Studies on Bi-heterocyclic Compounds. II.[1] 5-Substituted Thiazolones[2]

Hiroaki YAMAZAKI,* Hidenori HARADA, Kenichi MATSUZAKI, Kimitomo YOSHIOKA, Muneaki TAKASE, and Eiji OHKI

Research Laboratory, Zenyaku Kogyo Co., Ltd., 33-7, Ohizumimachi 2-chome, Nerima-ku, Tokyo 178, Japan. *Received June 3, 1989*

Reactions of 4-methyl-2(3*H*)-thiazolones (5) with various *N*-alkoxycarbonyl pyridinium salts (6a—f) led to (*N*-alkoxycarbonyl dihydropyridyl)thiazolones (7a—f), oxidation of which yielded a new class of 5-pyridylthiazolones (8a—f). These reactions were applied to the synthesis of other azaarylthiazolones. Some of these azaarylthiazolones, particularly 5-(4-pyridyl)thiazolones (8b, c) and 5-(4-quinolyl)thiazolones (14a, b), showed positive inotropic activity with little chronotropic effect on guinea pig left atria.

Keywords thiazolone; dihydropyridine; dihydropyridylthiazolone; pyridylthiazolone; *N*-acylpyridinium salt; oxidation; positive inotropic activity; congestive heart failure; bi-heterocyclic compound

In the preceding paper[1] we reported the synthesis and inotropic activities of various 6-pyridylthiazinones (**1**) which were easily prepared by the reaction of 5-methyl-2*H*-1,4-thiazinones (**2**) with *N*-alkoxycarbonyl pyridinium salts (**3**) followed by oxidation of the resulting 6-(*N*-alkoxycarbonyl dihydropyridyl)thiazinones (**4**). From these results, we assumed that other heterocyclic compounds containing an ene-amide structure like that of **2** in the skeleton might also be attacked by pyridinium cations. During our extensive synthetic study on dihydrothiazinones or thiazolones, it was found that **5** also undergoes electrophilic substitution reactions at the 5-position to give **7a**—**f**. We report here the synthesis of various 5-substituted thiazolones by the use of the same reactions. Some of the 5-substituted thiazolones thus obtained showed a potent positive inotropic activity with little chronotropic effect on guinea pig left atria.

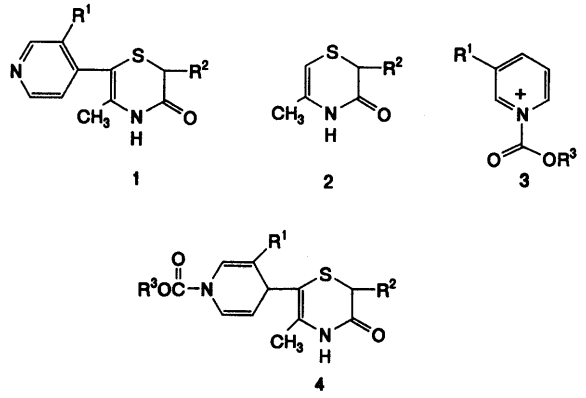

Chart 1

4-Methyl-2(3*H*)-thiazolone (**5**) was prepared by the method of Tcherniac[3] and was treated with 2,2,2-trichloroethyl chloroformate and pyridine in acetonitrile. The reaction proceeded smoothly at room temperature to afford **7a** in 31% yield. The infrared (IR) spectrum of **7a** exhibited absorptions at 1730 and 1680 cm^{-1}, indicating the presence of urethane and amide carbonyl moieties, respectively. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **7a** showed a singlet at δ 2.06 due to the 4-methyl protons. In addition, the absence of the signal due to the 5-proton at δ 5.60 suggests the existence of a 5-substituent in **7a**. Further, a doublet at δ 6.95 with a coupling constant (J) of 8.8 Hz may be ascribed to H-2 and H-6 of the α,β-unsubstituted dihydropyridine ring, reflecting the 4-substituted 1,4-dihydropyridine structure of **7a**. The signals of H-3 and H-5 of the dihydropyridine appear as a multiplet at δ 4.77—5.03 (4H), which overlaps with signals due to the methylene protons of the trichloroethyl group, while the H-4 signal appears as a multiplet at δ 4.28.

