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

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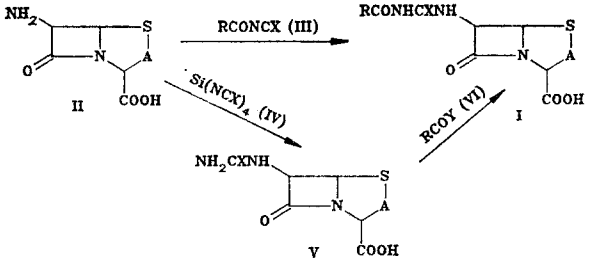
New N-acylureido and N-acylthioureido derivatives of β-lactam antibiotics were obtained by the reaction of 6-ureido and 6-thioureidopenicillanic and 7-thioreidodeacetoxycephalosporanic acids with acyl halides of carboxylic acids and benzoyl isocyanate. 6-Carbamoylhydroxypenicillanic acid, 6-thiocarbamoylhydroxypenicillanic 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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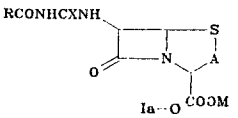
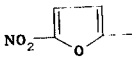
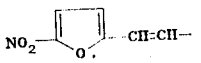
TABLE 1. Physicochemical and Antibacterial Properties of N-Acylureido and N-Acylthioureido Derivatives of β-Lactam Antibiotics Ia-o



Compound*	R	X	A	M	IR spectrum, C=O, cm^{-1} β-lactam	CONH	COOH	COO⁻	MIC†, St. aureus 209P, g/mm	Yield, %
Ia	C_6H_5 ‡	O	$-C(CH_3)_2-$	H	1770	1710, 1680	1730	—	12,5	72
Ib	$C_6H_5CH_2$ ‡	O	$-C(CH_3)_2-$	H	1770	1690	1730	—	200	62
Ic	$C_6H_5CH_2$	S	$-C(CH_3)_2-$	H	1780	1660	1730	—	25	48
Id	$C_6H_5OCH_2$	S	$-C(CH_3)_2-$	H	1780	1670	1730	—	12,5	56
Ie	$C_6H_5(NH_2)CH$	S	$-C(CH_3)_2-$	K	1770	1660	—	1600	200	43
If	Ad	O	$-C(CH_3)_2-$	K	1760	1720, 1640	—	1600	200	50
Ig	Ad	S	$-C(CH_3)_2-$	H	1780	1670	1730	—	25	53
Ih	Ad	S	$-CH_2CCH_3=$	H	1780	1670	1710	—	200	40
Ii	$BrCH_2$	S	$-C(CH_3)_2-$	K	1780	1660	—	1600	200	87
Ij		O	$-C(CH_3)_2-$	K	1760	1730, 1670	—	1600	200	50
Ik	„ „	S	$-C(CH_3)_2-$	H	1780	1670	1730	—	50	70
Il	„ „	S	$-CH_2CCH_3=$	H	1780	1670	1710	—	200	43
Im		O	$-C(CH_3)_2-$	K	1770	1720, 1670	—	1600	50	35
In	„ „	S	$-C(CH_3)_2-$	H	1770	1670	1730	—	12,5	76
Io	C_6H_5CONH	O	$-C(CH_3)_2-$	K	1770	1710, 1670	—	1600	50	50

*Compounds Ia-h and Ih-p were synthesized by the acid chloride method, Ii was synthesized by the bromo halide method, and Io was synthesized by the isocyanate method.

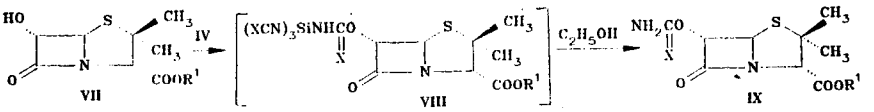
†The letters "MIC" pertain to the minimal inhibiting concentration.

‡The synthesis of Ia,b by the acyl isocyanates method was presented in [1].

The reaction of ureido acids V [A = $-C(CH_3)_2-$ and $-CH_2CCH_3=$] with alkyl halides of carboxylic acids and benzoyl isocyanate was realized in a nonaqueous medium with the aid of trimethylsilyl protection of the carboxy group. Analogs of antibiotics Ia-o (see Table 1) were isolated in the form of acids or potassium salts. Their structures were confirmed by the results of IR spectroscopy, and their homogeneity was confirmed by TLC.

