A New Selective Preparation of Ethyl 7-Aminopteridine-6- carboxylate Derivatives and Related Compound

Yoichi Yamada,* Heinosuke Yasuda, Yuichi Yoshihara, and Kazue Yoshizawa

Department of Chemistry, Faculty of Education, Utsunomiya University, Mine, Utsunomiya 321-8505, Japan

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A series of ethyl 7-amino-2,4-dioxopteridine-6-carboxylates **4** and ethyl 7-amino-4-oxo-2-thioxopteridine-6-carboxylates **5**, of interest biologically, has been prepared in one step from the reaction of such *vicinal*-diamines as 1,3-dialkyl-5,6-diaminouracils **2** or 1,3-dialkyl-5,6-diamino-2-thiouracils **3** with diethyl (*E*)-2,3-dicyanobutenedioate (**1**). Moreover, ethyl 3-amino[1,2,4]triazino[2,3-*a*]-1*H*-benzimidazole-2-carboxylate (**11**) was also obtained from the reaction between 1,2-diamino-1*H*-benzimidazole (**10**) and **1**. The structural studies of **4**, **5**, and **11** prepared were carried out by nmr experiments in some details.

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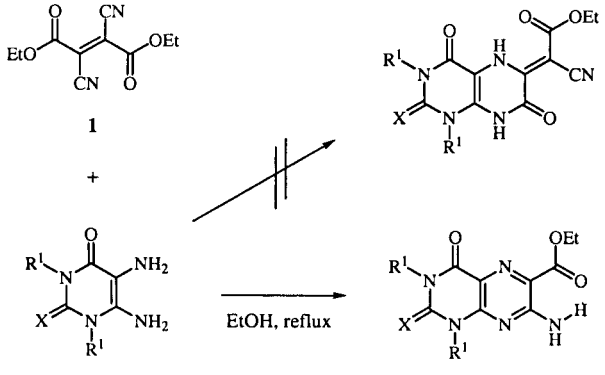
Pteridine ring systems are reported [1-5] to be useful in a variety of fields, such as, in pharmaceutics [6] as drugs, in biology as a base component of several nucleosides [7] or nucleotides [8], and in other biological activity [9]. In previous papers we described a new method leading to excellent yields of dialkyl (*E*)-2,3-dicyanobutenedioates **1** [10] and a novel synthesis of various heterocyclic compounds such as 1,6-diamino-2-pyridones, [1,2,4]triazolo-[1,5-*a*]pyridines [11], 1-substituted 5-aminopyrazoles, and pyrazolo[1,5-*a*]-s-triazine [12] starting from **1**.

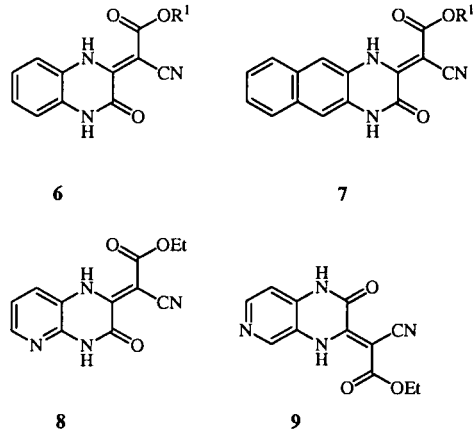
Scheme 1



2, 4	R^1	2, 4	R^1	3, 5	R^1
a	Me	f	Am	a	Me
b	Et	g	*i*-Am	b	Et
c	Pr	h	Hex	c	Pr
d	Bu	i	Hep	d	Bu
e	*i*-Bu				

In connection with our interest in investigating the preparation of nitrogen-containing heterocycles starting from **1**, we have designed a synthesis using heterocyclic *vicinal*-diamines such as 1,3-dialkyl-5,6-diaminouracils **2** and 1,3-dialkyl-5,6-diamino-2-thiouracils **3** as building blocks (Scheme 1). Compounds of this type, **2** and **3**, would appear to be ideal substrates for the present purpose.

We have recently shown [13] that various 1,2,3,4-tetrahydroquinoxalines **6**, 3,4-dihydrobenzo[*g*]quinoxalin-2(1*H*)-ones **7**, 1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one derivative **8**, and 3,4-dihydro-1*H*-pyrido[3,4-*b*]pyrazin-2-one derivative **9**, bearing α-cyano-α-alkoxycarbonylmethylene group were easily prepared by the reaction of **1** with such *vicinal*-diamines as *o*-phenylenediamine, 2,3-diaminonaphthalene, 2,3-diaminopyridine, or 3,4-diaminopyridine, respectively, either in acetonitrile at room temperature or in ethanol under reflux.



