Articles

Oxidative Synthesis of Benzoylpteridines from Benzylpteridines by Potassium Permanganate

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6- and 7-Benzylpteridine derivatives have been converted to the corresponding 6- and 7-benzoylpteridines by the oxidation reaction with $KMnO_4$. The newly synthesized compounds have been characterized by pKa determinations, UV, and ^{1}H-NMR spectra.

Keywords : Benzylpteridines, Benzoylpteridines, Diphenylmethane derivatives, Oxidation of pteridines.

Introduction

The various pteridines have been isolated from many living things: including amphibia,[1] fish,[2] microorganisms,[3] insects[4] and mammals, including humans.[5,6] The conversion of the side chain of pteridines is very useful and important for the synthesis of naturally occurring pteridine derivatives. For instance, the 6-methyl group in 6-methylpterin [2-amino-6-methylpteridin-4(3*H*)-one] is converted into the formyl group via the dibromomethyl group, and then the reaction with 4-aminobenzoyl-1-glutamic acid produces folic acid, which acts as a growth cofactor in the human body.[7] On the other hand, the oxidation of 6- and 7-substituted pteridine derivatives provides the corresponding pteridine 6- and 7-carboxylic acid,[8] which shows different absorption bands in the UV spectrum.[9,10] The oxidation reaction of natural pteridines, therefore, presents important information for structural elucidation.

In the present study, we prepared several 6- and 7-benzylpteridines that could be expected to have analogues chemical reactivities to the diphenylmethane derivatives that are easily converted into the corresponding diaryl ketones by oxidation with potassium permanganate or potassium dichromate.[11] 6- and 7-Benzylpteridines have the methylene group between the pyrazine, 6-membered heteroaromatic, and the phenyl. Thus, treatment of 6- and 7-benzylpteridines with oxidant can provide the synthetic method for the preparation of 6- and 7-aroylperidines.

Results and Discussion

The reaction of 4,5-diamino-1,3-dimethyluracil (**1**) with benzylglyoxal (**2**)[12] in ethanol formed a Schiff base, which was converted to a mixture of 6- (**3**) and 7-benzyl-1,3-dimethyllumazine (**4**) by intramolecular cyclization in 50% acetic acid. The obtained isomer mixture was separated by column chromatography over silica gel eluting with toluene : ethyl acetate to give 6- (**3**, 28%) and 7-benzyl-1,3-dimethyllumazine (**4**, 59%), respectively. In the pteridine ring system, the electron density of C-7 is lower than that of C-6 due to the conjugation with the 4-oxo group.[13,14]

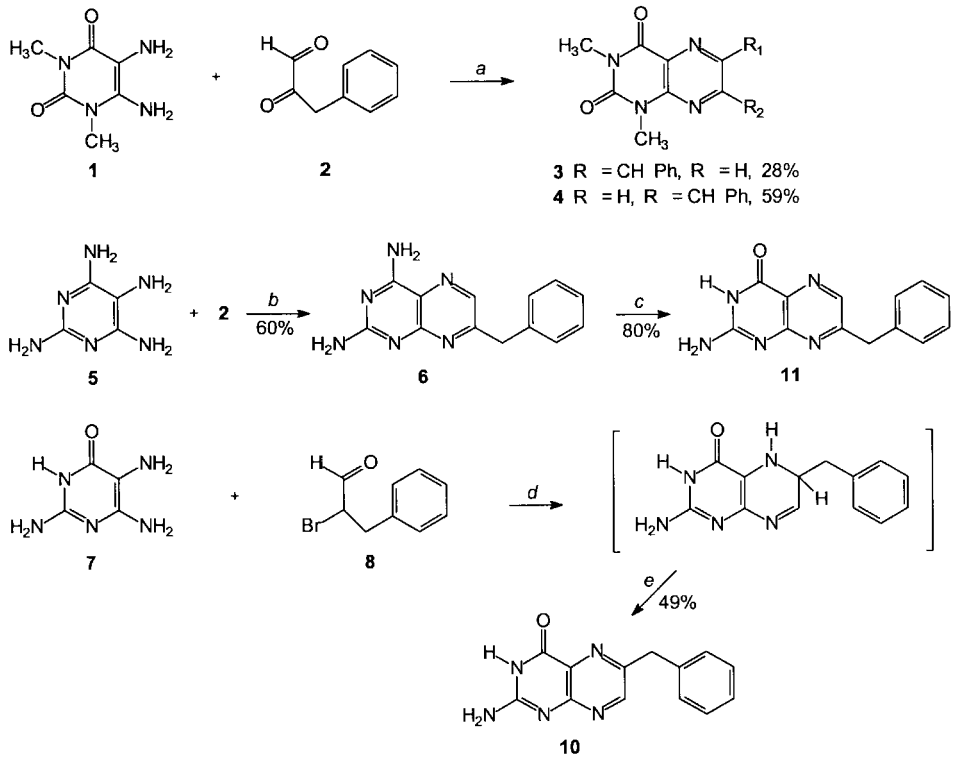
The C-7-H of 6-benzyl-1,3-dimethyl-lumazine (**3**) was low-field shifted to 8.43 ppm, and C-6-H of 7-benzyl-1,3-dimethyllumazine (**4**) appeared at 8.41 ppm.

