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Studies on 2-Substituted Thiazolines. II.[1,2] Reactions with Rhodanines

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2-Alkylthiothiazolines were reacted with heterocycles such as rhodanines and thiazolidine-2,4-dione in acetic anhydride to give the condensed products, (Va) and (X). The intermediates, (IIIa), (IVa) and (IX) were also obtained. The structures of these compounds were established by spectral data.

In the previous paper, we reported the reactions of 2-substituted thiothiazolines with aliphatic compounds (*e.g.* ethyl cyanoacetate) having an active methylene group. In this paper, the reactions of 2-alkylthiothiazolines with heterocyclic compounds having an active methylene group are described. The mass spectral study of their condensation products is also described.

5-(2′-Thiazolidinylidene)rhodanine (IIa) was obtained in a high yield by refluxing 2-ethylthiothiazoline (Ia) with rhodanine in acetic acid in the presence of sodium acetate for several hours. However this drastic condition was not suitable for other unstable compounds.

With a view to activate the 2-position of the thiazoline ring toward nucleophiles, 2-methylthio-3-methylthiazolinium iodide (VIa)[4] was prepared. As was expected, the condensation of VIa with rhodanine took place under the milder condition by refluxing them in ethanol in the presence of triethylamine for about one hour to give the N′-methyl derivative (VIIa). In the same manner, N-methyl- and N-phenylrhodanine gave (VIIb) and (VIIc), respectively.

2-Methylthio-3-benzylthiazolinium iodide (VIb)[5] also reacted with rhodanine, N-methyl- and N-phenylrhodanine to give the N′-benzyl derivatives (VIIIa—c), respectively.

When the reaction was carried out in acetic anhydride in place of acetic acid, much interesting phenomena were observed. For example, 2-ethylthiothiazoline reacted with N-methylrhodanine at room temperature to give an intermediate (IIIb) and at elevated temperature to give an intermediate (IVb) and the condensed product (Vb). The intermediates (IIIb) and (IVb) had the same molecular formula and showed the presence of a $>N\text{-}CH_2\text{-}CH_2\text{-}S$-, a -SEt and an acetyl groups in the infrared (IR) and the nuclear magnetic resonance (NMR) spectra, but their structures could not be assigned by the above spectral data. For the assignment of their structures, the ultraviolet (UV) and the mass spectra were very useful. Thus, the UV spectrum of IIIb showed the maxima at 267 and 296.5 nm and was similar to those of N-methylrhodanine (259 and 294 nm). However, that of IVb showed the maxima at 293.5 and 399 nm and was similar to those of IIb (274.5 and 393 nm). Furthermore, the mass spectrum of IIIb showed the characteristic peak at *m/e* 62 (C_2H_5SH) and IVb at *m/e* 86 ($\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CO\text{-}CH_3$). IIIb was converted to IVb by warming and the latter by removal of ethylmercaptan gave Vb which gave IIb in a high yield by hydrolysis.

1) Part I: Y. Sakurai, M. Kurumi, T. Okutome, S. Sato and K. Yamaguchi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1426 (1973).
2) Presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April, 5—7, 1972.
3) Location: *3-14-3, Minami-Yawata, Ichikawa, Chiba.*
4) K. Hirai and Y. Kishida, *Tetrahedron Letters*, **1972**, 2743.
5) A.D. Clark and P. Sykes, *J. Chem. Soc.* (*C*), **1971**, 103.

