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Studies on Heterocyclic Compounds. XIX.[1] The Reaction of the Thiazolo[3,2-*b*]pyridazinium Perchlorates with Carbanions[2]

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On reaction with sodium salts of such active methylene compounds as ethyl cyanoacetate, malononitrile, ethyl malonate and phenylacetonitrile, thiazolo[3,2-*b*]pyridazinium perchlorates (I) furnish anhydro-8-(α,α-disubstituted methylene)-5,8-dihydrothiazolo[3,2-*b*]pyridazinium hydroxides (IV, V, VI, and VII). On treatment with sodium hydrosulfide as a nucleophile, I affords anhydro-8-mercaptothiazolo[3,2-*b*]pyridazinium hydroxide (X).

The reaction is initiated by the nucleophilic addition of the reagents at the 8-position, and subsequent oxidation by atmospheric oxygen *via* radical intermediates gives rise to the ylide compounds.

Keywords——thiazolo[3,2-*b*]pyridazinium salts; pyridazine derivatives; thiazolium *N*-imine; triplet oxygen; radical substitution reaction; nucleophilic addition; ^{13}C NMR

On reaction with such *C*-nucleophiles as carbanions and enamines, 2,3-dihydrothiazolo[2,3-*b*]thiazolium salts[3] or thiazolo[2,3-*b*]benzothiazolium salts,[1] which are a kind of pi-deficient condensed thiazole derivatives, were attacked by the reagents at the polarized $\rangle C=\overset{+}{N}\langle$ bond to afford 2-substituted thiazoles or pyrrolo[2,1-*b*]benzothiazole ring. The reaction of oxazolo[3,2-*b*]pyridazinium salts[4] with carbanions was also initiated by the nucleophilic attack of the reagent on C_{8a} at the polarized $\rangle C=\overset{+}{N}\langle$ bond to give pyrrolo[1,2-*b*]pyridazines. In contrasts, thiazolo[3,2-*b*]pyridazinium salts (I)[5] gave, on reaction with potassium cyanide, 8-cyano-4,7-dihydrothiazolo[3,2-*b*]pyridazine-7-ones (II) and anhydro-7-cyano-5,8-dihydrothiazolo[3,2-*b*]pyridazinium hydroxides (III) through nucleophilic addition which takes place at either the C_8- or C_7-position and subsequent oxidation by atmospheric oxygen. In the reaction of thiazolo[2,3-*a*]phthalazinium salts with carbanions, the position attacked is dependent on the reagent used.[2,6] On reaction with sodium salts of ethyl cyanoacetate, the phthalazinium salts afforded 6-(α-cyano-α-ethoxycarbonyl)methylidene ylide through an addition elimination mechanism, nucleophilic addition taking place at the C_6-position to form a thiazole *N*-imine type intermediate. These results led us to examine the reaction mode of thiazolo[3,2-*b*]pyridazinium salts (I) with carbanions to see whether the initial attack of the reagent occurs either at the C_{8a}-position, or at the C_7- or C_8-position.

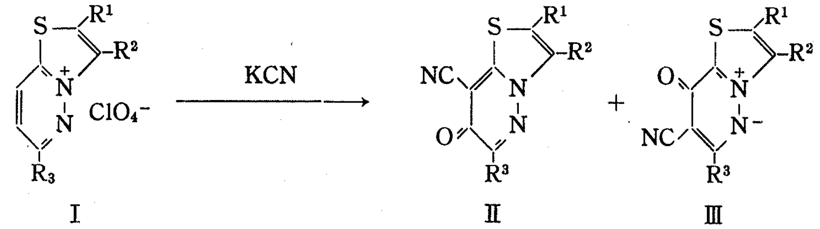
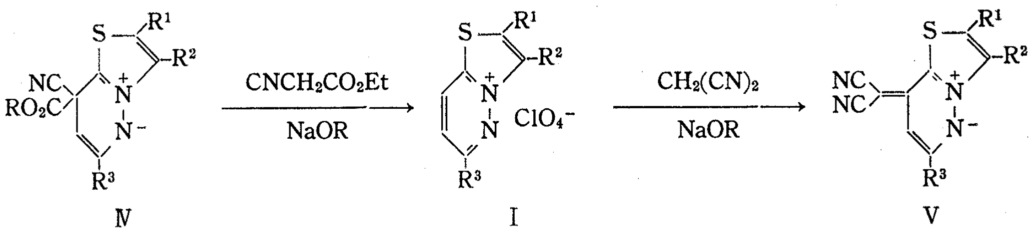


Chart 1

3,6-Dimethylthiazolo[3,2-*b*]pyridazinium perchlorate (Ib) furnished yellow crystals on treatment with the sodium salt of ethyl cyanoacetate in absolute methanol at room temperature for 4 h under air. This compound (IVb), mp 290—292°C, had the empirical formula



IV I V

	R^1	R^2	R^3	R
IVa:	H	H	CH_3	CH_3
IVb:	H	CH_3	CH_3	CH_3
IVc:	H	CH_3	CH_3	C_2H_5
IVd:	-$(CH_2)_4$-		CH_3	CH_3
IVe:	H	H	C_6H_5	CH_3
IVf:	H	H	C_6H_5	C_2H_5
IVg:	H	CH_3	C_6H_5	CH_3
IVh:	H	CH_3	C_6H_5	C_2H_5
IVi:	H	C_6H_5	C_6H_5	CH_3
IVj:	H	CH_3	SCH_3	CH_3

