ACYLAMINE-CONTAINING PENAMIC AND CEPHEMIC DERIVATIVES CONTAINING 1-[2H]ISOQUINOLINONE AND 1H-2-BENZOPYRAN-1-ONE RINGS

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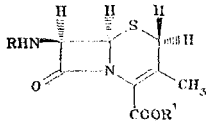
UDC 547.789.1.4.61'718'869.1'814.5'833.3.7.8.07:543.422

New penamic and cephemic derivatives that contain a 1-[2H]isoquinolinone or 1H-2-benzopyran-1-one ring in an acylaminoside chain were synthesized. It was established that compounds in the form of carboxylic acids or sodium salts display activity *in vitro* with respect to pathogenic microorganisms.

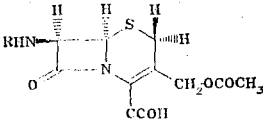
Many semisynthetic penicillins and cephalosporins that are used in medical practice have an N-acyl group, in the composition of which various heteroaromatic rings are included [1, 2]. Heterorings are introduced by acylation of the amino group by heteroaromatic or heteroarylacetic acids [3, 4]. The structure of the acylamino substituent is an important factor in determining the medicobiological properties of penicillins and cephalosporins, as a consequence of which intensive research on the creation of new "classical" [5] semisynthetic β-lactam antibiotics [6, 7] is continuing

In the preent paper we will examine the acylation of 7-aminodeacetoxycephalosporanic acid (Ia) and its esters IIIa-Va, 7-aminocephalosporanic acid (VIa), 6-aminopenicillanic acid (VIIa), and ampicillin (Xa) by acids XIII, XV, 2R-XVII, XIX, XXI, and XXIII. They all contain a 1-[2H]isoquinolinone (isocarbostyryl) or 1H-2-benzopyran-1-one (isocoumarin) ring. Derivatives of these biologically valuable heterocyclic systems are encountered in nature [8, 9] or are used in therapy [10, 11]. Most of the acids mentioned above have become accessible only recently, since simple and convenient methods for their preparation have been created [12-15].

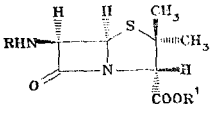
The N-acylation of Ia-VIIa and Xa was carried out by means of widely used methods [4, 16, 17]; in some cases Ia, VIIa, and Xa were subjected to the reaction with prior protective silylation [18] of the carboxy group.



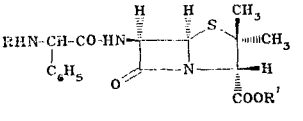
I–V



VI a,f,g



VII–IX



X–XII

I–XII a R=H, b R=XIV, c R=XVI, d R=2R-XVIII, e R=XX, f R=XXII, g R=XXIV; I a,b,f,g R^1=H; II b R^1=CH_3; III a-d R^1=$CH_2C_6H_4NO_2$-*p*; IV a,e R^1=$C(CH_3)_3$; V a,g R^1=CH_2CCl_3; VIIa,f R^1=H; VIIIf R^1=Na; IXf R^1=CH_3; X a,f R^1=H; XIf R^1=Na; XIIf R^1=CH_3

In previous studies some of us established that only acids XIII, XV, and XXI are readily converted to acid chlorides [10] and that acylation by them can be carried out in aqueous or nonaqueous media in the presence of bases. Under the influence of thionyl chloride, oxalyl chloride, and other chlorides acids 2R-XVII, XIX, and XXIII are converted to complex mixtures of reaction products. We observed a correspondence between the chemical properties of

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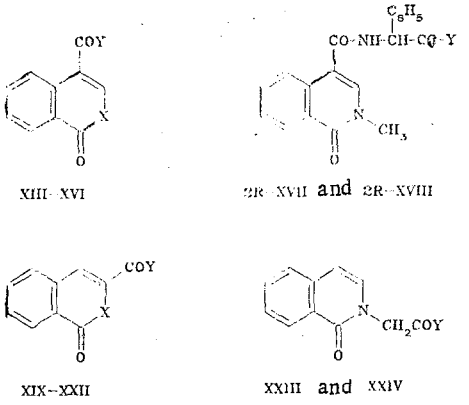
 0009-3122/84/2003-0256$08.50

the examined 1-[2H]isoquinolinone-containing carboxylic acids and the chemical shifts of the carbonyl carbon atoms in the ^{13}C NMR spectra. Acylation by acids 2R-XVII, XIX, and XXIII takes place readily via the carbodiimide method [19].

