

## Azole Chemistry. V (1). Synthesis and Spectral Properties of Thiazolo[3,2-*d*]tetrazolium Salts

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Received September 15, 1972

Thiazolo[3,2-*d*]tetrazolium salts were obtained by treatment of 5-mercapto-1-phenyl-1,2,3,4-tetrazole with  $\alpha$ -bromo ketones followed by cyclodehydration. The spectral properties of the salts and the  $\beta$ -keto sulfide precursors were investigated.

The synthesis of heteroaromatic salts containing a fused thiazole ring has been a subject of considerable interest in recent years (2-8). This paper describes the preparation and spectral properties of a series of thiazolo[3,2-*d*]tetrazolium salts, formed by annelation of a thiazole ring to a tetrazole ring.

Although much work has been done on simple tetrazoles (9), relatively few publications have appeared in the literature concerning a tetrazolium ring fused to at least one other heterocyclic ring (10). Attainment of the title salts was not only of interest from a synthetic point of view, but previous findings (9) (on simpler tetrazoles and tetrazolium salts) indicated potential uses of such salts as medicinal agents and in photographic processes. It was also of interest to investigate the spectral characteristics of the salts.

Our approach to the synthesis of the thiazolo[3,2-*d*]tetrazolium salts (4) is presented in Scheme 1. Condensation of a mercaptotetrazole with an  $\alpha$ -bromo ketone

(2) would give the  $\beta$ -keto sulfide and subsequent dehydration of the latter under strongly acidic conditions would result in formation of 4.

Treatment of 5-mercapto-1-phenyl-1,2,3,4-tetrazole (1) with an equimolar quantity of 2 in refluxing tetrahydrofuran (THF) gave 3 in generally good yields. We found THF to be superior to all other solvents (e.g., 2-butanone) (1a) for effecting condensation reactions of this kind both because of ease of reaction and product purity (in several instances, the precipitated product was analytically pure and required no further purification). Rearrangement of 1 to 5-anilino-1,2,3,4-thiazotriazole did not occur under the reaction conditions (11). The melting points, yields, and analytical data for the tetrazolyl  $\beta$ -keto sulfides are given in Table I. Pertinent spectral data is presented in Tables II and III.

The infrared (ir) carbonyl stretching band (potassium bromide disc) for 3, when R is aromatic, occurs in the region of 1660-1683  $\text{cm}^{-1}$  while the same absorption appears at 1703-1715  $\text{cm}^{-1}$  when R is aliphatic or cyclic (Table II). None of the  $\beta$ -keto sulfides exhibited absorption bands in the 1335-1390  $\text{cm}^{-1}$  region characteristic of thiocarbonyl stretching of a tetrazolinethione (except 3, R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> which shows  $\nu_{\text{SNO}_2}$  1348  $\text{cm}^{-1}$ ) (12). However, inspection of the data in Table II for the 1260-960  $\text{cm}^{-1}$  region reveals good agreement of the position of the bands in 3 with the reported data for 5-methylthio-1-phenyl-1,2,3,4-tetrazole (11).

The nuclear magnetic resonance (nmr) spectra (Table III) displayed singlet absorption at  $\delta$  4.32-5.25 due to the methylene protons on the sulfur and carbonyl bearing carbon atom. For aromatic R groups, the nature of the *para*-substituent had little effect on the position of the signal for the methylene protons. The mass spectra for 3, R = aromatic group, showed abundant molecular ion peaks

