[Chem. Pharm. Bull. 23(12)3254—3265(1975)]

UDC 547.789.6.04 : 547.422.3.04

Studies of Heterocyclic Compounds. VII.[1] The Reactions of 5,6-Dihydrothiazolo[2,3-*b*]thiazolium Salts with Carbanions

Hiroko Ohtsuka, Tadashi Miyasaka, and Kiichi Arakawa

School of Pharmaceutical Sciences, Showa University[2]

(Received May 23, 1975)

The reaction of 5,6-dihydrothiazolo[2,3-*b*]thiazolium salt (**1**) with the sodium salt of acetylacetone furnished 3-(2-thiazolyl)-acetylacetone (**2**) with elimination of thiirane and 2-acetonylidene-3-acetylthioethyl-4-thiazoline (**3**). The reaction of **1** with the sodium salt of ethyl acetoacetate gave ethyl 2-(2-thiazolyl)-acetoacetate (**12**) and the reaction of **1** with the sodium salts of ethyl cyanoacetate and malononitrile gave 2-substituted thiazole (**16**), 3-(2-mercaptoethyl)-thiazoline (**17**) and/or its disulfide (**18**). The tautomeric forms of **2**, **12** and **16** are discussed on the basis of the structures of the methylated products and of their spectrophotometric properties.

In the preceding papers we have reported that the reaction of 5,6-dihydrothiazolo[2,3-*b*]-thiazolium salt (**1**) with nucleophiles is initiated by the addition of the reagent on C_{7a} at the polarized $>C=\overset{+}{N}<$ bond. If the nucleophile is not efficient enough as a leaving group, the adduct is converted either into thiazole derivative with elimination of thiirane, or into 3-mercaptoethylthiazoline derivative with cleavage of the C_{7a}–S_7 bond of the thiazolidine moiety. Of further interest are the reaction of **1** with carbanions and the chemical and physical properties of the reaction products.

Treatment of **1a** with the sodium salt of acetylacetone in dimethylformamide and benzene at 70° furnished two products. An acidic product, mp 140—142°, whose elemental analysis was in good accord with the empirical formula $C_{14}H_{13}O_2NS$ gave a red complex with methanolic ferric chloride and showed absorption bands at 3440, 3060 (NH or OH), and 1588 cm^{-1} (C=O) in the infrared (IR) spectrum and showed fragments of *m/e* 259 (M^+), 244, 217, 202, and 188 in the mass spectrum. These results are best accommodated by 3-(4-phenylthiazol-2-yl)-acetylacetone (**2a**). The nuclear magnetic resonance (NMR) spectrum was in good agreement with the assigned structure and exhibited a complex pattern due to tautomerism (more will be discussed about this later). The alkaline hydrolysis of **2a** afforded 2-acetonyl-4-phenyl-thiazole (**4**) as an oil which showed a carbonyl band at 1724 cm^{-1} in the IR spectrum and showed three singlets at δ 2.29 (3H), 4.17 (2H), and 7.40 ppm (1H) in the NMR spectrum. The acetylation of **2a** with acetic anhydride afforded an unstable acetate (**5**) which showed carbonyl bands at 1765 (ester) and 1710 cm^{-1} (conjugated ketone) in the IR spectrum and exhibited three individual methylsinglets at δ 2.24, 2.31 and 2.54 ppm in the NMR spectrum.

The second product isolated from the organic layer as yellow prisms, mp 141—142°, had the empirical formula, $C_{16}H_{17}O_2NS_2$ which was compatible with that of the 1:1 adduct, and on strongly alkaline hydrolysis gave 2-acetonylthiazole (**4**). The IR spectrum of the second product showed two bands at 1683 and 1598 cm^{-1} in the carbonyl region and the NMR spectrum showed peaks at δ 2.20 (s, 6H), 3.05 (double d, 2H), 3.90 (double d, 2H), 6.04 (s, 1H,

1) Part VI: H. Ohtsuka, T. Miyasaka, and K. Arakawa; *Chem. Pharm. Bull.* (Tokyo), **23**, 3243 (1975).
2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*

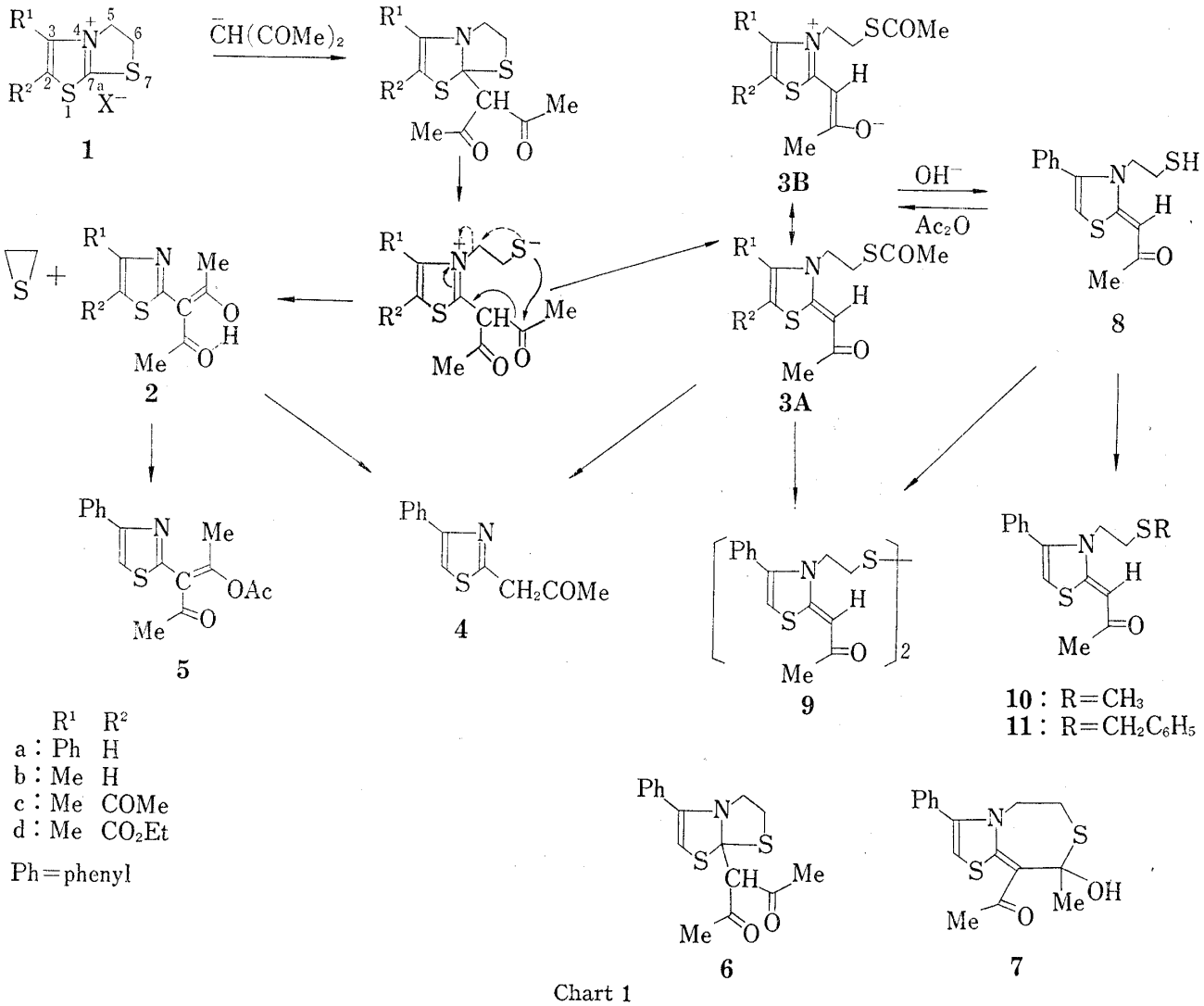
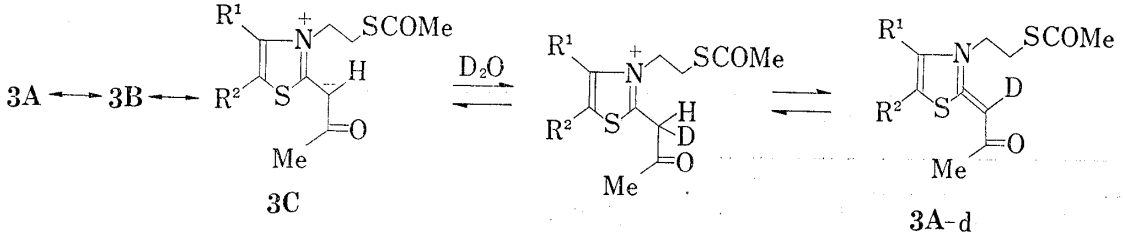


