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UREIDO AND THIOUREIDO DERIVATIVES OF β-LACTAM ANTIBIOTICS

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6-Ureido- and 6-thioureidopenicillanic acids and 7-ureido- and 7-thioureidodeacetoxycephalosporanic acids were obtained by the reaction of 6-aminopenicillanic acid and 7-aminodeacetoxycephalosporanic acids with tetraisocyanatosilane or tetraisothiocyanatosilane. N-Carbamoyl derivatives of ureido- and thioureidopenicillanic acids were isolated after repeated treatment of 6-ureido- and 6-thioureidopenicillanic acids with the indicated isocyanatosilanes.

Ureido and thioureido derivatives of β-lactam antibiotics Ia-c are usually obtained by the reaction of amino acids with alkali metal isocyanates or thiocyanic acid [1-5].

7-Ureidodeacetoxycephalosporanic acid (Id), the ureido group in which is directly adjacent to the β-lactam ring, has also been synthesized by means of potassium cyanate [6]. However, the corresponding penicillin analog Ie could not be obtained by this method, since modification of the amino group in aqueous solution at elevated temperatures is accompanied by destruction of the β-lactam ring of the heterocyclic amino acids.

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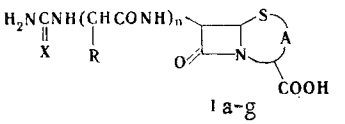


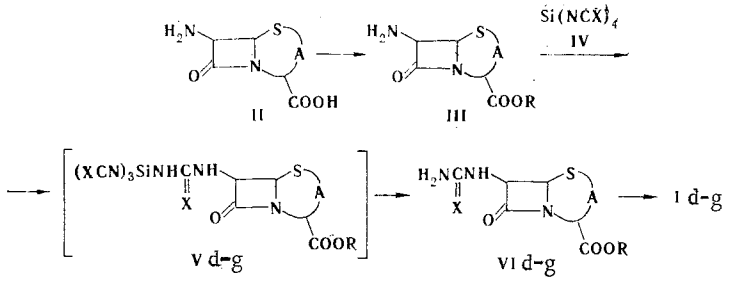
I a-g

I a A=—$C(CH_3)_2$—, X=O, n=1, R=Ar, Alk, etc.; b A=—$C(CH_3)_2$—, X=S, n=1, R=C_6H_5; c A=—$CH_2C(CH_2COOCH_3)$—, X=O, n=1, R=Ar, Alk, etc.; d A=—$CH_2C(CH_3)$=, X=O, n=0; e A=—$C(CH_3)_2$—, X=O, n=0; f A=—$C(CH_3)_2$—, X=S, n=0; g A=—$CH_2C(CH_3)$=, X=S, n=0

To obtain Ie-g it seemed expedient to use isocyanoto- and isothiocyanatosilanes, which, according to the literature data [7], have high reactivities at low temperatures in aprotic solvents, i.e., under conditions that promote retention of the β-lactam ring of amino acids II, as the reagents.

In view of the low solubilities of starting amino acids II in aprotic solvents, we used their trimethylsilyl and p-nitrobenzyl esters III. In addition to increasing the solubilities, they ensure protection of the carboxy group from side reactions with the isocyanato- and isothiocyanatosilanes.

An attempt to use trimethylisocyanatosilane in the reaction with trimethylsilyl esters III was unsuccessful. The reagents did not react at room temperature, and the predominant process above 30°C was destruction of the β-lactam ring. We were able to accomplish the reaction only with tetraisocyanatosilane (IV, X = O), which reacts with amino acid esters III at room temperature virtually quantitatively without the formation of side products.



II III V d-g VI d-g I d-g

III, V, VI R=$SiMe_3$, $CH_2C_6H_4$—NO_2-p; IV X=S, O; II, III A=—$CH_2C(CH_3)$=, —$C(CH_3)_2$—; V, VI d A=—$CH_2C(CH_3)$=, X=O; e A=—$C(CH_3)_2$—, X=O; f A=—$C(CH_3)_2$—, X=S; g A=—$CH_2C(CH_3)$=, X=S

