Benzothiazoline Derivatives. II. Preparation of *N*-Substituted Derivatives of 2-Benzothiazolinethione by Thiation of the 2-Oxo Analogs (1)

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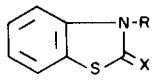
Thiation of the benzoate and acetate esters of 3-(2-hydroxyethyl)-2-benzothiazolinone (Ig) gave the corresponding thiones. The benzoate was then deblocked to yield 3-(2-hydroxyethyl)-2-benzothiazolinethione (Ik), a compound not accessible by direct addition or substitution. Attempts to introduce a chlorine (or bromine) atom in place of the hydroxyl group in the latter compound or its *S*-isomer, 2-(2-hydroxyethylthio)benzothiazole (IIa), gave 2,3-dihydrothiazolo-[2,3-*b*]benzothiazolium chloride (or bromide) (IIIa or b). The latter compound undergoes dihydrothiazolo ring opening when treated with sodium hydroxide or sodium sulfide to give bis[2-(2-benzothiazolinon-3-yl)ethyl]disulfide (IVc) or bis[2-(2-benzothiazolinethion-3-yl)ethyl] disulfide (IVb), respectively. 2-Benzothiazolinethione reacted with ethylenimine and with *N*-phenylethylenimine to give *S*-substituted derivatives. Addition to vinyl *n*-butyl ether gave the expected *N*-substituted derivative, which was found to undergo removal of the butyoxyethyl group when subjected to conventional conditions for ether cleavage.

The direct attachment of functional groups to the nitrogen atom of 2-benzothiazolinethione (Ia) may be accomplished only by means of Mannich reactions, conjugate additions to vinyl acceptor agents, or thermal rearrangement of the corresponding *S*-isomers. Each of these methods suffers from specific limitations as to the nature of the moiety that may be introduced when it is utilized. In the present work it was our intention to synthesize an *N*-substituted derivative of 2-benzothiazolinethione in which the substituent consists of an extendable two-carbon chain.

No example of the above mentioned reactions has been reported to produce such a derivative. The nature of the Mannich reaction precludes the possibility of such a product, and the extension of a one-carbon chain (such as a chloromethyl group) required conditions too drastic to permit retention of the benzothiazoline ring system. All attempts to bring about thermal $S \rightarrow N$ rearrangements of the easily obtainable *S*-isomers were unsuccessful, presumably due to interferences by reactive groups located at the β-position of the side chain. Among the obvious choice of acceptors for our purpose, the compounds vinyl chloride and vinyl benzoate were found to give no reaction with 2-benzothiazolinethione, even at high temperatures, and vinyl acetate reacted sluggishly to give only a trace of its addition compound, as detected in the ultraviolet spectrum of the crude product. The addition product with vinyl *n*-butyl ether, while obtained in reasonable yield, was found to undergo loss of the entire substituent under conventional conditions for ether cleavage.

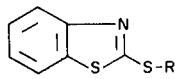
In the search for acceptable alkylating agents it was hoped that ethylene oxide or ethylenimine might follow the pattern of vinyl addition under the proper conditions. The former reagent had been reported to effect *S*-hydroxyethylation of Ia in neutral solvents (2). In acetic acid *N*-hydroxyethylation occurred but was accompanied by replacement of the exocyclic sulfur atom by oxygen (3). In the present work ethylenimine and *N*-phenylethylenimine were seen to give *S*-substitution exclusively.

In contrast to 2-benzothiazolinethione, its oxo analog, 2-benzothiazolinone (Ib), undergoes direct *N*-alkylation with a variety of reagents, including alkyl halides. This distinction in reactivity may be explained as a consequence of the greater nucleophilic reactivity of sulfur as compared with oxygen. This naturally suggests an approach in which the desired side chain is first attached to the *N*-atom of 2-benzothiazolinone, followed by thiation of the carbonyl to give the desired *N*-substituted thione. Precedent for this general approach may be found in the pyridazinethione series, where the *N*-substituted derivatives are not



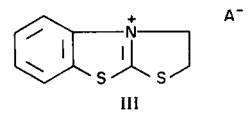
I

Compound	R	X
Ia	H	S
Ib	H	O
Ic	CH_3	O
Id	CH_3	S
Ie	CH_2NHPh	S
If	CH_2NHPh	O
Ig	CH_2CH_2OH	O
Ih	$CH_2CH_2OCOCH_3$	O
Ii	CH_2CH_2OCOPh	O
Ij	CH_2CH_2OCOPh	S
Ik	CH_2CH_2OH	S
Il	CH_2CH_2Cl	O
Im	$CH_2CH_2OCOCH_3$	S
In	CH_2CH_2OTs	S
Io	$CH_2CH_2OC_4H_9$-*n*	S



II

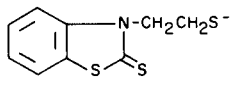
Compound	R
IIa	CH_2CH_2OH
IIb	$CH_2CH_2NH_3^+Cl^-$
IIc	CH_2CH_2NHPh
IId	CH_3



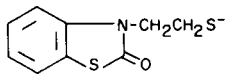
III

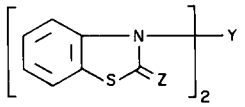
Compound	A⁻
IIIa	Cl^-
IIIb	Br^-
IIIc	TsO^-

IIId



IIIe





IV

Compound	Y	Z
IVa	$CH_2CH_2N(Ph)CH_2CH_2$	O
IVb	$CH_2CH_2SSCH_2CH_2$	S
IVc	$CH_2CH_2SSCH_2CH_2$	O

Ph = phenyl
Ts = *p*-toluenesulfonyl

accessible by direct substitution, but are prepared instead by thiation of the corresponding pyradazinones (4).

In order to test this method, pairs of known oxo-thione analogs were chosen for thiation studies. Thus it was found that 3-methyl-2-benzothiazolinone (Ic) (5) was converted in 64% yield to 3-methyl-2-benzothiazolinethione (Id) (phosphorus pentasulfide, pyridine, 3 day reflux). Similarly, 2-benzothiazolinone (Ib) gave 67% of 2-benzothiazolinethione (Ia) (See Table I). Another known compound, 3-anilinomethyl-2-benzothiazolinethione (Ie) (6) could not be prepared by thiation due to loss of the anilinomethyl side chain at the required temperatures (7). An analogous compound, *N,N*-bis-[2-(2-benzothiazolinon-3-yl)ethyl]aniline (IVa), in which the nitrogen atoms are separated by *two* methylene groups, proved stable but unreactive under the thiating conditions utilized.

For the purposes of the present work the β-hydroxyethyl group was conceived as an extendable two-carbon unit. A derivative of 2-benzothiazolinone containing this side chain, 3-(2-hydroxyethyl)-2-benzothiazolinone (Ig), was readily available (3). In order to preserve the hydroxyl group the acetyl and benzoyl esters (Ih and Ii) were prepared and then successfully thiated. For large scale preparations the benzoyl group was chosen because of its easy removability. Alkaline hydrolysis of the resulting 3-(2-benzoyloxyethyl)-2-benzothiazolinethione (Ij) was easily accomplished. The compound thus obtained, 3-(2-hydroxyethyl)-2-benzothiazolinethione (Ik), fulfills the stated goal of this work of attaching an extendable two-carbon unit to 2-benzothiazolinethione at the 3-position. To substantiate the structure of Ik, its immediate precursor Ij was prepared from it by means of benzoyl chloride in pyridine.

