SEMISYNTHETIC CEPHALOSPORINES. SYNTHESIS OF SOME SUBSTITUTED TETRAZOLYL ACETIC AND PROPIONIC ACIDS

Ľubomír JANDA[a], Zdeno VOTICKÝ[b], Jozefína JAKUBCOVÁ[a], Jan SVĚTLÍK[a], Jaroslava GRIMOVÁ[c] and Eva MATUROVÁ[c]

[a] *Drug Research Institute, Modra, 811 04 Bratislava,*
[b] *Institute of Chemistry, Slovak Academy of Sciences, 842 38 Bratislava, and*
[c] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague*

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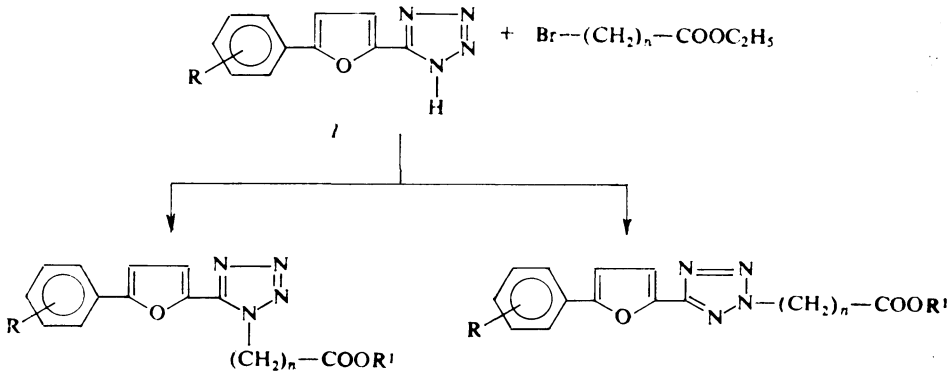
The N-alkylation of 5-[5-(substituted phenyl)-2-furyl]-1*H*-1-tetrazoles with ethyl bromoacetate or ethyl 3-bromopropionate afforded a mixture of 5-substituted ethyl 1- and 2-tetrazoyl acetates or propionates, which were separated and hydrolyzed to the corresponding 1- and 2-acetic or propionic acids, and used as intermediates for the synthesis of semisynthetic cephalosporine antibiotics. The prepared tetrazolyl acetic acids exhibited antiinflammatory activity.

The 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetic acids *VIa – VIi*, 5-[5-(substituted phenyl)-2-furyl]-2-tetrazolylacetic acids *IXa–IXi* and 3-{5-[5-(3-chlorophenyl)-2-furyl]-1- and -2-tetrazolyl}propionic acids *VIIIa* and *XIa*, prepared by hydrolysis of the corresponding esters *IIa–IIi*, *IVa–IVi*, *IIIa*, and *Va*, were used for acylation of 7-aminocephalosporanic acid aiming to get new semisynthetic antibiotics modified in position $C_{(7)}$ of the cepheme backbone. The afore-mentioned esters were synthesized by N-alkylation of 5-[5-(substituted phenyl)-2-furyl]-1*H*--1-tetrazoles[1,2] *I* with ethyl bromoacetate or 3-bromopropionate and chromatographic separation of position isomers formed (Scheme 1). Tetrazoles *I* were obtained from 5-(substituted phenyl)-2-furaldehydes[3] *via* 5-(substituted phenyl)-2-furonitriles[1–3].

The N-alkylation of 5-substituted 1*H*-1-tetrazoles has already been described[4–8]. The alkylation proceeds in relation to the both character of the substituent at $C_{(5)}$ of the tetrazole ring, and the reaction medium. Thus, 5-phenyl derivative is alkylated in ethanol exclusively into position $N_{(2)}$ (ref.[8]), whilst the $C_{(5)}$-thienyl, furyl, or alkyl derivatives afford in the same solvent a mixture of 1- and 2-isomers in various ratio[5,7]; in acetone, one gets a mixture of 1- and 2-isomers regardless the character of the substituent at $C_{(5)}$ (ref.[5,7]). In general, a replacement of an aromatic substituent at $C_{(5)}$ of the tetrazole ring for aliphatic one lowered the representation of 2-isomer[7] in the mixture. As evident, the ratio of the isomers formed is strongly influenced

by inductive effects of substituents at the carbon atom of the tetrazole ring; electron-accepting properties of the substituent preferentially orient the N-alkylation to $N_{(2)}$ atom[9-11]. The alkylation course of tetrazoles *I* is in accordance with these findings. Alkylation of 5-[5-(substituted phenyl)-2-furyl]-1*H*-1-tetrazoles *I* afforded a mixture of esters in an approximately 1 : 0·75 ratio in favour of the 1-isomer; were the benzene



IIa—IIi: $R^1 = C_2H_5$, n = 1
IIIa: $R^1 = C_2H_5$, n = 2
VIa—VIi: R^1 = H, n = 1
VIIa—VIIh: R^1 = K, n = 1
VIIIa: R^1 = H, n = 2