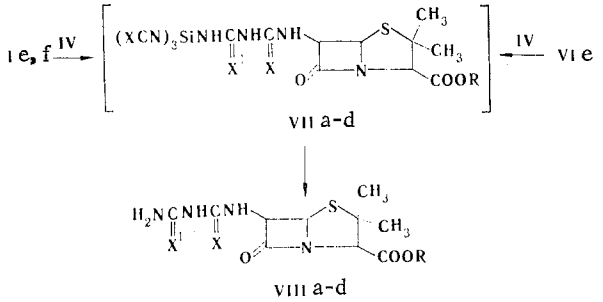
A study of the effect of the ratio of the reagents and their concentrations on the yields of ureido acids Id-e showed that up to two isocyanato groups of the isocyanato molecule enter into the reaction as the solution is diluted, whereas only one such group undergoes the reaction in more concentrated solutions. The maximum yield was obtained at an amino acid ester III:tetraisocyanotosilane:solvent (benzene, methylene chloride) ratio of 1:1:100. Subsequent treatment of intermediate N-silyl-substituted ureido acid ester V (X = O) with water or lower alcohols leads to splitting out of the silylisocyanato grouping. In the case of the trimethylsilyl ester the carboxy group is simultaneously liberated, and the desired ureido acids Id-e are isolated in the form of the free acids or the potassium salts. In the case of the p-nitrobenzyl ester the final product was isolated in the form of ureido acid ester VIe.

Similarly, 6-thioureidopenicillanic acid (If), its p-nitrobenzyl ester VIf, and 7-thioureidodeacetoxycephalosporanic acid (Ig) were obtained by treatment of esters III with tetraisothiocyanatosilane (IV, X = S).

The presence of a ureido group in the penicillin and deacetoxycephalosporin molecules is confirmed by the appearance in the IR spectra of a strong absorption band at 1660-1670 cm^{-1}. In contrast to the ureido group, the thioureido group in If, Ig, and VIf is characterized by an absorption band of medium intensity at 1550-1560 cm^{-1}. The compositions and structures of the synthesized compounds were also confirmed by the PMR spectroscopic data and the results of elementary analysis.

A study of the biological activity of ureido and thioureido acids Id-g conducted in the Scientific-Research Institute for the Biological Testing of Chemical Compounds showed that they display only moderate antibacterial activity with respect to a penicillin-sensitive staphylococcus.

In view of the high reactivities of tetraisocyanatosilane and tetraisothiocyanatosilane, we studied the possibility of obtaining biuret and thiobiuret derivatives of penicillanic acid (VIIIa-c) by means of them.



VII, VIII a $R=CH_2C_6H_4NO_2$-p, $X^1=X=O$; b $R=K$, $X^1=X=O$; c $R=K$, $X^1=O$, $X=S$; d $R=K$, $X^1=X=S$

As in the preparation of ureido acids Id-g, 6-ureido- and 6-thioureidopenicillanic acids and p-nitrobenzyl ester VIe were treated with the corresponding isocyanatosilane IV, and, after completion of the reaction, the N-silylisocyanato group was split out with a lower alcohol. However, because of the lower basicities of the ureido and thioureido groups as compared with the amido group, this reaction, in contrast to the preceding reaction, proceeds slowly and gives the product in considerably lower yield. In the reaction of 6-ureidopenicillanic acid Ie with tetrathioisocyanatosilane (IV, X = S) we observed cleavage of the β-lactam ring and were unable to isolate a substance with the penicillin structure. The similarity in the physicochemical properties of the starting compounds and the final products hinders the isolation and purification of the 6-N-carbamoylureidopenicillanic acids and the p-nitrobenzyl ester (VIIIa-d).

The IR spectra of these substances contain characteristic absorption bands of β-lactam, carboxy, and ester groups. In addition, the biuret structure in VIIIa,b is characterized by splitting of the primary amide band (1710 and 1680 cm^{-1}), and in the spectrum of VIIIc, as compared with that of the starting 6-thioureidopenicillanic acid, one observes the appearance of a band at 1670 cm^{-1}. The structure of VIIIa,d were also confirmed by data from the PMR spectra.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 580B spectrometer. The PMR spectra of solutions of most of the compounds in D_2O were recorded with a WH-90 spectrometer (90 MHz) with 3-(trimethylsilyl)propanesulfonic acid as the internal standard; the PMR spectra of o-nitrobenzyl esters VIe and VIIIa were obtained from solutions in d_6-DMSO with tetramethylsilane as the internal standard. The source of the reaction and the purities of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol plates in the following systems: A) isopropyl alcohol–dioxane–methanol (2:3:5); B) n-butyl alcohol–water–acetic acid (4:1:1). The chromatograms were developed by spraying with a 1% solution of sodium azide in a 0.005 N solution of iodine (white spots on a violet background).

