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Synthesis, Spectral Characteristics and Structure of 1,3- and 1,4-Disubstituted Tetrazolinones

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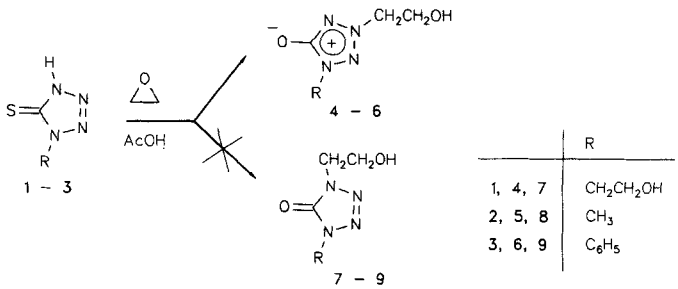
Abstract. Reaction of ethylene oxide with 1-alkyl- or 1-aryl-1,4-dihydrotetrazole-5-thiones in acetic acid affords the corresponding mesoionic 1-alkyl- or 1-aryl-3-(2-hydroxyethyl)-tetrazolium-5-olates **4–6**. The X-ray structure of one of these compounds (**5**) is presented. On the other hand, the reaction of tetrazolinones with 2-chloroethanol in the presence of potassium hydroxide affords a mixture of the corresponding 1,3- and 1,4-disubstituted isomers. The isomers can be distinguished easily by their IR, ^1H or ^{13}C NMR spectra. The fragmentation of these compounds in the mass spectrometer is discussed.

1,4-Dialkyl-1,4-dihydro-5H-tetrazol-5-ones [1,2] or 1-alkyl-4-aryl-analogues [3-5] are generally prepared by the alkylation of the respective 1-alkyl- or 1-aryl-1,4-dihydro-5H-tetrazol-5-ones. It has been reported that reaction of monosubstituted tetrazolinethiones with ethylene oxide affords 1,4-disubstitued 1,4-dihydro-5H-tetrazol-5-ones [6]. In an attempt to synthesize 1,4-dihydro-1,4-bis(2-hydroxyethyl)-5H-tetrazol-5-one (**7**), 1,4-dihydro-1-(2-hydroxyethyl)-5H-tetrazole-5-thione (**1**) was treated with ethylene oxide in a manner similar to that reported for the synthesis of the similar compound **9** from **3** and ethylene oxide [6] (Scheme 1).



Scheme 1

The resulting product with the correct elemental analysis and molecular ion (Table 1, Scheme 1) was found to be different in its spectroscopic properties from the 1,4-disubstituted tetrazolinones (Table 2). The C=O stretching frequency of our compound is found at 1668 cm^{-1}, lower than that of about 1710–1720 cm^{-1} (in KBr) reported for monosubstituted derivatives [7] and also found in our present work for the 1,4-disubstituted tetrazolinones. The ^{13}C chemical shift of C-5 of the tetrazolinone ring is in the range of 150–152 ppm [8], but it is found for our compound at about 161 ppm. The ^1H NMR spectrum shows six signals for the two hydroxyethyl groups, indicating that this compound is not symmetric, being the 1,2- or the 1,3-disubstituted mesoionic product.

In order to explore the structure of this compound, we have prepared another two compounds by the same method with methyl and phenyl groups at position 1, the latter (mp. 144 °C) is the one that was reported [6] to have the 1,4-structure (Scheme 1). These compounds were found to have spectroscopic properties (Table 2) similar to that of compound **4** which differ from those of the 1,4-disubstituted tetrazolinones. The three compounds **4–6** are soluble in ethanol and water but completely insoluble in chloroform or other non polar solvents.

In order to determine the structures of these compounds, an X-ray structure analysis was done for compound **5**, which revealed that this compound is 1,3- and not 1,4-disubstituted, thus being a mesoionic tetrazolium-5-olate of type A after the classification of Ollis et al. [9]. In analogy we can conclude that compounds **4** and **6** are also 1,3-disubstituted tetrazolium-5-olates. This ionic structure explains the solubility of these compounds in polar solvents like water and ethanol. The molecular structure of **5** is shown in Figure 1. The ring is planar according to the X-ray analysis and AM1 [10] calculations. PM3 [11] calculations, how-