On the other hand, in the present study, it was found that the reaction between **1** and the heterocyclic *vicinal*-diamines such as 5,6-diaminouracils **2** and **3** did not give the corresponding compounds of the types **6–9**, but ethyl 1,3-dialkyl-7-amino-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylates **4** or ethyl 1,3-dialkyl-7-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylates **5** were isolated. We now wish to describe new, a general method for the selective one step synthesis of ethyl 7-amino-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylates **4** and the 7-amino-4-oxo-2-thioxo derivatives **5** by the reaction of 5,6-diaminouracils **2** or 5,6-diamino-2-thiouracils **3** with **1** (Scheme 1). This method consists of

allowing **1** to react with **2** or **3** in a 1:1 molar ratio in ethanol under reflux for one hour.

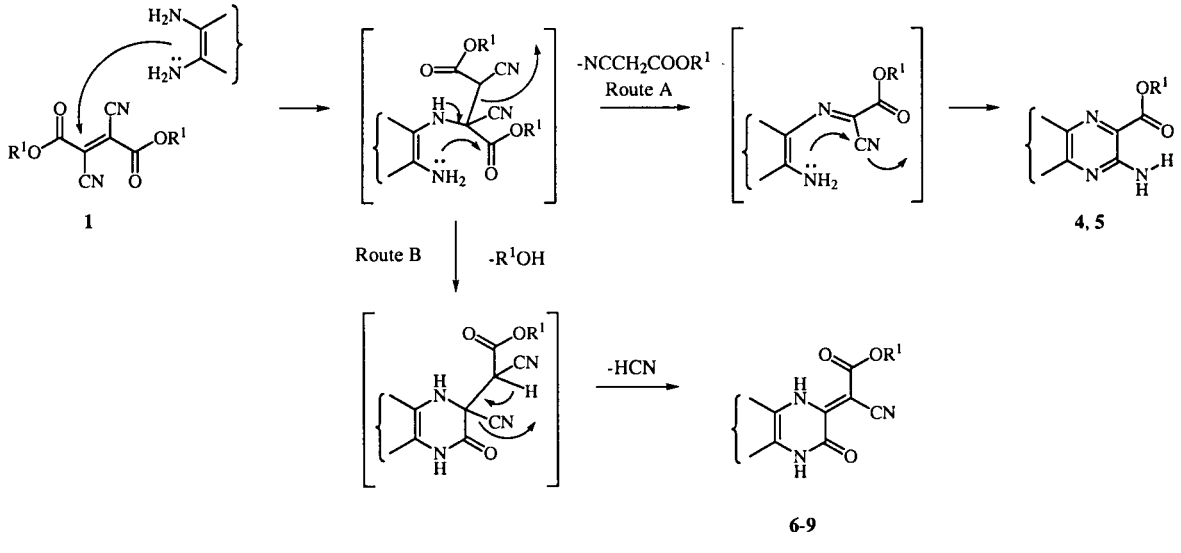
A series of 7-aminopteridine systems, **4** and **5**, is thus obtained in fair to good yields. A possible reaction process is depicted in Scheme 2. Presumably, a Michael 1,4-addition of reactive 5-amino group of *vicinal*-diamines **2** and **3** to the ethylenic double bond of **1** leads to an adduct. The resulting adduct undergoes an elimination of one molecule of ethyl cyanoacetate, followed by the intramolecular nucleophilic attack at the cyano group, to form pteridine type products **4** and **5** (Route A). On the other hand, tetrahydroquinoxaline type compounds **6-9** were obtained from cyclization of the adduct by intramolecular nucleophilic attack at the ester group, followed by an elimination of a cyano group (Route B).

These were assigned to the amino protons. Appearance of the ester carbonyl band at about 1700 cm^{-1} and one of the amino protons at δ 8.33-8.58 would indicate that both compounds **4** and **5** had chelate hydrogen-bond structures.

