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Synthesis of N-Free 4-Hydroxy-2-thiazoline as an Intermediate in the Hantzsch Thiazole Synthesis[1]

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4-Hydroxy-2-thiazolines were prepared by interrupting the Hantsch thiazole synthesis at the stage of cyclization. The chemical behavior of the tertiary amines, as well as the AB-quartet pattern at around 3.5 ppm in the NMR spectra, supported the cyclic structure (VII). Thioliminoester structure (VIIIa) proposed by M. Steude was unambiguously denied by the present paper.

The need of 2-thiazoline base for our other synthetical purposes and our interest in the reactivity of nitrogen and sulfur in un-aromatized heterocycles have led us to investigate the establishment of a general synthetic pathway of N-free 4-hydroxy-2-thiazoline. Although a couple of reports have been disclosed concerning syntheses of 4-hydroxy-2-thiazolines,[3–6] any general method for N-free compounds has not appeared. We have now planned to isolate the suspected intermediate of the Hantzsch thiazole synthesis.[7] The reaction has been postulated to proceed stepwise from thioamide (I) and α-haloketone (II) *via* thioiminoester hydrohalide (III) and 4-hydroxy-2-thiazoline salt (IV) to dehydrate into thiazole hydrohalide (V) through steps *a*, *b* and *c*[8,9] as shown in Chart 1, however, not many reports have been published on isolation of N-alkyl-4-hydroxy-2-thiazolinium salt synthesized from secondary thioamide and α-haloketone.[10a–e,11] Much fewer observations have been disclosed on the liberation and structure determination of the intermediate salt from primary thioamide.[5,12] M. Steude first reported isolation of the liberated base from the salt (X) obtained from the reaction of thioacetamide (Ia, R_1=-CH_3) and ethyl γ-bromoacetoacetate (IIa, R_2=-CH_2CO_2-C_2H_5, R_3=H) in absolute ethanol.[13] He concluded that the crystalline base (XI) $C_8H_{13}O_3$-NS [mp 94°] had the open-chain structure (VIIIa, R_1=-CH_3, R_2=-$CH_2CO_2C_2H_5$, R_3=H)

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[2] Location: *Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*

[3] K. Miyatake and T. Yoshikawa, *J. Pharm. Soc. Japan*, **75**, 1054 (1955).

[4] S. Gronowitz, B. Mathiasson, R. Dahlbom, B. Holmberg and K.A. Jensen, *Acta Chem. Scand.*, **19**, 1215 (1968).

[5] H. Baganz and J. Rüger, *Chem. Ber.*, **101**, 3872 (1968).

[6] E. Haruki, S. Izumida and E. Imoto, *Nippon Kagaku Zasshi*, **89**, 942 (1965).

[7] A. Hantzsch, *Ann.*, **250**, 257, 281 (1889).

[8] Cf. R.H. Wiley, D.C. England and L.C. Behr, "Organic Reactions," Vol. 6, ed. by R. Adams, John Wiley and Sons Inc., New York, 1951, p. 367.

[9] Cf. R.C. Elderfield, "Heterocyclic Compounds," Vol. 5, ed. John Wiley and Sons Inc., New York, 1950, p. 496.

[10] *a*) A.R. Todd, F. Bergel and Karimullah, *Chem. Ber.* **B**, **69**, 217 (1936); *b*) P.M. Kochergin and M.N. Schukina, *J. Gen. Chem., USSR*, **26**, 483, 3233 (1956); *c*) K. Murav'eva and M.N. Schukina, *Zh. Obsch. Khim.*, **30**, 2327, 2334 (1960); *d*) A. Takamizawa, K. Hirai, T. Ishiba and Y. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 731 (1967); *e*) B.M. Regan, F.T. Galysh and R.N. Morris, *J. Med. Chem.*, **10**, 649 (1967).

[11] R.S. Egan, J. Tadanier, D.L. Garmaise and A.P. Gaunce, *J. Org. Chem.*, **33**, 4422 (1968).

[12] The intermediate salts were formerly reported to be too unstable to permit liberation and structure determination. *cf. a*) F.E. Hopper and T.B. Johnson, *J. Am. Chem. Soc.*, **56**, 484 (1934); *b*) E.H. Huntress and K. Pfister, 3rd, *ibid.*, **65**, 1667 (1943).