IVa—IVi: $R^1 = C_2H_5$, n = 1
Va: $R^1 = C_2H_5$, n = 2
IXa—IXi: R^1 = H, n = 1
Xa—Xg: R^1 = K, n = 1
XIa: R^1 = H, n = 2

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

SCHEME 1

ring substituted by a nitro group in position 2, the alkylation product was a mixture of isomers in roughly the same ratio, but with the 2-isomer as a major product. The required tetrazolylacetic and propionic acids were in principle prepared according to[7], describing an alkaline hydrolysis of ethyl 5-(2-furyl)-1- and 2-tetrazolyl acetates in methanol at an ambient temperature. Since the ethyl esters of substituted phenylfuryl-1- and 2-tetrazolyl acetic acids *II* and *IV* are methanol insoluble at room temperature, they were hydrolyzed under reflux with an excess of 3M-KOH. This modification proved disadvantageous, because potassium salts began to precipitate during hydrolysis and therefore, 50%-ethanol was used. The potassium salts are well soluble in this solvent down to approximately 60°C, and consequently, the corresponding acids must be liberated above this temperature. Yield of potassium salts, which can be isolated before acidification by filtration and washing with 75%-ethanol, depended on their solubility and varied within 50 to 70%. The yield of acids without

preceding isolation was virtually quantitative; crystallization from ethanol consumed about 10% of the yield.

Melting points of compounds substituted at $N_{(1)}$ of the tetrazole ring were higher than those of the corresponding $N_{(2)}$ isomers. This property has been preserved even with esters, acids and their potassium salts. This general finding was consistent with that of Norris[9] and Raap[12], but, nevertheless inconsistent with that of Sorensen and Klitgaard[7]. Of all pairs of isomers presented in this paper only ethyl-5[5-(2--methoxyphenyl)-2-furyl -2-tetrazolyl acetate (*IVg*) melted by 4°C higher than the corresponding 1-isomeric ester *IIg*. This anomaly, however, disappeared with the corresponding acid, and, in accordance with the other pairs of isomers, the -1-tetrazolyl acetic acid *VIg* had a higher melting point than the -2-tetrazolyl acetic acid *IXg*. The melting point differences between the respective isomeric pairs of esters, acids and salts were found to be 10 to 70°C.

The IR spectra of these ethyl esters, acids and their salts were characteristic of absorption bands of a medium strong to strong intensity in the 1 280 to 1 266 cm^{-1} and 1 036–1 019 cm^{-1} ranges, associated with the asymmetric and symmetric stretching vibrations of furan ring[13,14]. Moreover, all spectra had a narrow band of weaker intensity at 902–871 cm^{-1} belonging to out-of-plane bending vibrations of C—H bonds of furan[15,16]. Further absorption bands due to stretching vibrations of the tetrazole ring and $\nu(C{=}C)_{arom}$ appeared at 1 624–1 464^{-1}. A comparison of IR spectra with those of model substances (ethyl 1*H*-1-tetrazolyl acetate[17], ethyl 5-(2-furyl)-1-tetrazolyl acetate and ethyl 5-(2-furyl)-2-tetrazolyl acetate[7]) made it possible to ascribe unambiguously the following bands: those at 1 624–1 600 cm^{-1} to stretching vibrations of tetrazole, those at lower wavelengths between 1 598–1 579 cm^{-1} and 1 489–1 464 cm^{-1} to $\nu(C{=}C)_{arom}$. Absorptions at about 1 334 cm^{-1} reflected stretching vibrations of the tetrazole ring[18]. A medium strong absorption band at 1 116–1 092 cm^{-1} characterized skeletal vibrations of tetrazole[18,19]. Dominating two absorption bands in the 1 754–1 734 cm^{-1} and 1 246 to 1 208 cm^{-1} regions of compounds *IIa–IIi* and *IVa–IVi* were ascribed to stretching vibrations of the carbonyl group[20], and stretching vibrations of the ester group[21,22], respectively. Acids *VIa–VIi* and *IXa–IXi* revealed a slight wavelength decrease of the dominating carbonyl absorption band down to 1 743–1 716 cm^{-1}. The presence of carboxyl groups was backed by medium strong absorption bands of C—O stretching vibrations at 1 455–1 427 cm^{-1}, and by strong absorptions of in-plane bending vibrations of the C—O—H bond angle at 930 cm^{-1} (ref.[23]). The IR spectra were measured in KBr pellets and therefore the O—H streching vibrations[24] could not be mentioned. Vibrations of the carbonyl ion were observed with the spectra of potassium salts of the respective acids at 1 620–1 600 cm^{-1}, and at 1 419 to 1 383 cm^{-1}, both being diagnostic of asymmetric and symmetric stretching vibrations of this ion[25].

