The Reaction of *N,N*-Dimethyldichloromethyleniminium Chloride (Phosgeniminium Chloride) with 6-*N*-Arylaminouracils. A New and Convenient "One Pot" Synthesis of 1,3-Dimethyl-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones, 1,3-Dimethyl-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones and 3-Methyl-10-alkyl-5-chloropyrimido[4,5-*b*]quinoline-(3*H*,10*H*)-2,4-diones (3-Methyl-10-alkyl-5-chloro-5-deazaflavins)

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The 1,1,1-tricondensation of *N,N*-dimethyldichloromethyleniminium chloride (phosgeniminium chloride) with various 1,3-dimethyl-6-*N*-arylaminouracils and 3-methyl-6-*N*-(alkylaryl)aminouracils, which gives only 5-dimethylaminopyrimido[4,5-*b*]quinoline-2,4-diones when performed in the presence of triethylamine, affords also the corresponding 5-chloropyrimido[4,5-*b*]quinoline-2,4-diones, including 3-methyl-10-alkyl-5-chloro-5-deazaflavins, when carried out in the absence of a base and under appropriate solvent and temperature reaction conditions. With regard to the selectivity of the transformation, these reaction conditions have been found to be especially dependent on the nature and the position of the starting arylaminouracil substituents.

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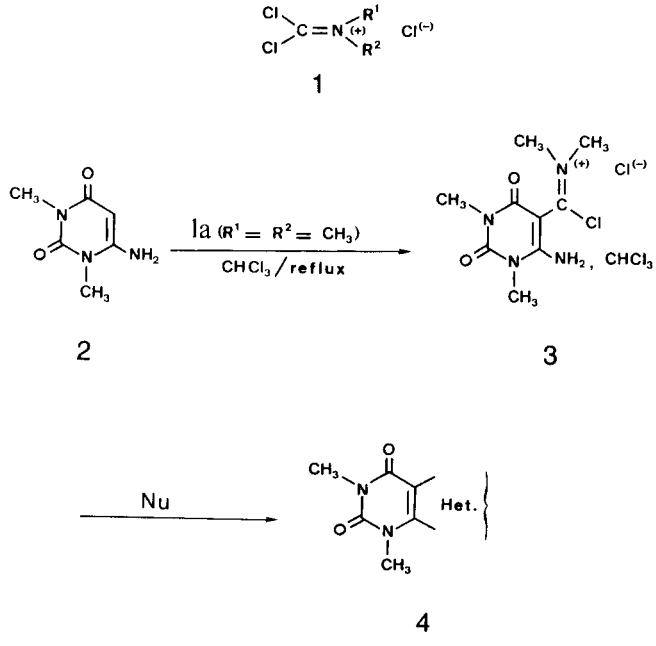
Phosgeniminium chlorides **1** (Scheme 1) are valuable strong electrophilic one carbon atom reagents. They possess three very mobile chlorine atoms and condense readily with nucleophiles to give amide chlorides, chloroenamines, *etc.*, which can react further to produce, through either inter or intramolecular processes, various types of functionalized 5, 6 and 7 membered ring systems [2-6].

Thus, while focusing on the use of uracil derivatives as starting materials to prepare new heterocyclic compounds of biological interests, we found earlier that the condensation of **1a** ($R^1 = R^2 =$ methyl) with the 1,3-dimethyl-6-aminouracil **2**, affords the thermally stable amide chloride **3** (Scheme 1). The latter was conveniently converted, *via* reaction with nucleophiles (Nu), into various fused pyrimidines **4** including thieno[3,4-*d*], pyrido[2,3-*d*] and pyrimido[4,5-*d*]pyrimidines, pyrido[1,2-*a*] and benzo[*c*]pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidines, *etc.*, [7-13] (Scheme 1).

Scheme 1

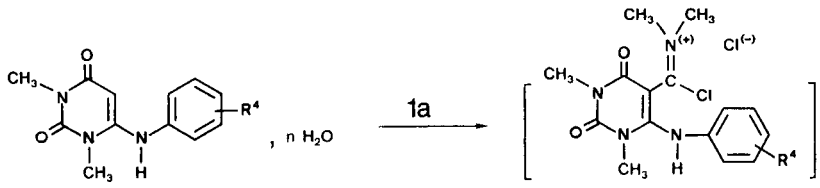


Further study of the above transformation showed that **1a** condenses as well with 6-*N*-(aryl) and 6-*N*-(alkylaryl)aminouracils **5** and **6** to form the thermally unstable amide chlorides of types **7** and **8** respectively (Schemes 2 and 3).

When heated in a dry solvent, these amide chlorides **7** and **8** undergo an intramolecular quinoline ring closure, affording the corresponding pyrimido[4,5-*b*]quinolines (5-deazaalloxazines and 5-deazaisoalloxazines) **9** to **11** in very good yields (Scheme 4). Pyrimido[4,5-*b*]quinolines of types **11** are structurally similar to flavins (pyrimido[4,5-*b*]-quinoxalines or isoalloxazines) and are usually referred to as 5-deazaflavins.

Electrophiles such as the nitrous anion [14,15], acyl halides [16], the Vielsmeyer-Haack-Arnold reagent [17], *etc.*, are known to condense with barbituric acids and 6-aminouracils, producing 5-substituted uracils, and of course, phosgeniminium chlorides **1** are no exception. Besides, well known very useful procedures starting from 6-*N*-arylaminouracils of types **5** and **6** and affording pyrimido[4,5-*b*]quinolines, including 5-deazaflavins, through reaction with one carbon atom reagents such as the Vielsmeyer-Haack-Arnold reagent for instance, have been reported [18]. However, due to the structure of the latter, only 5-unsubstituted pyrimido[4,5-*b*]quinolines can generally be prepared when using these procedures while corre-

Scheme 2



5a–j

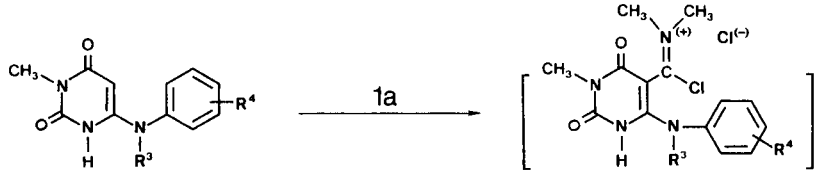
n = 0 , 5b, d, e, g, j.

n = 1 , 5a, c, f, h, i.

7a–j

	R^4		R^4
5a , 7a	H	5f , 7f	4′–Cl
5b , 7b	3′–CH_3	5g , 7g	3′–Cl
5c , 7c	4′–OCH_3	5h , 7h	2′–Cl
5d , 7d	3′–OCH_3	5i , 7i	2′,3′–Cl_2
5e , 7e	3′,4′–$(CH_3)_2$	5j , 7j	3′,4′–Cl_2

Scheme 3



6a–i

$R^3 = CH_3$, 6, 8a–g

$R^3 = C_2H_5$, 6, 8h–i

8a–i

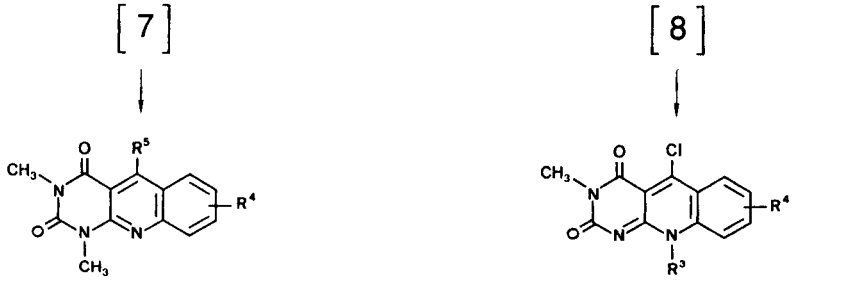
	R^4		R^4
6a , 8a	H	6f , 8f	4′–C_2H_5
6b , 8b	4′–CH_3	6g , 8g	3′,4′–$(CH_3)_2$
6c , 8c	3′–CH_3	6h , 8h	H
6d , 8d	4′–OCH_3	6i , 8i	3′–CH_3
6e , 8e	3′–OCH_3		

sponding 5-functionalized derivatives are expected when similar transformations involve the phosgeniminium chlorides **1**.

