Reactions of Ethylenethiourea with α- and β-Halo Acids and Derivatives[1]

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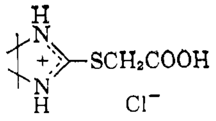
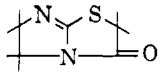
Previous work on the products of the reaction of ethylenethiourea with chloroacetic acid has been confirmed, and the postulated intermediate, 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one (II), was isolated. Ethylenethiourea was found to react with β-halo propionic acids to produce 3-(β-aminoethyl)-1,3-thiazane-2,4-dione salts (XII) in aqueous solution, but in acetone or ethanol the products were 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) salts. XI was obtained in quantitative yield from ethylenethiourea and β-propiolactone in aqueous solution. The probable precursor of XI and XII, 2-(β-carboxyethylmercapto)imidazoline (X), was obtained as its hydrochloride by treatment of ethylenethiourea with acrylic acid in acidic acetone. 2-(β-Cyanoethylmercapto)imidazoline hydrochloride (XVII) was obtained in high yield by the neat reaction of β-chloropropionitrile with ethylenethiourea, but no reaction occurred when the reagents were refluxed in ethanol. The proof of structure and interconversion of X, XI, and XII are described.

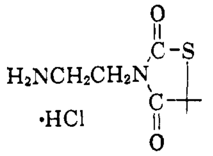
Johnson and Edens[3] refluxed ethylenethiourea with 2 equiv. of chloroacetic acid in water for 3 hr. and isolated a crystalline salt melting at 223°, to which they assigned the structure 2-carboxymethylmercaptoimidazoline hydrochloride (I). Later VanAllan[4] reinvestigated this synthesis and showed that the compound was actually the hydrochloride of 3-β-aminoethylthiazolidinedione (III), formed by ring closure of I to the postulated bicyclic intermediate, 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one (II), followed by acid hydrolysis of the dihydroimidazo ring at position 7–7a to yield III. Evidence for structure III included formation of a monobenzoyl derivative (IV), trimethylammonium salt on exhaustive methylation, a benzal derivative (V), and similarity of the ultraviolet and infrared spectra of 2,4-thiazolidinedione.



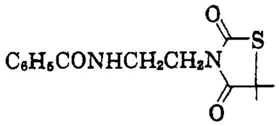
I



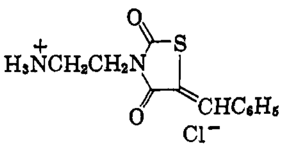
II



III



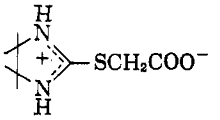
IV



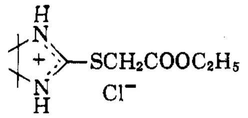
V

We have confirmed the work of VanAllan, by converting the zwitterion VI into I (m.p. 129–130°) by treatment with hydrochloric acid. Our inability to convert the chloroacetic acid–ethylenethiourea adduct into the zwitterion VI by neutralization with sodium acetate or on a basic ion-exchange column is also evidence against structure I for this adduct, especially in view of the fact that II hydrochloride could be hydrolyzed to VI in the presence of aqueous sodium acetate.

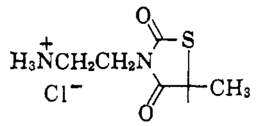
Stephen and Wilson[5] claimed to have prepared II, melting at 159°, by refluxing ethylenethiourea with ethyl chloroacetate in pyridine. We were unable to repeat this preparation, but have obtained an authentic sample of VanAllan's postulated intermediate, II, melting at 94°, by treating an ethanolic solution of 2-(carbethoxymethylmercapto)imidazoline hydrochloride (VII) with ammonia. II forms a picrate and a hydrochloride and also was converted to the same benzylidene derivative prepared by VanAllan[4] from VI. II hydrochloride also was obtained from VI by heating with concentrated acid. VII was obtained by refluxing ethylenethiourea and ethyl chloroacetate in ethanol, or by stirring these reactants in pyridine at room temperature. Crystallization of hydrochloride VII from pyridine indicates that S-carbethoxymethylethyleneisothiourea is a stronger base than pyridine, even though ethylenethiourea itself does not form a hydrochloride.[6]



VI



VII



VIII

Reaction of ethylenethiourea with chloroacetyl chloride in benzene or cold ether did not yield isolable products, but, from refluxing acetone, the hydrochloride III was obtained on crystallization. Treatment of III with ammonia forms among other things a white amorphous polymeric substance insoluble in water or common organic solvents.

As further confirmation of the structure assignments of the compounds obtained from ethylenethiourea and

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[2] This work is taken from a thesis submitted by M. C. W. to Indiana University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1961.

[3] T. B. Johnson and C. D. Edens, *J. Am. Chem. Soc.*, **64**, 2708 (1942).

[4] J. A. VanAllan, *J. Org. Chem.*, **21**, 24, 193 (1956).

