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PURINS, PYRIMIDINES, AND RELATED CONDENSED SYSTEMS. 22.* SYNTHESIS AND HETEROCYCLIZATION OF 7-ALKYNYL- AND 6,7-DIALKYNYLLUMAZINES

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The reaction of 6,7-dichloro-1,3-dimethyllumazine with terminal alkynes under Sonogashira conditions gave 7-alkynyl-6-chloro- and 6,7-dialkynyl-1,3-dimethyllumazines. It was found that the alkynyllumazines readily add primary and secondary alkylamines at the 7-alkynyl group to form stable enamines, hydrolysis of which gives 7-(β-hydroxyvinyl)lumazines. The heterocyclization of 7-(β-aminovinyl)- and 7-(β-hydroxyvinyl)lumazines has been carried out to give pyrrolo-, pyrido-, furo-, and pyranopteridines.

Keywords: 1-alkynes, 7-alkynyl-6-chloro-1,3-dimethyllumazines, 6,7-dialkynyl-1,3-dimethyllumazines, 6,7-dichloro-1,3-dimethyllumazine, enamines, pyrano[2,3-*g*]pteridine-2,4(1H,3H)-diones, pyrano-[3,4-*g*]pteridine-2,4(1H,3H)-diones, pyrido[3,4-*g*]pteridine-2,4(1H,3H)-diones, pyrrolo[2,3-*g*]pteridine-6,8(5H,7H)-diones, furo[2,3-*g*]pteridine-6,8(5H,7H)-diones, Sonogashira cross conjugation, metallocomplex catalysis.

Recent years have been marked by a real revival in the chemistry of acetylenes. Efficient methods have been devised for their synthesis based on transition metal catalyzed reactions of cross conjugated organohalides and triflates with 1-alkynes [2], alkynylboronic acids [3], and alkynylstannanes [4]. With the growing availability of the acetylenes they are used successfully in the synthesis of various carbo- and heterocyclic compounds [5-8]. Because of the discovery of the enediyne antibiotics, great attention has been attached to the so-called Bergman cyclization of (*Z*)-3-en-1,5-diones as well as to the synthesis of compounds containing this fragment [9, 10].

We have recently described the synthesis of 6-alkynyl-1,3-dimethyllumazines and their heterocyclization to pyrrolo[3,2-*g*]- and thieno[3,2-*g*]pteridine-5,7(6H,8H)-diones [11]. In extending this work we have set ourselves the task of carrying out the synthesis and studying the cyclization reaction (including the Bergman) for the 7-alkynyl- and 6,7-dialkynyl-1,3-dimethyllumazines. In this article we report the results of our study of the synthesis and heterocyclization of alkynyllumazines. The results for the Bergman cyclization will be presented in a separate communication.

* For Communication 21 see [1].

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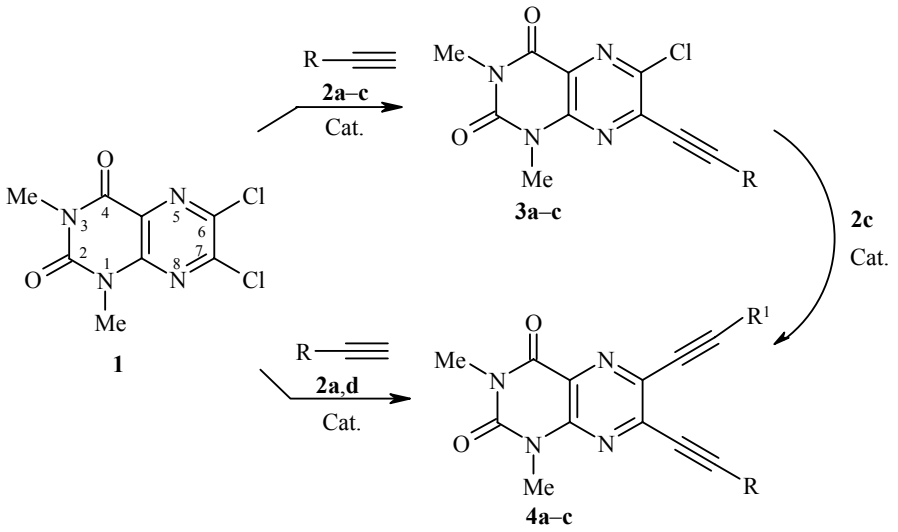
6,7-Dichloro-1,3-dimethyllumazine (**1**) [12] was selected as the starting material since the different mobility of the chlorine atoms can result in both mono-, and disubstitution [13]. We have found that the reaction of compound **1** with an equimolar amount of the alkyne **2a-c** under Sonogashira [2] conditions at 20-30°C gives the 7-alkynyl derivatives **3a-c** in 20-64% yields. The reaction of the dichlorolumazine **1** with a twofold excess of the acetylenes **2a,b** at a higher temperature (90-100°C) gives a 23-33% yield of the 6,7-dialkynyllumazines **4a,b**. Combination of the 6-chloro-7-phenylethynyllumazine **3a** with 1-piperidinocyclohexylacetylene **2c** at 90-100°C gives a 36% yield of compound **4c**.



Cat. = Pd_2dba_3, PPh_3, CuI, K_2CO_3, DMF, Ar;
2, **3 a** R = Ph, **b** R = 1-hydroxycyclohex-1-yl, **c** R = 1-piperidinocyclohex-1-yl;
2 d R = $SiMe_3$; **4 a** R = R^1 = Ph; **b** R = R^1 = $SiMe_3$; **c** R = Ph, R^1 = 1-piperidinocyclohex-1-yl

