A Novel Synthesis of Pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-Deazaflavins) and Analogues by the Oxidative Cyclization of 5,5′-Arylmethylenebis-(6-alkylamino-3-methyluracils)

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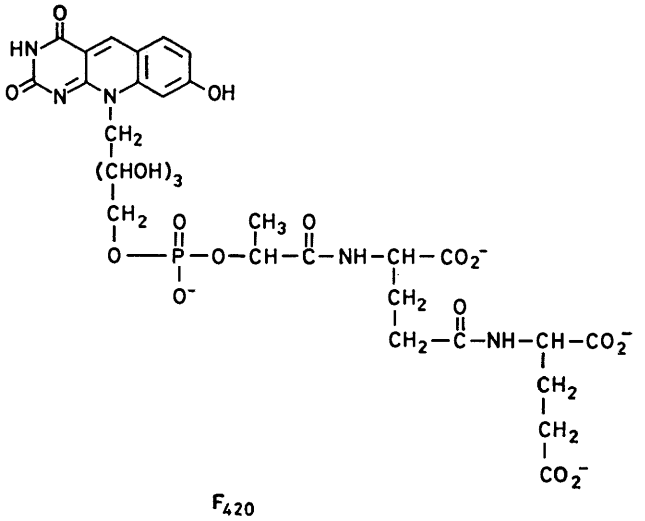
The oxidative coupling of 5,5′-arylmethylenebis-(6-alkylamino-3-methyluracils), prepared by the condensation of 6-alkylamino-3-methyluracils and arenecarbaldehydes, with diethyl azodiformate afforded the corresponding pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-deazaflavins). This synthetic method was successfully applied to the preparation of 5-deazaflavin-type compounds such as a benzologue, a thiophen analogue, or a nitrogen analogue of 5-deazaflavin. The 8-chloro-5-deazaflavin was converted into the corresponding 8-amino-derivatives by treatment with amines.

PYRIMIDO[4,5-*b*]QUINOLINE-2(3*H*),4(10*H*)-DIONES (5-deazaflavins), where N-5 of the flavin is replaced by CH, have aroused further great interest, because of the recent discovery that F_{420}, which possesses a 5-deazaflavin moiety, is the coenzyme of methane-producing bacteria.[1]



SCHEME

5-Deazaflavins have previously been synthesized by the condensation of anthranilaldehydes with barbituric acid,[2] the cyclization of 6-(*N*-alkylanilino(uracils with one-carbon reagents including the Vilsmeier reagent,[3] and by the condensation of 6-chloro-5-formylpyrimidines with *N*-alkylanilines.[3] We now report a novel and general synthesis of 5-deazaflavins which consists of the oxidative coupling of 5,5′-arylmethylenebis-(6-alkylamino-3-methyluracils) with diethyl azodiformate (DAD).[4]

The starting materials, 5,5′-arylmethylenebis-(6-alkylamino-3-methyluracils) (IIa—m) † were synthesized by heating 6-alkylamino-3-methyluracils (Ia—d) with the appropriate arenecarbaldehydes in refluxing acetic acid (Table 1).[5,‡] The structures of compounds (II) were established based on the satisfactory analytical and spectral data. They revealed a characteristic signal for the methane proton substituted by an aryl group and two 6-alkylamino-3-methyluracil moieties at δ 9.8—9.9.

Fusion of compound (IIa) with excess of DAD (5 equiv.) at 160 °C caused the oxidative cyclization to give rise to 3,10-dimethylpyrimido[4,5-*b*]quinoline-2(3*H*),4-(10*H*)-dione (3,10-dimethyl-5-deazaflavin) (IIIa). The reaction is equally applicable to compounds (IIb—m) to afford the corresponding 5-deazaflavins (IIIb—m) (Table 2).

The above synthetic method was successfully applied to the preparation of the 5-deazaflavin-type compounds such as a benzologue, a thiophen analogue, or a nitrogen analogue. Thus, the condensation of (Ia) with 2-naphthaldehyde, thiophen-2-carbaldehyde, and pyridine-3-carbaldehyde gave the corresponding substituted 5,5′-methylenebis-(6-methylamino-3-methyluracil)s (IIn—p)