Chart 1

exchangeable with deuterioxide), 6.24 (s, 1H), and 7.3—7.6 ppm (m, 5H).[3] Several alternative structures (*i.e.*, **3a**, **6** and **7**) for the second product may be drawn on the basis of these considerations and one of these structures, **3a**, was proved to be correct by examination of the mass spectrum and the chemical behaviors of the second product. The mass spectrum showed fragments of *m/e* 319 (M^+), 276 (M^+-COCH_3), 244 ($M^+-SCOCH_3$), 217 ($M^+-\overline{\overset{+}{S}}-COCH_3$), *etc*, where the fragments of *m/e* 244 and 217 led to the structure [**3a**, 2-acetonylidene-3-(2-acetylthioethyl)-4-phenyl-4-thiazoline. Treatment of **3a** with hydrochloric acid in methanol

3) The deuterium-exchange of the vinyl proton at the α-carbon of **3** proceeded fairly rapidly. By shaking the 10% solution of **3** in $CDCl_3$ with a few drops of D_2O the exchange was almost complete in a few minutes at room temperature. The α-carbon of 2-acetonylthiazolium betain (**3C**) looks like to be easily deuterated to give **3A-d** under such a mild condition. For other examples of deuterium-exchange of vinyl protons see W. von Philipsborn, H. Sterlin, and W. Traber, *Helv. Chim. Acta*, **46**, 259 (1963); S. Takahashi and H. Kanō, *Tetrahedron Letters*, **1965**, 3789; *ibid.*, *Chem. Pharm. Bull.* (Tokyo), **14**, 375 (1966) and R. Breslow, *J. Am. Chem. Soc.*, **79**, 1762 (1957).



gave its hydrochloride and **3a** gave mercaptan (**8**) by treatment with potassium carbonate for 10 minutes in methanol but gave disulfide (**9**) under the same condition except for several hours or by treatment with aqueous ammonia. Mercaptan (**8**) was converted into **3a** on acetylation, into methyl sulfide (**10**) on methylation, and into benzyl sulfide (**11**) on benzylation. According to the spectroscopic data, the structure of **3a** appears to be best represented as the resonance hybrid, **3A** and **3B**; the IR spectrum of **3a** exhibited an enolizable and polarizable conjugated carbonyl band at 1598 cm^{-1} and the NMR spectrum exhibited a deuterioxide-exchangeable peak at δ 6.04 ppm due to a vinyl proton of C_2-side chain. The structures of **8**, **9**, **10**, and **11** were determined by analytical and spectroscopic data. The IR spectrum of **9**, **10**, and **11** were analogous to that of **3a** except of disappearance of a carbonyl band at 1683 cm^{-1}, but that of **8** showed in addition SH streching vibration at 2520 cm^{-1}. The NMR spectrum of **8** exhibited a triplet at δ 1.55 ppm (SH) and that of **10** exhibited a singlet at δ 1.79 ppm (S–CH_3). The reactions of **1b**, **1c** and **1d** with the sodium salt of acetylacetone similarly furnished two products, **2** and **3**, in various yield. The yields and the physical properties are summarized in Table I. The productions of **2** and **3** are probably best envisaged as attack by the reagent on C_{7a}, followed by the elimination of thiirane to give **2** and followed by concerted or stepwise migration of acetyl group from C_{2a} to S_7 to give **3** as shown in Chart 1.

On reaction of **1** with the sodium salt of ethyl acetoacetate the sole product which could be isolated was ethyl 2-(2-thiazolyl)-acetoacetate (**12**). The IR spectrum of **12a** showed bands at 1626 and 1573 cm^{-1} in the carbonyl region and the mass spectrum showed a molecular ion (*m/e* 289) and a structurally consistent fragmentation pattern [*m/e* 243 (M^+—EtOH), 201 (M^+—EtOH, CH_2=C=O), 134 (), 102 (Ph–C≡CH)]. Alkaline hydrolysis of **12a** gave 2-thiazolylacetic acid (**13**), which, on thermolysis, decarboxylated to give 2-methylthiazole (**14**). Treatment of **12a** with aqueous ammonia afforded 2-thiazolylacetamide (**15**). The physical properties of **13** and **14** agreed exactly with those described in the literatures.[4,5]

Chart 2

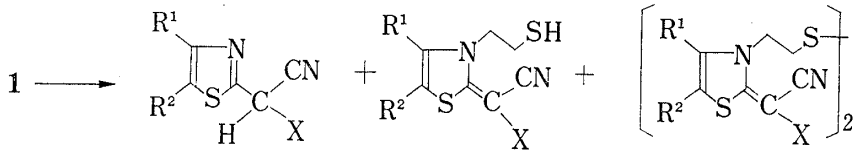
Table I. Reaction of **1** with the Sodium Salt of Acetylacetone

	R^1	R^2	2 yield (%)	2 mp	2 $\nu_{C=O}$ cm^{-1} [a]	3 yield (%)	3 mp	3 $\nu_{C=O}$ cm^{-1} [a]	3 δCH_3 ppm [b]
a	C_6H_5	H	70.5	140—142°	1588	21.0	141—142°	1683 1598	2.20 (6H)
b	CH_3	H	11.0	116—119°	1584	48.0	112.5—117°	1695 1586	2.19 (3H) 2.29 (3H) 2.40 (3H)
c	CH_3	$COCH_3$	48.6	185—187°	1672 1600	34.1	153.5—155°	1690 1658 1602	2.24 (3H) 2.41 (6H) 2.67 (3H)
d	CH_3	$CO_2C_2H_5$	13.2	136—137°[c] 161—170°	1716 1598	9.5	153.5—157°	1710 1687 1603	1.33 (3H) 2.22 (3H) 2.41 (3H) 2.66 (3H)

a) in KBr disk *b*) in deuteriochloroform *c*) double melting point

4) C. Scherschener, *C.A.*, **58**, 5655 (1963).
5) E. Erlenmeyer, *Helv. Chim. Acta.*, **30**, 2058 (1947).

On the other hand, the reactions of **1** with the sodium salts of ethyl cyanoacetate and malononitrile furnished 2-substituted thiazole (**16**) which was formed by elimination of thiirane, mercaptan (**17**), and/or disulfide (**18**), which were produced by the attack of the carbanion at C_{7a}, followed by the cleavage of C_{7a}–S_7 bond. Mercaptan (**17**) yielded **18** on oxidation and yielded methyl sulfide (**19**) on methylation.



16	R^1	R^2	X
a :	Ph	H	CO_2Et
b :	Ph	H	CN
c :	Me	H	CO_2Et
d :	Me	COMe	CO_2Et

17 **18**

Chart 3

As compounds **2**, **12**, and **16** had several sites which could be alkylated and the alkylation was needed to the determination of these tautomeric forms, we have investigated the methylation of these compounds. The methylation of **2a** with iodomethane for 30 minutes in the presence of potassium carbonate in acetonitrile gave 2-(1,1-diacetylethyl)-thiazole (**20**) as an unstable oil which showed singlets at δ 1.86 (3H) and 2.275 ppm (6H) in the NMR spectrum, whereas methylation of **2a** in methanol or for more than an hour in acetonitrile furnished 3-(4-phenylthiazol-2-yl)-2-butanone (**21**) as an oil, 3-hydroxy-3-(4-phenylthiazol-2-yl)-2-butanone (**22**) as an oil, and 2-acetyl-4-phenylthiazole (**23**) as crystals in 17.5, 30.7, and 16.8% yield, respectively. Methanolic solution of **20** was allowed to stand with a base at room temperature to give the same products as **21**, **22** and **23**. Methylation of **12** and **16a** in acetonitrile for 1.5—3 hours gave $C_{2\alpha}$-methylated products, **24** and **25**, whereas methylation in methanol overnight gave **26** and **27**, which were also produced from **24** and **25** in the presence of a base in methanol. On alkaline hydrolysis **22** furnished 1-(4-phenylthiazol-2-yl)-ethanol and **25** furnished a known compound, 2-ethyl-4-phenylthiazole.[6] Accordingly on treatment of **2**, **12** and **16a** with iodomethane in the presence of a base methylation took place only on $C_{2\alpha}$. However, in case of **16b** methylation in the same manner in acetonitrile furnished N_3-methylated product **28** and C_2-methylated product **29** in 12.6 and 78.6% yield. The structures of **28** and **29** were confirmed by spectroscopic data; **28** showed singlets at δ 3.64 (CH_3) and 6.53 ppm (C_5-vinyl H), but **29** showed singlets at δ 2.32 (CH_3) and 7.85 ppm (C_5-aromatic H) in the NMR spectrum. The UV spectrum of **28** was superimposable with that of **17**, but that of **29** was analogous to that of **14**.