The UV spectra of 1-substituted esters *IIa–IIi* showed a K-band at 311–324 nm,

TABLE I

Antiinflammatory effect of acids *VIa*—*VIi* and *IXa*—*IXh*

Compound	mg kg^{-1}	Inflammation inhibition, %		
		Caolin. oedema	Carrageenin. oedema	Adjuv. oedema
VIa	25	11	13	19
	100	21	3	23
VIb	25	4	0	37[a]
	50	—	1[b]	23[a]
	100	0	11[b]	31[a]
VIc	25	26	0	19
	100	2	14	22
VId	25	21	0	18
	100	9	0	10
VIe	25	19	0	0
	100	0	8	0
VIf	25	2[b]	0[b]	5[b]
	100	18[a]	15[b]	7[b]
VIg	25	19	8	4
	100	16	6	21
VIh	25	12	0	17
	100	0	6	13
VIi	25	15[b]	13[b]	28[a]
	50	—	22[b]	11[b]
	100	6[b]	19[b]	36[a]
IXa	25	28[a]	0	31[a]
	100	7	0	23[a]
IXb	25	0	11	25[a]
	100	19	16	33[a]
IXc	25	18	11	11
	100	22	7	26
IXd	25	12	0[b]	28[a]
	50	—	4[b]	36[a]
	100	2	14[b]	36[a]
IXe	25	12	8	13
	100	22	12	16
IXf	25	13[b]	0[b]	19[a]
	100	17[b]	0[b]	25[a]
IXg	25	12	0[b]	8[b]
	100	10	5[b]	0[b]
IXh	25	0	10	18
	100	0	9	10
Ibuprofen	25	51[a]	50[a]	39[a]
	100	49[a]	50[a]	41[a]

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

whilst the 2-isomers *IVa–IVi* have this band hypsochromically shifted to 308 to 319 nm. Both isomeric ethyl 5-[(2-nitrophenyl)-2-furyl]tetrazolyl acetates (*IIh* and *IVh*) displayed a hypsochromic shift of this band to 292 nm. This phenomenon can be rationalized by a discontinuance of coplanarity and thereby also by discontinuation of conjugation of the molecule due to the steric hindrance of nitro group. A similar hypsochromic shift can also be observed in the spectra of 4-, 3- and 2-chloro derivatives, where the K-band is shifted by 2–3 nm between the respective position isomers at benzene ring in the given sequence. This shift display the 1- and the 2-isomeric series of these compounds. The bathochromic shift of the isomeric ethyl 5-[5-(methoxyphenyl)-2-furyl]tetrazolyl acetates (*IIg* and *IVg*) by 2–3 nm relative to the corresponding 4-methoxy derivatives *IIf* and *IVf* might be due to an influence of the methoxy group in position 4 of the phenyl ring. Of nine esters of the 1-isomeric series four derivatives were substituted in position 4 of the benzene ring. The greatest effect upon the K-band shift was seen with the methoxy groups (λ_{max} 323 nm), followed by bromo and chloro derivatives; the lowest effect showed the unsubstituted ethyl 5-(5-phenyl-2-furyl)-1-tetrazolyl acetate (λ_{max} 314 nm). Four esters of the 2-isomeric series of total nine compounds displayed the effect due to the substituent in position 4 of the benzene ring. Even this group of substances had the hypsochromic shift in the same sequence, the differences in the K-band position being 1–3 nm.

The ^{1}H NMR spectral data of ethyl esters *IIa–IIi* and *IVa–IVi* accord with the reported data for 1,5- and 2,5-substituted tetrazoles[26,27]. Protons of the methylene group attached to tetrazole ring in position 1 resonate in higher field than those of the 2-isomer with the exception of both 5-[5-(3-chlorophenyl)-2-furyl]tetrazolyl

TABLE II

Acute oral toxicity of acids *VIa– Vi* and *IXa– IXh*

Compound	Mortality[a] %	Compound	Mortality[a], %
VIa	0	*IXa*	20
VIb	10	*IXb*	20
VIc	10	*IXc*	10
VId	20	*IXd*	0
VIe	10	*IXe*	0
VIf	0	*IXf*	0
VIg	0	*IXg*	30
VIh	0	*IXh*	0
VIi	0	Ibuprofen	20

[a] Group of ten animals.

acetates *IIb* and *IVb*. A like trend was preserved by the ethyl group of ester function (Table III). Another characteristic feature revealed signals of furan protons; the H_3 one was always downfield shifted due to ring anisotropy of tetrazole ring. The difference between chemical shift values of the isomeric pair is very small ($\Delta\delta$ = 0·02 to 0·05 ppm for —CH_2—N) and consequently, insufficient for a general distinction in comparison with compounds *IIj* and *IVj* (Scheme 2), where $\Delta\delta$ = 0·14 ppm (ref.[7]). Correctness of the signal assignment to the particular isomers was verified by ^{1}H NMR spectral data of six 1-isomeric esters *IIa*, *IIb*, *IIc*, *IId*, *IIf*, and *IIi* prepared by an unequivoval synthesis from the corresponding imidoyl chloride and azide ion[28]. Reliable and general information on the assignment of position

