Conversion of 1,3-Thiazolidine and its Sulfoxide to Dihydro-1,4-thiazine

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Two methods for constructing dihydro-1,4-thiazine **4** were described. 1,3-Thiazolidines **5** were converted to dihydro-1,4-thiazines **4** by chlorinolysis through the unisolable chlorosulfonium salt **10** and sulfenyl chloride **11**. Oxidation of the sulfides **5** gave a mixture of pairs of diasteromers **6**. In the presence of acid catalyst, both sulfoxides were converted to dihydrothiazine **4** through sulfenic acid **22**. In this reaction the stepwise ring opening involving carbocation **23** seems more probable. The structures of **4** were proven by the independent synthesis involving 3-bromo-2-oxobutanoic acid derivatives.

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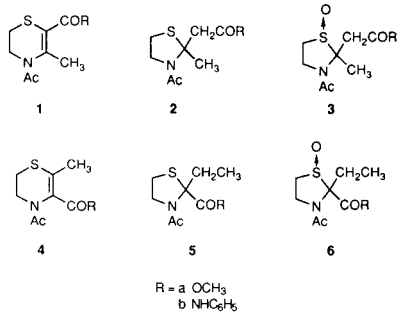
Synthetic methods available for the construction of heterocyclic molecules can be used to affect a number of valuable synthetic transformations. In our previous paper [1,2], we reported a synthesis of dihydro-1,4-thiazine **1** by chlorinolysis of 1,3-thiazolidine **2** and by rearrangement of 1,3-thiazolidine sulfoxides **3**. As an extension of our studies of the reactivity and synthetic uses of dihydro-1,4-thiazines, we now report two methods for constructing dihydro-1,4-thiazine **4** that is a structural isomer of compound **1**, which is transposed just with N and S. An important feature of the 1,3-thiazolidine **5** and its sulfoxide **6** is the absence of carbonyl activated methylene hydrogens β to the C-S bond being ruptured. Thus, in considering the structural difference, it seems to be interesting to investigate the rearrangement of these new thiazolidines and their sulfoxides and to compare the previous results.



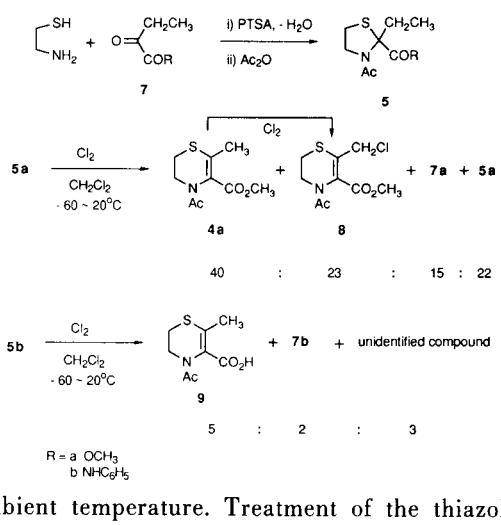
R = a OCH_3
b NHC_6H_5

Results and Discussion.

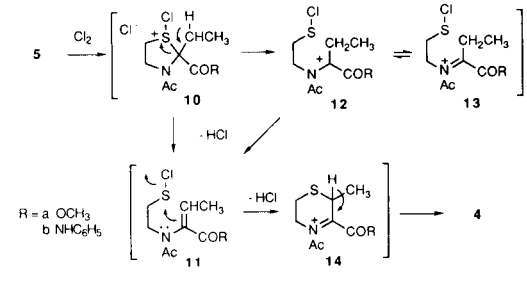
Chlorinolysis of 1,3-Thiazolidines.

As shown in Scheme 1, the starting 1,3-thiazolidines **5** were prepared by the acid catalyzed condensation of 2-aminoethanethiol with α-ketobutyric acid derivatives **7** followed by acetylation. The chlorinolysis reactions were carried out in the methylene chloride solution at -60 ~ -20° to ambient temperature. Treatment of the thiazolidine ester **5a** with 1 equivalent of chlorine gave a 40:23:15:22 mixture of dihydro-1,4-thiazine **4a**, chloromethyl compound **8**, methyl 2-ketobutyrate **7a** and starting material **5a**, respectively. A similar chlorinolysis reaction of the thiazolidine anilide **5b** resulted in a 5:2:3 mixture of dihydro-1,4-thiazine carboxylic acid **9**, α-ketobutananilide **7b** and an unidentified compound, respectively.