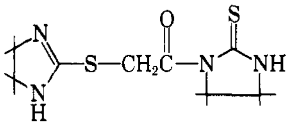
[5] H. W. Stephen and F. J. Wilson, *J. Chem. Soc.*, 2531 (1926).

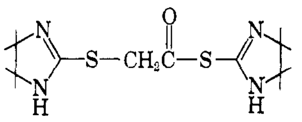
[6] P. C. Guha and D. N. Dutta, [*J. Indian Chem. Soc.*, **6**, 65 (1929)] in connection with the reactions of ethylenediamine and diethylxanthic formic ester (sic) report the isolation of ethylenethiourea hydrochloride, m.p. 304–305°. These authors do not report any elemental analysis. However, according to A. W. Hofman [*Ber.*, **5**, 240 (1872)] ethylenethiourea crystallizes unchanged from acids. We have confirmed Hofman's observation. It is probable that Guha and Dutta mistook ethylenediamine dihydrochloride (m.p. 345° dec.) for ethylenethiourea hydrochloride.

chloroacetic acid, VanAllan's benzoyl derivative (IV) was prepared unequivocally by the condensation of the potassium salt of 2,4-thiazolidinedione[7] with β-benzamidoethyl bromide.[8] The melting points, mixture melting point, and infrared spectra of these two benzoyl derivatives obtained by the two different routes were identical.

Reaction of ethylenethiourea and α-chloropropionic acid in water led to the formation of a high-melting salt, assigned the structure of 3-β-aminoethyl-5-methyl-2,4-thiazolidinedione hydrochloride (VIII), on the basis of the infrared spectrum, which was very similar to that of III.

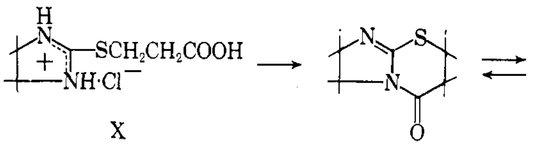
Several rather interesting related reactions have been observed. Passing an aqueous solution of III over an ion-exchange column containing the hydroxide form of Dowex^R 1-X8, in an effort to convert it to the zwitterion VI, led instead to the formation of ethyleneurea. This suggests that under basic conditions, III may again be converted to II, which may then be further hydrolyzed. The reaction of ethylenethiourea and ethyl chloroacetate in ethanol in the presence of sodium acetate was carried out in the hope of isolating the free base of VII. Instead, a compound having two moieties of ethylenethiourea was isolated, which must have structure IXa or b. Such a compound can only arise by reaction of ethylenethiourea with the free base of VII, or with the reactive bicyclic compound II. The latter is more likely, since esters are not known to react with ethylenethiourea. It was not possible to distinguish between IXa and IXb by infrared analysis, since amide and thiol ester carbonyl absorption bands overlapped. Treatment with hydrochloric acid converted IX to II hydrochloride, which suggests that the more readily hydrolyzable IXb is the more likely structure.

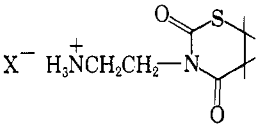

IXa


IXb

Although Baer and Lockwood[9] reported that ethylenethiourea did not react with β-halo propionic acids or derivatives in refluxing ethanol, we have found that reaction does occur between these reagents under a variety of experimental conditions to give three types of products, represented by X, XI, and XII. This represents a series of related compounds similar to I, II, and III, in that XI may be formed by cyclization of X, and XII by ring opening of XI.

Refluxing β-halo propionic acids with ethylenethiourea in either water or alcohol led to 3-(β-aminoethyl)-1,3-thiazane-2,4-dione salts (XIIa or b) in low yield. XIIa was subjected to benzoylation under aqueous conditions and a dibenzoyl derivative (XIII) was obtained. Formation of a dibenzoyl derivative indicates the compound cannot have structure X, which could only form a monobenzoyl derivative. Assignment of XII as the structure of this product is further supported by the fact that benzoylation in pyridine gave a monobenzoyl derivative (XIV), whose infrared spectrum showed a strong -NH band at 3430 cm.$^{-1}$, and by the synthesis of 3-(β-benzamidoethyl)-1,3-thiazane-2,4-dione (XIV) from a salt of 1,3-thiazane-2,4-dione and β-benzamidoethyl bromide.