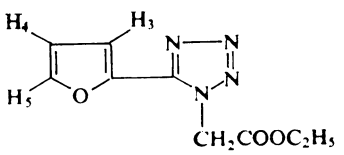
TABLE III

Ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates *IIa*—*IIi*

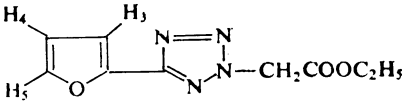
Compound R	Formula (M_r)	Calculated/Found			M.p., °C (yield, %)	λ_{max}, nm (log ε)	R_F
		% C	% H	% N			
IIa	$C_{15}H_{13}ClN_4O_3$[a]	54·14	3·93	16·83	166—167	316 (4·55)	0·35
4-Cl	(332·7)	54·26	3·93	16·80	(52)	332 sh (4·34)	
IIb	$C_{15}H_{13}ClN_4O_3$[b]	54·14	3·93	16·83	140—141	313 (4·50)	0·15
3-Cl	(332·7)	53·98	3·97	16·85	(50)	328 sh (4·30)	
IIc	$C_{15}H_{13}ClN_4O_3$[c]	54·14	3·93	16·83	128—129	311 (4·36)	0·18
2-Cl	(332·7)	54·17	4·01	16·85	(50)	327 sh (4·11)	
IId	$C_{15}H_{13}BrN_4O_2$[d]	47·76	3·47	14·85	170—172	318 (4·52)	0·26
4-Br	(377·2)	47·82	3·40	14·80	(51)	333 sh (4·33)	
IIe	$C_{16}H_{16}N_4O_3$	61·53	5·16	17·93	132—133	313 (4·48)	0·10
3-CH_3	(312·3)	61·30	5·12	17·58	(50)	328 sh (4·20)	
IIf	$C_{16}H_{16}N_4O_4$	58·53	4·91	17·06	143—145	323 (4·42)	0·22
4-CH_3O	(328·3)	58·20	5·02	17·12	(52)	338 sh (4·28)	
IIg	$C_{16}H_{16}N_4O_4$	58·53	4·91	17·06	105—107	324 (4·38)	0·25
2-CH_3O	(328·3)	58·43	4·87	16·98	(47)	340 sh (4·25)	
IIh	$C_{15}H_{13}N_5O_5$	52·48	3·81	20·40	113—114	292 (4·26)	0·04
2-NO_2	(343·3)	52·46	3·78	20·61	(40)		
IIi	$C_{15}H_{14}N_4O_3$	60·39	4·73	18·78	128—129	314 (4·43)	0·30
H	(298·3)	60·54	4·61	18·82	(52)	327 sh (4·22)	

[a] Calculated: 10·65% Cl, found: 10·78% 3l; [b] calculated: 10·65% Cl, found: 10·70% Cl; [c] calculated 10·65% Cl, found: 10·78% Cl; [d] calculated: 21·18% Br, found: 21·04% Br.

isomers of esters *IIa–IIi* and *IVa–IVi* was adduced from the ^{13}C NMR data reported separately[29].



IIj



IVj

SCHEME 2

TABLE IV

Ethyl 5-[5-(substituted phenyl)-2-furyl]-2-tetrazolyl acetates *IVa–IVi*

Compound R	Formula (M_r)	Calculated/Found % C	% H	% N	M.p., °C (yield, %)	λ_{max}, nm (log ε)	R_F
IVa 4-Cl	$C_{15}H_{13}ClN_4O_3$[a] (332·7)	54·14 54·38	3·93 3·84	16·83 16·93	99–101 (37)	312 (4·54) 328 sh (4·34)	0·72
IVb 3-Cl	$C_{15}H_{13}ClN_4O_3$[b] (332·7)	54·14 54·22	3·93 3·81	16·83 16·88	126–127 (41)	310 (4·23) 324 sh (4·23)	0·30
IVc 2-Cl	$C_{15}H_{13}ClN_4O_3$[c] (332·7)	54·14 54·24	3·93 3·91	16·83 16·89	88–89 (42)	308 (4·34) 323 sh (4·11)	0·38
IVd 4-Br	$C_{15}H_{13}BrN_4O_3$[d] (377·2)	47·76 47·81	3·47 3·54	14·85 14·77	105–106 (39)	314 (4·51) 329 sh (4·32)	0·80
IVe 3-CH_3	$C_{16}H_{16}N_4O_3$ (312·3)	61·53 61·49	5·16 5·20	17·93 17·94	96–97 (32)	309 (4·42) 324 sh (4·20)	0·26
IVf 4-CH_3O	$C_{16}H_{16}N_4O_4$ (328·3)	58·53 58·50	4·91 5·03	17·06 17·10	90–92 (38)	317 (4·44) 333 sh (4·24)	0·38
IVg 2-CH_3O	$C_{16}H_{16}N_4O_4$ (328·3)	58·53 58·51	4·91 4·98	17·06 17·10	109–110 (40)	319 (4·43) 335 sh (4·31)	0·45
IVh 2-NO_2	$C_{15}H_{13}N_5O_5$ (343·3)	52·48 52·44	3·81 3·90	20·40 20·46	100–101 (52)	292 (4·27)	0·10
IVi H	$C_{15}H_{14}N_4O_3$ (298·3)	60·39 60·42	4·73 4·60	18·78 18·64	84–86 (39)	308 (4·13) 324 sh (3·90)	0·60

