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The Synthesis of Some New ω-Substituted 1-Vinyltetrazole Derivatives

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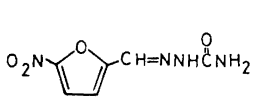
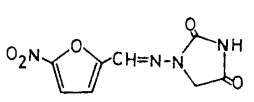
Azidolytic transformation of some 5-oxazolones followed by a copper-quinoline induced decarboxylation of the resulting α-(1-tetrazolyl)acrylic acids has led to a series of new 1,5-disubstituted tetrazoles.

In some cases the decarboxylation procedure gave rise to a mixture of the *cis*- and *trans*-isomers of the tetrazoles. The geometrical isomerism is discussed on the basis of ^{1}H NMR- and IR-spectra.

Many furan derivatives are known as antibacterial compounds and some of them are used in medicine, *e.g.* (5-nitrofurfurylidenamino)carbamide (Furacin®) (I) and 1-(5-nitrofurfurylidenamino)imidazolidinedione-(2,4) (Furadantin®) (II), which are included in the Nordic Pharmacopoea. Moreover, 1-alkyl- and 1-aryl-5-(5-nitro-2-furyl)tetrazoles (III) are shown to possess a high antibacterial activity. This together with our current interest in the chemistry of the tetrazoles prompted us to synthesize some new 1-vinyltetrazole derivatives (VI) which have some constitutional similarity to I and II.



I



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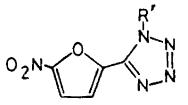


III

The *1-vinyltetrazole* derivatives were obtained by azidolysis of appropriately substituted 4-methylene-5-oxazolones (IV) followed by decarboxylation of the α-(1-tetrazolyl)acrylic acids (V). The first step of the synthesis was performed according to a method of Awad *et al.*[2] who found that 4-arylmethylene-5-oxazolones (IV, R = aryl) were transformed into α-(1-tetrazolyl)cinnamic acid derivatives (V, R = aryl) by treatment with hydrazoic acid in aqueous acetic acid. The compounds VI, the intermediates V in Table 1 and the oxazolones IVe and IVm have not previously been described.

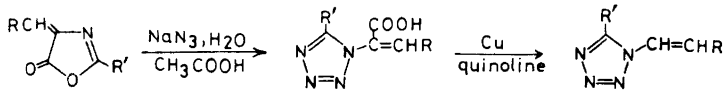
Table 1. New α-(1-tetrazolyl)acrylic acid derivatives (V).

Compound	Method	Reaction time, h	Recryst. from	Yield %	M.p.,°C[a]	Formula	Analysis (C,H,N,S)
Vb	A	1	amyl acetate	69	200–202	$C_{14}H_{10}N_4O_3$	Found: 59.80; 3.65; 20.00; Calc.: 59.57; 3.57; 19.85;
Vc	A	1	amyl acetate-petroleum ether	54	202–212	$C_{14}H_{10}N_4O_2S$	Found: 56.41; 3.50; 18.87; 10.98; Calc.: 56.37; 3.38; 18.78; 10.75;
Ve	A and B	2	–	0[b]	–	$C_9H_8N_4O_3$	
Vf	B	2	amyl acetate	69	206–208	$C_9H_8N_4O_2S$	Found: 45.65; 3.52; 23.53; 13.68; Calc.: 45.75; 3.41; 23.72; 13.57;
Vh	A	1	ethyl acetate-petroleum ether	62	194–197	$C_{14}H_9N_5O_5$	Found: 51.25; 2.84; 21.54; Calc.: 51.38; 2.77; 21.40;
Vj	B	2	ethyl acetate-petroleum ether	73	185–188	$C_{14}H_9N_5O_4S$	Found: 49.24; 2.74; 20.62; 9.29; Calc.: 48.98; 2.64; 20.40; 9.34;
Vk	B	1	ethyl acetate-petroleum ether	75	194–197	$C_{11}H_9N_5O_4$	Found: 47.95; 3.34; 25.96; Calc.: 48.00; 3.30; 25.45;
Vl	A	1	DMF–water	42	226–229	$C_9H_7N_5O_5$	Found: 40.90; 2.75; 26.65; Calc.: 40.76; 2.66; 26.41;
Vm	B	2	ethyl acetate-petroleum ether	85	205–207	$C_9H_7N_5O_4S$	Found: 38.46; 2.61; 25.01; 11.09; Calc.: 38.44; 2.51; 24.91; 11.40;