Within the framework of this investigation we established that acid XXIII reacts regioselectively with ethyl chloroformate under the conditions of the low-temperature preparation of mixed anhydrides with alkylcarbonic acids. Acid XXIII activated in this way was used for N-acylation in aqueous or nonaqueous media in the presence of bases.



XIII, XIV, XIX, XX X=NCH_3; XV, XVI, XXI, XXII X=O; XIII, XV, 2R-XVII, XIX, XXI, XXIII Y=OH; XIV, XVI, 2R-XVIII, XX, XXII without Y

Acids XIII, XV, 2R-XVII, XIX, XXI, and XXIII were investigated as acylating agents for β-lactamthiazolidine and β-lactamidihydrothiazine systems containing an amino group in the case of acylation of the readily accessible and stable p-nitrobenzyl (IIIa), tert-butyl (IVa), and trichloroethyl (Va) esters of Ia. This method was used to obtain the corresponding IIIb-d, IVe, and Vg. the protection of the carboxy group can be readily removed by means of known methods [4, 20].

N-(1-[2H]Isoquinolinonyl-4-carboxy) derivative Ib was obtained by acylation of Ia with acid XIII. This compound was characterized in the form of corresponding methyl ester IIb.

Compounds If and VIf, respectively, were obtained by acylation of Ia and VIa with 1H-2-benzopyran-1-one-3-carboxylic acid (XXI), and the corresponding VIIIf and Xf were obtained from VIIa or ampicillin. Compounds VIIIf and IXf were isolated in the form of sodium salts. Free acids VIIf and Xf were characterized without isolation from the reaction mixtures in the form of methyl esters IXf and XIIf.

The structure of the examined group of compounds is similar to the structure of the β-lactam antibiotic sefamandol [4], which is used in medical practice and contains a hydroxy group that is intramolecularly acylated and included in an isocoumarin ring.

Compounds Ig and VIg, respectively, were obtained by acylation of Ia and VIa with 1-[2H]isoquinolinonyl-2-acetic acid (XXIII). With respect to the type of substitution they are similar to the β-lactam antibiotic cephalothin [4], which has long been used in medical practice.

The expected retention of the cis configuration of the β-lactam ring was confirmed by the PMR specra of the newly obtained compounds.

The compounds obtained in the form of free acids or sodium salts display activity *in vitro* relative to pathogenic microorganisms such as *Ps. aeruginosa, P. vulgaris, P. mirabilis, Staph. aureus, E. coli,* and *Klebsiella.*

EXPERIMENTAL

The melting points of the analytically pure substances were determined with a Boetius heating stage and were not corrected. All of the newly obtained substances were investigated by means of thin-layer chromatography (TLC) on Merck GF-254 silica gel in a hexane–ethyl acetate–methanol–ammonia system (120:100:15:10) (upper layer). The IR spectra of 1% solutions in chloroform (if other conditions are not indicated) were recorded with Zeiss Specord IR71 and Zeiss UR-10 spectrometers. The PMR spectra were recorded with JEOL-PS-100, Tesla

BS-487-C (80 MHz), the Tesla BS-467 (60 MHz) spectrometers with tetramethylsilane and hexamethyldisiloxane as the internal standards. The angles of rotation were determined with a Roussel JOUAN polarimeter.

2-Methyl-1-[2H]isoquinolinone-4-carboxylic acid (XIII) was obtained by the method in [12], 2-methyl-1-[2H]isoquinolinone-3-carboxylic acid (XIX) was obtained by the method in [21], 1-H-2-benzopyran-1-one-4-carboxylic acid (XV) was obtained by the method in [14], and 1H-2-benozpyran-1-one-3-carboxylic acid (XXI) was obtained by the method in [15]. N-(2-Methyl-1-[2H]isoquinolinonyl-4-carbonyl)glycine (2R-XVII) was obtained by the method in [19], and the chlorides of acids XIII, XV, and XXI were synthesized with thionyl chloride by the method in [22].

