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Studies of Heterocyclic Compounds. IX.[1] The Synthesis and the Properties of Thiazolo[3,2-*b*]pyridazin-4-ium Perchlorates

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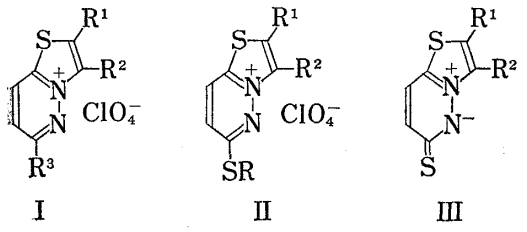
Eleven 6-methyl- and 6-phenyl-thiazolo[3,2-*b*]pyridazin-4-ium perchlorates (I) are synthesized by acid-cyclization of the corresponding ketosulfides (VI) and thioacetonitriles (VII) which are prepared from 6-methyl- and 6-phenyl-pyridazine-3(2*H*)thiones (IVa, b) by alkylation with α-haloketones (V) and α-chloroacetonitrile, respectively. Treatment of the quarternary salts (I) with potassium hydroxide or secondary amines furnishes 2-(2- mercaptovinyl)pyridazine-3(2*H*)-ones (XII), nucleophilic attack of the hydroxide ion taking place at the C_{8a}-position of the thiazolo[3,2-*b*]pyridazinium system.

Keywords——Hantzsch thiazole Synthesis; pyridazine derivatives; thiazolopyridazine derivatives; nucleophilic addition; NMR

In connection with our research on the synthesis and the reactivity of pi-deficient heteroaromatic compounds, interest and need for thiazolium salts condensed with another heteroaromatic nucleus have led us to prepare thiazolo[3,2-*b*]pyridazin-4-ium salts (I) and to examine their chemical properties especially toward nucleophilic reagents. The present paper reports the synthesis of 6-methyl- and 6-phenyl-thiazolo[3,2-*b*]pyridazin-4-ium perchlorates (I; R^3=CH_3, C_6H_5) and their reactions with hydroxide ion.



I II III

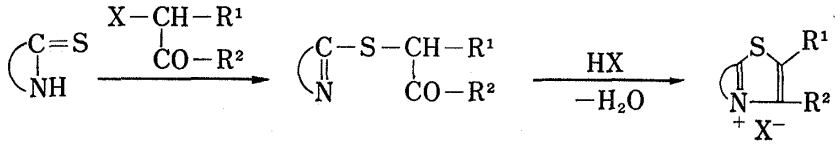


Chart 1

Since Bradsher and a coworker synthesized condensed thiazolopyridinium salts by acid-cyclization of α-hetarylthioketones in 1964,[3] a lot of papers have appeared on the preparation of thiazolopyridinium,[4] -pyrimidinium,[5] -pyrazinium,[5] -pyridazinium[6] salts through the modified Hantzsch thiazole synthesis[7] (Chart 1). 6-Mercaptothiazolo[3,2-*b*]pyridazinium per-

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2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) C.K. Bradsher and D.F. Lohr, Jr., *Chem. Ind.* (London), **1964**, 1801.
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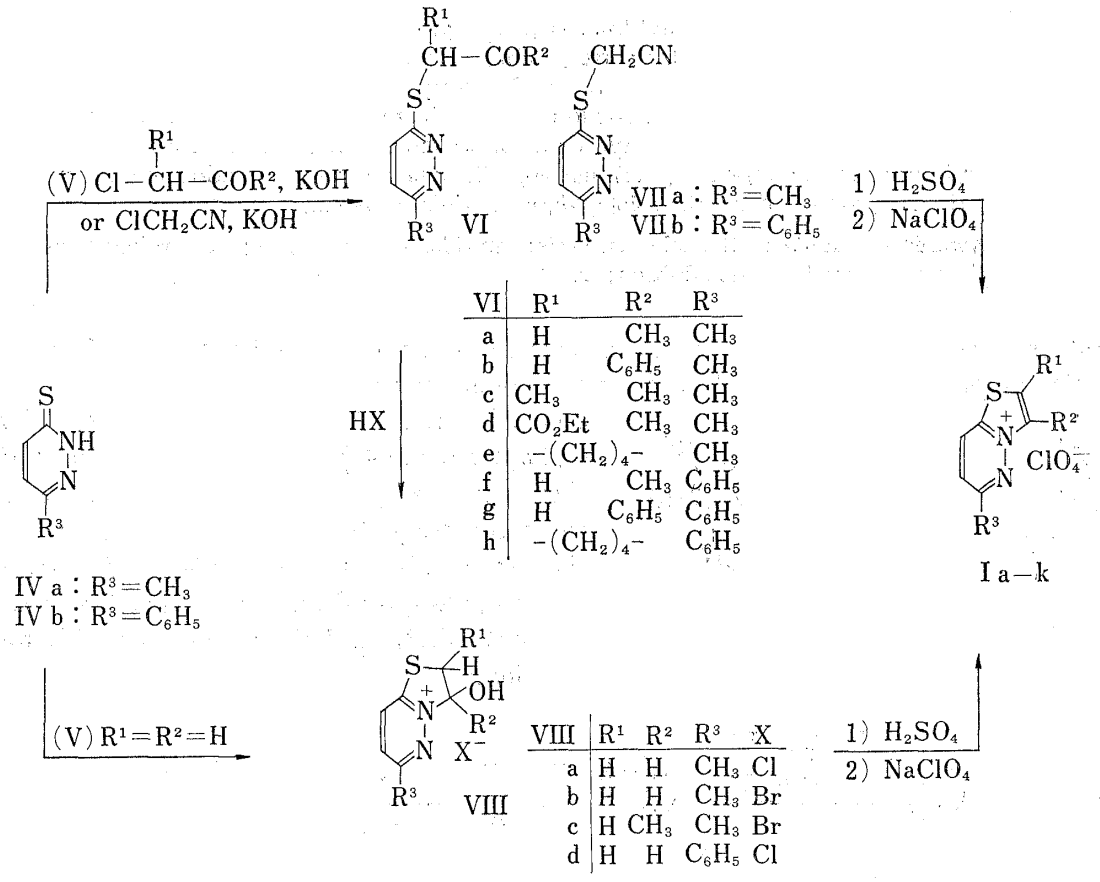
7) A. Hantzsch, *Ann.*, **250**, 281 (1889).

