Condensed *as*-Triazines. Synthesis of 7-Aryl-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one

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Ring closure of 6-amino-3-oxo-*as*-triazine-5-thione with α-haloketones provides the thiazino[2,3-*e*]-1,2,4-triazines which dehydrate *via* an unusual pathway to give 7-aryl-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-ones.

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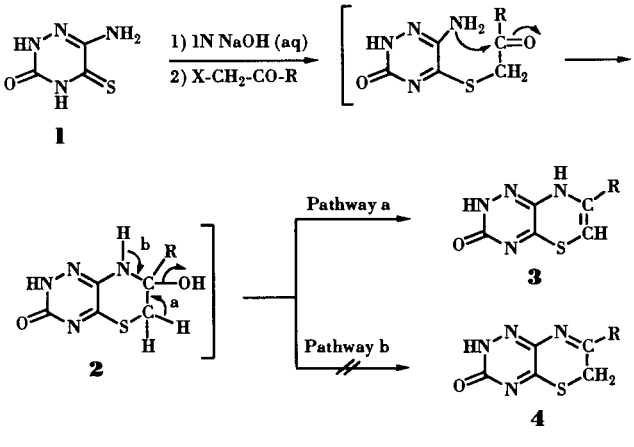
An examination of numerous antitumor agents from both natural and synthetic origin suggests that a common chemical structural pattern of the 2-phenylnaphthalene-type ring system is necessary for designing compounds of this type. The 2-phenylnaphthalene-type ring systems could either be carbocyclic or heterocyclic, with nitrogen, oxygen and/or sulfur atoms placed at selected positions [1]. We have synthesized a number of *as*-triazines [2-3] and its condensed heterocycles, pyrazino[2,3-*e*]-1,2,4-triazine [4] and imidazo[4,5-*e*]-1,2,4-triazine [5-6] and studied their chemical and biological properties. *as*-Triazine-3,5-dione (6-azauracil) has proved to possess a broad spectrum of therapeutic effects which include antiviral [7-8], antitumor [9-10], and antifungal activities [11]. The present report describes the preparation of another novel thiazino[2,3-*e*]-1,2,4-triazine which provides the first example of condensed *as*-triazine belonging to the antitumor 2-phenylnaphthalene-type ring system.

6-Amino-3-oxo-*as*-triazine-5-thione (**1**) [12], previously prepared in our laboratory, was reacted with α-haloketones in the presence of sodium acetate as described by Kim *et al* [13]. This reaction resulted in the formation of complicated products which were difficult to separate. Faced with this dilemma, we explored a more effective route for the preparation of this heterocycle. It was found that when the sodium salt of 3-oxo-*as*-triazine-5-thione in dry ethanol was alkylated with an α-haloketone it cyclized *in situ* to provide thiazino[2,3-*e*]-1,2,4-triazine (**2**) as the sole product. Depending on the mode of dehydration of **2**, two tautomers are possible, *i.e.* 8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3**) and 6*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**4**).

Scheme 1



3a, R = C_6H_5
3b, R = *p*-OCH_3-C_6H_4
3c, R = *p*-Cl-C_6H_4
3d, R = *p*-C_6H_5-C_6H_4
3e, R = CH_3

According to Kim *et al* [13], reaction of 2,5,6-triamino-4-thiopyrimidine with α-haloketones gave substituted 7*H*-pyrimido[4,5-*b*][1,4]thiazines which resemble tautomer **4**. Nair [14] and Henrie [15] have also reported the preparation of 2-amino-4(3*H*)-oxo-6-phenylpyrimido[4,5-*b*][1,4]-thiazine from 2,5-diamino-6-mercaptopyrimidone and α-bromoacetophenone. Faced with a similar situation, we could have reached the same conclusion, *i.e.*, that the dehydration product was **4** (pathway **b**, Scheme 1). However, after careful examination of the nmr spectra it became apparent that only **3** (pathway **a**) fit the data. The proton nmr spectra of the dehydration product showed a vinyl signal at 4.6-4.9 ppm and no evidence for allylic protons. The C-13 nmr showed only a tertiary and no methylene carbon lent additional support for the tautomer **3**. In order to provide a more definitive structural assignment, we decided to synthesize 7-methyl-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3e**) and examine its proton nmr. The long range coupling (J = 1.2 Hz) of its vinylic proton and the protons of the methyl substituent further confirmed our assignment. Based on above nmr spectral data, we conclude that the dehydration occurs *via* pathway **a** to give tautomer **3**.

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 spec-

trometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. The progress of reaction was followed by thin-layer chromatography (tlc) on silica gel 60 F-254 plates purchased from E. Merck. Flash column chromatography was performed with silica gel 60 (230-400 mesh) from E. Merck. All compounds were analyzed for C, H, and N. The results were within 0.4% of the calculated theoretical values.

7-Phenyl-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3a**).

