Mesoionic 5-Acylimino-2-methylthiothiazoles

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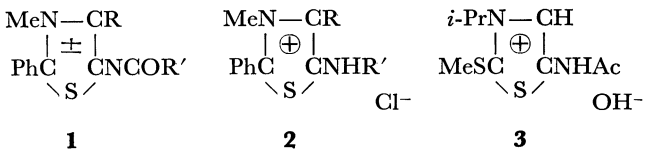
Treatment of 5-acylamino-4-thiazoline-2-thiones (**6**) with methyl iodide followed by treatment with an alkali gave the corresponding mesoionic 5-acylimino-2-methylthiothiazoles (**8**) instead of the corresponding thiazolium salts. The reactions of 2-methylthiothiazoles (**8**) with nucleophiles gave 2-substituted 5-acylamino-4-thiazolines.

We reported[1] on the preparation of mesoionic 5-acyliminothiazoles (**1**) by treatment of 3-substituted 5-acylaminothiazolium chlorides (**2**) with an alkali. Cook and Cox[2] claimed the preparation of 5-acetamido-2-methylthio-3-isopropylthiazolium hydroxide (**3**) by the reaction of 5-acetamido-3-isopropyl-4-thiazoline-2-thione and methyl iodide in the presence of sodium hydroxide. Although their results of elemental analyses agreed with those of thiazolium hydroxide structure, the substance might be assumed to actually have the corresponding anhydro-base or mesoionic structure, since the method of preparation is similar in principle to the one we employed for the preparation of mesoionic 5-iminothiazoles. The present study was initiated with the view of establishing the structure of the product obtained by Cook and Cox.

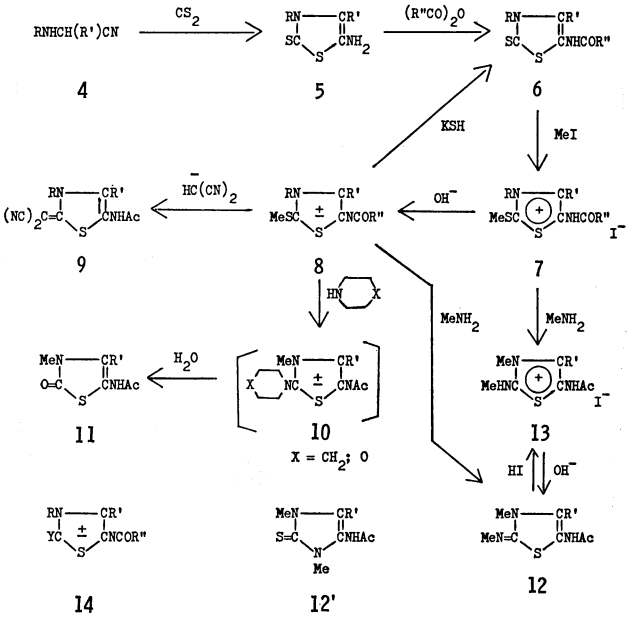


The reactions between aminoacetonitriles (**4a—c**) and carbon disulfide gave 5-amino-4-thiazoline-2-thiones (**5a—c**), which, on treatment with acetic anhydride or benzoic anhydride, gave the corresponding acylamino-4-thiazoline-2-thiones (**6a—d**). Treatment of **6a—d** with methyl iodide gave the corresponding 5-acylamino-2-methylthiothiazolium iodides (**7a—d**), which gave the free bases **8a—d** on treatment with aqueous alkali.

The elemental analyses of the final products agreed with the anhydro-bases **8** but not with the thiazolium hydroxides of type **3**. A considerable bathochromic shift of the ultraviolet absorption maxima is observed with **8** in comparison with iodides **7**. The infrared spectra of **7** show an amide carbonyl band at 1650—1675 cm^{-1} whereas the free bases **8** show no carbonyl band above 1600 cm^{-1}.

From the results including spectral data (Table 2), we might conclude that the compounds obtained by treatment of iodides **7** with alkali are mesoionic 5-acylimino-2-methylthiothiazoles (**8**).

