4-Azapteridines. I. Covalent Addition Products of the Pyrazino[2,3-*e*]-*as*-triazine Ring System

Cherng Chyi Tzeng and Raymond P. Panzica*

Departments of Medicinal Chemistry and Chemistry, University of Rhode Island, Kingston, Rhode Island 02881

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Ring closure of 5,6-diamino-3-methylthio-*as*-triazine with 40% aqueous glyoxal provided the 6,7-dihydrate of the pyrazino[2,3-*e*]-*as*-triazine (4-azapteridine) ring system. The C7 hydroxy group of this dihydrate underwent exchange in methanol or ethanol affording the 7-alkoxy, 6-hydroxy derivatives.

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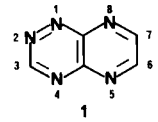
As part of our program to synthesize novel bicyclic nitrogen heterocycles, we initiated a study to prepare the unknown pyrazino[2,3-*e*]-*as*-triazine ring system (**1**, 4-azapteridine). 5,6-Diamino-3-methylthio-*as*-triazine (**2**) [1] was selected as starting material for this project.



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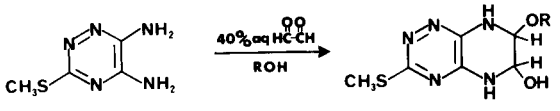
Reacting **2** with 40% aqueous glyoxal under neutral or acidic conditions gave the 2:1 σ adduct 6,7-dihydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**3a**) [2]. The structure of **3a** was confirmed by ^{1}H nmr and elemental analyses. The ^{1}H nmr spectrum of **3a** was quite similar to those reported for certain 5,6,7,8-dihydrated pteridines [3].



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3a: R=H
b: R=CH_3
c: R=CH_2CH_3

When this adduct was dissolved in methanol and stirred at room temperature for 1.5 hours, a new compound formed and was shown by ^{1}H nmr to be the monomethoxy, monohydroxy adduct **3b**. This adduct could be easily converted back to the dihydrate **3a** by employing the same reaction conditions and using water as solvent. In fact, the methoxy-**3b** or ethoxy-**3c** adducts were obtained exclusively during ring closure of **2** if methanol or ethanol, respectively, was used as a solvent [4]. To our knowledge this exchange phenomenon has not been observed in the pteridine series.

To establish the position of the alkoxy group, *i.e.*, whether attachment was to the C6 or C7 position, a synthetic and ^{1}H nmr study was undertaken. 6-Amino-5-methylamino-3-methylthio-*as*-triazine (**4**) [1] and 5-amino-6-methylamino-3-methylthio-*as*-triazine (**5**) were prepared and used to assign the chemical shifts of the N(5)H and N(8)H protons of **3** [5]. Inspection of the ^{1}H nmr spectra of **4** and **5** easily identified the NH protons of the amino and methylamino groups, by their splitting patterns and integration, and established their chemical shifts (Table I). We assumed that the electronic and magnetic environment of

Table I

Pertinent ^{1}H NMR Chemical Shift Data (a)

Compound	N5	N6	N8(H)	C6(OH)	C7(OH)	C6(H)	C7(H)	OCH_3	NCH_3
2	7.12 s (b) (NH_2)	5.96 s (NH_2)							
4	7.38 q (NH)	5.92 s (NH_2)							2.82 d
5	7.02 s (NH_2)	6.12 q (NH)							2.85 d
3a	8.72 d (NH)		7.68 d	5.95 d	5.80 d	4.64 m	4.64 m		
3b	8.82 d (NH)		8.22 d	6.05 d		4.76 m	4.35 m	3.15 s	
3c	8.78 d (NH)		8.15 d	6.00 d		4.70 m	4.40 m		
6			8.30 d	6.40 d		4.82 m	4.38 m	3.19 s	3.05 s
7	8.80 d (NH)			6.10 d	6.02 d	4.65 m	4.65 m		3.00 s

(a) All samples were run in DMSO-d_6 and the chemical shifts are expressed in δ units downfield from TMS. (b) s = singlet, d = doublet, q = quartet, m = multiplet.

