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REDUCTION BY A MODEL OF NAD(P)H. XII. EFFECT OF SUBSTITUENTS ON THE STEREOSPECIFICITY OF THE REACTION

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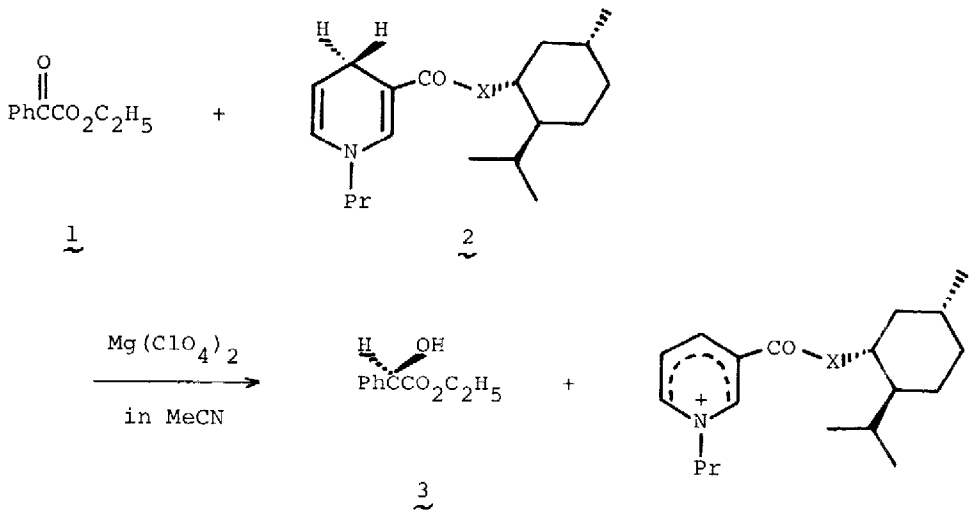
It has been reported that optically active N-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide and its analogs react with α-ketoesters,[1] α,α,α-trifluoroacetophenone,[2] or 2-acylpyridines[3] to give the corresponding chiral alcohols in the coexistence of magnesium perchlorate. The reaction is the first example which has demonstrated the discriminative use of prochiral C_4-hydrogens in an NAD(P)H model compound.

Despite the separation of the reaction center by five atoms from the chiral center, the stereospecificity of the reaction is fairly satisfactory and it is interesting to obtain an insight into the mechanism of stereospecific participation of a substituent on the 1,4-dihydropyridine ring. The present paper concerns to the result on this particular subject.

Ethyl benzoylformate (1) was reacted with an equimolar amount of a model compound (2)[4] in the presence of a twice molar amount of magnesium perchlorate in acetonitrile at 30°C for 44 hr in a dark. Techniques for isolation and purification of products have been described previously.[1] The yield of 3 was quantitative based on the reacted 1. Conversions of 1 and optical yields of 3 are listed in Table 1.

The present result indicates that the stereospecificity of the reaction decreases with the decrease of the basisity of carbonyl-oxygen,[5] which may be



1 2 3

Table 1. Stereospecific Reduction of Ethyl Benzoylformate.

X in 2	Conversion of 1, %	e.e. in 3, %
NH	99	26
CH_2	30	9
O	55	2

interpreted as following: the more basic the carbonyl-oxygen and the stronger the coordination onto the magnesium ion, the larger becomes the double-bond character between the carbonyl-carbon and an X atom. The double-bond character thus induced tends to fix the configuration (and thence conformation, too[6]) of the chiral group on the X atom. Consequently, the participation by the chiral group becomes more stereospecific than when there is no (or little) double-bond character between the carbonyl-carbon and an X atom. Thus, the existence of the amide group in the model compound is essential to exert a high stereospecificity with the present biomimetic reaction. The present conclusion agrees with the previously observed results,[2,3,7] *i.e.*, without magnesium ion, no asymmetric reduction takes place even with a chiral model compound.

Nevertheless, we do not believe that the coordination of the carbonyl-oxygen onto the magnesium ion is the primary interaction between a model compound and

magnesium ion. Physico-chemical results[8-11] suggest that the main interaction between two species is the *coordination* with the 1,4-dihydropyridine ring and the coordination of the carbonyl-oxygen is only supplmentary.[12] The more precise expression for the "coordination of a carbonyl-oxygen" may be the "polarization of a carbonyl group induced by a magnesium ion."[13-15]

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