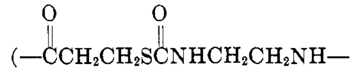

X
XI


XIIa, X = Cl
b, X = Br

Salts of XII were easily cleaved at the imide linkage in weakly acid or basic solution. For example, heating XIIa in a large volume of alcohol, and allowing it to stand overnight, converted it to an open-chain ester salt, whose analysis and infrared spectrum were consistent with either XVa or b. Warming XV in 1 *N* hydrochloric acid reconverted it to XIIa, a reaction which can be considered as evidence favoring structure XVa for the structure of this product. The alternate, XVb, would be expected to cleave at the thio ester linkage under these conditions. Treatment of XIIb with aqueous base converted it to a white amorphous insoluble high-melting solid, which may be a polymer of structure XVI. XVI could be formed by intermolecular aminolysis of the thiazanedione ring by the free base XII.


$$C_2H_5O\overset{O}{\overset{\|}{C}}CH_2CH_2S\overset{O}{\overset{\|}{C}}NHCH_2CH_2CH_2NH_3{}^+Cl^-$$
XVa


$$C_2H_5O\overset{O}{\overset{\|}{C}}SCH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_2CH_2CH_2NH_3{}^+Cl^-$$
XVb


$$(-\overset{O}{\overset{\|}{C}}CH_2CH_2S\overset{O}{\overset{\|}{C}}NHCH_2CH_2NH-)_x$$
XVI

Thiourea hydrochloride reacts with α,β-unsaturated acids to produce addition products.[10a] Although ethylenethiourea does not form a hydrochloride salt, we have now found that treatment of an acetone solution of ethylenethiourea and acrylic acid with dry hydrogen chloride at room temperature causes the formation of 2-carboxyethylmercaptoimidazoline hydrochloride (X). This compound is distinctly different from its isomer, XIIa, and can be cyclized to the bicyclic XI hydrochloride[10b] by refluxing in ethanol, but not in refluxing acetone. Although VI was quite easily isolated,[4] attempts to convert the hydrochloride X to the homologous zwitterion were unsuccessful. Instead, XI was apparently formed and further hydrolyzed during these experiments.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) and its salts are formed readily. Refluxing

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(7) C. Lo and E. Y. Shropshire, *J. Org. Chem.*, **22**, 999 (1957).

(8) S. Gabriel, *Ber.*, **32**, 2222 (1899).

(9) J. E. Baer and R. G. Lockwood, *J. Am. Chem. Soc.*, **76**, 1162 (1954).

(10) (a) H. Behringer and P. Zillikens, *Ann.*, **574**, 140 (1951); (b) C. G. Overberger and H. A. Friedman [*J. Org. Chem.*, **29**, 1720 (1964)] report the isolation of XI by the reaction of ethylenethiourea and acrylyl chloride in acetone. We wish to thank Dr. Overberger for the opportunity to examine his manuscript before publication.

ethylenethiourea with β-chloropropionic acid in ethanol or acetone gave only traces of XI hydrochloride, but β-bromopropionic acid in these solvents or in water gave moderate yields of XI hydrobromide. However, when ethylenethiourea was heated with an equimolar amount of the appropriate β-halo acid or ester in an open flask without solvent, it was converted in good yield to a salt of XI. The free base of XI was obtained in nearly quantitative yield from ethylenethiourea and β-propiolactone in aqueous solution, but in acidic ethanol this reaction was unsuccessful.

It was possible to obtain XI from XII in low yield by careful neutralization of salts of XII and immediate extraction into chloroform. Apparently the extraction technique produces the free base of XII in high dilution, so that cyclization occurs, rather than the intermolecular reaction to form XVI. X was also converted to XI under similar conditions, as shown by extraction of a small amount of XI by chloroform, or isolation of the picrate of XI if the reaction were carried out in ethanol.

Since XI salts can be converted into XII salts by refluxing in aqueous acid, we have now isolated and characterized the three new compounds, X, XI, and XII, and have shown that X can be converted to XI and XII, XI can be converted to XII, and XII back to XI, but we have been unable to convert either XII or XI back to X. On the basis of these experiments, and the earlier work of VanAllan,[4] it seems reasonable to presume that XII salts are formed from ethylenethiourea and β-halo propionic acids in aqueous solution by initial alkylation of sulfur to form X salts, followed by cyclization to XI and hydrolysis to XII. In contrast to the sequence I → II → III, in which II is obtained only with difficulty, XI, which contains the 5,6-fused ring system, is much more stable and easily isolated.

The analog of X, 2-(β-cyanoethylmercapto)imidazoline hydrochloride (XVII) was obtained in excellent yield by the neat reaction of ethylenethiourea and β-chloropropionitrile. However, when these reagents were refluxed in ethanol for 16 hr., ethylenethiourea was recovered unchanged. Since boiling XVII in water led to the formation of some XI hydrochloride, it is probable that initial hydrolysis of the cyano group leads to cyclization in this case.

A homolog of XI, 7-methyl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one hydrochloride (XVIII) was obtained in good yield from the reaction of ethylenethiourea with either 3-chlorobutyric acid neat, or by the acid-catalyzed addition to crotonic acid in ethanol. Apparently the methyl group enhances the ring closure in this case, since the open-chain system X was obtained with acrylic acid under these conditions. Refluxing ethylenethiourea and 3-chlorobutyric acid in aqueous solution produced the thiazanedione XIX in satisfactory yield.

