# Syntheses of 5-Deazaflavines

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Treatment of 6-(*N*-alkylanilino)uracils with Vilsmeier-type reagents (dimethylformamide–phosphoryl chloride or dimethylformamide–ethyl chloroformate) gave 5-deazaflavines {10-alkylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones}; this cyclization was also achieved with triethyl orthoformate. Treatment of 3-methylbarbituric and barbituric acids with dimethylformamide–phosphoryl chloride gave 6-chloro-5-formyl-3-methyluracil and 2,4,6-trichloro-5-formylpyrimidine, respectively. Reactions of these 6-chloro-5-formylpyrimidines with *N*-substituted anilines gave directly the corresponding 5-deazaflavines.

THE 5-deazaflavine {pyrimido[4,5-*b*]quinoline-2,4-(3*H*,10*H*)-dione} ring system, wherein N-5 of the flavine (isoalloxazine) is replaced by CH, has become of considerable interest because of the discovery that its oxidation–reduction properties are similar to those of flavine.[1-5] The 5-deazaflavines have previously been synthesized by condensation of substituted anthranilaldehydes with barbituric acid,[6] and the synthesis of the closely related 2,3-dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-*b*]quinolin-4(10*H*)-one has been reported.[7] However, treatment of this compound with nitrous acid

TABLE 1

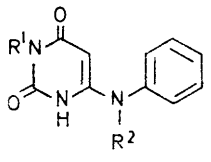
5-Deazaflavines

| Compd. | Recryst. solvent | M.p. (°C) | Yield (%) | Synthetic method [a] | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (IIa) | EtOH | 327 | 96 | A | 64.6 | 4.65 | 17.35 | $C_{13}H_{11}N_3O_2$ | 64.7 | 4.6 | 17.4 |
| | | | 95 | B | | | | | | | |
| | | | 75 | C | | | | | | | |
| | | | 68 | D | | | | | | | |
| (IIb) | EtOH | 283 | 88 | A | 65.9 | 5.2 | 16.25 | $C_{14}H_{13}N_3O_2$ | 65.85 | 5.15 | 16.45 |
| | | | 90 | B | | | | | | | |
| | | | 82 | C | | | | | | | |
| | | | 63 | D | | | | | | | |
| (IIc) | EtOH | 267 | 86 | A | 66.9 | 5.65 | 15.8 | $C_{15}H_{15}N_3O_2$ | 66.9 | 5.6 | 15.6 |
| | | | 64 | D | | | | | | | |
| (IId) | EtOH | 245 | 89 | A | 67.85 | 6.25 | 14.9 | $C_{16}H_{17}N_3O_2$ | 67.8 | 6.05 | 14.85 |
| | | | 96 | B | | | | | | | |
| | | | 85 | C | | | | | | | |
| | | | 53 | D | | | | | | | |
| (IIe) | AcOH | 359 | 95 | A | 63.3 | 3.85 | 18.35 | $C_{12}H_9N_3O_2$ | 63.45 | 4.0 | 18.5 |
| | | | 57 | D | | | | | | | |
| (IIf) | AcOH | 353 | 87 | A | 64.95 | 4.45 | 17.65 | $C_{13}H_{11}N_3O_2$ | 64.7 | 4.6 | 17.4 |
| | | | 92 | B | | | | | | | |
| | | | 63 | D | | | | | | | |
| (IIg) | AcOH | 318 | 90 | A | 65.75 | 5.2 | 16.3 | $C_{14}H_{13}N_3O_2$ | 65.85 | 5.15 | 16.45 |
| | | | 60 | D | | | | | | | |
| (IIh) | EtOH–AcOH | 302 | 92 | A | 66.75 | 5.65 | 15.35 | $C_{15}H_{15}N_3O_2$ | 66.9 | 5.6 | 15.6 |
| | | | 90 | B | | | | | | | |
| | | | 57 | D | | | | | | | |
| (IIi) | EtOH | 320 | 58 | D | 66.75 | 5.5 | 15.6 | $C_{15}H_{15}N_3O_2$ | 66.9 | 5.6 | 15.6 |
| (IIj) | AcOH | >360 | 52 | D | 65.8 | 5.15 | 16.55 | $C_{14}H_{13}N_3O_2$ | 65.85 | 5.15 | 6.45 |
| (IIk) | AcOH | >360 | 80 | A | 65.8 | 5.2 | 16.6 | $C_{14}H_{13}N_3O_2$ | 65.85 | 5.15 | 16.45 |
| (IIl) | AcOH–$H_2O$ | 284 | 43 | D | 58.55 | 5.75 | 10.6 | $C_{19}H_{23}N_3O_6$ | 58.6 | 5.95 | 10.8 |
| (IIm) | $H_2O$ | 291 | 57 | C | 57.45 | 5.65 | 11.15 | $C_{18}H_{21}N_3O_6$ | 57.6 | 5.65 | 11.2 |
| | | | 37 | D | | | | | | | |

