

2-Aminothiazoline-4-one * and 2-Iminothiazolidine-4-one Derivatives

Part I. The Reaction of Chloroacetic Acid with N-Monoalkylthiourea

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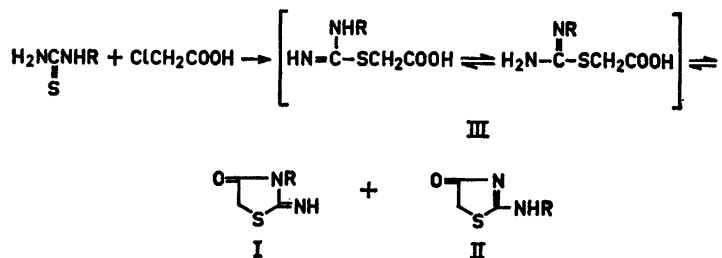
The reaction of chloroacetic acid with N-alkylthioureas in the presence of sodium acetate gave 2-alkylaminothiazoline-4-ones (II). The same reaction performed in the absence of a base gave varying results depending on the size of the alkyl substituent. Thus, with N-methylthiourea, 2-imino-3-methylthiazolidine-4-one (I) was obtained. With N-ethyl- and N-propylthiourea, the corresponding 3-alkyl-2-iminothiazolidine-4-one (I) and 2-alkylaminothiazoline-4-one (II) were both obtained in the proportions 3-4:1. The reaction with N-isopropylaminothiourea gave exclusively 2-isopropylaminothiazoline-4-one (II).

In acidic media, the 2-alkylamino compounds (II) rearranged to the 3-alkyl compounds (I) while under alkaline conditions the reaction was reversed. The isopropylamino derivative (II) did not rearrange.

The reaction of thiourea or alkylthiourea with chloroacetic acid is a general method for the preparation of 2-aminothiazoline-4-one and 2-iminothiazolidine-4-one derivatives. This reaction, when applied to a N-monoalkylthiourea derivative and chloroacetic acid, can in theory give two products, namely 3-alkyl-2-iminothiazolidine-4-one (I) and 2-alkylaminothiazoline-4-one (II).

Only a few rather incomplete studies of such reactions have been published and the results are contradictory. Andreasch^{2,3} reported that 3-methyl- and 3-allyl-2-iminothiazolidine-4-one were obtained by reacting chloroacetic acid with N-methyl- and N-allylthiourea, respectively. The structures were assigned by analogy with the corresponding phenyl derivative obtained by reacting chloroacetic acid with N-phenylthiourea.^{2,4}

* These derivatives can theoretically exist in two possible tautomeric forms; 2-aminothiazoline-4-one and 2-iminothiazolidine-4-one. In this paper they were given the amino structure in accordance with the results obtained in Part II of this study.



However, the structure of the phenyl derivative was later proved ⁵ to be 2-phenyliminothiazolidine-4-one and not 2-imino-3-phenylthiazolidine-4-one as earlier believed. In accordance with this, Andreasch's methyl- and allylthiazolidone derivatives, when reported in Beilstein,⁶ were given the structures 2-methylimino- and 2-allyliminothiazolidine-4-one, respectively. Andreasch ⁷ also reported later that 2-ethyliminothiazolidine-4-one was obtained from the corresponding reaction with N-ethylthiourea. However, in no case was any attempt made to verify the alkylimino structure.

Subsequently Eberly *et al.*⁸ reported that 3-allyl-2-iminothiazolidine-4-one was obtained by reacting N-allylthiourea with chloroacetic acid.

In view of these incomplete and contradictory results it was found desirable to make further studies of the reaction of chloroacetic acid with some N-monoalkylthiourea derivatives.

Method. Chloroacetic acid was allowed to react with a N-monoalkylthiourea derivative in water at 50°C and at 100°C in the presence and absence of base. The reaction was performed with N-methyl-, N-ethyl-, N-propyl-, and N-isopropylthiourea. The base used was sodium acetate. The reaction products were analysed by thin layer chromatography and by this means the minor reaction products were identified.

Results. The reaction of chloroacetic acid with a N-monoalkylthiourea in the presence of sodium acetate gave exclusively product II with the alkyl substituent on the exocyclic nitrogen. Although yields did not exceed 50–74 %, no other product could be isolated. However, traces of 3-alkyl-2-iminothiazolidine-4-one (I) could be detected by thin layer chromatography. Analogous results were obtained with different alkylthioureas suggesting that the result of the reaction is independent of the size of the alkyl substituent.

