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SYNTHESIS AND STUDY OF AROMATIC DERIVATIVES OF 5,6-DIHYDRO-4-PTERIDINOL

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The reaction of 4-hydroxy-5,6-diamino- and 2,5,6-triaminopyrimidines with substituted α-bromoacetophenones gives aryl derivatives of 5,6-dihydro-4-pteridinols. The course of these reaction is discussed and the physicochemical characteristics of these products were studied.

Keywords: diaminopyrimidine, dihydro-4-pteridinol, luminescence, stability.

Diaminopyrimidines are valuable synthones in fine organic synthesis, in particular, in the synthesis of purines, which often display high pharmacological activity [1]. In the present work, we studied the products of the cyclization of 4-hydroxy-5,6-diaminopyrimidine (**1**) and 4-hydroxy-2,5,6-triaminopyridimine (**2**) with substituted α-bromoacetophenones **3a-g**.

The desired products **4a-e**, **5a,b,d-g** were obtained by heating diamine **1** or the hydrochloride of triamine **2** with ketones **3a-g** in the presence of catalytic amounts of potassium acetate in ethanol at reflux. Products **4a-e, 5a,b,d-g** are light yellow or orange crystalline compounds stable upon storage in the air, which display luminescence in the crystal and ethanolic solution. In the case of ketones **3a,b,d**, aromatization products **6a,b,d** were also isolated from the reaction mixtures (Table 1). The yield of pteridines **6** increases with increasing reflux time and pteridine **6f** was obtained exclusively in the reaction of **1** with ketone **3f**.

The hydrochloride salt of triamine **2** was used in the synthesis of **5a,b,d-g** in light of the better solubility of this salt. While the formation of pteridines **4** or **6** was observed after only 10-30 min, products **5** could be isolated after heating for 12-15 h at reflux and only in low yields. Up to 30% of the starting compounds remained in the reaction mixture and traces of aromatization products **7** appeared. The much lower reactivity of triamine **2** is most likely related to its low solubility. Pteridines **7a,b,d** were also obtained in the reaction of **2** with α,α-dibromoacetophenones **8a,b,d**.

The structures of products **4-7** were in accord with their elemental analyses, ^{1}H NMR, UV, and IR spectra (Table 1), and, in the case of **4e, 5f,g,** and **6d**, mass spectra. The $\nu_{C=N}$ band in the IR spectra of dihydropteridines **4a-e** is insensitive to the electronic effect of substituent R^1. A significant shift toward lower frequencies is seen for **6a,b,d,f** (Table 1). Three strong bands are found at 3100-3660 cm^{-1}. The high-frequency and low-frequency bands should be assigned to the stretching vibrations of free and intermolecularly-bound hydroxyl group, respectively, while the band at 3300 cm^{-1} should be assigned to the stretching vibrations of the secondary amino group. These assignments are supported by the IR spectra of **4a,d**,**e** taken for solutions in carbon tetrachloride and chloroform, which show free bands ν_{OH} (3521-3528 cm^{-1}) and ν_{NH} (3410-3412 cm^{-1}),