The heterocyclisation of polynucleophiles *via* a 1,1,1-tricondensation with **1**, usually affords 5, 6 and 7 membered ring systems bearing a dialkylamino group whether or not the reaction is carried out in the presence of an organic base which traps the three equivalents of hydrogen chloride released by **1** pending the condensation/cyclisation process. Accordingly, we actually thought that the reaction of **1a** ($R^1 = R^2$ = methyl) with **5** and **6** would only produce 5-dimethylaminopyrimido[4,5-*b*]quinolines. As a matter of fact, while this is always the case when the reaction is carried out in the presence of an excess of triethylamine, quite surprisingly, in the absence of such a base, the transformation gives 5-chloropyrimido[4,5-*b*]quinolines of types **10** and **11** as well, along with one equivalent of dimethylamine which is quantitatively trapped into the reaction mixture as dimethylammonium chloride.

Further investigation of this transformation enabled us: 1/ to develop original "one pot" procedures to prepare selectively such compounds as 1,3-dimethyl-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones **9**, 1,3-dimethyl-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones **10** and 3-methyl-10-alkyl-5-chloropyrimido[4,5-*b*]-quinoline-(3*H*,10*H*)-2,4-diones (3-methyl-10-alkyl-5-chloro-5-deazaflavines) **11**, starting from easily available 6-*N*-aryl-aminouracils, and 2/ to point out a curious property of the

Scheme 4



9 $[R^5 = N(CH_3)_2]$, 10 $[R^5 = Cl]$

11a–g $[R^3 = CH_3]$, 11h–i $[R^3 = C_2H_5]$

	R^4		R^4
9a , 10a	H	9g , 10g	8 – Cl
9b , 10b	8 – CH_3	9h , 10h	9 – Cl
9c , 10c	7 – OCH_3	9i	8,9 – Cl_2
9d , 10d	8 – OCH_3	9j 10j	7,8 – Cl_2
10e	7,8 – $(CH_3)_2$	9k	6,7 – Cl_2
9f , 10f	7 – Cl		

	R^4		R^4
11a	H	11f	8 – C_2H_5
11b	7 – CH_3	11g	7,8 – $(CH_3)_2$
11c	8 – CH_3	11h	H
11d	7 – OCH_3	11i	8 – CH_3
11e	8 – OCH_3		

Table 1

Analytical Data of 1,3-Dimethyl-5-Dimethylaminopyrimido[4,5-*b*]quinoline(1*H*,3*H*)-2,4-Diones (9)

	R^4		R^4		R^4
9a	H	9f	7-Cl	9i	8,9-Cl_2
9b	8-CH_3	9g	8-Cl	9j	7,8-Cl_2
9c	7-OCH_3	9h	9-Cl	9k	6,7-Cl_2
9d	8-OCH_3				

No	Formula (M^+)	Mp [a]	Analysis (%)		Calcd./Found	
			C	H	Cl	N
9a	$C_{15}H_{16}N_4O_2$ (284)	202	63.38	5.63		19.71
			63.60	5.59		19.63
9b	$C_{16}H_{18}N_4O_2$ (298)	164 [b]	64.42	6.04		18.79
			64.35	6.02		18.61
9c	$C_{16}H_{18}N_4O_3$ (314)	216	61.14	5.73		17.83
			60.96	5.78		17.75
9d	$C_{16}H_{18}N_4O_3$ (314)	258	61.14	5.73		17.83
			61.00	5.84		17.56
9f	$C_{15}H_{15}ClN_4O_2$ (318)	216	56.51	4.70	11.14	17.58
			56.68	4.45	11.30	17.37
9g	$C_{15}H_{15}ClN_4O_2$ (318)	206 [c]	56.51	4.70	11.14	17.58
			56.46	4.70	11.57	17.46
9h	$C_{15}H_{15}ClN_4O_2$ (318)	174	56.51	4.70	11.14	17.58
			56.68	4.77	11.11	17.40
9i	$C_{15}H_{14}Cl_2N_4O_2$ (352)	222	50.99	3.96	20.11	15.86
			50.43	3.96	19.78	15.84
9j	$C_{15}H_{14}Cl_2N_4O_2$ (352)	236	50.99	3.96	20.11	15.86
			51.15	4.08	20.06	15.72
9k	$C_{15}H_{14}Cl_2N_4O_2$ (352)	176	50.99	3.96	20.11	15.86
			50.90	3.92	20.12	15.62

Table 2

^{1}H-nmr of 1,3-Dimethyl-5-Dimethylaminopyrimido[4,5-*b*]quinoline(1*H*,3*H*)-Diones (9) [a]

No	R^4	
9a	H	3.28 (s, 6H), 3.48 (s, 3H), 3.75 (s, 3H), 7.20-8.0 (m, 3H), 8.15 (dd, 1H, J = 8.0, J = 2.0).
9b	8-CH_3	2.50 (s, 3H), 3.26 (s, 6H), 3.48 (s, 3H), 3.75 (s, 3H), 7.20 (dd, 1H, J = 9.0, J = 2.0), 7.65 (br s, 1H), 8.05 (d, 1H, J = 9.0).
9c	7-OCH_3	3.27 (s, 6H), 3.52 (s, 3H), 3.75 (s, 3H), 3,96 (s, 3H), 7.35 (br d, 1H, J = 8.0), 7.45 (br s, 1H), 7.80 (br d, 1H, J = 8.0).
9d	8-OCH_3	3.22 (s, 6H), 3.48 (s, 3H), 3.76 (s, 3H), 3.98 (s, 3H), 7.05 (dd, 1H, J = 9.0, J = 3.0), 7.25 (d, 1H, J = 3.0), 8.05 (d, 1H, J = 9.0).
9f	7-Cl	3.20 (s, 6H), 3.42 (s, 3H), 3.70 (s, 3H), 7.65 (dd, 1H, J = 9.0, J = 3.0), 7.80 (d, 1H, J = 9.0), 8.10 (d, 1H, J = 3.0).
9g	8-Cl	3.28 (s, 6H), 3.48 (s, 3H), 3.70 (s, 3H), 7.25 (dd, 1H, J = 10.0, J = 2.0), 7.80 (d, 1H, J = 2.0), 8.05 (d, 1H, J = 10.0).
9h	9-Cl	3.25 (s, 6H), 3.46 (s, 3H), 3.78 (s, 3H), 7.30 (t, 1H, J = 8.0), 7.82 (dd, 1H, J = 8.0, J = 2.0), 8.10 (dd, 1H, J = 8.0, J = 2.0).
9i	8,9-Cl_2	3.22 (s, 6H), 3.45 (s, 3H), 3.78 (s, 3H), 7.38 (d, 1H, J = 9.0), 7.95 (d, 1H, J = 9.0).
9j	7,8-Cl_2	3.30 (s, 6H), 3.48 (s, 3H), 3.72 (s, 3H) 7,92 (s, 1H), 8.20 (s,1H).
9k	6,7-Cl_2	3.15 (s, 6H), 3.45 (s, 3H), 3.70 (s,3H), 7.60 (s, 2H).