2,4,5,6-Tetraaminopyrimidine (**5**) has four amino groups. In particular, among the four amino groups, 2-, 4-, and 6-amino groups have low nucleophilicities due to the stabilization by guanidine resonance with ring N-1 and N-3 atoms. Only the 5-amino group has enough nucleophilicity to attack the carbonyl group of benzylglyoxal (**2**). From the pH-controlled condensation of 2,4,5,6-tetraaminopyrimidine (**5**) with **2** in pH 9-10 we obtained the isomer free 2,4-diamino-7-benzylpteridine (**6**), which was hydrolyzed to 7-benzylpterin (**11**) by heating under reflux in sodium hydroxide solution. On the other hand, the reaction below pH 8 gave a mixture of 2,4-diamino-6- and 7-benzylpteridine. This can be explained by the fact that the nucleophilicity of the 5-amino group in pyrimidine **5** was decreased by protonation below pH 8.

The pH-controlled condensation of 4,5-diamino-1,3-dimethyluracil (**1**) with **2** in pH 9-10 was also tried, but the reaction did not proceed due to the cleavage of **1** in alkaline medium, and many inseparable products were obtained.

The isomeric mixture of 6- (**10**) and 7-benzylpterin (**11**) was synthesized from the reaction of 2,4,5-triamino-6-oxo-dihydropyrimidine sulfate with 1,1-dimethoxy-3-phenyl-2-propanone by Roswosky, and the isomer free 6-benzylpterin (**10**) was obtained, after a series of recrystallizations, in low yield.[15] Some of 6-substituted pterins were prepared from the reaction of 2,4,5-triamino-6-oxo-dihydropyrimidine (**7**) and a-halo aldehyde or a-halo ketone.[16,17] In a similar process, the reaction of **7** with 2-bromo-3-phenylpropionaldehyde monohydrate (**8**)[18] provided 6-benzyl-5,6-dihydropterin (**9**), which was oxidized to 6-benzylpterin (**10**) *in situ* by treatment with hydrogen peroxide (Scheme 1).

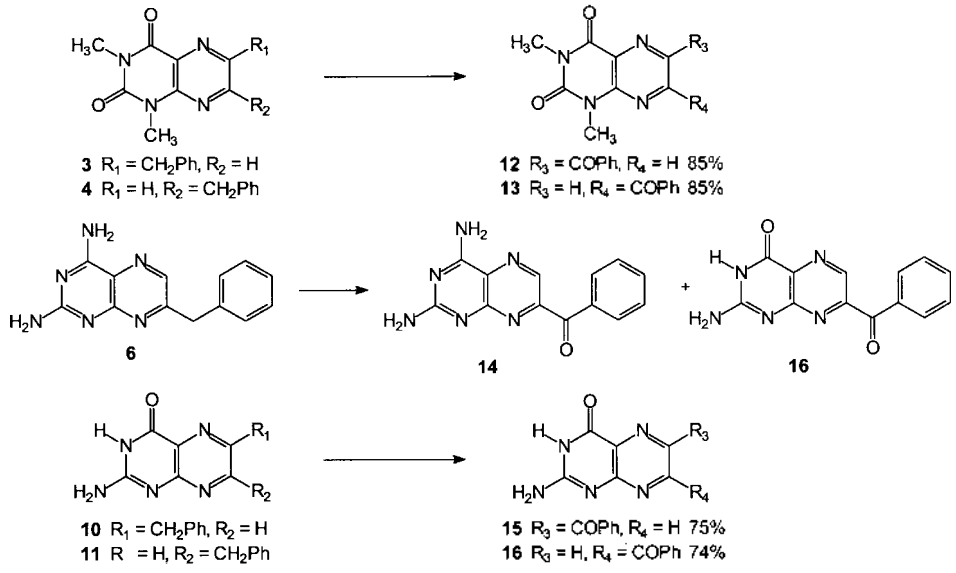
As expected, the oxidation reaction of 6- and 7-benzyl-