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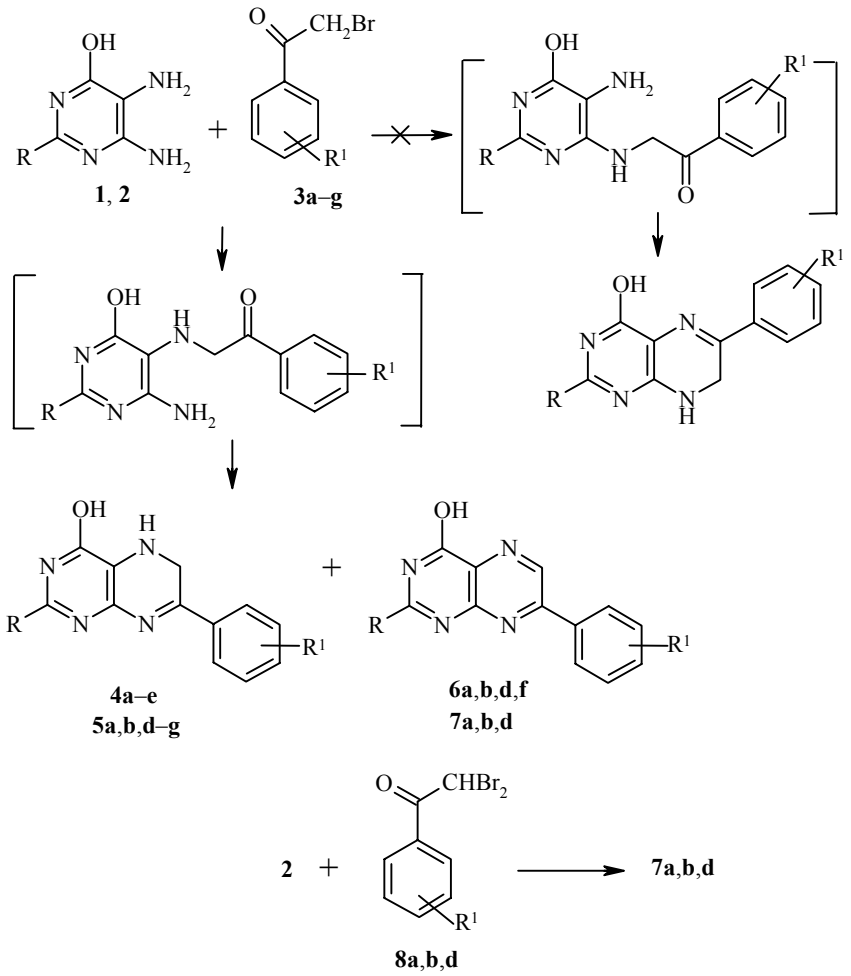
while the bands for bound groups are not seen. The IR spectra of aromatization products **6a,b,d,f** lack these bands but show a strong band at 1700 cm^{-1}, which is related to the lactim–lactam equilibrium in the pyrimidine ring and is in accord with literature data [2].



1, **4**, **6** R = H; **2** R = NH_2·HCl; **5**, **7** R = NH_2; **3a-g**, **4a-e**, **5a**,**b**,**d-g**, **6a**,**b**,**d**,**f**, **7**, **8** **a** R^1 = H, **b** R^1 = Me-*p*, **8c** R^1 = OMe-*p*, **d** R^1 = Br-*p*, **e** R^1 = NO_2-*p*, **f** R^1 = Ph-*p*, **g** R^1 = NO_2-*m*

A reliable assignment of these compounds to dihydro derivatives **4** and **5** or to their aromatic analogs **6** and **7** was made using their ^{1}H NMR spectra. Thus, the spectra of dihydropteridines **4a-e** show a two-proton singlet for the methylene group at 5.4-5.5 ppm, a broad two-proton singlet assigned to the OH and NH groups at 7.2-7.5 ppm, downfield singlet for 2-H at 7.9-8.3 ppm, and aromatic proton multiplet at 7.6-8.6 ppm. The spectra of **6a,b,d,f** show aromatic proton multiplets, broad signal for the hydroxyl group at 12.7-12.9 ppm, and singlet for pyrazine 6-H at 9.4-9.5 ppm. The spectra of pteridines **5a,b,d-g, 7a,b,d** show a doubled singlet for the amino group at 6.5-7.0 ppm instead of the singlet for 2-H (Table 2).

The direction of formation of **4a-e, 5a**,**c-g** was determined experimentally. The reaction of diamine **1** and specific oxidation of pteridine **4a** gave the same product identical to **6a**. Thus, the more nucleophilic 5-NH_2 group takes part both in the condensation at the aldehyde group and phenacylation with cyclization to give 1,2-dihydropteridines. This conclusion is in accord with the greater nucleophilicity of the amino group at $C_{(5)}$ in the pyrimidine ring [3].

