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THE ACID CATALYSED C3 EPIMERIZATION OF RESERPINE AND DESERPIDINE

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Abstract The epimerization at C3 of reserpine and deserpidine catalysed by acetic acid has been studied. 3-Deuterio-isoreserpine epimerizes without loss of label. Reserpine and isoreserpine methosalts do not epimerize at C3 in acetic acid. 3-Deuterio-isodeserpidine dedeuterates faster than it epimerizes. It is concluded that epimerization in these alkaloids involves initial C2 protonation according to Scheme II.

Epimerization of Reserpine

Background. It has been recognized for some time that epimerization of alkaloids of the reserpine[1,2] (I) type at C3 is possible by treatment with organic acids,[3] mineral acids[4] and acetic anhydride.[5] Examples of base promoted C3 epimerization have been reported,[4,6] though the conditions required were vigorous and consequently poor yields were obtained. The relative stability of a particular pair of α- and β-epimers depends on the stereochemistry of the D/E ring junction and the orientation and size of substituents on the E ring. This fact was neatly utilized in the final stages of the total synthesis of reserpine.[2] The ease of epimerization does not depend upon these steric features but rather upon electronic factors associated with substitution of the benzene ring.[5]

Three mechanisms have been suggested[4,7] to account for the acid catalysed epimerization of reserpine to isoreserpine[3] (II). The three possibilities, involving initial protonation at one of three atoms, are represented in Schemes I, II and III. In Scheme I a proton is first added[8] to the indole β-position,[9] C7. A series of enamine-immonium equilibria, proceeding through an intermediate III possessing a trigonal C3, could then allow epimerization. Scheme II represents the possible

[1] J. Müeller, E. Schlittler and H. J. Bein, *Experientia* **8**, 338 (1952); L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. Müeller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta* **37**, 59 (1954).

[2] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[3] H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. André, *J. Am. Chem. Soc.* **77**, 1071 (1955).

[4] E. Wenkert and Liang H. Liu, *Experientia* **11**, 302 (1955).

[5] H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and R. E. Ulshafer, *J. Am. Chem. Soc.* **77**, 4335 (1955).

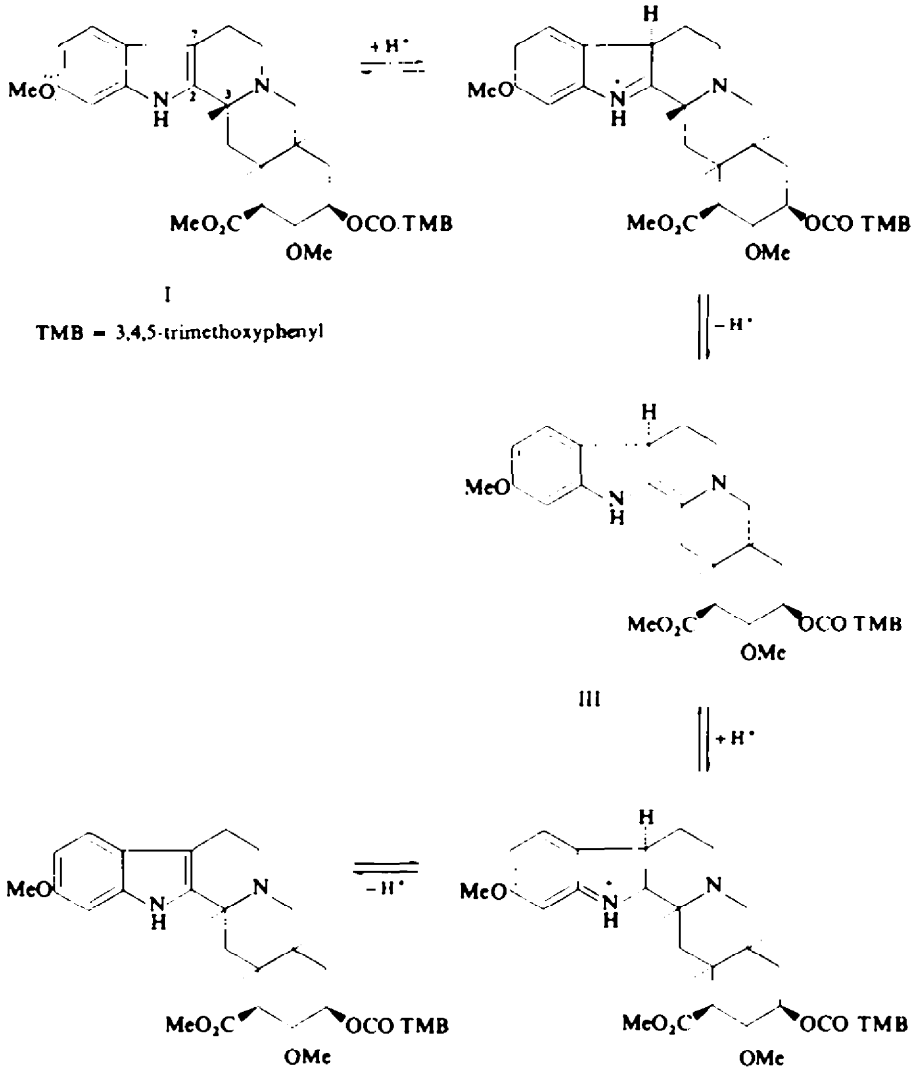
[6] M-M. Janot, R. Goutarel and M. Amin, *C.R. Acad. Sci., Paris* **230**, 2541 (1950).

