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New Aromatic Systems Having a Fused Thiazolium Ring (1)

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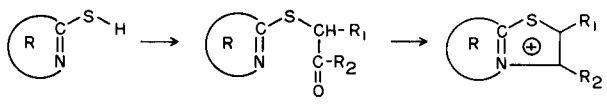
The method developed for the synthesis of thiazolo[3,2-*a*]pyridinium salts has been extended to the first synthesis of simple thiazolo[3,2-*a*]pyrimidinium, thiazolo[3,2-*a*]-pyrazinium and thiazolo[2,3-*b*]benzo[*d*]thiazolium salts. No method could be found for the cyclization of 4'-bromo-2-(2-benzoxazolylthio)acetophenone to the thiazolo[2,3-*b*]-benzoxazolium system.

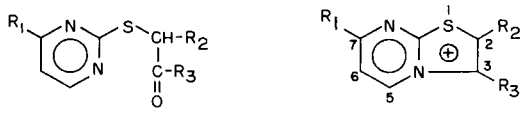
The discovery by Babichev and Bubnovskaya (2) and independently by Bradsher and Lohr (3) that sulfides (II, R = pyridine) formed by reaction of 2-mercaptopyridines with α-halo ketones and acetals of α-halo aldehydes can be cyclized to form thiazolo[3,2-*a*]pyridinium salts (III, R = pyridine), raised the question whether this was a general reaction which could be extended to any heterocyclic system (I) having a mercaptan (thione) group adjacent to a ring nitrogen. It has already been reported that the synthesis can be applied to mercaptoquinolines, mercaptoisoquinolines and mercaptophenanthridines (3) as well as to mercaptothiazoles (4). This paper describes our efforts to extend the reaction to mercaptopyrimidines, mercaptopyrazines, mercaptobenzothiazoles and mercaptobenzoxazoles.

The pyrimidine derivatives were prepared from 2-mercapto- and 2-mercapto-4-methylpyrimidine (Table I). While no difficulty was encountered in the synthesis of 2,3-dialkyl- or 3-alkyl or aryl thiazolopyrimidinium (V) perchlorates, no conditions could be found for cyclization of 2-(2-pyrimidylthio)-acetaldehyde (IV, $R_1 = R_2 = R_3 = H$) diethyl acetal to the parent compound (V, $R_1 = R_2 = R_3 = H$). It is interesting that in 2,3-dimethylthiazolo[3,2-*a*]-pyrimidinium perchlorate, the two methyl groups have a similar magnetic environment and are the origin of a single 6-proton peak at δ 2.81 in the nmr spectrum. A single signal was likewise reported (3b) for the methyl protons of 2,3-dimethylthiazolo[3,2-*a*]pyridinium salts (III, R = pyridine, $R_1 = R_2 = CH_3$).

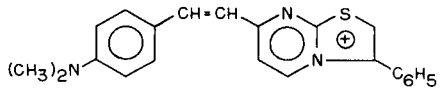
It has been shown earlier (5,2) that methyl groups *para* to a bridgehead quaternary nitrogen atom will undergo condensation with an aromatic aldehyde. The new 7-methyl-3-phenylthiazolo[3,2-*a*]pyrimidinium (V, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_6H_5$) perchlorate likewise condenses with *p*-*N*,*N*-dimethylaminobenzaldehyde to afford a maroon product believed to be VI.



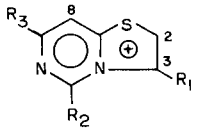
I II III



IV V

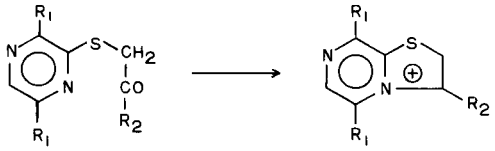


VI



VII

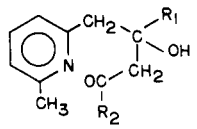
a. R_1 = p-BrC_6H_4, $R_2 = R_3 = NH_2$



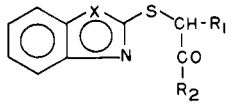
IX X

a. $R_1 = CH_3$, $R_2 = CH_3$

b. $R_1 = CH_3$, R_2 = p-BrC_6H_4

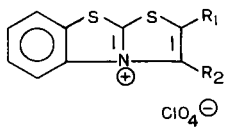


XI



XII, X = S

XIII, X = O



XIV

It might be predicted from the general equation II ⟶ III that 4-mercaptopyrimidines might be used for the synthesis of the thiazolo[3,2-*c*]pyrimidinium system (VII). Subsequent to the completion of this work, Roth (6) has reported an example of this type of synthesis leading to 3-(*p*-bromophenyl)-5,7-diaminothiazolo[3,2-*c*]pyrimidinium (VIIa) sulfate.