Table 1. Physical and Analytical Data of Compounds **4–10**

Compd.	Yield (%)	m.p. [°C]	Mol. Formula [M]$^+$	Calcd. / Found (%) C	H	N
4	28	oil	$C_5H_{10}N_4O_3$	34.48	5.79	32.17
	32[a]		174	34.57	6.18	32.04
5	44	109–110	$C_4H_8N_4O_2$	33.33	5.59	38.87
			144	33.78	5.62	39.38
6	56	143–144	$C_9H_{10}N_4O_2$	52.42	4.89	27.17
			206	52.58	4.84	27.30
7	60	42–43	$C_5H_{10}N_4O_3$	34.48	5.79	32.17
			174	34.40	6.11	31.99
8	34	50–51	$C_4H_8N_4O_2$	33.33	5.59	38.87
			144	32.69	5.62	38.16
9	64	36–37	$C_9H_{10}N_4O_2$	52.42	4.89	27.17
			206	52.54	5.00	26.73
10	60	41–42	$C_5H_{10}N_4O_2S$	31.57	5.30	29.45
			190	31.57	5.32	29.69

[a] Synthesized by the method of Scheme 4

Table 2. Selected IR and NMR Data of Compounds **4–10**

	IR (KBr)	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm)
4	3410	4.35 (t, 2H, N^3CH_2, J = 5.1)	58.57 (N^3CH_2)
	1668	3.82 (dt, 2H, $N^3CH_2\mathbf{CH_2}OH$)	58.33 ($N^3CH_2\mathbf{CH_2}OH$)
		3.97 (t, 2H, N^1CH_2, J = 5.6)	46.97 (N^1CH_2)
		3.68 (dt, 2H, $N^1CH_2\mathbf{CH_2}OH$)	58.25 ($N^1CH_2\mathbf{CH_2}OH$)
			161.34 (C=O)
5	3312	4.38 (t, 2H, NCH_2, J = 5.1)	30.60 (CH_3)
	1661	3.85 (dt, 2H, CH_2OH)	58.57 (NCH_2)
		3.56 (s, 3H, CH_3)	58.33 (CH_2OH)
			161.40 (C=O)
6	3298	4.51 (t, 2H, NCH_2, J = 4.7)	59.36 (NCH_2)
	1667	3.90 (dt, 2H, CH_2OH)	58.44 (CH_2OH)
			159.37 (C=O)
7	3376	3.94 (t, 2H, NCH_2, J = 4.5)	47.38 (NCH_2)
	1713	3.70 (dt, 2H, CH_2OH)	58.29 (CH_2OH)
			150.89 (C=O)
8	3408	3.95 (t, 2H, NCH_2, J = 5.5)	31.11 (CH_3)
	1709	3.72 (dt, 2H, CH_2OH)	47.49 (NCH_2)
		3.54 (s, 3H, CH_3)	58.26 (CH_2OH)
			150.89 (C=O)
9	3453	4.06 (t, 2H, NCH_2, J = 5.4)	47.84 (NCH_2)
	1705	3.79 (dt, 2H, CH_2OH)	58.19 (CH_2OH)
			149.11 (C=O)
10	3382	4.31 (t, 2H, NCH_2, J = 5.3)	49.92 (NCH_2)
	3317	3.76 (dt, 2H, $NCH_2\mathbf{CH_2}OH$)	58.86 ($NCH_2\mathbf{CH_2}OH$)
		3.33 (t, 2H, SCH_2, J = 6.3)	35.83 (SCH_2)
		3.65 (dt, 2H, $SCH_2\mathbf{CH_2}OH$)	59.51 ($SCH_2\mathbf{CH_2}OH$)
			154.35 (C^5-S)

ever, show it to have a pyramidal N^1, where the sum of angles around this atom is 354.9°.

Mesoionic 1,3-disubstituted tetrazolium-5-olates with aromatic substituents at positions 1 and 3 have been reported before [12]. But little is known about aliphatic 1,3-disubstituted tetrazolium-5-olates. Horwitz et al. [1] reported that the methylation of 5-tetrazolinone or 1-methyl-5-tetrazolinone gives, in addition to the 1,4-dimethyl-5-tetrazolinone, a very small amount of a compound that has a carbonyl absorption at 1673 cm^{-1}, which they considered to be the 1,2- or the mesoionic 1,3-dimethyl product. Now, from the reported carbonyl absorption of this compound at 1673 cm^{-1}, it can be concluded that it is 1,3-dimethyl-tetrazolium-5-olate, and recently a chemical shift of 161.1 ppm (C-5) was reported for this compound [13]. The other compounds are 1-aryl-3-benzyl-5-tetrazolium-5-olates (**13**), which are formed in low yield in the rearrangement of 1-aryl-5-benzyloxytetrazoles (**11**) into the 1-aryl-4-benzyltetrazolinones (**12**) (Scheme 2) or by benzylation of the anion of the corresponding 1-aryltetrazolinone [14].

