Synthesis of 2*H*-Chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (10-Oxa-5-deazaflavins) and Their Use in the Oxidation of Benzyl Alcohol

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Treatment of 6-phenoxyuracil derivatives with the Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) gave the corresponding 5-formyl-6-phenoxyuracil derivatives or their equivalents (5-dimethylaminomethylene-6-phenoxyuracil derivatives). Dehydrative cyclization of the above 5-formyluracils or 5-dimethylaminomethyleneuracils with polyphosphoric acid gave the corresponding 2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (10-oxa-5-deazaflavins). These 10-oxa-5-deazaflavins showed strong oxidizing power in oxidizing benzyl alcohol even under neutral conditions (without base) to give benzaldehyde, while they were hydrogenated to 1,5-dihydro-10-oxa-5-deazaflavins.

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Previously we have reported that 10-thia-5-deazaflavins (I), in which the nitrogen atom at position 10 of the 5-deazaflavins (II) is replaced by a sulfur atom, revealed a similar oxido-reductive behaviour to that of II (1). Subsequently we have synthesized the 2*H*-chromeno[2,3-*d*]-pyrimidine-2,4(3*H*)-diones (10-oxa-5-deazaflavins) (III) which possess a structure isosteric and isoelectronic with both I and II (2). Compounds III were expected to have strong oxidizing power, since the oxygen atom possesses stronger electronegativity than nitrogen and sulfur atoms. However, 10-oxa-5-deazaflavin derivatives had been little studied, either synthetically or for their chemical properties. The only analog in the literature prior to 1979 was a benzo derivative (IV) synthesized from 2-hydroxy-1-naphthaldelhyde and barbituric acid (3). Recently, Blythin, *et al.*, described a one-step synthesis of 10-oxa-5-deazaflavin derivatives from salicyl aldehydes and *N*-cyanoacetylurethane (4). In connection with this ring system, 2-aryl-2,3-dihydro-2-deoxo-5-deazaflavins (V) have been synthesized by the condensation of 3-carbamoyl-2-iminochromen with arylaldehydes (5). We now present the experimental details of our synthetic route to 10-oxa-5-deazaflavins (III) and their use in the oxidation of benzyl alcohol (2).

Scheme 1

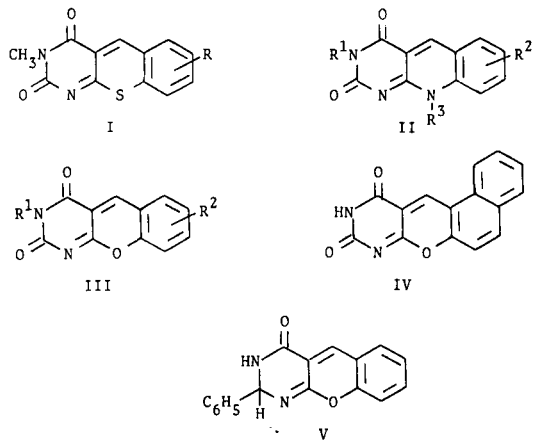
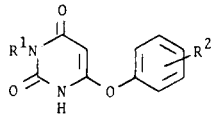


