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SYNTHESIS OF A NEW TYPE OF 5-DEAZAFLAVOQUINONE. (HYBRID MODEL COMPOUND OF 5-DEAZAFLAVIN AND COENZYME PQQ).

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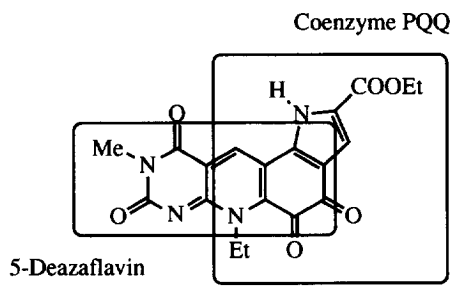
Abstract. A novel chemical hybrid model compound of 5-deazaflavin and PQQ was designed and synthesized via the suitably substituted 5-deazaflavin (5-deazaisoalloxazine) intermediate, followed by the oxidation to introduce orthoquinone group; the obtained model compound showed higher autorecycling oxidizing ability for benzylamine than usual 5-deazaflavins.

5-Deazaflavin, which is thought to be a chemical hybrid of NAD and flavin, functions as an electron transferring agent similar to both NAD and flavin. Syntheses of various 5-deazaflavin derivatives and nonenzymatic autorecycling oxidation of amines to corresponding carbonyl compounds using them have been reported by Yoneda et al.[1,2,3]. Recently 5-deazaflavo-6,9-quinone derivatives (5-dFlQ), which are regarded as a chemical hybrid of 5-deazaflavin and coenzyme Q, were synthesized and their catalytic oxidizing properties were reported by Kimachi et al.[4].

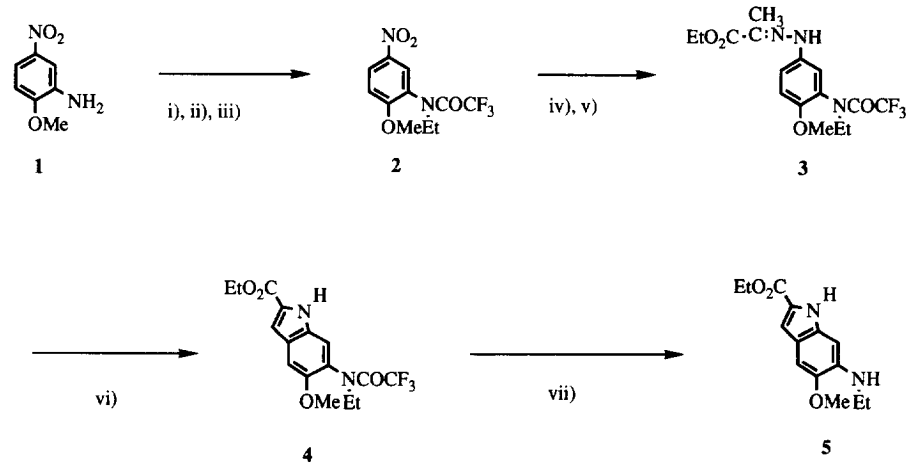


Scheme 1. Heterosis of 5-Deazaflavin and PQQ

In the series of our studies to search for stronger autorecycling oxidizing catalysts , we have designed a novel 5-deazaflavoquinone which can be regarded as a chemical hybrid compound of 5-deazaflavin and coenzyme

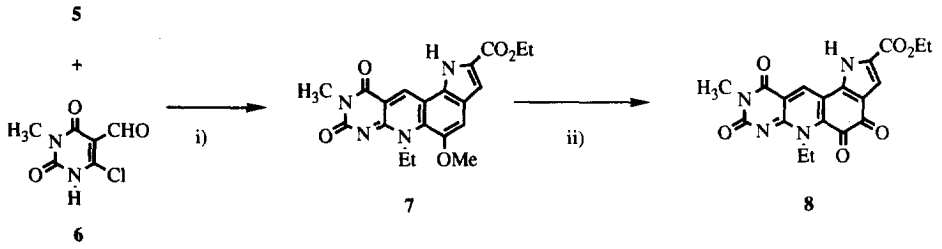
PQQ (Scheme 1). PQQ is known as a coenzyme of alcohol dehydrogenase originated from methylotrophic bacteria and is working as an oxidizing catalyst which oxidizes methanol to formaldehyde or formic acid[5-10]. We descibe herein the synthesis and catalytic amine oxidation of the hybrid model compound of 5-deazaflavin and PQQ.

