AZOLIDINE-4-THIONES - THEIR DERIVATIVES AND ANALOGY IX.* STUDY OF THE SYNTHESIS OF SOME 1,3-THIAZAN-4-ONES

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The conditions for the synthesis of thiazan-2,4-diones by the condensation of β -chloropropionic, β -chloro- and β -bromobutyric, and β -chloroisobutyric acids with thiourea in acetic anhydride, water, and formic and acetic acids were studied. S-Guanylmercaptohydracrylic acids, 2-imino- and 2-acetyliminothiazan-4-ones and their hydrochlorides, and thiazan-2,4-diones were isolated. Their interconversions were studied.

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1,3-Thiazan-2,4-diones are chemically inert, but their activation by sulfuration to thiazan-4-thiones [1] and thiazan-2,4-dithiones [2] makes them valuable starting compounds for the preparation of various 1, 3-thiazan derivatives [3]. In this connection, we investigated the synthesis of unsubstituted thiazan-2,4-dione (VI) and its homologs (XI and XII).



 $\begin{array}{c} \mathbf{I} \ \mathbf{R}=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}\cdot\mathbf{H}\mathbf{C}\mathbf{I}; \ \mathbf{II} \ \mathbf{R}=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{HII} \ \mathbf{R}=\mathbf{C}\mathbf{H}_3, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{IV} \ \mathbf{R}=\mathbf{R}'=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}\cdot\mathbf{H}\mathbf{C}\mathbf{I}; \\ \mathbf{V} \ \mathbf{R}=\mathbf{R}'=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{VI} \ \mathbf{R}=\mathbf{R}'=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{C}\mathbf{O}\mathbf{C}\mathbf{H}_3, \ \mathbf{H}=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{VI} \ \mathbf{R}=\mathbf{R}'=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{VI} \ \mathbf{R}=\mathbf{R}'=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{C}\mathbf{O}\mathbf{C}\mathbf{H}_3, \ \mathbf{H}=\mathbf{H}, \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{X}=\mathbf{N}; \ \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{X}=\mathbf{N}; \ \mathbf{X}=\mathbf{N}\mathbf{H}; \mathbf{X}=\mathbf{N}\mathbf{H}; \ \mathbf{X}=\mathbf{N}\mathbf{H}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{N} = \mathbf{N}; \mathbf{N}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \ \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{N}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{N}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{N}; \mathbf{N}=\mathbf{N}; \mathbf{N}; \mathbf{$

In a search for the optimum conditions for the synthesis of VI, which was first obtained from xanthogenamide and iodopropionic acid [4], we decided upon the condensation of the readily accessible β -chloropropionic acid with thiourea in water, or acetic or formic acids, rejecting the reaction in acetic anhydride [5], since the yield of VI is only 22%. Other methods [6-8] are also inefficient.

By changing the medium and the condensation time, we obtained various related compounds (I-XIII) of similar composition that also had a number of similar properties (melting points, color, and crystal form); this made their identification difficult. The formation of picrolonates, which is peculiar only to imino compounds II and V, is useful in this case. The principal transformations are presented in the scheme. It turned out that acetic anhydride is necessary for the preparation of 2-iminothiazans IV and V and acetyl-iminothiazans VII and VIII [7,9]. At the same time, the best medium for the synthesis of dione VI and its homolog (XI) proved to be 85% formic acid, while water was the best medium for dione XII (85% yield); VI and XI are also formed in reasonable yields (44 and 47%) in water. When β -bromopropionic acid and thiourea are used, the imino group is not hydrolyzed, and dione VI is not obtained. (See scheme on following page.) This is in agreement with the literature data [5,10], but is not general in character, since dione XII is formed in high yield with both β -chloro- and β -bromobutyric acids. In formic acid, the transition from chlorine to bromine raises the yield of XII from 64 to 76%, but reduces it from 88 to 72% in water. It was also noted that XII is formed more readily from β -chlorobutyric acid than XI is formed from β -chlorobutyric acid; i.e., a methyl group in the α -position relative to the carboxyl group hinders the cyclization by weakening (by the +I effect) the electrophilicity of the carboxyl carbon. The conversion of VIII to I dem-

* See [14] for communication VIII.

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onstrated that a dione is not always formed during acid hydrolysis and that the possibility of ring opening should be taken into account.

EXPERIMENTAL

<u>S-Guanylmercaptohydracrylic Acid (II) [7,12,13].</u> A mixture of 6.6 g (0.02 mole) of β -chloropropionic acid, 6.0 g of thiourea, and 6 ml of water was heated until an exothermic reaction commenced and was then poured into a dish and dried in a vacuum desiccator. Crystallization from acetic acid-dioxane gave snow-white, rhombic plates of hydrochloride I with mp 139-140 deg. Neutralization with 25% aqueous so-dium acetate gave 7.8 g (88%) of oval, acicular plates of II with mp 173 deg (from water). Compound II is also formed in formic or acetic acids or from bromopropionic acid in water. Found: N 18.96; S 21.34%. C₄H₈N₂O₂S. Calculated: N 18.91; S 21.34%. The picrolonate was obtained in acetic acid as golden "compass needles" with mp 203-205 deg (dec., from methanol).

<u>S-Guanyl- β -mercaptobutyric Acid (III)</u>. This was similarly obtained in 45% yield from β -chlorobutyric or β -bromobutyric acid and thiourea. The square plates melted at 182 deg (from water). Found: N 16.88; S 20.17%. C₅H₁₀N₂O₂S. Calculated: N 17.26; S 19.77%.

