CONDENSED *as*-TRIAZINE II[1]: SYNTHESIS OF 7-PHENYLDIHYDRO- AND TETRAHYDROPYRAZINO-[2,3-*e*]-*as*-TRIAZINES

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Abstract- Certain derivatives of dihydro- and tetrahydropyrazino[2,3-*e*]-*as*-triazines were prepared by ring closure of 5,6-diamino-*as*-triazines with phenylglyoxal in methanol. These 4-azapteridines experience an addition of the alcohol at C(7), and N(8) underwent an unusual methylation under acidic conditions affording the 7-methoxy-8-methyl-6-phenyldihydropyrazino derivative. Regioselective control by the aldehyde-binding reagent, sodium hydrogen sulfite and sodium sulfite, tends to direct the phenyl group to the C(7). Hinsberg reaction of 5,6-diamino-*as*-triazines with phenacyl bromide proceeded in regiospecific fashion to give the *E*-form Schiff bases which then isomerize to the corresponding enamines.

The expectation that azapteridines might exhibit biological and/or chemotherapeutic activity[2,3] has stimulated a number of synthetic studies leading

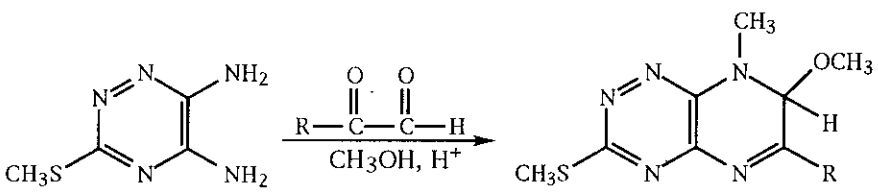
to derivatives of the 7-azapteridine (pyrimido[5,4-*e*]-*as*-triazine),[2,4] 6-azapteridine (pyrimido[4,5-*e*]-*as*-triazine),[4,5] and 4,7-diazapteridine (*as*-triazino[6,5-*e*]-*as*-triazine)[6,7] ring systems. We have synthesized a number of *as*-triazines[8,9] and their condensed heterocycles, pyrazino[2,3-*e*]-*as*-triazine[10] and imidazo[4,5-*e*]-*as*-triazine.[11,12] Recently, we reported the synthesis of 7-aryl-8*H*-[1,4]thiazino[2,3-*e*]-*as*-triazin-3(2*H*)-one[1] which provides the first example of condensed *as*-triazine belonging to the antitumor 2-phenylnaphthalene-type ring system.[13] The present report describes the preparation of another antitumor 2-phenylnaphthalene-type condensed *as*-triazine, i.e., phenylpyrazino[2,3-*e*]-*as*-triazines, their solvent exchange at position C(7) with alcohols, and the unusual alkylation at position N(8).

RESULTS AND DISCUSSION

The most straightforward synthesis of the target compounds is the Gabriel-Isay reaction[14,15] involving the condensation of 5,6-diamino-*as*-triazines and appropriate α,β-dicarbonyl compounds. Our previous studies on the preparation of free 4-azapteridine ring failed since it experienced a very fast addition process with alcohol molecule at C(7).[10] We envisaged that with an appropriate bulky group substituted at C(6) or C(7), the free 4-azapteridine could be obtained due to the steric and inductive effects which prevent the process of nucleophilic addition to occur across the 7,8-azomethine bond. Thus, 5,6-diamino-3-methylthio-*as*-triazine (**1a**) and phenylglyoxal were condensed in dry methanol under acidic conditions (Scheme 1). The resulting precipitate was collected and crystallized with a mixed solvent of dimethyl sulfoxide and methanol to give pale yellow crystals. The ^{1}H nmr spectrum of this compound showed three singlets at δ 3.08, 2.99 and 2.53 ppm corresponding to three methyl groups, OCH_3, NCH_3 and SCH_3, respectively. The remaining one proton singlet at δ 4.53 (unexchangeable with D_2O), and a five proton multiplet at δ 7.41-7.53 were attributed to the tertiary CH and the phenyl group