A study of the biological activity of Ia-o *in vitro* carried out at the Scientific-Research Institute at BIKhS demonstrated that they primarily display moderate or weak activity with respect to *Staphylococcus aureus* (see Table 1). Appreciable intensification of the antibacterial activity on passing from ureido derivatives Ib,f,j,m (X = O) to the corresponding thioureido derivatives Ic,g,l,p (X = S) is characteristic for compounds with an identical acyl group.

In contrast to N-carbamoylation, the analogous modification of the hydroxy group in β-lactam molecules of antibiotics is rarely encountered. One of the examples of its utilization is the carbamoylation of 3-hydroxymethylcephalosporin, including also by way of trimethylsilyl isocyanate [5]. It seemed of interest to use tetraisocyanatosilanes IV for the modification of 6-hydroxypenicillanic acid (VII).



VII—IX R^1=H, CH_2CCl_3; VIII, IX X=O, S

6-Hydroxypenicillanic acid and its trichloroethyl ester VII were obtained by the methods in [6, 7]. Slightly soluble intermediate 6-N-silylcarbamoyloxypenicillanates (VIII) are formed in their reaction with IV in methylene chloride at room temperature. Splitting out of the silylisocyanato groups in VIII by ethanol leads to the production of 6-thiocarbamoyloxypenicillanic acid (IX, X = S) and its trichloroethyl ester (IX, X = S, $R^1 = CH_2CCl_3$).

The IR spectrum of IX (X = O, R^1 = H) is characterized by the appearance of an intense absorption band of a carbamoyl group at 1720 cm^{-1}. Replacement of the oxygen atom by a sulfur atom in IX (X = S, R^1 = H) leads to a 30 cm^{-1} shift of the C=O vibrations of the β-lactam carbonyl group to lower frequencies. The absorption band at 1600 cm^{-1}, which is related to the C=O bond of the ionized carboxy group, is evidently due to the betaine structure of IX (R^1 = H).

The structure of ester IX (X = S, $R^1 = CH_2CCl_3$) was confirmed by the PMR spectrum and mass-spectrometric analysis.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 580B spectrometer. The PMR spectra of solutions in d_6-DMSO were recorded with a WH-90 spectrometer (90 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectrum was recorded with a Kratos MS-50 spectrometer (70 eV). The homogeneity of the compounds was monitored by means of TLC on Silufol plates in an n-butanol–water–ethanol–acetic acid system (5:2:1.5:1.5). The chromatograms were developed with a 1% solution of sodium azide in a 0.005 N solution of iodine (white spots on a violet background).

Acid Halide Method for the Preparation of 6-N-Acylureido-, Thioureidopenicillanic, and 7-N-Acylthioureidodeacetoxycephalosporanic Acids (Ia-n) (Table 1). A 3.82-ml (3 mmoles) sample of trimethylchlorosilane and 0.66 ml (3 mmoles) of hexamethyldisilazane were added to a suspension of 3 mmoles of ureido- or thioureido acid V in 80 ml of dry benzene, and the mixture was stirred at room temperature for 4 h until the solids had dissolved completely. A 5.3-ml (3.5 mmoles) sample of triethylamine and a solution of 3 mmoles of the carboxylic acid chloride in 20 ml of benzene were added at −5°C, and the mixture was stirred at room temperature for 1 h. It was then diluted with 30 ml of water, and the precipitated antibiotic I in the acid form (M = H) was removed by filtration, washed with water, and dried in a vacuum desiccator.

To obtain the potassium salts the acid forms of the antibiotics were dissolved in ethanolic potassium acetate solution, and the resulting precipitates were removed by filtration, washed with ethyl acetate, and dried *in vacuo*.

Potassium 6-[3-(Benzamidocarbonyl)ureido]penicillanate (Io) (Table 1). A mixture of 1.04 g (4 mmoles) of 6-thioureidopenicillanic acid and 0.82 g (4 mmoles) of bis(trimethyl)-silylacetamide in 40 ml of THF was stirred at room temperature for 1 h, after which 1.05 ml (8 mmoles) of benzoyl isocyanate in 10 ml of THF was added to the resulting solution, and the reaction mixture was stirred at room temperature and allowed to stand overnight. Ethanol (20 ml) was then added, and the mixture was stirred for 1 h. The solvent was evaporated at room temperature, and the residue was dissolved in 10 ml of ethanol. The solution was filtered, and 500 ml of diethyl ether was added with stirring. The resulting precipitate was removed by filtration, dried, and dissolved in ethanol. The solution was neutralized with an ethanolic solution of potassium acetate, and the resulting precipitate was removed by filtration and dried *in vacuo*.