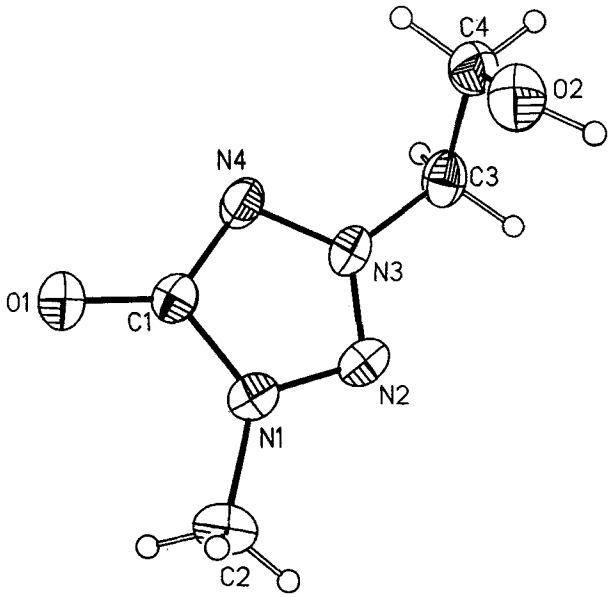
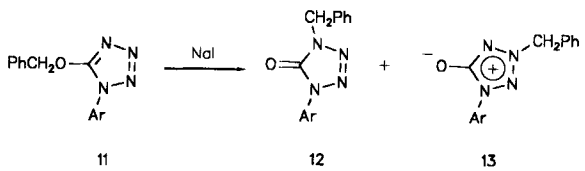


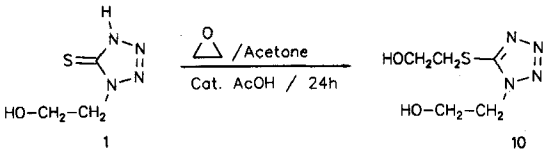
Figure 1. Thermal ellipsoid plot (50%) of **5** with the numbering scheme, selected distances (Å) and angles (°).
C1-O1 1.231(3), C1-N1 1.365(3), C1-N4 1.350(3), N1-N2 1.324(3), N1-C2 1.442(4), N2-N3 1.276(3), N3-N4 1.320(2), N3-C3 1.456(3), C3-C4 1.499(4), C4-O2 1.396(4)
C1-N1-N2 111.1(2), N1-N2-N3 102.8(2), N2-N3-N4 116.7(2), N3-N4-C1 103.5(2), N4-C1-N1 105.9(2), O1-C1-N1 125.3(2), O1-C1-N4 128.9(2), C1-N1-C2 126.4(2), C2-N1-N2 122.5(2), N2-N3-C3 122.2(2), N4-N3-C3 121.1(2), N3-C3-C4 110.0(2), C3-C4-O2 112.1(2), N2-N3-C3-C4 -119.9(2), N4-N3-C3-C4 58.6(3), N3-C3-C4-O2 60.2(3).



Scheme 2

It is worth noting that the alkylation of 1,5-disubstituted tetrazoles gives both the 1,3- and the 1,4-disubstituted tetrazolium ions depending on the alkylating reagent and the steric properties of the substituent at position 1 [2,15,16], and hence it is believed in this

case that the alkylation occurs first at the sulphur atom giving 5-alkylthiotetrazole, and this is then alkylated at position 3 and hydrolysed. This was demonstrated in one case where 1-(2-hydroxyethyl)-5-(2-hydroxyethylthio)tetrazole (**10**) was separated from the reaction of **1** and ethylene oxide with a catalytic amount of acetic acid in acetone after one day (Scheme 3). The physical data of compound **10** are given in Table 1 and the spectroscopic data are given in Table 2. Similar (hydroxyalkylthio)tetrazoles are reported from the reaction of tetrazolinethiones with substituted ethylene oxides [17]. The mechanism of this reaction proposed by Vlasova and Postovskii [6] seems to be questionable.

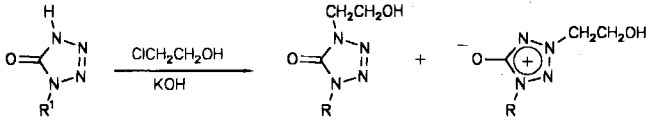


1 10

Scheme 3

The synthesis of tetrazolinones having the hydroxyethyl group at position 4 is found in the literature to proceed through the alkylation of the anion of the 1-substituted tetrazolinone with 2-haloethanol [5,18,19,21]. In all these references the 1,4-disubstituted isomer was reported as the only product of this reaction.

