INVESTIGATION OF THE REACTIVITIES AND TAUTOMERISM OF AZOLIDONES.

52.* SYNTHESIS OF 2- AND 3-ALLYL-SUBSTITUTED PSEUDOTHIOHYDANTOINS

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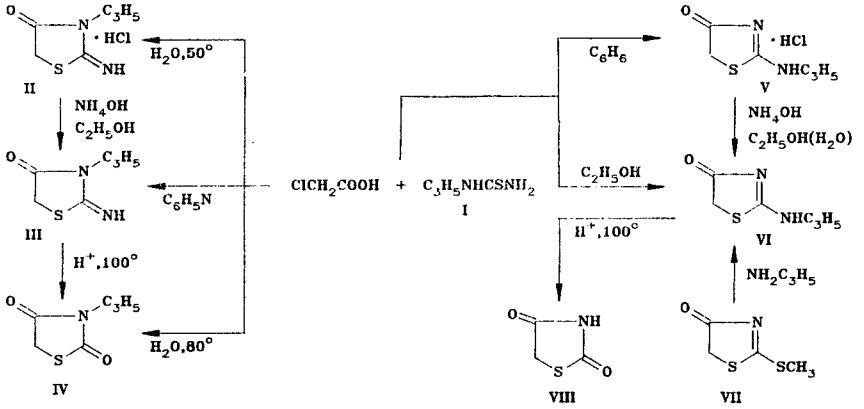
The effect of the solvent on the cyclization of N-allylthiourea with monochloroacetic acid was studied; the structures of the products were proved by alternative synthesis, as well as by acidic hydrolysis.

It is known that the condensation of N-alkylthiourea with monochloroacetic acid may proceed with the formation of two isomers, viz., the alkylated pseudothiohydantoin 2-alkylaminothiazolin-4-one and 2-imino-3-alkylthiazolidin-4-one [2]. A determining effect on the ratio of the isomeric products is exerted by the pH of the medium, which is regulatable by the addition of catalytic amounts of sodium acetate [3, 4]. As regards the reaction of N-allylthiourea (I) with monochloroacetic acid, the literature contains contradictory data [3-5], and for this reason we also studied it. Carrying out the cyclization reaction in polar (water) and nonpolar solvents leads to contradictory results. Thus in the case of condensation in water at 50°C one observes the formation of 2-imino-3-allythiazolidin-4-one (II), and base III was isolated by treatment of II with an alcohol solution of ammonia. An increase in the temperature of the reaction mixture to 80°C leads to 3-allylthiazolidine-2,4-dione (IV) [6] as a result of the hydrolysis of the imino group in the 2 position [4]. The cyclization of allylthiourea with monochloroacetic acid in anhydrous pyridine gives exclusively 2-imino-3-allylthiazolidin-4-one (III).



Condensation in benzene, chloroform, or dioxane leads to 2-allylamino-Δ^2-thiazolin-4-one hydrochloride (V); base VI was isolated by treatment of V with an alcohol or aqueous solution of ammonia. The structure of VI was confirmed by alternative synthesis from 2-methylmercaptothiazolin-4-one (VII) and allylamine, as well as by hydrolysis to 3-allylthiazolidin-2,4-dione (VIII) [4, 7]. The cyclization proceeds peculiarly in ethanol: 2-allylamine-Δ^2-thiazolidin-4-one (V) was isolated in the case of refluxing for 0.5 h, whereas in the case of refluxing for 3 h hydrochloride II was isolated, i.e., one observes V → II isomerization, which proceeds intramolecularly via a Claisen rearrangement [8].

*See [1] for Communication 51.

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EXPERIMENTAL

The UV spectra (10^{-5} M) were recorded with a Hitachi EPS-3T spectrophotometer. The IR spectra of mineral oil suspensions and KBr pellets were recorded with a Perkin–Elmer 283 spectrometer. Substances II-VIII were purified by two recrystallizations from suitable solvents. The individuality of the compounds was confirmed by chromatography on Silufol UV-254 plates in an acetone–hexane system (1:1).

