**Studies of Heterocyclic Compounds. V.¹⁾ Synthesis of 5,6-Dihydrothiazolo-
[2,3-*b*]thiazolium Salts and Their Reactions with Amines.
A New Synthesis of 2-Aminothiazoles²⁾**

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5,6-Dihydrothiazolo[2,3-*b*]thiazolium salts (**1a—d**) were synthesized from 2-mercaptothiazoline and α -haloketones. The reaction of **1** with a secondary amine gave 2-aminothiazole (**7a—l**) with the liberation of thiirane (**9**) *via* an unstable adduct, 7a-amino-2,3,5,6-tetrahydrothiazolo[2,3-*b*]thiazole (**8a—g**). The reaction of **1** with a primary amine afforded 3-(2-mercaptoethyl)-4-thiazolin-2-imine (**10**) and/or its disulfide (**11**). The reaction of **1** with an amine was concluded to be initiated by the attack of the reagent on C-7a.

In recent years the reactivity of the carbonium ions stabilized by three adjacent heteroatoms have been the subject of a lot of investigations and Nakai has classified the chemical properties of the systems with a carbonium ion adjacent to such heteroatoms as S, S,N; S,N,N; N,N,N; O,O,N; S,S,S; N,N,Cl; N,S,Cl⁵⁾ whereas almost no publication has appeared concerning the reactivity of the partially aromatized bicyclic system with a carbonium ion adjacent to S,S and N.⁶⁾

In connection with our research on the synthesis and the reactivity of pi-deficient heteroaromatic compounds four 5,6-dihydrothiazolo[2,3-*b*]thiazolium salts (**1**) have been prepared and the chemical properties, especially the reactions toward nucleophilic reagents, have been examined. As shown in Chart 1, the resonance formulae of the system suggest that the positions 1, 6, 7, and 7a are susceptible toward nucleophilic attack.

Chart 1

Since Bogolyubskaya and coworkers first synthesized **1a** and **1b** in 1966,⁷⁾ the preparation of quarternary salts (**1**) have been described in a few papers.^{6,8)} However, their chemical properties have not thoroughly been examined except alkaline hydrolysis of **1a**.

The synthesis of the 5,6-dihydrothiazolo[2,3-*b*]thiazolium salts (**1**) were carried out according to the reported method.⁶⁻⁸⁾

Treatment of 2-mercaptothiazoline (**2**) with 3-chloroacetylacetone (**3c**) in dimethylformamide at room temperature afforded **4c** as colorless crystals, which showed a red-brown

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- 2) Presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April, 1971.
- 3) To whom inquiries are to be sent.
- 4) Location: 1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.
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color with methanolic ferric chloride and showed carbonyl bands typical of 1,3-diketones at 1680—1557 cm^{-1} in the infrared (IR) spectrum and a singlet peak at δ 2.35 ppm (6H) in the nuclear magnetic resonance (NMR) spectrum. When the reaction was carried out at 70°, 5,6-dihydrothiazolo[2,3-*b*]thiazolium chloride (**1c**) was obtained quantitatively, which was also obtained from **4c**, by refluxing its ethanolic solution.

The structure of the aromatized bicyclic compound (**1c**) was confirmed by the two individual singlet peaks at δ 2.57 (3H) and 2.69 (3H) ppm in the NMR spectrum and by a sharp carbonyl band at 1680 cm^{-1} in the IR spectrum.

Treatment of **2** with ethyl 3-chloroacetoacetate (**3d**) afforded **1d** directly in quantitative yield. Thiazolium salts, (**1a**) and (**1b**), were synthesized from **2** and monochloroacetone (**3a**) and phenacylbromide (**3d**) respectively according to Bradsher's procedure.

Chart 2

Methanolic solution of **1c** was treated with piperidine (2eq. mole) to afford orange-yellow crystals, which did not show the presence of ethylene group of thiazoline moiety of **1** in the NMR spectrum. This compound offered good agreement with 5-acetyl-4-methyl-2-piperidinylthiazole (**7h**) which was synthesized through the route of Hantzsch thiazole synthesis⁹⁾ using 3-chloroacetylacetone and N,N-pentamethylenethiourea. It was thus proved that, on reaction of α -halo ketone with 2-mercaptothiazoline as well, the initial alkylation took place on the sulfur in stead of the nitrogen to give **1** and the alternative structure (**5**) was, therefore, ruled out. As we would expect, reactions of **1a**, **1b**, **1c**, and **1d** with dimethylamine, piperidine, and morpholine similarly furnished 2-N,N-disubstituted aminothiazoles (**7**) in good yield.

Chart 3

Compounds (**7a** and **7b**) were identified by comparing the spectroscopic data described in the literature.¹⁰⁾ The physical properties of **7** are summarized in Table I.

On reaction of **1c** and **1d** with secondary amines under controlled mild conditions unstable amine-adducts could be isolated, which were considered to be the precursor of the aromatized 2-aminothiazoles, **7c** and **7d** respectively. After an ice-cold methanolic solution of **1c** was

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TABLE I. Physical Properties of 2-Aminothiazole (7)

