4-Azapteridines. 2 [1]. Spectral, Chromatographic, and X-Ray Crystallographic Studies Concerning the Mode of Covalent Addition to the Pyrazino[2,3-*e*]-*as*-triazine Ring System

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The first examples of the unknown pyrazino[2,3-*e*]-*as*-triazine ring system, that is, the 6,7-dihydroxy-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazines, have been prepared by ring closure of selected 5,6-diamino-*as*-triazines with 40% aqueous glyoxal. These 4-azapteridines experience a novel exchange process with alcohols at the C(7)-position. When dissolved in alcohol and stirred at room temperature, the 7-alkoxy, 6-hydroxy analogues are formed and isolated. In fact, during ring closure, if alcohols are used as the solvent, only the latter compounds are obtained. Initially, cyclization of the *ortho*-diamino-*as*-triazines with glyoxal proceeds in a stereoselective manner giving rise to both the *cis* and *trans* adducts. A single-crystal X-ray diffraction study has determined the predominant and most stable adduct to be the *trans (R,R* or *S,S)* isomer. Spectroscopy (nmr) has verified the intermediacy of the *cis* adduct, but because of the aforementioned exchange process only the *trans* isomer is isolated. The site of exchange on these σ-adducts has been rigorously established as C(7). A plausible reaction mechanism by which this exchange process occurs is presented.

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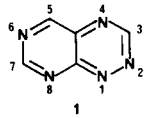
The expectation that azapteridines might exhibit biological and/or chemotherapeutic activity [3,4] has stimulated a number of synthetic studies leading to derivatives of the 7-azapteridine (pyrimido[5,4-*e*]-*as*-triazine, **1**) [4,5], 6-azapteridine (pyrimido[4,5-*e*]-*as*-triazine, **2**) [5,6], and 4,7-diazapteridine (*as*-triazino[6,5-*e*]-*as*-triazine, **3**) [7,8a] ring systems. Many of the synthetic approaches to the 6-aza- and 7-azapteridines and all to the 4,7-diazapteridine system utilize *as*-triazines as precursors. It was anticipated that with an appropriate 5,6-diamino-*as*-triazine another



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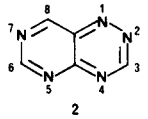

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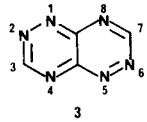

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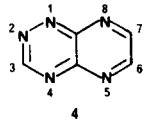

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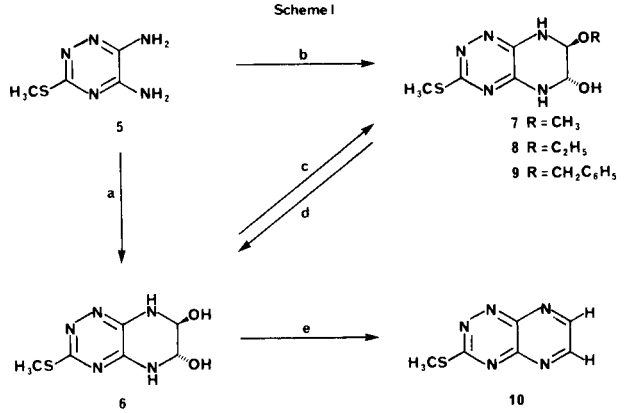
azapteridine system could be realized, *i.e.*, 4-azapteridine (pyrazino[2,3-*e*]-*as*-triazine, **4**), and provide for the first time an aza analogue of pteridine which maintained the integrity of the pyrazine ring. At the time this study was initiated, only a few 5,6-diamino-*as*-triazines were described [8,9]; all but one contained alkylated exocyclic amino groups, and most of them were prepared *via* rearrangement and ring opening of certain 7-azapteridines [9]. Therefore, a synthetic program [10] was designed specifically to provide a practical, efficient method for the preparation of 5,6-diamino-*as*-triazines which on cyclization with appropriate α,β-dicarbonyl compounds would furnish derivatives of the desired 4-azapteridine ring system. The present paper describes the condensation of the *as*-triazines **5**, **14**, **15**, and **24** with 40% aqueous glyoxal in water and alcohols, the 6,7-dihydroxy-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazines formed, their exchange at position C(7) with alcohols, and the mechanism by which this exchange process occurs.

Results and Discussion.

Reacting **5** 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 (**6**, Scheme 1). The structure of **6** was established by nmr (^{1}H and ^{13}C) and elemental analyses. The proton and carbon chemical shifts of **6** were quite similar to those reported [11,12] for certain 5,6,7,8-dihydrated pteridines.

When **6** was dissolved in an excess of 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, monohydroxyl adduct **7**. This adduct was easily converted back to the dihydrate **6** by employing similar reaction conditions and using water as solvent. In fact, the methoxy (**7**) or ethoxy (**8**) adducts were obtained exclusively during cyclization of **5** if methanol or ethanol, respectively, was used as a solvent. An equilibrium between **6** and **7** was

Scheme I

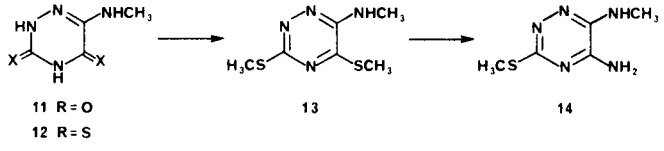


(a) 40% aqueous glyoxal/H_2O (acidic or neutral); (b) 40% aqueous glyoxal/alcohol; (c) alcohol/acidic or neutral; (d) H_2O/acidic or neutral; (e) dimethyl-d_6 sulfoxide at boil (30 seconds).

achieved instantaneously. When an aliquot of a solution of **7** in dry methanol [13] was added to an equal volume of glass-distilled water and a sample of this solution immediately injected into a high-performance liquid chromatograph (*ca.* 30 seconds), the resulting integrated chromatogram indicated near-equal amounts of both **6** and **7**. There was no significant change in the ratio of these adducts over a two hour period.

To establish the position of the alkoxy group, *i.e.*, whether attachment was to the C(6) or C(7) position, a rigorous synthetic and ^{1}H nmr study was undertaken. 5-Amino-6-methylamino-3-methylthio-*as*-triazine (**14**, Scheme 2) and 6-amino-5-methylamino-3-methylthio-*as*-triazine (**15**) [10] were prepared and used to assign the chemical shifts of the N(5)H and N(8)H protons of **6** [14]. Examination of the ^{1}H nmr spectra of **14** and **15** [10] easily identified the NH protons of the amino and methylamino groups, by their characteristic spin patterns and integration, and thus established their chemical shifts. It was assumed that the electronic and magnetic environment of the N(5)H and

Scheme II



N(6)H protons in **14** and **15**, respectively, would be similar to those of the N(5)H and N(8)H protons of **6**. Thus, the doublet at δ 8.72 was assigned to the N(5)H proton and the upfield doublet at δ 7.68 to the N(8)H proton (Table 1). Subsequent ring closure of **14** to **20** and **15** to **16** and inspection of their ^{1}H nmr spectra confirmed these assignments. It is worth mentioning that this assignment is identical to that established for the adducts of pteridine [11, 15,16]. Next, a series of selective spin decoupling experiments were conducted on **7** 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 C(7).