The yield of **7a** was modest compared with that of **4** ($R^1=R^2=H$, $R^3=Cl_3CCH_2$–)[1] but this reaction proceeded regioselectively without formation of the possible 2-pyridyl isomers and unchanged **5** was easily recovered from the water-soluble part of the reaction products.

These results indicate that **5** and 2*H*-1,4-thiazinones (**2**)[4] have similar reactivity to pyridinium cations. Compound **7a** thus obtained was readily oxidized with sulfur at 140—150 °C to provide **8a** in 62% yield. The structure of **8a** was assigned on the basis of spectral evidence. The IR spectrum of **8a** lacked the absorption due to the urethane group. The

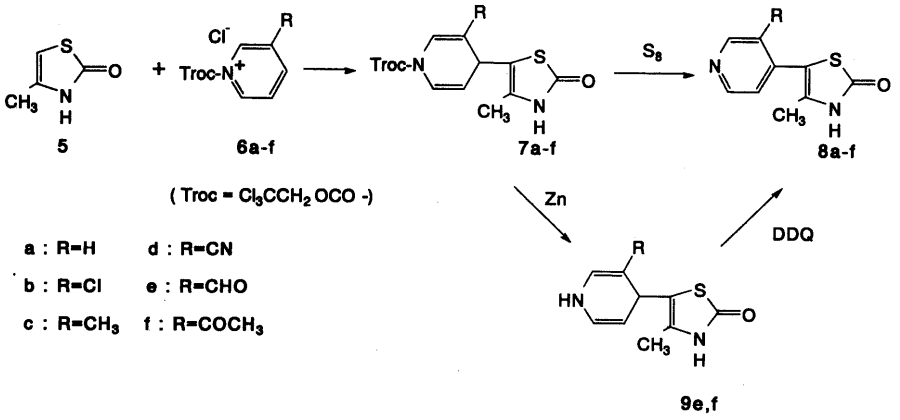

Chart 2

presence of a 4-substituted pyridine ring in **8a** was shown by its ^{1}H-NMR signals at δ 7.31 (2H, J=4.4 Hz, H-3 and H-5) and δ 8.55 (2H, J=4.4 Hz, H-2 and H-6).

When using 3-substituted pyridines, such as 3-chloro-, 3-methyl-, 3-cyano-, 3-formyl- and 3-acetylpyridine, the corresponding 5-[1,4-dihydro-3-substituted-1-(2,2,2-trichloroethoxycarbonyl)-4-pyridyl]thiazolones (**7b—f**) were obtained. Oxidation of **7b—d** with sulfur provided the corresponding 3-substituted pyridylthiazolones (**8b—d**). On the other hand, the 3-formyl and 3-acetyl derivatives (**7e** and **7f**) were treated with sulfur to give a complex tar from which no desired product could be isolated. Treatment of **7e** and **7f** with zinc powder in aqueous tetrahydrofuran (in the case of **7f**, at pH 4—5) afforded 1,4-dihydropyridyl thiazolones (**9e** and **9f**, respectively). The structures of **9e** and **9f** were confirmed by the absence of the urethane absorption in the IR. These dihydropyridine compounds **9e** and **9f** were readily oxidized by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in acetonitrile to give **8e** and **8f**, respectively. As shown above, it seems that the latter procedure *via* *N*-dealkoxycarbonylation with zinc followed by aromatization with DDQ is advantageous when an electron-attracting group is substituted on the pyridine ring.