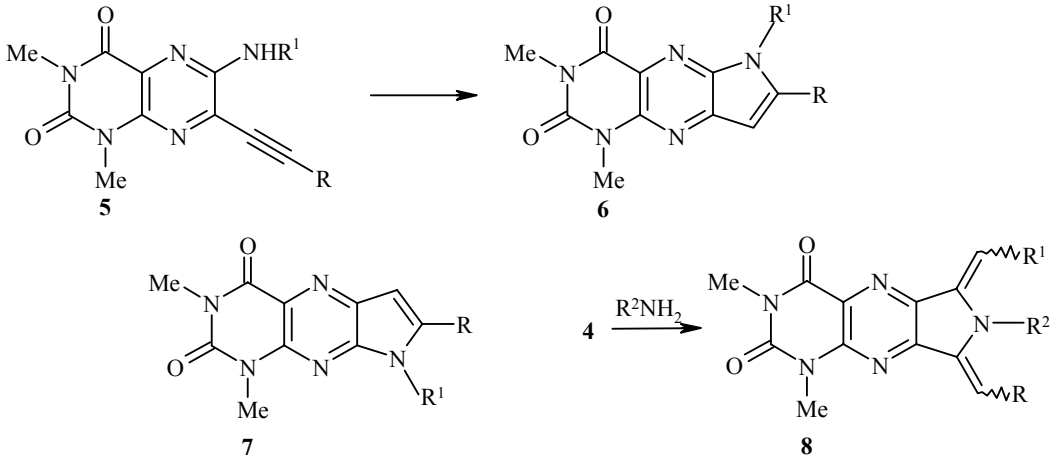
The structures of compounds **3** and **4** were confirmed by spectroscopic data and by elemental analysis (see Tables 1-3). The IR spectra of the monoacetylenes **3** show a $\nu_{C\equiv C}$ band of medium intensity at 2207-2223 cm^{-1}. The IR spectra of the dialkynyllumazines **4** show two signals for the triple bonds of moderate intensity; in the case of the trimethylsilyl derivative **4b** this signal is absent.

In spite of the lower yields, the method proposed by us for the preparation of the 6,7-dialkynyl-1,3-dimethyllumazines **4** has the advantage over the recently reported method based on the cyclization of 5,6-diamino-1,3-dimethyluracil with diethynyl-1,2-diketones [14] in that it allows the subsequent introduction of different alkyl groups in the molecule **1**.

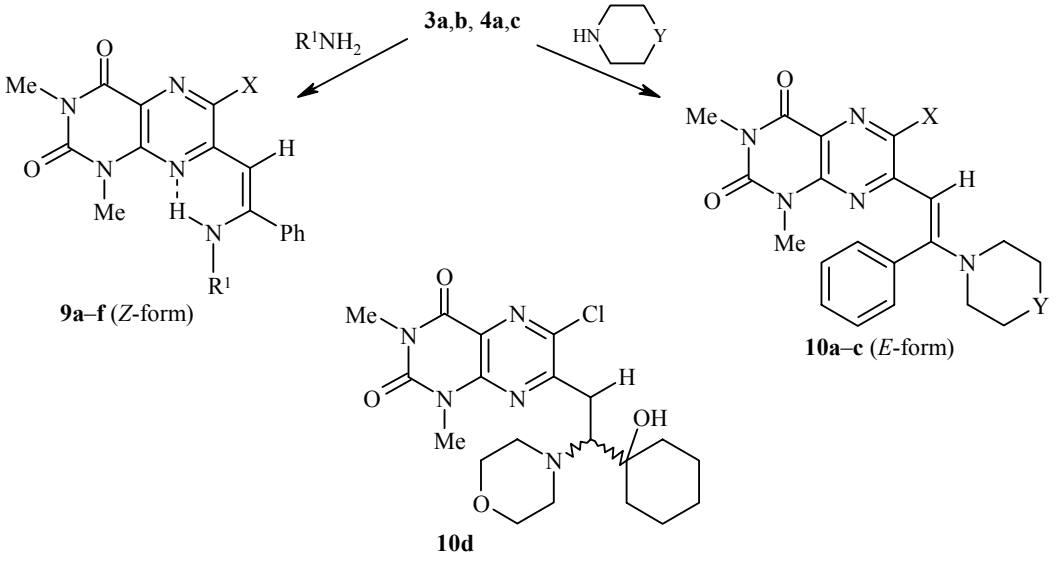
Based on the data in [15] we had expected that the substitution of the chlorine atom by an amino group in the monoacetylenes **3** and the subsequent heterocyclization of amine **5** would give the pyrrolo[3,2-*g*]-pteridine-6,8(5H,7H)-dione **6**, isomeric with the previously prepared pyrroles **7** [11]. It was also expected that the reaction of the 6,7-dialkynyllumazines **4** with amines would yield the [*c*]-condensed pyrroles **8** (cf. [16]) (Scheme 1).

However, it was found that both at 20°C and also upon refluxing the 6-chloro-7-phenylethynyllumazine **3a** in propylamine gave the enamine **9a** in 93% yield (Tables 1,3) instead of the expected amino derivative **5** (R = Ph, R^1 = Pr). The ^{1}H NMR spectrum of compound **9a** shows a one proton singlet for the vinyl proton at 5.73 ppm and a poorly resolved triplet for the NH proton at 10.13 ppm. The position of the latter signal points to the presence in the molecule of **9a** of an intramolecular hydrogen bond between the $N_{(8)}$ atom of the lumazine ring and the NH proton of the alkylamino group. The formation of enamine **9a** is evidently favored by the fact that the alkynyl group in compound **3a** is conjugated to the $C_{(4)}$=O carbonyl and thus is activated towards nucleophilic attack whereas the chlorine atom is passive due to the donor effect of the $N_{(1)}$ heteroatom.

Scheme 1



The 6,7-dialkynyllumazines **4a,c** react similarly with amines even at -10 to 25°C to give the enamines **9b-f** (Tables 1-4). Although the $\nu_{C\equiv C}$ bands are extremely weak or absent altogether in the IR spectra of the latter, comparison of the ^{13}C NMR spectra of the diacetylene **4a** and the addition product **9d** do not cast doubt on the correctness of structure **9** (Table 2). Hence the spectrum of 6,7-di(phenylethynyl)lumazine **4a** shows four *sp*-hybridized carbon atom signals for the two acetylene bonds, two singlets at 85.4 and 86.3 ppm, and two triplets at 96.0 ($^3J_{C,H}$ = 5.8 Hz) and 99.9 ppm ($^3J_{C,H}$ = 4.9 Hz) which are assigned to the carbon atoms directly bound to the phenyl ring and interacting with its *ortho*-protons. The spectrum of the enamine **9d** shows a singlet at 86.0 ppm and triplet at 94.5 ppm ($^3J_{C,H}$ = 5.3 Hz) from the acetylenic carbons of the 6-alkynyl group, a doublet for the methine carbon atom at 93.2 ppm ($^1J_{C,H}$ = 163.7 Hz), and a doublet at 132.4 ppm ($^2J_{C,H}$ = 3.6 Hz) from other carbon atom of the vinyl group. The appearance of the signal for the bridging $C_{(4a)}$ atom as a doublet with $^3J_{C,H}$ = 3 Hz is very significant in interpreting the structure of **9d** since it points to an interaction of the $C_{(4a)}$ nucleus with the NH proton of the alkylamino group *via* the hydrogen bond.