Acid Chloride Method. A) A 1-mmole sample of triethylamine was added to a solution of the p-nitrobenzyl ester of Ia (1 mmole) in 25 ml of chloroform, the acid chloride obtained from acid XIII or XV (1 mmole) was added to the solution in parts with stirring and cooling to 0°C, and the mixture was stirred for an additional 1-2 h at room temperature. After this, the chloroform solution was washed successively with 5% hydrochloric acid, 10% sodium bicarbonate solution, and water, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was treated with absolute ether or petroleum ether, and the precipitate was removed by filtration and purified by recrystallization.

p-Nitrobenzyl 7-(2-Methyl-1-[2H]isoquinolinonyl-4-carboxamido)-3-methylceph-3-eme-4-carboxylate (IIIb). The reaction of 203 mg of XIII through the chloride gave 340 mg (64%) of IIIb with mp 214-215°C (methylene chloride–ether) and $[\alpha]_D^{23}$ = +116° (c 0.28, $CHCl_3$). IR spectrum: 1350 (NO_2), 1660 (broad band, amide CO), 1730 (ester CO), 1790 (β-lactam CO), and 3400 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 80 MHz): 2.15 (3H, s, CCH_3), 3.45 (2H, dd, SCH_2, J = 18.0 Hz), 3.46 (3H, s, NCH_3), 5.10 (1H, d, 6-H, J_{67} = 5.0 Hz), 5.32 (2H, s, OCH_2), 5.9 (1H, m, 7-H), and 7.4-8.9 ppm (10H, aromatic and NH protons). Found: C 58.2; H 4.6%. $C_{26}H_{22}N_4O_7S$. Calculated: C 58.4; H 4.2%.

p-Nitrobenzyl 7-(1H-2-Benzopyran-1-onyl-4-carboxamido)-3-methylceph-3-eme-4-carboxylate (IIIc). The reaction of 190 mg of XV through the chloride gave 370 mg (71%) of IIIc with mp 241-242°C (methylene chloride–ether) and $[\alpha]_D^{20}$ = +106° (c 0.25, DMF). IR spectrum (Nujol): 1340 (NO_2), 1660 (amide CO), 1780 (broad band, ester and β-lactam CO), and 3320 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 80 MHz): 2.25 (3H, s, CCH_3), 3.0-3.6 (2H, m, SCH_2), 5.17 (1H, d, 6-H, J_{67} = 5.0 Hz), 5.40 (2H, s, OCH_2), 5.90 (1H, q, 7-H, J_{67} = 5.0, $J_{7\text{-H,NH}}$ = 8.0 Hz), 7.5-8.5 (3H, m, aromatic protons), and 9.40 ppm (1H, d, NH, $J_{7\text{-H,NH}}$ = 8.0 Hz). Found: C 57.4; H 3.6%. $C_{25}H_{19}N_3O_8S$. Calculated: C 57.5: H 3.6%.

B) 7-[1H-2-Benzopyran-1-onyl-3-carboxamido]-2-acetoxymethylceph-3-eme-4-carboxylic Acid (VIf). A 0.28-ml (2 mmole) sample of triethylamine and 190 mg (1 mmole) of the chloride obtained from acid XXI were added successively with cooling to 0°C and stirring to 272 mg (1 mmole) of VIa in 70 ml of acetone and 0.5 ml of water, and the mixture was stirred with cooling for 30 min and at room temperature for 2 h. Water (4 ml) was added after the first hour. Acidification with dilute hydrochloric acid gave a solid substance, which was removed by filtration and recrystallized from n-butanol to give 290 mg (65%) of VIf with mp 167-170°C and $[\alpha]_D^{20}$ = 88.1° (c 0.32, DMF), IR spectrum (Nujol): 1730 (broad band with an inflection at 1780 cm^{-1}, acid, δ-lactone, and β-lactam CO) and 3400 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 80 MHz): 2.08 (3H, s, OCH_3), 3.6-4.0 (2H, m, SCH_2), 4.8-5.4 (3H, m, OCH_2 and 6-H), 5.9 (1H, m, 7-H), 7.6-8.0 (5H, m, aromatic and NH protons), 8.2 (1H, m, 8-H), and 9.7 ppm (1H, m, OH). Found: N 6.5; S 7.4%. $C_{20}H_{16}N_2O_8S$. Calculated: N 6.3; S 7.2%.