In our work to prepare similar hydroxyethyl derivatives using chloroethanol and the tetrazolinones **14–16** as described by the method reported by Quast et al. [19], we found that this reaction gives a mixture of the 1,3- (**4–6**) and the 1,4-disubstituted products (**7–9**) depending on the substituent at position 1 (Scheme 4). The separation and purification of these isomers is described in the Experimental Part. The physical and analytical data for **7–9** are summarized in Table 1 and the spectroscopic data in Table 2.



14 – 16 7 – 9 4 – 6

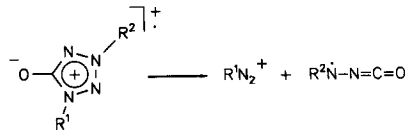
	R^1
14	H
15	CH_3
16	Ph

	R	Ratio
7 / 4	CH_2CH_2OH	65 / 35
8 / 5	CH_3	82 / 18
9 / 6	Ph	87 / 13

Scheme 4

1,3-Disubstituted tetrazolium-5-olates are reported to fragment in the mass spectrometer in the following manner [20] (Scheme 5).

This fragmentation pattern is clear in compounds **5** and **6** giving rise to the peaks at m/z = 43 as the base peak and 101 in compound **5**. In compound **6** the benzenediazonium cation peak at 105 and its Ph^+ cation



Scheme 5

fragment at 77 (base peak) are observed. The spectrum of **4** is complex due to the elimination of small molecules such as H_2O, CH_2O, and $CH_2{=}CH_2$ and the fragment $C_2H_3O^+$ (calcd. 43.0190, found 43.0184). On the other hand, tetrazolinones are reported to decompose via [3 + 2]-cycloreversion in the mass spectrometer [2,3,21]. This path is clear for **9**, however, high resolution measurements showed that compounds **7** and **8** lose a $C_2H_3O^+$ fragment before they completely decompose under 1,3-cycloreversion.

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Experimental

Melting points (uncorrected) were determined with a Büchi 510 instrument. Infrared spectra were recorded on a Perkin Elmer 1600 FT spectrophotometer. NMR spectra (in DMSO-d_6) were measured with a Varian XL 200 or a Bruker AMX 300 spectrometer. Mass spectra were obtained with a Prospec 3000 instrument from Fisons company. The X-ray structure determination was done with a Siemens R3m/V diffractometer connected with a Micro Vax II computer.

Compounds **1** [22], **2** [23], **3** [23], **14** [24], **15** [25], and **16** [26] were prepared according to known literature procedures.

Synthesis of 1,3-Bis(2-hydroxyethyl)tetrazolium-5-olate (4), 3-(2-Hydroxyethyl)-1-methyltetrazolium-5-olate (5) and 3-(2-Hydroxyethyl)-1-phenyltetrazolium-5-olate (6)

Compounds **1–3** (30 mmol) were dissolved in acetic acid (30 ml), and ethylene oxide (20 ml) was added to this solution. The reaction mixture was kept at room temperature for 3–5 d. It was then diluted with water (100 ml) and extracted with diethyl ether (3×50 ml). The aqueous layer was completely evaporated under vacuum at 60 °C. The residue was then further purified as follows: Compound **6** was crystallized from ethyl acetate. The purification of compounds **4** and **5** was achieved using column chromatography. A column was filled with a slurry of silica gel (0.2–0.5 mm, 100 g) in chloroform, and 2 g of the residue in ethanol (5 ml) was added. The compound was eluted with chloroform/ethanol (50:50 v/v). The solvent was then evaporated under vacuum. Compound **4** was further dried under vacuum (0.5 Torr) at 50 °C for 2 h to give the analytically pure compound as an oil. Compound **5** was crystallized from ethyl acetate. No indication for the formation of other products like **7–9** was found by TLC.

The yields and physical properties of compounds **4–6** are given in Table 1.