The same **8a** was isolated when **6a** was treated with methyl iodide in aqueous sodium hydroxide as described by Cook and Cox.[2] Treatment of **8a** with water did not afford hydroxide **3**. The melting points of **8a** (178—179°C) and its hydriodide **7a** (159—160°C) did not agree with the reported values (83°C and 182—183°C respectively).



a: R=*i*-Pr, R′=H, R″=Me
b: R=Me, R′=Me, R″=Me
c: R=Me, R′=Ph, R″=Me
d: R=Me, R′=Ph, R″=Ph

The NMR chemical shifts of the substituents of **8** (Table 2) appear at a region close to the values of the corresponding thiazolium salts **7**. The signal for the methylthio group of **8** is also shifted downfield in comparison with thioanisole (δ 2.47) and 2-methylthiopyrimidines (δ around 2.5).[3] These spectral values are very close to those of mesoionic 2-phenyl-5-acyliminothiazoles.[1] For the sake of comparison, 5-acetylimino- and 5-benzoylimino-3,4-dimethyl-2-phenylthiazole (**1b**: R=R′=Me; **1c**: R=Me, R′=Ph) were prepared by the method reported,[1] and the results are shown in Tables 1 and 2. The NMR data, together with the solvent dependent electronic spectra (See Table 2) and the lack of infrared carbonyl absorption in the normal infrared region suggest that the ring bears a considerable positive charge, and the acylimino group is strongly polarized; *i.e.*, there is a large contribution from resonance structures such as **8′** and **8″**.

1) T. Shiba and H. Kato, This Bulletin, **44**, 1864 (1971).
2) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, **1949**, 2337.
3) N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., Vol. 1 (1962); Vol. 2 (1963).

