

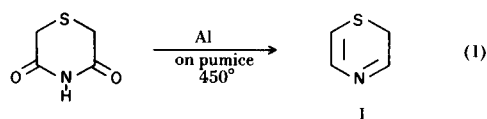
New Derivatives of 1,4-Thiazine (1)

Carl R. Johnson and C. B. Thanawalla

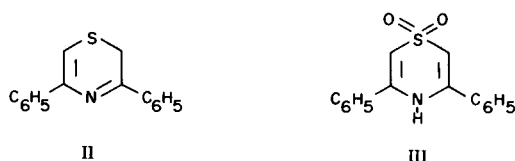
Department of Chemistry, Wayne State University

Although there has been considerable effort in the field of 1,4-thiazines fused with aromatic nuclei, very little is known of the chemistry of the fundamental heterocycle. Most of the publications pertaining to the heterocycle describe only its dihydro- or tetrahydro-derivatives (2-7). The sparsity of investigations of 1,4-thiazines coupled with the relationship of these materials to the well-known phenothiazine psychotherapeutic agents prompted this study.

The parent heterocycle (1) was reported to be prepared in small yield by the reductive dehydration of the corresponding imide (eq. 1) (8). The 2,4-diene formulation



of the product was based on its failure to provide a sulfonamide derivative. The other derivatives known, for example, 3,5-diphenyl-1,4-thiazine (II) and its 1,1-dioxide (III), were prepared from phenacyl sulfides or sulfones and ammonia (9-11).



Thioamidates react with a variety of nucleophilic reagents, such as Grignard reagents, to give products wherein the $-C=N-$ linkage is retained (12). Utilizing such an approach we have been able to prepare some interesting new derivatives of 1,4-thiazine (Scheme 1).

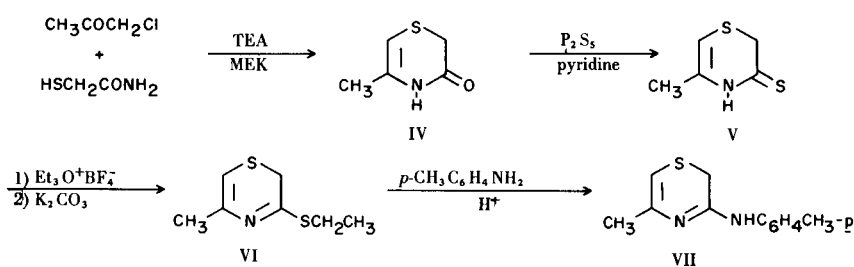
The synthesis of 5-methyl-2,3-dihydro-4*H*-1,4-thiazine-3-one (IV) was carried out by a modification of the procedure of Sokol and Ritter (13). These workers, however, assigned the compound the lactim structure based on analogy with the corresponding five-membered ring. Compound IV has a very intense carbonyl band at 1685 cm^{-1} indicating that the substance exists mainly in the lactam form.

Reaction of IV with phosphorus pentasulfide in pyridine (14) afforded the thiolactam V in yields of 40 to 50%. Alkylation of the thiolactam with triethyloxonium tetrafluoroborate provided 3-ethylthio-5-methyl-2*H*-1,4-thiazine (VI).

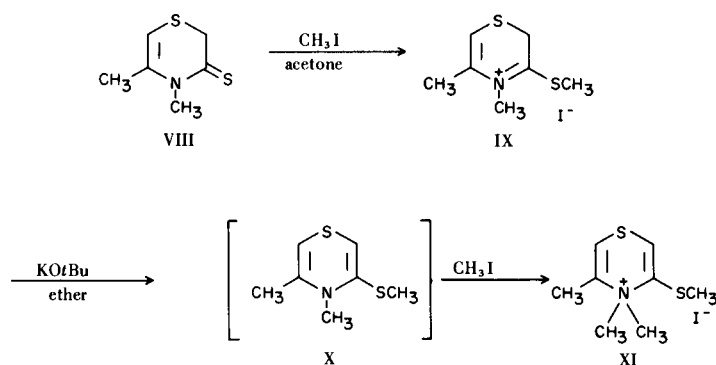
In the presence of a trace of acid VI readily reacts with *p*-toluidine to afford 3-*p*-tolylamino-5-methyl-2*H*-1,4-thiazine (VII) with loss of a molecule of ethyl mercaptan. It was anticipated that a similar reaction might be achieved with Grignard reagents to produce 3,5-dialkyl-1,4-thiazines. However, treatment of VI with methyl magnesium iodide in ether or tetrahydrofuran resulted only in the recovery of starting material.