Since the structures of **2**, **12** and **16** had some tautomers, we diagnosed the tautomeric state of 4-phenyl derivatives, **2a**, **12a**, **16a** and **16b**, by NMR, UV and IR spectroscopy. In general, 4-phenylthiazole derivatives (*i.e.*, **4**, **27**, **29**) have an absorption maximum of the longest wave length at *ca.* 255 nm, whereas 4-phenyl-4-thiazoline derivatives (*i.e.*, **3**, **28**) have one at *ca.* 330 nm. The shape of the UV spectrum of **16b**, whose structure is representative as tautomeric forms, **A** (thiazole form) and **B** (thiazoline form), is very similar to that of **28** rather than that of **29** as shown in Fig. 1, it follows that **16b** exists as thiazoline form, **B**. The IR and NMR spectra also support it. The IR spectrum exhibits strong conjugated CN bands at 2201 and 1988 cm^{-1} and the NMR spectrum (90 MHz) shows a doublet at δ 7.28 ppm (J=1.4 Hz) due to C_5–H besides a multiplet due to aromatic protons. Addition of deuterioxide

6) F. Asinger, M. Thiel, and W. Horingklee, *Ann.*, **610**, 49 (1957).

changes the doublet to a singlet, so the doublet is inferred to couple with N_3–H which can not be observed. The long range coupling of C_5–H to N_3–H in thiazoline form is distinctly observed in case of **16a** which has λ_{max} 330.6 nm in the UV spectrum and shows a doublet at δ 6.70 ppm (1H, J=1.7 Hz) due to C_5–H and a broad singlet at δ 12.46 ppm (exchangeable with deuterioxide) due to hydrogen-bonded N_3–H in the NMR spectrum. Irradiation at

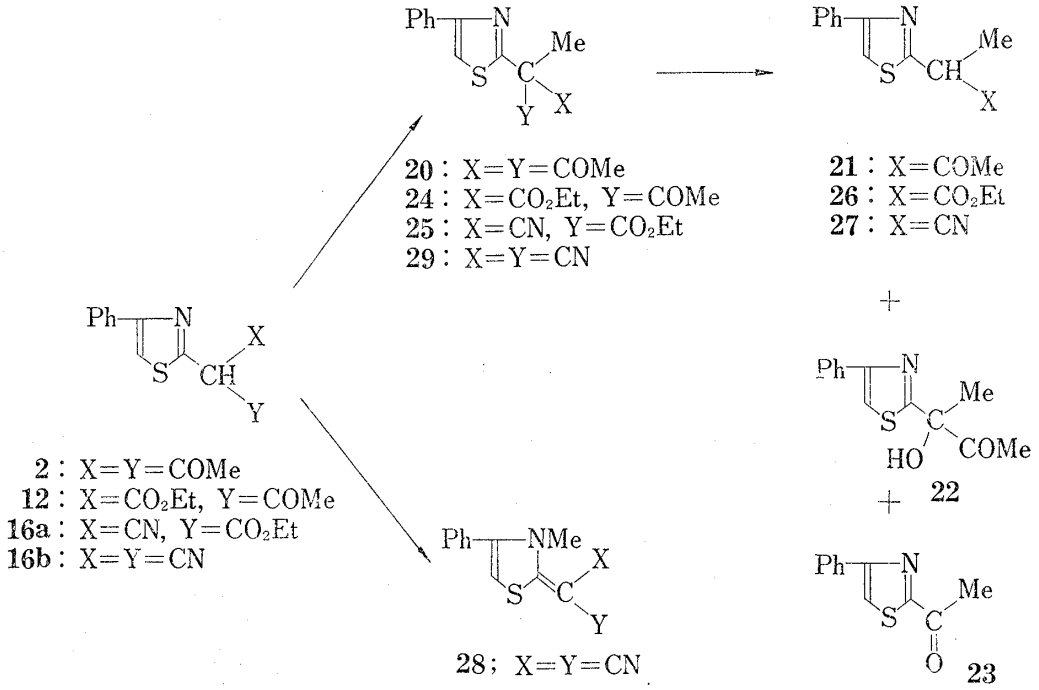


Chart 4

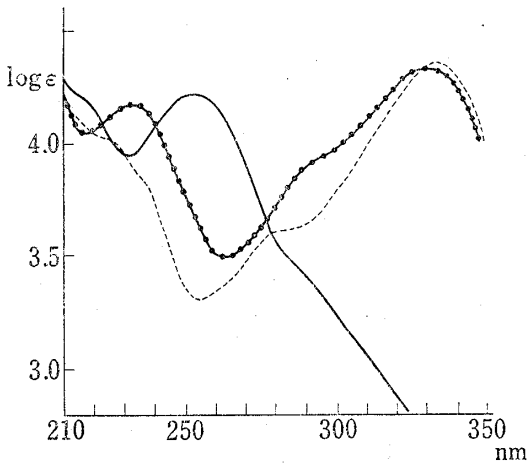


Fig. 1. Ultraviolet Absorption Spectra (in MeOH)

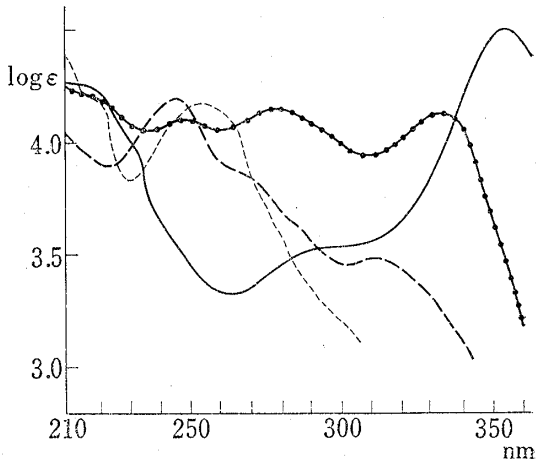
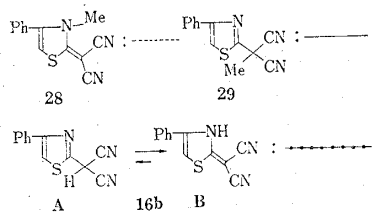
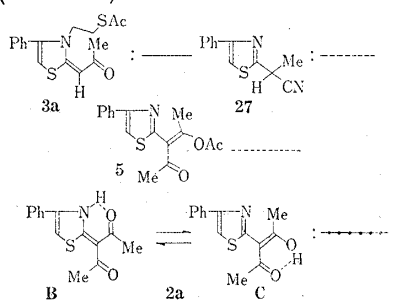


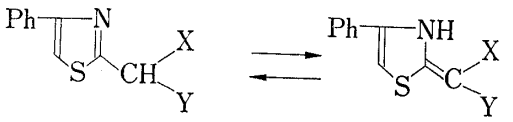
Fig. 2. Ultraviolet Absorption Secptra (in MeOH)





δ 12.46 ppm or addition of deuterioxide leads to the collapse of the δ 6.70 doublet to a singlet (Fig. 3). Similar long range coupling of analogous six-membered ring system, tetrahydro-1,4-thiazine, has been reorpted (J=1.05 Hz).[7]

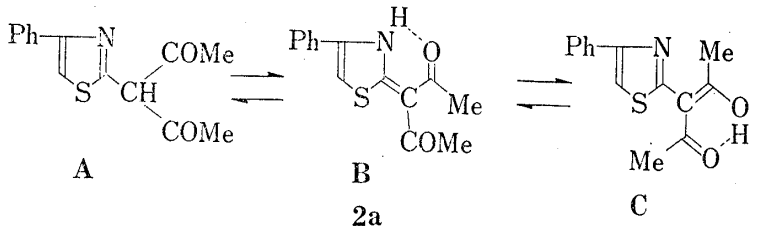
The IR spectrum of **16a** shows strong bands at 2210 (CN) and 1658 cm^{-1} (COOEt) and that of 2-(α-cyano-α-ethoxycarbonyl)methylenethiazolidine has been reported to exhibit strong bands at 2215 (CN) and 1665 cm^{-1} (COOEt) by Hirai and coworkers.[8] The shape of the UV spectrum of **2a**, whose structure can be represented as tautomeric forms, **A**, **B** and **C**, is complex and is not analogous to



A(thiazole type) B(thiazoline type)

16b : X=Y=CN
16a : X=CN, Y=CO_2Et
12a : X=COMe, Y=CO_2Et

Chart 5



2a

Chart 6

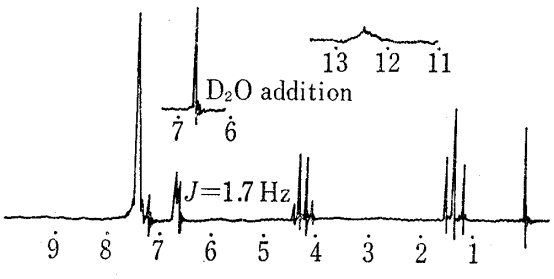


Fig. 3. NMR Spectrum of Ethyl 2-(4-Phenylthiazol-2-yl)-cyanoacetate (**16a**) (90 MHz)