TABLE 1. PROPERTIES OF 5-AMINOTHIAZOLE AND 5-AMINO-4-THIAZOLINE DERIVATIVES

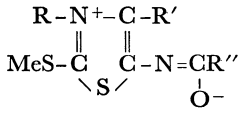
Compd.	Appearance	Solvent of Recryst.	Yield %	Mp °C	Formula	Anal. Found / Calcd. C	H	N
5b	colorless needles	dimethylformamide	77	263.5—264	$C_5H_8N_2S_2$	37.80 37.50	4.85 5.04	17.15 17.50
5c	yellow needles	ethyl acetate	79	138—139	$C_{10}H_{10}N_2O_2$	53.79 54.01	4.50 4.54	12.82 12.60
6b	colorless needles	methanol	91	214.5—215.5	$C_7H_{10}N_2OS_2$	41.32 41.56	5.20 4.98	13.39 13.69
6c	colorless prisms	acetone	88	272—272.5	$C_{12}H_{12}N_2OS_2$	54.68 54.55	4.61 4.58	10.32 10.60
6d	pale yellow needles	dimethylformamide	93	273—274	$C_{17}H_{14}N_2OS_2$	62.56 62.55	4.35 4.32	8.88 8.58
7a	colorless leaflets	ethanol	91	159—160[g]	$C_9H_{15}N_2OS_2I$	30.08 30.18	4.27 4.22	7.54 7.82
7b	colorless prisms	methanol	88	183.5—184.5	$C_8H_{13}N_2OS_2I$	28.13 27.92	3.88 3.81	7.99 8.14
7c	yellow prisms	ethanol	96	267.5—268	$C_{13}H_{15}N_2OS_2I$	38.52 38.44	3.81 3.72	6.61 6.90
7d	pale yellow needles	dimethylformamide	75	268—270	$C_{18}H_{17}N_2OS_2I$[i]	45.87 46.17	3.42 3.66	6.23 5.98
8a	colorless prisms	ethyl acetate	90	178—179[h]	$C_9H_{14}N_2OS_2$	46.67 46.97	6.24 6.13	11.80 12.17
8b	pale yellow needles	acetone	88	175—176	$C_8H_{12}N_2OS_2$	44.34 44.44	5.52 5.55	12.51 12.91
8c	yellow prisms	ethanol	96	212—213	$C_{13}H_{14}N_2OS_2$	56.46 56.11	5.32 5.07	9.77 10.07
8d	yellow leaflets	dimethylformamide	73	244.5—246	$C_{18}H_{16}N_2OS_2$	63.62 63.50	4.63 4.74	8.18 8.23
2a[a]	yellow prisms	2-propanol	57	243—244 dec	$C_{11}H_{13}N_2SCl$	54.70 54.81	5.55 5.44	11.64 11.64
2a, pic[b]	yellow needles	ethanol		150.5—151	$C_{17}H_{15}N_5O_7S$	47.22 47.11	3.52 3.52	15.79 16.16
2b[c]	colorless prisms	ethanol-acetone	90	228—230	$C_{13}H_{15}N_2OSCl$	55.01 55.31	5.48 5.31	9.62 9.92
2b, pic[b]	yellow needles	ethanol		167.5—168	$C_{19}H_{17}N_5O_8S$	48.30 48.00	3.81 3.60	14.56 14.73
2c[d]	colorless prisms	ethanol	58	175—176	$C_{18}H_{17}N_2OSCl$	62.36 62.70	5.20 4.97	7.96 8.13
2c, pic[b]	yellow prisms	ethanol		182—183	$C_{24}H_{19}N_5O_8S$	53.98 53.63	3.20 3.57	13.21 13.02
1b[c]	yellow prisms	ethanol	48	218.5—219	$C_{13}H_{14}N_2OS$	63.12 63.38	5.83 5.74	11.10 11.37
1c[d]	yellow needles	methanol	90	250—251	$C_{18}H_{16}N_2OS$	68.89 70.12	5.12 5.23	8.80 9.09
9a	colorless needles	dimethylformamide	89	>350	$C_{11}H_{12}N_4OS$	53.50 53.22	5.10 4.88	22.27 22.57
9b	colorless needles	dimethylformamide	74	307—308	$C_{10}H_{10}N_4S$	51.42 51.28	4.19 4.30	24.12 23.92
9c	colorless needles	ethanol	89	212.5—213.5	$C_{15}H_{12}N_4OS\cdot H_2O$[j]	57.05 57.30	4.75 4.50	18.12 17.82
11b	pale yellow prisms	ethanol	84[e]; 98[f]	186—187	$C_7H_{10}N_2O_2S$	44.91 45.14	5.54 5.41	14.57 15.01
11c	colorless needles	ethanol	72[e]; 81[f]	200—201	$C_{12}H_{12}N_2O_2S$	58.34 58.04	4.82 4.87	10.93 11.28
12b	colorless prisms	acetone	72	156—157	$C_8H_{13}N_3OS$	47.99 48.23	6.52 6.58	20.95 21.09
12c	colorless prisms	acetone	81	180—182	$C_{13}H_{15}N_3OS$	59.51 59.76	5.53 5.79	16.29 16.08
13b	colorless prisms	ethanol	80	303—304.5	$C_8H_{14}N_3OSI$	29.16 29.37	4.22 4.31	13.15 12.85
13c	colorless prisms	ethanol	79	230—232	$C_{13}H_{16}N_3OSI$	40.18 40.12	4.41 4.14	10.78 10.81

a) 5-Amino-3,4-dimethyl-2-phenylthiazolium chloride; R=Me, R′=H. b) The corresponding picrate. c) R=R′=Me. d) R=Me, R′=Ph. e) From piperidine. f) From morpholine. g) Reported mp: 182—183°C.[2] h) Reported mp for the corresponding hydroxide: 83°C.[2] i) This contains a molecule of dimethylformamide of crystallization before being dried in a vacuum at 200°C. j) Water content: 5.6% (Karl Fisher; calcd 5.73%).