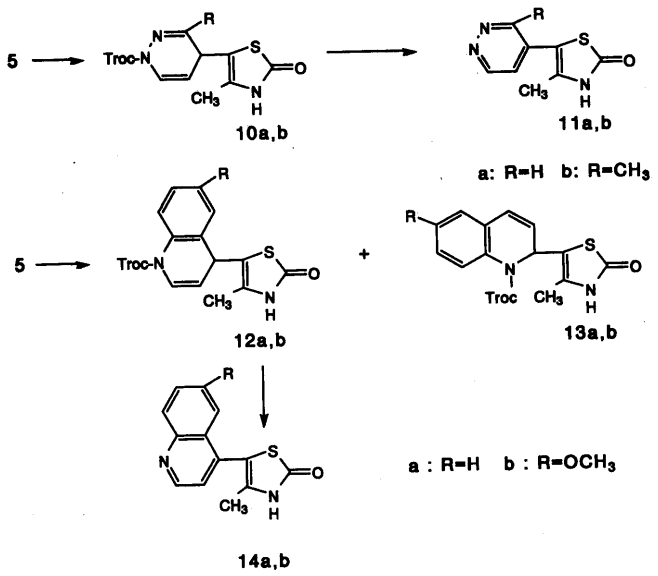

Chart 3

Next, we examined the substitution reaction of **5** with pyridazinium and quinolinium salts derived from other heterocycles such as pyridazine and quinoline. An analogous treatment of **5** with pyridazine or 3-methyl pyridazine in the presence of 2,2,2-trichloroethyl chloroformate gave the dihydropyridazinylthiazolones (**10a** and **10b**), and oxidation of these compounds with sulfur provided the 5-pyridazinylthiazolones (**11a** and **11b** respectively). The ^{1}H-NMR spectra of **11a** and **11b** confirmed these structures.

Different from these regiospecific substitutions, the reaction of **5** with quinolinium cation gave a mixture of (1,4-dihydro-4-quinolyl)thiazolone (**12a,b**) and (1,2-dihydro-2-quinolyl)thiazolone (**13a,b**) in a ratio of 1:3. The ^{1}H-NMR spectrum of **12a** showed a doublet at δ 4.78 (J=4 Hz) due to H-4, a doublet of doublets at δ 5.44 (J=4, 8 Hz) due to H-3, and multiplets at δ 7.10—7.58 due to H-2 and aromatic protons. Further oxidation of **12a** gave 4-quinolylthiazolone **14a**, whose ^{1}H-NMR spectrum showed a doublet at δ 7.53 (J=4.4 Hz) due to H-3 and a doublet at δ 8.94 (J=4.4 Hz) due to H-2, supporting the 4-substituted quinoline structure in **14a**. The ^{1}H-NMR spectrum of the isomeric dihydroquinolylthiazolone **13a** showed a doublet at δ 6.67 (J=9 Hz) due to H-4, a doublet of doublets at δ 6.07 (J=6, 9 Hz) due to H-3 and a doublet at δ 6.30 (J=6 Hz) due to H-2.

Biological Results

We reported previously[1] that pyridylthiazinones (**1**) were found to have a potent inotropic activity on the left atria of guinea pig. The structural similarity of the bi-heterocyclic compounds described above prompted us to study their pharmacological properties, particularly in regard to cardiac activity.

We tested these compounds preliminarily for inotropic activity using the isolated left atria of guinea pig. The results of this screening are given in Table I. Several thiazolone derivatives, **8a—c**, **11a—b** and **14a—b**, showed potent inotropic activity. Replacement of the 3-substituent on the pyridine ring in **8a** by an electron-attracting group such as formyl, cyano or acetyl, reduced the activity. From these results of preliminary screening, compounds **8a—c**, **11a—b** and **14a—b** were selected for further pharmacological evaluation.

TABLE I. Effects of Thiazolone Derivatives on Developed Tension on the Guinea Pig Left Atrium[a]

Compd.[b]	Change in developed tension[c] (mg)
8a	313± 13
8b	694±130
8c	550± 52
8d	134± 39
8e	120± 71
8f	102±100
11a	525±155
11b	400±130
14a	672± 96
14b	520± 99

a) Suspended in Krebs–Henseleit solution bubbled with 95% O_2 and 5% CO_2 at 30 °C. *b*) Concentration, 10^{-4} M in HCl. *c*) The left atrium, whose resting tension was adjusted to 500 mg, was stimulated by square pulses of 5-ms duration, at a voltage of 20% above the threshold and a stimulating rate of 0.5 Hz. Contractive forces were measured as absolute changes in developed tension.

