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Benzologs of the Thiazolo[3,2-*a*]pyridinium System (1)

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By use of concentrated sulfuric acid rather than hydrobromic acid as the cyclizing medium, good yields of the thiazolo[3,2-*a*]quinolinium ion and its derivatives may be obtained from α-(2-quinolylthio) ketones or acetals. In the same way, α-(1-isoquinolylthio) and α-(6-phenanthridylthio) ketones afford thiazolo[2,3-*a*]isoquinolinium and thiazolo[3,2-*f*]phenanthridinium salts.

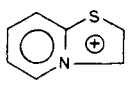
In the first paper to describe the synthesis of thiazolo[3,2-*a*]pyridinium salts (I), Babichev and Bubnovskaya (2) reported a single attempt to prepare a benzolog of the system. They found that (2-quinolylthio)propanone (II, $R_1 = R_2 = H$, $R_3 = CH_3$) in boiling hydrobromic acid was largely destroyed and only a 15% yield of the desired product III, $R_1 = R_2 = H$, $R_3 = CH_3$) was obtained. In our independent discovery (3) of the thiazolo[3,2-*a*]pyridinium synthesis, we found concentrated sulfuric acid to be an effective cyclizing agent, and it seemed desirable to determine whether (2-quinolylthio)propanone (Ib) and its analogs could be cyclized in this medium in reasonable yields. As may be known from Table I, this proved to be the case.

Babichev and Bubnovskaya (2) have shown that simple thiazolo[3,2-*a*]pyridinium salts having a methyl group attached to the six-membered ring at a position *para* to the quaternary nitrogen atom would undergo condensation reactions at the methyl group. We have found that a methyl group (presumably that at position 5) of 1,5-dimethylthiazolo[3,2-*a*]quinolinium perchlorate (IIIf) readily condenses with 4-*N*,*N*-dimethylbenzaldehyde in boiling acetic anhydride affording a maroon powder. A similar product was obtained from the 5-methyl-1-phenyl analog (IIIg), but the latter product was not obtained in a state of analytical purity.

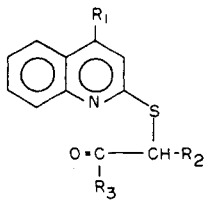
The β-oxo sulfides (IV) obtained from 1-mercaptoisoquinoline may be cyclized in good yield to thiazolo[2,3-*a*]isoquinolinium salts (VI). While these are the first such salts to be reported, Krȍhnke and Steuernagel (4) have reported a simple synthesis of betaines (V) having this ring system. The β-oxo sulfides (VII) from 6-mercaptophenanthridine served as intermediates for the preparation of thiazolo[3,2-*f*]phenanthridinium salts (VIII).

EXPERIMENTAL

The elemental analyses were by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany or Dr. C. Janssen, Research Laboratorium, Beerse, Belgium. Melting points were taken in capillaries using a Laboratory Devices Mel-Temp block and are corrected. All ultraviolet absorption spectra were observed in 95% ethanol using a Cary Model 14 spectrophotometer.



I



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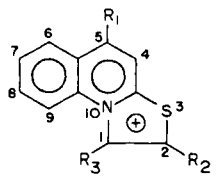

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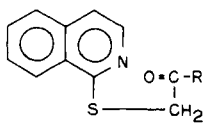
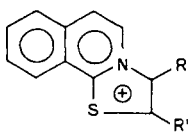
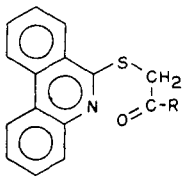


IV

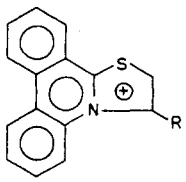


V, R' = S^-

VI, R' = H



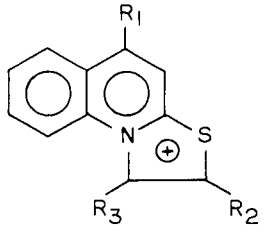
VII



VIII

TABLE I

Synthesis of Thiazolo[3,2-*a*]quinolinium Perchlorates (IIIa-g)



