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Synthesis of 10-Arylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)diones (10-Aryl-5-deazaflavins) and Their Use in Oxidations of Alcohols and Amines

Fumio Yoneda, Kinshiro Tsukuda, Kazuo Shinozuka, Fumitoshi Hirayama, Kaneto Uekama,[1a] and Akira Koshiro[1b]

Faculty of Pharmaceutical Sciences, Kumamoto University,[1a] and Department of Pharmacy, Yamaguchi University Hospital[1b]

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Treatment of aryl-bis(6-anilino-3-methyluracil-5-yl)methanes, which were prepared by the condensation of 6-anilino-3-methyluracils with arylaldehydes, with diethyl azodicarboxylate (DAD) in the presence of sulfolane led to the formation of the corresponding 10-arylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (10-aryl-5-deazaflavins). Heating of the methanes alone in sulfolane without DAD gave the corresponding 5-aryl-5-deaza-alloxazines.

The oxidizing abilities of the 10-aryl-5-deazaflavins thus obtained were examined from both kinetic and synthetic viewpoints. The oxidations of benzyl alcohol and benzylamine by these 5-deazaflavins have been shown to recycle automatically, and more than 100% yield of benzaldehyde (based on the 5-deazaflavins) was obtained.

Keywords——pyrimido[4,5-*b*]quinoline; 5-deazaflavin; alcohol oxidation; amine oxidation; diethyl azodicarboxylate; aryl-bis(6-anilinouracil-5-yl)methane; 5-deaza-alloxazine; turn-over catalyst; biomimetic oxidation

Recently, we have found that pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (5-deazaflavins) oxidize alcohols under strongly alkaline conditions, even in the dark, to yield the corresponding carbonyl compounds, while they themselves are hydrogenated to 1,5-dihydro-5-deazaflavins.[2] More interestingly, it was found that 5-deazaflavin-dependent oxidation of alcohols automatically recycles under less basic conditions.[3] For example, in the presence of potassium carbonate, the 1,5-dihydro-5-deazaflavins initially formed were reoxidized to the original 5-deazaflavins by air, so that the 5-deazaflavins acted as a turn-over catalyst. The 5-deazaflavins were also effective reagents for the oxidation of amines to carbonyl compounds.[4] The 5-deazaflavin ring system has generated considerable interest, because of the finding that coenzyme F_{420} from methane-producing bacteria possesses a 5-deazaflavin nucleus.[5,6]

In a previous paper, we reported a novel synthetic route to 5-deazaflavins by the oxidative cyclization of aryl-bis-(6-alkylamino-3-methyluracil-5-yl)methanes with diethyl azodicarboxylate (DAD).[7] The present paper describes a synthesis of previously unknown 10-arylpyrimido-[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (10-aryl-5-deazaflavins) by an application of the above synthetic methodology and their use as a turn-over catalyst in oxidations of alcohols and amines. It should be noted here that the known cyclization[8] of 6-(N-alkylanilino)uracils to the corresponding 10-alkyl-5-deazaflavins with one-carbon reagents, including the Vilsmeier reagent,