a. i) EtOH, rt, 1 h ii) 50% AcOH, reflux, 30 min b. pH 9~10, reflux, 1 h c. i) 0.1*N* NaOH, reflux, 1 h ii) pH 5~6
d. i) EtOH, rt, 30 min ii) reflux, 1 h e. 30% H_2O_2, rt, 16 h

Scheme 1

pteridine derivatives with potassium permanganate gave the corresponding 6- and 7-benzoylpteridine derivatives in good yield. The methylene group between the pyrazine and phenyl ring of 6- and 7-benzylpteridine derivatives was converted to carbonyl group by treatment with $KMnO_4$ to provide the corresponding 6- and 7-benzoylpteridine derivatives. Further oxidation of benzoylpteridines to the corresponding carboxylic acid did not occur due to the absence of α-hydrogen. In the case of 2,4-diamino-7-benzylpteridine (**6**). from the ^{1}NMR spectrum the isolated oxidative products were identified as a mixture of 2,4-diamino-7-benzoylpteridine (**14**) and 7-benzoylpterin (**16**) which was obtained *in situ* by hydrolysis of 4-amino group of **14** in alkaline medium. The separation of the obtained mixture by column chromato-



General reaction condition: $KMnO_4$ / H_2O, reflux, 30 min.

Scheme 2

Table 1. UV-Vis spectrum of pteridine derivatives

Compounds	pK_a	UV-absorption spectrum								*p*H	form[a]
		λ_{max} (nm)				*log* ε_{max}					
1,3-Dimethyllumazine[17]		236			331	4.19			3.88	MeOH	O
2,4-Diaminopteridine[18]		240	284	332	(345)	4.10	3.73	3.98	(3.90)	3	+
		224	255		364	4.07	4.32		3.86	8	O
6-Benzyl-1,3-dimethyllumazine (**3**)		240			338	4.32			3.91	MeOH	O
7-Benzyl-1,3-dimethyllumazine (**4**)		238			332	4.22			4.07	MeOH	O
2,4-Diamino-7-benzylpteridine (**6**)	4.99 ± 0.06	242	282	334	(345)	4.02	3.72	4.13	(4.08)	3	+
		217	255	(279)	366	4.15	4.32	(3.72)	3.97	8	O
6-Benzylpterin (**10**)	2.23 ± 0.12	(230)	248	325	(340)	(4.12)	4.14	3.95	(3.83)	0	+
	8.13 ± 0.08	(232)	274	348	(368)	(4.12)	4.23	3.82	(3.69)	5	O
		254	(278)		366	4.41	(3.88)		3.89	11	−
7-Benzylpterin (**11**)	2.12 ± 0.07	(244)		320	(332)	(3.93)		4.10	(4.02)	0	+
	8.42 ± 0.12	(233)	274	342	(360)	(4.08)	4.04	3.87	(3.79)	5	O
		252	(278)		360	4.33	(3.73)		3.97	11	−
6-Benzoyl-1,3-dimethyllumazine (**12**)		257	285		330	4.23	4.22		4.05	MeOH	O
7-Benzoyl-1,3-dimethyllumazine (**13**)		233	(255)		347	4.23	(4.10)		3.97	MeOH	O
6-Benzoylpterin (**15**)	1.17 ± 0.05	(233)	272		320	(4.03)	4.10		4.10	−1	+
	7.27 ± 0.08	236	(258)	308	351	4.10	(4.01)	4.18	4.05	4	O
		247	282	(352)	378	4.08	4.21	(4.02)	4.14	10	−
7-Benzoylpterin (**16**)	1.55 ± 0.06	(247)			333	4.32			4.09	−1	+
	7.50 ± 0.07	242	278		367	4.27	4.20		3.84	4	O
		250	(276)		389	4.32	(4.19)		3.86	10	−

[a]Molecular form; O, neutral form; +, cation; −, anion.

graphy failed because **14** and **16** are insoluble in water or organic solvents. Without separation, the mixture of **14** and **16** was heated in 1*N* NaOH aqueous solution under reflux. Spectroscopic data of isolated product were identical in many respects with those of the compound obtained from the oxidation of 7-benzylpterin (**11**) by potassium permanganate.