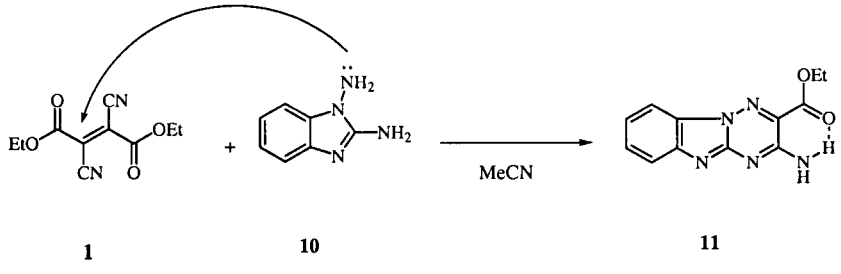
Recently, it was reported [8] that pteridine ring systems have a strong fluorescent property, which can be applied for labeling experiments in biochemistry and molecular biology. A series of pteridine of the type **4** prepared is also showed strong fluorescence and some absorption in the uv region (Table 2).

Finally, according to our approach for the preparation of fused heterocycles, ethyl 3-amino[1,2,4]triazino[2,3-*a*]-1*H*-benzimidazole-2-carboxylate (**11**) can also be obtained selectively by the reaction of **1** with 1,2-diamino-1*H*-benzimidazole (**10**) (Scheme 3). This reaction may be assumed to proceed similarly with those of the compounds of types

Scheme 2



Scheme 3



The ir spectra of **4** and **5** showed absorption bands due to an amino group in the 3410-3429 and 3252-3280 cm^{-1} region and an ester and amide carbonyl groups at 1700-1709 and at 1655-1690 cm^{-1}, respectively. But these compounds, **4** and **5**, exhibit no characteristic band for a cyano group. On the other hand, ^1H nmr spectra of **4** and **5** revealed signals at δ 8.00-8.12 and 8.33-8.58 each corresponding to one proton.

4 and **5** (Scheme 2). The ir spectrum of **11** shows peaks due to an ester carbonyl band at 1703 cm^{-1} and an amino group at 3390 and 3258 cm^{-1}, but it gave no absorption band for a cyano group as well as the compounds of types **4** and **5**. The ^1H nmr spectrum revealed signals at δ 1.40 (3H) and 4.46 (2H) for an ethoxy group and at δ 7.33-7.85 (4H) for an aromatic ring respectively.