TABLE 1. Characteristics of Compounds **4-7***

Compound	Empirical formula	Found, % / Calculated, %	mp, °C	IR spectrum, cm^{-1} (KBr)		UV spectrum λ_{max}, nm ($\varepsilon \times 10^{-3}$), ethanol	λ_{lum}, nm (Stokes shift, cm^{-1})	Yield, %
				$\nu_{C=N}$ ($\nu_{C=O}$)	$\nu_{NH\ (OH)}$			
1	2	3	4	5	6	7	8	9
4a	$C_{12}H_{10}N_4O$	24.8 / 24.76	227-229	1644	3296, 3163 (3462)	345 (13.8), 227 (16.6)	434 (5900)	85
4b	$C_{13}H_{12}N_4O$	23.4 / 23.32	235-237	1640	3300, 3160 (3475)	350 (13.5), 255 (11.7)	454 (6800)	63
4c	$C_{13}H_{12}N_4O_2$	21.9 / 21.86	239-240	1644	3303, 3150 (3424)	357 (3.7), 266 (11.9)	478 (7100)	81
4d	$C_{12}H_9BrN_4O$	18.4 / 18.36	242-243	1644	3307, 3160 (3483)	354 (13.3), 253 (13.9)	430 (5000)	76
4e	$C_{12}H_9N_5O_3$	25.8 / 25.82	290 (dec.)	1644	3305, 3110 (3424)	380, 252	435 (3400)	80
5a	$C_{12}H_{11}N_5O$	29.1 / 29.03	>300	1658	3316, 3146 (3370)	364 (18.7), 286 (8.3)	467 (6000)	50
5b	$C_{13}H_{13}N_5O$	27.3 / 27.43	>300	1660	3276, 3109 (3409)	364 (13.2), 289 (9.2)	458 (5600)	38
5d	$C_{12}H_{10}BrN_5O$	22.0 / 21.88	>300	1659	3356, 3163 (3496)	368 (11.3), 287 (5.5)	434 (4300)	40
5e	$C_{12}H_{10}N_6O_3$	29.2 / 29.36	>300	1658	3298, 3069 (3069)	—	—	75

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
5f	$C_{18}H_{15}N_5O$	22.1 22.07	>300	1648	3266, 3083 (3449)	379 (16.4), 289 (9.1)	457 (5100)	40
5g	$C_{12}H_{10}N_6O_3$	29.3 29.36	>300	1658	3293, 3192 (3436)	375 (11.2), 280 (6.9)	434 (3700)	36
6a	$C_{12}H_8N_4O$	24.9 24.89	>300 (dec.)	1602 (1702)		333 (18.5), 250 (23.5)	444 (6500)	29
6b	$C_{13}H_{10}N_4O$	22.2 22.12	>300 (dec.)	1604 (1712)		342 (19.7), 256 (24.1)	415 (5100)	20
6d	$C_{12}H_7BrN_4O$	18.5 18.48	>300 (dec.)	1637 (1708)		345 (3.4), 276 (20.2)	445 (6500)	20
6f	$C_{18}H_{12}N_4O$	18.5 18.48	>300 (dec.)	1608 (1710)		354 (7.6), 259 (11.6)	480 (7400)	26
7a	$C_{12}H_9N_5O$	29.2 29.27	>300	1688		370 (3.4), 299 (10.0)	456 (5100)	35
7b	$C_{13}H_{11}N_5O$	27.7 27.65	>300	1688		372 (3.2), 300 (9.5)	458 (5200)	32
7d	$C_{12}H_8BrN_5O$	22.1 22.01	>300	1688		370 (4.4), 303 (9.3)	458 (5200)	33

* Mass spectrum of **4e**: M^+ 271(3), 269(3), 121(2), 97(4); **5f**: M^+ 317(100), 179(21), 178(16), 158(6), 151(8), 138(47), 112(27), 92(7), 91(16); **5g**: M^+ 288(4), 287(11), 286(64), 256(6), 159(8), 138(40), 112(79), 102(11), 91(7), 80(9), 75(8); **6d**: 304(86), M^+ 302(81), 223(5), 185(9), 182(13), 151(23), 121(100), 102(10), 75(13).

