

Reactions of 1,3-Thiazine-2,6-dithiones. Part 6 [1].
 Synthesis of 2-Alkylthio-2,3-dihydro-1,3-thiazine-6-thiones
 by Reductive Alkylation of 1,3-Thiazine-2,6-dithiones

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2-Alkylthio-2,3-dihydro-1,3-thiazine-6-thiones **4** are synthesized by the reductive alkylation of 1,3-thiazine-2,6-dithiones with thiolate anions.

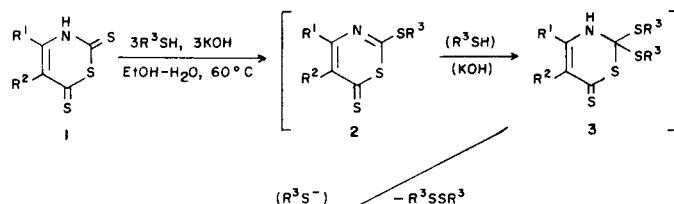
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We have reported several types of reactions of the 1,3-thiazine-2,6-dithiones; synthesis of imidazo- and pyrimido[2,1-*b*]pyrimidine derivatives [2], pyrimido[2,1-*b*] [1,3]diazepine derivatives [2], 3-aminopyrimidine-2,4-dithiones [3], pyrazoline-3-thiones [3], and 1,2,4-triazolo[1,5-*a*]pyrimidine-2,7-dithiones [3] by the reactions with 1, ω -diamines, hydrazines, and thiosemicarbazide. In addition, we reported that 2,5,6-trisubstituted pyrimidine-4(3*H*)-thiones are also synthesized by another type of reaction of the thiazinedithiones with enaminonitriles and -sulfones [4]. Other utility of the 1,3-thiazine-2,6-dithiones for synthesizing new hetero ring compounds, 1,3,5-thiadiazine-4-thiones, has also been reported in the reaction with thioureas [5]. In contrast, the thiazinedithiones took another course in the reaction with enaminonitriles in a polar aprotic solvent such as dimethylformamide in the presence of 4 molar equivalents of strong base to produce 4-thiopyridones *via* the formation of 2-cyanomethyldihydro-1,3-thiazine-6-thiones [1].

Our present finding is reductive *S*-alkylation of the 1,3-thiazine-2,6-dithiones by thiolate anions and we wish to report the formation reaction of 2-alkylthio-2,3-dihydro-1,3-thiazine-6-thiones **4a-h** by the reductive *S*-alkylation

reaction of the thiazinedithiones. Thus the thiazinedithiones, when treated with 3 molar equivalents of thiolate anion, produced 2-alkylthio-2,3-dihydro-1,3-thiazine-6-thiones **4a-h**. When the reaction was carried out with the thiolate less than 2 molar equivalents, the yield was extraordinarily poor. In addition, thiols, without base, never reacted with the thiazinedithiones.

Scheme 1



	R^1	R^2	R^3
4a	C_6H_5	$C_6H_5SO_2$	CH_3
4b	C_6H_5	$C_6H_5SO_2$	$C_6H_5CH_2$
4c	C_6H_5	$C_6H_5SO_2$	C_2H_5
4d	C_6H_5	$C_6H_5SO_2$	$n-C_3H_7$
4e	$m-CH_3C_6H_4$	CH_3SO_2	CH_3
4f	$m-CH_3C_6H_4$	CH_3SO_2	C_2H_5
4g	$m-CH_3C_6H_4$	CH_3SO_2	$n-C_3H_7$
4h	$m-CH_3C_6H_4$	CH_3SO_2	$C_6H_5CH_2$

Scheme 2 (a)

