Synthesis of some substituted tetrazolylacetic acids

[a]Ľ. JANDA and [b]Z. VOTICKÝ

[a]*Drug Research Institute, CS-900 01 Modra*

[b]*Institute of Chemistry, Centre for Chemical Research, Slovak Academy of Sciences, CS-842 38 Bratislava*

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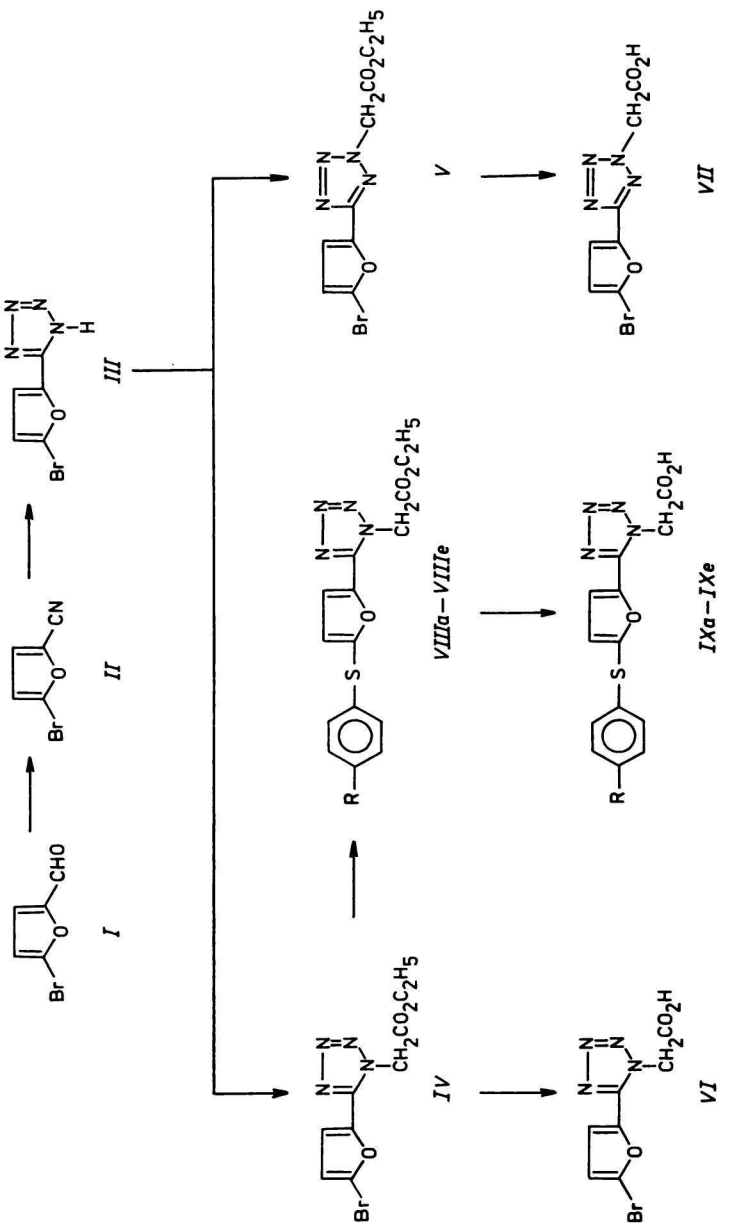
Alkylation of 5-(5-bromo-2-furyl)-1*H*-tetrazole with ethyl bromoacetate afforded a mixture of ethyl 5-(5-bromo-2-furyl)-1-tetrazolylacetate and ethyl 5-(5-bromo-2-furyl)-2-tetrazolylacetate; these were chromatographically separated and the ester substituted in position 1 was the substrate for the nucleophilic substitution with 4-substituted thiophenols. The resulting ethyl 5-[5-(4-R-phenylthio)-2-furyl]-1-tetrazolylacetates were hydrolyzed to corresponding acids.

