

**MODEL STUDIES ON INTERCONVERSION OF ROXBURGHINE-TYPE
ALKALOIDS. ACID-CATALYSED EPIMERIZATION OF C-12B
SUBSTITUTED INDOLO[2,3-*a*]QUINOLIZIDINE DERIVATIVES**

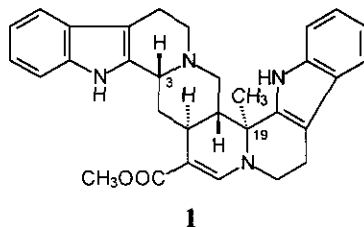
Mauri Lounasmaa,* Mathias Berner, Anders Månsus, and Arto Tolvanen

Laboratory for Organic and Bioorganic Chemistry

Technical University of Helsinki, P. O. Box 6100, HUT-02015 Espoo, Finland

Abstract – C-12b Methyl substituted indolo[2,3-*a*]quinolizidines possessing different structural features were prepared as model compounds to investigate whether different roxburghine alkaloids can be obtained by acid-catalysed epimerization. When they were subjected to epimerization under strongly acidic conditions (TFA), indoloquinolizidines (7) and (8) and lactams (12) and (13) epimerized as expected but the vinylogous urethanes (4) and (5) remained unaffected. The results indicate that the mechanism starting with protonation at the β -position of indole (Mechanism 1) is active in the acid-catalysed epimerization of vinylogous urethanes. This further suggests that roxburghine alkaloids do not epimerize at C-19.

In our on-going investigation of the acid-catalysed epimerization of indoloquinolizidines,¹⁻³ the C-12b substituted derivatives constitute an important group of compounds. First of all, these compounds play an important role in the total synthesis of the biogenetically interesting indole alkaloid roxburghine D (1),⁴ which consists of two indoloquinolizidine substructures.



It is commonly accepted that indoloquinolizidines epimerize at C-12b⁵ (corresponding to C-3 and C-19 in compound (1)⁶) and on this basis it would be logical to assume that roxburghine D possesses two epimerizable centers, capable of providing easy access to other members of the roxburghine group. The

facility is underlined by the different nature of the two centers: epimerization at C-3 requires refluxing in strong acid⁷ whereas epimerization at C-19 should easily occur at room temperature (*vide infra*). In the literature, however, epimerization of the roxburghine alkaloids has only been reported at C-3.⁸

In addition to being synthetically useful, the C-12b substituted indoloquinolizidines, when subjected to epimerization conditions, could be expected to provide useful information about the mechanism involved in the acid-catalysed epimerization. If the substituted compounds epimerize under acidic conditions, Mechanism 1 of the three generally accepted mechanisms is ruled out. If, on the other hand, the alkyl substituent at C-12b prevents epimerization, Mechanism 1 must be active. Recently, the acid-catalysed epimerization reaction has been interpreted to proceed mainly by Mechanism 2.^{2,9} The main intermediates of the three mechanisms are shown in Figure 1.^{1,10}

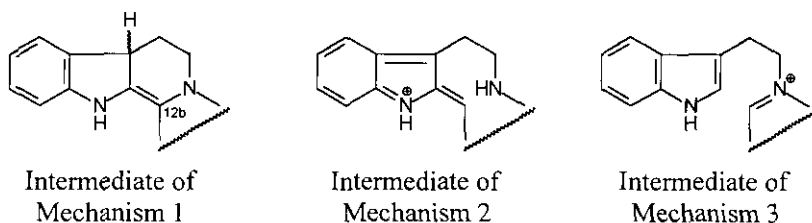
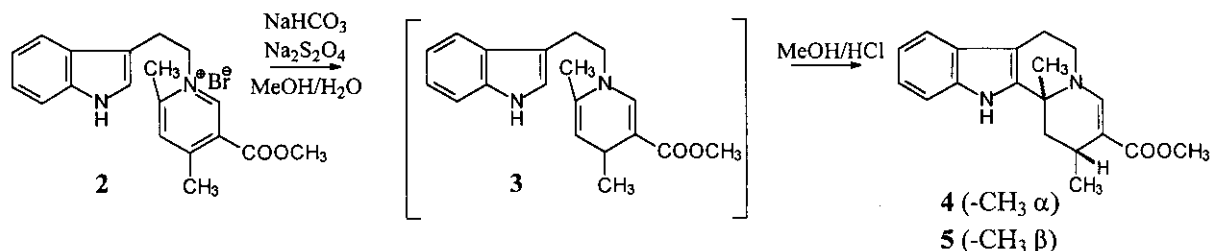