[a] in Chloroform-d

Table 3

Analytical Data of 1,3-Dimethyl-5-Chloropyrimido[4,5-*b*]quinoline(1*H*,3*H*)-2,4-Diones (**10**)

	R^4		R^4		R^4
10a	H	**10d**	8-OCH_3	**10g**	8-Cl
10b	8-CH_3	**10e**	7,8-OCH_3	**10h**	9-Cl
10c	7-OCH_3	**10f**	7-Cl	**10j**	7,8-Cl_2

No	Formula (M^+)	Mp	Analysis (%)		Calcd./Found	
			C	H	Cl	N
10a	$C_{13}H_{10}ClN_3O_2$ (275)	200 [a]	56.62	3.62	12.88	15.24
			56.46	3.69	12.72	15.05
10b	$C_{14}H_{12}ClN_3O_2$ (289)	220 [b]	58.03	4.14	12.26	14.50
			58.19	4.06	12.38	14.25
10c	$C_{14}H_{12}ClN_3O_3$ (305)	218 [c]	54.99	3.92	11.62	13.74
			54.83	3.87	11.78	13.57
10d	$C_{14}H_{12}ClN_3O_3$ (305)	268 [c]	54.99	3.92	11.62	13.74
			54.70	3.94	11.67	13.44
10e	$C_{15}H_{14}ClN_3O_2$ (303)	228 [d]	59.30	4.61	11.69	13.83
			59.37	4.56	11.91	13.64
10f	$C_{13}H_9Cl_2N_3O_2$ (309)	240 [e]	50.32	2.90	22.90	13.54
			50.46	2.74	23.15	13.47
10g	$C_{13}H_9Cl_2N_3O_2$ (309)	210 [e]	50.32	2.90	22.90	13.54
			50.47	2.70	22.66	13.40
10h	$C_{13}H_9Cl_2N_3O_2$ (309)	180 [a]	50.32	2.90		13.54
			50.48	3.06		13.66
10j	$C_{13}H_8Cl_3N_3O_2$ (343)	192 [f]	45.28	2.32	30.91	12.19
			45.34	2.23	31.67	12.16

[a], [b], [c],[d], [e], [f] Recrystallized from [a] éthyl acetate, [b] 2-propanol, [c] butanone, [d] ethyl acetate (50%) / 1-propanol (50%) mixture, [e] dichloroethane, [f] 1-propanol.

Table 4

^{1}H-nmr of 1,3-Dimethyl-5-Chloropyrimido[4,5-*b*]quinoline(1*H*,3*H*)-2,4-Diones (**10**) [a]

No	R^4	
10a	H	3.50 (s, 3H), 3.80 (s, 3H), 7.35-7.95 (m, 3H), 8.35 (br d, 1H, J = 9.0).
10b	8-CH_3	2.60 (s, 3H), 3.50 (s, 3H), 3.75 (s, 3H), 7.35 (dd, 1H, J = 9.0, J = 2), 7.65 (br s, 1H), 8.20 (d, 1H, J = 9.0).
10c [b]	7-OCH_3	3.70 (s, 3H), 4.10 (s, 3H), 4.18 (s, 3H), 7.95 (dd, 1H, J = 9.0, J = 3), 8.08 (br s, 1H), 8.35 (d, 1H, J = 9.0).
10d [b]	8-OCH_3	3.65 (s, 3H), 4.05 (s, 3H), 4.15 (s, 3H), 7.55-7.80 (m, 2H), 8.70 (d, 1H, J = 10.0).
10e	7,8-$(CH_3)_2$	2.42 (s, 6H), 3.46 (s, 3H), 3.70 (s, 3H), 7.55 (s, 1H), 7.98 (s, 1H).
10f	7-Cl	3.50 (s, 3H), 3.76 (s, 3H), 7.70 (br s, 2H), 8.35 (br s, 1H).
10g	8-Cl	3.48 (s, 3H), 3.72 (s, 3H), 7.45 (dd, 1H, J = 10.0, J = 3.0), 7.88 (d, 1H, J = 3.0), 8.30 (d, 1H, J = 10.0).
10h	9-Cl	3.50 (s, 3H), 3.78 (s, 3H), 7.40 (t, 1H, J = 9.0), 7.90 (dd, 1H, J = 9.0, J = 2.0), 8.28 (dd, 1H, J = 9.0, J = 2.0).
10j	7,8-Cl_2	3.53 (s, 3H), 3.80 (s, 3H), 7.98 (s, 1H), 8.38 (s, 1H).

[a] in Chloroform-d except [b] in Trifluoroacetic acid-d

5-dimethylaminopyrimido[4,5-*b*]quinolines, that is to be converted into their 5-chloro counterparts, upon treatment with hydrogen chloride and therefore, through reaction with the chloride anion.

Thus, as already mentioned, when carried out in the presence of triethylamine, the transformation of **5** and **6** affords only the 5-dimethylamino derivatives. In this context however, the 5-dimethylamino-5-deazaflavins, formed when starting from **6**, have always been obtained in very poor yields. Furthermore, due to their instability, these compounds could not be properly purified using standard procedures and, since no elemental analysis data can be offered for them at this time, their synthesis is not taken into consideration in this paper.

Conversely, in the absence of a base and depending on the solvent and temperature reaction conditions, the arylaminouracils of type **5** can afford either the only 5-dimethylaminopyrimido[4,5-*b*]quinolines **9** or the only 5-chloropyrimido[4,5-*b*]quinolines **10** or mixtures containing both compounds **9** and **10** while the cyclisation of the alkylarylaminouracils **6** leads to nearly pure 5-chloro-5-deazaflavins **11**.

The synthesis of the pyrimido[4,5-*b*]quinolines **9** to **11** using 6-arylaminouracils **5** and **6** and phosgeniminium chloride (**1a**), proceeds *via* two distinct steps, namely the formation and the cyclisation of the corresponding amide chlorides **7** and **8** (Schemes 2-4). In the absence of a base, the latter are usually formed cleanly and quantitatively at very moderate temperatures including room temperature, in such solvents as dichloromethane and chloroform. Their heterocyclisation into pyrimido[4,5-*b*]quinolines however, may require more drastic temperature reaction conditions which, depending on the starting aminouracils, have been found to vary from room temperature in dichloromethane to 120-130° in chlorobenzene.

The amide chlorides **7** and **8** are very hygroscopic materials readily converted into stable amides by facile hydrolysis. Thus, to avoid any inadvertent interference of atmospheric moisture, especially during workups, we chose to cyclise them *in situ* without prior isolation and further purification and therefore, to perform the overall conversion of the arylaminouracils **5** and **6** under "one pot" reaction conditions.

Reactions involving the phosgeniminium salt **1a** which, although very stable in dry atmosphere may decompose when extensively heated in an inert solvent, even at temperatures lower than 70°, are usually carried out at room

to reflux temperatures, in dry dichloromethane or dry chloroform. These two solvents however, were proved to be rather unsuitable for the transformation of **5** and **6** into pyrimido[4,5-*b*]quinolines, since they do not always allow: 1/ the achievement of the second step of the transformation that is to say, the cyclisation of the amide chlorides **7** and **8** or, when the latter is possible in such conditions, 2/ the selective formation of the 5-chloropyrimidoquinolines. For instance, some amide chlorides of type **7**, heterocyclise in refluxing chloroform yielding to mixtures of 5-dimethylamino and 5-chloropyrimido[4,5-*b*]quinolines **9** and **10** while they afford the only 5-chloro derivatives **10** when heated in chlorobenzene at 90-100°. Similarily, amide chlorides corresponding to the 6-*N*-(chlorophenyl)aminouracils **5f-j** and to the 6-*N*-(alkylaryl)aminouracils **6** do cyclise only when heated in refluxing dichloroethane (bp = 82°) and at 110-120° in chlorobenzene (bp = 131°) respectively.