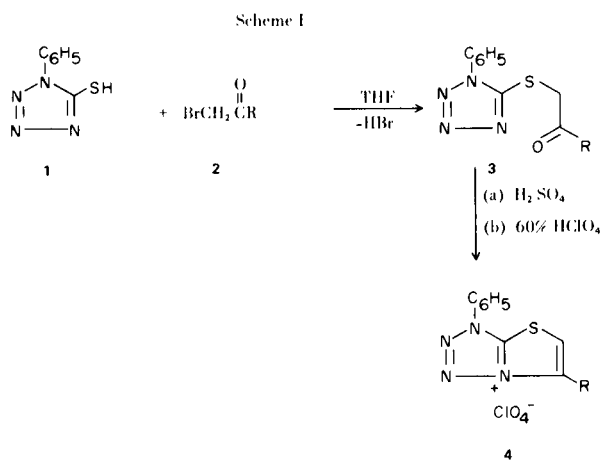


TABLE I  
 Yields, Melting Points, and Analytical Data for **3**

<b>3</b> , R =	Formula	Yield, %	M.p., °C	Calcd., %			Found, %			
				C	H	N	C	H	N	S
$C_6H_5$	$C_{15}H_{12}N_4OS$	65	97-99	60.79	4.08	18.91	61.05	4.06	19.01	10.86
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$C_{15}H_{11}ClN_4OS$	53	180-181	54.46	3.35	16.94	54.57	3.31	17.10	9.61
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	$C_{15}H_{11}BrN_4OS$	73	179-185	48.01	2.95	14.93	48.34	2.76	14.92	8.65
<i>p</i> -C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	$C_{21}H_{16}N_4OS$	37	148-150	67.72	4.33	15.04	67.48	4.31	15.10	8.78
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	$C_{16}H_{14}N_4O_2S$	78	163.5-164.5	58.88	4.32	17.16	58.28	4.28	17.30	9.64
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	$C_{15}H_{11}N_5O_3S$	74	174-176	52.78	3.25	20.52	52.74	3.18	20.60	9.44
1-Adamantyl	$C_{19}H_{20}N_4OS$	58	98-99	64.75	5.72	15.90	64.52	6.14	15.94	9.08
(CH <sub>3</sub> ) <sub>3</sub> C	$C_{13}H_{16}N_4OS$	63	72-73	56.50	5.84	20.27	56.55	6.07	20.38	11.93
$C_2H_5$	$C_{11}H_{12}N_4OS$	12	138-139	53.21	4.87	22.56	52.96	4.86	22.77	12.81

TABLE II  
 Pertinent Solid-State (Potassium Bromide Disc) Infrared Absorption Bands for **3**(a)

<b>3</b> , R =	$\nu_{CO}, cm^{-1}$	Absorption Bands (b), 1260-960 $cm^{-1}$		
$C_6H_5$	1660s	1247m	1158w	1092ms
	1672s	1244m	1176m	1096s
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1675s	1245m	1177m	1090ms
	1676s	1242m	1160w	1089s
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	1673s	1251m	1139mw	1097m
	1683s	1241m	1151m	1092s
1-Adamantyl	1703s	1251s	1178m	1088s
	1704s	1241s	1159m	1092ms
$C_2H_5$	1715s	1243m	1157mw	1091ms

(a) Absorption intensities: vs = very strong; s = strong; m = medium strong; ms = medium strong; mw = medium weak; w = weak. Ketone bands in the 1260-960  $cm^{-1}$  region are not included. (b) 5-Methylthio-1-phenyl-1,2,3,4-tetraazole shows the following bands in the 1260-960  $cm^{-1}$  region (potassium bromide disc): 1245s, 1167w, 1096s, 1078s, 1064w, 1044m, 1015ms, 988ms, 978s.