Experimental[11]

Preparation of the Zwitterion 2-Carboxymethylmercaptoimidazoline (VI).—This compound, originally prepared by Rylander,[12] has since been described by VanAllan.[4] A mixture of 20 g. (0.21 mole) of chloroacetic acid, 21.6 g. (0.21 mole) of ethylenethiourea, and 10 g. (0.21 mole) of sodium acetate in 150 ml. of ethanol was refluxed for 30 min. The alcohol was evaporated under reduced pressure, dilute sodium bicarbonate was added, and 23 g. (67%) of a precipitate, which after two recrystallizations from dilute ethanol melted at 182–183° dec., was obtained; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 3448 (NH), 2857 (CH), 3135 and 2632 (NH$^+$), 1538 (C=NH$^+$), 1600, 1364 (COO$^-$).

Anal. Calcd. for $C_5H_8N_2O_2S$: C, 37.46; H, 4.96; N, 17.48; S, 19.97. Found: C, 37.72; H, 4.92; N, 17.41; S, 20.18.

2-Carboxymethylmercaptoimidazoline Hydrochloride (I).—One gram of finely powdered VI was suspended in 25 ml. of ether and treated with a few drops of concentrated hydrochloric acid. When ethanol was added dropwise with constant stirring to the oily mass, the hydrochloride melting at 128–129°, as reported by VanAllan,[4] crystallized in almost quantitative yield (1.1 g.).

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one Hydrochloride (II·HCl). A. From VI.—A solution of 1 g. of VI in 2.5 ml. of concentrated hydrochloric acid was heated on a steam bath for 5 min., according to the direction of VanAllan[4] for preparing I. However, on evaporation of the solution under reduced pressure, and recrystallizing the residue from isopropyl alcohol, 0.5 g. of II·HCl, melting at 205–206° dec., was obtained.

B. From IX.—A suspension of 0.2 g. of IX in 25 ml. of ether was treated with a few drops of concentrated hydrochloric acid. Ether was decanted from the oily mass which separated, and it was triturated with ethanol to produce 0.1 g. (69%) of white crystals of II hydrochloride.

C. From II.—A benzene solution of II (see below) was treated with a few drops of concentrated hydrochloric acid, and the sticky oily mass which separated was washed with ethanol, giving a pure white product which melted to a red oil at 205–206°; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 3509, 2469 (NH$^+$), 2941 (CH), 1751 (CO), 1610 (C=N).

Anal. Calcd. for $C_5H_7ClN_2OS$: N, 15.69; S, 18.02. Found: N, 15.59; S, 18.28.

Hydrolysis of II Hydrochloride to Form VI.—An aqueous solution (5 ml.) of 0.177 g. (1.0 mmole) of II·HCl and 0.136 g. (1.0 mmole) of sodium acetate was refluxed for 0.5 hr., evaporated, and the residue was treated with 2 ml. of ice-cold water. The compound insoluble in cold water melted at 182–183° (0.060 g., 37%) and was identified as VI by comparison of infrared spectra.

2-Carbethoxymethylmercaptoimidazoline Hydrochloride (VII). A. From Ethanol.—A solution of 20.4 g. (0.2 mole) of ethylenethiourea and 24.5 g. (20.1 ml., 0.2 mole) of ethyl chloroacetate in 150 ml. of absolute ethanol was refluxed for 2 hr. Excess solvent was removed under reduced pressure, and the crude product (35 g., 80%) crystallized from ethanol as needles melting at 143–144°.

B. From Pyridine.—A pyridine solution (50 ml.) of 10 g. (0.1 mole) of ethylenethiourea and 12.2 g. (10 ml., 0.1 mole) of ethyl chloroacetate was stirred at room temperature for 7 hr. On scratching the sides of the reaction flask, 8 g. (35%) of VII separated, m.p. 143–144°, identical with the above; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 3096, 2273 (NH$^+$), 2941 (CH), 1721 (CO), 1563 (C=NH$^+$).

Anal. Calcd. for $C_7H_{13}ClN_2O_2S$: Cl, 15.78; N, 12.47; S, 14.27. Found: Cl, 15.90; N, 12.88; S, 13.98.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one (II).—Three grams of VII in 50 ml. of absolute ethanol was treated with ammonia gas for a few minutes. The precipitated ammonium chloride was filtered and removal of ethanol under reduced pressure at room temperature gave 1.15 g. (60%) of II, which after crystallization from ethyl acetate melted at 94–95°; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 3003 (CH), 1712 (CO), 1629 (C=N).

Anal. Calcd. for $C_5H_6N_2OS$: N, 19.7; S, 22.55. Found: N, 19.44; S, 22.44.

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazol-3-one Picrate.—Finely ground II was stirred into a saturated ethanolic solution of picric acid, and a precipitate formed immediately. It recrystallized from absolute ethanol as golden yellow needles melting at 184–185° dec. The same picrate was also obtained in small amounts from the concentrated mother liquors from the preparation of VI and VII.

Anal. Calcd. for $C_{11}H_9N_5O_8S$: N, 18.86; S, 8.62. Found: N, 18.97; S, 8.76.