[13] M. Steude, *Ann.*, **261**, 22 (1891).

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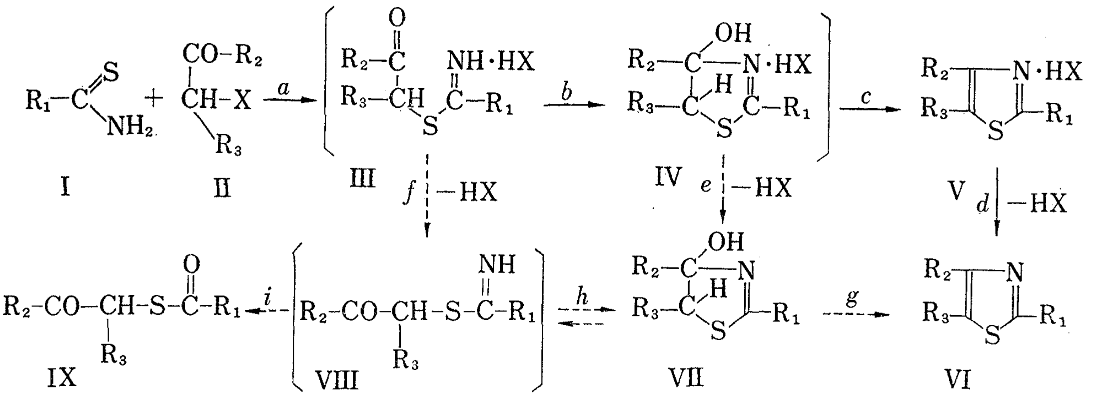

Chart 1

on the basis of the observations that the hydrobromide (X) gave ethyl γ-(acetylmercapto)-acetoacetate (IXa, R_1=$-CH_3$, R_2=$-CH_2CO_2C_2H_5$, R_3=H) by warming in water and that the base XI could not be converted to thiazole derivative with dehydrating agents.

We now re-examined Steude's experiment to inspect the validity of his observation from the present point of view. By treating the hygroscopic hydrobromide (X) with cold solution of sodium carbonate there were obtained colorless crystals [mp 91.7—93°, IR ν_{max}^{KBr} 1607 cm^{-1}, NMR δ (ppm in $CDCl_3$) 1.275 (3H, t, J=7 Hz.), 2.25 (3H, s), 2.825 (2H, s), 3.45 (2H, AB-quartet, J=12 Hz), 4.195 (2H, q, J=7 Hz), 5.55 (1H, broad s, exchangeable with D_2O)]. This compound offered good agreement with the Steude's specimen with respect to the elemental analysis datum as well as the melting point, however, the chemical and spectroscopic properties suggested that it had an isomeric cyclic structure, ethyl 4-hydroxy-2-methyl-2-thiazoline-4-acetate (VIIa, R_1=$-CH_3$, R_2=$-CH_2CO_2C_2H_5$, R_3=H) rather than α-thioketone or ethyl γ-(α-iminoethylmercapto)-acetoacetate (VIIIa), for it formed orange-red precipitation with Dragendorff's reagent and reacted neithr with 2,4-dinitrophenylhydrazine nor with ferric chloride solution, indicating the absence of ketonic carbonyl or enolic group.[14] In contrast to his observation, it was quantitatively dehydrated by heating in acetic acid to give ethyl 2-methylthiazole-4-acetate (VIa), and by treating the salt (X) with hot water there was obtained a mixture of VIa and IXa in a 2.2:1.0 ratio.[15] The presence of -C=N-rather than -C=O group was supported by a strong infra-red absorption band at 1607 cm^{-1},[16] and unequivalency of the two protons at C_5-position was clearly demonstrated by the quartet pattern centered at 3.45 ppm in the nuclear magnetic resonance (NMR) spectrum.[17]