TABLE I

Thiation of Various Benzothiazolinones

Product	Reactant/ grams	P_2S_5/ grams	Pyridine, ml.	Reflux Time, days	Crystallization Solvent	Yield %	M.p.	Analysis Calcd. C	H	N	S	Found C	H	N	S
Ia	Ib/3.4	9	100	3	AcOH	67	177-180 lit., 181 (a)								
Id	Ic/2	5	60	3	EtOH	64	87-89 lit., 91.5 (a)	53.01	3.89	7.73	35.38	52.87	3.82	7.90	35.61
Im	Ih/6	10	100	3	EtOAc	15	75-77	52.15	4.38	5.53	25.32	52.27	4.36	5.49	25.70
Ij	Ii/95	220	1900	4	EtOH	69	90-92	60.93	4.15	4.44	20.33	61.18	4.12	4.69	20.10
IVb	Ig/5	20	170	3	$CHCl_3$/EtOH	23	158-160 (b)	47.75	3.56	6.19	42.50	47.57	3.70	6.22	42.66

(a) H. Larivé, A. J. Chambonnet and J. Metzger, *Bull. Soc. Chim. France*, 1675 (1963). (b) NMR spectrum (C_5D_5N): τ 2.4-2.9 (multiplet, 8-H, C_6H_4), 5.19 (triplet, J = 7.5 Hz, 4-H, NCH_2), 6.73 ppm (triplet, J = 7.5 Hz, 4-H, SCH_2), mass spectrum, molecular ion, m/e 452.

TABLE II

Ultraviolet Absorption Spectra (in Methanol)

No.	Formula	λ max (mμ)	$\epsilon \times 10^{-3}$
		Structure A	
Ia	$C_7H_5NS_2$	326	25.8
		237.5	14.4
		232.5	14.2
Id	$C_8H_7NS_2$	325	26.8
		257	5.5
		240	14.0
		230	14.0
		207.5	15.0
Ie	$C_{14}H_{12}N_2S_2$	325	26.7
		240	27.0
Ij	$C_{16}H_{13}NO_2S_2$	326	25.6
		282	3.1
		229	25.7
Ik	$C_9H_9NOS_2$	325	26.3
		239	13.3
		230	14.6
		207.5	17.5
Im	$C_{11}H_{11}NO_2S_2$	325	24.0
		240	12.5
		229	13.6
Io	$C_{13}H_{17}NOS_2$	326	25.5
		278	2.3
		240	12.5
		229	14.2
IVb	$C_{18}H_{16}N_2S_6$	325	42.0
		229	27.8
		Structure B	
Ib	C_7H_5NOS	289	2.9
		282	2.9
		243	10.2
		213	39.8
Ic	C_8H_7NOS	289	3.1
		282.5	3.1
		245	5.7
		215	48.0

TABLE II (continued)

No.	Formula	λ max (mμ)	ε x 10^{-3}
If	$C_{14}H_{12}N_2OS$	288	4.4
		282	4.2
		242	19.6
		213	44.6
Ig	$C_9H_9NO_2S$	290	2.8
		283	2.8
		246	5.7
		215	44.0
Ih	$C_{11}H_{11}NO_3S$	289	2.8
		282	2.9
		244	5.5
		215	44.8
Ii	$C_{16}H_{13}NO_3S$	289	2.8
		282	3.4
		215	46.0
Il	C_9H_8ClNOS	289	2.8
		282.5	2.8
		244	5.5
		214	44.0
IVa	$C_{24}H_{21}N_3O_2S_2$	287.5	4.4
		250	32.7
		213	62.0
IVc	$C_{18}H_{16}N_2O_2S_4$	290	5.6
		282.5	5.6
		245	11.2
		215	81.0
	Structure C		
IIa	$C_9H_9NOS_2$	301	9.1
		290	11.5
		280	13.0
		244	8.6
		225	20.4
IIb	$C_9H_{11}ClN_2S_2$	300	7.5
		289	10.0
		276	12.2
		242.5	8.7
		223	20.5
IIc	$C_{15}H_{14}N_2S_2$	301	12.1
		291	14.0
		282.5	14.4
		246	20.8
		226	25.0
IId	$C_8H_7NS_2$	300	9.2
		289	11.8
		278	13.5
		243	9.1
		225	22.4
	Structure D		
IIIa	$C_9H_8ClNS_2$	311	14.6
		258	7.0
		251.5	5.5
		225	8.3
IIIb	$C_9H_8BrNS_2$	311	15.4
		258	7.2
		252	5.6
		224	9.1
IIIc	$C_{16}H_{15}NO_3S_3$	311	15.3
		258	7.4
		252	5.8
		222.5	20.3
IIId	$C_{18}H_{16}N_2S_5$	322	27.4
		257	10.0
		225	32.0
IIIe	$C_{18}H_{16}N_2OS_4$	309	8.6
		291	7.5
		285	6.3
		256	7.7
		247	9.3
		215	68.4

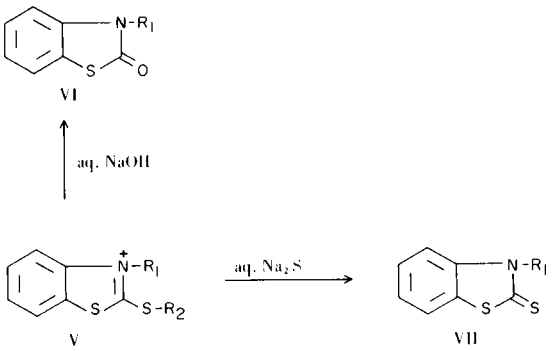
From a synthetic point of view it was considered desirable to prepare the corresponding chloroethyl derivative of Ik. Reaction conditions (thionyl chloride, chloroform, 0.5 hour reflux) were first tested on the oxo analog (Ig), and as a result 3-(2-chloroethyl)-2-benzothiazolinone (Il) was prepared. However, when these conditions were applied to the thione Ik, a water soluble product was obtained. Varying the reflux time or the use of other solvents (1 minute reflux; dioxane, pyridine) did not alter the course of the reaction. The product was identified as 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium chloride (IIIa) by comparison of its ultraviolet and infrared

spectra with those of an authentic sample of the corresponding bromide IIIb, prepared according to the method of Stanovnik and Tišler (8), which involves reaction of 2-benzothiazolinethione with ethylene dibromide. Subsequently, the bromide IIIb was itself prepared by treatment of Ik with phosphorus tribromide and the product found to be identical with authentic material (mixture melting point; infrared and ultraviolet spectra). The structure of the product recalls the related work of Sexton (9) on the formation of benzothiazolium salts from *N*- and *S*-methyl derivatives of 2-benzothiazolinethione, in which it was shown that the same product was obtained when either of these isomers was treated with methyl iodide. From these results it may be inferred that the present cyclization reaction (Ik→IIIa *or* IIIb) may proceed through an unstable covalent halide which rapidly cyclizes as a result of nucleophilic displacement of halogen by the exocyclic sulfur atom. The resultant product is seen to bear a close structural resemblance to the previously described benzothiazolium salts. The findings of Sexton regarding salt formation from isomeric *N*- and *S*-methyl derivatives prompted phosphorus tribromide treatment of compound IIa, which is the *S*-isomer of Ik. Using the same conditions as before, compound IIIb was obtained again, although in lower yield. With more vigorous conditions the yield was found to be closer to that previously observed with the *N*-isomer. In some experiments it was possible to isolate the uncyclized halide derivative of IIa as an oil. This could not be purified due to its facile conversion to the solid salt. The *N*-chloroethyl isomer, however, could not be isolated at all, due to the rapidity of its cyclization.