Алкилирование 5-(5-бром-2-фурил)-1*H*-тетразола этилбромацетатом привело к смеси этил-5-(5-бром-2-фурил)-1-тетразолилацетата и этил-5-(5-бром-2-фурил)-2-тетразолилацетата. Смесь была хроматографически разделена, и эфир, замещенный в положении 1, подвергся нуклеофильному замещению с замещенными в положении 4 тиофенолами. Образовавшиеся в результате этил-5-[5-(4-R-фенилтио)-2-фурил]-1-тетразолилацетаты были затем гидролизованы в соответствующие кислоты.

Our preceding paper [1] concerning the preparation of new semisynthetic cephalosporin antibiotics, presented the synthesis of 5-[5-(4-R-phenylthio)-2--furyl]-1-tetrazolylacetic acids by the imidoyl chloride method in low yields. Preparation of acids *IXa—IXe* proceeded *via* a six-step synthesis from 5-bromo--2-furaldehyde (*I*) [2] through 5-bromo-2-furonitrile (*II*) [3], 5-(5-bromo-2--furyl)-1*H*-tetrazole (*III*) [4], ethyl 5-(5-bromo-2-furyl)-1-tetrazolylacetate (*IV*), and ethyl 5-[5-(4-R-phenylthio)-2-furyl]-1-tetrazolylacetates (*VIIIa—VIIIe*), as shown in Scheme 1.

The product of alkylation depends on the character of the substituent at C-5 of the tetrazolyl ring [5—7] and on the reaction medium [5, 6], as follows from papers [5—9] reporting on the alkylation of 5-R-1*H*-tetrazoles. The ratio of isomers is substantially influenced by induction effects of substituents at the tetrazole carbon atom; their electron-accepting properties orientate the S_E alkylation preferentially to N-2 [10—12]. Alkylation of *III* with ethyl bromoacetate in ethanol led to a mixture of position isomers *IV* and *V* in an approximately 2 1 mass ratio in favour of the 2-isomer. This finding is in agreement with papers published so far on alkylation of tetrazoles [10—12].



Scheme 1

For *VIIIa–VIIIe* and *IXa–IXe*

The nucleophilic substitution to position 5 of a 2,5-disubstituted furan is known to proceed most easily with sulfur-containing reactants, which replace bromine, iodine, and chlorine [13—15], and also nitro groups [16—18] providing the reacting furan derivative bears an electron-accepting group at C-2 [19]. The halogen atom is best replaced with 5-halo-2-nitrofurans [20]; nevertheless, a nitrogen-containing heterocycle, as *e.g.* benzimidazole [21] can play an activating role for this S_N reaction as well. Our experiments show that electron-accepting effect of 1-substituted alkyltetrazole in position 2 of 2,5-disubstituted furan is sufficient to promote the nucleophilic replacement of bromine atom for sulfur-containing nucleophiles in position 5 of the furan skeleton. Ethyl 5-(5--bromo-2-furyl)-1-tetrazolylacetate (*IV*) employed for S_N reaction with sodium salts of 4-substituted thiophenols afforded after a 5 h reflux in absolute ethanol ethyl 5-[5-(4-R-phenylthio)-2-furyl]-1-tetrazolylacetates (*VIIIa—VIIIe*) in 82—87 % yield. Ethyl 5-(5-bromo-2-furyl)-2-tetrazolylacetate (*V*) was not utilized for S_N reactions.

For antibacterial tests the most interesting compounds were considered the 1-substituted tetrazolylacetic acids, since 7-(5-R-1-tetrazolyl)acetamidocephalosporan derivatives derived from them reveal a higher antibacterial activity than those of the corresponding 7-(5-R-2-tetrazolyl)acetamidocephalosporan [22]. Tetrazolylacetic acids (*IXa—IXe*) were prepared by alkaline hydrolysis of the corresponding ethyl esters *VIIIa—VIIIe* with hot methanolic potassium hydroxide ($c(\mathrm{KOH}) = 3\ \mathrm{mol\ dm^{-3}}$). From ethyl esters *IV* and *V* also 5-(5-bromo-2-furyl)-1-tetrazolylacetic (*VI*) and 5-(5-bromo-2-furyl)-2-tetrazolylacetic (*VII*) acids were obtained under the above-mentioned conditions.