9 a X = Cl, R^1 = Pr; **b** X = phenylethynyl, R^1 = Et; **c** X = phenylethynyl, R^1 = Pr; **d** X = phenylethynyl, R^1 = Bu; **e** X = 1-piperidinocyclohexyl-1-ethynyl, R^1 = Et; **f** X = 1-piperidinocyclohexyl-1-ethynyl, R^1 = Bu; **10 a** X = Cl, Y = CH_2; **b** X = Cl, Y = O; **c** X = phenylethynyl, Y = O

TABLE 1. Spectroscopic Characteristics of the Compounds Synthesized

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)
		C=O	C≡C	
1	2	3	4	5
3a	3.52 (3H, s, CH_3-3); 3.71 (3H, s, CH_3-1); 7.46 (3H, m, H_{Ph}); 7.69 (2H, m, H_{Ph})	1663, 1727	2207	
3b*	1.5-1.8 (6H, m, 3CH_2 cyclohexyl); 2.10 (5H, m, 2CH_2 cyclohexyl + OH); 3.51 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1)	1660, 1723	2223	
3c	1.55 (12H, m, 3CH_2 cyclohexyl + β- and γ-CH_2 piperidino); 2.15 (4H, m, 2CH_2 cyclohexyl); 2.71 (4H, m, α-CH_2 piperidino); 3.51 (3H, s, CH_3-3); 3.68 (3H, s, CH_3-1)	1600, 1714	2207	
4a	3.53 (3H, s, CH_3-3); 3.73 (3H, s, CH_3-1); 7.46 (6H, m, H_{Ph}); 7.69 (4H, m, H_{Ph})	1663, 1714	2200, 2213	264 (4.42), 316 (4.45), 405 (4.28)
4b	0.27 (9H, s, $Si(CH_3)_3$); 0.32 (9H, s, $Si(CH_3)_3$); 3.50 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1)	1675, 1724	—	288 (4.31), 305 (4.32), 380 (4.12)
4c	1.34 (2H, m, cyclohexyl); 1.57 (12H, m, 3CH_2 cyclohexyl + β- and γ-CH_2 piperidino); 2.13 (2H, m, cyclohexyl); 2.66 (4H, m, α-CH_2 piperidino); 3.53 (3H, s, CH_3-3); 3.71 (3H, s, CH_3-1)	1663, 1720	2207, 2233	299 (4.30), 385 (4.31)
9a*[2]	0.93 (3H, t, *J* = 7.1, $CH_2CH_2\underline{CH_3}$); 1.60 (2H, m, $CH_2\underline{CH_2}CH_3$); 3.26 (2H, m, $\underline{CH_2}CH_2CH_3$); 3.49 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1); 5.73 (1H, s, =CH); 7.47 (5H, m, C_6H_5); 10.13 (1H, m, NH)	1667, 1713	—	340 (3.89), 445 (4.36), 460 (4.44)
9b*[2]	1.26 (3H, t, *J* = 7.3, $CH_2\underline{CH_3}$); 3.33 (2H, m, $\underline{CH_2}CH_3$); 3.51 (3H, s, CH_3-3); 3.69 (3H, s, 1-CH_3); 5.94 (1H, s, =CH); 7.31 (3H, m, H_{Ph}); 7.49 (7H, m, H_{Ph}); 10.01 (1H, m, NH)	1675, 1710	—	293 (4.48), 383 (4.30), 455 (4.51), 468 (4.52)
9c*[2]	0.92 (3H, t, *J* = 7.3, $CH_2CH_2\underline{CH_3}$); 1.65 (2H, m, $CH_2\underline{CH_2}CH_3$); 3.27 (2H, m, $\underline{CH_2}CH_2CH_3$); 3.51 (3H, s, CH_3-3); 3.69 (3H, s, CH_3-1); 5.95 (1H, s, =CH); 7.31 (3H, m, H_{Ph}); 7.47 (m, 7H, H_{Ph}); 10.02 (1H, m, NH)	1660, 1707	2205 (weak)	294 (4.44), 383 (4.25), 452 (4.15), 460 (4.45)
9d*[2]	0.87 (3H, t, *J* = 7.1, $CH_2CH_2CH_2\underline{CH_3}$); 1.34 (2H, m, $CH_2CH_2\underline{CH_2}CH_3$); 1.54 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$); 3.30 (2H, m, $\underline{CH_2}CH_2CH_2CH_3$); 3.52 (3H, s, CH_3-3); 3.69 (3H, s, CH_3-1); 5.95 (1H, s, =CH); 7.32 (3H, m, H_{Ph}); 7.45 (m, 7H, H_{Ph}); 10.01 (1H, m, NH)	1663, 1700	—	293 (4.45), 384 (4.28), 455 (4.35), 470 (4.38)
9e*[2]	1.26 (3H, t, *J* = 7.3, $CH_2\underline{CH_3}$); 1.40-1.85 (14H, m, cyclohexyl + β- and γ-CH_2 piperidino); 2.05 (2H, m, cyclohexyl); 2.57 (4H, m, α-CH_2 piperidino); 3.50 (3H, s, CH_3-3); 3.68 (3H, s, CH_3-1); 5.98 (1H, s, =CH); 7.43 (5H, s, C_6H_5); 9.94 (1H, m, NH)	1665, 1713	2213 (weak)	260 (4.39), 365 (4.13), 446 (4.47), 465 (4.50)
9f*[2]	0.85 (3H, t, *J* = 7.1, $CH_2CH_2CH_2\underline{CH_3}$); 1.20-1.75 (18H, m, $CH_2\underline{CH_2}CH_2CH_3$ + cyclohexyl + β- and γ-CH_2 piperidino); 2.03 (2H, m, cyclohexyl); 2.56 (4H, m, α-CH_2 piperidino); 3.30 (2H, m, $\underline{CH_2}CH_2CH_2CH_3$); 3.50 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1); 6.00 (1H, s, =CH); 7.43 (5H, s, C_6H_5); 9.92 (1H, m, NH)	1660, 1700	2195 (weak)	374 (4.18), 463 (4.42)
10a	1.68 (6H, m, β- and γ-CH_2 piperidino); 2.56 (3H, s, CH_3-1); 3.31 (4H, m, α-CH_2 piperidino); 3.36 (3H, s, CH_3-3); 5.99 (1H, s, =CH); 7.25 (2H, m, H_{Ph}); 7.40 (3H, m, H_{Ph})	1660, 1710	—	337 (3.85), 458 (4.43)

