Tetrahedron Letters,Vol.26,No.42,pp 5183-5186,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

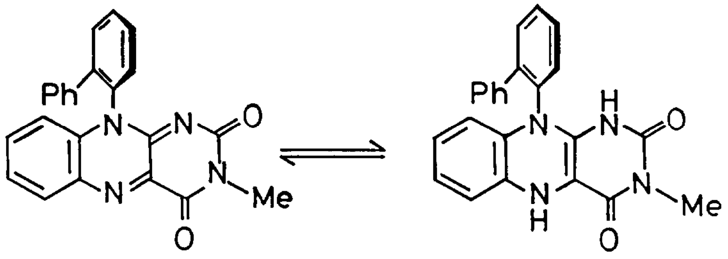
SYNTHESIS AND OPTICAL RESOLUTION OF A NEW FLAVIN WITH AXIAL CHIRALITY AND REDOX-DEPENDENT RACEMIZATION

Seiji SHINKAI,* Hideki NAKAO, and Osamu MANABE
Department of Industrial Chemistry, Faculty of Engineering,
Nagasaki University, Nagasaki 852, Japan

A new flavin (3-methyl-10-(2'-phenyl)phenylisoalloxazine) with restricted rotation about the C(1')-N(10) single bond was synthesized and optically resoluted for the first time. (+)-Isomer (100% enantiomeric purity) did not racemize at ambient conditions, whereas it racemized invariably when it was reduced (by four different methods). The kinetic studies proved that the novel racemization mode is attributed to conversion of the "planar" oxidized form to the "bent" reduced form.

In the past, many papers have reported on the synthesis and the resolution of optical isomers caused by restricted rotation about the C-C single bond.[1)] To the best of our knowledge, however, few precedents exist for such atropisomers including restricted rotation about the C-N single bond.[2-5)] For instance, aryl-substituted heterocyclic compounds such as 1-aryl-2-methyl-3-methoxy-4-pyrone and 1-aryl-4,6-dimethylpyrimidin-2(1H)-one are the rare examples.[4,5)] Although the optical resolution has been attained, in some cases, by the formation of the diastereomeric brucine salts,[2)] a liquid chromatographic method (LC method) using an optically active sorbent is not yet successfully applied because it results in the partial optical resolution.[3,4)]

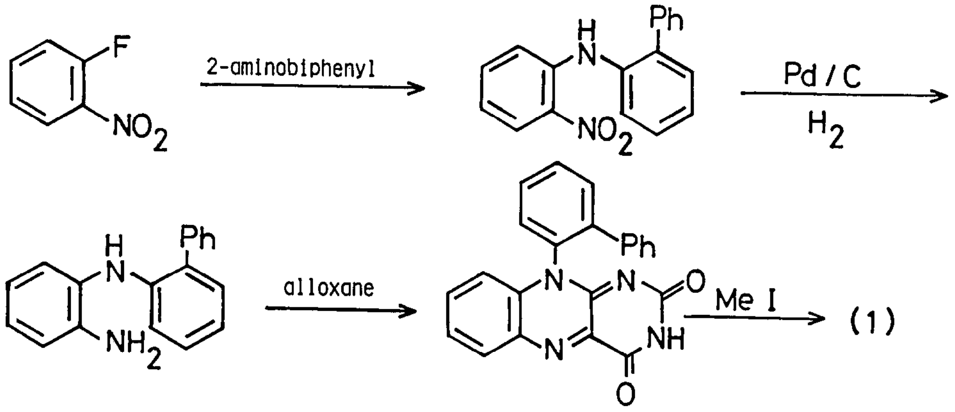
In the course of our studies on flavin chemistry,[6)] we noticed that in 10-phenylflavin the rotation of the phenyl group around the C(1')-N(10) bond may be restricted when proper substituents are introduced. There are two examples for the synthetic flavins bearing optically active substituents,[7,8)] but there are no reported data about atropisomeric flavins with axial chirality. We thus synthesized a new flavin, 3-methyl-10-(2'-phenyl)phenylisoalloxazine (1) and succeeded in its optical resolution with a LC method. Furthermore, we found that chiral (1), which cannot be racemized at ambient conditions, rapidly racemizes when (1) is converted to the reduced form (1_{red}).



(1) (1red)

(1) (mp 308-309 °C) was synthesized from o-fluoronitrobenzene according to scheme 1 and identified by IR, NMR, and elemental analysis: λ_{max}(MeCN) 332 nm(ε 6000), 438 nm(ε 7020).

