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

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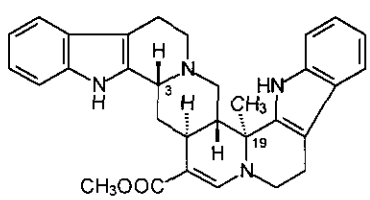
Abstract – C-12b Methyl substituted indolo[2,3-*a*]quinolizidines possessing different structural features were prepared as model compounds to investigate whether different roxburghine alkaloids can be obtained by acid-catalysed epimerization. When they were subjected to epimerization under strongly 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.



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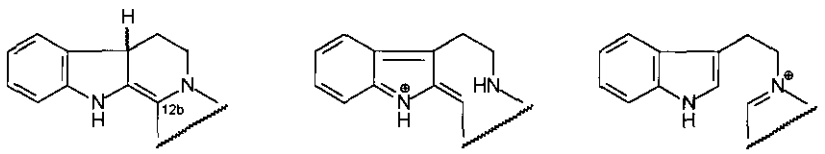
It is commonly accepted that indoloquinolizidines epimerize at C-12b[5] (corresponding to C-3 and C-19 in compound (**1**)[6]) and on this basis it would be logical to assume that roxburghine D possesses two epimerizable centers, capable of providing easy access to other members of the roxburghine group. The

facility is underlined by the different nature of the two centers: epimerization at C-3 requires refluxing in strong acid[7] 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]

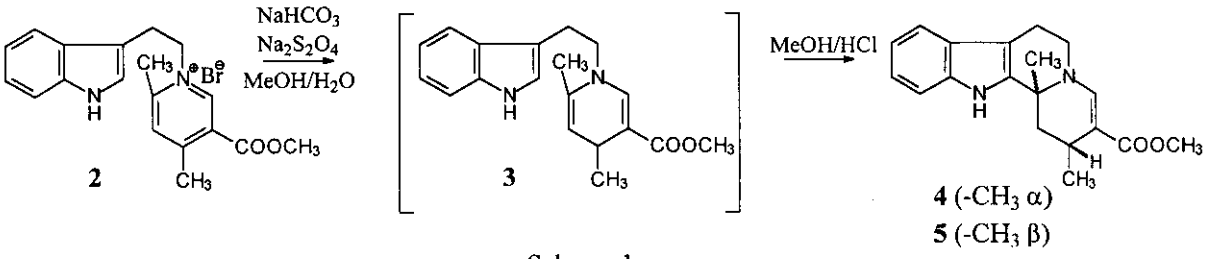


Intermediate of Mechanism 1 | Intermediate of Mechanism 2 | Intermediate of Mechanism 3

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]

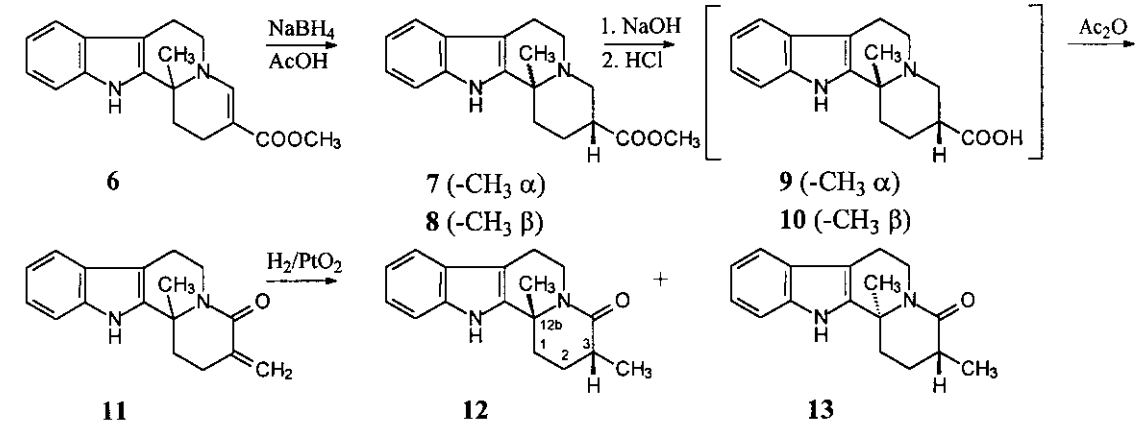
In view of the above findings, we investigated whether the introduction of a methyl group at C-12b to an indoloquinolizidine containing a vinylogous urethane moiety could prevent the epimerization. We note, in addition, that indoloquinolizidines containing a methyl group at C-12b, which exhibit promising pharmacological properties, have recently been of interest.[13] Therefore salt (**2**) (prepared from tryptophyl bromide and methyl 4,6-dimethylnicotinate[14]) was reduced with sodium dithionite[15] in refluxing aqueous methanol for 1.5 h followed by acid treatment to give in low yield urethanes (**4**) and (**5**) (Scheme 1).[16]



Scheme 1

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**).

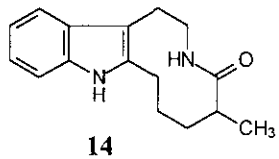


Scheme 2

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 ^{1}H 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 ^{1}H 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]



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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.

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16. Selected ^{1}H NMR data: Compound (**4**): δ 1.63 (s, 3H, -CH_3 at C-12b), 1.36 (d, 3H, J = 7 Hz, -CH_3); Compound (**5**): δ 1.49 (s, 3H, -CH_3 at C-12b), 1.23 (d, 3H, J = 6.5 Hz, -CH_3).
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20. Selected ^{1}H NMR data: Compound (**7**): δ 3.71 (s, 3H, -$COOCH_3$), 1.38 (s, 3H, -CH_3 at C-12b); Compound (**8**): δ 3.60 (s, 3H, -$COOCH_3$), 1.50 (s, 3H, -CH_3 at C-12b).
21. Selected ^{1}H NMR data: Compound (**12**): δ 1.68 (s, 3H, -CH_3 at C-12b), 1.24 (d, 3H, J = 7.5 Hz, -CH_3); Compound (**13**): δ 1.66 (s, 3H, -CH_3 at C-12b), 1.32 (d, 3H, J = 7 Hz, -CH_3).
22. α-Position of lactam (C-3-H) does not epimerize under the employed conditions.[2]

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