	R ¹	R ²	R ₂ N-	yield (%)	mp
7a	H	CH ₃	(CH ₃) ₂ N-	92	(oil)
7b	H	CH ₃	N-	61	(oil)
7c	H	CH ₃	N-	26	(oil)
7d	H	C ₆ H ₅	(CH ₃) ₂ N-	89	(oil)
7e	H	C ₆ H ₅	N-	96	71.5—72.5°
7f	H	C ₆ H ₅	N-	87	76—78.5°
7g	COCH ₃	CH ₃	(CH ₃) ₂ N-	77	64—65.5°
7h	COCH ₃	CH ₃	N-	80	74—76.5°
7i	COCH ₃	CH ₃	N-	84	149—150.5°
7j	COOC ₂ H ₅	CH ₃	(CH ₃) ₂ N-	76	35—39°
7k	COOC ₂ H ₅	CH ₃	N-	53	(oil)
7l	COOC ₂ H ₅	CH ₃	N-	49	101.5—102°

treated with one equivalent amount of dimethylamine for 5 minutes, addition of ice-water caused precipitation of the adduct **8a** in 54% yield. The A₂B₂ pattern of the methylene-protons on C₅ and C₆ of the starting thiazolium salt (**1**) was observed at around δ 4.06—4.87 ppm, whereas the spectrum of the adduct **8a** exhibited fairly complex peaks at the range of δ 2.81—4.82 ppm (4H), among which the peaks at δ 3.40 ppm (1H) and at δ 4.13 ppm (1H) were distinguishable as two separate octet signals. The Dreiding model of the molecule indicated that this bicyclo[2,2,0]octene system with the bridge-headed sp₃ carbon and nitrogen constituted rigid and convex configuration and that the two endo-protons at C₅ and C₆ were located perpendicularly upward over the pi-orbital of the C₂—C₃ double bond and the other two exo-protons were, on the other hand, far remote below from the orbital (Fig. 1). All the adduct **8** exhibited this sort of ABCD pattern in the NMR spectra. The structure of **8** was also confirmed by the mass spectroscopy. For example, **8c** exhibited peaks of m/e 286 (M⁺), 243 (M⁺—COCH₃), 226 (M⁺—S), and 200 (M⁺—N—O). The physical properties of **8** are summarized in Table II.

TABLE II. Physical Properties of 7a-Amino-4,5,6,8-tetrahydrothiazolo[2,3-b]thiazole (8)

	R ¹	R ²	R ₂ N-	yield(%)	mp	$\nu_{C=O}$ cm ⁻¹ (a)	δ C _{5,6} -H ^{b)} (center of octet)	
8a	COCH ₃	CH ₃	(CH ₃) ₂ N-	54.0	75—78°	1565	3.40	4.13
8b	COCH ₃	CH ₃	N-	69.5	86—87°	1553	3.41	4.17
8c	COCH ₃	CH ₃	N-	85.8	108—111.5°	1560	3.37	4.11
8d	CO ₂ C ₂ H ₅	CH ₃	(CH ₃) ₂ N-	81.5	80—83°	1593	3.41	— ^{c)}
8e	CO ₂ C ₂ H ₅	CH ₃	N-	83.9	88.5—89.5°	1582	— ^{c)}	— ^{c)}
8f	CO ₂ C ₂ H ₅	CH ₃	N-	92.5	114—115.5°	1583	— ^{c)}	— ^{c)}

a) in KBr disk

b) in deuteriochloroform

c) undistinguishable peaks

These intermediates **8** were smoothly converted into **1** by treatment with excess iodomethane or with 47% aqueous hydrobromic acid, whereas a solution of **8** in chloroform was allowed to stand at room temperature to furnish corresponding 2-N,N-disubstituted aminothiazole (**7**) with the liberation of thiirane (**9**) which was detected by NMR spectroscopy and gas chromatography; when the solution in deuterated chloroform was heated in a sealed tube for 10 minutes, in addition to the peaks due to **7a**, a singlet at δ 2.30 ppm due to ethylene group of thiirane was observed in the NMR spectrum (Fig. 1). After heating **8** in a sealed tube as a suspension in *n*-hexane, an aliquot amount was withdrawn and examined by the method of gas chromatography combined with mass spectrometry (GC-MS method). The retention time of the first peak (2.5 minutes on tricresyl phosphate column at 65°) was identical with that observed with the authentic specimen of thiirane, and the fragmentation pattern by electron impact agreed exactly with that of thiirane.¹¹⁾

Consequently it was proved that **7** was produced from **1** *via* the intermediate **8** with the elimination of thiirane (**9**), but in the case of $R^1=H$ the rate was too fast to isolate the intermediate **8**.

On reaction of **1c** with primary amines there were obtained 3-(2-mercaptoethyl)-thiazolin-2-imines (**10**) and/or the corresponding disulfides (**11**). The product-ratio varied owing to the applied amines and as well as to the reaction conditions. When a weak base such as aniline was used, the mercaptan (**10a**) was the only product isolated, which showed SH stretching vibration at 2520 cm^{-1} in the IR spectrum and showed a triplet at δ 1.47 ($J=9\text{ Hz}$, SH), a multiplet at δ 2.91 (2H, $-\text{CH}_2-\text{SH}$), and a double doublet at δ 4.06 (2H, $\text{N}-\text{CH}_2-\text{CH}_2$) ppm in the NMR spectrum. On oxidation with hydrogen peroxide it gave disulfide (**11a**) and on methylation with iodomethane at room temperature it gave **12a**, however, further reaction of **12a** in refluxing methanol with excess iodomethane for 2 hours yielded 2-acetyl-3-methyl-7-phenyl-2,3-dihydroimidazo[2,3-*b*]thiazolium iodide (**13**). When benzylamine was used, disulfide (**11b**) was the only product isolated and the corresponding mercaptan could not be isolated in spite of trials under various conditions. When methylamine was applied, on the contrary, either mercaptan (**10b**) or disulfide (**11c**) was selectively obtained by changing the reaction conditions: by stirring in methanolic solution at room temperature disulfide (**11c**), mp $131.5\text{--}133^\circ$, was obtained, whereas by stirring in an ice-cold mixture of water and chloroform mercaptan (**10b**) was obtained as a syrup from the chloroform-layer, which, on methylation with iodomethane in the presence of potassium carbonate, furnished crystalline methylsulfide (**12b**), mp $104\text{--}105^\circ$.