chlorates (II; R=H, CH_3) and anhydro-6-mercaptothiazolo[3,2-*b*]pyridazinium hydroxide (III) have also been synthesized in this laboratory.[6c] We have now synthesized eleven thiazolo[3,2-*b*]pyridazinium perchlorates (Ia—k) by the application of Bradsher's procedure.[4,5] The reaction of 6-substituted pyridazine-3(2*H*)-thiones (IVa, b) and α-chloroketones (V) in the presence of potassium hydroxide afforded α-(6-substituted pyridazin-3-ylthio)-ketones (VIa—h). A similar reaction of 6-substituted pyridazinethiones (IVa, b) and α-chloroacetonitrile afforded α-(6-substituted pyridazin-3-ylthio)-acetonitriles (VIIa, b). α-Pyridazinylthioketones (VI) and α-pyridazinylthioacetonitriles (VII) gave the desired 6-substituted thiazolo[3,2-*b*]-pyridazin-4-ium perchlorates (I) by heating in sulfuric acid.



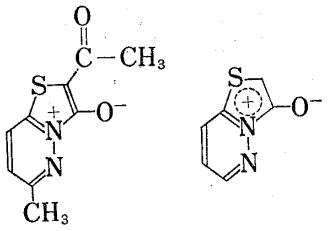
VI	R^1	R^2	R^3
a	H	CH_3	CH_3
b	H	C_6H_5	CH_3
c	CH_3	CH_3	CH_3
d	CO_2Et	CH_3	CH_3
e	$-(CH_2)_4-$		CH_3
f	H	CH_3	C_6H_5
g	H	C_6H_5	C_6H_5
h	$-(CH_2)_4-$		C_6H_5

VIII	R^1	R^2	R^3	X
a	H	H	CH_3	Cl
b	H	H	CH_3	Br
c	H	CH_3	CH_3	Br
d	H	H	C_6H_5	Cl

Chart 2

When the reaction of 6-substituted pyridazine-3(2*H*)-thiones (IV) with α-haloketones (V) was conducted in the presence of potassium hydroxide, the corresponding ketosulfides (VI) were most efficiently prepared. When chloroacetonitrile was used instead of V, 6-substituted 3-pyridazinylthioacetonitrile (VII) was obtained. The infrared (IR) spectrum of ketosulfides (VI) showed carbonyl bands at 1690—1730 cm^{-1}. Nitrile bands of VII appeared at 2220 cm^{-1} ($R^3=CH_3$) and 2250 cm^{-1} ($R^3=C_6H_5$). 3-(6-Methyl-3-pyridazinylthio)-2-butanone (VIc) was obtained by the reaction of pyridazinethione (IVa) with 3-chloro-2-butanone (Vc) in the presence of potassium hydroxide. The nuclear magnetic resonance (NMR) spectrum of VIc in carbon tetrachloride showed a doublet at δ 1.49 ppm (J=7.5 Hz) assigned to the methyl group at the side chain and a quartet at δ 4.88 ppm (J=7.5 Hz) assigned to the –S–CH< proton. The IR spectrum lacked absorption at the region of hydroxyl group but showed carbonyl absorption at 1727—1719 cm^{-1}. These data suggested that VIc assumed to be present as keto form in solution. On the other hand the NMR spectrum of ethyl 2-(6-methyl-3-pyridazinylthio)-3-oxobutyrate (VId) in carbon tetrachloride had a signal at δ 13.85 ppm (–OH) and the IR spectrum showed an absorption at 3420 cm^{-1} (νOH). VId gave brown

coloration with ferric chloride in methanol. These data suggested that VId was likely to exist as enol form in solution. The oily ketosulfide was also prepared by heating α-chloroacetoacetate and IVa in refluxing ethanol. The yellow crystals formed at the same time revealed to be 3,6-dimethylthiazolo[3,2-*b*]pyridazinium-2-carboxylate (IX), which was also obtained from VId by refluxing in ethanol. As a possible alternative for IX, 2-acetyl structure (X) would also be considered. However as a ketone is usually more susceptible to the attack of a nucleophile than an ester, it seems to be reasonable to consider that internal attack of the nuclear nitrogen at the ketone-carbonyl occurred predominantly. In fact, the condensation of ethyl α-chloroacetoacetate with thioamide yielded 4-methyl-5-ethoxycarbonylthiazole as the Hantzsch thiazole synthesis. Ohta and a coworker reported that the mesoionic compound (XI) was readily hydrolyzed in polar solvents to give the corresponding α-(pyridazine-3-ylthio)-acetic acid.[8] The IR spectrum of IX showed main absorption at 1667, 1600, and 1380 cm^{-1}: no hydrazone was formed with 2,4-dinitrophenylhydrazine. These facts supported the structure of IX.