The IR, UV, and ^{1}H NMR spectral data of ethyl 5-[5-(4-R-phenylthio)-2--furyl]-1-tetrazolylacetates (*VIIIa—VIIIe*) are listed in our preceding paper [1]. The IR spectrum of ethyl 5-(5-bromo-2-furyl)-1-tetrazolylacetate (*IV*) revealed bands characteristic of asymmetric and symmetric stretching vibrations of a disubstituted furan at $\tilde{\nu} = 1012$ and $1224\ \mathrm{cm^{-1}}$, respectively, and another one, corresponding to out-of-plane C—H bond vibrations of furan ring at $\tilde{\nu} = 930\ \mathrm{cm^{-1}}$ The presence of a disubstituted tetrazole in the molecule of *IV* was corroborated by appearance of the band at $\tilde{\nu} = 1619\ \mathrm{cm^{-1}}$ indicative of stretching vibrations of a disubstituted tetrazole, and another one associated with skeletal vibrations of disubstituted tetrazole at $\tilde{\nu} = 1108\ \mathrm{cm^{-1}}$ Stretching vibrations of the carbonyl group appeared as a significant band at $\tilde{\nu} = 1750\ \mathrm{cm^{-1}}$ The IR spectrum of the 2-isomeric compound *V* was characterized by absorption bands due to a disubstituted furan at $\tilde{\nu} = 930$, 1010, and $1220\ \mathrm{cm^{-1}}$, and disubstituted tetrazole at $\tilde{\nu} = 1120$ and $1628\ \mathrm{cm^{-1}}$ Stretching vibrations of the carbonyl group appeared at $\tilde{\nu} = 1744\ \mathrm{cm^{-1}}$

The UV spectrum of *IV* possesses a K band at $\lambda = 272$ nm, whilst that of the isomeric *V* was hypsochromically shifted to $\lambda = 265$ nm. This phenomenon is

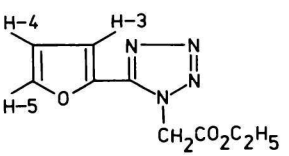
associated with extension of conjugation, which is possible with 1-isomers to a greater extent [23].

The ^{1}H NMR spectra of compounds *IV* and *V* are in line with those of isomeric tetrazoles [23, 24]. Protons of the methylene group attached to the tetrazole ring in position 1 resonate in higher field than those of the 2-isomeric compound *V* Another characteristic feature in the spectrum are signals of protons at the furan ring; that of H-3 was downfield shifted due to ring anisotropy of the tetrazole ring. The difference in the chemical shift values of ethyl esters *IV* and *V* ($\Delta\delta = 0.15$ ppm) is sufficient enough to distinguish both isomers; moreover, this difference is almost identical with that for compounds *X* and *XI* ($\Delta\delta = 0.14$ ppm) [8]. The ^{1}H NMR data of isomeric pairs *IV*, *V* and *X*, *XI* are presented in Table 1.

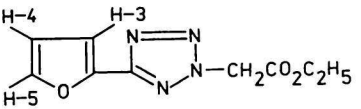
Table 1

Chemical shift data (δ/ppm) for protons of esters *IV*, *V*, *X*, and *XI*

Compound	CH_3 (Ester)	CH_2 (Ester)	CH_2—N	Furan ring protons
IV	1.21	4.21	5.74	6.95 (d, 1H, H-4), 7.44 (d, 1H, H-3)
V	1.22	4.21	5.89	6.85 (d, 1H, H-4), 7.28 (d, 1H, H-3)
X	1.17	4.19	5.75	6.80 (dd, H-4), 7.40 (d, H-3), 8.06 (dd, H-5)
XI	1.22	4.21	5.89	6.73 (dd, H-4), 7.23 (d, H-3), 7.95 (dd, H-5)



