Synthesis of some substituted tetrazolylacetic acids

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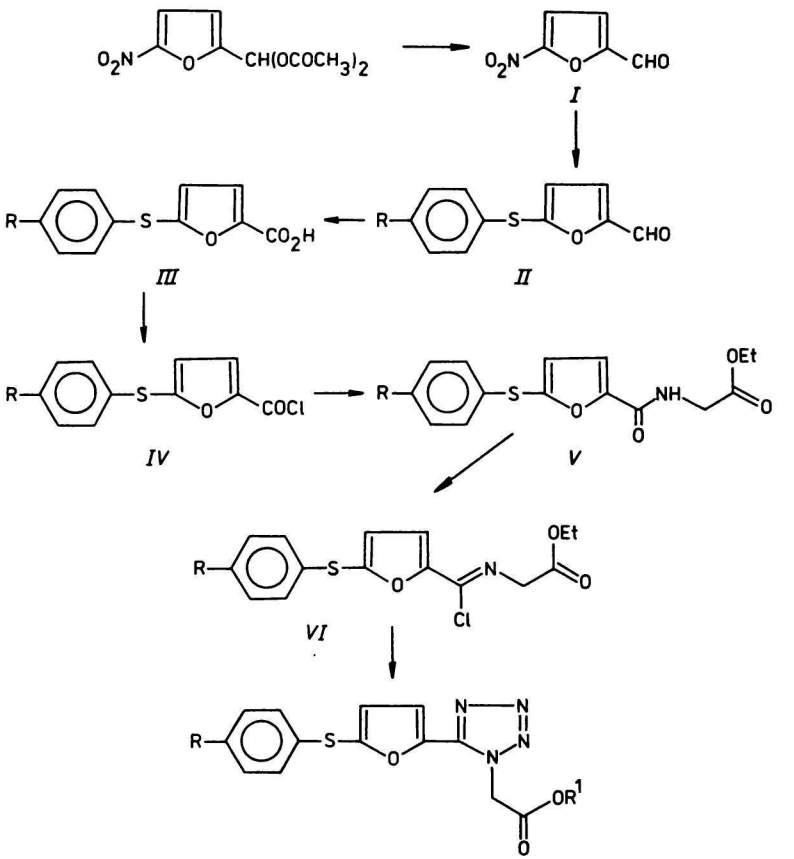
5-[5-(Substituted phenylthio)-2-furyl]tetrazol-1-ylacetic acids were prepared from ethyl 5-(substituted phenylthio)-2-furylcarbamidoacetates and phosphorus pentachloride *via* the corresponding imidoyl chlorides, which on treatment with sodium azide afforded the appropriate ethyl 5-[5-(substituted phenylthio)-2-furyl]tetrazolylacetates. Free acids serving as an intermediate in preparation of semisynthetic cephalosporins were obtained by an alkaline hydrolysis.

5-[5-(Замещенные фенилтио)-2-фурил]тетразол-1-илуксусные кислоты были получены из этил-5-(замещенных фенилтио)-2-фурилкарбамидоацетатов и пятихлористого фосфора через соответствующие имидоилхлориды, которые реакцией с азидом натрия образовали соответствующие этил-5-[5-(замещенные фенилтио)-2-фурил]тетразолилацетаты. Путем их щелочного гидролиза были синтезированы упомянутые кислоты как промежуточные продукты синтеза новых полусинтетических цефалоспорановых антибиотиков.

Our preceding paper [1] concerned the synthesis of 5-[5-(substituted phenyl)-2-furyl]tetrazol-1-ylacetic acids and their ethyl esters from the corresponding imidoyl chlorides and azide ion. 5-[5-(Substituted phenylthio)-2-furyl]tetrazol-1-ylacetic acids *VIII* were prepared by an analogous eight-step synthesis starting from 5-nitro-2-furaldehyde (*I*) *via* the 5-(4-substituted phenylthio)-2-furaldehydes *II*, 5-(4-substituted phenylthio)-2-furancarboxylic acids *III*, 5-(4-substituted phenylthio)-2-furylcarboxylic chlorides *IV*, ethyl 5-(4-substituted phenylthio)-2-furylcarbamidoacetates *V*, substituted imidoyl chlorides *VI*, and the final ethyl 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetates *VII* as illustrated in Scheme 1.