Table 1

NMR Data of Compounds **4**, **5**, and **11** in Dimethyl-d_6 Sulfoxide at 30°C

Product	^{1}H-NMR, δ (ppm), J (Hz)	^{13}C-NMR, δ (ppm)
4a	1.34 (t, 3H, J = 7.1, CH_3), 3.27(s, 3H, NCH_3), 3.45 (s, 3H, NCH_3), 4.36 (q, 2H, J = 7.1, OCH_2), 8.06 (br s, 1H, NH), 8.41 (br s, 1H, NH)	14.2 (OCH_2CH_3), 28.1, 28.8 (each NCH_3), 61.2 (OCH_2), 116.8 (C4a), 120.7 (C6), 149.6 (C8a), 150.8 (C2),156.2 (C7), 158.6 (C4), 165.0 (COO)
4b	1.22 (t, 3H, J = 7.0, CH_3), 1.23 (t, 3H, J = 7.1, CH_3), 1.27 (t, 3H, J = 7.0, CH_3), 4.18 (q, 4H, J = 7.1, $2NCH_2$), 4.40 (q, 2H, J = 7.1, OCH_2), 8.18 (br s, 1H, NH), 8.55 (br s, 1H, NH)	12.7, 12.8 (each NCH_2CH_3), 14.1 (OCH_2CH_3), 36.1, 36.8 (each NCH_2), 61.1 (OCH_2), 116.8 (C4a), 120.9 (C6), 149.0 (C8a), 149.7 (C2), 156.2 (C7), 158.1 (C4), 164.9 (COO)
4c	0.88 (t, 3H, J = 7.2, CH_3), 0.90 (t, 3H, J = 7.1, CH_3), 1.34 (t, 3H, J = 7.1, CH_3), 1.58, 1.65 (each sextet, 2H, J = 7.3, CH_2), 3.86, 4.05 each t, 2H, J = 7.3, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.03 (br s, 1H, NH), 8.38 (br s, 1H, NH)	10.8, 10.9 (each $NCH_2CH_2CH_3$), 13.9 (OCH_2CH_3), 20.2, 20.3 (each NCH_2CH_2), 42.3, 42.8 (each NCH_2), 60.9 (OCH_2), 116.5 (C4a), 120.7 (C6), 149.1 (C8a), 150.0 (C2), 156.0 (C7), 158.1 (C4), 164.7 (COO)
4d	0.90 (t, 3H, J = 7.3, CH_3), 0.92 (t, 3H, J = 7.3, CH_3), 1.27-1.36 (m, 7H, CH_3 and $2CH_2$), 1.52-1.60 (m, 4H,CH_2), 3.89 (t, 2H, J = 7.2, NCH_2), 4.08 (t, 2H, J = 7.4, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.03 (br s, 1H, NH), 8.36 (br s, 1H, NH)	13.58, 13.62 (each $NCH_2CH_2CH_2CH_3$), 14.1 (OCH_2CH_3), 19.4, 19.5 (each $NCH_2CH_2CH_2$), 29.2, 29.3 (each NCH_2CH_2), 40.6, 41.3 (each NCH_2), 61.1 (OCH_2), 116.7 (C4a), 120.9 (C6), 149.2 (C8a), 150.1 (C2),156.1 (C7), 158.2 (C4), 164.9 (COO)
4e	0.86 (d, 6H, J = 6.5, $2CH_3$), 0.89 (d, 6H, J = 6.1, CH_3), 1.34 (t, 3H, J = 7.1, CH_3), 1.97-2.11 (m, 2H, 2CH), 3.76 (d, 2H, J = 7.4, NCH_2), 3.95 (d, 2H, J = 7.3, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.02 (br s, 1H, NH), 8.37 (br s, 1H, NH)	14.1 (OCH_2CH_3), 19.8, 19.9 (each $CH(CH_3)_2$), 26.55, 26.59 (each $CH(CH_3)_2$), 47.7, 48.2 (each NCH_2), 61.1 (OCH_2), 116.6 (C4a), 121.0 (C6), 149.5 (C8a), 150.7 (C2), 156.0 (C7), 158.5 (C4), 164.9 (COO)
4f	0.87 (t, 6H, J = 6.8, $2CH_3$), 1.26-1.36 (m, 11H, $4CH_2$ and CH_3), 1.56-1.62 (m, 4H, CH_2), 3.88, 4.08 (each t, 2H, J = 7.4, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2),8.02 (br s, 1H, NH), 8.36 (br s, 1H, NH)	13.5, 13.6 (each $NCH_2CH_2CH_2CH_2CH_3$), 13.9 (OCH_2CH_3), 21.5, 21.6, 26.5, 26.6, 28.1, 28.2 (each CH_2), 40.7, 41.3 (each NCH_2), 60.9 (OCH_2), 116.5 (C4a), 120.7 (C6), 149.0 (C8a), 149.9 (C2), 156.0 (C7), 158.0 (C4), 164.7 (COO)
4g	0.92 (d, 6H, J = 7.0, $2CH_3$), 0.94 (d, 6H, J = 6.7, $2CH_3$), 1.34 (t, 3H, J = 7.1, CH_3), 1.43-1.61 (m, 6H, $3CH_2$), 3.91,4.09 (each t, 2H, J = 7.5, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.04 (br s, 1H, NH), 8.33 (br s, 1H, NH)	14.1 (OCH_2CH_3), 22.3, 22.4 (each $CH(CH_3)_2$), 25.5, 25.6 (each $CH(CH_3)_2$), 35.9, 36.1 (each NCH_2CH_2), 39.5, 40.2 (each NCH_2), 61.6, (OCH_2), 116.8 (C4a), 120.9 (C6), 149.1 (C8a), 150.0 (C2), 156.1 (C7), 158.2 (C4), 164.9 (COO)