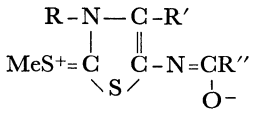
Table 2. Spectra of 5-aminothiazole and 5-amino-4-thiazoline derivatives

Compd.	λ_{max}^{EtOH}(nm) (log ε)	NMR (δ) of substituents at respective positions 2	3	4	5	IR (cm^{-1})
7a	319(4.036)	2.97	1.64 d[d] 4.73 sept	8.68	2.40	~3420 (NH), 1675 (C=O)
7b	324(4.042)	3.00	3.92	2.62	2.28[e]	3085—2990 (NH), 1660 (C=O)
7c	264(3.852) 322(4.056)					3010—2880 (NH), 1660 (C=O)
7d						3200—2800 (NH), 1650 (C=O)
8a	264(3.717)[c]	2.80	1.56 d[d] 4.82 sept	7.40	2.25	1560 (C=N or C=O)
8b	262(3.804)[c] 363(3.885)	2.77	3.83	2.62	2.28	1580 (C=N or C=O)
8c	234(3.910)[c] 305(3.915) 362(3.970)	2.82	3.71	7.52	2.20	1555 (C=N or C=O)
8d	230(4.303) 330(4.061) 382(4.211)	2.77	3.70	7.30—7.75 m (8H) 8.20—8.35 m (2H)		1540 (C=N or C=O)
1b[a]	250(3.975) 365(3.929)	7.58	3.88	2.67	2.30	1560 (C=N or C=O)
1c[b]	298(3.855) 382(4.250)	7.58	3.92	2.96	7.40—7.70m (3H) 8.35—8.50m (2H)	1560 (C=N or C=O)
11b			3.25	2.11	2.02	3400—2800 (NH), 1675 (C=O), 1660 (C=O), 1615 sh, 1600 (C=C)
11c			3.08	7.25—7.60m	1.99	3300—2800 (NH), 1670 (C=O), 1640 (C=O), 1600, 1590 sh (C=C)
12b		2.96	3.22	2.10	1.97	3240—3050, 2900 (NH), 1655 (C=O), 1635 (C=N), 1610 (C=C)
12c		3.03	3.08	7.30—7.63m	2.01	3300—2700 (NH), 1680 (C=O), 1640 (C=N), 1605 (C=C)
13b		3.06	3.57	2.37	2.18[e]	3350—2800 (NH), 1665, 1655 sh (C=O)
13c		3.19	3.71	—[f]	2.14	3400—2700 (NH), 1655 (C=O)

a) R=R′=Me. b) R=Me, R′=Ph. c) λ_{max} in pyridine: **8a**: 377 (4.047); **8b**: 391 (4.074); **8c**: 327 (3.929), 387 (4.030). λ_{max} in tetrahydrofuran: **8a**: 382 (4.055); **8b**: 395 (4.091); **8c**: 326 (3.970), 392 (4.031). d) J=7 Hz. e) In $CDCl_3$—DMSO-d_6 (2 : 3). f) Because of the low solubility of **13c**, this multiplet signal could not be measured with accuracy.



8′



8″

The mass spectra (see Experimental) of **8b** and **8c** show, besides the molecular ion peak, prominent fragmentation peaks corresponding to $(MeSCS)^+$, $(MeNCSMe)^+$, and $(MeNCR')^+$ as well as peaks of fragmentation at the ring substituents. It is to be noted that both **8b** and **8c** give fragment ion peaks corresponding to (M—133) with a considerable relative intensity.[4]

Since the spectral study suggested that the thiazole ring is positively charged, it was expected that the methylthio group of **8** would be readily replaced by nucleophiles.

Mesoionic 5-acylimino-2-methylthiothiazoles (**8a**—**c**) readily reacted with potassium hydrosulfide at room temperature to give the corresponding 5-acetamido-4-thiazoline-2-thiones (**6a**—**c**). The reaction between **8a**—**c** and dicyanomethide ion also gave the corresponding 2-dicyanomethylene derivatives **9a**—**c**. Methylthiothiazoles **8b** and **c** and their hydriodides **7b** and **c** reacted with piperidine and morpholine on heating in ethanol. However, the expected mesoionic 2-piperidino and 2-morpholino derivatives **10b** and **c** were not isolated, which apparently underwent hydrolysis to give the corresponding 5-acetamido-4-thiazolin-2-ones (**11b** and **c**) as the final products.