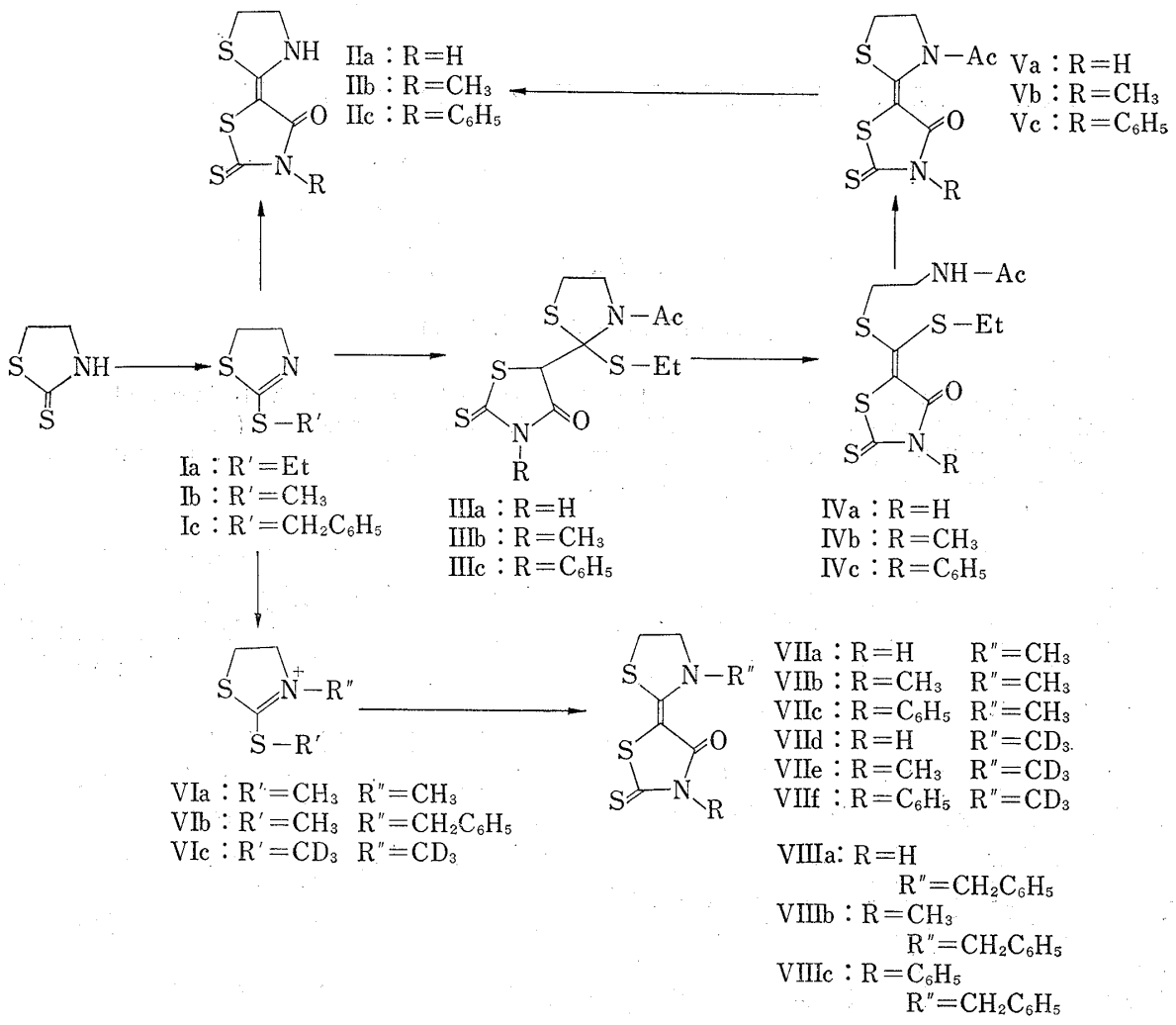


Chart 1

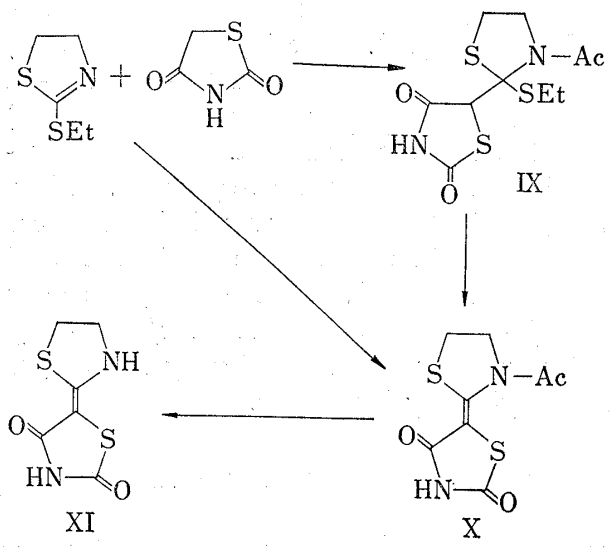


Chart 2

The compounds IIIa, IVa and Va were also obtained from rhodanine and IIIc, IVc and Vc from N-phenylrhodanine. Although the problems of stereoisomers are remained for IIa—c, IIIa—c, IVa—c and Va—c, there are no detailed data at present.