Experimental

Melting points were determined on a Yamato MP-1 apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL FX-270 spectrometer with tetramethylsilane as the reference, and IR spectra were recorded on a Hitachi 260-10 spectrometer. The results of detailed characterization (yields, elemental analyses, IR, and ^{1}H-NMR spectra) of the bi-heterocyclic compounds reported here are summarized in Tables II and III. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel 60F_{254} precoated, layer thickness 0.2 mm (E. Merck) and spots were detected under ultraviolet (UV) irradiation. Column chromatography was done on Wakogel C-200 and the developing solvents are shown in parentheses. Zinc powder, sulfur, and DDQ used in the present work were obtained commercially and used without further purification. 4-Methyl-2(3*H*)-thiazolone (**5**) was prepared from chloroacetone and potassium thiocyanate by the procedure developed by Tcherniac.[3]

4-Methyl-5-[1,4-dihydro-1-(2,2,2-trichloroethoxycarbonyl)-4-pyridyl]-2(3*H*)-thiazolone (7a) and Its Analogs 7b—f As a typical example, the preparation of **7a** is described. 2,2,2-Trichloroethyl chloroformate (4.68 g, 22 mmol) was added dropwise to a stirred solution of pyridine (1.6 g, 20 mmol) in dry acetonitrile (20 ml) at 0 °C and the mixture was stirred at the