Scheme 1



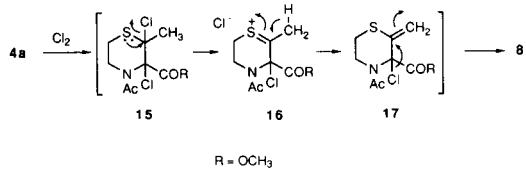
Scheme 2



The ring expansion of thiazolidine by action of chlorine undoubtedly proceeds *via* an unisolable transient sulfenyl chloride as generated from the initially formed chlorosulfonium salt **10** [3] (Scheme 2). The ring opening of **10** would occur by either a concerted β-elimination involving the methylene hydrogen to produce **11** or a stepwise mechanism to form **11** through the carbocation **12** or imminium ion **13**. The highly reactive sulfenyl chloride **11** was converted to the imminium ion **14** by a nucleophilic attack of the internal double bond to the sulfur atom [4]. This could then lose the C-2 proton to produce the dihydro-1,4-thiazine **4**. When the reaction mixture was allowed to stir in the chlorinolysis reaction at below -20° to room temperature, hydrogen chloride evolution started at -13 ~ -15°, suggesting that the ring opening of chlorosulfonium salt **10** to the sulfenyl chloride **11** occurred at this temperature.

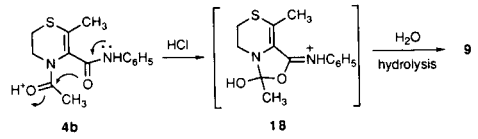
It seems likely that chloromethyl compound **8** arose by further chlorination of the dihydro-1,4-thiazine **4a** (Scheme 3). In fact, compound **8** was obtained when dihydro-1,4-thiazine **4a** was treated with 1 equivalent of chlorine under the same reaction conditions. Dichloride **15** most likely formed by addition of chlorine to dihydro-1,4-thiazine **4a** which was produced in the chlorinolysis reaction of 1,3-thiazolidine **5a**. The sulfur is postulated to attack the anomeric 2-halo carbon of **15** to give sulfonium ion **16** which would be converted to exo methylene **17**, followed by allylic chlorination to give the chloromethyl compound **8**. Formation of analogous dichlorides and chloromethyl compounds was observed previously in the chlorinolysis of oxathiolane [5] and thiazolidine [1]. The formation of methyl 2-ketobutyrate **7a** undoubtedly resulted from the hydrolysis of imminium ion **13**.

Scheme 3



While the dihydrothiazine **4a** was isolated after the chlorinolysis as described above, the anilide **4b** was unstable under the same reaction conditions to give the carboxylic acid **9**. The unusual mildness of hydrolysis of the carboxanilide group [6] is attributable to the internal neighboring carbonyl group (Scheme 4). The facile hydrolysis of the amide **4b** in comparison with ester **4a** may be effected by the anilide nitrogen lone paired electrons, the results of which suggest that the protonation [7] took place on the amide oxygen rather than anilide oxygen to form intermediate **18**. Indeed, the **4b** obtained by the independent synthesis discussed later was smoothly converted to carboxylic acid **9** by treatment of hydrogen chloride at room temperature. The structures of dihydrothiazines **4** were confirmed by various spectra and independent syntheses discussed later.

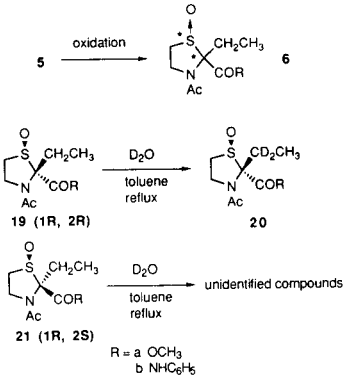
Scheme 4



Thiazolidine Sulfoxides and Conversion to Dihydro-1,4-thiazines.