[a] Calculated: 10·65% Cl, found: 10·72% Cl; [b] calculated: 10·65% Cl, found: 10·69% Cl; [c] calculated: 10·65% Cl, found: 10·66% Cl; [d] calculated: 21·18% Br, found: 21·11% Br.

TABLE V

Proton chemical shift values of esters *IIa*—*IIj*, *IVa*—*IVj*, *IIIa*, and *Va*

Compound	CH_3 (ester)	CH_2 (ester)	CH_2—N	H_{arom}	Other
IIa	1·12	4·15	5·91	7·53, 7·61, 7·77, 7·86 (AA'BB', 4 H, C_6H_4) 7·35 (d, H-4), 7·55 (d, H-3)	—
IVa	1·23	4·22	5·93	7·47, 7·56, 7·78, 7·86 (AA'BB', 4 H, C_6H_4) 7·25 (d, H-4), 7·36 (d, H-3)	—
IIb	1·14	4·17	5·93	7·41—7·85 (m, 6 H, C_6H_4 + H-4)	—
IVb	1·22	4·22	5·90	7·28—7·80 (m, 6 H, C_6H_4 + H-3 + H-4)	—
IIc	1·07	4·12	5·90	7·37—7·89 (m, 6 H, C_6H_4 + H-3 + H-4)	—
IVc	1·23	4·22	5·94	7·29—7·96 (m, 6 H, C_6H_4 + H-3 + H-4)	—
IId	1·12	4·15	5·90	7·73 (s, eclipsed AA'BB', 4 H, C_6H_4) 7·36 (d, H-4), 7·54 (d, H-3)	—
IVd	1·26	4·26	5·95	7·63, 7·72, 7·76, 7·86 (AA'BB', 4 H, C_6H_4) 7·28 (d, H-4), 7·39 (d, H-3)	—
IIe	1·12	4·16	5·90	7·17—7·63 (m, 4 H, C_6H_4) 7·27 (d, H-4), 7·54 (d, H-3)	2·38 (CH_3—)
IVe	1·23	4·22	5·92	7·08—7·64 (m, 4 H, C_6H_4) 7·19 (d, H-4), 7·35 (d, H-3)	2·37 (CH_3—)
IIf	1·13	4·16	5·88	7·02, 7·11, 7·70, 7·78 (AA'BB', 4 H, C_6H_4) 7·14 (d, H-4), 7·50 (d, H-3)	3·82 (CH_3O—)
IVf	1·23	4·22	5·91	6·99, 7·08, 7·71, 7·79 (AA'BB', 4 H, C_6H_4) 7·04 (d, H-4), 7·32 (d, H-3)	3·80 (CH_3O—)
IIg	1·13	4·15	5·91	7·18—7·82 (m, 6 H, C_6H_4 + H-3 + H-4)	3·96 (CH_3O—)
IVg	1·25	4·25	5·95	7·13—7·93 (m, 6 H, C_6H_4 + H-3 + H-4	3·97 (CH_3O—)
IIh	1·06	4·12	5·90	7·74—8·07 (m, 4 H, C_6H_4) 7·20 (d, H-4), 7·58 (d, H-3)	—
IVh	1·22	4·22	5·93	7·58—8·03 (m, 4 H, C_6H_4) 7·14 (d, H-4), 7·40 (d, H-3)	—
IIi	1·13	4·15	5·90	7·38—7·89 (m, 5 H, C_6H_5) 7·30 (d, H-4), 7·54 (d, H-3)	—
IVi	1·27	4·26	5·96	7·40—7·91 (m, 5 H, C_6H_5) 7·24 (d, H-4), 7·39 (d, H-3)	—
IIj	1·17	4·19	5·75	6·80 (dd, H-4), 7·40 (d, H-3), 8·06 (dd, H-5)	—

TABLE V
(*Continued*)

Compound	CH_3 (ester)	CH_2 (ester)	CH_2—N	H_{arom}	Other
IVj	1·22	4·21	5·89	6·73 (dd, H-4), 7·23 (d, H-3), 7·95 (dd, H-5)	—
IIIa	1·18	4·10	5·00	7·35—7·87 (m, 6 H, C_6H_4 + H-3 + H-4)	3·18 (CH_2CO_2)
Va	1·05	4·05	5·01	7·43—7·92 (m, 6 H, C_6H_4 + H-3 + H-4	3·15 (CH_2CO_2)

