Synthesis and Structure of 6- and 7-(Acylmethyl)pteridines

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6-(Acylmethyl)-7-hydroxypteridines **7-14** as well as the isomeric 7-(acylmethyl)-6-hydroxypteridines **15-22** were prepared by condensation of 5,6-diaminouracils **1** and **2** with ethyl aroylpyruvates **3-6** in pyridine and hydrochloric acid, respectively. The structures of the newly synthesized compounds were confirmed by their hydrolysis into the 7-hydroxy-6-methyl- **23, 24** and 6-hydroxy-7-methylpteridines **25** and **26**. The synthesis of the 2-(methylthio) derivative **28** is also described.

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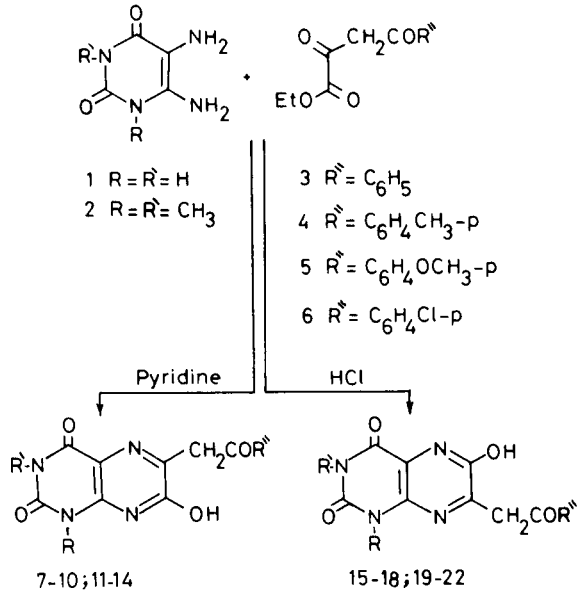
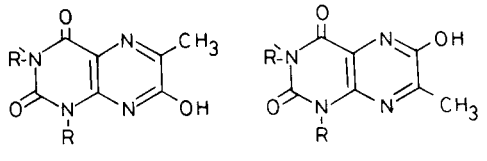
Pteridines constitute an important class of compounds that possess a wide range of pronounced biological activities [1-4]. The most widely used method for the synthesis of such ring system involves the condensation of a 5,6-diaminouracil with a 1,2-dicarbonyl compound [5]. It seemed of interest to investigate the possible condensation between some 5,6-diaminouracils and ethyl aroylpyruvates and to study the mode of cyclization under acidic and basic conditions.

As a point of departure we chose the simplest compound, *i.e.*, 5,6-diaminouracil. Thus, condensation of **1** with ethyl benzoylpyruvate (**3**) and its *p*-substituted derivatives **4-6** may produce 6-(acylmethyl)-7-hydroxypteridines **7-10** or their isomeric 7-(acylmethyl)-6-hydroxy analogues **15-18** depending on the *p*H under which the condensation was carried out. We have found that, when the diaminouracil **1** was heated under reflux with esters **3-6** in dry pyridine we obtained 6-(acylmethyl)-7-hydroxy-2,4(1*H*,3*H*)-pteridinediones **7-10**. On the other hand, when the condensation was conducted in hydrochloric acid 7-(acylmethyl)-6-hydroxy-2,4 (1*H*,3*H*)-pteridinediones **15-18** were obtained.



7,15 R=R'=H ; R''=C_6H_5
8,16 R=R'=H ; R''=$C_6H_4CH_3$-p
9,17 R=R'=H ; R''=$C_6H_4OCH_3$-p
10,18 R=R'=H ; R''=C_6H_4Cl-p
11,19 R=R'=CH_3 ; R''=C_6H_5
12,20 R=R'=CH_3 ; R''=$C_6H_4CH_3$-p
13,21 R=R'=CH_3 ; R''=$C_6H_4OCH_3$-p
14,22 R=R'=CH_3 ; R''=C_6H_4Cl-p

To ascertain the structures of the obtained pteridines, the position of the phenacyl groups in **7-10** was confirmed by the following facts: 1) When **7-10** were subjected to alkaline hydrolysis they converted into 7-hydroxy-6-methyl-2,4(1*H*,3*H*)-pteridinedione (**23**) and the corresponding aromatic acid. Similar hydrolysis of **15-18** gave 6-hydroxy-7-methyl-2,4(1*H*,3*H*)-pteridinedione (**25**). Compounds **23** and **25** were found identical with samples prepared according to the reported procedures [6,7]. 2) Acid hydrolysis of 7-hydroxy-2-(methylthio)-6-phenacyl-4(3*H*)-pteridinone (**28**), obtained by the condensation of 5,6-diamino-2-(methylthio)-4(3*H*)-pyrimidinone (**27**) with ethyl benzoylpyruvate (**3**) in dry pyridine gave **7**.