TABLE II. Data for (1,4-Dihydro-4-pyridyl)thiazolones

Compd.	mp (°C) Solvent	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ[a]	Analysis (%) Calcd (Found) C	H	N	Formula	Yield (%)
7a	174—175 EtOH	3200, 3060, 1730, 1680, 1640	2.06 (3H, s), 4.28 (1H, m), 4.77—5.03 (2H+2H, m), 6.95 (2H, d, J=8.8 Hz), 9.72 (1H, s)	38.99 (38.73	2.99 2.96	7.57 7.51)	$C_{12}H_{11}Cl_3N_2O_3S$	31
7b	181—183 EtOH	3190, 3060, 2880, 1730, 1670, 1640	2.11 (3H, s), 4.40 (1H, d, J=4 Hz), 4.78—5.11 (2H+1H, m), 6.97 (1H, s), 7.17 (1H, d, J=8.3 Hz), 9.89 (1H, s)	35.66 (35.46	2.49 2.41	6.93 6.82)	$C_{12}H_{10}Cl_4N_2O_3S$	66
7c	173—174 EtOH	3170, 3050, 2880, 1730, 1700, 1650	1.64 (3H, s), 2.08 (3H, s), 4.09 (1H, d, J=3 Hz), 4.76—5.01 (2H+1H, m), 6.77 (1H, d, J=8.3 Hz), 6.94 (1H, d, J=8.3 Hz), 9.61 (1H, s)	40.69 (40.55	3.32 3.39	7.30 7.27)	$C_{13}H_{13}Cl_3N_2O_3S$	26
7d	139—140 EtOH	3150, 3030, 2870, 2225, 1740, 1650	2.17 (3H, s), 4.53 (1H, d, J=4 Hz), 4.96 (2H, s), 5.19 (1H, dd, J=4, 8 Hz), 7.04 (1H, d, J=8 Hz), 7.69 (1H, s), 10.35 (1H, s)	39.56 (39.73	2.55 2.51	10.64 10.59)	$C_{13}H_{10}Cl_3N_3O_3S$	61
7e	185—186 EtOH	3290, 3080, 2850, 1740, 1670, 1610	2.18 (3H, s), 4.63 (1H, d, J=5 Hz), 5.03 (2H, s), 5.33 (1H, dd, J=5, 8 Hz), 7.08 (1H, dd, J=2, 5 Hz), 7.90 (1H, d, J=2 Hz), 9.53 (1H, s), 10.21 (1H, s)	39.26 (39.40	2.78 2.84	7.04 7.12)	$C_{13}H_{11}Cl_3N_2O_4S$	30
7f	170.5—171.5 EtOH	3240, 1750, 1680	2.25 (3H, s), 2.33 (3H, s), 4.66 (1H, d, J=5 Hz), 4.95 (2H, s), 5.30 (1H, dd, J=5, 8 Hz), 7.05 (1H, d, J=8 Hz), 8.05 (1H, s), 10.00 (1H, s)	40.84 (40.62	3.18 3.16	6.80 6.87)	$C_{14}H_{13}Cl_3N_2O_4S$	48
10a	138—140 ab. EtOH	3200, 3050, 1750, 1670	2.10 (3H, s), 4.15 (1H, d, J=4.9 Hz), 4.94 (2H, s), 5.05 (1H, dd, J=4.9, 8.3 Hz), 6.90 (1H, s), 7.19 (1H, d, J=8.3 Hz), 9.95 (1H, s)	35.64 (35.56	2.71 2.73	11.33 11.25)	$C_{11}H_{10}Cl_3N_3O_3S$	55
10b	85—87 ab. EtOH	3200, 3050, 1730, 1660	1.92 (3H, s), 2.01 (3H, s), 4.38 (1H, d, J=4.4 Hz), 5.05 (2H, s), 5.17 (1H, dd, J=4.4, 8 Hz), 7.15 (1H, d, J=8 Hz), 11.05 (1H, s)[b]	37.46 (37.22	3.14 3.11	10.92 10.79)	$C_{12}H_{12}Cl_3N_3O_3S$	57
12a	>120[c]	3160, 3030, 2950, 2860, 1730, 1650	2.16 (3H, s), 4.78 (1H, d, J=4 Hz), 4.99 (2H, s), 5.44 (1H, dd, J=4, 8 Hz), 7.10—7.58 (3H+1H, m), 8.07—8.30 (1H, m), 10.28 (1H, s)	45.78 (45.80	3.12 3.02	6.67 6.80)	$C_{16}H_{13}Cl_3N_2O_3S$	24
12b	187—189 EtOH	3200, 2950, 2850, 1720, 1650, 1620	2.14 (3H, s), 3.78 (3H, s), 4.70 (1H, d, J=4 Hz), 4.93 (2H, s), 5.34 (1H, dd, J=4, 8 Hz), 6.62 (1H, d, J=3 Hz), 6.85 (1H, dd, J=3, 9 Hz), 7.21 (1H, d, J=8 Hz), 8.07 (1H, d, J=9 Hz), 10.06 (1H, s)	45.40 (45.41	3.36 3.43	6.23 6.11)	$C_{17}H_{15}Cl_3N_2O_4S$	24
13a	197—199.5 EtOH	3140, 3030, 2860, 1710, 1660	2.19 (3H, s), 4.93 (2H, ABq, J=12 Hz), 6.07 (1H, dd, J=6, 9 Hz), 6.30 (1H, d, J=6 Hz), 6.67 (1H, d, J=9 Hz), 7.11—7.79 (4H, m), 10.39 (1H, s)	45.78 (45.88	3.12 3.11	6.67 6.73)	$C_{16}H_{13}Cl_3N_2O_3S$	60
13b	194.5—196 EtOH	3150, 3010, 2960, 2880, 1700, 1635	2.20 (3H, s), 3.85 (3H, s), 4.91 (2H, ABq, J=12 Hz), 6.10 (1H, dd, J=6, 9 Hz), 6.30 (1H, d, J=6 Hz), 6.65 (1H, d, J=9 Hz), 6.81 (1H, d, J=2 Hz), 6.89 (1H, dd, J=2, 9 Hz), 7.60 (1H, d, J=9 Hz), 10.16 (1H, s)	45.40 (45.14	3.36 3.71	6.23 5.87)	$C_{17}H_{15}Cl_3N_2O_4S$	32

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. *b*) Measured as a solution in DMSO-d_6. *c*) Purified by column chromatography.

same temperature for 5 min. Then, **5** (2 g, 17.4 mmol) was added portionwise and the mixture was stirred at 0 °C for 40 min and successively at room temperature for 3.5 h. The resulting precipitates were collected, washed with acetonitrile and recrystallized from EtOH to give **7a** (2 g, 31%) as colorless needles, mp 174—175 °C. The spectral data and elemental analyses are given in Table II. By using 3-substituted pyridine, compounds **7b**—**f** were obtained in the same manner as above. In these cases, products were purified by column chromatography on silica gel (ethyl acetate–hexane) prior to recrystallization. Their melting points, yields, spectral data and elemental analyses are given in Table II.