1) Location: *a) Oe-honmachi, Kumamoto 862, Japan; b) Kogushi, Ube 755, Japan.*
2) F. Yoneda, Y. Sakuma, and P. Hemmerich, *J. Chem. Soc. Chem. Comm.*, **1977**, 825.
3) F. Yoneda in "Lectures in Heterocyclic Chemistry," Vol. 5 ed. by R.N. Castle and S.W. Schneller, HeteroCorporation, Orem, Utah, 1980, p. 73.
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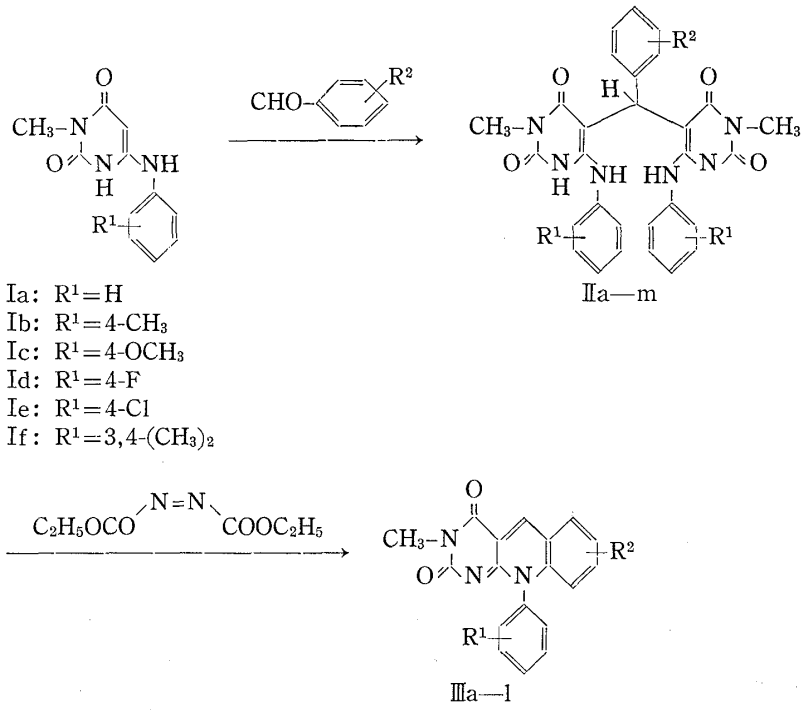


Ia: R^1=H
Ib: R^1=4-CH_3
Ic: R^1=4-OCH_3
Id: R^1=4-F
Ie: R^1=4-Cl
If: R^1=3,4-$(CH_3)_2$

Chart 1

could not be applied to the synthesis of 10-aryl-5-deazaflavins, because the intermediary 6-(N-arylanilino)uracils were not available by the usual condensation of 6-chlorouracils with diphenylamines.

Synthesis of 10-Aryl-5-deazaflavins

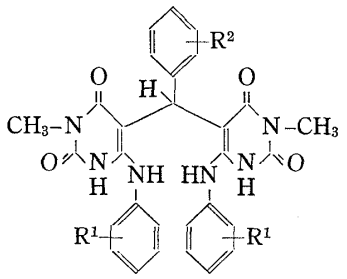
The requisite starting materials, aryl-bis(6-anilino-3-methyluracil-5-yl)methanes (IIa—m) were readily obtained by heating 6-anilino-3-methyluracils (Ia—f) with appropriate arylaldehydes in refluxing acetic acid (Table I). The structures of compounds II were established based on the satisfactory analytical and spectral data. They showed a characteristic signal of the methane proton on the carbon carrying the aryl group and two 6-anilino-3-methyluracil moieties in the 6.5 ppm region in deuterochloroform. These adducts are thermally labile, as indicated by their mass spectra, which show no parent ion but give two large peaks corresponding to 6-anilino-3-methyluracil and 5-benzylidene-6-anilino-3-methyluracil.

Fusion of compound IIa with excess diethyl azodicarboxylate (DAD) in the presence of sulfolane (as a high-boiling solvent) at 180° caused oxidative cyclization to give rise to 10-phenyl-3-methylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (10-phenyl-3-methyl-5-deazaflavin) (IIIa). The reaction is equally applicable to compounds IIb—m to afford the corresponding 10-aryl-5-deazaflavins (IIIb—l) (Table II).

The light absorption spectra showed typical bands of the 5-deazaflavin ring system,[8] namely one band in the 400 nm region and another in the 320 nm region in ethanolic solution (Table III). The C-5 proton chemical shifts of the 10-aryl-5-deazaflavins vary according to the nature of the 7- and 8-substituents, as shown in Table III. On the other hand, the substituents on the 10-aryl moiety seem to have no significant influence upon the C-5 proton chemical shifts.

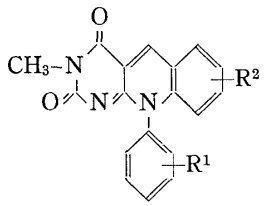
This new synthesis of 10-aryl-5-deazaflavins can be rationalized in terms of the initial addition of DAD to compounds II. Subsequent cyclization with concomitant elimination of 6-anilino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyluracil would provide the 10-aryl-1,5-dihydro-5-deazaflavins. The latter could be readily dehydrogenated by excess DAD to give the final 10-aryl-5-deazaflavins. The eliminated 6-anilino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyluracil is presumably thermally decomposed to unidentified compounds.

