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NAD(P)$^+$-NAD(P)H MODELS. 50. STEREO-CONTROLLED REDUCTION OF METHYL 2-OXO-3-METHYLPENTANOATE

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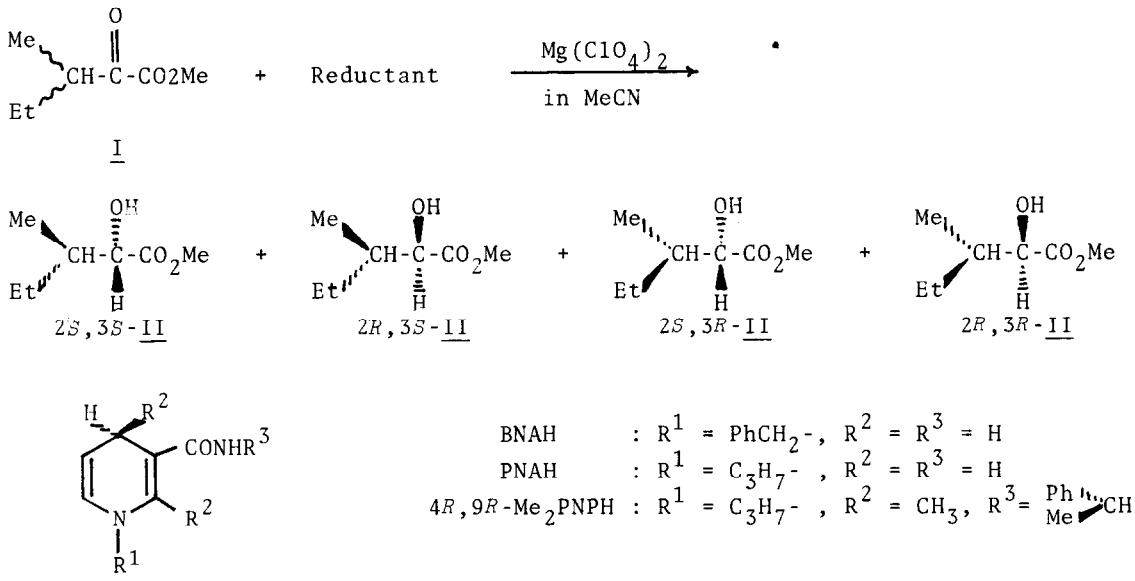
Summary : Racemic and optically active title compound was reduced with chiral and achiral NAD(P)H models. The composition of diastereomers in the product was determined and the steric relationship is discussed.

In previous papers of the series from our laboratory, it was reported that reduction of carbonyl compounds with a chiral NAD(P)H model, N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH), is a promising method to induce a chirality onto the carbon atom bearing a hydroxyl group (*1*). Since chiral hydroxyl group is one of important functions in bio-active compounds, especially in antibiotics (*2*), if one can apply the method to induce multi-asymmetric center into a product, synthetic utility of Me_2PNPH might



BNAH : R^1 = $PhCH_2$-, R^2 = R^3 = H
PNAH : R^1 = C_3H_7- , R^2 = R^3 = H
4*R*,9*R*-Me_2PNPH : R^1 = C_3H_7- , R^2 = CH_3, R^3 = Ph(Me)CH-

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Table 1. Reduction of Methyl 2-oxo-3-methylpentanoate (I) with PNAH, BNAH, and $NaBH_4$

Reductant (mmole)	Substrate (mmole)	$Mg(ClO_4)_2$ (mmole)	Reaction Time, hr	Total Yield,%	Composition,% *syn*	*anti*
	racemic-I					
PNAH (0.050)	(0.105)	0.050	44	91	42	58
BNAH (0.050)	(0.100)	0.052	96	75	39	61
$NaBH_4$ (0.050)	(0.105)	none	5	100	42	58[a]
	S-I					
PNAH (0.050)	(0.100)	0.056	44	90	42	58
BNAH (0.050)	(0.100)	0.050	86	70	38	62
$NaBH_4$ (0.050)	(0.100)	none	5	100	40	60[a]

a) Reaction in methanol.

Table 2. Reduction of Methyl 2-oxo-3-methylpentanoate (I) with 4*R*,9*R*-Me_2PNPH

Reductant mmole	Substrate (mmole)	$Mg(ClO_4)_2$ mmole	Reaction Time, hr	Total Yield,%	Composition,% *syn*	*anti*
	racemic-I					
0.025	(0.100)	0.027	18	100	45	55
0.025	(0.100)	0.028	23	100	46	54[a]
	S-I					
0.025	(0.050)	0.025	20	100	90	10
0.025	(0.053)	0.025	18	100	90	10

a) Reaction at 0°C.