[7] Footnote on p. 19 of Ref. 2.

[8] Both Scheme I and Scheme II postulate the protonation of reserpine at a centre other than the aliphatic nitrogen. In acetic acid solution most of the reserpine will be present as its N_b^+-hydrogen salt. It is an implicit assumption of these two reaction schemes, that they proceed through an equilibrium concentration of the free base.

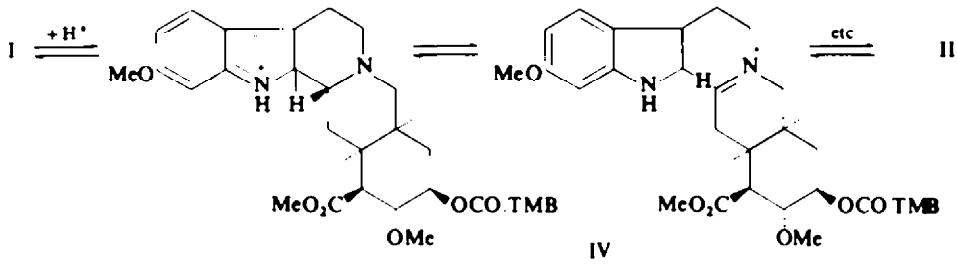
[9] R. I. Hinman and E. B. Whipple, *J. Am Chem Soc* **84**, 2535 (1962).

sequence of events following initial attack by a proton at the indole α-position,[10] C2. A ring opened intermediate IV possesses a planar C3 atom and thus could permit reclosure of the system to reserpine or isoreserpine. Scheme III suggests that a medium-sized ring intermediate V is formed by the opening of N_b-protonated reserpine. This intermediate contains a trigonal C3 and, as before, could lead on reclosure, to either of the epimeric bases.

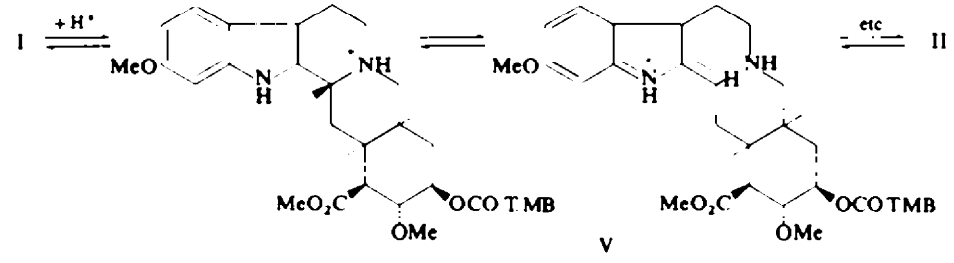


Scheme 1

[10] J. Harley-Mason and W. R. Waterfield, *Tetrahedron* **19**, 65 (1963); A. Z. Britten, J. A. Joule and G. F. Smith, *Tetrahedron* **23**, 1971 (1967).



Scheme II



Scheme III

Equilibration of reserpine

The interconversion of reserpine and isoreserpine is a true equilibrium. Both bases, on treatment with acetic acid at reflux, gave the same mixture. Isoreserpine, which has the bulky indole substituent equatorial to ring C, was 3·5 times more abundant than reserpine at equilibrium. The ratio of the two bases was unchanged by prolonged treatment with acetic acid at 140°.

3-*Deuterio-isoreserpine*

Scheme I. Examination of the three proposed mechanisms reveals that only Scheme I involves direct fision of the C3-hydrogen bond. Neither of the remaining two schemes contains an intermediate which could reasonably be expected to exchange this atom with a proton from the solvent. The Cα hydrogen atom of the part structure VI did not exchange in acidic media.[11] In order to discover whether Scheme I is operative in the epimerization of reserpine, isoreserpine labelled at C3 was prepared.

Sodium borodeuteride reduction[12] of 3-dehydroreserpine perchlorate[13] gave 3-deuterio-isoreserpine in high yield. The labelled base was treated with acetic acid at 118°. Reserpine and isoreserpine were isolated from samples withdrawn from the reaction mixture. The last sample was withdrawn after 3½ hr at which time the reaction had proceeded more than half way to equilibrium. All the reserpine and isoreserpine samples showed no mass spectroscopically detectable loss of deuterium

[11] D. W. Thomas, H. Achenbach and K. Biemann, *J. Am. Chem. Soc.* **88**, 1537 (1966).