	R^1	R^2	R^3
Ia:	H	H	CH_3
Ib:	H	CH_3	CH_3
Ic:	-$(CH_2)_4$-		CH_3
Id:	H	H	C_6H_5
Ie:	H	CH_3	C_6H_5
If:	H	C_6H_5	C_6H_5
Ig:	H	CH_3	SCH_3
Ih:	H	C_6H_5	CH_3

	R^1	R^2	R^3
Va:	H	H	CH_3
Vb:	H	CH_3	CH_3
Vc:	-$(CH_2)_4$-		CH_3
Vd:	H	H	C_6H_5
Ve:	H	CH_3	C_6H_5
Vf:	H	CH_3	SCH_3

Chart 2

of $C_{12}H_{11}N_3O_2S$ and showed a sharp nitrile band at 2158 cm^{-1} and a strong carbonyl band at 1643 cm^{-1} in the infrared (IR) spectrum. The nuclear magnetic resonance (NMR) spectrum of IVb showed two methyl signals at δ 2.56 (3H, s) and 2.64 (3H, d, J=*ca.* 1 Hz) ppm, the latter being coupled with a methine proton, whose signal appeared at δ 8.23 (1H, q) ppm. A single peak was also observed at δ 8.19 ppm, which was assigned to the C_7- or C_8-proton of the pyridazine ring. In the NMR spectrum of IVa a methine signal of the pyridazine ring was observed at δ 8.21 ppm as a singlet peak which was not coupled with the C_6-methyl protons at δ 2.99 ppm, and accordingly the singlet methyl signal at δ 2.56 ppm of IVb ought to be assigned to the methyl group at the C_6-position. The C_2-proton of the enamine type compound II (R^1=H, R^2=R^3=CH_3) appeared at δ 7.33 ppm and that of the ylide type compound III (R^1=H, R^2=R^3=CH_3) at δ 8.23 ppm in the NMR spectra (in DMSO-d_6). The above NMR

Table I. Reaction Products of I with Carbanion of Ethyl Cyanoacetate

IV	R^1	R^2	R^3	R	mp (°C)	React. Time (h)	Yield (%)	IR cm^{-1} C≡N C=O	NMR (δ)					Solvent
									C_2	C_3	C_6	C_7	R	
a	H	H	CH_3	CH_3	275—277	16	22	2160 1648	8.61	8.88	2.99	8.21	4.02	CF_3COOH
b	H	CH_3	CH_3	CH_3	290—292	4	47	2158 1684	8.23	2.64	2.56	8.19	3.69	DMSO-d_6
c	H	CH_3	CH_3	C_2H_5	218—219	4	32	2170 1650	7.49	2.62	2.48	8.16	1.16 4.20	$CDCl_3$
									8.19	2.59	2.52	8.11	1.22 4.10	DMSO-d_6
d	-$(CH_2)_4$-		CH_3	CH_3	285—286	3	47	2160 1670	1.97 (4H,m) 2.93 (4H,m)		2.48	8.08	3.64	DMSO-d_6
e	H	H	C_6H_5	CH_3	286—287	3	65	2160 1675	8.75 ($J_{2,3}$=4.5 Hz)	9.07		8.70	1.22 4.11	DMSO-d_6
f	H	H	C_6H_5	C_2H_5	228—229	2	62	2170 1650	8.47 ($J_{2,3}$=4.5 Hz)	8.86		8.70	1.22 4.14	DMSO-d_6
g	H	CH_3	C_6H_5	CH_3	296—297	16	72	2160 1658	8.30	2.72		8.82	3.70	DMSO-d_6
h	H	CH_3	C_6H_5	C_2H_5	275—277	2	54	2165 1650	8.24	2.50		8.78	1.20 4.21	DMSO-d_6
i	H	C_6H_5	C_6H_5	CH_3	287—289	40	18	2170 1670	8.88			8.62	3.64	DMSO-d_6
j	H	CH_3	SCH_3	CH_3	280—282	2	15	2150 1660	8.25	2.63	2.63	8.24	3.66	DMSO-d_6

spectral data suggested that IVb was an ylide type compound. The mass spectrum displayed a molecular ion at *m/e* 261 and fragment ions at *m/e* 230 ($M^+ - OCH_3$) and at *m/e* 203 (230-CO). As shown in Fig. 1, the ultraviolet (UV) spectrum of IVb showed an absorption maximum at 342.5 nm in methanol, which was at *ca.* 10 nm shorter wavelength compared to the maximum in tetrahydrofuran. The UV spectra of II and III are also shown in Fig. 1 for comparison. The UV spectrum of IVb in a strongly acidic medium in the presence of perchloric acid resembled that of the quaternary salt (Ib). The UV spectral data further supported the view that this compound is anhydro-8-(α-cyano-α-methoxycarbonyl)methylidene-5,8-dihydro-3,6-dimethylthiazolo[3,2-*b*]pyridazinium hydroxide, an ylide structure with a methylidene substituent at the C_8-position. When the reaction was carried out in ethanol, the ethyl ester (IVc) was obtained instead by transesterification. A similar reaction of Ia—g with the sodium salt of ethyl cyanoacetate gave the corresponding ylides (IVa—j) in 15—72% yields. The physical data and the elemental analyses of these compounds (IVa—j) are shown in Table I and in Table III, respectively.