respectively. The ^{13}C nmr spectrum supported the ^{1}H nmr spectrum in confirming the presence of three methyl carbons appeared at δ 40.45, 38.53 and 13.32 ppm and a tertiary carbon at δ 69.38 ppm. Elemental analysis was in accord with the molecular formula $C_{14}H_{15}N_5OS$ which, taken together with spectral evidences, suggests a structure of 7-methoxy-8-methyl-3-methylthio-6-phenyl-7,8-dihydropyrazino[2,3-*e*]-*as*-triazine (**2a**). The phenomena of the solvent attacking at C(7) had been previously described.[10,16] The methylation at N(8), however, is quite unusual. In order to established and to further confirm this novel condensation, **1a** was reacted with pyruvic aldehyde in dry methanol and dil. HCl to give 7-methoxy-6,8-dimethyl-3-methylthio-7,8-dihydropyrazino[2,3-*e*]-as-triazine (**2b**) in 72 % yield. The structure of **2b** was also established by nmr spectral and elemental analyses.

Scheme 1



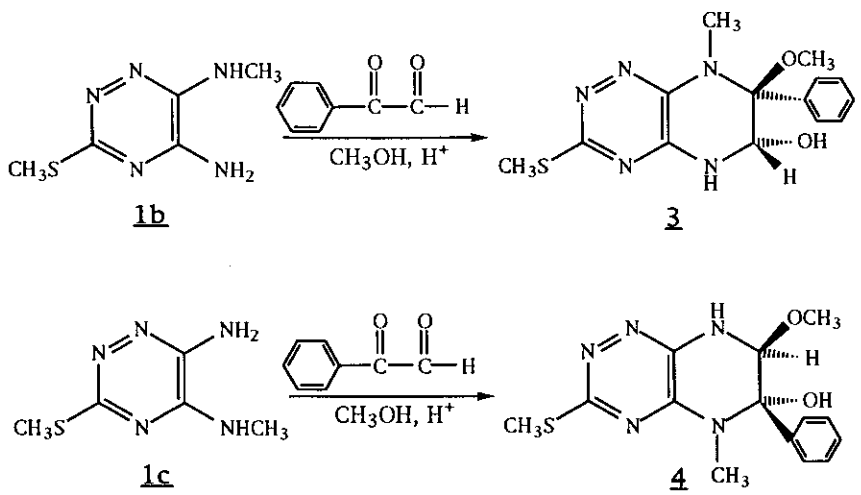
1a

2a : R = C_6H_5
2b : R = CH_3

Our next concern was to synthesize **2a** *via* a direct and unequivocal route. 5-Amino-6-methylamino-*as*-triazine (**1b**) and 6-amino-5-methylamino-*as*-triazine (**1c**) were prepared according to the known procedures.[17] Reaction of **1b** with phenylglyoxal in dry methanol under acidic conditions gave *threo*-6-hydroxy-7-methoxy-8-methyl-3-methylthio-7-phenyl-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**3**), with no **2a** detected by uv or nmr analysis (Scheme 2). In the

condensation reaction leading to **3** as well as the exchange with methanol, only one product was observed and isolated. The ^1H nmr spectrum of **3** showed a coupling of tertiary CH proton with N(5)H (J= 4.16 Hz) and C(6)OH (J=7.68 Hz) indicating that the cyclization process was regiospecific and the addition of methanol occurred at C(7).[10] Because of the steric hindrance exerted by the methylamino group at position C(6), the amino group at C(5) played more important role in attacking the aldehyde portion of phenylglyoxal leaving another carbonyl group for the methylamino to give **3**. Initially, cyclization of **1b** with phenylglyoxal proceeded in a stereoselective manner giving rise to both *threo* and *erythro* diols. Both isomers were then dehydrated to give the intermediate with a 7,8-azomethine double bond which immediately underwent a *trans* addition of methanol leading to the formation of *threo* adducts (**3**).[10] A similar reaction sequence has been previously described.[18] Accordingly, *threo*-6-hydroxy-7-methoxy-5-methyl-3-methylthio-6-phenyl-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**4**) was prepared from **1c** and phenylglyoxal in 54 % yield.