This difference in reactivity is in agreement with the findings of Morgan (10) who upon repeating the benzothiazolium salt syntheses of Sexton noted that the *S*-methyl isomer reacted more slowly with methyl iodide (or methyl sulfate) than did the corresponding *N*-methyl compound.

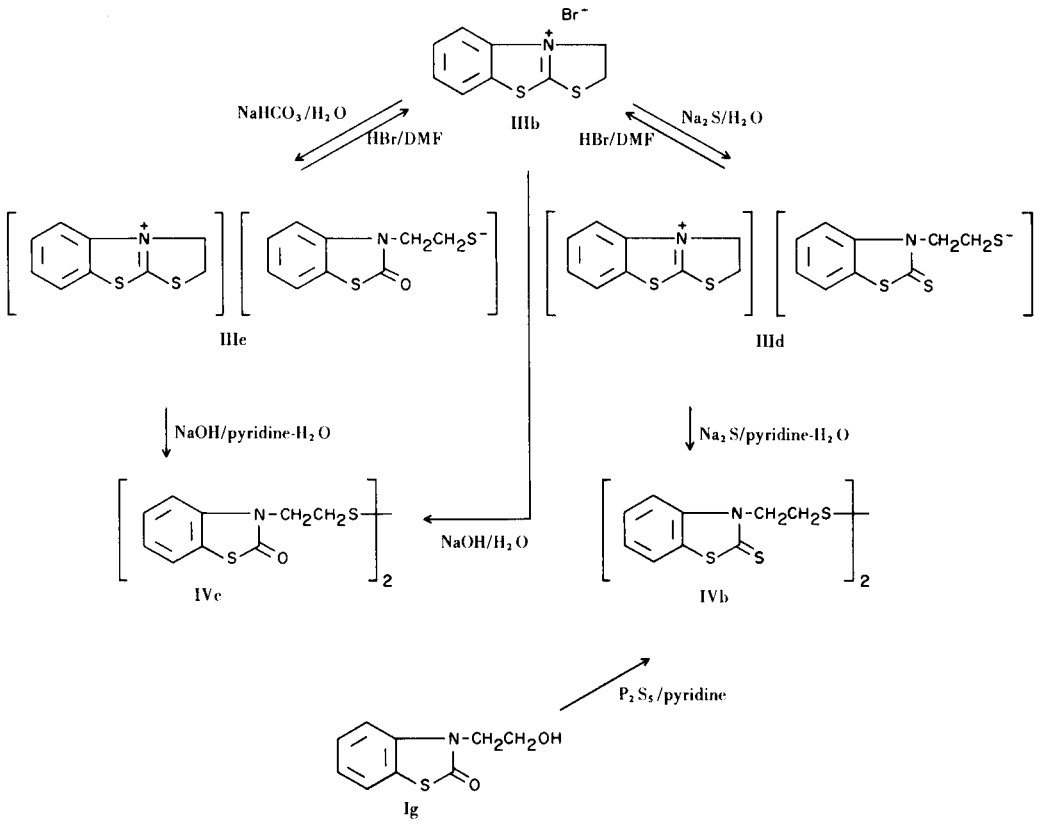
Cyclization of the isomeric *N*- and *S*-haloethyl derivatives to give the 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium ion may be explained as resulting from participation of the available heteroatom, thereby facilitating halide ion formation. The tosylate ester (In), prepared from Ik, also changed on standing for three days to the tosylate salt IIIc, presumably by way of a similar mechanism.

The structural similarity between salts having structure III and the benzothiazolium salts described in the earlier literature suggested that established degradative pathways could be used to substantiate the structure of this unusual fused ring system. Thus Sexton (9) noted that various *N*,*S*-dialkyl salts (V) experienced bond rupture of the alkylthio group when treated with aqueous solutions of either sodium hydroxide or sodium sulfide. This resulted in replacement of the alkylthio group by either oxygen or sulfur, to give the corresponding *N*-substituted compounds VI and VII, as shown below.



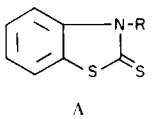
In order to provide chemical proof for the structure of IIIb, probe runs were performed in which the compound was subjected alternatively to the hydroxide and sulfide decomposition conditions described by Sexton (9). In our initial experiments, performed at room temperature using aqueous solutions, the major products precipitated from the reaction mixtures, and were shown to have structures IIId (from sulfide decomposition) and IIIe (from hydroxide decomposition). These unusual benzothiazolium salts were identified by elemental analyses, uv and ir spectra, and reconversion to IIIb by treatment with hydrogen bromide in dimethylformamide. In addition to the major products, IIId and IIIe, the sulfide and hydroxide decompositions also yielded small amounts of IVb and IVc, respectively. Their presence in the reaction mixtures suggested that IIId and IIIe might function as intermediates in the decomposition sequences, having been isolated in the probe runs only because of their insolubility in water. Subsequently it was found that IIId and IIIe were indeed readily converted in homogenous solutions (pyridine-water) by means of sulfide and hydroxide to the final products IVb and IVc. Substitution of sodium bicarbonate for sodium hydroxide in the transformation of IIIb to IIIe gave the same result, only in higher yield. For purposes of comparison, an independent synthesis of IVb was performed by treatment of the hydroxyethyl compound Ig with phosphorus pentasulfide in pyridine (See Table I). The products obtained by the two separate routes were found to be identical.

Mass spectra of the salts IIId and IIIe revealed parent peaks at m/e 420 and 404, respectively. These results may be interpreted as resulting from thermally induced combination of the ions present in the salts prior to electron bombardment; the resultant molecular species

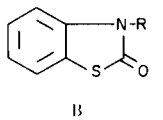


then being free to vaporize from the source into the ionizing region of the instrument. Mass spectrometry was also used to verify the molecular weights of compounds IVa, IVb and IVc, the result for each compound being the same as the corresponding calculated value.

