Department of Chemistry, Duke University

Thiazolo[3,2-a]pyridinium Salts (1,2)

C. K. Bradsher and D. F. Lohr, Jr.

The sulfides formed by the reaction of α-halo ketones or α-halo acetals with 2-mercaptopyridine may be cyclized in good yield to form thiazolo[3,2-a]pyridinium salts. The presence of chloro or nitro substituents on the pyridine ring does not interfere with the synthesis. Nitration of 3-methylthiazolo[3,2-a]pyridinium perchlorate has been found to occur at position 8.

From earlier work (3) done with 1-alkyl- or 1-arylimidazo[1,2-a]pyridinium salts (I) it appeared that there should exist a family of resonance-stabilized quinolizinium analogs in which X was an element or group having an unshared pair of electrons. The present paper describes our first test of this hypothesis, the synthesis of thiazolo[3,2-a]pyridinium salts (II).

The new aromatic system was prepared in a simple two step synthesis. First the sodium salt of 2-mercaptopyridine was allowed to react with an α-halo ketone to form a sulfide (III). It had already been established (4) that phenacyl bromide reacts with 2-mercaptopyridine at the sulfur atom, yielding IIIb, and it is assumed that this mode of alkylation is general.

Boiling hydrochloric acid had little effect on 2-pyridylthioacetone (IIIa), but concentrated sulfuric acid readily brought about cyclization (89% yield). The infrared absorption spectrum of the perchlorate salt (IVa) of the product showed no significant absorption in the carbonyl region. The ultraviolet absorption maximum was at 312 mμ as compared with 290 mμ for the starting material (IIIa). The nuclear magnetic resonance spectrum of IVa showed a singlet at 7.17 τ corresponding to the protons of the methyl group, and as would be predicted, the remaining five protons appeared in the aromatic region.

The acid-catalized cyclization of a keto-sulfide (III) to yield a thiazolo[3,2-a]pyridinium salt is a special case of aromatic cyclodehydration (5) in which acid-catalyzed attack of the carbonyl group occurs on an aromatic heterocyclic nitrogen atom rather than carbon. Although the first known instance (6) of the preparation of a compound containing a quinolizinium nucleus involved such a cyclization, as yet no reaction mechanism has been suggested. While it would be expected that the conjugate acid (V) would cyclize readily, the great ease with which the protonation of the pyridine nitrogen could take place would mean that the equilibrium concentration of V would be extremely low. It now appears more likely that there is a concerted (7) reaction involving a cation (VI) originating from the hydrogen-bonded nitrogen-protonated salt.

3-Methylthiazolo[3,2-a]pyridinium (IVa) perchlorate seemed quite stable. It could be heated to its melting point (178-179.5°) and recovered unchanged from the melt. The ultraviolet absorption spectrum of the perchlorate in 0.001 *M* aqueous alkali appeared unchanged after 48 hours. Attempts to bring about condensation of the methyl group at position 3 with aromatic aldehydes in the presence of piperidine,

