ACID-CATALYSED C-3 EPIMERIZATION OF RESERPINE AND OTHER INDOLO[2,3-*a*]QUINOLIZIDINES

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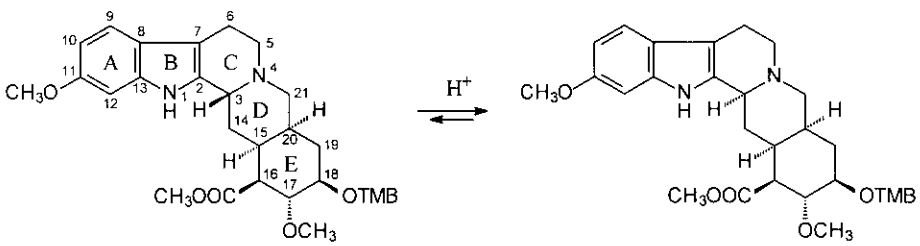
Abstract - The acid-catalysed C-3 epimerization of the indole alkaloid reserpine (**1**) and other closely related indolo[2,3-*a*]quinolizidines is reviewed. The three mechanisms that have been proposed and relevant experimental findings are discussed. Representative examples of C-3 epimerization reactions are included.

CONTENTS

I EARLY EPIMERIZATION STUDIES ON RESERPINE

The biologically active constituent of the Indian snake-root, *Rauwolfia serpentina* Benth., named as reserpine (**1**), was first isolated in the early 1950's.[1,2] In the course of an intensive structure elucidation, this new pharmacologically important indole alkaloid of yohimbine type was found to be chemically labile. Under acid (or base) catalysis, it was found to equilibrate to a mixture of **1** and its epimer, isoreserpine (**2**).[3]



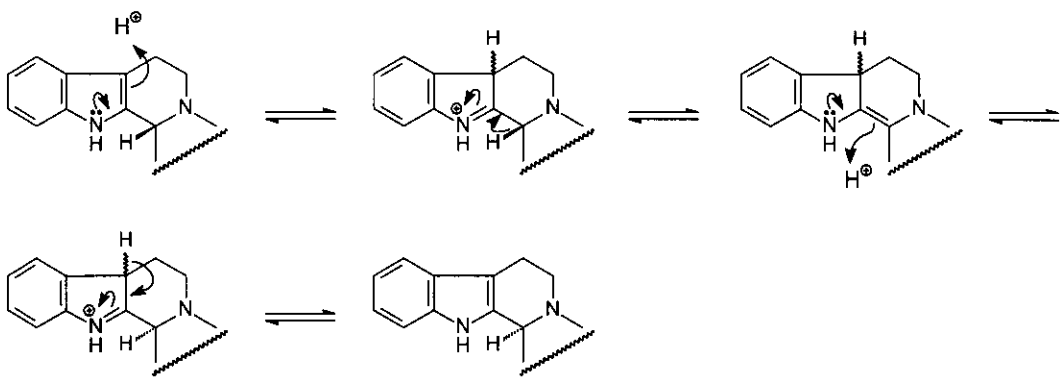
TMB = 3,4,5-trimethoxybenzoyl

1 **2**

The epimerization played an important role in the structure elucidation of reserpine.[4] Originally, MacPhillamy *et al.*[5] used acetic anhydride in the epimerization reaction. Refluxing **1** in acetic anhydride for 18 h they obtained **2** in 20% yield. When the anhydride was replaced by the corresponding acid, the epimerization became more efficient (yield 60%)[5] and the method could be applied to the more important backwards conversion: the formation of reserpine (**1**) from isoreserpine (**2**). Refluxing **2** in acetic acid for 24 h furnished an equilibrium mixture of **1** and **2**, from which **1** was isolated in 15% yield.[6] It was very soon recognized that the configurationally labile carbon in **1** was C-3,[7] as a few years earlier Cookson[8] had suggested that C-3 is the centre of epimerization in the base-catalysed equilibration of yohimbine-type alkaloids.[9] Moreover, the electron donating methoxy group in the indole part of reserpine was found to facilitate the epimerization, as deserpidine (11-demethoxyreserpine) was epimerized much more slowly.[5]

