NOVEL NADH MODELS[1]. STEROIDS BEARING PENDENT 1,4-DIHYDRONICOTINAMIDES

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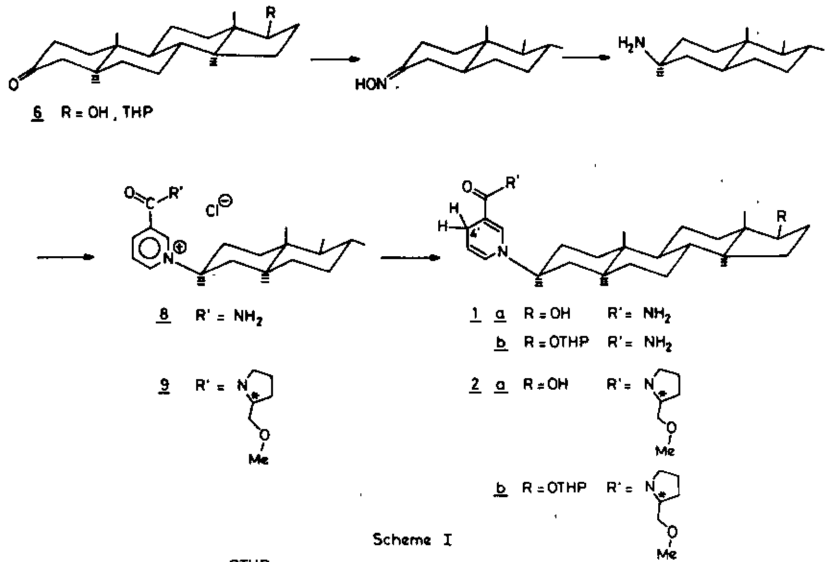
Abstract. Steroids bearing 1,4-dihydronicotinamides at the 3-position have been synthesized and studied as potential chiral reducing agents.

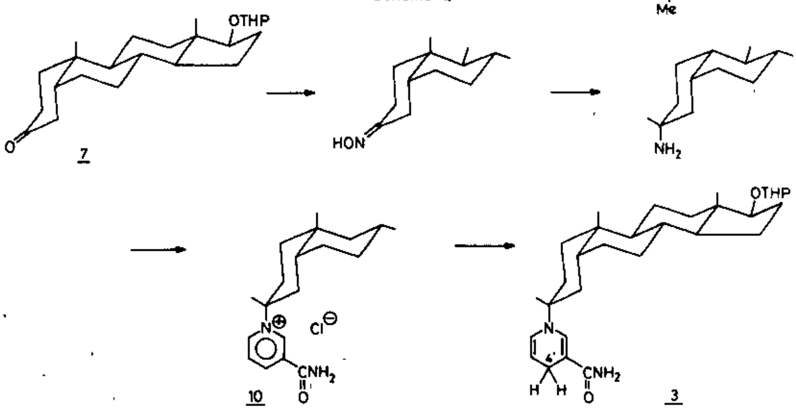
An important aspect of the study of NADH models is the potential asymmetric reduction of prochiral substrates, by 1,4-dihydropyridine derivatives possessing chiral substituents. A number of examples of asymmetric reductions by chiral NADH models have been recorded in recent years[3].

In enzymatic reductions, utilizing NADH as coenzyme, the stereochemical course of the hydrogen transfer process is determined by the alignment of both the substrate and the NADH molecule at the template of the active site[4].

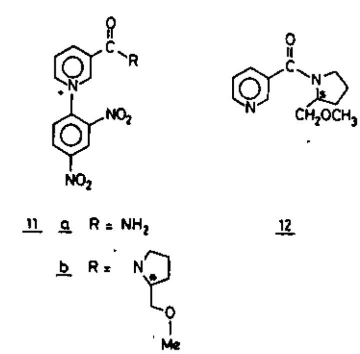
This mechanistic description suggests that the stereochemical interactions within the enzyme-coenzyme-substrate complex may be conceptually mimicked by the reaction between a substrate and a dihydronicotinamide residue attached to a chiral, structurally well-defined, multifunctional "molecular matrix". The spatial and functional properties of such a matrix would give rise to steric, polar and hydrophobic interactions, with both the dihydronicotinamide and the substrates, and as a result, exert a "template effect", i.e. stereochemical constraints, upon the transition state of the reduction reaction. While à priori the choice of potential template systems possessing the desired characteristics is large[5], we have, at present, directed our attention to steroidal systems which possess well-established stereochemistry and which are accessible to suitable functionalization via known methodology. In this communication we present the synthesis of a few members of steroidal dihydronicotinamides (1-3) (Schemes I and II) and discuss the stereochemistry of the reduction of phenylglyoxalate (4) and trifluoroacetophenone (5) by these NADH models. It was hoped that the study of compounds 1-3 would provide useful information on the influence of both, steric factors in the steroid skeleton and chiral functionality in the dihydronicotinamide moiety, upon the stereochemic-



Scheme I



Scheme II



al course of the reduction.