Compound VIII prepared by a method analogous to that for V reacted with methyl iodide in acetone to afford the ammonium iodide IX. The latter was treated with potassium *t*-butoxide in ether to provide 3-methylthio-4,5-

SCHEME 1



SCHEME 2



dimethyl-4*H*-1,4-thiazine (X) as a highly unstable oil. Whereas Gompper and Elser (15) found that simpler α -alkylthioenamines with hydrogen(s) on the β -carbon react with electrophilic reagents at the β -carbon, the only product that could be isolated from the reaction of X with methyl iodide was the *N*-alkylated salt XI (Scheme 2).

EXPERIMENTAL

All melting and boiling points are uncorrected. The nmr spectra were obtained at 60 MHz using a Varian HR-60 instrument. Mass spectra were determined with an Atlas CH-4 spectrometer using an ionizing potential of 70 e.v. The infrared spectra were obtained on a Perkin-Elmer 137B instrument. Ultraviolet spectra were run on a Cary model 14 spectrophotometer.

5-Methyl-2,3-dihydro-4*H*-1,4-thiazine-3-one (IV).

Crude thioglycolamide (35.0 g., 0.38 mole), prepared by ammonolysis of methyl thioglycolate according to the procedure of Sokol and Ritter (13), and 37.0 g. (0.40 mole) of chloroacetone were dissolved in 250 ml. of methyl ethyl ketone. The solution was added to a cold solution of 40.4 g. (0.40 mole) of triethylamine in 100 ml. of methyl ethyl ketone over a period of 30 minutes. After the addition, the reaction mixture was warmed with hot water for 30 minutes, cooled and filtered. The residue was washed with cold dry benzene and the combined filtrate was evaporated to a small volume (100 ml.) under reduced pressure, washed with water and dried over anhydrous sodium sulfate. On evaporation of the solvent, there was obtained 51.5 g. (95%) of a straw colored oil, ν max (neat) 1720 cm^{-1} . Without further purification, the product was dissolved in 250 ml. of dry benzene and the solution was refluxed for 18 hours with a trace of *p*-toluenesulfonic acid using a Dean-Stark water separator. On evaporation of the solvent and crystallization of the residue from benzene, there was obtained 33.5 g. (75%) of 5-methyl-2,3-dihydro-4*H*-1,4-thiazine-3-one, m.p. 144-145° [lit. (13) m.p. 144°].

5-Methyl-2,3-dihydro-4*H*-1,4-thiazine-3-thione (V).

A mixture of 2.6 g. (20 mmoles) of the lactam IV and 4.4 g. (22 mmoles) of phosphorous pentasulfide in 40 ml. of dry pyridine was refluxed for 1 hour. During this time, the mixture became deep blue and then turned brown. The hot reaction mixture was poured into 500 ml. of vigorously stirred methylene

chloride. The solution was separated from the black, tarry mass by decantation. The latter was shaken with an additional 500 ml. of methylene chloride and the combined extract was distilled under reduced pressure to a small volume (10 ml.) and then passed rapidly through a base-washed alumina column using methylene chloride as the solvent. On removal of the solvent from the eluents, there was obtained a coffee-colored crystalline solid. Sublimation under reduced pressure (0.2 mm.) at 50° afforded 1.3 g. (45%) of a yellow crystalline solid, m.p. 107-109°; ν max (chloroform), 1485, 1500, 1110 cm^{-1} ; λ max (ethanol) 205 (ϵ , 7,650), 273 (ϵ , 5,660), and 351 $\text{m}\mu$ (ϵ , 3,190).

Anal. Calcd. for $\text{C}_5\text{H}_7\text{NS}_2$: C, 41.39; H, 4.82. Found: C, 41.71; H, 4.83.

3-Ethylthio-5-methyl-2*H*-1,4-thiazine (VI).

The thione V (1.47 g., 10 mmoles) was dissolved in 7 ml. of methylene chloride. To this solution was added with stirring a solution of 2.24 g. (12 mmoles) of triethyloxonium tetrafluoroborate in 10 ml. of methylene chloride. The reaction mixture was stirred for 18 hours and treated with 10 ml. of 50% (w/v) potassium carbonate solution. The organic layer was decanted, dried over anhydrous potassium carbonate and evaporated to provide a dark, red oil. The latter was fractionated to afford 1.2 g. (69%) of a light yellow oil, b.p. 64° (0.2 mm.); n_D^{27} 1.5876, ν max (neat), 780, 1065, 1152, 1230, 1550, 1575 cm^{-1} ; λ max (ethanol), 212 (ϵ , 5,190), 251 (ϵ , 6,790), 336 $\text{m}\mu$ (ϵ , 4,050). The nmr was consistent with the assigned structure.

Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{NS}_2$: C, 48.55; H, 6.40. Found: C, 48.96; H, 6.54.

3-*p*-Tolylamino-5-methyl-2*H*-1,4-thiazine (VII).

3-Ethylthio-5-methyl-2*H*-1,4-thiazine (0.075 g., 0.5 mmole) was dissolved in 0.5 ml. of diethyl ether. To the solution was added 0.117 g. (1.1 mmoles) of *p*-toluidine and a trace of triethylamine hydrochloride. The reaction mixture was stirred for 36 hours. The precipitate was filtered and crystallized from benzene-hexane to afford 0.08 g. (80%) of 3-*p*-tolylamino-5-methyl-2*H*-1,4-thiazine, m.p. 139-143°, ν max (chloroform), 1640, 1620 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{S}$: C, 66.01; H, 6.46. Found: C, 65.89; H, 6.50.

4,5-Dimethyl-2,3-dihydro-1,4-thiazine-4-one.

A solution of 2-mercapto-*N*-methylacetamide (7.85 g., 75 mmoles) and 6.93 g. (75 mmoles) of chloroacetone in 30 ml. of methyl ethyl ketone was added dropwise to a solution of 7.57 g.

(75 mmoles) of triethylamine in 45 ml. of methyl ethyl ketone over a period of 30 minutes. After the addition, the mixture was warmed with hot water for 15 minutes, cooled and filtered. The residue was washed with cold benzene. The combined filtrates were concentrated to a small volume (25 ml.), washed with water, dried and evaporated to give 11.4 g. (94%) of a light orange-colored oil. This oil (7 g.) was dissolved in 125 ml. of dry toluene and the solution was refluxed for 18 hours with a trace of *p*-toluenesulfonic acid using a Dean-Stark water separator. On evaporation of the solvent and fractionation of the residual oil, there was obtained 4.1 g. (65%) of a light-yellow colored oil, b.p. 65-67° (0.05 mm.), $n_D^{25.8}$ 1.5640; ν max (neat), 1660, 1620, 1320 cm^{-1} .

Anal. Calcd. for $\text{C}_6\text{H}_9\text{NOS}$: C, 50.32; H, 6.32. Found: C, 50.30; H, 6.52.

4,5-Dimethyl-2,3-dihydro-1,4-thiazine-3-thione (VIII).

This compound was prepared from 4,5-dimethyl-2,3-dihydro-1,4-thiazine-3-one in the same manner as 5-methyl-2,3-dihydro-2*H*-1,4-thiazine-3-thione (V). After chromatographic purification, the product was sublimed at 50° under reduced pressure (0.2 mm.) to provide a light yellow crystalline solid in 37.3% yield, m.p. 48-50°, ν max (chloroform), 1460, 1440, 1360, 1075 cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{NS}_2$: C, 45.25; H, 5.70. Found: C, 45.38; H, 5.66.

3-Methylthio-4,5-dimethyl-2*H*-1,4-thiazinium iodide (IX).

A solution of 4,5-dimethyl-2,3-dihydro-1,4-thiazine-3-thione (VIII) (1.59 g., 10 mmoles) and 1.42 g. (10 mmoles) of methyl iodide in 25 ml. of anhydrous acetone was stirred for 18 hours at room temperature. A yellow precipitate was filtered, washed with ether and dried to give an almost quantitative yield of the thiazinium iodide.

3-Methylthio-4,5-dimethyl-1,4-thiazine (X).

The iodide IX was treated with potassium *t*-butoxide in ether after the procedure of Gompper and Elser (15). A dark red oil was obtained in 79% yield; ν max (neat), 1640, 1550. Attempts to purify the product by distillation under reduced pressure resulted in its decomposition. Vapor phase chromatography on silicon gum rubber indicated the product to be one substance. The product soon became a tar on exposure to air.

3-Methylthio-4,4,5-trimethyl-1,4-thiazinium iodide (XI).

A small amount of the crude 3-methylthio-4,5-dimethyl-1,4-

thiazine was treated with excess methyl iodide. The mixture was warmed for 2 minutes. The product was filtered and recrystallized from methyl alcohol-ethyl acetate mixture to provide needles, m.p. 125-126° (d); ν max (chloroform), 1620, 1600 cm^{-1} . The nmr spectrum was consistent with the proposed structure.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{INS}_2$: C, 30.48; H, 4.48. Found: C, 30.71; H, 4.50.

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Detroit, Michigan 48202