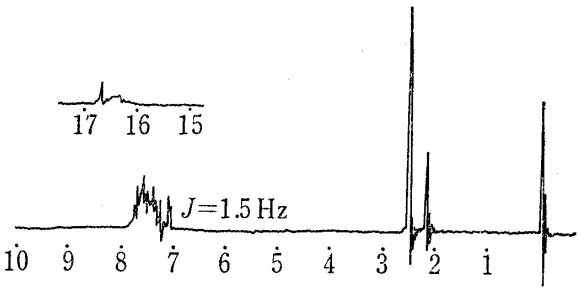


Fig. 4. NMR Spectrum of 3-(4-Phenylthiazol-2-yl)-acetylacetone (**2a**) (90 MHz)

those of any compound as shown in Fig. 2. Therefore, **2a** seems likely to exist as a mixture of the tautomers and it is proved by NMR spectroscopy. Its spectrum (Fig. 4) shows two singlets at δ 2.09 (1.5 H, CH_3 of form **C**) and 2.61 ppm (4.5H, CH_3 of form **B**), a doublet at δ 7.04 ppm (0.75H, J=1.5 Hz, C_5–H of form **B**), a broad singlet at δ 16.60 (0.75H, NH of form **B**) and a sharp singlet at δ 16.86 ppm (0.25H, OH of form **C**). The peaks at δ 16.60 and 16.86 ppm are exchangeable with deuterioxide and indicate the protons hydrogen-bonded. Irradiation at δ 16.60 ppm or addition of deuterioxide leads to the collapse of the δ 7.04 doublet to a singlet. From these results **2a** is confirmed to exist as a mixture of **B** and **C** forms (3: 1) in solution. The IR spectrum of **2a** in KBr disk shows a carbonyl band at 1588 cm^{-1} whereas that of 2-(diacetylmethylene)-thiazoline has been reported to show one at 1625 cm^{-1}.[8] In connection of **12a**, the NMR spectrum exhibits to exist as the thiazoline form (δ 7.20 ppm, d, J=1.2 Hz, C_5–H), but the shape of the UV spectrum is complex to appear to exist as a mixture.

7) R.F.C. Brown and I.D. Rae, *Aust. J. Chem.*, **18**, 1071 (1965).
8) K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.* (Tokyo), **20**, 97 (1971).

Experimental[8)]

Reaction of 3-Phenyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Bromide (1a) with Carbanion of Acetylacetone——50% oily NaH (480 mg) was added to a stirred ice-cold solution of acetylacetone (1.0 g) in benzene (20 ml) and the resulted suspension was stirred for 10 min at room temperature. Three g of **1a** and hot dimethylformamide (DMF) (70°, 50 ml) were added with stirring to the suspension. After stirring for 5 hr at 70°, the solvent was evaporated and the residue was taken up in $CHCl_3$ and extracted with 2% KOH. The alkaline layer was acidified with 10% HCl to deposit crystals (1.81 g, 70.5%) which were filtered. Recrystallization from MeOH gave 1.409 g of 3-(4-phenylthiazol-2-yl)-acetylacetone (**2a**), mp 140—142°. IR ν_{max}^{KBr} cm^{-1}: 3440, 3060, 1588, 1480, 1470, 1377, 1334, 960, 741. NMR (in $CDCl_3$) δ: 2.09 (s, 1.5H), 2.61 (s, 4.5H), 7.04 (d, 0.75H, $J=1.5$ Hz) 7.35—7.75 (m, 5H), 16.60 (broad s, 0.75H), 16.86 (s, 0.25H). UV λ_{max}^{MeOH} nm (log ε): 218 sh (4.20), 249.6 (4.10), 278 (4.15), 333 (4.12). Mass Spectrum *m/e*: 259 (M^+), 244, 217, 202, 188, 134, 102. *Anal.* Calcd. for $C_{14}H_{13}O_2NS$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.89; H, 5.05; N, 5.36.

The $CHCl_3$ layer was evaporated and the residue was crystallized from benzene-*n*-hexane to furnish yellow prisms of 2-acetonylidene-3-(2-acetylthioethyl)-4-phenyl-4-thiazoline (**3a**), 670 mg, 21.0%, mp 141—142°. IR ν_{max}^{KBr} cm^{-1}: 1683, 1598, 1498, 1486, 1453, 1366, 1210, 1184, 940. NMR (in $CDCl_3$) δ: 2.20 (s, 6H), 3.05 (m, 2H), 3.90 (m, 2H), 6.04 (s, 1H, exchangeable with D_2O), 6.24 (s, 1H), 7.3—7.5 (m, 5H). UV λ_{max}^{MeOH} nm (log ε): 217 (4.24), 264 (3.32), 295 (3.52), 355 (4.48). Mass Spectrum *m/e*: 319 (M^+), 276, 244, 233, 217, 202, 175, 134. *Anal.* Calcd. for $C_{16}H_{17}O_2NS_2$: C, 60.19; H, 5.33; N, 4.39. Found: C, 60.11; H, 5.40; N, 4.40.

Reaction of 3-Methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Bromide (1b) with Carbanion of Acetylacetone——Into a stirred suspension of carbanion of acetylacetone (1.00 g) in benzene (10 ml) there were added **1b** (2.38 g) and DMF (30 ml). After stirring overnight at room temperature the resulted orange-red solution was evaporated, taken up in $CHCl_3$, and extracted with 2% KOH. The alkaline layer was acidified with 10% HCl. The emulsified mixture was extracted with CH_2Cl_2 and the CH_2Cl_2 extracts were dried and evaporated to give syrup (420 mg). Chromatography on SiO_2 with $CHCl_3$ containing 2% MeOH gave 216 mg (11.0%) of 3-(4-methylthiazol-2-yl)-acetylacetone (**2b**), mp 116—119°. IR ν_{max}^{KBr} cm^{-1}: 1584, 1549, 1488, 1377, 1326, 962. NMR (in $CDCl_3$) δ: 2.38 (d, 3H), 2.57 (s, 6H), 6.51 (broad s, 1H), 15.45 (broad s, 1H). *Anal.* Calcd. for $C_9H_{11}O_2NS$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.69; H, 5.62; N, 7.32.

The $CHCl_3$ layer was washed with water, dried, and evaporated. The residual syrup (2.61 g) was purified by chromatography on SiO_2 with $CHCl_3$ containing 2% MeOH and by recrystallization from benzene–*n*-hexane to furnish 1.236 g (48%) of 2-acetonylidene-3-(2-acetylthioethyl)-4-methyl-4-thiazoline (**3b**), mp 112.5—117°. IR ν_{max}^{KBr} cm^{-1}: 3090, 1695, 1586, 1420—1496, 1195, 943. NMR (in $CDCl_3$) δ: 2.19 (s, 3H), 2.29 (broad s, 3H), 2.40 (s, 3H), 3.08 (m, 2H), 3.91 (m, 2H), 5.88 (broad s, 1H, exchangeable with D_2O), 6.02 (broad s, 1H). *Anal.* Calcd. for $C_{11}H_{15}O_2NS_2$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.49; H, 5.91; N, 5.54.

Reaction of 2-Acetyl-3-methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Chloride (1c) with Carbanion of Acetylacetone——Into a stirred suspension of carbanion of acetylacetone (700 mg) in benzene (10 ml) there were added **1c** (1.11 g) and DMF (30 ml). After stirring overnight, the solvent was evaporated and the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl to deposit crystals, which were filtered and recrystallized from benzene–*n*-hexane. 3-(5-Acetyl-4-methylthiazol-2-yl)-acetylacetone (**2c**), 580 mg (48.6%), mp 185—187°. IR ν_{max}^{KBr} cm^{-1}: 1672, 1600, 1554, 1476, 1380, 1340. NMR (in $CDCl_3$) δ: 1.33 (t, 3H), 2.44 (s, 3H), 2.59 and 2.63 (s, each; 3H, altogether), 4.23 and 4.27 (q, each; 2H, altogether), 11.36 and 11.94 (broad s, each; 1H, altogether, exchangeable with D_2O). *Anal.* Calcd. for $C_{11}H_{13}O_3NS$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.30; H, 5.45; N, 6.00.

The $CHCl_3$ layer was washed with water, dried, and evaporated. The residual oil (940 mg) was purified by chromatography on SiO_2 with $CHCl_3$ to yield 510 mg (34%) of 2-acetonylidene-5-acetyl-3-(2-acetylthioethyl)-4-methyl-4-thiazoline (**3c**), mp 153.5—155°. IR ν_{max}^{KBr} cm^{-1}: 1690, 1658, 1602, 1564, 1480, 1361. NMR (in $CDCl_3$) δ: 2.24 (s, 3H), 2.41 (s, 6H), 2.67 (s, 3H), 3.12 (m, 2H), 3.97 (m, 2H), 6.08 (s, 1H, exchangeable with D_2O). *Anal.* Calcd. for $C_{13}H_{17}O_3NS_2$: C, 52.17; H, 5.73; N, 4.68. Found: C, 52.23; H, 5.72; N, 4.77.