When the same reaction was performed in water at 50°C and in the absence of a base different products were obtained depending on the size of the alkyl substituent. The reaction of chloroacetic acid with N-methylthiourea gave 2-imino-3-methylthiazolidine-4-one (I) and traces of 2-methylaminothiazolidine-4-one (II). The latter compound was detected by thin layer chromatography.

The reaction of chloroacetic acid with N-ethyl- and N-propylthiourea gave both I and II in the ratio 3–4:1. Finally, when the same reaction was performed with N-isopropylthiourea, 2-isopropylaminothiazolidine-4-one (II) was the only product obtained.

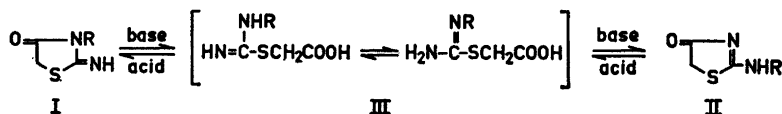
The structures of the two derivatives I and II have been determined by comparing the UV-spectra of 3-alkyl-2-iminothiazolidine-4-ones (I) with

those of 3-alkyl-2-alkyliminothiazolidine-4-ones. Further, the 2-alkylamino derivatives (II) are weak acids, which can be titrated with base unlike the imino derivatives (I).

In the absence of a base and at higher temperature (100°C) the products undergo some hydrolysis thus affording thiazolidine-2,4-dione derivatives.

It is reported⁹ that derivatives of type I and II with an aryl substituent in position 5 are interconvertible by treatment with a base and an acid, respectively.

In accordance with these results, 2-alkylaminothiazoline-4-ones (II) with methyl, ethyl or propyl substituents rearranged to 3-alkyl-2-iminothiazolidine-4-ones when treated with dilute, ethanolic hydrochloric acid at 80°C for 3 h. When the rearrangement was performed in a more concentrated acid, the imino group was hydrolyzed, giving the thiazolidine-2,4-dione derivatives. However, even after 23 h at 80°C 2-isopropylaminothiazoline-4-one failed to rearrange.



3-Alkyl-2-iminothiazolidine-4-ones (I) were found to rearrange to the 2-alkylaminoderivatives (II) when treated with a base (*e.g.* sodium ethoxide or sodium acetate) or simply on warming in water. In the last case the rearrangement was incomplete.

DISCUSSION

The first step in the reaction of chloroacetic acid with N-monoalkylthioureas is assumed to be the attack of the α -carbon atom of chloroacetic acid on the sulphur atom of the N-monoalkylthiourea giving an N-alkyl-S-carboxymethylisothiurea (III). These derivatives were isolated when the reaction was performed at room temperature in the presence of sodium acetate. The interconversion of the alkylamino compounds (II) and imino compounds (I) implies that ring closure of III is reversible.

In *acid* media I and II are stabilized by protonation. When both derivatives are present, the iminocompound (I), having the higher basicity,¹⁰ will be preferentially protonated. This explains why in the absence of a base the imino compounds are the main products of the reaction between chloroacetic acid and N-alkylthioureas. The effect of different alkyl substituents on the proportion of I:II is understood in terms of the resulting stabilities of the corresponding protonated species. However, the ringclosure of S-carboxymethyl-N-isopropylisothiurea (III) to 2-imino-3-isopropylthiazolidine-4-one (I) is probably prohibited on steric grounds.

In *basic* media, the alkylaminocompounds (II) are stabilized by conversion to their anions unlike the iminocompounds (I) which have no acid properties.

Finally, in *neutral* media where no change of the equilibrium can occur by salt formation, the alkylaminocompounds (II) are found to be more stable

than the corresponding iminocompounds (I). Consequently, the pH of the reaction medium determines the proportion in which the products I and II are obtained.

