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FORMATION OF 4a,5-DIHYDRO-4a-HYDROXY-5-DEAZAFLAVINS IN THE REACTION OF 1,5-DIHYDRO-5-DEAZAFLAVINS WITH *m*-CHLOROPERBENZOIC ACID AND THEIR PYRIMIDINE RING CONTRACTION WITH BASE

Fumio Yoneda,*[,a] Kiyoshi Tanaka,[a] Yoshiharu Sakuma,[b] Hironori Yoshino,[b]
and Masayuki Takamoto[c]
Faculty of Pharmaceutical Sciences, Kyoto University,[a] Yoshida, Sakyo-ku, Kyoto 606, Japan, Faculty of Pharmaceutical Sciences, Kumamoto University,[b] Oe-honmachi, Kumamoto 862, Japan, and Central Research Division, Takeda Chemical Industries, Ltd.,[c] Juso-honmachi, Yodogawaku, Osaka 532, Japan

A new class of 4a,5-dihydro-4a-hydroxy-5-deazaflavins, which are isosteric and isoelectronic with the flavin pseudobase, was synthesized by the reaction of 1,5-dihydro-5-deazaflavins with *m*-chloroperbenzoic acid. The base catalyzed hydrolysis of the 4a,5-dihydro-4a-hydroxy-5-deazaflavins was carried out to give the corresponding 9,9a-dihydro-oxazolo[4,5-*b*]quinolin-2(4*H*)-ones.

KEYWORDS ——— 1,5-dihydro-5-deazaflavin; *m*-chloroperbenzoic acid oxidation; 4a,5-dihydro-4a-hydroxy-5-deazaflavin; ring contraction; oxazolo[4,5-*b*]quinolin-2(4*H*)-one; 3,4-dihydro-3-hydroxyquinolin-2(1*H*)-one

5-Deazaflavins, in both free[1)] and enzyme-bound[2)] state, react with peroxides in the same way to give birth to the corresponding 4a,5-epoxy derivatives. The exposure of the 4a,5-epoxy-5-deazaflavins to alkaline conditions causes a remarkable ring contraction reaction to give oxazolo[4,5-*b*]quinolin-2(4*H*)-ones,[3,4)] which undergo further hydrolysis to yield 3-hydroxy-2-quinolin-2(1*H*)-one.[3)] The above ring contraction reaction appears analogous to the reaction observed with the enzyme-bound 4a,5-epoxy-5-deazaflavin at neutral conditions.[1,2)]

In the meantime, it would be of interest and of concern to know the behavior of reduced-type 5-deazaflavins towards peroxides, because the 5-deazaflavins shuttle between the oxidized forms and the reduced forms in both biological and model redox reactions. This communication describes the *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of 1,5-dihydro-5-deazaflavins giving the corresponding 4a,5-dihydro-4a-hydroxy-5-deazaflavins and the base catalyzed hydrolysis of these 4a-hydroxy derivatives.

For example, stirring of 1,5-dihydro-10-methyl-5-deazaflavin (Ia)[5)] (4.1 mmol) with *m*-CPBA (6.2 mmol) in chloroform (30 ml) at room temperature for 10 h in the dark, followed by concentration of the reaction mixture in vacuo and the trituration of the residue in ether yielded crude product, which was filtered off and recrystallized from ethanol to give 4a,5-dihydro-4a-hydroxy-10-methyl-5-deazaflavin (IIa) as pale yellow prisms, mp 223°C, in 55% yield. [^{1}H-NMR (DMSO-d_6), δ 3.13 (3H, s, N_{10}-Me), 3.14 (1H, d, J = 17 Hz, C_5-H_a), 3.33 (1H, d, J = 17 Hz, C_5-H_b), 3.55 (3H, s, N_3-Me), 7.02 (1H, s, C_{4a}-OH, exchangeable with D_2O), 7.09-7.35 (4H, m, ArH). ^{13}C-NMR (DMSO-d_6), δ 27.18 (N_{10}-Me), 31.97 (N_3-Me), 32.47 (C-5), 62.16 (C-4a), 116.04 (Ar-C), 123.25 (C-5a), 124.10 (Ar-C), 127.45 (Ar-C), 129.26 (Ar-C), 138.20 (C-9a), 155.48 (C-10a), 165.41 (C-2 or 4), 169.59 (C-4 or 2)]. The NMR data and other spectral data, however, could not exclude the possibility of the product possessing 4a,10a-epoxy-1,5-dihydro-5-deazaflavin structure. Therefore, the structure of IIa was finally determined by X-ray crystallographic analysis (Fig. 1). Similarly, 10-ethyl-4a,5-dihydro-4a-hydroxy-5-deazaflavin (IIb), mp 225°C, was prepared by treatment of 10-ethyl-1,5-dihydro-3-methyl-5-deazaflavin (Ib)$^{5)}$ with m-CPBA in 69% yield.

