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Cyanoethylation. II. Cyanoethylation of 2-Thiazoline-2-thiol

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In the presence of basic catalysts 2-thiazoline-2-thiol (IX) undergoes cyanoethylation exclusively on the heterocyclic nitrogen atom to give 2-thioxo-3-thiazolidinepropionitrile (XI). This compound is readily hydrolyzed to 2-thioxo-3-thiazolidinepropionic acid. Further hydrolysis, with resulting scission of the heterocyclic nucleus, occurs with great difficulty. Treatment of 2-thioxo-3-thiazolidinepropionitrile with mercuric oxide in hot acetic acid produces 2-oxo-3-thiazolidinepropionamide by desulfurization and concomitant partial hydrolysis of the nitrile.

It has been shown that the cyanoethylation of 4,5-dialkylthiazole-2-thiols (I, Fig. 1) occurs on the ring nitrogen rather than on the thiol sulfur atom.[2,3]

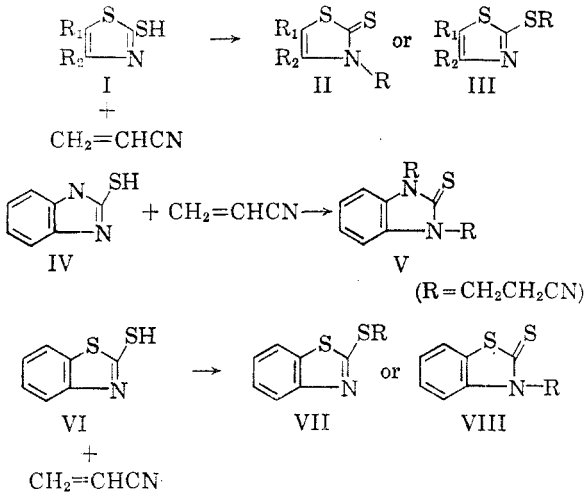
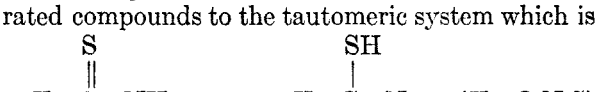


Figure 1

This is somewhat surprising inasmuch as the formation of a 4-thiazoline-3-propionitrile (II) destroys the aromaticity of the thiazole ring. Efros[4a] also reports, with reservation, that the cyanoethylation of 2-mercaptobenzimidazole (IV) results in substitution on both nitrogen atoms to give V. Other authors assign, with insufficient evidence, the 2-(2-cyanoethylthio)-structure (III) to the reaction products of various 2-mercaptothiazoles[4b] and 2-mercaptobenzothiazoles[5] with acrylonitrile. Sprague and Land,[6] however, express the opinion that the product from 2-mercaptobenzothiazole (VI) and acrylonitrile may actually have the *N*-cyanoethylated structure VIII. Considerable confusion exists regarding the structures of the products arising from the addition of various unsaturated compounds to the tautomeric system which is



present in a large number of heterocyclic-2-thiols. We wish to report some observations on the reaction of 2-thiazoline-2-thiol (IX) with acrylonitrile.

Initially the cyanoethylation product of 2-thiazoline-2-thiol was thought to be 2-(2-cyanoethylthio)-2-thiazoline (X); however, it was quickly apparent that the chemical behavior and infrared spectrum were not compatible with that expected of a 2-alkylthio-2-thiazoline. The product was insoluble in dilute acid and could be readily hydrolyzed in excellent yield to the corresponding carboxylic acid. Cleavage of the ring resulted only after prolonged heating with concentrated hydrochloric acid. Neither the nitrile (XI) nor the acid (XII) exhibited a C=N infrared absorption band at approximately 1560 cm.$^{-1}$. In addition, treatment of the nitrile with mercuric oxide in hot acetic acid[7] produced 2-oxo-3-thiazolidinepropionamide (XIV) as inferred from analytical data and infrared absorption bands at 3510, 3250 and 1640 cm.$^{-1}$, attributable to a primary amide, and at 1690 cm.$^{-1}$, attributable to the ring carbonyl group. The concurrent formation of amide during the desulfurization reaction was probably due to a mercuric ion catalyzed hydration of the nitrile by the water formed in the neutralization of the mercuric oxide.