EXPERIMENTAL

2-Methylaminothiazoline-4-one. 4.5 g (0.05 mole) of N-methylthiourea, 8.2 g (0.1 mole) of sodium acetate and 4.7 g (0.05 mole) of chloroacetic acid were dissolved in 15 ml of water. The solution was refluxed for 45 min. On cooling, 3.7 g of 2-methylaminothiazoline-4-one precipitated. The mother liquor was evaporated to dryness and the residue boiled with chloroform. From the chloroform solution a further crop of 1.1 g was obtained after evaporation. Total yield: 4.8 g (74 %). The substance was recrystallized from water. M.p. 196–199°C. (Found: C 37.0; H 4.9; N 21.4; S 24.6. Calc. for $C_4H_8N_2OS$ (130.1): C 36.9; H 4.6; N 21.5; S 24.7).

One, one and a half and two equivalents of sodium acetate were used without any significant increase in yield.

2-Imino-3-methylthiazolidine-4-one. 725 g (8.05 moles) of N-methylthiourea were added to 1700 ml of water in a three-necked round-bottomed flask. The mixture was warmed to 45°C and 760 g (8.05 moles) of chloroacetic acid, dissolved in 1000 ml of water, were added through a dropping funnel. The reaction temperature was kept at 50°C. After complete addition, the solution was warmed at 50°C for 35 min. The solution was then cooled and neutralized. 855 g (81.6 %) of 2-imino-3-methylthiazolidine-4-one precipitated. M.p. 140–143°C. Recrystallization from water did not raise the melting point. (Found: C 37.0; H 4.8; N 21.3; S 24.6. Calc. for $C_4H_8N_2OS$ (130.1): C 36.9; H 4.6; N 21.5; S 24.7).

Thin layer chromatography of the reaction solution showed that traces of 2-methylaminothiazoline-4-one were present.

By increasing the reaction temperature to 100°C, the yield of 2-imino-3-methylthiazolidine-4-one was lowered as a result of hydrolysis of this substance to 3-methylthiazolidine-2,4-dione. M.p. 36–38°C. (Found: C 36.8; H 3.8; N 10.6. Calc. for $C_4H_6N_2O_2S$ (131.1): C 36.6; H 3.8; N 10.7; S 24.5).

S-Carboxymethyl-N-methylisothiourea. 4.7 g (0.05 mole) of chloroacetic acid, 4.5 g of N-methylthiourea and 6.2 g (0.075 mole) of sodium acetate were added to 15 ml of water in a beaker. After 30 min the temperature had risen to 30°C and all substances had dissolved. After 3 h 7.8 g of a white substance had precipitated. This was treated with 100 ml of warm ethanol and 5.6 g of S-carboxymethyl-N-methylisothiourea remained undissolved. M.p. 191–192°C (decomp.). (Found: C 32.4; H 5.6; N 19.0; S 21.7. Calc. for $C_4H_8N_2O_2S$ (148.1): C 32.4; H 4.6; N 18.9; S 21.7).

2-Ethylaminothiazoline-4-one. 10.4 g (0.1 mole) of N-ethylthiourea and 12.3 g (0.15 mole) of sodium acetate were dissolved in 40 ml of water. 9.45 g (0.1 mole) of chloroacetic acid, dissolved in 10 ml of water, were added dropwise to the solution, which was refluxed for 45 min. On cooling, 9.2 g (64 %) of 2-ethylaminothiazoline-4-one precipitated, which was recrystallized from benzene. M.p. 143.5–145.5°C. (Found: C 41.7; H 5.3; N 19.5; S 22.1. Calc. for $C_5H_8N_2OS$ (144.2): C 41.6; H 5.6; N 19.4; S 22.3).

2-Ethylaminothiazoline-4-one and 3-ethyl-2-iminothiazolidine-4-one. 10.4 g (0.1 mole) of N-ethylthiourea and 9.5 g (0.1 mole) of chloroacetic acid were dissolved in 30 ml of water. The solution was warmed at 50°C for 45 min. After cooling, the solution was neutralized giving 8.8 g (61 %) of 3-ethyl-2-iminothiazolidine-4-one. After recrystallization from toluene it had m.p. 33–35.5°C. (Found: C 41.7; H 5.8; N 19.4; S 22.2. Calc. for $C_5H_8N_2OS$ (144.2): C 41.6; H 5.6; N 19.4; S 22.3).