TABLE III

Nmr and Mass Spectral Data for 3

3, R =	nmr, ppm (a)				Jom, cps		Others		mass spectral data, m/e	
	Solvent (b)	-SCH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> N	H <sub>0</sub> (c)	H <sub>m</sub> (d)					
C <sub>6</sub> H <sub>5</sub>	D	4.90s	7.38s	7.30	7.80m		7.30-7.80m, H <sub>p</sub> (e)		296, 268, 254, 222, 178, 163, 151, 135, 118	
p-ClC <sub>6</sub> H <sub>4</sub>	D	5.16s	7.72s	8.07d	7.66d	8			331, 303, 289, 257, 186, 163, 140, 127, 118	
p-BrC <sub>6</sub> H <sub>4</sub>	D	5.16s	7.71s	8.02d	7.80d	8			376, 374, 348, 346, 334, 332, 302, 300, 185, 183, 171, 169, 163, 157, 155, 135, 118	
p-C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	D	5.22s	7.76s	8.05d	7.54d	8			326, 298, 284, 252, 178, 163, 135, 118	
p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	D	5.15s	7.70s	8.05d	7.10d	7	3.90s, OCH <sub>3</sub>		341, 313, 299, 297, 267, 163, 150, 135, 118	
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	D	5.25s	7.70m	7.837s						
1-Adamantyl	C	4.54s	7.65m				1.70, 1.94, Adamantane skeleton			
(CH <sub>3</sub> ) <sub>3</sub> C	C	4.58s	7.54s				1.20s, (CH <sub>3</sub> ) <sub>3</sub> C		118, 104, 93, 91, 64, 44	
C <sub>2</sub> H <sub>5</sub>	T	4.32s	7.48s				1.12t, CH <sub>3</sub> 2.63q, CH <sub>2</sub>			

(a) Chemical shifts in parts per million ( $\delta$ ) relative to TMS; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. (b) D = dimethyl sulfoxide-d<sub>6</sub>; C = deuteriochloroform; T = carbon tetrachloride. (c) H<sub>0</sub> = protons on carbons *ortho* to carbon bearing carbonyl group. (d) H<sub>m</sub> = protons *meta* to carbonyl carbon. (e) H<sub>p</sub> = proton *para* to carbonyl carbon.

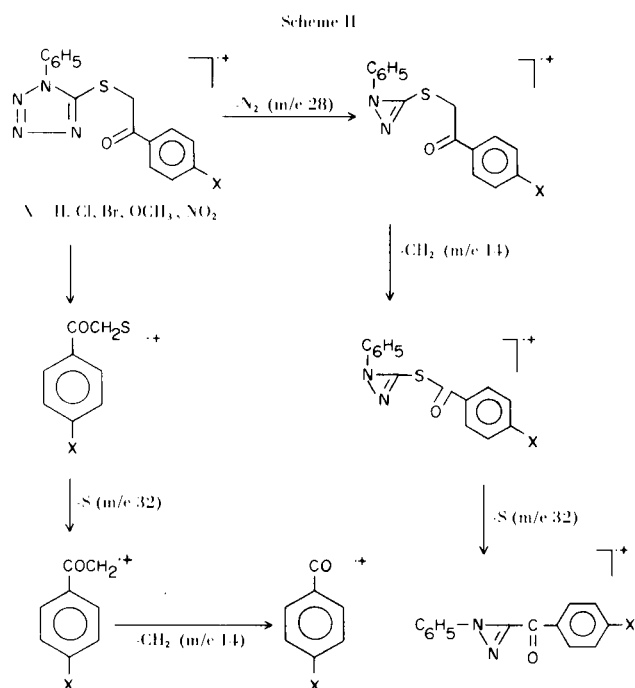
TABLE IV

Yields, Melting Points, and Analytical Data for 4(a)

4, R =	Formula	Yield, %	M.p., °C	Calcd., %			Found, %				
				C	H	N	C	H	N	S	
C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>11</sub> ClN <sub>4</sub> O <sub>4</sub> S	87	201-203	47.56	2.93	14.79	8.47	47.59	2.75	14.83	8.20
p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub> S	53	180-181 (b)	43.60	2.44	13.56	7.76	43.32	2.27	13.47	8.14
p-BrC <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>10</sub> BrClN <sub>4</sub> O <sub>4</sub> S	63	201-205	39.36	2.20	12.24	7.01	39.40	2.09	12.13	7.51
p-C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>21</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub>	57	>290	55.74	3.56	12.38	14.17	55.80	3.24	12.15	13.94
p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub>	34	280° dec.	47.28	3.47	13.78	15.78	47.69	3.31	13.84	16.00
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>10</sub> ClN <sub>5</sub> O <sub>6</sub> S	31	189-194	42.51	2.38	16.53	7.57	42.65	2.29	16.41	7.56
1-Adamantyl	C <sub>19</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>4</sub> S	85	199-202	52.23	4.84	12.82	7.34	51.84	5.05	12.65	7.46
(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>13</sub> H <sub>15</sub> ClN <sub>4</sub> O <sub>4</sub> S	60	191-194	43.52	4.21	15.61	8.94	43.12	3.96	15.54	8.94
C <sub>2</sub> H <sub>5</sub>	C <sub>11</sub> H <sub>11</sub> ClN <sub>4</sub> O <sub>4</sub> S	42	194-196	39.95	3.35	16.94	9.69	40.33	3.37	17.08	9.51