C) A 1-mmole sample of Ia, VIIa, or ampicillin (Xa) in 15 ml of methylene chloride was treated with 0.23 ml (1 mmole) of hexamethyldisilazane, and the reaction mixture was refluxed until the substances had dissolved completely. After this, the solution was cooled to −5°C, and 0.14 ml (1 mmole) of triethylamine and (with stirring) 1 mmole of the chloride obtained from acid XIII or XXI were added successively. The mixture was stirred for another hour at room temperature, after which the solvent was removed by distillation *in vacuo*. Ethyl acetate (10 ml) was added to the residue, and the mixture was cooled to −5°C. Water (2 ml) was added, the mixture was acidified to pH 2 with concentrated HCl, and the organic layer was dried with Na_2SO_4. An equimolar amount of a saturated alcohol solution of sodium acetate was added, or the organic layer was extracted with a 3% aqueous solution of sodium bicarbonate, and the product was precipitated by acidification.

7-(2-Methyl-1-[2H]isoquinolonyl-4-carboxamido)-3-methylceph-3-eme-4-carboxylic Acid (Ib) and Its Methyl Ester (IIb). The reaction of 214 ml of Ia and chloride XIII gave 190 mg (47%) of Ib with mp 204-206°C (from n-butanol) and $[\alpha]_D^{20}$ = +69.44 (c 0.17, DMF). IR

spectrum (Nujol): 1640 (amide CO), 1710 (acid CO), 1790 (β-lactam CO), 3230 (NH), and 3450 cm^{-1} (OH). PMR spectrum (d_6-DMSO, 60 MHz): 2.43 (3H, s, CCH_3), 3.93 (3H, s, NCH_3), 5.53 (1H, d, 6-H, J_{67} = 5.0 Hz), 6.1 (1H, m, 7-H, d, after exchange with D_2O), 7.7-8.8 (4H, m, aromatic and NH protons), and 9.59 ppm (1H, d, OH, vanished after exchange with D_2O); and SCH_2 protons were not identified because of overlapping of the signals. Found: N 10.2; S 8.2%. $C_{19}H_{17}N_3O_5S$. Calculated: N 10.5; S 8.0%.

The action of an ether solution of diazomethane on 90 mg of Ib gave 70 mg of ester IIb with mp 233-235°C (chloroform–ether) and $[\alpha]_D^{20}$ = +152.88 (c 0.1, DMF). IR spectrum (Nujol): 1650 (broad, amide CO), 1720 (ester CO), 1780 (β-lactam CO), and 3200 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 80 MHz): 2.18 (3H, s, CCH_3), 3.25 (2H, dd, SCH_2, J = 18.0 Hz), 3.52 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 5.10 (1H, d, 6-H, J_{67} = 4.5 Hz), 5.9 (1H, m, 7-H), 7.2-7.9 (4H, m, aromatic protons), and 8.1-8.6 ppm (2H, m, 8-H, and NH). Found: C 55.5; H 5.1%. $C_{20}H_{19}N_3O_7S \cdot 0.5H_2O$. Calculated: C 55.7; H 4.9%.

7-(1H-2-Benzopyran-1-onyl-3-carboxamido)-3-methylceph-3-eme-4-carboxylic Acid (If). The reaction of Ia and chloride XXI gave 270 mg (64%) of If with mp 150-152°C (from n-butanol) and $[\alpha]_D^{20}$ = +159.78 (c 0.31, DMF). IR spectrum (Nujol): 1680 (amide CO), 1780 (broad band with an inflection at 1740 cm^{-1}, acid, δ-lactone, and β-lactam CO) and 3340 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 80 MHz): 2.35 (3H, s, CCH_3), 3.4-3.9 (2H, m, SCH_2), 5.40 (1H, d, 6-H, J_{67} = 5.0 Hz), 5.93 (1H, m, J_{67} = 5.0 Hz), 7.8-8.6 (6H, m, aromatic and NH protons), and 9.90 ppm (1H, m, OH). Found: N 6.4; S 7.1%. $C_{18}H_{14}N_2O_6S \cdot 2H_2O$. Calculated: N 6.6; S 7.5%.

