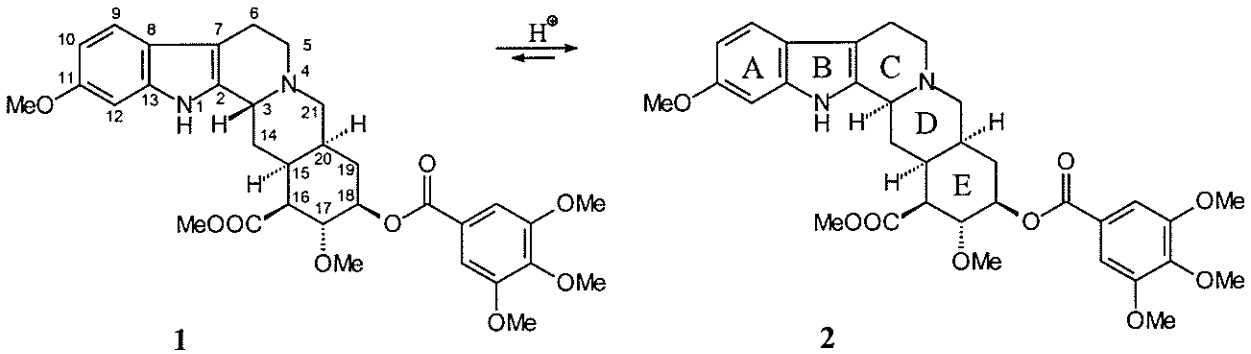
DEUTERIUM INCORPORATION INTO RESERPINE‡

Mauri Lounasmaa*, Mathias Berner, Arto Tolvanen, and Reija Jokela

Laboratory for Organic and Bioorganic Chemistry
Technical University of Helsinki, P.O.Box 6100, FIN-02015 HUT Espoo, Finland

Abstract – Treatment of reserpine (**1**) with TFA-*d* under various conditions demonstrated that deuterium incorporation proceeds much more slowly than the epimerization. Indirect evidence was thereby obtained for the mechanism of the acid-catalysed epimerization of reserpine (**1**) that proceeds through C-3–N_b bond cleavage. Furthermore, the effectiveness of TFA as an epimerization reagent was demonstrated.

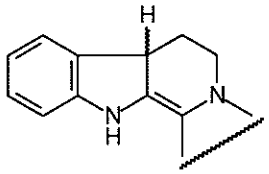
Reserpine (**1**),[1] one of the principal members of the yohimboid class of indole alkaloids, has been a classic compound for the study of acid-catalysed epimerization of indolo[2,3-*a*]quinolizidines.[2] Already in the 1950's this reaction was utilized to isomerize reserpine (**1**) to its more stable C-3 epimer isoreserpine (**2**).[3]



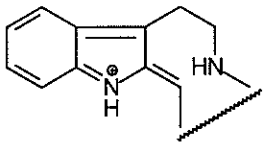
1 **2**

In connection with their ingenious total synthesis of reserpine in 1958, Woodward *et al.*[4] presented three different intermediates to explain the inversion of an isoreserpine derivative to the reserpine derivative. Gaskell and Joule[5] carried out a thorough investigation of the mechanistic aspects of the epimerization reaction of reserpine (**1**) in 1967, and Cook and co-workers[6] conducted a reinvestigation of the same subject in 1989. The main intermediates of the three mechanisms that were proposed are shown in Figure 1.

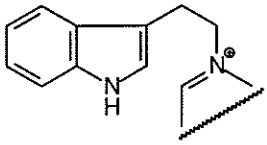
‡ Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 73rd birthday.