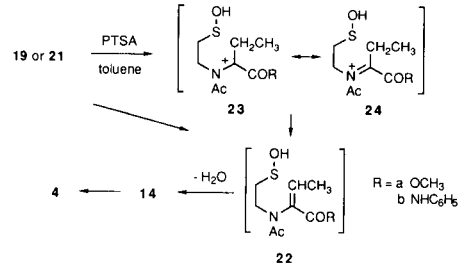
Oxidation of the sulfides **5** gave a mixture of pairs of diasteromers **6** [9] and they were separated from each other by fractional crystallization or preparative tlc. Assignments of the stereochemistry of each isomer were based on the result of deuterium incorporation reaction [2,10]. Thus, when the **19** (1*R*,2*R*) separated from the diasteromeric mixture **6** was refluxed in the presence of a large excess of deuterium oxide in toluene solution, methylene hydrogens of the CH_2CH_3 group were deuterated to give **20** (Scheme 5). It was thus concluded that the sterochemistry of **19** was the sulfoxide oxygen and the CH_2CH_3 group is on the same face of the thiazolidine ring. The other isomer **21** (1*R*,2*S*) gave a mixture of unidentified compounds under the same reaction conditions.

Scheme 5



It is not necessary to separate them from each other for the preparation of dihydrothiazine **4**. In the presence of an acid catalyst, both the sulfoxides **19** and **21** were converted to dihydrothiazine **4** (Scheme 6). The ring expan-

Scheme 6

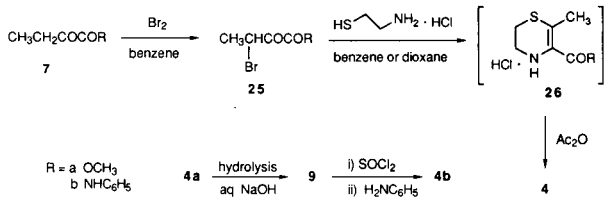


sion reaction undoubtedly proceeds through sulfenic acid **22** [11]. The ring opening of the protonated sulfoxides would occur by either a concerted β-elimination or a stepwise mechanism *via* a similar pathway in the chlorinolysis reaction described above to form carbocation **23** or iminium ion **24** followed by loss of a proton to give **4**. In view of the previously reported [10] carbocation intermediacy in the acid catalyzed rearrangement of cyclic sulfoxide, the stepwise ring opening involving **23** seems more probable. When both sulfoxides **19** and **21** were heated separately with *p*-toluenesulfonic acid as a catalyst in refluxing toluene, it was found that isomerization of the sulfoxides indeed occurred, the results being consistent with carbocation intermediacy **23**. The cyclization of sulfenic acid **22** to imminium ion **14** assisted by the nitrogen lone pair seems to be caused by the electrophile component of the sulfenic acid predominating over the nucleophilic character [13] for an internal double bond in this reaction condition. This imminium ion **14** could then lose the C-2 proton to give the dihydrothiazine **4**.

Independent Synthesis of Dihydro-1,4-thiazine.

The independent syntheses of dihydrothiazines **4** are summarized in Scheme 7. 3-Bromo-2-oxobutanoic acid derivatives **25** were prepared by bromination of 2-ketobutanoic acid derivatives **7** respectively. The bromide **25b** was reacted with 2-aminoethanethiol in benzene or dioxane solution to give intermediate **26b** as a white amorphous solid, which was treated with excess acetic anhydride to afford the desired dihydrothiazines **4b**. A similar result was obtained for the preparation of ester **4a**. As expected, coupling of carboxylic acid **9** prepared by the hydrolysis of **4a** with aniline gave **4b**.

Scheme 7



EXPERIMENTAL

All melting points were obtained with an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 735B or JASCO IR-810 spectrophotometer. All ^1H and ^{13}C nmr spectra were recorded on a Varian Model EM 360 at 60 MHz or Varian Gemini 300 spectrometer at 300 and 78.5 MHz, respectively, with tetramethylsilane as an internal standard and are reported in δ units. Mass spectra were performed using Hitachi Perkin Elmer RMV-6E. All elemental analysis of new compounds was performed with a Perkin-Elmer 240 DS analyzer. All flash chromatographic isolations were accomplished by Kieselgel GF 254 (230-400 mesh) silica gel.

Methyl 3-Acetyl-2-ethyl-1,3-thiazolidine-2-carboxylate (**5a**).