II MECHANISMS

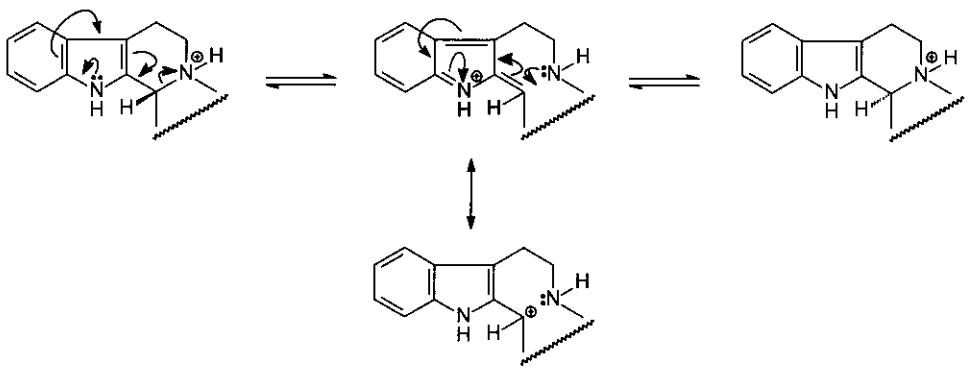
The mechanisms for the C-3 epimerization of reserpine were proposed almost immediately. In reporting the details of the first total synthesis of reserpine, Woodward *et al.*[10] included a short discussion of the main intermediates of the mechanisms. In their mechanism 1 (Scheme 1) protonation takes place at C-7 (the ß-position of indole) and is then followed by enamine formation *via* proton abstraction at C-3. Enamine protonation and subsequent proton cleavage at C-7 complete the sequence, which leads to the change of configuration at C-3.



Scheme 1 (Mechanism 1)

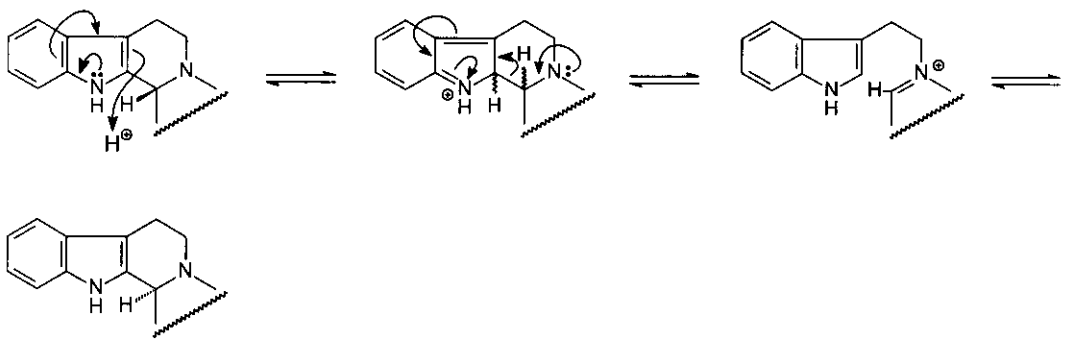
Mechanism 2 (Scheme 2), which was first proposed by Wenkert and Liu,[11] starts with protonation at N_b, the most basic site and so the most likely to be protonated first. In mechanisms 1 and 3 (*vide infra*) the

reactions are supposed to proceed instead *via* an equilibrium concentration of the free base. As seen in Scheme 2, after protonation the C-3 - N_b bond is cleaved as a result of the participation of the indole nitrogen lone pair, giving a carbocation intermediate. Ring reclosure assisted by the N_b lone pair then effects the inversion at C-3.



Scheme 2 (Mechanism 2)

Mechanism 3 (Scheme 3) involves initial protonation at C-2 and the formation of an intermediate where cleavage of the C-2 - C-3 bond to give an iminium ion is possible. Acid-induced recyclization of the iminium species gives rise to the epimerized product.



Scheme 3 (Mechanism 3)

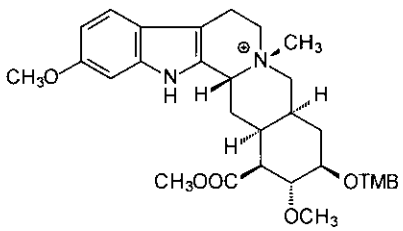
In inspecting the three alternatives described above, it should be noted that only in mechanism 1 (Scheme 1) is the proton at C-3 cleaved allowing the possibility of deuteration experiments. As will be discussed in the following, only mechanisms 2 and 3 have received experimental support.

III PIONEER WORK ON THE EPIMERIZATION MECHANISM: GASKELL AND JOULE

The first systematic investigation of the acid-catalysed epimerization reaction was conducted by Gaskell and Joule,[12] who examined in detail the three mechanisms described above to see if any of them could be experimentally demonstrated to operate in the epimerization of reserpine.