Intermediate of Mechanism 1



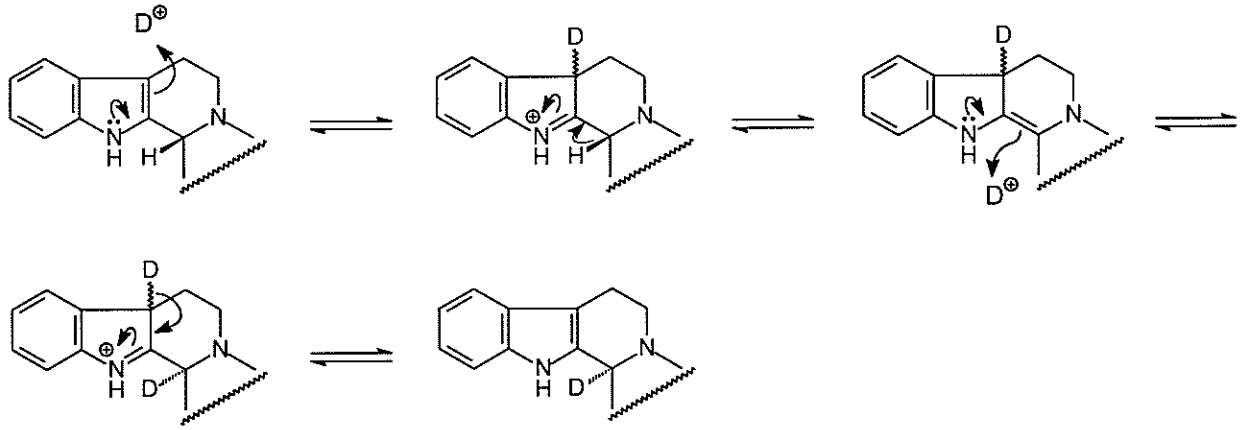
Intermediate of Mechanism 2



Intermediate of Mechanism 3

Figure 1

Recently, indirect evidence has been presented for Mechanism 1.[7,8] Treatment of reserpine (**1**) under strong acidic conditions results in protonation at C-7, which is a prerequisite for Mechanism 1. Since only Mechanism 1 results in hydrogen cleavage at C-3, further evidence for Mechanism 1 should be available through epimerization studies with a deuterated acid. We have previously reported[9] deuterium incorporation at C-12b (corresponds to C-3) in 2-ethyl substituted indolo[2,3-*a*]quinolizidines under vigorous conditions (refluxing in TFA-*d* overnight). Similar hydrogen exchange was observed by Rosentreter and co-workers[10] in their studies. Deuterium incorporation *via* Mechanism 1 is depicted in Scheme 1.



Scheme 1

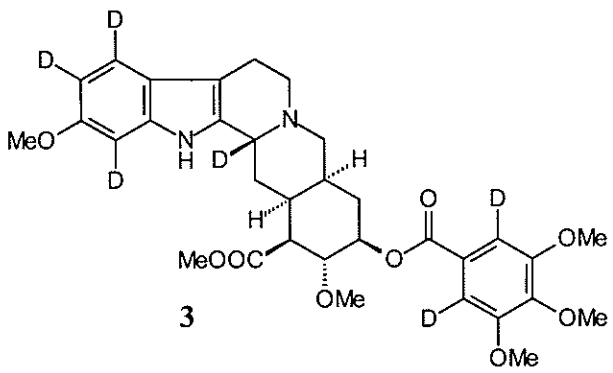
However, mere deuterium incorporation at C-3 is not sufficient evidence for Mechanism 1 being primarily responsible for the acid-catalysed epimerization reaction: the rates of deuterium incorporation and epimerization should be identical. We investigated this problem by monitoring the epimerization rate in a deuterated acid.

RESULTS AND DISCUSSIONS

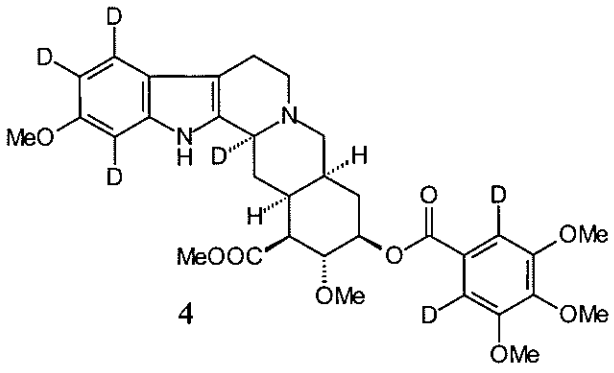
It is attractive in epimerization studies to work with a compound that isomerizes rapidly. Reserpine (**1**), which epimerizes easily due to the electron donating methoxy group in the A ring,[3] was accordingly chosen as target molecule. Besides the nature of the compound, also the employed acid affects the

epimerization rate. Having found in previous studies[11] that TFA is an efficient epimerization reagent, we decided to utilize this acid in our present work. Reserpine epimerizes remarkably fast in TFA: when reserpine (**1**) was refluxed in TFA at 90°C for 10 min the equilibrium ratio of 15:85 (**1**:**2**) was achieved. Tracking the epimerization rate more accurately we found that when reserpine (**1**) was refluxed in TFA for 1 min, a ratio of 48:52 (**1**:**2**) was obtained, and after just 5 min the ratio was 15:85 (**1**:**2**). Thus, with use of a strong acid, the reaction time of the acid-catalysed epimerization reaction of reserpine (**1**) can be shortened dramatically relative to the reaction times given in the literature.[5,6] As a representative example, when reserpine (**1**) was treated with 1% HCl/MeOH for 12 h at 68°C the ratio was only 42:58 (**1**:**2**).[6] In addition, the yields with TFA are nearly quantitative. To confirm that the ratio 15:85 (**1**:**2**) indeed is the equilibrium ratio, we refluxed isoreserpine (**2**) in TFA for 10 min. The ratio was the same.