TABLE 1

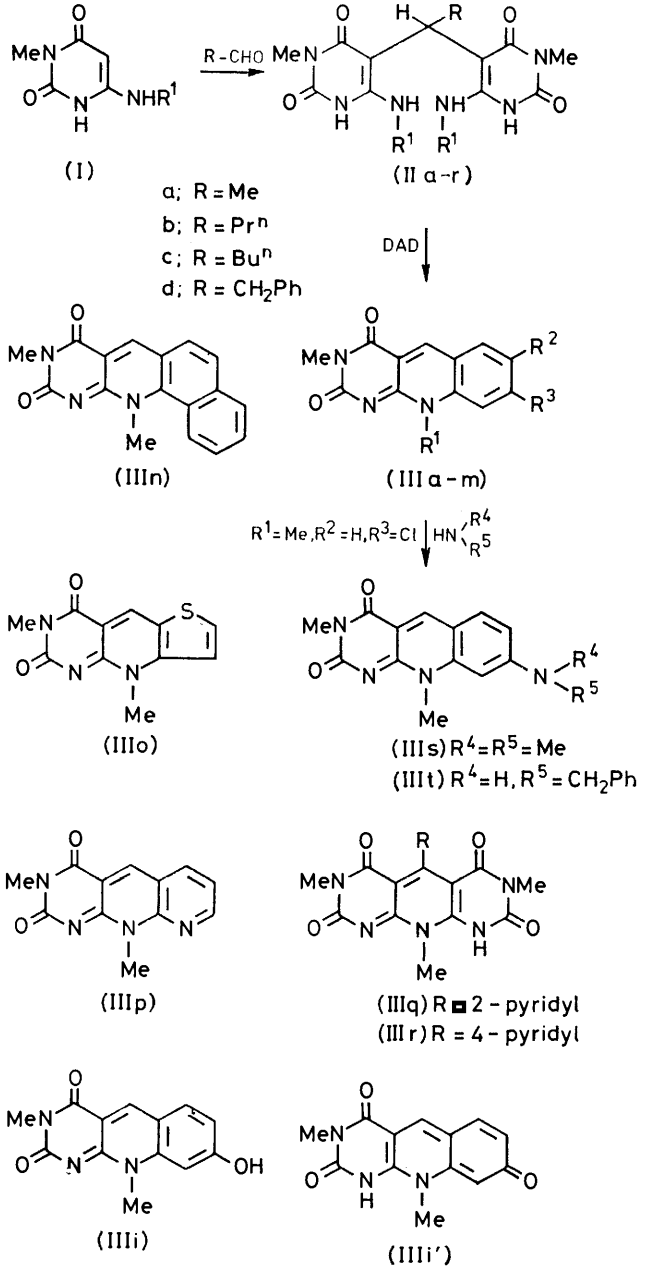
Formation of the substituted 5,5′-methylenebis-(6-alkylamino-3-methyluracils) (II) by the reaction of 6-alkylaminouracils (I) with aromatic aldehydes

Compound	R^1	R	M.p. (°C)	Recrystallisation solvent	Yield (%)
(IIa)	Me	Ph	294	AcOH	80
(IIb)	Me	3-Cl-C_6H_4	278	AcOH	75
(IIc)	Me	4-Cl-C_6H_4	289	AcOH	90
(IId)	Me	3,4-$Cl_2C_6H_3$	295	AcOH	82
(IIe)	Me	4-CN-C_6H_4	311	AcOH	82
(IIf)	Me	3-Me-C_6H_4	282	AcOH	75
(IIg)	Me	4-Me-C_6H_4	290	AcOH	74
(IIh)	Me	4-MeO-C_6H_4	273	AcOH	72
(IIi)	Me	4-OH-C_6H_4	280	AcOH	89
(IIj)	Me	3,4-$CH_2O_2C_6H_3$	278	AcOH	88
(IIk)	Pr^n	Ph	266	EtOH	89
(IIl)	Bu^n	Ph	230	EtOH	83
(IIm)	CH_2Ph	Ph	235	AcOH	85
(IIn)	Me	2-Naphthyl	285	AcOH	83
(IIo)	Me	2-Thienyl	255	AcOH	74
(IIp)	Me	3-Pyridyl	234	EtOH	78
(IIq)	Me	2-Pyridyl	239	EtOH	75
(IIr)	Me	4-Pyridyl	263	EtOH	76

† In the earlier communication,[4] these compounds were reported as 6-alkylamino-5-benzylidene-3-methyluracils, which structures have proved to be wrong.

‡ Tables of analytical data for compounds (II) and (III) are available as Supplementary Publication No. SUP 22691 (6 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

respectively (Table 1). These compounds were likewise treated with an excess of DAD to give rise to the 5-deazaflavin-type compounds, 3,12-dimethylpyrimido-[4,5-*b*]benzo[*h*]quinoline-2(3*H*),4(12*H*)-dione (IIIn), 3,9-dimethylthieno[3,2-*f*]pyrido[2,3-*d*]pyrimidine-2-(3*H*),4(9*H*)-dione (IIIo), and 3,10-dimethylpyrimido-[4,5-*b*]-1,8-naphthyridine-2(3*H*),4(10*H*)-dione (IIIp).



