SYNTHESIS OF 1,6-DIMETHYLPYRIMIDO[4,5-c]PYRIDAZINE-5,7-(1H,6H)-DIONE (4-DEAZATOXOFLAVIN) DERIVATIVES AND THEIR USE IN THE OXIDATION OF ALCOHOLS

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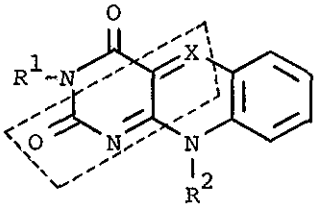
Treatment of 3-methyl-6-(1-methylhydrazino)uracil (I) with phenacyl bromides afforded the corresponding 3-aryl-1,6-dimethylpyrimido[4,5-c]pyridazine-5,7(1H,6H)-diones (3-aryl-4-deazatoxoflavins) (IIa-c) and 3-aryl-1,7-dimethyl-6,8-dioxo-1,4,6,7,8-pentahydropyrimido[4,3-c]-as-triazines (IIIa-c). The reaction of arylaldehyde N-methyl-N-(3-methyluracil-6-yl)hydrazones (IVa-e) with triethyl orthoformate in DMF also gave the respective 4-deazatoxoflavins (IIa-e).

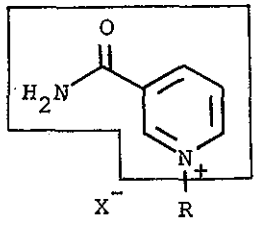
3-Phenyl-4-deazatoxoflavin (IIa) thus obtained oxidized alcohols under alkaline conditions in the dark to yield the corresponding carbonyl compounds, while it is itself hydrogenated to 4,8-dihydro-3-phenyl-4-deazatoxoflavin (V).

1,6-Dimethylpyrimido[4,5-c]pyridazine-5,7(1H,6H)-dione (4-deazatoxoflavin) where N-4 of the antibiotic toxoflavin[1] is replaced by CH, has a similar conjugated system to those of flavin and pyrimido[4,5-b]quinoline-2,4(3H,10H)-dione (5-deazaflavin)[2,3] in the molecule. Furthermore one of canonical forms of its resonance can

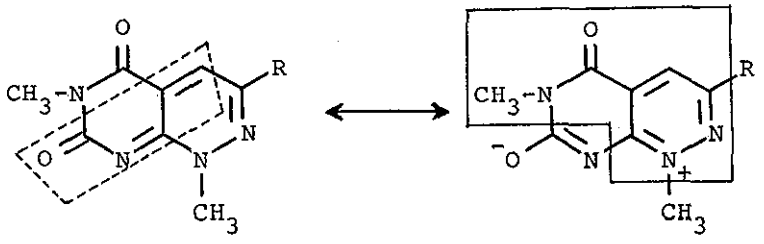
be considered as a model of the 6-aza analog of nicotinamide nucleotide. Therefore it would be expected that 4-deazatoxoflavin derivatives might abstract hydrogen equivalents from hydrogen donors under certain conditions.