To ensure full deuterium incorporation, we commenced our studies by refluxing reserpine (**1**) in TFA-*d* at 90°C overnight. Hexadeuterated reserpine (**3**)[12] and isoreserpine (**4**)[13] were obtained in the ratio 15:85 (determined by ^{1}H NMR integration). The deuterium incorporation at C-3 indicates that Mechanism 1 could be active under the employed conditions.

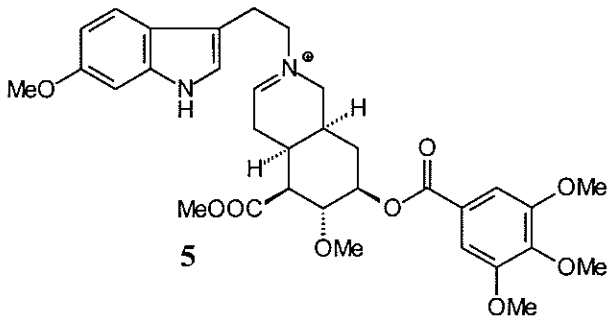


3



4

In a second experiment we used a much shorter reaction time: reserpine (**1**) was refluxed in TFA-*d* at 90°C for just 5 min. Epimerization occurred (21:79), but this time only the hydrogens at C-10 and C-12 were exchanged, and virtually no deuterium was incorporated at C-3. Similar results were obtained when reserpine was stirred in TFA-*d* overnight at room temperature. Thus, the rapid epimerization without deuterium incorporation at C-3 provides strong evidence that Mechanism 1 is not the main route by which reserpine (**1**) undergoes epimerization. In addition, Martin and co-workers[14] have reported that under acidic conditions the iminium compound (**5**) cyclizes primarily to reserpine (**1**) and not isoreserpine (**2**), demonstrating that Mechanism 3 cannot be the major pathway in the epimerization reaction of reserpine (**1**). If only the three mechanisms noted above are considered, one can then conclude that Mechanism 2 is primarily responsible for the epimerization reaction. This result supports the conclusions of Cook and co-workers.[6]



5

CONCLUSIONS

We have shown that, in the case of reserpine (**1**), deuterium incorporation proceeds much more slowly than epimerization. Thus, Mechanism 1 cannot be primarily responsible for the acid-catalysed epimerization of reserpine (**1**). Since Mechanism 3 likewise cannot be primarily responsible for the epimerization (*vide supra*), it must be Mechanism 2 that is active in the isomerization process. As also demonstrated here, TFA is a highly effective epimerization reagent: with use of TFA the epimerization reaction times of reserpine (**1**) were reduced dramatically relative to the conventionally used reagents.

REFERENCES AND NOTES

1. Biogenetic numbering: J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**,508.
2. For a review, see: M. Lounasmaa, M. Berner, and A. Tolvanen, *Heterocycles*, 1998, **48**, 1275.
3. H.B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André, and P. R. Ulshafer, *J. Am. Chem. Soc.*, 1955, **77**, 4335.
4. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1.
5. A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.
6. L.-H. Zhang, A. K. Gupta, and J. M. Cook, *J. Org. Chem.*, 1989, **54**, 4708.
7. M. A. Muñoz, C. Carmona, J. Hidalgo, and M. Balón, *Heterocycles*, 1989, **29**, 1343.
8. M. Royer, M. D. de Maindreville, J.-Y. Laronze, J. Lévy, and R. Wen, *Tetrahedron*, 1996, **52**, 9069.
9. M. Lounasmaa, L. Miikki, and A. Tolvanen, *Tetrahedron*, 1997, **53**, 5349.
10. U. Rosentreter, L. Born, and J. Kurz, *J. Org. Chem.*, 1986, **51**, 1165.
11. M. Lounasmaa, M. Berner, M. Brunner, H. Suomalainen, and A. Tolvanen, *Tetrahedron*, 1998, **54**, 10205.
12. Selected MS data of compound (**3**): 616 (33), 615 (57), 614 (M^+, 73), 613 (43), 612 (27), 611 (16), 450 (60), 419 (18), 418 (23), 417 (19), 403 (13), 402 (25), 401 (35), 400 (31), 399 (30), 398 (28), 386 (18), 385 (22), 384 (19), 364 (17), 363 (25), 362 (23), 252 (50), 214 (96), 197 (100).
13. Selected MS data of compound (**4**): 617 (15), 616 (43), 615 (83), 614 (M^+, 100), 613 (59), 612 (33), 611 (10), 403 (10), 402 (20), 401 (32), 400 (26), 399 (26), 398 (20), 397 (7), 387 (5), 386 (12), 385 (18), 384 (15), 383 (7), 382 (4), 197 (72).
14. S. F. Martin, H. Rüeger, S. A. Williamson, and S. Grzejszczak, *J. Am. Chem. Soc.*, 1987, **109**, 6124.

Received, 5th April, 1999