In contrast, 2-alkylthio- or 2-arylthio-2-thiazolines, *e.g.* XIII, are soluble in dilute acid, are readily cleaved by hydrochloric acid to alkyl- or aryl 2-aminoethyl dithiolcarbonate hydrochlorides,[8,9] and possess a characteristic C=N infrared band at about 1560 cm.$^{-1}$.

The above data lead us to conclude that the cyanoethylation of 2-thiazoline-2-thiol had not

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(4) (a) A. M. Efros, *Zhur. Obshchei Khim.*, 28, 617 (1958).

(4) (b) A. M. Clifford and J. G. Lichty, U. S. Patent 2,407,138 (1946).

(5) C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, 69, 2328 (1947).

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(9) J. C. Crawhall and D. F. Elliot, *J. Chem. Soc.*, 2071 (1951); 3094 (1952).

occurred on the thiol sulfur atom but on the ring nitrogen to give 2-thioxo-3-thiazolidinepropionitrile (XI). Mild hydrolysis produced 2-thioxo-3-thiazolidinepropionic acid (XII) and prolonged hydrolysis gave *N*-(2-mercaptoethyl)-β-alanine hydrochloride (XV). These reactions are outlined in Fig. 2.

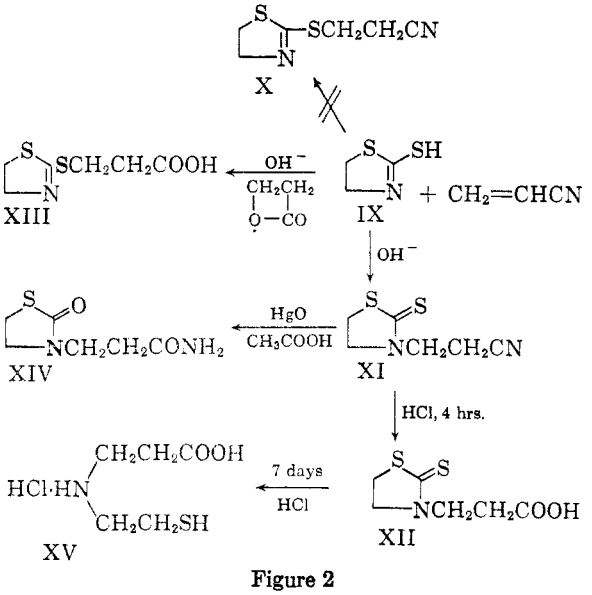

Figure 2

The structure of the acid XII was confirmed by comparison with authentic 2-(2-carboxyethylthio)-2-thiazoline (XIII) prepared from an aqueous solution of the sodium salt of 2-thiazoline-2-thiol and β-propiolactone.[10] The amphoteric behavior of

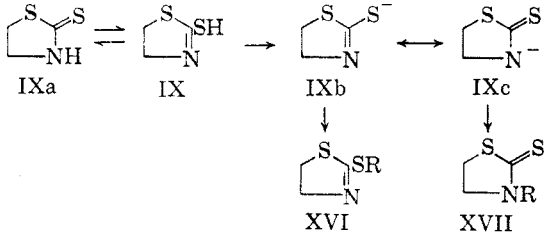

Figure 3

the acid XIII, the pronounced difference in the melting points of the acids XII and XIII, and the presence of a C=N absorption band in the infrared spectrum of XIII indicated that the cyanoethylation product of 2-thiazoline-2-thiol and the corresponding acid are correctly formulated as XI and XII respectively.

