A CONVENIENT SYNTHESIS OF 3-(ARYL)SUBSTITUTED 2,4(1*H*,3*H*)-PTERIDINEDIONES AND THEIR ABSORPTION AND FLUORESCENCE SPECTROSCOPIC CHARACTERISTICS+

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Abstract --- 3-(Aryl)substituted 2,4(1*H*,3*H*)-pteridinediones are synthesized in high yields by addition and simultaneous cyclization of methyl 3-amino-2-pyrazinecarboxylate with isocyanates. The remarkable difference in the reactivity is observed among heterocumulenes. The absorption and fluorescence spectroscopic characteristics of the titled compounds are also discussed.

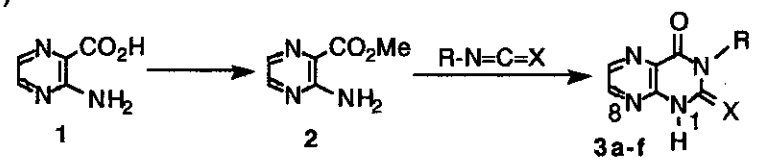
Substituted pyrazines widely occur in nature and include quite attractive heterocyclic nuclei for the design of pharmaceuticals and pesticides.[1,2] 2,4(1*H*,3*H*)-Pteridinediones and their derivatives have been prepared in various paths; reaction of 3-aminopyrazinamide with phenyl isocyanate,[3] that of 3-methylaminopyrazine-2-carbonitrile with methyl isocyanate followed by hydrolysis of the resulting 1,3-dimethyl-4-iminopteridin-2-one,[4] and treatment of methyl 3-isothiocyanato-2-pyrazinecarboxylate with a variety of amines.[5] To the best of our knowledge, their synthesis by combination of alkyl 3-amino-2-pyrazinecarboxylate and isocyanates has not been reported. As a part of our studies on pteridines, we now describe a convenient synthesis of 3-(aryl)substituted 2,4(1*H*,3*H*)-pteridinediones.

Synthesis of 3-(Aryl)substituted 2,4(1*H*,3*H*)-Pteridinediones.

The starting material, methyl 3-amino-2-pyrazinecarboxylate (**2**), was attempted to prepare according to the reported methods,[6-8] but could not be obtained in satisfactory yields. A modified

+ Dedicated to Professor Edward C. Taylor, Princeton University, on the occasion of his 70th birthday.

procedure was then applied to give the compound (**2**) in 57% yield with an appreciable repeatability. (Scheme 1)



Scheme 1

A mixture of methyl 3-amino-2-pyrazinecarboxylate (**2**) and phenyl isocyanate was refluxed for 2 h to afford 3-phenyl-2,4(1*H*,3*H*)-pteridinedione (**3a**) in 81% yield. Ir spectrum of the product (**3a**) shows absorption bands at 3450, 1740 and 1640 cm^{-1}, attributed to NH and two amide C=O stretching vibrations, respectively. ^1H Nmr spectrum exhibits a new phenyl proton signal in addition to typical vicinal protons of the parent pyrazine ring. Similarly the reaction with other isocyanates and an isothiocyanate was carried out, and the results are summarized in Table 1.

Table 1 3-(Aryl)substituted 2,4(1*H*,3*H*)-pteridinediones (**3a-f**)

Product	R	X	Reaction conditions	Yield(%)
3a	C_6H_5	O	pyridine, reflux, 2 h	81
3b	3-ClC_6H_4	O	pyridine, reflux, 6 h	94
3c	3-MeC6H4	O	pyridine, reflux, 5 h	71
3d	4-$MeOC_6H_4$	O	pyridine, reflux, 3 h	84
3e	$C_6H_5CH_2$	O	pyridine, reflux, 6 h	0
			benzene, reflux, 3 h	13
3f	C_6H_5	S	pyridine, reflux, 6 h	0
			4-picoline, reflux, 72 h	14

In case of aryl isocyanates, the desired 3-aryl-2,4(1*H*,3*H*)-pteridinediones (**3a-d**) were obtained in high yields. In contrast, the reaction with benzyl isocyanate or phenyl isothiocyanate under the same conditions recovered the starting material (**2**) almost unreacted. Both compounds (**3e**) and (**3f**) were obtained in low yields by using benzene or 4-picoline instead of pyridine as a solvent. (Table 1) Thus, it is worthy to note that the reactivity of the compound (**2**) toward heterocumulenes depends, to a large extent, on the sort of used heterocumulenes and solvents, though the reason remains uncertain.