The symmetry of pyrazine is such that any β-keto sulfide (IX) which is derived from pyrazine and which will undergo cyclization on aromatic nitrogen will afford derivatives of the thiazolo[3,2-*a*]pyrazinium system (X). Starting with 2-mercapto-3,6-dimethylpyrazine (7) the expected sulfides (IX) were obtained in good yield, but cyclization in sulfuric acid failed, and only moderate yields of the thiazolopyrazinium salts (X) were obtained when the cyclization was carried out in polyphosphoric acid. The difficulty in ring closure recalls that observed by Hansen and Amstutz (8) in their effort to produce 4,6-disubstituted quinolizinium salts through the cyclization of a carbonyl group at a ring nitrogen flanked by a methyl group. It seems likely that in our system (IX) as with theirs (XI) the attack of the ring nitrogen on the carbonyl group (or its conjugate acid) is impeded by non-bonded interactions between the 6-methyl group and the R group of the ketone.

One of the most readily available aromatic thiols is 2-mercaptobenzo[*d*]thiazole. The anion of 2-mercaptobenzothiazole reacts readily with α-chloro ketones and with bromoacetaldehyde diethyl acetal. The resulting sulfides (XII) cyclize in excellent yield to produce the first thiazolo[2,3-*b*]benzo[*d*]thiazolium salts (XIV) in good yield (Table II).

It was noted earlier in this paper that protons on the two adjacent methyl groups attached to the thiazolo ring of the 2,3-dimethylthiazolo[3,2-*a*]-pyrimidinium ion like those of 2,3-dimethylthiazolo-[3,2-*a*]pyridinium ion give rise to a single 6-proton peak in the n.m.r. spectrum. It was observed that the protons of 2,3-dimethylthiazolo[2,3-*b*]benzo[*d*]-thiazolium perchlorate (XIV, $R_1 = R_2 = CH_3$) give rise to two distinct peaks at δ 2.25 and δ 3.12, each with an area corresponding to three protons. This difference does not arise simply because the thiazolo ring bearing the two methyl groups is fused to a thiazolium ring, because the methyl protons of 2,3-dimethylthiazolo[2,3-*b*]thiazolium (III, R = thiazole, $R_1 = R_2 = CH_3$) perchlorate give rise to a single signal at δ 2.76 in the n.m.r. spectrum (9). It is believed that the disturbing effect of fusing a benzenoid ring to the thiazolo[2,3-*b*]-thiazolium system (as in XIV, $R_1 = R_2 = CH_3$) is due wholly or in part to a steric or ring current effect of the benzenoid ring on the methyl group at position 3.

Only a single sulfide (XIII, R_1 = H, R_2 = *p*-BrC_6H_4) was prepared from 2-mercaptobenzoxazole. This compound was extremely resistent to cyclization, the starting material being recovered even after a week in polyphosphoric acid at 100°.

EXPERIMENTAL

The elemental analyses were by Dr. C. Janssen Research Laboratorium, Beerse, Belgium. Melting points were taken in capillaries using a Laboratory Devices Mel-Temp apparatus and are corrected. Unless otherwise indicated all ultraviolet absorption spectra were observed in 95% ethanol using a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer.

α-(2-Pyrimidylthio) Ketones (IV) and Diethyl Acetal.

To a sodium alkoxide solution prepared by dissolving 4.60 g. (0.20 g.-atom) of sodium metal in 400 ml. of absolute methanol or ethanol (with bromoacetaldehyde diethyl acetal), 0.1 mole of 2-mercaptopyrimidine hydrochloride (12) or of 2-mercapto-4-methylpyrimidine hydrochloride was added. To the resulting solution containing the mercaptide anion, 0.1 mole of the α-chloro ketone or bromoacetaldehyde diethyl acetal was added. After about 18 hours at room temperature in the case of the halo ketones, or 48 hours refluxing in the case of the bromoacetaldehyde diethyl acetal, the mixture was poured into water and extracted with methylene chloride. The product was isolated from the dried methylene chloride solution by one of three methods: crystallization of the base, precipitation and crystallization of the hydrochloride, or distillation. The results of these reactions are recorded in Table III.