X



XI

Experimental

Melting points were determined on a Kofler micro hot-stage. The IR spectra of esters and acids ($w = 0.3$—0.4 %) were measured in KBr pellets with a Perkin—Elmer, model 457, spectrophotometer, the UV spectra of esters in dioxan ($c = (4.0$—$6.0) \times 10^{-4}$ mol dm^{-3}) were taken with a Perkin—Elmer, model 340, apparatus in the range of $\lambda_{max} = 220$—350 nm. The ^{1}H NMR spectra of hexadeuterodimethyl sulfoxide solutions containing tetramethylsilane as internal reference were recorded with an FX-100

(Jeol) instrument operating at the frequency 100 MHz. Isomeric esters *IV* and *V* were separated with a preparative chromatograph PrepLC/System 500 A (Waters) using Prep-PAK-500/SILICA column, mobile phase dichloromethane, flow rate 250 $cm^3 min^{-1}$, pressure 1.5—2.0 MPa, retention time for 2-isomer *V* 4—5 min, for 1-isomer *IV* 16—20 min, feed 20 g. Separation was monitored by thin-layer chromatography on Silufol 254 (Kavalier, Czechoslovakia) sheets, with dichloromethane.

5-Bromo-2-furaldehyde (*I*) was prepared by a direct bromination of a distilled fresh 2-furaldehyde in dichloroethane under catalysis of sulfur and hydroquinone [2]. 5-Bromo-2-furonitrile (*II*) was obtained by condensation of 5-bromo-2-furaldehyde (*I*) with hydroxylamine in pyridine and dehydration of the intermediate oxime with acetic anhydride *in situ* [3].

5-(5-Bromo-2-furyl)-1H-tetrazole (III)

5-Bromo-2-furonitrile (172 g; 1 mol), sodium azide (71.5 g; 1.1 mol), and ammonium chloride (58.8 g; 1.1 mol) in dimethylformamide (500 cm^3) were stirred at 100 °C for 4 h, the solvent was removed under reduced pressure and the oily residue was dissolved in water (150 cm^3). Charcoal was added to the solution, which was filtered, cooled and acidified with hydrochloric acid (w = 15 %). The precipitated tetrazole was filtered off, washed with water and crystallized from the mixture ethanol—water. Yield = 161.3 g (75 %), m.p. = 163—164 °C.

For $C_5H_3BrN_4O$ (M_r = 215.0) w_i(calc.): 27.93 % C, 1.40 % H, 26.06 % N, 37.17 % Br; w_i(found): 28.06 % C, 1.48 % H, 26.08 % N, 37.12 % Br. UV spectrum (dioxan), λ_{max}/nm (log (ε/(m^2 mol^{-1}))): 266 (4.21).

Ethyl 5-(5-bromo-2-furyl)-1-tetrazolylacetate (IV) and 5-(5-bromo-2-furyl)-2-tetrazolylacetate (V)

5-(5-Bromo-2-furyl)-1*H*-tetrazole (112.9 g; 0.7 mol) was added to a solution of sodium metal (16.1 g; 0.7 mol) in dry ethanol (2450 cm^3), the solution was heated to reflux for 5 min, and ethyl bromoacetate (77.9 cm^3; 0.7 mol) was successively added. The mixture was refluxed for 16 h, the solvent was distilled off and the remaining oily mixture containing crystals was extracted with dichloromethane (250 cm^3); crystalline NaBr was filtered off and the filtrate was washed with aqueous sodium hydrogencarbonate and water, dried with sodium sulfate and the solvent was removed. The remaining mixture of esters (196 g; 93 %) was separated with a preparative chromatograph to give the respective esters *IV* and *V* Their ^{1}H NMR spectral values and characteristic data are presented in Tables 1 and 2, respectively.