TABLE VI
Ethyl 3-{5-[5-(3-chlorophenyl)-2-furyl]-1- and -2-tetrazolyl}propionates *IIIa* and *Va*, and 3-{5-[5-(3-chlorophenyl)-2-furyl]-1- and -2-tetrazolyl}propionic acids *VIIIa* and *XIa*

Compound R	Formula (M_r)	Calculated/Found % C	% H	% N	M.p., °C (yield, %)	λ_{max}, nm (log ε)	R_F
IIIa	$C_{16}H_{15}ClN_4O_3$[a] (346·7)	55·42 / 55·56	4·36 / 4·34	16·15 / 16·09	89—91 (52)	314 (4·27) 329 sh (4·23)	0·22
Va	$C_{16}H_{15}ClN_4O_3$[b] (346·7)	55·42 / 55·48	4·36 / 4·34	16·15 / 16·20	61—62 (40)	309 (4·17) 323 sh (4·10)	0·27
VIIIa	$C_{14}H_{11}ClN_4O_3$[c] (318·7)	52·76 / 52·72	3·47 / 3·50	17·57 / 17·56	247—248 (89)	—	—
XIa	$C_{14}H_{11}ClN_4O_3$[d] (318·7)	52·76 / 52·77	3·47 / 3·50	17·57 / 17·58	235—237 (91)	—	—

[a] Calculated: 10·22% Cl, found: 10·23% Cl; [b] calculated: 10·22% Cl, found: 10·18% Cl; [c] calculated: 11·12% Cl, found: 11·10% Cl; [d] calculated: 11·12% Cl, found: 11·15% Cl.

The antiinflammatory effect of 5-substituted 2-furylacetic acids[30-32] and 5-substituted 1- and 2-tetrazolyl acetic acids has already been reported[8]. Tetrazolyl acetic acids *VIa—VIi* and *IXa—IXh* were subjected to an orientative screening test on three experimental inflammation models (caoline[33], carrageenine[34] and adjuvant[35]). A statistically significant antiinflammatory effect showed acids *VIb*, *VIi*, *IXa*, *IXb*, and *IXd*; it was, however, less pronounced when compared with that

of the standard Ibuprofen and was manifested preponderantly on one model of the experimental inflammation (adjuvant oedema, Table I). As evident from results of the acute oral toxicity, heterocyclic acids *VIa–VIi* and *IXa–IXh* are at peroral administration very little toxic and the LD_{50} value would exceed the dosis 1 g kg^{-1} for all substances under investigation (Table II).

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage, the IR spectra were measured with a Perkin–Elmer, model 457 apparatus in KBr at 2–3 mg per 20 mg concentration unless stated otherwise. The UV spectra were recorded with a Perkin–Elmer, model 340 spectrophotometer in the 220–350 nm range; concentration 4·0–6·0 . 10^{-4} mol l^{-1}, dioxane. The ^{1}H NMR spectra of hexadeuteriodimethyl sulfoxide solutions containing tetramethylsilane as reference were run with a Jeol FX-100 instrument operating at 100 MHz. Position isomers were separated

TABLE VII

5-[5-(Substituted phenyl)-2-furyl]-1-tetrazoylacetic acids *VIa–VIi*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Hal	
VIa	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	231–232
4-Cl	(304·7)	51·22	2·98	18·42	11·43	(94)
VIb	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	249–250
3-Cl	(304·7)	51·27	2·92	18·34	11·38	(94)
VIc	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	221–222
2-Cl	(304·7)	51·28	2·99	18·41	11·68	(93)
VId	$C_{13}H_9BrN_4O_3$	44·72	2·59	16·04	22·88	243–245
	(349·2)	44·76	2·62	16·09	22·78	(94)
VIe	$C_{14}H_{12}N_4O_3$	59·15	4·25	19·70	—	270–271
3-CH_3	(284·3)	59·14	4·31	19·78	—	(92)
VIf	$C_{14}H_{12}N_4O_4$	56·00	4·02	18·65	—	223–224
4-CH_3O	(300·3)	56·06	4·06	18·71	—	(94)
VIg	$C_{14}H_{12}N_4O_4$	56·00	4·02	18·65	—	258–259
2-CH_3O	(300·3)	56·02	4·12	18·70	—	(92)
VIh	$C_{13}H_9N_5O_5$	49·53	2·87	22·21	—	214–216
2-NO_2	(315·3)	49·54	2·90	22·30	—	(89)
VIi	$C_{13}H_{10}N_4O_3$	57·77	3·72	20·73	—	227–229
H	(270·2)	57·58	3·80	20·71	—	(91)

with a preparative chromatograph Prep LC/System 500 A (Waters) using PrePAK—500/Silica columns, the mobile phase being dichloromethane at a 250 ml min^{-1} flow rate and 1·5—2 MPa solvent pressure; retention time for 2-isomers was 4—5 min, for 1-isomers 6—20 min, injection 15—30 g depending on the separation capacity for the given pair and on the solubility of the mixture of esters. The process of separation was monitored by thin-layer chromatography, the R_F values refer to Silufol 254 sheets (Kavalier, Czechoslovakia); solvent system: dichloromethane.