When using solvents such as dichloroethane and chlorobenzene, inadvertent thermal decomposition of **1a** prior its expected condensation with **5** and **6**, was prevented through careful monitoring of the reaction temperatures. Thus, reaction mixtures containing starting aminouracils and **1a** were heated first not higher than 50-60° until the formation of the amide chlorides was completed and the temperature raised up afterwards as high as needed, to go on with the following and last step of the transformation which as a matter of fact, appears to subdivide itself into two distinct but somehow overlapped processes: the ring closure and the formation of 5-chloro and/or 5-dimethylaminopyrimido[4,5-*b*]quinolines.

The reaction conditions for this last step of the transformation depend very much on the structure of the starting aminouracils. For instance, undermost and uppermost temperature conditions for the overall conversion of arylaminouracils of type **5**, correspond to the 6-*N*-(3′-methoxyphenyl)aminouracil **5d** and to the 6-*N*-(dichlorophenyl)-aminouracils **5i** and **5j**, having respectively, the most and the less activated 2′-position in their aryl moiety. Besides, according to our results, it appears that in the absence of a base, the 5-dimethylaminopyrimido[4,5-*b*]quinolines **9** would be formed at lower temperatures than their 5-chloro counterparts. Thus, amide chlorides **7a-e** are the easiest to cyclise but, although **7d** can be formed and cyclised at

Table 5

Analytical Data of 3-Methyl-10-Alkyl-5-Chloro-5-Deazaflavins (**11**)

	R^3	R^4		R^3	R^4
11a	CH_3	H	**11f**	CH_3	7-C_2H_5
11b	CH_3	7-CH_3	**11g**	CH_3	7,8-$(CH_3)_2$
11c	CH_3	8-CH_3	**11h**	C_2H_5	H
11d	CH_3	7-OCH_3	**11i**	C_2H_5	8-CH_3
11e	CH_3	8-OCH_3			

No	Formula (M^+)	Mp° [a] (dec.)	Analysis (%) Calcd./Found		
			C	H	N
11a	$C_{13}H_{10}ClN_3O_2$ (275)	> 280	56.62	3.62	15.24
			56.76	3.64	15.35
11b	$C_{14}H_{12}ClN_3O_2$ (289)	> 280	58.03	4.14	14.50
			57.81	4.20	14.29
11c	$C_{14}H_{12}ClN_3O_2$ (289)	> 280	58.03	4.14	14.50
			57.87	4.27	14.39
11d	$C_{14}H_{12}ClN_3O_3$ (305)	279	54.99	3.92	13.74
			55.02	4.15	13.74
11e	$C_{14}H_{12}ClN_3O_2$ (305)	> 280	54.99	3.92	13.74
			55.28	4.14	13.41
11f	$C_{15}H_{14}ClN_3O_2$ (303)	263	59.30	4.61	13.83
			59.59	4.78	13.86
11g	$C_{15}H_{14}ClN_3O_2$ (303)	> 280	59.30	4.61	13.83
			59.61	5.10	13.98
11h	$C_{14}H_{12}ClN_3O_2$ (289)	260	58.03	4.14	14.50
			58.18	4.17	14.51
11i	$C_{15}H_{14}ClN_3O_2$ (303)	> 280	59.30	4.61	13.83
			59.27	4.72	13.86

[a] Due to their instability, these compounds could not be recrystallized

Table 6

^{1}H-nmr of 3-Methyl-10-Alkyl-5-Chloro-5-Deazaflavins (**11**) [a]

No	R^3	R^4	
11a	CH_3	H	3.58 (s, 3H), 4.50 (s, 3H), 8.05-8.45 (m, 3H), 8.95 (br d, 1H, J = 8.0).
11b	CH_3	7-CH_3	2.72 (s, 3H), 3.62 (s, 3H), 4.54 (s, 3H), 8.10-8.20 (m, 2H), 8.70 (br s, 1H).
11c	CH_3	8-CH_3	2.85 (s, 3H), 3.68 (s, 3H), 4.55 (s, 3H), 7.98 (br d, 1H, J = 9.0), 8.15 (d, 1H, J = 2.0), 8.85 (d, 1H, J = 9.0).
11d	CH_3	7-OCH_3	3.70 (s, 3H), 4.18 (s, 3H), 4.58 (s, 3H), 8.05-8.40 (m, 3H).
11e	CH_3	8-OCH_3	3.62 (s, 3H), 4.22 (s, 3H), 4.45 (s, 3H), 7.60 (m, 2H), 8.85 (d, 1H, J = 9.0).
11f	CH_3	7-C_2H_5	1.45 (t, 3H, J = 7.0), 3.05 (q, 2H, J = 7.0), 3.60 (s, 3H), 4.52 (s, 3H), 8.10-8.30 (m, 2H), 8.70 (br s, 1H).
11g [b]	CH_3	7,8-$(CH_3)_2$	2.46 (s, 3H), 2.52 (s, 3H), 3.42 (s, 3H), 4.10 (s, 3H), 7.40 (s, 1H), 8.15 (s, 1H).
11h [b]	C_2H_5	H	1.48 (t, 3H, J = 7.0), 3.45 (s, 3H), 4.85 (q, 2H, J = 7.0), 7.35-8.10 (m, 3H), 8.55 (dd, 1H, J = 8.0, J = 2.0).

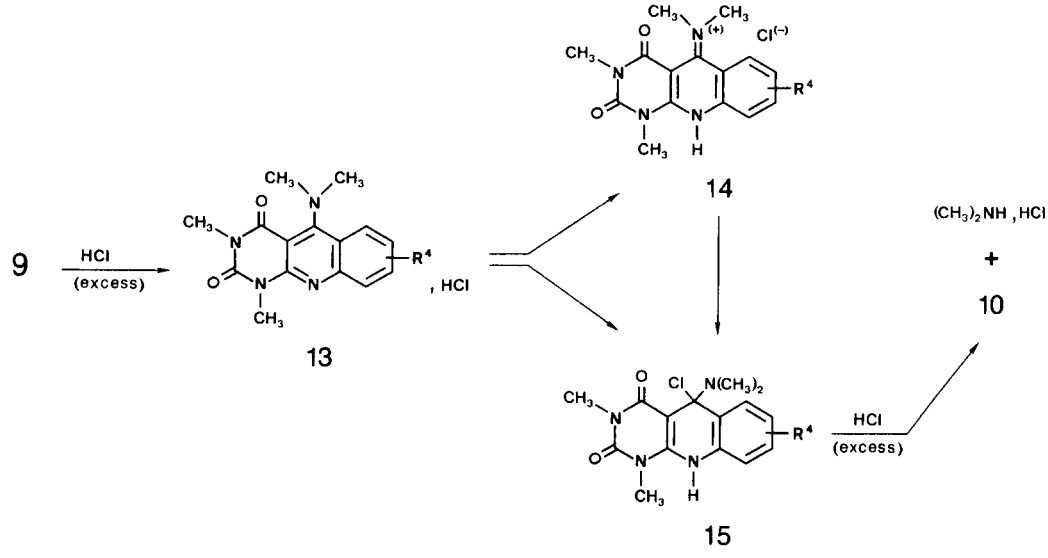
[a] in Trifluoroacetic acid-d except [b] in Chloroform-d.

room temperature in dry dichloromethane, affording the only 5-chloropyrimido[4,5-*b*]quinoline **10d**, analogs **7a-c,e** cyclise in refluxing chloroform leading to mixtures of 5-chloro and 5-dimethylamino derivatives. By contrast, all of them produce pure 5-chloropyrimidoquinolines when heated in dry chlorobenzene at 90-100°. Similarly, the amide chlorides **7f-j** do cyclise when heated either in refluxing dichloroethane, to form the 5-dimethylaminopyrimidoquinolines **9**, or at 120-130° in chlorobenzene, to produce the corresponding 5-chloro derivatives **10**. Under these reaction conditions, the 6-*N*-(3',4'-dichlorophenyl)-aminouracil **5j** affords respectively, mixtures of the isomeric 5-dimethylamino-7,8-dichloro and 5-dimethylamino-6,7-dichloropyrimidoquinolines **9j** and **9k** in dichloroethane, and mixtures containing the 5-chloro-7,8-dichloropyrimidoquinoline (5,7,8-trichloropyrimidoquinoline) **10j** and the 5-dimethylamino-6,7-dichloropyrimidoquinoline **9k**, which is not converted into its 5-chloro counterpart, in chlorobenzene. As for the amide chlorides **8**, they usually cyclise only when heated at 110-120° in dry chlorobenzene, producing very good yields of rather unstable but nearly analytically pure 5-chloro-5-deazaflavins **11**. In this case, the formation at lower temperatures of the corresponding 5-dimethylamino derivatives, could not be clearly established.

