SEMISYNTHETIC CEPHALOSPORINS. THE SYNTHESIS OF 7-(HETEROARYLACETAMIDO)-3-ACETOXYCEPHALOSPORANIC ACIDS

Ľubomír JANDA[a], Zdeno VOTICKÝ[b], Ján ŠIPOŠ[a] and Marta MÚČKOVÁ[a]

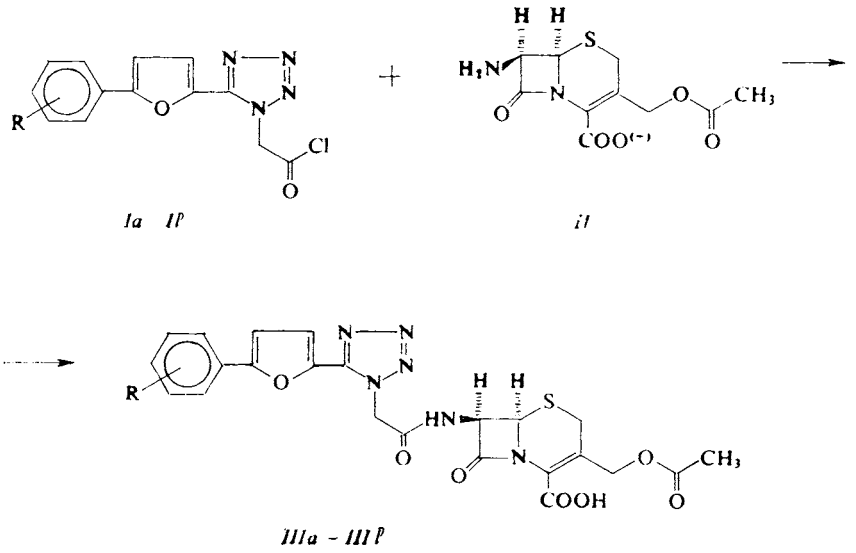
[a] *Drug Research Institute, Modra, 811 04 Bratislava and*
[b] *Institute of Chemistry,*
Slovak Academy of Sciences, 842 38 Bratislava

Received June 4th, 1984

7-(5-(5-Aryl-2-furyl)-1- and -2-tetrazolylacetamido)cephalosporanic acids and their sodium salts were prepared by N-acylation of 7-aminocephalosporanic acid with derivatives of 5-(5-aryl--2-furyl)-1- and -2-tetrazolylacetic acids. The final products tested *in vitro* on the Gram-positive and Gram-negative strains of microorganisms showed an activity comparable or better than that of reference substances.

1*H*-Tetrazole substituted at $N_{(1)}$ or at $N_{(1)}$ and $C_{(5)}$ is often embodied in a 7-heteroarylacetamide[1-4], or a 3-heteroarylthiomethyl substituent[5-8] of semisynthetic cephalosporins related to 7-aminocephalosporanic acid (7-ACA). Enhancement of the antibacterial activity of cephalosporin antibiotics, when compared with that of their 3-acetoxymethyl derivatives, is primarily due to the 1-alkyl-1*H*-5-tetrazolylthiomethyl group at $C_{(3)}$ of the cepheme backbone; this has been rationalized by their lowered metabolization in the organism to the less active 3-hydroxymethyl group[9]. Semisynthetic cephalosporins prepared from 7-ACA and having a 1*H*-1-tetrazolylacetamide grouping at $C_{(7)}$ of the cepheme backbone are widely used in medicine. Cefazolin[2] and ceftezol[1] are those well known cephalosporins with a 1,5-substituted 1*H*-tetrazole at $C_{(3)}$ of the cepheme skeleton are represented *e.g.* by cefamandol[5], ceforanid[6] cefotiam, cefazaflur[7], and cefoperazon[8].