<u>2-Imino-1,3-thiazan-4-one (V)</u>. A mixture of 3 ml of acetic anhydride, 0.04 mole of chloropropionic acid, and 0.04 mole of thiourea was heated for 1 h. The hot mixture was diluted with ethanol and heated, and 0.46 g of NH₄Cl was removed by filtration. The crystals that precipitated after cooling were treated with boiling dichloroethane to give 3.6 g (60%) of hydrochloride IV. Recrystallization from acetic acid gave polyhedrons with mp 194-198 deg. A 1-g sample of IV was introduced into a saturated aqueous NaHCO₃ solution to give 0.55 g (64%) of V with mp 168 deg (from methanol). Found: N 21.58; S 24.37%. C₄H₆N₂OS. Calculated: N 21.52; S 24.62%. The picrolonate was obtained as pale yellow crystals with mp 209 deg that were slightly soluble in methanol.

<u>2-Imino-5-methylthiazan-4-one (X)</u>. Hydrochloride IX was obtained like IV from thiourea and β - chloroisobutyric acid (0.04 mole each) in 43% yield and had mp 187-190 deg (from ethanol). Neutralization of 0.5 g of IX gave 0.32 g (74%) of X. Recrystallization from dichloroethane gave colorless rectangular plates with mp 165 deg. Found: N 19.78; S 21.87%. C₄H₈ON₂S. Calculated: N 19.40; S 22.22%.

2-Imino-6-methylthiazan-4-one (XIII). This was obtained by refluxing a mixture of 0.04 mole each of β -chlorobutyric acid and thiourea in 3 ml of acetic anhydride for 2 h. Addition of excess ethanol to the cooled reaction solution precipitated 1.46 g (23.3%) of long plates with mp 218 deg (from methanol). The product was soluble in hot water and ethanol. Found: N 19.60; S 22.52%. C₅H₈N₂OS. Calculated: N 19.40; S 22.23%.

 $\frac{2-\text{Acetyliminothiazan-4-one (VIII). A)}{\text{ml of acetic anhydride. After 20 min, the solution was cooled, and the precipitate was filtered and washed with dichloroethane to give 2.5 g (75%) of oval plates of VII with mp 163-167 deg (from acetic acid) gave colorless prisms of VIII with mp 199-200 deg. Substance VIII did not form a picrolonate.$

B) Crystallization of II from acetic anhydride gave 65-70% of VIII. Found: N 16.12; S 18.89%. C_6H_8 -N₂O₂S. Calculated: N 16.2; S 18.62%.

Evaporation of a solution of VIII in 15% HCl gave 60% of I.

1,3-Thiazan-2,4-diones (VI, XI, and XII). A mixture of 0.1 mole of β -halocarboxylic acid, 0.13 mole of thiourea, and 10 ml of 85% formic acid (or 7.5 ml of water or 6 ml of glacial acetic acid) was refluxed for 5-6 h and cooled. The precipitate was filtered and washed with a small amount of water to give 42% of VI in formic acid (mp 161-162 deg); 55% of XI from β -chloroisobutyric acid in formic acid [mp 111 deg (from water)]. Found: N 9.85; S 22.07%. C₅H₇NO₂S. Calculated: N 9.65; S 22.09%. XII was obtained from β -chlorobutyric acid in formic acid (76% yield), and in formic acid (64% yield). It was also obtained from β -bromobutyric acid in formic acid (76% yield) and in water (72% yield). The product was obtained as rectangular plates with mp 129 deg (from water and then from methanol). Found: N 9.67; S 22.17%. C₅H₇NO₂S. Calculated: N 9.65; S 22.09%.

LITERATURE CITED

- 1. A. P. Grishchuk, G. I. Roslaya, and S. N. Baranov, Khim. Geterotsikl. Soedin., 661 (1967).
- 2. A. P. Grishchuk and G. I. Roslaya, Khim. Geterotsikl. Soedin., 537 (1966).
- 3. G. I. Roslaya, Khim. Geterotsikl. Soedin., 438 (1968).
- 4. N. Langlet, Ber., 24, 3848 (1891).
- 5. E. V. Vladzimirskaya and N. M. Turkevich, Dokl. Akad. Nauk Ukr. SSR, 80 (1962).
- 6. E. V. Vladzimirskaya, Ukr. Khim. Zh., 30, 941 (1964).
- 7. E. V. Vladzimirskaya and Yu. M. Pashkevich, Zh. Obshch. Khim., 33, 3149 (1963).
- 8. S. Wintrop and G. Garin, Can. J. Chem., <u>36</u>, 879 (1958).
- 9. A. L. Misra, J. Org. Chem., <u>23</u>, 897 (1958).
- 10. E. Campaigne and M. Wani, J. Org. Chem., 29, 1715 (1964).
- 11. R. Taborsky, J. Org. Chem., 23, 1779 (1959).
- 12. R. Andreasch, Monatsh., 6, 821 (1885).
- 13. V. A. Vasilevskii, V. M. Fedoseev, and A. V. Silaev, Zh. Obshch. Khim., 32, 2269 (1962).
- 14. A. P. Grishchuk and I. D. Komaritsa, Data of the Second Scientific-Technical Conference on Chemistry [in Russian], Vol. 2, L'vov (1969), p. 22.