Chemistry of 2,4-Dioxothiazolidine. II. Ammonolysis of 2,4-Dioxothiazolidine and its Derivatives

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It is found that the ammonolysis of 2,4-dioxothiazolidine gives 5-amino-2,3-dithiacaprohydroxamic acid, while 3-phenyl-2,4-dioxothiazolidine is transformed in glycolic acid N-(2-amino-1-hydroxyethyl)-anilide. The product of ammonolysis of 3-(3,4-dichlorophenyl)-2,4-dioxothiazolidine proved to be 3,4-dichlorophenylcarbamide.

Many derivatives of 2,4-dioxothiazolidine are known as substances with bacterostatic, bactericide, insecticide, local anesthetic, antispasmat or anticancer properties. The effect of 2,4-dioxothiazolidine derivatives on Mycobacterium tuberculosis is specially investigated. In our complex study of 2,4-dioxothiazolidine chemistry we directed our attention to the behaviour of this type of compounds to ammonia. There is the communication of Erlemann and Knetsch, where the reaction between 2,4-dioxothiazolidine (I) and ammonia or amines is treated. The authors reported that they obtained thioglycolic acid (II) and their amide (III) as a result of the reaction between 2,4-dioxothiazolidine and ammonia.

\[
\text{S-CH}_2\text{O}_2\text{C} \xrightarrow{2\text{NH}_3} \text{HS-CH}_2\text{COOH} + \text{HS-CH}_2\text{CONH}_2
\]

In our experiments we have found some differences which do not in agreement with the quoted results. Therefore, we studied the reaction in aqueous medium between (a) 2,4-dioxothiazolidine (I), (b) 3-phenyl-2,4-dioxothiazolidine (IV), and (c) 3-(3,4-dichlorophenyl)-2,4-dioxothiazolidine (V).

The reaction between ammonia and 2,4-dioxothiazolidine and their mentioned derivatives is carried out by heating the suspended compound in 25% aqueous ammonia under the reflux condenser on the water bath. The compounds are very easily dissolved during heating. In the ammonolyses of 3-substituted derivatives at the end of reaction, crystalline products are spontaneously separated. The reaction product of 2,4-dioxothiazolidine must be isolated by azeotropic distillation.

The infrared spectra of all three products were essentially different. None of isolated compounds was thioglycolic acid or its amide, what is opposite to

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communication of Erlemann and Knetsch. On the basis of IR, MS spectra and other characteristics we found that each examined derivative reacted with ammonia on its own way resulting in different products.

2,4-Dioxothiazolidine (I) in the ammonolysis is transformed in 5-amino-2,3-dithiacaprohydroxamic acid (VI). It could be proposed an opening of heterocyclic ring with fusion of two fragments followed by an oxido-reduction.

\[
\begin{align*}
\text{I} & \quad \text{NH}_2\text{OH} \\
S\text{-CH}_2\text{CO-NHOH} & \quad S\text{-CH}_2\text{-CH}_2\text{NH}_2
\end{align*}
\]

3-Phenyl-2,4-dioxothiazolidine (IV) in the reaction with ammonia is transformed in glycolic acid N-(2-amino-1-hydroxyethyl)-anilide (VII). It could be proposed an opening of the heterocyclic ring in two different ways, followed by extrusion of sulfur, reduction and combination of fragments.

\[
\begin{align*}
\text{IV} & \quad \text{NH}_2\text{OH} \\
S\text{-CH}_2\text{CO-NHOH} & \quad S\text{-CH}_2\text{-CH}_2\text{NH}_2
\end{align*}
\]

3-(3,4-Dichlorophenyl)-2,4-dioxothiazolidine (V) in the ammonolysis gave 3,4-dichlorophenylcarbamide (VIII), which is formed by the degradation of the heterocyclic ring and subsequent reaction between the intermedier fragment and ammonia.

The comparison of these three results of the ammonolysis of 2,4-dioxothiazolidine and its derivatives indicates that the flow of the ammonolysis and the type of the final product in the investigated cases depends not only upon the heterocyclic ring but also upon the substituent in the position >3× (e.g. on the nitrogen), which has a substantive influence on the whole reaction.