5-Phenylthio-2-furaldehydes and 5-(4-acetamidophenylthio)-2-furaldehydes were obtained by a nucleophilic substitution reaction from 5-bromo-2-furaldehyde and the corresponding thiolate in aqueous ethanol according to a procedure describing the preparation of this type of aldehydes [2]. Further and also already known aldehydes were synthesized from the same starting material in acetone in the presence of an equimolar amount of potassium carbonate [3].



Scheme 1

5-(4-Chlorophenylthio)-2-furaldehyde was also reported [4] to be prepared by an S_N reaction of 5-nitro-2-furaldehyde with sodium 4-chlorophenylthiolate in ethanol; the yield of this synthesis was, however, lower than that with 5-bromo--2-furaldehyde under these conditions. 5-(4-Substituted phenylthio)-2-furaldehydes *IIa*—*IIe* were obtained by an S_N reaction of 5-nitrofuraldehyde with the respective substituted thiophenols in acetone in the presence of an equimolar amount of potassium carbonate by a 7 h-stirring at room temperature. Yields of

aldehydes *IIa—IId* were by only 10 % lower than those from 5-bromo-2-furaldehyde as starting material under the same conditions [3]. 5-(4-Substituted phenylthio)-2-furancarboxylic acids *IIIa—IIIe* were synthesized according to [5] with the difference of modifying the temperature from ambient to 50—60 °C. The isolation was simplified and the recovery of acids was higher by addition of ethanol into the hot reaction mixture prior to filtration of silver, since ethanol increased the solubility of sodium salts of acids being formed. This step avoided losses due to a partial removal of insoluble salts of acids together with the metallic silver. Acids freed in the presence of ethanol were thus purer. 5-(4-Substituted phenylthio)-2-furylcarboxylic chlorides *IVa—IVe* obtained in high yields and fair purity by chlorination of the corresponding acids with phosphorus pentachloride in the absence of reaction medium were directly used for preparation of ethyl 5-(4-substituted phenylthio)-2-furylcarbamidoacetates *Va—Ve* by an *N*-acylation of glycine ethyl ester in chloroform in the presence of trimethylamine in a 100 % excess. The corresponding imidoyl chlorides *VI* were synthesized by heating the equimolar mixture of amides *V* with phosphorus pentachloride in benzene, where hydrogen chloride was vigorously freed already at 60 °C. The formation of chlorides was finished within 5 min after the benzene solution began to boil, when the evolution of hydrogen chloride ceased. The chlorides *VI* dissolved in dimethylformamide were added to a suspension of a 100 % excess of sodium azide and the mixture was worked up to afford ethyl 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetates *VIIa—VIIe* in 29 to 35 % yields. The 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetic acids *VIIIa—VIIIe* resulted from an alkaline hydrolysis of the corresponding ethyl esters with 3 mol dm^{-3} methanolic potassium hydroxide. The potassium salts should be acidified when cool in order to obtain the freed acids in crystalline form; acidification of hot solutions may lead to oily products. The acids were obtained in 100 % yields, losses due to crystallization were up to 10 %. The low melting points of azides *V* prevented their purification by crystallization in reasonable yields and therefore, they were used for further reaction with phosphorus pentachloride in crude state.

