Kinetics and Mechanism of Reserpine Oxidation by Nitrous Acid. A Reinterpretation of Recent Results[1]

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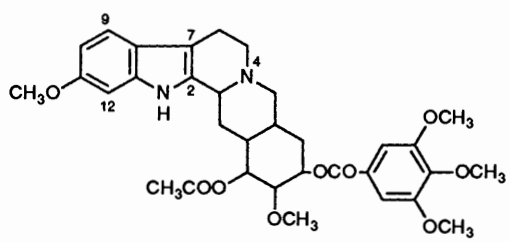
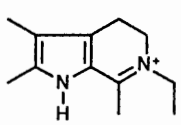
Recently reported kinetic results from the reaction of reserpine and nitrous acid (to give 3,4-dehydroreserpine) are reinterpreted. Two possible mechanisms are consistent with the experimental observations involving either (*a*) the rapid and reversible formation of N^1-nitrosoreserpine (**3**), which then undergoes a rate-limiting acid-catalysed rearrangement to yield the product, or (*b*) the rapid and reversible attack at the tertiary *N*-atom yielding a quaternary nitrosamine ion, which breaks down in an acid-catalysed rate-limiting process, which takes place in parallel with the reversible and rapid formation of **3**. Mechanism (*b*) has a close analogy to that involved in the nitrosation of simpler tertiary amines.

Recently[1] some of us have published the results of a kinetic study of the reaction of the Rauwolfia alkaloid reserpine (**1**) with nitrous acid, where the product is believed[2] to be 3,4-dehydroreserpine (**2**); a mechanism was postulated. However it now appears that details of the mechanistic interpretation are flawed, and that another mechanism is equally consistent with the results. This paper sets out to present these two mechanisms in a more appropriate fashion.



Reserpine **1**



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Results

Reactions were carried out in 20% methanol–water (and in some cases in 30% methanol–water) using hydrochloric acid as a catalyst. Reactions were followed spectrophotometrically (mostly at 25 °C) measuring the appearance of the product at 380 nm. The experimental results are summarised as follows.

(i) With the initial $[HNO_2] \gg$ initial [**1**] the kinetics fitted a first-order rate equation.

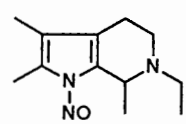
(ii) Using a range of [HCl] the reaction was first-order in [HCl].

(iii) With a range of $[HNO_2]$, the measured first-order rate constant, k_{obs}, was found to take the form given in eqn. (1).

$$k_{obs} = a[HNO_2][H^+]/(1 + b[HNO_2]) \quad (1)$$

(iv) No catalysis was detected by the addition of Cl^-, Br^- or SCN^- (1×10^{-2} mol dm^{-3}).

(v) At very low acidity N^1-nitrosoreserpine (**3**) was isolated and characterised. At higher acidity **3** reacted to give **2**.



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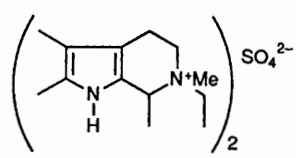

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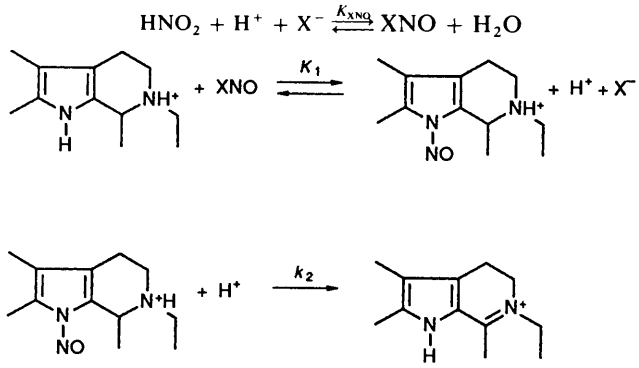
(vi) N^4-Methylreserpine sulphate (**4**) reacted with nitrous acid to give a N^1-nitroso derivative which did not rearrange at higher acidity to give a dehydro derivative.