6-Ureidopenicillanic Acid and Its Potassium Salt (Ie). A mixture of 6.48 g (0.03 mole) of 6-aminopenicillanic acid with 4.93 g (0.03 mole) of hexamethylsilazan and 50 mg of concentrated H_2SO_4 was refluxed in 200 ml of dry benzene for 2 h, after which a solution of 5.90 g (0.03 mole) of tetraisocyanatosilane in 40 ml of benzene was added to the resulting solution at room temperature, and the mixture was stirred at room temperature for 48 h. The solvent was evaporated in vacuo, a mixture of 50 ml of ethanol in 500 ml of ether was added to the residue, and the resulting precipitate was stirred for 3 h, removed by filtration, and dissolved in ethanol. The solution was filtered, and the filtrate was poured into 1 liter of ether. The resulting precipitate was removed by filtration and dried to give 6.3 g (81%) of a product with R_f 0.72 (system A) and 0.80 (system B). Found: C 41.5; H 5.2; N 15.9%. $C_9H_{13}N_3O_4S$. Calculated: C 41.7; H 5.1; N 16.2%.

To obtain the potassium salt, 6.3 g of acid Ie was dissolved in methanol, and the solution was neutralized with a methanol solution of potassium acetate. The precipitate was removed by filtration and dried to give 5.6 g (78%) of the potassium salt of Ie. IR spectrum 1770 (C=O, β-lactam), 1670 (CONH), and 1610 cm^{-1} (COO^-). PMR spectrum 1.50 (3H, s, 2-CH_3),

1.61 (cH, s, 2-CH_3), 4.24 (1H, s, 3-H), 5.47 (1H, d, J = 4.4 Hz, 5-H), and 5.59 ppm (1H, d, J = 4.4 Hz, 6-H).

6-Thioureidopenicillanic Acid (If) and Its Potassium Salt. This acid, with R_f 0.83 (system B), was obtained in 70% yield by the reaction of 6-aminopenicillanic acid with tetrathioisocyanatosilane by the method presented for acid Ie. Found: C 39.4; H 5.0; N 15.1%. $C_9H_{13}H_3O_3S_2$. Calculated: C 39.3; H 4.8; N 15.3%.

Acid If was converted to the potassium salt in 81% yield by the method used for Ie. IR spectrum: 1770 (C=O, β-lactam), 1600 (COO^-), and 1560 cm^{-1} (CSNH). PMR spectrum: 1.50 (3H, s, 2-CH_3), 1.59 (3H, s, 2-CH_3), 1.59 (3H, s, 2-CH), 4.24 (1H, s, 3-H), 5.48 (1H, d, J = 4.4 Hz, 5-H), and 5.59 ppm (1H, d, J = 4.4 Hz, 6-H).

7-Ureidodeacetoxycephalosporanic Acid (Id) and Its Potassium Salt. This acid with R_f 0.65 (system A) and 0.40 (system B), was obtained in 77% yield by the reaction of 7-aminodeacetoxycephalosporanic acid with tetraisocyanatosilane by the method presented for acid Ie. IR spectrum 1760 (C=O, β-lactam), 1690 (COOH), and 1670 cm^{-1} (CONH).

Acid Id was converted to the potassium salt in 79% yield by a method similar to that used for Ie. Found: C 36.4; H 3.6; N 14.2%. $C_9H_{10}KN_3O_4S$. Calculated: C 36.6; H 3.4; N 14.2%.

7-Thioureidodeacetoxycephalosporanic Acid (Ig) and Its Potassium Salt. The acid, with R_f 0.34 (system B), was obtained in 83% yield by the reaction of 7-aminodeacetoxycephalosporanic acid with tetraisothiocyanatosilane by the method presented for Ie.