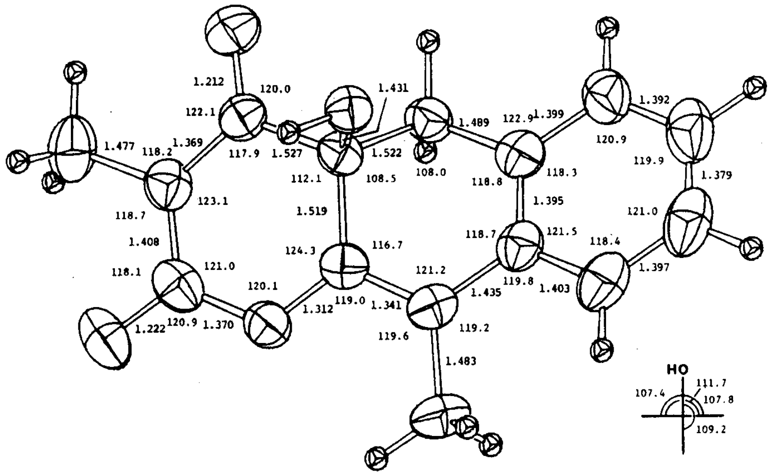


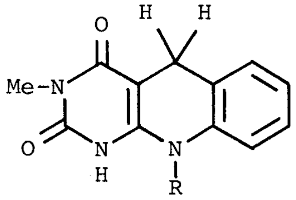
Fig. 1. Molecular Structure of 4a,5-Dihydro-4a-hydroxy-5-deazaflavin (IIa)

Crystal Data

Crystal System	Monoclinic
Cell Dimensions	a = 10.556(3) Å
	b = 7.670(2) Å
	c = 15.282(5) Å
	β = 98.52(3) Å
Cell Volume	1223.6(6) Å^3
Space Group	$P2_1/c$
Number of Formula Units in the Unit Cell	Z = 4
Calculated Density	1.407 g/cm^3

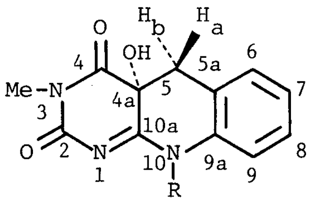
The final R value was 0.065 for 1372 observed reflections.

Compounds II are considerably stable against acid but unstable with base, and are readily hydrolyzed to yield the corresponding 9,9a-dihydrooxazolo[4,5-b]quinolin-2(4H)-ones (III). Namely, stirring of IIa (3.9 mmol) with potassium carbonate (7.7 mmol) in water (10 ml) at room temperature for 20 h precipitated hydrolyzed product, which was filtered off and recrystallized from ethanol to give 9,9a-dihydro-4-methyloxazolo[4,5-b]quinolin-2(4H)-one (IIIa) as colorless needles, mp 213°C, in 60% yield. [^{1}H-NMR (CDCl$_3$), δ 2.93 (1H, t, J = 14 Hz, C_9-H_a), 3.36 (1H, dd, J = 14 and 7 Hz, C_9-H_b), 3.63 (3H, s, N_4-Me), 4.90 (1H, dd, J = 14 and 7 Hz, C_{9a}-H), 6.90-7.57 (4H, m, ArH)]. 4-Ethyl-9,9a-dihydrooxazolo[4,5-b]quinolin-2(4H)-one (IIIb), mp 201°C, was likewise obtained form IIb in 50% yield. Next, IIIa was further hydrolyzed with aqueous potassium carbonate at 80°C for 1 h, and the reaction mixture was acidified with hydrochloric acid and extracted with chloroform. Evaporation of the chloroform extracts and recrystallization of the residue from hexane gave 3,4-dihydro-3-hydroxy-1-methylquinolin-2(1H)-one (IVa) as colorless needles, mp 90°C, in 85% yield. [^{1}H-NMR (DMSO-d$_6$), δ 3.05 (1H, t, J = 14 Hz, C_4-H_a), 3.22 (1H, dd, J = 14 and 7 Hz, C_4-H_b), 3.43 (3H, s, N_1-Me), 3.98 (1H, d, J = 2.5 Hz, OH (chelated)), 4.27 (1H, ddd, J = 14, 7, and 2.5 Hz, C_3-H), 6.85-7.51 (4H, m, ArH). 1-Ethyl-3,4-dihydro-3-hydroxyquinolin-2(1H)-one (IVb), mp 79°C, was likewise obtained from IIIb in 37% yield.



(Ia) R = Me

(Ib) R = Et



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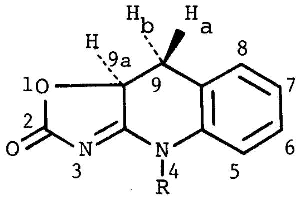
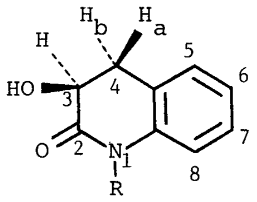


(IIIa) R = Me

(IIIb) R = Et



(IVa) R = Me

(IVb) R = Et

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