[12] L. D. Antonnacio, N. A. Fereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, L. J. Durham and C. Djerassi, *J. Am. Chem. Soc.* **84**, 2161 (1962).

[13] J. Beyer and L. Szporny, *Magyar. Kém. Folyoirat* **65**, 24 (1959).

during the reaction. This result establishes that epimerization of reserpine in acetic acid at 118° does not involve the route depicted in Scheme I.

More vigorous treatment of 3-deuterio-isoreserpine did allow exchange of the labelled atom. Heating in acetic acid at 140° for 3 days gave totally unlabelled reserpine and isoreserpine in the equilibrium proportions. Treatment of the labelled base with acetic acid at 140° for only 1½ hr gave an almost totally equilibrated mixture which, however, retained more than 95% of the label. Thus, even under conditions which allow slow exchange of the C3 hydrogen of reserpine, the mechanism important for epimerization does not involve this process.[14]

Methosalts

Schemes II and III. Inspection of the remaining two schemes reveals an important difference in the role of the basic nitrogen. In Scheme II, participation of the lone pair of electrons on N_b is necessary for the reverse Mannich step leading to the intermediate IV. In contrast, Scheme III utilises reserpine acetate leading to an intermediate V in both of which the lone pair of electrons is involved in a covalent bond to hydrogen. No means would be available for the epimerization of reserpine and isoreserpine methosalts if the inversion required the operation of the route illustrated in Scheme II. Even if initial C2 protonation of the quaternary salts took place, the reverse Mannich C2–C3 fission would be blocked by the lack of an available lone pair of electrons on N_b. On the other hand the methosalts could be expected to epimerize, possibly even in the absence of acids, by the route envisaged in Scheme III. Stuart models show that the size of an N_b-methyl grouping in the intermediate V would not prohibit the necessary passage of the nitrogen atom to the alternate side of the molecule.

Reserpine and isoreserpine react with methyl iodide to give the salts VII (X = I) and VIII (X = I) respectively, in which the aliphatic nitrogen atoms adopt the same configurations as in the corresponding free bases. The structures VII (X = I) and VIII (X = I) can be assigned to the two methiodides on the basis of their relative rates of formation.[15] These formulations are confirmed by the NMR spectra of the two salts. The *cis* fused salt VII (X = I) displayed an N^+-methyl signal at τ 7·6 and the *trans* fused salt VIII (X = I) a corresponding signal at τ 7·92. These assignments are in accord with the relative positions demonstrated for the signals of N^+-methyl groups in simpler *cis* and *trans* N^+-methyl quinolizidinium ions.[15a, 16]

Since both methiodides were insoluble in benzene, they were converted to the corresponding methacetates. Heating VII (X = OAc) and VIII (X = OAc) in benzene solution at 140° led, in each case, to dequarternization[17] presumably via nucleo-

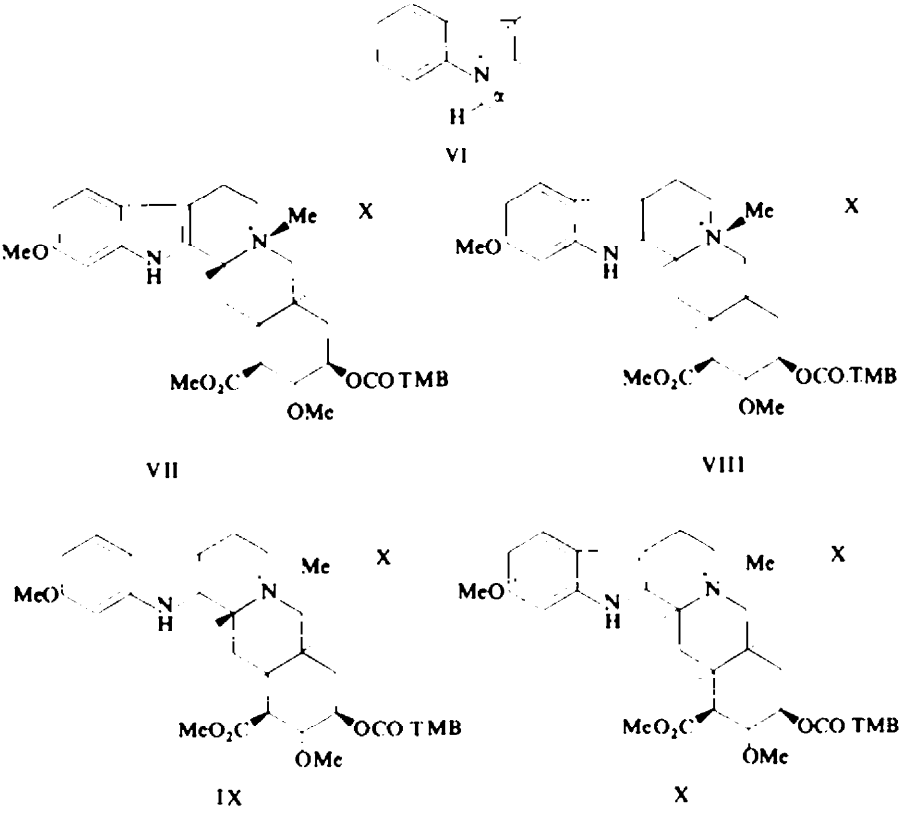
[14] The methacetate of 3-deuterio-isoreserpine showed no loss of label on heating in acetic acid at 140°. This result seems to rule out an ylid as an alternative to Scheme I to explain the exchange of the C3-hydrogen. If exchange were to proceed through the ylid having the part structure (C2 N_b^+ H) it would be anticipated that the methosalts would exchange via an ylid with part structure (C2 N_b^+—CH_3) with at least equal ease.

