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SYNTHESIS OF A FIXED PARAQUINOID TAUTOMER OF 8-HYDROXY-5-DEAZAFLAVIN

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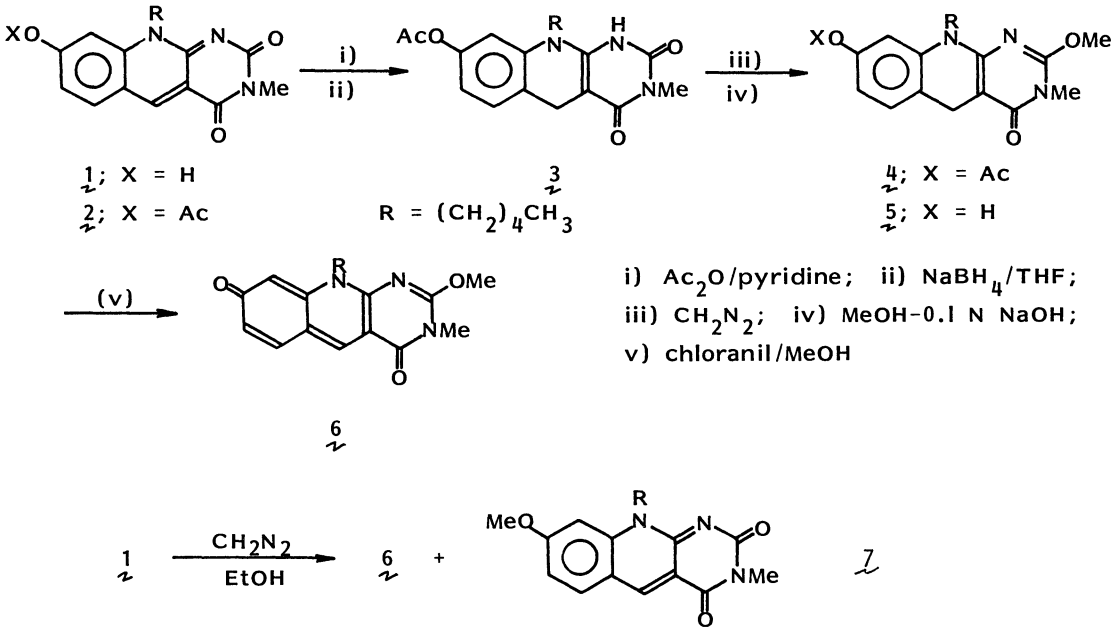
A fixed paraquinoid tautomer of 8-hydroxy-5-deazaflavin has been synthesized by five-step sequence. The existence of paraquinoid-phenolic tautomerism in ethanolic solution was demonstrated by trapping experiment.

Considerable attention has been focussed on the chemistry of 8-hydroxy-5-deazaflavin owing to its biological occurrence as F_{420} in anaerobic methane-producing bacteria.[1,2] The 8-hydroxy-5-deazaflavin system can be represented either in a phenolic structure or in its tautomeric paraquinoid form, and the monoanion was suggested to exist predominantly as paraquinoid form.[2] It is therefore important to establish unambiguously the spectral properties of both tautomers by preparing appropriate model compounds in which the tautomeric form is "blocked" by substitution. We report herein the first synthesis of a derivative of paraquinoid 5-deazaflavin and the result confirming the existence of the paraquinoid-phenolic tautomerism in ethanolic solution.

N^{10}-*n*-Amyl-N^{3}-methyl-8-hydroxy-5-deazaflavin (1) was prepared from 3-methyl-6-chlorouracil and N-(*n*-amyl)-*m*-aminophenol according to the published procedure.[3] Acetylation (acetic anhydride/pyridine) followed by $NaBH_4$ reduction in THF gave 1,5-dihydro-5-deazaflavin 3.[4] Methylation of 3 in MeOH-CH_2Cl_2 (1 : 1) with diazomethane produced 4 which without purification was converted to 5 with MeOH-0.1 N NaOH (20 : 1). Oxidation of 5 with chloranil in MeOH gave 6[4,5] as brilliant yellow needles (Chart 1). Overall yield of 6 from 1 was 50%. 6: mp 212-214 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (3 H, t, J = 7 Hz), 1.40-2.20 (6 H, m), 3.60 (3 H, s), 4.40 (3 H, s), 4.70 (2 H, t, J = 7 Hz), 6.42 (1 H, d, J = 2 Hz), 6.79 (1 H, dd, J = 9, 2 Hz), 7.89 (1 H, d, J = 9 Hz), 8.56 (1 H, s); IR (Nujol) 1674, 1634, 1592 cm^{-1}; UV (EtOH) (log ε) 433 nm (4.28), 303 (4.20), 252 (4.41); Em_{max}(EtOH) 496 nm (435 nm excit).

Chart 1



Evidence for the existence of undissociated paraquinoid tautomer in ethanolic solution of 1 was obtained by the following trapping experiment. A solution of 1 in a large volume of dry ethanol was treated with excess diazomethane in CH_2Cl_2. After evaporation of the solvent, 6 and 7 were obtained in a ratio of 1:3. The structure of 7 was confirmed by independent synthesis from 1 by conventional methylation ($DMF/K_2CO_3/CH_3I$). It is interesting to note here that 1 did not react with diazomethane in aqueous ethanol at pH 7.0 or at pH 8.5, indicating that the undissociated paraquinoid form is reacting with diazomethane.[6] From the foregoing evidence it is now obvious that the phenolic form of 8-hydroxy-5-deazaflavin is equilibrated with its paraquinoid form in organic solvent such as ethanol.

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References

1) L. D. Eirich, G. D. Vogels and R. S. Wolf, Biochem., 17, 4583 (1978).
2) C. Walsh, Accounts Chem. Res., 13, 148 (1980).
3) W. T. Ashton, R. D. Brown, F. Jacobson, and C. Walsh, J. Am. Chem. Soc., 101, 4419 (1979).
4) All new compounds gave consistent spectral data and correct elemental analyses.
5) ^{13}C NMR ($CDCl_3$) δ 157.1 (C-2), 159.9 (C-4), 119.4 (C-4a), 134.9 (C-5), 100.8 (C-5a), 132.9 (C-6), 129.1 (C-7), 183.0 (C-8), 102.5 (C-9), 144.0 (C-9a), 150.9 (C-10a), 28.9 (NMe), 56.4 (OMe). The signals of *n*-amyl group are omitted. The ^{13}C NMR data clearly eliminate a 4-methoxy structure for 6. The assignments are based on off-resonance spectra and comparison of the chemical shifts with those of F_{420}.[1]
6) The pK_a for the dissociation of phenolic 8-hydroxyl group of 1 was determined to be 6.5 ± 0.2.

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