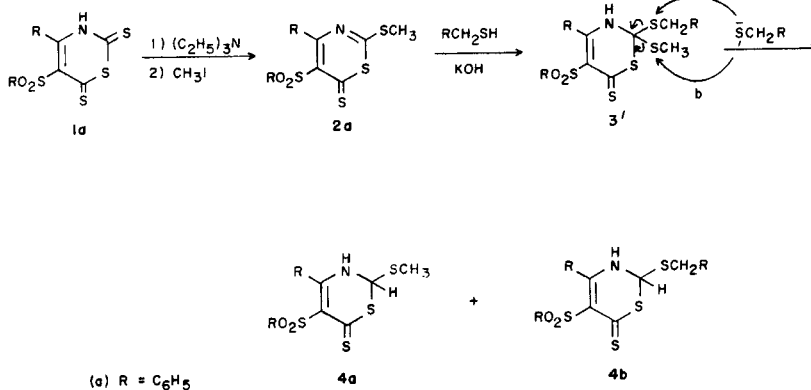
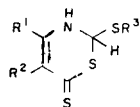
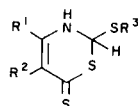


Table 1
2-Alkyl- and 2-Aralkylthio-2,3-dihydro-1,3-thiazine-6(6*H*)-thiones **4a-h**



Compound	R ¹	R ²	R ³	Yield (%)	Mp, °C	Molecular Formula	C	Analyses %		
								Calcd./Found	H	N
4a	C ₆ H ₅	C ₆ H ₅ SO ₂	CH ₃	79	204-205	C ₁₇ H ₁₅ NO ₂ S ₄	51.88	3.84	3.56	32.59
							51.96	3.92	3.92	32.31
4b	C ₆ H ₅	C ₆ H ₅ SO ₂	C ₆ H ₅ CH ₂	80	181	C ₂₃ H ₁₉ NO ₂ S ₄	58.82	4.08	2.98	27.33
							58.61	3.97	3.22	27.63
4c	C ₆ H ₅	C ₆ H ₅ SO ₂	C ₂ H ₅	63	186	C ₁₈ H ₁₇ NO ₂ S ₄	53.03	4.21	3.44	31.45
							53.29	4.19	3.38	31.09
4d	C ₆ H ₅	C ₆ H ₅ SO ₂	<i>n</i> -C ₃ H ₇	72	165-166	C ₁₉ H ₁₉ NO ₂ S ₄	54.13	4.54	3.32	30.42
							54.13	4.60	3.46	30.18
4e	<i>m</i> -CH ₃ C ₆ H ₄	CH ₃ SO ₂	CH ₃	57	189.5	C ₁₃ H ₁₅ NO ₂ S ₄	45.19	4.38	4.06	37.12
							45.47	4.50	3.96	37.25
4f	<i>m</i> -CH ₃ C ₆ H ₄	CH ₃ SO ₂	C ₂ H ₅	69	170	C ₁₄ H ₁₇ NO ₂ S ₄	46.77	4.77	3.90	35.67
							46.80	4.77	3.73	35.38
4g	<i>m</i> -CH ₃ C ₆ H ₄	CH ₃ SO ₂	<i>n</i> -C ₃ H ₇	73	153-154	C ₁₅ H ₁₉ NO ₂ S ₄	48.23	5.13	3.75	34.33
							48.53	5.18	3.77	34.61
4h	<i>m</i> -CH ₃ C ₆ H ₄	CH ₃ SO ₂	C ₆ H ₅ CH ₂	27	168-169	C ₁₉ H ₁₉ NO ₂ S ₄	54.13	4.55	3.32	30.41
							53.89	4.27	3.05	30.72