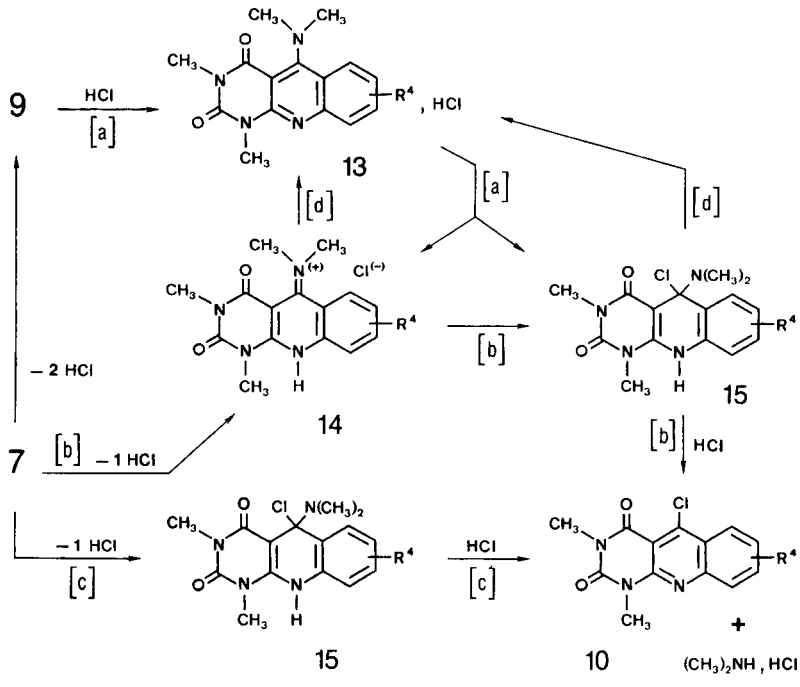
Pending the overall transformation of **5** and **6**, only three equivalents of the chloride anion, all three coming from **1a**, are going to be available to form the 5-chloro derivatives **10** and **11**, and we must note that when the latter are produced quantitatively, at least two out of these three chlorine atoms have to be involved since every time these 5-chloro derivatives are formed, one equivalent of dimethylammonium chloride is present as well in the crude reaction mixtures. Compounds such as the 5-dimethylaminopyrimido[4,5-*b*]quinolines **9** are yellow solids usually soluble in aqueous acidic medium while the 5-chloro derivatives **10** are not and it is generally quite easy to isolate quantitatively the latter from mixtures of both derivatives in diluted aqueous hydrochloric acid, by filtration and/or extraction with an organic solvent, as long as the whole sequence is performed at room temperature. Then, the 5-dimethylaminopyrimidoquinolines **9** can be recovered from the colorless acidic filtrates, through neutralization with potassium hydrogen carbonate followed by filtration and/or extraction with chloroform or dichloromethane. At higher temperature, the compounds **9** are likely to be converted more or less easily, into their 5-chloro and/or 5-hydroxy counterparts. A similar transformation may occur as well when bubbling an excess of hydrogen chloride into solutions of 5-dimethylaminopyrimidoquinolines in dry chloroform, dichloroethane or chlorobenzene. At room temperature the corresponding salts **13** do generally separate as colorless needles when adding dry ether, but they may decompose slowly at room temperature pending their isolation by filtration in the presence of atmospheric moisture or afterwards when treated with water, giving back the starting 5-dimethylamino derivatives **9** and hydrochloric acid. Conversely, they are converted into the 5-chloropyrimidoquinolines **10** when warmed *in situ* at 70-100° *via* probably, formation of such intermediates as **14** and **15** (Scheme 5).

In this context, when using only 2-3 equivalents of hydrogen chloride, instead of an excess, to be as close as possible of the corresponding concentration of the reaction mixtures during the cyclisation of amide chlorides when it affords the 5-chloro derivatives, the transformation was usually found to be sluggish and rather difficult to achieve.

Scheme 5



Scheme 6



As for these observations, whether or not the 5-dimethylamino derivatives are eventually found in the crude reaction mixtures, we may believe: 1/ that they are not necessarily the precursors or the only precursors, of the 5-chloropyrimidoquinolines (Scheme 6, pathway [a]), and 2/ that other intermediates such as for instance, the imminium chlorides **14** and the 5-chloro-5-dimethylamino derivatives **15** which may be formed in the first place when the amide chlorides do cyclise, would also afford the 5-chloropyrimidoquinolines and possibly, faster than the 5-dimethylamino derivatives themselves (Scheme 6, pathway [b] and [c]). As a matter of fact, whether or not they are obtained selectively, evidence of the formation *in situ* of **10** and **11** *via* formation first of their 5-dimethylamino counterparts, could not be established.

During the cyclisation process, any loss as free hydrogen chloride, of part of the two chlorine atoms attached to the amide chloride, would compete with the formation of the 5-chloro derivative and allow the presence of the 5-dimethylaminopyrimidoquinoline in the reaction mixture. Therefore, whenever the 5-chloro derivatives **10** and **11**, as well as their by-product the dimethylammonium chloride, are quantitatively produced, it is obvious that the whole of these two chlorine atoms must have been quantitatively trapped *in situ* under a much stabler form than volatil hydrogen chloride especially of course, when the reaction is carried out in chlorobenzene at 90 to 120-130°. However, neither the reasons why some amide chlorides would cyclise into mixture of 5-dimethylamino and 5-chloropyrimidoquinolines when heated in refuxing chloroform and into pure 5-chloropyrimidoquinolines instead, when heated at 90 to 120-130° in chlorobenzene, nor the fact that the latter 5-chloro derivatives would usually be produced at higher temperature than their 5-dimethylamino counterparts, are really understood yet and no clear explanation of these results can be given at this time.

A synthesis of a pyrimido[4,5-*b*]quinoline from a barbituric acid and the 2-aminobenzaldehyde, was first reported by Conrad and Reinbach in 1901 [19]. As a matter of fact, probably because very less attention has been paid to this heterocyclic system for about one-half of a century afterwards, the Conrad and Reinbach's procedure has remained, until about 20 years ago, the main one being referred to for the preparation of pyrimido[4,5-*b*]quinoline derivatives. In recent years, following the discovery in 1978, of a naturally occurring 5-deazaflavin [20-23], a dramatically increasing interest in the 5-deazaflavin chemistry has developed and new and convenient methodologies to synthesize a great variety of pyrimido[4,5-*b*]quinolines and especially 5-deazaflavins, have been reported most of them by Yoneda and co-workers [11,18,24].