2-Methylmercaptothiazolin-4-one (VIII) was obtained by the method in [9].

2-Imino-3-allylthiazolidin-4-one hydrochloride (II). A 10.4-g (0.11 mole) sample of monochloroacetic acid was added at 50°C to 11.6 g (0.1 mole) of allylthiourea in 20 ml of water, and the mixture was retained at this temperature for 12 h. The precipitate was removed by filtration and crystallized from acetic acid to give 15.6 g (81%) of a product with mp 189-191°C (176°C [4]). IR spectrum (thin layer): 1750 [$C_{(4)}O$]; 1672, 1570, 1500 cm^{-1} (C=C, C=N). UV spectrum (water), λ_{max} (log ε): 216 nm (4.02). Found: N 14.6; S 16.6%. $C_6H_8N_2OS$. HCl. Calculated: N 14.6; S 16.6%.

2-Imino-2-allylthiazolidin-4-one (III). A 10.4-g (0.11 mole) sample of monochloroacetic acid was added to 11.6 g (0.1 mole) of allylthiourea in 25 ml of anhydrous pyridine, and the mixture was refluxed for 6 h. The solvent was then removed by distillation, and the residue (oil) was fractionated *in vacuo* to give 3.1 g (20%) of a product with bp 116-117°C (4 mm). IR spectrum: 3280 (NH); 1710 (C=O); 1620, 1608 cm^{-1} (C=N, C=C). UV spectrum (ethanol), λ_{max} (log ε): 208 (4.10) and 213 nm (4.08). Found: N 17.9; S 20.5%. $C_6H_8N_2OS$. Calculated: N 18.0; S 20.5%.

2-Allylamino-Δ^2-thiazolin-4-one hydrochloride (V). A 10.3-g (0.15 mole) sample of monochloroacetic acid was added to 11.6 g (0.1 mole) of allylthiourea in 50 ml of benzene, and the mixture was stirred at 100°C for 2 h. The precipitate was removed by filtration and crystallized from acetic acid to give 15.5 g (80%) of a product with mp 142-143°C. IR spectrum: 1745 [$C_{(4)}$=O)]; 1650, 1575, 1530 cm^{-1} (C=C, C=N). UV spectrum (ethanol), λ_{max} (log ε): 233 (4.26) and 250 nm (shoulder, 4.07). Found: N 14.5; S 16.5%. $C_6H_8N_2OS \cdot HCl$. Calculated: N 14.5; S 16.6%.

The reaction in dioxane and chloroform was carried out similarly at 100°C, 50°C, and 20°C. The analytical data for the compound obtained were in agreement with the data for V.

2-Allylamino-Δ^2-thiazolin-4-one (VI). A) A 12.3-g (0.15 mole) sample of sodium acetate and 10.4 g (0.11 mole) of monochloroacetic acid were added to 11.6 g (0.1 mole) of allylthiourea in 50 ml of water, after which the mixture was heated with stirring at 95°C for 1.5 h. The precipitate was removed by filtration and recrystallized from isopropyl alcohol to give 12.5 g (80%) of a product with mp 102-103°C (103°C [5]). IR spectrum: 1700 [$C_{(4)}$=O]; 1645, 1600, 1528 cm^{-1} (C=C, C=N). UV spectrum (in ethanol), λ_{max} (log ε): 232 (4.28) and 247 nm (shoulder, 4.09). Found: N 18.1; S 20.4%. $C_6H_8N_2OS$. Calculated: N 18.0; S 20.5%.

The reaction was carried out similarly in ethanol, dioxane, benzene, and chloroform. The analytical data and the physicochemical characteristics of the product were in agreement with those for VI. The result did not change when equimolar amounts of pyridine were used in place of sodium acetate.

B) A 0.6-g (0.01 mole) sample of allylamine was added to a solution of 1.6 g (0.01 mole) of 2-methylmercapto-Δ^2-thiazolin-4-one (VIII) in 30 ml of chloroform, and the mixture was heated with constant stirring at 50°C for 1.5 h. The solvent was removed by vacuum distillation, and the residue was recrystallized from isopropyl alcohol.