[a] An evolution of nitrogen took place some degrees below the melting point. [b] See p. 268.

Synthesis of the oxazolones (IV) and the α-(1-tetrazolyl)acrylic acid derivatives (V). Most of the oxazolones were obtained by the Erlenmeyer oxazolone synthesis [3] involving the condensation of either *N*-acetylglycine or hippuric acid and an appropriate aldehyde in the presence of acetic anhydride and fused sodium acetate. In the case of the new 2-methyl-4-furfurylidene-5-oxazolone (IVe) the crude product was separated by preparative layer chromatography to give two compounds one of which was IVe in a 43 % yield while the other turned out to be 2-[β-(2-furyl)vinyl]-4-furfurylidene-5-oxazolone (VII) in a 7 % yield.

As concerns the new 2-methyl-4-(5-nitrothenylidene)-5-oxazolone (IVm) the only isolable products of the Erlenmeyer synthesis were unreacted *N*-acetylglycine and the diacetate of 5-nitro-2-thiophenecarbaldehyde formed by a

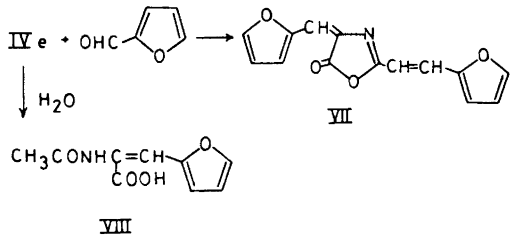


IV V VI

	R	R′		R	R′
a	C_6H_5	C_6H_5	g	p-$NO_2C_6H_4$	C_6H_5
b	2-furyl	C_6H_5	h	5-nitro-2-furyl	C_6H_5
c	2-thienyl	C_6H_5	j	5-nitro-2-thienyl	C_6H_5
d	C_6H_5	CH_3	k	p-$NO_2C_6H_4$	CH_3
e	2-furyl	CH_3	l	5-nitro-2-furyl	CH_3
f	2-thienyl	CH_3	m	5-nitro-2-thienyl	CH_3

Scheme 1.

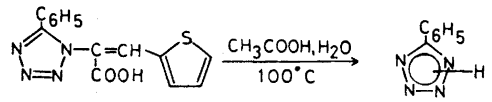
reaction of the aldehyde with acetic anhydride. A modification of the Erlenmeyer synthesis involving addition of the aldehyde to the intermediate 2-methyl-5-oxazolone [4] resulted in a 65 % yield of IVm.



Scheme 2.

Regarding the preparation of the α-(1-tetrazolyl)acrylic acid derivatives (V) the method of Awad *et al.*[2] proved to be fully applicable giving yields ranging from 50 % to 85 % (reaction conditions and analytical data are summarized in Table 1). Ve could not be prepared as a consequence of the easy hydrolysis of IVe [5] leading to 2-acetamido-3-(2-furyl)acrylic acid (VIII, Scheme 2).

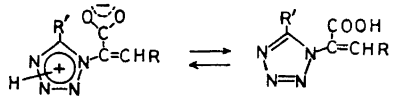
During the isolation of (Vc) a small amount of 5-phenyltetrazole (IX) was isolated probably as a result of partial hydrolysis of Vc. This indicates enamine character of Vc and will be the subject of further investigations in our laboratory.



Vc IX

Scheme 3.