IIIa-g

	R_1	R_2	R_3	Yield II, %	Yield III, %	U. V. λ max (mμ)
a	H	H	H	71 (a)	97	227 (4.34), 237 sh (4.33), 249 (4.12), 260 sh (3.89), 313 sh (3.98), 327 (4.23), 342 (4.38)
b	H	H	CH_3	84	51 (b)	214 (4.34), 246 (4.27), 252 (4.24), 336 (4.19), 349 (4.28)
c	H	H	C_6H_5	80	88	253 (4.31), 337 sh (4.14), 347 (4.25)
d	H	CH_2-CH_2-CH_2		66	73	215 (4.31), 248 (4.35), 254 (4.45), 343 (4.25), 357 (4.31)
e	CH_3	H	H	88 (a)	83	227 sh (4.33), 240 (4.77), 258 sh (3.90), 268 sh (3.68), 313 sh (4.01), 318 sh (4.02), 327 (4.24), 342 (4.57)
f	CH_3	H	CH_3	79	85	214 (4.34), 244 (4.38), 250 (4.38), 324 sh (4.01), 336 (4.24), 348 (4.33)
g	CH_3	H	C_6H_5	85	91	201 (5.26), 247 (4.64), 337 sh (4.16), 347 (4.26)

(a) Diethyl acetal of the aldehyde. (b) Babichev and Bubnovskaya (Ref. 2) obtained only a 15% yield using boiling hydrobromic acid as the cyclizing medium.

α-(2-Quinolylthio) Ketones and Acetals.

The procedure was essentially that described earlier (3). To 350 ml. of absolute methanol to which had been added 4.60 g. (0.20 g.-atom) of sodium, 0.20 mole of the 2-mercaptoquinoline or 2-mercapto-4-methylquinoline (5) was added. When the mercaptan had dissolved, 0.20 mole of the α-halo ketone was added slowly with stirring and the mixture allowed to stand for about 18 hours at room temperature. The salt was removed by filtration, the solution concentrated under vacuum and the residue taken up in chloroform or methylene chloride. The organic solution was washed with dilute alkali, water, and then dried over magnesium sulfate. Concentration of the solution afforded a solid or an oil which solidified and purification was carried out by crystallization from ether-hexane.

The acetals were prepared similarly except that absolute ethanol was used as the solvent and, after addition of the bromoacetaldehyde diethyl acetal (0.20 mole), the mixture was refluxed for 48 hours. Experimental results are summarized in Table II.

Thiazolo[3,2-*a*]quinolinium Perchlorates (III).

Ten grams of the keto sulfide (II) was dissolved in about 50 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 24 hours. If an acetal was used, it was first allowed to stand overnight in 6*M* hydrochloric acid, the acid then removed under vacuum on a steam bath, and the residue (presumably the aldehyde) dissolved in sulfuric acid to effect cyclization. At the end of 24 hours, the sulfuric acid was poured cautiously into 1 liter of cold anhydrous ether and the mixture placed in the refrigerator for several hours. The ether was then decanted, the residue dissolved in a small quantity of water, and the aqueous solution treated with charcoal and filtered. Addition of 35% perchloric acid to the filtered solution precipitated the thiazoloquinolinium salt which was crystallized from methanol. The results of the cyclization reactions are summarized in Table III.

1-Methyl-5-(4-*N*,*N*-dimethylaminostyryl)thiazolo[3,2-*a*]quinolinium Perchlorate (III, R_1 = *p*-$(CH_3)_2NC_6H_4CH$=CH-, R_2 = H, R_3 = CH_3).

A solution containing 1.0 g. of 1,5-dimethylthiazolo[3,2-*a*]quinolinium perchlorate (IIIf) and 0.48 g. of 4-*N*,*N*-dimethylaminobenzaldehyde in 15 ml. of acetic anhydride was refluxed for 1 hour. The volume of the solution was reduced to approximately 5 ml. under reduced pressure using a rotary evaporator, and 10 ml. of methanol was added. The cooled solution afforded 0.37 g. (25%) of a maroon microcrystalline powder, which was obtained as bronze needles, m.p. > 300°, when recrystallized from acetone-methanol.

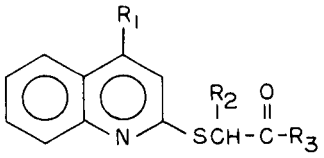
Anal. Calcd. for $C_{22}H_{21}ClN_2O_4S$: C, 59.38; H, 4.76; N, 6.30. Found: C, 59.49; H, 4.63; N, 6.27.