In the condensation reactions leading to **6** (pathway a, Scheme 1) as well as the exchange with alcohols (pathways b and c, Scheme 1), only one isomer was observed and iso-

Table 1

Summary of Proton Chemical Shifts (δ, ppm) [a]

Compound	N(5)H	N(8)H	C(6)OH	C(7)OH	C(6)H	C(7)H	Other
6	8.72 (d)	7.68 (d)	5.95 (d)	5.80 (d)	4.64 (m)	4.64 (m)	—
7	8.82 (d)	8.22 (d)	6.05 (d)	—	4.76 (m)	4.35 (m)	3.15 (s, OCH_3)
8	8.78 (d)	8.15 (d)	6.00 (d)	—	4.70 (m)	4.40 (m)	3.50 (q, OCH_2)
							1.00 (t, CH_3)
9	8.90 (d)	8.40 (d)	6.12 (d)	—	4.81 (m)	4.50 (m)	4.50 (s, OCH_2)
							7.29 (s, C_6H_5)
10	—	—	—	—	9.30 (d)	9.11 (d)	2.71 (s, SCH_3)
16	—	7.79 (d)	6.29 (d)	5.90 (d)	4.70 (m)	4.70 (m)	3.08 (s, NCH_3)
17	—	7.51 (d)	—	—	—	—	2.97 (s, NCH_3)
18	—	8.30 (d)	6.40 (d)	—	4.82 (m)	4.38 (m)	3.05 (s, NCH_3)
							3.19 (s, OCH_3)
19	—	8.29 (d)	6.40 (d)	—	4.82 (m)	4.50 (m)	3.08 (s, NCH_3)
							3.48 (q, OCH_2)
							1.02 (t, CH_3)
20	8.80 (d)	—	6.10 (d)	6.02 (d)	4.65 (m)	4.65 (m)	3.00 (s, NCH_3)
21	8.49 (d)	—	—	—	—	—	2.90 (s, NCH_3)
22	8.92 (d)	—	6.19 (d)	—	4.81 (m)	4.60 (d)	3.20 (s, NCH_3)
							3.31 (s, OCH_3)
23	8.92 (d)	—	6.19 (d)	—	4.83 (m)	4.69 (m)	3.18 (s, NCH_3)
							3.59 (q, OCH_2)
							1.08 (t, CH_3)

[a] s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Table 2

Summary of Carbon-13 Chemical Shifts (δ, ppm)

Compound	C(3)	C(4a)	C(8a)	C(6)	C(7)	Other
6	159.7_7	144.2_9	143.5_0	75.2_1	74.6_1	13.1_0 (SCH_3)
7	160.2_9	144.1_7	142.9_3	82.0_9	73.3_5	13.2_2 (SCH_3), 53.5_5 (OCH_3)
8	160.1_9	144.1_6	142.9_4	80.6_2	73.6_0	13.2_1 (SCH_3), 61.3_0 (OCH_2), 15.1_4 (CH_3)
9	160.3_1	144.1_4	142.9_9	80.2_0	73.4_9	13.1_9 (SCH_3), 67.2_6 (OCH_2), 138.0_1 (Cl'), 128.3_4 (C2'), 127.7_5 (C3'), 127.5_7 (C4')
16	159.7_3	143.4_7	144.0_1	74.3_3	82.2_9	13.3_5 (SCH_3), 33.2_5 (NCH_3)
17	—	—	—	72.8_9	78.8_1	29.6_4 (NCH_3)
18	160.3_6	142.9_7	143.9_5	80.2_9	81.8_6	13.3_2 (SCH_3), 32.9_6 (NCH_3), 53.6_1 (OCH_3)
19	160.2_5	143.0_6	143.9_9	80.4_2	80.5_4	13.3_1 (SCH_3), 33.0_1 (NCH_3), 61.4_2 (OCH_2), 15.1_4 (CH_3)
21	—	—	—	78.9_6	74.2_4	33.4_1 (NCH_3)
22	160.3_4	144.2_2	143.0_1	89.4_9	72.4_5	13.2_8 (SCH_3), 36.2_4 (NCH_3), 56.0_8 (OCH_3)
23	160.3_4	144.2_3	143.1_2	88.2_4	73.0_3	13.2_8 (SCH_3), 35.8_4 (NCH_3), 64.0_1 (OCH_2), 15.4_8 (CH_3)

Table 3

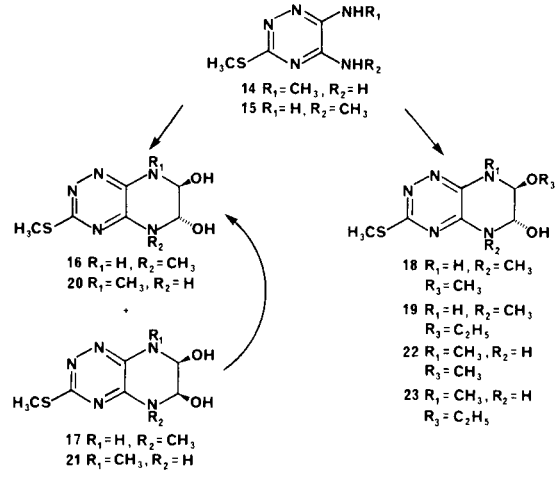
Selected Bond Lengths (Å) in *trans*-6,7-Dihydroxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**16**, $C_7H_{11}N_5O_2S$)

Atoms	Distance	Atoms	Distance
S—C(3)	1.752(3)	N(5)—C(6)	1.453(4)
S—C(9)	1.762(5)	N(5)—C(4a)	1.342(3)
N(1)—N(2)	1.374(3)	N(8)—C(7)	1.432(4)
N(1)—C(8a)	1.307(3)	N(8)—C(8a)	1.345(3)
N(2)—C(3)	1.312(3)	C(6)—O(6)	1.396(4)
N(4)—C(3)	1.343(3)	C(6)—C(7)	1.514(4)
N(4)—C(4a)	1.313(3)	C(7)—O(7)	1.409(4)
N(5)—C(5)	1.453(4)	C(8a)—C(4a)	1.439(4)

lated. If ring closure of **5** with 40% aqueous glyoxal in water occurred in a random fashion a mixture of *cis* and *trans* isomers would result, whereas if cyclization was stereospecific only one form would be realized. Likewise, depending on the mode of addition of alcohol to the C(7) position, this process too, could be stereoselective or stereospecific. Therefore, in an attempt to understand the mode of ring closure and the exchange mechanism the following questions were addressed: (i) are the cyclization and the exchange processes either stereospecific or stereoselective, (ii) what is the stereochemistry of products formed, and (iii) what is the mechanism of addition of alcohols to the C(7) position?