X = N: flavin
X = CH: 5-deazaflavin



nicotinamide nucleotide

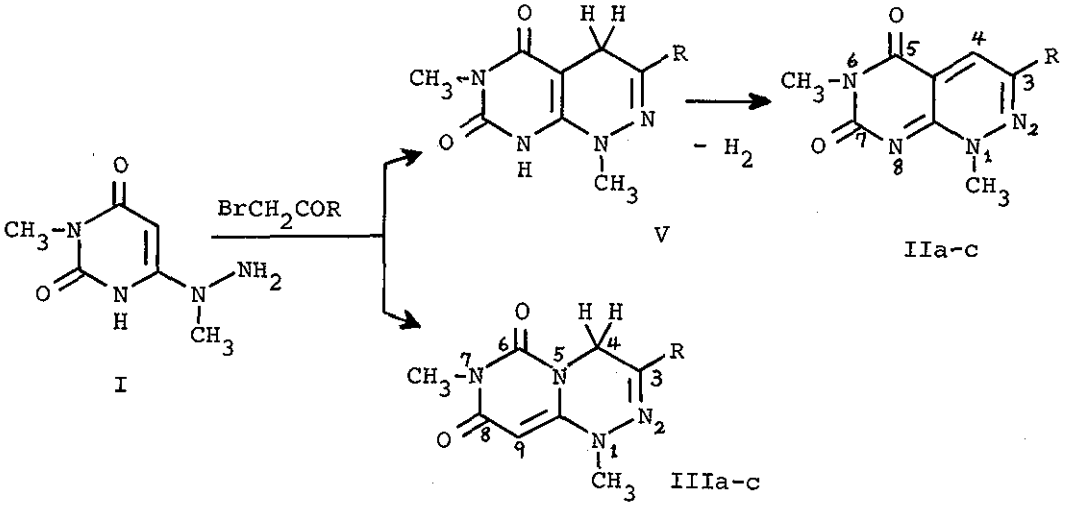


4-deazatoxoflavin

4-Deazatoxoflavin and its analogs have first been synthesized by Castle et al.[4] by the condensation of 3-methyl-6-(1-methylhydrazino)uracil[5] with appropriate α-diketones. We now present two new synthetic methods of 4-deazatoxoflavin derivatives and oxidation of alcohols by them under alkaline conditions.

Synthetic Method A Refluxing of 3-methyl-6-(1-methylhydrazino)uracil (I) with an equimolar amount of phenacyl bromide in ethanol for 5 hr afforded a mixture of 1,6-dimethyl-3-phenylpyrimido[4,5-c]pyridazine-5,7(1H,6H)-dione (3-phenyl-4-deazatoxoflavin) (IIa) and 1,7-dimethyl-6,8-dioxo-3-phenyl-1,4,6,7,8-pentahydro-

pyrimido[4,3-c]-as-triazine (IIIa). The initial reaction mixture included an intermediate for IIa, 4,8-dihydro-1,6-dimethyl-3-phenyl-pyrimido[4,5-c]pyridazine-5,7(1H,6H)-dione (4,8-dihydro-3-phenyl-4-deazatoxoflavin) (V) (vide infra), besides IIa and IIIa. The compound IIIa was separated out from the reaction mixture, while the compound IIa was isolated by evaporation of the filtrate. The assigned structures of these products were derived on the basis of elemental analyses, molecular weights as determined by mass spectro-



metry, and IR spectra and especially by NMR data [(CF_3COOH) δ IIa: 3.63 (3H, s, N^6-CH_3), 4.73 (3H, s, N^1-CH_3), 7.56-8.23 (5H, m, aromatic protons), 9.39 (1H, s, C^4-H). IIIa: 3.62 (3H, s, N-CH_3), 3.73 (3H, s, N-CH_3), 5.02 (2H, s, C^4-H_2), 5.80 (1H, s, br, C^9-H), 7.45-7.95 (5H, m, aromatic protons)]. Other 4-deazatoxoflavins (IIb,c) and pyrimido[4,3-c]-as-triazine derivatives (IIIb,c) were similarly prepared by refluxing I with the corresponding phenacyl bromides in ethanol (see Tables 1 and 2).

TABLE 1. 3-Substituted 4-Deazatoxoflavins

Compd. No.	3-Substituent (R)	Mp (°C)[a]	Yield (%) Method A	Method B
IIa	C_6H_5	250	43	35
IIb	4-Cl-C_6H_4	248	27	36
IIc	4-Br-C_6H_4	255	28	33
IId	3,4-$(CH_3O)_2$-C_6H_3	303		30
IIe	3,4-CH_2O_2-C_6H_3	287		43

a) All compounds were recrystallized from ethanol.

