Biomimetic Stereospecific Reduction of αβ-Unsaturated Iminium Salts[1]

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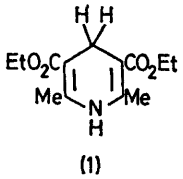
Summary Reaction of the iminium perchlorates (**2a**—**c**) with 1,4-dihydropyridine derivatives, followed by hydrolysis, results in stereospecific formation of the *cis*-ring fused ketones (**3a**—**c**).

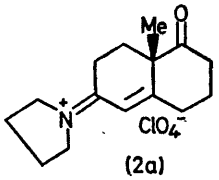
REDUCTION of electrophilic olefins with dihydropyridine derivatives (NADH models) is a model reaction of biological interest, and we have recently reported the homogeneous reduction of αβ-unsaturated acyl halides with the Hantzsch ester (**1**).[2] We report here reduction of the αβ-unsaturated iminium salts (**2a**—**c**) to the corresponding dihydro-systems (**3a**—**c**) with 1,4-dihydropyridine derivatives.

The crystalline iminium perchlorates [(**2a**), m.p. 208—212°; (**2b**), m.p. 235—237° (decomp.); (**2c**), m.p. 254—261°] were readily obtained by treatment of the corresponding dienamines with 70% $HClO_4$–AcOH.[3] Typically, a solution of the iminium salt and the Hantzsch ester (**1**) (1·2—1·8 equiv.) in MeCN was refluxed for *ca.* 20 h until the starting

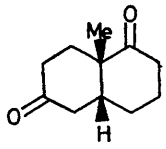
perchlorate could not be detected (as the corresponding $\alpha\beta$-unsaturated ketone) by t.l.c. After evaporation the residue was extracted with ether and the resulting product† was hydrolysed to give the saturated ketone (*ca.* 70%). The ketones (**3a**—**c**) were found to be *single* isomers in each case. Essentially similar results were obtained when (**2a**) and (**2c**) were reduced with 1-benzyl-1,4-dihydronicotinamide.



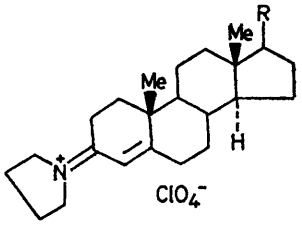
(1)



(2a)

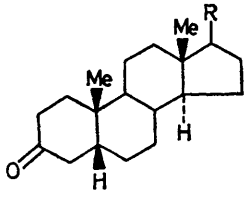


(3a)



(2b) R = C_8H_{17}

(2c) R = OAc



(3b) R = C_8H_{17}

(3c) R = OAc

The structures of the saturated ketones (**3a**—**c**) were established as follows. The i.r. and n.m.r. spectra of (**3a**) were identical with those of an authentic sample of *cis*-8a-methyl-3,4,4a,7,8,8a-hexahydronaphthalene-1(2*H*),6(5*H*)-dione, prepared by catalytic reduction of the corresponding $\Delta^{4a,5}$ derivative.[4] Particularly significant in identifying the *cis*-isomer was the singlet at δ 1·33 due to 8a-Me. The structure of the reduction product of (**2b**) was shown by its ^{13}C n.m.r.[5] and mass spectra.[6] The stereochemical purity of this product (before purification) was established by comparison of these spectra with those of authentic 5β-cholestanone and with the spectrum of a mixture of 5α- and 5β-cholestanones obtained by catalytic reduction (H_2–Pd, $CaCO_3$) of Δ^4-cholesten-3-one. The latter mixture is known to contain the 5α-isomer as the minor component. The ^{13}C n.m.r. resonances ascribed to C(18) and C(19) in the 5α-isomer[5] were absent in the product of the homogeneous reduction. The product of reduction of (**2c**) with (**1**) was also a single isomer, according to its ^1H n.m.r. spectrum. Purification of the latter led to a crystalline compound whose m.p. (140—145°) corresponded to that of 5β,6-dihydrotestosterone acetate.[7] Although a comparison of the ^1H n.m.r. spectrum of the reduction product with that reported for 5α,6- and 5β,6-dihydrotestosterone acetates does not allow unequivocal stereochemical assignment at C(5), analogy with the reduction of (**2b**) and the observed m.p. strongly argues in favour of structure (**3c**). The overall reaction discussed above represents the stereospecific homogeneous reduction of an $\alpha\beta$-unsaturated carbonyl compound to its saturated derivative, by an NADH analogue. While the detailed mechanism and scope of this stereospecific 'biomimetic reduction' is being investigated, we suggest that the pyridine nucleotide-mediated microbiological reduction of Δ^4-3-oxo-steroids may proceed *via* the sequence C=C–C=O→C=C–C=N$^+$→C–C=C–N→C–C–C=O. In view of the fact that enzymes have recourse only to primary amine functions (from amino-acid residues) for the formation of iminium salts, it is of interest that preliminary studies have shown that conjugated imines derived from $\Delta^{4a,5}$-(**3a**) and $\Delta^{4,5}$-(**3c**) undergo reduction, as the corresponding protonated species, with (**1**) or 1-benzyl-1,4-dihydronicotinamide.

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† The intermediate reduced iminium perchlorates could be isolated as crystalline products.

[1] Taken in part from the forthcoming Ph.D. thesis of F. R. Mas Cabré, University of Amsterdam.
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