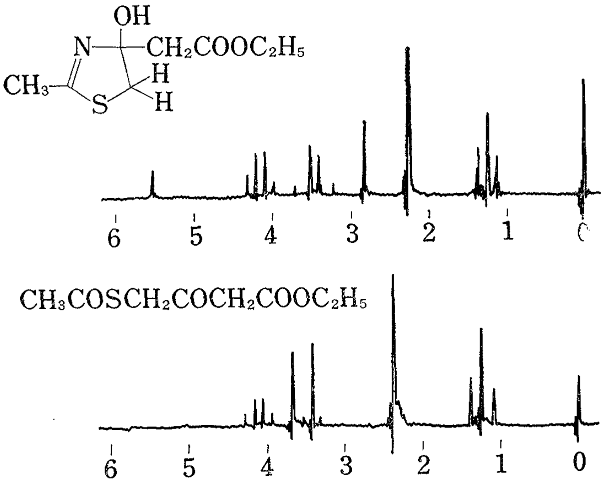

Fig. 1

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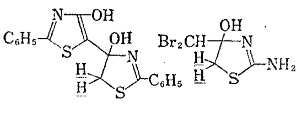
[14] The structurally related α-thioketone (IXa) forms hydrazones and gives red coloration with ferric chloride solution.

[15] This may be accounted for by assuming equilibrium between the hydrobromides, IIIa and IVa. *cf.* ref. 11.

[16] W. Otting and F. Drawert, *Chem. Ber.*, **88**, 1469 (1955).

[17] Similar observations have been reported as shown on the right.[4,5] On the other hand, IXa presents two sharp singlet peaks at δ (ppm in $CDCl_3$) 3.57 ($-COC\underline{H}_2-S-$) and 3.83 ($-COC\underline{H}_2CO_2C_2H_5$).



δ(ppm):	3.70	4.00
J_{AB}(Hz):	1.53	13.0
solvent:	DMSO-d_6	CH_3CO_2H

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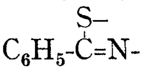
The hydrobromide $C_{13}H_{16}O_3NSBr$ [mp 81.5—83°], separated from the reaction of IIa and thiobenzamide (Ib, R_1=-C_6H_5) in ethanol, was similarly treated with aqueous sodium carbonate to give crystalline base (VIIh) $C_{13}H_{15}O_3NS$ [mp 86—86.8°; IR $\nu_{\max}^{\mathrm{KBr}}$ 1605, 1583 cm^{-1}; NMR δ (ppm in $CDCl_3$) 3.475 (2H, AB-quartet, J_{AB}=12.3 Hz); UV $\lambda_{\max}^{\mathrm{EtOH}}$: 244 mμ (12,900), 275 mμ (inflex., 2,200)]. The ultraviolet (UV) spectrum was analogous to that of 4-hydroxy-5-(α-hydroxyethyl)-2-phenyl-2-thiazoline,[6] showing both contained the same chromophoric group,  $C_6H_5\text{-}\overset{S-}{C}\text{=N-}$, as a common structural unit.

Now that chemical as well as spectroscopic properties of VIIa and VIIh clarified that they existed not as iminoester (VIII) but as 4-hydroxy-2-thiazoline at least in solutions, Ia and Ib were, then, treated with monochloroacetone (IIb), 1,3-dichloroacetone (IIc), phenacyl bromide (IId), ethyl bromopyruvate (IIe), 1-bromo-2,3-butanedione 3-oxime (IIf) and 1,5-dibromoacetylacetone (IIg). It was important to choose such a reaction medium as to have the salt (IV) precipitate before subsequent elimination of water to give V. Absolute ethanol- or acetone-ether was satisfactorily applied not to diminish the rate of the steps *a* and *b* too much at lower temperature. After the separated hydrohalide was treated with cold sodium carbonate or bicarbonate solution, the liberated base was collected by filtration or by extraction with ether. Recrystallization afforded pure materials in 62—92% yield. Their physical properties were summarized in Table I. Cyclic configuration of every compound was supported by the AB-quartet pattern in the range of 3.0—3.6 ppm in the NMR spectrum.