**EXPERIMENTAL**

The structures of all the products were established by elemental analysis, molecular weight determination by mass spectrometry, and by spectral data. The infrared spectra were measured with a Perkin-Elmer spectrophotometer Model 437. The
mass spectra were taken with a Varian MAT CH 5 apparatus. The melting points are uncorrected.

The Ammonolysis of 2,4-Dioxothiazolidine (I)

In a 100 ml flask, fitted with reflux condenser, 350 mg (0.003 mol) of 2,4-dioxothiazolidine (origin Fluka AG) is suspended in 15 ml of aqueous ammonia (25%) and heated 3 h in the water bath. Suspended compound is soon dissolved. After heating the corresponding amount of ethanol and benzene is added and water is removed by azeotropic distillation. Remaining oil is transferred in a Petri-dish and in short time crystallised 5-amino-2,3-dithiacaproyl hydroxamic acid (VI). The crystals are carefully washed with absolute ethanol. Yield 100 mg, m. p. 167–8 °C.

Anal. C₄H₁₀N₂O₂S₂ (182.2) calc'd.: C 26.36; H 5.53; N 15.37%  
found: C 26.11; H 5.46; N 15.42%

Characteristic IR bands: 3220–2800, 1580–1560, 1455, 1430, 1380–1370, 1210 cm⁻¹.  
MS: 182 (M⁺), 164, 137, 119, 109, 79 m/e.

The Ammonolysis of 3-Phenyl-2,4-dioxothiazolidine (IV)

In a 50 ml flask, fitted with reflux condenser, 385 mg (0.002 mol) of 3-phenyl-2,4-dioxothiazolidine (IV) is suspended in 15 ml of aqueous ammonia (25%) and heated 3 h in the water bath. The suspension is very soon dissolved and only a few minutes after heating crystals started to separate. Complete amount of crystals is separated after cooling. The crystals of glycolic acid N-(2-amino-1'-hydroxyethyl)-anilide (VII) are carefully washed with absolute ethanol. Yield 80 mg, m. p. 148 °C.

Anal. C₁₀H₁₄N₂O₃ (210.2) calc'd.: C 57.13; H 6.71; N 13.33%  
found: C 56.82; H 6.81; N 13.65%

Characteristic IR bands: 3440–3420, 3340–3270, 3220, 3100, 3060, 3040, 2890, 1670–1640, 1615, 1590, 1565–1530, 1500, 1450, 1355, 1305, 1290, 1265–1245, 1150, 1130–1110, 1075, 1035, 905, 860, 775, 750 cm⁻¹. MS: 210 (M⁺), 180, 165, 134, 117, 93, 77 m/e.

The Ammonolysis of 3-(3,4-Dichlorophenyl)-2,4-dioxothiazolidine (V)

Ammonolysis of 390 mg (0.1115 mol) of 3-(3,4-dichlorophenyl)-2,4-dioxothiazolidine (V) was carried out in the same way. The reaction yielded 110 mg of 3,4-dichlorophenylcarbamide (VIII), m. p. 158 °C. The melting point is in agreement with the published data.

Anal. C₇H₆N₂OCl₂ (204.9) calc'd.: C 41.00; H 2.95; N 13.67%  
found: C 39.69; H 2.78; N 13.40%

Characteristic IR bands: 3495, 3430, 3340–3270, 2920, 2850, 1680–1640, 1610, 1580, 1540–1530, 1475, 1395, 1382, 1340, 1125, 1025 cm⁻¹. MS: 204 (M⁺), 186, 161, 145, 133, 125, 75 m/e.

REFERENCES
SAŽETAK

Kemija 2,4-dioksotiazolidina. II. Amonoliza 2,4-dioksotiazolidina i njegovih derivata

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Nađeno je da se amonolizom 2,4-dioksotiazolidina dobija 5-amino-2,3-ditiakaprohidroksamska kiselina, dok 3-fenil-2,4-dioksotiazolidin prelazi u N-(2-amino-1-oksietil)-anilid glikolne kiseline. Proizvod amonolize 3-(3-4-dihlorfenil)-2,4-dioksotiazolidina je 3,4-dihlorfenilkarbamid.

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