Sodium Salt (VIIIf) and Methyl Ester (IXf) of 6-(1H-2-Benzopyran-1-onyl-3-carboxamido)-2,2-dimethylpenam-3-carboxylic Acid. The reaction of 216 mg of VIIa and chloride XXI gave 310 mg (75%) of salt VIIIf with mp 247-250°C (dec.) and $[\alpha]_D^{20}$ = +135.15 (c 0.26, DMF). IR spectrum (Nujol): 1560 (COO^-), 1660 (amide CO), 1760 (broad band with an inflection at 1780, δ-lactone and β-lactam CO), and 3400 cm^{-1} (NH). The iodometric activity was 1405 units/mg (the percentage of the principal substance was 97.1%).

The reaction of the same amount of VIIa and XXI gave free acid VIIf, which, without isolation, was treated with an ether solution of diazomethane to give 300 mg (75%) of ester IXf with mp 164-166°C and $[\alpha]_D^{20}$ = +146.0 (c 0.25, $CHCl_3$). IR spectrum: 1700 (ester CO), 1760 (δ-lactone CO), 1800 (β-lactam CO), and 3400 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 100 MHz): 1.40 (3H, s, CCH_3), 1.60 (3H, s, CCH_3), 3.68 (3H, s, OCH_3), 4.40 (1H, s, 4-H), 5.6-5.7 (2H, m, 5-H and 6-H), 7.6-7.9 (4H, m, aromatic protons), 8.12 (1H, d, 8-H), and 8.9 ppm (1H, m, NH). Found: N 6.8: S 8.2%. $C_{19}H_{18}N_2O_6S$. Calculated: N 6.9; S 7.9%.

Sodium Salt (XIf) and Methyl Ester (XIIf) of 6-[N-(1H-2-Benzopyran-1-onyl-3-carbonyl)-2R-2-aminophenylacetamide]-2,2-dimethylpenam-3-carboxylic Acid. The reaction of 349 mg of ampicillin (Xa) and chloride XXI gave 395 mg (73%) of salt XIf with mp 234-235°C (dec.) and $[\alpha]_D^{20}$ = +136.19 (c 0.21, DMF). IR spectrum (Nujol): 1590 (COO^-), 1670 (amide CO), 1760 (broad band, δ-lactone and β-lactam CO), and 3300 cm^{-1} (NH). The iodometric activity was 1089 units/mg (the percentage of the principal substance was 100%).

The reaction of the same amounts of Xa and XXI gave free acid Xf, which, without isolation, was treated with an ester solution of diazomethane to give 380 mg (71%) of ester XIIf with mp 167-169°C (from isopropyl alcohol) and $[\alpha]_D^{20}$ = +128.40 (c 0.26, $CHCl_3$). IR spectrum 1690 (ester CO), 1730 (δ-lactone CO), 1790 (β-lactam CO), and 3400 cm^{-1} (NH). Found: N 8.0; S 6.1%. $C_{27}H_{25}N_2O_7S$. Calculated: N 7.9; S 6.0%.

Carbodiimide Method. A 1-mmole sample of N-(1-[2H]isoquinolinonyl-4-carbonyl)glycine (2R-XVII) or 1-[2H]isoquinolinone-3-carboxylic acid (XIX) was suspended in 10 ml of dry methylene chloride, a solution of 226 mg (1.1 mmole) of dicyclohexylcarbodiimide in 5 ml of dry methylene chloride was added, and the mixture was stirred at room temperature for 10 min. A 1-mmole sample of p-nitrobenzyl ester IIIa or 1 mmole of tert-butyl ester IVa in 5-10 ml of dry methylene chloride was added, and the mixture was stirred at room temperature for 12 h. The resulting dicyclohexylcarbamide was removed by filtration, and the solution was concentrated and treated with absolute ether. The resulting precipitate was removed by filtration and purified by recrystallization.