The synthetic approaches to build the pyrimido[4,5-*b*]-quinoline skeleton up, may roughly be classified into two types of methods involving respectively, as ultimate step of the preparation, either a central pyridine ring closure process or the creation of the lateral pyrimidine ring of the

molecule.

The central pyridine ring closure process to synthesize pyrimido[4,5-*b*]quinolines including 5-deazaflavins, has by far, been the most used. It consists mostly in condensing barbituric acids with various 2-aminobenzaldehydes, as in the original procedure by Conrad and Reinbach [19,25], isatine, 2-nitrobenzaldehydes, *etc.*, or primary aminouracils with dimedone, alkylaldehydes and hydroxymethylenecycloalcanones, or alkyl and arylaminouracils with 2-halogenobenzaldehydes and benzaldehydes in the presence of diethylazodicarboxylate, or arylaminouracils with one carbon atom reagents, including the Vielsmeyer-Haack-Arnold reagent and carbon disulfide. In this context, a few procedures allowing the direct synthesis of 5-substituted pyrimido[4,5-*b*]quinolines, including 5-substituted 5-deazaflavins, and starting from 6-arylaminouracils of types **5** and **6** and such reagents as carbon disulfide [26], carbonyldiimidazole [27a], activated trifluoroacetic acid [27b], and aromatic aldehydes [28a,b] have been proposed. Some other procedures, starting from 5-substituted barbituric acids and 5-substituted aminouracils and involving reagents such as arylisocyanates, dimethylaminocyclohexenone, cyclohexenedione, polyphosphoric and sulfuric acids, *etc.*, have also been reported [11,18]. An indirect route to 5-chloro-5-deazaflavins of type **11**, starting from 5-deazaflavins *via* formation first of corresponding 4a,5-epoxy-5-deazaflavins, and then reaction with the Vielsmeyer reagent (phosphorus oxychloride in dimethylformamide), has been developed by Yoneda [28c].

The formation of the pyrimido[4,5-*b*]quinoline skeleton using properly 3-substituted-2-aminoquinolines *via* a lateral pyrimidine ring closure process seems to have been less frequently used than the previous one. It was however, successfully applied to the preparation of various deazaalloxazines starting from 3-(carboxamido, cyano, aminomethyl, carbethoxy, *etc.*,) -2-aminoquinolines and such reagents as acetic anhydride, formamide, ureas, arylisocyanates, *etc.*, [29-31]. Conversely, only one procedure affording 5-deazaflavins has, so far, been reported [32].

Pyrimido[4,5-*b*]quinolines of deazaalloxazine type, which can be seen as diazaacridines and non redox analogs of riboflavins, were first prepared as potential anti-cancer agents and potential agonists and antagonists of riboflavins and acridines, the latter being already known as amine oxidase and acetylcholinesterase inhibitors, and as useful antiseptics and antipaludics [33].

Tautomeric isomers of 5-deazaalloxazines known as 5-deazaflavins, were first synthesized [25] as potential flavin antagonists and have been extensively studied afterwards in both enzimatic and model systems. They are structurally similar to flavins and nicotinamide nucleotides (NADH$^+$) and have often been referred to as "flavin shaped NAD analogs". However, it is now well established that they are chemically closer to nicotinamide nucleotides than to flavins. Since the discovery of the 8-hydroxy-5-deazaflavin moiety as being part of the redox coenzyme factor F 420 from the anaerobic methane producing bacteria, several other cofactors containing the same 5-deazaflavin skeleton, have been isolated from various sources. Final and unambiguous proof of the structure of some of these cofactors has recently been provided through total synthesis by Yoneda's group who, over the last 15 years, has also pointed out and studied the most important biofonctional properties of the 5-deazaflavin system. Thus 5-deazaflavins have been proved to possess strong oxidizing power and to behave as NAD$^+$ model in non enzymatic oxidation of alcohols and amines, acting as autorecycling turnover catalyst in corresponding reactions. Conversely, autorecycling reduction with 1,5-dihydro-5-deazaflavins using 5-deazaflavins in formic acid, was successfully applied to the conversion of carbonyl compounds into alcohols, to the reductive amination of α-ketoacids into α-aminoacids and to the specific 1,4-reduction of α,β-insaturated carbonyl compounds [18,24]. Recently, some 5-amino-5-deazaflavin derivatives prepared either from 5-unsubstituted-5-deazaflavins or from 5-chloro-5-deazaflavins of type **11**, have been found to exhibit interesting anti-tumor activities [34].

EXPERIMENTAL

Melting points were taken with a Kofler bench and are uncorrected. The ^{1}H nmr spectra have been recorded on a R 24 Hitachi Perkin-Elmer 60 MHz spectrometer and/or an E.M. 390 Varian 90 MHz spectrometer using chloroform-d, dimethyl sulfoxide-d_6 or trifluoroacetic acid-d as solvents (see tables 2, 4 and 6) and tetramethylsilane as internal reference. Chemical shifts are given in ppm and coupling constants in Hz. The following abbreviations are used: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quadruplet, m = multiplet, br = broad. Elemental analysis have been performed by the "service Central d'Analyse du C.N.R.S.", Vernaison, France. Mass spectra have been obtained on a Nermag R 10-10C mass spectrometer.

Preparation of the Starting Materials.

All starting materials were prepared according to the literature [35-40]. Thus, the 1,3-dimethyl-6-*N*-(aryl) and 3-methyl-6-*N*-(alkylaryl)aminouracils of types **5** and **6** were synthesized by condensing 1,3-dimethyl and 3-methyl-6-chlorouracils with primary and secondary anilines respectively. The 6-chlorouracils were obtained from 1,3-dimethyl and 3-methylbarbituric acids *via* reaction with phosphorus oxychloride. Both barbituric acids were prepared by condensing malonic acid with *N,N'*-dimethylurea and *N*-methylurea respectively [35-40]. Non commercially available secondary anilines were obtained by reduction of corresponding formamides readily prepared by reaction between primary anilines and acetic formic anhydride [41].

1,3-Dimethyl-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones **9a-d, 9f-i**.

Procedure 1. In the Presence of a Base (General Procedure).

An excess of phosgeniminium chloride (**1a**) (1.0 g, approxi-

mately 0.006 mole [42-43], see Scheme 2), was added slowly to a mixture of 1,3-dimethyl-6-arylaminouracil (**5**) (0.005 mole), triethylamine (3.1 g, approximately 0.030 mole [44], see Scheme 2), and 1/ dry chloroform (50 ml) for **5a-d** or 2/ dry dichloroethane (50 ml) for **5f-i**. The stirring suspension, protected from atmospheric moisture was allowed to stand at room temperature for 2 hours, heated first at 40-50° for 2 hours and then at reflux for 2 hours. After cooling at room temperature, the solvent was removed *in vacuo* and water added to the residue. The resulting 5-dimethylaminopyrimido[4,5-*b*]quinoline **9**, was isolated by filtration using a glass filter, washed with water (3 x 20 ml) and dried *in vacuo*. An additional small quantity of **9** was occasionally extracted from the filtrate with chloroform, overall yield, 90-92% (Tables 1 and 2).

1,3-Dimethyl-8,9-dichloro-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**9i**).

Procedure 2. In the Absence of a Base.

To a suspension of **1a** (2.0 g, approximately 0.012 mole [42,43], see Scheme 2) in dry dichloroethane (50 ml) was added the 1,3-dimethyl-6-*N*-(2',3'-dichlorophenyl)aminouracil **5i** (1.59 g, 0.005 mole). The stirring mixture protected from atmospheric moisture, was allowed to stand at room temperature for 2 hours, heated first at 40-50° for 2 hours and then at reflux until the evolution of hydrogen chloride had ceased (5-6 hours). After cooling, the solvent was removed *in vacuo*, the residue mixed with water (50 ml) and potassium hydrogen carbonate added slowly until the evolution of carbon dioxide had ceased. The precipitate of nearly pure 5-dimethylaminopyrimido[4,5-*b*]quinoline **9i**, was isolated by filtration using a glass filter, and treated as before in the procedure 1, yield 1.44 g, approximately 82% (Tables 1 and 2).