Scheme 2



1b **3**

1c **4**

We have postulated that the acetal formation is responsible for the production of **2** (Figure 1). Nucleophilic addition of methanol across the 7,8-azomethine bond is the driving force for the π-electron to attack acetal furnished alkylated products.

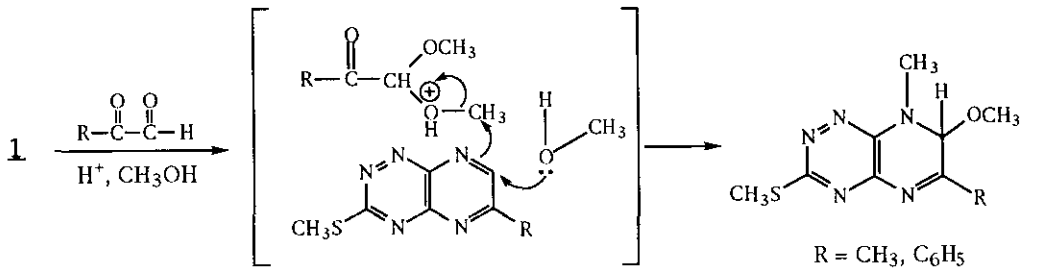
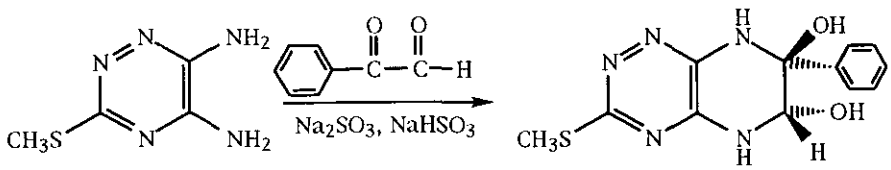


Figure 1 The proposed mechanism of solvent exchange and N(8) methylation

The regioselective control to influence the orientation of the phenyl group by using aldehyde-binding reagents such as sodium hydrogen sulfite and sodium sulfite tends to direct the phenyl group into the 7-position as depicted in Scheme 3.[19,20] Thus, *threo*-6,7-dihydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (**5**) was synthesized from **1a** and phenylglyoxal with sodium hydrogen sulfite and sodium sulfite as aldehyde-binding reagents. The ring cyclization is regiospecific but not stereospecific. Through the exchange process, dehydration of the initial product at C(7) followed by the *trans* addition of H_2O, only *threo* form was obtained.[10]