As a test for mechanism 1, Gaskell and Joule prepared and carried out experiments with 3-deuteroisoreserpine. Heating of the labelled compound with acetic acid showed that the epimerization reaction took place much faster than the dedeuteration process. The exchange of the deuterium required very vigorous reaction conditions (heating at 140°C for 3 days). When an analogous experiment was conducted with 3-deuterodeserpidine, the results were exactly the opposite: epimerization was *slower* than the loss of the deuterium label. Gaskell and Joule concluded that two processes are operative: the first is the epimerization process, which does not involve loss of the deuterium label and the second is a dedeuteration process, which does not lead to epimerization. Mechanism 1 was accordingly discredited.

Gaskell and Joule also prepared metho salts (**3**) and (**4**), which they treated with acetic acid at 140°C for 3 days. No epimerization occurred at C-3, but instead new salts (**5**) and (**6**) were formed *via* inversion at N_b.



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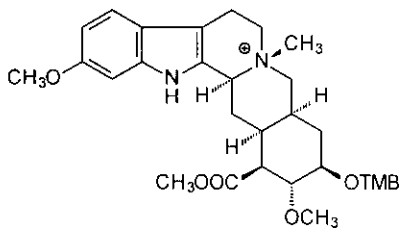

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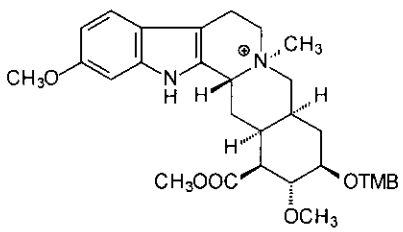

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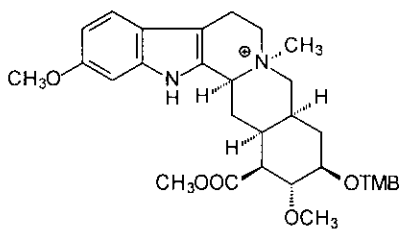
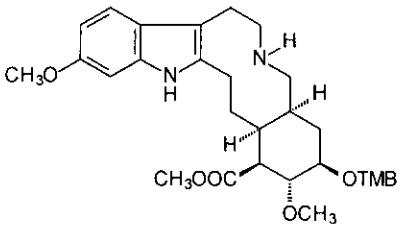


6

The original bases (**1**) and (**2**) were recovered from the corresponding salts (**5**) and (**6**) by high vacuum pyrolysis. Gaskell and Joule proposed that the inversion at N_b occurred through a mechanism involving C-3 - N_b bond scission. However, the failure of the metho salts (**3**) and (**4**) to epimerize at C-3 led them to reject mechanism 2.

Gaskell and Joule next introduced an important experiment to obtain possible mechanistic intermediates by treating reserpine (**1**) with zinc in acetic acid. Besides reserpine (**1**) and isoreserpine (**2**), two products were isolated: 3,4-secoreserpine (**7**) as a result of bond cleavage at C-3 - N_b and 2,3-secoreserpine (**8**) through cleavage at C-2 - C-3.[12,13]



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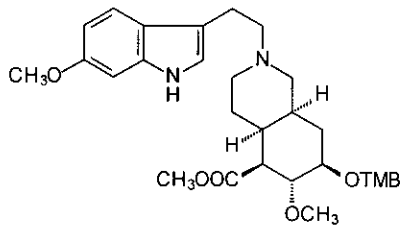
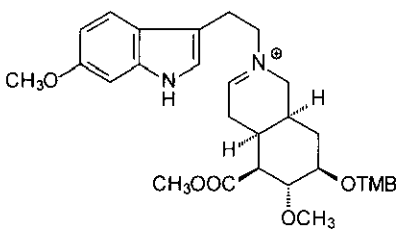


8

In regard to their other results Gaskell and Joule concluded that the epimerization reaction occurred *via* mechanism 3, even though compound (**7**) was obtained in a much higher yield than compound (**8**). In mechanism 3 the main intermediate in the acid-catalysed epimerization of reserpine should be the iminium species (**9**).



9

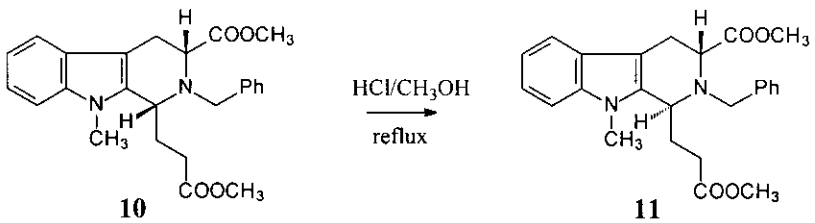
Mechanism 3, as supported by Gaskell and Joule, has received general acceptance. Schiffl and Pindur[14] have discussed the cyclization of intermediate (**9**) in terms of stereoelectronic control. Moreover, Sakai and Ogawa[15] have cleaved the C-2 – C-3 bond of reserpine with formic acid and formamide,[16] under which conditions intermediate (**9**) was reduced to 2,3-secoreserpine (**8**). However, other experimental information about the acid-induced cyclization of **9** has compelled further investigation of the mechanism.

