Reduction of the $>C{=}\overset{+}{N}<$ Bond by an NADH Model

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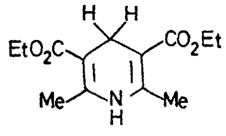
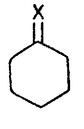
Summary Reduction of the iminium salts (**2a**), (**3a**), and (**4a**—**c**), with the Hantzsch ester (**1**), gives the corresponding ammonium salts, the reaction proceeding stereospecifically in the case of the steroidal systems (**4a**—**c**).

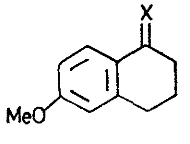
RECENTLY we communicated the stereospecific reduction of the carbon–carbon double bonds of $\alpha\beta$-unsaturated iminium salts with 1,4-dihydropyridine derivatives.[1] We report now the homogeneous reduction of the iminium chromophore, to the corresponding amine system, with the Hantzsch ester (**1**) (NADH model).[2a,b] The iminium perchlorates (**2**), m.p. 246—250 °C, and (**3**), m.p. 175 °C,[3] were prepared from the corresponding enamines, while the salts (**4a—c**) were obtained by reduction of the conjugated iminium systems[1]† which, in turn, were derived from the appropriate Δ^4-3-keto-steroids. Reduction was carried out by refluxing the substrate iminium salt with compound (**1**) (1·2 equiv.) in MeCN until the starting iminium perchlorates could not be detected (i.r absence of $C{=}N^+$ and/or t.l.c.). Evaporation and addition of ether gave the ammonium salts as crystalline products in excellent yields (> 90%). The structures of (**2b**) and (**3b**) were confirmed by liberation of the free amines (1M $NaHCO_3$) and their comparison with authentic samples prepared by $NaBH_4$ reduction of (**2a**), and (**3a**). While reduction of (**4a—c**) can, in principle, lead to isomeric steroidal amines, the product in each case was found to be a single compound. The gross structures of (**5a—c**) were deduced from their spectroanalytical data.‡ In view of the line-broadening of 3-H (and the pyrrolidine α-methylene hydrogens) due to quadrupole coupling, information on the stereochemistry of the pyrrolidine ring was derived from ^{13}C n.m.r. spectra of the compounds. Particularly relevant to the stereochemical assignment of the C-3 substituent were the chemical shifts of C-1 and C-5, which, owing to the steric compression involving $\alpha\alpha'$-pyrrolidinyl- and C-1 and C-5 (axial) protons, underwent an expected upfield shift.§ The stereochemical course of the reduction may be rationalized in terms of the sterically favoured α-approach of the reagent. However, this point requires further attention.



(1)

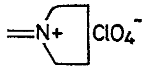


(2)



(3)

a; X =



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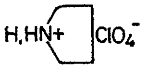
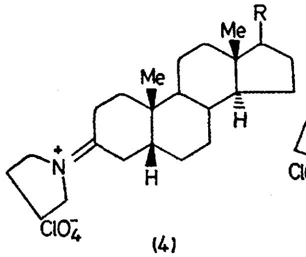
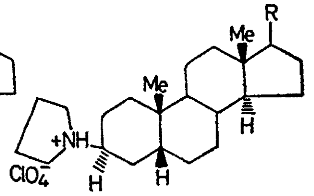




(4)



(5)

a, R = C_8H_{17}
b; R = OAc
c, R = Ac

Pyridine nucleotide-mediated enzymatic reduction of the $>C{=}N-$ linkage is an important type of transformation in numerous biological processes. The facility with which iminium salts are reduced by NADH models strongly suggests that a protonated imine species may be involved in these reductions.

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† The salt (**4c**), m.p. 234—237 °C, was prepared analogously to (**4a**), m.p. 225 °C, and (**4b**), m.p. 245—247 °C. See ref. 1.

‡ Satisfactory spectral and microanalytical data have obtained for (**5a—c**); (**5a**), m.p. 281—283 °C; (**5b**), m.p. 270—271 °C; (**5c**) m.p. 266—267 °C.

§ ^{13}C n.m.r. ($CDCl_3$), (**5a**): C-1 29·0, C-5 35·7; (**5b**): C-1 28·9, C-5 36·1; (**5c**): C-1 29·0, C-5 35·6 p.p.m. The chemical shifts for C-1 and C-5 are at a higher field (± 8·9 and ± 8·5 p.p.m., respectively) than in 5β-steroids without a C-3 substituent. C-3 α-substituents are known to cause only small diamagnetic shifts (1—2 p.p.m.) for C-1 and C-5. (D. Leibfritz and J. D. Roberts, *J. Amer. Chem. Soc.*, 1973, **95**, 4996). An example of a C-3 β-substituted 5β-steroid is reported to involve a high field shift of 7·9 p.p.m. at C-5. (G. Lukacs and C. R. Bennett in '^{13}C N.m.r. Spectroscopy,' Methods and Applications, Ed. E. Breitmaier and W. Voelter, Verlag Chemie, Weinheim 1974). A detailed discussion of the ^{13}C n.m.r. spectra will be presented elsewhere.

[1] U. K. Pandit, F. R. Mas Cabré, R. A. Gase, and M. J. de Nie-Sarink, *J.C.S. Chem. Comm.*, 1974, 627.
[2] (a) A part of this work was communicated by us at the 9th Int. Symp. on the Chemistry of Natural Products, Ottawa, Canada, 1974. (b) For a related example see S. Shinkai and T. Kunitake, *Chem. Letters*, 1974, 1113.
[3] U. K. Pandit, F. A. van der Vlugt, and A. C. van Dalen, *Tetrahedron Letters*, 1969, 3697.