TABLE I. Aryl-bis(6-anilino-3-methyluracil-5-yl)methanes



Compd. No.	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIa	H	H	302	94	$C_{29}H_{26}N_6O_4$	66.65	5.02	16.08	66.36	5.14	15.95
IIb	4-CH_3	H	268	90	$C_{31}H_{30}N_6O_4$	67.62	5.49	15.26	67.81	5.51	15.46
IIc	4-OCH_3	H	293	90	$C_{31}H_{30}N_6O_6$	63.90	5.19	14.43	63.69	5.10	14.31
IId	4-F	H	293	84	$C_{29}H_{24}F_2N_6O_4$	62.14	4.32	15.35	62.25	4.59	15.46
IIe	4-Cl	H	298	87	$C_{29}H_{24}Cl_2N_6O_4$	58.69	4.08	14.50	58.51	4.16	14.54
IIf	3,4-$(CH_3)_2$	H	307	89	$C_{33}H_{34}N_6O_4$	68.49	5.92	14.52	68.76	5.87	14.63
IIg	H	4-CH_3	331	92	$C_{30}H_{28}N_6O_4$	67.15	5.26	15.66	67.36	5.41	15.45
IIh	H	4-OCH_3	259	91	$C_{30}H_{28}N_6O_5$	65.20	5.10	15.21	64.93	5.24	15.08
IIi	H	4-F	321	85	$C_{29}H_{25}FN_6O_4$	64.20	4.64	15.86	64.03	4.61	15.18
IIj	H	4-Cl	285	89	$C_{29}H_{25}ClN_6O_4$	62.31	4.51	15.39	62.59	4.75	15.18
IIk	H	3-CH_3	294	93	$C_{30}H_{28}N_6O_4$	67.15	5.26	15.66	67.02	5.37	15.69
IIl	H	3-OCH_3	293	90	$C_{30}H_{28}N_6O_5$	65.20	5.10	15.21	65.04	5.18	15.00
IIm	H	3-Cl	319	90	$C_{29}H_{25}ClN_6O_4$	62.31	4.51	15.39	62.39	4.40	15.09

TABLE II. 10-Aryl-3-methyl-5-deazaflavins



Compd. No.	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIIa	H	H	>360	66	$C_{18}H_{13}N_3O_2$	71.27	4.32	13.86	70.91	4.41	13.91
IIIb	4-CH_3	H	346	57	$C_{19}H_{15}N_3O_2$	71.91	4.76	13.24	71.86	4.63	13.13
IIIc	4-OCH_3	H	323	52	$C_{19}H_{15}N_3O_3$	68.46	4.54	12.61	68.38	4.51	12.32
IIId	4-F	H	>360	49	$C_{18}H_{12}FN_3O_2$	67.28	3.76	13.08	67.04	3.87	12.79
IIIe	4-Cl	H	>360	62	$C_{18}H_{12}ClN_3O_2$	64.00	3.58	12.44	63.85	3.57	12.16
IIIf	3,4-$(CH_3)_2$	H	>360	61	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.51	5.04	12.72
IIIg	H	8-CH_3	>360	60	$C_{19}H_{15}N_3O_2$	71.91	4.76	13.24	71.77	4.70	12.99
IIIh	H	8-OCH_3	>360	65	$C_{19}H_{15}N_3O_3$	68.46	4.54	12.61	68.38	4.55	12.27
IIIi	H	8-Cl	>360	70	$C_{18}H_{12}ClN_3O_2$	64.00	3.58	12.44	63.85	3.50	12.19
IIIj	H	7-CH_3	>360	74	$C_{19}H_{15}N_3O_2$	71.91	4.76	13.24	72.04	4.77	13.12
IIIk	H	7-OCH_3	358	82	$C_{19}H_{15}N_3O_3$	68.46	4.54	12.61	68.55	4.53	12.78
IIIl	H	7-Cl	>360	87	$C_{18}H_{12}ClN_3O_2$	64.00	3.58	12.44	63.77	3.50	12.17