The mother liquor was shaken with ether to extract the remaining 3-ethyl-2-iminothiazolidine-4-one. Ethanolic hydrogen chloride solution was added to the ether solution and 1.8 g (10 %) of the hydrochloride of 3-ethyl-2-iminothiazolidine-4-one precipitated. M.p. 227°C (decomp.). (Found: C 33.3; H 5.0; Cl 20.3; N 15.3; S 17.5. Calc. for $C_5H_8ClN_2OS$ (180.7): C 33.2; H 5.0; Cl 19.7; N 15.5; S 17.8).

The mother liquor was then extracted with chloroform to dissolve the 2-ethylaminothiazoline-4-one. The chloroform solution was evaporated leaving 3 g (21 %) of 2-ethylaminothiazoline-4-one which was recrystallized from benzene. M.p. 143–145°C.

On further cooling of the mother liquor 0.55 g of N-ethyl-S-carboxyethylisothiurea precipitated. After recrystallization from water it had m.p. 197–198°C (decomp.). (Found: C 37.2; H 6.0; N 17.1; S 19.7; Calc. for $C_5H_{10}N_2O_2S$ (162.1): C 37.0; H 6.2; N 17.3; S 19.8.

2-Propylaminothiazoline-4-one. 11.8 g (0.1 mole) of N-propylthiourea and 12.3 g of sodium acetate were dissolved in 25 ml of water. 9.45 g (0.1 mole) of chloroacetic acid, dissolved in 35 ml of water were dropwise added to the solution which was then refluxed for 45 min. On cooling, 7.9 g (50 %) of 2-propylaminothiazoline-4-one precipitated. M.p. 89–93°C. Recrystallization from toluene did not raise the melting point. (Found: C 45.4; H 6.2; N 17.5; S 20.0. Calc. for $C_6H_{10}N_2OS$ (158.2): C 45.5; H 6.4; N 17.7; S 20.3).

Only traces of 2-imino-3-propylthiazolidine-4-one could be detected by thin layer chromatography.

2-Propylaminothiazoline-4-one and 2-imino-3-propylthiazolidine-4-one. 11.8 g (0.1 mole) of N-propylthiourea and 9.45 g (0.1 mole) of chloroacetic acid, were dissolved in 30 ml of water. The solution was warmed at 50°C for 45 min. On cooling, 5.5 g (28.3 %) of the hydrochloride of 2-imino-3-propylthiazolidine-4-one precipitated. This substance decomposed above 200°C. (Found: C 37.1; H 5.5; Cl 18.4; N 14.5; S 16.6. Calc. for $C_6H_{11}ClN_2OS$ (194.7): C 37.0; H 5.7; Cl 18.2; N 14.4; S 16.4).

The free base was obtained by dissolving the salt in water, neutralizing and extracting with ether. The ether solution was evaporated. Distillation of the residue afforded 2-imino-3-propylthiazolidine-4-one. B.p. 78°C/0.3 torr. (Found: C 45.7; H 6.3; N 17.8; S—. Calc. for $C_6H_{10}N_2OS$ (158.2): C 45.5; H 6.4; N 17.7; S 20.3).

A further crop of 2-imino-3-propylthiazolidine-4-one was obtained by neutralizing the mother liquor and shaking it with ether. By addition of ethanolic hydrogen chloride to the ether solution 6.7 g (34.4 %) of the hydrochloride of 2-imino-3-propylthiazolidine-4-one precipitated. Thin layer chromatography showed that this product was contaminated with 2-propylaminothiazoline-4-one.

The mother liquor was then evaporated to dryness and the residue boiled with chloroform. Evaporation of the chloroform afforded 2.9 g (14.9 %) of 2-propylaminothiazoline-4-one.

2-Isopropylaminothiazoline-4-one. Method A. 7.1 g (0.06 mole) of N-isopropylthiourea, 5.7 g (0.06 mole) of chloroacetic acid and 7.4 g (0.09 mole) of sodium acetate were dissolved in 25 ml of water. The solution was warmed at 90°C for 1.5 h. On cooling, 6.0 g (63.3 %) of 2-isopropylaminothiazoline-4-one precipitated. M.p. 144.5–152°C. Recrystallization of the substance from ethyl acetate raised the melting point to 151.5–154°C. (Found: C 45.6; H 6.3; N 17.7; S 20.3. Calc. for $C_6H_{10}N_2OS$ (158.2): C 45.5; H 6.4; N 17.7; S 20.3).