Absorption and Fluorescence Spectra of 3-Substituted 2,4(1*H*,3*H*)-Pteridinediones.

The absorption and fluorescence spectra of 1-methyl- and 3-methyl-2,4(1*H*,3*H*)-pteridinediones and their related compounds have been reported in detail by Lippert[9] and Klein.[10] These spectra of 3-

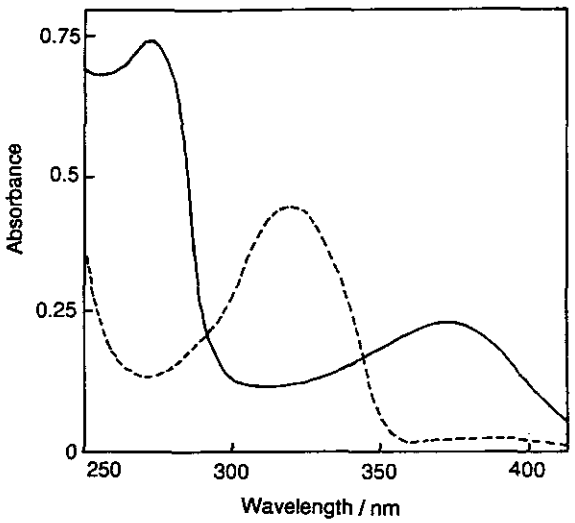


Figure 1. Absorption spectra of 3-phenyl-2,4(1*H*,3*H*)-pteridinedione (**3a**): in EtOH (——), [**3a**]=7.3x10^{-5} M; in MeCN (-----), [**3a**]=1.1x10^{-4} M.

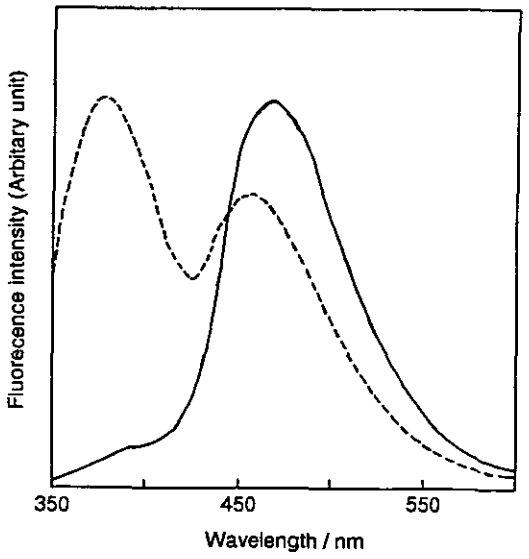
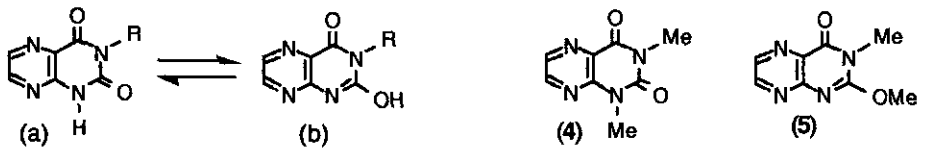


Figure 2. Fluorecence spectra of 3-phenyl-2,4(1*H*,3*H*)-pteridinedione (**3a**): in EtOH (——), in MeCN (- - - -); excitation wavelength=320 nm.