Reaction of 2-Ethoxycarbonyl-3-methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Chloride (1d) with Carbanion of Acetylacetone——Into a stirred suspension of carbanion of acetylacetone (550 mg) in benzene (7 ml), there were added **1d** (1.33 g) and DMF (20 ml). After stirring overnight at 70°, the solvent was evaporated and the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl to precipitate crystals, which were collected by filtration. Recrystallization from EtOH yielded 175 mg (13.2%) of 3-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-acetylacetone (**2d**), mp 136.5—137°, 161—170°. IR ν_{max}^{KBr} cm^{-1}: 1716, 1598, 1552, 1460, 1370, 1266, 998. NMR (in $CDCl_3$) δ: 1.375 (t, 3H), 2.58 (s, 6H), 2.67

9) All melting points were measured in capillary tubes and were uncorrected. NMR spectra were measured by a HITACHI R-20 60 MHz and R-22 90 MHz spectrophotometer, using tetramethylsilane as the internal reference. IR and UV spectra were measured on a JASCO IR-A spectrophotometer and on a HITACHI EPS-3 UV spectrometer respectively.

(s, 3H), 4.36 (q, 2H), 15.50 (broad s, 1H). *Anal.* Calcd. for $C_{12}H_{15}O_4NS$: C, 53.53; H, 5.62; N, 5.20. Found: C, 52.83; H, 5.25; N, 5.28.

The $CHCl_3$ layer was washed with water, dried, and evaporated. The residue (1.65 g) was crystallized from MeOH to give yellow powder (700 mg) which didn't dissolve in various organic solvent and water and the structure of which couldn't be determined. The filtrate was concentrated to dryness and the residue was crystallized from benzene–*n*-hexane to afford 155 mg (9.5%) of 2-acetonylidene-3-(2-acetylmercaptoethyl)-5-ethoxycarbonyl-4-methyl-4-thiazoline (**3d**), mp 153.5—157°. IR ν_{max}^{KBr} cm^{-1}: 1710, 1687, 1603, 1484, 1263. NMR (in $CDCl_3$) δ: 1.33 (t, 3H), 2.22 (s, 3H), 2.41 (s, 3H), 2.66 (s, 3H), 3.08 (m, 2H), 3.94 (m, 2H), 4.27 (q, 2H), 6.01 (s, 1H, exchangeable with D_2O). *Anal.* Calcd. for $C_{14}H_{19}O_4NS_2$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.94; H, 5.62; N, 4.13.

Ethyl 2-(4-Phenylthiazol-2-yl)-acetoacetate (12a)——Into a suspension of carbanion of ethyl acetoacetate (prepared from ethyl acetoacetate (1.30 g) and 50% oily NaH (480 mg) in benzene) in benzene there were added **1a** (3.00 g) and hot DMF (70°, 70 ml) with stirring. After stirring overnight at room temperature, the solvent was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated to give tar (3.44 g), which was recrystallized twice from MeOH to furnish 1.73 g (60.1%) of **12a**, mp 98.5—99.5°. IR ν_{max}^{KBr} cm^{-1}: 1626, 1573, 1486, 1375, 1336, 1323. NMR (in $CDCl_3$) δ: 1.40 (t, 3H, J=7 Hz), 2.59 (s, 3H), 4.32 (q, 2H, J=7 Hz), 7.20 (d, 1H, J=1.2 Hz), 7.3—7.77 (m, 5H). UV λ_{max}^{MeOH} nm (log ε): 225 (4.16), 245 (4.20), 262 sh (4.11), 333 (4.26). Mass Spectrum *m/e*: 289 (M^+), 243, 201, 134, 102. *Anal.* Calcd. for $C_{15}H_{15}O_3NS$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.11; H, 5.40; N, 5.02.

Ethyl 2-(4-Methylthiazolin-2-yl)-acetoacetate (12b)——Hot DMF (70°, 25 ml) and **1b** (2.3 g) were added to a suspension of carbanion of ethyl acetoacetate (1.5 g) in benzene (10 ml) with stirring. After stirring for 5 hr, the solvent was evaporated and the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to give 490 mg (21.6%) of **12b**, mp 60.5—64°. IR ν_{max}^{KBr} cm^{-1}: 1637, 1549, 1479, 1373, 1340, 1305, 1127. NMR (in $CDCl_3$) δ: 1.39 (t, 3H), 2.36 (d, 3H), 2.55 (s, 3H), 4.33 (q, 2H) 6.39 (broad s, 1H, exchangeable with D_2O). Mass Spectrum *m/e*: 227, 212, 185, 182, 181, 168. *Anal.* Calcd. for $C_{10}H_{13}O_3NS$: C, 52.86; H, 5.77; N, 6.17. Found: C, 53.06; H, 5.47; N, 6.30.

Ethyl 2-(5-Acetyl-4-methylthiazol-2-yl)-acetoacetate (12c)——Into a stirred suspension of carbanion of ethyl acetoacetate (570 mg) in benzene (10 ml) there were added **1c** (886 mg) and DMF (20 ml). After stirring for 30 min at 70°, the solvent was evaporated and the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl to deposit yellow precipitation (610 mg), which was filtered and recrystallized from EtOH to yield 490 mg (45.5%) of **12c**, mp 111—112°. IR ν_{max}^{KBr} cm^{-1}: 3090, 1674, 1586, 1574, 1496. NMR (in $CDCl_3$) δ: 1.40 (t, 3H), 2.50 (s, 3H), 2.56 (s, 3H), 2.64 (s, 3H), 4.35 (q, 2H). *Anal.* Calcd. for $C_{12}H_{15}O_4NS$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.34; H, 5.55; N, 5.19.

Ethyl 2-(5-Ethoxycarbonyl-4-methylthiazol-2-yl)-acetoacetate (12d)——Into a stirred suspension of the carbanion of ethyl acetoacetate (737 mg) in benzene (10 ml) there were added **1d** (1.33 g) and DMF (30 ml). After stirring at 70° for 5 hr, the solvent was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and evaporated to give a solid (1.81 g), which was crystallized from MeOH to afford yellow feathers of **12d**, 429 mg (14.3%), mp 104—106.5°. IR ν_{max}^{KBr} cm^{-1}: 1714, 1584, 1480, 1467, 1271, 1238. NMR (in $CDCl_3$) δ: 1.37 (t, 3H), 1.39 (t, 3H), 2.56 (s, 3H), 2.65 (s, 3H), 4.35 (q, 4H). *Anal.* Calcd. for $C_{13}H_{17}O_5NS$: C, 52.17, H, 5.73; N, 4.68. Found: C, 52.40; H, 5.50; N, 4.84.

Ethyl (4-Phenylthiazol-2-yl)-cyanoacetate (16a)——50% oily NaH (350 mg) was added to a stirred ice-cold solution of ethyl cyanoacetate (790 mg) in benzene (15 ml) and the mixture was stirred for 10 min at room temperature. Into this stirring suspension there were added **1a** (1.80 g) and DMF (30 ml). After stirring overnight the solvent was evaporated and the residue was taken up in benzene and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl to leave crystals, which were collected by filtration and recrystallized from benzene to give 487 mg (29.6%) of **16a**, mp 157—158°. IR ν_{max}^{KBr} cm^{-1}: 3440, 2210, 1658, 1530, 1420, 1314. NMR (in $CDCl_3$) δ: 1.34 (t, 3H), 4.26 (q, 2H), 6.70 (d, 1H, J=1.7 Hz) 7.47 (s, 5H), 12.46 (broad s, 1H, exchangeable with D_2O). UV λ_{max}^{MeOH} nm (log ε): 231 (4.28), 330.6 (4.37). Mass Spectrum *m/e*: 272, 244, 226, 200, 172, 134, 102. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2S$: C, 61.76, H, 4.44; N, 10.29. Found: C, 61.92; H, 4.29; N, 10.02.

Reaction of 1a with Carbanion of Malononitrile——Three g of **1a** was added with stirring to a suspension of carbanion of malononitrile (prepared from malononitrile (660 mg) and 50% oily NaH (480 mg) in benzene) in benzene (10 ml) and then DMF (50 ml) was added dropwise with stirring. The resulted precipitation was collected by filtration after stirring for 7 hr and washed with H_2O and hot MeOH to yield 188 mg (6.6%) of bis[2-(2-dicyanomethylene-4-phenyl-4-thiazolin-3-yl)ethyl] disulfide (**18b**), mp>230°. IR ν_{max}^{KBr} cm^{-1}: 2200, 2180, 1505, 1456, 1344. NMR (in DMSO-d_6) δ: 3.39 (m, 4H), 4.21 (m, 4H), 7.10 (s, 2H), 7.50 (s, 10H). *Anal.* Calcd. for $C_{28}H_{20}N_6S_4$: C, 59.15; H, 3.55; N, 14.78. Found: C, 59.18; H, 3.76; N, 14.87.