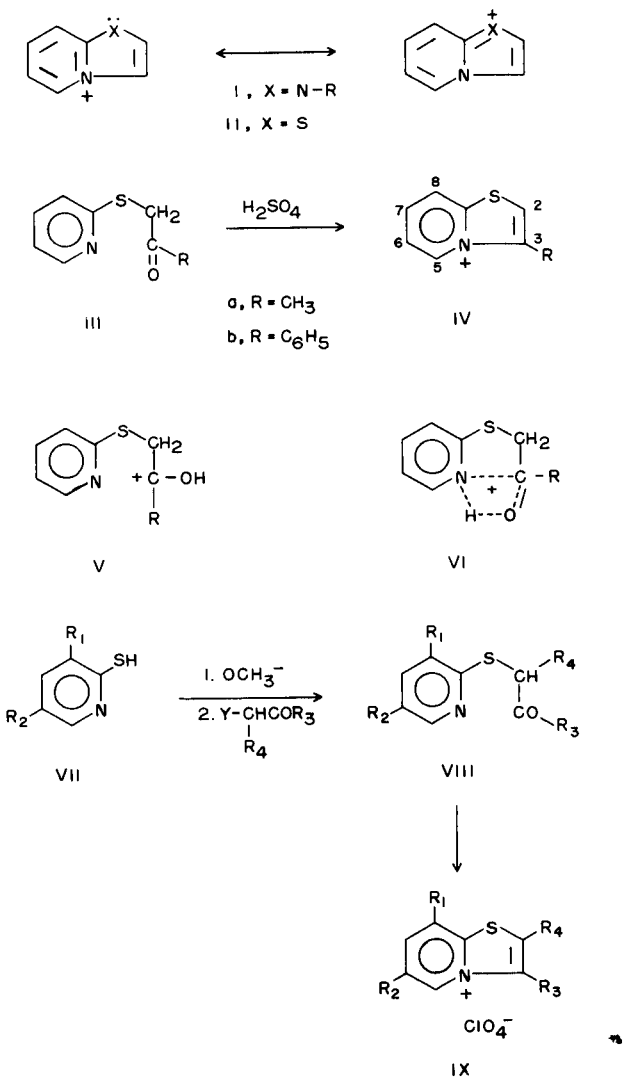

TABLE I

Synthesis of Thiazolo[3,2-a]pyridinium Salts

	R_1	R_2	R_3	R_4	Y	Yield VIII, %	Yield IX, % (a)	IX λ max, mμ (log ε)
a	-	-	-	-	Br	91 (b)	80 (c) (52)	208 (d) (4.00), 224 (4.08), 228sh (4.02), 295 (4.11), 306 (4.24)
b	-	-	CH_3	-	Cl	83 (83)	89 (50)	207sh (d) (3.99), 233 (4.10), 308sh (4.10), 312 (4.20)
c	-	-	C_6H_5	-	Br	83 (e) (86)	85 (55)	230 (d) (4.24), 311 (4.07)
d	-	-	*p*-BrC_6H_4	-	Br	68	75	234 (4.38), 312 (4.08)
e	-	-	CH_3	CH_3	Br	72 (49)	55 (71)	213 (d) (4.08), 239 (4.01), 305sh (4.10) 314 (4.22)
f	-	-	CH_3	$COCH_3$	Cl	60	68	237 (4.11), 306sh (4.03), 314 (4.16), 327sh (3.68)
g	-	-	C_6H_5	CH_3	Br	81	91	239 (4.21), 314 (4.17)
h	-	-	C_6H_5	C_6H_5	Cl	82 (78)	86 (f)	251sh (4.09), 318 (4.26)
i	-	-	$-(CH_2)_4-$		Cl	79 (73)	63 (92)	213 (4.09), 242 (4.03), 306sh (4.12), 316 (4.24)
j	-	-	$-(CH_2)_3-$		Cl	75	42	212sh (4.07), 244 (3.99), 318 (4.25)
k	-	NO_2	H	H	Br	- (g)	80 (h)	213 (3.89), 329 (3.08)
l	-	NO_2	CH_3	H	Cl	58	95	214 (4.01), 246 (4.12), 312 (3.92)
m	-	NO_2	*p*-BrC_6H_4	H	Br	93	92	254 (4.36), 331 (3.82)
n	-	NO_2	CH_3	$COCH_3$	Br	31	64	249 (3.99), 324 (3.93)
o	-	NO_2	$-(CH_2)_4-$		Cl	36	92	251 (4.15), 323 (3.93)
p	NO_2	-	CH_3	-	Br	52	79	222 (3.87), 267 (3.72), 307 (3.88), 409 (4.22)
q	NO_2	-	*p*-BrC_6H_4	-	Br	51	95	230 (4.27), 305 (4.02), 413 (4.28)
r	-	Cl	-	-	Br	75 (g)	52	257 (4.20), 303 (3.65)
s	-	Cl	*p*-BrC_6H_4	-	Br	41	91	199 (5.17), 215sh (4.76), 222sh (4.72), 244 (4.82), 321 (4.04)
t	-	Cl	CH_3	-	Br	78	36	221 (4.20), 245 (4.20), 314sh (4.07), 323 (4.16)
u	Cl	-	-	-	Br	98	48	249 (4.07), 298 (3.67), 318sh (3.01)
v	Cl	-	CH_3	-	Cl	-	36 (h)	242 (4.20), 312sh (4.06), 322 (4.20)
w	Cl	-	C_6H_5	-	Br	98	86	238 (4.26), 321 (4.08)