As an exception, the oxidative cyclization of 5,5′-(2-pyridyl)- (IIq) and 5,5′-(4-pyridyl)-methylenebis-(6-methylamino-3-methyluracil) (IIr), prepared from (Ia) and pyridine-2- and -4-carbaldehydes, with DAD failed to give the desired 5-deazaflavin-type compounds, and self-condensation occurred to afford 5-(2-pyridyl)- (IIIq) and 5-(4-pyridyl)-3,7,10-trimethylpyrido[2,3-*d*:6,5-*d*′]-dipyrimidine-2(1*H*),4(3*H*),6(7*H*),8(9*H*)-tetraone (IIIr) respectively.

Next, 8-chloro-3,10-dimethylpyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-dione (IIIc) was treated with dimethylamine and benzylamine in hexamethylphosphoramide

TABLE 2

Oxidative cyclization of substituted 5,5′-methylenebis-(6-alkylamino-3-methyluracils) (II) to the corresponding 5-deazaflavins (III) with diethyl azodiformate (DAD)

Compound	R^1	R^2	R^3	M.p. (°C)	Recryst-allisation solvent	Yield (%)
(IIIa) [3]	Me	H	H	327	EtOH	49
(IIIb)	Me	Cl	H	>360	AcOH	50
(IIIc)	Me	H	Cl	328	DMF	63
(IIId)	Me	Cl	Cl	>360	DMF	53
(IIIe)	Me	H	CN	>360	AcOH	68
(IIIf)	Me	Me	H	330	EtOH	45
(IIIg)	Me	H	Me	309	AcOH	55
(IIIh)	Me	H	OMe	345	EtOH	55
(IIIi)	Me	H	OH	>360	AcOH	58
(IIIj)	Me	—O—CH$_2$—O—		>360	EtOH	52
(IIIk)	Pr^n	H	H	267	EtOH	75
(IIIl) [3]	Bu^n	H	H	245	EtOH	70
(IIIm) [3]	CH$_2$Ph	H	H	287	EtOH	80

(HMPA) to give the corresponding 8-dimethylamino- (IIIs) and 8-benzylamino-5-deazaflavin (IIIt).

The chemical shifts of the C-5 protons of the 5-deazaflavins varied according to the nature of the 8-substituents as shown in Table 3. On the other hand, the substituent of the 7-position seems have no significant influence upon the chemical shifts of the C-5 protons [compare (IIIb) with (IIIf)]. The similarity

TABLE 3

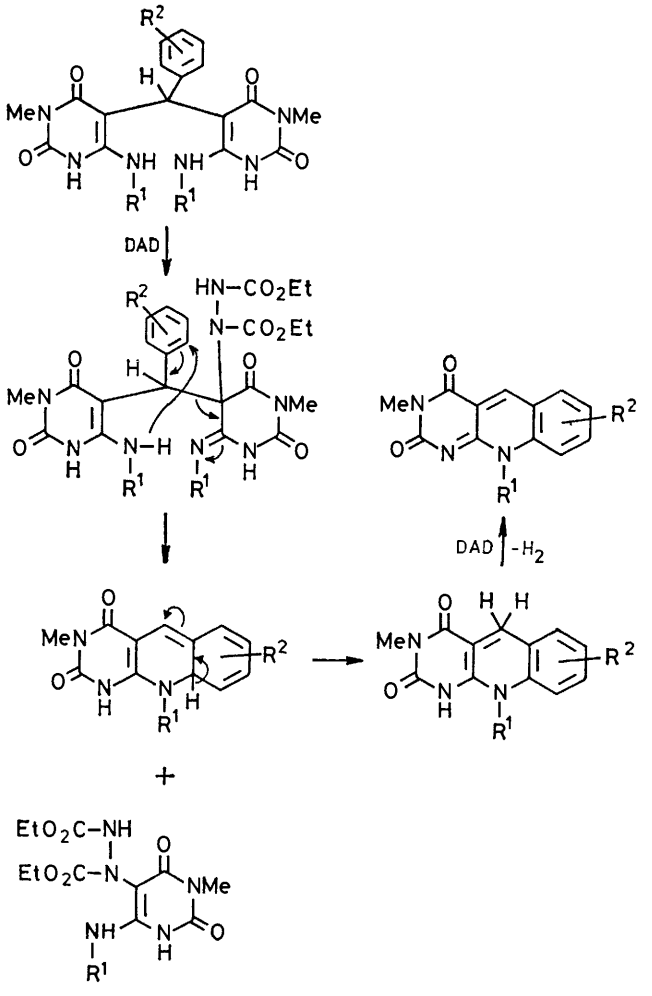
Chemical shifts of C-5 protons of the 5-deazaflavins and analogues

