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SYNTHESIS AND PROPERTIES OF 1-BENZOTHIOPYRANO[2,3-d]PYRIMIDINE-2,4(3H)-DIONE (5-DEAZA-10-THIAFLAVIN)

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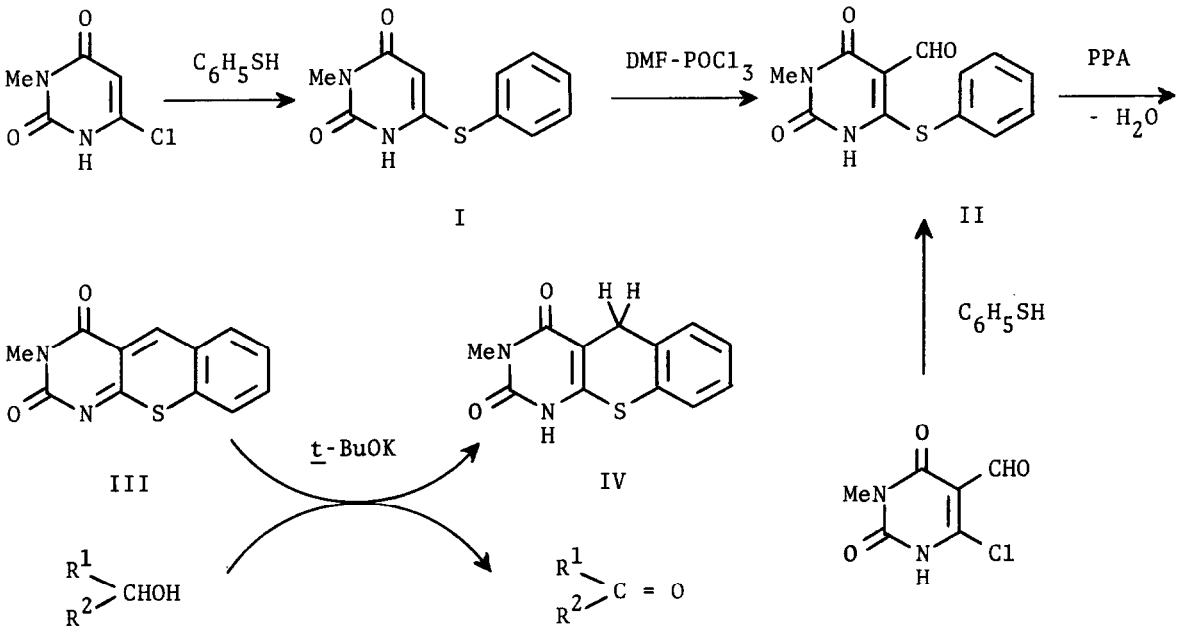
1-Benzothiopyrano[2,3-d]pyrimidine-2,4(3H)-dione (5-deaza-10-thiaflavin) has an isosteric and isoelectronic structure of the biologically interesting 5-deazaflavin (pyrimido[4,5-b]quinoline-2,4(3H,10H)-dione)[1,2] which has been considered as a model not only of flavin nucleotide[3-16] but also of nicotinamide nucleotide protected by annelation.[17] Therefore, it would be expected that the 5-deaza-10-thiaflavin has some chemical and biological analogies to the 5-deazaflavin, however no report has been described on the synthesis of this ring system so far. This paper describes a synthesis of 3-methyl-5-deaza-10-thiaflavin and oxidation of alcohols by it under alkaline conditions. Additionally we wish to report the alkaline hydrolysis of this compound, which brought about the disproportionation into oxidation-reduction products.

3-Methyl-6-(phenylthio)uracil (I),[18] mp 218°, (2 mmol), prepared in 95% yield by condensation (2 hr reflux) of 6-chloro-3-methyluracil and thiophenol in ethanol in the presence of potassium hydroxide, was treated with a mixture of dimethylformamide (40 mmol) and phosphorous oxychloride (4 mmol) at 90° for 2 hr. The reaction mixture was diluted with water to cause the separation of 5-formyl-3-methyl-6-(phenylthio)uracil (II), mp 207°, in 92% yield. Compound II was also obtained in 80% yield by refluxing of 6-chloro-5-formyl-3-methyluracil[2] (2 mmol) with thiophenol (2 mmol) in ethanol in the presence of potassium carbonate. Heating of the 5-formyluracil (II) (3 mmol) thus obtained in polyphosphoric acid (3 ml) at 120° for 2 hr, followed by dilution with water, afforded 3-methyl-

1-benzothipyrano[2,3-d]pyrimidine-2,4(3H)-dione (3-methyl-5-deaza-10-thiaflavin) (III) as yellow prisms (from acetic acid or dimethylformamide), mp 318°, in 82% yield: NMR (CF_3COOH) δ 3.68 (3H, s, N-Me), 8.05-8.85 (4H, m, ArH), and 10.05 (1H, s, C^5-H); UV λ_{max}^{EtOH} nm (log ε) 283 (3.98), 346 (2.98), and 421.8 (2.92); IR ν_{max}^{Nujol} cm^{-1} 1695m (C=O), 1643s (C=O), 1590s, and 1512s.