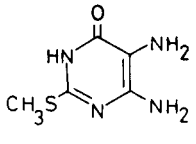
23 R=R'=H
24 R=R'=CH_3

25 R=R'=H
26 R=R'=CH_3

In an attempt to synthesize the 1,3-dimethyl derivatives of compounds **7-10** and **15-18** respectively, we investigated the reaction between 5,6-diamino-1,3-dimethyluracil (**2**) and ethyl aroylpyruvates **3-6**. Thus, condensation of **2** with **3-6** in dry pyridine afforded 6-(acylmethyl)-7-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pteridinediones **11-14**. However, condensation of **2** with **3-6** in hydrochloric acid led

to the formation of the 7-(acylmethyl)-6-hydroxy isomers **19-22**.

The structures of the isomeric pteridines **11-14** and **19-22** have been differentiated and established by the fact that **11** was hydrolyzed into 7-hydroxy-1,3,6-trimethyl-2,4-(1*H*,3*H*)-pteridinedione (**24**) while similar treatment of **19** gave 6-hydroxy-1,3,7-trimethyl-2,4(1*H*,3*H*)-pteridinedione (**26**) [6,8].



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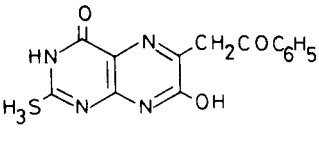

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Furthermore, the 7-hydroxy-6-phenacylpteridines **7** and **11** exhibit similar uv absorption spectra with a characteristic λ max at 346 nm. On the other hand, the 6-hydroxy-7-phenacylpteridines **15** and **19** extend their absorption to λ max above 400 nm.

From what has been said, we come to the conclusion that the previous findings are in accordance with the reported behaviour of 5,6-diaminouracils [5,6,9]. Because of their different position with respect to the 4-oxo group and to the nitrogen atoms in the ring, condensation with the 5- and 6-amino groups is *p*H dependent. Thus, in pyridine the 5-amino group of the pyrimidine condenses with the 2-keto group of the carbonyl component and the 6-amino group condenses with the ester carbonyl. However, in 1*N* hydrochloric acid the 6-amino group condenses with the 2-keto function and the 5-amino group condenses with the ester carbonyl leading to the isomeric products.

Table 1

Yields and Analytical Characterization of Compounds **7-10** and **15-18**

Products [a]	Yield %	Formula (Molecular Weight)	Analyses % [b] Calcd./Found C	H	N
7	75	$C_{14}H_{10}N_4O_4$	56.38	3.38	18.79
		(298.26)	55.90	3.50	18.60
8	80	$C_{15}H_{12}N_4O_4$	57.69	3.87	17.94
		(312.28)	57.80	4.00	18.10
9	83	$C_{15}H_{12}N_4O_5$	54.88	3.68	17.07
		(328.28)	55.00	3.80	16.90
10	85	$C_{14}H_9ClN_4O_4$	50.54	2.73	16.84
		(332.70)	50.70	2.50	16.70
15	30	$C_{14}H_{10}N_4O_4$	56.38	3.38	18.79
		(298.26)	56.50	3.50	19.00
16	40	$C_{15}H_{12}N_4O_4$	57.69	3.87	17.94
		(312.28)	57.70	3.90	17.80
17	35	$C_{15}H_{12}N_4O_5$	54.88	3.68	17.07
		(328.28)	54.80	3.70	17.00
18	32	$C_{14}H_9ClN_4O_4$	50.54	2.73	16.84
		(332.70)	50.70	3.00	16.60

[a] Compounds **7**, ms: m/e 298 (M^+); uv: λ max (log ε max): 346 nm (5.03); **15**, ms: m/e 298 (M^+); uv: λ max (log ε max): 308 (5.10), 438 nm (5.18). [b] Compounds **10**: Cl, Calcd: 10.66. Found: 10.40; **18**, Cl, Calcd: 10.66. Found: 10.80.

Table 2

Yields and Analytical Characterization of Compounds **11-14** and **19-22**

Products [a]	Mp °C [b]	Yield %	Formula (Molecular Weight)	Analyses % [c] Calcd./Found C	H	N
11	275	60	$C_{16}H_{14}N_4O_4$	58.89	4.32	17.17
			(326.31)	59.20	4.20	16.90
12	298	55	$C_{17}H_{16}N_4O_4$	59.99	4.73	16.46
			(340.34)	60.10	4.60	16.20
13	270	50	$C_{17}H_{16}N_4O_5$	57.30	4.52	15.72
			(356.34)	57.50	4.30	15.60
14	283	70	$C_{16}H_{13}ClN_4O_4$	53.27	3.63	15.53
			(360.76)	53.40	3.80	15.40
19	290	35	$C_{16}H_{14}N_4O_4$	58.89	4.32	17.17
			(326.31)	59.20	4.10	17.30
20	305	40	$C_{17}H_{16}N_4O_4$	59.99	4.73	16.46
			(340.34)	60.00	4.70	16.30
21	308	32	$C_{17}H_{16}N_4O_5$	57.30	4.52	15.72
			(356.34)	57.40	4.70	15.50
22	303	30	$C_{16}H_{13}ClN_4O_4$	53.27	3.63	15.53
			(360.76)	53.10	3.70	15.20

[a] Compounds **11**, ms: m/e 326 (M^+); uv: λ max (log ε max): 346 nm (5.03); **19**, ms: m/e 326 (M^+); uv: λ max (log ε max): 306 (4.65), 420 nm (4.82). [b] All compounds melted with decomposition. [c] Compounds **14**: Cl, Calcd: 9.83. Found: 10.10; **22**, Cl, Calcd: 9.83. Found: 9.70.