To a suspended solution of 2-aminoethanethiol hydrochloride (46.28 g, 0.407 mole) and triethylamine (56.8 ml, 0.407 mole) in benzene was added methyl α-ketobutyrate (**7a**) [15] (43 g, 0.37 mole) and *p*-toluenesulfonic acid monohydrate (PTSA) (3.52 g) while stirring. The reaction mixture was refluxed for 6 hours with a Dean-Stark water trap. The reaction mixture was cooled, washed with 0.1 *N* sodium hydroxide solution, water, and then dried (sodium sulfate). Evaporation of the solvent gave methyl 2-ethyl-1,3-thiazolidine-2-carboxylate (52 g, 80%) as a light yellow liquid. A mixture of this 1,3-thiazolidine (35.0 g, 0.2 mole) and acetic anhydride (70 ml) was stirred for 24 hours at room temperature. The excess acetic anhydride was removed under reduced pressure to give a yellow viscous liquid. Fractional distillation under reduced pressure gave 1,3-thiazolidine **5a** (16.9 g, 39%) as a colorless viscous liquid, bp 182-184°/7 mm Hg; ^1H nmr (300 MHz, deuteriochloroform): δ 0.95 (t, J = 5.6 Hz, 3H, ethyl CH_3), 2.13 (s, 3H, CH_3CO), 3.74 (s, 3H, OCH_3), 1.69-4.21 (m, 6H, ethyl CH_2 and SCH_2CH_2N); ^{13}C nmr (deuteriochloroform): δ 8.01, 24.00, 26.42, 29.85, 52.70, 53.92, 75.06, 168.44, 172.53; ir (potassium bromide): 2950, 1735, 1650 cm^{-1}.

3-Acetyl-2-ethyl-*N*-phenyl-1,3-thiazolidine-2-carboxamide (**5b**).

This compound was prepared by the same procedure as described for **5a**. Thus, a mixture of α-ketobutananilide (**7b**) [16] (4.4 g, 25 mmoles), 2-aminoethanethiol (2.87 g, 37 mmoles) and PTSA (0.24 g) was refluxed for 24 hours with a Dean-Stark water trap. After work up, a colorless oily liquid (5.48 g) was crystallized from ethyl acetate and petroleum ether to give 2-ethyl-*N*-phenyl-1,3-thiazolidine-2-carboxamide (4.63 g, 79%) as colorless needles. A solution of this 1,3-thiazolidine (3.17 g, 13.4 mmoles) and pyridine (5 drops) in acetic anhydride (5 ml) was heated in an oil bath (60-65°) for 70 hours. The reaction mixture was cooled and the white precipitate was filtered, washed with ethyl ether and then dried to give 1,3-thiazolidine **5b** (3.5 g, 94%). Crystallization from chloroform afforded white plates, mp 194-197°; ^1H nmr (300 MHz, deuteriochloroform): δ 1.02 (t, J = 6.5 Hz, 3H, ethyl CH_3), 2.10-4.10 (m, 6H, 4-CH_2, 5-CH_2 and ethyl CH_2), 2.14 (s, 3H, CH_3CO), 7.05-7.53 (m, 5H, ArH), 8.36 (br s, 1H, CONH); ir (potassium bromide): 3300, 1680, 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.30; H, 6.40; N, 9.85.

Chlorinolysis of 1,3-Thiazolidine Ester **5a**.

To a solution of 1,3-thiazolidine **7a** (1.09 g, 5 mmoles) in methylene chloride (50 ml) at -20° with dry ice-acetone cooling bath was added dropwise a solution of chlorine (0.355 g, 5 mmoles) dissolved in methylene chloride (14 ml) for 5 minutes. The cooling bath was removed and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was washed with saturated sodium bicarbonate solution, water, and dried (sodium sulfate). Evaporation of the solvent gave a brown oily residue (1.154 g), which was a 40:23:15:22 mixture of dihydro-1,4-thiazine **4a**, chloromethyl compound **8**, methyl α-ketobutyrate **7a**, and starting material **5a**, respectively, by ^1H nmr spectrum. This mixture was separated by preparative chromatography with *n*-hexane/ethyl acetate, 7/3 as an eluent to give dihydro-1,4-thiazine **4a** (0.34 g) and **8** (0.17 g).