The structural assignment of V was confirmed by elemental analyses besides IR-spectroscopy, which lend some support to the structures proposed by Awad *et al.*[2] involving the formation of a normal associated form or a zwitterionic form (X) in equilibrium with a non-polar monomer form (XI). The configuration about the double bond of V was not considered.



X XI

Scheme 4.

Decarboxylation of α(1-tetrazolyl)acrylic acid derivatives (V). It is generally accepted that α,β-unsaturated carboxylic acids only decarboxylate with difficulty. Thus some preliminary attempts to decarboxylate V by heating the solid acids in Table 1 to a few degrees below the melting points gave rise to a vigorous liberation of nitrogen accompanied by the formation of the corresponding oxazolones (IV). Addition of copper powder combined with heating under reduced pressure [6] gave the same result. Using α-(5-phenyl-1-tetrazolyl)cinnamic acid (Va) as a model compound a series of attempts to carry out an alkali induced decarboxylation failed. Refluxing in piperidine [7] or pyridine [8] for 24 h gave unchanged starting material together with small amounts of IVa. Elevation of the temperature by heating in quinoline [8] to about 160° for a few hours resulted in a mixture of the geometric isomers of IVa.[9] Acid catalyzed decarboxylation of Va or decarboxylative dehydrobromination [10,11] did not proceed either.

Finally, the decarboxylation was accomplished by heating a solution of Va in quinoline to a temperature of 30° below the melting point in the presence of catalytic amounts of copper powder.[12] The 1-vinyltetrazole derivatives (VI), however, polymerized completely within 5 – 10 min under the above mentioned conditions. This problem was overcome by adding *p*-methoxyphenol as an antipolymerization agent [17] and by cooling the reaction mixture to room temperature immediately after the carbon dioxide evolution had ceased. This method was successfully used for the decarboxylation of 9 out of 12 α-(1-tetrazolyl)acrylic acids (Table 2). Low yields were mainly caused by polymerization and to a smaller extent by oxazolone formation as shown by TLC. Those

Table 2. New 1-vinyltetrazole derivatives (VI).

Compound	Reaction		Recryst. from	Yield %	M.p.,°C	TLC-eluent: benzene-ethyl acetate	Formula	Analysis (C,H,N,S)
	Time min.	Temp. °C						
VIa (*cis*)	60	167	cyclohexane	50	75–77	9:1	$C_{15}H_{12}N_4$	Found: 72.35; 5.02; 22.50; Calc.: 72.56; 4.89; 22.57;
VIb (*cis*)	35	170	tetrachloro-methane petroleum ether	30	97–99	9:1	$C_{13}H_{10}N_4O$	Found: 64.90; 4.29; 23.27; Calc.: 65.53; 4.23; 23.52;
VIc (*cis*)	50	175	hexane	50	58–60	8:2	$C_{13}H_{10}N_4S$	Found: 61.41; 4.00; 22.10; 12.57; Calc.: 61.40; 3.96; 22.03; 12.61;
VId (*cis*)	30	175	cyclohexane	65	99–101	9:1	$C_{10}H_{10}N_4$	Found: 64.55; 5.43; 30.06; Calc.: 64.50; 5.41; 30.09;
VIf (*cis*)	30	160	cyclohexane	70	99–100	8:2	$C_8H_8N_4S$	Fonud: 49.80; 4.19; 28.88; 16.64; Calc.: 49.98; 4.19; 29.15; 16.68;
VIk (*trans*)	25	160	benzene-cyclohexane	25[a]	174–176	1:1	$C_{10}H_9N_5O_2$	Found: 52.35; 4.08; 30.10; Calc.: 51.94; 3.92; 30.29;
VIk (*cis*)	25	160	tetrachloro-methane	25[a]	152–154	1:1	$C_{10}H_9N_5O_2$	Found: 51.90; 4.04; 30.25; Calc.: 51.94; 3.92; 30.29;
VI l (*trans*)	30	152	tetrachloro-methane	10[a]	178–180	1:1	$C_8H_7N_5O_3$	Found: 43.25; 3.32; 31.40; Calc.: 43.44; 3.19; 31.67;
VIm (*trans*)	30	145	ethanol	55[a]	228–230	1:1	$C_8H_7N_5O_2S$	Found: 40.64; 3.06; 29.07; 13.40; Calc.: 40.50; 2.98; 29.52; 13.51;