4-Methyl-5-(4-pyridyl)-2(3*H*)-thiazolone (8a) and Its Analogs 8b—d As a typical example, the preparation of **8a** is described. A mixture of **7a** (12.5 g, 33.8 mmol), sublimed sulfur (7 g, 218.8 mmol) and dimethylformamide (DMF) (87 ml) was refluxed for 1 h. The mixture was concentrated *in vacuo*, and then the residue was extracted with 2 N HCl solution (40—50 ml). The insoluble material was filtered off. The filtrate was washed with $CHCl_3$ and neutralized with 2 N NaOH solution below 0 °C. The resulting precipitates were collected, washed with water and recrystallized from EtOH with the use of active carbon to give **8a** (4 g, 61.5%) as pale yellow prisms, mp 269—271 °C. Compounds **8b**—**d** were also obtained in the same manner. In these cases, the products were purified by column chromatography on silica gel, using ethyl acetate–hexane or $CHCl_3$–MeOH as the eluant, followed by recrystallization. The melting points, yields, spectral data and elemental analyses are given in Table III.

5-(3-Formyl-4-pyridyl)-4-methyl-2(3*H*)-thiazolone (8e) A mixture of **7e** (398 mg, 1.0 mmol), zinc powder (327 mg, 5.0 mmol) and tetrahydrofuran (THF)–H_2O (1 ml, 1 : 1, v/v) was refluxed for 45 min. After cooling, the insoluble materials were filtered off and the filtrate was extracted twice with ethyl acetate. The combined extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$–hexane) and recrystallized from MeOH to give 5-(3-formyl-1,4-dihydro-4-pyridyl)-4-methyl-2(3*H*)-thiazolone (**9e**) (187 mg, 84%) as pale yellow needles, mp 180.5—182.5 °C. IR (KBr): 3350, 3180, 3060, 1640, 1630, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.99 (3H, s), 4.51 (1H, d, J=5 Hz), 4.79 (1H, dd, J=5, 8 Hz), 6.22 (1H, dd, J=5, 8 Hz), 7.23 (1H, d, J=5 Hz), 8.95 (1H, br), 9.05 (1H, s), 10.66 (1H, s).

A suspension of **9e** (240 mg, 1.08 mmol) and DDQ (245 mg, 1.08 mmol) in acetonitrile (25 ml) was stirred at room temperature for 15 min. The mixture was evaporated to dryness *in vacuo*, the residue was extracted with 2 N HCl solution and the insoluble materials were filtered off. The filtrate was washed with ethyl ether and neutralized with 2 N NaOH solution, and then the resulting precipitates were extracted twice with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Recrystallization from EtOH gave **8e** (182 mg, 76.9%) as pale yellow needles, mp 225—226 °C. The spectral data and elemental analyses are given in Table III.