Compound **4a** had mp 77-80°; ^1H nmr (60 MHz, deuteriochloroform): δ 1.93 (s, 3H, 4-acetyl), 2.37 (s, 3H, 2-CH_3), 3.13-3.37 (m, 2H, 6-CH_2), 3.93 (s, 3H, OCH_3), 3.93-4.00 (m, 2H, 5-CH_2); ir (po-

tassium bromide): 1720, 1657 cm^{-1}; ms: m/z 215 (M^+).

Anal. Calcd. for $C_9H_{13}NO_3S$: C, 50.2; H, 6.09; N, 6.51. Found: C, 50.4; H, 6.14; N, 6.45.

Compound **8** had mp 114-118°; ^1H nmr (300 MHz, deuteriochloroform): δ 1.96 (s, 3H, 4-acetyl), 3.17 (m, 2H, CH_2S), 3.80 (m, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2Cl); ^{13}C nmr (deuteriochloroform): δ 22.38, 30.47, 38.81, 42.28, 52.44, 125.62, 141.18, 162.54, 169.97; ms: (20 eV) m/z 249.7 (M^+), 206.7, 172.2, 112.2.

Anal. Calcd. for $C_9H_{12}ClNO_3S$: C, 43.3; H, 4.84; N, 5.61. Found: C, 43.4; H, 4.87; N, 5.69.

Chlorinolysis of 1,3-Thiazolidine Anilide **5b**.

To a solution of 1,3-thiazolidine **5b** (1.00 g, 0.36 mmole) in methylene chloride (200 ml) at -20° with a dry ice-acetone cooling bath was added dropwise a solution of chlorine (0.255 g, 0.36 mmole) dissolved in methylene chloride (9.8 ml) for 2 minutes. The reaction mixture was stirred for 1.5 hours at or below 10°. The insoluble precipitate was filtered off and filtrate was washed with saturated sodium bicarbonate solution, water, and then dried (sodium sulfate). Evaporation of the solvent gave a brown oily residue (0.88 g), which was a 5:2:3 mixture of dihydrothiazinecarboxylic acid **9**, α-ketobutanalide (**7b**), and an unidentified compound, respectively, by the ^1H nmr spectra. This mixture was separated by preparative chromatography with benzene/ethyl acetate, 7/3 to give **9** (242 mg), **7b** (47 mg), and an unidentified compound (194 mg), respectively.

Compound **9** had mp 155-157°; ^1H nmr (60 MHz, deuteriochloroform): δ 2.01 (s, 3H, 4-acetyl), 2.43 (s, 3H, 2-CH_3), 3.00-3.17 (m, 2H, 6-CH_2), 3.73-3.93 (m, 2H, 5-CH_2), 10.1 (s, 1H, OH); ir (potassium bromide): 3050, 1720, 1600, 1420, 1220 cm^{-1}; ms: m/z 201 (M^+).

Methyl 4-Acetyl-2-chloromethyl-5,6-dihydro-1,4-thiazine-2-carboxylate (**8**).

To an ice cooled solution of dihydrothiazine **4a** (1.075 g, 5 mmoles) in methylene chloride at 0-5° was added dropwise a solution of chlorine (0.373 g, 5.25 mmoles) dissolved in methylene chloride (14.3 ml) for 2 minutes 20 seconds. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was washed with saturated sodium bicarbonate solution, water, dried (sodium sulfate), and then decolorized with charcoal. Evaporation of solvent gave a light yellow oily residue (1.14 g). Crystallization from benzene afforded the chloromethyl compound **8** (1.0 g, 80%) as light yellow needles, which had identical ^1H nmr and ir spectra with those obtained by the chlorinolysis of 1,3-thiazolidine **5a**.

Preparation of Methyl 3-Acetyl-2-ethyl-1,3-thiazolidine-2-carboxylate, *S*-Oxide (**6a**).