Table III. UV and Visible Maxima and C-5 Proton Chemical Shifts of 10-Aryl-5-deazaflavins

Compd No.	λ_{max}^{EtOH} (log ε)	δ (CF_3COOH)
IIIa	417sh(4.03), 400(4.08), 382sh(3.98), 321(4.03), 264(4.56)	9.93
IIIb	420sh(3.97), 400(4.06), 384sh(3.94), 319(4.00), 264(4.62)	9.92
IIIc	419sh(3.94), 402(4.03), 320(4.00), 264(4.58)	9.92
IIId	419sh(4.00), 401(4.50), 380sh(3.91), 320(4.00), 263(4.51)	9.94
IIIe	420sh(3.94), 400(4.03), 320(3.98), 316sh(3.97), 264(4.56)	9.95
IIIf	417sh(3.69), 401(3.79), 389sh(3.70), 320(3.76), 264(4.38)	9.92
IIIg	414sh(3.90), 399(3.97), 322(3.96), 263(4.40)	9.82
IIIh	422(3.96), 395(3.99), 336(3.53), 257(4.16)	9.70
IIIi	419sh(3.51), 397(3.78), 322(3.82), 256(4.30)	9.90
IIIj	429sh(4.01), 409(4.09), 388sh(3.93), 325(4.05), 318sh(4.04), 266(4.65), 224(4.48)	9.86
IIIk	427(3.87), 409sh(3.75), 329(3.85), 313(3.94), 263(4.42), 225(4.26)	9.83
IIIl	423sh(3.87), 409(3.96), 393sh(3.89), 319sh(3.95), 307(3.99), 268(4.64), 226(4.44)	9.87

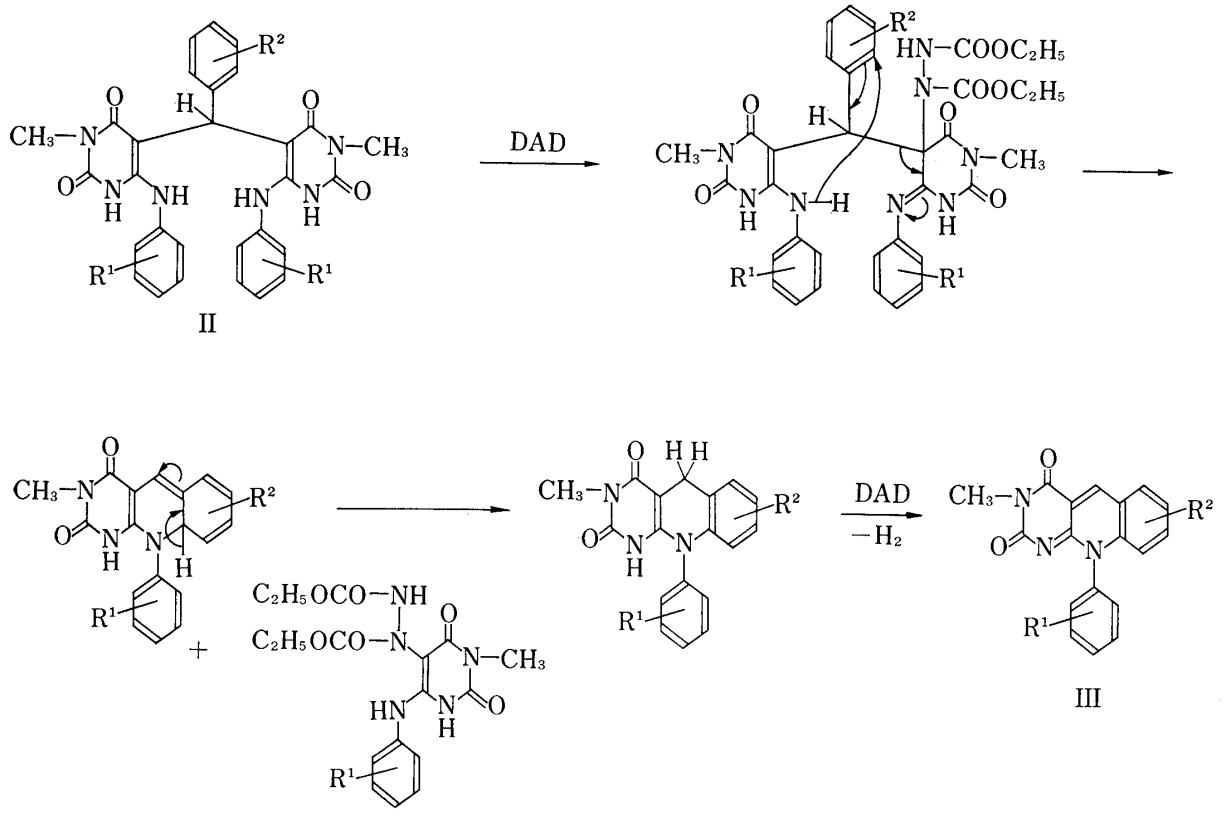
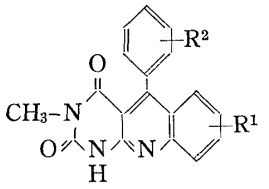