Thiazolo[3,2-*a*]pyrimidinium Perchlorates.

The cyclization reactions were carried out in sulfuric acid at room temperature as described for thiazolo[3,2-*a*]pyridinium salts (3b). Physical constants and analyses are recorded in Table IV.

7-(*p*-*N*,*N*-Dimethylaminostyryl)-3-phenylthiazolo[3,2-*a*]pyrimidinium (VII) Perchlorate.

A solution of 1 g. of 7-methyl-3-phenylthiazolo[3,2-*a*]pyrimidinium (V, $R_1 = CH_3$, R_2 = H, $R_3 = C_6H_5$) perchlorate and 0.46 g. of *p*-*N*,*N*-dimethylaminobenzaldehyde in 15 ml. of acetic anhydride was refluxed for 2 hours. The mixture was concentrated under reduced pressure (rotary evaporator) to a volume of approximately 5 ml., and 10 ml. of methanol was added. The maroon powder which separated was recrystallized from acetone-methanol as maroon flakes, m.p. 245-251° dec., yield 1.35 g. (95%). The analytical sample melted at 247-251°.

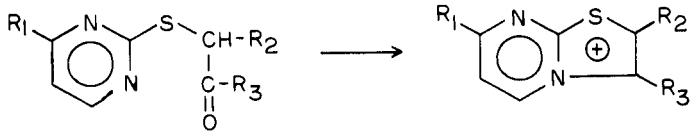
Anal. Calcd. for $C_{22}H_{20}ClN_3O_4S$: C, 57.70; H, 4.40; N, 9.18. Found: C, 57.94; H, 4.59; N, 8.98.

(3,6-Dimethyl-2-pyrazylthio)propanone (IXa) Methiodide.

The reaction of 2.78 g. of chloroacetone with the anion from 4.27 g. of 2-mercapto-3,6-dimethylpyrazine (7) was carried out essentially

TABLE I

Synthesis of Thiazolo[3,2-*a*]pyrimidinium Perchlorates



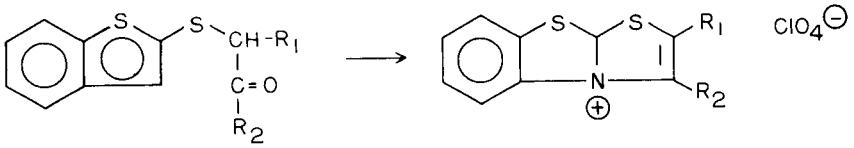
IV a-f Va-f

	R_1	R_2	R_3	X (a)	Yield IV, %	Yield V, %	Overall Yield, %
a	H	H	H	Br	81 (b)	0 (c)	0
b	H	H	CH_3	Cl	74	81	60
c	H	CH_3	CH_3	Br	68 (d)	63	43
d	H	H	*m*-$NO_2C_6H_4$	Cl	75 (d)	88	66
e	CH_3	H	CH_3	Cl	-- (e)	38 (f)	38
f	CH_3	H	C_6H_5	Cl	84	85	71

(a) Halo atom of α-halo ketone or α-haloacetaldehyde diethyl acetal. (b) Diethyl acetal which has been submitted to a previous hydrolysis by allowing it to stand overnight with dilute hydrochloric acid. Omission of this step usually reduces the cyclization yield. (c) Failed with polyphosphoric as well as with sulfuric acid. Decomposition of the starting material was observed. (d) Crude. (e) Not isolated. (f) Overall yield.

TABLE II

Synthesis of Thiazolo[2,3-*b*]benzo[*d*]thiazolium Perchlorates XIV



XII a-e XIV a-e

	R_1	R_2	Yield XII, %	Yield XIV, %	Overall Yield, %
a	H	H	60 (a)	96	57
b	$CH_2CH_2CH_2CH_2$		89 (b,c)	92	82
c	H	CH_3	71 (b,d)	85	60
d	H	C_6H_5	88	88	77
e	CH_3	CH_3	71	91	65

(a) Diethylacetal of XII (R_1 = R_2 = H) obtained by the reaction of bromoacetal with the anion of mercaptobenzothiazole. All other sulfides were prepared from chloro ketones except IVe which was prepared from 3-bromo-2-butanone. (b) Previously reported. (c) Reference 10. (d) Reference 11.

