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SYNTHESIS AND REACTION OF A NEW TYPE OF 5-DEAZAFLAVIN WITH AXIAL AND PLANAR CHIRALITY[1)]

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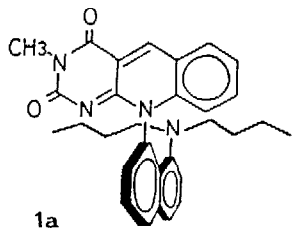
Summary: A new type of 5-deazaflavin derivative with axial and planar chirality was synthesized as a flavoenzyme model. A novel optical resolution gave an enantiomeric pair of the 5-deazaflavins **1a,b**. Compounds **1a,b** were optically stable and effectively discriminated PNPH enantiomers in a model reaction of intercoenzyme hydrogen transfer.

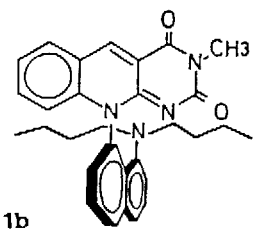
A concept has generally been accepted that a coenzyme is located and fixed in some geometry at the active site of the enzyme concerned and one face of the coenzyme is heavily guarded by the wall of the protein, consequently, an approach and interaction with the substrate is possible only on the other face. Such an environment exerts stereoselectivity and has an important bearing on chiral recognition.

As a part of our continuing studies on functional coenzyme model compounds, a new type of chiral 5-deazaflavin **(1)**,[2)] bearing both axial and planar chirality was designed (Scheme 1). In the flavoenzyme model **1**, 10-(8'-N,N-dibutylaminonaphth-1'-yl)-3-methylpyrimido[4,5-b]quinoline-2,4(3H,10H)-dione, one of 5-deazaflavin planes containing the reaction center at C(5) position may be covered with bulky N,N-dibutylamino group and the rotation around C-N(10) bond should be prevented. Therefore, compound **1** can be regarded as a model for flavoenzyme. As to redox coenzyme models in this category, Shinkai and co-workers introduced a cyclophane structure into a 5-deazaflavin and a flavin,[3)] and demonstrated interesting redox reactions by these (5-deaza)flavinophanes.[4)]



1a

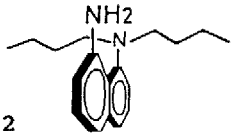
Scheme 1



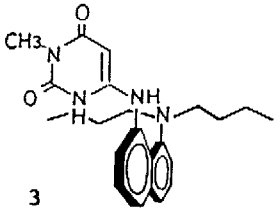
1b

In trials introducing an element of chirality in flavoenzyme models[3,5], an application of atropisomers was also reported[6], but so far successful chiral recognition is rare for an acyclic model. The present paper reports the first example of synthesis and reaction of the acyclic model compound with both axial and planar chirality, which is optically stable under the reaction conditions.

The racemate of the 5-deazaflavin **(1)** was prepared in 50 % yield according to Yoneda's method[7,8] from o-fluorobenzaldehyde and 6-(8'-N,N-dibutylaminonaphth-1'-yl)-amino-3-methyluracil **(3)** which was obtained by treatment of N,N-dibutyl-1,8-diamino-naphthalene **(2)**[9] with 3-methyl-6-chlorouracil in 55 % yield (Scheme 2).



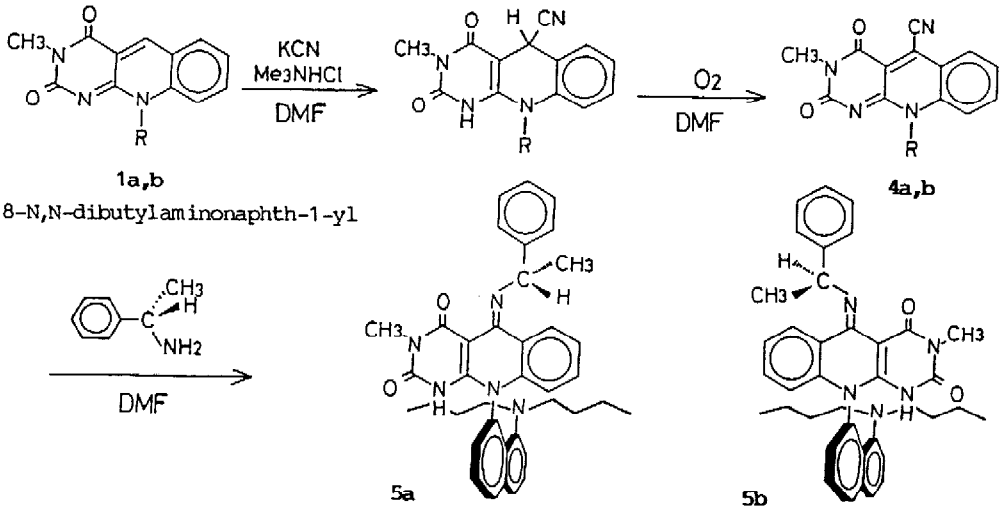
2



3

Scheme 2

A novel optical resolution method was developed for the racemate utilizing the commercially available primary amine as a chiral auxiliary. Hydrocyanation in the presence of trimethylammonium chloride[10] and subsequent spontaneous air oxidation of the racemic adduct afforded the cyanide **(4a,b)**, which was treated with (S)-(-)-α-methyl-benzylamine to yield an easily separable mixture of diastereomers **(5a,b)**. Practically, this transformation can be effectively achieved in one-pot procedure. Chromatographic separation of the mixture on silica gel resulted in satisfactory isolation of each diastereomer, whose purity is more than 99.8 % judging from h.p.l.c. analysis (Scheme 3).