(a) The numbers in brackets under Yield are the yields reported by Babichev and Bubnovskaya (Ref. 2). (b) This product was the diethyl acetal obtained by refluxing bromoacealdehyde diethyl acetal for 48 hours in ethanol with the sodium salt of 2-mercaptopyridine. Babichev and Bubnovskaya (Ref. 2) appear to have prepared the aldehyde (VIIIa) although no physical constants or analytical data were reported. (c) Prior to cyclization the acetal was allowed to remain in 6 *N* hydrochloric acid overnight to effect hydrolysis of the acetal linkage. (d) Spectrum measured in water. (e) Prepared by Djerassi and Pettit (Ref. 4). (f) The Russians (Ref. 2) reported the formation of the keto sulfide (VIII, $R_1 = R_2 = H$, $R_3 = R_4 = C_6H_5$), but do not report its cyclization. (g) The crude diethyl acetal prepared as was VIIIa was not isolated as the pure base or a derivative. (h) Overall yield from sulfide (VIII).

TABLE II

α-(2-Pyridyl) Ketones

VIII	B.P. (mm.) (a)	Derivative	M.P.	Formula	C,%		H,%		N,%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
b	89-93 (0.4)	MeI (b)	116-117 (c,d)	$C_9H_{12}INOS$	34.96	34.92	3.91	3.92	4.53	4.30
c	161-169 (0.4)	MeI (e)	166-168 (d,f)	$C_{14}H_{14}INOS$	45.29	45.11	3.80	3.86	3.77	3.63
d	- (g)	Base	113-115 (h,i)	$C_{13}H_{10}BrNOS$	50.66	50.65	3.27	3.42	4.55	4.32
e	125-133 (0.2)	Pic (j,k)	140-141.5 (c,i)	$C_{15}H_{14}N_4O_8S$	43.90	43.93	3.44	3.53	13.65	13.83
f	103-109 (0.2)	MeI	121-123 (i,m)	$C_{11}H_{14}INO_2S$	37.62	37.64	4.02	4.18	3.99	4.00
g	144-148 (0.4)	Pic	148-149 (c,i)	$C_{20}H_{16}N_4O_8S$	50.84	51.00	3.41	3.47	11.86	12.11
h	-	Base (m)	79.5-81 (i,n)							
i	-	Base (k)	43-44 (h,o)	$C_{11}H_{13}NOS$	63.74	63.97	6.32	6.50	6.76	6.81
j	116-122 (0.6)	Pic	140-143 (i,l)	$C_{16}H_{14}N_4O_8S$	45.50	45.76	3.34	3.33	13.27	13.13
l	-	Base	88-89 (i,p)	$C_8H_8N_2O_3S$	45.27	45.57	3.80	3.93	13.20	13.30
m	-	Base	147-149 (h,i)	$C_{13}H_9BrN_2O_3S$	44.20	44.56	2.57	2.83	7.93	8.00
n	-	Base	131.5-132.5 (i,l)	$C_{10}H_{10}N_2O_4S$	47.23	47.13	3.96	3.98	11.02	11.23
o	-	Base	113-114 (l,o)	$C_{11}H_{12}N_2O_3S$	52.39	52.26	4.80	4.66	11.11	11.41
p	-	Base	70-71 (l,q)	$C_8H_8N_2O_3S$	45.27	45.34	3.80	3.83	13.20	13.54
q	-	Base	138.5-140 (i,l)	$C_{13}H_9BrN_2O_3S$	44.20	44.31	2.57	2.41	7.93	7.52
s	-	Base	107-107.5 (i,p)	$C_{13}H_9BrClNOS$	45.57	45.51	2.65	2.67	4.09	4.36
t	-	Base	57-57.5 (o,p)	C_8H_8ClNOS	47.64	47.64	4.00	4.05	6.95	6.97
w	-	Base	105.5-106.5 (i,r)	$C_{13}H_{10}ClNOS$	59.20	59.47	3.82	3.89	5.31	5.46

(a) Observed b.p. of material used in cyclization reaction. In most cases it was not convenient to prepare pure samples of the bases so solid derivatives were prepared for analysis. (b) Methiodide. (c) Yellow prisms. (d) From methanol-ether. (e) The base has been characterized previously as the hydrobromide (Refs. 2,4). (f) Yellow microcrystalline powder. (g) Purified by recrystallization. (h) Colorless needles. (i) From methanol. (j) Picrate. (k) This keto sulfide was previously characterized as the hydrochloride (Ref. 2). (l) Yellow needles. (m) From acetone-ether. (n) Reported previously by Babichev and Bubnovskaya (Ref. 2), m.p. 78°. (o) From ether. (p) Platelets. (q) From ether-petroleum ether. (r) Prisms.