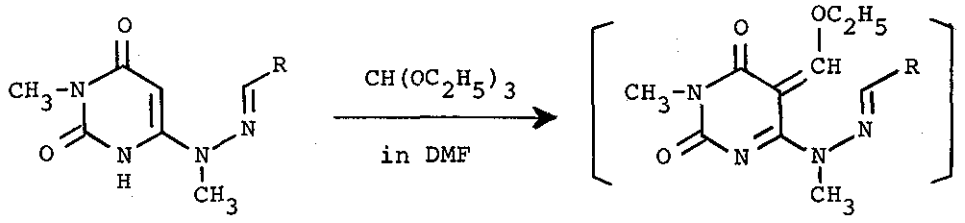
TABLE 2. 3-Substituted 1,7-Dimethyl-6,8-dioxo-1,4,6,7,8-pentahydropyrimido[4,3-c]-as-triazines

Compd. No.	3-Substituent (R)	Mp (°C)[a]	Yield (%)
IIIa	C_6H_5	235	45
IIIb	4-Cl-C_6H_4	276	52
IIIc	4-Br-C_6H_4	284	50

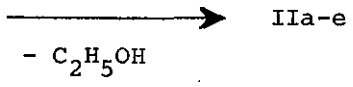
a) All Compounds were recrystallized from ethanol.

Synthetic Method B Heating of arylaldehyde N-methyl-N-(3-methyluracil-6-yl)hydrazones (IVa-e)[1] (0.01 mol) with excess triethyl orthoformate (10 ml) in DMF (20 ml) at 160° for 10 hr resulted in the formation of the corresponding 4-deazatoxoflavins (IIa-e), which were identical with the samples prepared by Synthetic Method A (Table 1).

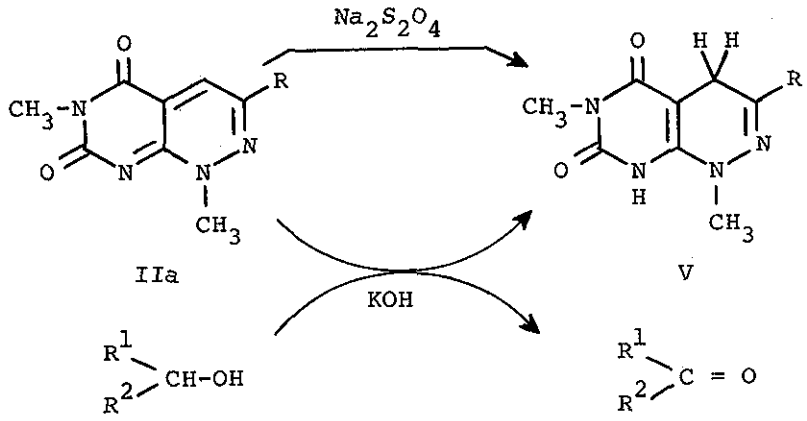
It is noted that neither the Vilsmeier reagent nor dimethylformamide dimethylacetal was effective for the cyclization of IV to II under various conditions.



IVa-e



Oxidation of Alcohols by 4-Deazatoxoflavin The 4-deazatoxoflavin (IIa) (2 mmol) and KOH (9 mmol) were added to a mixture of benzyl alcohol (3 g), DMF (3 ml) and water (2 ml), and then the mixture was warmed at 80° for 1 hr in the dark. From the reaction mixture benzaldehyde was detected in 75% yield by gas chromatography. The reaction mixture was diluted with water and acidified with acetic acid to cause the separation of 4,8-dihydro-3-phenyl-4-deazatoxoflavin (V) as yellow powder, mp > 300°, in 80% yield [NMR (CF_3COOH) δ V: 3.53 (3H, s, N-CH_3), 3.74 (3H, s, N-CH_3), 3.94 (2H, s, C^4-H_2), 7.40-7.90 (5H, m, aromatic protons)]. Compound V was identical with the authentic sample prepared by reduction of IIa with sodium dithionite in the presence of ammonia. The reaction of IIa with benzhydrol under the same conditions afforded benzophenone (70%, not optimum), while IIa was reduced to V. 4-Deazatoxoflavin oxidation of other alcohols are currently under investigation.



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