The filtrate was evaporated and the residue was taken up in $CHCl_3$ and extracted with 1% KOH. The alkaline layer was acidified with 10% HCl to deposit crystals which were collected by filtration. Recrystallization from EtOH afforded 408 mg (18.2%) of 2-(4-phenylthiazol-2-yl)-malononitrile (**16b**) as grey flakes, mp>230°. IR ν_{max}^{KBr} cm^{-1}: 2201, 1988, 1549, 1416, 1330, 883. NMR (in DMSO-d_6) δ: 7.28 (d, 1H, J=1.4 Hz),

7.42—7.53 (m, 3H), 7.68—7.79 (m, 2H). UV λ_{max}^{MeOH} nm (log ε): 234 (4.16), 290 sh (3.90), 331.5 (4.33). *Anal.* Calcd. for $C_{12}H_7N_3S$: C, 64.00; H, 3.13; N, 18.66. Found: C, 63.98; H, 3.34; N, 18.46.

The $CHCl_3$ layer was concentrated to dryness and the residue was applied on chromatography on SiO_2 with $CHCl_3$ containing 2% MeOH. The first oily fraction gave 46 mg of 2-dimethylaminothiazole and the second crystalline fraction was recrystallized from benzene–*n*-hexane to leave 142 mg (4.8%) of 2-dicyanomethylene-3-(2-mercaptoethyl)-4-phenyl-4-thiazoline (**17b**), mp 180° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2516, 2198, 2170, 2162, 1503, 1455. NMR (in $CDCl_3$) δ: 1.55 (t, 1H), 2.44—2.94 (m, 2H), 4.22 (m, 2H), 6.55 (s, 1H), 7.30—7.65 (m, 5H). *Anal.* Calcd. for $C_{14}H_{11}N_3S_2$: C, 58.94; H, 3.89; N, 14.73. Found: C, 58.71; H, 4.14; N, 14.46.

Reaction of 1c with Carbanion of Ethyl Cyanoacetate——Into a stirred ice-cold suspension of ethyl cyanoacetate (565 mg) in benzene (15 ml) was added **1c** (1.107 g) and then DMF (30 ml) was added dropwise. After stirring overnight at room temperature, the resulted white powder was filtered (355 mg) and recrystallized from $CHCl_3$–EtOH to yield 135 mg (8.6%) of bis[2-{5-acetyl-2-(α-cyano-α-ethoxycarbonyl)methylene-4-methyl-4-thiazolin-3-yl)}-ethyl] disulfide (**18d**), mp 220.5—224° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2199, 1679, 1663, 1493, 1465, 1296. *Anal.* Calcd. for $C_{26}H_{30}O_6N_4S_4$: C, 50.11; H, 4.81; N, 8.99. Found: C, 49.94; H, 4.63; N, 8.79.

The filtrate was concentrated to dryness and the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified with 10% HCl to separate crystals which were collected by filtration. Recrystallization from benzene afforded 297 mg (16.9%) of ethyl (5-acetyl-4-methylthiazol-2-yl)-cyanoacetate (**16d**), mp 188—197°. IR ν_{max}^{KBr} cm^{-1}: 2200, 1679, 1659, 1539, 1300, 1264. NMR (in $CDCl_3$) δ: 1.33 (t, 3H), 2.44 (s, 3H), 2.61 (d, 3H), 4.27 and 4.23 (q, each; 2H altogether), 11.36 and 11.94 (broad s, each; 1H altogether, exchangeable with D_2O). *Anal.* Calcd. for $C_{11}H_{12}O_3N_2S$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.37; H, 4.78; N, 11.00.

The mother liquor of **16d** was evaporated and the residue was purified by chromatography on SiO_2 with $CHCl_3$ containing 2% MeOH to yield 284 mg (18.2%) of 5-acetyl-2-(α-cyano-α-ethoxycarbonyl)methylene-3-(2-mercaptoethyl)-4-methyl-4-thiazoline (**17d**), mp 119.5—126°. IR ν_{max}^{KBr} cm^{-1}: 2555, 2198, 1680, 1661, 1497. NMR (in $CDCl_3$) δ: 1.21 (t, 3H), 1.75 (t, 1H), 2.29 (s, 3H), 2.55 (s, 3H), 2.83 (m, 2H), 4.13 (q, 2H), 4.36 (m, 2H). *Anal.* Calcd. for $C_{13}H_{16}O_3N_2S_2$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.96; H, 5.31; N, 8.74.

Reaction of 1b with Ethyl Cyanoacetate——Into a suspension of carbanion of ethyl cyanoacetate (1.30 g) in benzene (10 ml) there were added **1b** (2.38 g) and DMF (10 ml), and the mixture was stirred for 5 hr. After evaporation the residue was taken up in $CHCl_3$ and extracted with 3% KOH. The alkaline layer was acidified to separate crystals which were collected by filtration and recrystallized from benzene–*n*-hexane. Ethyl (4-phenylthiazol-2-yl)-cyanoacetate (**16c**), 620 mg (29.4%), mp 194—195°. IR ν_{max}^{KBr} cm^{-1}: 2200, 1658, 1548, 1315, 1129. NMR (in $CDCl_3$) δ: 1.32 (t, 3H), 2.31 (d, 3H), 4.26 (q, 2H), 6.26 (broad s, 1H), 11.19 (broad s, 1H). *Anal.* Calcd. for $C_9H_{10}O_2N_2S$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.41; H, 4.89; N, 13.06.

The chloroform layer was washed with H_2O and concentrated to dryness. The residue was purified by chromatography on SiO_2 to furnish 492 mg (18.3%) of bis[2-{2-(α-cyano-α-ethoxycarbonyl)methylene-4-methyl-4-thiazolin-3-yl}ethyl] disulfide (**18c**) as pale yellow powder, mp 225—227°. IR ν_{max}^{KBr} cm^{-1}: 2185, 1664, 1496, 1086. NMR (in DMSO-d_6) δ: 1.27 (t, 3H), 2.37 (broad s, 3H), 3.17 (m, 2H), 4.19 (q, 2H), 4.65 (m, 2H), 6.71 (broad s, 1H). *Anal.* Calcd. for $C_{22}H_{26}O_4N_4S_4$: C, 49.07; H, 4.87; N, 10.41. Found: C, 48.67; H, 4.79; N, 10.57.

Methylation of 2a——a) Into a stirred suspension of **2a** (260 mg) and K_2CO_3 (140 mg) in CH_3CN (10 ml) there was added CH_3I (1 g) and the mixture was stirred for 30 min. After evaporation the residue was extracted with $CHCl_3$, washed with 2% KOH and H_2O, dried, and evaporated to yield red oil (231 mg). Chromatography on SiO_2 with $CHCl_3$ gave 166 mg of 2-(1,1-diacetylethyl)-4-phenylthiazole (**20**) as an unstable oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1712, 1487, 1447, 1360. NMR (in $CDCl_3$) δ: 1.86 (s, 3H), 2.275 (s, 6H), 7.31—7.42 (m, 3H), 7.51 (s, 1H), 7.80—7.97 (m, 2H). Mass Spectrum *m/e*: 273 (M^+), 230 (M^+-COCH_3).

b) Potassium carbonate (140 mg) and CH_3I (1 g) were added to a methanolic solution of **2a** (260 mg) and the mixture was stirred for 20 hr. After evaporation the residue was dissolved in $CHCl_3$, washed with H_2O, dried, and evaporated to yield oil (200 mg) which was applied on chromatography on SiO_2 with $CHCl_3$ containing 1% MeOH. The earlier fractions (4—6) were recrystallized from *n*-hexane to leave 34 mg (16.8%) of 2-acetyl-4-phenylthiazole (**23**), mp 77.5—78°. IR ν_{max}^{KBr} cm^{-1}: 1676, 1479, 1432, 1359, 1264. NMR (in $CDCl_3$) δ: 2.78 (s, 3H), 7.37—7.55 (m, 3H), 7.77 (s, 1H), 7.88—8.05 (m, 2H). Mass Spectrum *m/e*: 203, 188, 175, 161, 134, 102. λ_{max}^{MeOH} nm: 213 sh, 242, 260 sh, 274.5 sh, 327. *Anal.* Calcd. for $C_{11}H_9ONS$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.29; H, 4.45; N, 6.42.