X

XI

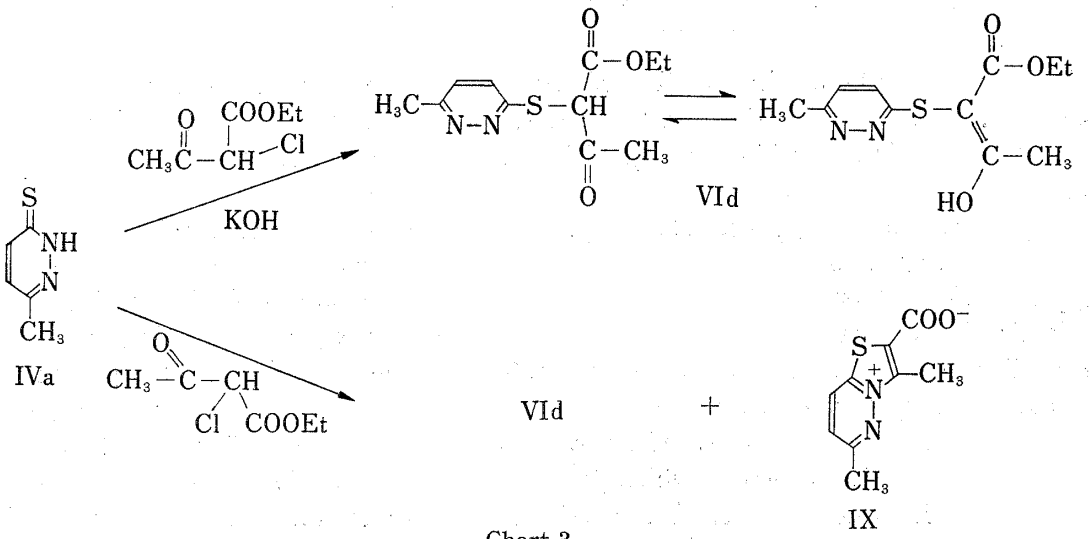
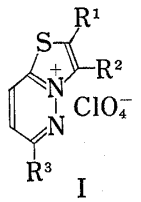


Chart 3

Attempt to form the aldosulfide by the reaction of pyridazinethiones (IVa, b) with chloroacetoaldehyde (V; $R^1=R^2=H$) in the presence of potassium hydroxide was unsuccessful. In spite of separation of potassium chloride, only the formation of tarry material was observed. However, heating of IVa, b and V ($R^1=R^2=H$) in refluxing methanol under neutral condition gave 3-hydroxy-2,3-dihydrothiazolium chloride (VIIIa, d) in good yield. The IR spectrum of VIIIa, d showed a strong broad absorption at 3100—3400 cm^{-1} (νOH) and lacked carbonyl band. The NMR spectrum of VIIIa showed a signal at δ 9.22 ppm (OH) and a signal at δ 6.52 ppm (C_3–H). On the basis of the above spectral data and the analytical data, the structure of VIII was assigned. Heating of 6-methyl-3-acetonylthiopyridazine (VIa) in 47% hydrobromic acid at 80° for 30 minutes gave 3-hydroxy-3,6-dimethyl-2,3-dihydrothiazolo[3,2-*b*]-pyridazin-4-ium bromide (VIIIc) in 38% yield, the IR spectrum of which did not show carbonyl band any more but exhibited a hydroxyl band at 3100 cm^{-1}. Treatment of the pyridazinium chloride (VIIIa) with 47% hydrobromic acid only caused halide-exchange reaction to give the pyridazinium bromide (VIIIb). These hydroxythiazolium salts (VIII) were stable under condition of recrystallization and unchanged after prolonged standing at room temperature, although 6-chloro-derivatives[6a] were reported to be unstable.

8) M. Ohta and K. Kishimoto, *Bull. Chem. Soc. Japan*, **34**, 142 (1961).

TABLE I



I

	R^1	R^2	R^3	mp (°C)	Yield (%)	ν_{max}^{KBr} cm^{-1}		λ_{max}^{MeOH} (log ε)	
a	H	H	CH_3	171.5—175	86	1428	1368	232.5(4.09)	291.0(3.96)
b	H	CH_3	CH_3	165 —166	69	1430	1357	238.5(4.00)	302.5(3.94)
c	H	C_6H_5	CH_3	168 —170	70	1425	1352	242.0(4.30)	317.0(3.74)
d	CH_3	CH_3	CH_3	140 —141	31	1435	1362	244.0(3.90)	310.0(3.99)
e	H	NH_2	CH_3	173 —173.5	60	1420	1380	259.0(3.74)	386.0(3.80)
f	$-(CH_2)_4-$		CH_3	199 —200.5	58	1425	1380	245.5(3.91)	312.0(4.09)
g	H	H	C_6H_5	214 —216.5	69	1420	1367	271.0(4.44)	
h	H	CH_3	C_6H_5	182 —185	62	1425	1360	274.0(4.42)	
i	H	C_6H_5	C_6H_5	225 —227	68	1426	1360	246.0(4.39)	270.0(4.36)
j	H	NH_2	C_6H_5	290 —294	62	1430	1390	259.0(4.33)	387.0(3.75)
k	$-(CH_2)_4-$		C_6H_5	294 —295	52	1423	1345	274.0(4.40)	

The reaction of keto-sulfides (VIa—h) with sulfuric acid almost completed within 10 minutes at 80°. Treatment of the resulting sulfates with sodium perchlorate afforded thiazolo[3,2-*b*]pyridazin-4-ium perchlorates (I). The yield and the melting point of I are given in Table I.