4h	0.86 (t, 6H, J = 6.8, $2CH_3$), 1.24-1.31 (m, 12H, $6CH_2$), 1.34 (t, 3H, J = 7.1, CH_3), 1.52-1.64 (m, 4H, CH_2), 3.88, 4.08 (each t, 2H, J = 7.1, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.04 (br s, 1H, NH), 8.36 (br s, 1H, NH)	13.78, 13.81 (each $NCH_2CH_2CH_2CH_2CH_2CH_3$), 14.1 ($OCH_2CH_3$), 21.9, 22.0, 25.8, 25.9, 27.0, 27.1, 29.1, 30.9 (each CH_2), 40.9, 41.6 each NCH_2), 61.1 (OCH_2), 116.7 (C4a), 120.9 (C6), 149.2 (C8a), 150.1 (C2), 156.2 (C7), 158.3 (C4), 164.9 (COO)
4i	0.85 (t, 6H, J = 6.6, $2CH_3$), 1.23-1.30 (m, 16H, $8CH_2$), 1.36 (t, 3H, J = 7.1, CH_3), 1.53-1.63 (m, 4H, CH_2), 3.88, 4.08 (each t, 2H, J = 7.1, NCH_2), 4.36 (q, 2H, J = 7.1, OCH_2), 8.04 (br s, 1H, NH), 8.37 (br s, 1H, NH)	13.85, 13.86 (each $NCH_2CH_2CH_2CH_2CH_2CH_2$ CH_3), 14.1 (OCH_2CH_3), 21.9, 22.0, 26.1, 26.2, 27.1, 27.2, 28.3, 28.4, 31.1, 31.2 (each CH_2), 40.9, 41.6 (each NCH_2), 61.1 (OCH_2), 116.7 (C4a), 120.9 (C6), 149.2 (C8a), 150.1 (C2), 156.2 (C7),158.3 (C4), 164.9 (COO)
5a	1.39 (t, 3H, J = 7.1, CH_3), 3.70 (s, 3H, N-CH_3), 3.92 (s, 3H, NCH_3), 4.37 (q, 2H, J = 7.1, OCH_2), 8.12 (br s, 1H, NH), 8.55 (br s, 1H, NH)	14.2 (OCH_2CH_3), 35.4, 36.2 (each NCH_3), 61.5 (OCH_2), 118.1 (C4a), 122.9 (C6), 149.2 (C8a), 156.0 (C4), 156.9 (C7), 164.7 (COO), 177.9 (C2)
5b	1.23, 1.28 (each t, 3H, J = 6.8, CH_3), 1.34 (t, 3H, J = 7.1, CH_3), 4.37 (q, 2H, J = 7.1, OCH_2), 4.51 (q, 2H, J = 6.8, NCH_2), 4.73 (q, 2H, J = 6.8, NCH_2), 8.11 (br s, 1H, NH), 8.58 (br s, 1H, NH)	11.7, 11.9 (each CH_3), 14.1(CH_3), 43.0, 43.7 (each NCH_2), 61.5 (OCH_2), 118.2 (C4a), 123.0 (C6), 148.5 (C8a), 156.2 (C7), 156.3 (C4), 164.7 (COO), 176.6 (C2)
5c	0.90 (t, 3H, J = 7.3, CH_3), 0.94 (t, 3H, J = 7.3, CH_3), 1.34 (t, 3H, J = 6.5, CH_3), 1.71 (sextet, 4H, J = 7.5, CH_2), 4.37 (q, 2H, J = 6.5, OCH_2), 4.40 (t, 2H, J = 7.3, NCH_2), 4.62 (t, 2H, J = 7.3, NCH_2), 8.09 (br s, 1H, NH), 8.51 (br s, 1H, NH)	10.9, 11.0 (each CH_3), 14.0 (CH_3), 19.3, 19.4 (each CH_2), 48.9, 49.5 (each NCH_2), 61.4 (OCH_2), 117.94 (4a), 122.9 (C6), 148.6 (C8a), 156.0 (C7) , 156.3 (C4), 164.5 (COO), 176.9 (C2)
5d	0.92 (t, 3H, J = 7.5, CH_3), 0.94 (t, 3H, J = 7.5, CH_3), 1.34 (sextet, 2H, J = 7.1, CH_2), 1.35 (t, 3H, J = 7.1, CH_3), 1.38 (sextet, 2H, J = 7.1, CH_2), 1.65, 1.69 (each quintet, 2H, J = 7.1, CH_2), 4.38 (q, 2H, J = 7.1, OCH_2), 4.45,4.66 (each t, 2H, J = 7.5, NCH_2), 8.09, 8.50 (each br s, 1H, NH)	13.68, 13.71 (each CH_3), 14.1 (CH_3), 19.5, 19.6 (each CH_2), 28.1, 28.2 (each CH_2), 47.3, 48.0 (each NCH_2), 61.4 (OCH_2), 118.0 (C4a), 123.1 (C6), 148.7 (C8a), 156.1 (C7), 156.4 (C4), 164.61 (COO), 176.9 (C2)
11	1.40 (t, 3H, J = 7.1, CH_3), 4.46 (q, 2H, J = 7.1, OCH_2), 7.33 (ddd, 1H, J = 8.0, 7.1, 1.0), 7.44 (ddd, 1H, J = 8.0, 7.1, 1.0), 7.64 (d, 1H, J = 8.0), 7.85 (d, 1H, J = 8.0)	13.7 (CH_3), 62.1 (OCH_2), 110.1 (C9), 118.1 (C6), 120.9 (C8), 125.8 (C7), 127.1 (C9a), 128.3 (C5a), 143.3 (C4a), 146.5 (C2), 152.2 (C3), 162.6 (COO)