[a] Yields calculated after separation by preparative layer chromatography.

compounds (V) which did not undergo decarboxylation all contained R′ = C_6H_5 and R = *p*-NO_2-C_6H_4 (Vg), R = 5-nitro-2-furyl (Vh), R = 5-nitro-2-thienyl (Vj), respectively.

The preferred configuration of VI was the *cis*-form. However VIk, VI l, and VIm were obtained as mixtures of the geometric isomers. Among these compounds only the *cis*-isomer of VIk could be isolated in a pure state whereas the *cis*-isomers of VI l and VIm partly rearranged to the *trans*-isomers. Reaction conditions and analytical data of VI are summarized in Table 2.

Assignment of the configuration of VI. The configuration about the double bond of the 1-vinyltetrazoles (VI) was established by ^{1}H NMR- and IR-spectroscopy (spectroscopic data are summarized in Table 3). The vicinal coupling constants for the *cis*-isomers were found in the range of 8.2 – 9.3 Hz and for the *trans*-isomers in the range of 14.2 – 14.5 Hz. The assigned *trans*-configurations were all correlated with medium to strong absorption in the infrared region about 950 cm^{-1} characteristic of *trans*-ethylenic double bonds.[13] This band was absent in the *cis*-isomers.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 337 spectrophotometer (KBr discs) and the ^{1}H NMR spectra were recorded at 60 MHz on a Varian A 60 spectrometer and at 100 MHz on a Varian HA – 100 spectrometer. Melting points are uncorrected and were determined with a hot stage microscope (Mikroskop-Heiztisch, 350 Ernst Leitz G.m.b.H., Wetzlar). The microanalyses were made by Preben Hansen, Micro-analytical Department of Chemical Laboratory II, University of Copenhagen.

2-Methyl-4-furfurylidene-5-oxazolone (IVe) and 2-[β-(2-furyl)vinyl]-4-furfurylidene-5-oxazolone (VII). A mixture of 58.5 g (0.5 mol) of *N*-acetylglycine, 48 g (0.5 mol) of 2-furaldehyde, 41 g (0.5 mol) of fused sodium acetate, and 150 g of acetic anhydride was heated on a steam bath for 2 h. After cooling to room temperature the precipitate formed was collected and washed successively with small amounts of ethanol and water. Yield 65 % of crude product, which was used for further preparations. A TLC-analysis of the crude product revealed the presence of 2 compounds one of them constituting the main product (IVe).

For analytical purposes 600 mg of crude product was chromatographed on a preparative silica gel PF_{254} (Merck) plate using benzene-ethyl acetate (9:1) as an eluent. Recrystallization of the main product from cyclohexane provided 400 mg (corresponding to an overall yield of 43 %) of IVe, m.p. 95 – 97°C. (Found: C 60.80; H 4.05; N 7.84. Calc. for $C_9H_7NO_3$: C 61.01; H 3.98; N 7.91). IR spectrum (cm^{-1}): 3140w and 3070w (=C–H stretching frequencies of the furan protons and the vinyl protons, respectively [14]), 1800s, 1780s, 1670s, and 1615s (the four characteristic bands of unsaturated oxazolones [17]). Recrystallization of the by-product from cyclohexane provided 65 mg (7 %) of 2-[β-(2-furyl)vinyl]-4-furfurylidene-5-oxazolone VII, m.p. 213 – 216°C. (Found: C 65.65; H 3.69; N 5.47. Calc. for $C_{14}H_9NO_4$: C 65.88; H 3.55; N 5.49). IR spectrum (cm^{-1}): 3140w and 3070w, 1800s, 1780s, 1660s, and 1620s.