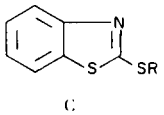
Throughout this work, ultraviolet absorption spectra were of particular utility in establishing whether a substituent was attached to nitrogen or to the exocyclic sulfur atom of the potentially tautomeric 2-benzothiazolinethione ring system. Previous workers (10, 11) established the existence of clearly different and easily recognizable ultraviolet absorption curves for various isomeric *N*- or *S*-substituted pairs of compounds. We have found that the ultraviolet curves of pertinence to the present work may be grouped into four distinct patterns, corresponding to structures A,B,C, and D (see Table II and Figures I-IV).



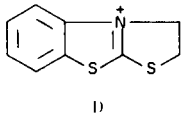
A



B



C



D

In agreement with the findings of previous authors, the *N*-substituted thiones exhibit an absorption maximum at 325 mμ due to the thione grouping. This band is absent in the other compounds, thereby providing a valuable distinguishing feature. A characteristic pattern was observed for our benzothiazolium salts (Structure D), consistent with the findings of Morgan (10) for structurally similar *N*,*S*-dialkyl benzothiazolium salts.

The NMR spectra were also useful in supporting *N*- *vs.* *S*- structural assignments. We have confirmed the findings of Halasa and Smith (12) regarding the observation of either a two-envelope (*S*-substituted) or compressed (*N*-substituted) aromatic multiplet with isomeric pairs of compounds (See Table III). In accordance with expectation, the *N*-substituted oxo-analog Ig also showed the same characteristic compressed multiplet as was observed in the thione series. It is of interest that the benzothiazolium salt IIIb was found to have an aromatic multiplet of the two-envelope form. The presence of $-CH_2CH_2-$ side chains was established in each case by the observation of a characteristic A_2B_2 splitting pattern. Coupling of N-H

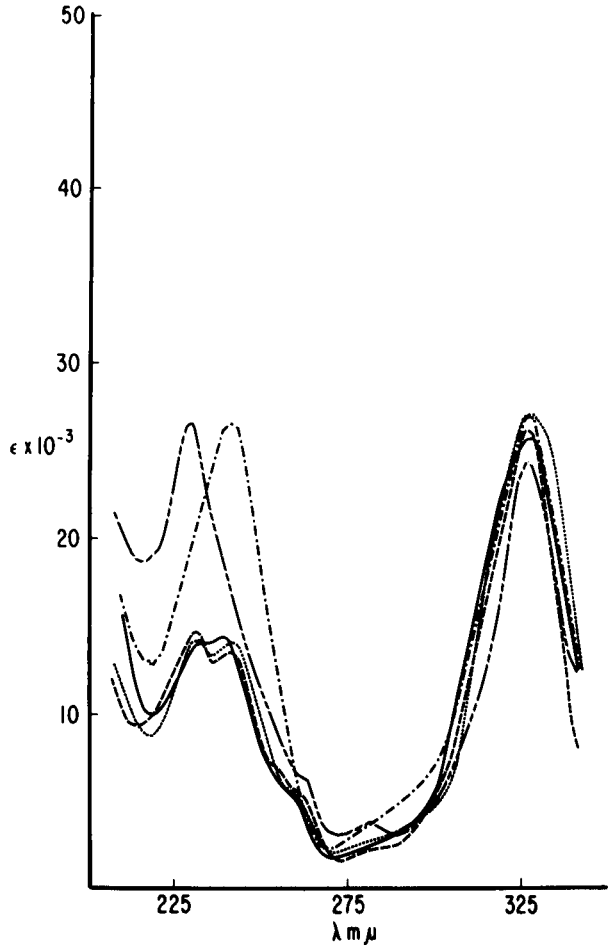


Figure I. Ultraviolet spectra in methanol. Compounds of structural type A; Ia,——; Id, · · · · ·; Ie,·····; Ij, ·····; Ik, ·····.

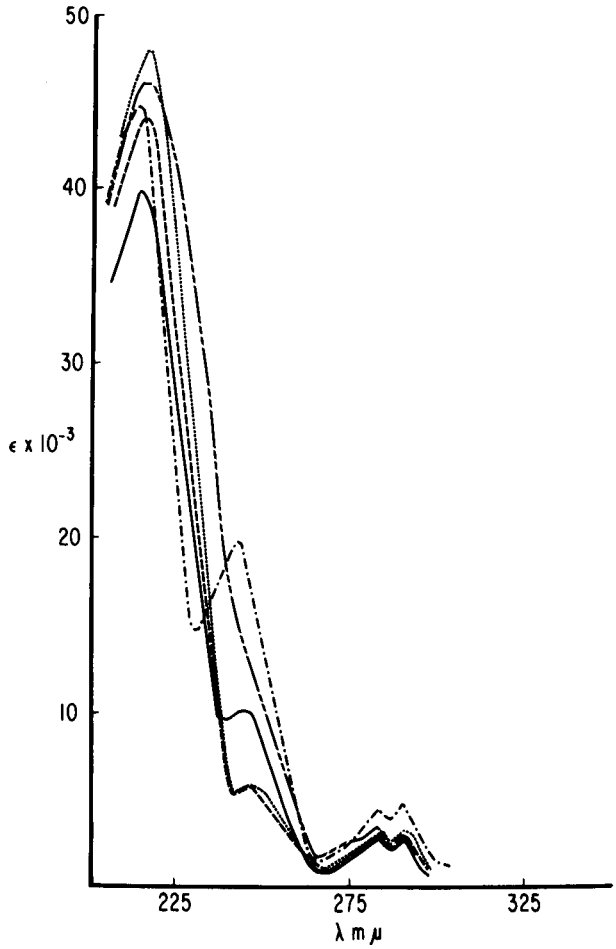


Figure II. Ultraviolet spectra in methanol. Compounds of structural type B; Ib,——; Ic,. . . .; If, ·····; Ig, -----; Ii, ·····.

functions with adjacent methylene groups was observed with compounds Ie and If, as evidenced by the conversion of a doublet into a singlet upon addition of deuterium oxide to the solutions.

Infrared spectra were of value in following the course of thiation reactions due to the disappearance of a strong carbonyl absorption in the 6 μ region as the reactions progressed. In other respects, the compounds studied had the expected infrared spectra, showing the characteristic thioamide or amide absorption at 6.5-6.8, 6.8-7.0, and 7.4-7.6 μ, in agreement with the findings of Ettlinger (14) for similar structural arrangements.

EXPERIMENTAL (15)

3-(2-Butoxyethyl)-2-benzothiazolinethione (Io).

A solution consisting of 30 g. (0.18 mole) of 2-benzothiazolinethione (Ia) and 130 g. (50 ml., 0.3 mole) of vinyl *n*-butyl ether in 400 ml. of glacial acetic acid was refluxed overnight. The clear brown solution was then concentrated to a semisolid and flushed with water. A methylene chloride (1 l.) solution of the residue was washed with 5% sodium hydroxide and saturated sodium chloride solutions. The organic layer was treated with Darco G-60, filtered, and dried over sodium sulfate. After removal of the drying agent and evaporation of the solvent a clear oil (25.1 g., 53%) was obtained. The product had an infrared spectrum clearly different from those of the starting materials. The ultraviolet spectrum showed a maximum at 326 mμ, indicative of *N*-substitution. The product was next distilled (b.p. 142-170°/ 0.1-0.3 mm) to give an oil which was found to contain a small amount of 2-benzothiazolinethione, probably formed during distillation. Final purification was achieved by dissolving the impure oil in hexane and washing again with 5% sodium hydroxide solution. After washing to neutrality with water the hexane layer was dried over sodium sulfate, treated with Darco KB, filtered and evaporated to dryness to give 15.1 g. (32%) of product.