Starting from 2-methoxy-5-nitroaniline (**1**), N-ethyl-N-trifluoroacetylanisidine derivative **2** was prepared by acetylation, reduction with borane methyl sulfide complex and trifluoroacetylation. The reduction with catalytic hydrogenolysis led the nitro substituent to the amine. Cyclization of arylhydrazone intermediate **3** obtained from aniline derivative by usual procedure, afforded desired indole **4** in totally 61.5% from starting nitroanisidine. Reductive detrifluoroacetylation using sodium borohydride led the amide to the indole **5** in 41.9 % (Scheme 2).

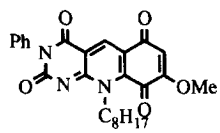
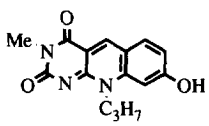


Scheme 2. *Reagents and Conditions:* i) Ac_2O, Py. r.t., 1 h, 96.4 %; ii) BMS, THF, reflux, 5h, 96.8 %; iii) TFAA, Py. 0°C, 3h, 99 %; iv) H_2/PtO_2, EtOH, r.t., 3 days, 98.8 %; v) 1) $NaNO_2$/HCl, 0°C, 5 min, 2) $CH_3CO(CH_3)CO_2C_2H_5$/KOH, EtOH/H_2O, 0°C, 8h, 71.3 %; vi) HCOOH, 90°C, 5h, 94.4 %;vii) $NaBH_4$, EtOH, r.t., 1h, 41.9 %.

Condensation of **5** thus obtained and 6-chloro-5-formyluracil **6** [11] afforded the desired 5-deazaflavin **7** after 2 days heating at 140°C in DMF. The 5-deazaflavin **7** was exposed to several oxidizing conditions to convert the orthoquinone **8**, but it was only successful when silver (II) oxide and nitric acid were used in THF at room temperature for 5 hours (Scheme 3). In the electrochemical study, hybrid model compound **8**[12] was changed to the more electrically positive state than usual 5-dFl, namely redox potential of the compound **8** shifted to -0.48 V from -1.09 V (for 5-dFl) (vs Ag/AgCl, 0.5 mM in 20 ml of DMF containing 0.1 M n-$Bu_4N^+Cl^-$). But it will not be so easy to compare the redox potential between compound **8** and PQQ, because PQQ shows rather complicated redox potential in DMF ,that is, -0.05, -0.71, -0.94, -1.53 (eV)[13].



Scheme 3. *Reagents and Conditions*:i) DMF, 140°C, 2 days, 17.8 %; ii) AgO, HNO_3, THF, r.t., 5h, 10.5 %.

Oxidizing agent	Yield (%)[a)]
8	1767
	776
	262

a) Based on initial amount of oxidizing agent.

Table 1. Oxidation of benzylamine with 5-deazaflavin and PQQ hybrid model **8** and other compounds in acetonitrile: conditions, [oxidizing agent] = 22 mM, [benzylamine] = 4.59 M, ambient air, reaction time: 40 h. reaction temp. 60°C.

The compound **8** thus obtained was used for benzylamine oxidation in acetonitrile as the model reaction for amine oxidase[14]. At room temperature, the reaction was slow and did not act as an autorecycling catalyst. But at the condition described in Table 1, a catalytic amount of **8** strongly oxidized benzylamine to the corresponding benzaldehyde and showed higher autorecycling turnover in the amine oxidizing ability than any other 5-deazaflavin derivatives. However, the autorecycling oxidizing ability of compound **8** was about one-third of that of coenzyme PQQ (PQQTME, tetramethyl ester of PQQ oxidized benzylamine in 5000 % at room temperature[14]). Even under O_2 atmosphere, the reaction was not accelerated. Finally chemical hybridization between 5-deazaflavin and PQQ got the moderate oxidizing ability against benzylamine.

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12. Spectral data. δ_H (270 MHz, $CDCl_3$) 1.39 (t, 3H, J=7.0 Hz), 1.44 (t, 3H, J=7.0 Hz), 3.44 (s, 3H), 4.39 (q, 2H, J=7.0 Hz), 5.06 (q, 2H, J=7.0 Hz), 6.94 (s, 1H), 8.68 (s, 1H), 11.80 (bs, 1H). MS, m/z for $C_{19}H_{16}O_6N_4$ 396.1083 (Calcd. 396.1093). UV visible (chloroform), λ max (ε), nm ($M^{-1}cm^{-1}$); 289 (3.73×10^4), 395 (3.22×10^4), 550 (0.16×10^4).
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