(a) Perchlorate salts, except for 4, R = p-C<sub>6</sub>H<sub>5</sub>C<sub>6</sub>H<sub>4</sub>, p-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, which are bisulfate salts. (b) Explosive at high temperature (>200°).

and some characteristic fragmentation patterns (proposed structures of fragment ions are given in Scheme 2). Also observed in all spectra were fragments at  $m/e$  163 and



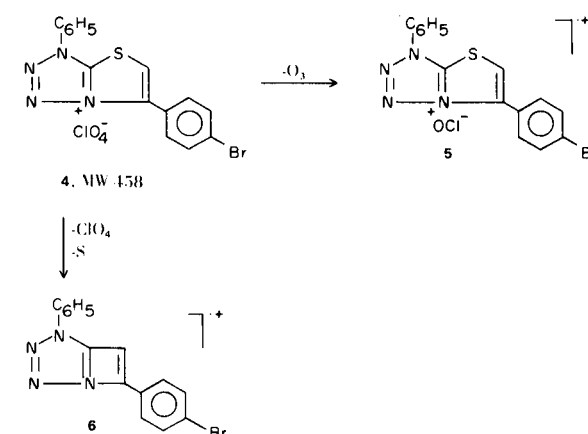
$m/e$  118 (C<sub>6</sub>H<sub>5</sub>NHCN<sup>+</sup>). The latter fragment was the most abundant ion for **3**, R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> but for R = other aromatic substituents, the fragment of greatest abundance was assigned to RCO<sup>+</sup>. No molecular ion was observed in the mass spectrum of **3**, R = (CH<sub>3</sub>)<sub>3</sub>C.

Cyclization of **3** to **4** was achieved by treatment of the  $\beta$ -keto sulfide with concentrated sulfuric acid at room temperature. In several instances the formed thiazolo[3,2-*d*]tetrazolium derivative was characterized as its bisulfate salt but it was usually converted to the less hygroscopic perchlorate analogue. The melting points, yields, and analytical data of **4** are given in Table IV.

The ir spectra (Table V) of **4** show an absorption band of medium-high intensity at 1513-1526 cm<sup>-1</sup> and a weak band at 1561-1576 cm<sup>-1</sup>. These bands, which are absent in **1** and **3**, are assigned to stretching vibrations of the bicyclic heterocycle. There are, of course, additional bands in the 1450-1000 cm<sup>-1</sup> region but the complexity of the spectra in this region render assignments difficult at this time (similarly for the 900-650 cm<sup>-1</sup> region). Intense bands characteristic of perchlorate and bisulfate groups (13) were also observed.

The proton on the thiazole ring of **4** gave a singlet absorption in the nmr at low field (Table V). The protons of the benzene ring attached to nitrogen showed absorption, as expected, at lower field than the corresponding signal in **3**.

Thiazolo[3,2-*d*]tetrazolium salts are fairly high melting solids of low volatility and therefore do not generally lend themselves to mass spectral analysis. However, **4** R = *p*-BrC<sub>6</sub>H<sub>4</sub> (perchlorate salt), did undergo ionization and fragmentation to give a reproducible spectrum showing the following features: no molecular ion; an abundant fragment (**5**) at  $m/e$  410, corresponding to the loss of ozone from **4**; and an ion of high abundance at  $m/e$  326 (assigned structure **6**).