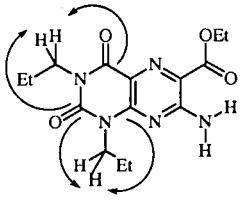
The molecular formula of compounds **4**, **5**, and **11**which were obtained and confirmed by elemental analysis and ms data. The structure of the compounds **4**, **5**, and **11** was also confirmed by some 1D- and 2D-nmr techniques, such as DEPT (determination of methyl, methylene, methine, or quaternary carbon), HMQC ($^1J_{CH}$ correlation), and HMBC ($^2J_{CH}$ or $^3J_{CH}$ correlation). The ^{1}H-detected $^3J_{CH}$ coupling correlative

Table 2

Ultraviolet and Fluorescence Spectral Data of Compounds **4**

	Ultraviolet λ_{max}, nm (ε)	Fluorescence λ_{max}, nm
4a	267 (35300), 285 (34300), 362 (36000)	413
4b	232 (24325), 273 (7361), 290 (7239), 364 (11503)	409
4c	232 (30803), 273 (9766), 288 (9431), 364 (15384)	410
4d	233 (33782), 272 (10945), 289 (10255), 365 (17091)	409
4e	233 (38687), 274 (12989), 291 (12486), 365 (20335)	411
4f	234 (38906), 274 (12422), 291 (11718), 366 (19492)	410
4g	233 (36641), 274 (11953), 289 (11250), 365 (18438)	410
4h	234 (34686), 274 (11297), 291 (10711), 365 (17155)	410
4i	233 (28661), 273 (9464), 290 (8884), 365 (14018)	410

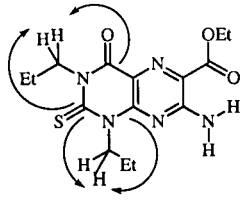
data (HMBC) for **4c** and **5c** are illustrated in Figures 1-2, respectively.



4c

	Irradiated Nucleus	$^3J_{CH}$ Correlated Proton(s)
C2	149.7 ppm	3.86 and 4.05 ppm (3- and 1-CH_2)
C4	158.1	3.86 (3-CH_2)
C8a	149.1	4.05 (1-CH_2)

Figure 1. ^{1}H-detected long range $^3J_{CH}$ correlation (HMBC) in **4c**.



5c

	Irradiated Nucleus	$^3J_{CH}$ Correlated Proton(s)
C2	176.9 ppm	4.40 and 4.62 ppm (3- and 1-CH_2)
C4	156.3	4.40 (3-CH_2)
C8a	148.5	4.62 (1-CH_2)

Figure 2. ^{1}H-detected long range $^3J_{CH}$ correlation (HMBC) in **5c**.

The principal advantages of the method described here are that the time of reaction is short, the work up is convenient, and the reaction is easily carried out and proceeds under mild conditions to give 7-aminopteridine type compounds selectively.

EXPERIMENTAL

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. The ir spectra were recorded in potassium bromide on a Perkin-Elmer FT-IR 1000 PC spectrophotometer. The uv and fluorescence spectra were taken on either a Hitachi 124 or a Hitachi 320 spectrophotometer in ethanol. The ^{1}H nmr spectra were recorded on either a JEOL EX-400 (400 MHz) or a Varian VXR-300 (300 MHz) instrument. The ^{13}C nmr (100 MHz) were taken on a JEOL EX-400 instrument in dimethyl-d_6 sulfoxide with tetramethylsilane as internal reference. The distortionless enhancement by polarization transfer (DEPT) spectra were run in a standard manner, using θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. Moreover, the signals caused by quaternary carbons were identified by the comparison between ^{13}C NMR and DEPT spectra. The ^{1}H-detected heteronuclear multiple-quantum coherence (HMQC, using C-H spin-spin coupling constant $^1J_{CH}$ = 140 Hz), and ^{1}H-detected multiple-bond heteronuclear multiple-quantum coherence (HMBC, using C-H long range coupling constant $^nJ_{CH}$ = 8 Hz) experiments were also carried out with a JEOL EX-400 instrument. Mass spectra were obtained with a JEOL AX-500 spectrometer (EI: 70 eV). Elemental analyses were performed on a Perkin-Elmer 240 instrument.

