Azole Chemistry. VI. (1). Tetrazolo[5,4-*b*][1,3]thiazinium Salts.

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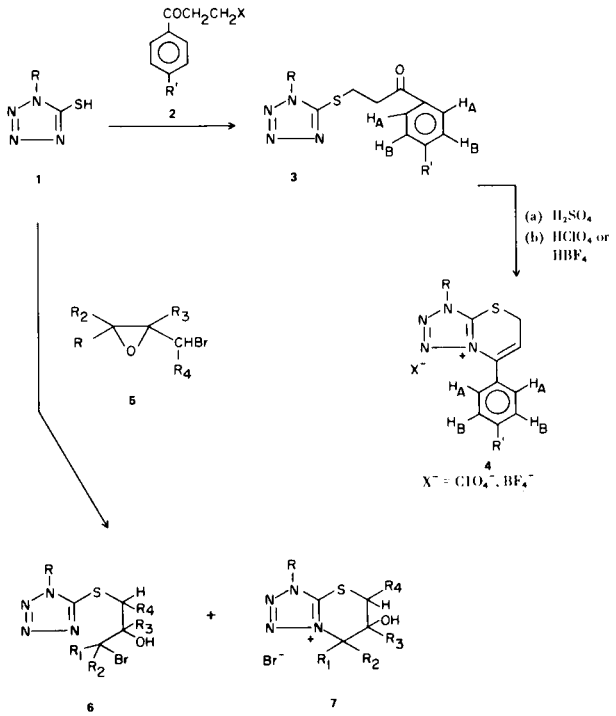
Cyclodehydration of tetrazolyl γ-keto sulfides, prepared by treatment of β-halo ketones with 5-mercapto-1-substituted-1,2,3,4-tetrazoles (**1**), gave 1,5-diaryl-7*H*-tetrazolo[5,4-*b*][1,3]thiazinium salts in reasonable yields. Reaction of **1** with epoxy bromides afforded 6-hydroxy-1-substituted-6,7-dihydro-5*H*-tetrazolo[5,4-*b*][1,3]thiazinium bromides. The spectral properties of the fused thiazinium salts are discussed.

There has been considerable interest from a medicinal chemistry viewpoint in the synthesis of various simple and fused 5-substituted tetrazoles (2). Since a number of 1,3-thiazine derivatives have demonstrated physiological activity (3), it seemed conceivable that a heterocyclic system containing a 1,3-thiazine ring fused to a 5-substituted tetrazole ring might exhibit interesting pharmacological properties. This paper reports two synthetic approaches to the tetrazolo[5,4-*b*][1,3]thiazine system which, to our knowledge, has not been previously described.

SCHEME I



Results and Discussion.

Tetrazolo[5,4-*b*][1,3]thiazinium salts were prepared by annelation of a thiazine ring to a tetrazole ring (Scheme I). One approach involved initial condensation of a 5-mercapto-1-substituted-1,2,3,4-tetrazole (**1**) with a β-halo ketone (**2**) in refluxing tetrahydrofuran (THF) to form a tetrazolyl γ-keto sulfide (**3**) in 35-82% yield. The yields, melting points, and analytical data for **3** are listed in Table I.

All of the γ-keto sulfides exhibited intense carbonyl stretching in the infrared (ir) at 1675-1680 cm^{-1} (Table

TABLE I

Yields, Melting Points and Analytical Data for **3**

3 R =, R' =	Formula	Yield, %	M.p. °C	Calcd., % C	H	N	S	Found, % C	H	N	S
C_6H_5, H	$C_{16}H_{14}N_4OS$	68	98-100	61.93	4.55	18.05	10.31	62.01	4.58	18.43	10.38
C_6H_5, Br	$C_{16}H_{13}BrN_4OS$	35	129-130	49.37	3.36	14.39	8.24	49.08	3.40	14.49	8.61
C_6H_5, F	$C_{16}H_{13}FN_4OS$	70	109-111	58.53	3.99	17.06	9.77	58.71	3.79	17.04	10.02
p-ClC_6H_4, F	$C_{16}H_{12}ClFN_4OS$	82	106-107	52.97	3.33	15.44	8.84	53.34	3.30	15.18	9.02
p-ClC_6H_4, Br	$C_{16}H_{12}BrClN_4OS$	51	154-155	45.35	2.85	13.22	7.57	45.35	2.60	13.27	7.81
p-ClC_6H_4, Cl	$C_{16}H_{12}Cl_2N_4OS$	70	138-139	50.67	3.19	14.77	8.45	50.65	3.10	14.71	8.26
C_6H_{11}, F	$C_{16}H_{19}FN_4OS$	60	117-118	57.47	5.73	16.75	9.59	57.48	5.89	16.48	9.81