IV ANOTHER PROPOSAL FOR THE MECHANISM: COOK AND CO-WORKERS

Strong arguments against mechanism 3 (Scheme 3) have been advanced by Cook *et al.*,[17,18] who were prompted to reinvestigate the question by a detail in the synthesis of reserpine performed by Martin *et*

al.[19] As the final step in this synthesis, the acid-induced cyclization of intermediate (**9**) gave mainly reserpine (**1**) and not isoreserpine (**2**) (the ratio was 4.4:1). The predominance of reserpine (**1**) in the cyclization reaction of intermediate (**9**) had in fact already been reported by Sakai and Ogawa.[16,20] This experimental result is in contradiction with mechanism 3 because the major product in the acid-catalysed epimerization of reserpine (**1**) should then be reserpine (**1**) and not, as is the case, isoreserpine (**2**).

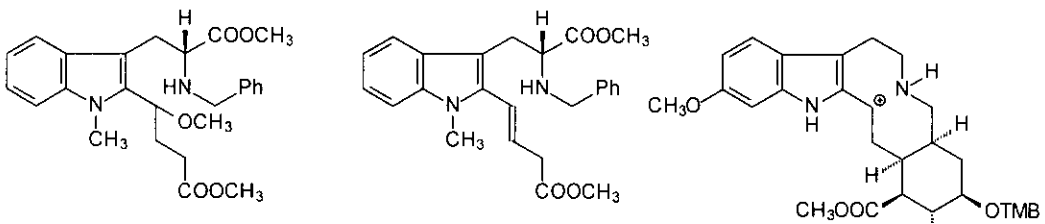
Thus, Cook *et al.* came to the conclusion that intermediate (**9**) could not be the predominating species in the epimerization reaction. Previously, the same group had studied the acid-catalysed epimerization of β-carboline derivative (**10**),[17] and found that when compound (**10**) was treated with HCl/CH_3OH its more stable epimer (**11**) was obtained (Scheme 4).



10 **11**

Scheme 4

Besides **11**, also the two open intermediates (**12**) and (**13**) were isolated, and the formation of these compounds strongly supports mechanism 2 (Scheme 2). In analogy, Cook *et al.* suggested that the acid-catalysed epimerization reaction of reserpine (**1**) would occur through the same mechanism. Thus, through mechanism 2, the main intermediate in the acid-catalysed epimerization reaction of **1** would be carbocation (**14**).



12 **13** **14**

When Cook *et al.* repeated some experiments performed already by Gaskell and Joule they obtained similar results. When they tried to trap the intermediates of the epimerization reaction with acetic acid and zinc, they obtained the same compounds (**7**) and (**8**). To explain the behaviour of the metho salts Cook *et al.* concluded that an inversion had taken place occurring *via* a mechanism that involved C-3 - N_b bond

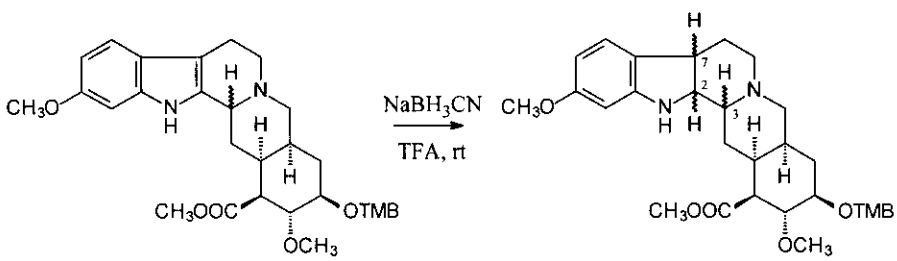
scission (the same mechanism as in the epimerization reaction). This was confirmed through consideration of the stereochemistries of the different metho salts (**3**-**6**).[21]

Even at various temperatures, Cook *et al.* failed to trap any intermediates when using HCl/MeOH in the epimerization reaction. Their explanation was that the epimerization occurred too rapidly.