All heterocyclic *vicinal*-diamines, such as 1,3-dialkyl-5,6-diaminouracils **2** [14], 1,3-dialkyl-5,6-diamino-2-thiouracils **3** [15], and 1,2-diaminobenzimidazole (**10**) [16, 17], were obtained according to the literature.

General Procedure for the Preparation of 1,3-Dialkyl-7-amino-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylates **4**.

A mixture of 0.22 g (1.0 mmole) of diethyl (*E*)-2,3-dicyanobutenedioate (**1**) and 1.0 mmole of 1,3-dialkyl-5,6-diaminouracils **2** were refluxed in ethanol (10 ml) for one hour. The reaction mixture was cooled to room temperature and was allowed to stand overnight. The deposited solid was isolated by filtration and recrystallized from pyridine-ethanol (2:1) to give **4a-i** as yellow to orange crystals.

Ethyl 7-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**4a**).

This compound was obtained as yellowish brown crystals, 0.18 g, 65% yield, mp 265-267°; ir: ν 3415, 3270 (NH), 1685 (COO), 1648 (N-C=O); ms: m/z 279 (M^+), 207.

Anal. Calcd. for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.07. Found: C, 47.32; H, 4.79; N, 25.22.

Ethyl 7-Amino-1,3-diethyl-2,4-dioxo-1.2,3,4-tetrahydropteridine-6-carboxylate (**4b**).

This compound was obtained as yellow crystals, 0.19 g, 62% yield, mp 254.5-255.5°; ir: ν 3415, 3280 (NH), 1705 (COO), 1660 (N-C=O); ms: m/z 307 (M^+), 234.

Anal. Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.46; H, 5.58; N, 22.68.

Ethyl 7-Amino-2,4-dioxo-1,3-dipropyl-1,2,3,4-tetrahydropteridine-6-carboxylate (**4c**).

This compound was obtained as yellow crystals, 0.20 g, 60% yield, mp 194-194.5°; ir: ν 3420, 3280 (NH), 1700 (COO), 1665 (N-C=O); ms: m/z 335 (M^+), 262.

Anal. Calcd. for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 53.96; H, 6.22; N, 20.69.

Ethyl 7-Amino-1,3-dibutyl-2,4-dioxo-1.2,3,4-tetrahydropteridine-6-carboxylate (**4d**).

This compound was obtained as yellow crystals, 0.13 g, 36% yield, mp 184-185°; ir: ν 3420, 3280 (NH), 1700 (COO), 1663 (N-C=O); ms: m/z 363 (M^+), 290.

Anal. Calcd. for $C_{17}H_{25}N_5O_4$: C, 56.19; H, 6.93; N, 19.27. Found: C, 56.21; H, 6.84; N, 19.48.

Ethyl 7-Amino-1,3-diisobutyl-2,4-dioxo-1.2,3,4-tetrahydropteridine-6-carboxylate (**4e**).

This compound was obtained as orange crystals, 0.20 g, 55% yield, mp 210-211°; ir: ν 3415, 3280 (NH), 1700 (COO), 1660 (N-C=O); ms: m/z 363 (M^+), 290.

Anal. Calcd. for $C_{17}H_{25}N_5O_4$: C, 56.19; H, 6.93; N, 19.27. Found: C, 56.01; H, 6.95; N, 19.27.

Ethyl 7-Amino-1,3-diamyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**4f**).

This compound was obtained as orange crystals, 0.22 g, 56% yield, mp 181-183°; ir: ν 3420, 3280 (NH), 1700 (COO), 1660 (N-C=O); ms: m/z 391 (M^+), 318.

Anal. Calcd. for $C_{19}H_{29}N_5O_4$: C, 58.29; H, 7.46; N, 17.88. Found: C, 58.41; H, 7.55; N, 18.10.

Ethyl 7-Amino-1,3-diisoamyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**4g**).

This compound was obtained as orange crystals, 0.21 g, 54% yield, mp 176.5-178.5°; ir: ν 3418, 3280 (NH), 1700 (COO), 1660 (N-C=O); ms: m/z 391 (M^+), 318.

Anal. Calcd. for $C_{19}H_{29}N_5O_4$: C, 58.29; H, 7.46; N, 17.88. Found: C, 58.24; H, 7.16; N, 17.87.

Ethyl 7-Amino-1,3-dihexyl-2,4-dioxo-1.2,3,4-tetrahydropteridine-6-carboxylate (**4h**).

