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PREPARATION OF CHIRAL 5-DEAZAFLAVIN DERIVATIVES AND THEIR ASYMMETRIC REDUCTION OF ETHYL BENZOYLFORMATE

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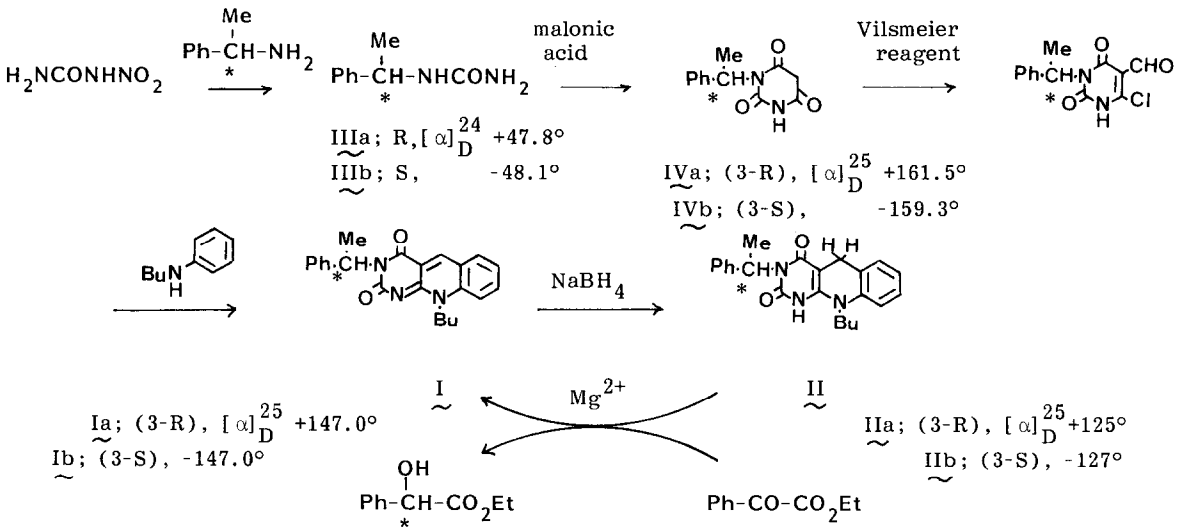
Summary: 1,5-Dihydro-5-deazaflavin derivatives possessing a chiral substituent at N(3) position were synthesized, with which moderate asymmetric induction was observed in the reduction of ethyl benzoylformate.

In recent years, 5-deazaflavin derivatives (e.g. coenzyme F_{420}[1]) have been given much attention because of their significant role in redox reaction of biological systems. We have previously reported that 1,5-dihydropyrimido[4,5-*b*]-quinoline-2,4[3*H*,10*H*]-dione (1,5-dihydro-5-deazaflavin), which is a model of 1,5-dihydroflavin nucleotide as well as NADH, reduced simple carbonyl compounds to yield the corresponding alcohols under the acidic condition[2]. The stereoselective nonenzymatic reductions of carbonyl group by modified 1-benzyl-1,4-dihydronicotinamide (BNAH) with chiral substituents at 1,3,4 or 5 positions as a model for NAD(P)H have been extensively investigated and remarkable results so far reported by many groups[3].

We, in this communication, wish to report the synthesis of the chiral 5-deazaflavin derivatives (Ia,b),(IIa,b) and their use in asymmetric reduction of ethyl benzoylformate in the presence of magnesium perchlorate.



Scheme I. Preparation of the chiral 5-deazaflavins (Ia,b) and the reduction of ethyl benzoylformate.

Synthesis of the 5-deazaflavin derivatives (Ia,b) was undertaken by the method shown in Scheme I. Thus, starting from nitrourea and R-(+)- or S-(-)-α-phenylethylamine, 3-R-(+)- and 3-S-(-)-α-phenylethylbarbituric acids (IVa,b)[4] were obtained in 65-75 % yield. Construction of the 5-deazaflavin skeleton[5] was achieved by the treatment of IVa,b with Vilsmeier reagent followed by successive treatment of *N*-butylaniline in DMF to afford Ia and Ib[6] in 40-50 % yield respectively. The 5-deazaflavins (Ia,b) were converted to the corresponding 1,5-dihydro derivatives (IIa,b)[6] by the reduction with sodium borohydride in ethanol quantitatively.

The reduction of ethyl benzoylformate with equimolar amount of 1,5-dihydro-5-deazaflavins (IIa,b) was carried out in the presence of magnesium perchlorate (1 eq.) in a mixture of acetonitrile and acetic acid (1:1) at room temperature for 7 days under atmosphere of argon in the dark. Ethyl mandelate was obtained in moderate chemical[7] and optical yield together with recovered benzoylformate and 5-deazaflavins (Ia,b). These results are summarized in Table I.

Table I. Asymmetric reduction of ethyl benzoylformate.

1,5-dihydro-5-deazaflavin	ethyl mandelate (product)			
	chemical[a] yield (%)	configuration	$[\alpha]_D^{20}$ [b]	optical[c] yield (%)
IIa	12	S	+14.2°	14
IIb	15	R	-21.8°	21

a) not optimum[7] b) ethanol, c = 0.15 c) pure ethyl mandelate $[\alpha]_D^{24} = -104°$

This is a first example of the synthesis of the chiral 5-deazaflavin derivatives having redox potential and use in enantioselective reduction. This synthesis described above also opens the way to the synthesis of the 5-deazaflavin derivatives bearing a variety of substituents at N(3) position. Synthesis of another type of the chiral 5-deazaflavins and their application for asymmetric reducing agent are under progress.

REFERENCES AND NOTES

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3) For example; J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, *101*, 2759 (1979); A. Ohno, M. Ikeguchi, T. Kimura and S. Oka, *ibid.*, *101*, 7036 (1979); T. Endo, H. Kawasaki and M. Okawara, *Tetrahedron Lett.*, 23, (1979); T. Makino, T Nunozawa, N. Baba, J. Oda and Y. Inouye, *J. Chem. Soc., Perkin Trans. I*, 7 (1980).

4) All new compounds were fully characterized spectroscopically and by combustion.

5) F. Yoneda, Y. Sakuma, S. Mizumoto and R. Ito, *J. Chem. Soc., Perkin Trans. I*, 1085 (1976).

6) Ia: mp 114-116° C. IR ($CHCl_3$) 1695, 1640, 1617, 1568 and 1532 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.02 (3H,*t*,J = 8 Hz), 1.94 (3H, *d*, J = 7 Hz), 4.72 (2H,*bt*), 6.40 (1H, *q*, J = 7 Hz), 7.15-7.90 (9H,*m*), 8.78 (1H,s). Ib: mp 114- 116° C. IIa: mp 83-84° C. IR ($CHCl_3$) 3430, 1690 and 1620 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (3H, *t*, J = 8 Hz), 1.90 (3H, *d*, J = 7 Hz), 3.66 (2H, *m*), 3.77 (2H, *s*), 6.34 (1H, *q*, J = 7 Hz), 6.82-7.42 (9H, *m*), MS *m/z*: 394 (M^+). IIb: mp 85° C.

7) Since 1,5-dihydro derivatives (IIa,b) are extremely sensitive to atmospheric oxygen which regenerates 5-deazaflavins (Ia,b), exact chemical yield could not be determined.

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