TABLE II

IR Carbonyl Stretching Bands (Potassium Bromide) and NMR Spectral Data for **3**

3 R =, R′ =	ir, ν_{CO}, cm^{-1}	nmr [solvent] (a), ppm
C_6H_5, H	1675	3.72 (s, 4H, $SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.65 (s, 5H, C_6H_5N-), 7.40-8.05 (m, 5H, H_A, H_B, R′ = H) [CD_3NO_2]
C_6H_5, Br	1678	3.72 (t, 4H, -$SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.57 (s, 5H, C_6H_5N-), 7.60 (d, 2H, H_B, J_{AB} = 9.0 H_z), 7.87 (d, 2H, H_A) [$CDCl_3$]
C_6H_5, F	1680	3.68 (s, 4H, -$SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.33 (t, 2H, H_B, $J_{AB} \sim J_{B\text{-}F^{19}}$ = 8.5 H_z), 7.67 (s, 5H, C_6H_5N-), 8.08 (dd, 2H, H_A, $J_{A\text{-}F^{19}}$ = 5.7 H_z) [$(CD_3)_2SO$]
p-ClC_6H_4-, F	1679	3.72 (t, 4H, -$SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.15 (t, 2H, H_B, $J_{AB} \sim J_{B\text{-}F^{19}}$ = 8.0 H_z), 7.53 (s, 4H, *p*-ClC_6H_4N-), 8.02 (dd, 2H, H_A, $J_{A\text{-}F^{19}}$ = 5.5 H_z) [$CDCl_3$]
p-ClC_6H_4⁻, Br	1678	3.67 (s, 4H, -$SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.65 (s, 4H, *p*-$ClC_6H_4N$-), 7.67 (d, 2H, H_B, J_{AB} = 9Hz), 7.93 (d, 2H, H_A) [$(CD_3)_2SO$]
p-ClC_6H_4⁻, Cl	1679	3.70 (t, 4H, -$SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.47 (d, 2H, H_B, J_{AB} = 9.0 H_z), 7.59 (s, 4H, *p*-ClC_6H_4N-), 7.95 (d, 2H, H_A) [$(CD_3)_2SO$]
C_6H_{11}, F	1680	1.20-2.20 (m, 10H, $(CH_2)_5$), 3.20-3.45 (m, 1H, >CHN-), 3.70 (s, 4H, $SCH_2CH_2\overset{O}{\overset{\|\|}{C}}$-), 7.27 (t, 2H, H_B, $J_{AB} \sim J_{B\text{-}F^{19}}$ = 8.5 H_z), 8.05 (dd, 2H, H_A, $J_{A\text{-}F^{19}}$ = 5.5 H_z) [$(CD_3)_2SO$]

(a) Chemical shifts in parts per million (δ) relative to TMS: s = singlet; d = doublet; t = triplet; dd = doublet of doublets; m = multiplet.

TABLE III

Yields, Melting Points and Analytical Data for **4**

4 R =, R′ =, X^- =	Formula	Yield, %	M.p. °C dec.	Calcd. % C	H	N	S	Found, % C	H	N	S
C_6H_5, H, BF_4	$C_{16}H_{13}BF_4N_4S$	51	201-203	50.55	3.45	14.73	8.43	50.81	3.43	14.94	8.07
C_6H_5, Br, ClO_4	$C_{16}H_{12}BrClN_4O_4S$	47	242-244	40.74	2.56	11.88	6.80	40.51	2.45	11.78	7.33
C_6H_5, F, ClO_4	$C_{16}H_{12}ClFN_4O_4S$	30	210-212	46.78	2.94	13.64	7.80	47.01	2.84	13.48	7.76
p-$ClC_6H_4^-$, F, BF_4	$C_{16}H_{11}BClF_5N_4S$	29	205-206	44.42	2.56	12.95	7.41	44.81	2.82	13.09	7.64
p-$ClC_6H_4^-$, Br, ClO_4	$C_{16}H_{11}BrCl_2N_4O_4S$	49	213-215	37.97	2.19	11.07	6.33	38.03	1.97	10.97	6.61
p-$ClC_6H_4^-$, Cl, ClO_4	$C_{16}H_{11}Cl_3N_4O_4S$	46	200-202	41.62	2.40	12.13	6.94	41.39	2.26	12.20	6.80