Figure 1

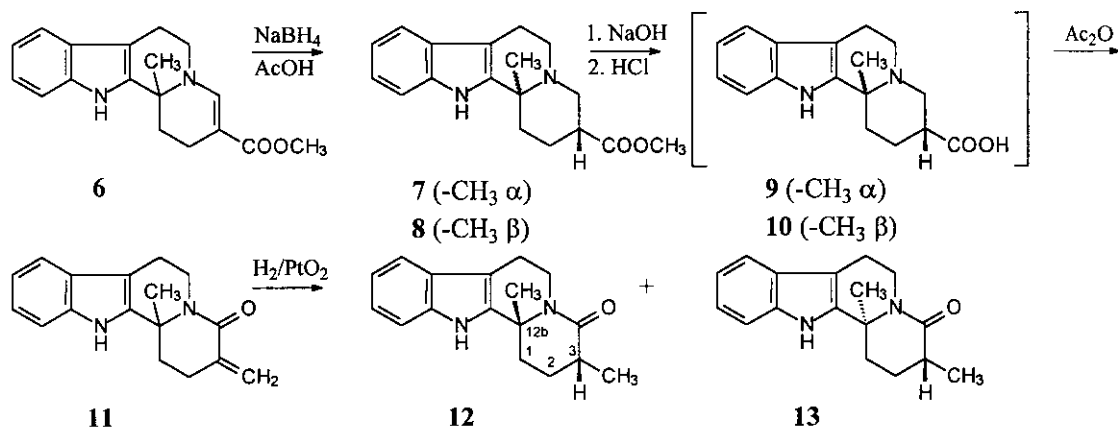
Acid-catalysed epimerization reactions conducted with vinylogous urethanes lacking a methyl group at C-12b (corresponding to C-19) have been reported earlier.^{11,12} One of the striking features of these reactions is the great ease with which the epimerization occurs. Treatment of different vinylogous urethanes with trifluoroacetic acid (TFA) at room temperature for 2 h gave the corresponding epimers in high yield.¹¹ Another important detail is provided by a deuterium experiment conducted with TFA-*d*, which resulted in deuterium incorporation at C-12b. Since only Mechanism 1 results in proton cleavage at C-12b, it was considered to be active.¹²

In view of the above findings, we investigated whether the introduction of a methyl group at C-12b to an indoloquinolizidine containing a vinylogous urethane moiety could prevent the epimerization. We note, in addition, that indoloquinolizidines containing a methyl group at C-12b, which exhibit promising pharmacological properties, have recently been of interest.¹³ Therefore salt (2) (prepared from tryptophyl bromide and methyl 4,6-dimethylnicotinate¹⁴) was reduced with sodium dithionite¹⁵ in refluxing aqueous methanol for 1.5 h followed by acid treatment to give in low yield urethanes (4) and (5) (Scheme 1).¹⁶



Treatment of different mixtures of epimers (4) and (5) with de-aired TFA at room temperature for 16 h left the ratios unchanged. Thus, the methyl group at C-12b prevented the epimerization reaction under the employed conditions. This result, together with the deuterium incorporation at C-12b,¹² strongly indicates that Mechanism 1 is responsible for the epimerization of vinylogous urethanes.

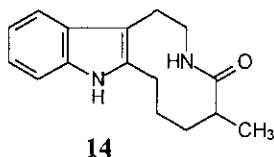
C-12b Methyl substituted lactams are important precursors in the total synthesis of roxburghine D.⁴ Epimers (7) and (8) were obtained from urethane (6)¹⁷ by sodium borohydride reduction and converted *via* methylenelactam rearrangement^{18,19} to lactam (11). Hydrogenation of lactam (11) yielded the desired epimers (12) and (13).



Not only epimers (12) and (13) but also (7) and (8) can provide useful information when subjected to epimerization conditions. When compounds (7) and (8) were refluxed in de-aired TFA overnight, an equilibrium ratio of *ca.* 55:45 (*cis:trans*; determined by ¹H NMR integration) was obtained.²⁰ This demonstrates that Mechanism 1 is not operative in the epimerization of these compounds.