The characteristic bands in IR spectra of ethyl 5-(4-substituted phenylthio)-2--furylcarbamidoacetates *Va—Ve* and ethyl 5-[5-(4-substituted phenylthio)-2--furyl]tetrazol-1-ylacetates *VIIa—VIIe* are listed in Tables 5 and 6, respectively. The IR spectra of esters *VIIa—VIIe* revealed in the $\tilde{\nu} = 1622—1478\ cm^{-1}$ region several absorption bands belonging to stretching vibrations of C=N, C=C, and N=N bonds; an interaction leading to merging of bands could not be excluded. The bands could unequivocally be ascribed only after preparation and taking the IR spectra of ethyl 1*H*-tetrazol-1-yl acetate [6] and ethyl 5-(2-furyl)tetrazol-1-ylacetate [7], which show that bands at $\tilde{\nu} = 1622—1617\ cm^{-1}$ belong to stretching vibrations of C=N bonds, while those of C=C bonds

appeared at lower values at $\tilde{\nu} = 1599—1588\,cm^{-1}$ and $\tilde{\nu} = 1499—1478\,cm^{-1}$. The most intense carbonyl band of 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetates was downfield shifted to $\tilde{\nu} = 1740—1719\,cm^{-1}$ when compared with the corresponding esters. The UV spectra of esters *VIIa—VIIe* show a feeble band at $\lambda_{max} = 271—273\,nm$.

The ^1H NMR spectral data of esters *VIIa—VIIe* are listed in Table 7, and as seen, they are in line with those of 1-isomeric tetrazoles [1, 8]. The effect of substituents in *para* position at the benzene ring on chemical shifts of protons was not manifested.

Experimental

The IR spectra of amides, esters, and acids ($c = (5.5—6.5) \times 10^{-6}\,mol\,dm^{-3}$) were measured in KBr, those of chlorides ($c = (2.0—2.5) \times 10^{-4}\,mol\,dm^{-3}$) were recorded in chloroform on a Perkin—Elmer, model 457 spectrophotometer. The UV spectra of dioxan solutions ($c = (2.0—2.5) \times 10^{-4}\,mol\,dm^{-3}$) were recorded in the $\lambda_{max} = 220—350\,nm$ range with a Perkin—Elmer, model 340 apparatus. Melting points were determined on a Kofler micro hot-stage.

5-Nitro-2-furaldehyde (I)

This compound was obtained by an acid hydrolysis of a commercially available (Merck—Schuchardt) 5-nitro-2-furyldiacetate according to [23].

5-(4-Fluorophenylthio)-2-furaldehyde (IIe)

A solution of 5-nitro-2-furaldehyde (14.1 g; 0.1 mol) in acetone (100 cm^3) was poured into the stirred mixture of 4-fluorothiophenol (12.8 g; 0.1 mol) and potassium carbonate (13.8 g; 0.1 mol) in acetone (200 cm^3) at room temperature. The mixture was stirred for additional 7 h, heated with charcoal, filtered and the filtrate was evaporated to dryness. The oily residue was dissolved in ethyl acetate (100 cm^3), washed with water (25 cm^3), dried over sodium sulfate, purified with charcoal, filtered and the filtrate was evaporated and crystallized from ether—light petroleum. The yield of *II* was 16.7 g (75 %), m.p. = 30—31 °C.

For $C_{11}H_7FO_2S$ ($M_r = 222.2$) w_i(calc.): 59.45 % C, 3.17 % H, 14.42 % S; w_i(found): 59.51 % C, 3.23 % H, 14.38 % S. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1681 (ν(C = O)).

5-(4-Fluorophenylthio)-2-furancarboxylic acid (IIIe)

Silver nitrate (47.56 g; 0.28 mol) dissolved in water (210 cm^3) was added at room temperature to sodium hydroxide (22.4 g; 0.56 mol) in water (160 cm^3) in one portion. 5-(4-Fluorophenylthio)-2-furaldehyde (15.55 g; 70 mmol) dissolved in ethanol (17.5 cm^3) was poured at once into the brown precipitate of silver oxide and the mixture was stirred at 50 °C for 1 h within which silver became to separate (the mixture turned black and the flask was coated with silver mirror). Ethanol (70 cm^3) was added to the hot mixture and after 5 min the suspension was filtered off and the warm filtrate was acidified with 15 % hydrochloric acid. The precipitated and cooled 5-(4-fluorophenylthio)-2-furancarboxylic acid was filtered off, washed with water and crystallized from 50 % aqueous ethanol. Yield = 15.2 g (91 %), m.p. = 147—149 °C.

