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SYNTHESIS OF 2H-CHROMENO[2,3-d]PYRIMIDINE-2,4(3H)-DIONES (5-DEAZA-10-OXAFLAVINS) AS AN AUTORECYCLING OXIDIZING AGENT

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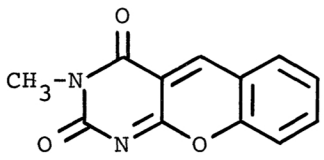
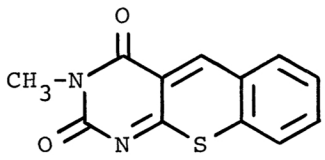
Treatment of 3-methyl-6-phenoxyuracils with the Vilsmeier reagent gave the corresponding 5-formyl-3-methyl-6-phenoxyuracils. Dehydrative cyclization of the above 5-formyluracils with polyphosphoric acid gave 3-methyl-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-diones (3-methyl-5-deaza-10-oxaflavins). These 5-deaza-10-oxaflavins showed strong oxidizing power in oxidizing benzyl alcohol even under neutral conditions to give benzaldehyde, while they were hydrogenated to 1,5-dihydro-5-deaza-10-oxaflavins.

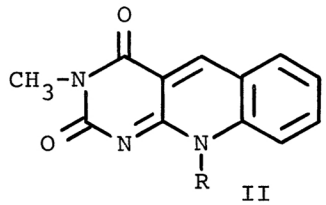
Recently we have reported that 5-deaza-10-thiaflavin,[1] in which the nitrogen atom at the position 10 of the 5-deazaflavin (II) is replaced by a sulfur atom, revealed a similar oxido-reductive behaviour to that of II.[2] For example, 3-methyl-5-deaza-10-thiaflavin (III) oxidized benzyl alcohol to benzaldehyde in the presence of a strong base. Furthermore, the compound III showed an oxidation-reduction at the 5-position in its hydrolysis. On the basis of the above observations, we have planned to synthesize a new ring system, 2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (5-deaza-10-oxaflavin) (I), which has a structure isosteric and isoelectronic with both II and III. The compound I would be expected to have strong oxidizing power, since oxygen atom possesses stronger electronegativity than nitrogen and sulfur atom.



I



III

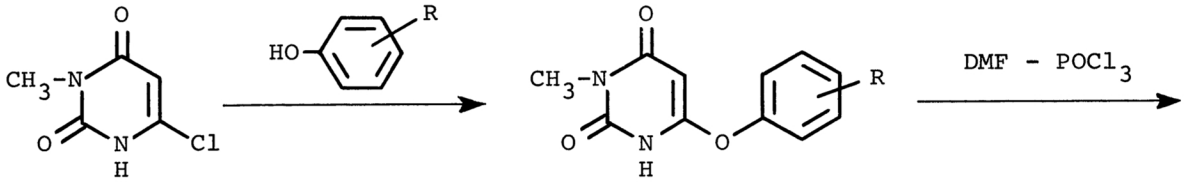


II

Scheme 1

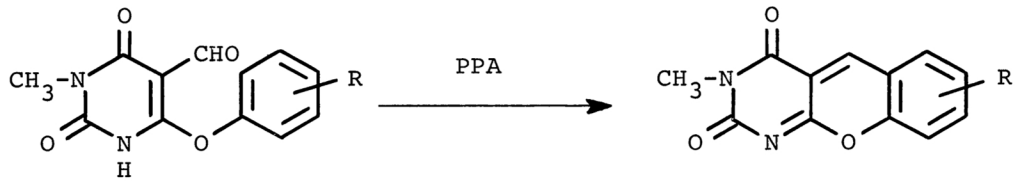
This paper describes a synthesis of 5-deaza-10-oxaflavin derivatives and a preliminary attempt to oxidize benzyl alcohol with them.

Heating of 6-chloro-3-methyluracil (IV)[3] (10 mmol) with appropriate phenols (50 mmol) in dimethylformamide (20 ml) in the presence of potassium carbonate (50 mmol) for 10 hr under reflux gave 3-methyl-6-phenoxyuracils (Va-e), which were recrystallized from ethanol. The compounds V (5 mmol) were treated with a mixture of dimethylformamide (5 ml) and phosphorus oxychloride (1 ml) (the Vilsmeier reagent) at 90 °C for 2 hr and then the reaction mixtures were poured into ice water (100 ml) to separate the corresponding 5-formyl-3-methyl-6-phenoxyuracils (VIa-e). The 5-formyluracils (VI) thus obtained were unstable on recrystallization from solvents and were used for further step without purification.



IV a; R = H
b; R = 4-Cl
c; R = 3-Cl
d; R = 4-CH_3
e; R = 3-CH_3

Va (mp 243 °C, 65%)
Vb (mp 250 °C, 65%)
Vc (mp 232 °C, 80%)
Vd (mp 258 °C, 51%)
Ve (mp 216 °C, 69%)



VIa (84%)
VIb (90%)
VIc (79%)
VId (81%)
VIe (89%)