On the other hand, 2-ethylthiothiazoline condensed with thiazolidine-2,4-dione in acetic anhydride in the presence of sodium acetate at room temperature to give an only product (IX) which gave (X) by acid treatment. When this reaction was carried out at elevated temperature, X was directly obtained. X was easily hydrolyzed to the secondary amine (XI).

From these results, the reaction mechanism in acetic anhydride could be explained as follows:

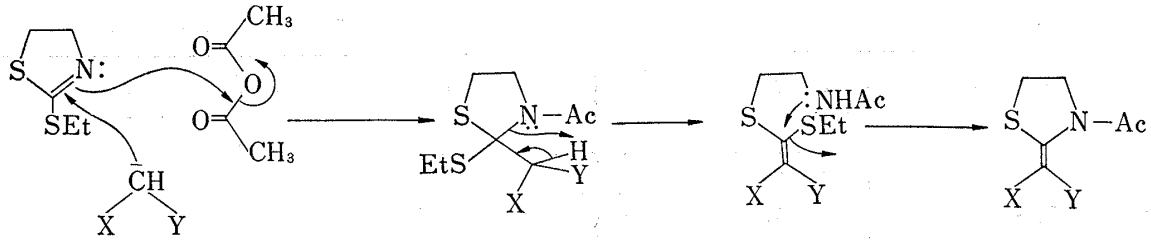
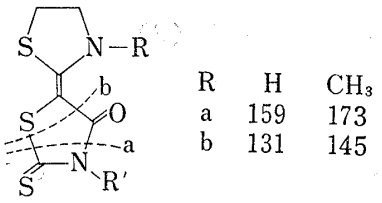


Chart 3

The mass spectra of the compounds IIa—c, Va—c, VIIa—c and VIIIa—c are discussed here. For IIa—c, the common fragments were observed at *m/e* 159 and 131 and for VIIa—c at *m/e* 173 and 145 due to the cleavages of the rhodanine nucleus (a and b). However, in the latter case, the N'-methyl derivatives, one additional fragment at *m/e* 144 was observed, which suggested the participation of N'-methyl group in VIIa—c to the fragmentation. So the deuterium derivatives (VIId—f) were prepared and their fragmentation patterns were studied.



	R	H	CH_3
a		159	173
b		131	145

Chart 4

Comparison of the fragmentation pattern of VIId—f with that of VIIa—c revealed that the fragment at *m/e* 144 in the latter shifted only by two units to *m/e* 146, although the fragments at *m/e* 173 and 145 in the latter shifted by three units to *m/e* 176 and 148, respectively. On the basis of these observation, the fragment at *m/e* 144 was considered to be the results of five membered ring formation with one hydrogen releasing from the N'-methyl group.

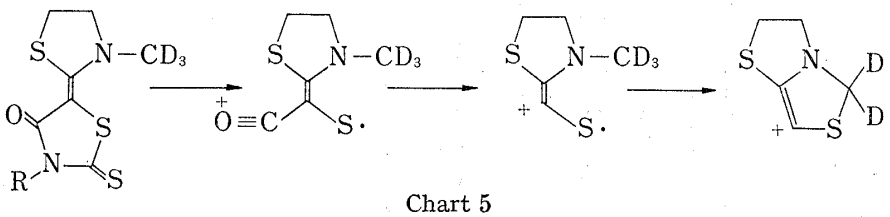


Chart 5

Furthermore, for the N'-benzyl derivatives (VIIIa—c), the fragments at *m/e* 249 and 221 due to the cleavages (a) and (b) were observed, and the fragment at *m/e* 220 resulted from the formation of five membered ring was also observed. Therefore, the fragmentation pattern of VIIIa—c was considered to be similar to that of VIIa—c.

On the other hand, the fragmentation of the N'-acetyl compounds (Va—c) seemed to proceed by an initial deacetylation followed by the cleavages (a) and (b), since the peaks except the molecular ion peaks were identical with those of the corresponding N'H-derivatives (IIa—c).

Table I.