TABLE III

Thiazolo[3,2-a]pyridinium Perchlorates

IX	M.P.	Formula	C		H		N	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
a	280-283 (a)	Lit. (2) (b) m.p. 270°						
b	178-179.5 (c)	Lit. (2) m.p. 176°						
c	200-201	Lit. (2) m.p. 200°						
d	238-239 (d)	$C_{13}H_9BrClNO_4S$	39.97	40.24	2.32	2.46	3.59	3.71
e	141.5-143	Lit. (2) 141°						
f	159.5-160.5	$C_{10}H_{10}ClNO_5S$	41.17	41.43	3.46	3.32	4.80	4.94
g	185-187 (e)	$C_{14}H_{12}ClNO_4S$	51.61	51.95	3.71	3.67	4.30	4.07
h	214.5-216 (f,g)	$C_{19}H_{14}ClNO_4S$	58.84	59.07	3.64	3.71	3.61	3.87
i	181.5-182.5	Lit. (2) m.p. 180°						
j	155.5-156.5	$C_{10}H_{10}ClNO_4S$	43.56	43.86	3.66	3.66	5.08	5.32
k	205-209 (h,i)	$C_7H_5ClN_2O_6S\cdot CH_3OH$	30.72	30.77	2.90	2.83	8.96	9.19
l	200-201 (i)	$C_8H_7ClN_2O_6S$	32.60	32.22	2.40	2.21	9.51	9.77
m	270-272 (j)	$C_{13}H_8BrClN_2O_6S$	35.84	36.19	1.85	1.76	6.43	6.58
n	228.5-230.5 (k)	$C_{10}H_9ClN_2O_7S$	35.67	35.86	2.69	2.76	8.32	8.48
o	205-206	$C_{11}H_{11}ClN_2O_6S$	39.47	39.57	3.31	3.28	8.37	8.51
p	233-234.5 (c,h)	$C_8H_7ClN_2O_6S$	32.60	32.56	2.40	2.39	9.51	9.77
q	294-295 (d,l)	$C_{13}H_8BrClN_2O_6S$	35.84	35.92	1.85	1.88	6.43	6.58
r	155-156	$C_7H_5Cl_2NO_4S\cdot CH_3OH$	31.80	31.88	3.00	2.96	4.63	4.81
s	300.5-303 (a)	$C_{13}H_8BrCl_2NO_4S$	36.73	36.95	1.90	1.93	3.30	3.37
t	190.5-191.5 (m)	$C_8H_7Cl_2NO_4S$	33.82	33.96	2.48	2.55	4.93	5.11
u	156-157 (c)	$C_7H_5Cl_2NO_4S\cdot CH_3OH$	31.80	32.17	3.00	3.22	4.63	4.88
v	226-227	$C_8H_7Cl_2NO_4S$	33.82	33.92	2.48	2.43	4.93	5.03
w	225.5-227	$C_{13}H_9Cl_2NO_4S$	45.10	45.21	2.62	2.57	4.05	4.43

(a) Melted with decomposition (evacuated capillary). (b) Analysis of each of the five compounds made by Babichev and Bubnovskaya (Ref. 2) and duplicated here gave satisfactory results. (c) Platelets. (d) Yellow. (e) Flakes. (f) Prisms. (g) The intermediate (VIIIh) needed for the preparation of this thiazolopyridinium salt was described by the Russian authors (Ref. 2), but it does not appear to have been cyclized. (h) Light buff. (i) Prisms. (j) From ethanol-acetonitrile. (k) From methanol-acetonitrile. (l) Irregular crystals from acetonitrile. (m) From methanol-ether.

sodium hydroxide or sodium methoxide produced no condensation product, but in each case led to recovery of at least 50% of the starting material. Attempts to effect catalytic reduction at atmospheric pressure using Adams' catalyst failed.