This compound was obtained as yellow crystals, 0.14 g, 33% yield, mp 179.5-180°; ir: ν 3435, 3245 (NH), 1688 (COO), 1668 (N-C=O); ms: m/z 419 (M^+), 346.

Anal. Calcd. for $C_{21}H_{33}N_5O_4$: C, 60.12; H, 7.92; N, 16.69. Found: C, 59.92; H, 8.14; N, 16.97.

Ethyl 7-Amino-1,3-diheptyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**4i**).

This compound was obtained as orange crystals, 0.14 g, 31% yield, mp 184-186°; ir: ν 3425, 3280 (NH), 1705 (COO), 1665 (N-C=O); ms: m/z 447 (M^+), 374.

Anal. Calcd. for $C_{23}H_{37}N_5O_4$: C, 61.72; H, 8.33; N, 15.64. Found: C, 61.61; H, 8.11; N, 15.80.

General Procedure for the Preparation of Ethyl 1,3-Dialkyl-7-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylates **5**.

A mixture of 0.18 g (0.80 mmole) of diethyl (*E*)-2,3-dicyanobutenedioate (**1**) and 0.80 mmoles of 1,3-dialkyl-5,6-diamino-2-thiouracils **3** were refluxed in ethanol (10 ml) for one hour. The reaction mixture was cooled to room temperature, and then allowed to stand overnight. The deposited solid was collected by filtration, washed with cold ethanol, and recrystallized from pyridine-ethanol (2:1) to give **5a-d** as yellow to brown crystals.

Ethyl 7-Amino-1,3-dimethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**5a**).

This compound was obtained as brown crystals, 80 mg, 34% yield, mp 297.5-298.5°; ir: ν 3410, 3270 (NH), 1705 (COO), 1690 (N-C=O); ms: m/z 295 (M^+), 222, 195.

Anal. Calcd. for $C_{11}H_{13}N_5O_3S$: C, 44.74; H, 4.44; N, 23.71; S, 10.86. Found: C, 44.71; H, 4.42; N, 23.58; S, 10.93.

Ethyl 7-Amino-1,3-diethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**5b**).

This compound was obtained as brown crystals, 85 mg, 33% yield, mp 273-275°; ir: ν 3412, 3275 (NH), 1709 (COO), 1685 (N-C=O); ms: m/z 323 (M^+), 250, 195.

Anal. Calcd. for $C_{13}H_{17}N_5O_3S$: C, 48.28; H, 5.29; N, 21.65; S, 9.91. Found: C, 48.34; H, 5.30; N, 21.60.

Ethyl 7-Amino-1,3-dipropyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**5c**).

This compound was obtained as brown crystals, 98 mg, 35% yield, mp 179-180°; ir: ν 3410, 3280 (NH), 1702 (COO), 1685 (N-C=O); ms: m/z 351 (M^+), 278, 195.

Anal. Calcd. for $C_{15}H_{21}N_5O_3S$: C, 51.27; H, 6.02; N, 19.93; S, 9.12. Found: C, 51.13; H, 6.01; N, 19.84.

Ethyl 7-Amino-1,3-dibutyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropteridine-6-carboxylate (**5d**).

This compound was obtained as yellow crystals, 139 mg, 46% yield, mp 188.5-189.5°; ir: ν 3429, 3252 (NH), 1700 (COO), 1681 (N-C=O); ms: m/z 379 (M^+), 306, 195.

Anal. Calcd. for $C_{17}H_{25}N_5O_3S$: C, 53.80; H, 6.64; N, 18.45; S, 8.44. Found: C, 53.71; H, 6.79; N, 18.53.

Ethyl 3-Amino-1*H*-[1,2,4]triazino[2,3-*a*]benzimidazole-2-carboxylate (**11**).

To a solution of 1.0 g (4.5 mmoles) of diethyl (*E*)-2,3-dicyanobutenedioate (**1**) in dimethyl sulfoxide (5 ml), 0.66 g (4.5 mmoles) of 1,2-diaminobenzimidazole (**10**) dissolved in dimethylsulfoxide (10 ml) was added with stirring. After stirring was continued for four hours at room temperature, the solution was poured into water (40 ml). The deposited products were collected by filtration, washed with water and recrystallized from ethanol to give **11** as yellow crystals, 0.26 g, 20% yield, mp 227-228°; ir: ν 3390, 3258 (NH), 1703 (COO); ms: m/z 257 (M^+), 185, 158, 133, 105, 90.

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.02; H, 4.30; N, 27.22. Found: C, 55.91; H, 4.18; N, 27.37.

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