Table II. Reaction Products of I with Carbanion of Malononitrile

V	R^1	R^2	R^3	mp (°C)	React. Time (h)	Yield (%)	IR C≡N	C=C or C=N	NMR (δ)				Solvent
									C_2	C_3	C_6	C_7	
a	H	H	CH_3	290—292	17	36	2190	1545	8.46	8.81	2.48	6.74	DMSO-d_6
							2165	1540		($J_{2,3}$=4.5 Hz)			
b	H	CH_3	CH_3	253—254	6	32	2190	1545	7.63	2.72	2.55	6.87	$CDCl_3$
							2170	1540	8.29	2.64	2.55	6.80	DMSO-d_6
									7.20	2.81	2.72	7.84	CF_3COOH
c	-$(CH_2)_4$-		CH_3	288—290	16	45	2180	1545	2.04 (4H,m)		2.48	6.71	$CDCl_3$
							2160	1535	2.96 (4H,m)				
d	H	H	C_6H_5	288—289.5	2	52	2195	1550	8.55	8.96	—	7.10	DMSO-d_6
							2170	1535	8.23	8.68	—	7.64	CF_3COOH
e	H	CH_3	C_6H_5	>300	2	60	2190	1545	8.30	2.70	—	7.09	DMSO-d_6
							2170	1535					
f	H	CH_3	SCH_3	258—259.5	2	20	2205	1538	8.27	2.51	2.63	7.50	DMSO-d_6
							2190	1530					

Table III. Analytical Data for IV and V

Compd.	Molecular formula	Analysis (%)					
		Calcd			Found		
		C	H	N	C	H	N
IVa	$C_{11}H_9N_3O_2S$	53.43	3.67	16.99	53.27	3.75	16.70
IVb	$C_{12}H_{11}N_3O_2S$	55.16	4.24	16.08	55.10	3.75	16.37
IVc	$C_{13}H_{13}N_3O_2S$	56.71	4.76	15.26	56.95	4.58	14.98
IVd	$C_{15}H_{15}N_3O_2S$	59.78	5.02	13.94	59.67	5.20	14.21
IVe	$C_{16}H_{11}N_3O_2S$	62.12	3.58	13.58	62.29	3.87	13.47
IVf	$C_{17}H_{13}N_3O_2S$	63.14	4.05	12.99	62.87	4.15	12.71
IVg	$C_{17}H_{13}N_3O_2S$	63.14	4.05	12.99	62.85	4.20	12.88
IVh	$C_{18}H_{15}N_3O_2S$	64.08	4.48	12.45	63.87	4.69	12.19
IVi	$C_{22}H_{15}N_3O_2S$	68.55	3.92	10.90	68.19	3.81	10.82
IVj	$C_{21}H_{11}N_3O_2S_2$	49.13	3.78	14.41	49.44	3.86	14.54
Va	$C_{10}H_6N_4S$	56.06	2.82	26.15	56.26	2.80	26.75
Vb	$C_{11}H_8N_4S$	57.88	3.53	24.54	57.70	3.67	24.80
Vc	$C_{14}H_{12}N_4S$	62.66	4.51	20.88	62.36	4.48	20.61
Vd	$C_{15}H_8N_4S$	65.21	2.92	20.28	65.37	2.99	19.99
Ve	$C_{16}H_{10}N_4S$	66.19	3.47	19.29	65.91	3.55	19.44