Pertrifluoroacetic acid appeared to have no effect on the 3-methylthiazolo[3,2-a]pyridinium cation, and while oxidation in concentrated sulfuric acid with sodium dichromate appeared to take place, the mixture of products could not be separated. Refluxing the salt (IV) for a week with 8 *M* nitric acid was without effect, but refluxing for 24 hours with concentrated nitric acid having a few chips of anthracite coal suspended in it resulted in a small yield (14%) of a mononitration product. Similar results could be obtained without the coal chips if nitric oxide was bubbled through the solution. No means was found for increasing the yield of nitration product and the majority of the starting material was unaccounted for. By comparison with the product obtained by cyclization of 1-(3-nitro-2-pyridylthio)-propanone (VIIIp), it was shown that the nitration product was 8-nitro-3-methylthiazolo[3,2-a]pyridinium perchlorate (IXp).

The nitration of the thiazolopyridinium cation has no parallel in the quinolizinium series, where substitution reactions have been observed (8) only when activating groups are present. It is of interest that it is the *pyridinium* ring of the thiazolopyridinium cation which undergoes substitution, suggesting that electrophilic substitution of the parent quinolizinium ion may not be impossible.

The anion from 2-mercaptopyridine is a potent nucleophile and a wide variety of α-halo ketones and α-halo acetals can be brought into reaction with it. Yields of ten sulfides (VIII) produced by this reaction are given in Table I. Cyclization of the sulfides was brought about at room temperature in concentrated sulfuric acid, and it is felt that under most circumstances this medium is to be preferred

over the boiling 48% hydrobromic acid used by Babichev and Bubnovskaya (2). While our yields are superior in only three out of the five instances in which we prepared the same cyclization products, it is significant that 2-phenyl-2-(2-pyridylthio)-acetophenone (VIIIh), but not its cyclization product (IXh), was reported by the Russian workers; we have found that the ketosulfide (VIIIh) is cyclized in sulfuric acid in 86% yield.

Of particular interest are the thiazolopyridinium salts (IXk-w) which have a chlorine atom or nitro group in the pyridine ring. Since the pyridine nitrogen of the intermediate keto sulfides (VIIIk-w) would be made less basic by the inductive effect associated with the nitro and chlorine substituents, one might anticipate difficulty in cyclization. While the cyclizations may be slower, the overall yields of the substituted thiazolopyridinium salts (IXk-w) as a group, are as high as of the unsubstituted (IXa-h) cations. The nitrothiazolopyridinium salts (IXk-q) are of particular interest since these may lead to amines and perhaps to diazonium salts.

One further observation was that 2-carboxy-3-methylthiazolo[3,2-a]pyridinium perchlorate (IX, R_1 = R_2 = H, R_3 = CH_3, R_4 = COOH) the first carboxylic acid in this series, may be prepared by the nitric acid oxidation of 2-aceto-3-methylthiazolo[3,2-a]-pyridinium perchlorate (IXn).

Additional nuclear magnetic resonance spectra of some thiazolo[3,2-a]pyridinium perchlorates indicate that the system is aromatic as would be expected if there were some delocalization of charge from nitrogen to sulfur (II). The spectrum of the unsubstituted parent compound (II) shows no non-aromatic protons (all < 2.50 τ). The NMR spectrum of 2,3-dimethylthiazolo[3,2-a]pyridinium perchlorate shows but a single unsplit peak for the six protons of the two methyl groups with the correct ratio (0.67) to the aromatic protons. This equivalence of the two methyl groups might be interpreted as an indication that the positive charge is delocalized as represented by II.

EXPERIMENTAL

The elemental analyses were by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany, Galbraith Laboratories, Knoxville, Tennessee, or 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 noted, 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.

2-Mercaptopyridines.

2-Mercaptopyridine (VII, R_1 = R_2 = H) is available from the Aldrich Chemical Company. The preparation of 2-mercapto-5-nitropyridine (VII, R_1 = H, R_2 = NO_2) (9), 2-mercapto-3-nitropyridine (VII, R_1 = NO_2, R_2 = H) (10) and 5-chloro-2-mercaptopyridine (VII, R_1 = H, R_2 = Cl) (11) have been described. It was found more convenient to prepare 2-mercapto-3-nitropyridine via the isothiuronium salt.

