SEMISYNTHETIC CEPHALOSPORINES. THE SYNTHESIS OF SOME SUBSTITUTED TETRAZOLYLACETIC ACIDS

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5-[5-(Substituted phenyl)-2-furyl]-1-tetrazolylacetic acids were synthesized from ethyl 5-(substituted phenyl)-2-furylcarbamidoacetates and phosphorus pentachloride *via* the corresponding imidoyl chlorides, which gave with sodium azide the respective ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates. A positive antiinflammatory effect was found when testing the acids obtained by hydrolysis of the acetates prepared.

Our preceding paper[1] dealt with the preparation of 5-[5-(substituted phenyl)-2-furyl]--1- and -2-tetrazolylacetic acids needed for acylation of 7-aminocephalosporanic acid; this paper presents an alternative synthesis of these substituted acetic acids.

A general method for preparation of esters of 5-substituted 1-tetrazolylacetic acids, the reaction of alkyl carbamidoacetates with phosphorus pentachloride followed by a cycloaddition of azoimide to the imidoyl chloride formed, afforded yields not exceeding 40% (ref.[2-4]). Another method to obtain a 1,5-disubstituted tetrazole is the 1,3-dipolar cycloaddition of an azide ion to imidoyl chlorides in a polar aprotic solvent; this procedure has been utilized for preparation of 1,5-diaryltetrazoles[5] only in approximately 85% yields. We obtained esters of 5-[5-(substituted phenyl)-2-furyl]--1-tetrazolylacetic acids in 60 to 70% yields by substituting azoimide by sodium azide thus excluding the poisonous azoimide from the reaction. The preparation of 5-(substituted phenyl)-2-furancarboxylic acids *I* was described in our preceding communication[6]; 5-(substituted phenyl)-2-furancarboxylic acid chlorides *II* were synthesized according to[7,8] with the difference that the reaction of acids with thionyl chloride was catalyzed by dimethylformamide. As a consequence, the reaction time was substantially reduced and the required chlorides were obtained in higher both purity and yield. Without being purified, these chlorides were N-acylated with ethyl-ester of glycine in chloroform in the presence of a two-fold excess of triethylamine to give ethyl 5-(substituted phenyl)-2-furylcarbamidoacetates *IIIa*–*IIIk* similarly, as in[9,10]. The corresponding imidoyl chlorides *IV* were prepared by a successive

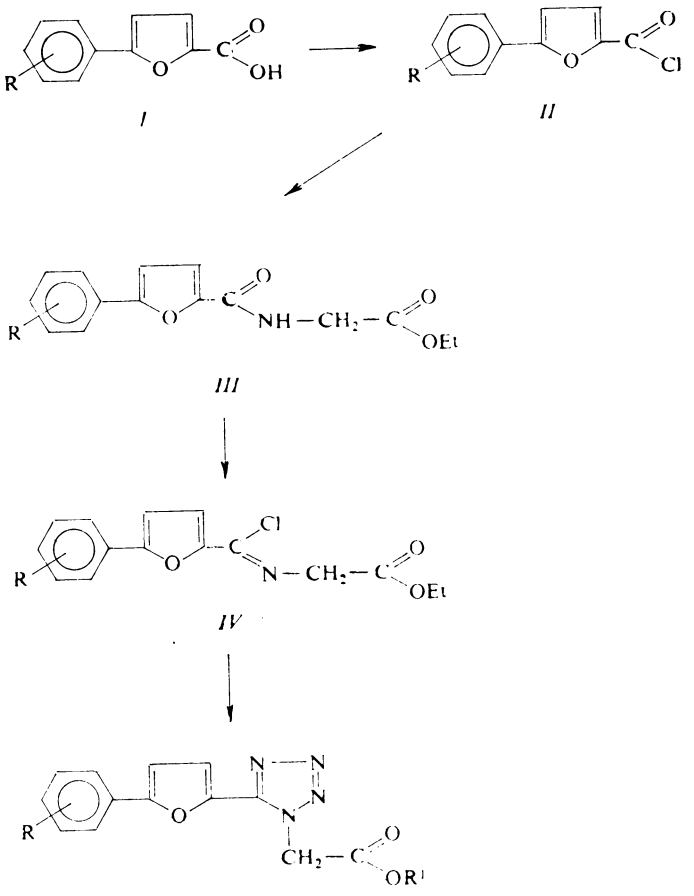
heating of an equimolar mixture of the respective amides *III* with phosphorus pentachloride in benzene. Hydrogen chloride began to evolve at 60°C; at the reflux temperature and after 5 min the evolution of hydrogen chloride ceased indicating the end of reaction. The raw product was left to react with sodium azide and the resulting ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates *Va – Vk* were crystallized from ethanol. Acids *VIa – VIk* were obtained by alkaline hydrolysis of the corresponding esters *Va – Vk*. The 2- and 2,6-substituted ethyl esters were hydrolyzed by methanolic potassium hydroxide, since the originating salts are methanol-soluble. The majority of potassium 3- and 4-substituted 1-tetrazolyl acetates is methanol-insoluble and therefore, they were hydrolyzed in 50% aqueous ethanol under reflux. The potassium tetrazolyl acetates *VII* crystallized after cooling in a 50 to 70% yield depending on their solubility.