Table I. Physical Properties of 2-Methyl- and 2-Phenyl-4-hydroxy-2-thiazolines[a]

	Compounds			mp (°C)	IR $\nu_{\max}$ (cm^{-1})		NMR δ (ppm)			
VII	R_1	R_2	R_3		O–H	C=N, arom.	C_2-CH_3	$C_5\langle^{H_A}_{H_B}$	(J_{AB} Hz)	C_4-O-H [b]
a	$-CH_3$	$-CH_2CO_2C_2H_5$	H	91.7—93	3160	1607[c]	2.25	3.45	(12)	5.55[d]
b	$-CH_3$	$-CH_3$	H	64.5—66.5	3540, 3180	1635[e]	2.18	3.19	(11)	5.84[f]
c	$-CH_3$	$-CH_2Cl$	H	88—89.3	3535, 3120	1620[e]	2.275	3.45	(12)	5.76[d]
d	$-CH_3$	$-C_6H_5$	H	104.5—106	3530, 3145	1620— 1630[e]	2.13	3.44	(12)	5.325[d]
e	$-CH_3$	$-CO_2C_2H_5$	H	67.5—71	3510, 3150	1623[e]	2.295	3.60	(12.2)	5.22[d]
f	$-CH_3$	$-C(NOH)CH_3$	H	114—116.5	3290	1600[c]	2.14	3.535	(11.8)	6.21[g]
g	$-CH_3$	$-CH_2-$	H	142	3290	1627[c]	2.27	3.37	(12)	7.37[d]
h	$-C_6H_5$	$-CH_2CO_2C_2H_5$	H	85—86.8		1605, 1583[e]		3.475	(12.3)	[d]
i	$-C_6H_5$	$-CH_3$	H	125—126.8		1600, 1578[e]		3.40	(12)	[d]
j	$-C_6H_5$	$-CH_2Cl$	H	131—133.2		1598, 1575[e]		3.08	(12.2)	[d]

a) The composition and empirical formulae assigned to all new compounds were supported by satisfactory elemental analyses.
b) The NMR spectra were taken with TMS as the internal reference using a 60 Mc spectrometer.
c) in KBr tablet *d*) in deuteriochloroform *e*) in chloroform *f*) in carbontetrachloride *g*) in DMSO-d_6

In contrast to the hydrohalide (IV), which is hygroscopic and susceptible to dehydration to thiazole salt (V), the free base (VII) is comparatively stable at room temperature even in acetic acid. The dehydration of VII could be performed by heating in acetic acid to the corresponding thiazole (VI) in almost quantitative yield. The nitrogen atom of VII is reactive enough to be quarternarized readily at room temperature. Thus, 4-hydroxy-2-methyl-4-phenyl-2-thiazoline (VIId) was converted to 4-hydroxy-2,3-dimethyl-4-phenyl-2-thiazolinium iodide [mp 124—128.5° (decomp.)] with iodomethane in quantitative yield.

We consider the present synthesis provides a general method for preparing N-free 4-hydroxy-2-thiazoline, starting from primary thioamide and α-haloketone, popularly used for the Hantzsch thiazole synthesis.

Experimental[18]

Ethyl 4-Hydroxy-2-methyl-2-thiazoline-4-acetate (VIIa)——By following M. Steude's method,[13] using absolute ethanol as solvent, crude hydrobromide (IVa) was obtained in 79.9% yield. By using acetone-ether as reaction medium a better yield was attained.

To an ice-cold suspension of thioacetoamide (Ia) (2.65 g) in acetone (10 ml, dried over $CaCl_2$) was added dropwise to a solution of ethyl γ-bromoacetoacetate[19] (IIa) (5.78 g) in acetone (10 ml) with stirring, followed by addition of ether (10 ml). Soon Ia dissolved into solution and yellow powder precipitated. After another 30 minutes' stirring the precipitate was collected by filtration and washed with ether to give crude hydrobromide (IVa) (6.83 g, 87.3% yield), which was dissolved in water and neutralized with 10% Na_2CO_3, there was obtained ethyl 4-hydroxy-2-methyl-2-thiazoline-4-acetate (VIIa) as colorless crystals (quantitative yield from IVa), which was recrystallized from ethanol-ether to give pure sample. mp 91.7—93°. UV λ_{max}^{EtOH} mμ: 231.5, 243 (inflex.). IR ν_{max}^{KBr} cm^{-1}: 1723, 1607, 1419, 1368, 1332, 1193, 1152, 1064, 1025. NMR (in $CDCl_3$) δ: 1.275 (3H, t), 2.25 (3H, s), 2.825 (2H, s), 3.45 (2H, q), 4.195 (2H, q), 5.55 (1H, broad s). *Anal.* Calcd. for $C_8H_{13}O_3NS$: C, 47.29; H, 6.45; N, 6.89; S, 15.75. Found: C, 47.76; H, 6.47; N, 7.12; S, 15.85.