At first it appeared that the condensation reaction was stereospecific and furnished a single adduct [17], but an nmr spectral examination of the material isolated from the cyclization of **15** indicated an approximate 4:1 mixture [18] of adducts (**16** and **17**, Scheme 3). Stirring or dissolving the mixture in water led exclusively to one isomer. In fact, the nmr sample (in dimethyl-d_6 sulfoxide) on standing gave the same results.

Scheme III



The *cis* and *trans* forms of certain 1,4-dioxane-2,3-diols [19,20] and 1,3-dioxolane-4,5-diols [20], compounds prepared from glyoxal, can be distinguished and assigned through their ^{13}C nmr spectra. The carbon chemical shifts of the *cis* diol carbons appear upfield to those of the *trans* isomers. Thus, based on this spectral characteristic, the predominant adduct (**16**, Table 2) would be the *trans* isomer. However, we were reluctant to make this critical structural assignment founded only on this evidence and therefore we sought a more definitive answer; an X-ray crystallographic analysis of **16**. A view of a single molecule of **16** is given in Figure 1. As can be seen in the figure, the hydroxyl groups are *trans* and the isomer has the *R,R* configuration, but in this centrosymmetric space group there is an equal number of *S,S* forms.

The bond lengths in the *as*-triazine ring suggest a prefe-

Table 4

Selected Bond Angles (degrees) in *trans*-6,7-Dihydroxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**16**, $C_7H_{11}N_5O_2S$)

Atoms	Angles	Atoms	Angles
C(3)—S—C(1)	103.0(2)	C(7)—C(6)—O(6)	109.5(3)
N(2)—N(1)—C(8a)	119.3(2)	N(5)—C(6)—C(7)	110.4(3)
N(1)—N(2)—C(3)	117.1(3)	C(6)—C(7)—N(8)	110.1(3)
C(3)—N(4)—C(4a)	115.7(3)	C(6)—C(7)—O(7)	107.5(3)
C(5)—N(5)—C(6)	117.7(3)	N(8)—C(7)—O(7)	113.0(3)
C(5)—N(5)—C(4a)	119.1(3)	N(1)—C(8a)—N(8)	121.0(3)
C(6)—N(5)—C(4a)	120.5(3)	N(1)—C(8a)—C(4a)	120.5(3)
C(7)—N(8)—C(8a)	120.1(3)	N(8)—C(8a)—C(4a)	118.5(3)
N(2)—C(3)—N(4)	127.3(2)	N(4)—C(4a)—N(5)	120.2(3)
S—C(3)—N(4)	118.4(2)	N(4)—C(4a)—C(8a)	119.8(3)
S—C(3)—N(2)	114.3(2)	N(5)—C(4a)—C(8a)	120.0(3)
N(5)—C(6)—O(6)	111.0(3)		

Table 5

Positional Parameters for *trans*-6,7-Dihydroxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**16**, $C_7H_{11}N_5O_2S$)

Atom	X	Y	Z
S	0.8426(1)	0.40950(8)	0.2174(3)
O(6)	0.0353(3)	0.2038(2)	−0.2721(5)
O(7)	0.2825(3)	0.0080(2)	−0.5088(5)
N(1)	0.6095(4)	0.1609(2)	0.2409(6)
N(2)	0.7293(4)	0.2392(2)	0.2940(6)
N(4)	0.5509(3)	0.3089(2)	−0.1149(6)
N(5)	0.2955(4)	0.2262(2)	−0.4037(6)
N(8)	0.3387(4)	0.0875(2)	−0.0195(6)
C(3)	0.6918(4)	0.3077(2)	0.1186(7)
C(5)	0.2637(5)	0.3060(3)	−0.5848(8)
C(6)	0.1481(4)	0.1591(3)	−0.4240(7)
C(7)	0.2131(4)	0.0644(2)	−0.3017(7)
C(8a)	0.4662(4)	0.1580(2)	0.0228(7)
C(4a)	0.4387(4)	0.2327(2)	−0.1714(7)
C(9)	0.7510(5)	0.4886(3)	−0.0458(9)
H(O6)	−0.062(4)	0.218(2)	−0.389(6)
H(O7)	0.324(5)	−0.051(3)	−0.425(8)
H(5)	0.174(4)	0.281(2)	−0.775(7)
H(5′)	0.211(4)	0.360(2)	−0.508(6)
H(5″)	0.371(4)	0.324(2)	−0.612(7)
H(6)	0.089(3)	0.142(2)	−0.623(5)
H(7)	0.114(3)	0.027(2)	−0.268(6)
H(8)	0.342(3)	0.049(2)	0.113(6)
H(9)	0.835(4)	0.545(2)	−0.009(7)
H(9′)	0.757(5)	0.459(3)	−0.237(9)
H(9″)	0.648(4)	0.511(3)	−0.020(7)

rence for the canonical structure of **16** illustrated in Scheme 3 with N(1)-N(2) as a single bond. Thus, the N(1)-C(8a), N(2)-C(3), and N(4)-C(4a) bonds are in the narrow range of 1.307(3) to 1.313(3) Å with an average value of 1.311(3) Å while the nominally single bond N(4)-C(3) is significantly longer at 1.343(3) Å. The N(1)-N(2) distance of 1.374(3) Å is considerably longer than the values found for the (partial) double bonds in substituted *v*-triazoles (1.293 to 1.307 Å) [21-23] and is similar to the values of 1.346 to 1.380 Å found for the nominal single N-N bonds in those molecules. Moreover, it is slightly longer than the values of 1.351 to 1.365 Å found for the analogous bond in substituted *as*-triazines [24-26]. It is noteworthy that this canonical form is also that calculated for the unsubstituted *as*-triazine molecule [27]. Selected bond lengths and angles and positional parameters for **16** are listed in Tables 3, 4, and 5, respectively.

The six-atom triazine ring is approximately planar, the largest deviations from the least-squares plane being ±0.026 Å at the ring fusion atoms C(8a) and C(4)a. The sulfur atom is significantly out of this plane, lying 0.131(1) Å below it. Atom N(8) of the substituted tetrahydropyrazine ring is also substantially out of the triazine plane, lying 0.156(3) Å below it. This lends further support to our view of a largely localized structure for the bonding in the triazine ring, since in a delocalized model, atoms N(5) and N(8) would be expected to lie in the ring plane. Atom N(5) sits 0.062(3) Å above the plane.