[15] [a] M. Shamma and J. Moss Richey, *J. Am. Chem. Soc.* **85**, 2507 (1963);
[b] M. Shamma and J. B. Moss, *Ibid.* **83**, 5038 (1961);
[c] M. Shamma and E. F. Walker, *Chem. & Ind.* 1866 (1962).

[16] M. Moynehan, R. A. Y. Jones, K. Schofield and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).

[17] The low temperature pyrolysis of quaternary ammonium acetates is under investigation as a general means of dequaternization.

philic attack by acetate ion on the quaternary methyl groups. Neither the reserpine nor the isoreserpine recovered from these reactions contained detectable amounts of the other isomer.

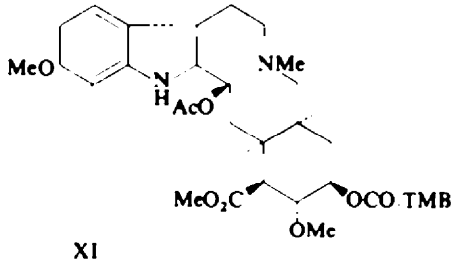


Heating the two methacetates in acetic acid also failed, in both cases, to cause epimerization at C3. When reserpine methacetate was heated at 140° in acetic acid solution for 3 days, an N_b epimeric salt IX (X = OAc) of reserpine was produced. The two salts, VII (X = ClO_4) and IX (X = ClO_4) were shown to be different by m.p. and IR comparisons. Recovery of the base from the new salt IX (X = Cl) by high vacuum pyrolysis gave reserpine with *no trace of isoreserpine*. The NMR spectrum of the new salt IX (X = I) showed an N^+-methyl singlet at τ 7·72. This represents an upfield shift from the corresponding value in the spectrum of the original reserpine methosalt VII (X = I). On the basis of the established[15a, 16] relationship between ring junction stereochemistry and chemical shift of ring junction alkyl substituent, the new salt must contain the alternative *trans* fused C/D ring junction and possess structure IX.[18] The new conformation is derived from 7 by inversion of N_b but *not of* C3.

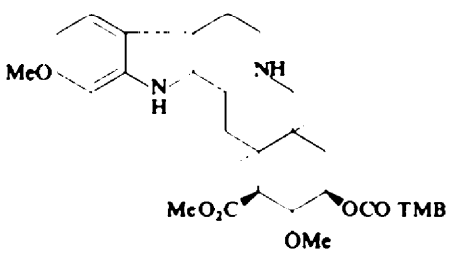
Isoreserpine methacetate was converted by an identical acetic acid treatment to a new salt X (X = OAc) of isoreserpine. Here again m.p. and IR comparisons showed

[18] It seems likely that ring E exists as a boat in this salt to allow the three substituents on it to take up equatorial orientations

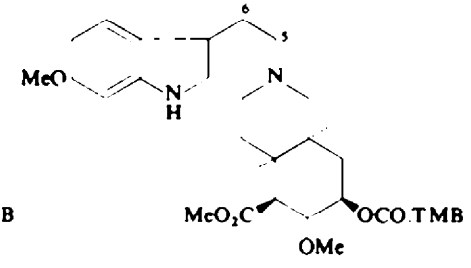
the new product X (X = ClO_4) to be different from the original isoreserpine salt VIII (X = ClO_4) and also from the salt, IX (X = ClO_4). High vacuum pyrolysis of this new salt, IX (X = Cl^-) gave isoreserpine in good yield, with no trace of reserpine. These results are important in the light of the fortuitous coincidence, at τ 7·72, of the chemical shifts of the N^+-methyl signals of both new salts. The downfield shift observed in going from the original isoreserpine salt VIII (X = I) to the new salt X (X = I) suggests a change in the stereochemistry of the C/D ring junction. This change, which involves a *trans* fused system becoming a *cis* fused system, necessitates inversion of N_b but *not of* C3. The failure of the methosalts of reserpine and isoreserpine to epimerize at C3 on heating in acetic acid is conclusive evidence against the mechanism depicted in Scheme III.