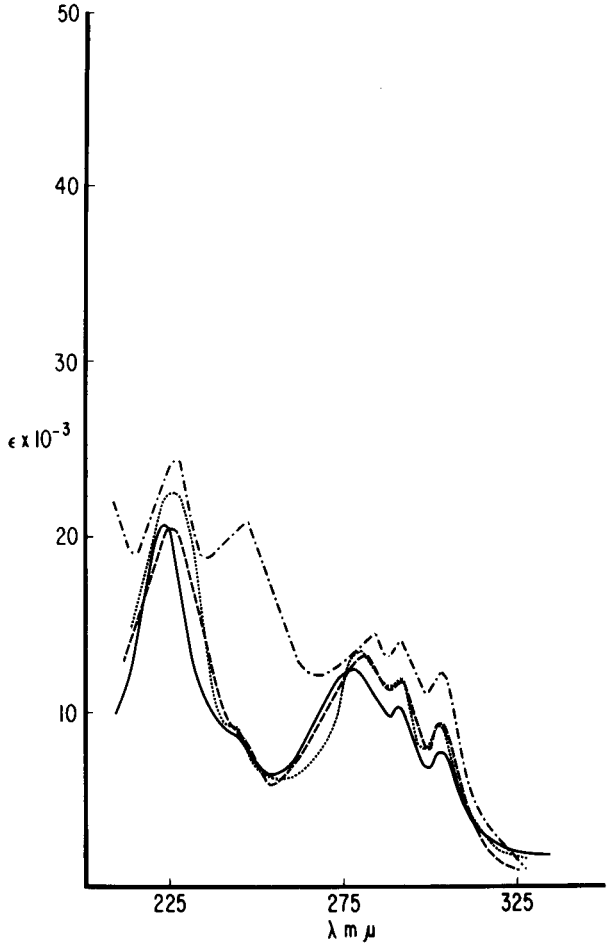


Figure III. Ultraviolet spectra in methanol. Compounds of structural type C; IIa, -----; IIb, ——; IIc, ·····; IId, ...

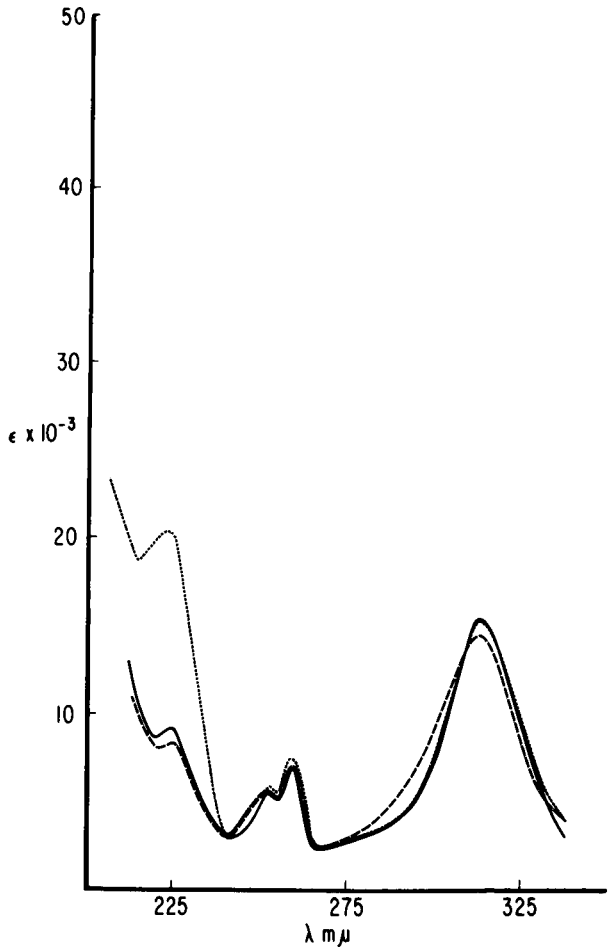


Figure IV. Ultraviolet spectra in methanol. Compounds of structural type D; IIIa, -----; IIIb, ——; IIIc, ...

Anal. Calcd. for $C_{13}H_{17}NOS_2$: C, 58.39; H, 6.41; N, 5.24; S, 23.98. Found: C, 58.14; H, 6.63; N, 5.44; S, 24.44.

In attempts to effect ether cleavage, it was found that the product was converted to Ia upon treatment with either hot 57% aqueous hydriodic acid or concentrated sulfuric acid at room temperature.

2-(2-Aminoethylthio)benzothiazole hydrochloride (IIb).

A solution of 20.0 g. (0.120 mole) of Ia and 40 ml. (0.77 mole) of ethylenimine in 200 ml. of ethanol was stirred and refluxed for 3.5 hours. The reaction mixture was concentrated *in vacuo*, flushed with benzene, and dissolved in methylene chloride. This solution was washed with 5% sodium hydroxide, with saturated sodium chloride, decolorized with Darco G-60, dried over sodium sulfate, and concentrated.

The oily residue was next dissolved in 100 ml. of isopropyl alcohol and treated dropwise with 12 ml. of concentrated hydrochloric acid. The solid hydrochloride was kept at 5° overnight and filtered. This was next crystallized from ethanol and washed with ether to give 12.25 g. (42%) of IIb, m.p. 177-178.5°; nmr (deuterium oxide) τ 1.95-2.20, 2.30-2.60 (multiplet, 4-H, C_6H_4), 6.22-6.43 ppm (multiplet, 4-H, CH_2CH_2).

Anal. Calcd. for $C_9H_{11}ClN_2S_2$: C, 43.80; H, 4.49; N, 11.35; S, 25.99; Cl, 14.37. Found: C, 43.69; H, 4.41; N, 11.21; S, 25.93; Cl, 14.41.

2-(2-Anilinoethylthio)benzothiazole (IIc).

Method A.

A solution of 3.75 g. (0.022 mole) of Ia and 2.7 g. (0.023 mole) of freshly prepared *N*-phenylethylenimine (16) in 60 ml. of ethanol was refluxed under nitrogen for 5 hours. The yellow solution was concentrated to an oily residue which solidified on trituration with ether and petroleum ether. The crude product (4 g.) obtained in this manner was crystallized from ether to give 2.6 g. (41%) of pure product, m.p. 72-74°; nmr (acetone-d_6) τ 2.0-3.6 (multiplet, 9-H, C_6H_4 and C_6H_5), 4.67-4.92 (broad, 1-H, NH), 6.38 ppm (multiplet, 4-H, CH_2CH_2).