To a stirred solution of 6-amino-3-oxo-*as*-triazine-5-thione (**1**, 144 mg, 1 mmole) in absolute ethanol (15 ml) at 40° was added 1*N* sodium hydroxide solution (1 ml). While adding sodium hydroxide solution, **1** dissolved, and after several minutes a small quantity of the sodium salt precipitated. The stirred solution was cooled to room temperature then α-bromoacetophenone (239 mg, 1.2 mmoles) was added slowly under nitrogen atmosphere. The progress of the reaction was monitored by using tlc (methanol:dichloromethane = 1:10). During the reaction period (*ca.* 20 hours), the pale orange product gradually precipitated. The solid was collected by filtration, washed with ethanol, then recrystallized from methanol to give 167 mg of **2a** as pale yellow fine needles (68%), mp 186-187°; ^{1}H nmr (DMSO-d_6): δ 4.90 (s, 1H, vinyl proton), 5.97 (br s, 1H, N8 H), 7.54-8.09 (m, 5H, C_6H_5), 11.74 (br s, 1H, N2 H); ^{13}C nmr (DMSO-d_6): δ 129.40 (C-6), 129.39, 129.88, 134.81, 136.72 (C_6H_5), 143.22 (C-7), 152.24 (C-4a), 166.68 (C-8a), 193.82 (C-3); uv: λ max (nm) 232 (methanol), 225, 232 (0.1*N* sodium hydroxide), 207 (0.1*N* hydrochloric acid).

Anal. Calcd. for $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.94. Found: C, 54.20; H, 3.69; N, 22.88.

7-(4′-Methoxyphenyl)-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3b**).

This compound was prepared by the same method as **3a** except the pure product was obtained by flash column chromatography (methanol:dichloromethane = 1:5), followed by recrystallization from ethanol to yield 148 mg (54%), mp 194-196°; ^{1}H nmr (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 4.84 (s, 1H, vinyl proton), 5.93 (br s, 1H, N8 H), 7.07-8.06 (m, 4H, C_6H_4), 11.72 (br s, 1H, N2 H); ^{13}C nmr (DMSO-d_6): δ 55.92 (OCH_3), 114.34, 128.72, 131.05, 163.85 (C_6H_4), 131.10 (C-6), 142.35 (C-7), 151.33 (C-4a), 165.71 (C-8a), 190.79 (C-3); uv: λ max (nm) 270 (methanol), 232 (0.1*N* sodium hydroxide), 267 (0.1*N* hydrochloric acid).

Anal. Calcd. for $C_{12}H_{10}N_4O_2S$ (274.29): C, 52.55; H, 3.67; N, 20.43. Found: C, 52.31; H, 3.79; N, 20.21.

7-(4′-Chlorophenyl)-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3c**).

This compound was obtained as an orange powder, 103 mg (37%), mp 240-241°; ^{1}H nmr (DMSO-d_6): δ 4.87 (s, 1H, vinyl proton), 5.95 (br s, 1H, N8 H), 7.63-8.10 (m, 4H, C_6H_4), 11.73 (br s, 1H, N2 H); ^{13}C nmr (DMSO-d_6): δ 129.22, 130.56, 134.65, 138.90 (C_6H_4), 130.60 (C-6), 142.33 (C-7), 151.26 (C-4a), 165.52 (C-8a), 191.74 (C-3); uv: λ max (nm) 232 (methanol), 232 (0.1*N* sodium hydroxide), 259 (0.1*N* hydrochloric acid).

Anal. Calcd. for $C_{11}H_7N_4OSCl$ (278.71): C, 47.40; H, 2.53; N, 20.10. Found: C, 47.66; H, 2.37; N, 20.09.

7-(4′-Phenylphenyl)-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3d**).

This compound was obtained by a method similar to that described for **3a** except the reaction was carried out in dry methanol. After recrystallization from methanol and small amount of dimethyl sulfoxide, the pure **3d** separated in 43% yield, mp 215-218°; ^{1}H nmr (DMSO-d_6): δ 4.92 (s, 1H, vinyl proton), 5.97 (br s, 1H, N8 H), 7.40-8.16 (m, 9H, C_6H_4-C_6H_5), 11.76 (br s, 1H, N2 H); ^{13}C nmr (DMSO-d_6): δ 127.20, 127.26, 129.24, 129.39, 134.68, 139.06, 145.34 (C_6H_4-C_6H_5), 128.78 (C-6), 142.38 (C-7), 151.35 (C-4a), 165.63 (C-8a), 192.09 (C-3); uv: λ max (nm) 227 (methanol), 221, 224 (0.1*N* sodium hydroxide), 208 (0.1*N* hydrochloric acid).

Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.36): C, 63.74; H, 3.77; N, 17.49. Found: C, 63.85; H, 3.99; N, 17.09.

7-Methyl-8*H*-[1,4]thiazino[2,3-*e*]-1,2,4-triazin-3(2*H*)-one (**3e**).

This compound was obtained as a dark red powder (ethanol), 97 mg (53%), mp 281-282°; ^{1}H nmr (DMSO-d_6): δ 1.72 (d, 3, CH_3, J = 1.2 Hz), 4.65 (q, 1, vinyl proton, J = 1.2 Hz), 9.04 (br s, 1, N8 H), 11.34 (br s, 1, N2 H); ^{13}C nmr (DMSO-d_6): δ 19.52 (CH_3), 81.61 (C-6), 134.53 (C-7), 139.08 (C-4a), 152.80 (C-8a), 168.25 (C-3); uv: λ max (nm) 232 (methanol), 232, 300 (0.1*N* sodium hydroxide), 208, 297 (0.1*N* hydrochloric acid).

Anal. Calcd. for $C_6H_6N_4OS$ (182.20): C, 39.55; H, 3.32; N, 30.75. Found: C, 39.48; H, 3.62; N, 31.04.

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