2-(3-Nitropyridyl)isothiuronium Hydrochloride.

A solution of 7.95 g. of 2-chloro-3-nitropyridine and 3.81 g. of thiourea in 60 ml. of ethanol was refluxed for one hour. The isothiuronium salt separated from the solution and was collected, yield 8.89 g. (76%) of colorless prisms, m.p. 185-188° dec. The analytical sample, m.p. 187-189° dec., was crystallized from methanol.

Anal. Calcd. for $C_6H_7ClN_4O_2S$: C, 30.71; H, 3.01; N, 23.88. Found: C, 30.58; H, 3.13; N, 23.66.

The picrate crystallized from methanol as yellow needles, m.p. 190-191.5°.

Anal. Calcd. for $C_{12}H_9N_7O_9S$: C, 33.72; H, 2.12; N, 22.95. Found: C, 33.86; H, 2.21; N, 23.27.

2-Mercapto-3-nitropyridine (VII, R_1 = NO_2, R_2 = H).

A slight excess of an aqueous sodium carbonate solution was added to 4.00 g. of 2-(3-nitropyridyl)isothiuronium hydrochloride. The resulting orange precipitate was collected and recrystallized from methanol as bright orange needles, m.p. 172-174° (lit. (10) 174-175°), yield 2.52 g. (95%).

3-Chloro-2-mercaptopyridine (VII, R_1 = Cl, R_2 = H).

The procedure was based upon that recommended by Thirtle (12) for the preparation of 2-mercaptopyridine, with the additional precaution that a nitrogen atmosphere was used. From 14.8 g. of 2,3-dichloropyridine, 12.7 g. (88%) of product was obtained, m.p. 194-202°.

The analytical sample crystallized from methanol as yellow needles which melted at 197-206° and gave no improvement in melting point range when repeatedly recrystallized and sublimed under vacuum.

Anal. Calcd. for C_5H_4ClNS: C, 41.24; H, 2.77; N, 9.62. Found: C, 41.41; H, 2.93; N, 9.90.

α-(2-Pyridylthio)ketones.

To 350 ml. of absolute methanol containing 4.60 g. (0.20 gram-atom) of sodium, 0.20 mole of the mercaptopyridine (VII) was added. When the mercaptan had dissolved, 0.20 mole of the α-haloketone was added in portions while the flask was swirled. The mixture was allowed to stand at room temperature for about 18 hours. After removal of the sodium halide by filtration, the solution was concentrated. To the oily residue 40 ml. of water and 10 ml. of sodium hydroxide were added, and the oil extracted with methylene chloride or chloroform. The combined extracts were washed with water and dried over magnesium sulfate. After removal of the solvent, the residue (if not a solid) was purified by distillation under reduced pressure. The results are summarized in Table II.

2-(2-Pyridylthio)acetaldehyde Diethyl Acetal Methiodide.

To a sodium ethoxide solution formed by addition of 1.15 g. of sodium metal to 30 ml. of absolute ethanol, 5.55 g. of 2-mercaptopyridine was added. To the resulting solution, 9.85 g. of bromoacetaldehyde diethyl acetal in 75 ml. of absolute ethanol was added and the mixture refluxed for 48 hours. The sodium bromide was removed by filtration and the solution concentrated under reduced pressure. The residue was taken up in chloroform and the solution washed with dilute sodium hydroxide and water. The dried solution was concentrated and the residue distilled, yielding 10.45 g. (91%) of a light yellow oil, b.p. 99-101° (0.5 mm.).

The methiodide was recrystallized from acetone-ether as irregular colorless crystals, m.p. 89-91°.

Anal. Calcd. for $C_{12}H_{20}INO_2S$: C, 39.03; H, 5.46. Found: C, 38.76; H, 5.30.

2-(2-Pyridylthio)acetaldehyde Dimethyl Acetal Methiodide.