Anal. Calcd. for $C_{15}H_{14}N_2S_2$: C, 62.90; H, 4.93; N, 9.78. S, 22.39. Found: C, 62.93; H, 5.10; N, 9.85; S, 22.35.

Method B.

To 400 ml. of stirred ethanol was dissolved, in order, 5.5 g. (0.136 mole) of sodium hydroxide, 11.4 g. (0.068 mole) of Ia and 19.0 g. (0.068 mole) of β-bromoethylaniline hydrobromide (17).

TABLE III

Chemical Shifts of Aromatic Multiplets
(60 MHz; ambient temperature)

Compound	Solvent	Chemical Shift τ (ppm)
IId (13)	$CDCl_3$	2.01-2.33 2.38-2.93
Id	$CDCl_3$	2.38-2.93
IIa	$CDCl_3$	2.05-2.42 2.44-2.98
Ik	C_5D_5N	2.23-2.83
Ig	$CDCl_3$	2.45-2.95
IIIb	D_2O	1.90-2.15 2.20-2.60

The clear solution was allowed to stand for 4 hours, then concentrated *in vacuo* to an oil. The residue was partitioned between 600 ml. of methylene chloride and 600 ml. of water, the organic layer was washed with 5% sodium hydroxide and saturated sodium chloride solution, dried over sodium sulfate, and the solvent was removed. The oily residue was dissolved in ether, treated with Darco G-60, and the ether was distilled at atmospheric pressure just to the point of cloudiness. After cooling, the solid was filtered and washed with ether and petroleum ether to give 13.1 g. of crude product. This was crystallized again in the same way to give 10.4 g. (53%) of IIc. The product gave satisfactory elemental analyses and was shown to be identical with the material prepared by the alternate method by mixture melting point determination and comparison of their uv, ir, and nmr spectra.

N,N-Bis[2-(2-benzothiazolinon-3-yl)ethyl]aniline (IVa).

A 500 ml. round-bottomed flask was fitted with a stirring shaft, thermometer, and a system for purging with nitrogen. The flask was charged with 25 ml. of aniline, 0.05 g. of copper powder and 0.725 g. (0.0316 atom) of metallic sodium (18). The system was closed, protected from moisture, purged with nitrogen, then stirred and heated under reflux until the sodium metal had completely dissolved (approximately one hour). After cooling, the reaction mixture was diluted with 50 ml. of toluene without exposing the contents of the flask to the outside atmosphere. Observing the same precaution, a solution of 6.75 g. (31.6 mmoles) of 3-(2-chloroethyl)-2-benzothiazolinone (II) in 100 ml. of toluene was added. This was refluxed for 0.5 hour to give a solid precipitate, which was filtered and washed with toluene. The wash liquors and the filtrate were combined, concentrated *in vacuo*, and flushed with water to remove traces of unreacted aniline. The glass which remained was triturated with ethanol to give 4.85 g. of crude product. Pure IVa was obtained by crystallization from ethanol, yielding 4.1 g. (59%), m.p. 136-138°; nmr (pyridine-d_5) τ 1.9-3.1 (multiplet, 13-H, C_6H_4 and C_6H_5), 5.6-6.8 ppm (multiplet, 8-H, CH_2CH_2), mass spectrum, molecular ion, m/e 447.

Anal. Calcd. for $C_{24}H_{21}N_3O_2S_2$: C, 64.40; H, 4.73; N, 9.39; S, 14.33. Found: C, 64.40; H, 4.69; N, 9.36; S, 14.49.

3-Anilinomethyl-2-benzothiazolinone (If).

To a stirred solution of 7.9 g. (52 mmoles) of Ib and 4.7 g. (52 mmoles) of aniline in 40 ml. of ethanol was added 3.9 ml. (4.2 g., 52 mmoles) of 37% aqueous formaldehyde solution. After stirring for 15 minutes a white solid precipitated from the clear solution. The reaction was brought to completion by stirring and warming at 40° for 0.5 hour, after which it was cooled and filtered. The product was crystallized from ethanol, washed first with cold ethanol, then with petroleum ether, and dried to give 8.0 g. (60%) of If, m.p. 159-161°; nmr (acetone-d_6) τ 2.3-3.5 (multiplet, 9-H, C_6H_4 and C_6H_5), 3.6-4.0 (broad, disappears with deuterium oxide, 1-H, NH), 4.5 ppm (doublet, J = 7 Hz, converted to singlet with deuterium oxide, 2-H, CH_2).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.81; H, 4.77; N, 10.81; S, 12.49.

3-(2-Benzoyloxyethyl)-2-benzothiazolinone (Ii).

A solution was prepared by dissolving 20.0 g. (0.102 mole) of Ig in 150 ml. of pyridine. To this was added dropwise with stirring 12.8 ml. (15.4 g., 0.11 mole) of benzoyl chloride over a period of 5 minutes. After stirring for 0.5 hour, the mixture was cooled and 450 ml. of water was added. This first caused a clear solution and then a white precipitate. The solid was washed with water, air-dried, and crystallized from ethanol, using Darco G-60. The product was washed with cold ethanol and with petroleum ether, then dried to give 26.3 g. (86%), m.p. 92-93°; nmr (pyridine-d_5) τ 1.8-3.1 (multiplet, 9-H, C_6H_4 and C_6H_5), 5.17-5.75 ppm (multiplet, A_2B_2, 4-H, CH_2CH_2).

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68; S, 10.71. Found: C, 64.30; H, 4.29; H, 4.64; S, 10.63.

3-(2-Acetoxyethyl)-2-benzothiazolinone (Ih).

This procedure was similar to that used for the preparation of Ii. Compound Ig (4.2 g.) in 15 ml. of pyridine was treated with 15 ml. of acetic anhydride to give 2.9 g. (57%) of Ih, m.p. 60-61°.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.73; H, 4.53; N, 6.08; S, 13.56.

Thiation of 2-Benzothiazolinones (Table I). General Procedure.

The benzoate Ii (95.0 g., 0.317 mole) in pyridine (1.9 l.) was combined with 220 g. of phosphorus pentasulfide, the latter being added in small portions with stirring over a period of approximately one minute. Using a condenser equipped with a drying tube, the mixture was stirred and heated under vigorous reflux for 4 days. It was then cooled and diluted with 9 l. of water (external cooling was necessary). The resulting dark mixture was allowed to stand overnight, after which the granular solid was collected by filtration, then washed with water using a Waring blender. After air-drying there was obtained 90 g. of pulverized solid which was further purified by precipitation from pyridine (800 ml.) by the addition of water (2400 ml.). The fine precipitate obtained was washed again with water, then air-dried and crystallized from ethanol using Darco G-60. The product was washed with cold ethanol and petroleum ether, then dried to give 57 g. of cream-colored crystals. A second crop (12 g.) was subsequently obtained from the mother liquors, bringing the total yield of Ij to 69 g. (69%).