1a,b

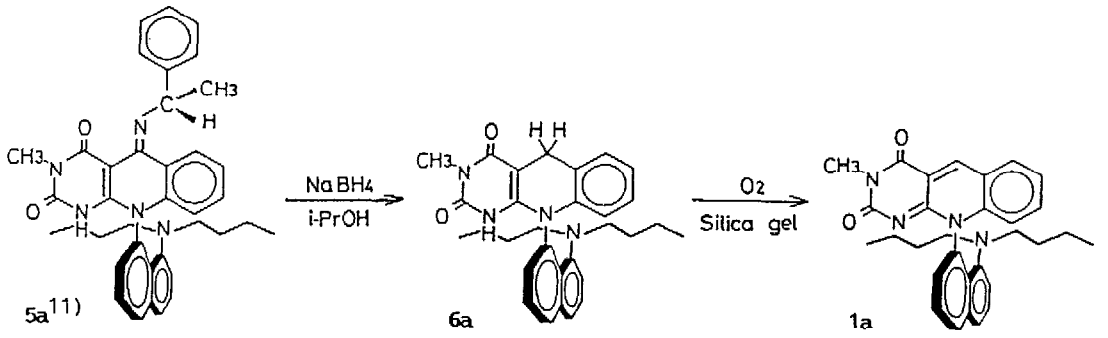
R= 8-N,N-dibutylaminonaphth-1-yl

4a,b

5a

5b

Scheme 3



Scheme 4

Table 1. Specific rotation values of 5 and 1 **

5	1
+161.4°	+296°
+43.6°	-293°

** in chloroform c=1.01 at 20°C

Each of the diastereomers **(5a,b)** was converted by sodium borohydride into 1,5-dihydro-5-deazaflavin **(6a,b)**, which was oxidized by air on silica gel to give the optically pure 5-deazaflavin **(1a,b)** in good overall yield (Scheme 4). Of unusual interest is the fact that the 5-deazaflavin **(1)** emits essentially no fluorescence on photoexition at 360nm, while, its reduced form, 1,5-dihydro-5-deazaflavin **(6)**, gives strong fluorescence.

Generally, 1,5-dihydro-5-deazaflavin has a "relaxed" butterfly wing like structure[12)] folded through C(5) and N(10), and this is believed to cause "redox induced racemization".[6)] Nevertheless, it is interesting to note that all the compounds **5,6** and **1** are optically stable during the transformation and no racemization was observed at ambient or even at higher temperature (100°C) (checked by h.p.l.c. analysis). Specific rotation values of compounds 5 and 1 are shown in Table 1. Elucidation of the absolute structure is under investigation.

Oxidation reaction[4b,13)] of PNPH (N-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide) with (+)-**1** isomer was carried out in the presence of magnesium perchlorate

Table 2. Discrimination factor and the estimated pseudo-first-order rate constants (k_ψ min^{-1}) *** 14)

temperature	Initial rate:(+)-1 and (R)-PNPH / Initial rate:(+)-1 and (S)-PNPH	k_ψ (R)-PNPH	k_ψ (S)-PNPH
30°C	1.6	8.81×10^{-4}	5.35×10^{-4}
16°C	2.2	5.43×10^{-4}	2.42×10^{-4}
0°C	5.3	2.51×10^{-4}	4.77×10^{-5}

*** $[(+)\text{-}1] = 1.00 \times 10^{-4}$M, $[PNPH] = 5.00 \times 10^{-4}$M, $[Mg(ClO_4)_2] = 1.25 \times 10^{-3}$M

in acetonitrile under nitrogen stream, and initial rates of the reduction of (+)-**1** were measured by monitoring the decrease of absorption at 430 nm.[14] The ratio of the initial rates between the reactions of (+)-**1** with (R)-PNPH and (S)-PNPH are listed in Table 2. As Table 2 shows, (+)-**1** has a marked ability of chiral recognition, that is, (+)-**1** oxidizes (R)-isomer of PNPH more rapidly than (S)-isomer. Interestingly enough, the degrees of the discrimination by (+)-**1** increased at low temperature, giving k_R/k_S ratio of 1.6 at 30 °C and 5.3 at 0 °C.

In this model reaction of asymmetric intercoenzyme hydrogen transfer, an intervention of a ternary complex [PNPH•Mg(II)•(+)-**1**] was suggested. The detailed kinetic and mechanistic studies will be reported in the near future.

References and Notes

1. This paper is dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March 1989.
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8. All new compounds in this paper were unambiguously characterized by spectroscopic and elemental analyses.
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10. Ammonium chloride gave 5-imino derivative in substantial quantity, probably through addition-elimination reaction involving **4**.
11. For the compounds **5,6,** and **1**, one of the enantiomers is shown for the convenience.
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14. Decomposition of PNPH during the reaction prohibited the monitoring of the reaction at a high coversion. Division of initial rate by initial concentration of the substrate gives the pseudo-first-order rate constant. In a separate experiment where a high concentration of PNPH allows a trace of the reaction up to 2-3 half-lives, Guggenheim analysis and the initial rate method gave essentially identical pseudo-first-order rate constant. At a reasonably low conversion, 5 fold excess of the reagent guarantees $[PNPH]=[PNPH]_0$ and $[Mg(ClO_4)_2]=[Mg(ClO_4)_2]_0$, which are the necessary condition of the pseudo-first-order reaction.

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