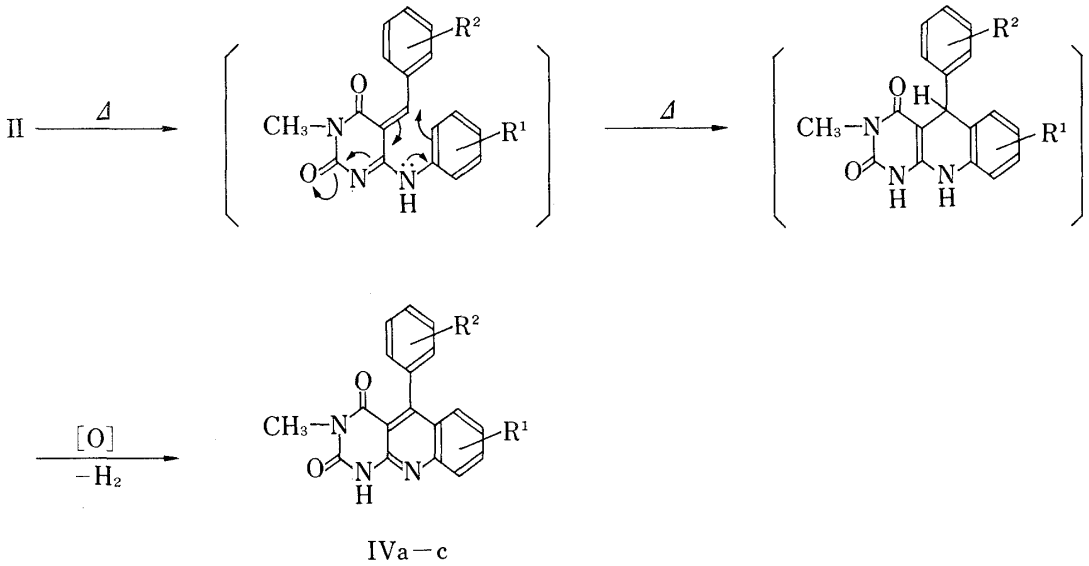
Chart 2

When the fusion of compounds II with excess DAD was carried out at more than 200°, the by-product 5-aryl-3-methyl-5-deazaalloxazines (IV) were obtained in addition to the corresponding 5-deazaflavins (III). Heating compounds IIa, b, f alone in sulfolane at 250° without DAD also gave the same 5-aryl-5-deazaalloxazines (IVa, b, c) (Table IV). It appears that the 5-benzylidene-6-anilino-3-methyluracil fragment derived from II by thermal decomposition (suggested by mass spectrometry, as described above) underwent cyclization followed by dehydrogenation to give compounds IV, as depicted in Chart 3. The structures of compounds IV were determined by mass spectrometry, the absence of the C-5 proton in their NMR spectra, and their light absorption spectra (Table IV).