TABLE 1 (continued)

1	2	3	4	5
10b	2.59 (3H, s, CH_3-1); 3.28 (4H, m, $N(CH_2)_2$ morpholino); 3.38 (3H, s, CH_3-3); 3.76 (4H, m, $O(CH_2)_2$ morpholino); 6.00 (1H, s, =CH); 7.26 (2H, m, H_{Ph}); 7.41 (3H, m, H_{Ph})	1666, 1700	—	443 (4.46)
10c	2.62 (3H, s, CH_3-1); 3.28 (4H, m, $N(CH_2)_2$ morpholino); 3.40 (3H, s, CH_3-3); 3.77 (4H, m, $O(CH_2)_2$ morpholino); 6.30 (1H, s, =CH); 7.25 (2H, m, H_{Ph}); 7.40 (6H, m, H_{Ph}); 7.59 (2H, m, H_{Ph})	1665, 1715	—	294 (4.51), 369 (4.29), 445 (4.47)
10d	1.80-2.05 (3H, m, CH_2 cyclohexyl + OH); 2.87 (4H, m, $2CH_2$ cyclohexyl); 3.35 (4H, m, $N(CH_2)_2$ morpholino); 3.47 (3H, s, CH_3-3); 3.66 (3H, s, CH_3-1); 3.67 (4H, m, $2CH_2$ cyclohexyl); 3.75 (4H, m, $O(CH_2)_2$ morpholino); 5.95 (1H, s, H-9)	1663, 1695	—	351 (3.83), 464 (3.71)
11a*[3]	For **11a**: 3.52 (3H, s, CH_3-3); 3.61 (3H, s, CH_3-1); 4.77 (2H, s, CH_2); 7.40-7.70 (3H, m, H_{Ph}); 8.05 (2H, m, H_{Ph}); for **11'a**: 3.50 (3H, s, CH_3-3); 3.72 (3H, s, CH_3-1); 6.76 (1H, s, =CH); 7.40-7.70 (3H, m, H_{Ph}); 8.00 (2H, m, H_{Ph}); 14.04 (1H, s, OH)	1660, 1723	—	250 (4.30), 337 (3.93), 427 (4.25), 450 (4.21)
11b*[3]	For **11b**: 3.53 (3H, s, CH_3-3); 3.63 (3H, s, CH_3-1); 4.85 (2H, s, CH_2); 7.40-7.90 (10H, m, H_{Ph}); for **11'b**: 3.51 (3H, s, CH_3-3); 3.72 (3H, s, CH_3-1); 6.93 (1H, s, =CH); 7.40-7.90 (10H, m, H_{Ph}); 8.00 (2H, m, H_{Ph}); 13.94 (1H, s, OH)	1680, 1725	2210	257 (4.34), 287 (4.38), 356 (4.31), 435 (4.33), 448(4.31)
12a	0.71 (3H, t, J = 7.5, $CH_2CH_2\underline{CH_3}$); 1.69 (2H, m, $CH_2\underline{CH_2}CH_3$); 3.56 (3H, s, CH_3-7); 3.80 (3H, s, CH_3-5); 4.44 (2H, t, J = 7.5, $\underline{CH_2}CH_2CH_3$); 6.68 (1H, s, H-3); 7.55 (5H, m, C_6H_5)	1660, 1717	—	371 (4.41)
12b	0.73 (3H, t, J = 7.3, $CH_2CH_2CH_2\underline{CH_3}$); 1.11 (2H, m, $CH_2CH_2\underline{CH_2}CH_3$); 1.62 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$); 3.57 (3H, s, CH_3-7); 3.80 (3H, s, CH_3-5); 4.48 (2H, t, J = 7.5, $\underline{CH_2}CH_2CH_2CH_3$); 6.68 (1H, s, H-3); 7.53 (5H, m, C_6H_5)	1673, 1700	—	373 (4.41)
13	3.56 (3H, s, CH_3-7); 3.78 (3H, s, CH_3-5); 7.24 (1H, s, H-3); 7.54 (3H, m, H_{Ph}); 7.98 (2H, m, H_{Ph})	1660, 1713	—	344 (4.20), 378 (4.58), 398 (4.65)
14	1.50-2.10 (10H, m, cyclohexyl); 3.22 (4H, m, $N(CH_2)_2$ morpholino); 3.48 (3H, s, CH_3-3); 3.64 (3H, s, CH_3-1); 3.80 (4H, m, $O(CH_2)_2$ morpholino); 5.87 (1H, s, H-9)	1640, 1682	—	334 (3.78), 426 (4.43)
15a	0.53 (3H, t, J = 7.5, $CH_2CH_2\underline{CH_3}$); 1.36 (2H, m, $CH_2\underline{CH_2}CH_3$); 3.29 (2H, t, J = 7.1, $\underline{CH_2}CH_2CH_3$); 3.52 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1); 6.05 (1H, s, =CH); 7.14 (1H, s, H-9); 7.37 (2H, m, H_{Ph}); 7.45-7.65 (8H, m, H_{Ph})	1676, 1720	—	273 (4.59), 371 (4.06), 520 (3.11)
15b	0.55 (3H, t, J = 7.3, $CH_2CH_2CH_2\underline{CH_3}$); 0.92 (2H, m, $CH_2CH_2\underline{CH_2}CH_3$); 1.30 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$); 3.32 (2H, t, J = 7.1, $\underline{CH_2}CH_2CH_2CH_3$); 3.52 (3H, s, CH_3-3); 3.67 (3H, s, CH_3-1); 6.04 (1H, s, =CH); 7.15 (1H, s, H-9); 7.37 (2H, m, H_{Ph}); 7.45-7.65 (8H, m, H_{Ph})	1660, 1714	—	273 (4.59), 372 (4.05), 520 (3.08)
16	3.50 (3H, s, CH_3-3); 3.66 (3H, s, CH_3-1); 6.51 (1H, s, =CH); 7.12 (1H, s, H-9); 7.38 (3H, m, H_{Ph}); 7.52 (3H, m, H_{Ph}); 7.78 (2H, m, H_{Ph}); 7.88 (2H, m, H_{Ph})	1660, 1717	—	275 (4.52), 399 (4.08), 498 (4.08)

* ν_{OH} 3415 cm^{-1}.