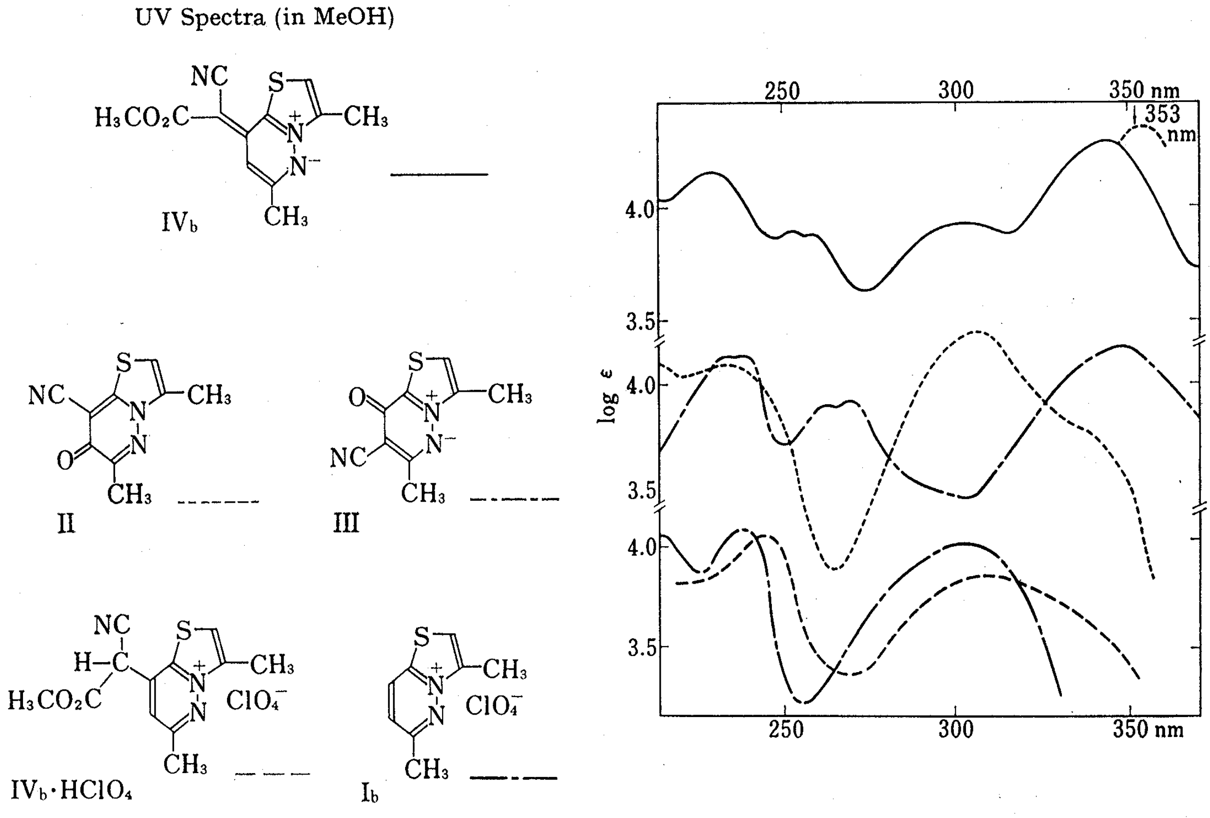


Fig. 1

On treatment with the sodium salt of malononitrile in a similar manner, Ib furnished yellow crystals of Vb in 32% yield, which melted at 253—254°C and showed two bands at 2190 and 2170 cm^{-1} in the IR spectrum. The NMR spectrum of Vb displayed a doublet peak at δ 2.64 ppm ($J=ca.$ 1 Hz, C_3–$C\underline{H}_3$) coupled with a quartet peak at δ 8.29 ppm (C_2–$\underline{H}$) and two singlet peaks at δ 2.55 (C_6–$C\underline{H}_3$) and 6.80 ppm (C_7–$\underline{H}$). In the case of V, the reaction was also initiated by the addition of the nucleophile at the C_8-position of I, followed by a substitution reaction due to atmospheric oxygen to form anhydro-8-α,α-dicyanomethylidene-thiazolo[3,2-*b*]pyridazinium hydroxide (V). On reaction with the sodium salt of ethyl malonate and phenylacetonitrile, Ie similarly gave anhydro-8-α,α-di(ethoxycarbonyl)methylidene- and anhydro-8-(α-cyano-α-phenyl)methylidene-3-methyl-6-phenylthiazolo[3,2-*b*]pyridazinium hydroxides (VI and VII) in 34% and 35% yields, respectively. The NMR spectra of VI and VII in trifluoroacetic acid showed signals of the methine proton of the side chain of their conjugate acids at δ 5.51 and δ 6.04 ppm, respectively.

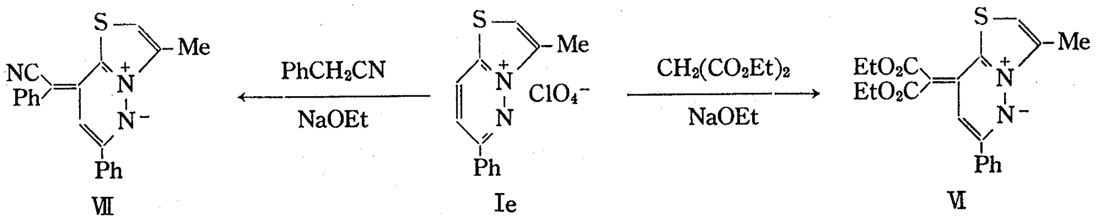


Chart 3

IVb was treated with sulfuric acid at room temperature for 3 d to give anhydro-8-(α-carboxamido-α-methoxycarbonyl)methylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium hydroxide (VIII), the cyano group being hydrolyzed. Hydrolysis of IVb in boiling 10% hydrochloric acid furnished anhydro-8-(α-cyano)methylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium hydroxide (IX) in 58% yield as a result of hydrolysis and decarboxylation of the methoxycarbonyl group. IX was also obtained by the hydrolysis of Vb in boiling 20% hydrochloric acid. It showed a strong nitrile band at 2150 cm^{-1} in the IR spectrum. The NMR spectrum of IX showed a vinylidene methine signal at δ 3.69 ppm. The strongly shielded vinylidene methine signal near δ 3.7 ppm has also been observed in the case of conjugated enamine nitriles.[7)]

Concerning the *E–Z* configuration of the unsymmetrically substituted vinylidene compounds IVa—j and VII, the less bulky cyano group seems likely to be oriented *endo* to the condensed thiazolium moiety. In contrast to the dicyanomethylidene derivative (Ve, δ 7.09 ppm), the cyanoester (IVh, δ 8.19 ppm), the cyanophenyl compound (VII, δ 8.31 ppm) and the diester derivative (VI, δ 8.36 ppm) all showed the C_7–H signal at more than 1 ppm lower field owing to the anisotropic effect of the *cis*-oriented carbonyl or phenyl group.