Treatment of epimers (12) and (13) with de-aired TFA at room temperature for 2 h resulted in an equilibrium ratio of *ca.* 65:35 (*cis:trans*; determined by ¹H NMR integration).^{21,22} Similar results were obtained by Winterfeldt and co-workers with lactams containing a methyl group at the corresponding

carbon.⁴ This is in accordance with our recently published result, where we trapped the intermediate (14) in the acid-catalysed epimerization reaction of an analogous lactam with a hydrogen at C-12b.²



In conclusion, this first systematic study to provide information about the epimerization behavior of different C-12b methyl substituted indolo[2,3-*a*]quinolizidine derivatives has shown that C-12b methyl substituted vinylogous urethanes (e.g. 4), which are model compounds for roxburghine alkaloids, do not epimerize under acidic conditions. On this basis we conclude that roxburghine alkaloids do not epimerize at C-19. In a synthesis, however, the epimerization can be performed at a suitable stage to obtain the desired isomers. Furthermore, this result provides for the first time strong evidence in favor of Mechanism 1. Mechanism 1 cannot, on the other hand, operate in the epimerization reaction of lactams (e.g. 12) and indoloquinolizidines (e.g. 7) that contain a methyl group at C-12b. Evidently, Mechanism 2 is responsible for the epimerization reaction of such compounds.

REFERENCES AND NOTES

1. For a review, see: M. Lounasmaa, M. Berner, and A. Tolvanen, *Heterocycles*, 1998, **48**, 1275.
2. M. Lounasmaa, M. Berner, M. Brunner, H. Suomalainen, and A. Tolvanen, *Tetrahedron*, 1998, **54**, 10205.
3. M. Lounasmaa, M. Berner, and A. Tolvanen, *Heterocycles*, 1999, **50**, 243.
4. G. Benz, H. Riesner, and E. Winterfeldt, *Chem. Ber.*, 1975, **108**, 248.
5. A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.
6. Biogenetic numbering: J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
7. M. Lounasmaa, L. Miikki, and A. Tolvanen, *Tetrahedron*, 1997, **53**, 5349.
8. L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron*, 1970, **26**, 2259.
9. E. D. Cox, L. K. Hamaker, J. Li, P. Yu, K. M. Czerwinski, L. Deng, D. W. Bennett, J. M. Cook, W. H. Watson, and M. Krawiec, *J. Org. Chem.*, 1997, **62**, 44.
10. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1.
11. E. Wenkert, P. D. R. Moeller, and Y.-J. Shi, *J. Org. Chem.*, 1988, **53**, 2383.
12. U. Rosentreter, L. Born, and J. Kurz, *J. Org. Chem.*, 1986, **51**, 1165.
13. J. J. Li, B. K. Trivedi, J. R. Rubin, and B. D. Roth, *Tetrahedron Lett.*, 1998, **39**, 6111.
14. J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield, and J. F. Whidby, *J. Org. Chem.*, 1981, **46**, 3040.
15. M. Lounasmaa, P. Juutinen, and P. Kairisalo, *Tetrahedron*, 1978, **34**, 2529.
16. Selected ¹H NMR data: Compound (4): δ 1.63 (s, 3H, -CH₃ at C-12b), 1.36 (d, 3H, *J* = 7 Hz, -CH₃); Compound (5): δ 1.49 (s, 3H, -CH₃ at C-12b), 1.23 (d, 3H, *J* = 6.5 Hz, -CH₃).
17. E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, 1976, **98**, 3645.
18. D. L. Lee, C. J. Morrow, and H. Rapoport, *J. Org. Chem.*, 1974, **39**, 893.
19. A. R. Stoit and U. K. Pandit, *Tetrahedron*, 1988, **44**, 6187.
20. Selected ¹H NMR data: Compound (7): δ 3.71 (s, 3H, -COOCH₃), 1.38 (s, 3H, -CH₃ at C-12b); Compound (8): δ 3.60 (s, 3H, -COOCH₃), 1.50 (s, 3H, -CH₃ at C-12b).
21. Selected ¹H NMR data: Compound (12): δ 1.68 (s, 3H, -CH₃ at C-12b), 1.24 (d, 3H, *J* = 7.5 Hz, -CH₃); Compound (13): δ 1.66 (s, 3H, -CH₃ at C-12b), 1.32 (d, 3H, *J* = 7 Hz, -CH₃).
22. α-Position of lactam (C-3-H) does not epimerize under the employed conditions.²

Received, 16th November, 1998