Biomimetic inversion of C-3 in monoterpenoid indole alkaloids has been proposed to involve the C-3 - N_b bond cleavage analogously to mechanism 2.[22] There is thus a considerable amount of evidence in support of mechanism 2. However, other reactions (*vide infra*) reported in the literature nevertheless evoke confusion, which has not yet been totally dissipated.

V RELATED OBSERVATIONS ON THE MECHANISM

Although Hinman and Whipple[23] showed back in 1962 that protonation of indole derivatives takes place mainly at the 3-position (corresponding to C-7 of reserpine), mechanism 1, starting with protonation at C-7, has not received general acceptance as the operative mechanistic route in the acid-catalysed epimerization of reserpine and related compounds. Some relevant points may be noted, however. Recently, protonation of indolo[2,3-*a*]quinolizidines at C-7 has been confirmed by several research groups. Balón and co-workers,[24] while investigating the protonation site of *Rauwolfia* alkaloids, showed through ^{13}C NMR studies that protonation takes place at C-7 in 18M H_2SO_4. Moreover, Royer *et al.*[25] showed that reserpine (**1**) and isoreserpine (**2**) are transformed into the corresponding 2,7-dihydro compounds (**15**) (55%) and (**16**) (87%) by $NaBH_3CN$ in trifluoroacetic acid (TFA) at room temperature. Such a transformation is only possible through protonation at C-7. Further evidence was obtained by deuterium incorporation at C-7 when TFA-*d* was used in analogous reactions.

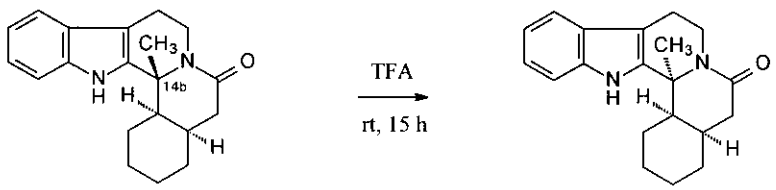


1 (H-3β)
2 (H-3α)

15 (H-2β, H-3β, H-7β)
16 (H-2α, H-3α, H-7α)

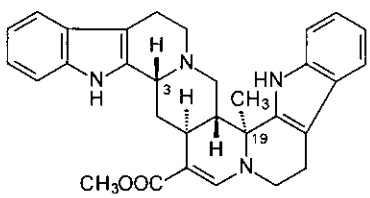
Scheme 5

Examples of epimerizations of indolo[2,3-*a*]quinolizidines of various types show how differing structural features affect the epimerization. Winterfeldt and co-workers[26] have epimerized some indolo[2,3-*a*]quinolizidin-4-one derivatives. In connection with a synthesis of the biogenetically interesting indole alkaloid roxburghine D (**19**), for example, they treated lactam (**17**) with TFA at room temperature to give lactam (**18**) in 90% yield (Scheme 6). The important feature of compound (**17**) is that it contains a methyl group at C-14b (C-3), which means that, for it at least, mechanism 1 (Scheme 1) is ruled out.



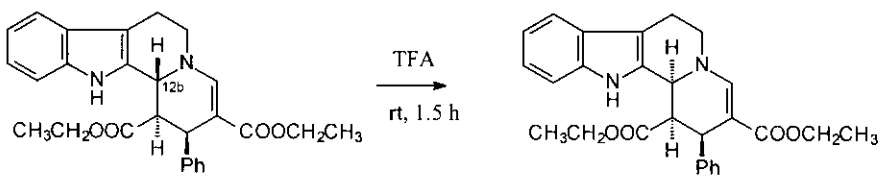
17 **18**

Scheme 6



19

The roxburghines, such as roxburghine D (**19**),[27] are a group of indole alkaloids containing two epimerizable centres in the sense discussed here. It would be expected that, besides C-3, also C-19 in roxburghines would be epimerized easily. Compounds which, like **19**, contain a vinylogous urethane moiety, constitute a notable group in regard to their epimerization behaviour. As a representative example, Rosentreter *et al.*[28] epimerized vinylogous urethane (**20**) at room temperature in TFA (Scheme 7). Epimer (**21**) was obtained in 70% yield. When the reaction was repeated with TFA-*d* deuterium was incorporated at C-12b.