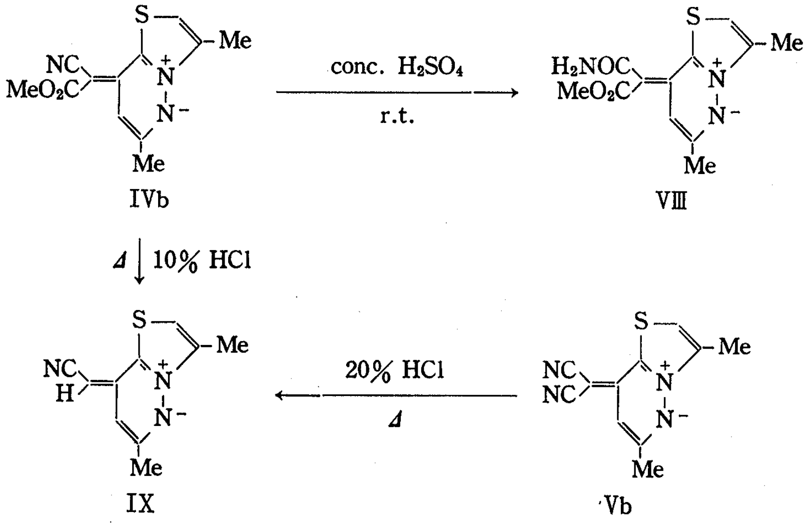
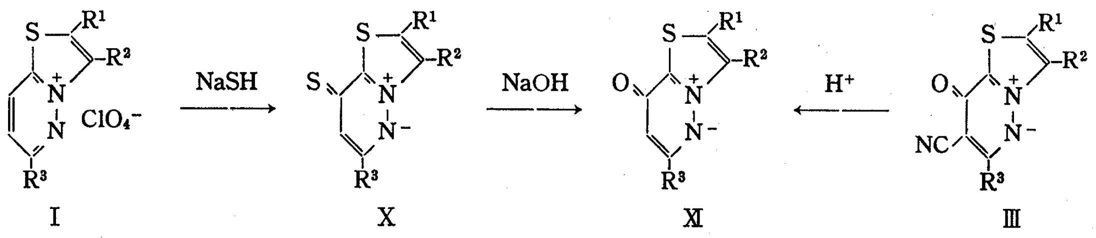


Chart 4

On reaction with sodium hydrosulfide as a nucleophile ,the salts (I) afforded yellow crystals of 8-thione ylides (X), anhydro-8-thiothiazolo[3,2-*b*]pyridazinium hydroxides, in good yields. In this case, the attack of the reagent may have occurred initially at the C_8-position. Hydrolysis of Xa with sodium hydroxide and hydrogen peroxide gave 8-oxo ylide (XIa), which was identical with the sample prepared by the previous method.[5)] 8-Oxo ylide (XIb) obtained by alkaline hydrolysis of Xc was not identical to the 7-oxo compound, which was previously obtained by acid hydrolysis of the 8-cyano-7-oxo compound (II).

We found a remarkable difference in the chemical shifts of the C_2-methine protons in the NMR spectra of these thiazolo[3,2-*b*]pyridazine derivatives in their NMR spectra. In contrast



	R^1	R^2	R^3
Xa:	H	CH_3	CH_3
Xb:	H	C_6H_5	CH_3
Xc:	H	CH_3	C_6H_5
Xd:	H	CH_3	SCH_3

	R^1	R^2	R^3
IIa, IIIa, XIa:	H	CH_3	CH_3
IIb, IIIb, XIb:	H	CH_3	C_6H_5

Chart 5

to the 8-cyano-4,7-dihydrothiazolo[3,2-*b*]pyridazine-7-ones (II), which display the methine signal at around δ 7.3 ppm, the quaternary salts (I) and the 7-cyano-8-oxo-pyridazinium ylides (III) display the methine signals at around δ 8.8 ppm and δ 8.2 ppm, respectively, in at least 0.9 ppm lower field. A low-field shift is also observed in the carbon magnetic resonance spectra of ^{13}C at the 2-position. As shown in Table IV, the chemical shifts of C_2 of the compounds (III, IV, V, VI, VII, IX, and X) are 116—120 ppm, which are in approximately 10 ppm lower field compared to those of the former compounds (II), which do not bear a positive charge on the nitrogen at the 4-position. These observations seem to support the strongly polarized structure of anhydro-5,8-dihydro-8-methylidene-thiazolo[3,2-*b*]pyridazinium hydroxide obtained in the present investigation.

Table IV. ^{13}C Chemical Shifts of I—X

Product No.	C-2	C-7	C-8
Ib	130.8	121.9	127.0
IIa	106.8	164.3	89.4
IIb	107.4	164.0	93.0
IIIa	119.7	91.0	164.5
IIIb	120.1	90.8	165.4
IVb	118.7	108.7	143.0
Vb	118.8	106.2	145.0
Ve	118.8	102.6	143.6
VI	118.0	108.2	140.9
VII	116.2	97.5	140.9
IX	115.6	100.4	144.2
Xa	119.2	123.6	167.2
Xc	119.8	120.4	168.5

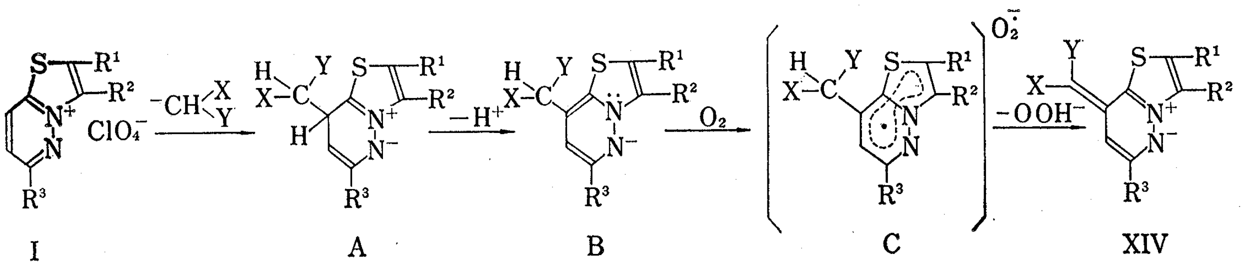


Chart 6

A plausible mechanism for the formation of the ylides (IV, V, VI, VII) by the reaction of the quaternary salts (I) with carbanions is shown in Chart 6. The nucleophilic attack of a carbanion at the C_8-position forms an adduct A, which might be more stable, due to thiazolium *N*-imine resonance, than the alternative C_7-adduct. The pi-sufficient anion (B), which is formed from A by deprotonation in the basic medium, couples with atmospheric oxygen to furnish a radical anion (C), from which hydroperoxide is eliminated to yield the ylide (XIV).[8] The reaction seems to proceed in a similar manner to that reported in the case of cyanide as a nucleophile,[5,9] with respect to the substitution reaction with oxidation of the pi-deficient thiazolium salt with a carbon nucleophile in the presence of atmospheric oxygen.