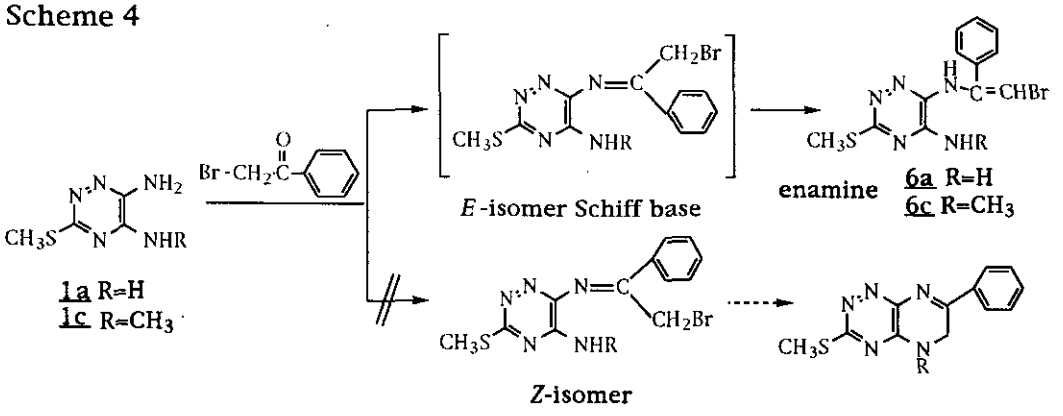
Scheme 3

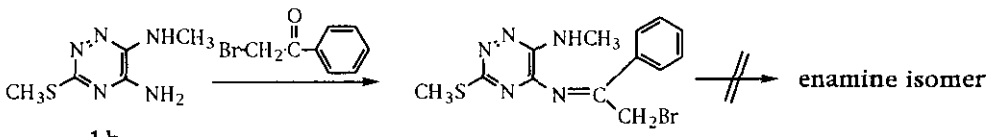


1a **5**

An alternative synthetic approach leading to the 7-phenyl-4-azapteridine ring is the cyclization of **1** and phenacyl bromide (Scheme 4).[21, 22] Treatment of **1a** with phenacyl bromide in methanol gave 5-amino-6-(2-bromo-1-phenylethylenylamino)-3-methylthio-*as*-triazine (**6a**) which is believed to be obtained from the isomerization of its *E*-form Schiff base. Positional isomer (*Z*-form) does not exist in this case indicating that the condensation of **1a** is regiospecific. The structure of **6a** was established by the ^{1}H nmr, ^{13}C nmr, and elemental analyses. Reaction of **1c** with phenacyl bromide is also proceeded in a regiospecific fashion leading to the formation of 6-(2-bromo-1-phenylethylenylamino)-5-methylamino-3-methylthio-*as*-triazine (**6c**). Hinsberg reaction of **1b** with phenacyl bromide, however, did not give expected enamine product and only 5-(2-bromomethyl-1-phenylimino)-6-methylamino-3-methylthio-*as*-triazine (**6b**) was obtained. Steric effect of the 6-methylamino group is supposed to be responsible for the unusual result. The Hinsberg condensation of certain bifunctional carbonyl compounds, such as glyoxylic acid, pyruvic acid and phenylglyoxylic acid with *o*-phenylenediamines, such as 2,3-diaminopyridine and 4,5-diaminopyrimidine in a regioselective fashion has been previously described.[18, 23, 24, 25]

Scheme 4





1b

6b *E*-isomer Schiff base

EXPERIMENTAL

Melting points were determined in capillary tubes on a Fargo apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian XL-GEM 200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard; ultraviolet spectra were obtained on a Shimadzu UV-160A UV-Visible Recording Spcetrophotometer; The progress of reaction was followed by thin-layer chromatography (tlc) on silica gel 60 F-254 plates purchased from E. Merck and short-wave ultraviolet light (254 nm) was used to detect the uv-absorbing spots.

7-Methoxy-8-methyl-3-methylthio-6-phenyl-7,8-dihydropyrazino[2,3-*e*]-*as*-triazine (2a)

5,6-Diamino-3-methylthio-*as*-triazine (**1a**) (471 mg, 3 mmol) was dissolved in 15 ml of anhydrous methanol and to this solution was added phenylglyoxal (502 mg, 3.3 mmol) and 0.3 ml of 0.2N hydrochloric acid. The mixture was stirred at room temperature for 24 h and the resulting precipitate was collected by filtration. The solid was washed with cold solvent and dried in an drying oven (Büchi TO-51) at 60 °C for 12 h. This material was suitable for elemental analyses. This was recrystallized from dimethyl sulfoxide and methanol to give 615 mg of **2a** (68 %); mp 185-187 °C; ^1H nmr (methanol-d_4): δ 2.53 (3 H, s, SCH_3), 2.99 (3 H, s, NCH_3), 3.08 (3 H, s, OCH_3), 4.53 (1H, s, C7-H), 7.41-7.53 (5 H, m, C_6H_5); ^{13}C nmr (methanol-d_4): δ 13.62 (SCH_3), 38.53 (NCH_3), 40.45 (OCH_3), 69.38 (C7), 132.15 (C6), 128.31, 128.42, 128.98, 129.14 (C_6H_5), 144.77 (C8a), 145.54 (C4a), 163.11 (C3). Uv λmax (log ε):

327.9 [sh] (3.92), 265.0 (4.45) (0.1N HCl/CH_3OH); 362.6 (4.41), 276.4 [sh] (4.17), 244.2 (4.33) (CH_3OH); 383.8 (4.27), 300.9 [sh] (4.04), 253.8 (4.41) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{14}H_{15}N_5OS$: C, 55.79; H, 5.02; N, 23.24. Found: C, 55.46; H, 5.09; N, 23.58.