In the UV spectra of 6- and 7-benzylpteridine derivatives, there are similar spectra for the corresponding 6- and 7-unsubstituted pteridines.[19,20] 2,4-Diamino-7-benzylpteridine (**6**) has a basic pKa of 4.99, which resulted from protonation at N-1 and provided a distinct hypsochromic shift of long wave absorption band. 6- (**10**) and 7-Benzylpterin (**11**) displayed two pKa values in normal pH range. The pKa of 2.23 from **10** was assigned from the basic character of N-1. The pKa of 8.13 from **10** corresponded to the anion formation at N-3 and caused a characteristic bathochromic shift of the long wave absorption band (Table 1). 6- (**15**) and 7-benzoylpterin (**16**) showed lower basic pKa values at 1.17 and 1.55 than those of 6- (**10**) and 7-benzylpterin (**11**) because the basicity at N-1 of **15** and **16** was decreased by the benzoyl group.

Experimental Section

Materials and instruments. All chemicals used were analytical grade purchased from commercial sources. The solvents were purified by distillation, and the other reagents were used without further purification. ^{1}H NMR spectra were measured at 300 MHz using a Varian Unity Plus 300 spectrometer. The chemical shift values are reported as δ downfield from TMS as an internal standard. Melting points were determined on a Büchi 530 and a Mettler FP62 melting point apparatus and were uncorrected. UV spectra were performed on a Perkin Elmer Lambda 7, and the samples were prepared as a concentration of 10^{-2} molL^{-1}. Elemental analyses were performed by Fisions EA 1108.

6-Benzyl-1,3-dimethyllumazine (3) and 7-benzyl-1,3-dimethyllumazine (4). A solution of benzylglyoxal (**2**, 2.6 g, 17.5 mmol) in ethanol (80 mL) was added dropwise to a stirred suspension of 5,6-diamino-1,3-dimethyluracil (**1**, 2 g, 11.7 mmol) in ethanol (100 mL). The resulting reaction mixture was then stirred at ambient temperature for 1 h. After the solvent was removed by rotary evaporation, the residue was heated with 50% acetic acid (*aq*. 100 mL) under reflux for 30 min. After being cooled to room temperature, the solution was neutralized with ammonia water and extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated. The obtained isomeric mixture of **3** and **4** was separated by column chromatography over silica gel, using a toluene-ethyl acetate (10 : 1, v/v) as the eluent, affording **3** (940 mg, 28%) as the least polar and **4** (1.98 g, 59%) as the most polar component. For **3**: mp. 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H, 3-N-CH_3), 3.65 (s, 3H, 1-N-CH_3), 4.32 (s, 2H, -CH_2-), 7.28 (m, 5H, phenyl), 8.43 (s,1H, 7-C-H); Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C 63.88, H 4.76, N 19.63. For **4**: mp. 147-148 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H, 3-N-CH_3), 3.68 (s, 3H, 1-N-CH_3), 4.22 (s, 2H, -CH_2-), 7.28 (m, 5H, phenyl), 8.41 (s, 1H, 6-C-H); Anal. Found: C, 63.61; H, 4.65; N, 19.47.

2,4-Diamino-7-benzylpteridine (6). A solution of benzylglyoxal (**2**, 3.47 g, 23 mmol) in ethanol (100 mL) was added

dropwise to a stirred suspension of 2,4,5,6-tetraaminopyrimidine dihydrochloride (**5**, 5 g, 23 mmol) in water (250 mL), and the pH was adjusted to 9-10 with ammonia water. The reaction mixture was heated under reflux for 1 h. After being cooled to room temperature, the precipitate was collected by filtration, washed with water and acetone, and dried on a vacuum pump at 100 °C to afford **6** (3.56 g, 60%) as a yellow solid: mp. 284 °C; ^{1}H NMR (DMSO-d_6) δ 4.13 (s, 2H, -CH_2-), 6.56 (bs, 2H, 2-NH_2), 7.27 (m, 5H, phenyl), 7.60 (bs, 2H, 4-NH_2), 8.24 (s, 1H, 6-C-H); Anal. Calc for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.31. Found: C, 61.87; H, 4.98; N, 32.95.