On the other hand, **1a** and **1b** did not react with aniline. They reacted with benzylamine to give disulfides (**11d**) and (**11e**) respectively. The spectroscopic data of these compounds were in good agreement with the assigned structures. As for the UV spectra, the curves of **10a**, **10b**, **11a**, **11b**, **11c**, **12a** and **12b** were almost superimposable on that of 5-acetyl-3-ethyl-4-methylthiazolin-2-ethylimine which was synthesized from 3-chloroacetylacetone and *sym*-

Fig. 1. a) NMR Spectrum (90MHz) of 2-Acetyl-7a-dimethylamino-3-methyl-4,5,6,8-tetrahydrothiazolo [2,3-*b*] thiazole (**8a**) (Right after Dissolving it in CDCl_3)
b) NMR Spectrum of the Same Solution after Keeping it at Room Temperature for 2 Hours

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Chart 4

diethylthiourea. The curves of **11d** and **11e** were analogous to those of 4-methyl- and 4-phenyl-3-alkyl-substituted thiazolin-2-alkylimine reported in the literature.¹⁰⁾

In the recent publications on the other systems of the carbonium ion adjacent to S,S,N like N,N-dimethyl-S,S'-dimethyldithiocarbamidium ion,¹²⁾ 2-dialkylamino-1,3-dithiolanylium ion,¹³⁾ 2,3,5,6-tetrahydrothiazolo[2,3-*b*]thiazolium ion,^{5,14)} and monocyclic S,N-disubstituted 2-mercaptothiazolium ion,^{5,15)} the position of the nucleophilic attack depends upon the used reagent: some nucleophiles including primary and secondary amines attack exclusively upon the carbonium ion and the others do not attack upon the same carbonium ion. In the case of the 5,6-dihydrothiazolo[2,3-*b*]thiazolium ion (**1**), a partially aromatized bicyclic system, the reaction of amines with (**1**) is now confirmed to be initiated by the attack of the reagent on the 7a-position of the polarized $>C=N^+$ bond to form an adduct and to proceed *via* *AE*-mechanism to yield 2-aminothiazole (**7**) with the liberation of thiirane.

Experimental¹⁶⁾

3-(2-Thiazolin-2-ylthio)-pentan-2,4-dione Hydrochloride (4c)—3-Chloroacetylacetone (538 mg) was added dropwise with stirring to a solution of 2-mercaptothiazoline (476 mg) in dimethylformamide (DMF) (5 ml). After stirring for 10 min, it was left aside at room temperature overnight. The resulted crystals were collected by filtration, washed with a small amount of EtOH to give hydrochloride (**4c**), 578 mg, 55.5%, mp 199–200.5° (decomp.). IR ν_{max}^{KBr} cm⁻¹: 2900, 2740, 1680, 1640, 1557, 1408, 1362, 1300, 1159. NMR (in DMSO-*d*₆) δ : 2.35 (6H, s), 3.47 (2H, double d), 4.28 (2H, double d), 6.55 (1H, s). Anal. Calcd. for: C₈H₁₂O₂NS₂Cl: C, 37.87; H, 4.73; N, 5.52. Found: C, 38.05; H, 4.84; N, 5.71.

2-Acetyl-3-methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Chloride (1c)—A solution of 2-mercaptothiazoline (2.38 g) and 3-chloroacetylacetone (2.79 g) in DMF (9 ml) was heated at 70° for 3.5 hr to deposit crystals. After cooling, the crystals were collected by filtration, washed with ether, and recrystallized from

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15) A.D. Clark and P. Sukes, *J. Chem. Soc.*, **1971**, 103.

16) All melting points were measured in capillary tubes and were uncorrected. NMR spectra were measured on a HITACHI R-20 60 MC spectrophotometer, using tetramethylsilane as the internal reference. IR and UV spectra were measured on a JASCO IRA-I spectrophotometer and on a HITACHI EPS-3 UV spectrophotometer, respectively. GC-MS method was carried out on a HITACHI RMS-4 mass spectrometer combined with a K53-gas spectrometer.

MeOH-ether to give **1c**, 3.53 g, 68.1%, mp 218° (decomp.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1680, 1560, 1410, 1380, 1350, 1160, 1040, 965. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 315.5 (14500), 270 sh (1400), 228.0 (5300). $\lambda_{\text{max}}^{5\% \text{ KOH}}$ nm (ϵ): 344.4 (13600). NMR (in DMSO-*d*₆) δ : 2.57 (3H, s), 2.69 (3H, s), 4.07 (2H, double d), 4.81 (2H, double d). Anal. Calcd. for C₈H₁₀ONS₂Cl: C, 40.76; H, 4.25; N, 5.94. Found: C, 40.59; H, 4.06; N, 6.10.

2-Ethoxycarbonyl-3-methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Chloride (1d)—A solution of 2-mercaptothiazoline (1.19 g) and ethyl 3-chloroacetoacetate (1.64 g) in DMF (5 ml) was allowed to stand at room temperature to separate crystals gradually. After standing for 3 days, the crystals were collected by filtration and ether was added to the filtrate to afford crystals. The crystals were combined, washed with ether, and recrystallized from EtOH-ether to give white needles, 840 mg, 69%, mp 185–185.5°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1720, 1605, 1390, 1292, 1190, 1110, 760. NMR (in DMSO-*d*₆) δ : 1.33 (3H, t), 2.69 (3H, s), 4.35 (2H, q), 4.87 (2H, double d), 4.06 (2H, double d). Anal. Calcd. for C₉H₁₂O₂NS₂Cl: C, 40.67; H, 4.52; N, 5.20. Found: C, 40.40; H, 4.78; N, 5.52.

2-Dimethylamino-4-methylthiazole (7a)—To a solution of **1a** (582 mg) in MeOH (20 ml) was added with stirring 30% aqueous dimethylamine (1.35 g). After 2 hr the solvent was evaporated, and the residue was taken up in H₂O and extracted with benzene. The benzene layer was dried, and evaporated to give **7a** as an oil, 390 mg, 92.2%. Picrate: mp 155–159°. Anal. Calcd. for C₆H₁₀N₂S·C₆H₃O₇N₃ (picrate): C, 38.82; H, 3.52; N, 18.87. Found: C, 38.73; H, 3.63; N, 18.48.