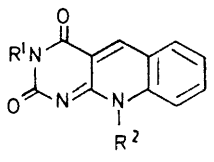
[a] A, cyclization with dimethylformamide–phosphoryl chloride; B, cyclization with dimethylformamide–ethyl chloroformate; C, cyclization with triethyl orthoformate; D, condensation of a 6-chloro-5-formylpyrimidine with an *N*-substituted aniline.

[1] D. E. Edmondson, B. Barman, and G. Tollin, *Biochemistry*, 1972, **11**, 1133.
[2] M. Brüstlein and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 6548.
[3] S. Shinkai and T. C. Bruice, *J. Amer. Chem. Soc.*, 1973, **95**, 7526.
[4] S. Shinkai, T. Kunitake, and T. C. Bruice, *J. Amer. Chem. Soc.*, 1974, **96**, 7140.
[5] M. S. Jorns and L. B. Hersh, *J. Amer. Chem. Soc.*, 1974, **96**, 4012.
[6] D. E. O'Brien, L. T. Weinstock, and C. C. Cheng, *J. Heterocyclic Chem.*, 1970, **7**, 99.
[7] E. J. Reist, H. P. Hanlow, I. G. Junga, R. M. Silverstein, and B. R. Baker, *J. Org. Chem.*, 1960, **25**, 1368.

failed to yield the corresponding 5-deazaflavine.[7] We now describe two new synthetic approaches to 5-deazaflavines, which are notable for their simplicity.[8]

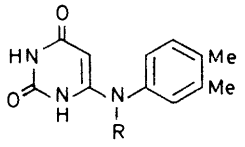


(I)

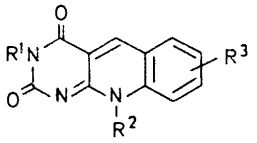


(II)

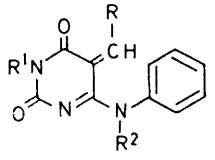
a; $R^1$ = Me, $R^2$ = Me
b; $R^1$ = Me, $R^2$ = Et
c; $R^1$ = Me, $R^2$ = $Pr^n$
d; $R^1$ = Me, $R^2$ = $Bu^n$
e; $R^1$ = H, $R^2$ = Me
f; $R^1$ = H, $R^2$ = Et
g; $R^1$ = H, $R^2$ = $Pr^n$
h; $R^1$ = H, $R^2$ = $Bu^n$



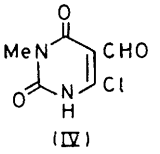
(Ik) R = Me
(Im) R = $CH_2 \cdot [CHOH]_3 \cdot CH_2OH$



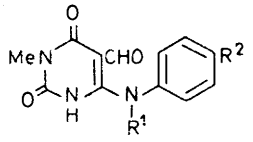
(IIi) $R^1$ = Me, $R^2$ = Et, $R^3$ = 7-Me
(IIj) $R^1$ = H, $R^2$ = Et, $R^3$ = 7-Me
(IIk) $R^1$ = H, $R^2$ = Me, $R^3$ = 7,8-$Me_2$
(IIl) $R^1$ = Me, $R^2$ = $CH_2 \cdot [CHOH]_3 \cdot CH_2OH$, $R^3$ = 7,8-$Me_2$
(IIm) $R^1$ = H, $R^2$ = $CH_2 \cdot [CHOH]_3 \cdot CH_2OH$, $R^3$ = 7,8-$Me_2$