2-Benzylidene-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one.—A solution of 0.426 g. (3.0 mmoles) of II, 0.318 g. (3.0 mmoles) of benzaldehyde, and 0.358 g. (3.0 mmoles) of piperidine in 10 ml. of ethanol was refluxed for 8 hr. The excess solvent was removed under reduced pressure, and the crystalline pale yellow residue (0.120 g., 17%) was washed several times with ether and melted at 179–180° as reported by VanAllan.[4]

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[11] All melting points are corrected. Analyses were by Midwest Microlab, Inc., Indianapolis, Ind.

[12] P. N. Rylander, Ph.D. thesis, Indiana University, 1948.

3-(β-Aminoethyl)-2,4-thiazolidinedione Hydrochloride (III).—A solution of 5.1 g. (0.05 mole) of ethylenethiourea and 9.4 g. (0.1 mole) of chloroacetic acid in 50 ml. of water was refluxed for 3 hr., and then concentrated to a sirup. On pouring the cooled concentrate into 50 ml. of cold methanol, 8 g. (81%) of needles separated, which melted at 225–227°.[3,4]

A similar reaction in 95% ethanol gave a 51% yield of III, and refluxing ethylenethiourea with chloroacetyl chloride in acetone also produced III, in 23% yield. Saturating a solution of 1.61 g. of VI in 50 ml. of 95% ethanol with dry hydrogen chloride produced needles of pure III in 25% yield after 3 days. Concentration of the mother liquor in this case led to intractable oils; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3448, 2519 (NH^+), 2941, 2841, 2762 (CH), 1701, 1629 (CO), 1587 (NH_3^+).

Anal. Calcd. for $C_5H_9ClN_2O_2S$: C, 30.53; H, 4.58; N, 18.05. Found: C, 30.59; H, 4.54; N, 18.00.

3-(β-Benzamidoethyl)-2,4-thiazolidenedione (IV). **A. Benzoylation of III.**—To a stirred solution of 5 g. of III and 6 g. of sodium acetate in 25 ml. of water was added slowly and with stirring 4 g. of benzoyl chloride at 15–20°. After 2 hr., 4 g. of sodium bicarbonate was added and stirring was continued for 0.5 hr. more. The white solid which had separated was removed by filtration, resuspended in a dilute aqueous solution of sodium bicarbonate and again filtered. Two crystallizations from ethanol yielded 6 g. (80%) of white crystals, m.p. 135–136°.[4]

B. **From 2,4-Thiazolidinedione.**—Five grams of 2,4-thiazolidinedione was dissolved in 20 ml. of hot ethanol containing 2.62 g. of potassium hydroxide, stirred for 2 hr., and then cooled in an ice bath. The crystalline potassium salt (6 g.) was collected, washed with ethanol, and air-dried. A mixture of 1.55 g. of this salt[7] (0.01 mole) in 25 ml. of dimethylformamide and 2.28 g. (0.01 mole) of β-benzamidoethyl bromide,[8] was heated on a steam bath for 4 hr., excess solvent was removed under reduced pressure, and the residue was treated with 20 ml. of ice-cold water and 2 ml. of concentrated hydrochloric acid. The product (0.87 g., 33%) melting at 135–136° after two crystallizations from ethanol was identical with the one prepared by method A, by mixture melting points and infrared spectra.

3-β-Aminoethyl-5-methyl-2,4-thiazolidinedione Hydrochloride (VIII).—When 9.4 g. (0.09 mole) of α-chloropropionic acid was treated with ethylenethiourea in water as described for III, 85% of crude white solid separated, which melted at 249–251° after recrystallization from ethanol in plates; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3425, 3125, 2551 (NH^+), 2933, 2841, 2762 (CH), 1718, 1653 (CO), 1582 (C=N).

Anal. Calcd. for $C_6H_{11}ClN_2O_2S$: Cl, 16.8; N, 13.3. Found: Cl, 16.6; N, 13.7.

Preparation of IX.—A solution of 10.2 g. (0.1 mole) of ethylenethiourea, 10 ml. (0.1 mole) of ethyl chloroacetate, and 8.2 g. (0.1 mole) of fused sodium acetate in 225 ml. of anhydrous ethanol was refluxed for 45 min. On cooling, undissolved sodium acetate and sodium chloride were removed by filtration, and the solution was concentrated under reduced pressure. The residue was crystallized three times from ethyl acetate to give 2.5 g. (21%) of crystals melting at 129–130°; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3500 (NH), 2941 (CH), 1701 (CO), 1580 (C=N).

Anal. Calcd. for $C_8H_{12}N_4OS_2$: C, 39.3; H, 4.95; N, 22.93; S, 26.25. Found: C, 39.43; H, 5.05; N, 22.93; S, 26.16.