4-Methyl-2-piperidinylthiazole (7b)—To a solution of **1a** (714 mg) in MeOH (15 ml) was added piperidine (511 mg). After stirring for 4 hr at room temperature, the solvent was distilled off and the residue was extracted with chloroform. The chloroform layer was dried, and evaporated to give crude oil (460 mg). Chromatography on SiO₂ using chloroform gave **7b** as a pale yellow oil, 328 mg. Picrate: mp 147–149°. NMR (in CCl₄) δ : 1.63 (6H, broad s), 2.15 (3H, d), 3.2–3.55 (4H), 5.92 (1H, q). Anal. Calcd. for C₉H₁₄N₂S·C₆H₃O₇N₃ (picrate): C, 43.80; H, 4.17; N, 17.03. Found: C, 43.68; H, 4.15; N, 17.08.

4-Methyl-2-morpholinylthiazole (7c)—Morpholine (530 mg) was added with stirring to a solution of **1a** (714 mg) in MeOH (10 ml). After 30 minutes, solvent was distilled off and the residue was taken up in chloroform. The chloroform layer was washed with water and dried over MgSO₄. After removal of the solvent, the residual oil (260 mg) was purified by chromatography on SiO₂ to give **7c** as an oil, 130 mg, 25.5%. Picrate: mp 136–140°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 2940, 2890, 2840, 1646, 1505, 1448, 1383, 1306, 1118, 885. NMR (in CCl₄) δ : 2.19 (3H, d), 3.25–3.50 (4H, m), 3.61–3.82 (4H, m), 6.01 (1H, q). Anal. Calcd. for C₈H₁₂ON₂S·C₆H₃O₇N₃ (picrate): C, 40.68; H, 3.66; N, 16.95. Found: C, 40.72; H, 3.57; N, 17.03.

2-Dimethylamino-4-phenylthiazole (7d)—To a suspension of **1b** (299 mg) in EtOH (10 ml) was added dropwise with stirring 30% aqueous dimethylamine (450 mg), and stirring was continued for 2 hr. After evaporation, the residue was taken up in H₂O and extracted with chloroform. The chloroform layer, to which was added SiO₂ (1 g), was stirred for 1 hr. The insoluble material was removed by filtration and filtrate was concentrated to give 2-dimethylamino-4-phenylthiazole (**7d**) as a pale yellow oil, 270 mg, 89%. Picrate: mp 160–170 (decomp.). NMR (in CDCl₃) δ : 3.10 (6H, s), 6.57 (1H, s), 7.12–7.85 (5H, m). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 237, 265 sh, 289.5. $\lambda_{\text{max}}^{\text{H}^+}$ nm: 271. Anal. Calcd. for C₁₁H₁₂N₂S·C₆H₃O₇N₃ (picrate): C, 47.12; H, 3.49; N, 16.16. Found: C, 47.27; H, 3.70; N, 15.91.

4-Phenyl-2-piperidinylthiazole (7e)—To a suspension of **1b** (897 mg) in EtOH (5 ml) was added dropwise with stirring piperidine (1666 mg). After 2 hr the resulted solution was evaporated and the residue was taken up in H₂O and extracted with chloroform. The chloroform layer was dried, and evaporated to give white solid, which was crystallized from MeOH, 700 mg, 96%, mp 71.5–72.5°. Anal. Calcd. for C₁₄H₁₆N₂S: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.57; H, 6.49; N, 11.04.

2-Morpholinyl-4-phenylthiazole (7f)—To a suspension of **1b** (598 mg) in MeOH (5 ml) was added morpholine (348 mg) and the mixture was stirred for 2 hr. After evaporation, the residue was taken up in H₂O and extracted with chloroform. The chloroform layer was dried and distilled to give an oil (640 mg). Chromatography on SiO₂ using 5% MeOH in chloroform gave 2-morpholinyl-4-phenylthiazole, which was crystallized from benzene-*n*-hexane, 430 mg, 87%, mp 76–78.5°. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 237.5, 264 sh, 283 sh. $\lambda_{\text{max}}^{\text{H}^+}$ nm: 223, 273.5. Anal. Calcd. for C₁₃H₁₄ON₂S: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.10; H, 5.51; N, 11.15.

5-Acetyl-2-dimethylamino-4-methylthiazole (7g)—To a solution of **1c** (1.772 g) in MeOH (10 ml) 30% aqueous dimethylamine (3.6 g) was added dropwise over a period of 10 min. After stirring for 2.5 hr, the solvent was evaporated and the residue was extracted with chloroform. The chloroform layer was dried and evaporated to give yellow crystals, which were recrystallized from pet. ether, 830 mg, 77.3%, mp 64–65.5°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1645, 1560, 1480, 1410, 1360, 1305, 1265, 1025, 890. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 335.2 (22000), 224.6 (5800). $\lambda_{\text{max}}^{5\% \text{ HCl}}$ nm (ϵ): 302.6 (17500), 254.1 (6700), NMR (in CDCl₃) δ : 3.14 (6H, s), 2.56 (3H, s), 2.41 (3H, s). Anal. Calcd. for C₈H₁₂ON₂S: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.22; H, 6.35; N, 15.17.