For $C_{11}H_7FO_3S$ (M_r = 238.2) w_i(calc.): 55.45 % C, 2.96 % H, 13.45 % S; w_i(found): 55.51 % C, 2.89 % H, 13.42 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1710 (ν(C=O)).

5-(4-Substituted phenylthio)-2-furancarboxylic chlorides IVa—IVe

5-(4-Substituted phenylthio)-2-furancarboxylic acid (60 mmol) and phosphorus pentachloride (1.236 g; 60.7 mmol) were plunged into a 60 °C hot water bath with stirring. After 5 min the green-yellow liquid was evaporated to dryness, benzene (10 cm^3) poured into the oily distillation residue was distilled off together with the remnants of phosphorus oxychloride. The solid rest was extracted with chloroform (20 cm^3), the extract was purified with charcoal, filtered and the solvent was removed. The product can be crystallized from heptane. Yields of crude chlorides varied within 91 and 94 %. Characteristic data of chlorides *IVa—IVe* are presented in Table 1.

Ethyl 5-(4-substituted phenylthio)-2-furyl-carbamidoacetates Va—Ve

Triethylamine (11.4 cm^3; 80 mmol) was added to a suspension of ethyl glycinium chloride (5.58 g; 40 mmol) in chloroform cooled to −5 °C at temperature not exceeding 0 °C. After the mixture had clarified 5-(4-substituted phenylthio)-2-furancarboxylic chloride (40 mmol) in chloroform (20 cm^3) was added at −5 to 0 °C. The stirred mixture was kept at this temperature for 30 min and then at an ambient temperature for 1 h. The chloroform solution was successively washed with 5 % hydrochloric acid, water, 5 % sodium carbonate, and water to neutral reaction. The chloroform solution was dried with sodium sulfate, filtered and the solvent was evaporated. The product can be crystallized from aqueous ethanol. Yields of crude amides varied from 91 to 96 %. Characteristic data of compounds *Va—Ve* are listed in Table 2.

Table 1

Characteristic data of chlorides *IVa*—*IVe*

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.	ν(C=O) $\tilde{\nu}$(CHCl$_3$)/cm^{-1}
				C	H	S	Cl	%	°C	
IVa	H	$C_{11}H_7ClO_2S$	238.7	55.35	2.96	13.43	14.85	93	35—36	1745
				55.43	3.02	13.40	14.77			
IVb	CH_3	$C_{12}H_9ClO_2S$	252.7	57.03	3.58	12.68	14.03	91	69—70	1745
				56.92	3.64	12.70	14.12			
IVc	CH_3O	$C_{12}H_9ClO_3S$	268.7	53.64	3.36	11.93	13.19	92	64—65	1750
				53.76	3.46	12.05	12.96			
IVd	Cl	$C_{11}H_6Cl_2O_2S$	273.1	48.37	2.21	11.74	25.96	94	58—60	1749
				48.50	2.18	11.78	26.05			
IVe	F	$C_{11}H_6ClFO_2S$	256.7	51.47	2.35	12.49	13.81		48—49	1747
				51.56	2.31	12.42	13.78			