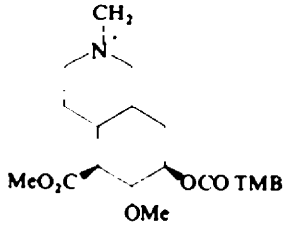
XI



XII



XIII



XIV

The route which allows inversion of the aliphatic nitrogen atom in the transformations of these salts must involve fission of a carbon-N_b bond with subsequent reclosure. The benzylic C3–N_b bond seems to be the most likely to undergo such a change. The reaction is envisaged therefore as a series of equilibria proceeding through an intermediate XI in the reserpine case and through the C3 epimer of XI in the

isoreserpine case. The intermediate XI would be formed by nucleophilic displacement of N_b^+ by acetate at C3. The intervention of an intermediate such as XI would allow inversion of N_b, but not C3, to take place. Precedents for the nucleophilic displacement of a positively charged N_b from C3 by acetate have been recorded.[19]

Reduction of reserpine

Scheme II. The data presented so far are consistent only with Scheme II for the epimerization of reserpine. Positive evidence for the intervention of the intermediate IV was obtained by reduction of reserpine. The presence of zinc in an acetic acid solution of the alkaloid at 118° allowed trapping of intermediate species present. Reserpine, isoreserpine, a crystalline dihydroreserpine (XII)[20] and an amorphous dihydroreserpine (XIII) were obtained from such a reaction. The amorphous dihydroreserpine (XIII) displayed the same UV absorption as reserpine showing that the original chromophore was intact. It gave an instantaneous blue coloration with Ehrlichs reagent. The mass spectrum of the compound was dominated by a peak at *m/e* 450 due to a species $C_{23}H_{32}NO_8$. This peak is not present in the spectra of reserpine, isoreserpine or the dihydroreserpine (XIII). The molecular formula of this ion is consistent with a fragment XIV, the anticipated result of the highly favourable fission between C5 and C6 of the molecular ion of XIII.

The detection of XIII from treatment of reserpine with zinc in acetic acid, is strong evidence in support of the presence, in the reaction mixture, of intermediate IV. It is concluded that reserpine and isoreserpine epimerize in acetic acid by the mechanism represented in Scheme II.

Epimerization of Deserpidine

Equilibration of deserpidine

Deserpidine[21] (des-11-methoxy-reserpine) which differs from reserpine only in lacking an indolic methoxyl group, epimerizes much more slowly[5] than reserpine (Experimental) but eventually yields an equilibrium mixture of analogous composition. The faster rate in the reserpine series is entirely consistent with the mechanism developed above involving initial C2 protonation. It has been clearly demonstrated[22] that electron release at the α-position of an indole is considerably facilitated by the presence of a methoxyl group at the 6-position. Such electron release would lower the activation energy necessary for the initial step depicted in Scheme II. This provides an explanation of the faster rate of epimerization of reserpine as compared with deserpidine.

3-*Deuterio-isodeserpidine*

Dedeuteration without epimerization. The presence or absence of a methoxyl at the 6-position of an indole would not be expected to have a marked effect on the ease

[19] L. J. Dolby and Shin-ichiro Sakai, *J. Am. Chem. Soc.* **86**, 1890 (1964); G. H. Foster, J. Harley-Mason and W. R. Waterfield, *Chem. Comm.* 21 (1967); K. Freter, H. H. Huebner, H. Merz, H. D. Schroeder and K. Zeile, *Liebigs. Ann.* **684**, 159 (1965).

[20] Evidence for the structure of the crystalline dihydro-reserpine as XII and a rationalization of its mode of formation will be presented elsewhere.

[21] E. Schlittler, P. R. Ulshafer, M. L. Pandow, R. M. Hunt and L. Dorfman, *Experientia* **11**, 64 (1955).

[22] J. B. Hester, *J. Org. Chem.* **29**, 2864 (1964).

of addition of a proton at the β-position. In the much slower equilibration of deserpidine epimerization by proton loss could represent the dominant reaction path. In order to test this thesis, 3-deuterio-isodeserpidine was prepared and treated with acetic acid at 118°. Samples were withdrawn and separated into deserpidine and isodeserpidine.[23] Each isomer was then analysed mass spectroscopically. The results show that loss of label takes place faster than epimerization and that the percentage of label lost from deserpidine is always the same as that lost from isodeserpidine. These results are consistent with the operation of two processes. The first of these is an *epimerization* by Scheme II *not involving loss of label*. The second is a *dedeuteration* process which *does not lead to epimerization*. In order to rationalize these findings it is necessary only to assume that the intermediate III of Scheme I reprotonates stereospecifically. A re-examination of Scheme I makes this a highly plausible explanation. The initial C7 protonation postulated for this mechanism would probably be stereospecific. Thus the same intermediate III *is not formed* from both deserpidine and isodeserpidine. Reversal of the step which forms III would then lead back only to the original base and no epimerization would be possible by this route even though C3 hydrogen exchange could take place. Since the failure of Scheme I, though operative, to cause epimerization, is due to steric factors, it is reasonable to extrapolate the conclusions drawn above from deserpidine to reserpine.