Thiazolo[2,3-*a*]isoquinolinium Perchlorate (VI, R = H).

The crude undistilled 2-(1-isoquinolylthio)acetaldehyde (IV, R = H) diethyl acetal, prepared from 4.84 g. of 1-mercaptoisoquinoline (6)

TABLE II

Preparation of α-(2-Quinolylthio) Ketones (II) and Diethyl Acetals



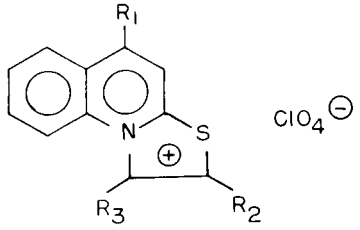
II a-g

II	M.P.	Crystalline form	Halide used (a)	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	------ (b)	------ (c)	Br	$C_{16}H_{22}INOS_2$ (d)	45.83	45.97	5.29	5.32		
b	57-57.5	flakes	Cl	$C_{12}H_{11}NOS$ (e)	66.33	66.74	5.10	5.08	6.45	6.64
c	81-81.5	needles (f)	Br	$C_{17}H_{13}NOS$	73.09	73.38	4.69	4.46	5.02	5.09
d	102-103	prisms (g)	Cl	$C_{14}H_{13}NOS$	69.11	69.04	5.38	5.28	5.76	5.96
e	50-50.5	flakes	Br	$C_{16}H_{21}NO_2S$	65.94	66.10	7.26	7.11	4.81	4.77
f	84-85	flakes	Cl	$C_{13}H_{13}NOS$	67.50	67.34	5.66	5.66	6.06	6.29
g	100.5-101	needles (f)	Cl	$C_{18}H_{15}NOS$	73.69	73.94	5.15	5.17	4.78	4.81

(a) Halogen present in acetal or ketone used for reaction with mercaptide ion. (b) Diethyl acetal of the aldehyde. (c) Liquid, b.p. 150-153° (4 mm.). (d) The analysis is of the methiodide, m.p. 142-144.5° and obtained from acetone-ether as irregular crystals. (e) Although the perchlorate salt has been reported (ref. 2), the free base does not appear to have been described. (f) From methanol. (g) Pale yellow.

TABLE III

Thiazolo[3,2-*a*]quinolinium Perchlorates (IIIa-g) (d)



IIIa-g

III	M.P.	Form	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	181-182.5	needles	$C_{11}H_8ClNO_4S$	46.24	46.23	2.82	2.96	4.90	5.29
b	176-177 (a)	needles	$C_{12}H_{10}ClNO_4S$	48.08	48.36	3.36	3.35		
c	245.5-246	needles	$C_{17}H_{12}ClNO_4S$	56.43	56.34	3.34	3.39	3.87	4.10
d	214-215 (b)	needles	$C_{14}H_{12}ClNO_4S$	51.61	51.88	3.71	3.82	4.30	4.41
e	252-254 (b)	needles	$C_{12}H_{10}ClNO_4S$	48.08	48.28	3.36	3.65	4.67	4.76
f	170-171	flakes	$C_{13}H_{12}ClNO_4S$	49.76	49.56	3.86	3.83	4.47	4.78
g	247-248.5 (b,c)	plates	$C_{18}H_{14}ClNO_4S$	57.52	57.32	3.75	3.71	3.73	3.90

(a) Lit. (ref. 2) m.p. 175°. Since the Russian authors have reported analyses only for nitrogen and sulfur, our analytical results for carbon and hydrogen are reported. (b) With decomposition. (c) This cyclization was carried out in 24 hours at steam bath temperature. (d) See Table I for substituents R_1, R_2, R_3.

as in the case of the isomer IIa, was cyclized as in the preparation of IIIa, affording 5.66 g. (66%) of buff-colored needles, m.p. 233-235°. The analytical sample, m.p. 233.5-235° was crystallized from methanol.

Anal. Calcd. for $C_{11}H_8ClNO_4S$: C, 46.24; H, 2.82; N, 4.90. Found: C, 46.43; H, 2.95; N, 4.93.

3-Methylthiazolo[2,3-*a*]isoquinolinium Perchlorate (VI, R = CH_3).