*[2] $\nu_{N-H\ ac}$ 3100-3500 cm^{-1}.

*[3] $\nu_{O-H\ ac}$ 3100-3500 cm^{-1}.

TABLE 2. ^{13}C NMR Spectra of Compounds **4a, 9d**

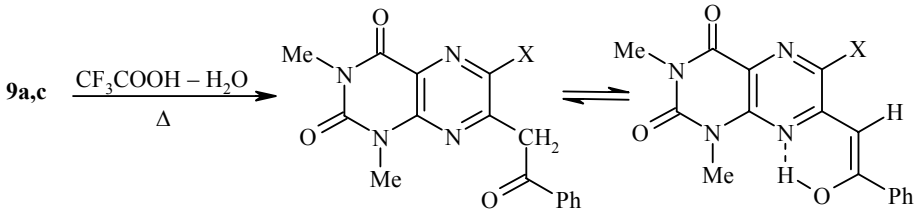
Com-pound	Chemical shift, δ, ppm. (*J*, Hz)										
	C-2	C-4	C-4a	C-6	C-7	C-8a	C≡C(6)	C≡C(7)	C=C	C_{Ph}	Other signals
4a	150.25 (m)	158.87 (q, ^3J = 2.4)	143.91	125.12	136.96	145.48 (q, ^3J = 2.6)	85.39, 96.02 (t, ^3J = 5.8)	86.33, 99.94 (t, ^3J = 4.9)	—	120.88 (t, ^2J = 8.3); 121.57 (t, ^2J = 7.9); 128.50 (dm, ^1J = 155.3); 128.64 (dm, ^1J = 163.7); 129.62 (dt, ^1J = 151.8, ^2J = 7.8); 130.47 (dt, ^1J = 162.1, ^2J = 7.8); 132.47 (dt, ^1J = 164.0, ^2J = 6.6); 132.04 (dt, ^1J = 165.7, ^2J = 6.7)	29.02 (q, ^1J = 142.7, CH_3-3); 29.50 (q, ^1J = 143.0, CH_3-1)
9d	163.86 (m)	159.31 (q, ^3J = 2.4)	156.89 (d, ^3J = 3.0)	117.80	145.50 (m)	150.89 (m)	85.98, 94.46 (t, ^3J = 5.3)	—	93.22 (d, ^1J = 163.7), 132.39 (d, ^2J = 3.6)	122.09 (t, ^2J = 7.7); 127.75 (dm, ^1J = 161.0); 128.28 (dm, ^1J = 162.1); 128.56 (dm, ^1J = 160.9); 128.96 (dt, ^1J = 161.6, ^2J = 7.3); 129.60 (dm, ^1J = 164.0); 131.80 (dm, ^1J = 163.4); 136.14 (m)	13.52 (q, ^1J = 125.2, CH_3); 19.78 (t, ^1J = 122.3, CH_2); 28.65 (q, ^1J = 142.1, CH_3-3); 29.23 (q, ^1J = 141.5, CH_3-1); 33.09 (t, ^1J = 118.0, CH_2); 45.27 (t, ^1J = 138.1, CH_2)

TABLE 3. Characteristics of the Compound Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl		
3a	$C_{16}H_{11}ClN_4O_2$	58.65 / 58.81	3.43 / 3.37	17.01 / 17.15	11.05 / 10.87	241-243	64
3b	$C_{16}H_{17}ClN_4O_3$	54.92 / 55.09	5.03 / 4.88	16.19 / 16.07	10.12 / 10.19	202-205	46
3c	$C_{21}H_{26}ClN_5O_2$	60.64 / 60.65	6.33 / 6.26	16.67 / 16.85	8.38 / 8.54	148-150	20
4a	$C_{24}H_{16}N_4O_2$	73.56 / 73.47	3.94 / 4.08	14.10 / 14.29	—	225-227	33
4b	$C_{18}H_{24}N_4O_2Si_2$	56.45 / 56.25	6.14 / 6.25	14.61 / 14.58	—*	175-177	23
4c	$C_{29}H_{31}N_5O_2$	72.34 / 72.35	6.31 / 6.44	14.49 / 14.55	—	214-216	54
9a	$C_{19}H_{20}ClN_5O_2$	58.98 / 59.14	5.40 / 5.19	18.03 / 18.16	9.39 / 9.21	181-183	93
9b	$C_{26}H_{23}N_5O_2$	71.47 / 71.40	5.13 / 5.26	16.00 / 16.02	—	230-233	54
9c	$C_{27}H_{25}N_5O_2$	71.91 / 71.84	5.42 / 5.54	15.49 / 15.52	—	197-199	93
9d	$C_{28}H_{27}N_5O_2$	72.18 / 72.26	5.88 / 5.81	15.23 / 15.05	—	195-197	84
9e	$C_{31}H_{38}N_6O_2$	70.63 / 70.72	7.36 / 7.22	15.81 / 15.97	—	185-188	54
9f	$C_{33}H_{42}N_6O_2$	71.31 / 71.48	7.75 / 7.58	15.04 / 15.16	—	165-167	80
10a	$C_{21}H_{22}ClN_5O_2$	61.41 / 61.24	5.29 / 5.35	17.13 / 17.01	8.70 / 8.63	216-218	95
10b	$C_{20}H_{20}ClN_5O_3$	58.22 / 58.04	5.01 / 4.84	17.06 / 16.93	8.71 / 8.59	276-278	99
10c	$C_{28}H_{25}N_5O_3$	70.05 / 70.14	5.29 / 5.22	14.53 / 14.61	—	215-217	99
10d	$C_{20}H_{26}ClN_5O_4$	55.23 / 55.11	6.06 / 5.97	16.26 / 16.07	7.94 / 8.15	191-193	97
11a	$C_{16}H_{13}ClN_4O_3$	55.84 / 55.73	3.65 / 3.77	16.36 / 16.25	10.31 / 10.30	118-220	98
11b	$C_{24}H_{18}N_4O_3$	70.31 / 70.24	4.34 / 4.39	13.74 / 13.66	—	225-227	90
12a	$C_{19}H_{19}N_5O_2$	65.40 / 65.33	5.62 / 5.44	19.93 / 20.06	—	192-194	60
12b	$C_{20}H_{21}N_5O_2$	66.03 / 66.12	5.91 / 5.78	19.45 / 19.28	—	186-188	73
13	$C_{16}H_{12}N_4O_3$	62.47 / 62.34	4.06 / 3.90	18.00 / 18.16	—	273-275	65
14	$C_{20}H_{25}N_5O_4$	60.09 / 60.15	6.43 / 6.27	17.70 / 17.54	—	278-280	55
15a	$C_{27}H_{25}N_5O_2$	72.01 / 71.84	5.70 / 5.54	15.39 / 15.52	—	278-280	88
15b	$C_{28}H_{27}N_5O_2$	72.33 / 72.26	5.96 / 5.81	14.87 / 15.05	—	198-200	85
16	$C_{24}H_{18}N_4O_3$	70.42 / 70.24	4.25 / 4.39	13.74 / 13.66	—	292-294	67