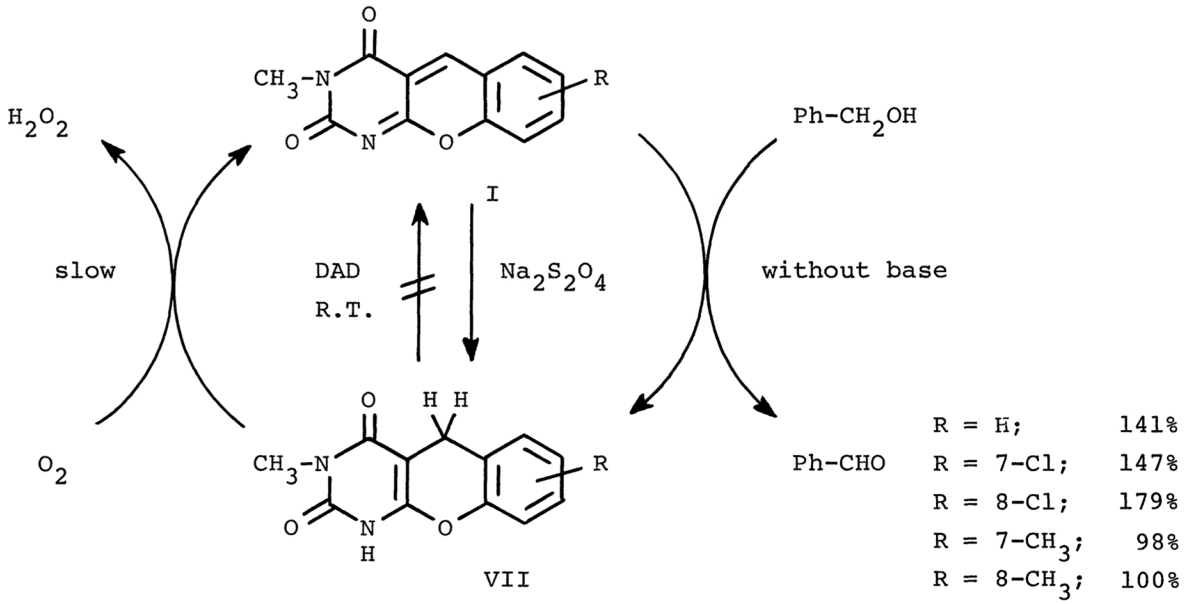
Ia; R = H (mp 261 °C, 82%, yellow needles)
Ib; R = 7-Cl (mp 336 °C, 90%, yellow plates)
Ic; R = 8-Cl (mp 273 °C, 95%, yellow plates)
Id; R = 7-CH_3 (mp 317 °C, 90%, yellow needles)
Ie; R = 8-CH_3 (mp 293 °C, 92%, yellow needles)

Scheme 2

Heating of 5-formyluracils (VI) (5 mmol) in polyphosphoric acid (7 ml) at 120 °C for 2 hr, followed by dilution with ice water (100 ml), afforded 3-methyl-2H-chromeno-[2,3-d]pyrimidine-2,4(3H)-diones (3-methyl-5-deaza-10-oxaflavins) (Ia-e), which were recrystallized from a mixture of acetic acid and acetic anhydride (10:1). The

structures of Ia-e were assigned by elemental analyses and satisfactory spectral data, especially by the presence of the characteristic C-5 proton signal at 9.9 region in the NMR (CF_3COOH).

We have found that the compounds I have remarkable oxidizing ability in oxidizing benzyl alcohol under neutral conditions (in the absence of base)[4] to give benzaldehyde, while the compounds I themselves are reduced to 1,5-dihydro-5-deaza-10-oxaflavins (VII). In some cases, a recycling of the oxidation was observed and more than 100% yield of benzaldehyde (based on the 5-deaza-10-oxaflavin) was obtained.



Scheme 3

For example, a mixture of 3-methyl-5-deaza-10-oxaflavin (Ia) (0.5 mmol) and benzyl alcohol (10 mmol) was stirred at 90 °C for 10 hr under aerobic conditions and the reaction mixture was diluted with ether. The 1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (VIIa) thus separated (R = H, mp 258 °C, ca 50%) was filtered off and the filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2N hydrochloric acid to cause the separation of benzaldehyde 2,4-dinitrophenylhydrazone, mp 237 °C, in 141% yield based on Ia. Other 5-deaza-10-oxaflavins (Ib-e) also oxidized benzyl alcohol to give benzaldehyde under neutral conditions in the yields indicated in Scheme 3. In this series, the presence of the 8-chloro substituent enhanced the oxidizing power. Although the compounds I showed remarkable oxidizing power even in the absence of base, recycling of the reaction was not so excellent as

was expected. This may be attributable to considerable stability of the compounds VII initially formed in aerobic media and their slow reoxidation to the original 5-deaza-10-oxaflavins (I) by air. In fact, the compound VIIa (R = H) alternatively synthesized by the sodium dithionite reduction of Ia was very stable and even diethyl azodicarboxylate (DAD)[5] did not reoxidize it to the original Ia under usual conditions.[6]

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1) F. Yoneda, M. Kawazoe, and Y. Sakuma, Tetrahedron Letters, 1978, 2803.

2) F. Yoneda, Y. Sakuma, and P. Hemmerich, J. Chem. Soc., Chem. Comm., 1977, 825.

3) G. Nübel and W. Pfleiderer, Chem. Ber., 95, 1605 (1962).

4) Alcohol oxidations by 5-deazaflavins[2] or 5-deaza-10-thiaflavins[1] required the presence of base.

5) Oxidation reactions by diethyl azodicarboxylate (DAD) have recently been reviewed; F. Yoneda, Yuki Gosei Kagaku Kyokai Shi, 38, 679 (1980).

6) DAD oxidized readily 1,5-dihydro-5-deazaflavins at room temperature to give the original 5-deazaflavins in quantitative yields; F. Yoneda, K. Mori, Y. Sakuma, and H. Yamaguchi, J. Chem. Soc. Perkin I, 1980, 978.

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