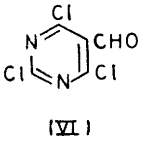
(III) R = $NMe_2$ or OEt



(IV)



(V) a; $R^1$ = Me, $R^2$ = H
b; $R^1$ = Et, $R^2$ = H
c; $R^1$ = $Pr^n$, $R^2$ = H
d; $R^1$ = $Bu^n$, $R^2$ = H
i; $R^1$ = Et, $R^2$ = Me



(VI)

*Cyclization of* 6-(N-*Alkylanilino*)*uracils with One-carbon Reagents.*—Treatment of 3-methyl-6-(*N*-methylanilino)uracil (Ia) [9] with dimethylformamide–phosphoryl chloride at 90 °C for 2 h gave 3,10-dimethylpyrimido-[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (IIa) in good yield. Similar treatment of the 6-(*N*-alkylanilino)uracils (Ib—h and k) also gave the corresponding 5-deazaflavines (II) (Table 1). This cyclization was also achieved by refluxing in dimethylformamide–ethyl chloroformate for 5 h, in almost the same yields (Table 1). This is an application of a known variation of the Vilsmeier reaction.[10]

Ethyl orthoformate was also effective for the cyclization of the uracil derivatives (I). For example, refluxing compound (Ia) with triethyl orthoformate in dimethylformamide for 1 h gave the 5-deazaflavine (IIa) (Table 1). However refluxing compound (Ia) in triethyl orthoformate alone, for a longer time, did not give the deazaflavine (IIa); starting material was recovered. This method was successfully applied to the cyclization of 6-(*N*-D-ribityl-3,4-dimethylanilino)uracil (Im) [9] to yield 5-deazariboflavine (IIm).[6] The Vilsmeier-type reagents were not suitable for the synthesis of this compound (IIm); they gave rise to dehydration in the D-ribityl group.

All these reactions presumably involve 5-methylene-substituted intermediates (III), which cyclize with elimination of dimethylamine or ethanol.

*Condensation of* 6-*Chloro*-5-*formylpyrimidines with* N-*Substituted Anilines.*—The Vilsmeier reagent (dimethylformamide–phosphoryl chloride) is known to react with cyclohexanone to give 1-chloro-2-formylcyclohexene.[11] This type of formylation–chlorination was carried out on 1,3-dimethylbarbituric acid to yield 6-chloro-5-formyl-1,3-dimethyluracil.[12] We have applied this reaction to 3-methylbarbituric acid to afford 6-chloro-5-formyl-3-methyluracil (IV).

Stirring compound (IV) in an excess of *N*-methylaniline with warming, followed by dilution with ether, caused separation of the deazaflavine (IIa). Similarly, treatment of (IV) with other *N*-alkylanilines in excess under the same conditions gave the corresponding 5-deazaflavines (IIb—d and i) (Table 1). When the reaction was carried out in ether at room temperature, 6-(*N*-alkylanilino)-5-formyl-3-methyluracils (Va—d and i) were obtained (Table 3). Simply warming these products (V) in a small amount of concentrated sulphuric acid gave the deazaflavines (II).

Treatment of barbituric acid with dimethylformamide–phosphoryl chloride under reflux for 8 h gave 2,4,6-trichloro-5-formylpyrimidine (VI), identical from its i.r., mass, and n.m.r. spectra ($\nu_{CO}$ 1708 $cm^{-1}$; $M + 2$, $M + 4$, and $M + 6$ peaks in the mass spectrum; CHO n.m.r. signal but none for H-5). Compound (VI) was likewise treated with *N*-alkylanilines with warming to give directly the respective 5-deazaflavines (IIe—h and

[8] Preliminary report, F. Yoneda and Y. Sakuma, *J.C.S. Chem. Comm.*, 1976, 203.
[9] F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *J. Amer. Chem. Soc.*, 1976, **98**, 830.
[10] K. Ikawa, F. Takami, Y. Fukui, and K. Tokuyama, *Tetrahedron Letters*, 1969, 3279.
[11] L. A. Paquette, B. A. Johnson, and F. M. Hinga, *Org. Synth.*, 1966, **46**, 18.
[12] S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, *Yakugaku Zasshi*, 1971, **91**, 1372.

j) (Table 1), with concomitant hydrolysis of the 2- and 4-chloro-substituents of the pyrimidine.