## 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 PCR, Inc. The infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. Nmr spectra were recorded on Varian A-60 or HA-100 spectrometers. Commercial chemicals were purified by standard methods. Mr. E. C. H. Keung provided 1-bromo-2-butanone and 1-bromo-3,3-dimethyl-2-butanone (1b).

General Procedure for Reaction of 5-Mercapto-1-phenyl-1,2,3,4-tetrazole with  $\alpha$ -Bromo Ketones.

Equimolar quantities of the mercaptotetrazole and the  $\alpha$ -bromo ketone were refluxed in dry THF for 3 minutes to 4 days (45 minute reaction times were used in most instances). The solution was cooled, the product precipitated by addition of water or methanol, and collected by suction filtration. Recrystallization of **3**, if necessary, was effected from either benzene, THF/water, or THF/methanol mixtures. The melting points, yields, and analyses of these compounds are listed in Table I.

### Thiazolo[3,2-*d*]tetrazolium Salts (4).

The  $\beta$ -keto sulfides (**3**) were dissolved in concentrated sulfuric acid at room temperature (20 ml. of concentrated sulfuric acid per g. of **3**). The solution was magnetically stirred for 2-5 days at room temperature. The reaction was worked-up by one of the following techniques: (a) 60% perchloric acid was added to the *ice-cold* mixture until the solution became cloudy or until an equal volume of 60% perchloric acid had been added. Subsequent addition of water gave a precipitate which was collected by

TABLE V  
Pertinent Ir (Potassium Bromide Disc) and Nmr Data for 4

4, R =	ir, cm <sup>-1</sup>		nmr, ppm (b)		H <sub>0</sub> (e)	Others		
	$\nu_{\text{ClO}_4^-}$	$\nu_{\text{HSO}_4^-}$	A (a)	Solvent (c)			CH	C <sub>6</sub> H <sub>5</sub> N
C <sub>6</sub> H <sub>5</sub>	1095		1523, 1561	D	8.63s	7.60	8.30m	
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1085		1513, 1571	D	8.70s	7.82s	7.73d	8.18d
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	1094		1513, 1570	D	8.70s	7.96s	7.83d	8.13d
<i>p</i> -C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>		1118, 1037 857	1514, 1568	F	8.16s	7.40	8.10m	
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>		1161, 1032 843	1521, 1574	F	8.81s	7.90s	7.45d	8.38d
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>			1521 (f), 1567	D	8.93s	7.90s	8.52s	
1-Adamantyl	1096		1523, 1572	D	7.60	8.05m		1.85, 2.22, Adamantane skeleton
(CH <sub>3</sub> ) <sub>3</sub> C	1095		1526, 1574	D	7.60	8.00m		1.51s, (CH <sub>3</sub> ) <sub>3</sub> C
C <sub>2</sub> H <sub>5</sub>	1092		1517, 1576	D	8.00s	7.81m		1.42t, CH <sub>3</sub> 3.22d, CH <sub>2</sub>

(a) Heterocyclic ring stretching vibrations. (b) Chemical shifts measured in parts per million ( $\delta$ ) relative to TMS; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. (c) D = dimethyl sulfoxide-d<sub>6</sub>; F = deuterio trifluoroacetic acid. (d) H<sub>m</sub> = protons *meta* to heterocyclic bearing carbon. (e) H<sub>0</sub> = protons *ortho* to heterocyclic bearing carbon. (f) Includes  $\nu_{3s}$  NO<sub>2</sub>.

filtration; (b) the mixture was poured over crushed ice, and the resulting milky precipitate filtered (bisulfate salt). It was then converted to the perchlorate salt by stirring in 60% perchloric acid for 1-2 days at room temperature.

Further purification of **4** was effected from either dimethyl sulfoxide/methanol or from THF. Analyses, yields, and melting points for **4** are listed in Table IV.

Acknowledgements.

We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are indebted to Hoffmann-LaRoche, Inc. for carrying out most of the elemental analyses and mass spectral determinations. We are also grateful to Ms. R. Cartmell of this department for running the nmr spectra on the HA-100 spectrometer.

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