The 7-ACA is most frequently N-acylated by chlorides[10] and mixed anhydrides[11,12] of heterocyclically substituted acetic acids. Although the mixed anhydrides are less reactive than chlorides of the corresponding acids, the modified Schotten–Baumann acylation afforded good yields even with cephalosprins. The N-acylation with mixed anhydrides is limited by solubility of the heterocyclically substituted acetic acids and their organic salts especially in acetone and tetrahydrofuran. Since the solubility of 5-(5-aryl-2-furyl)-1- and -2-tetrazolylacetic acids was unsatisfactory in these solvents, what would result in a change of conditions for every compound, dichloromethane well soluble chlorides were prepared by reacting the respective acids with phosphorus trichloride in phosphorus trichloride oxide.



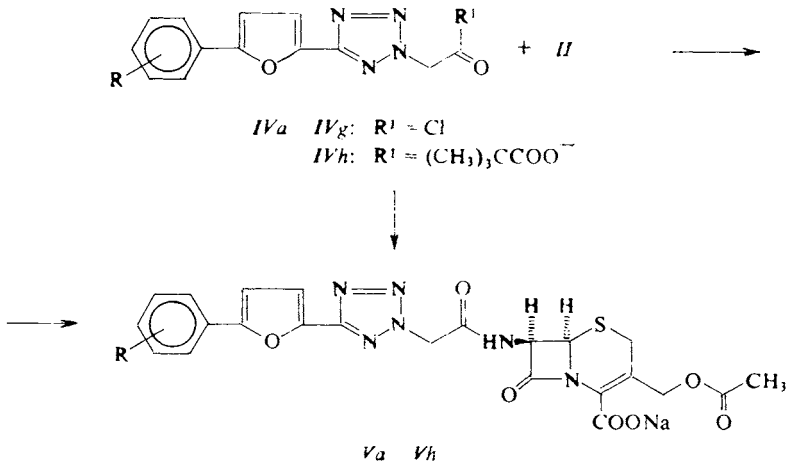
Ia–Il *II* *IIIa–IIIl*

a: R = 4-Cl, *b*: R = 3-Cl, *c*: R = 2-Cl, *d*: R = 4-Br, *e*: R = 3-CF_3, *f*: R = 2-CF_3, *g*: R = 4-CH_3O, *h*: R = 2-CH_3O, *i*: R = H, *j*: R = 3-CH_3, *k*: R = 2-NO_2, *l*: R = 2,6-Cl_2

SCHEME 1

The 7-(5-(5-aryl-2-furyl)-1-tetrazolylacetamido)cephalosporanic acids *IIIa–IIIl* were prepared by N-acylation of triethylammonium salt of 7-ACA (*II*) with 5-(5-aryl-2-furyl)-1-tetrazolylacetyl chlorides (*Ia–Il*) in dichloromethane at −5°C (Scheme 1). Sodium 7-(5-(5-aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanates *Va–Vg* were obtained by N-acylation of the the triethylammonium salt of 7-ACA (*II*) with 5-(5-aryl-2-furyl)-2-tetrazolylacetyl chlorides *IVa–IVg* in dichloromethane at −5°C (Scheme 2). The sodium 7-(5-(5-(4-chlorophenyl)-2-furyl)-2-tetrazolylacetamido)-cephalosporanate (*Vh*) was alternatively prepared by N-acylation of triethylammonium salt of 7-ACA (*II*) with a mixed anhydride of 5-(5-(4-chlorophenyl)-2-furyl)-2-tetrazolylacetic and pivalic acids (*IVh*) in aqueous acetone at −25°C (Scheme 2).

The IR spectra of cephalosporins *IIIa–IIIl* revealed absorption bands due to stretching vibrations of carbonyl groups at 1 780 to 1 530 cm^{-1}, evidencing the integrity of the β-lactam ring (1 780 to 1 760 cm^{-1}), a secondary amide at $C_{(7)}$ of the cepheme ring (1 677 to 1 664 cm^{-1} and 1 554 to 1 530 cm^{-1}), a free carboxylic acid at $C_{(4)}$ (1 625 to 1 610 cm^{-1}), and a free acetomethoxyl group at $C_{(3)}$ (1 746 to 1 708 cm^{-1}) tending to form the unwanted γ-lactone[13]; all these data are in accord with those reported[14]. Cephalosporins *Va–Vh* also displayed noticeable absorption bands associated with stretching vibrations of carbonyl groups; the β-lactam carbonyl (1 765 to 1 758 cm^{-1}), the secondary amide carbonyl (1 674 to