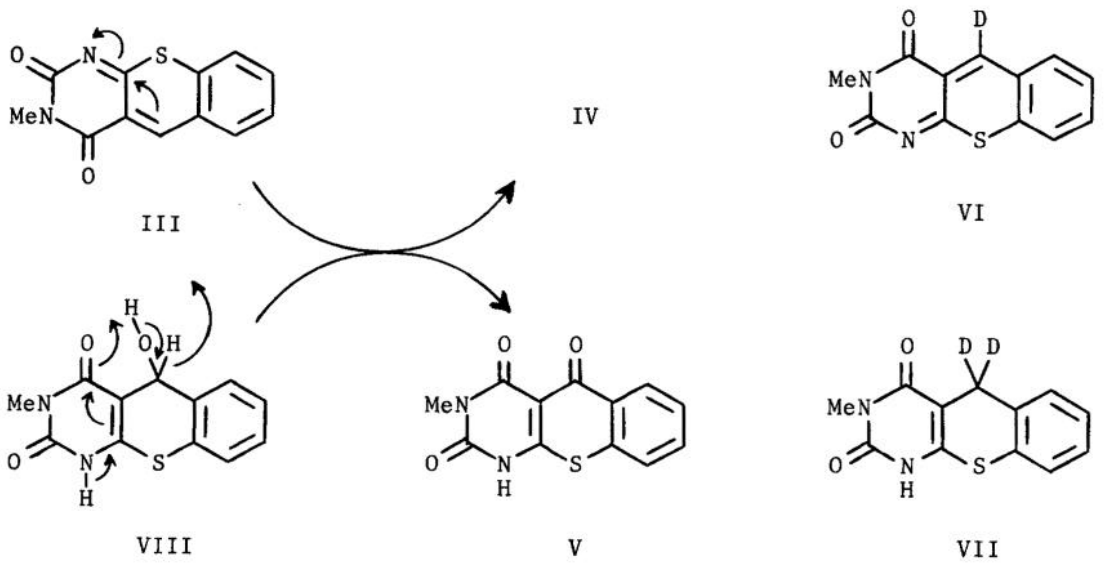
The 5-deaza-10-thiaflavin (III) (2 mmol) was added to benzyl alcohol (4 ml) including potassium t-butoxide (4 mmol) and the mixture was heated at 80° for 2 hr in the dark. The reaction mixture was diluted with ether and the crystals which separated were filtered off to give the potassium salt of IV (vide infra). This salt was dissolved in water and neutralized with acetic acid to give 1,5-dihydro-3-methyl-1-benzothiopyrano[2,3-d]pyrimidine-2,4(3H)-dione (1,5-dihydro-3-methyl-5-deaza-10-thiaflavin) (IV) as colorless crystals (from ethanol), mp >300°, in 90% yield: NMR (CF_3COOH) δ 1.33 (1H, s, NH), 3.53 (3H, s, N-Me), 3.87 (2H, s, C^5-H_2), and 7.29 (4H, s, ArH); UV λ_{max}^{EtOH} nm (log ε) 225 (4.07), 248.5 (3.97), and 296 (3.78); IR ν_{max}^{Nujol} cm^{-1} 3150 (NH), 1700s (C=O), and 1605s (C=O). The filtrate was treated with 4-phenylsemicarbazide to precipitate

benzaldehyde 4-phenylsemicarbazone, mp 181°, in 75% yield. Similarly, benzhydrol was oxidized by the compound III in the presence of potassium t-butoxide to give benzophenone (78% as the oxime, mp 140°) and IV (90%).

Stirring of III (1 mmol) in 20% aqueous potassium hydroxide (3 ml) at 60° for 1 hr, followed by neutralization with acetic acid, caused the separation of a mixture of IV (47%) and 1,5-dihydro-3-methyl-5-deaza-10-thiaflavin-5-one (V) (46%) as colorless needles (from ethanol), mp >300°: NMR (CF_3COOH) δ 3.67 (3H, s, N-Me) and 8.16 (4H, s, ArH); IR ν_{max}^{Nujol} cm^{-1} 3100 (NH), 1722s (C=O), 1660s (C=O), 1582w, 1540w, and 1505w.

Furthermore, treatment of 5-deuterio-3-methyl-5-deaza-10-thiaflavin (VI)[19] with 20% aqueous potassium hydroxide under the same conditions gave the corresponding 5,5-dideuterio-derivative (VII) and the ketone (V) in almost quantitative yields.

Therefore, this disproportionation is rationalized in terms of initial nucleophilic attack of a hydroxide ion on the 5-position of III giving the 5-hydroxy-1,5-dihydro-5-deaza-10-thiaflavin (VIII). Subsequent transfer of a hydrogen equivalent from the 5-position of VIII to the 5-position of III affords the corresponding products IV and V.



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18) Satisfactory analytical and spectral data were obtained for all compounds.

19) Prepared by the treatment of 3-methyl-6-(phenylthio)uracil (I) with a mixture of [$^{2}H_{7}$]dimethylformamide and phosphorous oxychloride, followed by dehydrative cyclization with polyphosphoric acid.