Table 2

Characteristic data of substituted ethyl carbamidoacetates *Va*—*Ve*

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
				C	H	N	Hal	%	°C
Va	H	$C_{16}H_{15}NO_4S$[a]	305.4	59.00	4.95	4.58		96	100—101
				58.92	5.10	4.62			
Vb	CH_3	$C_{16}H_{17}NO_4S$[b]	319.4	60.17	5.36	4.38		93	50—52
				60.22	5.40	4.41			
Vc	CH_3O	$C_{16}H_{17}NO_5S$[c]	335.2	57.28	5.11	4.12		91	65—67
				57.33	5.08	4.19			
Vd	Cl	$C_{15}H_{14}ClNO_4S$	339.8	53.02	4.15	4.12	9.43	94	89—91
				53.08	4.17	4.11	9.50		
Ve	F	$C_{15}H_{14}FNO_4S$	324.3	55.54	4.35	4.31	9.88	95	77—79
				55.67	4.41	4.34	9.92		

a) w_S(calc.) = 10.50 %, w_S(found) = 10.43 %; *b*) w_S(calc.) = 10.03 %, w_S(found) = 9.89 %; *c*) w_S(calc.) = 9.56 %, w_S(found) = 9.67 %.

Table 3

Characteristic data of substituted ethyl tetrazolylacetates *VIIa*—*VIIe*

Compound	R	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield	M.p.	λ_{max}/nm	log (ε/(m^2 mol^{-1}))
				C	H	N	S	%	°C		
VIIa	H	$C_{15}H_{14}N_4O_3S$	330.4	54.53	4.27	16.27	9.70	30	84—86	272	3.18
				54.62	4.30	16.94	9.71				
VIIb	CH_3	$C_{16}H_{16}N_4O_3S$	344.4	55.80	4.68	16.26	9.31	31	90—91	272	3.19
				55.88	4.60	16.30	9.36				
VIIc	CH_3O	$C_{16}H_{16}N_4O_4S$	360.4	53.32	4.47	15.54	8.89	29	85—87	273	3.16
				53.32	4.50	15.60	8.84				
VIId	Cl	$C_{15}H_{13}ClN_4O_3S$[a]	364.8	49.38	3.59	15.35	8.78	33	92—93	271	3.20
				49.42	3.64	15.25	8.90				
VIIe	F	$C_{15}H_{13}FN_4O_3S$	348.4	51.72	3.76	16.08	9.20	31	88—89	273	3.18
				51.76	3.69	16.06	9.28				

a) w_{Cl}(calc.) = 9.71 %, w_{Cl}(found) = 9.68 %.

Table 4

Characteristic data of substituted tetrazolylacetic acids *VIIIa*—*VIIIe*

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
				C	H	N	S	%	°C
VIIIa	H	$C_{13}H_{10}N_4O_3S$	302.3	51.64	3.33	18.53	10.60	91	131—132
				51.63	3.39	18.60	10.76		
VIIIb	CH_3	$C_{14}H_{12}N_4O_3S$	316.3	53.15	3.82	17.71	10.13	90	159—161
				53.23	3.94	17.80	10.18		
VIIIc	CH_3O	$C_{14}H_{12}N_4O_4S$	332.3	50.59	3.63	16.85	9.64	91	169—171
				50.66	3.68	16.80	9.52		
VIIId	Cl	$C_{13}H_9ClN_4O_3S$[a]	336.8	46.36	2.69	16.63	9.52	90	114—116
				46.42	2.74	16.60	9.51		
VIIIe	F	$C_{13}H_9FN_4O_3S$	320.3	48.74	2.83	17.49	10.01	90	94—95
				48.79	2.91	17.50	10.08		

a) w_{Cl}(calc.) = 10.52 %, w_{Cl}(found) = 10.68 %.