Scheme 1



The enantiomers were optically resolved by a LC method using a chiral packing column (Sumipax OA-2000). The method resulted in a satisfactory separation of the enantiomers. We separated the eluent into three fractions and obtained 30 mg of (+)-(1) from the first fraction and 35 mg of (-)-(1) from the last fraction with enantiomeric purities of 100% and 92.2%, respectively, from 100 mg of racemic (1). (+)-(1) gave unusually large specific rotation $[\alpha]_D^{30}$ = +760°(MeOH:water = 1:1 v/v, c = 0.038):CD spectrum (MeOH) $[\theta]_{439}$ = +16300, $[\theta]_{334}$ = -7050.

First, we corroborated that (+)-(1) does not racemize at 30 °C at pH 3-11. Similarly, photoirradiation by a 17 W fluorescent lamp did not mediate the racemization. We reduced (+)-(1) (5.14×10^{-5} M) in anaerobic aqueous solution by four different reagents, 1-benzyl-1,4-dihydronicotinamide (BNAH: 5.01×10^{-4} M), 1,4-butanedithiol (4.99×10^{-4} M), furoin (9.97×10^{-5} M),

Table 1. Chromatographic analysis of reoxidized (1)[a]

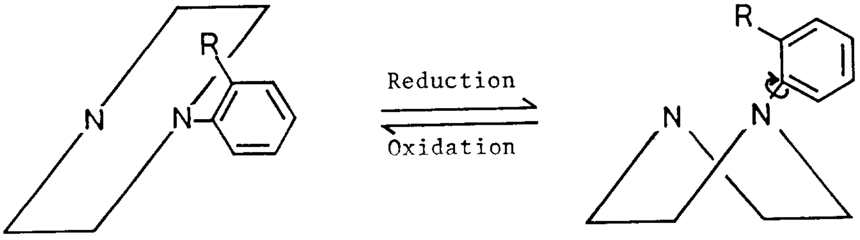
Reducing agent	pH	Reacion time (min)	Recovered (1)	
			(+)-(1)	(-)-(1)
BNAH	8.60	10	50.6	49.4
1,4-Butanedithiol	8.60	90	49.5	50.5
Furoin	8.60	1	49.7	50.3
EDTA(light)	10.13	50	49.5	50.5

[a] [(+)-(1)] = 5.14 × 10^{-5} M, 30 °C.

and visible light irradiation in the presence of EDTA. After completion of the reduction (1_{red}) was oxidized by molecular oxygen and the aqueous solution was extracted with chloroform. (1) was recovered quantitatively in the chloroform layer, which was subjected to the LC analysis using a chiral packing column (vide supra). As summarized in Table 1, recovered (1) was racemized "completely" (within the experimental error). It is now clear that chiral (1), which cannot be racemized in the oxidized form, easily racemizes in the reduced form.

It is unequivocally established that oxidized flavins are planar, whereas reduced flavins are folded along the N(5)-N(10) axis like butterfly wings.[9] Examination of molecular models suggests, as illustrated in scheme 2, that in reduced (1) the rotation of the (2'-phenyl)phenyl group around the C(1')-N(10) axis easily occurs owing to the bent isoalloxazine structure.

Scheme 2



planar oxidized (1)   bent reduced (1)

If the racemization process involves the rate-limiting reduction of (+)-(1) followed by the rapid rotation of the C(1')-N(10) single bond, the racemization rate should be equal to the reduction rate. We measured the aerobic reaction rate between (+)-(1) (3.50×10^{-4} M) and BNAH (7.62×10^{-5} M) at 30 °C (in water(pH 9.5):methanol = 4.3:4.5 v/v by following the disappearance of the absorption band of BNAH at 352 nm and compared it with the racemization rate determined under identical reaction conditions.[10] The two pseudo-first-order rate constants showed good agreement within the experimental error: $k_{reduction} = 8.82 \times 10^{-5}\ s^{-1}$; $k_{racemization} = 8.42 \times 10^{-5}\ s^{-1}$. The result clearly supports the racemization mechanism in scheme 2.

In conclusion, the present paper is a novel example for atropisomers with the C-N axis, the rotation of which can be induced by the redox reaction. Further characterization of these and related flavin derivatives is now under intensive investigation. Of particular interest is to evaluate whether the similar redox-induced racemization occurs in 5-deazaflavin analogues.

We thank Professor S. Kawano for helpful discussions.

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10) (1_{red}) is reoxidized instantaneously under aerobic conditions, so that one can assume the concentration of (1) to be constant.

(Received in Japan 30 July 1985)