Table IV. 5-Aryl-3-methyl-5-deazaalloxazines



Compd. No.	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	λ_{max}^{EtOH} (log ε)
IVa	H	H	300 (sublim)	92	$C_{18}H_{13}N_3O_2$	71.27 (71.01	4.32 4.60	13.86 14.01)	413sh(3.82), 383(3.86), 377sh(3.62), 312(3.98), 259(4.57), 244(4.42)
IVb	H	4-CH_3	315 (sublim)	89	$C_{19}H_{15}N_3O_2$	71.91 (71.82	4.76 4.86	13.24 13.10)	374sh(3.75), 361(3.81), 310(3.98), 313sh(3.94), 254(4.46), 242(4.65)
IVc	7,8-$(CH_3)_2$	H	313 (sublim)	90	$C_{20}H_{17}N_3O_2$	72.49 (72.12	5.17 5.04	12.68 12.73)	381(3.36), 365(3.50), 318(3.69), 260(4.40), 247(4.31)



IVa–c

Chart 3

Dehydrogenation of Alcohols and Amines by 10-Aryl-5-deazaflavins

Table V shows the apparent oxidation rates of alcohols by these 10-aryl-5-deazaflavins in both 0.2 N sodium hydroxide in 50 v/v% ethanol and 0.2 N sodium hydroxide in 50 v/v% isopropanol at 60°. The lowest line shows the rate with 10-ethyl-3-methyl-5-deazaflavin for comparison. In general, a significant substituent effect was not observed, but 7-chloro-3-methyl-10-phenyl-5-deazaflavin (IIIl) did show exceptional behavior: the rate for this compound was so high that it could not be determined by conventional spectroscopic methods under these conditions.

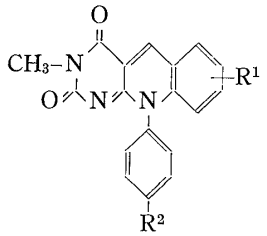
Under much milder conditions, such as pH 11.5 in 50 v/v% isopropanol at 60°, 7-chloro-3-methyl-10-phenyl-5-deazaflavin (IIIl) (2.97×10^{-1} min^{-1}) oxidized isopropanol about 10 times faster than 3-methyl-10-phenyl-5-deazaflavin (IIIa) (3.75×10^{-2} min^{-1}).

Judging from these data, the 10-aryl-5-deazaflavins seem to be strong oxidizing agents. Thus, oxidations of alcohols and amines were carried out on a larger scale in order to examine

their oxidizing abilities from a practical synthetic point of view.

Table VI shows the results of oxidations of benzyl alcohol and cyclohexanol into benzaldehyde and cyclohexanone by selected 10-aryl-5-deazaflavins (III) in the presence of potassium carbonate. In this series, the presence of an 8-chloro group considerably enhanced the oxidizing power, while the presence of a 7-chloro group rather decreased it, contrary to our expectation based on the above kinetic data. This means that compound IIIl oxidizes substrates very rapidly in the initial stage, but recycling of the reaction is rather poorer than with other

Table V. Apparent Oxidation Rates of Alcohols by 10-Aryl-5-deazaflavins at 60°



Compd. No.	R^1	R^2	$k'(min^{-1})^{a)}$	$k'(min^{-1})^{b)}$
IIIa	H	H	0.12	0.28
IIIb	H	CH_3	0.10	0.26
IIIc	H	OCH_3	0.10	0.22
IIId	H	F	0.10	0.31
IIIe	H	Cl	0.098	0.26
IIIg	8-CH_3	H	0.064	0.18
IIIh	8-OCH_3	H	0.062	0.13
IIIi	8-Cl	H	0.15	0.18
IIIl	7-Cl	H	—c)	—c)
10-Ethyl-3-methyl-5-deazaflavin			0.043	0.10

a) 0.2N NaOH in 50 v/v% ethanol–water.
b) 0.2N NaOH in 50 v/v% isopropanol–water.
c) Too fast to determine by the conventional spectroscopic method.