Synthesis of compounds 7–9

Compounds **14–16** (20 mmol) and 85% KOH (2 g, 30 mmol) were dissolved in ethanol (30 ml) and water (15 ml), and the

solution was stirred and heated to 50 °C. 2-Chloroethanol (3.2 g, 40 mmol) was added dropwise to the hot solution and the reaction mixture refluxed for 24 h. (The ratio of KOH and 2-chloroethanol is doubled in case of compound **14**). The solvent was then completely evaporated under vacuum and the residue digested with warm absolute acetone (4×50 ml). The acetone fractions were collected and the solvent evaporated under vacuum. The residual oil was then purified as follows:

a) 1,4-Dihydro-1,4-bis-(2-hydroxyethyl)-5H-tetrazol-5-one (**7**)

The residual oil was purified using preparative chromatography plates (20 × 20 cm silica gel plates, GF_{254}, Merck Ø = 10–40 μm) and chloroform/ethanol (80:20 v/v). The higher fraction is that of the desired compound **7** (2.02 g, 58%) and the second is that of the 1,3-disubstituted tetrazolium-5-olate isomer **4** (1.10 g, 32%). The total yield is 3.12 g (90%). Compound **7** was crystallized from ethyl acetate. It is recommended to prepare compound **4** by this method and not by the first method using ethylene oxide.

b) 1,4-Dihydro-1-(2-hydroxyethyl)-4-methyl-5H-tetrazol-5-one (**8**)

The ^1H NMR spectrum of the oil showed it to contain both the 1,4- and the 1,3-isomers in the ratio 82:18% as deduced from the intensities of the methyl signals at 3.53 and 3.58 ppm, respectively. The oil was dissolved in diethyl ether and drops of isopropanol, left in the refrigerator at −40 °C for 1 d, where the 1,3-isomer **5** precipitated (0.17 g), and found to be identical with a sample of this compound prepared by the other method through TLC, mp., and mixed mp. The filtrate was evaporated under vacuum to give a sample that was almost pure (1.0 g, 34%), this was distilled under vacuum to give the analytically pure product **8** as an oil (0.63 g) bp. 137 °C/1 Torr. After 1 d this oil solidified. The solid was triturated with a small amount of diethyl ether and collected (0.42 g), mp. 50–51 °C.

c) 1,4-Dihydro-1-(2-hydroxyethyl)-4-phenyl-5H-tetrazol-5-one (**9**)

The residual oil (3.4 g) was crystallized from diethyl ether/pentane. A small amount of solid crystallized which was collected (0.40 g, 10%) and found to be identical with a sample of the 1,3-isomer **6** through TLC, mp., and mixed mp. The filtrate was treated with active charcoal, filtered and the solvent evaporated under vacuum. The residual oil was crystallized from a minimum amount of diethyl ether to give the pure product **9** (2.65 g, 64%), mp. 36–37 °C.

Synthesis of 1-(2-hydroxyethyl)-5-(2-hydroxyethylthio)tetrazole (10)

Compound **1** (2 g, 14 mmol) was dissolved in acetone (30 ml) and acetic acid (2 ml). Ethylene oxide (15 ml) was added at room temperature. After 1 d the solvent was evaporated and the residue diluted with water (30 ml) and extracted with diethyl ether (2×50 ml). The aqueous layer was then collected and the water evaporated under vacuum. The residual oil was crystallized from ethyl acetate/hexane to give pure crystals of compound **10** (1.6 g, 60%), mp. 41 °C. The correlation of the ^1H and ^{13}C NMR data for this compound was determined through a HMQC (inverse CH-Cosy) 2D-NMR experiment (Table 2).

Crystal data for compound 5

$C_4H_8N_4O_2$, crystal size 0.53×0.39×0.31 mm^3, orthorhombic, space group *P*bca (no. 61), a = 7.721(2), b = 10.023(2), c = 16.887(4) Å, V = 1306.8(8) $Å^3$, Z = 8, F(000) = 608, ρ_{calc} = 1.465 Mg/m^3, μ = 0.12 mm^{-1}, graphite monochromized Mo-K_α-radiation, Siemens R3m/V diffractometer, T = 296 K, $2\Theta_{max}$ = 50°, 2622 intensities measured, 1894 unique (R_{int} = 0.030), 1271 observed ($F_o \geq 4.0\ \sigma(F)$), SHELXTL-Plus program package [27], structure solution with Direct Methods, Full-Matrix Least Squares on $\Sigma w(F_o-F_c)^2$, extinction correction χ = 0.0014(7), where $F^* = F[1+0.002\chi F^2/\sin(2\Theta)]^{-1/4}$, weighting scheme $w^{-1} = \sigma^2(F) + 0.002F^2$, hydrogen atoms isotropic without constraints, all other atoms anisotropic, 127 parameters refined, R = 0.0609, R_w = 0.0772, maximum residual electron density 0.28 $eÅ^3$. Lists of structural factors, anisotropic thermal parameters, atom coordinates, bond distances and angles, details of X-ray measurements and crystal data may be obtained through Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, Germany, on quoting the depository number CSD 404182, the names of the authors and the journal citation.

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