CONDENSED 1,2,4-TRIAZINES: SYNTHETIC AND MOLECULAR MODELING STUDIES OF 5,8-DIHYDRO-7-METHYLPYRAZINO[2,3-*e*]-1,2,4-TRIAZINES

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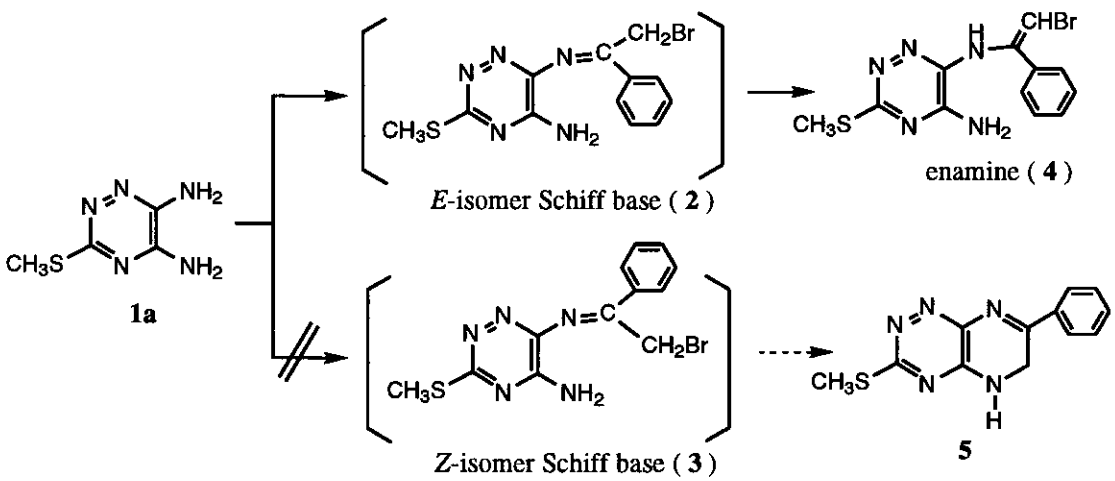
Abstract - 5,8-Dihydro-7-methylpyrazino[2,3-*e*]-1,2,4-triazines (dihydroazapteridines) were prepared by Hinsberg reaction of 5,6-diamino-1,2,4-triazines with bromoacetone *via* a regiospecific fashion. The initial *Z*-form Schiff base intermediates cyclized to give 5,6-dihydro-7-methylpyrazino[2,3-*e*]-1,2,4-triazines which underwent π redistribution to afford 5,8-dihydro-7-methylpyrazino[2,3-*e*]-1,2,4-triazines as final products.

7-Azapteridine antibiotics (pyrimido[5,4-*e*]-1,2,4-triazine),[1-3] such as toxoflavin and fervenulin have been isolated and proved to possess broad-spectrum antibacterial, antifungal, antiparasitic, and antineoplastic activities. The isomeric 6-azapteridine (pyrimido[4,5-*e*]-1,2,4-triazine),[3,4] and 4,7-diazapteridine (1,2,4-triazino[6,5-*e*]-1,2,4-triazine)[5,6] ring systems were also disclosed. However, 4-azapteridine (pyrazino[2,3-*e*]-1,2,4-triazine), an aza analogue of pteridine which maintained the integrity of the pyrazine ring, is still unknown. Our previous studies on the preparation of 4-azapteridine ring failed since it experienced a fast addition process with solvent molecule at C(7).[7,8] An alternative synthetic approach leading to the 7-phenyl-4-azapteridine ring was the oxidation of its 5,6-dihydro precursor (**5**) which should be obtained *via* Hinsberg reaction of 5,6-diamino-3-methylthio-1,2,4-triazine (**1a**)[9] and 2-bromoacetophenone. However,

only the open-chain enamine, 5-amino-6-(2-bromo-1-phenylethylenylamino)-3-methylthio-1,2,4-triazine (**4**), which is believed to be obtained from the isomerization of the *E*-form Schiff base (**2**), was isolated (Scheme 1).[8] Similar results were reported during the preparation of 2-phenylpyrido[2,3-*b*]pyrazin-3(4*H*)-one from 2,3-diaminopyridine and benzoylformic acid.[10,11] Steric hindrance exerted by the phenyl group of the benzoylformic acid is supposed to be responsible for the difficulties in ring cyclization. On the other hand, 2-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one was obtained easily from 2,3-diaminopyridine and pyruvic acid.[12,13] Therefore, we decided to use bromoacetone instead of 2-bromoacetophenone as a cyclization reagent for the preparation of 7-methyl-4-azapteridines. The computer modeling studies to calculate the relative stability of Schiff bases and enamine are also described.