Acidification of hot solutions gave rise to acids *VII* in almost quantitative yield; crystallization from ethanol consumed about 10% of the product (Scheme 1).

The IR spectra of ethyl 5-(substituted phenyl)-2-furylcarbamidoacetates *IIIa – IIIk* revealed characteristic $\nu(C{=}O)_{amide\,II}$ and $\nu(N{-}H)_{assoc}$ absorption bands at 1 650 to 1 638 cm^{-1} and 3 350 to 3 265 cm^{-1}, respectively (ref.[11,12]). The presence of an ester group was backed by appearance of a $\nu(C{=}O)$ vibration at 1 750 to 1 730 cm^{-1} (ref.[13]) and a $\nu(C{-}O)$ one at 1 210 to 1 200 cm^{-1} (ref.[14,15]). Asymmetric and symmetric[16,17] stretching vibrations of the C—O—C grouping in furan were seen at 1 282 to 1 272 cm^{-1} and at 1 030 to 1 019 cm^{-1}. The 2,5-substitution at furan ring was evidenced by bands at 880 to 858 cm^{-1} associated with the out-of-plane C—H bond vibration[18,19]. Bands indicative of an aromatic ring occurred in the 1 602 to 1 470 cm^{-1} region. Intense bands at 820 to 755 cm^{-1} diagnostic of deformation out-of-plane C—H bond vibrations confirmed the presence of a disubstituted benzene ring[20]. Dominating bands at 1 753 to 1 737 cm^{-1} and 1 247 to 1 208 cm^{-1} of ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates *Va – Vk* were attributed to stretching vibrations of carbonyl and ester groups, respectively. An unambiguous assignment of C=N, C=C and N=N stretching vibrations could be done after synthesizing model substances ethyl 1*H*-1-tetrazolyl acetate[21] and 5-(2-furyl)-1-tetrazolyl acetate[4]; their IR spectra showed that the bands at 1 621 to 1 602 cm^{-1} belong to C=N stretching vibrations, those at 1 598 to 1 580 cm^{-1} and at 1 490 to 1 465 cm^{-1} to C=C ones. The bands in the 1 335 cm^{-1} region are also due to stretching vibrations of tetrazole ring[22]. The IR spectra of esters *V*, acids *VI* and their potassium salts *VII* revealed a medium strong band at 1 114 to 1 094 cm^{-1} associated with the skeletal vibration of tetrazole[22,23] and further bands at 1 282 to 1 265 cm^{-1} and 1 038 to 1 017 cm^{-1} ascribable to asymmetric and symmetric stretching vibrations of the furan skeleton. Acids *VI* showed a mild wavelength drop of the dominating carbonyl band to 1 744 to 1 717 cm^{-1}, when compared with that of the esters. The carboxyl groups of acids were evidenced by the appearance of C—O stretching vibrations at 1 455 to 1 426 cm^{-1}, bending in-plane O—H vibrations at 1 241 to

1 205 cm^{-1} and bending out-of-plane C—O—H bond angle vibrations at about 930 cm^{-1} (ref.[24]). The KBr technique avoided to observe the O—H bond vibrations[25]. Potassium salts *VII* displayed asymmetric and symmetric stretching vibrations of the carboxyl ion at 1 620 to 1 599 cm^{-1} and at 1 420 to 1 384 cm^{-2} (ref.[26]).