Ethyl 4-Hydroxy-2-phenyl-2-thiazoline-4-acetate (VIIh)——To an ice-cold suspension of thiobenzamide (Ib) (1.40 g) in ethanol (20 ml) was added dropwise with stirring a solution of IIa (5.22 g) in ether (20 ml). After addition was over further 40 ml of ether was added. The white emulsified mixture deposited precipitation. After stirring another hour, the mixture was poured into ice-water and extracted with ether (30 ml × 3). The extracts were combined and left overnight to deposit crystals of IVh (1.40 g, 26.5% yield). Recrystallization from ethanol-ether afforded pure sample mp. 81.5—83°. *Anal.* Calcd. for $C_{13}H_{16}O_3NSBr$: C, 45.11; H, 4.66; N, 4.05. Found: C, 45.08; H, 4.66; N, 4.52.

An ice-cold solution of the hydrobromide (IVh) (700 mg) in 1N HCl solution (20 ml) was basified with aqueous Na_2CO_3 solution to give crystalline precipitation, which was recrystallized from ether. Coloress crystals (380 mg). mp 86—86.8°. UV λ_{max}^{EtOH} mμ (ε): 244 (12900), 275 (inflex, 2200). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3460, 3060, 1736, 1605, 1583, 1379, 1194, 1020, 942. NMR (in CCl_4) δ: 1.21 (3H, t), 2.78 (2H, s), 3.475 (2H, q), 4.08 (2H, q), 5.13 (1H, broad s), 7.23—7.90 (5H, m). *Anal.* Calcd. for $C_{13}H_{15}O_3NS$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.81; H, 5.63; N, 5.48.

2,4-Dimethyl-4-hydroxy-2-thiazoline (VIIb)——Thioacetamide (Ia) (1.8 g) was added to an ice-cold solution of monochloroacetone (IIb) (2.14 g) in acetone (5 ml). After the crystals dissolved completely the mixture was allowed to stand at room temperature for half an hour to deposit crystals. After 3 hours' standing at room temperature, it was cooled in a refrigerator overnight and the crystals were collected by filtration, followed by washing with ether to give hydrochloride (IVb) (2.46 g, 62.5% yield) mp 95.5—98.5°, 1 g of which, without further purification, was dissolved in ice-water and basified with 10% aqueous Na_2CO_3 to give white emulsified mixture. The mixture was extracted with ether (20 ml × 3), dried and evaporated to give white solid (630 mg). Recrystallization from petroleum-ether afforded pure sample of VIIb as colorless needles. mp 64.5—66.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1428, 1370, 1178, 1141, 940, 914. NMR (in CCl_4) δ: 1.50 (3H, s), 2.18 (3H, s), 3.19 (2H, q), 5.84 (1H, broad s). *Anal.* Calcd. for C_5H_9ONS: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.93; H, 6.96; N, 10.85.

4-Chloromethyl-4-hydroxy-2-methyl-2-thiazoline (VIIc)——The isolation of IVc was performed by following the procedure described in *ref.* 10a).

1,3-Dichloroacetone (IIc) (2.6 g) and Ia (1.5 g) were dissolved in as little acetone as possible (*ca.* 4 ml) in a small flask, which was stoppered tightly, and left at room temperature. Within 30 minutes the solution deposited crystals, which were collected by filtration after standing further 4 hours, to give hydrochloride (IVc), mp 117—119° (decomp.), (3.8 g, 92.9% yield).

A solution of IVc (3.8 g) in ice-water was basified with aqueous $NaHCO_3$ solution to give white emulsion, which was extracted with ether (30 ml × 3). The extract was washed with water, dried over $MgSO_4$ and evaporated to give white solid. Recrystallization from ether and petroleum-ether afforded VIIc in quantitative yield. mp 88—89.3°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1435, 1380, 1257, 1170, 818. NMR (in $CDCl_3$) δ: 2.275 (3H, s), 3.45 (2H, q), 3.66 (2H, s), 5.76 (1H, s). *Anal.* Calcd. for C_5H_8ONSCl: C, 36.26; H, 4.87; N, 8.46. Found: C, 36.47; H, 4.83; N, 8.63.