IVa *IVg*: $R^1 = Cl$
IVh: $R^1 = (CH_3)_3CCOO^-$

Va *Vh*

a: R = 3-Cl, *b*: R = 2-Cl, *c*: R = 4-Br, *d*: R = 3-CH_3, *e*: R = 4-CH_3O, *f*: R = 2-CH_3O, *g*: R = 2-NO_2, *h*: R = 4-Cl.

SCHEME 2

1 663 cm^{-1} and 1 550–1 530 cm^{-1}), the free carboxyl ion carbonyl (1 622–1 615 cm^{-1}), and the ester carbonyl (1 742–1 728 cm^{-1}). All cephalospirons showed absorption bands of N—H stretching vibrations (3 290–3 305 cm^{-1}), and of C—O bonds of ester groups (1 238–1 253 cm^{-1}). The 5-(5-aryl-2-furyl)-1- and -2-tetrazolylacetyl chlorides *Ia–Il* displayed a diagnostic absorption band of the carbonyl group (1 792 to 1 732 cm^{-1}); the IR spectra of the latter are not presented in detail, since they can be found in our previous papers[15,16].

Tests of the *in vitro* antibacterial activity of cephalosporins *IIIa–IIIl* and *Va–Vh* showed that the majority of these compounds has a comparable or even a better effect than cefalotin, cefazolin and cefamandol. The compounds under investigation are active against following bacterial strains: *Bacillus subtillis*, *B. cereus*, *B. pumilis*, *Sarcina lutea*, *S. subflava*, *Escherichia coli*, *Staphylococcus aureus*, *S. pyogenes*, and *S. epidermis*; their activity against *Pseudomonas aeruginosa*, *Proteus mirabilis* and *P. vulgaris* was found to be very low. Consequently, these compounds can be classified into the first and second generation of cephalosporin antibiotics. The 7-(5-(5-(4-chlorophenyl)-2-furyl-1-tetrazolylacetamido)cephalosporanic acid (*IIIa*) was found to be the most efficient substance of this series. Results of antibacterial activity show that 7-(5-(3-aryl-2-furyl)-1-tetrazolylacetamido)cephalosporanic acids *III* are more effective than sodium 7-(5-(5-aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanates *V*. The minimum inhibition concentrations of substituted cephalosporanic acids *IIIa–IIIl* are listed in Table I, those of sodium salts *Va–Vh* in Table II.

TABLE I

in vitro Antibacterial activities of 7-(5-(5-aryl-2-furyl)-1-tetrazolylacetamido)cephalosporanic acids *IIIa*—*IIIl*

Microorganism	MIC, μg/ml											
	IIIa	*IIIb*	*IIIc*	*IIId*	*IIIe*	*IIIf*	*IIIg*	*IIIh*	*IIIi*	*IIIj*	*IIIk*	*IIIl*
Bacillus subtilis Bs 5/58	0·125	0·125	0·125	2	1	0·125	0·125	1	2	0·125	0·125	0·125
B. cereus Bcm 4/58	0·125	0·125	0·125	1	1	0·5	0·125	0·5	8	0·125	0·125	0·125
B. pumilis Bac 2/65	0·125	0·25	0·125	4	2	0·125	0·125	1	2	0·125	0·125	0·125
Sarcina lutea Sar 5/58	0·125	0·125	0·125	2	8	0·5	0·5	4	16	0·5	0·5	0·125
S. subfiava Sar 6/58	0·125	0·5	0·125	4	32	0·125	4	8	16	2	0·125	0·125
Escherichia coli Esk 67/59	0·125	0·5	0·125	4	16	0·125	0·125	4	16	0·125	0·125	0·125
Staphylococcus aureus Man 78/71	0·125	0·25	32	16	16	64	128	16	32	64	32	32
S. epidermis M 12/63	0·125	>128	0·125	>128	>128	0·125	>128	>128	>128	>128	>128	0·125
Streptococcus pyogenes A 1/49	0·125	64	0·125	128	64	0·125	128	8	128	128	128	0·125
Pseudomonas aeruginosa Pa 133/71	>128	128	>128	128	>128	>128	128	>128	128	128	>128	>128
Proteus mirabilis Prmi 7/44	>128	>128	>128	>128	>128	>128	128	>128	>128	>128	128	>128
P. vulgaris Prh 4/42	128	>128	128	>128	>128	128	128	>128	128	128	128	128