A solution of 1,3-thiazolidine **5a** (2.5 g, 11.5 mmoles) in methylene chloride (50 ml) and benzeneseleninic acid (0.1 g) was treated with 30% hydrogen peroxide solution in water (1.95 ml, 17.25 mmoles) for 48 hours at room temperature [17]. The reaction mixture was washed with saturated sodium bicarbonate solution and water, and then dried (sodium sulfate). Evaporation of the solvent gave a colorless oily residue, which was a 1:9 diasteromeric mixture of sulfoxides **19a** and **21a**, respectively, by ^1H nmr and tlc. Separation of this diasteromeric mixture by preparative tlc with chloroform/methanol, 100/2, gave sulfoxides **19a** (0.26 g) and **21a** (1.35 g) as viscous oils respectively.

Compound **19** (1*R*,2*R*) (R_f = 0.25) had ^1H nmr (300 MHz, deuteriochloroform): δ 1.05 (t, J = 7.5 Hz, ethyl CH_3), 2.26 (s, 3H, $COCH_3$), 2.38-2.90 (m, 2H, ethyl CH_2), 3.12-3.33 (m, 2H, 5-CH_2), 3.80 (s, 3H, OCH_3), 4.19-4.62 (m, 2H, 4-CH_2).

Compound **21a** (1*R*,2*S*) (R_f = 0.15) had ^1H nmr (300 MHz, deuteriochloroform): δ 0.82 (t, J = 7.5 Hz, 3H, ethyl CH_3), 2.19 (s, 3H, $COCH_3$), 2.52 and 2.79 (2q x 2, J = 7.5 Hz, J = 15.2 Hz, 2H, ethyl CH_2), 3.09-3.16 (m, 2H, 5-CH_2), 3.79 (s, 3H, OCH_3), 4.09-4.46 (m, 2H, 4-CH_2).

Preparation of 3-Acetyl-2-ethyl-*N*-phenyl-1,3-thiazolidine-2-carboxamide, *S*-Oxide (**6b**).

This compound was prepared by the same procedure as described for **6a**. Thus, a solution of 1,3-thiazolidine **5b** (2.5 g, 8.99 mmoles) and benzeneseleninic acid (85 mg) in chloroform (100 ml) was treated with 30% hydrogen peroxide solution in water (1.53 ml, 13.48 mmoles) for 30 minutes at room temperature. After work up, a diasteromeric mixture of sulfoxide **6b** was obtained as a white solid (2.52 g, 95%). Separation of this mixture by the preparative tlc with chloroform/methanol, 95/5, gave sulfoxides **21b** (1.61 g) and **19b** (0.35 g).

Compound **19b** (1*R*,2*R*) (R_f = 0.24) had mp 184-186°; ^1H nmr (300 MHz, deuteriochloroform): δ 1.12 (t, J = 7.4 Hz, 3H, ethyl CH_3), 1.92-3.24 (m, 2H, ethyl CH_2), 2.19 (s, 3H, $COCH_3$), 3.05-3.11 (m, 2H, 5-CH_2), 4.05-4.45 (m, 2H, 4-CH_2), 7.03-7.43 (m, 5H, ArH), 10.25 (br s, 1H, NH); ir (potassium bromide): 1670, 1600, 1060, 750 cm^{-1}.

Compound **21b** (1*R*,2*S*) (R_f = 0.10) had mp 204-205° dec; ^1H nmr (300 MHz, deuteriochloroform): δ 1.12 (t, J = 7.4 Hz, 3H, ethyl CH_3), 1.64 (s, 3H, $COCH_3$), 1.98 and 3.18 (2q x 2, J = 7.4 Hz, J = 14.8 Hz, 1H, ethyl CH), 3.05-3.10 (m, 2H, 5-CH_2), 4.07-4.53 (m, 2H, 4-CH_2), 7.06-7.54 (m, 5H, ArH), 8.08 (br s, 1H, NH); ir (potassium bromide): 1680, 1630, 1065, 750 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 56.80; H, 6.21; N, 9.54; S, 10.90.

Acid-catalyzed Ring Expansion of 1,3-Thiazolidine Sulfoxide Ester (**6a**).

The diasteromeric mixture of sulfoxide **6a** (300 mg, 1.29 mmoles) and PTSA (12 mg) in benzene (40 ml) was refluxed with a Dean-Stark water trap for 7 hours. The reaction mixture was cooled, washed with saturated sodium bicarbonate solution, water, and then dried (sodium sulfate). Evaporation of the solvent gave an oily residue (250 mg). Flash chromatography with chloroform/methanol, 100/2, gave **4a** (110 mg, 40%), which had identical ^1H nmr spectra with those obtained by the chlorinolynolysis of **5a**.