3-(β-Aminoethyl)-1,3-thiazane-2,4-dione (XII) Hydrohalides. A. Hydrochloride (XIIa).—An aqueous solution (100 ml.) of 10.2 g. (0.1 mole) of ethylenethiourea and 10.84 g. (0.1 mole) of β-chloropropionic acid was refluxed for 3 hr. Excess solvent was removed under reduced pressure, the oily residue was dissolved in ethanol, and ether was added. The white solid (6.6 g., 31%) that separated was recrystallized from ethanol containing 1 drop of concentrated hydrochloric acid and melted at 157–159°. No other identifiable product could be obtained from the ethanolic mother liquor. Refluxing these reagents in ethanol for 40 hr. (at the end of 20-hr. reflux period unchanged ethylenethiourea could still be isolated) gave only 5% of XIIa after recrystallization; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 2941 (CH), 2755, 2370 (NH_3^+), 1701, 1629 (CO).

Anal. Calcd. for $C_6H_{11}ClN_2O_2S$: N, 13.30; S, 15.22. Found: N, 13.51; S, 15.31.

B. Hydrobromide (XIIb).—An aqueous solution (50 ml.) of 5.1 g. (0.05 mole) of ethylenethiourea and 7.5 g. (0.05 mole) of β-bromopropionic acid, refluxed for 3 hr., gave 5.2 g. (40%) of XIIb melting at 185–186° after crystallizing from isopropyl alcohol. The infrared spectrum was identical with that of XIIa, above. An aqueous solution (15 ml.) of 2.37 g. (0.01 mole) of XI hydrobromide and 1 ml. of 48% hydrobromic acid, refluxed for 24 hr., concentrated, and recrystallized from isopropyl alcohol, gave 1.25 g. (50%) of crystals identical in melting point and infrared spectrum with XIIb.

Anal. Calcd. for $C_6H_{11}BrN_2O_2S$: N, 10.98; S, 12.54. Found: N, 10.89; S, 12.66.

3-(β-Dibenzoylaminoethyl)-1,3-thiazane-2,4-dione (XIII).—To a stirred solution of 5.25 g. (0.025 mole) of XIIa and 6.8 g. (0.05 mole) of sodium acetate in 25 ml. of water was added slowly with stirring 4 g. of benzoyl chloride at 15–20°. After 2 hr., 4 g. of sodium bicarbonate was added and stirring was continued for 3 hr. more. The yellow sticky solid which had separated was removed by filtration, resuspended in a dilute aqueous solution of sodium bicarbonate and again filtered and washed with water. Three recrystallizations from methanol yielded 1.5 g. (15%) of XIII melting at 172–173°. The infrared spectrum of this compound is characterized by the absence of NH stretch in the 3400-cm.$^{-1}$ region; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 2940 (CH), 1701, 1629 (broad, CO).

Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.71; N, 7.33; S, 8.37. Found: C, 62.38; H, 4.82; N, 7.45; S, 8.40.

3-(β-Benzamidoethyl)-1,3-thiazane-2,4-dione (XIV).—To a solution of 0.525 g. (0.0025 mole) of XIIa in 5 ml. of dry pyridine and 10 ml. of dry benzene was added, dropwise, 0.5 ml. of benzoyl chloride. The resulting mixture was heated on a steam bath at 60–70° for 0.5 hr. and then was poured into 100 ml. of cold water. The benzene layer was separated and the aqueous solution was washed once with 10 ml. of benzene. The combined benzene solutions were washed with 5% sodium carbonate solution and with water and dried with anhydrous magnesium sulfate. The oily residue left after benzene was removed under reduced pressure was treated with 2 ml. of ethanol and 25 ml. of petroleum ether (b.p. 30–60°). The white product (0.200 g., 28%) melted at 160° after recrystallization from dilute ethanol; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3436 (NH), 3155, 3012 (CH), 1704, 1629 (CO).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: N, 10.08; S, 11.51. Found: N, 10.32; S, 11.62.

To a solution of 3.93 g. (0.03 mole) of 1,3-thiazane-2,4-dione, prepared by the method of Hendry[13] in 83% yield, in 20 ml. of dimethylformamide was added slowly and under constant stirring over a period of 1 hr. 1.6 g. (slight excess) of 52.7% sodium hydride in mineral oil.[14] The resulting suspension of sodium salt was treated with 6.8 g. of β-benzamidoethyl bromide[8] in 10 ml. of dimethylformamide, and the reaction mixture was heated on a steam bath under constant stirring for 4 hr. Excess solvent was removed under reduced pressure, 200 ml. of cold water was added, the aqueous suspension was extracted with 25 ml. of ether, and the residue (0.520 g., 6%) insoluble in water and ether crystallized from dilute ethanol. It melted at 159–160°, and the infrared spectrum of this compound is identical with that of XIV, above.

Ethanolysis of XIIa.—A white pasty mass of crude XIIa, obtained from 1.0 mole of each of the reagents in a liter of water (see above) and melting at 152–154° after drying *in vacuo*, was dissolved in 750 ml. of 95% ethanol and, on cooling overnight, 90 g. (34%) of a colorless crystalline solid XV melting at 109–110° was obtained; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3280 (NH), 2965 (CH), 2750, 2375 (NH_3^+), 1725, 1635 (CO), 1504 (C=N).