2-Methyl-4-(5-nitrothenylidene)-5-oxazolone (IVm). 9.0 g (0.077 mol) of *N*-acetylglycine and 6.3 g (0.077 mol) of fused sodium acetate were suspended in 26 ml acetic anhydride and heated on a steam bath until a clear yellow solution was formed. 12.1 g (0.077 mol) of 5-nitro-2-thiophenecarbaldehyde was added and the heating was continued for 2 h. The reaction mixture was then kept at 5 – 10°C for several hours and the solid formed was collected and washed twice with small portions of acetic acid and once with water. The air-dried product was pure enough for further use. Yield 65 %, m.p. 215 – 218°C. For analytical purposes the oxazolone was recrystallized from methyl ethyl ketone. M.p. 216 – 218°C. (Found: C 45.46; H 2.63; N 11.48; S 13.49. Calc. for $C_9H_6N_2O_4S$: C 45.38; H 2.54; N 11.76; S 13.46). IR spectrum (cm^{-1}): 3100m (=C–H stretching frequencies of the thiophene protons [14]) and 1790s, 1760s, 1650s, and 1590s (unsaturated oxazolones [15]) and 1490s and 1320s (N=O stretching frequencies [13]).

An attempt to recrystallize IVm from ethanol resulted in a cleavage of the oxazolone ring giving ethyl 2-acetamido-3-(5-nitro-2-thienyl)-acrylate. M.p. 204 – 206°C. (Found:

Table 3. ^{1}H NMR-[a] and IR-data of 1-vinyltetrazole

Compounds	Substituents		Chemical shift in τ-values			
	R'_C	R_D	H_B; H_A[b]	H_D		
				1	2	3
VIa (*cis*)	C_6H_5		2.64; 2.89	all in the region 2.00–3.30		
VIa[c,d] (*trans*,)	C_6H_5		2.14; 2.45	all in the region 2.00–2.70		
VIb[d] (*cis*)	C_6H_5		2.81; 3.00	3.59	3.59	2.35–2.55
VIc[h] (*cis*)	C_6H_5		2.58; 2.80[f]	2.77	2.98	2.35–2.55
VId[g] (*cis*)	CH_3		3.16; 3.20	2.70–2.79	3.11–3.21	2.70–2.79
VIf[h] (*cis*)	CH_3		2.61; 2.83[f]	2.70	2.90	2.42
VIk[i] (*trans*)	CH_3		1.90; 2.48	2.05	1.82	–
VIk[i] (*cis*)	CH_3		2.68; 2.88	2.70	1.88	–
VI l (*trans*)	CH_3		2.03; 2.55	2.82	2.23	–
VIm (*trans*)	CH_3		1.93; 2.32	2.44	1.92	–

[a] The spectra were recorded in DMSO at 20° with TMS as an internal standard. All the spectra were recorded at 60 MHz with field sweep and some of the spectra in addition at 100 MHz with frequency sweep.

[b] The vinyl-protons all showed an AB-quartet.

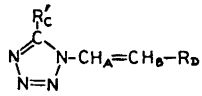
[c] This compound was synthesized from another work going on in this laboratory.

[d] The experimental values for the chemical shifts and coupling constants were confirmed both by the 100 MHz and 60 MHz spectra.

[e] The *o*- and *p,m*-protons, respectively.

C 46.25; H 4.21; N 9.69; S 11.21. Calc. for $C_{11}H_{12}N_2O_5S$: C 46.29; H 4.27; N 9.89; S 11.32). IR spectrum (cm^{-1}): 3240m, 3000m, 1720s, 1670s, and 1640m (amide [16]), 1510s, and 1330s.