In retrospect a better choice of co-solvent would have been dioxane, since methanol substantially converts nitrous acid into methyl nitrite which is not a nitrosating agent under these conditions.[3] This certainly accounts for the reduction in rate constants when the solvent composition is changed from 20% methanol to 30% methanol. The use of hydrochloric acid as the acid catalyst can cloud the issue of possible chloride ion catalysis. Certainly the addition of Cl^- (1×10^{-2} mol dm^{-3}) hardly changes the $[Cl^-]$ in most of the runs. However, from previous experience where nucleophilic catalysis does occur SCN^- (1×10^{-2} mol dm^{-3}) should produce an appreciable effect, so it is safe to assume in the present case that there is in fact no nucleophilic catalysis.

Discussion

Two mechanisms are equally consistent with the results; (*a*) where **3** is an intermediate on the pathway to product **2**, and (*b*) where rapid and reversible formation of **3** occurs in parallel with the pathway to the products.

Mechanism (a).—This is set out in Scheme 1 and is essentially the mechanism outlined earlier in ref. 1, although the quantitative treatment previously given is in error. We include the possible reaction *via* the general nitrosating agent XNO (produced from HNO_2 and X^- *e.g.* Cl^-, Br^- and SCN^-); in the absence of added X^- ($X^- = H_2O$) the reagent is $H_2NO_2^+$ or NO^+ which are indistinguishable kinetically. It is assumed that nitrosation at the indole nitrogen atom is rapid (compared with subsequent reactions) and reversible, with equilibrium constant K_1. This is a reasonable assumption given the published results on the closely related tryptophan system,[4] where the measured



Scheme 1

equilibrium constant ($= K_{XNO}K_1$) is 850 $dm^3\ mol^{-1}$. The rate equation expected from Scheme 1 is given in eqn. (2), where [S]

$$\text{Rate} = \frac{k_2K_1K_{XNO}[HNO_2][H^+][S]}{1 + K_1K_{XNO}[HNO_2]} \quad (2)$$

is the stoichiometric concentration of substrate (reserpine). With $[HNO_2]_0 \gg [S]_0$ the measured first-order rate constant k_{obs} (defined by Rate $= k_{obs}[S]$) is given by eqn. (3), which

$$k_{obs} = \frac{k_2K_1K_{XNO}[HNO_2][H^+]}{1 + K_1K_{XNO}[HNO_2]} \quad (3)$$

takes the same form as the experimental eqn. (1). The double reciprocal plot of $(k_{obs})^{-1}$ *vs.* $[HNO_2]^{-1}$ yields a straight line (ref. 1) and a value for k_2 of 7.6×10^{-3} $dm^3\ mol^{-1}\ s^{-1}$ and of K_1K_{XNO} of 136 $dm^3\ mol^{-1}$ in the 20% methanol solvent system, and corresponding values of 3.4×10^{-3} $dm^3\ mol^{-1}\ s^{-1}$ and 193 $dm^3\ mol^{-1}$ for reaction in the 30% methanol solvent.

The product K_1K_{XNO} is independent of the concentration and nature of X^-, so it is impossible to establish what the actual nitrosating agent is in this case. The same situation exists for the nitrosation of amides and of other nitrogen sites containing powerful electron-attracting substituents.[5] This will always be true when there is a rapid and reversible nitrosation step followed by a rate-limiting step.

The detailed mechanism of the final step in Scheme 1 is probably as outlined earlier[1] involving the elimination of HNO, although it is a matter of speculation. The case would be strengthened by the identification of N_2O in the products.

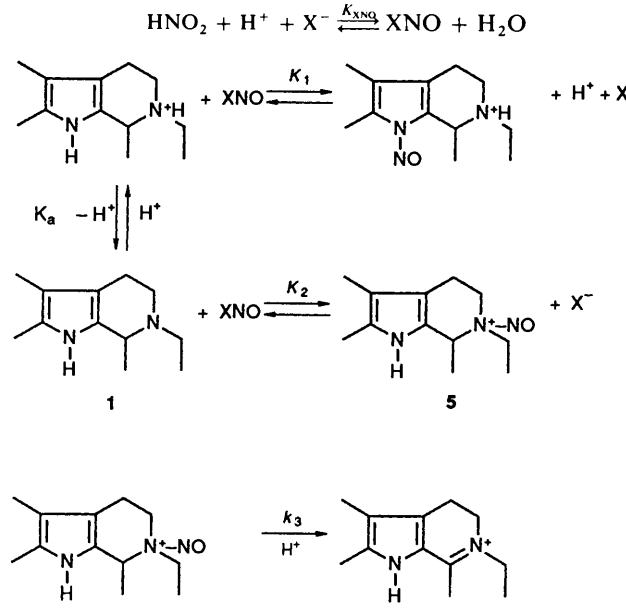
Mechanism (b).—The detection of an intermediate in a reaction does not necessarily mean that the intermediate is on the pathway to the observed products. Such an intermediate could be formed reversibly and in parallel with a reaction leading to products. Scheme 2 outlines a mechanism where rapid and reversible nitrosation at the indole nitrogen atom occurs in parallel with direct attack at the tertiary-*N* atom. In this case we propose a rapid and reversible formation of the quaternary nitrosonium ion **5** (in low concentration), followed by a rate limiting reaction involving a proton to yield the product.