DISCUSSION

2-Thiazoline-2-thiol (IX) has been shown to exist in the thioamide form (IXa)[11] in the solid and in neutral or slightly acidic solutions in organic solvents. In basic solution, on the other hand, it exists as a resonance stabilized anion in which the canonical forms IXb and IXc are the major contributors. Under basic conditions 2-thiazoline-2-thiol will behave as an ambient anion[12] and whether an *S*-substituted (XVI) or *N*-substituted (XVII) product results from its reactions will depend upon both the reaction conditions and the mechanism which is operative.

In all S_N2-type alkylations, e.g., with alkyl halides, dialkyl sulfates, β-propiolactone, etc., of an alkali metal salt of 2-thiazoline-2-thiol the products are invariably *S*-alkylated (XVI).[10,13,14] Whether the use of the silver salt of 2-thiazoline-2-thiol would shift the alkylation to the nitrogen in a manner analogous to the alkylation of silver nitrite[12,15] is not known but is worth investigating.

On the other hand, there is no agreement in the literature as regards the structure of the products arising from the addition, under basic conditions, of 2-thiazoline-2-thiol (IX) to various unsaturated systems. For example, IX and phenylvinylsulfone are reported to give the *S*-adduct (XVI, R = $C_6H_5SO_2CH_2CH_2$—).[16] We have shown that the addition to acrylonitrile produces 2-thioxo-3-thiazolidinepropionitrile (XI). The addition products of IX with formaldehyde plus an alcohol or an amine have been variously assigned either the *S*-substituted (XVI, R = CH_2OR_1, $CH_2NR_1R_2$)[17,18] or the *N*-substituted (XVII, R = CH_2OR_1, $CH_2NR_1R_2$)[19] structure. Similarly, acylation of 2-thiazoline-2-thiol under Schotten-Baumann conditions has, by implication, been reported to give the *S*-acylated compounds (XVI, R = ArCO—).[20,21] Clapp and Watjen,[22] however, prepared the *p*-nitrobenzoates of 2-thiazoline-2-thiol and several alkyl substituted 2-thiazoline-2-thiols and cited infrared data which clearly indicated that acylation had occurred on the imino nitrogen atom (XVII, R = *p*-$NO_2C_6H_4$-CO—).

Nitrogen substitution has been shown to occur in the reaction of 2-thiazoline-2-thiol with acrylonitrile and *p*-nitrobenzoyl chloride. It may also occur in additions of formaldehyde, phenylvinyl-

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sulfone and other unsaturated compounds to 2-thiazoline-2-thiol; however, only a careful re-examination of this problem can ascertain whether addition has, in fact, produced 3-substituted-2-thiazolidinethiones (XVII).

EXPERIMENTAL[23]

2-Thioxo-3-thiazolidinepropionitrile (XI). A mixture of 119 g. (1.0 mole) of 2-thiazoline-2-thiol, 5 ml. of 35% methanolic Triton B (benzyltrimethylammonium hydroxide) and 500 ml. of chloroform was warmed to 40°. Acrylonitrile (106 g., 2.0 moles) was added to the stirred solution over a period of 25 min. When about one-half the acrylonitrile had been added, an exothermic reaction commenced and necessitated external cooling to keep the temperature at 40–50°. The final solution was stored at 25° for 18 hr., washed with 100 ml. of 1*N* hydrochloric acid and three 200-ml. portions of water, dried, filtered and concentrated to give 163 g. (94.8%) of orange oil. Vacuum distillation afforded 156 g. (90.3%) of pure product as a light yellow oil, b.p. 176–178° (0.25 mm.), n_D^{25} 1.6344, which slowly crystallized to a wax-like solid, m.p. 29–31°.

Anal. Calcd. for $C_6H_8N_2S_2$: C, 41.83; H, 4.68; N, 16.27. Found: C, 41.94; H, 4.78; N, 16.56.