4-Hydroxy-2-methyl-4-phenyl-2-thiazoline (VIId)——Thioacetamide (Ia) (0.45 g) was added to an ice-cold solution of phenacyl bromide (IId) (0.94 g) in acetone (7 ml). The solution deposited white preci-

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18) All melting points were uncorrected. NMR spectra were measured by HITACHI R-20 60MC spectrophotometer, using tetramethylsilane as the internal reference. IR and UV spectra were measured on a JASCO IRS spectrophotometer and on a HITACHI EPS-3 UV spectrophotometer, respectively.

19) M. Conrad, *Chem. Ber.*, 29, 1042 (1896).

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pitate instantly, which, after cooling with ice-water for 20 minutes, separated by filtration, washed with dry ether to give hydrobromide (IVd) (1.25 g, 91% yield). mp 74—77° (decomp.). The hydrobromide (700 mg), without further purification, was dissolved in ice-water (15 ml) and basified with 10% aqueous Na_2CO_3 to give crystals (425 mg, 87% yield). Recrystallization from ether and petroleum–ether afforded VIId. mp 104.5—106°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3530, 3145, 1620—1630, 1450, 1425, 1376, 1164, 1059, 1021, 948. NMR (in $CDCl_3$) δ: 2.13 (3H, s), 3.44 (2H, q), 5.325 (1H, s), 7.1—7.35 (3H, m). *Anal.* Calcd. for $C_{10}H_{11}ONS$: C, 62.16; H, 5.74; N, 7.25; S, 16.55. Found: C, 62.34; H, 5.75; N, 7.34; S, 16.25.

Ethyl 4-Hydroxy-2-methyl-2-thiazoline-4-carboxylate (VIIe).——Thioacetamide (Ia) (800 mg) was added into a solution of ethyl bromopyruvate (IIe) (1.95 g) in acetone (5 ml). The mixture solidified instantly to give pale yellow solid, which was filtered and washed with dry ether. The separated hydrobromide (IVe) (2.12 g, 79% yield) was dissolved in ice-water and basified with $NaHCO_3$ to give white emulsified mixture, which was extracted with ether (20 ml × 3), dried with $MgSO_4$ and freed from solvent by evaporation. The residual solid was recrystallized from ether and petroleum–ether to give VIIe in quantitative yield. mp 67.5—71°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3510, 3150, 1754, 1623, 1443, 1384, 1263; $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1752, 1603, 1433, 1275, 1185, 1080, 1060, 839, 810, 757, 723. NMR δ (in $CDCl_3$): 1.30 (3H, t), 2.295 (3H, s), 3.60 (2H, q), 4.225 (2H, q), 5.22 (1H, broad s). *Anal.* Calcd. for $C_7H_{11}O_3NS$: C, 44.44; H, 5.86; N, 7.41; S, 16.92. Found: C, 44.73; H, 5.92; N, 7.54; S, 16.54.

4-Acetyl-4-hydroxy-2-methyl-2-thiazoline Oxime (VIIf)——1-Bromo-2,3-butanedione 3-oxime (IIf) (0.9 g) and Ia (0.4 g) were dissolved in acetone (7 ml). The solution soon emulsified and deposited crystals. After standing at room temperature for 7 hr and cooling in a refrigerator overnight, the crystals were collected by filtration and washed with ether to give hydrobromide (IVf) (1.06 g, 81.5% yield). mp 90° (decomp.). The hydrobromide was dissolved in ice-water and neutralized with aqueous $NaHCO_3$ solution, followed by intensive extraction with ether (20 ml × 5). After working-up in a usual manner, crystalline residue was obtained in quantitative yield. Recrystallization from ethanol–ether afforded pure sample of VIIf. mp 113.8—116.5° (decomp.). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3290, 3050, 1600, 1420, 1372, 1184, 1172, 1073, 996, 903, 770, 710. NMR δ (in DMSO-d_6): 1.35 (3H, s), 2.14 (3H, s), 3.535 (2H, q), 6.21 (1H, s), 10.57 (1H, s). *Anal.* Calcd. for $C_6H_{10}O_2N_2S$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.64; H, 5.74; N, 16.05.