Although **8b** and **8c** did not react with aniline even on heating, they reacted with methylamine to give substitution products, the elemental analyses of which agreed with 2-methylimino derivatives (**12b** and **c**). However, an imidazoline-2-thione structure **12′** should also be considered as a possible structure of the reaction products since a similar skeletal rearrangement has been observed by the reactions of 5-methylthiothiazolium[5] and 5-methylthiothiadiazolium[6] salts and methylamine.

4) The high resolution mass spectrum of **8c** measured by Prof. Fukiko Yamada, Kansai University, gave the composition $C_9H_9N_2$ for this fragment.

5) T. Shiba and H. Kato, This Bulletin, **43**, 3491 (1970); P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *Chem. Commun.*, **1972**, 696.

6) M. Ohta, H. Kato, and T. Kaneko, This Bulletin, **40**, 579 (1967).

Comparison of the NMR spectra of the reaction products and their hydriodides, formed either by the treatment of **12b** and **c** with hydriodic acid or directly by the reaction of methylthiothiazolium iodides **7b** and **c** and methylamine, shows that one methyl signal is shifted to a considerably lower magnetic field in going from the free base to the hydriodide, but the other remains almost unchanged. This suggests that one methyl group is substituted on a ring nitrogen atom while the other is substituted on an exocyclic nitrogen atom. This, together with the lack of infrared bands often observed with an N–C=S group,[6,7] supports the view that the reaction products have a 2-methyliminothiazoline structure **12b** and **c**. Although the mass spectra of **12b** and **c** do not provide information as to the choice of structure between **12** and **12'**, they show a strong peak corresponding to (M−116) which probably has the same composition as the (M−133) peak of **8**.

That the products of nucleophilic displacement reactions have 5-acetamido-4-thiazoline structures (**6**, **9**, **11**, **12**) rather than the corresponding mesoionic 2-substituted 5-acetyliminothiazole structures (**14**) was supported, *inter alia*, by the presence of the amide carbonyl band at a normal infrared region and the presence of an NH stretching frequency band. This shows that 4-thiazoline structures are thermodynamically more stable than the corresponding mesoionic thiazole structures.

Experimental[8]

*5-Amino-4-thiazoline-2-thiones (**5**).* A solution of 0.21 mol of aminoacetonitriles (**4**) and 16 g (0.21 mol) of carbon disulfide in 150 ml of ethyl acetate was allowed to stand at room temperature for two days. The solvent was concentrated and the residue was recrystallized. IR: **5b**: ~3300 (NH), 1620 (C=C), 1092, 1300 (C=S); **5c**: 3380—3300 (NH), 1620 (C=C), 1105, 1295 (C=S).

*5-Acylamino-4-thiazoline-2-thiones (**6**).* One part of 5-aminothiazolinethione (**5**) was dissolved in 20 parts of acetic anhydride and the resulting precipitate was collected. Benzoylation of **5c** was effected by heating equimolar amounts of **5c** and benzoic anhydride in benzene for twenty minutes. IR: **6a**: 3200—3100 (NH), 1665 (C=O), 1595 (C=C) 1075, 1290 (C=S); **6b**: ~3280 (NH), 1670 (C=O), 1630 (C=C), 1105, 1275 (C=S); **6c**: ~3320 (NH), 1650 (C=O), 1610 (C=C), 1120, 1294 (C=S); **6d**: ~3210 (NH), 1660 (C=O), 1610 (C=C), 1105, 1294 (C=S).

*5-Acylamino-5-methylthiothiazolium Iodides (**8**).* A solution of 5-acylamino-4-thiazoline-2-thione (**6**) and two molar equivalents of methyl iodide in methanol was heated under reflux; the solvent was concentrated and the residue was recrystallized.

*Mesoionic 5-Acylimino-2-methylthiothiazoles (**8**).* An aqueous solution (or suspension) of 5-acylamino-2-methylthiothiazolium iodide (**7**) was made alkaline with potassium carbonate and the crystals which separated out were collected and recrystallized. MS: **8b**: 216 (30) M, 201 (41) [M–Me], 91 (73) MeSCS, 88 (21) MeNCSMe, 83 (30) [M−MeSCS−Ac+H], 56 (88) MeNCMe, 43 (100) Ac. **8c**: 278 (41) M, 263 (38) [M−Me], 145 (19) [M−MeSCS−Ac+H], 118 (80) MeNCPh, 91 (97) MeSCS, 88 (32) MeNCSMe, 77 (48) Ph, 43 (100) Ac.