Stirring compounds (IV) and (VI) with a slight excess of *N*-D-ribityl-3,4-xylidine in dimethylformamide at room temperature, followed by dilution with ether, caused separation of 3-methyl-5-deazariboflavine (III) and 5-deazariboflavine (IIm), respectively.

The 5-deazaflavines obtained were identified by elemental analyses and molecular weight determination (mass spectrometry). M.p.s and u.v. spectra of compounds (IIe and m) agreed with those of authentic samples.[6] The assigned structures were confirmed by n.m.r. spectra [available as Supplementary Publication No. SUP 21800 (3 pp.) *]. All showed a characteristic low-field H-5 singlet (δ 9.46—9.75), implying that the 5-position is the most electron-deficient and very reactive to nucleophiles; this will be discussed in a later paper. The light absorption spectra (Table 2) show one band in the 400 nm region, another in the 320 nm region, and two in the u.v. region (in ethanolic solution). On protonation the *ca.* 400 nm maxima are shifted to shorter wavelength, and the *ca.* 320 nm bands to longer wavelength; these shifts are similar to the behaviour of flavines.[13]

TABLE 2

U.v.–visible maxima of 5-deazaflavines

| Compd. | $\lambda_{max.}$(EtOH)/nm (log ε) | $\lambda_{max.}$(5N-HCl in 50% EtOH)/nm (log ε) |
|---|---|---|
| (IIa) | 398 (4.08), 319.4 (4.00), 262.6 (4.66), 219.8 (4.53) | 333.2 (4.21), 256 (4.54), 215.6 (4.41) |
| (IIb) | 398 (4.02), 320.2 (3.93), 263 (4.62), 221 (4.49) | 333.2 (4.16), 256 (4.49), 216 (4.35) |
| (IIc) | 398.5 (4.11), 320 (4.03), 263.3 (4.71), 220.8 (4.57) | 333.2 (4.26), 256.5 (4.58), 215.6 (4.45) |
| (IId) | 398.6 (3.97), 320.2 (3.89), 263.3 (4.56), 220.4 (4.42) | 333.4 (4.11), 256.2 (4.43), 215.8 (4.28) |
| (IIe) | 397.5 (3.96), 318 (3.83), 262 (4.44), 219.5 (4.29) | 333.5 (4.08), 257 (4.40), 215 (4.29) |
| (IIf) | 396.4 (4.03), 319.4 (3.89), 262 (4.51), 220.8 (4.50) | 334 (4.21), 257.2 (4.53), 215.8 (4.42) |
| (IIg) | 397.2 (4.15), 320 (4.02), 262.2 (4.63), 221.2 (4.61) | 333.8 (4.30), 257.6 (4.62), 215.8 (4.50) |
| (IIh) | 397.5 (4.05), 320 (3.92), 262.5 (4.52), 221 (4.49) | 334.2 (4.22), 257.2 (4.50), 216 (4.39) |
| (IIi) | 405 (4.06), 324.2 (4.01), 264.2 (4.69), 223.8 (4.53) | 333.6 (4.23), 259 (4.60), 220.2 (4.39) |
| (IIj) | 403.5 (3.89), 323.2 (3.87), 261.2 (4.44), 223.8 (4.43) | 333.8 (4.10), 261.5 (4.45), 218.4 (4.34) |
| (IIk) | 402.2 (3.69), 324 (3.95), 260.8 (4.25), 225.4 (4.32) | 347 (4.03), 261.8 (4.32), 220 (4.23) |
| (III) | 403.2 (4.00), 333 (3.98), 263.6 (4.49), 226.6 (4.44) | 354.8 (4.23), 261.8 (4.50), 224.8 (4.33) |
| (IIm) | 402 (4.07), 332.2 (4.02), 264.3 (4.45), 226.8 (4.52) | 355 (4.27), 263.2 (4.53), 224 (4.38) |