* Found, Si 14.38%, Calculated Si 14.58%.

The enamines **9** are extremely stable substances and do not hydrolyze, even when refluxed in 20% sulphuric acid solution. However, when heated in 50% trifluoroacetic acid, compounds **9a,c** form the ketones **11** which are in equilibrium with the enols **11'**. According to ^{1}H NMR data the ratio for **11a**:**11'a** is 1.6:1 and for **11b**:**11'b** is 1: 4.8



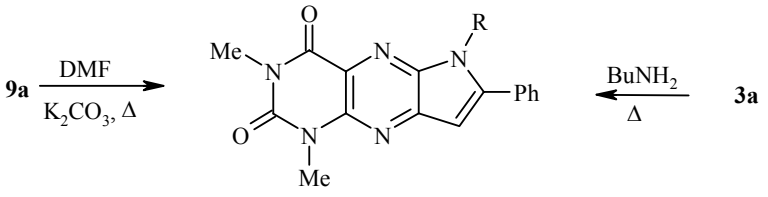
11a,**b** **11'a**,**b**

11 a X = Cl, **b** X = phenylethynyl

7-Alkynyl- (**3**) and 6,7-dialkynyllumazines **4** also form the stable enamines **10a-d** with secondary amines (piperidine and morpholine). However, in contrast to the enamines **9a-f**, the compounds **10a-c** have the *E*-configuration as shown by their ^{1}H NMR spectra (Table 1). Hence the signal for the $N_{(1)}$-methyl group protons in compound **10** (δ 2.6 ppm) lies about 1 ppm to higher field than the lumazines **3**, **4**, **9** and this can only be related to a shielding effect of the benzene ring. By comparing the enamines **9** and **10** it is apparent that their stability is achieved not so much by the intramolecular hydrogen bond as by conjugation of the amino group with the heterocycle.

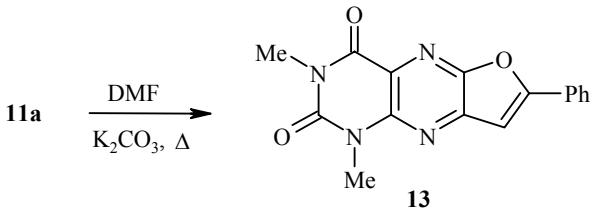
Overall, the reactivity of the 7-alkynyl-6-chloro- and 6,7-dialkynyl-1,3-dimethyllumazines relative to the amines resembles their quinoxaline analogs [17, 18]. They differ in that the chlorine atom in the 2-alkynyl-3-chloroquinoxalines is more mobile and in the dialkynylquinoxalines both C≡C bonds can add amines to give readily hydrolysing enamines.

In contrast to the reaction with propylamine (which does not form the tricyclic product **12a**) we found that prolonged refluxing of 6-chloro-7-phenylethynyllumazine **3a** in butanol gives the pyrrolopteridine **12b** in 73% yield, evidently being formed via a type **9** enamine. This is supported by the fact that enamine **9a** gives the pyrrolopteridine **12a** in 60% yield when treated with potassium carbonate in DMF. Under the same conditions, the ketone **11a** and compound **10d** cyclize to the furopteridine **13** (65%) and pyranopteridine **14** (55%) respectively. Characteristics of compounds **12-14** are given in Tables 1 and 3.



12a,**b**

12 a R = Pr, **b** R = Bu



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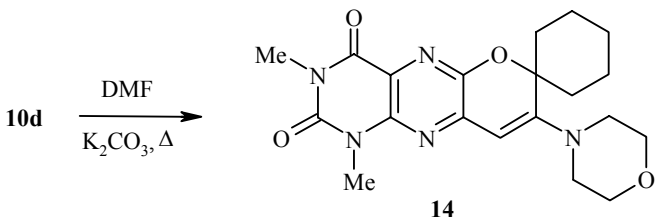

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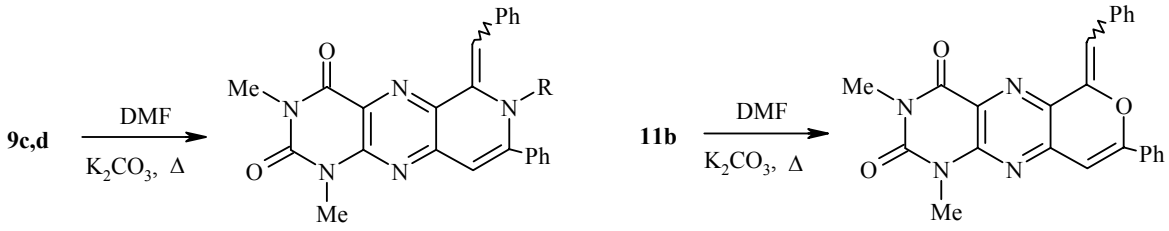
When heated with K_2CO_3 in DMF, the enamines **9c,d** give the pyridopteridines **15a,b** in high yield. Compound **11b** cyclizes to the pyran **16** (67%) under the same conditions. In contrast to the orange starting materials **9**, **11b** (λ_{max} 450-470 nm) the methylene anhydrobases **15** and **16** are deep-purple in color (λ_{max} 498-520 nm).