Acid-catalyzed Ring Expansion of 1,3-Thiazolidine Sulfoxide Anilide (**6b**).

This reaction was performed by the same procedure as described for the ring expansion of **6a**. Thus, a solution of 1,3-thiazolidine sulfoxide **6b** (250 mg, 0.85 mmole) and PTSA (8 mg) in ethyl acetate (110 ml) was refluxed with a Dean-Stark water trap for 70 hours. After work up, an oily residue (201 mg) was separated by preparative tlc (Kiesel gel DF 254), using benzene/ethyl acetate, 7/3, as an eluent to give 1,4-thiazine **4b** (54 mg, 23%), mp 150-154°; ^1H nmr (300 MHz, deuteriochloroform): δ 2.11 (s, 3H, CH_3CO), 2.44 (s, 3H, 2-CH_3), 3.10 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.75-3.93 (m, 2H, 5-CH_2), 7.11-7.55 (m, 5H, ArH), 7.77 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 20.2, 22.7, 29.4, 39.9,

120.2, 124.4, 124.9, 137.9, 139.2, 161.8, 172.2; ir (potassium bromide): 3280, 1660 cm^{-1}; ms: m/z 276 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.8; H, 5.83; N, 10.1. Found: C, 60.9; H, 5.87; N, 9.96.

Independent Synthesis of Dihydro-1,4-thiazine Ester **4a**.

To a solution of methyl α-ketobutyrate (**7a**) (30 g, 0.258 mole) in benzene (30 ml) at 60° was added dropwise bromine (43.4 g, 0.271 mole) for 30 minutes. The reaction mixture was placed in oil bath (70-75°) for 2 hours while stirring. The reaction mixture was cooled, diluted with benzene (60 ml), and then dried (magnesium sulfate). The solvent was removed under reduced pressure to give methyl 3-bromo-2-ketobutyrate (**25a**) as a light brown liquid (27.9 g, 55%). To the ice-cooled bromide (4.92 g, 25.2 mmoles) was added dropwise a suspended solution of 2-aminoethanthiol hydrochloride (2.86 g, 25.2 mmoles) and pyridine (4 ml) in methanol (10 ml) for 40 minutes. Stirring was continued for 2 hours at room temperature. The reaction mixture was concentrated, diluted with benzene, washed with water, and then dried (sodium sulfate). The solvent was evaporated to give a brown oily liquid (5.94 g), which was treated with acetic anhydride (24 ml) and pyridine (2 ml) for 48 hours at room temperature. The excess acetic anhydride was removed under reduced pressure and the reaction mixture was poured into a saturated potassium carbonate solution, and extracted with chloroform. The organic phase was washed with water, dried (sodium sulfate), and concentrated to give a dark brown oil (4.35 g). Flash chromatography with *n*-hexane/-ethyl acetate, 1/1, gave dihydro-1,4-thiazine **4a** (3.32 g, 61%), which had identical ^1H nmr and ir spectra with those obtained by the previous method.

Independent Synthesis of Dihydro-1,4-thiazine Anilide **4b**.

A solution of 3-bromo-2-ketobutananilide (**7b**) [16] (0.614 g, 2.4 mmoles) in dioxane (2 ml) was treated with 2-aminoethanthiol hydrochloride (0.273 g, 2.4 mmoles) for 2 days at room temperature. The precipitate was collected and washed with petroleum ether. The white solid, **26** (0.415 g), was treated with pyridine (0.25 ml) and acetic anhydride (0.15 ml) for half an hour at room temperature. The excess acetic anhydride was hydrolyzed with aqueous potassium carbonate solution. The reaction mixture was taken into methylene chloride, washed with 2 *N* hydrochloric acid and then water. The organic phase was dried (magnesium sulfate) and evaporated to give an oily residue, which was separated by flash chromatography on silica gel to provide **4b** as a yellow solid (0.312 g, 47%), which had identical ^1H nmr spectra with those obtained by the previous method.

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