p-Nitrobenzyl 7-[N-(2-Methyl-1-[2H]isoquinolinonyl-4-carbonyl)2R-2-aminophenylacetamido]-3-methylceph-3-eme-4-carboxylate (IIId). The reaction of 336 mg of acid 2R-XVII and IIIa gave 400 mg (51%) of IIId with mp 202-204°C (chloroform–hexane) and $[\alpha]_D^{20}$ = +41.5 (c 0.13, DMF). IR spectrum: 1350 (NO_2), 1660 (amide CO), 1720 (ester CO), 1790 (β-lactam CO), and 3400 cm^{-1} (NH). Found: N 9.6; S 5.0%. $C_{34}H_{29}N_5O_8S$. Calculated: N 10.4; S 4.8%.

tert-Butyl 7-(2-Methyl-1-[2H]isoquinolinolyl-3-carboxamido)-3-methylceph-3-eme-4-carboxylate (IVe). The reaction of 203 mg (1 mmole) of acid XIX and 270 mg of tert-butyl ester IVa gave 290 mg (64%) of IVe with mp 195-197°C (from isopropyl alcohol) and $[\alpha]_D^{20}$ = +12.60 (c 0.30, DMF). IR spectrum (Nujol): 1640 (broad band with an inflection at 1670 cm^{-1}, amide CO), 1720 (ester CO), 1790 (β-lactam CO), and 3380 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 100 MHz): 1.44 [9H, s, $C(CH_3)_3$], 1.96 (3H, s, CCH_3), 3.0-3.7 (5H, m, SCH_2 and NCH_3), 5.12 (1H, d, 6-H, J_{67} = 5.0 Hz), 5.64 (1H, q, 7-H, J_{67} = 5.0 Hz, $J_{7\text{-H,NH}}$ = 8.0 Hz), 6.6-7.7 (4H, m, aromatic protons), 8.1 (1H, m, 8-H), and 9.76 ppm (1H, m, NH, $J_{NH,7\text{-H}}$ = 8.0 Hz; underwent exchange with D_2O). Found: N 9.2; S 6.7%. $C_{23}H_{25}N_3O_5S$. Calculated: N 9.2; S 7.0%.

Method of Mixed Anhydrides. A 203-mg (1 mmole) sample of acid XXIII was suspended in 1.7 ml of dry acetone, 0.14 ml (1 mmole) of triethylamine was added, and the temperature was lowered to −30 to −35°C. A 1-ml sample of a solution of N-methylmorpholine (0.17 ml of N-methylmorpholine in 100 ml of acetone) and 0.1 ml of ethyl chloroformate were added successively, and the mixture was stirred at −30°C for 30 min. A 1-mmole sample of a cooled (to 0°C) suspension of Ia or VIa in 0.6 ml of water and 0.8 ml of acetone and ∿0.5 ml of 2 M aqueous NaOH neutralized to pH 7.8 were added to the resulting mixed anhydride, and the reaction mixture was stirred at room temperature for 1 h. During the first 30 min, the gaseous reaction products were removed *in vacuo*. The solvent was evaporated *in vacuo*, and the residue was dissolved in 5 ml of water. The aqueous solution was acidified to pH 2 with 10% hydrochloric acid, and the precipitate was immediately removed by filtration and washed with water, acetone, and ether.

7-(1-[2H]Isoquinolinonyl-2-acetamido)-3-methylceph-3-eme-4-carboxylic Acid (Ig). The reaction of acid XXIII and Ia gave 250 mg (63%) of Ig with mp 200-201°C (after washing with hot butanol). IR spectrum (Nujol): 1660 (broad band, amide CO), 1720 (acid CO), 1770 (β-lactam CO), and 3260 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 100 MHz): 2.12 (3H, s, CCH_3), 3.3-3.7 (2H, dd, SCH_2, J = 18.0 Hz), 4.76 (2H, s, NCH_2), 5.10 (1H, d, 6-H, J_{67} = 4.50 Hz), 5.6-5.8 (1H, m, 7-H), 6.64 (1H, d, 4-H, J_{34} = 7.0 Hz), 7.2-7.9 (4H, m, aromatic protons), 8.22 (1H, d, 8-H), and 9.24 ppm (1H, d, NH; underwent exchange with D_2O). Found: N 10.4; S 8.4%. $C_{19}H_{17}N_3O_5S$. Calculated: N 10.5; S 8.0%.