The UV spectra of esters *V* showed the K band in the 300–348 nm region; this was observed to be hypsochromically shifted in 4-, 3- and 2-chloro derivatives



I *II* *III* *IV*

V, R^1 = Et
VI, R^1 = H
VII, R^1 = K

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

SCHEME 1

by 2 to 3 nm between the respective position isomers at benzene ring in the given sequence. Even a more significant hypsochromic shift was found between 3- and 2-trifluoro derivatives reaching up to 13 nm. The greatest shift revealed ethyl 5-[5-(2,6-dichlorophenyl)-2-furyl]-1-tetrazolyl acetate (*Vk*), where the K-band value decreased to 280 nm. This phenomenon could be rationalized by a discontinuance of coplanarity and thereby also conjugation of the molecule due to a steric hindrance of substituents in *ortho* position of the benzene ring. The discontinuance of coplanarity of 2,6-dichloro derivative is much greater than that of 2-chloro or 2-trifluoromethyl derivative. Six of eleven esters were substituted in position 4 of the benzene ring; the highest value of the K-band wavelength had the 4-nitro derivative *Vj* (348 nm) and the lowest one the unsubstituted ethyl 5-(5-phenyl-2-furyl)-1-tetrazolyl acetate (*Vg*) −314 nm. The sequence was a follows: 4-NO_2>, 4-CH_3O > 4-Br>, 4-CH_3>, 4-Cl>, 4-H. The extension of conjugation in 4-nitro derivative *Vj* was manifested by a noticeable bathochromic shift by 25 to 34 nm, when compared with other derivatives, the difference among them being maximum 8 nm.

The ^{1}H NMR spectra data of ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates *Ve*, *Vf*, *Vh*, *Vj*, and *Vk*, listed in Table I, are in accordance with those reported for 1-substituted tetrazoles[1,27,28]. The chemical shift values of protons of these esters are in the same range as those of ethyl 1-alkylated 5-[5-(substituted phenyl)-2-furyl]-1*H*-1-tetrazoles[1]. The ^{1}H NMR data of the other esters *Va* – *Vd*, *Vg* and *Vi* are presented in the preceding paper[1].

TABLE I

^{1}H NMR Values of chemical shifts (δ, ppm) of esters *Ve*, *Vf*, *Vh*, *Vj* and *Vk*

Compound	CH_3-ester CH_2-ester	CH_2—N=	H_{arom}
Ve	1·08 4·13	5·95	7·74—8·12 (m, 4 H, C_6H_4) 7·14 (d, H-4), 7·40 (d, H-3)
Vf	0·99 4·08	5·79	7·64—8·16 (m, 4 H, C_6H_4) 7·09 (d, H-4), 7·50 (d, H-3)
Vh	1·14 4·16	5·79	7·18, 7·34, 7·59, 7·74 (AA'BB', 4 H, C_6H_4) 7·13 (d, H-4), 7·45 (d, H-3)
Vj	1·11 4·16	5·92	7·91, 8·07, 8·26, 8·41 (AA'BB', 4 H, C_6H_4) 7·59 (s, eclipsed AB, H-3 + H-4)
Vk	0·96 4·05	5·70	7·50—7·70 (m, 3 H, C_6H_4) 7·07 (d, H-4), 7·60 (d, H-3)

The antiinflammatory effect of 5-substituted-2-furylacetic acid[29-31] and 5-substituted 1- and 2-tetrazolylacetic acids[32] has been reported. Screening of tetrazolylacetic acids *VIe*, *VIk* and *VIk* showed a statistically significant antiinflammatory activity; the first acid had a weaker one relative to standard Ibuprofen in one experimental inflammatory model (adjuvant oedema). All the acids tested have a very low toxicity at oral administration, the LD_{50} being greater than 1 g kg^{-1}.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage, the IR spectra (3 mg/200 mg KBr) were measured with a Perkin–Elmer, model 457 spectrophotometer, the UV spectra of 4·0 to $6{\cdot}0 \cdot 10^{-4}$ mol l^{-1} dioxane solutions were recorded with a Perkin–Elmer, model 340 apparatus

TABLE II

Acute oral toxicity of acids *VIe*, *VIf* and *VIk*

Compound	*VIe*	*VIf*	*VIh*	Ibuprofen
Mortality, %[a]	10	0	20	20

[a] Group of ten animals.