The crude undistilled 2-(1-isoquinolylthio)propanone obtained from 4.83 g. of 1-mercaptoisoquinoline, as in the case of the isomer IIb, was cyclized in the usual way affording 6.11 g. (68%) of pale yellow irregular crystals, m.p. 211-213°. The analytical sample, m.p. 212-214°, was crystallized from methanol.

Anal. Calcd. for $C_{12}H_{10}ClNO_4S$: C, 48.08; H, 3.36; N, 4.67. Found: C, 48.13; H, 3.46; N, 4.74.

4-Bromo-α-(1-isoquinolylthio)acetophenone (IV, R = *p*-BrC_6H_4).

Following the usual procedure but starting with 1.61 g. of 1-mercaptoisoquinoline and 2.77 g. of α,4-dibromoacetophenone, the title compound crystallized from methanol as irregular orange crystals, m.p. 115-117°, yield 2.63 g. (73%). The analytical sample, m.p. 116-117°, was crystallized from ether-hexane.

Anal. Calcd. for $C_{17}H_{12}BrNOS$: C, 56.99; H, 3.38; N, 3.91. Found: C, 57.11; H, 3.42; N, 4.02.

3-*p*-Bromophenylthiazolo[2,3-*a*]isoquinolinium Perchlorate (VI, R = *p*-BrC_6H_4).

Cyclization of 1.0 g. of 4-bromo-α-(1-isoquinolylthio)acetophenone was carried out as usual affording 1.15 g. (93%) of pale yellow irregular crystals, m.p. 250-252°. The analytical sample, m.p. 251-253° was crystallized from methanol.

Anal. Calcd. for $C_{17}H_{11}BrClNO_4S$: C, 46.33; H, 2.52; N, 3.18. Found: C, 46.47; H, 2.49; N, 3.11.

α-(6-Phenanthridylthio)acetophenone (VII, R = C_6H_5).

The mercaptide ion was prepared in methanol in the usual way from 2.11 g. of 6-mercaptophenanthridine (7), and to the resulting suspension, 1.99 g. of α-bromoacetophenone was added, and the mixture refluxed for 3 hours. The orange solid which formed was collected and recrystallized from methylene chloride–hexane, as pale yellow irregular crystals, m.p. 159.5-161.5°, yield 2.55 g. (78%). The analytical sample melted at 162-164°.

Anal. Calcd. for $C_{21}H_{15}NOS$: C, 76.57; H, 4.59; N, 4.25. Found: C, 76.58; H, 4.64; N, 4.43.

(6-Phenanthrydylthio)propanone (VII, R = CH_3).

The general procedure used in making the phenyl analog (VII, R = C_6H_5) was followed, except that 0.93 g. of chloroacetone was used instead of bromoacetophenone. From the cooled reaction mixture, 2.09 g. (75%) of colorless needles, m.p. 94-96°, separated. The analytical sample, m.p. 95-96°, was crystallized from methanol.

Anal. Calcd. for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 72.27; H, 4.98; N, 5.24.

3-Phenylthiazolo[3,2-*f*]phenanthridinium Perchlorate (VIII, R = C_6H_5).

Following the usual procedure, the α-(6-phenanthridylthio)acetophenone (VII, R = C_6H_5) cyclized in 97% yield, affording fine colorless needles, m.p. 316-318° dec. The analytical sample, m.p. 317-319° dec. (evacuated capillary), was crystallized from acetonitrile-methanol.

Anal. Calcd. for $C_{21}H_{14}ClNO_4S$: C, 61.24; H, 3.43; N, 3.40. Found: C, 61.44; H, 3.53; N, 3.28.

3-Methylthiazolo[3,2-*f*]phenanthridinium Perchlorate (VII, R = CH_3).

The cyclization of (6-phenanthridylthio)propanone (VII, R = CH_3) afforded a quantitative yield of the title salt as irregular colorless crystals, m.p. 300-304°. The analytical sample, m.p. 302-304° was crystallized from acetonitrile-methanol.

Anal. Calcd. for $C_{16}H_{12}ClNO_4S$: C, 54.94; H, 3.46; N, 4.01. Found: C, 55.03; H, 3.42; N, 4.10.

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(1) This investigation was supported by Public Health Research Grant No. CA-05509 of the National Cancer Institute of the National Institutes of Health.

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