The substituted tetrahydropyrazine ring is, as expected, not planar, but it does not readily lend itself to any of the classical descriptions for six membered rings. Thus, the best four atom plane passes through the atoms N(8), C(8a), C(4a), and C(6), [maximum deviation 0.013(3) Å] and both N(5) and C(7) lie on the same side of this plane [deviations 0.165(3) and 0.529(3) Å, respectively]. The ring geometry can best be described as being intermediate between the "half-chair" and the "sofa" conformations. In the former description, the four-adjacent atoms N(8), C(8a), C(4a), and N(5) form the base plane [maximum deviation 0.024(3) Å] with C(6) 0.220(3) Å below the plane and C(7) 0.386(3) Å above it. In the sofa description, the five atoms in the "plane" are N(8), C(8a), C(4a), N(5), and C(6) [maximum deviation 0.083(3) Å] with C(7) sitting 0.532(3) Å above the plane. The bond lengths in this ring are unremarkable. The two C-O single bonds are of similar lengths [1.396(4) and 1.409(4) Å]. As was noted above, the hydroxyl groups are *trans* diaxial, the torsion angle O(6)-C(6)-C(7)-O(7) of 163.3° being close to the idealized values of 180° [28].

There is extensive hydrogen bonding in the crystals, with all potential donors participating. The hydroxyl group O(6)-H(6) forms a hydrogen bond to N(2) of an adjacent molecule, with O(6)...N(2), H(6)...N(2) distances of 2.806(3) and 1.96(3) Å, and associated O(6)-H(6)...N(2) angle of 170(3)°. The other hydroxyl group interacts with N(1) of a different neighboring molecule, the O(7)...N(1), H(7)...N(1), and O(7)-H(7)...N(1) distances and angle being 2.791(3) Å, 1.84(3) Å, and 174(3)°. The protonated N(8)-H(8) moiety interacts with O(7) of an adjacent molecule, with N(8)...O(7), H(8)...O(7), and N(8)-H(8)...O(7) values of 2.935(3) Å, 2.13(3) Å, and 154(2)°.

It is worth mentioning that the potential acceptor N(4) is not involved in hydrogen bonding. In order to investigate this further, we calculated the residual charges on the

Table 6

Ultraviolet Spectra for Certain *as*-Triazines and Pyrazino[2,3-*e*]-*as*-triazines [a]

Compound	pH	λ max (nm)	ε × 10^{-3}	λ min (nm)	ε × 10^{-3}
6	1	329 sh [b]	3.44		
		263	25.40		
	H_2O	330.5	5.70	293	2.91
		266 sh	13.13	231.5	8.82
		253.5	16.14		
		221	10.98		
	11	330	6.03	294	3.19
		267 sh	12.05	225	7.53
		253	15.45		
7	1	327 sh	3.76		
		263	27.97		
	MeOH	331	6.65	290	2.93
		267 sh	13.07	231	9.45
		252	17.19		
		221	13.30		
	11	333	6.56	295	3.26
		269 sh	13.07	226	6.88
		255	16.85		
8	1	329 sh	3.41		
		264	27.25		
	EtOH	330	6.45	289.5	2.68
		264 sh	13.50	230.5	9.24
		251.5	16.67		
		220	12.65		
	11	332.5	6.81	293	3.65
		265.5 sh	14.72	222	6.81
		253.5	17.40		
12	1	301	28.58	227	3.31
		249 sh	6.97		
	MeOH	304	27.53	228	2.09
		253 sh	6.27		
	11	327	10.80	312	10.11
		284	19.86	238	9.41
		233	10.28		
13	1	315 sh	8.90	239	5.26
		274	21.85		
	MeOH	362	3.64	310	1.21
		267	23.06	232	3.64
	11	355	3.84	313	2.83
		267	22.05		
14	1	259	23.22	231	7.02
	MeOH	326	4.88	293	3.25
		265 sh	13.01		
		249	14.83		
	11	322	4.93	295	3.77
		268 sh	12.50		
		249	14.73		
16	1	329 sh	3.90		
		267	26.14		
	H_2O	328	6.19	296	4.13
		266 sh	15.59	235	9.86
		257.5	16.74		
		225	11.00		
	11	328	7.06	298	4.36
		264 sh	14.21	222	6.42
		257	15.13		

Table 6 continued

Compound	pH	λ max (nm)	ε × 10^{-3}	λ min (nm)	ε × 10^{-3}
18	1	327 sh	4.18		
		267	25.55		
	MeOH	329	6.33	293	3.36
		268 sh	12.89	235	9.20
		255	15.72		
		224	12.41		
	11	328	6.81	297	2.97
		270 sh	12.16	223.5	6.81
		257	14.48		
19	1	328 sh	3.86		
		267	27.53		
	EtOH	328	6.81	291.5	3.65
		268 sh	14.15	234	10.29
		254	17.50		
		223.5	13.90		
	11	329	7.00	297	4.50
		272.5 sh	12.87	222	6.18
		257	16.21		
20	1	333 sh	3.44		
		264.5	25.31		
	MeOH	330	5.55	294.5	2.98
		270 sh	11.46	230.5	8.71
		252	15.36		
		221	11.00		
	11	332	5.46	298	3.10
		271 sh	11.23	224.5	5.27
		253.5	14.90		
22	1	330 sh	3.02		
		265	26.37		
	MeOH	330	6.08	293	3.41
		269 sh	12.07	230	9.24
		251	16.18		
		220	11.92		
	11	332	6.57	296	4.01
		271 sh	12.94	222	6.81
		253	16.79		
23	1	332 sh	2.68		
		265.5	27.28		
	EtOH	330	6.30	292	3.45
		269 sh	12.22	230	9.52
		251	16.73		
		221	12.48		
	11	332	6.30	297	3.47
		270 sh	12.87	223	5.15
		254	16.34		

[a] Each compound was dissolved in the specified alcohol (10 mg/100 ml) and from this stock solution the final dilution was made with the appropriate solvent. [b] sh = shoulder.

atoms in this molecule using the CNDO/2 method of Pople and coworkers [29,30]. The calculated charge density of −0.20 e at N(4) is significantly higher than those of −0.12 and −0.11 e at N(1) and N(2), respectively. Thus, it appears probable that the absence of hydrogen bonding at N(4) is due to stereochemical rather than electronic fac-