Scheme 1

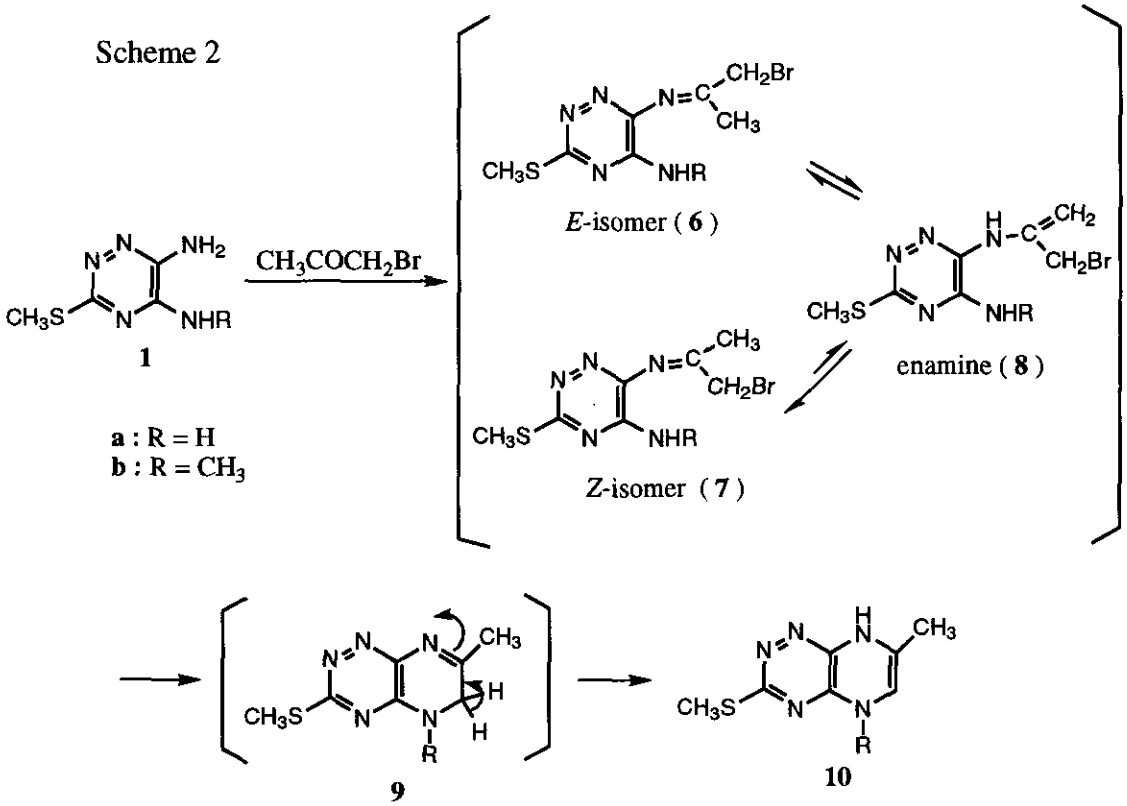


RESULTS AND DISCUSSION

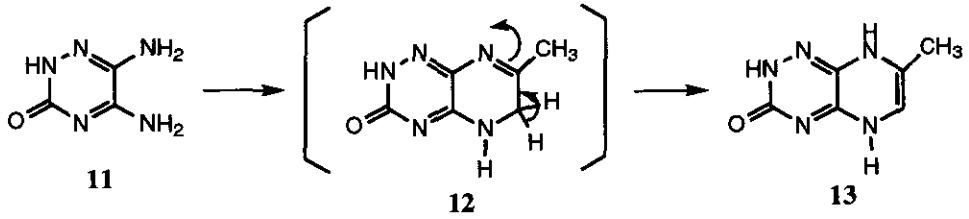
5,6-Diamino-3-methylthio-1,2,4-triazine (**1a**) was treated with bromoacetone in dry methanol under anhydrous conditions (Scheme 2). The resulting precipitate was collected and crystallized from methanol to give pale yellow crystals. The ^{1}H nmr spectrum of this compound showed four singlets (δ 2.37, 2.40, 8.68 and 11.48 ppm) and a doublet (δ 7.92 ppm, J = 0.82 Hz) corresponding to CH_3, SCH_3, N(8)H, N(5)H, and C(6)H protons respectively. The proton-decoupled ^{13}C nmr and DEPT spectra indicated the presence of C(6) vinylic carbon resonated at δ 115.86 ppm suggesting a structure of 5,8-dihydro-7-methyl-3-methylthiopyrazino[2,3-*e*]-1,2,4-triazine (**10a**) instead of its 5,6-dihydro counterpart (**9a**). The relatively most stable *Z*-form Schiff base (**7**) was generated and cyclized to give 5,6-dihydro-7-methylpyrazino[2,3-