Table 2
Spectral Properties of Compounds **4a-h**



Compound	IR (KBr), cm ⁻¹	UV and Visible (EtOH) λ max (log ε), nm	¹ H NMR (CD ₃ COCD ₃) (δ, ppm)
4b	3200, 1628, 1495, 1485, 1444, 1310, 1286, 1143, 1066	260 (3.94), 353 (4.21)	7.58-7.32 (m, 15H, 3C ₆ H ₅), 7.14 (s, 1H, NH), 5.64 (d, 1H, CH), 4.19-4.07 (m, 2H, CH ₂)
4c	3160, 1625, 1480, 1445, 1311, 1288, 1144, 1071	263 (4.04), 352 (4.23)	7.59-7.27 (m, 10H, 2C ₆ H ₅), 7.14(br) (s, 1H, NH), 5.85 (s, 1H, CH), 2.92-2.82 (m, 2H, CH ₂), 1.38 (t, 3H, CH ₃)
4d	3200, 1622, 1480, 1444, 1310, 1288, 1148, 1071	249 (3.89), 352 (4.20)	7.60-7.27 (m, 10H, 2C ₆ H ₅), 7.14 (s, ca. 1H, NH), 5.83 (s, 1H, CH), 2.75-2.32 (m, 2H, SCH ₂), 1.84-1.72 (m, 2H, CH ₂ CH ₃), 1.05 (t, 3H, CH ₃)
4e	3260, 1620, 1477, 1316, 1124, 1065	258 (3.78), 348 (4.20)	7.38-7.35 (m, 5H, C ₆ H ₄ and NH), 5.56 (s, 1H, CH), 2.94 (s, 3H, SO ₂ -CH ₃), 2.40 (s, 3H, C ₆ H ₄ CH ₃), 2.35 (s, 3H, SCH ₃)
4f	3215, 1618, 1598, 1470, 1316, 1230, 1129, 1073	259 (3.93), 347 (4.19)	7.4(br) (ca. 5H, C ₆ H ₄ and NH), 5.62 (s, 1H, CH), 2.93 (s, 3H, SO ₂ -CH ₃), 2.91-2.79 (m, 2H, CH ₂ CH ₃), 2.39 (s, 3H, C ₆ H ₄ CH ₃), 1.34 (t, 3H, CH ₂ CH ₃)
4g	3200, 1620, 1477, 1311, 1136, 1069	258 (3.77), 349 (4.20)	7.36(br) (s, ca. 5H, C ₆ H ₄ and NH), 5.61 (s, 1H, CH), 2.93 (s, 3H, SO ₂ -CH ₃), 2.92-2.72 (m, 2H, SCH ₂), 2.40 (s, 3H, C ₆ H ₄ CH ₃), 1.78-1.69 (m, 2H, CH ₂ CH ₃), 1.03 (t, 3H, CH ₂ CH ₃)
4h	3200, 1624, 1600, 1479, 1451, 1315, 1264, 1138, 1070	257 (3.88), 348 (4.19)	7.68-7.27 (m, 10H, C ₆ H ₅ , C ₆ H ₄ and NH), 5.53 (s, 1H, CH), 4.13 and 4.11 (dd, 2H, SCH ₂), 2.86 (s, 3H, SO ₂ CH ₃), 2.38 (s, 3H, C ₆ H ₄ CH ₃)

These facts suggest that the 1,3-thiazine-2,6-dithiones first react with a thiolate to give 2-alkylthio-1,3-thiazine-6-thiones (**2**), which are followed by an addition of another mole of thiolate to **2** yielding 2,2-dialkylthio-2,3-dihydro-1,3-thiazine-6-thiones **3**. The latter compounds are desulfurized by other thiolate anion leading to end products **4** and disulfides.

To confirm this reaction route, an intermediate **2a** ($R^1 = \text{Ph}$, $R^2 = \text{SO}_2\text{Ph}$, $R^3 = \text{Me}$) was synthesized and treated with 2 molar equivalents of phenylmethanethiolate to afford a mixture of compounds **4a** (20%) and **4b** (35%). This fact supports that compounds **4a** and **4b** are produced by reductive desulfurization of transient intermediate **3'** which are formed by addition reaction of phenylmethanethiol to the intermediate **2a**. Oki and his co-workers have reported the reductive desulfurization of (α -alkylthio)carbonyl compounds with thiolate anions [6]. Ogura and his co-worker have also reported this type of desulfurization in the preparation of phenylglycine from α -methylthiophenylglycine [7]. It has been known that Schiff bases are reduced to produce corresponding secamines by refluxing with a thiol [8]. Thiol itself, however, never hydrogenated the intermediates **3** (Scheme 1 and 2).

Thiophenolate, in this reaction, showed no reactivity. 5-Cyano-1,3-thiazine-2,6-dithiones did not react with any thiolate. Physical properties of compounds **4a-h** here obtained are provided in Table 1 and IR, UV and Visible and ¹H-nmr spectral data are provided in Table 2.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were determined on a Nippon-Bunko IRA-1 infrared spectrophotometer. The ¹H-nmr spectra were recorded on a JEOL-JNM-GX 270 spectrometer with TMS as internal standard. The electronic absorption spectra were measured on a Shimadzu MPS-5000 multi-purpose spectrophotometer. 4-Phenyl-5-phenylsulfonyl- and 5-methylsulfonyl-4-(*m*-tolyl)-1,3-thiazine-2,6(3*H*)-dithiones **1a** and **1b**, were prepared by the published literature procedures [9].