Table 7

Synthesis of Certain Trihydro- and Tetrahydropyrazino[2,3-*e*]-*as*-triazines

Starting *as*-triazine	Solvent [a]	Product (% Yield)	Mp °C (dec)	Formula	Analyses (%) Calcd./Found C	H	N	S
5	water	**6** (70)	175-177	$C_6H_9N_5O_2S$	33.48	4.21	32.54	14.90
					33.70	3.91	32.69	14.92
5	methanol	**7** (68)	178-180	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
					36.63	4.84	30.34	13.94
5	ethanol	**8** (72)	162-164	$C_8H_{13}N_5O_2S$	39.50	5.39	28.79	13.18
					39.29	5.41	28.92	12.97
15	water	**16** (73)	184-186	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
					36.53	4.82	30.68	14.14
15	methanol	**18** (66)	183-185	$C_8H_{13}N_5O_2S$	39.50	5.39	28.79	13.18
					39.40	5.21	28.84	13.09
15	ethanol	**19** (71)	187-189	$C_9H_{15}N_5O_2S$	42.01	5.88	27.22	12.46
					41.88	5.90	27.61	12.28
14	water or methanol	**20** (64)	180-182	$C_7H_{11}N_5O_2S$	36.67	4.84	30.55	13.99
					36.54	4.84	30.64	13.88

[a] Solvent used during ring closure, washing, and recrystallization.

tors. Indeed, inspection of Figure 1 demonstrates that the methyl groups on N(5) and on the sulfur atom at C(3) effectively block approach of potential donors to N(4).

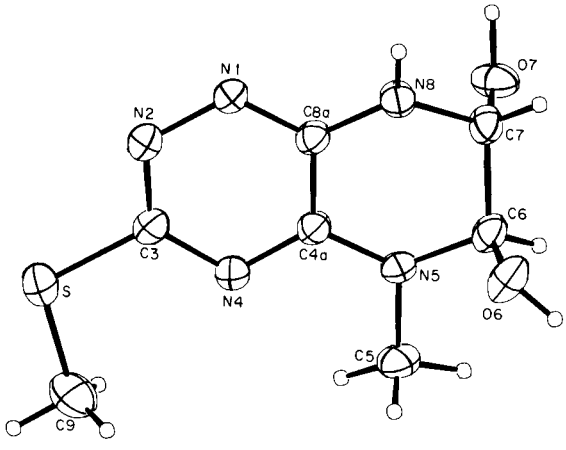
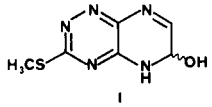


Figure 1

The spectral and crystallographic data provided concrete answers to two of the aforementioned questions. Cyclization of the 5,6-diamino-*as*-triazines **5**, **14**, **15**, and **24** with 40% aqueous glyoxal proceeds in a stereoselective fashion. The *cis* isomer, when formed, quickly converts to the more stable *trans* form, especially when the exocyclic amino groups are unsubstituted. Substitution on either of these amino groups seems to retard this process and allows isolation of the *cis* form. This again is borne-out during the cyclization of **14** which provides a 6:1 mixture [18] of the *trans*-**20** and *cis*-**21** adducts. As in the case of **16** and **17**, merely resuspending this mixture in water and allowing it to stir at room temperature gave the pure *trans* isomer **20** (Scheme 3). Besides identifying the *trans* isomer as the most stable form, the crystallographic study also shed considerable light on the mode of nucleophilic addition of water (or alcohols) to the C(7) position. The hydroxyl substituent at C(6) appears to control, stereospecifically, the approach of the in-coming nucleophile. Addition occurs on the opposite face of the pyrazine moiety and furnishes either the *trans R,R* or *S,S* enantiomers. An inspection of the ^1H and ^{13}C chemical shift data indicates that the C(7)-alkoxy derivatives prepared in this study enjoy the same *trans* relationship. Interconversion of the σ-adducts, *e.g.*, **6** ⇌ **7** or **16** ⇌ **18**, always provided a single component and in the case of **16** it was *trans* [31].

We now turned our attention to the final question; the mechanism by which the C(7) exchange process occurs. Initially, the reversibility experiments suggested that a plausible intermediate in this process was 3-methylthio-6-hydroxy-5,6-dihydropyrazino[2,3-*e*]-*as*-triazine (I) generat-



I

ed by a loss of water from the dihydrated σ-adduct. Once formed, nucleophilic reagents could then add across the 7,8-azomethine bond in a stereospecific manner providing the *trans*-adduct. This pathway seemed quite reasonable as even the CI mass spectrum of **16** indicated that the loss of water from the parent ion was a major event. Furthermore, when **14** was cyclized in a minimal amount of methanol and mild acidic conditions only **20** was isolated. This experimental evidence supported the intermediacy of I and the argumentation that only **20** was possible since loss of water across the C(7)-N(8) positions was not feasible.

However, a closer examination of the cyclization of **14** in water and methanol under different experimental conditions provided a more profound understanding of the mechanistic pathway.

As stated earlier, the *cis* adduct **21** was converted in water to the more stable *trans* compound **20**. In order for

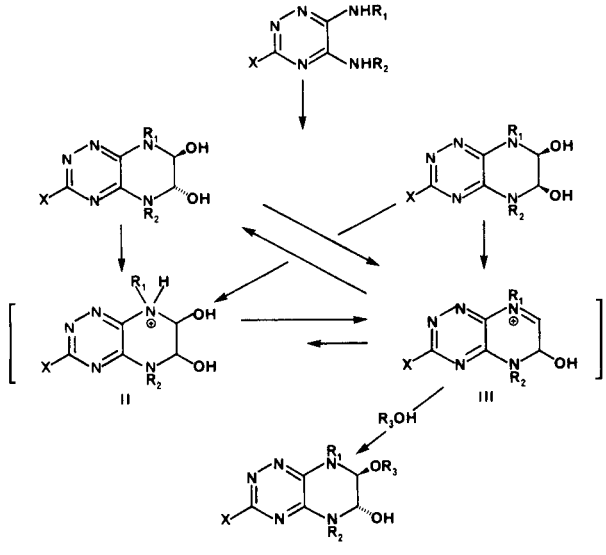
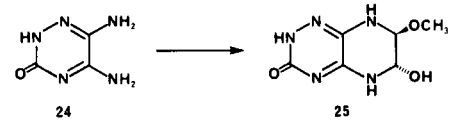


Figure 2. Proposed mechanism for the formation of 3-substituted-5,6-dihydroxy-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazines and covalent addition of nucleophiles across the 7,8-azomethine bond. The substituents are as follows: X = SCH_3 or OH; R_1, R_2 = H or CH_3; R = H, CH_3, C_2H_5 and $CH_2C_6H_5$. When R_1 = CH_3, R_2 = H and vice versa. Although both *trans (R,R* and *S,S)* and *cis (R,S* and *S,R)* forms are possible only one form is depicted. Also the lactim tautomer when X = OH is shown only for convenience.