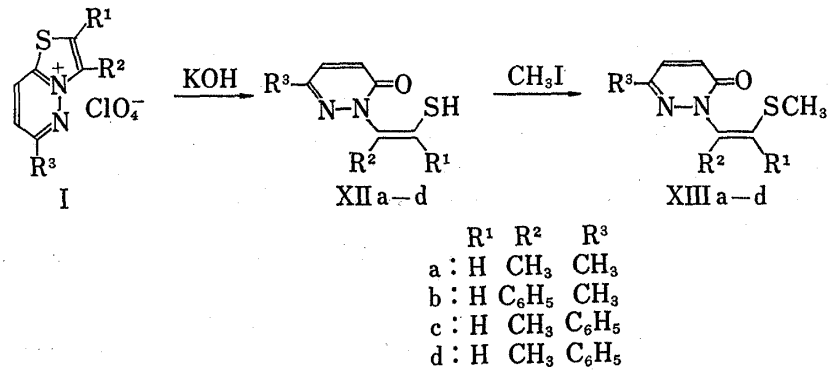
Bicyclic compounds (I) were also prepared by use of 47% hydrobromic acid or 70% perchloric acid. For example heating of VIg in 47% hydrobromic acid at 80° for 3 hours or in 70% perchloric acid for 2 hours gave the bromide or the perchlorate of I, respectively.

Cyclization of cyanomethylsulfides (VIIa, b) was carried out by heating in sulfuric acid in a similar manner to give 3-amino-6-methyl- and 6-phenyl-thiazolo[3,2-*b*]pyridazin-4-ium perchlorates (Ie, j). In addition to the typical AB-quartet pattern at around δ 8.0—9.2 ppm (C_7–H and C_8–H), there was observed an overlapped singlet peak at 7.20 ppm (1H, C_2–H and 2H, $-NH_2$) in the NMR spectrum, which diminished two-thirds of its area intensity by deuterium-exchange with heavy water. The corresponding 3-acetamino derivatives were obtained by heating Ie, j in acetic anhydride. The IR spectrum of 3-acetamino-6-methyl derivative

TABLE II. NMR Spectral Data of Thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (I) δ (in DMSO-d_6)

	R^1	R^2	R^3	C-7	C-8	$J_{7,8}$ (Hz)
a	8.74[a]	9.20	2.74	8.09	9.15	9.8
b	8.51[b]	2.75	2.84	8.08	9.15	9.8
c	8.76	7.52—7.94	2.75	8.10	9.19	9.5
d	2.69	2.78	2.83	8.05	9.12	9.7
e	7.13	—	2.80	7.91	9.00	9.6
f	1.98[c]	3.05[c]	2.70	8.03	9.09	9.6
g	8.81	9.35	7.58—7.80 8.11—8.37	8.79	9.37	9.8
h	8.76	2.90	7.50—7.80 8.17—8.40	8.76	9.37	9.8
i	8.85	7.46—8.23 (10H)		8.77	9.36	9.8
j	7.17	—	7.54—7.80 8.34—8.64	8.60	9.18	9.5
k	2.04[c]	3.11[c]	7.50—7.70 8.04—8.30	8.68	9.24	9.7

a) $J_{2,3}$=4.5 Hz *b*) $J_{2,3}$=1.1 Hz *c*) (m, 4H)



	R^1	R^2	R^3
a :	H	CH_3	CH_3
b :	H	C_6H_5	CH_3
c :	H	CH_3	C_6H_5
d :	H	CH_3	C_6H_5

Chart 4

showed the N-acetyl band at 1705 cm^{-1}; the NMR spectrum showed the methyl signal at δ 2.35 ppm and N–H proton at δ 11.30 ppm. These data suggested that Ie, j are in amino-form but not in imino-form.

The NMR spectral data of eleven thiazolo[3,2-*b*]pyridazinium perchlorates (I) are shown in Table II. Each exhibits a typical AB pattern for C_7 and C_8-protons with *ortho*-coupling constant of *ca.* 10 Hz. The IR spectrum showed characteristic bands at 1430, 1360, and at 1100 cm^{-1} (ClO_4). The IR and UV spectral data of I are shown in Table I.

The reaction of the salt (Ib) with potassium hydroxide in aqueous solution gave 2-(2-mercaptovinyl)pyridazin-3-one (XIIa); the NMR spectrum showed a doublet at δ 2.33 ppm H–C=C–C$\underline{H}_3$, J=1.1 Hz), a quartet at δ 6.31 ppm ($\underline{H}$–C=C–CH_3, J=1.1 Hz) and an AB-quartet pattern centered at 6.89 and 7.16 ppm (C_7–H and C_8–H, J=9 Hz). Treatment of XIIa with methyl iodide yielded S–methyl derivative (XIIIa); the NMR spectrum showed a singlet at δ 2.23 ppm (S–CH_3) and a peak at δ 6.06 ppm for the vinyl proton. The mass spectrum showed ions corresponding to *m/e* 196 (M^+), 181 (M^+-CH_3) and 149 (M^+-SCH_3). Treatment of Ib with dimethylamine in aqueous solution also gave XIIa. 3-Dimethylamino derivative could not be isolated. In case of aniline the starting material was recovered. In case where hydroxide ion was applied as a nucleophile, pi-deficient heteroaromatic compounds (I) were attacked by the reagent at the C_{8a}-position to form the unstable hydroxythiazoline intermediate, the C–S bond being cleaved spontaneously with formation of pyridazinone-N-vinylthiol (XII). As for the reaction of other nucleophiles such as cyanide and carbanions, more interesting results have been obtained, which will be discussed in the following paper.