Conclusions

It is concluded, therefore, that epimerization of reserpine and deserpidine occurs through initial C2 protonation followed by reverse Mannich fission of the C2 C3 bond. The alkaloid lacking an aromatic methoxyl at C11 epimerizes more slowly than the base possessing such a group. A mechanism (Scheme I) involving proton addition at C7 does operate, especially at higher temperatures, but is slow and stereospecific and does not lead to epimerization at C3. It is likely that a medium-sized ring intermediate (XI, N_b-hydrogen instead of N_b-methyl) is present in equilibrium with the bases in acetic acid solution, but is formed stereospecifically and can ring close only to the original base.

EXPERIMENTAL

Mass spectra were determined using an A.E.I. MS9 instrument. NMR spectra were determined using a Varian A60 spectrometer. The anions of quaternary salts were interchanged using an Amberlite I.R.A.400 resin. The salt in MeOH–$CHCl_3$ was passed down a column of the appropriately equilibrated resin, the eluate evaporated and the residue crystallized. TLC was performed using Kieselgel G as adsorbent and AcOEt as eluant except where otherwise stated.

Reserpine[1] was crystallized from CH_2Cl_2–MeOH, m.p. 247–252° (dec); λ_{max} (EtOH) 267, 296 mμ (ε 15,700, 9600); *m/e* 610 (5%), 609 (19), 608 (52, M⁺), 607 (32), 593 (10), 577 (6), 414 (20), 397 (25), 381 (25), 366 (18), 265 (15), 251 (38), 195 (100).

Reserpine methiodide[15c] was prepared by refluxing the base with MeI in benzene. Crystallized from MeOH–Et_2O, the iodide had m.p. 266–268° (dec); τ (CF_3CO_2H) 7·6 (3H singlet, N^+–$C\underline{H}_3$), 6·17 (3H singlet, $CO_2C\underline{H}_3$), 5·9 (15H, $OC\underline{H}_3$).

Reserpine methoperchlorate crystallized from MeOH–Et_2O, m.p. 302–305° (dec).

Reserpine methacetate crystallized from $CHCl_3$–Et_2O, m.p. 170–179° (dec); *m/e* 622 (5%), 608 (7, M⁺), 607 (4), 424 (3), 411 (3), 396 (8), 395 (7), 382 (22), 381 (21), 365 (6), 364 (9), 226 (100), 215 (74), 212 (41), 211 (39), 195 (39).

Reserpine methochloride crystallized from MeOH, m.p. 245° (dec).

[23] W. O. Godtfredsen and S. Vandegal, *Acta Chem. Scand.* **10**, 1414 (1956).

Preparation of isoreserpine[3] Reserpine (1·02 g) and AcOH (10 ml) were heated at 140° in an evacuated sealed tube for 3 days. The resulting mixture of bases was separated by chromatography on silica gel (Chromedia S.G.31). Elution with C_6H_6–$CHCl_3$ (1:9) gave isoreserpine (0·695 g) which was crystallized from MeOH, m.p. 147–150°; λ_{max}(EtOH) 267, 296 mμ (ε 15,700, 9600); *m/e* 610 (8%), 609 (36), 608 (100, M^+), 607 (50), 593 (6), 577 (5), 397 (12), 395 (19), 251 (6), 212 (6) and 195 (15).

Isoreserpine methiodide[1,3c] was prepared by heating the base in MeI under reflux. Crystallized from EtOH the salt had m.p. 228–231° (dec); τ (CF_3CO_2H) 7·92 (3H singlet, N^+–CH_3), 6·27 (singlet, CO_2CH_3), 6·0 (15H, OCH_3); *m/e* 608 (4%), 594 (95), 593 (55), 579 (15), 564 (9), 402 (31), 400 (16), 383 (65), 370 (28), 352 (21), 240 (40), 201 (18), 184 (100).

Isoreserpine methoperchlorate crystallized from Me_2CO–MeOH–Et_2O, m.p. 312–315° (dec).

Isoreserpine methacetate was an amorphous glass.

3-Deutero-isoreserpine methacetate had *m/e* 637 (6), 623 (41), 609 (100, M^+), 591 (13), 577 (13), 412 (13), 395 (20), 381 (15), 230 (20), 226 (15), 216 (74), 212 (30), 200 (22), 195 (45).