TABLE IV

Pertinent IR (Potassium Bromide) and NMR (DMSO-d_6) Spectral Data for **4**

4 R =, R′ =, X^- =	ir $\nu_{ClO_4^-}$	ir $\nu_{BF_4^-}$	nmr (a), ppm
		cm^{-1}	
C_6H_5, H, BF_4		1055	4.33 (d, 2H, SCH_2-), 6.57 (t, 1H, >CH=), 7.65 (s, 5H, H_A, H_B, R′ = H), 7.85 (s, 5H, C_6H_5N-)
C_6H_5Br, ClO_4	1085		4.28 (d, 2H, SCH_2), 6.66 (t, 1H, >CH=), 7.61 (d, 2H, H_B, J_{AB} = 8.5 Hz), 7.78 (s, 5H, C_6H_5N-), 7.89 (d, 2H, H_A)
C_6H_5, F, ClO_4	1080		4.13 (d, 2H, SCH_2-), 6.33 (t, 1H, >CH=), 7.20 (t, 2H, H_B, $J_{AB} \sim J_{B\text{-}F^{19}}$ = 8.0 Hz), 7.65 (s, 5H, C_6H_5N-), 7.30-7.90 (m, 2H, H_A)
p-$ClC_6H_4^-$, F, BF_4		1045	4.24 (d, 2H, SCH_2-), 6.47 (t, 1H, >CH=), 7.08 (t, 2H, H_B, $J_{AB} \sim J_{B\text{-}F^{19}}$ = 8.0 Hz), 7.51 (s, 4H, *p*-ClC_6H_4N-), 7.76 (dd, 2H, H_A, $J_{A\text{-}F^{19}}$ = 5.0 Hz)
p-$ClC_6H_4^-$, Br, ClO_4	1085		4.33 (d, 2H, SCH_2-), 6.62 (t, 1H, >CH=), 7.63 (d, 2H, H_B, J_{AB} = 9 Hz), 7.86 (d, 2H, H_A), 7.87 (s, 4H, *p*-ClC_6H_4N-)
p-$ClC_6H_4^-$, Cl, ClO_4	1090		4.37 (d, 2H, SCH_2-), 6.63 (t, 1H, >CH=), 7.70 (s, 4H, H_A, H_B), 7.93 (s, 4H, *p*-ClC_6H_4N-)

(a) Chemical shifts in parts per million (δ) relative to TMS: s = singlet; d = doublet; t = triplet; dd = doublet of doublets; m = multiplet.

TABLE V

Products Obtained from Reactions of Epoxy Bromides (**5**) with **1**

1, R =	**5** R_1 =, R_2 =, R_3 =, R_4 =	Yield, % **6**	Yield, % **7**	M.p. °C (a) **7**	Calcd., % C	Calcd., % H	Calcd., % N	Product	Found, % C	Found, % H	Found, % N
C_6H_5	H, H, H, H	47	46	170-172	38.11	3.51	17.77	**6**	38.05	3.74	17.93
								7	38.35	3.84	17.46
C_6H_5	H, H, H, CH_3	52	21	174-177	40.13	3.98	17.02	**6**	40.07	3.82	16.99
								7	39.91	4.23	16.93
C_6H_5	H, H, CH_3, H	74	8	233-235	40.13	3.98	17.02	**6**	40.11	4.23	17.24
								7	39.97	4.11	16.91
C_6H_5	CH_3, CH_3, H, H	68	26	208-210	41.95	4.41	16.33	**6**	42.00	4.34	16.17
								7	41.71	4.59	15.96
C_6H_{11}	H, H, H, H	63	28	194-195	37.39	5.33	17.44	**6**	37.07	5.54	17.28
								7	37.39	5.00	16.91
C_6H_{11}	H, H, CH_3, H	42	18	231-232	39.41	5.71	16.71	**6**	39.20	5.81	16.93
								7	39.07	6.03	16.76

(a) Compounds of structure **6** were oils which decomposed on attempted reduced pressure distillation.