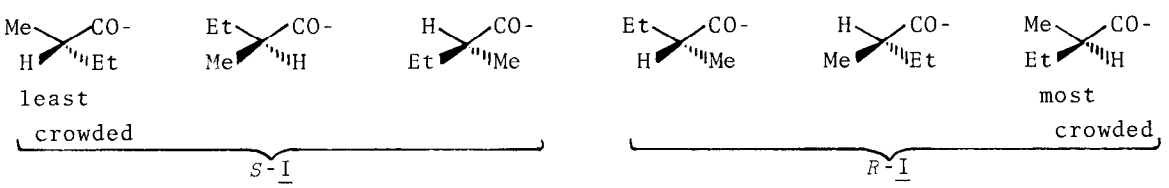
increase tremendously. As a model of multi-asymmetric synthesis, we studied the reduction of methyl 2-oxo-3-methylpentanoate (I) with 4*R*,9*R*-Me_2PNPH as well as 1-propyl-1,4-dihydronicotinamide (PNAH), 1-benzyl-1,4-dihydronicotinamide (BNAH), and sodium borohydride ($NaBH_4$). The reduction product, methyl 2-hydroxy-3-methylpentanoate (II), has two asymmetric centers on C2 and C3, respectively. Among the products, 2*S*,3*S*-II and 2*R*,3*R*-II will be abbreviated as *anti* hereafter. The remaining two will be called as *syn*.

The reduction was carried out by adding 1 mL of anhydrous acetonitrile solution of an appropriate amount of a reductant into 2 mL of anhydrous acetonitrile solution of appropriate amounts of I and magnesium perchlorate under argon atmosphere in the dark. The reaction was run at room temperature. The reduction products were analyzed on a VPC (80°C, PEG 20M, 1.5 m). The authentic 2*S*,3*S*-II was obtained by methylation of sodium L-2-hydroxy-3-methylvalerate (Sigma Chem. Co.). Results are summarized in Tables 1 and 2.

The diastereotopic selectivity observed in the reduction with achiral reductants is quite similar to that observed in the reduction of similar substrate by using microorganisms (2). Thus, it is apparent that recognition of steric effect in the substrate in average biochemical process does not differ very much from that in organic ones. BNAH exerts higher selectivity than PNAH, which is understandable in terms of reactivity-selectivity relationship. The fact that both *racemic*- and *S*-I afford the products with the same *syn/anti* ratio indicates that the chirality in the substrate does not induce the chirality onto the reaction center at all when an achiral reductant is employed.

When 4*R*,9*R*-Me_2PNPH is used, on the other hand, the *syn/anti* ratio from *S*-I differs largely from that from *racemic*-I. Calculation based on the ratios shown in Table 2 tells us that the *syn/anti* ratio from *R*-I should be 0/100 instead of 10/90 when 4*R*,9*R*-Me_2PNPH is employed as the reductant. Consequently, the enantiomeric excess in *syn*- and *anti*-products from *racemic*-I in the reduction with 4*R*,9*R*-Me_2PNPH are calculated to be 100% and 90%, respectively. Thus, when the reductant is chiral, the chirality in the substrate slightly affects the stereochemistry on the reaction center. The following scheme illustrates three possible conformations of alkyl groups in *S*-I and *R*-I,

Scheme



respectively. In order to induce *R*-configuration onto the reduction center,

reductant has to approach to the substrate from its *si*-phase. By doing so, the reductant might *feel* lager steric bulk for *R*-I than for *S*-I because the former involves the most crowded conformation, whereas the latter involves the least crowded one. Nevertheless, the calculation suggests that *R*-I exerts higher selectivity than *S*-I. Similar trend was observed previously. That is, methyl 2-oxo-3,3-dimethylbutanoate exerted larger enantiospecificity than methyl benzoylformate in the reduction with Me_2PNPH, although the former had bulkier substituent than the latter. Thus, selectivity and/or specificity exerted in the reduction of an α-keto ester with an NAD(P)H model is not a function of steric effect. Some other effects such as hydrophobicity or polarity seem to be operating.

Since the reduction of α-keto ester with 4*R*,9*R*-Me_2PNPH is known to induce *R*-configuration in large predominancy (*1*), the present result with *S*-I again confirms our proposal that polar substituent in a substrate faces against the carbamoyl group (a polar substituent) of the reductant at the transition state of the reduction (*1*,*3*). Although the magnesium ion seems to play a crucial role in exerting the stereospecificity, the detailed mechanism on its activity is not yet known. We have tentatively suggested that the coordination of magnesium ion onto the dihydropyridine-ring fixes the conformation of transition state (*4*,*5*).

Further studies to revise the selectivity as well as to apply the reduction to other substrates are in progress in our laboratory.

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REFERENCES

1. A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, 101, 7036 (1979).
2. T. Oishi and H. Akita, *J. Synth. Org. Chem. Jpn.*, 41, 1031 (1983). Cf. also T. Nakata, T. Kuwabara, T. Tani, and T. Oishi, *Tetrahedron Lett.*, 23, 1015 (1982).
3. A. Ohno, T. Goto, J. Nakai, and S. Oka, *Bull. Chem. Soc. Jpn.*, 54, 3478 (1981).
4. A. Ohno, j. Nakai, K. Nakamura, T. Goto, and S. Oka, *Bull. Chem. soc. Jpn.*, 54, 3482 (1981).
5. P. M. van Lier, G. H. W. M. Meulendijks, and H. M. Buck, *Rec. Trav. Chim. Pays-Bas*, 102, 337 (1983).

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