The expression for k_{obs} (defined previously) deduced from Scheme 2 is given in eqn. (4), which also takes the same form as

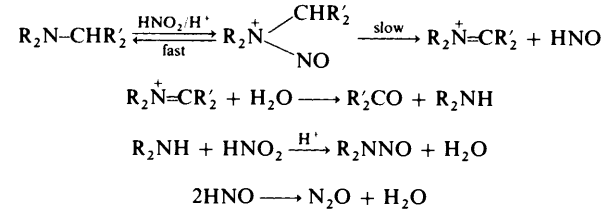
$$k_{obs} = \frac{k_3K_2K_aK_{XNO}[HNO_2][H^+]}{1 + K_1K_{XNO}[HNO_2]} \quad (4)$$

the experimentally observed eqn. (1), and is also independent of the nature of X^-.

Nitrosation of tertiary amines is now well-known, and the mechanism generally accepted[6] is set out in Scheme 3, for a simple straight chain system.

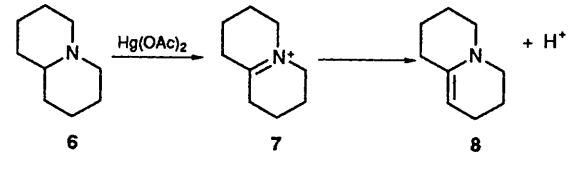


Scheme 2



Scheme 3

A quaternary nitrosonium ion is rapidly and reversibly formed, and breaks down slowly with the elimination of HNO to give the iminium ion, which in this case is readily hydrolysed to give a carbonyl compound and a secondary amine. In the present case it is likely that reaction would stop at the iminium ion stage because of the cyclic nature of the structure. In a closely related example, quinolizidine (**6**) is oxidised by mercuric acetate to the enamine **8** probably *via* the iminium ion **7**.[7] Similarly indolizidine systems in alkaloids are oxidised by *N*-bromosuccinimide to iminium ion structures.[8]



As is the case in mechanism (*a*), the case for (*b*) would be strengthened by the confirmation of N_2O in the reaction products. The experimental results obtained thus far do not allow the distinction between mechanisms (*a*) and (*b*); presumably this question could be answered by studies on the N^1-alkylated derivative of reserpine.

References

1 M. A. Munoz, D. González-Arjona and M. Balón, *J. Chem. Soc., Perkin Trans. 2*, 1991, 453.

2 R. P. Haycock, P. B. Sheth, T. Higuchi, W. J. Mader and J. Papppariello, *J. Pharm. Sci.*, 1966, **55**, 826.

3 S. E. Aldred, D. L. H. Williams and M. Garley, *J. Chem. Soc., Perkin Trans. 2*, 1982, 777; J. Casado, F. M. Lorenzo, M. Mosquera and M. F. R. Prieto, *Can. J. Chem.*, 1984, **62**, 136.

4 A. Castro, E. Iglesias, J. R. Leis, M. E. Peña, J. Vázquez Tato and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1165.
5 G. Hallett and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1372; J. K. Snyder and L. M. Stock, *J. Org. Chem.*, 1980, **45**, 886; J. Fitzpatrick, T. A. Meyer, M. O'Neill and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1984, 927.
6 D. L. H. Williams, *Nitrosation*, CUP, 1988, p. 99 and references therein.
7 N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *J. Am. Chem. Soc.*, 1955, **77**, 439.
8 K. V. Rao and L. S. Kapicak, *J. Heterocycl. Chem.*, 1976, **13**, 1073.

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