Fractions (9—12) gave 76 mg (30.7%) of 3-hydroxy-3-(4-phenylthiazol-2-yl)-butan-2-one (**22**) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1718, 1496, 1450, 1366. NMR (in $CDCl_3$) δ: 1.90 (s, 3H), 2.49 (s, 3H), 5.09 (broad s, 1H, exchangeable with D_2O), 7.3—7.5 (m, 4H), 7.8—7.95 (m, 2H). Mass Spectrum *m/e*: 247, 204, 162, 134, 102. *Anal.* Calcd. for $C_{13}H_{13}O_2NS$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.19; H, 5.23; N, 5.65.

Finally, the later fractions (13, 14) gave 40 mg (17.5%) of 3-(4-phenylthiazol-2-yl)-butan-2-one (**21**) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1139, 1106. NMR (in $CDCl_3$) δ: 1.57 (d, 3H, J=7.35 Hz), 2.23 (s, 3H), 4.24

(q, 1H, J=7.35 Hz), 7.22—7.34 (m, 4H), 7.71—7.88 (m, 2H). *Anal.* Calcd. for $C_{13}H_{13}ONS$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.77; H, 5.91; N, 5.96.

Hydrolysis of 21——After a solution of **21** (82 mg) in 10% KOH was heated under reflux for 3 hr with stirring, the resulted emulsion was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and evaporated. The residual crystals were recrystallized from *n*-hexane to afford 33 mg of 1-(4-phenylthiazol-2-yl)ethanol as yellow prisms, mp 73—75°. IR ν_{max}^{KBr} cm^{-1}: 3140, 3090, 1603, 1501. NMR (in $CDCl_3$) δ: 1.67 (d, 3H, J=7 Hz), 2.725 (s, 1H, exchangeable with D_2O), 5.17 (q, 1H, J=7 Hz), 7.29—7.47 (m, 4H), 7.77—7.94 (m, 2H). *Anal.* Calcd. for $C_{11}H_{11}ONS$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.35; H, 5.40; N, 6.75.

Methylation of 12a——a) Iodomethane (500 mg), K_2CO_3 (69 mg) and **12a** (145 mg) were added to CH_3CN (5 ml). After stirring for 3 hr, the solvent was evaporated and the residue was purified by chromatography on SiO_2 to yield 110 mg of ethyl 2-methyl-2-(4-phenylthiazol-2-yl)-acetoacetate (**24**) as an unstable oil. IR $\nu_{max}^{CH_3CN}$ cm^{-1}: 1740, 1725, 1485, 1447, 1254, 1190, 1020. NMR (in $CDCl_3$) δ: 1.32 (t, 3H), 1.92 (s, 3H), 2.27 (s, 3H), 4.32 (q, 2H), 7.32—7.45 (m, 3H), 7.51 (s, 1H), 7.82—8.00 (m, 2H). UV λ_{max}^{MeOH} nm: 257.5, 272 sh $\lambda_{max}^{H^+}$ nm: 255.5, 273 sh.

b) Iodomethane (500 mg) and K_2CO_3 (69 mg) were added to a solution of **12a** (145 mg) in a mixture (10 ml) of MeOH and CH_3CN (3: 1) and the mixture was stirred overnight. After evaporation of the solvent the residue was dissolved in $CHCl_3$, washed with H_2O, dried, and evaporated to furnish a mixture (200 mg) of ethyl 2-(4-phenylthiazol-2-yl)-propionate (**26**) and **24**. Chromatography on SiO_2 with $CHCl_3$ containing 1% MeOH gave 130 mg of **25** as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1743, 1497, 1450, 1179, 1138, 1107. NMR (in $CDCl_3$) δ: 1.23 (t, 3H), 1.68 (d, 3H, J=7.2 Hz), 4.20 (q, 2H), 4.23 (q, 1H, J=7.2 Hz), 7.31—7.50 (m, 4H; 7.37, C_5–H), 7.82—7.97 (m, 2H). *Anal.* Calcd. for $C_{14}H_{15}O_2NS$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.06; H, 5.65; N, 4.99.

Methylation of 16a——a) Into a solution of **16a** (215 mg) in CH_3CN (10 ml) there were added CH_3I (500 mg) and K_2CO_3 (35 mg) and the mixture was stirred for 1.5 hr. After evaporation the residue was taken up in H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated. The residue was purified by chromatography on SiO_2 with $CHCl_3$ containing 4% MeOH to yield 130 mg (58%) of ethyl 2-cyano-2-(4-phenylthiazol-2-yl)propionate (**25**) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2246 (w), 1757, 1491, 1447, 1386. NMR (in $CDCl_3$) δ: 1.325 (t, 3H), 2.15 (s, 3H), 4.34 (q, 2H), 7.32—7.45 (m, 3H), 7.52 (s, 1H), 7.82—7.99 (m, 2H). *Anal.* Calcd. for $C_{15}H_{14}O_2N_2S$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.82; H, 5.13; N, 9.43.

b) Iodomethane (1 g) and K_2CO_3 (138 mg) were added to a solution of **16a** (275 mg) in MeOH (7 ml) and the mixture was stirred overnight. After evaporation the residue was dissolved in $CHCl_3$, washed with water, and evaporated to yield mass (237 mg) which was purified by chromatography on SiO_2 with $CHCl_3$ containing 1% MeOH and by recrystallization from *n*-hexane to yield 105 mg of 2-(4-phenylthiazol-2-yl)-propionitrile (**27**), mp 75—76.3°. IR ν_{max}^{KBr} cm^{-1}: 2240, 1496, 1448, 1303, 1195, 788, 744. NMR (in $CDCl_3$) δ: 1.85 (d, 3H, J=7.5 Hz), 4.37 (q, 1H, J=7.5 Hz), 7.35—7.58 (m, 3H), 7.48 (s, 1H), 7.83—8.00 (m, 2H). *Anal.* Calcd. for $C_{12}H_{10}N_2S$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.30; H, 4.63; N, 12.75.

Methylation of 16b——Iodomethane (500 mg) and K_2CO_3 (40 mg) were added to a solution of **16b** (113 mg) in CH_3CN (15 ml) and the mixture was stirred overnight. After evaporation of the solvent the residue was dissolved in $CHCl_3$, washed with 3% KOH and H_2O, dried, and evaporated to yield tar (134 mg) which was crystallized from benzene–*n*-hexane. 2-Dicyanomethylene-3-methyl-4-phenyl-4-thiazoline (**28**), 15 mg (12.5%), mp 197—200°. IR ν_{max}^{KBr} cm^{-1}: 3096, 2200, 2170, 1515, 1424, 769. NMR (in $CDCl_3$) δ: 3.64 (s, 3H), 6.53 (s, 1H), 7.2—7.6 (m, 5H). UV λ_{max}^{MeOH} nm (log ε): 226 sh (4.00), 275 sh (3.58), 333.6 (4.34). *Anal.* Calcd. for $C_{13}H_{19}N_3S$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.45; H, 3.97; N, 17.81.

The mother liquor was condensed to 5 ml and left aside to give 82 mg (68.5%) of 2-methyl-2-(4-phenylthiazol-2-yl)-malononitrile (**29**), mp 66—67°. IR ν_{max}^{KBr} cm^{-1}: 3095, 2250 (w), 1486, 1447, 1184, 1088. NMR (in $CDCl_3$) δ: 2.32 (s, 3H), 7.30—7.41 (m, 3H), 7.58 (s, 1H), 7.75—7.92 (m, 2H). UV λ_{max}^{MeOH} nm (log ε): 218 sh (4.20), 252.5 (4.20). *Anal.* Calcd. for $C_{13}H_{19}N_3S$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.32, H, 3.92; N, 17.76.

Methylation of 17d——To a solution of **17d** (160 mg) in 5% KOH (25 ml) was added a solution of CH_3I (250 mg) in $CHCl_3$ (10 ml). After stirring for 2 hr, the $CHCl_3$ layer was separated, washed with H_2O, dried, and evaporated to give a solid (129 mg). Recrystallization from benzene–*n*-hexane afforded 108 mg of 5-acetyl-2-(α-cyano-α-ethoxycarbonyl)methylene-4-methyl-3-(2-methylthioethyl)-4-thiazoline (**19**), mp 103—105°. IR ν_{max}^{KBr} cm^{-1}: 2197, 1664, 1640, 1592, 1484. NMR (in $CDCl_3$) δ: 1.35 (t, 3H), 2.16 (s, 3H), 2.45 (s, 3H), 2.69 (s, 3H), 2.95 (m, 2H), 4.28 (q, 2H), 4.62 (m, 2H). *Anal.* Calcd. for $C_{14}H_{18}O_3N_2S_2$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.59; H, 5.35; N, 8.40.