2-Thioxo-3-thiazolidinepropionic acid (XII). A mixture of 65.7 g. (0.38 mole) of 2-thioxo-3-thiazolidinepropionitrile and 150 ml. of concd. hydrochloric acid was heated under reflux for 4 hr. Considerable crystalline material separated upon slight cooling. This was removed, washed free of ammonium chloride and dried to give 62.0 g. (85.4%) of crystalline acid. Further chilling of the filtrate gave an additional 4.4 g. for an over-all yield of 66.4 g. (91.5%). An analytical sample, m.p. 103.3–104.6°, was obtained by recrystallization from water.

Anal. Calcd. for $C_6H_9ON_2S_2$: C, 37.68; H, 4.74; N, 7.32; S, 33.52. Found: C, 37.93; H, 4.87; N, 7.03; S, 33.64.

2-(2-Carboxyethylthio)-2-thiazoline (XIII). The procedure of Jansen and Mathes[10] was employed, with slight modification, using one-half the specified quantities of reagents. One hour after the addition of β-propiolactone the solution was adjusted to *p*H 1.0 and a small quantity (3.0 g.) of starting material was removed. The filtrate was then adjusted to *p*H 4.5 and the yellow oil which separated was extracted with two 100-ml. portions of ether. The ethereal extract was washed with 50 ml. of cold water, dried, filtered and vacuum concentrated (*ca.* 15 mm.) without external heating. The resultant chilling caused partial crystallization. The solid was removed by suction filtration, washed rapidly with 25 ml. of ether and 15 ml. of petroleum ether (b.p. 30–60°) and dried to give 21.7 g. (23.9%) of colorless crystals, m.p. 76.6–77.5°. Further evaporation of the combined filtrates afforded an additional 33 g. of XIII as a pale yellow oil. The combined yield was 54.7 g. (60.3%).

2-Oxo-3-thiazolidinepropionamide (XIV). After the initial, mild exotherm had subsided, a stirred mixture of 34.4 g. (0.2 mole) of 2-thioxo-3-thiazolidinepropionitrile, 86.6 g. (0.4 mole) of mercuric oxide and 350 ml. of glacial acetic acid was held at 120° for 6 hr. Within 10 min. the red suspension turned white and after 2.5 hr. mercuric sulfide began to form. The hot mixture was vacuum filtered and the filtrate was concentrated to a colorless paste. This was digested with 150 ml. of boiling ethanol and filtered. The filter cake was washed with an additional 50 ml. of hot ethanol and the combined filtrates were vacuum concentrated to a yellow oil. Crystallization from approximately 150 ml. of ethanol, after removal of a small amount of insoluble material, afforded 10.4 g. of colorless crystals, m.p. 92.0–93.8°. An additional 4.0 g. of product was obtained by diluting the mother liquor with hexane for an over-all yield of 14.4 g. (41.3%). An analytical sample, m.p. 94.1–94.9°, was obtained after two recrystallizations from ethanol-hexane.

Anal. Calcd. for $C_6H_{10}O_2N_2S$: C, 41.36; H, 5.79; N, 16.08; S, 18.40. Found: C, 41.07; H, 5.54; N, 16.14; S, 18.23.

N-(2-Mercaptoethyl)-β-alanine hydrochloride (XV). A mixture of 66.0 g. (0.345 mole) of 2-thioxo-3-thiazolidinepropionic acid and 150 ml. of concd. hydrochloric acid was heated under reflux for 7 days. Upon chilling, 31.1 g. of starting material was recovered. Vacuum concentration (90°, 20 mm.) of the filtrate left a yellow syrup which was dissolved in 100 ml. of absolute ethanol and again concentrated. There was obtained 26.9 g. (79.4% corrected for recovered XII) of uncrystallizable, yellow syrup. Positive tests with sodium bicarbonate, silver nitrate and sodium nitroprusside and the infrared spectrum support the assigned structure.

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(23) All melting points are corrected; boiling points are uncorrected.