TABLE III

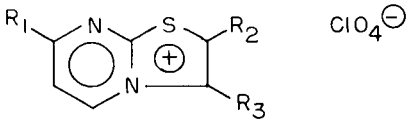
α-(2-Pyrimidylthio) Ketones (IV)

IV (a)	B.P. or M.P., °C (b)	Derivative (c)	M.P., °C (d)	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	118-121 (0.7 mm.)	Methiodide (Diethyl Acetal)	119.5-120.5 (e)	$C_{11}H_{19}IN_2O_2S$	35.68	35.49	5.17	5.04	7.57	7.93
b	125-128 (0.5 mm.)	DNP (f)	125-126 (g)	$C_{13}H_{12}N_6O_4S$	44.82	44.75	3.47	3.68	24.13	23.67
d	100-102	Base	101.5-102.5 (h)	$C_{12}H_9N_3O_3S$	52.36	52.52	3.29	3.37	15.27	15.69
f	68-70	Base	70-71 (i)	$C_{13}H_{12}N_2OS$	63.91	64.20	4.95	4.97	11.47	11.68

(a) Letters in this column refer to designation in Table I. (b) Physical constants of material used in subsequent reactions. Boiling points may be distinguished from melting points by the indication of pressure (mm.). (c) Derivative prepared for analysis. (d) M.p. of analytical sample of derivative. (e) From acetone-ether. (f) Dinitrophenylhydrazone. (g) From ethanol-ethyl acetate. (h) From methylene chloride-hexane. (i) From ether.

TABLE IV

Thiazolo[3,2-*a*]pyrimidinium (V) Perchlorates



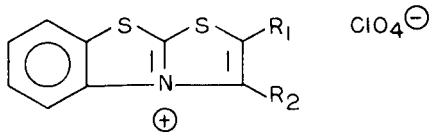
V

V (i)	M.P., °C	Form	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
b	192-193.5	flakes (a)	$C_7H_7ClN_2O_4S$	33.54	33.38	2.82	2.77	11.19	11.05
c	283-285 dec. (b)	needles (a)	$C_8H_9ClN_2O_4S$	36.30	36.27	3.43	3.40	10.59	10.66
d (c)	267-270 dec.	irregular (d, e)	$C_{12}H_8ClN_3O_6S$	40.29	39.90	2.25	2.27	11.75	12.05
e (f)	184-185	needles (a, e)	$C_8H_9ClN_2O_4S$	36.30	36.60	3.43	3.36	10.59	10.69
f (g)	240-242 dec.	platelets (a, h)	$C_{13}H_{11}ClN_2O_4S$	47.78	47.78	3.39	3.25	8.58	8.55

(a) From methanol. (b) The 3-(2-pyrimidylthio)-2-butanone from which Vc was prepared was never obtained in a state of analytical purity or converted to a pure derivative. The material used in the cyclization experiment was prepared from 3-bromo-2-butanone and had b.p. 100-102° (0.45 mm.). (c) λ max, mμ (log ε), 227 (4.32), 263 (4.31), 324 (4.41). (d) From acetonitrile. (e) Buff colored. (f) The crude (4-methyl-2-pyrimidylthio)propanone was cyclized without purification; λ max, mμ (log ε), 214 (3.97), 238 (4.19), 302 (3.87). (g) λ max, mμ (log ε), 237 (4.33), 327 (3.83). (h) Light yellow. (i) These letters correspond to the formulas in Table I.

TABLE V

Thiazolo[2,3-*b*]benzo[*d*]thiazolium Perchlorates (XIV)



XII	M.P., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a (a)	222-223 (b,c)	$C_9H_6ClNO_4S_2$	37.05	37.22	2.07	2.22	4.80	4.76
b	265.5-267.5 (d)	$C_{13}H_{12}ClNO_4S_2$	45.14	45.44	3.50	3.68	4.05	4.15
c	196-197 (e)	$C_{10}H_8ClNO_4S_2$	39.28	39.18	2.64	2.57	4.58	4.59
d	252-254	$C_{15}H_{10}ClNO_4S_2$	48.98	48.99	2.74	2.89	3.81	3.99
e	252.5-253.5	$C_{11}H_{10}ClNO_4S_2$	41.31	41.28	3.15	3.11	4.38	4.17