Experimental

All melting points were measured in capillary tubes and are uncorrected. The ^1H-NMR spectra were measured with a Hitachi R-22 90MC NMR spectrometer, using TMS as an internal reference. The ^{13}C-NMR spectra were measured with JEOL JNM FX60 (2500 Hz) and JNM-FX100 (4167 Hz) spectrometers. The

IR and UV spectra were measured on a JASCO IRA-I spectrometer and a Hitachi EPS-3 spectrometer, respectively. Mass spectra were recorded on a Hitachi RMS-4 instrument.

Reaction of Thiazolo[3,2-*b*]pyridazinium Perchlorates (I) with Carbanion of Ethyl Cyanoacetate. Formation of Anhydro-8-(α-cyano-α-ethoxycarbonyl)methylidene-thiazolo[3,2-*b*]pyridazinium Hydroxide (IV)——Into a solution of sodium ethoxide prepared from 55 mg (2.4 m gram atom) of metallic sodium and 15 ml of absolute EtOH, there were added 135 mg (1.2 mmol) of ethyl cyanoacetate and 1 mmol of perchlorate (I). The whole mixture was stirred at room temperature for 2—40 h. Yellow crystals that deposited were collected by filtration and recrystallized from benzene–hexane or from EtOH to give the ylides (IVc,f,h). When the reaction was carried out in MeOH, similar work-up gave the methyl esters (IVa,b,d,e,g,i,j). In the case of the reaction of Ig (R^1=H, R^2=CH_3, R^3=SCH_3), 28 mg (1.2 m gram atom) of sodium was used. Physical and analytical data are shown in Table I and Table III, respectively.

Reaction of Thiazolo[3,2-*b*]pyridazinium Perchlorates (I) with Carbanion of Malononitrile. Formation of Anhydro-8-dicyanomethylidene-thiazolo[3,2-*b*]pyridazinium Hydroxide (V)——The reaction and work-up were carried out in the same manner as described above. In the case of Ig (R^1=H, R^2=CH_3, R^3=SCH_3), the reaction was carried out with 28 mg (1.2 m gram atom) of sodium. Physical and analytical data are shown in Table II and Table III, respectively.

Reaction of Ie (R^1=H, R^2=CH_3, R^3=C_6H_5) with Carbanion of Ethyl Malonate. Formation of Anhydro-8-α,α-di(ethoxycarbonyl)methylidene-3-methyl-6-phenylthiazolo[3,2-*b*]pyridazinium Hydroxide (VI)——Into a solution of sodium ethoxide prepared from 55 mg (2.4 m gram atom) of sodium and 15 ml of absolute EtOH, there were added 192 mg (1.2 mmol) of ethyl malonate and 326 mg (1 mmol) of Ie. The mixture was stirred at room temperature for 20 h. Orange crystals that precipitated were collected by filtration and recrystallized from EtOH to give 130 mg (34% yield). mp 243—244°C (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1712 (sh), 1703, 1593. NMR (in DMSO-d_6) δ: 1.24 (6H, t, J=7.5 Hz), 2.70 (3H, d, J=*ca.* 1 Hz), 4.12 (4H, q, J=7.5 Hz), 8.22 (1H, m), 8.36 (1H, s). (in CF_3COOH) δ: 1.41 (6H, t, J=7.5 Hz), 3.15 (3H, d, J=*ca.* 1 Hz), 4.49 (4H, q, J=7.5 Hz), 5.51 (1H, s), 8.29 (1H, m), 8.71 (1H, s). UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 257 (4.44). $\lambda_{\max}^{\text{THF}}$ nm (log ε); 258 (4.41), 400 (4.09). MS *m/e*: 384 (M$^+$). *Anal.* Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.23; H, 5.36; N, 7.11.

Reaction of Ie (R^1=H, R^2=CH_3, R^3=C_6H_5) with Carbanion of Phenylacetonitrile. Formation of Anhydro-8-(α-cyano-α-phenyl)methylidene-3-methyl-6-phenylthiazolo[3,2-*b*]pyridazinium Hydroxide (VII)——Phenylacetonitrile (140 mg, 1.2 mmol) was added to 15 ml of absolute EtOH solution containing 55 mg (2.4 m gram atom) of sodium, then 326 mg (1 mmol) of Ie was added and the mixture was stirred at room temperature for 2 h. Red crystals that deposited were collected by filtration and recrystallized from EtOH to give 120 mg (35% yield), mp 216°C (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2140, 1538. NMR (in DMSO-d_6) δ: 2.58 (3H, d, J=*ca.* 1 Hz), 8.12 (1H, m), 8.31 (1H, s), (in CF_3COOH) δ: 2.99 (3H, d, J=*ca.* 1 Hz), 6.04 (1H, s), 8.17 (1H, m), 8.76 (1H, s), 7.58 (5H, arom.), 7.54—7.84 (3H, arom.), 8.11—8.34 (2H, arom.). UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 257 (4.42), 400 (4.22). $\lambda_{\max}^{\text{THF}}$ nm (log ε): 259 (4.39), 415 (4.22). MS *m/e*: 341 (M$^+$). *Anal.* Calcd for $C_{21}H_{15}N_3S$: C, 73.87; H, 4.43; N, 12.31. Found: C, 73.59; H, 4.70; N, 12.06.