TABLE 2. ^{1}H NMR Spectra of **4-7**, δ, ppm, Coupling Constant, *J* (Hz)

Compound	CH_2, s, 2H (6-H, s, 1H)	OH, NH, br. s, 2H (OH, s, 1H)	2-H, s, 1H (NH_2, s, 2H)	H_{Ar}
4a	5.47	7.21	7.97	7.69-8.10, m, 5H
4b	5.43	7.27	7.89	7.64 d and 8.06 d, 4H ^3J = 7.8
4c	5.45	7.22	7.92	7.66 d and 8.03 d, 4H ^3J = 8.0
4d	5.39	7.27	7.97	7.72 d and 8.06 d, 4H ^3J = 8.0, 4H
4e	5.55	7.47	8.30	8.42 d and 8.55 d, 4H ^3J = 8.0
5a	5.28	6.20	(6.53)	7.45-7.98 m
5b	5.51	6.25	(6.53)	7.31 d and 7.94 d, 4H ^3J = 7.8
5e·HCl	5.62	5.70	(6.55)	8.10 d and 8.45 d, 4H ^3J = 8.0
5f·HCl	5.54	3.30	(6.55)	7.40-8.12 m, 5H
5g·HCl	5.57	3.25	(6.50)	7.80-8.42 m, 5H
6a	(9.43)	(12.75)	8.37	7.65-8.32 m, 5H
6b	(9.40)	(12.70)	8.41	7.65 d and 8.33 d, 4H ^3J = 8.0
6d	(9.42)	(12.85)	8.44	7.70 d and 8.38 d, 4H ^3J = 7.5
6f	(9.47)	(12.75)	8.40	7.69-8.38 m, 5H
7a	(9.20)	(11.35)	(6.86)	7.50-8.12 m, 5H
7b	(9.22)	(11.40)	(6.86)	7.32 d and 8.05 d, 4H ^3J = 8.0
7d	(9.29)	(11.30)	(6.99)	7.69 d and 8.04 d, 4H ^3J = 7.5

The reactions of α-bromoacetophenones with *o*-phenylenediamine and its derivatives proceed under milder conditions involving brief heating of the starting compounds in ethanol at reflux in an inert atmosphere to give dihydroquinoxalines in satisfactory yield [4, 5]. These products are sensitive to atmospheric oxygen and readily oxidize to 2-arylquinoxalines. The stability of 1,2-dihydroquinoxalines is enhanced upon substitution at the NH or CH_2 group [6]. On the other hand, dihydropteridines **4a-e, 5a,b,d-g** are more stable than 1,2-dihydroquinoxalines. The stabilization of these compounds may be related to the formation of intermolecular associates since heating **4a-e, 5a,b,d,g** in acetone, DMSO, or DMF facilitates their oxidation to pteridines **6** or **7**, respectively. The presence of the electron-withdrawing pyrimidine ring in **4a-4e, 5a,b,d,g** is also a stabilizing factor.

Since an intramolecular hydrogen bond is impossible for dihydropteridines **4**, quantum-chemical *ab initio* (6-31G** [7]) calculations were carried out for model compounds **A** and **B** (Table 5). The results showed that there is no O···HN hydrogen bond since that the O···H distance is greater than the sum of the corresponding van der Waals radii. On the other hand, the shortening of the N···HO distance for form **B** is sufficient for hydrogen bond formation. The increase of the dipole moment for molecule **B** (up to 1.380) also supports this conclusion [8]. However, the only slight difference between the energies for **A** and **B** (4 kcal/mole in favor of form **A**) makes hydrogen bonding improbable.

