

of sodium hydroxide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After the solution was stirred for 5 min., there was added dropwise 1.09 ml. (1.22 g., 20 mmoles) of nitromethane. This solution was stirred for 15 min., after which time it was cooled to 5° while 20% hydrochloric acid was added dropwise until a pH of 3 was attained. After standing in the refrigerator for an hour, the reaction mixture was filtered. The precipitate, upon air-drying, provided 3.72 g. (96% yield) of product, m.p. 110–114°. Treatment with Darco in water gave white needles, m.p. 117–119°.

Two more recrystallizations from water provided a sample of analytical purity.

Anal. Calcd. for C₈H₈BNO₂: C, 49.78; H, 4.18; N, 7.26. Found: C, 49.81; H, 4.28; N, 7.09.

Preparation of α -Cyanoboronophthalide.—To a magnetically stirred, cooled (15–20°) solution of 1.04 g. (20 mmoles) of 95% sodium cyanide in water was added 3.00 g. (20 mmoles) of *o*-formylbenzeneboronic acid. After stirring for 15 min., the solution was cooled to 5° and acidified with concentrated hydrochloric acid to a pH of 5. The white precipitate thus formed was removed by filtration, and the filtrate was further acidified with 10% acid until no more precipitate formed. The two crops thus

obtained were found to weigh 3.52 g. (99+ % yield) upon air-drying. A recrystallization from water provided 2.81 g. (88% yield) of purified *o*-boronomandelonitrile (dehydration range, 60–65°). Dehydration of this material either by heating to 65° or by vacuum desiccation was found sufficient to cause lactone formation.

The analytical sample of the lactone (m.p. 107–109°) was prepared by twice recrystallizing from water, followed by drying over phosphorus pentoxide for 24 hr. *in vacuo*.

Anal. Calcd. for C₈H₆BNO₂: C, 60.43; H, 3.80; N, 8.81; mol. wt., 159. Found: C, 60.26; H, 3.79; N, 8.75; mol. wt. (in benzene), 160.

Preparation of α -Carboxyboronophthalide.—To a 15-ml. beaker containing 10 ml. of concentrated hydrochloric acid was added 159 mg. (1 mmole) of α -cyanoboronophthalide, and the mixture was allowed to stand for 24 hr. in the hood. The white crystalline product was separated by filtration, washed with two 10-ml. portions of acid, and dried, to provide 175 mg. (98% yield) of α -carboxyboronophthalide (m.p. 141–142°), which proved to be analytically pure.

Anal. Calcd. for C₈H₇BO₄: C, 53.99; H, 3.96; mol. wt., 178. Found: C, 53.76; H, 4.08; mol. wt. (in dioxane), 171.

The Interconversion of 2-Substituted 2-Oxazolines and 2-Thiazolines

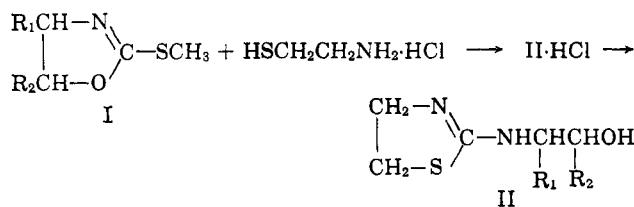
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The anomalous products obtained from the reaction of two 2-methylthio-2-oxazolines with 2-mercaptoethylamine hydrochloride were identified as 2-(2-hydroxyethylamino)-2-thiazolines. On standing in solution, the latter compounds undergo rearrangement to 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfides. The interconversion of 2-oxazolines containing a 2-mercaptoethylamino side chain and 2-thiazolines containing a 2-hydroxyethylamino side chain, possibly through a bicyclic intermediate, is thus demonstrated.