PhCOCOOMe $\quad\quad$ $PhCOCF_3$

4 $\quad\quad$ 5

The models 1-3 were synthesized, starting from the corresponding 3-ketosteroids (6 and 7) via the sequence of reactions described in Schemes I and II. The ketosteroids were converted into the 3-aminosteroids via their oximes, and the amine functions of the aforementioned intermediates transformed into the 3'-carbamoylpyridinium salts (8,9, Scheme I; 10, Scheme II), by reaction with the required Zincke reagents[6] (11a,b). In the case of compound 11b, the appropriate Zincke reagent was prepared by the reaction of nicotinamide derivative 12[7] with 2,4-dinitrochlorobenzene. Sodium dithionite reduction of the pyridinium salts 8-10 gave the dihydropyridines 1-3. Relevant characteristic data on the models 1-3 is presented in Table I. The spectral data in Table I show that whereas the C(4')-protons of the nicotinamide ring of 1a,b and 3 show no magnetic non-equivalence, in case of the models 2a and 2b, which carry a chiral prolinol ether substituent, the dissymmetry of the corresponding hydrogens is evidenced by the AB pattern. The latter becomes fully visible in the NMR spectrum when a small amount (0.1 eq.) of $Mg(ClO_4)_2$ is added to the system.

The reduction of the substrates 4 and 5 with the NADH models 1-3 was carried out in the presence of 1 equiv. of $Mg(ClO_4)_2$. In a typical experiment, a mixture of the substrate (1 eq.), the reductant (1 eq.) and $Mg(ClO_4)_2$ (1 eq.), in acetonitrile was allowed to stand at room temperature for 18 hours. The reduction product was isolated from the reaction mixture by column chromatography and the excess of one of the enantiomers was determined by polarimetric measurement. The results are described in Table II.

Inspection of the results presented in Table II indicates that the enantiomeric enhancements (e.e.) in the reductions of 4 and 5 by the stereoidal NADH-models are very modest; the highest e.e. value achieved by model 2a being 17%. Three aspects of the results are, however, significant. (1) The steroidal template has a distinct influence in directing the chiral transfer of the hydrogen. This is evidenced by, admittedly low, chiroselective reductions of 4 by 1a,b and 3. (2) Comparison of the reductions by 1b and 3 indicates that the stereochemistry of the A/B ring junction of the steroid skeleton and the relative orientation of the dihydro-

TABLE I

Compound	m.p.	Yield[a]	NMR Spectral characteristics Solvent	$C_4(H_2)$
1a	168-171° d	61%	$CDCl_3$	3.12 dd
1b	151-153° d	69%	$CDCl_3$	3.17 dd
2a	87-91°	54%	CD_3CN	2.96 d, 3.04 d, 3.30 br.s (AB pattern[6])
			CD_3CN	[(0.1 eq. $Mg(ClO_4)_2$ added)] 2.83 d, 2.91 d, 3.15, 3.27 (AB pattern)
2b	86-89°	52%	$CDCl_3$	2.93 d, 3.00 d, 3.27 br.s (AB pattern[6])
3	c	99%	$CDCl_3$	3.15 dd

[a] Yield refers to the dithionite reduction step.

[b] The fourth peak of the AB quartet is submerged under the signals of the prolinol ether substituent.

[c] not determined.

Table II

NADH Model	Substrate	Product	$[\alpha]_D$	Yield[a]		e.e.
1a	PhCOCOOMe(4)	PhCH(OH)COOMe	(-)8.4°	66%	(R)	6.3%
1b	"	"	(-)5.8°	36%	(R)	4.3%
2a	"	"	(-)12.7°	54%	(R)	9.5%
2b	"	"	(-)14.8°	26%	(R)	11.1%
3	"	"	(+) 8.7°	44%	(S)	6.6%
1a	$PhCOCF_3$(5)	$PhCH(OH)CF_3$	0	25%		-
2a	"	"	(+) 7°	40%	(S)	17%

[a] Besides the alcohols, varying quantities of the starting ketones were isolated from the reaction mixtures.

pyridine moiety is crucially involved in the geometry of the transition state of the reduction process. (3) A chiral substituent in the amine portion of the dihydronicotinamide moiety brings about a relative enhancement in the chiral induction (compare reductions by 1a,b with those by 2a,b).

The abovementioned implications of asymmetric reduction by NADH models involving 1,4-dihydropyridines attached to chiral templates are being actively investigated in our laboratory.

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