Synthesis of 2-Alkyl- and 2-Aralkylthio-2,3-dihydro-1,3-thiazine-6(6*H*)-thiones (**4a-h**).

Each 1,3-thiazine-2,6-dithione (1.33 mmoles) and thiol (4.00 mmoles) were added to an alcoholic potassium hydroxide (4.00 mmoles) in 15 ml of ethanol. Each solution was refluxed at 60° for 3 hours and cooled. Water (20 ml) was added to each reaction mixture and each aqueous solution was washed with ether, treated under reduced pressure to remove any ether remaining, and then acidified with 2*M* hydrochloric acid. Each yellow solid which separated was collected and purified by recrystallization from aqueous ethanol.

2-Methylthio-4-phenyl-5-phenylsulfonyl-1,3-thiazine-6(6*H*)-thione (**2a**).

Triethylammonium salt of compound **1a** was prepared as reddish

orange crystals by adding an excess of triethylamine to a suspension of **1a** in ethanol. 1.00 g (2.09 mmoles) of this salt was suspended in 20 ml of methanol and 0.700 g (4.93 mmoles) of methyl iodide was added to the methanolic suspension at room temperature. The suspension became clear solution. After standing for 30 minutes, a small amount of *n*-hexane was added carefully with stirring to increase the amount of the crystals which was separated. Resulting orange needles of **2a** were collected and washed with a mixed solvent of methanol and *n*-hexane, mp 167-172°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}_2\text{S}_4$: C, 52.15; H, 3.35; N, 3.58. Found: C, 51.96; H, 3.49; N, 3.62.

Reaction of **2a** with Phenylmethanethiolate Anion. Formation of 2,3-Dihydro-2-methylthio-4-phenyl-5-phenylsulfonyl-1,3-thiazine-6(6*H*)-thione (**4a**) and 2-Benzylthio-2,3-dihydro-4-phenyl-5-phenylsulfonyl-1,3-thiazine-6(6*H*)-thione (**4b**).

To an ethanolic solution (25 ml) containing 0.190 g (3.39 mmoles) of potassium hydroxide and 0.420 g (3.38 mmoles) of phenylmethanethiol, was added 0.650 g (1.66 mmoles) of compound **2a** and the mixture was heated at 60° for 3 hours. 0.1*M* hydrochloric acid (35 ml) was added in

To an ethanolic solution (25 ml) containing 0.190 g (3.39 mmoles) of potassium hydroxide and 0.420 g (3.38 mmoles) of phenylmethanethiol, was added 0.650 g (1.66 mmoles) of compound **2a** and the mixture was heated at 60° for 3 hours. 0.1*M* hydrochloric acid (35 ml) was added in small portions to the cooled reaction mixture and the aqueous solution was extracted with ether (50 ml \times 2). Combined ether extracts were washed with 0.5*M* aqueous ammonia (50 ml \times 3) and then with water. The ether, after dried over magnesium sulfate, was evaporated to dryness to give a mixture of solid and viscous oil, which was treated with a mixed solvent of *n*-hexane and ethanol (9:1). Resulting yellow solid was collected and washed with the mixed solvent to give compound **4b** (0.210 g, 35%). The mother liquor was diluted with ether and washed with 0.1*M* potassium hydroxide, then with water, and dried over magnesium sulfate. The solvent was evaporated to dryness and the remaining solid was washed with the above mixed solvent to afford white crystals (0.070 g, 26%) of dibenzyl disulfide. The combined aqueous ammonia layer was acidified with 2*M* hydrochloric acid to give yellowish orange solid, which was collected and washed with ethanol to obtain yellow solid of **4a** (0.100 g, 20%). Infrared spectra of those three compounds were identical with those of authentic samples respectively. Each purified compound also had satisfactory microanalyses.

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