this to happen an intermediate such as cation III depicted in Figure 2 must be evoked. This cation should provide the driving force for nucleophilic addition of water across the 7,8-azomethine bond. If III is formed, however, then addition of alcohols should also be possible. Evaporation and examination of the reaction filtrate from the cyclization of **14** in methanol by ^{1}H nmr revealed that a small amount of **22** was present. The 8-methyl dihydrates **20** and **21** are quite insoluble, as compared to **6**, **16**, and **17**, and when formed during the cyclization with glyoxal, precipitate out of solution. It was anticipated that the formation of either **22** or **23** from **20** could be augmented by increasing the acidity of the reaction media during cyclization and employing an excess of solvent (methanol or ethanol). The increased acidity of the reaction media should enhance the solubility of **20** *via* II and facilitate the loss of water to give III. Indeed, this was the case and the adducts **22** and **23** were isolated in good yield. The site of exchange was again corroborated by a ^{1}H nmr spin decoupling study.

Thus, the pathway illustrated in Figure 2 most probably represents the overall mechanism for the exchange process. It is worth mentioning that the cyclization of 5,6-diamino-*as*-triazine-3-one (**24**) in acidic methanol furnished the adduct 6-hydroxy-7-methoxy-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine-3-one (**25**) and it appears that the substituent residing at C(3) has little effect on the course of cyclization or exchange.



24 25

Lastly we would like to point out that **6** can be dehydrated to provide 3-methylthiopyrazino[2,3-*e*]-*as*-triazine (**10**). This was accomplished by rapidly bringing to boil (30 seconds) a solution of **6** in dimethyl-d_6 sulfoxide. By conducting this experiment in an nmr sample tube, we were able to acquire ^{1}H nmr spectral evidence for the existence of this heterocycle, but the time needed to obtain a reasonable ^{13}C nmr spectrum resulted in the decomposition of this 4-azapteridine. To date, all attempts to isolate **10** have failed.

EXPERIMENTAL

X-Ray Crystallography.

A colorless parallelepiped-shaped crystal of **16** with dimensions 0.50 × 0.30 × 0.13 mm was mounted on an Enraf-Nonius CAD-4/SDP diffractometer. A preliminary search of reciprocal space indicated that the crystals were triclinic, and this was confirmed by a Delauney reduction. The cell constants, based on twenty-five reflections with $18 \leq 2\theta$ (Mo) $\leq 36°$, were calculated to be a = 7.925(2), b = 13.590(5), c = 4.784(2) Å, α = 97.33(3), β = 106.22(2), γ = 90.20(2)°. Diffraction data were collected out to a maximum value of 2θ(Mo) = 50.0°, or $(\sin\theta/\lambda) = 0.594$ Å^{-1} at a temperature of 20°. The data were corrected for Lorentz-polarization effects, but not for absorption.

The structure was solved by direct methods and refined by least-squares techniques. The function minimized was $\Sigma w(|Fo|-|Fc|)^2$, the weights w being assigned as $4Fo^2/\sigma^2(Fo)^2$, where $\sigma(Fo)^2$ is given by $[\sigma^2(I) + (0.01I)^2]^{1/2}$ and $\sigma(I)$ is derived from counting statistics. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were refined isotropically. The final values of the conventional R-factors $R_1 = \Sigma||Fo|-|Fc||/\Sigma|Fo|$ and R_2 (or weighted R-factor) = $[\Sigma w(|Fo|-|Fc|)^2/\Sigma wFo^2]^{1/2}$ are 0.043 and 0.035, respectively, and the error in an observation of unit weight was 1.6. A final difference Fourier was featureless, with no peak higher than 0.16 Å^{-3}. Examination of the values of |Fo| and |Fc| suggested that no correction for secondary extinction was necessary. In the final least-squares cycle, no parameter moved by more than 0.03σ, which was taken as evidence of convergence. All computer programs used were those provided by Enraf-Nonius in the CAD-4/SDP package.

The refined positional parameters, along with their standard deviations as estimated from the inverse matrix, are presented in Table 5; the anisotropic librational parameters and listings of observed and calculated structure amplitudes are available as supplementary material from the authors.

HPLC Chromatography.

The hplc analyses were conducted on a Waters LCS-III High Performance Liquid Chromatograph. The components consisted of a V.6 K Injector, two Model 510 Pumps, a Model 680 Automated Gradient Programmer, and a Model 440 Absorbance Detector. The detection wavelength used was 254 nm. Integration of the peak areas was performed electronically using a Hewlett-Packard Model 3380-A integrator. A μ Bondpack C_{18} column was employed and the mobile phase was methanol (isocratic). The flow rate was 1 ml/min. The approximate sample size injected was 25 $\mu\ell$.

Mass Spectrometry.

The low resolution mass spectrum of **16** was obtained with a Finnigan 4500 quadrupole mass spectrometer. The sample was dissolved in 100 $\mu\ell$ of millipore water and a 1 $\mu\ell$ aliquot was evaporated on the tip of the filament of the direct exposure probe. The reagent gas was isobutane at 0.25 Torr.

NMR Spectroscopy.

Carbon-13 spectra were obtained with a Varian CFT-20 spectrometer. Compounds were dissolved in dry, spectroquality dimethyl-d_6 sulfoxide (DMSO-d_6) and chemical shifts are expressed in parts per million with respect to TMS. A flip angle of 45° was employed. Carbon assignments were made by analogy with model *as*-triazines prepared in the present study and references 10 and 32. The assignments for the carbons C(6) and C(7) were established by a spectral technique [33], which relies on changes in the chemical shifts of those carbon atoms α and β to the site of N-substitution. Proton spectra were determined using a Varian EM-390 spectrometer. All samples were dissolved in DMSO-d_6 containing 1% TMS. Chemical shifts are in parts per million with respect to TMS.

Synthetic Methods.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ultraviolet absorption spectra were obtained on a Beckman DB-GB grating spectrometer (Table 6). Thin-layer chromatography was run on precoated (0.25 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. SilicAR CC-4 (Mallinckrodt) suitable for chromatographic use was employed for column chromatography. All solvent proportions are by volume unless otherwise stated. Evaporations were performed with a Büchi Rotovapor at 50°. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

The use of 6-methylamino-*as*-triazine-3,5-dione (**11**) has been described in the literature [34], but to our knowledge no experimental details are available. Therefore, we have included our procedure for the synthesis of **11**.