e]-1,2,4-triazine (**9a**) which then underwent π redistribution (allylic rearrangement) leading to the formation of its 5,8-dihydro counterpart (**10a**). Accordingly, reaction of **1b** with bromoacetone is also proceeded in the same sequences leading to the formation of 5,8-dihydro-5,7-dimethyl-3-methylthiopyrazino[2,3-*e*]-1,2,4-triazine (**10b**) which was characterized by the presence of a vinylic carbon resonated at δ 116.26 ppm. In order to establish and to further confirm this cyclization pattern, 5,6-diamino-1,2,4-triazin-3-one (**11**) was condensed with bromoacetone to give 5,8-dihydro-7-methylpyrazino[2,3-*e*]-1,2,4-triazin-3-one (**13**) in 77% yield (Scheme 3). The structure of **13** was also established by ^{1}H nmr, ^{13}C nmr and elemental analyses.

Scheme 2

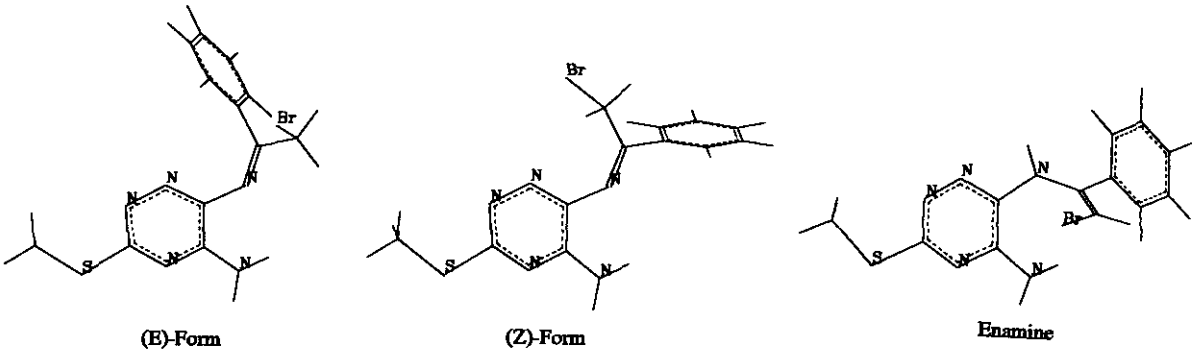


Scheme 3



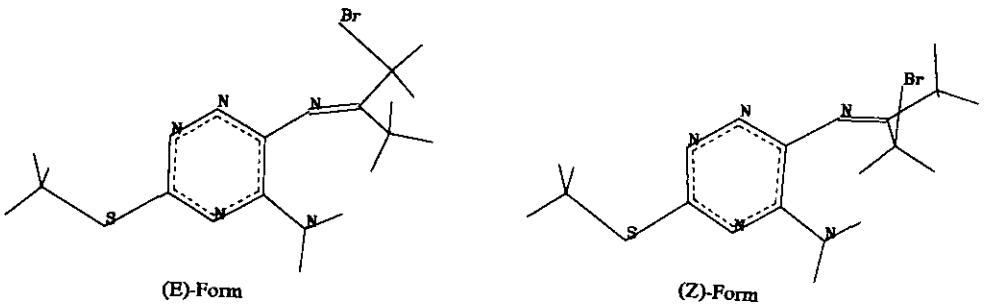
To better understand why the Hinsberg reaction of **1a** with 2-bromoacetophenone did not give the desired 7-phenyl-4-azapteridine (**5**) while the 7-methyl counterparts were easily obtained from **1** and bromoacetone, we initiated the computer modeling studies to calculate the conformation and the relative stability of the Schiff bases and the enamine. Figure 1 depicts the energy minimized conformation of the Schiff bases (**2**, **3**) and enamine (**4**). The global minimized energy showed 161.78 kcal, 163.27 kcal and 71.76 kcal corresponding to **2** (*E*-form), **3** (*Z*-form) and **4** (enamine) respectively. The distances between 5-amino and allylic bromomethyl carbon for both Schiff bases are 5.02 Å (*E*-form) and 5.23 Å (*Z*-form). The modeling graphics indicate that these distances are too far for either Schiff base (**2** or **3**) to undergo ring cyclization. We have postulated that the reaction pathway proceeded *via* the relatively stable *E*-form Schiff base (**2**) which was then isomerized into the relatively most stable enamine (**4**) as the final product.