6-α-Carbamoyloxpenicillanic Acid (IX, X = O, R^1 = H). A 0.72-ml (5.2 mmoles) sample of triethylamine was added to a suspension of 1.13 g (5.2 mmoles) of 6-α-hydroxypenicillanic acid in 50 ml of methylene chloride, after which, to the cooled (to 0°C) solution, a solution of 1.02 g (5.2 mmoles) of tetraisocyanatosilane in 10 ml of methylene chloride was added, and the mixture was stirred at room temperature for 4 h. The solvent was then removed by evaporation at reduced pressure, and the residue was dissolved in 20 ml of ethanol. The solution was poured with stirring into 500 ml of diethyl ether, and the resulting precipitate was removed by filtration and dried in a vacuum desiccator to give 0.7 g (54%) of a product with R_f 0.88 and $[\alpha]_D^{20}$ + 96° (c 1, DMSO). IR spectrum: 1770, 1720, 1670, and 1600 cm^{-1}.

Trichloroethyl 6-α-Thiocarbamoyloxypenicillinate (IX, X = X, $R^1 = CH_2CCl_3$). A solution of 1.1 g (4.3 mmoles) of tetraisothiocyanatosilane in 10 ml of methylene chloride was added

to a solution of 1.5 g (4.3 mmoles) of trichloroethyl 6-α-hydroxypenicillanate in 50 ml of dry methylene chloride, and the resulting solution was maintained at room temperature for 48 h. The solvent was then removed at reduced pressure, and the residue was dissolved in 20 ml of ethanol. The ethanol solution was filtered and poured with stirring into 500 ml of petroleum ether, and the resulting precipitate was removed by filtration and dried in a vacuum desiccator to give 0.8 g (47%) of a product with R_f 0.96 $[\alpha]_D^{20}$ + 31° (c 1, DMSO), and M^+ 406. IR spectrum: 1760 and 1740 cm^{-1}. PMR spectrum: 1.53 (3H, s, 2-CH_3), 1.69 (3H, s, 2-CH_3), 4.23 (1H, s, 3-H), 4.77 (2H, s, CH_2CCl_3), 5.24 (1H, d, J = 1 Hz, 5-H), 5.36 (1H, d, J = 1Hz, 6-H), and 8.41 ppm (2H, s, H_2NCS).

6-α-Thiocarbamoyloxypenicillanic Acid (IX, X = S, R^1 = H). A 0.6-ml (4.3 mmoles) sample of triethylamine was added to a suspension of 0.93 g (4.3 mmoles) of 6-α-hydroxypenicillanic acid in 40 ml of methylene chloride, the mixture was then cooled to 0°C, and a solution of 1.1 g (4.3 mmoles) of tetraisocyanatosilane in 10 ml of methylene chloride was added. The solution was maintained at room temperature for 48 h, after which the solvent was evaporated at reduced pressure, and the residue was dissolved in 20 ml of ethanol. The ethanol solution was filtered and poured with stirring into 500 ml of diethyl ether. The resulting precipitate was removed by filtration and dried *in vacuo* to give 0.65 g (48%) of a product with R_f 0.92 and $[\alpha]_D^{20}$ + 89° (c ~1, DMSO). IR spectrum: 1740 and 1600 cm^{-1}.

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SYNTHESIS OF 3,4,7,8-BIS(3-R-BENZO)-2,6-DITHIA-1,5-DIAZA-2,6-DIHYDROANTHRACENE 2,6-DIOXIDES

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Derivatives of a new heterocyclic quinoid system, viz., 3,4,7,8-bis(3-R-benzo)-2,6-dithia-1,5-diaza-2,6-dihydroanthracene 2,6-dioxide, were synthesized by the oxidation of 3,4,7,8-bis(3-R-benzo)-2,6-dithia-1,5-diaza-1,2,5,6-tetrahydroanthracene 2,6-dioxides with lead tetraacetate in acetic acid or with phenyliodoso diacetate in benzene.

N,N'-Diarylsulfonylquinonediimines are valuable intermediates in the synthesis of several indole derivatives [1]. It is known that in the indole series there exist compounds with high biological activity and medicinal preparations. Several dibenzo [c,e] [1, 2]-thiazine 5,5-dioxides also display biological activity [2]. In a continuation of our research [3] in order to find new biologically active substances that combine dibenzothiazine and indole rings we have synthesized heterocyclic quinoneimines of the 3,4,7,8-bis(3-R-benzo)-2,6-dithia-1,5-diaza-2,6-dihydroanthracene 2,6-dioxide (Va,b) series.

N,N'-Bis(arylsulfonyl)-1,4-phenylenediamines (Ia,b) were synthesized by the action of the corresponding arenesulfonyl chlorides on 1,4-phenylenediamine by the method in [4]:

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