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BIOMIMETIC REDUCTION WITH NON WATER-SENSIVIVE NADH MODELS

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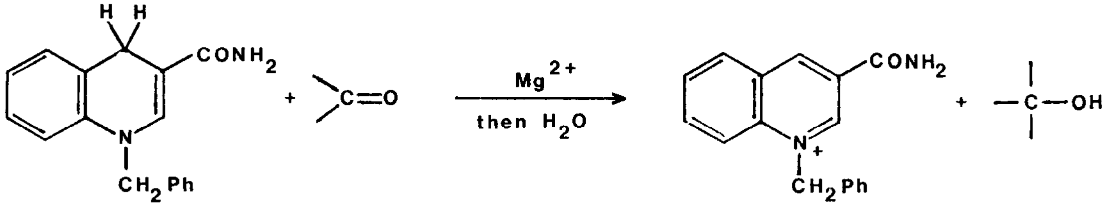
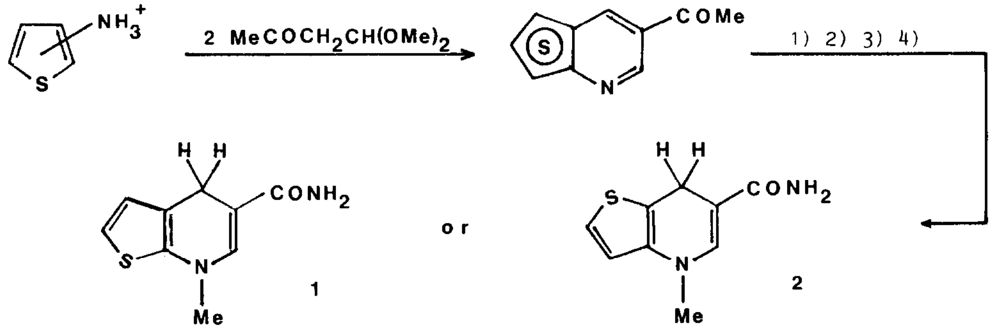
SUMMARY: Two NADH models were synthesized which are considerably less water-sensitive than classical-1,4 dihydronicotinamide derivatives such as N-benzyl-1,4 dihydronicotinamide (BNAH): these two models are reactive and more stable in the presence of water than previously reported models.

NADH analogous such as 1,4-dihydronicotinamide derivatives are water-sensitive compounds. N-Benzyl-1,4 dihydronicotinamide (BNAH) for example, undergoes reactions on the -5,6 double bond which cause a dramatic decrease in the efficiency of the reagent (1).

Models of NADH bearing a protected-5,6 double bond in a 1,4-dihydroquinoline structure were prepared (2). Unfortunately these models are known to be less reactive than the corresponding 1,4-dihydropyridine derivative (3). It is probably the withdrawing effect of the annelated benzene ring that hinders the departure of the hydrogen involved in the reduction of a carbonyl compound for example:



We synthesized (4) models with an annelated thiophene ring in order to protect the -5,6 double bond of the dihydropyridine part as well as to favor the departure of hydrogen through the electron donnating effect of the thiophenic ring.



1) NaOH/Br$_2$; 2) SOCl$_2$ than NH$_3$; 3) ICH$_3$; 4) Na$_2$S$_2$O$_4$/OH$^-$.

First we compared the behaviour of models 1 and 2 with that of BNAH or N-methyl-3 aminocarbonyl-1,4 dihydroquinoline (MeQAH). The reactions were performed in the same conditions: 1 mmole of NADH model, 1 mmole of magnesium perchlorate, 1 mmole of substrate in acetonitrile at 65°C.

Expt	Model (substrate *)	Reaction time	Water added	Yield of reduction
1	BNAH (a)	4 h	no	100 %
2	MeQAH (a)	4 h	–	25 %
3	1 (a)	4 h	–	77 %
4	2 (a)	4 h	–	40 %
5	1 (a)	17 h	–	100 %
6	2 (a)	17 h	–	100 %
7	MeQAH (a)	17 h	–	50 %
8	BNAH (a)	until no further reaction occurs	1 equiv.	76 %
9	BNAH (a)		2 equiv.	66 %
10	1 (a)		1,5 equiv.	100 %
11	2 (a)		1 equiv.	100 %
12	1 (b)		no	80 %
13	1 (b)		1 equiv.	80 %
14	BNAH (b)	–	no	70 %

*Substrate :

a) p-Nitrobenzaldehyde

b) -3 formylpyridine

As we can see the reactivity of 1,4-dihydro thieno pyridines 1 and 2 is much higher than that of MeQAH (expt 2,3,4,5,6). However BNAH is more reactive (compare expt 1 and 3 or 4): it appears that the access to the active site (4 position) for compounds 1 or 2 is more difficult due to the presence of the thiophenic ring in the vicinity of this site. The annelation effect of thiophene is perhaps greater than its electrodonating effect.

BNAH is extremely water-sensitive and the presence of water dramatically lowers the yields of reduction of p-nitrobenzaldehyde (entry 8 and 9, ref (5)). On the other hand we can see that the reactivity of 1 and 2 is always excellent in these conditions.

Moreover, some substrates which are less reactive towards BNAH, such as 3-formyl pyridine, and which are not reduced in classical conditions but only in drastic conditions can be reduced with 1 in excellent yields (expt 11). In technical grade acetonitrile (which contains 1 or 1,5 equivalent of water in our experimental conditions) the activity of 1 is always excellent. It is of interest to note that in the same conditions, the activity of BNAH is lowered.

In order to compare the stabilities of 1 and BNAH in water we performed the following experiment: NADH model 1 mmole, $Mg(ClO_4)_2$ 1 mmole in a mixture of acetonitrile and water (4/1). After 24 hours at 65°C, BNAH is totaly destroyed and 1 is recovered in 90 % yield.

We think that models 1 or 2 are promising for synthesis since they exhibit a good reactivity and they are much less sensitive than BNAH to side reactions. Further studies on extending the scope and limitations of these models, and their application to organic synthesis are in progress in our laboratory.

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3) A model having electron donnor substituent on the dihydropyridine ring such as N-methyl-2,4-dimethyl-3 aminocarbonyl-1,4-dihydroquinoline derivative, gives better results than unsubstituted models (A. OHNO, Y. ISHIHARA, S. USHIDA and S. OKA, Tetrahedron Letters, 3185 (1982). However the synthesis of this compound is rather difficult since the N-methylation has been performed under a 10 000 Kg/cm^2 pressure.

4) Synthesis, spectral and polarographic studies will be published later.

5) P. TINTILLIER, G. DUPAS, J. BOURGUIGNON and G. QUEGUINER, Submitted to publication.

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