Isoreserpine methochloride was an amorphous powder.

Deserpidine[2,1] had λ_{max}(EtOH) 271, 289 mμ (ε 17,900, 11,500); *m/e* 578 (100%, M^+), 577 (66), 563 (11·5), 547 (75), 448 (2), 383 (5), 367 (25), 366 (20), 365 (32), 351 (20), 335 (13), 291 (8), 221 (14), 212 (9), 195 (25).

Preparation of isodeserpidine. Deserpidine (48 mg) was heated under reflux in AcOH (5 ml) under N_2 for 5 days. Separation of the resulting mixture of bases by TLC gave isodeserpidine (30 mg) R_f 0·9: λ_{max} (EtOH) 271, 289 mμ (ε 17,900, 11,500); ν_{max}($CHCl_3$) 2700–2800 cm^{-1} (Bohlmann Absorption); *m/e* 578 (90%, M^+), 577 (75), 563 (15), 547 (8), 448 (2), 383 (7), 365 (100), 351 (36), 335 (17), 333 (39), 291 (8), 235 (15), 221 (41), 211 (21), 195 (65).

The equilibration of reserpine in acetic acid. Reserpine (50 mg) in AcOH (12 ml) was heated under reflux under N_2. Samples were withdrawn and each sample analysed by basification, $CHCl_3$ extraction and TLC of the total extract. Reserpine had R_f 0·5 and isoreserpine R_f 0·85. The bands corresponding to each base were thoroughly eluted and the relative quantities estimated by quantitative UV measurements.

Time (hr)	Reserpine (mg/ml)	Isoreserpine (mg/ml)	[a]Forward, pseudo unimolecular rate constant (hr^{-1})
0	4·17	0	–
1	2·38	1·79	$1·61 \times 10^{-1}$
2	1·39	2·78	$1·98 \times 10^{-1}$
4	1·35	2·82	$1·55 \times 10^{-1}$
24	0·94	3·23	

Mean pseudo unimolecular rate constant for the forward reaction, $1·7 \times 10^{-1}$ hr^{-1}.

Since K_{equil} = 3·5, the pseudo unimolecular rate constant for the back reaction is $5·05 \times 10^{-2}$ hr^{-1}.

The equilibration of deserpidine in acetic acid

Deserpidine was heated under reflux in AcOH under N_2 and analysed exactly as described for reserpine.

Time (hr)	Deserpidine (mg/ml)	Isodeserpidine (mg/ml)	Pseudo unimolecular rate constant (hr^{-1})
0	0·92	–	
26	0·61	0·31	$1·67 \times 10^{-2}$
120	0·19	0·73	

Since K_{equil} = 3·75, the pseudo unimolecular rate constant for the back reaction is $4·4 \times 10^{-3}$ hr^{-1}.

Preparation of 3-deuterio-isoreserpine

3-Dehydroreserpine perchlorate[13] (159 mg) in EtOH was treated with excess sodium borodeuteride at room temp. The soln was evaporated and the residue partitioned between $CHCl_3$ and water. The dried $CHCl_3$ extract was evaporated and the residue crystallized from MeOH to give *3-deuterio-isoreserpine* (105 mg), m.p. 147–150°; ν_{max} 2700–2800 cm^{-1} (Bohlmann absorption); *m e* 611 (11%), 610 (38), 609 (100, M^+), 608 (48), 607 (32), 594 (7), 578 (5), 398 (14), 395 (13), 251 (6) and 195 (25).

Preparation of 3-deuterio-isodeserpidine

3-Dehydrodeserpidine perchlorate[23] (130 mg) in MeOH was reduced with sodium borodeuteride to give an amorphous product (116 mg). Purification by TLC gave *3-deuterio-isodeserpidine* (42 mg), amorphous; λ_{max}(EtOH) 271, 289 mμ; *m e* 581 (3%), 580 (18), 579 (45, M^+), 578 (23), 577 (21), 564 (5), 377 (22), 275 (50), 351 (5), 333 (8), 330 (7), 329 (8), 235 (8), 221 (16), 212 (16), 197 (9), 195 (18), 168 (25), 164 (20), 151 (100), 138 (35)

The equilibration of 3-deuterio-isoreserpine

(a) 3-Deuterio-isoreserpine (56 mg) was heated under reflux in AcOH (9 ml) under N_2. Samples were withdrawn after 1, 2 and 3½ hr. Each sample was analysed as described above. All the isolated samples of isoreserpine had the same mass spectrum; *m e* 611 (10%), 610 (38), 609 (100), 608 (51), 607 (40), 594 (6), 578 (4), 398 (13), 395 (11), 381 (7), 254 (3), 251 (5), 215 (5), 212 (5), 207 (8), 200 (7), 195 (21).