Table 5

IR spectral data of substituted ethyl carbamidoacetates *Va—Ve*

Compound	$\tilde{\nu}$/cm^{-1}					
	ν(C=O)$_{\text{2nd band of amides}}$	ν(N—H)	ν(C=O)$_{\text{ester}}$	ν(C—O)$_{\text{ester}}$	ν(C—O—C)$_{\text{as}}$	ν(C—O—C)$_{\text{s}}$
Va	1640	3229	1740	1201	1288	1019
Vb	1645	3228	1739	1197	1290	1010
Vc	1648	3236	1751	1199	1282	1011
Vd	1644	3239	1747	1199	1296	1005
Ve	1644	3233	1749	1200	1298	1007

Table 6

IR spectral data of substituted ethyl tetrazolylacetates *VIIa—VIIe*

Compound	$\tilde{\nu}$/cm^{-1}						
	ν(C=O)	ν(C—O)	ν(C=N)	ν(C=C)	ν(tetrazole)$_{\text{skeleton}}$	ν(C—O—C)$_{\text{as}}$	ν(C—O—C)$_{\text{s}}$
VIIa	1748	1211	1621	1499	1110	1293	1016
VIIb	1750	1220	1618	1489	1093	1300	1020
VIIc	1750	1219	1622	1487	1112	1298	1021
VIId	1751	1228	1617	1492	1098	1299	1028
VIIe	1752	1226	1619	1478	1118	1310	1017

Table 7

^{1}H NMR chemical shift data (δ/ppm) of substituted ethyl tetrazolylacetates *VIIa—VIIe*

Compound	$CH_{3(ester)}$ $—CH_{2(ester)}$	$—CH_2—N=$	H_{fur}, H_{ar}	Others
VIIa	1.07 3.98	5.69	7.20—7.40 (m, 5H, phenyl protons)	—
VIIb	1.09 4.02	5.68	7.20 (s, 4H, eclipsed AA′BB′ system) 7.17 (d, H-4), 7.50 (d, H-3)	3.40 (CH_3—)
VIIc	1.13 4.07	5.67	6.92, 7.01, 7.32, 7.41 (4H, AA′BB′) 7.07 (d, H-4), 7.46 (d, H-3)	3.75
VIId	1.08 4.01	5.69	7.22, 7.31, 7.40, 7.50 (4H, AA′BB′) 7.29 (d, H-4), 7.55 (d, H-3)	—
VIIe	1.10 4.04	5.69	7.15—7.47 (m, 4H, AA′BB′) 7.22 (d, H-4), 7.52 (d, H-3)	—

Ethyl 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetates VIIa—VIIe

Powdered phosphorus pentachloride (6.25 g; 30 mmol) was added to the respective ethyl 5-(4-substituted phenylthio)-2-furylcarbamidoacetate covered with benzene (60 cm^3). Temperature of the stirred mixture was adjusted to 75 °C during 2 min and kept for 10 to 15 min; the mixture was evaporated to dryness and the oily imidoyl chloride was dissolved in dimethylformamide (30 cm^3). This solution was added during 45 min to a suspension of sodium azide (3.51 g; 54 mmol) in dimethylformamide (30 cm^3) at room temperature. The suspension was stirred for 30 min, the solvent was removed and acetone (60 cm^3) was added to the hot residue. Inorganic salts were removed, the filtrate was purified with charcoal and evaporated to dryness. Ethanol (10 cm^3) was added to the oily residue from which the respective esters crystallized within 24 h in 29—33 % yield. Characteristic data of esters *VIIa—VIIe* are summarized in Table 3.

5-[5-(4-Substituted phenylthio)-2-furyl]tetrazol-1-ylacetic acids VIIIa—VIIIe

Ethyl 5-[5-(4-substituted phenylthio)-2-furyl]tetrazol-1-ylacetate (7.5 mmol) was dissolved in hot ethanol (30 cm^3) to which potassium hydroxide (c = 3 mol dm^{-3}; 3 cm^3) was added. The mixture, from which the potassium salt separated was stirred at 60 °C for 1 h, ethanol was evaporated and the residue was dissolved in water (15 cm^3). The solution was purified with charcoal, acidified with 5 % hydrochloric acid, the separated organic acid was filtered off, washed with water and crystallized from ethanol. Characteristic data of acids *VIIIa—VIIIe* are listed in Table 4.

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