5-Acetyl-4-methyl-2-piperidinylthiazole (7h)—To a solution of **1c** (221.5 mg) in 1:1 mixture of H₂O and EtOH (20 ml) piperidine (170 mg) was added and stirred for 30 min. After evaporation, the residue was obtained. Recrystallization from *n*-hexane gave the orange-red crystals, 180 mg, 80%, mp 74–76.5°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1603, 1483, 1323, 1312, 1264, 1239, 1120, 973, 906. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 335.2 (22000), 224.6 (5800). $\lambda_{\text{max}}^{5\% \text{ HCl}}$ nm (ϵ): 302.6 (17500), 254.1 (6700). NMR (in CDCl₃) δ : 1.65 (6H, broad s), 2.37 (3H, s), 3.52

(4H, broad s). *Anal.* Calcd. for $C_{11}H_{16}ON_2S$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.69; H, 7.14; N, 12.09.

5-Acetyl-4-methyl-2-morpholinylthiazole (7i)—Morpholine (260 mg) was added to a solution of **1c** (221.5 mg) in MeOH (15 ml). After stirring at room temperature for 24 hr, the solvent was evaporated and the residue was worked up in a usual manner to afford a syrupy mass, which was crystallized from benzene-*n*-hexane, 190 mg, 84%, mp 149.5–150°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1623, 1520, 1305, 1256, 1114, 925, 906, 876. UV $\lambda_{\max}^{MeOH}$ nm: 333.4, 225.5. $\lambda_{\max}^{5\% HCl}$ nm: 303.8, 259.0. NMR (in $CDCl_3$) δ : 2.42 (3H, s), 2.54 (3H, s), 3.42–3.65 (4H, m), 3.68–3.95 (4H, m). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2S$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.16; H, 6.20; N, 12.08.

5-Ethoxycarbonyl-4-methyl-2-dimethylaminothiazole (7j)—30% Aqueous dimethylamine (600 mg) was added to a solution of **1d** (849 mg) in EtOH (15 ml). After stirring for 4 hr the solvent was distilled off and the residue was dissolved in H_2O , extracted with chloroform, and dried over $MgSO_4$. After working-up in a usual manner, red oil obtained was purified by chromatography on SiO_2 using chloroform to give **7j** as an oil which solidified for standing, 490 mg, 76%, mp 35–39°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1706, 1565, 1550, 1534. UV $\lambda_{\max}^{MeOH}$ nm (log ϵ): 213.7 (3.91), 310 (4.29). $\lambda_{\max}^{5\% HCl}$ nm (log ϵ): 245 (3.59), 285.5 (4.20). NMR (in CCl_4) δ : 1.31 (3H, t), 2.46 (3H, s), 3.09 (6H, s), 4.18 (2H, q). *Anal.* Calcd. for $C_9H_{14}O_2N_2S$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.31; H, 6.36; N, 12.92.

5-Ethoxycarbonyl-4-methyl-2-piperidinylthiazole (7k)—To a suspension of **1d** (849 mg) in EtOH (20 ml) was added with stirring piperidine (510 mg) at room temperature. After crystals dissolved completely, the mixture was allowed to stand for 3 hr. After evaporation, the residue was dissolved in H_2O and extracted with chloroform. The chloroform layer was dried and evaporated. The residual red-brown syrupy mass was purified by chromatography on SiO_2 to give **7k** as an oil which solidifies in a refrigerator, 400 mg. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1699, 1537, 1452, 1324, 1300, 1280, 1257. NMR (in $CDCl_3$) δ : 1.30 (3H, t), 1.64 (6H, broad s), 2.52 (3H, s), 3.49 (4H, broad s), 4.23 (2H, q). *Anal.* Calcd. for $C_{12}H_{18}O_2N_2S$: C, 56.70; H, 7.12; N, 11.12. Found: C, 56.68; H, 7.14; N, 11.02.

5-Ethoxycarbonyl-4-methyl-2-morpholinylthiazole (7l)—Morpholine (522 mg) was added to a solution of **1d** (849 mg) in MeOH (10 ml). After stirring for 3 hr the reaction mixture was left overnight, evaporated, taken up in H_2O , and extracted with chloroform (10 ml $\times$ 3). After evaporation, the residue was purified by chromatography on SiO_2 using 2% MeOH in chloroform to give crystals, which were recrystallized from benzene-*n*-hexane, 350 mg, mp 101–102°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1695, 1540, 1384, 1341, 1301, 1272, 1125, 1108, 898. NMR (in $CDCl_3$) δ : 1.31 (3H, t), 2.53 (3H, s), 3.4–3.65 (4H), 3.7–3.95 (4H), 4.24 (2H, q). *Anal.* Calcd. for $C_{11}H_{16}O_3N_2S$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.46; H, 6.31; N, 10.98.

2-Acetyl-7a-dimethylamino-3-methyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8a)—To an ice cold solution of **1c** (665 mg) in MeOH (5 ml) was added with stirring 30% aqueous dimethylamine (900 mg). After stirring for 5 min in an ice-water bath, ice-water (10 ml) was added to the solution. After stirring for another 10 min, the resulted precipitate was filtered, washed with water, and dried to yield pale yellow powder, 630 mg, 85%. Recrystallization from benzene-*n*-hexane gave orange crystals, 400 mg, 54%, mp 75–78°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1615, 1565, 1256, 1364, 1318, 1207, 1086, 1002, 975. UV $\lambda_{\max}^{MeOH}$ nm (ϵ): 317 (10800), 226.2 (5800). $\lambda_{\max}^{5\% HCl}$ nm (ϵ): 319 (14900), 229 (5300). $\lambda_{\max}^{5\% KOH}$ nm (ϵ): 348 (13400). NMR (in $CDCl_3$) δ : 2.18 (3H, s), 2.32 (3H, s), 2.35 (6H, s), 2.96 (2H, m), 3.40 (1H, o), 4.13 (1H, o). *Anal.* Calcd. for $C_{10}H_{16}OS_2N_2$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.30; H, 6.56; N, 11.71.