7-Methoxy-6,8-dimethyl-3-methylthio-7,8-dihydropyrazino[2,3-*e*]-*as*-triazine (2b)

Compound (**2b**) was prepared from **1a** (471 mg, 3 mmol) and pyruvic aldehyde (40 wt. % solution in water) (594 mg, 3.3 mmol) by the method similar to that described for **2a**. This compound can also be recrystallized from dimethyl sulfoxide and methanol. The pale yellow crystalline precipitate separated to give 517 mg of **2b** (72 %); mp 199-201 °C; ^1H nmr (methanol-d_4): δ 1.56 (3H, s, CH_3), 2.48 (3 H, s, SCH_3), 3.22 (3 H, s, NCH_3), 3.35 (3 H, s, OCH_3), 4.44 (1H, s, C7-H); ^{13}C nmr (methanol-d_4): δ 13.99 (SCH_3), 20.03 (CH_3), 36.61 (NCH_3), 54.88 (OCH_3), 84.99 (C7), 85.36 (C6), 143.96 (C8a), 146.38 (C4a), 163.74 (C3). Uv λmax (log ε): 332.7 [sh] (3.70), 264.0 (4.38) (0.1N HCl/CH_3OH); 333.6 (3.80), 252.6 (4.20), 219.2 (4.07) (CH_3OH); 322.1 [sh] (3.87), 251.0 (4.52) (0.1N NaOH). Anal. Calcd for $C_9H_{13}N_5OS$: C, 45.17; H, 5.47; N, 29.27. Found: C, 45.20; H, 5.19; N, 29.38.

6-Hydroxy-7-methoxy-8-methyl-3-methylthio-7-phenyl-5,6,7,8-tetrahydropyrazino-[2,3-*e*]-*as*-triazine (3)

This compound was prepared from 5-amino-6-methylamino-3-methylthio-*as*-triazine (**1b**) by the same reaction condition of **2a** to give white crystalline precipitate (54 %), mp 165-166 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.47 (3 H, s, SCH_3), 3.04 (3 H, s, NCH_3), 3.09 (3 H, s, OCH_3), 4.51 (1 H, m, C6-H), 6.29 (1 H, d, C6-OH, J= 7.68 Hz), 7.39-7.47 (5 H, m, C_6H_5), 9.18 (1 H, d, N5H, J= 4.16 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.40 (SCH_3), 34.83 (NCH_3), 51.77 (OCH_3), 77.39 (C7), 91.58 (C6), 128.00, 128.47, 129.51, 136.46 (C_6H_5), 144.34 (C8a), 144.45 (C4a),

160.59 (C3). Uv λmax (log ε): 332.9 [sh] (3.70), 265.2 (4.47) (0.1N HCl/CH_3OH); 333.0 (3.79), 253.0 (4.21), 217.4 (4.19) (CH_3OH); 330.2 (4.18), 254.0 (4.61) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{14}H_{17}N_5O_2S$: C, 52.65; H, 5.37; N, 21.93. Found: C, 52.43; H, 5.36; N, 21.67.