Table III. Analytical Data of Thiazolo[3,2-*b*]pyridazinium Perchlorates (I)

	Molecular formula	Calcd.			Found		
		C	H	N	C	H	N
a	$C_7H_7O_4N_2SCl$	33.55	2.82	11.18	33.15	2.94	10.90
b	$C_8H_9O_4N_2SCl$	36.31	3.43	10.59	36.30	3.50	10.13
c	$C_{13}H_{11}O_4N_2SCl$	47.79	3.39	8.57	47.82	3.37	8.82
d	$C_9H_{11}O_4N_2SCl$	38.78	3.98	10.05	38.57	3.93	10.28
e	$C_7H_8O_4N_3SCl$	31.65	3.04	15.82	31.43	3.11	15.89
f	$C_{11}H_{13}O_4N_2SCl$	43.46	4.30	9.19	43.42	4.51	9.45
g	$C_{12}H_9O_4N_2SCl$	46.08	2.90	8.96	46.33	2.94	9.05
h	$C_{13}H_{11}O_4N_2SCl$	47.79	3.39	8.57	47.76	3.61	8.87
i	$C_{18}H_{13}O_4N_2SCl$	55.61	3.37	7.21	55.54	3.57	7.53
j	$C_{12}H_{10}O_4N_3SCl$	43.72	3.06	13.35	43.90	3.02	13.44
k	$C_{16}H_{15}O_4N_2SCl$	52.39	4.12	7.64	52.32	4.27	7.35

Experimental[9]

6-Methylpyridazine-3(2*H*)-thione (IVa)——Into a solution of 6-methylpyridazine-3(2H)-one (11 g) in 100 ml of pyridine, there was added slowly phosphorus pentasulfide (10.6 g) and heated under reflux for 3 hours. The hot pyridine layer was decanted. The residue was heated under reflux for 10 min with 30 ml of pyridine. The combined pyridine solution was evaporated *in vacuo* and poured into ice water. The precipitated product was collected by filtration and crystallized from EtOH to give 7 g (55% yield) of yellow crystals with mp 197°. *Anal.* Calcd. for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.22. Found: C, 47.89; H, 4.83; N, 22.40.

6-Phenylpyridazine-3(2*H*)-thione (IVb)——Into a solution of 6-phenylpyridazine-3(2*H*)-one (17.2 g) in 100 ml of pyridine, there was added slowly phosphorus pentasulfide (16.9 g) and the reaction mixture was treated as described above under reflux for 3 hours. And the above described procedure gave 10 g (53.2%) of yellow crystals, mp 158—159°. *Anal.* Calcd. for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.51; H, 4.54; N, 14.70.

6-Methyl-3-acetonylthiopyridazine (VIa)——Into a solution of 6-methylpyridazine-3(2*H*)-thione (IVa) (630 mg) in 10 ml of EtOH containing potassium hydroxide (280 mg), there was added monochloroacetone (430 mg) under stirring. Immediately the crystals of potassium chloride precipitated. After an hour's stirring the crystals were filtered off and the filtrate was evaporated *in vacuo*. The residue was crystallized from *n*-hexane to give 500 mg (55%) of crystals which melted at 56.5—58°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1720 (C=O) NMR δ (in $CDCl_3$): 2.38 (3H, s), 2.64 (3H, s), 4.17 (2H, s), 7.08 (1H, d, $J=9$ Hz), 7.30 (1H, d, $J=9$ Hz). *Anal.* Calcd. for $C_8H_{10}ON_2S$: C, 52.71; H, 5.53; N, 15.37. Found: C, 52.86; H, 5.42; N, 15.64.

6-Methyl-3-phenacylthiopyridazine (VIb)——The compound was prepared by following the above procedure and purified by recrystallization from benzene and *n*-hexane. mp 92—93°, 67% yield. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR δ (in DMSO-d_6): 2.51 (3H, s), 4.89 (2H, s), 7.31 (1H, d, $J=9$ Hz), 7.54 (1H, d, $J=9$ Hz), 7.33—7.65 (3H, arom.), 7.94—8.16 (2H, arom.). *Anal.* Calcd. for $C_{13}H_{12}ON_2S$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.83; H, 4.89; N, 11.77.

3-(6-Methyl-3-pyridazinylthio)-2-butanone (VIc)——Into a solution of 6-methyl-pyridazine-3(2H)-thione (IVa) (630 mg) in 10 ml of EtOH containing potassium hydroxide (280 mg), there was added 3-chloro-2-butanone (580 mg) under stirring at room temperature. After further 2 hours' stirring, the precipitated potassium chloride was separated by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography through silica gel. The fraction which were eluted with 5% MeOH–$CHCl_3$ were collected to give 500 mg (51%) of oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1727, 1919 (C=O). NMR δ (in CCl_4): 1.49 (3H, d, $J=7$ Hz), 2.32 (3H, s), 2.61 (3H, s), 4.88 (1H, q, $J=7.5$ Hz), 7.13 (2H, s, pyridazine nucleus).

Ethyl 2-(6-Methyl-3-pyridazinylthio)-3-oxobutyrate (VId)——Into a solution of 6-methylpyridazine-3(2H)-thione (IVa) (630 mg) in 10 ml of EtOH containing potassium hydroxide (280 mg), ethyl α-chloroacetoacetate (900 mg) was added dropwise with stirring at room temperature. Soon potassium chloride precipitated. After another 30 minutes' stirring the precipitate was separated by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in 10% Na_2CO_3 soln. and extracted with $CHCl_3$. $CHCl_3$ layer was washed with water and dried over anhyd. $MgSO_4$. Removal of the solvent by evaporation gave 870 mg (68.5%) of oil which was almost pure. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3420 (OH), 1750 (sh), 1735 (C=O), 1630, 1595. NMR δ (in CCl_4): 1.17 (3H, t, $J=7.5$ Hz), 2.30 (3H, s), 2.60 (3H, s), 4.17 (2H, q, $J=7.5$ Hz), 7.07 (2H, s), 13.85 (1H, s). *Anal.* Calcd. for $C_{11}H_{14}O_3N_2S$: N, 11.02. Found: N, 10.88.