Anal. Calcd. for $C_{16}H_{13}NO_2S_2$: C, 60.93; H, 4.15; N, 4.44; S, 20.33. Found: C, 61.18; H, 4.12; N, 4.69; S, 20.10.

Recrystallization of a small sample of the product raised the melting point to 90-92°, and in some runs even higher melting (98-100°) samples could be obtained. The existence of two different crystalline forms of this compound, corresponding to the higher and lower melting samples, was established by X-ray diffraction. A mixture melting point was seen to be 98-100°. Further confirmation of the existence of two crystalline forms was provided by differential thermal analysis. However, no differences were detected in the solid state infrared spectra of the two forms.

3-(2-Hydroxyethyl)-2-benzothiazolinethione (Ik).

A solution of 57.3 g. (0.182 mole) of Ij in 140 ml. of acetone was warmed on a steam bath and to it was added 350 ml. of ethanol followed by a solution of 7.33 g. (0.182 mole) of sodium hydroxide in 18 ml. of water and 180 ml. of ethanol. Heating was continued for 5 minutes resulting in the formation of a gelatinous solid. This was treated with 1.8 l. of water to give momentary clearing, followed by crystallization. After cooling, the product was collected by filtration and washed with water. It was crystallized twice from chloroform, using Darco G-60 and dried to give 18.0 g. of product. The mother liquors yielded an additional 8.4 g. of the same quality, bringing the total yield of Ik to 26.5 g. (69%), m.p. 141-143°; nmr (pyridine-d_5) τ 2.3-2.9 (multiplet, 4-H, C_6H_4), 3.2-3.6 (singlet, 1-H, OH, exchanged with deuterium oxide), 5.26 (triplet, J = 5 Hz, 2-H, NCH_2), 5.76 ppm (triplet, J = 5 Hz, 2-H, CH_2O).

Anal. Calcd. for $C_9H_9NOS_2$: C, 51.13; H, 4.29; N, 6.63; S, 30.35. Found: C, 50.85; H, 4.24; N, 6.48; S, 30.62.

The product was converted back to its precursor Ij as follows. A stirred solution of 5.0 g. (2.4 mmoles) of Ik (from above) in 50 ml. of pyridine was treated dropwise over a 3-minute period with 2.8 ml. (2.4 mmoles) of benzoyl chloride. The solid obtained upon dilution with water was crystallized from ethanol to give 5.5 g. (79%) of Ij, m.p. 90-92°, undepressed when mixed with material obtained by thiation of Ii.

3-(2-Chloroethyl)-2-benzothiazolinone (Il).

Thionyl chloride (100 ml.) was combined with 10.0 g. (51.2 mmoles) of Ig in 50 ml. of chloroform and heated under reflux for 4 hours. Concentration of the resulting mixture gave an oily residue which was flushed with benzene, dissolved in methylene chloride and washed successively with water, 5% sodium bicarbonate, and saturated sodium chloride. After drying over sodium sulfate and vacuum concentration, the product was taken up in ether, filtered with Darco G-60, and the ether was distilled at atmospheric pressure until a volume of 40 ml. was obtained. Scratching produced crystals which were collected and washed with cold (-60°) ether and petroleum ether. After drying, 7.1 g. (55%) of Il was obtained, m.p. 65-66.5°; nmr (acetone-d_6); τ 2.2-3.0 (multiplet, 4-H, C_6H_4), 5.59 (multiplet, 2-H, NCH_2), 6.02 ppm (multiplet, 2-H, CH_2Cl).

Anal. Calcd. for C_9H_8ClNOS: C, 50.60; H, 3.78; N, 6.56; S, 15.01; Cl, 16.60. Found: C, 50.40; H, 3.61; N, 6.55; S, 14.83; Cl, 16.64.

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium chloride (IIIa).

A solution of Ik (2.1 g., 0.01 mole) and 0.87 g. (0.011 mole) of pyridine in 50 ml. of dioxane was cooled to 5° and treated dropwise with 1.55 g. (0.013 mole) of thionyl chloride, with stirring. After 2 hours at room temperature a solid had formed which was collected by filtration and crystallized from ethanol to give 0.9 g. (39%) of IIIa, m.p. 176-178°; uv and ir spectra were the same as for compound IIIb.

Anal. Calcd. for $C_9H_8ClNS_2$: Cl, 15.43. Found: C, 15.09.

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium bromide (IIIb).

Method A. (8)

By means of vigorous agitation (Waring blender), warming, and finally filtration, a solution was prepared from 33.4 g. (0.2 mole) of Ia, 13.8 g. (0.1 mole) of potassium carbonate and 4 l. of dimethylformamide. To the clear filtrate was added 37.6 g. (0.2 mole) of ethylene dibromide and the mixture was allowed to stand for one week at room temperature. The crystals which formed were collected and washed with dimethylformamide and with ether. After air-drying the product weighed 6.8 g., m.p. 255-257° (lit., (8) 255-257°). Pure material was obtained by treatment of an aqueous solution with Darco G-60, filtration, and precipitation by the addition of acetone. This gave 5.0 g. (9.6%) of IIIb having the same melting point; nmr (deuterium oxide), τ 1.90-2.15, 2.20-2.60 (multiplet, 4-H, C_6H_4), 4.8-5.8 ppm (multiplet, A_2B_2, 4-H, CH_2CH_2).

Anal. Calcd. for $C_9H_8BrNS_2$: C, 39.42; H, 2.94; N, 5.11; S, 23.39; Br, 29.14. Found: C, 39.11; H, 2.78; N, 5.03; S, 23.44; Br, 29.34.

The yield of this method was improved by the following modification. Compound Ia (50.3 g., 0.3 mole) in 300 ml. of dimethylformamide was neutralized with solid sodium hydroxide and the solution was added dropwise with stirring over a period of one hour to 540 g., (2.9 moles) of ethylene dibromide in 300 ml. of dimethylformamide at the temperature of a steam bath. Upon cooling, compound IIIb was deposited in 75% yield.

Method B.

To a cooled suspension of 1.0 g. (4.7 mmoles) of Ik in 50 ml. of chloroform was added 5.6 g. (21 mmoles) of phosphorus tribromide. This was refluxed for 0.5 hour and cooled. The yellow solid was collected by filtration, and washed with chloroform, dimethylformamide, and ether. This gave 1.2 g. of a crude solid which was crystallized from water-acetone with the aid of Darco G-60 to give 0.75 g. (58%) of IIIb, identical with authentic material (mixture melting point, uv and ir spectra).

Method C.

To a cooled stirred solution of 1.0 g. (4.7 mmoles) of IIa (19) in 50 ml. of dimethylformamide was added 0.9 g. (3.3 mmoles) of phosphorus tribromide. A clear solution resulted which was heated on a steam bath for 6 minutes, then allowed to stand at room temperature for 3 days. The white crystals were separated and washed with dimethylformamide and ether to give 0.57 g. of product. A second crop of crystals obtained from the mother liquors brought the total crude yield to 0.87 g. Crystallization from water-acetone provided 0.5 g. (38%) of IIIb, identical with authentic material (mixture melting point, uv and ir spectra).