Table 1

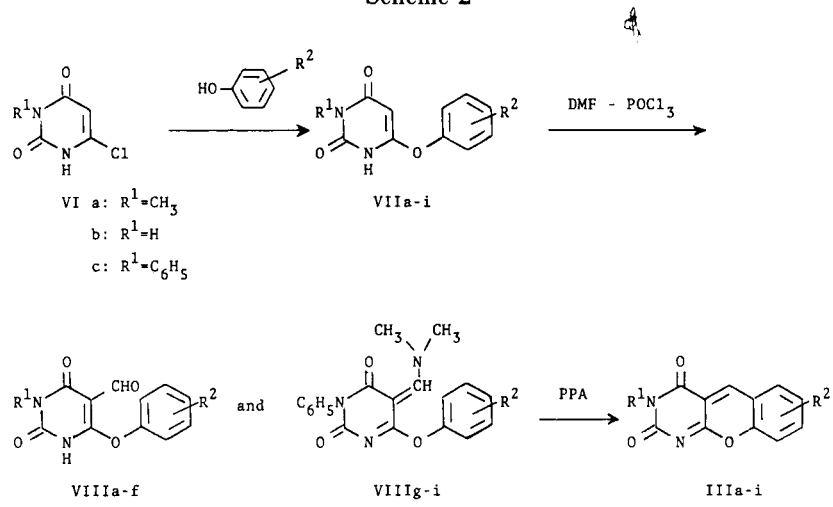
6-Phenoxyuracils



Compound No.	R¹	R²	Yield (%)	Mp (a) (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	CH_3	H	70	243	$C_{11}H_{10}N_2O_3$	60.54	4.62	12.84	60.55	4.71	12.68
VIIb	CH_3	3-CH_3	74	216	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.02	5.39	11.92
VIIc	CH_3	4-CH_3	61	258	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.18	5.11	12.20
VIId	CH_3	3-Cl	85	232	$C_{11}H_9ClN_2O_3$	52.29	3.59	11.09	52.39	3.76	11.27
VIIe	CH_3	4-Cl	70	250	$C_{11}H_9ClN_2O_3$	52.29	3.59	11.09	52.02	3.47	11.38
VIIf	H	H	53	270	$C_{10}H_8N_2O_3$	58.82	3.95	13.72	58.81	4.07	13.49
VIIg	C_6H_5	H	63	248	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.47	4.29	9.92
VIIh	C_6H_5	3-Cl	53	250	$C_{16}H_{11}ClN_2O_3$	61.06	3.52	8.90	61.10	3.53	8.72
VIIi	C_6H_5	4-Cl	49	260	$C_{16}H_{11}ClN_2O_3$	61.06	3.52	8.90	60.87	3.71	8.74

(a) Recrystallized from ethanol or acetic acid and obtained as colorless needles or plates.

Scheme 2



Synthesis of 10-Oxa-5-deazaflavins.

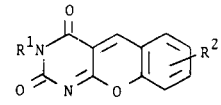
Heating of 6-chloro-3-methyluracil (VIa) (6) with appropriate phenols in demethylformamide in the presence of potassium carbonate under reflux gave the corresponding 3-methyl-6-phenoxyuracils (VIIa-e). Similarly, other 6-phenoxyuracils (VIIf-i) were synthesized from 6-chlorouracil (VIb) (7) or 6-chloro-3-phenyluracil (VIc) (8) and appropriate phenols (Table 1).

The compounds VIIa-f were heated with a mixture of dimethylformamide and phosphorus oxychloride (the Vilsmeier reagent) and then the reaction mixtures were treated with ice water to cause the separation of the corresponding 5-formyl-6-phenoxyuracils (VIIIa-f). In the case of the reaction of VIIg-i with the Vilsmeier reagent, the intermediary 5-dimethylaminomethylene-6-phenoxy-3-phenyluracils (VIIIg-i) were obtained as crude products. However these formyl and dimethylaminomethylene compounds thus obtained were unstable on recrystallization from solvents and were used for further steps without purification.

Heating of the 5-formyluracils (VIIIa-f) or the 5-dimethylaminomethyleneuracils (VIIIg-i) in polyphosphoric acid, followed by dilution with ice water, afforded the corresponding 2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (10-oxa-5-deazaflavins) (IIIa-i) (Table 2).

The structures of IIIa-i were assigned by elementary analyses and satisfactory spectral data, particularly by the presence of the characteristic C_5-H signal at 9.8-10.0 ppm region in the nmr (trifluoroacetic acid) (Table 3). The light absorption spectra of III showed a pattern similar to those of 5-deaza-flavins (9) and 10-thia-5-deazaflavins (I) (Table 3).

Table 2
10-Oxa-5-deazaflavins



Compound No.	R^1	R^2	Yield (%)	Mp (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	CH_3	H	82	261	yellow needles	$C_{12}H_8N_2O_3$	63.16	3.53	12.28	62.93	3.29	12.40
IIIb	CH_3	7-CH_3	90	317	yellow needles	$C_{12}H_{10}N_2O_3$	64.46	4.16	11.57	64.39	3.91	11.61
IIIc	CH_3	8-CH_3	92	293	yellow needles	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.57	64.10	4.09	11.38
IIId	CH_3	7-Cl	90	336	yellow plates	$C_{12}H_7ClN_2O_3$	54.87	2.67	10.67	54.47	2.57	10.78
IIIe	CH_3	8-Cl	95	273	yellow plates	$C_{12}H_7ClN_2O_3$	54.87	2.67	10.67	54.81	2.66	10.74
IIIf	H	H	86	325	yellow plates	$C_{11}H_6N_2O_3$	61.68	2.82	13.08	61.57	2.93	12.92
IIIg	C_6H_5	H	72	301	yellow needles	$C_{17}H_{10}N_2O_3$	70.34	3.47	9.68	70.33	3.50	9.75
IIIh	C_6H_5	7-Cl	70	311	yellow needles	$C_{17}H_9ClN_2O_3$	62.88	2.79	8.63	62.78	2.81	8.60
IIIi	C_6H_5	8-Cl	94	305	yellow needles	$C_{17}H_9ClN_2O_3$	62.88	2.79	8.63	62.86	2.76	8.72

(a) Recrystallized from a mixture of acetic acid and acetic anhydride (10:1).