Compound	Substituents		δ (CF_3CO_2H)
(IIIa)	H	10-Me	9.75
(IIIb)	7-Cl	10-Me	9.72
(IIIc)	8-Cl	10-Me	9.77
(IIId)	7,8-Cl$_2$	10-Me	9.71
(IIIe)	8-CN	10-Me	9.84
(IIIf)	7-Me	10-Me	9.72
(IIIg)	8-Me	10-Me	9.68
(IIIh)	8-OMe	10-Me	9.55
(IIIi)	8-OH	10-Me	9.56
(IIIj)	7,8-CH$_2$O$_2$	10-Me	9.48
(IIIk)	H	10-Pr^n	9.67
(IIIl)	H	10-Bu^n	9.70
(IIIm)	H	10-CH$_2$Ph	9.90
(IIIs)	8-NMe$_2$	10-Me	9.09
(IIIt)	8-NHCH$_2$Ph	10-Me	9.11
(IIIn)			9.73
(IIIo)			9.71
(IIIp)			9.82

between (IIIh and i) in both n.m.r. and u.v. spectra showed that the structure of (IIIi) is the 8-hydroxy-5-deazaflavin form rather than the paraquinonoid form (IIIi′) [6] [(IIIh), $\lambda_{max.}$ (EtOH) 402 (log ε 4.29), 254 (4.49), and 233 nm (4.56), $\lambda_{max.}$ (0.1N-HCl in 50% EtOH) 377 (log ε 4.39), 254 (4.52), and 233 nm (4.63); (IIIi), $\lambda_{max.}$ (EtOH) 407 (log ε 4.06), 251 (4.27), and 235 nm (4.18), λ_{max} (0.1N-HCl in 50% EtOH) 381 (log ε 4.11), 254

(4.21), and 233 nm (4.33)]. It is noteworthy that the signal for the N-12 methyl protons (δ 4.93) of (IIIn) underwent a paramagnetic shift due to anisotropy of the ring current or a steric compression effect by the naphthalene moiety.*

This novel synthesis of 5-deazaflavins can be rationalized in terms of the initial addition of DAD to compounds (II). Subsequent cyclization with concomitant elimination of the 6-amino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyluracil provides the 1,5-dihydro-5-deazaflavins. The latter could readily be dehydrogenated by excess of DAD to give the final 5-deazaflavins. In fact, the treatment of 1,5-dihydro-5-deazaflavins



prepared alternatively [7] with DAD gave immediately the corresponding 5-deazaflavins in quantitative yield at room temperature. The 6-amino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyluracils eliminated are thermally decomposed to unidentified compounds.

Attempts to cyclize compounds (II) to afford 5-deazaflavins with other oxidizing agents such as *N*-bromosuccinimide, thionyl chloride, bromine, or lead tetra-acetate were all unsuccessful.

* N.m.r. data for compounds (III) are available as Supplementary Publication No. SUP 22691.

EXPERIMENTAL

M.p.s were obtained with a Yanagimoto micro-apparatus. N.m.r. spectra were determined with JEOL PMX-60 spectrometer (tetramethylsilane as internal standard), and u.v. spectra were obtained with a JASCO Uvidec-1 spectrometer (1-cm quartz cells). The identity of the compounds was confirmed by comparison of i.r. spectra determined in Nujol with a JASCO IR-1A spectrometer.

6-Methylamino- (Ia),[8] 6-n-propylamino- (Ib),[9] 6-n-butylamino- (Ic),[9] and 6-benzylamino-3-methyluracil (Id) [8] were prepared according to known procedures.

Substituted 5,5'-Methylenebis-(6-alkylamino-3-methyluracils) (IIa—r). *General Procedure.*—A mixture of a 6-alkylamino-3-methyluracil (I) (0.01 mol) and an aromatic aldehyde (0.01 mol) in acetic acid (30 ml) was refluxed for 1 h. The mixture was evaporated *in vacuo* and the residue was recrystallized to give crystals (Table 1).

10-Alkyl-3-methylpyrimido[4,5-b]quinoline-2(3H),4(10H)-diones (10-Alkyl-3-methyl-5-deazaflavins) (IIIa—m). *General Procedure.*—Compounds (IIa—m) (0.001 mol) were mixed with diethyl azodiformate (DAD) (0.87 g, 0.005 mol) and the mixtures were heated at 160 °C for 30 min with stirring. After cooling, the mixtures were diluted with ethanol and allowed to stand at room temperature overnight to precipitate yellow crystals. Recrystallization from an appropriate solvent gave the corresponding 5-deazaflavins as a yellow microcrystalline powder (Table 2).