(a) The letters correspond to the formulas in Table II. (b) Flakes. (c) λ max, mμ (log ε), 216 (4.53), 258 (3.90), 300 sh (4.01), 306 (4.05). (d) From methanol-acetonitrile; λ max, mμ (log ε), 216 (4.42), 261 (3.90), 293 sh (3.62), 313 (4.03). (e) λ max, mμ (log ε), 214 (4.93), 260 (3.90), 283 sh (3.59), 307 (4.04), 312 (4.06).

as described for the mercaptopyrimidines, affording 4.62 g. (78%) of a yellow oil, b.p. 109-118° (1 mm.). This material was used for the cyclization, but a small sample was allowed to react for two weeks at room temperature with methyl iodide. The analytical sample crystallized from acetone-ether as irregular yellow crystals, m.p. 124-125°.

Anal. Calcd. for $C_{10}H_{15}IN_2OS$: C, 35.51; H, 4.47; N, 8.28. Found: C, 35.74; H, 4.47; N, 8.21.

2-(2-Benzothiazolylthio)acetaldehyde (XII, $R_1 = R_2 = H$) Diethyl Acetal.

The procedure was that used in making the pyrimidyl analog (IV, $R_1 = R_2 = R_3 = H$ diethyl acetal). From 8.36 g. of 2-mercaptobenzthiazole, 8.45 g. (60%) of a colorless oil, b.p. 146-149° (0.6 mm.) was obtained. The analytical sample was obtained by redistillation, b.p. 149° (0.6 mm.), n_D^{25} 1.5817.

Anal. Calcd. for $C_{13}H_{17}NO_2S_2$: C, 55.09; H, 6.05. Found: C, 54.86; H, 6.34.

2-(2-Benzothiazolylthio)acetophenone (XII, $R_1 = H$, $R_2 = C_6H_5$).

The reaction of 3.35 g. of 2-mercaptobenzothiazole with 2-chloroacetophenone was carried out in the usual way to afford 5.0 g. of product (88%) which crystallized from methanol as colorless needles, m.p. 111.5-113°.

Anal. Calcd. for $C_{15}H_{11}NOS_2$: C, 63.13; H, 3.89; N, 4.91. Found: C, 63.24; H, 3.76; N, 5.17.

3-(2-Benzothiazolylthio)-2-butanone (XII, $R_1 = R_2 = CH_3$) Dinitrophenylhydrazone.

Following the usual procedure, 8.36 g. of 2-mercaptobenzothiazole reacted with 3-bromo-2-butanone afforded 8.47 g. of a yellow oil, b.p. 142-146° (0.7 mm.). The 2,4-dinitrophenylhydrazone crystallized from ethanol-ethyl acetate as irregular yellow crystals, m.p. 173.5-174.5°.

Anal. Calcd. for $C_{17}H_{15}N_5O_4S_2$: C, 48.91; H, 3.62; N, 16.79. Found: C, 48.80; H, 3.62; N, 16.74.

Cyclization of 2-(2-Benzothiazolylthio) Ketones (XII) and Aldehydes (XII, $R_1 = R_2 = H$) Diethyl Acetal.

The cyclization procedures were as described earlier (3b) and, except as noted, the compounds were crystallized from methanol as colorless needles. The results are summarized in Table V.

4'-Bromo-2-(2-benzoxazolylthio)acetophenone (XIII, $R_1 = H$, $R_2 = p$-BrC_6H_4).

Following the usual procedure, 3.02 g. of 2-mercaptobenzoxazole reacted with α,4'-dibromoacetophenone afforded 5.12 g. (73%) of product which crystallized from methanol as colorless needles, m.p. 133-136° (135-136° when pure).

Anal. Calcd. for $C_{15}H_{10}BrNO_2S$: C, 51.73; H, 2.89; N, 4.02. Found: C, 51.85; H, 2.83; N, 4.18.

Several unsuccessful attempts were made to cyclize this ketone with sulfuric acid as well as with polyphosphoric acid. The isolation of starting material after heating the ketone for one week at 100° in polyphosphoric acid made it clear that the difficulty was due to resistance to cyclization rather than instability of the ketone in an acid medium.

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