2-(6-Methyl-3-pyridazinylthio)-cyclohexanone (VIe)——The compound was prepared by the general method mentioned above and the residue was submitted to column chromatog raphy on silica gel. The product eluted with 2% MeOH–$CHCl_3$ was recrystallized from EtOH. 48% yield mp 92—96°. IR ν_{max}^{KBr} cm^{-1}; 1715 (C=O). NMR δ (in $CDCl_3$): 2.61 (3H, s), 7.06 (1H, d, $J=9$ Hz), 7.28 (1H, d, $J=9$ Hz). *Anal.* Calcd. for $C_{11}H_{14}ON_2S$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.09; H, 6.40; N, 12.26.

6-Phenyl-3-acetonylthiopyridazine (VIf)——Into a solution of 6-phenylpyridazine-3(2*H*)-thione (IVb) (564 mg) in 15 ml of EtOH containing potassium hydroxide (168 mg), there was added monochloroacetone (278 mg) under stirring at room temperature. Immediately the precipitate was collected by filtration and the crystals were recrystallized from EtOH. 512 mg (70% yield) of the product was obtained. mp 142.5—143°. IR ν_{max}^{KBr} cm^{-1}: 1703 (C=O). NMR δ (in $CDCl_3$): 2.40 (3H, s), 4.28 (2H, s), 7.25—7.68 (5H, m), 7.82—8.15 (2H, arom.). *Anal.* Calcd. for $C_{13}H_{12}ON_2S$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.87; H, 5.04, N, 11.22.

6-Phenyl-3-phenacylthiopyridazine (VIg)——The compound was prepared by the above procedure. The crude product was recrystallized from EtOH. 81% yield mp 102—103°. IR ν_{max}^{KBr} cm^{-1}: 1703 (sh), 1690 (C=O). NMR δ (in $CDCl_3$): 5.03 (2H, s). *Anal.* Calcd. for $C_8H_{14}ON_2S$: C, 70.56; H, 4.61; N, 9.14. Found: C, 70.84; H, 4.73; N, 8.81.

9) Melting points were measured in capillary tubes and also on the Yanagimoto micro meltingpoint apparatus. All melting points were uncorrected. NMR spectra were measured by Hitachi R-20 60 MC and R-22 90MC NMR spectrophotometer, using tetramethylsilane as the internal reference. IR and ultraviolet (UV) spectra were measured on a JASCO IRA-I spectrophotometer and on a Hitachi EPS-3 UV spectrophotometer, respectively. Mass spectra were recorded on a Hitachi RMS-4 instrument.

2-(6-Phenyl-3-pyridazinylthio)-cyclohexanone (VIh)——The compound was prepared by following the above procedure and was purified by recrystallization from EtOH. 45% yield mp 146—147.5° IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{16}H_{16}ON_2S$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.25; H, 5.67; N, 9.69.

6-Methyl-3-pyridazinylthioacetonitrile (VIIa)——Into a solution of 6-methylpyridazine-3(2*H*)-thione (IVa) (630 mg) in EtOH containing potassium hydroxide (280 mg), there was added chloroacetonitrile (378 mg) under stirring at room temperature. After stirring for another hour, the precipitate was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH. 487 mg (59% yield) mp 88—89°. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N). NMR δ (in DMSO-d_6): 2.62 (3H, s), 4.39 (2H, s), 7.45 (1H, d, J=9 Hz), 7.69 (1H, d, J=9 Hz). *Anal.* Calcd. for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43. Found: C, 51.27; H, 4.50; N, 25.19.

6-Phenyl-3-pyridazinylthioacetonitrile (VIIb)——The compound was prepared by following the procedure of VIf. The crude product was recrystallized from MeOH. 71% yield mp 102—104°. IR ν_{max}^{KBr} cm^{-1}: 2250 (C≡N). NMR δ (in $CDCl_3$): 4.24 (2H, s). *Anal.* Calcd. for $C_{12}H_9N_3S$: C, 63.41; H, 3.99; N, 18.49. Found: C,63.16; H, 3.49; N, 18.11.

3-Hydroxy-6-methyl-2,3-dihydrothiazolo[3,2-*b*]pyridazin-4-ium Chloride (VIIIa)——A solution of 6-methylpyridazine-3(2*H*)-thione (IVa) (630 mg) and 30% chloroacetoaldehyde (1.5 g) in MeOH was refluxed for 3 hours. The solvent was again evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH. 780 mg (76% yield) of product was obtained. mp 169—170°. IR ν_{max}^{KBr} cm^{-1}: 3100 (broad), 1600, 1465. NMR δ (in DMSO-d_6): 2.70 (3H, s), 6.57 (1H, t), 8.22 (1H, d, J=9.8 Hz), 8.69 (1H, d, J=9.8 Hz), 9.22 (1H, broad s). *Anal.* Calcd. for $C_7H_9ON_2SCl$: C, 41.90; H, 4.51; N, 13.69. Found: C, 41.85; H, 4.45; N, 13.56.