6-Hydroxy-7-methoxy-5-methyl-3-methylthio-6-phenyl-5,6,7,8-tetrahydropyrazino-[2,3-*e*]-*as*-triazine (4)

This compound was prepared from 6-amino-5-methylamino-3-methylthio-*as*-triazine (**1c**) by the same method of **2a** to give yellow crystalline precipitate (54 %), mp 114-116 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.48 (3 H, s, SCH_3), 2.59 (3 H, s, NCH_3), 2.95 (3 H, s, OCH_3), 4.46 (1 H, d, C7-H, J= 2.34), 6.17 (1 H, s, C6-OH), 7.32-7.59 (5 H, m, C_6H_5), 8.18 (1 H, d, N8H, J=2.34); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.68 (SCH_3), 31.50 (NCH_3), 55.09 (OCH_3), 86.38 (C7), 85.00 (C6), 128.33, 128.64, 132.29, 135.02 (C_6H_5), 145.08 (C8a), 145.43 (C4a), 162.84 (C3). Uv λmax (log ε): 380.8 [sh] (3.69), 266.4 (4.40) (0.1N HCl/CH_3OH); 362.6 (4.02), 280.8 [sh] (3.84), 250.0 (4.22) (CH_3OH); 361.5 [sh] (4.11), 251.4 (4.37) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{14}H_{17}N_5O_2S$: C, 52.65; H, 5.37; N, 21.93. Found: C, 52.87; H, 5.50; N, 21.58.

6,7-Dihydroxy-3-methylthio-7-phenyl-5,6,7,8-tetrahydropyrazino[2,3-*e*]-*as*-triazine (5)

A suspension of **1a** (260 mg, 1.7 mmol) and sodium sulfite (2.6 g, 20.6 mmol) in water (20 ml) was heated at 60 °C for 20 min. and allowed to cool to room temperature. Phenylglyoxal (289 mg, 1.9 mmol) and sodium hydrogen sulfite (50 mg, 0.5 mmol) was added at one portion. The progress of the reaction was monitored by using tlc (dichloromethane : methanol = 10 : 1). During the reaction period, the yellow product gradually precipitated. The solid was collected by filtration, washed with cold water to give 357 mg of **5** as pale yellow solid (72 %), mp 149-152 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.50 (3 H, s, SCH_3), 4.58 (1 H, m, C6-H), 5.88 (1 H, d,

C6-OH, J= 7.84), 6.24 (1 H, s, C7-OH), 7.30-7.65 (5 H, m, C_6H_5), 7.85 (1 H, s, N8H), 9.00 (1 H, d, N5H, J= 4.08); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.43 (SCH_3), 78.40 (C7), 82.05 (C6), 1227.54, 127.80, 128.53, 129.33 (C_6H_5), 144.27 (C8a), 144.70 (C4a), 160.48 (C3). Uv λmax (log ε): 327.9 [sh] (4.11), 264.5 (4.42) (0.1N HCl/CH_3OH); 333.0 (3.86), 252.5 (4.24), 219.0 (4.18) (CH_3OH); 390.5 (3.84), 248.5 (4.37), 219.5 (4.19) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{12}H_{13}N_5O_2S$: C, 49.47; H, 4.50; N, 24.04. Found: C, 49.62; H, 4.37; N, 24.19.

5-Amino-6-(2-bromo-1-phenylethylenylamino)-3-methylthio-*as*-triazine (6a)

Phenacyl bromide (43.8 mg, 0.22 mmol) was added to a stirred solution of 5,6-diamino-3-methylthio-*as*-triazine (1a) (31.4 mg, 0.2 mmol) in anhydrous methanol (2 ml). The solution was stirred at room temperature under nitrogen atmosphere for 24 h. The yellow solid that deposited from the solution was collected by filtration and recrystallized from methanol. The filtrate was absorbed onto silica gel then purified by a flash column chromatography (E. Merck silica gel 60, 230-400 mesh) eluting with 20:1 dichloromethane-methanol. These two crops was combined to give 53 mg (78 %), mp 253-254 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.48 (3 H, s, SCH_3), 7.28-8.00 (5 H, m, C_6H_5), 7.44 (1H, s, enamine N<u>H</u>-C(C_6H_5)=CHBr), 8.25 (2 H, br s, NH_2), 8.54 (1H, s, enamine NH-C(C_6H_5)=C<u>H</u>Br); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.50 (SCH_3), 114.51 (enamine NH-<u>C</u>(C_6H_5)=CHBr), 125.61 (enamine NH-C(C_6H_5)=<u>C</u>HBr), 127.45, 128.09, 128.96, 133.56 (C_6H_5), 142.25, 152.33, 162.05 (*as*-triazine). Uv λmax (log ε): 314.4 [sh] (4.55), 259.0 (4.72) (0.1N HCl/CH_3OH); 312.0 (4.27), 256.5 (4.76) (CH_3OH); 313.5 [sh] (4.10), 256.5 (4.61), 219.5 (4.34) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{12}H_{12}N_5SBr$: C, 42.61; H, 3.58; N, 20.71. Found: C, 42.83; H, 3.72; N, 20.97.