Acid Ig was converted to the potassium salt in 77% yield by a method similar to that used for Ie. Found: C 33.5; H 3.0; N 13.7%. $C_9H_{10}KN_3O_3S_2$. Calculated: C 34.7; H 3.2; N 13.5%. IR spectrum: 1760 (C=O, β-lactam), 1600 (COO^-), and 1550 cm^{-1} (CSNH).

p-Nitrobenzyl 6-Ureidopenicillanate (VIe). To a solution of 1.5 g (5 mmole) of p-nitrobenzyl 6-aminopenicillanate in 50 ml dry methylene chloride was added 0.98 g (5 mmole) of tetraisocyanatosilane in 10 ml methylene chloride, and the mixture was stirred for 24 h at room temperature. To the reaction mixture was added, with stirring, 5 ml ethanol, and the precipitated residue filtered, dissolved in methanol, and reprecipitated with ether. Yield 1.1 g (66%) of VIe. mp 221-222°, R_f 0.77 (A), 0.96 (B). Found: C 48.6; H 4.8; N 14.0%. $C_{16}H_{18}N_4O_6S$. Calculated: C 48.7; H 4.6; N 14.2%. IR spectra: 1780 (C=O, β-lactam); 1730 (C=O, complex ether), 1670 cm^{-1} (CONH). PMR spectra: 1.42 (3H, s, 2-CH_3); 1.60 (3H, s, 2-CH_3); 4.50 (1H, s, 3-H); 5.37 (2H, s, CH_2); 5.37-5.60 (2H, m, 5-H and 6-H); 5.89 (2H, s, NH_2); 6.67 (1H, d, J = 9.0 Hz, NHCO); 7.80 (2H, d, C_6H_4); 8.24 ppm (2H, d, C_6H_4).

p-Nitrobenzyl 6-Thioureidopenicillate (VIf). This compound, with mp 151-152°C and R_f 0.79 (system β), was obtained in 71% yield by the reaction of p-nitrobenzyl 6-aminopenicillanate with tetraisocyanatosilane by the method presented for VIe. IR spectrum 1780 (C=O, β-lactam), 1740 (ester C=O), and 1550 cm^{-1} (CSNH).

p-Nitrobenzyl 6-[3-(Carbamoyl)ureido]penicillanate (VIIIa). This compound was obtained in 22% yield for p-nitrobenzyl 6-ureidopenicillanate and tetraisocyanatosilane by a method similar to that used to prepare ester VIe. IR spectrum: 1780 (C=O, β-lactam); 1730 (ester C=O); 1695, 1670 cm^{-1} (CONHCONH). PMR spectrum: 1.42 (3H, s, 2-CH_3), 1.60 (3H, s, 2-CH_3), 4.50 (1H, s, 3-h), 5.38 (2H, s, CH_2), 5.41-5.60 (2H, m, t-H and 6-H), 5.89 (2H, s, NH_2), 6.66 (1H, d, J = 9.0 Hz, NHCO), 7.80 (2H, d, C_6H_4), 8.27 (2H, d, C_6H_4), and 11.10 ppm (1H, s, CONHCO).

Potassium 6-[3-(Carbamoyl)ureido]penicillanate (VIIIb). A solution of 0.33 g (1.68 mmole) of tetraisocyanatosilane in 5 ml of benzene was added to a suspension of 0.5 g (1.68 mmole) of potassium 6-ureidopenicillanate in 20 ml of dry benzene, and the mixture was stirred at room temperature for 72 h. The solvent was then evaporated, and the residue was stirred for 3 h in a mixture of 10 ml of ether and 1 ml of ethanol. The solid material was removed by filtration and reprecipitated thre times from ether–methanol to give 0.1 g (18%) of product. IR spectrum: 1760 (C=O, β-lactam); 1710, 1670 (CONHCONH); 1600 cm^{-1} (COO^-).

Potassium 6-[3-(Carbamoyl)thioureido]penicillanate (VIIIc). This compound was similarly obtained in 21% yield. IR spectrum: 1770 (C=O, β-lactam), 1670 (CONH), and 1600 cm^{-1} (COO^-).

Potassium 6-[3-(Thiocarbamoyl)thioureido]penicillanate (VIIId). This compound was obtained in 25% yield by the method used to prepare salt VIIIb. IR spectrum: 1770 (C=O, β-lactam), 1610 (COO^-), and 1500 cm^{-1} (CSNH). PMR spectrum: 1.51 (3H, s, 2-CH_3), 1.63 (3H, s, 2-CH_3), 4.09 (1H, s, 3-H), 5.53 (kH, d, J = 4.4 Hz, 5-H), and 5.64 ppm (1H, d, J = 4.4 Hz, 6-H).

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