Compound	mp (°C)	Mass (*m/e*)	UV λ_{max}^{EtOH} nm (ε)	IR ν_{max}^{KBr} cm^{-1}	NMR (ppm)
Rhodanine	170.5—171		252.5(14100) 295 (17400)		
IIa	256—257(d)	218(M^+), 159, 131	274 (12300) 391 (35900)	1656, 1649, 1545	
IIb	263—269	232(M^+), 159, 131	274.5(13500) 393 (32800)	3275, 1640, 1535, 1510	
IIc	>270	294(M^+), 159, 131	283.5(12000) 395 (31900)	3260, 1644, 1569	
XI	>270(d)	202(M^+), 159, 131	249.5(4100) 334.5(21800)	3225, 1687, 1639, 1548	

Compound	mp (°C)	Mass (*m/e*)	UV λ_{max}^{EtOH} nm (ε)	IR ν_{max}^{KBr} cm^{-1}	NMR (ppm)
IIIa	150—152	322(M^+), 260, 62	261 (8800) 306 (19000)	1720, 1625	1.08(3H, t), 2.07(3H, s), [a] 2.92(2H, q), 2.97(2H, t), 3.75(2H, t)
IIIb	204—206	336(M^+), 274, 62	267 (11600) 296.5(16600)	1727, 1657	
IIIc	179—181	398(M^+), 336, 62	269 (9600) 303 (17000)	1735, 1660	
IX	155—160(d)	306(M^+), 244, 62	plane	1749, 1705, 1629	1.15(3H, t), 2.13(3H, s), [a] 2.85(2H, q), 3.03(2H, t), 4.02(2H, t), 6.29(1H, s)
IVa	198—200(d)	322(M^+), 86	286.5(12500) 390.5(34400)	3360, 1689, 1644	
IVb	131—133	336(M^+), 86	293.5(6900) 399 (18400)	3290, 1674, 1640	1.37(3H, t), 2.00(3H, s), [b] 3.15(2H, q), 3.27(4H, m), 3.47(3H, s), 6.01(1H, b)
IVc	153—154	398(M^+), 86	298.5(7400) 402 (27500)	3320, 1695, 1655	1.33(3H, t), 2.01(3H, s), [b] 3.15(2H, q), 3.40(4H, m), 6.01(1H, b), 7.43(5H, m)
Va	>230(d)	260(M^+), 218, 159, 131, 43	283.5(10700) 390 (28100)	1685, 1650, 1513	
Vb	220—222	274(M^+), 232, 159, 131, 43	285.5(11500) 392 (29100)	1690, 1667, 1515, 1503	
Vc	250—251	326(M^+), 294, 159, 131, 43	287.5(11000) 393 (30100)	1692, 1680, 1590, 1513	
X	230—232	244(M^+), 202, 159, 131	262.5(6200) 340 (15700)	1713, 1679, 1612, 1505	2.32(3H, s), 3.18(2H, t), [a] 4.12(2H, t)
VIIa	>265(d)	232(M^+), 173, 145, 144	277.5(12500) 394 (32600)	1633, 1525	
VIIb	234—235	246(M^+), 173, 145, 144	282.5(10100) 393 (34500)	1660, 1535	
VIIc	222—223	308(M^+), 173, 145, 144	281 (10900) 395 (25000)	1664, 1590, 1535	
VIId	>270(d)	235(M^+), 176, 148, 146	281.5(12600) 393 (35000)	1633, 1515	
VIIe	231—233	249(M^+), 176, 148, 146	277 (14000) 385 (33800)	1660, 1520	
VIIf	225—227	311(M^+), 176, 148, 146	280 (11200) 394 (32200)	1660, 1590, 1520	
VIIIa	>250(d)	308(M^+), 249, 221, 220, 91	283.5(14000) 395 (37200)	1645, 1515	
VIIIb	160—162	322(M^+), 249, 221, 220, 91	278.5(15600) 395 (35400)	1657, 1525	
VIIIc	198—200	384(M^+), 249, 221, 220, 91	282.5(11900) 397 (33300)	1658, 1525	

a) DMSO-d_6 *b*) $CDCl_3$

Experimental

5-(2′-Thiazolidinylidene)rhodanine (IIa)——A mixture of Ia (1.5 g), rhodanine (1.3 g) and anhydrous sodium acetate (0.8 g) in acetic acid was refluxed for 2 hr. After cooling, the precipitated crystals were collected and washed with water and EtOH. Recrystallization from N,N-dimethylformamide (DMF) gave IIa (1.3 g) as brown needles, mp 256—257° (decomp.). *Anal.* Calcd. for $C_6H_8ON_2S_3$: C, 33.04; H, 2.77; N, 12.84. Found: C, 33.44; H, 2.74; N, 12.76.