Table 2

Characteristic data of ethyl esters *IV* and *V* and acids *VI* and *VII*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.	λ_{max}/nm (log (ε/(m^2 mol^{-1})))	R_f
			C	H	N	%	°C		
IV	$C_9H_9BrN_4O_3$[a]	301.1	35.90	3.01	18.60	31	101 102	272	0.30
			36.01	3.04	18.57			(3.22)	
V	$C_9H_9BrN_4O_3$[a]	301.1	35.90	3.01	18.60	58	68 –69	265	0.44
			35.88	2.98	18.56			(3.25)	
VI	$C_7H_5BrN_4O_3$	273.1	30.79	1.84	20.51	93	175—177	—	—
			30.88	1.92	20.54				
VII	$C_7H_5BrN_4O_3$	273.1	30.79	1.84	20.51	95	201—203	—	—
			30.78	1.81	20.36				

a) Crystallized from ethanol.

Table 3

Characteristic data of ethyl esters *VIIIa*—*VIIIe*

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
				C	H	N	S	%	°C
VIIIa	H	$C_{15}H_{14}N_4O_3S$	330.4	54.53	4.27	16.95	9.70	82	84—86
				54.46	4.26	17.00	9.72		
VIIIb	CH_3	$C_{16}H_{16}N_4O_3S$	344.4	55.80	4.68	16.26	9.31	85	90—91
				55.76	4.70	16.32	9.32		
VIIIc	CH_3O	$C_{16}H_{16}N_4O_4S$	360.4	53.32	4.47	15.54	8.89	86	85—87
				53.30	4.46	15.55	8.93		
VIIId	Cl	$C_{15}H_{13}ClN_4O_3S$[a]	364.8	49.38	3.59	15.35	8.78	87	92—93
				49.41	3.62	15.32	8.80		
VIIIe	F	$C_{15}H_{13}FN_4O_3S$	348.4	51.72	3.76	16.08	9.20	86	88—89
				51.74	3.82	16.01	9.18		

a) w_{Cl}(calc.) = 9.71 %; w_{Cl}(found) = 9.69 %.

Ethyl 5-[5-(4-R-phenylthio)-2-furyl]-1-tetrazolylacetates (VIIIa—VIIIe)

A 4-substituted thiophenol (36 mmol) was dissolved in solution of sodium metal (0.83 g; 36 mmol) in dry ethanol (140 cm^3). Ethyl 5-(5-bromo-2-furyl)-1-tetrazolylacetate (10.54 g; 35 mmol) was poured into the clear solution of the proper sodium thiolate and the mixture was refluxed for 5 h. The separated sodium bromide was filtered off, the filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate (50 cm^3). The organic layer was washed with water (30 cm^3), dried with sodium sulfate, evaporated, and the oily or crystalline residue was crystallized from ethanol. Characteristic data for compounds *VIIIa—VIIIe* are listed in Table 3.

5-[5-(4-R-Phenylthio)-2-furyl]-1-tetrazolylacetic acids (IXa—IXe) and 5-(5-bromo-2-furyl)-1- and -2-tetrazolylacetic acids (VI and VII)

Methanolic potassium hydroxide (10 cm^3; $c(KOH) = 3\ mol\ dm^{-3}$) was added to a solution of substituted ethyl tetrazolylacetate (25 mmol) in hot methanol (100 cm^3). The mixture was stirred at 60 °C for 1 h, the solvent was distilled off and the residue was dissolved in water (50 cm^3) with charcoal added. After filtration the solution was acidified with hydrochloric acid ($w = 15$ %) to pH = 1, the separated acid was filtered off, washed with water and crystallized from dilute ethanol ($w = 50$ %). Characteristic data for acids *IXa—IXe* and *VI* and *VII* are given in our previous paper [1] and Table 2, respectively.

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