General Procedure for the Preparation of the *trans* σ-Adducts 6,7-Dihydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**6**), 6-Hydroxy-7-methoxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**7**), 7-Ethoxy-6-hydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino-[2,3-*e*]-*as*-triazine (**8**), 6,7-Dihydroxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**16**), 6-Hydroxy-7-methoxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**18**), 7-Ethoxy-6-hydroxy-5-methyl-3-methylthio-6,7,8-trihydropyrazino[2,3-*e*]-*as*-triazine (**19**), and 6,7-Dihydroxy-8-methyl-3-methylthio-5,6,7-trihydropyrazino[2,3-*e*]-*as*-triazine (**20**).

5,6-Diamino-3-methylthio-*as*-triazine (**5**) [10] (314.4 mg, 2 mmoles) was dissolved in 10 ml of solvent (see Table 7) and to this solution was added 0.4 ml (2.8 mmoles) of a 40 wt% glyoxal solution (Aldrich) and 0.2 ml of 0.2 *N* hydrochloric acid. 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 × 1 ml, as specified in Table 7) and dried in an Abderhalen for 12 hours at 80°. This material was suitable for elemental analyses and further experimentation. If desired, these compounds can be recrystallized by dissolving them in a minimal amount of dimethyl sulfoxide followed by addition of the specified solvent until a solvent ratio of *ca.* 2:1 (solvent:dimethyl sulfoxide) is reached. For the synthesis of **16, 18,** and **19, 5** was replaced by **15**. Compound **20** was prepared from **14**, as above, by using water or absolute methanol as solvent. The mp (°C, dec), yield (%), and elemental analyses of the title compounds are given in Table 7.

Preparation of 6-Hydroxy-7-methoxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**7**) and 7-Ethoxy-6-hydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**8**) from 6,7-Dihydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**6**).

Compound **6** (430 mg, 2 mmoles) was dissolved in 15 ml of solvent (for the preparation of **7**, absolute methanol; **8**, absolute ethanol) containing 0.4 ml of 1.0 *N* hydrochloric acid. The solution was stirred at room temperature and the reaction monitored by tlc (chloroform-methanol = 4:1). After 1.5 hours, the reaction was complete. The reaction was allowed to stir for an additional 2 hours and the resulting solid was collected by filtration, washed with cold solvent (3 × 1 ml), and air-dried to provide **7** (365 mg, 80% yield) or **8** (394 mg, 81% yield), respectively. These compounds were identical (^{1}H nmr, ^{13}C nmr) to those prepared from **5**.

For the reverse reaction (**7** → **6** or **8** → **6**), similar conditions were employed except distilled water was used as the solvent and either **7** or **8** was the starting material. The reverse reaction took 2 hours to reach completion and was then stirred an additional 4 hours. In either case **6** was obtained in 70% yield. The nmr (^{1}H and ^{13}C) spectra indicated that this heterocycle was identical with **6** prepared from **5**.

Either reaction can also be conducted without dissolving the starting material, but the total time required for completion of the reaction is longer, *i.e.*, **6** → **7** or **8** (4 hours) and **7** or **8** → **6** (16 hours).

7-Benzyloxy-6-hydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**9**).

To a suspension of **6** (430 mg, 2 mmoles) in distilled water (5 ml) and 1.0 *N* hydrochloric acid (0.5 ml) was added 15 ml of benzyl alcohol and the mixture stirred at room temperature for 4 hours. The resulting solution was mixed with silica gel (*ca.* 4 g), dried, and then evenly applied to a silica gel column (3 × 32 cm, slurry packed in 1:1 mixture of chloroform-acetone). The column was eluted with chloroform-acetone (1:1) and 50 ml fractions were collected. Fractions 8-27 were combined and evaporated under diminished pressure to provide analytically pure **9** (310 mg, 78%), mp 135-138° dec. Washing of the column with acetone (600 ml) provided 150 mg of unreacted **6**.

Anal. Calcd. for $C_{13}H_{15}N_5O_2S$: C, 51.13; H, 4.95; N, 22.93; S, 10.50. Found: C, 51.64; H, 5.05; N, 22.47; S, 10.13.

6-Methylamino-*as*-triazine-3,5-dione (**11**).

6-Bromo-*as*-triazine-3,5-dione [35] (19.2 g, 100 mmoles), copper powder (100 mg), and 40% aqueous methylamine solution (100 ml) were heated at 70° for 4 hours. After the reaction cooled, the precipitated copper powder was filtered off and the filtrate concentrated under diminished pressure to a small volume (*ca.* 20 ml) causing precipitation of the title compound. The precipitate was collected by filtration and washed with a minimal amount of cold, distilled water. The combined filtrate and wash was acidified to *p*H 4 with concentrated hydrochloric acid and on standing a second crop was obtained. The combined crops were resuspended in distilled water (300 ml) and dissolved by the dropwise addition of concentrated ammonium hydroxide, the solution filtered, and the colorless filtrate acidified to *p*H 4 with concentrated hydrochloric acid. The solid was collected by filtration, washed with distilled water and air-dried to furnish 14.0 g (99%) of **11**, mp >300°; ^{1}H nmr: δ 2.55 (d, 3, CH_3), 6.42 (q, 1, NH), 10.82 (s, 1, N2H), 11.58 (s, 1, N4H) [lit [34b] δ 2.68 (NCH_3), 6.25 (NH), 10.63 (N2H), 11.35 (N4H)]; ^{13}C nmr: 27.7$_5$ (NCH_3), 143.6$_6$ (C6), 148.9$_4$ (C5), 154.7$_4$ (C3) ppm; uv: ($\epsilon \times 10^{-3}$) λ max (*p*H 1) 306 nm (4.69), 232 (7.99), λ max (methanol) 307 nm (4.83), 233 (7.53), λ max (*p*H 11) 295 nm (4.02), 241 sh (7.82), 226.5 (10.91) [lit [34c] λ max (*p*H 1-7) 308 nm (4.07), λ max (*p*H 13) 298 nm (3.73)].

Anal. Calcd. for $C_4H_6N_3O_2$: C, 33.81; H, 4.26; N, 39.42. Found: C, 33.70; H,4.14; N, 39.57.

6-Methylamino-*as*-triazine-3,5-dithione (**12**).