H). The protons for the $-SCH_2CH_2\overset{O}{\overset{\|}{C}}-$ group gave a signal in the nuclear magnetic resonance (nmr) spectrum at δ 3.67-3.72 and the remainder of the spectrum was consistent with the assigned structure (Table II).

Reaction of **3** with concentrated sulfuric acid, followed by treatment with perchloric or tetrafluoroboric acid, gave the 1,5-diaryl-7*H*-tetrazolo[5,4-*b*][1,3]thiazinium perchlorate or tetrafluoroborate (**4**), respectively. The pertinent physical data are given in Tables III and IV. The nmr spectra gave a characteristic doublet absorption in the region of δ 4.13-4.37 which was assigned to the methylene protons. The vinylic proton appeared as a triplet at δ 6.33-6.66.

The second route to the titled compounds is based on the recently reported reaction of epoxy halides with mercaptoimidazoles and related compounds (4). Treatment of **1** with epoxy bromides of structure **5**, in hot 2-butanone, resulted in the formation of the bromo alcohol **6** and the 6-hydroxy-1-substituted-6,7-dihydro-5*H*-tetrazolo[5,4-*b*][1,3]thiazinium bromide (**7**) (Table V). A broad hydroxyl absorption was observed in the ir of **6** at 3350-3400 cm^{-1} while carbon-oxygen stretching occurred in the region of 1070-1078 (secondary alcohol) or 1144-1148 cm^{-1} (tertiary alcohol). Carbon-oxygen stretching was observed at 1123-1129 cm^{-1} for **7** when R_3 = CH_3, while the same type of vibration appeared in the region of 1078-1083 cm^{-1} when R_3 = H (for R_3 = H or CH_3, ν_{OH} = 3210-3260 cm^{-1}). The nmr spectral data for **6** and **7** are given in Table VI.

EXPERIMENTAL

General.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were carried out by Hoffmann-LaRoche Microanalytical Laboratory and by Pascher Mikroanalytisches Laboratorium, Bonn, Germany. The ir spectra were recorded on a Perkin-Elmer 457 spectrometer while a Varian A-60 spectrometer was used for nmr spectra.

General Procedure for the Reaction of **1** with beta-Halo Ketones (5).

A mixture of the mercaptotetrazole (**1**) and β-halo ketone (**2**-equimolar quantities) in dry THF was refluxed with stirring for 3-9 hours. The solution was cooled, filtered, and the filtrate evaporated *in vacuo*. The residue from flash evaporation was recrystallized from benzene/pentane, THF/pentane, or THF/ethanol to give analytically pure γ-keto sulfide (**3**). The melting points, yields, and analyses of these compounds are given in Table I.

1,5-Diaryl-7*H*-tetrazolo[5,4-*b*][1,3]thiazinium Salts (**4**).

A concentrated sulfuric acid solution of the γ-keto sulfide **3** (10-15 ml. of concentrated sulfuric acid/g. of **3**) was allowed to stand at room temperature for 3-7 days. In order to isolate **4** as the perchlorate salt, 60% perchloric acid was added to the *ice-cold* solution until it became cloudy. Subsequent addition of water precipitated out the thiazinium perchlorate which was recrystallized, if necessary, from methanol or THF/methanol. Addition of 48% HBF to the chilled sulfuric acid solution precipitated **4** as the tetrafluoroborate salt. The melting points, yields, and analytical data for **4** are listed in Table III.

General Procedure for the Preparation of 6-Hydroxy-1-substituted-6,7-dihydro-5*H*-tetrazolo[5,4-*b*][1,3]thiazinium Bromides (**7**).

Equimolar quantities of **1** and the epoxy bromides (**5**) were refluxed in 2-butanone for 1-2 days. The solution was cooled