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium *p*-toluenesulfonate (IIIc).

To a pyridine (30 ml.) solution of 2.1 g. (0.01 mole) of Ik were added 2.0 g. (10.5 mmoles) of *p*-toluenesulfonyl chloride with stirring and cooling. The solution was stirred at room temperature for 2 hours, whereupon it was diluted with 150 ml. of water and the resultant solid was collected by filtration, washed with water, and air-dried. The product (1.35 g.) had a melting point of 68-71°, but after standing for 3 days it was seen to have changed to 130-135° with concomitant changes in the ir spectra of the samples. Furthermore, the solid was no longer soluble in chloroform, but had become soluble in water. Finally, trituration with chloroform

and crystallization from ethanol gave 0.5 g. (14%) of IIIc, m.p. 215-218°.

Anal. Calcd. for $C_{16}H_{15}NO_3S_3$: C, 52.58; H, 4.14; N, 3.83; S, 26.32. Found: C, 52.54; H, 4.18; N, 3.82; S, 27.26.

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazoline-thion-3-yl)ethyl sulfide (IIId).

To an aqueous solution (100 ml.) of 3.0 g. (11 mmoles) of IIIb was added a solution of 6 g. (25 mmoles) of sodium sulfide (20) in 20 ml. of water with stirring at room temperature. The precipitate that formed immediately was stirred for 1 hour, removed by filtration and washed with water. The crude product (1.5 g., (65%), m.p. 139-142°) was crystallized from acetone to give 0.9 g. (40%) of pure IIId, m.p. 153-155°; nmr (deuteriochloroform), τ 2.6-3.4 (multiplet, 8-H, C_6H_4), 5.2-7.2 (multiplet, 8H, CH_2CH_2), mass spectrum, parent peak, m/e 420.

Anal. Calcd. for $C_{18}H_{16}N_2S_5$: C, 51.39; H, 3.83; N, 6.66; S, 38.11. Found: C, 51.16; H, 3.83; N, 6.66; S, 38.10.

The same product was obtained with sodium hydrosulfide or when the chloride or tosylate salts were used.

Bis[2-(2-benzothiazolinon-3-yl)ethyl]disulfide (IVc).

An aqueous solution (100 ml.) of 3.0 g. (11 mmoles) of IIIb was treated with Darco G-60 and to the clear, colorless filtrate was added a solution of 1.0 g. (25 mmoles) of sodium hydroxide in 20 ml. of water with vigorous stirring. A white precipitate formed immediately which was stirred for another hour at room temperature and then collected and washed with water. After air-drying the crude product (1.4 g., (61%), m.p. 123-125°) was crystallized from ethanol, yield, 0.6 g. (26%), m.p. 124-126°; nmr (deuteriochloroform), τ 2.5-3.4 (multiplet, 8-H, C_6H_4), 5.79 (triplet, J = 6.5 Hz, 4-H, NCH_2), 6.98 ppm (triplet, J = 6.5 Hz, 4-H, $-SCH_2$), mass spectrum, molecular ion, m/e 420.

Anal. Calcd. for $C_{18}H_{16}N_2S_4O_2$: C, 51.40; H, 3.83; N, 6.66; S, 30.49. Found: C, 51.56; H, 4.03; H, 6.78; S, 30.31.

The same compound (mixture melting points, infrared spectra) was obtained when the chloride and tosylate salts were similarly decomposed.

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazolinon-3-yl)ethyl sulfide (IIIe).

Aqueous solutions (50 ml.) of 1.8 g. (6.6 mmoles) of IIIb and 3.6 g. (43 mmoles) of sodium bicarbonate were combined with stirring at room temperature. After stirring for 2 hours the white precipitate was collected, washed with water and air-dried. The crude material (0.9 g., m.p. 122-126°) was extracted with ether. The combined ether extracts were diluted with 75 ml. of hexane and concentrated to cloudiness at atmospheric pressure. After cooling at 5° the resulting crystals were collected, washed with hexane and air-dried, yield, 0.4 g. (30%), m.p. 130-132°; nmr (deuteriochloroform) τ 2.6-3.5 (multiplet, 8-H, C_6H_4), 5.6-7.2 ppm (multiplet, 8-H, CH_2CH_2), mass spectrum, parent peak, m/e 404.

Anal. Calcd. for $C_{18}H_{16}N_2OS_4$: C, 53.44; H, 3.99; N, 6.92; S, 31.70. Found: C, 53.43; H, 3.92; N, 6.87; S, 31.79.

From the reaction mixture was isolated 0.57 g. (40%) of IVc, m.p. 125-127°, mixture melting point with IIIe, 110-115°. The chloride and tosylate benzothiazolium salts IIIa and IIIc behaved in the same manner.

Bis[2-(2-benzothiazolinethion-3-yl)ethyl]disulfide (IVb) from 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazoline-thion-3-yl)ethyl sulfide (IIId).

A solution of 0.09 g. (0.21 mmoles) of IIId in 6 ml. of warm pyridine was combined with a solution of 0.5 g. (20 mmoles) of sodium sulfide in 20 ml. of water and the resulting clear solution was heated on the steam bath until it turned cloudy (0.5 hour). After diluting with more water (100 ml.) and cooling, the mixture was filtered and the solid was washed with water and ethanol. The air-dried product weighed 0.07 g. (72%), m.p. 155-157°. Comparison of infrared spectra and mixture melting point showed this product to be identical with compound IVb obtained from the thiation of Ig (See Table I).

Bis[2-(2-benzothiazolinon-3-yl)ethyl]disulfide (IVc) from 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazolinon-3-yl)ethyl sulfide (IIIe).

The procedure was the same as in reaction IIId → IVb, except that the following amounts were used: 0.05 g. (0.124 mmole) of IIIe in 3 ml. of pyridine, 10 ml. of water and 1 drop of 50% sodium hydroxide solution. The white product (IVc) amounted to 0.04 g. (77%), m.p. 126-128°, undepressed when mixed with material obtained by the aqueous sodium hydroxide decomposition of IIIb (infrared spectra were superimposable).

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium bromide (IIIb) from 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazoline-thion-3-yl)ethyl sulfide (IIId) or 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium 2-(2-benzothiazolinon-3-yl)ethyl sulfide (IIIe).

A solution of 0.05 g. (0.119 mmole) of IIId or 0.05 g. (0.124 mmole) of IIIe in 2 ml. of dimethylformamide was combined with a freshly prepared solution of 3 drops of 47% hydrobromic acid in 2 ml. of dimethylformamide and the clear solution was allowed to stand for 0.5 hour. Crystals appeared which were thickened by the addition of ether (8 ml.). The product was isolated by filtration and washed with dimethylformamide and ether. The yield in the IIId → IIIb reaction was 0.03 g. (92%), m.p. 254-256° and in IIIe → IIIb reaction, 0.024 g. (70%), m.p. 255-257°. The products from both reactions were identical with an authentic sample of IIIb by comparison of infrared spectra and mixture melting points.

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