5-(2′-Thiazolidinylidene)methylrhodanine (IIb) and 5-(2′-thiazolidinylidene)phenylrhodanine (IIc) were prepared in the same manner. IIb, mp 263—269°. *Anal.* Calcd. for $C_7H_8ON_2S_3$: C, 36.21; H, 3.47; N, 12.07. Found: C, 36.57; H, 3.45; N, 12.22. IIc, mp>270°. *Anal.* Calcd. for $C_{12}H_{10}ON_2S_3$: C, 48.98; H, 3.43; N, 9.52. Found: C, 48.51; H, 3.38; N, 9.32.

5-[2′-(N′-Acetyl-2′-ethylthiothiazolidinyl)]rhodanine (IIIa)——A suspension of Ia (2.5 g), rhodanine (2.0 g) and anhydrous sodium acetate (1.5 g) was stirred for 24 hr at room temperature and the precipitated crystals were collected. After being washed with water, recrystallization from dioxane–EtOH gave IIIa (4.5 g) as pale yellow needles, mp 150—152°. *Anal.* Calcd. for $C_{10}H_{14}O_2N_2S_4$: C, 37.27; H, 4.38; N, 8.69. Found: C, 37.56; H, 4.54; N, 9.06.

IIIb and IIIc were prepared in the same manner. IIIb, mp 204—206°. *Anal.* Calcd. for $C_{11}H_{16}O_2N_2S_4$: C, 39.29; H, 4.76; N, 8.33. Found: C, 39.55; H, 4.92; N, 8.93. IIIc, mp 179—180°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_2S_4$: C, 48.28; H, 4.56; N, 7.03. Found: C, 48.23; H, 4.71; N, 7.36.

5-(Ethylthio-β-acetamidoethylthiomethylene)rhodanine (IVa)——a) A suspension of Ia (2.5 g), rhodanine (2.0 g) and anhydrous sodium acetate (1.5 g) in acetic anhydride was warmed for 30 min and the separated crystals were collected. After being washed with water, recrystallization from DMF gave IVa (4.0 g) as yellow needles, mp 198—200° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2S_4$: C, 37.27; H, 4.38; N, 8.69. Found: C, 37.43; H, 4.50; N, 9.21.

b) A suspension of IIIa and anhydrous sodium acetate in acetic anhydride was warmed for 30 min on a water bath and the separated crystals were collected.

IVb and IVc were prepared in the same manner. IVb, mp 131—133°. *Anal.* Calcd. for $C_{11}H_{16}O_2N_2S_4$: C, 39.29; H, 4.76; N, 8.33. Found: C, 39.24; H, 5.06; N, 8.61. IVc, mp 153—154°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_2S_4$: C, 48.24; H, 4.56; N, 7.03. Found: C, 48.45; H, 4.90; N, 7.30.

5-(N'-Methyl-2'-thiazolidinylidene)rhodanine (VIIa)——A solution of VIa (1.4 g) and rhodanine (0.8 g) in EtOH in the presence of Et_3N (1 ml) was refluxed for 30 min. After evaporation of the solvent, recrystallization from EtOAc gave VIIa (0.1 g) as yellow powder, mp>265° (decomp.). *Anal.* Calcd. for $C_7H_8ON_2S_3$: C, 36.21; H, 3.47; N, 12.07. Found: C, 36.17; H, 3.53; N, 12.07.

VIIb and VIIc were prepared in the same manner. VIIb, mp 234—235°. *Anal.* Calcd. for $C_8H_{10}ON_2S_3$: C, 39.03; H, 4.09; N, 11.38. Found: C, 38.88; H, 4.05; N, 11.23. VIIc, mp 222—223°. *Anal.* Calcd. for $C_{13}H_{12}ON_2S_3$: C, 50.65; H, 3.92; N, 9.09. Found: C, 50.62; H, 4.02; N, 9.03.

5-(N'-Acetyl-2'-thiazolidinylidene)rhodanine (Va)——A suspension of IVa (0.5 g) and Raney Nickel (W-2) (3 g) in dioxane was refluxed for 12 hr and the catalyst was filtered off in hot and then the filtrate was concentrated. Recrystallization of the residue from DMF–EtOH gave Va (0.1 g) as yellow plates, mp>230° (decomp.). *Anal.* Calcd. for $C_8H_8O_2N_2S_3$: C, 36.93; H, 3.10; N, 10.77. Found: C, 37.25; H, 3.08; N, 11.00.