5-(2-Bromomethyl-1-phenylimino)-6-methylamino-3-methylthio-*as*-triazine (6b)

This compound was prepared from **1b** by the same method of **6a** except the pure product was obtained by flash column chromatography (dichloromethane : methanol = 40 : 1), followed by recrystallization from methanol and small amount of dimethyl sulfoxide afforded **6b** as white needles in 68 % yield, mp 199-201 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.47 (3 H, s, SCH_3), 2.63 (3 H, d, $NHCH_3$, J= 4.98 Hz), 5.68 (2 H, s, imine N=C(C_6H_5)-CH_2Br), 7.16 (1 H, q, $NHCH_3$, J= 4.96 Hz), 7.57-8.09 (5 H, m, C_6H_5,); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.12 (SCH_3), 27.48 ($NHCH_3$), 61.53 (imine N=C(C_6H_5)-CH_2Br), 128.51, 129.33, 134.23, 134.77 (C_6H_5), 148.47, 156.13, 160.39 (*as*-triazine), 191.88 (imine N=C(C_6H_5)-CH_2Br). Uv λmax (log ε): 300.9 [sh] (4.18), 247.0 (4.50) (0.1N HCl/CH_3OH); 218.7 [sh] (4.15), 246.5 (4.44) (CH_3OH); 292.0 [sh] (3.96), 243.5 (4.29), 219.5 (4.35) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{13}H_{14}N_5SBr$: C, 44.32; H, 4.01; N, 19.88. Found: C, 44.63; H, 4.37; N, 20.15.

6-(2-Bromo-1-phenylethylenylamino)-5-methylamino-3-methylthio-*as*-triazine (6c)

This compound was obtained from **1c** by a method similar to that described for **6a**. The excess solvent was evaporated to give yellow oil residue then chromatographed on silica gel by using 50:1 dichloromethane-methanol as eluent. The eluent containing the product was combined and evaporated under reduced pressure to give **6c** in 82%. Recrystallization of a small sample from methanol yielded an analytical sample, mp 147-148 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.56 (3 H, s, SCH_3), 3.10 (3 H, d, $NHCH_3$, J= 5.10 Hz), 6.92 (1 H, q, $NHCH_3$, J= 5.10 Hz), 7.26 (1 H, s, enamine NH-C(C_6H_5)=CHBr), 7.32-7.87 (5 H, m, C_6H_5), 7.91 (1 H, s, enamine NH-C(C_6H_5)=CHBr); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.99 (SCH_3), 27.20 ($NHCH_3$), 113.38 (enamine NH-C(C_6H_5)=CHBr), 125.61 (enamine NH-C(C_6H_5)=CHBr), 127.91, 128.12, 128.85, 133.18 (C_6H_5), 142.73, 151.04, 162.77 (*as*-triazine). Uv λmax (log

ε): 319.2 [sh] (3.99), 261.5 (4.54) (0.1N HCl/CH_3OH); 320.2 (4.26), 257.0 (4.73) (CH_3OH); 310.0 [sh] (4.37), 257.0 (4.72), 220.0 (4.42) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_{13}H_{14}N_5SBr$: C, 44.32; H, 4.01; N, 19.88. Found: C, 44.28; H, 3.91; N, 18.98.