EXPERIMENTAL

All melting points are uncorrected. Mass spectra were recorded on Finnigan MAT 312 spectrometer. Ultraviolet spectra were obtained on Unicam SP 1720 spectrophotometer.

Compounds prepared by different procedures were identified by uv spectra (methanol) and R_f values.

6-(Acylmethyl)-7-hydroxy-2,4(1*H*,3*H*)-pteridinediones (**7-10**).

A mixture of 5,6-diaminouracil hydrochloride [10] (**1**·HCl) (10 mmoles) and the appropriate sodium salt of ethyl aroylpyruvate [11] **3-6** (10 mmoles) was heated under reflux in 50 ml of dry pyridine for 1 hour and cooled. The solid precipitated was collected, washed with ethanol and crystallized from DMF into compounds **7-10** respectively, mp >300° (Table 1).

7-(Acylmethyl)-6-hydroxy-2,4(1*H*,3*H*)-pteridinediones (**15-18**).

A suspension of 5,6-diaminouracil hydrochloride [10] (**1**·HCl) (10 mmoles) and the appropriate sodium salt of ethyl aroylpyruvate **3-6** (10 mmoles) was heated under reflux in 100 ml of 1*N* hydrochloric acid for 45 minutes and cooled. The solid precipitated was collected and purified [12] by dissolving in 100 ml of 5% sodium carbonate and reprecipitated by the addition of dilute hydrochloric acid. The process was repeated until a pure product (tlc) was obtained, mp >300° (Table 1).

7-Hydroxy-6-methyl-2,4(1*H*,3*H*)-pteridinedione (**23**).

Each of compounds **7-10** (3.0 g) was heated under reflux in 75 ml of 2*N* sodium hydroxide for 1 hour. The solution was cooled and acidified by the dropwise addition of boiling dilute sulfuric acid and left overnight at ambient temperature. The solid was crystallized from water into compound **23**, identical with an authentic sample prepared from **1** and ethyl pyruvate after the procedure of Pfleiderer [7].

6-Hydroxy-7-methyl-2,4(1*H*,3*H*)-pteridinedione (**25**).

This compound was obtained by hydrolyzing compounds **15-18**, respectively following the above procedure for obtaining **23**. Compound **25** was found identical with an authentic sample prepared from **1** and ethyl acetylpyruvate according to the reported procedure [8].

6-(Acylmethyl)-7-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pteridinediones (**11-14**).

These compounds were prepared from 5,6-diamino-1,3-dimethyluracil (**2**·HCl) (10 mmoles) and the appropriate sodium salt of **3-6** (10 mmoles), respectively as described for compounds **7-10** (Table 2).

7-(Acylmethyl)-6-hydroxy-1,3-dimethyl-2,4(1*H*,3*H*)-pteridinediones (**19-22**).

These compounds were prepared from **2**·HCl and the appropriate sodium salt of **3-6** respectively following the procedure for the preparation of compounds **15-18** (Table 2).

7-Hydroxy-1,3,6-trimethyl-2,4(1*H*,3*H*)-pteridinedione (**24**).

This compound was prepared by hydrolyzing **11** with 2*N* sodium hydroxide following the procedure described for the hydrolysis of **7-10**, yield 55%. Compound **24** was found identical with an authentic sample prepared from **2**·HCl and methyl pyruvate [8].

6-Hydroxy-1,3,7-trimethyl-2,4(1*H*,3*H*)-pteridinedione (**26**).

This compound was prepared by hydrolyzing **19** as described for **11**, yield 50%.

7-Hydroxy-2-(methylthio)-6-phenacyl-4(3*H*)-pteridinone (**28**).

A mixture of 5,6-diamino-2-(methylthio)-4(3*H*)-pyrimidinone (**27**) [13] (10 mmoles) and ethyl benzoylpyruvate (**3**) (10 mmoles) in 20 ml of dry pyridine was heated under reflux for 30 minutes, cooled and diluted with water. The precipitate was filtered off, washed with ethanol and crystallized from DMF into **28**, mp >300°, yield 80%.

Anal. Calcd. for $C_{15}H_{12}N_4O_2S$: (328.35): C, 54.87; H, 3.68; N, 17.06; S, 9.77. Found: C, 54.80; H, 3.70; N, 17.30; S, 9.90.

7-Hydroxy-6-phenacyl-2,4(1*H*,3*H*)-pteridinedione (**7**).

A suspension of 0.3 g (1.0 mmole) of **28** in 5 ml ethanol containing 3 ml of concentrated hydrochloric acid was heated under reflux until no methanethiol was evolved (1 hour) and cooled. The precipitate was filtered off and crystallized from DMF into **7** yield 50%.

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[12] Compounds **15-18** are practically insoluble in the usual solvents.

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