The dimethyl acetal was prepared from chloroacetaldehyde dimethyl acetal essentially as described for the diethyl except that methanol was used instead of ethanol. The acetal, b.p. 100-103° (0.2 mm.) was converted to the methiodide which crystallized from methanol-ethyl ether as irregular colorless crystals, m.p. 118-120°.

Anal. Calcd. for $C_{10}H_{16}INO_2S$: C, 35.20; H, 4.73; N, 4.11. Found: C, 35.26; H, 4.87; N, 4.05.

2-(3-Chloro-2-pyridylthio)acetaldehyde Diethyl Acetal.

The procedure was analogous to that used to prepare 2-(2-pyridylthio)acetaldehyde diethyl acetal. From 2.90 g. of 3-chloro-2-mercaptopyridine, 0.46 g. of sodium metal, and 3.94 g. of bromoacetaldehyde diethyl acetal in 50 ml. of absolute ethanol, there was obtained 5.11 g. (98%) of a light yellow oil, b.p. 115-120° (0.5-0.6 mm.), which solidified on standing.

The analytical sample crystallized from ether as colorless prisms, m.p. 50.5-51.5°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.16; N, 5.35. Found: C, 50.73; H, 6.35; N, 5.47.

3-Substituted Thiazolo[3,2-a]pyridinium Salts.

Ten grams of the keto sulfide (VIII) was dissolved in about 50 ml. of ice-cold concentrated sulfuric acid and the mixture allowed to stand at room temperature for 24 hours. The solution was then poured cautiously into 1 liter of cold anhydrous ether and the mixture placed in the refrigerator for several hours. The ether layer was decanted from the precipitated salt which might be either in the form of an oil or a solid. The material remaining after the ether was decanted was dissolved in a small quantity of water and the solution treated with Norite. Addition of 35% perchloric acid to the filtered and cooled solution caused precipitation of the perchlorate salt. The mixture was allowed to stand overnight and the product collected. Except as noted in Table III, all products were recrystallized from methanol and were obtained as colorless needles.

Thiazolo[3,2-a]pyridinium Salts (IX, R_3 = H) Unsubstituted at Position 3.

The cyclization of the 2-(2-pyridylthio)acetaldehyde acetals was not carried out directly, but the acetal was allowed to remain in 6 *N* hydrochloric acid solution overnight, the hydrochloric acid removed under vacuum at 100° and the residue (presumably the aldehyde) cyclized directly in concentrated sulfuric acid as recommended for the ketones. The isolation procedures were identical.

Nitration of 3-Methylthiazolo[3,2-a]pyridinium Perchlorate (IXb).

A solution of 1.00 g. of 3-methylthiazolo[3,2-a]pyridinium perchlorate was refluxed for 24 hours in 20 ml. of concentrated nitric acid with several small pieces of coal as boiling chips. The nitric acid was removed on the steam bath under reduced pressure (rotary evaporator) and the residue recrystallized from methanol. The yield was 0.17 g. (14%) of 3-methyl-8-nitrothiazolo[3,2-a]pyridinium perchlorate, identical with a sample prepared by cyclodehydration of 1-(3-nitro-2-pyridylthio)propanone (VIIIp). The nitration occurred in essentially the same manner if the coal was omitted and nitric oxide was bubbled through the solution during the refluxing period. Pure concentrated nitric acid afforded no nitration product.

2-Carboxy-3-methylthiazolo[3,2-a]pyridinium Bromide (IX, $R_1 = R_2$ = H, $R_3 = CH_3$, R_4 = COOH).

A solution of 1.0 g. of 2-acetyl-3-methylthiazolo[3,2-a]pyridinium perchlorate (IXp) in 20 ml. of 8 *M* nitric acid was refluxed for 8 hours. The nitric acid was removed under vacuum, the residue dissolved in 25 ml. of water and an excess of bromine-hydrobromic acid added. The orange tribromide salt precipitated and was collected from the chilled solution. The tribromide salt was converted to the bromide by refluxing in acetone. The product, 0.74 g. (77%), crystallized from acetone as irregular colorless crystals, m.p. 204–208° dec. The analytical sample, m.p. 207–210° dec., was crystallized from methanol-ether.

Anal. Calcd. for $C_9H_8BrNO_2S$: C, 39.43; H, 2.94; N, 5.11. Found: C, 39.34; H, 3.02; N, 4.87.

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