2-Acetyl-3-methyl-7a-piperidinyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8b)—To an ice cold suspension of **1c** (886 mg) in EtOH (6 ml) was added dropwise with stirring piperidine (696 mg). After 5 min cold water was added to the reaction mixture until no more emulsifying occurred. The resulted white suspension was stirred for 5 min to precipitate completely. The precipitate was filtered, dried, and dissolved in benzene (4 ml), *n*-hexane (25 ml) was added to the solution, which was kept in a refrigerator to give orange-yellow crystals, **8b**, 790 mg, 69.5%, mp 86–87°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1655, 1643, 1553, 1420, 1381, 1363, 1289, 1275, 1236, 1165, 1116, 947. UV $\lambda_{\max}^{MeOH}$ nm (ϵ): 226.9 (5400), 268 sh, 1400, 319 (11500), 350 sh (5300). $\lambda_{\max}^{5\% KOH}$ nm (ϵ): 343.3 (14900). $\lambda_{\max}^{5\% HCl}$ nm (ϵ): 229 (4900), 318 (15000). NMR (in CCl_4) δ : 1.52 (6H, broad s), 2.18 (3H, s), 2.32 (3H, s), 2.4–3.05 (6H, m), 3.14 (1H, o), 4.17 (1H, o). *Anal.* Calcd. for $C_{13}H_{20}ON_2S_2$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.76; H, 6.88; N, 9.98.

After a solution of **8b** in CCl_4 in a sealed tube was allowed to stand at room temperature for 24 hr, it was shown by NMR spectrum that **8b** decomposed to give 5-acetyl-4-methyl-2-piperidinylthiazole (**7h**) and thiirane (**9**). NMR (in CCl_4) δ : 1.675 (6H, broad s), 2.35 (s, $\sqrt{S}$), 2.39 (3H, s), 2.53 (3H, s), 3.54 (4H, broad s).

2-Acetyl-3-methyl-7a-morpholinyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8c)—To an ice cold solution of **1c** (443 mg) in MeOH (5 ml) was added cold morpholine (348 mg). The reaction mixture was stirred for 20 min to separate pale yellow crystals. After stirring in ice-water for 30 min, the crystals were collected by filtration (300 mg, mp 86–88°). After concentration, the filtrate was dissolved in H_2O and extracted with chloroform. The chloroform layer was dried and evaporated to give crystals, 340 mg. The crystals were combined and recrystallized from benzene-*n*-hexane to yield orange-yellow crystals, 490 mg, 85.8%, mp 108–110°. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1620, 1560, 1438, 1359, 1303, 1270, 1149, 1135, 1113, 1060, 1006, 970, 898, 834, 782. UV $\lambda_{\max}^{MeOH}$ nm (ϵ): 226.8 (5400), 261.2 sh (1700), 315.5 (11300). $\lambda_{\max}^{5\% KOH}$ nm (ϵ): 353.4 (14900).

NMR (90 MHz): 2.12 (3H, s), 2.25 (3H, s), 2.30—2.56 (2H, m), 2.73—3.02 (4H, m), 3.37 (1H, o), 3.62 (4H, t), 4.11 (1H, o). Mass Spectrum m/e : 286 (M^+), 285 ($M^+ - 1$), 252 ($M^+ - H_2S$), 243 ($M^+ - COCH_3$), 226 ($M^+ - S$), 200 ($M^+ - N$). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2S$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.56; H, 6.09; N, 9.73.

5-Acetyl-4-methyl-2-morpholinylthiazole from 8c—A solution of **8c** (50 mg) in EtOH (5 ml) was refluxed for 5 hr. After evaporation, the residue was crystallized from benzene-*n*-hexane to give **7i**, 20 mg.

2-Acetyl-3-methyl-5,6-dihydrothiazolo[2,3-*b*]thiazolium Iodide (1c; X=I) from 8c—a) To a suspension of **8c** (286 mg) in MeOH (10 ml) was added CH_3I (1 g) to become soon clear solution. The reaction mixture was stirred for 30 min at room temperature to separate orange-red crystals. After stirring for another 2 hr, the crystals were isolated and recrystallized from EtOH to yield (**1c** X=I), 180 mg, mp 221—224° (decomp.). b) A solution of **8c** (100 mg) in 48% aqueous hydrobromic acid was heated at 140° for 2 hr. After cooling, the solvent was removed and co-evaporated with EtOH to furnish a mass which was crystallized from EtOH to yield (**1c**; X=Br), 55 mg.

2-Ethoxycarbonyl-7a-dimethylamino-3-methyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8d)—To an ice cold solution of **1d** (849 mg) in MeOH (10 ml) was added with stirring cold 30% aqueous dimethylamine (900 mg). After 5 min ice-water (5 ml) was added to deposit precipitate, which was collected by filtration, washed with water, and dried to give yellow powder, 760 mg. The powder was dissolved in benzene (4—7 ml) and filtered. To the filtrate *n*-hexane (25 ml) was added and the solution was kept in a refrigerator to give yellow crystals, 605 mg, 81.5%, mp 80—83°. IR ν_{max}^{KBr} cm^{-1} : 1690, 1593, 1384, 1363, 1275, 1159, 1082, 798, 760. NMR (in $CDCl_3$) δ : 1.28 (3H, t), 2.32 (3H, s), 2.38 (6H, s), 2.8—3.05 (2H, m), 3.41 (1H, o), 4.15 (3H, m). *Anal.* Calcd. for $C_{11}H_{18}O_2N_2S_2$: C, 48.17; H, 6.62; N, 10.21. Found: C, 48.38; H, 6.59; N, 10.40.

2-Dimethylamino-5-ethoxycarbonyl-4-methylthiazole (7j) from 8d—After a solution of **8d** in chloroform was allowed to stand at room temperature for 2 hr, the solvent was evaporated to give oil which crystallized in a refrigerator, in quantitative yield, mp 35—39°.