7-(1H[2H]Isoquinolinonyl-2-acetamido)3-acetoxymethylceph-3-eme-carboxylic Acid (VIg). The reaction of acid XXIII and VIa gave 250 mg (55%) of VIg with mp 230-233°C (after washing with hot butanol). IR spectrum (Nujol): 1660 (broad band with an inflection at 1670 cm^{-1}, amide CO), 1790 (broad band, acid and β-lactam CO), and 3280 cm^{-1} (NH). PMR spectrum (d_6-DMSO, 100 MHz) 2.16 (3H, s, CH_3CO), 4.76 (2H, s, NCH_2), 5.0-5.2 (3H, m, 6-H and CH_2O), 5.6-6.0 (1H, m, 7-H), 6.64 (1H, d, 4-H, J_{34} = 7.0 Hz), 7.2-7.8 (4H, m, aromatic protons), 8.24 (1H, d, 8-H), and 9.3 ppm (1H, m, NH; underwent exchange with D_2O); overlapping of signals was observed for the SCH_2 group. Found: N 9.2; S 6.3%. $C_{21}H_{19}N_3O_7S$. Calculated: N 9.2; S 6.9%.

2,2,2-Trichloroethyl 7(1-[2H]Isoquinolinonyl-2-acetamido)-3-methylceph-3-eme-4-carboxylate (Vg). The mixed anhydride obtained from 203 mg (1 mmole) of acid XXIII was treated with a previously cooled (to 0°C) solution of 345.5 mg (1 mmole) of 2,2,2-trichloroethyl ester Va in 3 ml of chloroform, and the mixture was stirred at room temperature for 1 h; in the first 30 min the gaseous products were removed *in vacuo*. After this, the solvent was removed by distillation *in vacuo* to give 280 mg (51%) of a product with mp 198-200°C (methylene chloride–ether) and $[\alpha]_D^{20}$ = +81.93° (c 0.31, $CHCl_3$). IR spectrum: 1660 and 1700 (amide CO), 1790 (β-lactam CO with an inflection at 1750 cm^{-1}, ester CO), and 3450 cm^{-1} (NH). PMR spectrum ($CDCl_3$, 100 MHz): 2.15 (3H, s, CCH_3), 2.95-3.60 (2H, dd, SCH_2, J = 18.0 Hz), 4.4-5.6 (5H, m, 6-H, NCH_2, OCH_2), 5.80 (1H, q, 7-H, J_{67} = 5.0, $J_{NH,7\text{-H}}$ = 9.0 Hz), 6.60 (1H, d, 4-H, J_{34} = 7.0 Hz), 7.0-7.8 (4H, m, aromatic protons), 8.32 (1H, m, 8-H), and 8.72 ppm (1H, d, NH, $J_{NH,7\text{-H}}$ = 9.0 Hz). Found: C 47.4; H 3.8%. $C_{21}H_{18}Cl_3N_3O_5S$. Calculated: C 47.5; H 3.4%.

LITERATURE CITED

1. R. Reiner, in: Antibiotics, Vitamins, and Hormones, F. Korte and M. Goto, eds., Academic Press, New York (1977), p. 49.
2. D. Perlman (editor), Structure–Activity Relationship among the Semisynthetic Antibiotics, Academic Press, New York (1977).
3. D. Onken, Antibiotika: Chemie und Anwendung, Academie Verlag, Berlin (1979).
4. G. S. Rozenfeld and S. M. Navashin, Antibiotiki, 26, 860 (1981).
5. B. G. Christensen, in: β-Lactam Antibiotics: Mode of Action, New Developments, and Future Prospects, M. Salton and G. D. Shockman, eds., Academic Press, New York (1981), p. 101.