Anal. Calcd. for $C_8H_{17}ClN_2O_3S$: C, 37.65; H, 6.82; Cl, 13.84; S, 12.55. Found: C, 37.68; H, 7.19; Cl, 14.12; S, 12.57.

When 90 g. of XV was dissolved in 1 l. of 1 *N* hydrochloric acid, heated on a steam bath for 3 hr., and concentrated to one-third volume, the white solid which crystallized melted at 157–159° dec. and weighed 44 g. (60%). The infrared spectrum of this compound was identical with that of pure XIIa.

Hydrolysis of XIIb.—A concentrated aqueous solution of XIIb was treated with concentrated ammonium hydroxide. The white amorphous powder that separated was washed with water, ethanol, acetone, and ether. No suitable solvent to recrystallize the product could be found. It melted from 216–219°; $\nu_{\max}^{\text{KBr}}$ (cm.$^{-1}$): 3365 (NH), 2976 (CH), 1645 (CO).

Anal. Calcd. for $C_6H_{10}N_2O_2S$: N, 16.09; S, 18.42. Found: N, 15.94; S, 18.36.

2-β-Carboxyethylmercapto-2-imidazoline Hydrochloride (X).[15]—Hydrogen chloride gas was passed through a solution of 5.1 g.

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[13] C. M. Hendry, *J. Am. Chem. Soc.*, **80**, 973 (1958).

[14] G. deStevens, A. Halamondaris, and L. Dorfman, *ibid.*, **80**, 5198 (1958).

[15] L. Fedor, Ph.D. thesis, Indiana University, 1963.

(0.05 mole) of ethylenethiourea and 3.6 g. (0.05 mole) of acrylic acid in 500 ml. of acetone at 28° for 0.5 hr., at the end of which a white solid had precipitated. The compound was washed with acetone and a total of 7.9 g. (91%) of solid was obtained, m.p. 133–135°; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 2941 (CH), 2900, 2760 (w, NH$^+$), 1710 (CO), 1538 (C=N).

Anal. Calcd. for $C_6H_{11}ClN_2O_2S$: N, 13.30; S, 15.22. Found: N, 13.51; S, 15.60.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI) Hydrohalides. A. Hydrochloride.—A mixture of 10.1 g. (0.1 mole) of ethylenethiourea and 10.84 g. (0.1 mole) of β-chloropropionic acid was heated slowly to 115° in an open flask containing a thermometer. Ethylenethiourea went into solution completely accompanied by a rise in temperature to 160°. The reaction flask was cooled to 135° and maintained at this temperature for an additional 10 min. The cooled reaction mixture solidified and yielded 12 g. (63%) of XI hydrochloride, melting at 276–278° after recrystallizing from methanol; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 2933 (CH), 2703, 2326 (NH$^+$), 1721 (CO), 1587 (C=N).

Anal. Calcd. for $C_6H_9ClN_2OS$: N, 14.55; S, 16.62. Found: N, 14.81; S, 16.69.

When 1 g. (4.7 mmoles) of X was refluxed in ethanol for 4 hr., 0.65 g. (72%) of XI hydrochloride crystallized on cooling, as shown by mixture melting point (277–278°) and identity of infrared spectra. Similar treatment in refluxing acetone for 2 hr. gave only starting product. The neat reaction of ethylenethiourea and ethyl β-chloropropionate, heated to 150° for 15 min., gave only 36% of XI hydrochloride.

Attempted Reaction of Ethylenethiourea with β-Propiolactone.—A solution of 10.1 g. (0.1 mole) of ethylenethiourea in 50 ml. of ethanol previously saturated with hydrogen chloride was mixed with 7.2 g. (0.1 mole) of β-propiolactone and the reaction mixture was stirred at room temperature for 30 hr. From the oily mass left behind after the removal of 6.7 g. (67%) of ethylenethiourea, 0.20 g. (3%) of XI hydrochloride was isolated.

B. XI Hydrobromide.—When 5.1 g. (0.05 mole) of ethylenethiourea and 7.65 g. (0.05 mole) of β-bromopropionic acid was heated for 5 min. at 105° in an open flask with vigorous stirring, the reaction mixture solidified. The temperature of the mixture was raised slowly to 120° and stirring continued for an additional 10 min. It then was cooled to room temperature and stirred with 50 ml. of ethanol. The white crystals (8 g., 76%) melted at 285–286° after recrystallization from methanol and had an infrared spectrum identical with that of XI hydrochloride (above).

Anal. Calcd. for $C_6H_9BrN_2OS$: Br, 33.74; N, 11.84; S, 13.50. Found: Br, 33.91; N, 12.09; S, 13.84.

The preparation of this hydrobromide by refluxing the reagents in a solvent, such as water, ethanol, or acetone, was much less satisfactory.