4,4′-Dihydroxy-2,2′-dimethyl-4,4′-dithiazolinylmethane (VIIg)——The crude 1,5-dibromoacetylacetone (IIg),[20] prepared from ethyl γ,γ'-dibromodiacetoacetate (10 g), was dissolved in ether (30 ml) and this was added into a solution of Ia (4 g) in acetone (50 ml). Exothermic reaction occurred and after 3 hours' stirring at room temperature the precipitate was collected by filtration to give hydrobromide (IVg) (7.29 g, 70% yield). The crude hydrobromide (IVg) was dissolved in 0.1 N HCl and basification with Na_2CO_3 afforded fine crystals, which were separated by filtration. Recrystallization from ethanol gave VIIg in quantitative yield. mp 142°. IR $\nu_{\max}^{\mathrm{EtOH}}$ cm^{-1}: 1627, 1430, 1408, 1370, 1209, 1193, 1064, 1026, 869, 827, 637. NMR δ (in $CDCl_3$): 2.27 (6H, s), 2.33 (2H, s), 3.37 (4H, q), 7.37 (2H, s). *Anal.* Calcd. for $C_9H_{14}O_2N_2S_2$: C, 43.90; H, 5.73; N, 11.38; S, 25.99. Found: C, 43.99; H, 5.61; N, 11.36; S, 26.00.

4-Hydroxy-4-methyl-2-phenyl-2-thiazoline (VIIi)——Crystals separated from a solution of Ib (0.47 g) and monochloroacetone (IIb) (0.47 g) in a mixture of ether and acetone (8 ml + 2 ml) at room temperature. The separated crystals were collected by filtration after standing overnight and were washed with dry ether to give hydrochloride (IVi) (280 mg). mp 80—81°. The crude hydrochloride, without further purification, was dissolved in ice-water and basified with $NaHCO_3$. The emulsified mixture was extracted with ether (20 ml × 3) and the etheral extracts were combined and washed with water, dried, and evaporated to give crystals, which were recrystallized from ether and petroleum–ether. VIIi, mp 131—133.2°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1606, 1600, 1380, 1234, 1192, 1140, 926. NMR δ (in $CDCl_3$): 1.63 (3H, s), 3.40 (2H, q), 4.71 (1H, broad s), 7.31—7.50 (3H, m), 7.70—7.93 (2H, m). *Anal.* Calcd. for $C_{10}H_{11}ONS$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.20; H, 5.84; N, 7.34.

4-Chloromethyl-4-hydroxy-2-phenyl-2-thiazoline (VIIj)——A solution of 1,3-dichloroacetone (IIc) (0.65 g) and Ib (0.5 g) in acetone (5 ml) deposited in 15 minutes at room temperature yellow crystals, which were collected by filtration after stirring for an hour. When the hydrohalide was dissolved in water, the free base (VIIj) precipitated as fine needles (450 mg) in 40% yield. The analysis sample was obtained by recrystallization from a mixture of chloroform and ether. mp 125—126.8°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1239, 1050, 946, 811. NMR δ (in $CDCl_3$): 3.08 (2H, q), 3.70 (2H, s), 7.30—7.50 (3H, m), 7.70—7.94 (2H, m). *Anal.* Calcd. for $C_{10}H_{10}ONSCl$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.69; H, 4.50; N, 5.90.

Ethyl 4-Hydroxy-2-phenyl-2-thiazoline-4-carboxylate (VIIk)——To a stirred solution of Ib (0.5 g) in ether (7 ml), ethyl bromopyruvate (IIe) (1.95 g) was added dropwise. The orange-red syrupy mass, after the supernatant solution was decanted, was digested with water and ether (20 ml). The aqueous layer was extracted with two 20 ml ether. The etheral extracts were combined, washed with water, dried and evaporated to give solid (402 mg, 32% yield), which, after recrystallization from a mixture of chloroform and ether, afforded colorless crystals of VIIk. mp 106—106.5°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3485, 2978, 1746, 1592, 1570, 1264, 1183, 1090, 1046, 944. NMR δ (in CCl_4): 1.28 (3H, s), 3.63 (2H, q), 4.19 (2H, q), 7.22—7.40 (3H, m),

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7.69—7.90 (2H, m). *Anal.* Calcd. for $C_{12}H_{13}O_3NS$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.50; H, 5.28; N, 5.66.