## EXPERIMENTAL

M.p.s were obtained with a Yanagimoto micro-apparatus. N.m.r. spectra were determined with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as internal standard), and u.v.–visible spectra with a JASCO UVIDEC-1 instrument (1 cm quartz cells). Identity of compounds was confirmed by comparison of i.r. spectra (Nujol mulls) with a JASCO IR-1A spectrophotometer.

*Cyclization of* 6-(N-*Alkylanilino*)*uracils.*—(a) *With dimethylformamide–phosphoryl chloride.* A mixture of a 6-(*N*-alkylanilino)uracil (0.005 mol) and phosphoryl chloride (7.7 g, 0.05 mol) in dimethylformamide (10 ml) was heated at 90 °C for 2 h. After cooling it was diluted with water and neutralized with sodium hydrogen carbonate. The yellow crystals which separated were filtered off, washed with water, dried, and recrystallized (see Table 1).

(b) *With dimethylformamide–ethyl chloroformate.* A mixture of the 6-(*N*-alkylanilino)uracil (0.005 mol) and ethyl chloroformate (5.4 g, 0.05 mol) in dimethylformamide (5 ml) was refluxed for 5 h. Concentration of the mixture to a small volume and dilution with water precipitated yellow crystals, which were filtered off, washed with water, dried, and recrystallized.

(c) *With triethyl orthoformate.* A solution of the 6-(*N*-alkylanilino)uracil (0.005 mol) in triethyl orthoformate (5 ml) and dimethylformamide (5 ml) was refluxed for 1 h. After cooling, the crystals which separated were filtered off, washed with ether, and dried. The filtrate was evaporated to dryness and the residue was treated with a small amount of ethanol to give more product. The combined crystals were recrystallized.

*6-Chloro-5-formyl-3-methyluracil* (IV).—3-Methylbarbituric acid (8.5 g, 0.06 mol) was added to phosphoryl chloride (50 ml) and dimethylformamide (10 ml), and the mixture was refluxed for 5 h. The solution was evaporated and the residue poured on ice. The crystals which separated were rapidly filtered off, washed with ice–water, and dried *in vacuo* ($P_2O_5$) to give 6-chloro-5-formyl-3-methyluracil (7.5 g, 66%), m.p. 188°, *m/e* 188 ($M^+$), δ ($CF_3$·$CO_2H$) 3.48 (3 H, s, NMe) and 9.89 (1 H, s, CHO). This compound was very unstable and was used without recrystallization.

*2,4,6-Trichloropyrimidine-5-carbaldehyde* (VI).—Barbituric acid (8.5 g, 0.06 mol) was added to phosphoryl chloride (40 ml) and dimethylformamide (5 ml). The mixture was gently refluxed for 8 h, then treated as described above to give yellow crystals of the aldehyde (VI) (7 g, 55%), m.p. 186°, *m/e* 210 ($M^+$), δ ($CF_3$·$CO_2H$) 10.47 (1 H, s, CHO). This compound was also extremely unstable and was used without purification.

*Condensation of* 6-*Chloro-5-formylpyrimidines with* N-*Substituted Anilines; General Procedure.*—A mixture of the 6-chloro-5-formylpyrimidine (IV) or (VI) (0.001 mol) and the *N*-alkylaniline (0.05 mol) was heated at 95 °C for 20 min with stirring. Ether (10 ml) was added and the mixture was stirred for 2 h. The crystals which separated were filtered off, washed with water and ether, dried, and recrystallized (see Table 1).

6-(N-*Alkylanilino*)-5-*formyl*-3-*methyluracils* (Va—d *and* i)*; General Procedure.*—To a suspension of the aldehyde (IV) (0.5 g, 0.027 mol) in ether (10 ml) was added an *N*-alkylaniline (0.03 mol), and the mixture was stirred for 3 h at room temperature. The crystals which separated were filtered off, washed with water and ether, dried, and recrystallized from ethanol to give the product (V) (Table 3), δ 7.72—7.83 (in $CF_3$·$CO_2H$).