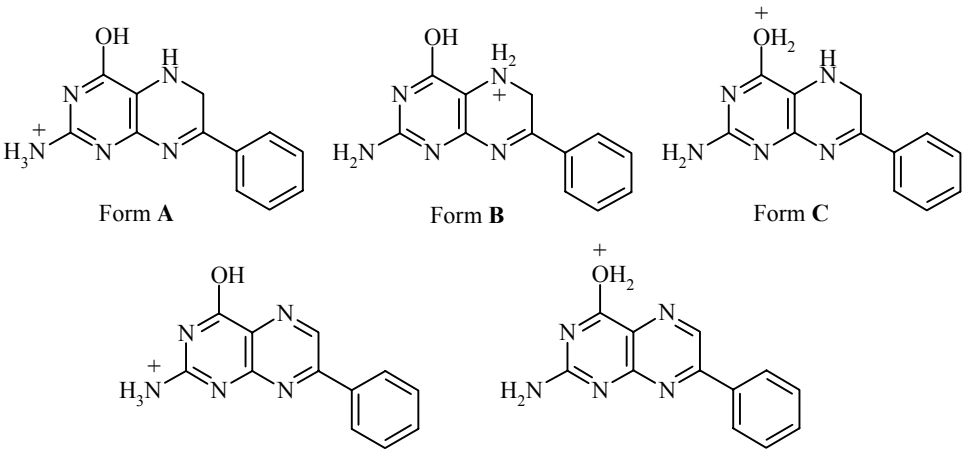
The electronic absorption spectra for **4a-e, 5a,b,d-g** show two rather resolved π–π* bands at 220-380 nm. The long-wavelength band undergoes a bathochromic shift upon introduction of substituent R^1 in the *para* position of the phenyl group and the greatest shift is seen for nitro derivative **4e** ($\Delta\lambda$ = 35 nm), which is characteristic for azomethine chromophores. Aromatization is regularly accompanied by a hypsochromic shift of λ_{max} of the long-wavelength band (Table 1). The addition of one or two drops of concentrated sulfuric acid to the solution measured for dihydro derivatives **5a,b,d,f,g** leads to a slight hypsochromic shift of the long-wavelength band and bathochromic shift of the short-wavelength band while both these bands undergo a hypsochromic shift for their aromatic analogs **7a,b**,**d** (Table 3). Comparison of the experimental data and results of CNDO/S calculations [9] for **5a** and **7a** suggested that protonation occurs at the primary amino group (Table 4).

The electronic spectra remain unchanged upon the addition of several drops of base such as ammonia or aqueous NaOH. However, an increase in the basicity of the medium has a marked effect on pterines **7a,b**,**d** and a new strong band appears in the short-wavelength region, which is independent of the base concentration (Table 3). This finding is probably the result of formation of enolate forms of **7a,b,d**.

TABLE 3. Electronic Absorption Spectra of Synthesized Compounds **5a,b,d,f,g, 7a,b,d**

Compound	λ_{max}, nm		
	neutral medium	acidic medium	basic medium
5a	364, 286	358, 295	364, 286
5b	364, 289	357, 292	364, 289
5d	368, 287	364, 296	368, 287
5f	379, 289	370, 299	379, 289
5g	375, 280	364, 287	375, 280
7a	370, 299	350, 278	379, 299, 279
7b	372, 300	358, 284	374, 300, 283
7d	370, 303	354, 285	379, 303, 283

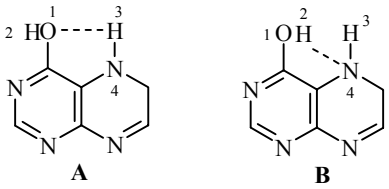
TABLE 4. Results of CNDO/S Calculations



Com-pound	λ_{max} (*f*)			
	nonprotonated form	form **A**	form **B**	form **C**
5a	365 (0.14) 232 (0.11)	355 (0.39) 257 (0.07)	371 (0.11) 242 (0.65)	376 (0.19) 236 (0.16)
7a	388 (0.0001) 277 (0.0037)	361 (0.0002) 267 (0.0021)		297 (0.0032) 293 (0.571)