The acute oral toxicity and the antiinflammatory effect was orientatively tested on mice (female, 19—22 g, Konárovice-breed S-strain) and on Wistar rats (150—170 g). The acute oral toxicity was estimated after a single administration of substances in gum arabic suspension in water (approx. 1/4 of the mass) to mice in a 1 g per 1 kg dose. The mortality of animals was determined in experimental groups of ten within 10 days from application. The antiinflammatory activity was tested by the scrrening method on rats after a peroral administration of substances to groups of four animals in 25, 50 and 100 mg kg^{-1} doses in form of a suspension with gum arabic in water. Tests with substances showing an antiinflammatory effect were complemented in a group of six animals and the results were statistically evaluated.

TABLE VIII

5-[5-(Substituted phenyl)-2-furyl]-2-tetrazoylacetic acids *IXa—IXi*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Hal	
IXa	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	198—200
	(304·7)	51·22	3·08	18·43	11·72	(94)
IXb	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	194—196
3-Cl	(304·7)	51·18	2·94	18·32	11·70	(96)
IXc	$C_{13}H_9ClN_4O_3$	51·24	2·97	18·38	11·63	221—224
2-Cl	(304·7)	51·34	3·06	18·45	11·83	(92)
IXd	$C_{13}H_9BrN_4O_3$	44·72	2·59	16·04	22·88	200—202
4-Br	(349·2)	44·64	2·51	16·14	22·68	(93)
IXe	$C_{14}H_{12}N_4O_3$	59·15	4·25	19·70*	—	165—167
3-CH_3	(284·3)	59·06	4·30	19·81	—	(90)
IXf	$C_{14}H_{12}N_4O_4$	56·00	4·02	18·65	—	180—182
4-CH_3O	(300·3)	56·08	4·10	18·64	—	(90)
IXg	$C_{14}H_{12}N_4O_4$	56·00	4·02	18·65	—	220—222
2-CH_3O)	(300·3)	56·02	3·98	18·70	—	(88)
IXh	$C_{13}H_9N_5O_5$	49·53	2·87	22·21	—	191—193
2-NO_2	(315·2)	49·48	2·98	22·34	—	(87)
IXi	$C_{13}H_{10}N_4O_3$	57·77	3·71	20·73	—	184—186
H	(270·2)	57·61	3·76	20·71	—	(92)

The 5-[5-(substituted phenyl)-2-furyl]-1*H*-1-tetrazoles (*I*) were prepared according to[1] as follows: 5-[5-(3-methylphenyl)-2-furyl]-1*H*-1-tetrazole (*Ia*) from 5-(3-methylphenyl)-2-furonitrile in a 81% yield, m.p. 236–237°C (ethanol). For $C_{12}H_{10}N_4O$ (226·2) calculated: 63·71% C, 4·46% H, 24·76% N; found: 63·86% C, 4·84% H, 24·72% N. UV spectrum, λ_{max}, nm (log ε); 308 (4·44), 325 sh (4·20). 5-[5-(2-methoxyphenyl)-2-furyl]-1*H*-1-tetrazole (*Ib*) from 5-(2-methoxyphenyl)-2-furonitrile, 79% yield, m.p. 190–192°C (ethanol). For $C_{12}H_{10}N_4O_2$ (242·2) calculated: 59·50% C, 4·16% H, 23·15% N; found: 59·32% C, 4·18% H, 23·20% N. UV spectrum, λ_{max}, nm (log ε); 322 (4·40), 336 sh (4·28).

Ethyl 5-[5-(Substituted phenyl)-2-furyl]-1- and -2-Tetrazolyl Acetates *IIa–IIi* and *IVa–IVi*

5-[5-(Substituted phenyl)-2-furyl]-1*H*-1-tetrazole (0·1 mol) was added to a stirred solution of sodium metal (2·3 g, 0·1 mol) in ethanol (350 ml) at room temperature. The solution was heated to the boiling temperature, and after 5 min ethyl bromoacetate (11·13 ml, 0·1 mol) was added and heating was continued for 16 h. A mixture of esters, crystallizing from the cooled solution was filtered off and washed with ethanol. The individual isomers were obtained by separation on a preparative chromatograph. The characteristic data of the title compounds are listed in Tables III and IV, their ^{1}H NMR data in Table V.

