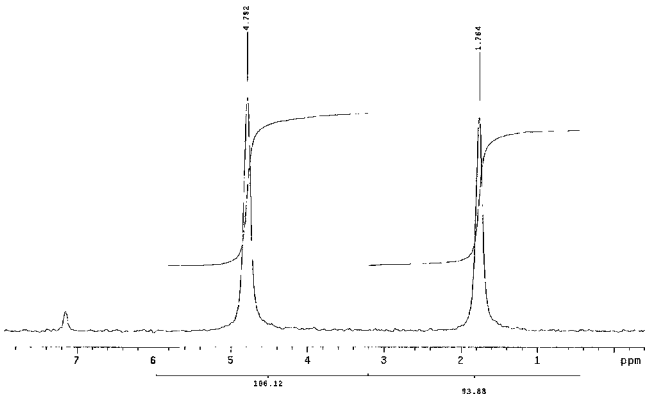


Figure 3. ^{2}H NMR of **27** and **28**.

label between C-2 and C-3 is *only* consistent with the intermediacy of the aziridinium ion **26**.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra of all new compounds, as well as X-ray crystallographic data for compounds **19** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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