A characteristic feature of the luminescence spectra of **4a-e, 5a,b,d-g, 6a,b,d,f, 7a,b,d** is higher sensitivity to the electronic effect of substituent R^1 than for the absorption spectra, which leads to variation in the values of the Stokes shifts (Table 1). Greater Stokes shifts are found for compounds with electron-donor groups (**4b,d,d**) or an extended π-system (**6f**). The fluorescence of nitro derivative **4c** is unexpected and probably results from a favorable relative positions of the *n*-π and π-π* levels in this molecule.

TABLE 5. Results of the Quantum-chemical Calculations for Model Forms of Dihydropteridines **A** and **B**



A **B**

Form	Interatomic distances		Total energy (*ab initio*), kcal/mole	Dipole moment D
	molecular mechanics, Å	*ab initio*, 6-31G**, Å		
A	O(1)···H(3) 2.57 (2.45)* N(4) ··H(2) 3.82 (2.66)*	O(1) ··H(3) 2.64 N(4) ··H(2) 3.75	-331179	4.36
B	O(1) ··H(3) 2.59 N(4) ··H(2) 2.38	O(1) ··H(3) 3.17 N(4) ··H(2) 2.30	-331175	5.74

* Sum of van der Waals radii [10].

EXPERIMENTAL

The IR spectra were taken on a Specord 75-IR spectrometer for KBr pellets and solutions in chloroform or carbon tetrachloride. The electronic absorption spectra were taken on a Specord M-40 spectrometer for ethanolic solutions with concentrations from $1 \cdot 10^{-5}$ to $5 \cdot 10^{-5}$ mol/l. The ^{1}H NMR spectra were registered on Bruker AM-300, Bruker WM-250, and Bruker AC-200 spectrometers for solutions in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Varian MAT-CH-6 mass spectrometer. The temperature of the ionization chamber was 100-300°C. The ionizing voltage was 70 eV and the emission current was 100 μA. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform, acetone, and ethyl acetate as the eluents.

7-(4-Methoxyphenyl)-5,6-dihydro-4-pteridinol (4c). A mixture of diamine **1** (0.38 g, 3 mmol), 4-methoxy-α-bromoacetophenone **3c** (0.7 g, 3 mmol), and a catalytic amount of potassium acetate in methanol (30 ml) was heated at reflux for 10 min. Cooling gave yellow crystalline pteridine **4c**, which was crystallized from 2:1 methanol–DMF.

Products **4a,b,d,e, 5a,b,d-g, 6a,b,d,f, 7a,b,d** were obtained analogously from diamine **1** and the corresponding ketone **3**. The reaction mixture was heated at reflux for 30 min in the synthesis of **4d,e** and for 12-15 h for **5a,b,** and **5d-g**.

2-Amino-7-phenyl-4-pteridinol (7a). A mixture of triamine hydrochloride **2** (0.5 g, 23 mmol) and α,α-dibromoacetophenone (0.64 g, 23 mmol) in methanol (30 ml) was heated at reflux for 20 h. Cooling gave **7a** as a powder, which was filtered off, washed with hot water, and crystallized from 2:1 methanol–DMF.

Products **7b,d** were synthesized analogously from triamine **2** and the corresponding substituted α,α-dibromoacetophenone **8**.

7-Phenyl-4-pteridinol (6a). A. A mixture of phenylglyoxal (0.1 ml, 5 mmol) and diamine **1** (1.9 g, 5 mmol) in methanol (30 ml) was heated at reflux for 30 min. Cooling gave crystalline **6a**, which was recrystallized from ethanol.

B. A sample of selenium dioxide (0.04 g, 0.4 mmol) was added to a solution of dihydropyrazine **4a** (0.1 g, 0.4 mmol) in dioxane (5 ml) and heated at reflux for 1 h. The selenium precipitate was separated. Cooling of the filtrate gave **6a**.

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