Table 3
UV and Visible Absorptions and NMR Spectra

Compound No.	λ max (Chloroform) nm (log ε)	δ (Trifluoroacetic Acid) ppm C_5-H
IIIa	322 (4.02), 371 (4.03), 388 (4.12), 408 (3.96)	9.93
IIIb	323 (4.12), 377 (4.07), 397 (4.19), 419 (4.07)	9.83
IIIc	334 (4.07), 373 (4.24), 391 (4.36), 414 (4.22)	9.86
IIId	317 (4.10), 380 (4.02), 399 (4.11), 420 (3.98)	9.81
IIIe	325 (4.04), 372 (4.20), 392 (4.29), 413 (4.10)	9.84
IIIf	319 ( ), 370 ( ), 387 ( ), 409 ( ) (a)	9.79
IIIg	325 (4.11), 370 (4.17), 389 (4.25), 410 (4.09)	9.99
IIIh	317 (4.09), 380 (4.05), 397 (4.15), 421 (3.99)	9.68
IIIi	316 (4.10), 378 (4.06), 397 (4.15), 420 (4.00)	9.77

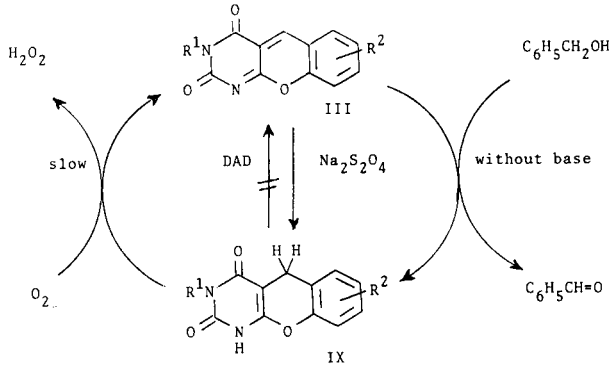
(a) Difficultly soluble in solvents.

Oxidation of Benzyl Alcohol by 10-Oxa-5-deazaflavins.

We have found that compounds III have oxidizing ability in oxidizing benzyl alcohol even under neutral conditions (in the absence of base) to give benzaldehyde, while the compounds III themselves are reduced to 1,5-dihydro-10-oxa-5-deazaflavins (IX). In some cases, a recycling of the oxidation was observed, and more than 100% yield (based on the 10-oxa-5-deazaflavin) of benzaldehyde was obtained.

For example, a mixture of 3-methyl-10-oxa-5-deazaflavin (IIIa) and 20 times excess benzyl alcohol was stirred at 90° for 10 hours. When the reaction mixture was diluted with ether, 1,5-dihydro-3-methyl-10-oxa-5-deazaflavin (IXa) was obtained as a precipitate. Compound IXa showed the characteristic C_5-H_2 signal at 3.8 ppm in the nmr (trifluoroacetic acid). Usually the reaction mixture was treated with 2,4-dinitrophenylhydrazine to separate benzaldehyde 2,4-dinitrophenylhydrazone. The yields of benzaldehyde obtained by the above procedure in the 10-oxa-5-deazaflavin-dependent oxidation of benzyl alcohol by several 10-oxa-5-deazaflavins (III) are indicated in Table 4.

Scheme 3



In this series, 7-chloro-3-phenyl-10-oxa-5-deazaflavin (IIIh) exhibited the highest yield of benzaldehyde. However the orderly correlation between the structure and oxidizing ability was not obtained. Although compounds III showed remarkable oxidizing power even in the absence of base, recycling of the reaction was not so good as was expected. This may be attributable to considerable stability of the 1,5-dihydro-10-oxa-5-deazaflavins (IX) initially formed in aerobic media and their slow reoxidation to the original 10-oxa-5-deazaflavins (III) by air. In fact, the compound IXa prepared by the sodium dithionite reduction of IIIa was very stable and even diethyl azodicarboxylate (DAD) (10) did not reoxidize IXa to the original IIIa under usual conditions (11).