Hydrolysis of Anhydro-8-(α-cyano-α-methoxycarbonyl)methylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium Hydroxide (IVb) with 10% Hydrochloric Acid——A suspension of the ylide (IVb, 100 mg) in 10% HCl (8 ml) was refluxed for *ca.* 1 h until IVb dissolved. After cooling, the resulting solution was basified with Na_2CO_3 to precipitate red crystals, which were collected by filtration. Recrystallization from benzene–hexane afforded 45 mg (58% yield) of anhydro-8-cyanomethylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium hydroxide (IX). mp 174—177°C (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2150, 1545. NMR (in $CDCl_3$) δ: 2.33 (3H, s), 2.60 (3H, d, J=*ca.* 1 Hz), 3.69 (1H, m), 6.44 (1H, s), 7.26 (1H, m), (in DMSO-d_6) δ: 2.30 (3H, s), 2.53 (3H, d, J=*ca.* 1 Hz), 3.75 (1H, s), 6.24 (1H, s), 8.00 (1H, m). UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 250 (3.98), 304 (4.12), 342.5 (4.27), 453 (3.62). *Anal.* Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 58.89; H, 4.70; N, 20.44.

Hydrolysis of Anhydro-8-(α-cyano-α-methoxycarbonyl)methylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium Hydroxide (IVb) with conc. Sulfuric Acid——A solution of the ylide (IVb, 100 mg) in 1 ml of conc. H_2SO_4 was allowed to stand at room temperature for 3 d. The mixture was poured into ice water and basified with Na_2CO_3. The resulting solution was extracted with $CHCl_3$ then the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give 110 mg of red crystals, which were recrystallized from benzene–hexane to yield 75 mg (71% yield) of anhydro-8-(α-carboxamido-α-methoxycarbonyl)methylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium hydroxide (VIII). mp 150—151°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3380, 1600 (br s). NMR (in $CDCl_3$) δ: 2.68 (3H, s), 2.69 (3H, d, J=*ca.* 1 Hz), 3.67 (3H, s), 7.59 (1H, m), 7.93 (1H, m). (in DMSO-d_6) δ: 2.65 (3H, s), 2.66 (3H, d, J=*ca.* 1 Hz), 3.53 (3H, s), 7.91 (1H, s), 8.29 (1H, m). *Anal.* Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.67; H, 4.79; N, 14.78. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 240 (4.26), 257.5 (4.22), 315 (3.91), 435 (3.62).

Hydrolysis of Anhydro-8-α,α-dicyanomethylidene-3,6-dimethylthiazolo[3,2-*b*]pyridazinium Hydroxide (Vb) with 20% Hydrochloric Acid——A suspension of the ylide (Vb, 90 mg) in 20% HCl (8 ml) was refluxed for *ca.* 1 h until Vb dissolved. After cooling, the resulting solution was basified with Na_2CO_3 to precipitate red crystals, which were collected by filtration to yield 80 mg. Recrystallization from benzene–hexane afforded 30 mg (37% yield), mp 174—177°C (dec.). The product did not show any depression of melting point on admixture with an authentic sample of the ylide prepared from IVb. The product was also identified by comparing its IR and NMR spectra with those of the authentic sample.

Reaction of Ib ($R^1=H$, $R^2=R^3=CH_3$) with Sodium Hydrosulfide. Formation of Anhydro-3,6-dimethyl-8-mercaptothiazolo[3,2-*b*]pyridazinium Hydroxide (Xa)——A solution of sodium ethoxide prepared from 161 mg (7 m gram atom) of metallic sodium in 25 ml of absolute EtOH was saturated with gaseous hydrogen sulfide under ice-cooling, then 795 mg (3 mmol) of the quaternary salt (Ib) was added all at once under stirring. The salt dissolved in the solution and yellow crystals precipitated after stirring for 1 h at room temperature. The solution was stirred for 24 h, then the yellow crystals were collected by filtration to give 415 mg. The mother liquor was evaporated to dryness *in vacuo* and the residue was shaken with $CHCl_3$–H_2O. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated to give a yellow oil. This oil was chromatographed on a silica gel column (2% MeOH–$CHCl_3$). The first fraction gave 40 mg of a yellow oil with mercaptan-like odor, which was not investigated further. The second fraction gave 100 mg of crystals, which were combined with the previous crystals; 87.6% total yield. Recrystallization from benzene and MeOH gave Xa, mp 229—230°C. IR ν_{max}^{KBr} cm^{-1}: 3060, 1480, 1428, 1390, 1383, 1320, 1283, 1180, 1133, 945, 880, 810. NMR (in $CDCl_3$) δ: 2.53 (3H, s), 2.69 (3H, d, $J=ca.$ 1 Hz), 7.61 (2H, s). *Anal.* Calcd for $C_8H_8N_2S_2$: C, 48.95; H, 4.10; N, 14.27. Found: C, 48.91; H, 3.93; N, 14.57.