5-(N'-Acetyl-2'-thiazolidinylidene)methylrhodanine (Vb)——A suspension of Ia (1 g), methylrhodanine (1 g) and anhydrous sodium acetate (0.6 g) in acetic anhydride was warmed for 3 hr. After cooling, the precipitates were collected. Recrystallization from DMF–EtOH gave Vb (1 g) as yellow needles, mp 220—222°. *Anal.* Calcd. for $C_9H_{10}O_2N_2S_3$: C, 39.42; H, 3.68; N, 10.22. Found: C, 39.32; H, 3.85; N, 9.98.

Vc was prepared in the same manner. Vc, mp 250—251°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2S_3$: C, 50.00; H, 3.60; N, 8.33. Found: C, 49.86; H, 3.75; N, 8.23.

5-(N'-Benzyl-2'-thiazolidinylidene)rhodanine (VIIIa)——A suspension of VIb (0.35 g) and rhodanine (0.14 g) in EtOH in the presence of Et_3N (0.5 ml) was refluxed for 1 hr and the solvent was evaporated. Recrystallization of the residue from DMF–EtOH gave VIIIa (0.1 g) as pale yellow powder, mp>250° (decomp.). *Anal.* Calcd. for $C_{13}H_{12}ON_2S_3$: C, 50.65; H, 3.92; N, 9.09. Found: C, 50.94; H, 4.22; N, 9.53.

VIIIb and VIIIc were prepared in the same manner. VIIIb, mp 160—162°. *Anal.* Calcd. for $C_{14}H_{14}ON_2S_3$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.34; H, 4.50; N, 8.93. VIIIc, mp 198—200°. *Anal.* Calcd. for $C_{19}H_{14}ON_2S_3$: C, 59.37; H, 4.20; N, 7.29. Found: C, 59.56; H, 4.36; N, 7.62.

5-[2'-(N'-Acetyl-2'-ethylthiothiazolidinyl)]thiazolidine-2,4-dione (IX)——A suspension of Ia (2.5 g), thiazolidine-2,4-dione (2.3 g) and anhydrous sodium acetate (0.16 g) in acetic anhydride was stirred for 48 hr at room temperature and, then, poured into water. The precipitates were collected and recrystallized from EtOH to give IX (1.8 g) as colorless prisms, mp 155—160° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}O_3N_2S_3$: C, 39.22; H, 4.61; N, 9.15. Found: C, 39.29; H, 4.86; N, 8.87.

5-(N'-Acetyl-2'-thiazolidinylidene)thiazolidine-2,4-dione (X)——a) A suspension of IX (0.5 g) in 10% HCl was warmed for 10 min. After cooling, the precipitated crystals were collected. Recrystallization from DMF–EtOH gave X (0.35 g) as yellow needles, mp 230—232°. *Anal.* Calcd. for $C_8H_8O_3N_2S_2$: C, 39.35; H, 3.30; N, 11.47. Found: C, 39.41; H, 3.30; N, 11.15.

b) A solution of Ia (4.2 g) and thiazolidine-2,4-dione (3.6 g) in acetic anhydride in the presence of anhydrous sodium acetate (2.5 g) was warmed for 4 hr and the solvent was evaporated under reduced pressure. After removal of sodium acetate, the oily residue was recrystallized from EtOAc to give X (1 g) as yellow needles.

5-(2'-Thiazolidinylidene)thiazolidine-2,4-dione (XI)——a) A suspension of X (0.2 g) in 10% NaOH was warmed for 30 min on a water bath and acidified with 10% HCl. The precipitates were collected and recrystallized from DMF–EtOH to give XI (0.1 g) as pale yellow powder, mp>270° (decomp.). *Anal.* Calcd. for $C_6H_6O_2N_2S_2$: C, 35.64; H, 2.99; N, 13.86. Found: C, 35.46; H, 2.80; N, 13.97.

b) A suspension of IX (1.5 g) in 25% NaOH was warmed for 30 min on a water bath and acidified with 10% HCl. The precipitates were collected and recrystallized from DMF–EtOH to give XI (1.1 g).

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