1,3-Dimethyl-7,8-dichloro-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**9j**), and 1,3-Dimethyl-6,7-dichloro-5-dimethylamino[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**9k**).

Procedure 3. In the Absence of a Base.

To a suspension of **1a** (0.59 g, approximately 0.0036 mole [42,43], see Scheme 2) in dry dichloroethane (50 ml) was added the 1,3-dimethyl-6-*N*-(3',4'-dichlorophenyl)aminouracil **5j** (0.90 g, 0.003 mole). The stirring mixture, protected from atmospheric moisture, was allowed to stand at room temperature for 2 hours and heated first at 50-60° for 2 hours, then at 75-80° for 2 hours and finally at reflux until the evolution of hydrogen chloride had ceased (4-5 hours). After cooling at room temperature, the solvent was removed *in vacuo*, the residue mixed with water (50 ml) and potassium hydrogen carbonate added slowly until the evolution of carbon dioxide had ceased. The precipitate was isolated by filration using a glass filter, washed with water (2 x 30 ml), air dried, washed with ether (6 x 25 ml) and the residue left on the glass filter, which is the 7,8-dichloro-5-dimethylaminopyrimido[4,5-*b*]-quinoline **9j**, dried *in vacuo* at room temperature, yield 0.65 g, approximately 61% (Tables 1 and 2). The ether was evaporated *in vacuo* and the residue mixed with water (20 ml). The resulting precipitate, which is the 6,7-dichloro-5-dimethylaminopyrimido-[4,5-*b*]quinoline **9k**, was isolated by filtration using a glass filter, washed with water (2 x 10 ml) and dried *in vacuo*, yield 0.19 g, approximately 18% (Tables 1 and 2).

1,3-Dimethyl-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones **10a-e**.

Procedure 4. In the Absence of a Base (General Procedure).

To a suspension of **1a** (1.0 g, approximately 0.006 mole [42,43], see Scheme 2) in dry chlorobenzene (50 ml), was added the 1,3-dimethyl-6-arylaminouracil **5** (0.005 mole). The stirring mixture, protected from atmospheric moisture, was allowed to stand at room temperature for 2 hours, heated first at 50-60° for 2 hours, then at 80° for 2 hours and finally at 95-100° for 4-5 hours. After cooling, the solvent was removed *in vacuo* and 10% aqueous hydrochloric acid (40 ml) added to the residue. The precipitate of nearly pure 5-chloropyrimidoquinoline **10**, was collected by suction using a glass filter, washed with a 5% aqueous potassium hydrogen carbonate (2 x 10 ml) then with water (4 x 30 ml), and dried *in vacuo* at room temperature, yield 88-89% (Tables 3 and 4). The acidic aqueous filtrate was neutralized with potassium hydrogen carbonate and very small quantity of the corresponding 5-dimethylaminopyrimidoquinoline derivative **9** occasionally recovered either by filtration or by extraction with chloroform, yield 0-2%.

1,3-Dimethyl-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones **10f-h**.

Procedure 5. In the Absence of a Base (General Procedure).

The 1,3-dimethyl-6-*N*-(chlorophenyl)aminouracils **5f-h** (0.005 mole) were treated as before in procedure 4 except for the temperature conditions, room temperature for 2 hours and then 80° for 2 hours, 95-100° for 1 hour and finally 125-130° for 4-5 hours, yield 85-87% (Tables 3 and 4).

1,3-Dimethyl-8-methoxy-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**10d**).

Procedure 6. In the Absence of a Base.

The aminouracil **5d** (1.30 g, 0.005 mole) was treated as before in procedure 4, except for the solvent and temperature conditions, overnight at room temperature in dichloromethane, yield 1.36 g, approximately 89% (Tables 3 and 4).

1,3-Dimethyl-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-diones (**10a,d,f-h**).

Procedure 7. From 5-Dimethylaminopyrimido[4,5-*b*]quinolines **9** *via* Reaction with Hydrogen Chloride.

The 5-dimethylamino derivative **9** (0.001 mole) was added to a 2% hydrogen chloride solution in dry chlorobenzene (25 ml). The resulting mixture was stirred at room temperature for 1 hour and then heated at 60° for 2 hours and at 100° for 2 hours. After cooling, the solvent was removed *in vacuo* and 5% aqueous hydrochloric acid (10 ml) added to the residue. The resulting insoluble 5-chloropyrimido[4,5-*b*]quinoline **10** was collected by filtration using a glass filter, and treated as before in procedure 4, yield 85-86%.

1,3-Dimethyl-7,8-dichloro-5-chloropyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**10j**), and 1,3-Dimethyl-6,7-dichloro-5-dimethylaminopyrimido[4,5-*b*]quinoline-(1*H*,3*H*)-2,4-dione (**9k**) (see also Procedure 3).

Procedure 8. In the Absence of a Base.

To a suspension of **1a** (1.0 g, approximately 0.006 mole) in dry chlorobenzene (50 ml), was added the 1,3-dimethyl-6-*N*-(3',4'-dichlorophenylamino)uracil **5j** (1.50 g, 0.005 mole). The stirring mixture, protected from atmospheric moisture, was allowed to

stand at room temperature for 2 hours and heated first at 50-60° for 2 hours, then at 80° for 2 hours, at 95-100° for one hour and finally at 120-130° for 4-5 hours. After cooling, the solvent was removed *in vacuo* and 10% aqueous hydrochloric acid (40 ml) added to the residue. The precipitate, which is the 7,8-dichloro-5-chloro (5,7,8-trichloro) derivative **10j**, was collected by suction, using a glass filter, washed with a 5% aqueous potassium hydrogen carbonate (2 x 20 ml) then with water (4 x 30 ml) and dried *in vacuo* at room temperature, yield 1.13 g, 66% (Tables 3 and 4). Potassium hydrogen carbonate was added slowly to the acidic aqueous filtrate until the evolution of carbon dioxide had ceased. The precipitate of nearly pure 6,7-dichloro-5-dimethylamino derivative **9k**, was collected by suction using a glass filter, washed with water and dried *in vacuo* at room temperature, yield 0.32 g, 18% (Tables 1 and 2).

3-Methyl-10-alkyl-5-chloropyrimido[4,5-*b*]quinoline-(3*H*,10*H*)-2,4-diones (3-Methyl-10-alkyl-5-chloro-5-deazaflavins) **11a-i**.

Procedure 9. In the Absence of a Base (General Procedure).

A stirring mixture of **1a** (1.0 g, approximately 0.006 mole) and 3-methyl-6-alkylarylaminouracil (**6**) (0.005 mole) in dry chlorobenzene (50 ml) protected from atmospheric moisture, was allowed to stand at room temperature for 2 hours and then heated at 50-60° for 2 hours, at 80° for 2 hours, at 100° for 1 hour and finally at 110-120° until the evolution of hydrogen chloride had ceased (4-5 hours). The heterogeneous mixture was cooled at room temperature and the precipitate of nearly pure 5-chloro-5-deazaflavin **11**, collected by filtration using a glass filter, washed with iced 5% aqueous potassium hydrogen carbonate (2 x 10 ml) then with methanol (2 x 20 ml) and ether (2 x 20 ml), and dried *in vacuo* at room temperature. An additional small fraction of the 5-chloro-5-deazaflavin **11** was occasionally separated from the filtrate after the latter was evaporated *in vacuo* and the oily residue mixed with methanol (10 ml) and the precipitate treated as before, with the iced aqueous potassium hydrogen carbonate, methanol and ether, yield 84-86% (Tables 5 and 6).