3-Allylthiazolidin-2,4-dione (IV). A) A 10.4-g (0.11 mole) sample of monochloroacetic acid was added to 11.6 g (0.1 mole) of allylthiourea in 50 ml of distilled water, after which the mixture was heated with stirring at 85°C for 1 h. The oil was separated and fractionated to give 9.6 g (61%) of a product with bp 100-101°C (3 mm) [130°C (12 mm) [7]]. IR spectrum: 1746 [$C_{(2)}$=O)] and 1700 cm^{-1} [$C_{(4)}$=O)]. UV spectrum (ethanol), λ_{max} (log ε): 224 (3.58) and 280 nm (shoulder, 2.40). Found: N 8.9; S 20.5%. $C_6H_7NO_2S$. Calculated: N 8.9; S 20.4%.

B) A 1.5-g (0.01 mole) sample of III was refluxed in 10 ml of 1 N HCL for 15 min, after which the oil was separated and fractionated to give 1.1 g (70%) of the product.

Thiazolidin-2,4-dione (VII). A 10-ml sample of concentrated HCl was added to 1.6 g (0.01 mole) of VI, and the mixture was refluxed with stirring for 2 h. The precipitate was removed by filtration and recrystallized from water to give 0.9 g (81%) of a compound with mp 124-125°C (123-125°C [6]).

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N- AND O-CARBAMOYL AND THIOCARBAMOYL DERIVATIVES OF β-LACTAM ANTIBIOTICS

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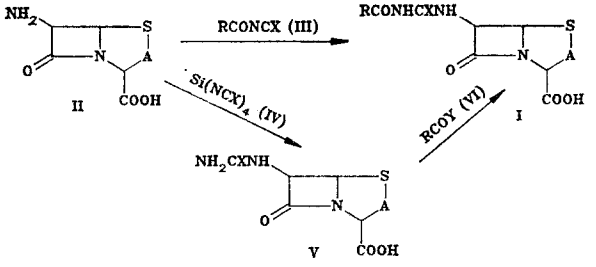
New N-acylureido and N-acylthioureido derivatives of β-lactam antibiotics were obtained by the reaction of 6-ureido and 6-thioureidopenicillanic and 7-thioreidodeacetoxycephalosporanic acids with acyl halides of carboxylic acids and benzoyl isocyanate. 6-Carbamoylhydroxypenicillanic acid, 6-thiocarbamoylhydroxypenicillanic acid, and its trichloroethyl ester were obtained by treatment of 6-α-hydroxypenicillanic acid and its trichloroethyl ester with isocyanatosilanes with subsequent hydrolysis of the N-silylcyanato groups.

The introduction into the side chain of penicillin and cephalosporin of an N-acylcarbamoyl or N-acylthiocarbamoyl group is a widespread method for the modification of β-lactam antibiotics, which is designed for the intensification of their antibacterial properties [1-3]. The chief method for the preparation of compounds I of this type with an acylureido group directly adjacent to the heterocyclic ring of the antibiotics is the reaction of 6-aminopencillanic or 7-aminocephalosporanic acid (II) with acyl isocyanates or acyl isothiocyanates (III) [1, 2]. The development of a method for the carbamoylation of amino acids II with tetraisocyanatosilane and tetraisothiocyantosilane IV [4] was accomplished by another accessible method for the synthesis of I based on the reaction of ureido derivatives V with chlorides of carboxylic acids, isocyanates, or other acylating agents VI.

This method was used in the present research for the synthesis of new ureido and thioureido derivatives of pencillin and deacetoxycephalosporin.



I, II, V A=$C(CH_3)_2$, CH_2CCH_3=, $CH_2C(CH_2OCOCH_3)$=; I, III—V X=O, S; VI Y=Cl, Br, NCO; I, III, VI R=C_6H_5, $C_6H_5CH_2$, 2-furyl

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