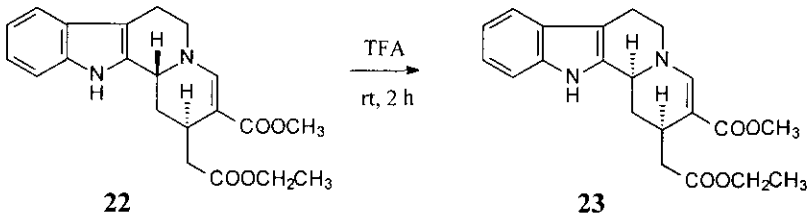


20 **21**

Scheme 7

The epimerization was postulated to take place *via* mechanism 1, for which the deuterium incorporation at C-12b was a strong indication. Rosentreter *et al.* also conducted reduction experiments with the vinylogous urethanes. Interestingly, only the double bond of the vinylogous urethane moiety was reduced. In contrast, no products corresponding to the 2,7-dihydro derivatives obtained by Royer *et al.*[25] (Scheme 5) were isolated even though the conditions used were similar.

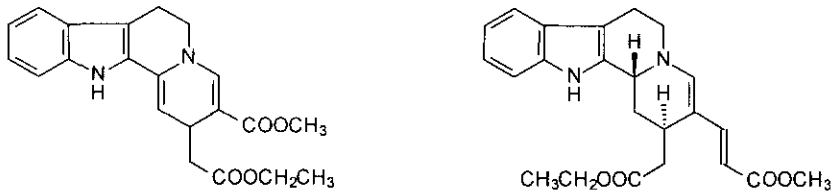
Subsequent to this, Wenkert and co-workers[29] conducted epimerization experiments on various vinylogous urethanes. The results were similar to those of Rosentreter and co-workers: the epimerization equilibrium with TFA was achieved at room temperature within 2 h. By way of example, Scheme 8 shows the transformation of compound (**22**) to compound (**23**) (80%).



22 **23**

Scheme 8

Wenkert *et al.* made two other observations: if TFA was not first degassed, bridgehead oxidation - leading to compound (**24**) - took place, and doubly vinylogous urethanes, such as **25**, did not epimerize.

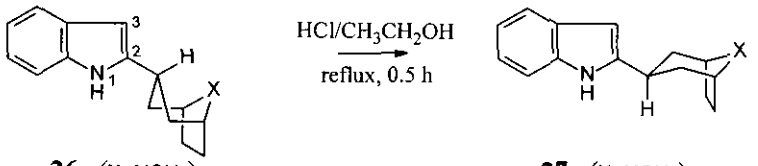


24 **25**

The common and very interesting feature in the epimerization of the lactams and vinylogous urethanes discussed above is that they are epimerized *at room temperature*. When other indolo[2,3-*a*]quinolizidines are epimerized, even with strong acids, *heat* is usually required.

A closely related example of compounds not possessing the indoloquinolizidine skeleton is worth noting. Repke and co-workers[30] found that indoles suitably substituted at the 2-position (**26a** and **26b** in Scheme 9) epimerized when treated with TFA. With TFA-*d*, deuterium incorporated immediately at the 3-position of indole and after a while at the epimeric centre. The fact that the incorporation of the two deuterium

atoms occurred faster than the epimerization was explained by the presence of a higher energy intermediate, which generally converts to the product but occasionally gives back the starting material. The epimerization rate was very similar for **26a** and **26b**, but the deuterium exchange at the C-3 of indole was significantly faster with the tropane derivative (**26a**).



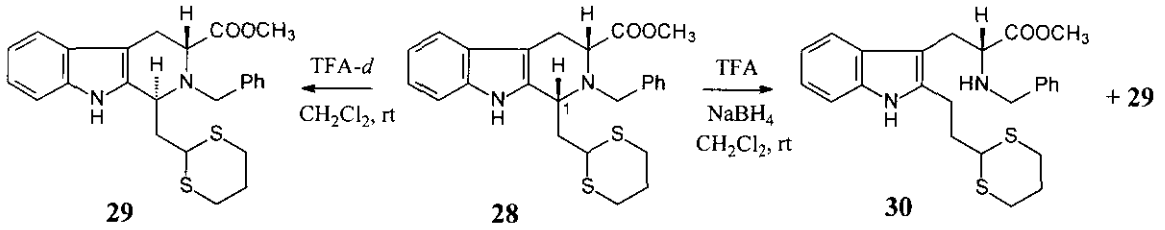
26a (X=NCH_3)
26b (X=CH_2)

27a (X=NCH_3)
27b (X=CH_2)

Scheme 9

Thus, in this case, the deuterium incorporation at the 3-position of indole (corresponding to C-7 in reserpine) suggests that mechanism 1 would be active.