phenyl-2,4(1*H*,3*H*)-pteridinedione (**3a**) in MeCN and in EtOH are shown in Figures 1 and 2, as a representative example. Compound (**3a**) showed two absorption bands at 320 and 390 nm in MeCN, the latter having a small molar absorption coefficient, and at 273 and 371 nm in EtOH. The similar spectra were obtained in case of other pteridinediones and the results are summarized in Table 2. It is well known that 3-substituted 2,4(1*H*,3*H*)-pteridinedione exists in tautomeric equilibrium between lactam (a) and lactim (b) as shown below. Then, the data of 3-substituted 2,4(1*H*,3*H*)-pteridine-



diones were compaired with those of model compounds for these two tautomers,[9] 1,3-dimethyl-2,4(1*H*,3*H*)-pteridinedione (**4**) and 2-methoxy-3-methyl-4(3*H*)-pteridinone (**5**). The absorption bands around 320 nm in MeCN and 270 nm in EtOH were observed on the spectra of model compounds (**4**) and (**5**), respectively, suggesting that 3-(aryl)substituted 2,4(1*H*,3*H*)-pteridinediones predominantly exist in the lactam form (a) in MeCN and in the lactim form (b) in EtOH. The absorption bands around 380 nm in both solvents, which were not previously observed under neutral conditions, may be attributable to the charge transfer from the benzene to pyrazine ring. In the fluorecence spectra, pteridinediones (**3a-e**) showed two emission bands at around 380 and 450 nm in MeCN, while they showed one

Table 2 Electronic Spectra of 3-Substituted 2,4(1*H*,3*H*)-Pteridinediones

	Uv/λ_{max} nm (ε)		Fluorescence/λ_{max} nm	
Compound	in MeCN	in EtOH	in MeCN	in EtOH
3a	320 (3900)	273 (10300)	376	467
	389 (260)	371 (3300)	450	
3b	319 (8000)	276 (11000)	376	468
	380 (150)	373 (4200)	440	
3c	319 (7500)	273 (17000)	375	466
	390 (370)	374 (5900)	460	
3d	317 (7900)	274 (19500)	377	469
	382 (360)	374 (6000)	471	
3e	321 (7400)	274 (12700)	375	465
	380 (370)	374 (5700)	443	

emission band at around 470 nm in EtOH when the excitation wavelength of 320 nm was applied. The emission bands around 460 nm are due to the N(8)-H phototautomer resulting from the N(1) to N(8) proton transfer in the excited state as proposed earlier by Klein.[10] In addition, the relative intensity of fluorescence in MeCN was found to be about one-tenth of that in EtOH.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus in open capillaries and are uncorrected. Ir spectra were recorded on a JASCO A-100 infrared spectrophotometer. Absorption and fluorescence spectra were recorded on a JASCO Ubest-50 and HITACHI F-4010 spectrophotometers, respectively. ^{1}H Nmr spectra were recorded on a JEOL GX-270 NMR spectrometer in either $CDCl_3$ or DMSO-d_6 and are reported in ppm (δ) downfield from internal TMS. Microanalyses were obtained using a YANACO MT-3 CHN corder.

Methyl 3-Amino-2-pyrazinecarboxylate (2): A mixture of 3-amino-2-pyrazinecarboxylic acid (**1**) (9.68 g, 69 mmol) and conc. H_2SO_4 (14 ml) in absolute MeOH (50 ml) was stirred for 2 h at 65 °C (bath temperature). After evaporation of the solvent, saturated Na_2CO_3 solution was added to the residue, and the pH was adjusted to 8-9. The solvent was evaporated to dryness, and the residual solid was subjected to continuous extraction with ether (200 ml) for 2 days. The resulting solid obtained by evaporation of ether was recrystallized from EtOH to give the product (**2**): yield 6 g (57%); mp 169-170 °C (lit.,[6] mp 170 °C). Ir (KBr) υ_{max}: 3420 and 1700 cm^{-1}; ^{1}H Nmr (DMSO-d_6) δ: 3.78 (3H, s), 7.22 (2H, br s), 7.85 (1H, d, J=2 Hz), and 8.21 ppm (1H, d, J=2Hz). Anal. Calcd for $C_6H_7N_3O_2$: C, 47.27; H, 4.59; N, 27.41. Found: C, 47.06; H, 4.58; N, 27.45. Commercially available methyl 3-amino-2-pyrazine-carboxylate (Aldrich: 27615-4) was purified by the continous extraction with ether before use.