The reaction of other substituted 5,5'-methylenebis-(6-methylamino-3-methyluracils) (IIn—p) (0.001 mol) with DAD (0.87 g, 0.005 mol) under the same conditions as above similarly yielded the 5-deazaflavin-type compounds, *3,12-dimethylpyrimido[4,5-b]benzo[h]quinoline-2(3H),4(12H)-dione* (IIIn), m.p. 301 °C (EtOH) (65%), *3,9-dimethylthieno-[3,2-f]pyrido[2,3-d]pyrimidine-2(3H),4(9H)-dione* (IIIo), m.p. >360 °C (AcOH) (55%), and *3,10-dimethylpyrimido-[4,5-b]-1,8-naphthyridine-2(3H),4(10H)-dione* (IIIp), m.p. >360 °C (AcOH) (61%).

5-(2-Pyridyl)-3,7,10-trimethylpyrido[2,3-d:6,5-d']dipyrimidine-2(1H),4(3H),6(7H),8(10H)-tetraone (IIIq).—A mixture of compound (IIa) (0.37 g, 0.001 mol) and DAD (0.87 g, 0.05 mol) was heated at 180 °C for 1 h. After cooling the mixture was diluted with ethanol to precipitate the crystals, which were filtered off and washed with ethanol. Recrystallization form acetic acid gave yellow *crystals* (0.21 g, 58%), m.p. >360 °C, M^+ 366 (δ (CF_3CO_2H), 3.40 (6 H, s, 3- and 7-Me), 4.42 (3 H, s, 10-Me), and 7.80—9.07 (4 H, aromatic H of 2-pyridyl) (Found: C, 55.6; H, 3.8; N, 22.7. $C_{17}H_{14}N_6O_4$ requires C, 55.75; H, 3.85; N, 22.95%).

5-(4-Pyridyl)-3,7,10-trimethylpyrido[2,3-d:6,5-d']dipyrimidine-2(1H),4(3H),6(7H),8(10H)-tetraone (IIIr).—A mixture of (IIr) (0.37 g, 0.001 mol) and DAD (0.87 g, 0.005 mol) was treated as described above to give yellow *crystals* (0.19 g, 52%), m.p. >360 °C, M^+ 366 (Found: C, 55.85; H, 3.9; N, 22.75. $C_{17}H_{14}N_6O_4$ requires C, 55.75; H, 3.85; N, 22.95%).

3,10-Dimethyl-8-dimethylaminopyrimido[4,5-b]quinoline-2(3H),4(10H)-dione (IIIs).—A mixture of compound (IIIc) (0.5 g, 0.001 8 mol) and 40% aqueous dimethylamine (0.61 ml, 0.005 4 mol) in HMPA (3 ml) was heated at 100 °C for 1 h and the mixture was allowed to stand overnight at room temperature to cause the separation of yellow *crystals*. Recrystallization from acetic acid gave yellow needles (0.48 g, 94%), m.p. >360 °C, M^+ 284 (Found: C, 63.25; H, 5.5; N, 19.5. $C_{15}H_{16}N_4O_2$ requires C, 63.35; H, 5.65; N, 19.7%).

8-*Benzylamino*-3,10-*dimethylpyrimido*[4,5-b]*quinoline*-2(3H),4(10H)-*dione* (IIIt).— A mixture of (IIIc) (0.5 g, 0.001 8 mol) and benzylamine (0.58 g, 0.005 4 mol) in HMPA (3 ml) was heated at 120 °C for 1 h and the mixture was set aside overnight at room temperature. The crystals thus separated were filtered off and recrystallized from acetic acid to give the yellow *needles* (0.58 g, 93%), m.p. 311 °C, M^+ 346 (Found: C, 69.5; H, 5.2; N, 16.05. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.25; N, 16.2%).

Oxidation of 3,10-*Dimethyl*-1,5-*dihydro*-5-*deazaflavin with DAD*.—A mixture of 3,10-dimethyl-1,5-dihydro-5-deazaflavin [7] (0.24 g, 0.001 mol) and DAD (0.52 g, 0.003 mol) was stirred for 5 min at room temperature. The mixture changed from pale to dark yellow. The crystals were collected by filtration, washed with ethanol, and recrystallized from acetic acid to give the 5-deazaflavin (IIIa) in quantitative yield.

Other 1,5-dihydro-5-deazaflavins can likewise be oxidized by DAD to the corresponding 5-deazaflavins.

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