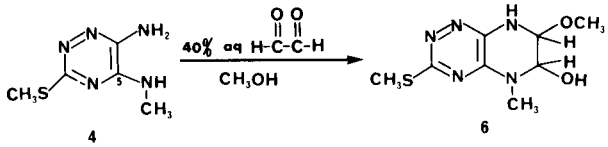
the N(5)H and N(6)H protons in **4** and **5**, respectively, would be similar to those of the N(5)H and N(8)H protons of **3**. Thus, the doublets at δ 8.72-8.82 in the spectra of **3a,b,c** were assigned to the N(5)H proton and the upfield doublets which appear in the range δ 7.68-8.15 to the N(8)H proton. Subsequent ring closure of **4** to **6** and **5** to **7** and examination of their ^{1}H nmr spectra corroborated these assignments. It is worth mentioning that this assignment is identical to that established for the adducts of pteridine [3,6,7]. Next, a series of selective spin decoupling experiments were conducted on **3b** to determine the position of the alkoxy substituent and to assign the remaining proton chemical shifts. These experiments indicated that attachment of the alkoxy group was at C7.

Table II

Analytical Results

Compound	Formula	Calcd./Found C	H	N	S
3a	$C_6H_9N_5O_2S$	33.48	4.21	32.54	14.90
		33.70	3.91	32.69	14.92
3b	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
		36.63	4.84	30.34	13.94
3c	$C_8H_{13}N_5O_2S$	39.50	5.39	28.79	13.18
		39.29	5.41	28.92	12.97
6	$C_8H_{13}N_5O_2S$	39.50	5.39	28.79	13.18
		39.40	5.21	28.84	13.09
7	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
		36.54	4.84	30.64	13.88
5	$C_5H_9N_5S$	35.07	5.30	40.90	18.73
		34.96	5.34	41.11	18.54
6-Methylamino-*as*-triazine-3,5-dithione					
	$C_4H_5N_4S_2$	27.57	3.47	32.15	36.80
		27.57	3.58	32.38	36.66
3,5-*bis*(Methylthio)-6-methylamino-*as*-triazine					
	$C_6H_{10}N_4S_2$	35.62	4.98	27.69	31.72
		35.72	5.06	27.88	31.72

Elemental analyses were performed by M-H-W, Phoenix, Arizona.



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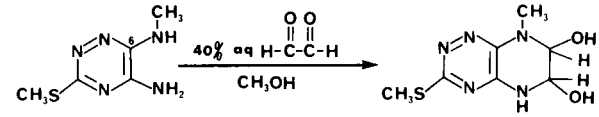
In view of the reversibility experiments, the formation of the alkoxy adducts most probably occurs *via* the 6-hydroxy-3-methylthio-5,6-dihydropyrazino[2,3-*e*]-*as*-triazine intermediate depicted in the final scheme. Additional evidence for this mechanistic pathway was provided by the syntheses of **6** and **7**. Ring closure of **4** with 40% aqueous glyoxal and using methanol as solvent, furnished the 7-methoxy adduct **6**, whereas **5** under the same reaction conditions provided only the dihyrate **7**. Loss of water and formation of the 7,8-azomethine bond is only possible in the case of **6**. Furthermore when **6** was dissolved in water and stirred at room temperature, the corresponding dihydrate derivative was formed.