In a previous paper¹ we have reported that products with anomalous properties are obtained from the reaction of 2-mercaptoethylamine hydrochloride with both 2-methylthio-2-oxazoline (Ia) and 2-methylthio-4-methyl-5-phenyl-2-oxazoline (Ib). The crystalline bases, IIa and IIb, afforded by these reactions have empirical formulas of C₅H₁₀N₂OS and C₁₂H₁₆N₂OS. We have now demonstrated that these compounds are 2-(2-hydroxyethylamino)-2-thiazoline and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline, respectively, as shown.



a, R₁ = R₂ = H
b, R₁ = CH₃; R₂ = C₆H₅

As reported previously,¹ the nuclear magnetic resonance spectrum of IIb contained a single sharp band that represented two protons at a frequency assignable to NH. This observation had suggested the possibility that a spiran such as V had been isolated, although the infrared spectrum strongly indicated that an unsaturated heterocyclic ring was present. The n.m.r. spectrum of the unsubstituted base, IIa, has been found to contain an analogous sharp signal with an

intensity corresponding to two protons. In both cases, this band shifted to higher field as a single sharp peak on dilution. However, in the n.m.r. spectrum of 2-ethylaminoethanol,² the NH and OH protons are assigned to a single band, presumably as a result of rapid proton exchange.³ We have found that the singularity of the NH–OH signal in 2-ethylaminoethanol is maintained over a wide range of concentrations and temperatures. Thus these two-proton signals in the spectra of IIa and IIb could arise from NH and OH rather than from two NH groups.

The infrared spectrum of IIb in chloroform had failed to show the presence of hydroxyl,¹ possibly, as previously suggested, because of hydrogen bonding. In dilute carbon tetrachloride solution it was indeed possible to observe a rather weak, though definite, free OH band at 2.76 μ . That both IIa and IIb contained an OH group was clearly demonstrated by near-infrared spectroscopy. The near-infrared spectra of the compounds showed the first overtone bands of both OH and NH.^{4,5}

Additional evidence for the presence of hydroxyl in IIa and IIb was obtained by acetylation with acetic anhydride and pyridine. In both cases the spectrum of

(2) "Varian N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 92.

(3) Other systems in which OH and amine NH protons undergo rapid proton exchange and give a single signal are discussed by J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 440 and 455.

(4) W. Kaye, *Spectrochim. Acta*, **6**, 281 (1954).

(5) K. Whetsel, W. E. Roberson, and M. W. Krell, *Anal. Chem.*, **29**, 1006 (1957).

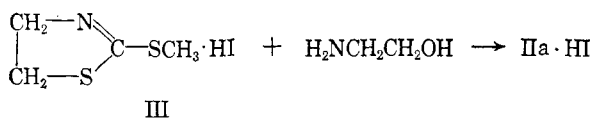
the acetylated product contained an ester carbonyl absorption at 5.75μ and indicated that O-acetylation had taken place.

With the identification of a hydroxyl group in the structures of IIa and IIb, the strong absorption in the infrared at 6.16μ can reasonably be assigned to the unsaturation in the 2-thiazoline ring.^{6,7} In the spectrum of the disulfide of 2-(2-mercaptoethylamino)-2-thiazoline,⁸ a similarly substituted 2-amino-2-thiazoline, the comparable band is identically located.

Interesting confirmatory evidence that the phenyl group is located in the side chain in IIb was provided by n.m.r. spectra. In the spectrum of IIb the proton bound to the carbon containing the phenyl group gave a doublet at τ 5.19. On acetylation, this signal was displaced to τ 4.02, a displacement to lower field of the predicted magnitude for the α -proton of a secondary alcohol on acylation.⁹ In the spectra of 4-methyl-5-phenyl-2-thioxazolidone and 2-methylthio-4-methyl-5-phenyl-2-oxazoline,¹ this doublet is at τ 3.99 and 4.28, respectively, electron-withdrawal effects apparently producing a similar displacement to lower field.