15a,**b**

15 a R = Pr, **b** R = Bu

16

It should finally be noted that the heterocyclizations **9→15** and **11b→16** are a novel way of synthesizing [*c*]-condensed pyrans and pyridines. In addition, the pyrans **14** and **16** prepared in this work have a hetero system isomeric with that found as the basis of the coenzyme molybdopterine **17**.

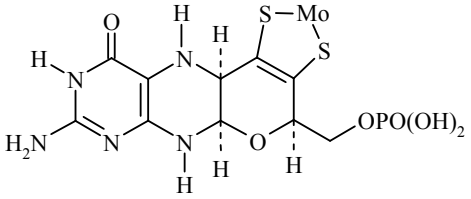


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TABLE 4. Mass Spectra of the Compounds

Com-pound	*m*/*z* (I_{real}, %)*
9c	452 $[M+1]^+$ (28), 451 $[M]^+$ (100), 450 $[M-1]^+$ (26), 437 $[M-CH_2]^+$ (10), 423 $[M-C_2H_4$ and $M-CO]^+$ (13), 410 (18), 423 $[M-C_3H_6]^+$ (16), 394 $[M-C_2H_5CH=NH$ and $[M-CH_3NCO]^+$ (10), 119 (20), 105 (15), 104 (40), 91 (20), 81 (18), 77 (20), 59 (30)
15a	452 $[M+1]^+$ (23), 451 $[M]^+$ (84), 450 $[M-1]^+$ (58), 410 (26), 409 $[M-C_3H_6]^+$ (96), 408 $[M-C_3H_7]^+$ (100), 394 $[M-C_2H_5CH=NH$ and $M-CH_3NCO]^+$ (10), 360 (17), 334 (13), 333 (55), 323 (14), 294 (11), 292 (11), 255 (12), 226 (12), 205 (24), 118 (23), 119 (24), 91 (78), 85 (32), 83 (49), 77 (26), 57 (18), 56 (14), 51 (13), 44 (35), 43 (55), 42 (22), 41 (48), 40 (20), 39 (18)
11b	410 $[M]^+$ (17), 105 (100), 77 (33), 44 (13)
16	411 $[M+1]^+$ (19), 410 $[M]^+$ (73), 409 $[M-1]^+$ (45), 395 $[M-CH_3]^+$ (16), 324 (13), 205 (31), 163 (10), 148 (11), 140 (10), 121 (11), 108 (12), 105 (49), 104 (16), 103 (15), 102 (10), 91 (55), 90 (19), 89 (18), 83 (18), 77 (100), 65 (12), 63 (13), 51 (27), 50 (12), 44 (20), 42 (16), 39 (17)

* Peaks with intensities less than 10% are omitted.

EXPERIMENTAL

IR spectra were obtained on a Specord IR-71 instrument using vaseline oil. ^{1}H NMR spectra were measured on a Bruker-250 (250 MHz) spectrometer using $CDCl_3$ at 20°C. The ^{13}C NMR spectra were taken on a Unity-300 spectrometer (75 MHz) using $CDCl_3$ and TMS as internal standard. UV Spectra were recorded on a Specord M-40 instrument using chloroform. Mass spectra (EI, 70 eV) were taken on an MX-1321A spectrometer. Chromatography was carried out on Brockmann activity grade III-IV Al_2O_3 with chloroform eluent and revealing using iodine vapour. Melting points were measured on a PTP instrument in a glass capillary and are not corrected.

Characteristics of the compounds prepared are given in Tables 1-3.

Preparation of Compounds 3a-c (General Method). A mixture of 1,3-dimethyllumazine (261 mg, 1 mmol), the corresponding alkyne **2a-c** (1.25 mmol), K_2CO_3 (103 mg, 0.75 mmol), Pd_2dba_3 (18.3 mg, 0.02 mmol), PPh_3 (41.9 mg, 0.16 mmol), and CuI (9.5 mg, 0.05 mmol) in absolute DMF (3 ml) was stirred at 25°C for 2 h in an argon atmosphere. The separation and purification were carried out differently (see below).

6-Chloro-1,3-dimethyl-7-phenylethynyllumazine (3a). The reaction mixture was cooled to 20°C and treated with water (5 ml). The precipitate was filtered off, washed on the filter with cold water and isopropanol, and recrystallized from isopropanol.

6-Chloro-7-(1-hydroxycyclohexylethynyl)-1,3-dimethyllumazine (3b). The reaction mixture was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.1 was collected. It was recrystallized from isopropanol.

6-Chloro-1,3-dimethyl-7-(1-piperidinocyclohexylethynyl)lumazine (3c). The reaction mixture was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the colorless fraction with R_f 0.5 was collected. It was recrystallized from methanol.

1,3-Dimethyl-6,7-di(phenylethynyl)lumazine (4a). A mixture of 6,7-dichloro-1,3-dimethyllumazine (261 mg, 1 mmol), phenylacetylene (0.28 ml, 2.5 mmol), K_2CO_3 (207 mg, 1.5 mmol), Pd_2dba_3 (18.3 mg, 0.02 mmol), PPh_3 (41.9 mg, 0.16 mmol), and CuI (9.5 mg, 0.05 mmol) in absolute DMF (3 ml) was stirred at 90-100°C for 1 h in an argon atmosphere. Phenylacetylene (0.14 ml, 1.25 mmol) was added and the stirring was continued for a further 1 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.5 was collected. It was recrystallized from isopropanol.

1**,3-Dimethyl-6,7-di(trimethylsilylethynyl)lumazine (4b).** A mixture of 6,7-dichloro-1,3-dimethyllumazine (261 mg, 1 mmol), trimethylsilylacetylene (0.35 ml, 2.5 mmol), Pd_2dba_3 (18.3 mg, 0.02 mmol), PPh_3 (41.9 mg, 0.16 mmol), and CuI (9.5 mg, 0.05 mmol) in Et_3N (10 ml) was heated in a sealed ampule at 100°C for 2 h under an argon atmosphere. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the light-yellow fraction with R_f 0.75 was collected. It was recrystallized from methanol.

1,3-Dimethyl-6-(piperidinocyclohexylethynyl)-7-phenylethynyllumazine (4c). A mixture of compound **3a** (326.5 mg, 1 mmol), alkyne **2c** (238.8 mg, 1.25 mmol), K_2CO_3 (103.5 mg, 0.75 mmol), Pd_2dba_3 (18.3 mg, 0.02 mmol), PPh_3 (41.9 mg, 0.16 mmol), and CuI (9.5 mg, 0.05 mmol) in absolute DMF (3 ml) was heated with stirring at 90-100°C for 2 h under an argon atmosphere. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.2 was collected. It was recrystallized from isopropanol.