6-Methylamino-*as*-triazine-3,5-dione (**11**, 5.68 g, 40 mmoles), flowers of sulfur (2.56 g, 10 mmoles), phosphorus pentasulfide (17.8 g, 80 mmoles), and 350 ml of ACS pyridine were heated at reflux for 6 hours with vigorous stirring. The reaction mixture was allowed to cool and stand at room temperature for 16 hours. The clear, reddish-brown solution was decanted from the reaction flask and the pyridine removed under diminished pressure (water bath, 60°), the residue which remained was covered with distilled water (*ca.* 200 ml), boiled for 10 minutes, and allowed to stand at room temperature for 18 hours. The precipitate was collected by filtration, resuspended in 200 ml of distilled water and basified to *p*H 10 with concentrated ammonium hydroxide. The mixture was treated with Norit (optional) and filtered through a Celite pad, and the pad was washed with two portions (2 × 20 ml) of basic water (*p*H 10). The combined filtrate and wash was carefully acidified with 6 *N* hydrochloric acid to *p*H 4 and **12** precipitated. The solid was collected by filtration, washed with cold, distilled water (3 × 50 ml), and air-dried to provide 5.5 g of **12** (79%), mp 252-254°; ^{1}H nmr: δ 2.79 (d, 3, CH_3), 6.65 (q, 1, NH), 12.99 (br s, 1, N2H), 14.05 (br s, 1, N4H); ^{13}C nmr: 28.6$_4$ (NCH_3), 149.7$_1$ (C6), 163.1$_0$ (C5), 174.0$_2$ (C3) ppm.

Anal. Calcd. for $C_4H_6N_3S_2$: C, 27.57; H, 3.48; N, 32.15; S, 36.80. Found: C, 27.57; H, 3.58; N, 32.38; S, 36.66.

6-Methylamino-3,5-dimethylthio-*as*-triazine (**13**).

To a stirred suspension of **12** (3.48 g, 20 mmoles) in 400 ml of absolute ethanol was added 40 ml of 1.0 *N* sodium hydroxide solution. After stirring at room temperature for 20 minutes, an excess of methyl iodide (10 ml) was added. The reaction mixture was allowed to stir at room temperature for 4 hours and then the excess solvent was removed under diminished pressure to furnish a crystalline residue. The solid was triturated with cold water (10 ml), collected by filtration, washed with cold distilled water (2 × 3 ml), and air-dried to afford 3.47 g of **13** (86%), mp 139-141°; ^{1}H nmr: δ 6.50 (q, 1, NH), 2.82 (d, 3, CH_3), 2.53 (s, 3, SCH_3), 2.50 (s, 3, SCH_3); ^{13}C nmr: 11.6$_6$ (SCH_3), 13.4$_5$ (SCH_3), 28.3$_0$ (NCH_3), 151.5$_5$ (C6), 154.3$_3$ (C5), 158.0$_2$ (C3) ppm.

Anal. Calcd. for $C_6H_{10}N_4S_2$: C, 35.62; H, 4.98; N, 27.69; S, 31.70. Found: C, 35.72; H, 5.06; N, 27.88; S, 31.72.

5-Amino-6-methylamino-3-methylthio-*as*-triazine (**14**).

6-Methylamino-3,5-dimethylthio-*as*-triazine (**13**, 2.02 g, 10 mmoles) and liquid ammonia (10 ml) were heated in a glass-lined stainless steel reaction vessel at 50° for 24 hours. The reaction vessel was allowed to cool to room temperature, and the excess gases were vented off to provide crystalline **14**, mp 228-230°; ^{1}H nmr: δ 7.02 (br s, 2, NH_2), 6.12 (q, 1, NH), 2.85 (d, 3, NCH_3), 2.40 (s, 3, SCH_3); ^{13}C nmr: 13.2$_3$ (SCH_3), 28.0$_2$ (NCH_3), 145.2$_5$ (C6), 147.4$_0$ (C5), 158.3$_1$ (C3) ppm.

Anal. Calcd. for $C_5H_9N_5S$: C, 35.07; H, 5.30; N, 40.90; S, 18.73. Found: C, 34.96; H, 5.34; N, 41.11; S, 18.54.

6-Hydroxy-7-methoxy-8-methyl-5,6,7-trihydropyrazino[2,3-*e*]-*as*-triazine (**22**) and 7-Ethoxy-6-hydroxy-8-methyl-5,6,7-trihydropyrazino[2,3-*e*]-*as*-triazine (**23**).

5-Amino-6-methylamino-3-methylthio-*as*-triazine (**14**) (342.5 mg, 2 mmoles) was dissolved in 30 ml solvent (for preparation of **22**, absolute methanol; **23**, absolute ethanol) and to this solution was added 0.4 ml (2.8 mmoles) of a 40 wt% glyoxal solution and 0.4 ml of 1.0 *N* hydrochloric acid. The mixture was stirred at room temperature for 24 hours and the resulting solution was evaporated under diminished pressure to a small volume (*ca.* 4 ml). The solution was allowed to stand at 4° for 18 hours and the off-white crystals collected by filtration, washed with cold solvent (3 × 1 ml) and dried in an Abderhalen for 12 hours at 80° to give **22** (326 mg, 67% yield), mp 168-170° dec or **23** (329 mg, 64% yield), mp 162-165° dec.

Anal. Calcd. for $C_8H_{13}N_5O_2S$ (**22**): C, 39.50; H, 5.39; N, 28.79; S, 13.18. Found: C, 39.57; H, 5.30; N, 28.89; S, 13.09.

Anal. Calcd. for $C_9H_{15}N_5O_2S$ (**23**): C, 42.01; H, 5.88; N, 27.22; S, 12.46. Found: C, 41.88; H, 5.68; N, 27.34; S, 12.31.

6-Hydroxy-7-methoxy-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine-3-one (**25**) [36].

5,6-Diamino-*as*-triazine-3-one (**24**) [10] (381.3 mg, 3 mmoles) was suspended in 15 ml of absolute methanol. To this well-stirred suspension was added 0.6 ml (4.2 mmoles) of a 40 wt% glyoxal solution and 1.0 ml of 1.0 *N* hydrochloric acid. The mixture was stirred at room temperature for 24 hours. The resulting solid was collected by filtration, washed with cold absolute methanol (3 × 1 ml), and air-dried to afford 390 mg (70%) of **25**. An analytical sample of **25** was prepared by column chromatography on silica gel, with chloroform-absolute methanol (3:1) as an eluent, mp 132-134° dec; ^{1}H nmr: δ 3.19 (s, 3, OCH_3), 6.65 (q, 1, NH), 4.28 (m, 1, C7H), 4.70 (m, 1, C6H), 6.15 (d, 1, OH), 7.80 (d, 1, N8H), 9.00 (br d, 1, N5H), 10.95 (br s, N2H); ^{13}C nmr: 53.9$_9$ (OCH_3), 73.7$_2$ (C7), 82.7$_4$ (C6), 134.3$_7$ (C8a), 150.7$_1$ (C4a), 155.5$_0$ (C=O) ppm.

Anal. Calcd. for $C_6H_9N_5O_3$: C, 36.18; H, 4.55; N, 35.16. Found: C, 35.93; H, 4.63; N, 35.30.

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