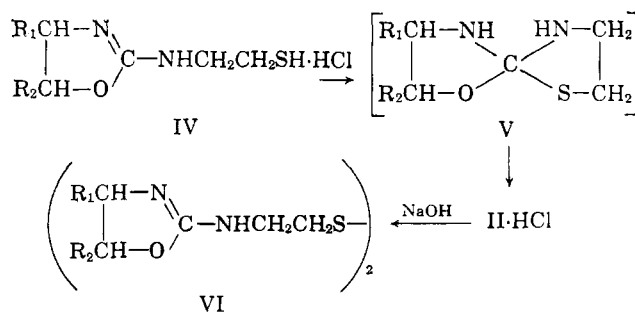
A distinction between the side-chain and ring locations of this CH-phenyl proton is indicated by the coupling constants of the doublet. For IIb and its acetyl derivative, the values of the constants are 3 and 3.5 c.p.s., whereas for the cyclic compounds, 4-methyl-5-phenyl-2-thioxazolidone and 2-methylthio-4-methyl-5-phenyl-2-oxazoline, the values are 8.5 and 9.5 c.p.s., respectively. Also, in the spectrum of IIb, the signal assigned to the methylene group adjacent to the sulfur atom is centered at τ 6.67, comparable to its position (τ 6.60) in the cyclic 2-methylthio-2-thiazoline¹⁰ rather than to the position (τ 7.06) of the acyclic methylene in the disulfide of 2-(2-mercaptoethylamino)-2-oxazoline.¹

Finally, we have obtained IIa in 50–60% yield from the reaction of 2-methylthio-2-thiazoline hydroiodide (III) and 2-aminoethanol. From the properties of the



compounds and this alternate synthesis, the formulation of IIa and IIb as 2-(2-hydroxyethylamino)-2-thiazoline and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline is established.

It can be presumed that 2-(2-mercaptoethylamino)-2-oxazoline hydrochlorides (IV) are formed initially in the reaction of the 2-methylthio-2-oxazolines (I) with 2-mercaptoethylamine hydrochloride. Rearrangement to the stable 2-(2-hydroxyethylamino)-2-thiazoline hydrochlorides (II·HCl) may then take place through such a bicyclic intermediate as V. This intermediate corresponds to the intermediate previously proposed for the reactions of transthiazolination⁸ and transoxazolination.¹ It is analogous to the cyclic intermediate



postulated by Doherty, *et al.*,¹¹ for the conversion of 2-(2-aminoethyl)-2-thiopseudourea (AET) to 2-mercaptoethylguanidine and similar rearrangements.

As previously reported,¹ the 2-(2-hydroxyethylamino)-2-thiazolines (IIa and IIb) undergo conversion to the 2-(2-mercaptoethylamino)-2-oxazolines, isolated as the disulfides (VI), on standing in solution in the air. This rearrangement, which proceeds more rapidly in alkaline solution, can be readily followed by the shift of the strong infrared band at 6.16μ to a wave length of 6.00μ , characteristic of oxazolines of type VI. It can again take place through the intermediate V. Removal of the initially formed mercaptan from the system by oxidation to the disulfide, catalyzed by base, apparently effects complete conversion to the disulfide.

The reactions involved in the rearrangements demonstrate the interconvertibility, under the proper conditions, of 2-oxazolines with 2-mercaptoethylamino side chains and 2-thiazolines with 2-hydroxyethylamino side chains.

Experimental

N.m.r. Spectra.—Spectra were determined in deuteriochloroform at 60 Mc. with a Varian Model A-60 spectrometer.

Spectra were run on 20-, 40-, 80-, 160-, and 320-mg. samples of 2-ethylaminoethanol, each diluted with 1 ml. of deuteriochloroform, and on the neat liquid. The NH-OH signal shifted progressively from τ 6.0 to 7.4. When spectra were recorded on the 80-mg. solution at temperatures from -40 to 60° , this signal shifted from τ 5.5 to 7.4.

Infrared Spectra.—The near-infrared spectra were taken in carbon tetrachloride in a Cary Model 14 spectrophotometer. Both 2-(2-hydroxyethylamino)-2-thiazoline (IIa) and 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline (IIb) gave bands at 1.41 (OH) and 1.48μ (NH). Comparative spectra were run on 2-ethylaminoethanol and benzyl alcohol. The former showed bands at 1.41 (OH) and 1.54μ (NH)¹²; the first OH overtone in benzyl alcohol is at 1.41μ .