Method B. 7.8 g (0.066 mole) of N-isopropylthiourea and 6.25 g (0.066 mole) of chloroacetic acid were dissolved in 25 ml of water. The solution was refluxed for 65 min. After cooling, the water solution was neutralized giving 4.7 g (45 %) of 2-isopropylaminothiazoline-4-one. M.p. 146–150.5°C. Recrystallization from ethyl acetate raised the melting point to 152–154°C. A further 3.6 g (34.5 %) were obtained by extracting the mother liquor with chloroform and evaporating the chloroform solution. Neither method A nor method B gave any 2-imino-3-isopropylthiazolidine-4-one.

S-Carboxymethyl-N-isopropylisothiurea. 3.5 g (0.03 mole) of N-isopropylthiourea, 2.9 g (0.03 mole) of chloroacetic acid and 3.7 g (0.045 mole) of sodium acetate were added to 15 ml of water in a beaker. No temperature rise was observed and there was undissolved material present all the time. After 3 days the mixture was filtered affording 4.7 g of a white substance which was treated with 200 ml of warm methanol. 3.5 g of S-carboxymethyl-N-isopropylthiourea remained. M.p. 182.5–184°C (decomp.). (Found: C 41.0; H 6.7; N 16.0; S 18.2. Calc. for $C_6H_{12}N_2O_2S$ (176.1): C 40.9; H 6.8; N 15.9; S 18.2).

Rearrangement of 2-methylaminothiazoline-4-one to 2-imino-3-methylthiazolidine-4-one. 0.5 g (3.85 mmoles) of 2-methylaminothiazoline-4-one was dissolved in 50 ml of ethanol and 6 ml of 5 M ethanolic hydrogen chloride. The solution was refluxed for 3 h. On cooling, the hydrochloride of 2-imino-3-methylthiazolidine-4-one precipitated. The free base was isolated by dissolving the hydrochloride salt in water and neutralizing the solution. The substance was identified by its IR-spectrum.

The rearrangement in acid medium of 2-ethylamino- and 2-propylaminothiazoline-4-one to 3-ethyl-2-iminothiazolidine-4-one and 2-imino-3-propylthiazolidine-4-one, respectively, could be affected in the same way. However, 2-isopropylaminothiazoline-4-one failed to rearrange despite a reaction time of 23 h.

Rearrangement of 2-imino-3-methylthiazolidine-4-one to 2-methylaminothiazoline-4-one.

(a) 0.5 g (3.85 mmoles) of 2-imino-3-methylthiazolidine-4-one was dissolved in a methanolic solution containing 3.85 mmoles of sodium methoxide. The solution was refluxed for 1 h. After cooling, the solution was neutralized giving 0.3 g of 2-methylaminothiazoline-4-one, which was identified by its IR-spectrum. Thin layer chromatography of the reaction solution showed that all 2-imino-3-methylthiazolidine-4-one had rearranged.

b) 2.6 g (0.02 mole) of 2-imino-3-methylthiazolidine-4-one and 3.3 g (0.04 mole) of sodium acetate were dissolved in 20 ml of water. The water solution was refluxed for 3 h. Thin layer chromatography of the reaction mixture showed that most of the 2-imino-3-methylthiazolidine-4-one had rearranged to 2-methylaminothiazoline-4-one.

c) 2.6 g (0.02 mole) of 2-imino-3-methylthiazolidine-4-one were dissolved in 20 ml of water and refluxed for 5 h. Samples were taken out after 1, 2, 3, 4 and 5 h. Thin layer chromatography revealed that some rearrangement of 2-imino-3-methylthiazolidine-4-one to 2-methylaminothiazoline-4-one had taken place. In addition to the latter compound S-carboxymethyl-N-methylisothiourea (III) was also isolated from the reaction mixture.

The rearrangement of 3-ethyl-2-iminothiazolidine-4-one and 2-imino-3-propylthiazolidine to 2-ethylamino- and 2-propylaminothiazoline-4-one, respectively, in the presence of sodium methoxide was studied in the same way.

Thin layer chromatography. The reactions and products were examined by thin layer chromatography on Silica gel GF 254. 2-Alkylaminothiazoline-4-one (II), 2-imino-3-alkylthiazolidine-4-ones (I) and 3-alkylthiazolidine-2,4-diones separated well when chromatographed in 2-butanol-formic acid-water (15:3:2). The spots were located in UV-light.

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