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REFERENCES AND NOTES

[1] Researcher at the Institut National de la Santé et de la Recherche Médicale (I.N.S.E.R.M.).

[2] Z. Janousek, Dissertation, U.C.L., Louvain-La-Neuve, Belgique, 1972.

[3] Z. Janousek and H. G. Viehe, Chemistry of Dichloromethyleniminium Salts (Phosgeniminium Salts) in Imminium Salts in Organic Chemistry, Advances in Organic Chemistry, Vol **9**, Part **1**, H. Böhme and H. G. Viehe, eds, John Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1976, p 343 and references cited therein.

[4] H. G. Viehe and Z. Janousek, *Angew. Chem.*, **85**, 837 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 806 (1973).

[5] H. G. Viehe, *Chem. Ind.*, 386 (1977).

[6a] V. P. Kukhar and V. I. Pasternak, *Synthesis*, 611 (1972); [b] V. P. Kukhar and V. I. Pasternak, *Synthesis*, 563 (1974).

[7] B. Kokel, C. Lespagnol and H. G. Viehe, *Bull. Soc. Chem. Belg.*, **89**, 651, (1980).

[8] B. Kokel, R. Royer, J. P. Declercq, G. Germain and M. Van Meerssch, *Tetrahedron Letters*, 449 (1981).

[9] B. Kokel, J. Guillaumel and R. Royer, *J. Heterocyclic Chem.*, **20**, 575 (1983).

[10] B. Kokel, G. Menichi, M. Hubert-Habart and J. Mercier, The 8th International Symposium on Medicinal Chemistry, Uppsala, Sweden, August 27-31, 1984, Proceedings, Vol **2**, 1985, p 483.

[11] B. Kokel, Thèse de Doctorat ès Sciences Physiques, Paris, France, 1987, and references cited therein.

[12] B. Kokel, M. Hubert-Habart, A. Cousson and B. Bachet, The 14th European Colloquium on Heterocyclic Chemistry, Toledo, Spain, October 1-3, 1990, Proceedings, 1990, p 222.

[13] A. Cousson, J. Proust, B. Bachet, B. Kokel and M. Hubert-Habart, *Acta Cryst.*, **C 48**, 76 (1992).

[14] W. Traube, *Ber.*, **33**, 3035 (1900).

[15] F. F. Blicke and H. G. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954).

[16] J. L. Bernier, A. Lefebvre, J. P. Henichart, R. Houssin and C. Lespagnol, *Bull. Soc. Chim. France*, 616 (1976).

[17] H. Bredereck, F. Effenberger and G. Simchen, *Chem. Ber.*, **97**, 1403 (1964).

[18] F. Yoneda and B. Kokel, Synthesis and Properties of 5-Deazaflavins in Chemistry and Biochemistry of Flavoenzimes, Vol **1**, F. Müller, ed, C.R.C. Press, Boca Raton, Ann Arbor, Boston, 1991, Chapter 4, p 121, and references cited therein.

[19] M. Conrad and H. Reinbach, *Ber.*, **34**, 1339 (1901).

[20] R. D. Eirich, G. D. Vogels and R. S. Wolfe, *Biochemistry*, **17**, 4583 (1978).

[21a] W. T. Ashton, R. D. Brown, F. Jacobson and C. Walsh, *J. Am. Chem. Soc.*, **101**, 4419 (1979); [b] C. Walsh, *Acc. Chem. Res.*, **19**, 216 (1986).

[22] A. P. M. Eker, A. Pol, P. van der Meyden and G. D. Vogels, FEMS, *Microbiol. Letters*, **8**, 161 (1980).

[23] J. R. D. Mc Cormick and G. O. Morton, *J. Am. Chem. Soc.*, **104**, 4014 (1982).

[24] F. Yoneda and K. Tanaka, The Biofunctional Chemistry of 5-Deazaflavins and Related Compounds in Medicinal Research Reviews, Vol **7**, John Wiley and Sons, Inc, 1987, p 477, and references cited therein.

[25a] D. E. O'Brien, L. T. Weinstock and C. C. Cheng, *Chem. Ind.*, 2044 (1967); [b] D. E. O'Brien, L. T. Weinstock and C. C. Cheng, *J. Heterocyclic Chem.*, **7**, 99 (1970).

[26a] Y. Tominaga, H. Okuda, M. Tochiki, Y. Matsuda and G. Kobayashi, *Heterocycles*, **15**, 679 (1981); [b] Y. Tominaga, H. Okuda, S. Kohra and H. Mazume, *J. Heterocyclic Chem.*, **28**, 1245 (1991).

[27a] R. W. Grauert, *Arch. Pharm.*, **316**, 476 (1983); [b] R. W. Grauert, *Arch. Pharm.*, **317**, 42 (1984).

[28a] F. Yoneda, T. Asano, K. Tsukuda and A. Koshiro, *Heterocycles*, **12**, 691 (1979); [b] F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980); [c] F. Yoneda and Y. Sakuma, *Tetrahedron Letters*, **22**, 3977 (1981).

[29] J. Lehmann and H. Wamhoff, *Chem. Ber.*, **106**, 3533 (1973).

[30] E. C. Taylor, Jr. and N. W. Kalenda, *J. Am. Chem. Soc.*, **78**, 5108 (1956).

[31] L. Capuano and V. Diehl, *Chem. Ber.*, **109**, 723 (1976).

[32] A. Lacroix and J. P. Fleury, *Tetrahedron Letters*, **19**, 3469 (1978).

[33] A. Lespagnol, C. Lespagnol and D. Lesieur, Précis de Pharmacie usuelle, Technique et Documentation, 1977, p 50.

[34a] T. Kimachi, F. Yoneda and T. Sasaki, *J. Heterocyclic Chem.*, **29**, 763 (1992); [b] B. Kokel, to be published.

[35] H. Biltz and H. Wittel, *Ber.*, **54**, 1035 (1921).

[36] W. Pfleiderer and K. H. Schündehütte, *Liebigs Ann. Chem.*, **612**, 158 (1958).

[37] G. Nübel and W. Pfleiderer, *Chem. Ber.*, **95**, 1605 (1962).

[38a] H. Goldner, G. Dietz and E. Carsten, *Liebigs Ann. Chem.*, **691**, 142 (1966); [b] H. Goldner, G. Dietz and E. Carsten, *Liebigs Ann. Chem.*, **694**, 142 (1966).

[39] Y. Sakuma, S. Matsumoto, T. Nagamatus and F. Yoneda, *Chem. Pharm. Bull.*, **24**, 338 (1976).

[40] F. Yoneda, Y. Sakuma, M. Ichiba and K. Shinomura, *J. Am. Chem. Soc.*, **98**, 830 (1976).

[41] C. F. Huebner, E. M. Donoghue, A. F. Plumer and P. A. Furness, *J. Med. Chem.*, **9**, 830 (1966).

[42] The 1,3-dimethyl-6-aminouracils **5a,c,f,h** and **i** crystallize with one molecule of water (n = 1) which has to be taken into consideration when calculating the quantity of phosgeniminium chloride (**1a**) to be used for the formation of corresponding amide chlorides **7** (see [43] and Scheme 2).

[43] Quantity of phosgeniminium chloride (**1a**) suitable only for non hydrated arylaminouracils (n = 0). When n = 1, another equivalent of **1a** (1.0 g approximately 0.006 mole) is required (see [42] and Scheme 2).

[44] This corresponds to 5 equivalents based on the quantity of Phosgeniminium chloride (**1a**) introduced in the reaction mixture for n = 0 (see [42,43] and Scheme 2).