β-Substituted α-(1-tetrazolyl)acrylic acids (V). General procedure. Method A. A solution of 0.15 mol of sodium azide in 25 ml of hot water was added to a suspension of 0.05 mol of the oxazolone in 100 ml of glacial acetic acid and the mixture was heated on a steam bath for 1–2 h (see Table 1). After cooling to room temperature the reaction mixture

derivatives (VI). 

Coupling constants in Hz					Moderately strong IR absorption about 950 cm^{-1}
H_C	J_{AB}	$J_{D(1)-D(2)}$	$J_{D(2)-D(3)}$	$J_{D(1)-D(3)}$	
	9.0				–
	14.4				+ (950)
2.00–2.20[g] 2.35–2.55	8.8				–
2.00–2.20[g] 2.35–2.55	8.2	3.7	5.0	1.1	–
7.93	8.9				–
7.60	8.4	3.7	5.0	1.1	–
7.28	14.2	9.2			+ (945)
7.57	9.3	8.6			–
7.30	14.2	3.8			+ (955)
7.32	14.5	4.5			+ (965)

[f] The low-field vinyl-proton showed coupling to the $H_{D(1)}$ and $H_{D(3)}$ protons why we assigned this to H_B.

[g] Recorded in CCl_4 at 100 MHz in order to obtain separation of the signals of H_A and H_B.

[h] Recorded at 100 MHz to obtain approximately an AMX pattern for the thiophene protons.

[i] The $H_{D(1)}$ and $H_{D(2)}$ protons were calculated as an AB quartet. A computer calculated AA'BB' pattern (the chemical shift and the *o*-coupling constant of $H_{D(1)}$ and $H_{D(2)}$ were taken from this table and the *m*-(2.4 Hz) and *p*-(0.5 Hz) coupling constants from the literature [18]) showed that this approximation was reasonable.

was poured on crushed ice, the precipitate was collected and dissolved in a saturated sodium bicarbonate solution. The aqueous solution was washed with ether and acidified with cold 4 N hydrochloric acid. The precipitate was collected, washed with water, and recrystallized from a suitable solvent (see Table 1).

Method B is a modified method A, the only modification being an evaporation of the reaction mixture after it has been heated. The residue was dissolved in a saturated sodium bicarbonate solution and the operation was completed as described above.

IR spectra (cm^{-1}) of the associated acids (Va-c, Vf, Vk, and Vm): 3000 – 2500m (H-bonded O – H stretching frequencies), 1680 – 90s (C = O stretching frequencies of compounds without the nitro group), 1730s (C = O stretching frequencies of compounds containing the nitro group). The monomer-zwitterionic form (Va-b, Vd, Vg-j, and Vl): 3440m (O – H stretching frequencies), 2500 – 2440m (N^+ – H stretching frequencies), 1900 – 1920m (N^+ – H stretching frequencies) 1680 – 90s, and 1730s.

ω-Substituted 5-methyl or 5-phenyl-1-vinyltetrazoles (VI). General procedure. A mixture of 10 mmol of (V), 10 % by weight of copper powder and 10 % by weight of *p*-methoxyphenol in 20 ml of quinoline was heated during 25 – 60 min at temperatures varying from 30 to 70°C below the melting points of V (see Table 2). The mixture was cooled and poured into 100 ml of 4 N hydrochloric acid and the precipitate was collected. The acidic filtrate was extracted with benzene until the benzene layer showed no further content of product as determined by TLC, using various proportions of benzene – ethyl acetate as the eluents (see Table 2). An additional amount of product was obtained by treating the solid from the acidification of the reaction mixture with 4 N hydrochloric acid at room temperature followed by extraction with benzene as described above. The combined benzene layers were dried and evaporated under reduced pressure leaving a residue which upon repeated crystallizations from a suitable solvent provided the compounds VI. Yields calculated from V and analytical data are summarized in Table 2. The compounds VIk-m, formed as mixtures of the geometric isomers were separated by preparative layer chromatography using the eluents given in Table 2.

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