The infrared spectrum of IIb showed the characteristic strong N=C-N absorption at 6.16μ in the solid state (potassium bromide pellet) as well as in solution, indicating that no rapid alteration has accompanied solution. In the hydrobromide of IIb this band was at 6.10μ (potassium bromide). The hydrobromide, which was not previously described, was obtained by treatment of IIb with an equivalent of anhydrous hydrogen bromide and melted at $129.5\text{--}131.5^\circ$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{BrN}_2\text{OS}$: C, 45.43; H, 5.40; S, 10.11. Found: C, 45.46; H, 5.36; S, 10.20.

2-(2-Hydroxyethylamino)-2-thiazoline (IIa).—The hydrochloride of IIa, obtained from 2-methylthio-2-oxazoline and 2-mercaptoethylamine hydrochloride,¹ was converted to the free base by treatment with sodium bicarbonate. To a solution of 530 mg. (2.9 mmoles) of the hydrochloride in 12 ml. of water was added 1.2 g. (14.3 mmoles) of sodium bicarbonate. The solid residue remaining after concentration of this solution under reduced pressure at $25\text{--}30^\circ$ was extracted successively with 6-ml. and

(11) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *ibid.*, **79**, 5667 (1957).

(12) The lower wave length for NH in IIa and b reflects the adjacent unsaturation.

(6) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4699 (1950).

(7) L. Long, Jr., R. C. Clapp, F. H. Bissett, and T. Hasselstrom, *J. Org. Chem.*, **26**, 85 (1961).

(8) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *ibid.*, **26**, 1666 (1961).

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 55.

(10) A. F. McKay, D. J. Whittingham, and M-E. Kreling, *J. Am. Chem. Soc.*, **80**, 3339 (1958).

two 3-ml. portions of absolute ethanol. The extracts were concentrated, and the concentrate was extracted with 6-ml. and 2-ml. portions of boiling ethyl acetate. From these extracts there was obtained 319 mg. (75%) of colorless crystals, m.p. 95–97°. Recrystallization from ethyl acetate afforded colorless flat crystals, m.p. 96–97.5°; $\lambda_{\max}^{\text{CHCl}_3}$ 2.89 (NH), 6.16 (N=C—N), and 6.66 μ .

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 41.07; H, 6.89; S, 21.93. Found: C, 41.33; H, 6.90; S, 21.74.

The ultraviolet spectrum in aqueous solution gave a maximum at 211–212 $m\mu$ (ϵ 11,170); the spectrum of 2-amino-2-thiazoline^{11,13} contained a maximum at 202–203 $m\mu$ (ϵ 8,470). For a solution of 54 mg. in 1 ml., the NH—OH band in the n.m.r. spectrum was at τ 4.67; at one-half this concentration it was at τ 5.00.

2-(2-Acetoxy-1-methyl-2-phenylethylamino)-2-thiazoline Picrate.—A solution of 300 mg. of 2-(2-hydroxy-1-methyl-2-phenylethylamino)-2-thiazoline (IIb)¹ in 7 ml. of pyridine and 7 ml. of acetic anhydride was allowed to stand at room temperature in an atmosphere of nitrogen for 17 hr. The solvent was removed under reduced pressure at a bath temperature of 40–50°. After the viscous concentrate had been washed with water, it was treated with ethanolic picric acid solution. Crystallization of the resulting crude picrate from ethanol gave 417 mg. of crystalline solid that melted from 192–197°. Recrystallization from ethanol yielded 366 mg. (57%) of fine yellow needles, m.p. 207–209°, $\lambda_{\max}^{\text{KBr}}$ 5.7 (s) and 6.15 (s) μ .

Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_9\text{S}$: C, 47.33; H, 4.17; S, 6.32. Found: C, 47.41; H, 4.04; S, 6.28.