Methylation of 3c——Into a methanolic solution of **3c** (130 mg) there were added CH_3I (200 mg) and K_2CO_3 (70 mg) and the mixture was stirred for 1 hr. After evaporation of the solvent the residue was dissolved in $CHCl_3$, washed with H_2O, dried, and evaporated to give a solid (139 mg). Recrystallization from benzene–*n*-hexane yielded 79 mg of 2-acetonylidene-5-acetyl-4-methyl-3-(2-methylthioethyl)-4-thiazoline, mp 90—92°. IR ν_{max}^{KBr} cm^{-1}: 1655, 1564, 1465, 1366, 1284, 1250. NMR (in $CDCl_3$) δ: 2.14 (s, 3H), 2.20 (s, 3H), 2.40 (s, 3H),

2.64 (s, 3H), 2.80 (m, 2H), 401 (m, 2H), 5.80 (broad s, 1H, exchangeable with D_2O). *Anal.* Calcd. for $C_{12}H_{17}O_2NS_2$: C, 53.13; H, 6.32; N, 5.16. Found: C, 52.88; H, 6.18; N, 5.15.

Acetylation of 2a——After a solution of **2a** (200 mg) in Ac_2O (15 ml) was heated on a boiling water-bath, the solvent was removed and co-evaporated with benzene to furnish acetate (**5**) as an oil. This oil was too unstable to purify to recover **2a**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1710, 1477, 1375, 1190, 1157, 1016. NMR (in $CDCl_3$) δ: 2.24 (s, 3H), 2.31 (s, 3H), 2.54 (s, 3H), 7.31—7.45 (m, 3H), 7.51 (s, 1H), 7.81—7.99 (m, 2H).

Hydrolysis of 2a. Formation of 2-Acetonyl-4-phenylthiazole (4)——Potassium carbonate (90 mg) was added into a methanolic solution of **2a** (200 mg), and the mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in $CHCl_3$, washed with 1% KOH and H_2O, dried and evaporated to furnish oil (100 mg), which was treated with active carbon to yield 47 mg of **4** as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724, 1640, 1598, 1450, 1368, 1165. NMR (in $CDCl_3$) δ: 2.29 (s, 3H), 4.17 (s, 2H), 7.30—7.47 (m, 4H; 7.40, C_5–H), 7.78—7.95 (m, 2H). *Anal.* Calcd for $C_{12}H_{11}ONS$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.82; H, 5.05; N, 6.78.

Hydrochloride of 3a——Two drops of conc. HCl were added to a methanolic solution of **3a** (100 mg) and the solution was heated under reflux for 2 hr. After cooling the solvent was evaporated and the residue was crystallized from MeOH-ether to give yellow prisms, mp 159—170°. IR ν_{max}^{KBr} cm^{-1}: 2230, 2280, 1688, 1612, 1571, 1399. *Anal.* Calcd. for $C_{16}H_{18}O_2NS_2Cl$: C, 54.01; H, 5.06; N, 3.93. Found: C, 54.00; H, 4.91; N, 4.23.

2-Acetonylidene-3-(2-methylthioethyl)-4-phenyl-4-thiazoline (10)——Iodomethane (400 mg) and K_2CO_3 (70 mg) were added to a methanolic solution of **3a** (165 mg). The solvent was evaporated after stirring for 4 hr, the residue was dissolved in AcOEt, washed with H_2O, dried, and evaporated to give oil (140 mg). Crystallization from benzene–*n*-hexane afforded 117 mg (78%) of **10**, mp 114—114.5°. IR ν_{max}^{KBr} cm^{-1}: 1583, 1492, 1485, 1453, 1421, 1365, 1197. NMR (in $CDCl_3$) δ: 1.79 (s, 3H), 2.20 (s, 3H), 2.64 (m, 2H), 3.92 (m, 2H), 5.78 (s, 1H, exchangeable with D_2O), 6.24 (s, 1H), 7.3—7.5 (m, 5H). *Anal.* Calcd. for $C_{15}H_{17}ONS_2$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.95; H, 5.54; N, 4.57.

2-Acetonylidene-3-(2-mercaptoethyl)-4-phenyl-4-thiazoline (8)——To a methanolic solution (15 ml) of **3a** (165 mg) was added K_2CO_3 (70 mg). After stirring for 10 min, water (20 ml) was added and the resulted solution was acidified with 10% HCl and then neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated to give oil (260 mg) which crystallized from benzene–*n*-hexane, 224 mg (81%), mp 119.5—124°. IR ν_{max}^{KBr} cm^{-1}: 2520, 1593, 1480, 1370, 1179. NMR (in $CDCl_3$) δ: 1.15 (t, 1H, exchangeable with D_2O), 2.18 (s, 3H), 2.40—2.92 (m, 2H), 3.88 (m, 2H), 5.69 (s, 1H, exchangeable with D_2O), 6.21 (s, 1H), 7.3—7.6 (m, 5H). *Anal.* Calcd. for $C_{14}H_{15}ONS_2$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.84; H, 5.33; N, 5.21.

Oxidation of 3a. Formation of Bis[2-(2-acetonylidene-4-phenyl-4-thiazolin-3-yl)ethyl] Disulfide (9)——One hundred mg of **3a** was dissolved in a mixture of aqueous NH_3 (20 ml) and MeOH (6 ml) and the solution was stirred overnight to deposit crystals, which were filtered and recrystallized from EtOH, 50 mg, mp 173.5—174.5°. IR ν_{max}^{KBr} cm^{-1}: 3420, 1596, 1478, 1450, 1365. NMR (in $CDCl_3$) δ: 2.20 (s, 3H), 2.57 (m, 2H), 3.97 (m, 2H), 5.80 (broad s, 1H, exchangeable with D_2O), 6.26 (s, 1H), 7.4 (broad s, 5H). *Anal.* Calcd. for $C_{28}H_{28}O_2N_2S_4$: C, 60.86; H, 5.11; N, 5.07. Found: C, 61.13; H, 4.98; N, 4.88.

Alkaline Hydrolysis of 3a. Formation of 4——The solution of **3a** (165 mg) in a mixture of MeOH (2 ml) and 20% NaOH (4 ml) was heated under reflux for 5 hr, and condensed to a half volume and extracted with AcOEt. The extract was dried and evaporated to yield oil (109 mg), which was purified by chromatography on SiO_2 with $CHCl_3$ containing 1% MeOH to give 46 mg of **4**.

Hydrolysis of 25. Formation of 2-Ethyl-4-phenylthiazole[5]——A suspension of **25** (100 mg) in 10% KOH (20 ml) was stirred for 5 hr at room temperature and extracted with $CHCl_3$. The $CHCl_3$ layer gave 32 mg of starting material (**25**). The aqueous layer was neutralized with 20% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and evaporated to yield 46 mg of 2-ethyl-4-phenylthiazole as an oil. Picrate: mp 127.5—128.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2975, 1499, 1448. NMR (in $CDCl_3$) δ: 1.41 (t, 3H, J=7.2 Hz), 3.08 (q, 2H, J=7.2 Hz), 7.3—7.5 (m, 4H; 7.32, C_5–H), 7.8—7.96 (m, 2H).

4-Phenylthiazole-2-acetic Acid (13)——After a suspension of **12a** (100 mg) in 10% KOH (2 ml) was heated on a boiling water bath until dissolving, the resulted solusion was left aside at room temperature for 30 min and acidified with 10% HCl under cooling to precipitate crystals which were collected by filtration. Recrystallization from *n*-hexane afforded 50 mg **13**, mp 90—91° (decomp.). [Lit.[3] mp 93° (decomp.).] IR ν_{max}^{KBr} cm^{-1}: 1708, 1489, 1436. NMR (in $CDCl_3$) δ: 4.19 (s, 2H, exchangeable with D_2O), 7.32—7.45 (m, 4H; 7.43, C_5–H), 7.74—7.92 (m, 2H), 9.57 (broad s, 1H, exchangeable with D_2O).

The filtrate was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated and the residue was purified by chromatography on SiO_2 to afford 26 mg of 2-methyl-4-phenylthiazole (**14**), mp 65°. (Lit.[4] mp 68.5°).

4-Phenylthiazole-2-acetamide (15)——A suspension of **12a** (145 mg) in a mixture of MeOH (3 ml) and aqueous NH_3 (15 ml) was stirred until the crystals were dissolved completely, and the resulted solution was allowed to stand at room temperature to precipitate white powders (86 mg), which was filtered and recrystallized from MeOH to yield 55 mg of **15**, mp—187.5°. IR ν_{max}^{KBr} cm^{-1}: 3350—3180, 1697, 1490, 1412,

1286. NMR (in DMSO-d_6) δ: 3.93 (s, 2H), 7.0—7.8 (m, 5H), 7.84 (s, 1H), 7.84—9.01 (m, 2H). *Anal.* Calcd. for $C_{11}H_{10}ON_2S$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.66; H, 4.90; N, 12.81.

Acknowledgement The authors are grateful to the members of the Central Analysis Room of this school for elemental analyses and NMR spectral measurement. This study was supported in part by a Grant-in-Aid Scientific Research from the Ministry of Education.