TABLE III. Data for 5-Substituted Thiazolones

Compd.	mp (°C) Solvent	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)[a]	Analysis (%) Calcd (Found) C	H	N	Formula	Yield (%)
8a	269—271 EtOH	3450, 3000, 1670, 1590, 1570	2.25 (3H, s), 7.31 (2H, dd, J=1.5, 4.4 Hz), 8.55 (2H, d, J=4.4 Hz), 11.60 (1H, s)[b]	56.23 (56.02	4.19 4.11	14.57 14.48)	$C_9H_8N_2OS$	62
8b	199—200.5 EtOH	3010, 1670, 1620, 1580	1.99 (3H, s), 7.50 (1H, d, J=4.9 Hz), 8.55 (1H, d, J=4.9 Hz), 8.72 (1H, s), 11.63 (1H, s)	47.68 (47.64	3.11 3.06	12.36 11.96)	$C_9H_7ClN_2OS$	58
8c	203.5—205 EtOH	3000, 1600, 1590	1.90 (3H, s), 2.26 (3H, s), 7.27 (1H, d, J=4.9 Hz), 8.41 (1H, d, J=4.9 Hz), 8.51 (1H, s), 11.45 (1H, br)	58.22 (57.98	4.88 4.85	13.58 13.32)	$C_{10}H_{10}N_2OS$	80
8d	257—258 EtOH	3010, 2220, 1695, 1580	2.09 (3H, s), 7.60 (1H, d, J=5.4 Hz), 8.83 (1H, d, J=5.4 Hz), 9.06 (1H, s), 11.80 (1H, br)	55.28 (55.27	3.24 3.21	19.34 18.99)	$C_{10}H_7N_3OS$	31
8e	225—226 EtOH	2990, 1675, 1620, 1595	1.93 (3H, s), 7.51 (1H, d, J=5.4 Hz), 8.80 (1H, d, J=5.4 Hz), 8.97 (1H, s), 10.12 (1H, s), 11.70 (1H, br)	54.53 (53.98	3.66 3.67	12.72 12.47)	$C_{10}H_8N_2O_2S$	77
8f	198—199 ab. EtOH	3000, 1690, 1620	1.88 (3H, s), 2.47 (3H, s), 7.45 (1H, d, J=5 Hz), 8.71 (1H, d, J=5 Hz), 8.88 (1H, s), 11.51 (1H, s)	56.39 (56.24	4.30 4.30	11.95 11.92)	$C_{11}H_{10}N_2O_2S$	23
11a	245—247 EtOH	3000, 1670	2.31 (3H, s), 7.58 (1H, dd, J=2.4, 5.4 Hz), 9.16 (1H, dd, J=1.0, 5.4 Hz), 9.23 (1H, dd, J=1.0, 2.4 Hz), 11.80 (1H, s)	49.72 (49.70	3.65 3.59	21.75 21.54)	$C_8H_7N_3OS$	19
11b	248—249 EtOH	3000, 2840, 2710, 1660	1.94 (3H, s), 2.26 (3H, s), 7.58 (1H, d, J=5.4 Hz), 9.11 (1H, d, J=5.4 Hz), 11.60 (1H, s)	52.15 (52.25	4.37 4.41	20.27 20.26)	$C_9H_9N_3OS$	47
14a	237—238.5 EtOH	3000, 2830, 2700, 1680, 1620, 1570	1.94 (3H, s), 7.53 (1H, d, J=4.4 Hz), 7.68 (1H, dd, J=7.8, 8.3 Hz), 7.83 (1H, dd, J=7.8, 8.3 Hz), 8.04 (1H, d, J=8.3 Hz), 8.11 (1H, d, J=8.3 Hz), 8.94 (1H, d, J=4.4 Hz), 11.69 (1H, s)	64.44 (64.67	4.16 4.20	11.56 11.23)	$C_{13}H_{10}N_2OS$	62
14b	223—224 EtOH	3140, 3020, 2860, 2720, 1690, 1680, 1620	1.97 (3H, s), 3.89 (3H, s), 7.28 (1H, d, J=3 Hz), 7.47 (1H, d, J=4.4 Hz), 7.48 (1H, dd, J=3, 8.8 Hz), 8.01 (1H, d, J=8.8 Hz), 8.76 (1H, d, J=4.4 Hz), 11.62 (1H, s)	61.74 (61.77	4.44 4.53	10.28 10.06)	$C_{14}H_{12}N_2O_2S$	78

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. b) Measured as a solution in $CDCl_3$.

5-(3-Acetyl-4-pyridyl)-4-methyl-2(3*H*)-thiazolone (8f) A mixture of **7f** (2.0 g, 4.9 mmol), zinc powder (1.4 g, 21.4 mmol) and THF–H_2O (10 ml, 1 : 1, v/v) was adjusted to pH 4 with 2 N HCl solution and then refluxed for 5 h. The mixture was treated in the same manner as described for **9e**, and **9f** was obtained (0.74 g, 74%) as colorless needles, mp 193—194 °C. IR (KBr): 3300, 3160, 1660, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.97 (3H, s), 2.07 (3H, s), 4.53 (1H, d, J=5 Hz), 4.74 (1H, dd, J=5, 7 Hz), 6.18 (1H, dd, J=5, 7 Hz), 7.42 (1H, d, J=6 Hz), 8.56 (1H, s), 10.59 (1H, s). A suspension of **9f** (0.7 g, 3.0 mmol) and DDQ (0.67 g, 3.0 mmol) in acetonitrile (30 ml) was stirred at 50 °C for 1 h. The mixture was worked up in the same manner as described for **8e** to give **8f** (0.16 g, 23%) as colorless needles, mp 198—199 °C. The spectral data and elemental analyses are given in Table III.