Table 4
Oxidation of Benzyl Alcohol by 10-Oxa-5-deazaflavins (a)

Compound No.	R^1	R^2	Yield of benzaldehyde (%) (b)
IIIa	CH_3	H	141
IIIb	CH_3	7-CH_3	98
IIIc	CH_3	8-CH_3	100
IIId	CH_3	7-Cl	147
IIIe	CH_3	8-Cl	179
IIIf	H	H	80
IIIg	C_6H_5	H	176
IIIh	C_6H_5	7-Cl	205
IIIi	C_6H_5	8-Cl	148

(a) Reaction conditions: 90°, 10 hours. (b) Isolated as the 2,4-dinitrophenylhydrazone.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Nmr spectra were determined with a JEOL JNM JH-60 spectrometer (tetramethylsilane as internal standard) and uv spectra were obtained with a JASCO UVIDEC-1 spectrometer (1-cm quartz cells). The identity of the compounds was confirmed by comparison of ir spectra determined in Nujol with a JASCO IR-A1 spectrometer.

6-Phenoxyuracils (VIIa-i). General Procedure.

A mixture of a 6-chlorouracil (10 mmoles), an appropriate phenol (30 mmoles) and potassium carbonate (50 mmoles) in dimethylformamide (20

ml) was refluxed for 10 hours under stirring. The reaction mixture was evaporated *in vacuo* and the residue was treated with ether to remove excess phenol. The crystals thus obtained were suspended in water, neutralized with acetic acid, and the crude product was filtered off. Recrystallization from ethanol or acetic acid gave colorless crystals (Table 1).

5-Formyl-6-phenoxyuracils (VIIIa-f). General Procedure.

A 6-phenoxyuracil (VIIIa-f) (5 mmoles) was added to a mixture of dimethylfromamide (5 ml) and phosphorus oxychloride (1 ml) and the mixture was heated at 90° for 2 hours. The reaction mixture was poured into ice water (100 ml) and the resulting precipitates were filtered off and dried on phosphorus pentaoxide in the desiccator. These compounds were unstable on recrystallization from solvents and were used for further steps without purification.

5-Dimethylaminomethylene-6-phenoxy-3-phenyluracils (VIIIg-i). General Procedure.

A 6-phenxoy-3-phenyluracil (VIIg-i) (5 mmoles) was added to a mixture of dimethylformamide (5 ml) and phosphorus oxychloride (1 ml) and the mixture was treated as above. These products showed the characteristic two methyl protons at 3.7 and 3.9 ppm regions and the methine proton at 8.8 ppm region (of the 5-dimethylaminomethylene group) in the nmr (trifluoroacetic acid). These compounds were also unstable on recrystallization from solvents and were used for futher steps without purification.

2*H*-Chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (10-Oxa-5-deazaflavins) (IIIa-i). General Procedure.

A 5-formyl-6-phenoxyuracil (VIIIa-f) or a 5-dimethylaminomethylene-6-phenoxyuracil (VIIIg-i) (5 mmoles) was suspended in polyphosphoric acid (7 ml) and the mixture was stirred at 120° for 2 hours. After cooling, the reaction mixture was diluted with ice water to cause the separation of cyrstals, which were collected by filtration and recrystallized from a mixture of acetic acid and acetic anhydride (10:1).

1,5-Dihydro-10-oxa-5-deazaflavin (IXa).

A mixture of IIIa (0.5 g, 2.2 mmoles) and sodium dithionite (0.57 g) was refluxed in water (5 ml) including 20% ammonia (1 ml) for 1 hour. The precipitate was filtered off, dried and recrystallized from acetic acid to give 1,5-dihydro-10-oxa-5-deazaflavin (IXa) as colorless powder (0.41 g, 81%), mp 258°; ms: m/e 230 (M^+); nmr (trifluoroacetic acid): ppm 3.53 ($N\text{-}CH_3$), 3.80 ($C_5\text{-}H_2$) and 7.23 (aromatic protons); ir (Nujol): cm^{-1} 3100 (NH), 1710, 1678, 1604.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.47; H, 4.41; N, 12.09.

Oxidation of Benzyl Alcohol by 10-Oxa-5-deazaflavins (III).

A 10-oxa-5-deazaflavin (III) (0.5 mmole) was added to benzyl alcohol (10 mmoles) and the mixture was heated at 90° for 10 hours with stirring. The reaction mixture was diluted with ether and the 1,5-dihydro-10-oxa-5-deazaflavin which separated was filtered off. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid to cause the separation of benzaldehyde 2,4-dinitrophenylhydrazone, mp 237°.

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