TABLE VI

Pertinent IR and NMR Spectral Data for **6** and **7**

6 or **7**	R =, R_1 =, R_2 =, R_3 =, R_4 =	Phase (a)	ir νOH, cm^{-1}	νCO	nmr [solvent] (b), ppm
6	C_6H_5, H, H, H, H	N	3370	1072	3.50-5.00 (m, 6H, -$CH_2$$\underset{\text{OH}}{\text{C}}HCH_2$-), 7.69 (s, 5H, C_6H_5) [$(CD_3)_2SO$]
7	C_6H_5, H, H, H, H	K	3240	1083	3.75 (s, 2H, SCH_2-), 4.81 (s(br), 3H, NCH_2-, >CH-O-), 6.22 (d, 1H, OH), 7.82 (s, 5H, C_6H_5) [$(CD_3)_2SO$]
6	C_6H_5, H, H, H, CH_3	N	3400	1078	1.81 (d, 2H, CH_3), 3.40-5.00 (m, 5H, SCH$\underset{\text{OH}}{\text{C}}HCH_2$Br), 7.66 (s, 5H, C_6H_5N) [$CDCl_3$]
7	C_6H_5, H, H, H, CH_3	K	3210	1082	1.71 (d, 2H, CH_3), 3.73 (d, 2H, NCH_2-), 4.60 (m, 1H, >CH-O-), 5.01 (m, 1H, >C*H*CH_3), 6.38 (d, 1H, OH), 7.87 (s, 5H, C_6H_5) [$(CD_3)_2SO$]
6	C_6H_5, H, H, CH_3, H	K	3390	1148	1.50 (s, 3H, CH_3), 3.57 (s, 2H, CH_2Br), 3.73 (s, 2H, SCH_2-), 7.58 (s, 5H, C_6H_5) [$CDCl_3$]
7	C_6H_5, H, H, CH_3, H	K	3260	1123	1.60 (s, 3H, CH_3), 3.65 (s, 2H, SCH_2-), 4.73 (q, 2H, NCH_2-), 6.07 (s, 1H, OH), 7.80 (s, 5H, C_6H_5) [$(CD_3)_2SO$]
6	C_6H_5, CH_3, CH_3, H, H	N	3380	1076	1.58 (s, 6H, CH_3), 3.71 (s, 2H, SCH_2-), 4.75 (m, 1H, >CH-O-), 7.62 (s, 5H, C_6H_5) [$CDCl_3$]
7	C_6H_5, CH_3, CH_3, H, H	K	3220	1078	1.78 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 3.72 (s, 2H, SCH_2-), 4.57 (m, 1H, >CH-O), 6.41 (d, 1H, OH), 8.00 (s, 5H, C_6H_5) [$(CD_3)_2SO$]
6	C_6H_{11}, H, H, H, H	N	3350	1070	1.20-2.20 (m, 10H, $(CH_2)_5$), 3.20-3.40 (m, 1H, >CHN<), 3.58 (d, 2H, -CH_2Br), 3.63 (d, 2H, SCH_2-), 3.80-4.10 (br, 1H, OH), 4.70-5.00 (m, 1H, >CH-O-) [$(CD_3)_2SO$]
7	C_6H_{11}, H, H, H, H	K	3245	1083	1.20-2.30 (m, 10H, $(CH_2)_5$) 3.20-3.40 (m, 1H, >CHN<) 3.72 (s, 2H, SCH_2), 4.75 (s(br), 3H, NCH_2, >CH-O), 6.18 (d, 1H, OH) [$(CD_3)_2SO$]
6	C_6H_{11}, H, H, CH_3, H	N	3395	1144	1.20-2.25 (m, 10H, $(CH_2)_5$), 1.54 (s, 3H, CH_3), 3.20-3.40 (m, 1H, >CHN<), 3.59 (s, 2H, CH_2Br), 3.67 (s, 2H, SCH_2) [$(CD_3)_2SO$]
7	C_6H_{11}, H, H, CH_3, H	K	3250	1129	1.55 (s, 3H, CH_3), 1.20-2.20 (m, 10H, $(CH_2)_5$), 3.20-3.40 (m, 1H, >CH-N<), 3.62 (s, 2H, SCH_2), 4.53 (s, 2H, NCH_2), 6.10 (s, 1H, OH) [$(CD_3)_2SO$]

(a) N = neat, K = potassium bromide. (b) Chemical shifts in parts per million (δ) relative to TMS: s = singlet; d = doublet; q = quartet, m = multiplet.

and the thiazinium bromide filtered, washed well with ether, and the washings added to the filtrate. The oil obtained on flash evaporation of the filtrate was chromatographed on Florisil or *neutral* alumina. Elution with benzene gave the bromoalcohol **6**. In Table V are listed yields, analytical data, and melting points for **6** and **7**.

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(5) The mercaptotetrazoles were purchased from Maybridge Chemical Company, Cornwall, England. The β-halo ketones were obtained from Aldrich Chemical Company, see reference 4 for sources of epoxy bromides.