TABLE II

in vitro Antibacterial activities of sodium 7-(5-(5-aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanates *Va*— *Vh*

Microorganism	MIC, μg/ml										
	Va	*Vb*	*Vc*	*Vd*	*Ve*	*Vf*	*Vg*	*Vh*	CEL[a]	CEZ[b]	CEM[c]
Bacillus subtilis Bs 5/58	0·5	4	1	4	1	1	16	2	0·125	0·125	0·25
B. cereus Bcm 4/58	4	2	2	1	0·5	1	8	1	0·125	0·125	0·125
B. pumilis Bac 2/65	2	2	1	64	1	2	8	2	0·125	0·125	0·125
Sarcina lutea Sar 5/58	8	4	16	1	1	1	16	2	0·125	2	0·125
S. subflava Sar 6/58	64	4	32	1	1	1	8	2	0·25	1	0·125
Escherichia coli Esk 67/59	2	1	2	4	2	2	16	2	0·25	0·5	0·25
Staphylococcus aureus Man 78/71	16	8	32	2	16	8	8	4	32	0·125	32
S. epidermis M 12/63	>128	>128	>128	>128	>128	>128	>128	>128	0·25	16	0·5
Streptococcus pyogenes A 1/49	8	128	64	128	8	128	>128	128	0·5	128	0·5
Pseudomonas aeruginosa Ps 133/71	128	128	128	128	128	128	128	128	128	128	128
Proteus mirabilis Prmi 7/44	>128	0·25	128	4	>128	128	16	4	129	4	1
P. vulgaris PrH 4/42	>128	>128	>128	>128	>128	>128	>128	>128	128	32	16

[a] Cefalotin; [b] cefalozin; [c] cefamandol.

EXPERIMENTAL

Melting points were measured on a Kofler micro hot-stage, the IR spectra were recorded with a Perkin-Elmer, model 457, spectrometer at a 3 mg per 200 mg KBr concentration in the 500 to 3 800 cm^{-1} range. 7-Aminocephalosporanic acid was prepared in the Drug Research Institute, Department of Fermentation Technology, Slovenská Ľupča. The products were tested *in vitro* against twelve Gram-negative and Gram-positive collection microorganisms (The Czechoslovak Collection of Microorganisms, J. E. Purkyně University, Brno) by a dilution technique according to Barry[17]. The antibacterial activity was expressed in minimum inhibition concentrations