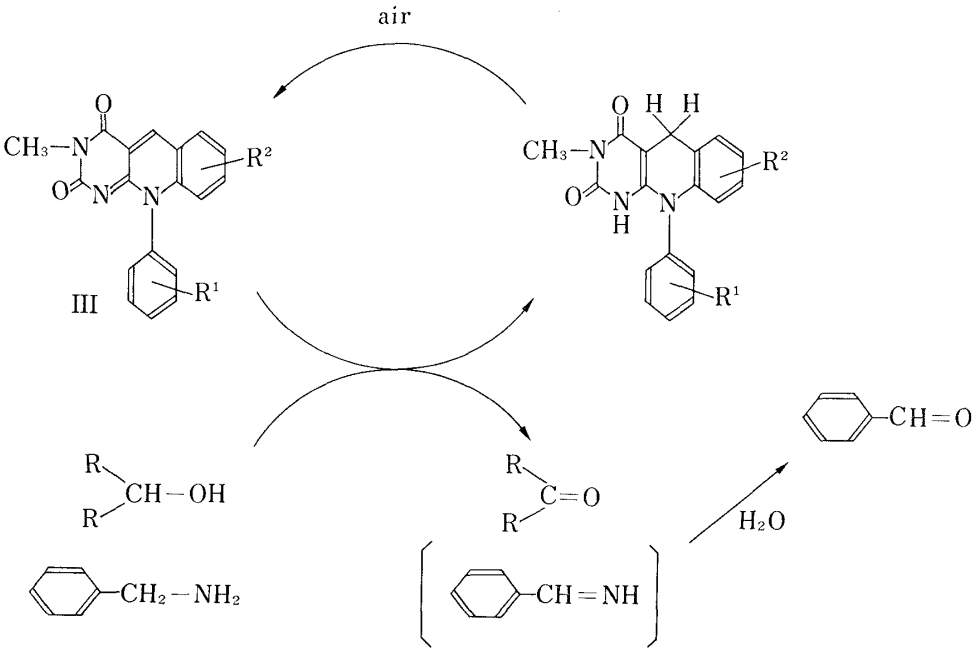
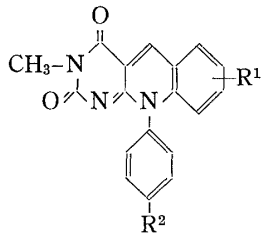


Chart 4

10-aryl-5-deazaflavins. In fact, even at 20° and 60° for just 5 minutes, compound IIIl oxidized benzyl alcohol into benzaldehyde in 122 and 144% yields, respectively, while in the oxidation by compound IIIa the yield of benzaldehyde was 57% after 1 hr at 60°.

Next, the oxidation of benzylamine by compounds III was carried out under aqueous conditions, and a similar substituent effect was observed (Table VI). It should be noted that the oxidation of benzylamine to benzaldehyde also shows considerably recycling; even under aqueous conditions the 10-aryl-1,5-dihydro-5-deazaflavins initially formed are reoxidized to the original 10-aryl-5-deazaflavins (III) by adventitious air.

Table VI. Oxidations of Benzyl Alcohol, Cyclohexanol and Benzylamine by 10-Aryl-5-deazaflavins



			Substrate		
			Benzyl alcohol	Cyclohexanol	Benzylamine
			Yield of Product (%)[a]		
			Benzaldehyde[b]	Cyclohexanone[c]	Benzaldehyde[c]
	R^1	R^2			
IIIa	H	H	296	38	212
IIIe	H	Cl	199	65	352
IIIi	8-Cl	H	399	76	423
IIIl	7-Cl	H	214	16	252

a) Based on the 10-aryl-5-deazaflavins.
b) 90°, 5 hr. Determined as the 2,4-dinitrophenylhydrazone.
c) 90°, 10 hr. Determined as the 2,4-dinitrophenylhydrazone.