3-Hydroxy-6-methyl-2,3-dihydrothiazolo[3,2-*b*]pyridazin-4-ium Bromide (VIIIb)——3-Hydroxy-6-methyl-2,3-dihydrothiazolo[3,2-*b*]pyridazin-4-ium chloride (VIIIa) (100 mg) and 1 ml of 47% HBr was heated at 80° for 30 min. The solvent was evaporated to dryness *in vacuo*. After adding a small amount of EtOH, the precipitate was collected by filtration. The crude product was recrystallized from EtOH to give 70 mg. mp 155—157°. IR ν_{max}^{KBr} cm^{-1}: 3090 (broad), 1600, 1458. NMR δ (in DMSO-d_6): 2.68 (3H, s), 6.61 (1H, broad t), 8.22 (1H, d, J=9.8 Hz), 8.63 (1H, d, J=9.8 Hz).

3-Hydroxy-3,6-dimethyl-2,3-dihydrothiazolo[3,2-*b*]pyridazin-4-ium Bromide (VIIIc)——6-Methyl-3-acetonylthiopyridazine (VIa) (100 mg) and 1 ml of 47% HBr was heated at 80° for 30 min. The reaction mixture was evaporated to dryness *in vacuo*. After adding a small amount of EtOH, the precipitate was collected by filtration and recrystallized from EtOH to give 55 mg (38% yield). mp 156°. IR ν_{max}^{KBr} cm^{-1}: 3100 (broad), 1600, 1450. NMR δ (in DMSO-d_6): 2.05 (3H, s), 2.71 (3H, s), 3.94 (2H, s), 8.21 (1H, d, J=9.8 Hz), 8.65 (1H, d, J=9.8 Hz). *Anal.* Calcd. for $C_8H_{11}ON_2SBr$: C, 36.52; H, 4.21; N, 10.65. Found: C, 36.70; H, 4.37; N, 10.88.

3-Hydroxy-6-phenyl-2,3-dihydrothiazolo[3,2-*b*]pyridazin-4-ium Chloride (VIIId)——A solution of 6-phenylpyridazine-3(2*H*)-thione (IVb) (564 mg) and 30% chloroacetoaldehyde (1.3 g) in 10 ml of MeOH was refluxed for 3 hours. The reaction mixture was worked up as the procedure of (VIIIa) and recrystallized from EtOH to give 684 mg (80% yield). mp 160—168°. IR ν_{max}^{KBr} cm^{-1}: 3400, 3100, 1592, 1442. NMR δ (in DMSO-d_6): 6.75 (1H, broad t), 7.44—7.80 (3H, arom), 8.05—8.34 (2H, arom) 8.86 (2H, s. pyridazine nucleus). *Anal.* Calcd. for $C_{12}H_{13}O_2N_2SCl$: C, 50.62; H, 4.60; N, 9.84. Found: C, 50.73; H, 4.92; N, 9.88.

General Method of the Preparation of 2,3,6-Trisubstituted Thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (I)——3-Alkylthiopyridazine (VI), (VII), (VIII) was added into about 10 times quantity of conc. H_2SO_4 and the mixture was heated at 80—85° for 1 hour. After cooling, the reaction mixture was poured into ice water. To this solution was added a thick solution of sodium perchlorate and the precipitated mixture was collected by filtration and recrystallized from EtOH or from MeOH. Physical properties and elemental analysis were summarized in Table I, Table II, and Table III.

3,6-Diphenylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (Ii)——6-Phenyl-3-phenacylthiopyridazine (VIg) (100 mg) and 1 ml of 60% $HClO_4$ was heated at 85° for 2 hours. After cooling, gum was obtained. A small amount of MeOH was added to this gum and the precipitated material was collected by filtration. Recrystallization from EtOH afforded pure sample. 45 mg (36% yield), mp 225—227°. The product did not show any depression in melting point when mixed with the authentic specimen of Ic prepared through the general method. The product was also identified by comparing its IR and NMR spectra.

3,6-Dimethylthiazolo[3,2-*b*]pyridazinium-2-carboxylate (IX)——Method a: A solution of 6-methylpyridazine-3(2*H*)-thione (IVa) (630 mg) and ethyl α-chloroacetoacetate (900 mg) in 15 ml of EtOH was refluxed for 5 hours. The solvent was evaporated *in vacuo* and the residue was passed through a column of silica gel and was eluted with 5% MeOH–$CHCl_3$. From the first eluate, 460 mg (36% yield) of VId was obtained, which was confirmed in comparison with the sample obtained in case of VId. From the second eluate, yellow crystals were obtained after recrystallization from EtOH. 125 mg (12%). mp 297—298° (d) IR ν_{max}^{KBr} cm^{-1}: 1667, 1612 (sh), 1600, 1452, 1380, 1203. NMR δ (in DMSO-d_6): 2.52 (3H, s), 2.70 (3H, s), 7.86 (1H, d, J=9.8 Hz), 8.68 (1H, d, J=9.8 Hz). *Anal.* Calcd. for $C_9H_8O_2N_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 52.36; H, 3.96; N, 13.01.

Method b: A solution of 150 mg of VId in 5 ml of EtOH was refluxed for 5 hours. The solvent was evaporated *in vacuo* and the residue was separated by column chromatography on silica gel. Elution with 5% MeOH–$CHCl_3$ afforded 70 mg of oil (containing VId) and yellow crystals of IX (20 mg).