TABLE III

5-(5-Aryl-2-furyl)-1-tetrazolylacetic acid chlorides *Ia*—*Il*

Compound	Formula (M_r)	Calculated/Found				M.p., °C (Yield, %)	ν(C=O) cm^{-1}
		% C	% H	% N	% Cl		
Ia 4-Cl	$C_{13}H_8Cl_2N_4O_2$ (323·1)	48·32 48·19	2·49 2·53	17·33 16·98	21·94 22·08	148—150 (95)	1 754
Ib 3-Cl	$C_{13}H_8Cl_2N_4O_2$ (323·1)	48·32 48·24	2·49 2·44	17·33 16·99	21·94 22·05	136—138 (94)	1 750
Ic 2-Cl	$C_{13}H_8Cl_2N_4O_2$ (323·1)	48·32 48·22	2·49 2·50	17·33 17·28	21·94 22·07	97—99 (92)	1 738
Id 4-Br	$C_{13}H_8BrClN_4O_2$ (367·7)	42·47 42·30	2·19 2·21	15·24 15·17	9·64 9·72	150—151 (94)	1 740
Ie 3-CF_3	$C_{14}H_8ClF_3N_4O_2$ (356·7)	47·14 47·21	2·26 2·16	15·70 15·91	9·93 —	151—153 (91)	1 753
If 2-CF_3	$C_{14}H_8ClF_3N_4O_2$ (356·7)	47·14 47·22	2·26 2·11	15·70 15·87	9·93 —	78—80 (93)	1 732
Ig 4-CH_3O	$C_{14}H_{11}ClN_4O_3$ (318·7)	52·75 52·66	3·47 3·50	17·57 17·64	11·12 11·16	128—130 (94)	1 757
Ih 2-CH_3O	$C_{14}H_{11}ClN_4O_3$ (318·7)	52·75 52·72	3·47 3·44	17·57 17·60	11·12 11·11	84—85 (93)	1 740
Ii H	$C_{13}H_9ClN_4O_2$ (288·7)	54·08 53·81	3·14 3·22	19·40 19·37	12·28 12·41	94—96 (96)	1 760
Ij 3-CH_3	$C_{14}H_{11}ClN_4O_2$ (302·7)	55·54 55·62	3·66 3·54	18·50 18·73	11·71 11·84	116—118 (96)	1 774
Ik 2-NO_2	$C_{13}H_8ClN_5O_4$ (333·7)	46·79 46·72	2·41 2·54	20·98 20·88	10·62 10·77	103—105 (87)	1 765
Il 2,6-Cl_2	$C_{13}H_7Cl_3N_4O_2$ (357·6)	43·66 43·82	1·97 2·01	15·66 15·60	29·74 29·90	111—113 (89)	1 733

(MIC, μg of the compound tested per 1 ml of the nutrition medium); the activity was compared with the reference cephalosporin antibiotics cefalotin, cefazolin and cefamandol (Eli Lilly, USA).

5-(5-Aryl-2-furyl)-1- and -2-tetrazolylacetic acids were prepared according to[15,16].

5-(5-Aryl-2-furyl)-1-tetrazolylacetyl Chlorides *Ia–Il* and
5-(5-Aryl-2-furyl)-2-tetrazolylacetyl Chlorides *IVa–IVg*

To the respective 5-(5-aryl-2-furyl)-1- and -2-tetrazolylacetic acid (10 mmol) phosphorus trichloride oxide (3 ml) and phosphorus trichloride (2·10 g, 10 mmol) were stepwise added and the mixture was stirred at 60°C for 15 to 30 min. The solvent was evaporated at this temperature during 10 min, then benzene (10 ml), added to the residue, was distilled off with the rest of phosphorus trichloride oxide. The distillation residue was taken into dichloromethane (20 to 50 ml), the extract was filtered, the solvent was distilled off and the crude chloride was crystallized from n-heptane if needed. Data of chlorides *Ia–Il* are listed in Table III, those of chlorides *IVa–IVg* in Table IV.

7-(5-(5-Aryl-2-furyl)-1-tetrazolylacetamido)cephalosporanic Acids *IIIa–IIIl*

To a suspension of 7-aminocephalosporanic acid (7-ACA, 1·36 g, 5 mmol) in dichloromethane (25 ml) triethylamine (0·84 ml, 6 mmol) was added at 0°C and the mixture stirred for 30–50 min till the 7-ACA became dissolved, was filtered and cooled to −5°C. Triethylamine (0·73 ml,