Cook *et al.*[31] conducted important epimerization studies with β-carboline derivatives. When compound (**28**) was epimerized with TFA-*d*, the corresponding epimer (**29**) was furnished in high yield (Scheme 10), but no deuterium was incorporated at C-1. When the epimerization reaction was then repeated with TFA/$NaBH_4$, the reaction products were the *trans*-epimer (**29**) and the reduced ring-cleavage intermediate (**30**) in approximately equal amounts. No traces of the starting material (**28**) were observed. A reduction experiment (TFA/$NaBH_4$ in CH_2Cl_2) with epimer (**29**) gave only starting material.

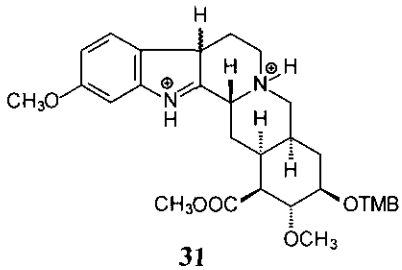


29 **28** **30**

Scheme 10

The fact that no deuterium had incorporated rules out mechanism 1. The ring-cleavage intermediate argues very strongly for mechanism 2.

As an interesting addition to the discussion on the mechanistic alternatives, Balón and co-workers[32] have recently shown that, under sufficiently strong acidic conditions (18M H_2SO_4), a dication intermediate (**31**) of reserpine is formed, protonated at both C-7 and N_b.



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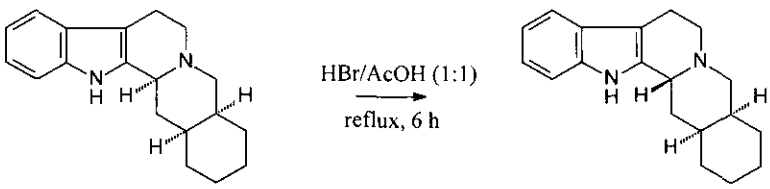
VI ACID-CATALYSED EPIMERIZATION OF INDOLO[2,3-*a*]QUINOLIZIDINES: A TOOL IN INDOLE ALKALOID SYNTHESIS?

We now present some examples of the acid-catalysed epimerization of indolo[2,3-*a*]quinolizidines having synthetic importance. The list is not intended to be exhaustive but rather to show that the reaction can actually be exploited in synthesis, a task for which it has generally been undervalued.

Like reserpine and many of its derivatives, the acid-catalysed epimerization of some yohimbine derivatives[33] was also under study in the 1950's. Wenkert and Liu[11] used concentrated hydrobromic acid/acetic acid in their epimerization experiments. Refluxing of alloyohimbane (**32**) or epialloyohimbane (**33**) with this reagent gave an equilibrium mixture (yield 74±5%), where epialloyohimbane (**33**) was the major isomer (*ca.* 78%) (Scheme 11). The epiallo skeleton is favoured when ring E does not contain bulky substituents.[34]

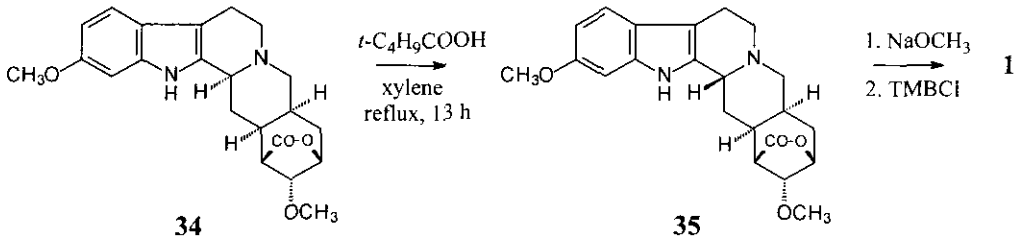


32 **33**

Scheme 11

One of the best-known examples of an acid-catalysed epimerization of indolo[2,3-*a*]quinolizidine derivatives is the culmination of the classic total synthesis of reserpine (**1**) reported by Woodward and co-workers.[10] Having arrived in their synthetic route at an isoreserpine derivative, their final step was to

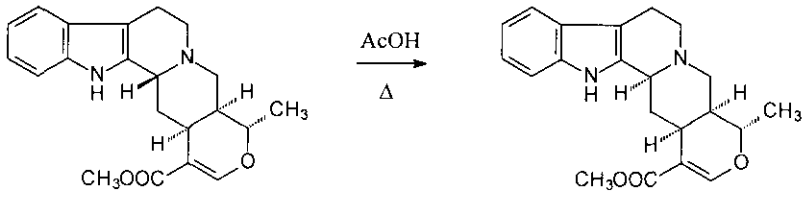
convert this intermediate to reserpine. The step was ingeniously executed - not by converting the derivative to isoreserpine (**2**) and then epimerizing - but by transforming it into isoreserpic acid lactone (**34**), which, for steric reasons, easily epimerized to reserpic acid lactone (**35**) in 79% yield upon treatment with pivalic acid (Scheme 12). The same idea was elaborated almost simultaneously by Schlittler and co-workers.[6]