Acetylation of 3-Amino-6-methylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (Ie)——A solution of 300 mg of Ie in 5 ml of acetic anhydride was heated at 80° for 3 hours. After cooling, the yellow precipitate was collected by filtration and recrystallized from MeOH. 200 mg (58% yield) mp 206—208°. IR ν_{max}^{KBr} cm^{-1}: 3440, 3360, 3230, 3130, 1712 (sh), 1705, 1598, 1518, 1360, 1255. NMR δ (in DMSO-d_6): 2.35 (3H, s), 2.86 (3H, s), 8.09 (1H, d, J=9.8 Hz), 8.57 (1H, s), 9.12 (1H, d, J=9.8 Hz), 11.30 (1H, broad s). *Anal.* Calcd. for $C_9H_{10}O_5N_3SCl$: C, 35.13; H, 3.28; N, 13.66. Found: C, 35.13; H, 3.34; N, 13.37.

The Reaction of Ib (R^1=H, R^2=R^3=CH_3) with KOH——A solution of 530 mg of Ib and 240 mg of KOH in water (10 ml) was stirred at room temperature for 20 hours. Brown crystals separated were filtered off, the filtrate was extracted with CH_2Cl_2. CH_2Cl_2 extracts were combined and dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. A small amount of oil (XIIa) was obtained. NMR of the oil, δ (in $CDCl_3$): 2.23 (3H, d, J=1.1 Hz), 2.39 (3H, s), 6.31 (1H, q), 6.89 (1H, d, J=9 Hz), 7.16 (1H, d, J=9 Hz). To the former aqueous solution was added 1 g of methyl iodide, the reaction mixture was stirred for 20 hours and then extracted with CH_2Cl_2. CH_2Cl_2 solution was dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. 210 mg of oil (XIIIa) was obtained. IR ν_{max}^{KBr} cm^{-1}: 3000, 2930, 1680, 1670, 1665, 1660, 1598, 1430, 1335, 1325, 840. NMR δ (in $CDCl_3$): 2.13 (3H, d, J=1.1 Hz), 2.23 (3H, s), 2.43 (3H, s), 6.06 (1H, q), 6.81 (1H, d, J=9 Hz), 7.05 (1H, d, J=9 Hz). Mass Spectrum M^+ m/e: 196, 181, 149 (base peak), 111. *Anal.* Calcd. for $C_9H_{12}ON_2S$: N, 14.27. Found: N, 13.85.

The Reaction of Ic(R^1=H, R^2=C_6H_5, R^3=CH_3) with KOH——A solution of 653 mg of Ic and 280 mg of KOH in 10 ml of a mixture of acetonitrile: water (1:1 v/v) was stirred for 2 hours. Brown crystals separated were filtered off and 1 g of methyl iodide was added to the filtrate. The reaction mixture was stirred for 3 hours, acetonitrile was distilled off. The residue was extracted with CH_2Cl_2. CH_2Cl_2 extracts were combined and dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from benzene and *n*-hexane, 150 mg (29% yield). mp 119—120°. IR ν_{max}^{KBr} cm^{-1}: 3030, 2920, 1672, 1662, 1658, 1590, 1443, 1345, 1323, 1178, 1145, 1100, 833, 760. NMR δ (in $CDCl_3$): 2.35 (3H, s), 2.39 (3H, s), 6.87 (1H, s), 6.95 (1H, d, J=9 Hz), 7.16 (1H, d, J=9 Hz), 7.22 (5H, arom). *Anal.* Calcd. for $C_{14}H_{14}ON_2S$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.40; H, 5.44; N, 11.07.

The Reaction of Ih(R^1=H, R^2=CH_3, R^3=C_6H_5) with KOH——A solution of 653 mg of Ih and 448 mg of KOH in 20 ml of a mixture of acetonitrile: water (1: 1 v/v) was stirred at room temperature for 24 hours. After 1 g of methyl iodide was added to the solution, the reaction mixture was stirred for further 5 hours. The solution was evaporated *in vacuo* to remove acetonitrile. The residue was extracted with $CHCl_3$. $CHCl_3$ extracts were combined and dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. 425 mg of oil (XIIIc) was obtained. IR ν_{max}^{KBr} cm^{-1}: 3000, 2930, 1675, 1670, 1660, 1658, 1590, 1445, 1340, 1330, 850. NMR δ (in $CDCl_3$): 2.24 (3H, d, J=1.1 Hz), 2.25 (3H, s), 6.16 (1H, q), 7.07 (1H, d, J=9.8 Hz), 7.70 (1H, d, J=9.8 Hz), 7.33—7.93 (5H, arom). *Anal.* Calcd. for $C_{14}H_{14}ON_2S$: C, 65.09; H, 5.46; N, 10.84. Found: C, 64.62; H, 5.43; N, 10.76.

The Reaction of Ii(R^1=H, R^2=R^3=C_6H_5) with KOH——A solution of 778 mg of Ii and 280 mg of KOH in a mixture of acetonitrile; water (1: 1 v/v) was stirred at room temperature for 19 hours. After 1 g of methyl iodide was added to the solution, the reaction mixture was stirred for further 3 hours. The solution was evaporated *in vacuo* to remove acetonitrile. The residue was extracted with $CHCl_3$. $CHCl_3$ extracts were evaporated to dryness *in vacuo*. The solid residue was recrystallized from EtOH to give pale yellow prisms, 300 mg (94% yield). mp 153—154°. IR ν_{max}^{KBr} cm^{-1}: 3050, 2930, 1690, 1680, 1670, 1663, 1590, 1440, 1340, 1200, 850, 840. NMR δ (in DMSO-d_6): 2.44 (3H, s), 7.18 (1H, d, J=9.8 Hz), 7.30 (5H, s), 7.42 (1H, s), 7.38—7.62 (3H, arom), 7.73—8.00 (2H, arom), 8.15 (1H, d, J=9.8 Hz).

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