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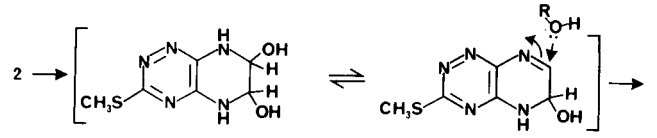

Nucleophilic addition of alcohol across the 7,8-azomethine bond can occur either *cis* or *trans* to the C6 hydroxy group and depending on stereochemistry at C6 furnish four possible stereoisomers. If addition occurs in a *cis* fashion the *R,S* and *S,R* enantiomers would be formed while *trans* addition would afford the racemic *R,R* and *S,S* mixture. Random addition of alcohol would lead to a diastereomeric mixture. Data from our laboratory suggest that addition of alcohol apparently takes place in a stereospecific manner. This assumption is based on the high pressure liquid chromatogram which shows **3b** to be a single component and the decoupled ^{13}C nmr spectrum of **3b** which exhibits single lines for the C6 and C7 carbons; a spectral characteristic atypical of diastereomeric mixtures [8]. Recently, a similar conclusion was reached for an adduct generated from a blocked deoxyguanosine derivative and glyoxal [9]. We are actively pursuing the stereochemical problem as well as examining the exchange process with other nucleophiles.

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[1] C. C. Tzeng, N. C. Motola and R. P. Panzica, *J. Org. Chem.*, **48**, 1271 (1983).

[2] We have used the nomenclature set forth in the pteridine series to describe the hydrate **3a**. The product formed from addition of nucleophilic reagents to the 5,6- and 7,8-azomethine bonds of a pteridine is referred to as a 2:1 σ adduct. See A. Albert (reference 7) and H. van der Plas (Lectures in Heterocyclic Chemistry, Vol 6, R. N. Castle and T. Kappe, eds, HeteroCorporation, Tampa, FL, 1982, p S1) for an in depth treatment of this terminology.

[3] A. Albert, T. J. Batterham and J. J. McCormack, *J. Chem. Soc. (B)*, 1105 (1966) and references cited therein.

[4] In a typical experiment, **2** [1] (314.4 mg, 2 mmoles) was dissolved in 15 ml of solvent (for the preparation of **3a**, distilled water; **3b, 6, 7**, AR methanol; **3c**, absolute ethanol) and to this solution was added 0.3 ml of 0.1 *N* hydrochloric acid and 0.4 ml (2.8 mmoles) of a 40 wt % glyoxal solution. The mixture was stirred at room temperature for 24 hours and

the resulting precipitate was collected by filtration. The solid was washed with cold solvent (4 × 5 ml, as specified above) and dried in an abderhalen for 12 hours at 80°. This material was suitable for analysis or could be recrystallized from the specified solvent. For the synthesis of compounds **6** and **7**, **2** was replaced by **4** and **5**, respectively. The adducts exhibited the following properties: **3a**, 70%, mp 175-177° dec; **3b**, 68%, mp 178-180° dec, uv: ($\epsilon \times 10^{-3}$) λ max (methanol) 330 nm (6.69), 252 (17.19); λ min (methanol) 290 nm (2.98), 231.5 (9.51); **3c**, 67%, mp 162-164° dec; **6**, 58%, mp 183-185° dec; **7**, 59%, mp 201-203° dec.

5-Amino-6-methylamino-3-methylthio-*as*-triazine (**5**) was synthesized by a similar pathway described for **4** [1]. 6-Methylamino-*as*-triazine-3,5-dione [10] was thiated to provide 6-methylamino-*as*-triazine-3,5-dithione (79%, mp 252-254°) which in turn was methylated to afford 3,5-*bis*(methylthio)-6-methylamino-*as*-triazine (86%, mp 139-141°). Treatment of the *bis*-(methylthio)-derivative with liquid ammonia in a stainless steel reaction vessel at 50° furnished **5** (95%, mp 228-230°).

Satisfactory analyses (C, H, N, S) were obtained for all new compounds.

[5] The N5 position of **3** is equivalent to the N5 position of **2**, **4**, or **5** and the N8 of pteridine.

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[9] M. Sekine, J. Matsuzaki and T. Hata, *Tetrahedron Letters*, **23**, 5287 (1982).

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