2-Ethoxycarbonyl-3-methyl-7a-piperidinyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8e)—To an ice-cold solution of **1d** (849 mg) in MeOH (10 ml) was added with stirring cold piperidine (510 mg) to deposit crystals. After 15 min, the crystals were collected by filtration, washed with water, and dried to give pale yellow powder, 790 mg, 83.9%, which was recrystallized from benzene-*n*-hexane to afford pale yellow prisms, 500 mg, mp 82—84°. IR ν_{max}^{KBr} cm^{-1} : 1679, 1582, 1390, 1368, 1276, 1160, 1113, 1068, 759. NMR (in $CDCl_3$) δ : 1.27 (3H, t), 1.52 (6H, broad s), 2.31 (3H, s), 2.5—3.6 (6H, m), 3.51 (1H, o), 4.16 (3H, m). *Anal.* Calcd. for $C_{14}H_{22}O_2N_2S_2$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.48; H, 6.94; N, 9.11.

2-Ethoxycarbonyl-3-methyl-7a-morpholinyl-4,5,6,8-tetrahydrothiazolo[2,3-*b*]thiazole (8f)—To an ice-cold solution of **1d** (849 mg) in MeOH (7 ml) was added with stirring cold morpholine (522 mg). After 7 min, white powder precipitated. After stirring for 20 min in an ice-water bath, the powder was collected by filtration, washed with a small amount of MeOH, and dried to give crude **8f**, 880 mg, 92%, mp 103°. Rapid recrystallization from MeOH gave yellow crystals, mp 114—115°. IR ν_{max}^{KBr} cm^{-1} : 1690, 1583, 1388, 1373, 1270. NMR (in $CDCl_3$) δ : 1.28 (3H, t), 2.31 (3H, s), 2.51—2.69 (2H, m), 2.76—3.10 (5H, m), 3.37 (1H, o), 3.61—3.76 (4H, m), 4.18 (2H, q). *Anal.* Calcd. for $C_{13}H_{20}O_3N_2S_2$: C, 49.36; H, 6.37; N, 8.86. Found: C, 49.11; H, 5.98; N, 8.76.

5-Acetyl-3-(2-mercaptoethyl)-4-methyl-4-thiazolin-2-phenylimine (10a)—Aniline (372 mg) was added to a solution of **1c** (443 mg) in MeOH (6 ml). After stirring for 8 hr, the solvent was distilled off to furnish crystalline residue, which was extracted with chloroform. The chloroform layer was dried and evaporated to give yellow solid, which, after recrystallization from EtOH- H_2O , yielded pale yellow prisms, 315 mg, 53.8%, mp 100—101°. IR ν_{max}^{KBr} cm^{-1} : 2520, 1610 sh, 1592, 1564, 1374, 1310, 1212, 1090, 990, 904, 784. UV λ_{max}^{MeOH} nm (log ϵ): 221 sh (4.41), 282 (3.91), 350.5 (4.07). $\lambda_{max}^{5\% HCl}$ nm (log ϵ): 261 (3.75), 308.5 (4.08). $\lambda_{max}^{5\% KOH}$ nm (log ϵ): 280 (3.92), 355.5 (4.14). NMR (in $CDCl_3$) δ : 1.47 (1H, t), 2.22 (3H, s), 2.61 (3H, s), 2.91 (2H, m), 4.06 (2H, double d), 6.85—7.50 (5H, m). *Anal.* Calcd. for $C_{14}H_{16}ON_2S_2$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.64; H, 5.48; N, 9.30.

Methylation of 10a—To a suspension of 5-acetyl-3-(2-mercaptoethyl)-4-methyl-4-thiazolin-2-phenylimine (242 mg) in MeOH (10 ml) was added K_2CO_3 (69 mg). After stirring for 5 min, iodomethane (284 mg) was added to the suspension and stirring was continued overnight. After evaporation, the residue was dissolved in H_2O and extracted with chloroform. The chloroform layer was dried and evaporated to give oily residue which was crystallized to leave **12a**, 275 mg, 90%, mp 55—58°. IR ν_{max}^{KBr} cm^{-1} : 1623 sh, 1610, 1558, 1405, 1300, 940, 776. UV λ_{max}^{MeOH} nm (log ϵ): 281 (3.92), 352 (4.10). $\lambda_{max}^{5\% HCl}$ nm (log ϵ): 224.0 sh (3.98), 256.6 sh (3.86), 306.4 (4.10). NMR (in $CDCl_3$) δ : 2.17 (3H, s), 2.24 (3H, s), 2.64 (3H, s), 2.88 (2H, double d), 4.15 (2H, double d), 6.9—7.4 (5H, m). *Anal.* Calcd. for $C_{15}H_{18}ON_2S_2$: C, 58.81; H, 5.92; N, 9.15. Found: C, 58.64; H, 6.04; N, 9.04.

Oxidation of 10a—To a solution of 5-acetyl-3-(2-mercaptoethyl)-4-methyl-4-thiazolin-2-phenylimine (100 mg) in MeOH (5 ml) was added 30% aqueous H_2O_2 (2 drops). The solution was left at room temperature to deposit crystals. After 8 hr yellow crystals were collected, **11a**, 35 mg, mp 125—127°. IR ν_{max}^{KBr} cm^{-1} :

1626 sh, 1610, 1566, 1406, 1362, 1290, 1080, 770. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 283.5, 352, $\lambda_{\text{max}}^{5\% \text{ HCl}}$ nm: 303. NMR (in CDCl_3) δ : 2.23 (3H, s), 2.61 (3H, s), 3.15 (2H, double d), 4.26 (2H, double d), 6.9–7.4 (5H, m). *Anal.* Calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_2\text{N}_4\text{S}_4$: C, 57.73; H, 5.19; N, 9.62. Found: C, 57.57; H, 5.26; N, 9.43.