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975. Index issue.

[13] O. Gawron, A. Rampal, and P. Johnson, *J. Amer. Chem. Soc.*, 1972, **94**, 5396.

*Cyclization of Compounds* (Va—d *and* i) *with Sulphuric Acid.*—Compound (V) (0.1 g) was added to concentrated sulphuric acid (2 ml). The mixture was warmed at 80 °C for *ca.* 10 s, then diluted with ice–water and set aside overnight. The 5-deazaflavine (IIa—d and i) separated in 70—90% yields.

To triethyl orthoformate (5 ml) and dimethylformamide (5 ml) was added 6-(*N*-D-ribityl-3,4-dimethylanilino)uracil (1.1 g, 0.03 mol). The mixture was refluxed for 2 h and then diluted with ether (10 ml) to cause separation of yellow crystals, which were collected, washed with ether, and recrystallized to give 5-*deazariboflavine* (0.7 g, 57%).

TABLE 3

6-(*N*-Alkylanilino)-5-formyl-3-methyluracils

| Compd. | M.p. (°C) | Yield (%) | Found (%) | | | Formula | Required (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| (Va) | 178 | 81 | 60.5 | 5.15 | 16.4 | $C_{13}H_{13}N_3O_3$ | 60.2 | 5.05 | 16.2 |
| (Vb) | 148 | 70 | 61.45 | 5.45 | 15.3 | $C_{14}H_{15}N_3O_3$ | 61.55 | 5.55 | 15.4 |
| (Vc) | 142 | 77 | 63.1 | 5.8 | 14.35 | $C_{15}H_{17}N_3O_3$ | 62.7 | 5.95 | 14.65 |
| (Vd) | 149 | 79 | 63.6 | 6.4 | 13.75 | $C_{16}H_{19}N_3O_3$ | 63.75 | 6.35 | 13.95 |
| (Vi) | 157 | 76 | 62.75 | 5.95 | 14.45 | $C_{15}H_{17}N_3O_3$ | 62.7 | 5.95 | 14.65 |

3,7,8-*Trimethyl*-10-(D-*ribityl*)*pyrimido*[4,5-b]*quinoline*-2,4(3H,10H)-*dione* (3-*Methyl*-5-*deazariboflavine*) (IIl).—A mixture of the aldehyde (IV) (1 g, 0.005 3 mol) and *N*-D-ribityl-3,4-xylidine (1.49 g, 0.005 8 mol) in dimethylformamide (5 ml) was stirred for 6 h at room temperature, then diluted with ether (20 ml), and again stirred for several h. The crystals which separated were filtered off, washed with water, dried, and recrystallized to give the yellow 3-*methyl*-5-*deazariboflavine* (0.89 g, 43%).

7,8-*Dimethyl*-10-(D-*ribityl*)*pyrimido*[4,5-b]*quinoline*-2,4(3H,10H)-*dione* (5-*Deazariboflavine*) (IIm).—*Method A.* To triethyl orthoformate (5 ml) and dimethylformamide (5 ml) was added 6-(*N*-D-ribityl-3,4-dimethylanilino)uracil (1.1 g, 0.03 mol). The mixture was refluxed for 2 h and then diluted with ether (10 ml) to cause separation of yellow crystals, which were collected, washed with ether, and recrystallized to give 5-*deazariboflavine* (0.7 g, 57%).

*Method B.* A mixture of compound (VI) (1 g, 0.005 mol) and 6-(*N*-D-ribityl-3,4-dimethylanilino)uracil (1.4 g, 0.005 5 mol) in dimethylformamide (5 ml) was stirred for 5 h at room temperature, then diluted with ether (10 ml) to precipitate the oily product. This was collected by decantation and solidified on treatment with water. Recrystallization gave 5-deazariboflavine (0.7 g, 37%).

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[6/446 *Received, 5th March,* 1976]