2-(2-Acetoxy-1-methyl-2-phenylethylamino)-2-thiazoline.—A solution of 611 mg. of the picrate in 30 ml. of chloroform was shaken twice with 10-ml. portions of cold 0.5 *N* sodium hydroxide solution. After it had been washed with water, the dried (anhydrous sodium sulfate) chloroform solution was concentrated to an oil. Addition of hexane to a solution of the oil in benzene yielded 281 mg. (84%) of nearly colorless crystals, m.p. 126–127.5°. Recrystallization from benzene–hexane gave colorless crystals, m.p. 126.5–128°; $\lambda_{\max}^{\text{CHCl}_3}$ 2.90 (NH), 5.75 (ester C=O), and 6.14 μ (N=C—N).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 60.40; H, 6.52; N, 10.07. Found: C, 60.58; H, 6.43; N, 10.02.

Acid hydrolysis (1.5 *N* hydrochloric acid on steam bath for 1 hr.) afforded the hydroxy compound, IIb. On treatment with alkali, the rearranged disulfide (VI, $\text{R}_1 = \text{CH}_3$; $\text{R}_2 = \text{C}_6\text{H}_5$) was obtained.

The acetyl derivative could not be obtained directly from the acetylation reaction; isolation required purification through the picrate.

(13) G. W. Raiziss and L. W. Clemence, *J. Am. Chem. Soc.*, **63**, 3124 (1941).

2-(2-Acetoxyethylamino)-2-thiazoline Picrate.—A solution of 800 mg. of 2-(2-hydroxyethylamino)-2-thiazoline hydrochloride (IIa·HCl) in 40 ml. of pyridine and 40 ml. of acetic anhydride was allowed to stand at room temperature in an atmosphere of nitrogen for 16 hr. After the solvent had been removed under reduced pressure, ethanolic picric acid solution was added. The crude picrate that precipitated crystallized from ethanol as yellow needles, 1.14 g. (62%), m.p. 145–147°, $\lambda_{\max}^{\text{KBr}}$ 5.7 (ester C=O) and 6.15 μ (N=C—N).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_5\text{O}_9\text{S}$: C, 37.41; H, 3.62; N, 16.78. Found: C, 37.66; H, 3.64; N, 16.70.

When a solution of the picrate in chloroform was treated with cold dilute sodium hydroxide, the base was obtained as an oil that failed to solidify. However, its infrared spectrum in chloroform showed the appropriate bands for O-acetylated IIa.

Alternate Synthesis of 2-(2-Hydroxyethylamino)-2-thiazoline (IIa).—A solution of 1.52 g. (5.82 mmoles) of 2-methylthio-2-thiazoline hydroiodide (III)¹⁰ and 356 mg. (5.83 mmoles) of 2-aminoethanol in 60 ml. of absolute ethanol was refluxed for 21 hr. Removal of the solvent under reduced pressure gave 1.70 g. of viscous concentrate. Water was added to a 1.55-g. portion of the concentrate, and a little insoluble oil was removed by shaking with ether. Treatment of a 10-ml. portion of the resulting 30 ml. of aqueous solution with ethanolic picric acid solution yielded 402 mg. (60%) of crystalline picrate, m.p. 140–143°. Recrystallization from ethyl acetate afforded yellow crystals, m.p. 142.5–144.5°, that were identical with the previously obtained¹ picrate of 2-(2-hydroxyethylamino)-2-thiazoline by mixture melting point and infrared spectrum.

The remaining 20 ml. of aqueous solution was made strongly alkaline with sodium hydroxide and aerated for about 14 hr. After concentration, 172 mg. (33%) of white solid, m.p. 130.5–133°, precipitated. Crystallization from ethyl acetate gave white crystals, m.p. 133–135°, of the disulfide of 2-(2-mercaptoethylamino)-2-oxazoline (VI, $\text{R}_1 = \text{R}_2 = \text{H}$). Identity was established by mixture melting point and infrared spectrum.

When 2-methylthio-2-thiazoline, 2-aminoethanol, and an equivalent of anhydrous hydrogen chloride were refluxed in absolute ethanol, crude IIa hydrochloride was obtained. However, the crude hydrochloride was somewhat hygroscopic and could not be efficiently purified.

Attempts to obtain IIb from the reaction of 2-methylthio-2-thiazoline and α -(1-aminoethyl)benzyl alcohol (norephedrine) hydrochloride were unsuccessful. After prolonged refluxing in ethanol, the starting materials were recovered.

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