6. E. I. Edwards, R. Epton, G. Marr, G. K. Rogers, and K. Y. Thompson, in: Recent Advances in the Chemistry of β-Lactam Antibiotics, Y. Elks, ed., Chem. Soc., London (1977), p. 92.
7. A. Y. Sweetman, Drugs Future, 5, 195 (1980).(1980).
8. M. Shamma and Y. L. Moniot, Isoquinoline Alkaloids: Research 1972-1977, Plenum Press, New York (1978), p. 103.
9. K. Maewkawa and H. Yoshikawa, in: Advances in Pesticide Science. Part 2, Geissbühler, ed., Pergamon Press, Oxford (1979), p. 104.
10. P. Y. Thorpe, Drugs Future, 7, 889 (1982).
11. K. Hiller, Drugs Future, 5, 135 (1980).
12. V. H. Belgaonkar and R. N. Usgaonkar, Tetrahedron Lett., No. 44, 3849 (1975).
13. V. H. Belgaonkar and R. N. Usgaonkar, Chem. Ind., No. 21, 954 (1976).
14. D. R. Bückle, B. C. C. Cantello, and H. Smith, West German Patent No. 2448387; Chem. Abstr., 83, 79080 (1975).
15. I. A. Mazur, I. Katkevich, A. I. Borodin, A. A. Martinovskii, and E. G. Knish, Farm. Zh., 31, 63 (1976).
16. M. M. Bodanszky, Y. S. Klausner, and M. A. Ondetti, Peptide Synthesis, Wiley-Interscience, New York (1976), p. 85.
17. Y. H. C. Nayler, in: Advances in Drug Research, N. Y. Harper and A. B. Simmons, ed., Vol. 7, Academic Press, New York (1973), p. 1.
18. G. A. Veinberg, L. I. Petrulyanis, and É. Ya. Lukevits, Khim. Geterotsikl. Soedin., No. 2, 147 (1982).
19. M. Haimova, I. Atanassova, E. Stanoeva, and S. Mihovska, Commun. Dept. Chem. Bulg. Acad. Sci. (1983, in press).
20. E. Guibe-Yampel and M. Wakselman, Synth. Commun., 12, 219 (1982).
21. E. Bamberger and W. Frew, Chem. Ber., 27, 203 (1894).
22. I. Atanassova, M. Haimova, and E. Stanoeva, Commun. Dept. Chem. Bulg. Acad. Sci. (in press).

REACTION OF AMINO THIOLS WITH CHLOROACETIC ACID AND ITS ESTERS

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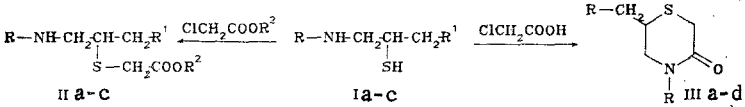
UDC 547.869.2'466.318'26'269.1.07:543.422

The reaction of amino thiols with chloroacetic acid esters leads to the formation of amino mercapto esters, whereas 6-alkyl(alkoxy)-N-aryltetrahydro-1,4-thiazine-3-ones are formed in the reaction with chloroacetic acid.

Tetrahydro-1,4-thiazine-3-ones or thiomorpholones are biologically active compounds [1-3]. Their synthesis is realized by the reaction of ethyleneimine with thioglycolic acid esters [4] or by the reaction of aminoethanethiol with haloacetic acid esters [5-8].

In the present research we set out to study the reaction between various amino thiols (I) and chloroacetic acid or its esters and to synthesize a number of new analogs of tetrahydro-1,4-thiazin-3-one. In contrast to [1, 8], we established that 1-anilino-2-propanethiol, 1-benzylamino-2-propanethiol, and other amino thiols react with chloroacetic acid esters to give amino mercapto esters and that the corresponding thiazinones are not formed.



II a-c Ia-c III a-d

I—III a R=Ph, R^1=H, R^2=Et; b R=CH_2Ph, R^1=H, R^2=Et; c R=Ph, R^1=BuO, R^2=Et(Bu); d R=CH_2Ph, R^1=BuO

In addition to this, as we have previously reported [9], thiazinones are formed in the reaction of the corresponding amino thiols with chloroacetic acid in the presence of sodium

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0009-3122/84/2003-0261$08.50