Experimental[9]

6-Anilino-3-methyluracil (Ia),[10] 6-(*p*-anisidino)-3-methyluracil (Ic),[11] 6-(*p*-chloroanilino)-3-methyluracil (Ie)[12] and 3-methyl-6-(3,4-xylidino)uracil (If)[11] were prepared according to the known procedures. Similarly, 3-methyl-6-(*p*-toluidino)uracil (Ib) and 6-(*p*-fluorophenyl)-3-methyluracil (Id) were obtained by the condensation of 6-chloro-3-methyluracil[13] with *p*-toluidine and *p*-fluoroaniline. Compound Ib gave mp 325° (89% from ethanol). *Anal.* Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.09; H, 5.57; N, 17.93. Compound Id gave mp 350° (86% from ethanol). *Anal.* Calcd for $C_{11}H_{10}FN_3O_2$: C, 56.17; H, 4.29; N, 17.87. Found: C, 55.90; H, 4.31; N, 17.59.

Aryl-bis(6-anilino-3-methyluracil-5-yl)methanes (IIa—m). General Procedure——A mixture of a 6-anilino-3-methyluracil (I) (0.005 mol) and an aromatic aldehyde (0.005 mol) in acetic acid (50 ml) was refluxed for 30 min. The reaction mixture was evaporated down *in vacuo* and the residue was recrystallized from acetic acid to give colorless needles (II) (see Table I).

10-Aryl-3-methylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones. (10-Aryl-3-methyl-5-deazaflavins) (IIIa—l). General Procedure——A mixture of compound II (0.003 mol), diethyl azodicarbozylate (0.009 mol) and sulfolane (0.5 g) was heated at 180—185° (oil bath) for 1 hr under stirring. After cooling, the reaction mixture was diluted with ethanol and allowed to stand at room temperature overnight to precipitate yellow crystals. Recrystallization from ethanol gave the corresponding 10-aryl-5-deazaflavin (III) as yellow needles (Table II).

9) All melting points are uncorrected. NMR spectra were determined with a JEOL-PMX 60 spectrometer (with tetramethylsilane as an internal standard). The identity of compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IR-A1 spectrometer.
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5-Aryl-3-methyl-5-deazaalloxazines (IVa—c). General Procedure——Compound II (0.003 mol) was heated in sulfolane (10 ml) at 220—230° for 3 hr. After cooling, the reaction mixture was diluted with water, and crystals separated. Recrystallization from ethanol gave colorless needles (IV) (Table III).

Determination of the Oxidation Rates of Alcohols by 10-Aryl-5-deazaflavins (III)——The rates of alcohol oxidation by a series of 10-aryl-5-deazaflavins (III), giving the corresponding carbonyl compounds and 1,5-dihydro-5-deazaflavins, have been studied in both 0.5 N NaOH in 50 v/v% ethanol–water and 50 v/v% isopropanol–water at 60° under aerobic conditions and at a concentration of 1.6×10^{-4} mol/l of 5-deazaflavins. These reactions were performed under pseudo first-order conditions (excess substrate) and the progress of the reaction was followed spectrophotometrically in terms of the decrease in absorbance at 400 nm. The pseudo first-order rates (k') were calculated using Eq. 1:

$$\log(A_t - A_\infty) = -k't + \log(A_0 - A_\infty) \quad (1)$$

where A_0, A_t and A_∞ are the absorbances at time 0, t and ∞ respectively.

Oxidation of Benzyl Alcohol and Cyclohexanol by 10-Aryl-5-deazaflavins——A mixture of a 10-aryl-5-deazaflavin (0.001 mol) and potassium carbonate (0.002 mol) in benzyl alcohol or cyclohexanol (3 ml) was stirred at 90° in the dark or in the light under aerobic conditions. The reaction mixture was diluted with ether (10 ml), and the separated 5-deazaflavin (III) was recovered by filtration. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid to separate benzaldehyde or cyclohexanone 2,4-dinitrophenylhydrazone.

Oxidation of Benzylamine by 10-Aryl-5-deazaflavins——A mixture of a 10-aryl-5-deazaflavin (0.002 mol), benzylamine (5 g, 0.047 mol) and water (5 ml) was heated at 100° for 10 hr under stirring. After diluting the reaction mixture with ether (10 ml), the separated 5-deazaflavin (III) was recovered by filtration. The filtrate was treated as described above to give the benzaldehyde 2,4-dinitrophenylhydrazone.

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