TABLE IV
5-(5-Aryl-2-furyl)-2-tetrazolylacetic acid chlorides *IVa–IVg*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (Yield, %)	ν(C=O) cm^{-1}
		% C	% H	% N	% Cl		
IVa 3-Cl	$C_{13}H_8Cl_2N_4O_2$ (323·1)	48·32 48·27	2·49 2·54	17·33 17·14	21·94 22·10	93–94 (95)	1 782
IVb 2-Cl	$C_{13}H_8Cl_2N_4O_2$ (323·1)	48·32 48·18	2·49 2·51	17·33 17·54	21·94 22·19	91–93 (94)	1 792
IVc 4-Br	$C_{13}H_8BrClN_4O_2$ (367·6)	42·47 42·35	2·19 2·21	15·24 15·35	9·64 10·00	94–95 (90)	1 744
IVd 3-CH_3	$C_{14}H_{11}ClN_4O_2$ (302·7)	55·54 55·66	3·66 3·58	18·50 18·66	11·71 11·78	103–105 (89)	1 791
IVe 4-CH_3O	$C_{14}H_{11}ClN_4O_3$ (318·7)	52·75 52·80	3·47 3·38	17·57 17·34	11·12 11·43	107–109 (91)	1 755
IVf 2-CH_3O	$C_{14}c_{11}ClN_4O_3$ (218·7)	52·75 52·89	3·47 3·44	17·57 17·78	11·12 11·06	96–97 (90)	1 741
IVg 2-NO_2	$C_{13}H_8ClN_5O_4$ (333·7)	46·79 46·82	2·41 2·50	20·98 21·18	10·62 10·89	87–89 (89)	1 732

5·25 mmol) was added again followed by addition of 5-(5-aryl-2-furyl)-1-tetrazolylacetyl chloride (5 mmol) in dichloromethane (10 to 25 ml) at a temperature not exceeding 0°C. The mixture was stirred 1 h at 0°C and 1 h at an ambient temperature, dichloromethane was distilled off, and water (30 ml) was added to the residue. A 15 min-stirring resulted in formatin of an emulsion, to which ethyl acetate (150 ml) was added; the stirred mixture was acidified with 15% hydrochloric acid to pH 2. The acetate layer was separated, dried with sodium sulfate, decoloured with charcoal, filtered and the solvent was evaporated. The crude 7-(5-(5-aryl-2-furyl)-1-tetrazolylacetamido)-cephalosporanic acid was dissolved in dimethylformamide (2·5 ml) at 40°C, diluted with ethanol (5 to 10 ml) and the separated crystals were filtered off, washed with ethanol, ether and dried in the air. Data of cephalosporanic acids *IIIa*—*IIIl* are listed in Table V.

TABLE V

7-(5-(5-Aryl-2-furyl)-1-tetrazolylacetamido)cephalosporanic acids *IIIa*—*IIIl*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (Yield, %)	(νC=O)$_{lactam}$ cm^{-1}
		% C	% H	% N	% Cl		
IIIa 4-Cl	$C_{23}H_{19}ClN_6O_7S$ (559·0)	49·42 49·19	3·42 3·56	15·03 15·26	6·34 6·12	199—200 (60)	1 767
IIIb 3-Cl	$C_{23}H_{19}ClN_6O_7S$ (559·0)	49·42 49·26	3·42 3·54	15·03 15·09	6·34 6·20	189—191 (61)	1 767
IIIc 2-Cl	$C_{23}H_{19}ClN_6O_7S$ (559·0)	49·42 49·21	3·42 3·48	15·04 15·17	6·34 6·22	176—177 (60)	1 756
IIId 4-Br	$C_{23}H_{19}BrN_6O_7S$ (603·4)	45·78 45·66	3·17 3·23	13·92 13·88	— —	198—199 (60)	1 778
IIIe 3-CF_3	$C_{24}H_{19}F_3N_6O_7S$ (592·5)	48·65 48·34	3·23 3·41	14·18 14·32	— —	187—189 (58)	1 777
IIIf 2-CF_3	$C_{24}H_{19}F_3N_6O_7S$ (592·5)	48·65 48·31	3·23 3·37	14·18 14·41	— —	178—180 (60)	1 743
IIIg 4-CH_3	$C_{24}H_{22}N_6O_8S$ (554·5)	51·98 51·75	3·99 4·10	15·15 15·32	— —	186—188 (59)	1·780
IIIh 2-CH_3O	$C_{24}H_{22}N_6O_8S$ (554·5)	51·98 51·76	3·99 4·08	15·15 15·28	— —	180—182 (60)	1 780
IIIi H	$C_{24}H_{20}N_6O_7S$ (524·5)	52·66 52·43	3·84 3·78	16·02 15·96	— —	182—184 (61)	1 762
IIIj 3-CH_3	$C_{24}H_{22}N_6O_7S$ (538·5)	53·52 53·36	4·11 4·14	15·60 15·54	— —	177—179 (61)	1 777
IIIk 2-NO_2	$C_{23}H_{19}N_7O_9S$ (569·5)	48·50 48·42	3·36 3·44	17·21 17·43	— —	131—132 (49)	1 767
IIIl 2,6-Cl_2	$C_{23}H_{18}Cl_2N_6O_7S$ (593·4)	46·55 46·59	3·05 3·10	14·16 14·02	11·94 11·88	201—202 (61)	1 766