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REFERENCES AND NOTES

1. Part I: K. H. Lee, B. R. Huang, Y. L. Chen, D. C. Wei, and C. C. Tzeng, J. Heterocycl. Chem., **1993**, 39, 293.
2. (a) For a review see: D. J. Brown and R. K. Lynn, "Chemistry and Biology of Pteridines" ed. by W. Pfleiderer and W. de Gruyter, New York, 1975; (b) W. Pfleiderer, J. Heterocycl. Chem., **1992**, 29, 583.
3. C. Kuchler, W. Kuchler, and L. Heinisch, Arzneim.-Forsch., **1966**, 16, 1122.
4. H. Neunhoeffer, "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, J. Wiley and Sons, Inc., New York, **1978**.
5. E. C. Taylor and S. F. Martin, J. Org. Chem.,**1972**, 37, 3985 and references cited therein.
6. H. Neunhoeffer and H. Hammann, Tetrahedron Lett., **1983**, 24, 1767.
7. K. Kaji, H. Nagashima, H. Oda, and M. Kawase, Heterocycles, **1976**, 4, 1846.
8. C. H. Han, Y. L. Chen, and C. C. Tzeng, Nucleosides and Nucleotides, **1991**, 10, 1390.
9. K. H. Lee, Y. L. Chen, B. R. Huang, Q. Y. Zhu, T. C. Chou, and C. C. Tzeng, Nucleosides and Nucleotides, **1991**, 10, 1407.
10. C. C. Tzeng, U. Rychlewska, D. J. Hodgson, and R. P. Panzica, J. Heterocycl. Chem., **1986**, 23, 33.
11. J. Riand, C. C. Tzeng, M. T. Chenon, and R. P. Panzica, J. Chem. Soc., Perkin Trans. 2, **1986**, 931.

12. C. J. Cheer, S. Kokkou, C. C. Tzeng, and R. P. Panzica, J. Chem. Soc., Perkin Trans. 2, **1987**, 1455.
13. C. C. Cheng, "Progress in Medicinal Chemistry", Vol. 25, ed. by G. P. Ellis and G. B. West, Elsevier Science Publishers, B. V. (Biomedical Division), **1988**, pp. 35-83.
14. (a) A. Albert, Q. Rer. Chem. Soc., **1952**, 6, 197.; (b) S. Gabriel and J. Colman, Ber., **1952**, 34, 1234; (c) O. Isay, Ber., **1906**, 39, 250.
15. F. Sachsand and G. Meyerheim, Ber., **1908**., 41, 3957.
16. C. C. Tzeng and R. P. Panzica, J. Heterocycl. Chem., **1983**, 20, 1123.
17. C. C. Tzeng, N. C. Motola, and R. P. Panzica, J. Org. Chem., **1983**, 48, 1271.
18. M. I. Abasolo, D. Bianchi, F. Atlasovich, C. Gaozza, and B. M. Fernandez, J. Heterocycl. Chem., **1990**, 27, 157.
19. D. R. Seeger, D. B. Cosulich, J. M. Smith. Jr., and M. E. Hultiquist, J. Am. Chem. Soc.,**1949**, 71, 1753.
20. W. Pfleiderer, "Comprehensive Heterocyclic Chemistry", Vol. 3, Part 2B, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, **1984**, p. 263.
21. A. Dornow, H. Menzel, and P. Marx, Chem. Ber., **1964**, 97, 2158.
22. A. Dornow, H. Menzel, and P. Marx, Chem. Ber., **1964**, 97, 2173.
23. M. I. Abasolo, C. H. Gaozza, and B. M. Fernandez, J. Heterocycl. Chem., **1987**, 24,1771.
24. D. G. Bekerman, M. I. Abasolo, and B. M. Fernandez, J. Heterocycl. Chem., **1992**, 29,129.
25. M. I. Abasolo and B. M. Fernandez, J. Heterocycl. Chem., **1992**, 29, 1279.

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