Hydrolysis of Ethyl 4-Hydroxy-2-methyl-2-thiazoline-4-acetate Hydrobromide (IVa)——A solution of the hydrobromide (IVa) (6.8 g) in water (50 ml) was heated on a boiling water-bath for 3 hr. After cooling the mixture was basified with $NaHCO_3$ and extracted with ether (20 ml × 3). The extracts were combined, dried over $MgSO_4$ and evaporated to give oily residue, which was extracted with 10% HCl (20 ml) and ether. The ethereal extract was separated, dried, evaporated and fractionated by distillation under vacuum to give ethyl γ-(acetylmercapto)-acetoacetate (IXa) (720 mg). bp 130—133° (3 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3009, 1740 (sh), 1712, 1700, 1310, 1212, 1137, 1020. NMR δ (in $CDCl_3$): 3.83 (2H, s), 3.57 (2H, s). *Anal.* Calcd. for $C_8H_{12}O_4S$: C, 47.06; H, 5.88. Found: C, 47.05; H, 5.98.

Acidic aqueous layer was basified with $NaHCO_3$ and extracted with ether (10 ml × 3). The extract was dried and evaporated to give oily residue, which was purified by vacuum distillation. Ethyl 2-methylthiazole-4-acetate (Va) (1.5 g). bp 140—144° (28 mmHg).[21] NMR δ (in $CDCl_3$): 1.27 (3H, t), 2.38 (3H, s), 3.57 (2H, s), 3.83 (2H, s), 4.17 (2H, q).

4-Hydroxy-2,3-dimethyl-4-phenyl-2-thiazolinium Iodide, Reaction of 4-Hydroxy-2-methyl-4-phenyl-2-thiazoline (VIId) with Iodomethane——To a solution of VIId (386 mg) in acetonitrile (50 ml) was added large excess amount of iodomethane (2 ml). After the reaction mixture was left at room temperature under interception of light for 7 days, the solution was condensed to 10 ml and the separated cyrstals were collected and dried under vacuum to give colorless crystals (290 mg). Dry ether was added to the filtrate to obtain second crop (250 mg). Both melted at 124—128.5°. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1604, 1463, 1265, 1232, 1200, 1064, 1005, 780, 748. *Anal.* Calcd. for $C_{11}H_{14}ONSI$: C, 39.42; H, 4.29; N, 4.18. Found: C, 40.06; H, 4.12; N, 4.46.

4-Ethoxycarbonylmethyl-4-hydroxy-2,3-dimethyl-2-thiazolinium Iodide, Reaction of Ethyl 4-Hydroxy-2-methyl-2-thiazoline-4-acetate (VIIa) with Iodomethane——Iodomethane (0.31 g) was added to a solution of VIIa (1 g) in acetonitrile (20 ml). After it was left aside at room temperature for 4 days, the reaction mixture was condensed to 10 ml, followed by addition of dry ether. After storing in a refrigerator the reaction mixture deposited N-methyl quarternary salt as white needles (900 mg). mp 110—116° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3185, 1717, 1603, 1218, 1151, 1058. *Anal.* Calcd. for $C_9H_{16}O_3NSI$: C, 31.31; H, 4.68; N, 4.06. Found: C, 31.64; H, 4.68; N, 4.33.

Dehydration of Ethyl 4-Hydroxy-2-methyl-2-thiazoline-4-acetate (VIIa), Ethyl 2-Methylthiazole-4-acetate——A solution of 4-hydroxythiazoline (VIIa) (800 mg) in acetic acid (20 ml) was heated in a boiling water-bath for 2 hr. After cooling, acetic acid was evaporated and the residual oil was distilled under reduced pressure to give ethyl 2-methylthiazole-4-acetate (500 mg, 69% yield) (bp 124—127°, 13 mmHg).

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[21] Identical with the specimen prepared through the reported method. *cf.* E.R.H. Jones, F.A. Robinson and M.N. Strachen, *J. Chem. Soc.*, **1946**, 87.

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