General Procedure for 3-Substituted 2,4(1*H*,3*H*)-Pteridinediones (3a-f). A mixture of compound (**2**) (2 mmol) and isocyanate (2 mmol) in the solvent (20 ml) was refluxed for 2-72 h. The precipitated product (**3**) was filtered and then recrystallized from an appropriate solvent.

3-Phenyl-2,4(1*H*,3*H*)-pteridinedione (3a): mp 359-360 °C (from MeOH); ir (KBr) υ_{max}: 3450, 1740, and 1640 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 7.42 (5H, s), 8.53 (1H, d, J=2 Hz), and 8.75 ppm (1H, d, J=2 Hz). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 59.55; H, 3.33; N, 23.15. Found: C, 59.51; H, 3.51; N, 22.85.

3-(*m*-Chloro)phenyl-2,4(1*H*,3*H*)-pteridinedione (3b): mp 278-279 °C (from EtOH-hexane); ir (KBr) υ_{max}: 3450, 1720, and 1680 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 7.25 (1H, dt, J=2 and 6.5 Hz), 7.35 (1H, dd, J=1 and 2 Hz), 7.47 (2H, m), 8.57 (1H, d, J=2 Hz), and 8.67 ppm (1H, d, J=2 Hz). Anal. Calcd for

$C_{12}H_7N_4O_2Cl$: C, 52.47; H, 2.57; N, 20.39. Found: C, 52.48; H, 2.81; N, 19.89.

3-*m*-Tolyl-2,4(1*H*,3*H*)-pteridinedione (3c): mp 275-276 °C (from AcOEt-hexane); ir (KBr) υ_{max}: 3450, 1720, and 1680 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.40 (3H, s), 7.12 (2H, m), 7.32 (1H, m), 7.43 (1H, m), 8.63 (1H, d, J=2 Hz), and 8.68 ppm (1H, d, J=2 Hz). Anal. Calcd for $C_{13}H_{10}N_4O_2 \cdot 0.1H_2O$: C, 60.98; H, 4.02; N, 21.88. Found: C, 61.17; H, 4.30; N, 21.59.

3-*p*-Anisyl-2,4(1*H*,3*H*)-pteridinedione (3d): mp 312-313 °C (from EtOH-hexane); ir (KBr) υ_{max}: 3450, 1720, and 1680 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 3.85 (3H, s), 7.05 (2H, d, J=9 Hz), 7.20 (2H, d, J=9 Hz), 8.57 (1H, d, J=2 Hz), and 8.67 (1H, d, J=2 Hz). Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.70; N, 20.74. Found: C, 57.56; H, 3.93; N, 20.72.

3-Benzyl-2,4(1*H*,3*H*)-pteridinedione (3e): mp 236-238 °C (from AcOEt-hexane); ir (KBr) υ_{max}: 3450, 1720, and 1680 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 5.25 (2H, s), 7.27 (3H, m), 7.53 (2H, m), 8.52 (1H, d, J=2 Hz), and 8.56 ppm (1H, d, J=2 Hz). Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.42; H, 3.94; N, 22.05. Found: C, 61.20; H, 4.17; N, 22.24.

3-Phenyl-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (3f): mp 352-353 °C (from AcOEt-hexane); ir (KBr) υ_{max}: 3450 and 1720 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 7.27 (2H, m), 7.52 (3H, m), 8.63 (1H, m), and 8.76 ppm (1H, m). Anal. Calcd for $C_{12}H_8N_4OS \cdot 0.6H_2O$: C, 53.97; H, 3.45; N, 20.99. Found: C, 54.09; H, 3.64; N, 20.70.

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