Sodium 7-(5-(5-Aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanates *Va*—*Vg*

The title salts were prepared according to procedure for cephalosporanic acids *IIIa*—*IIIl* from the respective 5-(5-aryl-2-furyl)-2-tetrazolylacetyl chlorides (5 mmol) with the difference that the crude cephalosporanic acids were not crystallized, but directly transformed into sodium salts: the crude 7-(5-(5-aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanic acid obtained by evaporation of the ethyl acetate extract was dissolved in methanol–acetone (20 and 15 ml) at 50°C; to this solution sodium acetate (0·41 g, 5 mmol) dissolved in methanol (10 ml) was added, the solution with a partly precipitated sodium salt of the respective cephalosporanic acid was concentrated to 1/4 of its volume, and the sodium salt, precipitated after addition of ethanol (25 ml) was filtered off, washed with ethanol, ether and dried. Diagnostic data of sodium salts *Va*—*Vg* are given in Table VI.

Sodium 7-(5-(5-(4-Chlorophenyl)-2-furyl)-2-tetrazolylacetamido)cephalosporanate (*Vh*)

Triethylamine (1·14 ml, 8·2 mmol) was added at 0°C to a suspension of 7-aminocephalosporanic acid (7-ACA, 1·36 g, 5 mmol) in 50% aqueous acetone (16 ml) and the mixture was stirred till all 7-ACA dissolved; stirring was continued at this temperature for additional 30 min, the solution was filtered and the triethylammonium salt of 7-ACA thus obtained was poured at −25°C

TABLE VI

Sodium 7-(5-(5-aryl-2-furyl)-2-tetrazolylacetamido)cephalosporanates *Va*—*Vh*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (Yield, %)	$\nu(C{=}O)_{lactam}$ cm^{-1}
		% C	% H	% N	% Cl		
Va	$C_{23}H_{18}ClN_6NaO_7S$	47·55	3·12	14·46	6·10	186—187	1 760
3-Cl	(581·0)	47·48	3·06	14·60	6·28	(67)	
Vb	$C_{23}H_{18}ClN_6NaO_7S$	47·55	3·12	14·46	6·10	180—181	1 755
2-Cl	(581·0)	47·45	3·08	14·52	6·21	(65)	
Vc	$C_{23}H_{18}BrN_6NaO_7S$	44·17	2·90	13·43	—	183—185	1 774
4-Br	(625·4)	44·26	3·06	13·33	—	(66)	
Vd	$C_{24}H_{21}N_6NaO_7S$	51·43	3·77	14·99	—	175—176	1 771
3-CH_3	(560·5)	51·56	3·62	15·21	—	(63)	
Ve	$C_{24}H_{21}N_6NaO_8S$	50·00	3·67	14·57	—	198—200	1 778
4-CH_3O	(576·5)	50·11	3·55	14·66	—	(60)	
Vf	$C_{24}H_{21}N_6NaO_8S$	50·00	3·67	14·57	—	190—192	1 776
2-CH_3O	(576·5)	50·18	3·47	14·70	—	(61)	
Vg	$C_{23}H_{18}N_7NaO^9S$	46·70	3·06	16·57	—	163—164	1 766
2-NO_2	(591·5)	46·61	3·00	16·72	—	(55)	
Vh	$C_{23}H_{18}ClN_6NaO_7S$	47·55	3·12	14·46	6·10	189—190	1 768
4-Cl	(581·0)	47·62	3·11	14·28	6·01	(47)	