*Mesoionic 5-Acylimino-3,4-dimethyl-2-phenylthiazoles (**1**).* The compounds were prepared by methods similar to those described earlier.[1]

*Reactions of **8a–c** with Potassium Hydrosulfide.* To a solution of 0.5 g of **8** in 15 ml of ethanol was added a solution of two molar equivalents of potassium hydrosulfide in 10 ml of ethanol, and the resulting solution was stirred at room temperature for one hour. The reaction mixture was poured into water and the precipitate was collected, recrystallized and identified to be 5-acetamido-4-thiazoline-2-thiones (**6**) by mixed mp and comparison of their infrared spectra. Yields: 99, 96, and 87% from **8a**, **b**, and **c** respectively.

*5-Acetamido-2-dicyanomethylene-4-thiazolines (**9**).* One gram of **8a–c** was added under an atmosphere of nitrogen to a solution of dicyanomethide anion in 20 ml of dimethyl sulfoxide prepared from an equimolar amount of malononitrile and sodium hydride. The resulting solution was stirred at room temperature for two hours, and poured into 20 ml of water. The precipitate was collected and recrystallized. IR: **9a**: 3300—2700 (NH), 2200, 2175 (CN), 1670 (C=O), 1625 (C=C); **9b**: 3260—2840 (NH), 2200, 2165 (CN), 1680 (C=O), 1640 (C=C); **9c**: 3700—2900 (NH), 2200, 2170 (CN), 1665 (C=O), 1630 (C=C).

*5-Acetamido-4-thiazolin-2-ones (**11**).* A solution of **8** or **7** and an equimolar amount of piperidine or morpholine was heated under reflux for ten hours. The solvent was concentrated and the crystals which separated out were collected.

*5-Acetamido-2-methylimino-4-thiazolines (**12**).* A solution of 0.5 g of **8** and 1.5 ml of 30% ethanolic methylamine in 10 ml of ethanol was stirred at room temperature for ten hours. The reaction mixture was concentrated and the crystals which separated out were collected and recrystallized. MS: **12b**: 199 (56) M, 156 (29) [M−Ac], 83 (78) [M−MeNCS−Ac], 56 (100) MeNCMe, 43 (60) Ac; **12c**: 261 (49) M, 219 (15) [M−Ac+H], 218 (10) [M−Ac], 145 (36) [M−MeNCS−Ac], 118 (100) MeNCPh, 77 (42) Ph, 43 (29) Ac.

*5-Acetamido-2-methylaminothiazolium Iodides (**13**).* The compounds were prepared either by the action of hydroiodic acid on **12**, or by treatment of **7** with an excess of ethanolic methylamine at room temperature for ten hours. The yields given in Table 1 refer to those from **7**. The free bases **12** were formed by treatment of **13** with potassium carbonate.

We are indebted to the staff of Kyorin Chemical Laboratories for elemental analyses and mass spectral measurements.

7) T. G. Stewart and L. B. Kier, *J. Pharm. Sci.*, **54**, 731 (1965); P. B. Talukdar and S. K. Sengupta, *J. Indian Chem. Soc.*, **47**, 49 (1970); and references cited therein.

8) The melting points were determined on a micro hot stage and are not corrected. The ultraviolet spectra were recorded on a Hitachi model ESP-2U spectrophotometer, and the infrared spectra were recorded as KBr disks on a Hitachi model EPI-SII spectrophotometer. Unless otherwise stated, the NMR spectra were obtained on a JEOLCO JNM-4H-100 (100 MHz) spectrometer in deuteriochloroform, and the chemical shifts are recorded (ppm) downfield from internal TMS. The mass spectra were measured on a Hitachi RMU-6 spectrometer at 75 eV using a direct inlet technique. The yields, properties and elemental analyses are given in Table 1, and the spectral data of some compounds in Table 2.