TABLE IX

Potassium 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetates *VIIa–VIIh*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Hal	
VIIa	$C_{13}H_8ClKN_4O_3$	45·55	2·35	16·34	10·34	338–340
4-Cl	(342·8)	45·48	2·30	16·41	10·46	(54)
VIIb	$C_{13}H_8ClKN_4O_3$	45·55	2·35	16·34	10·34	335–338
3-Cl	(342·8)	45·54	2·37	16·44	10·42	(56)
VIIc	$C_{13}H_8ClKN_4O_3$	45·55	2·35	16·34	10·34	328–330
2-Cl	(342·8)	45·58	2·40	16·43	10·29	(55)
VIId	$C_{13}H_8BrKN_4O_3$	40·32	2·08	14·46	20·63	336–338
4-Br	(387·3)	40·24	2·00	14·48	20·69	(61)
VIIe	$C_{14}H_{11}KN_4O_3$	52·16	3·43	17·37	—	332–333
3-CH_3	(322·4)	52·06	3·61	17·40	—	(70)
VIIf	$C_{14}H_{11}KN_4O_4$	49·69	3·27	16·55	—	326–328
4-CH_3O	(338·4)	49·60	3·32	16·56	—	(60)
VIIg	$C_{13}H_8KN_5O_5$	44·19	2·28	19·82	—	290–292
2-NO_2	(353·4)	44·21	2·30	19·88	—	(66)
VIIh	$C_{13}H_9KN_4O_3$	50·63	2·94	18·17	—	331–334
H	(308·4)	50·66	3·01	18·21	—	(58)

Ethyl 3-{5- 5-(3-chlorophenyl)-2-furyl]-1- and -2-tetrazolyl}propionates (*IIIa* and *Va*) were prepared as *IIa*—*IIi* and *IVa*—*IVi* with the exception that ethyl 3-bromopropionate was used instead of ethyl bromoacetate. Characteristic data of these compounds are presented in Table VI, their ^{1}H NMR data in Table V.

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

Ethanol (50 ml) and KOH (2·14 g, 37·5 mmol) in water (50 ml) was poured into ethyl 5-[5-(substituted phenyl)-2-furyl]-1-tetrazolyl acetate, the mixture was refluxed for 1 h, filtered and acidified with 15% hydrochloric acid while being hot. The separated acid was filtered off after cooling, washed with water and ethanol, and dried. Characteristic data of acids *VIa*—*VIi* are in Table VII, those of potassium salts *VIIa*—*VIIh* in Table IX.

5-[5-(Substituted phenyl)-2-furyl]-2-tetrazolylacetic Acids *IXa*—*IXi*

A 3M-methanolic KOH (10 ml) was poured into a solution of ethyl 5-[5-(substituted phenyl)--2-furyl] -2-tetrazolyl acetate (25 mmol) in hot methanol (100 ml). The separated potassium salt of the corresponding acid was dissolved by addition of water (50 ml) and heated for 1 h. The mixture was filtered off, the filtrate was acidified with 15% hydrochloric acid and the separated acid was filtered off and worked up as with compounds *VI*. Characteristic data of acids *IXa*—*IXi* are given Table VIII, those of potassium salts *Xa*—*Xg* in Table X.

TABLE X

Potassium 5-[5-(substituted phenyl)-2-furyl]-2-tetrazolyl acetates *Xa*—*Xg*

Compound R	Formula (M_r)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Hal	
Xa 4-Cl	$C_{13}H_8ClKN_4O_3$ (342·8)	45·55 45·51	2·35 2·38	16·34 16·38	10·34 10·42	317—319 (48)
Xb 3-Cl	$C_{13}H_8ClKN_4O_3$ (342·8)	45·55 45·50	2·35 2·38	16·34 16·32	10·34 10·26	310—312 (47)
Xc 2-Cl	$C_{13}H_8ClKN_4O_3$ (342·8)	45·55 45·49	2·35 2·37	16·34 16·28	10·34 10·56	303—304 (50)
Xd 4-Br	$C_{13}H_8BrKN_4O_3$ (387·3)	40·32 40·28	2·08 2·07	14·46 14·51	20·63 20·54	319—321 (54)
Xe 3-CH_3	$C_{14}H_{11}KN_4O_3$ (322·4)	52·16 52·21	3·43 3·44	17·37 17·41	— —	295—297 (65)
Xf 4-CH_3O	$C_{14}H_{11}KN_4O_4$ (338·4)	49·69 49·74	3·27 3·31	16·55 16·62	— —	302—303 (48)
Xg 2-NO_2	$C_{13}H_8KN_5O_5$ (353·4)	44·19 44·10	2·28 2·26	19·82 19·90	— —	275—277 (57)

3-{5-[5-(3-Chlorophenyl)-2-furyl]-1- and -2-tetrazolyl propionic}acids *VIIIa* and *XIa* were obtained by an alkaline hydrolysis of the corresponding esters *IIIa* and *Va* according to procedures for acids *VIa—VIi* and *IXa—IXi*. Characteristic data of these compounds are listed in Table VI.

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