5-Acetyl-4-methyl-3-(2-mercaptoethyl)-4-thiazolin-2-methylimine (10b)—To a stirred and cooled emulsion of **1c** (443 mg) in H_2O (10 ml) and chloroform (20 ml) 30% aqueous methylamine (412 mg) was added. After 15 min the aqueous layer was extracted with chloroform (15 ml $\times$ 3). The chloroform extracts were combined and washed with water, dried, and evaporated to give yellow viscous syrup, 470 mg, which was used for the next reaction without further purification.

Methylation of 10b—To an ice-cold solution of crude **10b** (470 mg) in MeOH (15 ml) were added iodomethane (383 mg) and K_2CO_3 (172 mg). After cooling with stirring for 1 hr, the reaction mixture was condensed and taken up in H_2O and extracted with chloroform. The chloroform layer was dried and evaporated to give orange-yellow oil, 500 mg, which was purified by column chromatography (2% MeOH in chloroform). Recrystallization from benzene-*n*-hexane gave **12b**, 120 mg, 24.5%, mp 104–105°. IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}): 1621, 1596, 1547, 1395, 1358, 1310, 1303, 1089, 978, 905. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 343.1 (12400), 252.5 (6000). $\lambda_{\text{max}}^{5\% \text{ HCl}}$ nm (ϵ): 299.0 (13500), 249.0 (3300). NMR (in CDCl_3) δ : 2.13 (3H, s), 2.31 (3H, s), 2.60 (3H, s), 2.78 (2H, double d), 3.00 (3H, s), 3.98 (2H, double d). *Anal.* Calcd. for $\text{C}_{10}\text{H}_{16}\text{ON}_2\text{S}_2$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.44; H, 6.44; N, 11.30.

Di-2-(5-acetyl-4-methyl-2-benzylimino-4-thiazolin-3-yl)-ethylidisulfide (11b)—When benzylamine (644 mg) was added to a suspension of **1c** (443 mg) in MeOH (5 ml), a clear solution was obtained instantly. The reaction mixture was stirred for 5 hr at room temperature to deposit crystals. After another 1 hr the resulting crystals were collected by filtration (220 mg, mp 99–104°) and the filtrate was condensed to dryness, washed with water, and dried to give crude crystals, 345 mg. The crystals were combined and recrystallized from EtOH, 428 mg, 69.8%, mp 103–105°. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{18}\text{ON}_2\text{S}_2$: C, 58.81; H, 5.92; N, 9.15. Found: C, 59.00; H, 5.77; N, 9.14.

Di-2-(5-acetyl-2-methylimino-4-thiazolin-3-yl)-ethylidisulfide (11c)—To an ice-cold solution of **1c** which, (443 mg) was added 30% aqueous methylamine (412 mg). The solution deposited white precipitate instantly, after cooling with stirring for 30 min, were collected by filtration to give crude **11c**, 390 mg, mp 131.5–133°. Recrystallization from chloroform-*n*-hexane afforded pure sample **11c**, mp 134–135°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1638, 1620, 1400, 1363, 1300, 1278, 1060, 950. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 244 sh, 342.5. $\lambda_{\text{max}}^{\text{H}^+}$ nm: 256, 295. NMR (in CDCl_3) δ : 2.30 (3H, s), 2.57 (3H, s), 2.97 (3H, s), 2.98 (2H), 4.07 (2H, double d). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{N}_4\text{S}_4$: C, 47.16; H, 5.72; N, 12.22. Found: C, 46.92; H, 5.82; N, 11.94.

Di-2-(2-benzylimino-4-methyl-4-thiazolin-3-yl)-ethylidisulfide (11d)—Benzylamine (214 mg) was added to a solution of **1a** (194 mg) in MeOH (15 ml). After stirring at room temperature for 3 hr, the resulted white crystals were collected by filtration to give crude **11d**, 190 mg, 72%, mp 117–118.5°. Recrystallization from EtOH gave pure **11d**, 180 mg, mp 120–121.5°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1628, 1600, 1343, 740. *Anal.* Calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_4\text{S}_4$: C, 59.31; H, 5.74; N, 10.64. Found: C, 59.05; H, 5.80; N, 10.33.

Di-2-(2-benzylimino-4-phenyl-4-thiazolin-3-yl)-ethylidisulfide (11e)—Benzylamine (428 mg) was added to a solution of **1b** (600 mg) in MeOH (5 ml). The solution was stirred at room temperature to separate syrupy mass. After 1 hr the supernatant solution was decanted and the mass was washed with MeOH (5 ml $\times$ 3) and purified by chromatography on SiO_2 using 5% MeOH in chloroform to give **11e** as viscous oil, 400 mg, 61.7%. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 257, 305 sh, $\lambda_{\text{max}}^{\text{H}^+}$ nm: 264. NMR (in CCl_4) δ : 2.61 (2H, m), 3.79 (2H, m), 4.20 (2H, s), 5.61 (1H, s), 7.2–7.4 (5H, m). *Anal.* Calcd. for $\text{C}_{36}\text{H}_{34}\text{N}_4\text{S}_4$: N, 8.61. Found: N, 8.44.

6-Acetyl-5-methyl-7-phenyl-2,3-dihydroimidazo[2,3-*b*]thiazolium Iodide (13)—To a methanolic solution of **12a** (310 mg) was added iodomethane (2 g) and the mixture was refluxed for 2 hr. After cooling iodomethane (1 g) was added again and the mixture was refluxed for 1 hr. The solvent was evaporated to give the crude **13** which was recrystallized from EtOH-ether, 240 mg, 61.2%, mp 235.5–237°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1650, 1583, 1529, 1305, 780. NMR (in $\text{DMSO}-d_6$) δ : 2.57 (3H, s), 2.67 (3H, s), 3.77 (2H, m), 4.78 (2H, m), 7.3–7.65 (5H, m). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{15}\text{ON}_2\text{SI}$: C, 43.53; H, 3.91; N, 7.25. Found: C, 43.23; H, 3.88; N, 7.16.

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