4-Methyl-5-(4-pyridazinyl)-2(3*H*)-thiazolone (11a) and Its Analog 11b A mixture of pyridazine (1.45 ml, 20 mmol), 2,2,2-trichloroethyl chloroformate (2.76 ml, 20 mmol), **5** (1.15 g, 10 mmol) and acetonitrile (30 ml) was worked up in the same manner as described for **7a**. The crude product was chromatographed on silica gel (ethyl acetate : hexane = 2 : 1), and then recrystallized from EtOH to give 4-methyl-5-[1,4-dihydro-1-(2,2,2-trichloroethoxycarbonyl)-4-pyridazinyl]-2(3*H*)-thiazolone (**10a**) (2.05 g, 55%) as colorless needles, mp 138—140 °C. Compound **10b** was also obtained in the same manner. The yields, melting points, spectral data and elemental analyses are given in Table II.

A mixture of **10a** (2.05 g, 1.1 mol) thus obtained, sublimed sulfur (1.0 g, 31.2 mmol) and DMF (20 ml) was worked up in the same manner as described for **8a**. The crude product was chromatographed on silica gel ($CHCl_3$: MeOH = 5 : 1) and then recrystallized from EtOH to give **11a** (0.2 g, 19%) as pale yellow plates, mp 245—247 °C. Compound **11b** was also obtained in the same manner. The yields, melting points, spectral data and elemental analyses are given in Table III.

4-Methyl-5-(4-quinolyl)-2(3*H*)-thiazolone (14a) and Its Analog 14b A mixture of quinoline (0.26 g, 2 mmol), 2,2,2-trichloroethyl chloroformate (0.30 ml, 2.2 mmol), **5** (0.12 g, 1.0 mmol) and acetonitrile (3 ml) was treated in the same manner as described for **7a**. The crude product was chromatographed on silica gel (ethyl acetate : hexane = 1 : 1) to give 4-methyl-5-[1,4-dihydro-1-(2,2,2-trichloroethoxycarbonyl)-4-quinolyl]-2(3*H*)-thiazolone (**12a**) (102 mg, 24.4%) and (1,2-dihydro-2-quinolyl)-2(3*H*)-thiazolone (**13a**) (253 mg, 60%) as pale yellow crystals. The *Rf* values on TLC were 0.3 for **12a** and 0.4 for **13a**. Compounds **12b** (*Rf* = 2.4) and **13b** (*Rf* = 3.4) were obtained in the same manner as described above. The melting points, spectral data and elemental analyses are given in Table II.

A mixture of **12a** (1.34 g, 3.20 mmol), sublimed sulfur (1.7 g, 53.1 mmol) and DMF (40 ml) was refluxed for 3 h, and worked-up in the same manner as described for **8a**. The crude product was chromatographed on silica gel (ethyl acetate : hexane = 4 : 1) and then recrystallized from EtOH with active carbon to give **14a** (0.48 g, 62.1%) as a colorless powder. Compound **14b** was also obtained in the same manner. The melting points, yields, spectral data and elemental analyses are given in Table III.

References

1) Part 1: H. Yamazaki, H. Harada, K. Matsuzaki, K. Yoshioka, M. Takase, and E. Ohki, *Chem. Pharm. Bull.*, **35**, 2243 (1987).
2) A part of this work was presented at the 7th Symposium on Medicinal Chemistry, Gifu, 1985.
3) J. Tcherniac, *J. Chem. Soc.*, **115**, 1071 (1919).
4) G. Venkat Rao, K. Szabo, and D. W. Grisely, Jr., *Synthesis*, **1972**, 136.