34 **35**

Scheme 12

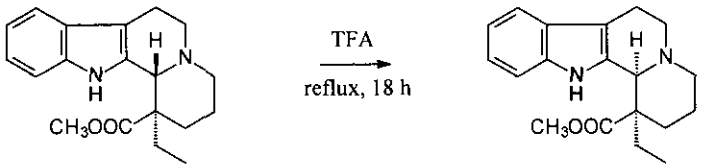
The equilibration of several corynantheine-type alkaloids in acetic acid was studied by Schmid and co-workers.[35] Some heteroyohimbines have been investigated by Salkin *et al.*[36] and Shamma and Moss Richey.[37] Akuammigine (**36**) in hot acetic acid was reported by Sakai and co-workers[38] to give tetrahydroalstonine (**37**), without stated yield (Scheme 13). However, replacing acetic acid with its stronger derivative, trifluoroacetic acid (TFA), has made the acid-catalysed epimerization of indolo[2,3-*a*]quinolizidines faster and consequently more useful for compounds that do not contain methoxy groups in the indole ring.



36 **37**

Scheme 13

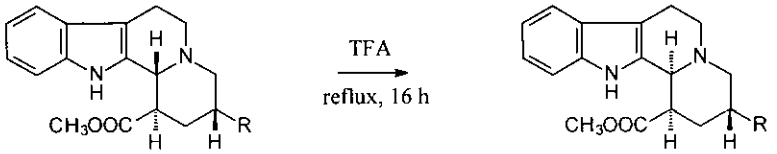
Rapoport and co-workers[39] utilized the acid-catalysed epimerization in preparing a key intermediate for the synthesis of the pharmacologically valuable indole alkaloid vincamine. The stereoselectivity in obtaining this intermediate has been a problem in the synthesis of eburnamine-vincamine alkaloids,[40] but Rapoport *et al.* showed that compound (**39**) could be isolated in 71% yield by equilibrating compound (**38**) in refluxing TFA (Scheme 14).



38 **39**

Scheme 14

Lounasmaa and co-workers have recently utilized the acid-catalysed epimerization as a tool to obtain important intermediates for the preparation of tacamine-type alkaloids. Ester (**40a**) ($R=C_2H_5$) gave ester (**41a**) ($R=C_2H_5$) in 79% yield when it was treated with TFA (Scheme 15).[41]



40a ($R=C_2H_5$) **41a** ($R=C_2H_5$)
40b (R=H) **41b** (R=H)

Scheme 15

In the same way, *trans*-ester (**40b**) (R=H) was epimerized in refluxing TFA to give the thermodynamic product *cis*-ester (**41b**) (R=H) as major epimer (78%). This reaction provides an easy access to both desethyleburnamonine isomers starting from the same precursor.[42] The first systematic epimerization study of 1-, 2-, and 3-ethyl substituted indolo[2,3-*a*]quinolizidines has also been carried out.[43] These examples show that in favourable cases tedious oxidation/reduction procedures can be avoided by utilizing the present epimerization reaction.

VII CONCLUSIONS

Despite the convincing evidence presented for mechanism 2, some confusion still exists. It has been shown that, in a strong acid, protonation takes place at C-7 and even a dication may exist, at least in the case of reserpine. The question then arises: why is mechanism 1 not operational? The reduction experiments with zinc in acetic acid resulted only in 2,3-secoreserpine (**8**) and 3,4-secoreserpine (**9**). No 2,7-dihydro compounds were formed. This would seem to indicate that with acetic acid protonation at C-7 does not occur easily. It is very likely that the choice of epimerization route depends on the strength of the

acid medium. The behaviour of reserpine and other indolo[2,3-*a*]quinolizidines in strong acids, such as TFA, presents an important subject for further study.

Further synthetic applications of the acid-catalysed C-3 epimerization can be predicted as it can provide an easy access to compounds, which otherwise may be difficult to reach. The different structural features of the compounds to be epimerized certainly have an effect on the epimerization reaction. Lactams and vinylogous urethanes epimerize relatively fast at room temperature, whereas other indolo[2,3-*a*]quinolizidines require more vigorous conditions. One possible explanation for this difference may be that the operating mechanisms are different. Many questions concerning the acid-catalysed C-3 epimerization indeed remain unresolved.

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Received, 2nd March, 1998