TABLE III

Antiinflammatory effect of acids *VIe*, *VIf* and *VIk*

Compound	Dose mg/kg	Inflammation inhibition, %		
		caolin. oedema	carrageenin. oedema	adjuvant oedema
VIe	25	6	5	17
	100	18	12	32[a]
VIf	25	14[b]	0[b]	4[b]
	100	14[b]	0[b]	12[b]
VIk	25	8	10	15
	100	8	20	25
Ibuprofen	25	51[a]	50[a]	39[a]
	100	49[a]	50[a]	41[a]

[a] Statistically significant effect, [b] statistically insignificant effect. The unspecified results were not statistically evaluated for an insufficient number of animals in the group.

in the 220—350 nm range, the ^{1}H NMR spectra of hexadeuteriodimethyl sulfoxide solutions containing tetramethylsilane as reference were run with an FX-100 (Jeol) instrument operating at 100 MHz.

The acute oral toxicity and the antiinflammatory activity were orientatively tested on mice (female, 19—22 g, S-strain, Konárovice breed), and Wistar rats (150—170 g). The acute oral toxicity was tested after a single administration of the substance in a gum arabic suspension with water (approx. 1/4 of the mass) to the mice in a 1 g kg^{-1} dose. The mortality of animals was investigated in experimental groups of ten within 10 days from application (Table II). The antiinflammatory activity was studied on three models of experimental inflammation, *i.e.* caolin[33], carrageenin[34] and adjuvant oedemas[35]. The screening method on rats in groups of four was used for evaluation of experimental data after oral administration of substances in aqueous

TABLE IV

Ethyl 5-(substituted phenyl)-2-furylcarbamidoacetates *IIIa*—*IIIk*

Compound R	Formula (M_r)	Calculated/Found % C	% H	% N	% Hal	M.p., °C (yield, %)
IIIa	$C_{15}H_{14}ClNO_4$	58·54	4·58	4·55	11·52	138—140
4-Cl	(307·7)	58·52	4·64	4·51	11·48	(91)
IIIb	$C_{15}H_{14}ClNO_4$	58·54	4·58	4·55	11·52	105—107
3-Cl	(307·7)	58·46	4·60	4·52	11·50	(93)
IIIc	$C_{15}H_{14}ClNO_4$	58·54	4·58	4·55	11·52	94—96
2-Cl	(307·7)	58·51	4·61	4·58	11·51	(94)
IIId	$C_{15}H_{14}BrNO_4$	51·15	4·00	3·97	22·68	126—128
4-Br	(352·2)	51·11	4·02	3·91	22·71	(89)
IIIe	$C_{16}H_{14}F_3NO_4$	56·31	4·13	4·10	—	107—109
3-CF_3	(341·3)	56·34	4·10	4·11	—	(88)
IIIf	$C_{16}H_{14}F_3NO_4$	56·31	4·13	4·10	—	88—90
2-CF_3	(341·3)	56·28	4·11	4·09	—	(86)
IIIg	$C_{15}H_{15}NO_4$	65·92	5·53	5·13	—	120—121
H	(273·3)	65·91	5·56	5·15	—	(94)
IIIh	$C_{16}H_{17}NO_4$	66·88	5·96	4·87	—	133—135
4-CH_3	(287·3)	66·84	5·98	4·78	—	(90)
IIIi	$C_{16}H_{17}NO_5$	63·35	5·64	4·61	—	118—119
4-CH_3O	(303·3)	63·36	5·70	4·54	—	(92)
IIIj	$C_{15}H_{14}N_2O_6$	56·60	4·43	8·80	—	174—175
4-NO_2	(318·3)	56·62	4·40	8·88	—	(82)
IIIk	$C_{15}H_{13}Cl_2NO_4$	52·65	3·82	4·09	20·72	60—62
2,6-Cl_2	(342·2)	52·58	3·88	4·02	20·73	(85)

suspension with gum arabic in 25, 50 and 100 mg doses per kg of the body mass. Those substances having an antiinflammatory effect were reexamined on a group of six animals and statistically evaluated (Table III).