Figure 1



The modeling effort based on these structures suggests that energetically accessible cyclization may exist for compounds bearing the less steric hindrance substitutents, such as a methyl group. The calculated energy difference between *Z*-form Schiff base (**7**) and its *E*-isomer (**6**) is approximately 0.56 kcal/mol in favor of *Z*-isomer. Moreover, the distance between 5-amino and allylic bromomethyl carbon is only 3.57 Å and 4.36 Å corresponding to *Z*-form and *E*-form Schiff base, respectively (Figure 2), which make the ring cyclization a possible event. The initial products (**9**) thus formed were then converted into the more stable final products (**10**) *via* π redistribution.

Figure 2



EXPERIMENTAL

Melting points were determined in capillary tubes on a MelTemp 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. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) packed in glass columns. All of the modeling techniques described herein were performed on Silicon Graphic IRIS INDIGO XS24-4000 workstation using the INSIGHT II /DISCOVER molecular modeling software from BIOSYM Technologies, Inc., 10065, Barnes Canyon Road, San Diego, California.

5,8-Dihydro-7-methyl-3-methylthiopyrazino[2,3-*e*]-1,2,4-triazine (10a)

To a stirred solution of 5, 6-diamino-3-methylthio-1,2,4-triazine (**1a**, 63 mg, 0.4 mmol) in dry methanol (2 ml) was added dropwise of bromoacetone (30 mg, 0.44 mmol), and the resulting mixture was stirred under an atmosphere of nitrogen at room temperature for 24 h. The progress of the reaction was monitored by tlc. Upon completion, the resulting precipitate was removed by filtration. The yellow filtrate was evaporated to give an oily residue which was absorbed onto silica gel. Purification by flash column chromatogrphy (silica gel, 10:1 CH_2Cl_2:CH_3OH, v/v) afforded a residual solid which was crystallized from dry CH_3OH to give **10a** (56 mg, 72 %) as pale yellow crystals. mp 258-260 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.37 (s, 3H, CH_3), 2.40 (s, 3H, SCH_3), 7.92 (d, 1H, C(6)H, J = 0.82 Hz), 8.68 (br s, 1H, N(8)H), 11.48 (br s, 1H, N(5)H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.81 (CH_3), 13.47 (SCH_3), 115.86 (C6), 124.94 (C7),

136.79 (C8a), 150.37 (C4a), 163.45 (C3). Uv λmax (log ε): 288 [sh] (3.69), 227.9 [sh] (4.06), 246 (4.24) (0.1N HCl/CH_3OH); 300.9 [sh] (3.70), 243 (4.46) (CH_3OH); 305.9 [sh] (3.58), 242 (4.38) (0.1N NaOH/CH_3OH). Anal. Cacld for $C_7H_9N_5S$: C, 43.06; H, 4.65; N, 35.87. Found: C, 43.33; H, 4.42; N, 35.90.

5,8-Dihydro-5,7-dimethyl-3-methylthiopyrazino[2,3-*e*]-1,2,4-triazine (10b)

Compound (**10b**) was prepared from 6-amino-5-methylamino-3-methylthio-1,2,4-triazine (**1b**, 63 mg, 0.4 mmol) by the same procedures as **10a** in 77% yield (64 mg). mp 60-61 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 3.08 (s, 3H, NCH_3), 7.51 (s, 1H, C(6)H), 8.22 (br s, 1H, N(8)H) ; ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.14 (CH_3), 13.36 (SCH_3), 27.75 (NCH_3), 116.26 (C6), 141.50 (C7), 141.49 (C8a), 151.98 (C4a), 164.16 (C3). Uv λmax (log ε): 283.3 [sh] (4.09), 247 (4.53) (0.1N HCl/CH_3OH); 307.8 [sh] (3.79), 244 (4.56) (CH_3OH); 303.9 [sh] (3.79), 244 (4.5), 224.5 [sh] (4.19) (0.1N NaOH/CH_3OH). Anal. Calcd for $C_8H_{11}N_5S$: C, 45.91; H, 5.30; N, 33.47. Found: C, 46.20; H, 5.11; N, 33.15.