Each sample of reserpine had the same mass spectrum; *m e* 611 (11%), 610 (39), 609 (100), 608 (57), 607 (42), 594 (11), 578 (8), 415 (5), 398 (20), 396 (21), 395 (41), 381 (10), 365 (6), 304 (3), 298 (5), 251 (15), 212 (11), 201 (8), 195 (21).

(b) 3-Deuterio-isoreserpine (100 mg) was heated in AcOH (10 ml) at 140° in an evacuated sealed tube for 3 days. Reserpine (23 mg) and isoreserpine (55 mg) were isolated as described above. The reserpine had *m e* 610 (5%), 609 (19), 608 (52), 607 (32), 593 (10), 577 (6), 414 (20), 397 (25), 381 (25), 366 (18), 265 (15), 251 (38), 195 (100) The isoreserpine had *m e* 610 (8%), 609 (36), 608 (100), 607 (50), 593 (6), 577 (5), 397 (12), 395 (19), 251 (6), 212 (6), 195 (15).

(c) Experiment (b) was repeated but the reaction was stopped after 1½ hr. Both reserpine and isoreserpine samples had mass spectra identical with those of the pure labelled bases.

The equilibration of 3-deuterio-isodeserpidine in acetic acid

3-Deuterio-isodeserpidine (40 mg) in AcOH (12 ml) was heated under reflux under N_2. Samples (4 ml) were withdrawn. Each sample was separated into its epimeric components and the mass spectrum of each determined

Time	Deserpidine					Calc % of	Isodeserpidine					Calc % of
	581	580	579	578	577	D species	581	580	579	578	577	D species
0	–	–	–	–		–	7	40	100	50	47	100
26	–	–	–	–		–	9	29	85	100	69	31
48	6	24	75	100	69	22	5	20	70	100	69	25
96	5	19	53	100	72	12	3	14	51	100	73	10

Mean pseudo unimolecular rate constant for loss of label is $3{\cdot}3 \times 10^{-2}$ hr^{-1}.

Experiments with reserpine methacetate

(a) Reserpine methacetate (43 mg) in benzene (5 ml) was heated at 140° for 3 days. The solvent was removed and the residue subjected to TLC. Reserpine (10 mg) was isolated. There was no isoreserpine present.

(b) Reserpine methacetate (50 mg) in AcOH (5 ml) was heated in an evacuated sealed tube for 3 days The solvent was removed under vacuum and the residue converted to the *perchlorate* IX (X = ClO_4), amorphous from MeOH—Et_2O, m.p. 196–210°.

The *iodide* IX (X = I), showed τ (CF_3CO_2H) 7·72 (3H singlet, N^+–CH_3), 6·3 (3H singlet, CO_2CH_3), 5·9 (15H, OCH_3).

The chloride IX (X = Cl; 43 mg) was pyrolysed at 220° and 10^{-5} mm Hg for 0·5 hr. The sublimate (27 mg) was purified by TLC to give reserpine (7·4 mg) and no isoreserpine.

Experiments with isoreserpine methacetate

(a) Isoreserpine methacetate (52 mg) in benzene (5 ml) was heated at 140° for 3 days. Purification as described above yielded isoreserpine (21 mg) and no reserpine.

(b) Isoreserpine methacetate (50 mg) in AcOH (5 ml) was heated in an evacuated sealed tube at 140° for 3 days. The solvent was removed in vacuum and the residue converted to the *perchlorate* X (X = ClO_4) which crystallized from MeOH–Et_2O, m.p. 282–290° (dec).

The *iodide* X (X = I) showed τ (CF_3CO_2H) 7·72 (3H singlet, $N^+-C\underline{H}_3$), 6·23 (3H singlet, $CO_2C\underline{H}_3$), 6·0 (15H, $OC\underline{H}_3$).

The *chloride* X (X = Cl) was pyrolysed as described above. The sublimate was crystallized from methanol to give isoreserpine, m.p. 246–250°. No reserpine was detectable by TLC.

Reduction of reserpine

Reserpine (1·87 g), Zn powder (3·75 g) and AcOH (75 ml) were heated under reflux under N_2 for 24 hr. The soln was filtered and evaporated. The residue was partitioned between dilute NH_3 and $CHCl_3$. The dried $CHCl_3$ layer was evaporated to give a gum which was purified by chromatography on silica gel (Chromeidia S.G.31). Elution with $CHCl_3$–MeOH (98:2) gave crystalline XII (180 mg), m.p. 236–239°. The residual materials from the column were subjected to TLC using EtOAc–MeOH (9:1) as eluant. Dihydroreserpine XIII (3 mg) was detected by means of Ehrlichs reagent, R_f 0·6; λ_{max}(EtOH) 267, 293 mμ; *m/e* 610 (19%, M^+), 608 (10), 595 (2), 579 (3), 450 (100), 399 (12), 395 (3), 256 (2), 238 (3), 225 (3), 212 (5), 195 (17).

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