5-(Substituted phenyl)-2-furancarboxylic Acid Chlorides *IIa*—*IIk*

To a 5-(substituted phenyl)-2-furancarboxylic acid (0·1 mol) in thionyl chloride (9·7 ml, 0·2 mol) two drops of dimethylformamide were added and the mixture was heated to its boiling point.

TABLE V

Ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolylacetates *Va*— *Vk*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Hal	
Va	$C_{15}H_{13}ClN_4O_3$	54·14	3·93	16·83	10·65	166—167
4-Cl	(332·7)	54·20	3·98	16·88	10·67	(63)
Vb	$C_{15}H_{13}ClN_4O_3$	54·14	3·93	16·83	10·65	140—141
3-Cl	(332·7)	54·16	3·90	16·86	10·66	(64)
Vc	$C_{15}H_{13}ClN_4O_3$	54·14	3·93	16·83	10·65	128—129
2-Cl	(332·7)	54·15	3·94	16·86	10·71	(62)
Vd	$C_{15}H_{13}BrN_4O_3$	47·76	3·47	14·85	21·18	170—172
4-Br	(377·2)	47·68	3·45	14·88	21·24	(62)
Ve[a]	$C_{16}H_{13}F_3N_4O_3$	52·46	3·57	15·29	—	110—111
3-CF_3	(366·3)	52·44	3·48	15·33	—	(67)
Vf[b]	$C_{16}H_{13}F_3N_4O_3$	52·46	3·57	15·29	—	90—92
2-CF_3	(366·3)	52·45	3·60	15·22	—	(67)
Vg	$C_{15}H_{14}N_4O_3$	60·39	4·73	18·78	—	128—129
H	(298·3)	60·44	4·78	18·81	—	(64)
Vh[c]	$C_{16}H_{16}N_4O_3$	61·53	5·16	17·93	—	183—184
4-CH_3	(312·3)	61·54	5·21	17·87	—	(66)
Vi	$C_{16}H_{16}N_4O_4$	58·53	4·91	17·06	—	143—145
4-CH_3O	(328·3)	58·50	5·01	17·12	—	(59)
Vj[d]	$C_{15}H_{13}N_5O_5$	52·48	3·81	20·40	—	177—180
4-NO_2	(343·3)	52·56	3·85	20·46	—	(55)
Vk[e]	$C_{15}H_{12}Cl_2N_4O_3$	49·06	3·24	15·25	19·31	89—93
2,6-Cl_2	(367·2)	49·18	3·16	15·21	19·50	(68)

[a] λ_{max} 313 nm (log ε 4·48), 328 sh (4·27); [b] λ_{max} 300 nm (log ε 4·26); [c] λ_{max} 317 nm (log ε 4·51), 332 sh (4·31); [d] λ_{max} 348 nm (log ε 4·40); [e] λ_{max} 280 nm (log ε 4·14).

The crystalline mass successively softened and liquidified within 30 min; the dark-green solution was simmered for 10 min, the excess of thionyl chloride was removed and the solid residue was dissolved in chloroform (50 ml), shortly boiled with charcoal, filtered and evaporated. Yields of chlorides vary between 70–90%.

Ethyl 5-(Substituted phenyl)-2-furylcarbamidoacetates *IIIa–IIIk*

Triethylamine (27·6 ml, 0·2 mol) was added to a suspension of ethyl aminoacetate hydrochloride (13·9 g, 0·1 mol) in chloroform (200 ml), cooled to −5°C so, as the temperature did not exceed 0°C. The solution became clear; then 5-(substituted phenyl)-2-furancarboxylic acid chloride (0·1 mol) in chloroform (50 ml) was added at −5 to 0°C. The mixture was stirred at this temperature for 30 min and at ambient one for 1 h. The chloroform solution was successively washed with a 5% aqueous hydrochloric acid, water, 5% potassium carbonate, and water to a neutral reaction. The organic layer was dried with sodium sulfate, the solvent was evaporated and the solid was crystallized from ethanol. Characteristic data of amides *IIIa–IIIk* are listed in Table IV.