2,3,6,7-Tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one (XI).—A mixture of 10 g. (0.1 mole) of ethylenethiourea and 7.2 g. (0.1 mole) of β-propiolactone in 50 ml. of water was stirred continuously for 45 min. Excess solvent was removed at reduced pressure, and the crude product (15 g., 96%) melted at 144–145° after two crystallizations from methanol; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 2941 (CH), 1664 (CO), 1587 (C=N).

Anal. Calcd. for $C_6H_8N_2OS$: N, 17.95; S, 20.51. Found: N, 17.99; S, 20.67.

When a cold solution of 2.62 g. (12.5 mmoles) of XIIa in 25 ml. of water was mixed with 5 ml. of water containing 1.7 g. (12.5 mmoles) of sodium acetate and the mixture was extracted immediately with 25 ml. of cold chloroform, 0.326 g. (16.7%) of XI was obtained on evaporation of the dried chloroform under reduced pressure. Similar treatment of XI hydrobromide produced XI in 30% yield, and by this means X was converted to XI in 5% yield.

Picrate.—A solution of XI in absolute ethanol was treated with an equal amount of a saturated ethanolic solution of picric acid, and a yellow picrate melting at 183–184° dec. crystallized on cooling. This same product was obtained in 16% yield when a solution of 1 g. of X (5 mmoles) in 20 ml. of absolute ethanol was stirred with 0.41 g. (5 mmoles) of sodium acetate, sodium chloride was filtered, the solvent was removed, and the resulting oil was redissolved in ethanol and treated with picric acid.[15]

Anal. Calcd. for $C_{12}H_{11}N_5O_8S$: N, 18.18; S, 8.31. Found: N, 18.43; S, 8.43.

2-(β-Cyanoethylmercapto)-2-imidazoline Hydrochloride (XVII).—The product of the neat reaction of 7 g. (0.07 mole) of ethylenethiourea in an excess (15 ml.) of β-chloropropionitrile was triturated with 25 ml. of ether. The white solid (13 g., 97%) melted at 134–135° after recrystallization from isopropyl alcohol; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 2941 (CH), 2632 (NH$^+$), 2273 (C≡N), 1550 (C=N).

Anal. Calcd. for $C_6H_{10}ClN_3S$: N, 21.94; S, 16.71. Found: N, 21.82; S, 16.60.

A solution of 3.6 g. (0.02 mole) of XVII was boiled in 10 ml. of water for 5 min. Removal of the water at reduced pressure and recrystallization of the residue from absolute ethanol gave 0.3 g. (7%) of XI hydrochloride, melting at 277–278°.

Picrate.—An alcoholic solution of XVII was mixed with a saturated solution of picric acid in ethanol, and golden yellow needles of XVII picrate, melting at 164–165° after recrystallization from ethanol, were collected.

Anal. Calcd. for $C_{12}H_{12}N_6O_7S$: N, 21.87; S, 8.33. Found: N, 22.29; S, 8.40.

7-Methyl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-one Hydrochloride (XVIII). A. From 3-Chlorobutyric Acid.—A mixture of 10 g. (0.1 mole) of ethylenethiourea and 12.25 g. (0.1 mole) of 3-chlorobutyric acid was heated slowly to 155° in a round-bottom flask. After 0.5 hr. the mixture was cooled and stirred with 50 ml. of absolute ethanol, giving a white solid (12 g., 58%) which melted at 262–264° after crystallization from methanol. No other product could be obtained from the ethanolic filtrate. The infrared spectrum was very similar to that of XI hydrochloride; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 2976 (CH), 3261, 2247 (NH$^+$), 1715 (CO), 1587 (C=N).

Anal. Calcd. for $C_7H_{11}ClN_2OS$: N, 13.56; S, 15.50. Found: N, 13.28; S, 15.63.

B. From Crotonic Acid.[15]—In a 100-ml. flask equipped with a condenser and gas inlet tube was placed 2.15 g. (0.025 mole) of crotonic acid, 2.55 g. (0.025 mole) of ethylenethiourea, and 50 ml. absolute ethanol. Hydrogen chloride gas was bubbled through the refluxing ethanolic solution for 2 hr. On cooling, the solution yielded 2.1 g. (40%) of white crystals, which on recrystallization from methanol melted at 262–263° and showed no depression of melting point when mixed with XVIII above. The infrared spectra of the two products were identical.

3-(β-Aminoethyl)-6-methyl-1,3-thiazane-2,4-dione Hydrochloride (XIX).—A solution of 5.1 g. (0.05 mole) of ethylenethiourea and 8.6 g. (0.05 mole) of 3-chlorobutyric acid in 50 ml. of water was refluxed for 4 hr. Work-up in the usual way and recrystallization from acetone gave 5.8 g. (43%) of XIX, melting at 161–163°; $\nu_{\max}^{\mathrm{KBr}}$ (cm.$^{-1}$): 3077 (NH$^+$), 3005 (CH), 1709, 1642 (CO).

Anal. Calcd. for $C_7H_{13}ClN_2O_2S$: N, 10.41; S, 11.91. Found: N, 10.47; S, 11.97.