6-Chloro-1,3-dimethyl-7-(2-propylamino-2-phenylvinyl)lumazine (9a). A solution of compound **3a** (163 mg, 0.5 mmol) and the amine (10 ml) was stirred at 25°C for 2 h. The amine was distilled off and the dried residue was extracted with chloroform (10 ml). The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.2-0.3 was collected. It was recrystallized from ethanol.

7-(2-Ethylamino-2-phenylvinyl)-1,3-dimethyl-6-phenylethynyllumazine (9b). A solution of compound **4a** (196 mg, 0.5 mmol) in ethylamine (50 ml) was stirred at -10°C for 2 h. The product was evaporated to dryness and the dried residue was extracted with chloroform (10 ml). The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.2-0.3 was collected. It was recrystallized from ethanol.

1,3-Dimethyl-6-phenylethynyl-7-(2-propylamino-2-phenylvinyl)lumazine (9c). A solution of compound **4a** (196 mg, 0.5 mmol) in propylamine (10 ml) was stirred at 25°C for 2 h. The amine was distilled off and the dried residue was extracted with chloroform (10 ml). The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.2-0.3 was collected. It was recrystallized from ethanol.

7-(2-Butylamino-2-phenylvinyl)-1,3-dimethyl-6-phenylethynyllumazine (9d) was prepared similarly to **9c** from compound **4a** and butylamine.

7-(2-Ethylamino-2-phenylvinyl)-1,3-dimethyl-6-(1-piperidinocyclohexyl)ethynyllumazine (9e) was prepared similarly to compound **9b** from compound **4c** and ethylamine.

7-(2-Butylamino-2-phenylvinyl)-1,3-dimethyl-6-(1-piperidinocyclohexyl)ethynyllumazine (9f) was prepared similarly to compound **9c** from compound **4c** and butylamine.

6-Chloro-1,3-dimethyl-7-(2-piperidino-2-phenylvinyl)lumazine (10a) was prepared similarly to compound **9a** from compound **3a** and piperidine.

6-Chloro-1,3-dimethyl-7-(2-morpholino-2-phenylvinyl)lumazine (10b) was prepared similarly to compound **9a** from compound **3a** and morpholine.

1,3-Dimethyl-7-(2-morpholino-2-phenylvinyl)-6-phenylethynyllumazine (10c) was prepared similarly to compound **9c** from compound **4a** and morpholine.

7-[2-(1-Hydroxycyclohexyl)-2-morpholinovinyl]-1,3-dimethyl-6-chlorolumazine (10d) was prepared similarly to compound **9a** from compound **3b** and morpholine.

6-Chloro-1,3-dimethyl-7-(2-oxo-2-phenylethyl)lumazine (11a). A solution of compound **9a** (192.8 mg, 0.5 mmol) in 50% trifluoroacetic acid (3 ml) was refluxed for 5 min and evaporated to dryness. The residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the bright-yellow fraction with R_f 0.35 was collected. It was recrystallized from ethanol.

1,3-Dimethyl-7-(2-oxo-2-phenylethyl)-6-phenylethynyllumazine (11b) was prepared similarly to compound **11a** from compound **9c**.

5,7-Dimethyl-2-phenyl-1-propylpyrrolo[2,3-*g*]pteridine-6,8(5H,7H)-dione (12a). A solution of compound **9a** (192.8 mg, 0.5 mmol) and K_2CO_3 (41.4 mg, 0.3 mmol) in DMF (10 ml) was heated at 120°C for 20 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the bright yellow fraction with R_f 0.35 was collected. It was recrystallized from ethanol.

1-Butyl-5,7-dimethyl-2-phenylpyrrolo[2,3-*g*]pteridine-6,8(5H,7H)-dione (12b). A solution of compound **3a** (163.3 mg, 0.5 mmol) and butylamine (50 ml) was refluxed for 5 days. After distilling the butylamine the dry product was extracted with chloroform (10 ml). The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the light-yellow fraction with R_f 0.35 was collected. It was recrystallized from ethanol.

5,7-Dimethyl-2-phenylfuro[2,3-*g*]pteridine-6,8(5H,7H)-dione (13). A solution of compound **11a** (174.5 mg, 0.5 mmol) and K_2CO_3 (41.4 mg, 0.3 mmol) in DMF (10 ml) was heated at 90°C for 2 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform eluent and the yellow fraction with R_f 0.4 was collected. It was recrystallized from isopropanol.

1,3-Dimethyl-8-morpholino-2,4-dioxo-1,2,3,4-tetrahydro-7-spirocyclohexane-7H-pyrano[2,3-*g*]-pteridine (14). A solution of compound **10d** (218 mg, 0.5 mmol) and K_2CO_3 (41.4 mg, 0.3 mmol) in DMF (5 ml) was heated at 100°C for 1 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform as eluent and the yellow fraction with R_f 0.15 was collected. It was recrystallized from ethanol.

6-Benzylidene-1,3-dimethyl-8-phenyl-7-propyl-6,7-dihydropyrido[3,4-*g*]pteridine-2,4(1H,3H)-dione (15a). A solution of compound **9c** (226 mg, 0.5 mmol) and K_2CO_3 (41.4 mg, 0.3 mmol) in DMF (5 ml) was refluxed for 1 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform as eluent and the purple fraction with R_f 0.6 was collected. It was recrystallized from ethanol.

6-Benzylidene-7-butyl-1,3-dimethyl-8-phenyl-6,7-dihydropyrido[3,4-*g*]pteridine-2,4(1H,3H)-dione (15b) was prepared similarly to compound **15a** from compound **9d**.

6-Benzylidene-1,3-dimethyl-8-phenyl-6H-pyrano[3,4-*g*]pteridine-2,4(1H,3H)-dione (16). A solution of compound **11b** (205 mg, 0.5 mmol) and K_2CO_3 (41.4 mg, 0.3 mmol) in DMF (5 ml) was refluxed for 1 h. The product was evaporated to dryness and the residue was extracted with chloroform. The extract was concentrated to about 5 ml and chromatographed on an Al_2O_3 column using chloroform as eluent and the dark red fraction with R_f 0.4 was collected. It was recrystallized from ethanol.

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