TABLE VI

5-[5-(Substituted phenyl)-2-furyl]-1-tetrazolylacetic acids *VIe*, *VIf*, *VIh*, *VIj*, and *VIk*, and salts *VIIe*, *VIIh*, *VIIj*

Compound R	Formula (M_r)	Calculated/Found			M.p., °C (yield, %)
		% C	% H	% N	
VIe[a] 3-CF_3	$C_{14}H_9F_3N_4O_3$ (338·3)	49·71 49·77	2·68 2·63	16·56 16·68	231–233 (92)
VIf[a] 2-CF_3	$C_{14}H_9F_3N_4O_3$ (338·5)	49·71 49·79	2·68 2·59	16·56 16·63	213–215 (92)
VIh[b] 4-CH_3	$C_{14}H_{12}N_4O_3$ (284·3)	59·15 59·08	4·25 4·31	19·70 19·78	219–221 (95)
VIj[b] 4-NO_2	$C_{13}H_9N_5O_5$ (315·3)	49·53 49·70	2·87 2·91	22·21 22·23	214–216 (89)
VIk[a,c] 2,6-Cl_2	$C_{13}H_8Cl_2N_4O_3$ (339·1)	46·04 46·12	2·37 2·34	16·52 16·49	246–248 (91)
VIIe 3-CF_3	$C_{14}H_8KF_3N_4O_3$ (376·4)	44·68 44·69	2·14 2·16	14·88 14·94	336–338 (58)
VIIh 4-CH_3	$C_{14}H_{11}KH_4O_3$ (322·4)	52·16 52·04	3·43 3·51	17·37 17·34	337–339 (58)
VIIj 4-NO_2	$C_{13}H_8KH_5O_5$ (353·4)	44·19 44·21	2·28 2·31	19·82 19·89	290–292 (51)

[a] Method A; [b] method B; [c] calculated: 20·90% Cl, found: 20·89% Cl.

Ethyl 5-[5-(Substituted phenyl)-2-furyl]-1-tetrazolylacetates *Va*— *Vk*

To an ethyl 5-(substituted phenyl)-2-furylcarbamidoacetate (50 mmol) under a benzene layer (100 ml) powdered phosphorus pentachloride (10·4 g, 50 mmol) was added with stirring. The temperature raised to 75°C within 2 min and stirring was continued at this temperature for additional 10 to 15 min. The solvent was evaporated and the formed oily imidoyl chloride *IV*, dissolved in dimethylformamide (50 ml) was added during 45 min to a suspension of sodium azide (5·8 g, 90 mmol) in dimethylformamide (50 ml). The suspension was then stirred for 30 min, formamide was distilled off and acetone (100 ml) was poured into the hot residue, the inorganic salts were filtered off and the filtrate was evaporated. The solid was crystallized from ethanol. Characteristic data of esters *Va*— *Vk* are presented in Table V.

5-[5-(Substituted phenyl)-2-furyl]-1-tetrazolylacetic Acids *VIa*— *VIk*

A) 3M-Methanolic KOH (10 ml) was added to a hot solution of ethyl 5-[5-substituted phenyl)-2-furyl]-1-tetrazolyl acetate (25 mmol) in methanol (100 ml). The separated potassium salt was dissolved by addition of water (50 ml) and heated for 1 h. The mixture was filtered, acidified with 15%-hydrochloric acid, the separated acid was filtered off after cooling, washed with water, ethanol, dried and crystallized from ethanol.

B) Ethanol (50 ml) and 0·75M-KOH (50 ml) were added to ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetate and refluxed for 1 h. A 15%-hydrochloric acid was added to the filtered hot solution and the separated acid was worked up as specified under *A*. Characteristic data of acids *VIa*— *VIk* and of potassium salts *VIIe*, *VIIh* and *VIIj* are listed in Table VI.

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