Reaction of Ih ($R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$) with Sodium Hydrosulfide. Formation of Anhydro-8-mercapto-6-methyl-3-phenylthiazolo[3,2-*b*]pyridazinium Hydroxide (Xb)——A solution of sodium ethoxide prepared from 161 mg (7 m gram atom) of metallic sodium in 25 ml of absolute EtOH was saturated with gaseous hydrogen sulfide under ice-cooling, then 978 mg (3 mmol) of the quaternary salt (Ih) was added all at once under stirring. After being stirred for 2 h at room temperature, the reaction mixture was colored brown. The solution was evaporated to dryness *in vacuo* after further stirring for 1.5 h and the residue was shaken with H_2O–$CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated to give a brown oil, which was chromatographed on a silica gel column (2% MeOH–$CHCl_3$). Both the first and the second fractions gave small amounts of yellow oils which were not investigated further. The third fraction gave 250 mg of yellow crystals, which were recrystallized from EtOH, mp 160.5—162°C. IR ν_{max}^{KBr} cm^{-1}: 3070, 1475, 1440, 1384, 1303, 1260, 1163, 1160, 940, 753, 682. NMR (in $CDCl_3$) δ: 2.45 (3H, s), 7.45—7.89 (7H, arom.). *Anal.* Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84. Found: C, 60.32; H, 4.21; N, 10.91.

Reaction of Ie ($R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$) with Sodium Hydrosulfide. Formation of Anhydro-8-mercapto-3-methyl-6-phenylthiazolo[3,2-*b*]pyridazinium Hydroxide (Xc)——A solution of sodium ethoxide prepared from 161 mg (7 m gram atom) of metallic sodium in 25 ml of absolute EtOH was saturated with gaseous hydrogen sulfide under ice-cooling, then 978 mg (3 mmol) of the quaternary salt (Ie) was added all at once under stirring. The salt dissolved into the solution and soon yellow crystals precipitated. The solution was stirred for 6 h at room temperature, then the crystals were collected by filtration to give 540 mg. The mother liquor was evaporated to dryness *in vacuo* and the residue was chromatographed on a silica gel column (2% MeOH–$CHCl_3$). The first fraction gave 50 mg of a yellow oil and the second gave 60 mg of yellow needles (mp 145—155°C), which were not investigated further. The third fraction gave 20 mg of yellow crystals which were identical with the above-mentioned precipitated crystals; 72.2% total yield. Recrystallization from benzene–$CHCl_3$ gave yellow needles, mp 259—263°C. IR ν_{max}^{KBr} cm^{-1}: 3100, 1480, 1385, 1325, 1280, 1220, 1180, 1125, 1100, 890, 870, 770, 685. NMR (in DMSO-d_6) δ: 2.71 (3H, d, $J=ca.$ 1 Hz), 8.00 (1H, s), 8.27 (1H, m). *Anal.* Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84. Found: C, 60.19; H, 3.97; N, 10.78.

Reaction of Ig ($R^1=H$, $R^2=CH_3$, $R^3=SCH_3$) with Sodium Hydrosulfide——A solution of sodium methoxide prepared from 46 mg (2 m gram atom) of metallic sodium in 15 ml absolute MeOH was saturated with gaseous hydrogen sulfide under ice-cooling, then 296 mg (1 mmol) of the quaternary salt (Ig) was added all at once under stirring. The salt dissolved into the solution and yellow crystals slowly precipitated after stirring for 3 h. The solution was stirred at room temperature overnight, then the yellow crystals were collected by filtration to give 110 mg. The filtrate was evaporated to dryness *in vacuo* and the residue was shaken with H_2O–$CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column (5% MeOH–$CHCl_3$). The first fraction gave 40 mg of crystals, which were identical with the above-mentioned crystals; 65.8% total yield. Recrystallization from EtOH gave yellow crystals, mp 210—210.5°C. NMR (in $CDCl_3$) δ: 2.60 (3H, s), 2.68 (3H, d, $J=ca.$ 1 Hz), 7.45 (2H, s). *Anal.* Calcd for $C_8H_8N_2S_3$: C, 42.11; H, 3.53; N, 12.28. Found: C, 42.57; H, 3.61; N, 12.62. The second fraction gave 14 mg (7.7% yield) of yellow crystals, which were identical with the material previously prepared.

Alkaline Hydrolysis of Xa——A suspension of the ylide (Xa, 100 mg) in 10 ml of acetone was treated with 2 ml of 10% aq. solution of NaOH and 1 ml of 30% H_2O_2. The ylide largely dissolved and the solution became colored slightly red. The solution was stirred for a further 1 h at room temperature, then a small amount of acetone was removed by evaporation to precipitate white feather-like crystals. Recrystallization from benzene gave anhydro-3,6-dimethyl-8-oxothiazolo[3,2-*b*]pyridazinium hydroxide (XIa), mp 177—180°C. XIa was identical with the material previously prepared.[5)]

Alkaline Hydrolysis of Xc——A suspension of the ylide (Xc, 100 mg) was treated with 3 ml of 10% aq. solution of NaOH and 1 ml of 30% H_2O_2, and the mixture was stirred for 2 h at room temperature. The reaction mixture was refluxed for *ca.* 30 min until the disappearance of the yellow color. After removal of small amounts of MeOH, white crystals that precipitated were collected by filtration, dried and recrystallized from benzene to give white needles, anhydro-3-methyl-8-oxo-6-phenylthiazolo[3,2-*b*]pyridazinium hydroxide (XIb), mp 153—154°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3500, 3400, 1562, 1550, 1485. NMR (in $CDCl_3$) δ: 2.73 (3H, d, *J*=*ca.* 1 Hz), 6.98 (1H, s), 7.50 (1H, m). *Anal.* Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.17; H, 4.19; N, 11.25.

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References and Notes

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