into the mixed anhydric prepared as follows: to 5-(5-(4-chlorophenyl)-2-furyl)-2-tetrazolylacetic acid (1·524 g, 5 mmol) dissolved in acetone (30 ml) triethylamine (0·8 g, 5·7 mmol) was added at 0° to 5°C and cooled to −10°C. To this solution pivaloyl chloride (0·81 g, 6·72 mmol) in acetone (5 ml) was added and the solution of the mixed anhydride was stirred at −10°C for 30 min. After both components were mixed the solution was stirred at −25°C for 1 h and then at room temperature for 2 h. Acetone was removed from this mixture and ethyl acetate (150 ml was added; the stirred emulsion was acidified with 15% hydrochloric acid to pH 2. The freed 7-(5-(5-(4--chlorophenyl)-2-furyl)-2-tetrazolylacetamido)cephalosporanic acid taken into the ethyl acetate layer was transformed into its sodium salt by procedure specified for sodium salts *Va*—*Vg*. Characteristic data of sodium salt *Vh* are presented in Table VI.

REFERENCES

1. Noto T., Nehashi T., Endo H., Saito M., Matsubara S., Harada Y., Suzuki S., Orawa H., Koyama K.: J. Antibiot. *29*, 1058 (1976).
2. Kariyone K., Harada H., Kurita M., Takano T.: J. Antibiot. *23*, 131 (1970).
3. Takano T., Kurita M., Nikaido H., Mera M., Konishi N., Nakagawa R.: S. African 68 04, 513 (1969); Chem. Abstr. *72*, 100 724 (1970).
4. Takano T., Kurita M., Nikaido H., Mera M., Konishi N., Nakagawa R.: S. African 69 07, 500 (1971); Chem. Abstr. *75*, 88 625 (1971).
5. Wick W. E., Preston P. A.: Antimicrob. Agents Chemother. *1*, 224 (1972).
6. Actor P., Sitrin R. D., Uri J. V.: *Annual Reports in Medicinal Chemistry*, (J. A. Weisbach. Ed.), Vol. 14, p. 103. Smith, Kline and French Lab., Philadephia 1979.
7. Roberts P. J.: Drugs Future *4*, 401 (1979).
8. Hinkle A.: Antimicrob. Agents Chemother. *17*, 423 (1980).
9. Wise R., Wills P. J., Andrews J. M., Bedford K. A.: Antimicrob. Agents Chemother. *17*, 84 (1980).
10. Stedman R. J., Swift A. C., Miller L. S., Dolan M. M., Hoover J. R. E.: J. Med. Chem. *10*, 363 (1967).
11. Morin R. B., Jackson B. G., Flynn E. H., Roeske R. W.: J. Amer. Chem. Soc. *84*, 3400 (1962).
12. Spencer J. L., Flynn E. H., Roeske R. W., Siu F. Y., Chauvette R. R.: J. Med. Chem. *9*, 746 (1966).
13. Onishi H. G., Daoust D. R.: Antimicrob. Agents Chemother. *5*, 38 (1974).
14. Green C. F. H., Page J. E., Staniforth S. E.: J. Chem. Soc. *1965*, 1595.
15. Janda L., Votický Z., Jakubcová J., Světlík J., Grimová J., Maturová E.: This Journal, in press.
16. Janda L., Votický Z., Světlík J., Grimová J., Maturová E.: This Journal *49*, 1505 (1984).
17. Barry A. L. in the book: *The Antimicrobic Susceptibility Test: Principles and Practices*, (Lea, Febinger, Eds), p. 92. Kimpton, London 1976.

Translated by Z. Votický.