5,8-Dihydro-7-methylpyrazino[2,3-*e*]-1,2,4-triazin-3-one (13)

The synthetic procedures are similar to that for the preparation of **10a** except 5, 6-diamino-1,2,4-triazin-3-one (**11**, 51 mg, 0.4 mmol) was used. The resulting pure product was precipitated from CH_3OH during the reaction period (*ca.* 24 h). Crystallization from dry CH_3OH gave **13** in 77% yield (51 mg). mp 244-245 °C; ^1H nmr (dimethyl sulfoxide-d6): δ 2.35 (s, 3 H, CH_3), 7.76 (d, 1H, C(6)H, J = 1.06 Hz), 10.91 (br s, 1H, N(8)H), 11.76 (br s, 2H, N(2)H, N(5)H); ^{13}C nmr (dimethyl sulfoxide-d6): δ 13.33 (CH_3), 111.68 (C6), 134.49 (C7), 144.06 (C8a), 149.29 (C4a), 154.82 (C3). Uv λmax (log ε): 313.7 [sh] (3.48), 237 (3.84) (0.1N HCl/CH_3OH); 298 [sh] (3.66), 235 (4.09) (CH_3OH); 305.9 [sh] (3.56), 236 (4.01), 222.5 [sh] (3.39) (0.1N NaOH/CH_3OH). Anal. Cacld for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.39; H, 3.99; N, 42.67.

Model development and comformational analyses

Automatic structure construction can be devided into two classes in trems of fundamental algorithm. One involves growing a molecule atom by atom, and other involves linking fragments that are prepared in the program. One of the advantages of the simple fragment method is that each generated structure should be

chemically acceptable because fragment structures familiar to medicinal chemists are used in the structure generation program.

All of the compounds were constructed *de novo* using where possible, the sketch option of the building module of INSIGHT II. Geometry optimization was performed using DISCOVER utilizing the CVFF (Consistent Valence Force Field) force field to an energy difference (RMSD) of 0.01 kcal/mol-A. The result were visualized using INSIGHT II running on a Silicon Graphic IRIS (SGI) INDIGO XS24-4000.

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REFERENCES

1. D. J. Brown and R. K. Lynn, "Chemistry and Biology of Pteridines" ed. by W. Pfleiderer and W. de Gruyter, New York, **1975**.
2. W. Pfleiderer, *J. Heterocycl. Chem.*, **1992**, *29*, 583.
3. H. Neunhoeffer, "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, J. Wiley and Sons, Inc., New York, **1978**.
4. E. C. Taylor and S. F. Martin, *J. Org. Chem.*,**1972**, *37*, 3985 and references cited therein.
5. H. Neunhoeffer and H. Hammann, *Tetrahedron Lett.*, **1983**, *24*, 1767.
6. K. Kaji, H. Nagashima, H. Oda, and M. Kawase, *Heterocycles*, **1976**, *4*, 1846.
7. C. C. Tzeng, U. Rychlewska, D. J. Hodgson, and R. P. Panzica, *J. Heterocycl. Chem.*, **1986**, *23*, 33.
8. K. H. Lee, B. R. Huang, Y. L. Chen, and C. C. Tzeng, *Heterocycles*, **1993**, *36*, 2577.
9. C. C. Tzeng, N. C. Motola, and R. P. Panzica, *J. Org. Chem.*, **1983**, *48*, 1271.
10. D. G. Bekerman, M. I. Abasolo, and B. M. Fernandez, *J. Heterocycl. Chem.*, **1992**, *29*, 129.
11. M. I. Abasolo and B. M. Fernandez, *J. Heterocycl. Chem.*, **1992**, *29*, 1279.
12. M. I. Abasolo, C. H. Gaozza, and B. M. Fernadez, *J. Heterocycl. Chem.*, **1987**, *24*, 1771.
13. M. I. Abasolo, D. Bianchi, F. Atlasovich, C. Gaozza, and B. M. Fernandez, *J. Heterocycl. Chem.*, **1990**, *27*, 157.

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