6-Benzylpterin (10). A solution of 2-bromo-3-phenylpropionaldehyde monohydrate (**8**, 24 g, 0.1 mol) in ethanol (400 mL) was added to a stirred suspension of 2,4,5-triamino-6-oxo-dihydropyrimidine dihydrochloride (**7**, 20 g, 0.1 mol) and $NaHCO_3$ (32 g, 0.38 mol) in water (250 mL). The reaction mixture was heated under reflux for 1 h and then cooled to room temperature. Hydrogen peroxide solution (30%, 100 mL) was added to the reaction mixture and stirred at ambient temperature for 16 h. The precipitate was collected by filtration, washed with water and acetone. Recrystallization of the crude product from acetic acid gave **10** (12.5 g, 49%) as a yellow solid: mp. >350 °C; ^{1}H NMR (DMSO-d_6) δ 4.16 (s, 2H, -CH_2-), 7.21 (m, 5H, phenyl), 7.76 (bs, 2H, 2-NH2), 8.52 (s, 1H, 6-C-H); Anal. Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.54; H, 4.31; N, 27.27.

7-Benzylpterin (11). **6** (2 g, 8 mmol) was heated with 0.1 N NaOH solution (300 mL) under reflux for 2 h. The pH of the hot resulting solution was adjusted to 5-6 with 50% acetic acid solution. After being cooled to room temperature, the precipitate was collected by filtration, washed with water and acetone. Recrystallization of the crude product from acetic acid gave **11** (1.6 g, 80%) as a yellow solid: mp. >350 °C; ^{1}H NMR (DMSO-d_6) δ 4.14 (s, 2H, -CH_2-), 7.23 (m, 5H, phenyl), 7.75 (bs, 2H, 4-NH_2), 8.28 (s, 1H, 6-C-H); Anal. Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.39; H, 4.32; N, 27.64.

6-Benzoyl-1,3-dimethyllumazine (12). A suspension of **3** (560 mg, 2 mmol) in water (300 mL) was heated with $KMnO_4$ (600 mg, 3.8 mmol) under reflux for 30 min. After being cooled to room temperature, the solution was extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated. Recrystallization of the crude product from ethanol provided **12** (490 mg, 85%) as a pale yellow needle: mp. 216-218 °C; ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 3H, 3-N-CH_3), 3.77 (s, 3H, 1-N-CH_3), 7.88 (m, 5H, phenyl), 9.34 (s, 1H, 7-C-H); Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.47; H, 4.11; N, 18.84.

7-Benzoyl-1,3-dimethyllumazine (13). **13** was obtained from **4**, according to the procedure described for **12**, as a pale yellow needle: yield 85%; mp. 190-191 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H, 3-N-CH_3), 3.67 (s, 3H, 1-N-CH_3), 7.78 (m, 5H, phenyl), 9.11 (s, 1H, 6-C-H); Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.99; H, 4.10; N, 18.80.

6-Benzoylpterin (15). A suspension of **10** (1.6 g, 6.3 mmol) in water (100 mL) was heated with $KMnO_4$ (2.6 g, 16.4 mmol) under reflux for 30 min. After being cooled to room temperature, the precipitate was removed by filtration on a celite pad, and the filtrate was acidified with 50% acetic acid solution. The precipitate was collected by filtration, washed with water and acetone, and dried on a vacuum pump at 100 °C to afford **15** (1.26 g, 75%) as a yellow solid: mp. >350 °C; ^{1}H NMR (DMSO-d_6) δ 7.35 (bs, 2H, 2-NH_2), 7.82 (m, 5H, phenyl), 9.22 (s, 1H, 6-C-H), 11.56 (bs, 1H, 3-N-H); Anal. Calcd for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.39; N, 26.21. Found: C, 58.02; H, 3.78; N, 25.75.

7-Benzoylpterin (16). **16** was obtained from **11**, according to the procedure described for **15**, as a pale yellow needle: yield 74%; mp. >350 °C; ^{1}H NMR (DMSO-d_6) δ 7.05 (bs, 2H, 2-NH_2), 7.79 (m, 5H, phenyl), 8.79 (s, 1H, 6-C-H), 11.61 (bs, 1H, 3-N-H); Anal. Calcd for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.39; N, 26.21. Found: C, 58.01; H, 3.64; N, 26.01.

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