Difference in Thermal Behaviour Between 1- and 2-Alkyl-5-(methoxycarbonyldiazomethyl)tetrazoles

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In continuation of previous work, isomeric diazoester-substituted alkyltetrazoles **5** and **6** have been synthesized by the diazo-transfer method and studied in thermolysis reactions. Whereas the N-1 alkyl derivatives **5** give norcaradienes **7** in benzene solution and imidazotetrazoles **12** in acetonitrile, the more thermostable N-2 alkyl isomers **6** yield fluxional norcaradiene-cycloheptatriene systems, **10** ⇌ **11**, and oxazoles **13**.

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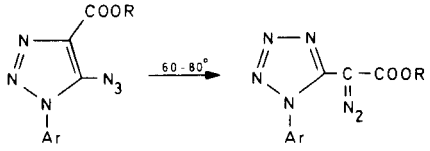
During studies on molecular rearrangements of 5-membered heterocycles, we have found that 5-azidotriazoles **1** bearing an ester function at the 4-position, rearrange thermally into 5-diazoester substituted 1-aryltetrazoles **2** [1].



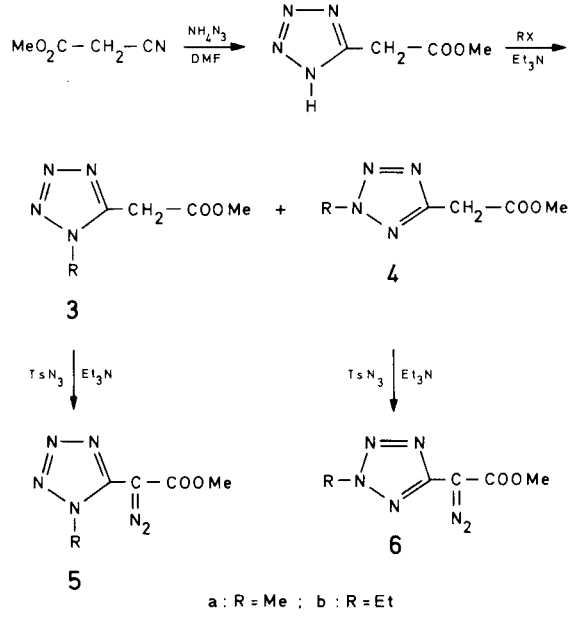
1 **2**

These compounds had not hitherto been prepared, although they constitute interesting starting materials for the synthesis of other heterocycles. It seemed therefore of interest to prepare them by direct methods and also to compare their thermal reactivity with that of the 2-substituted isomers. While this work was in progress, Moderhack and Goos [2] reported on the synthesis and thermolysis of 1- and 2-substituted 5-(diazomethyl)tetrazoles and concluded that the two isomers decomposed at different rates, but gave similar products (cycloheptatrienes in benzene and cyclohexylmethyl derivatives in cyclohexane solution respectively). Our investigation on the title compounds have also shown that the two isomers exhibit different thermal stabilities, and in addition furnish different reaction products in benzene or in acetonitrile.

Results and Discussion.

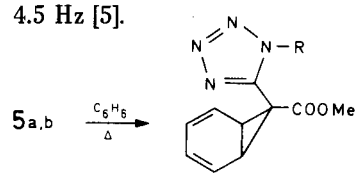
The diazo compounds **5a,b** and **6a,b** were obtained by a diazo transfer reaction of the corresponding activated methylene derivatives **3a,b** and **4a,b**, which themselves are available by a known procedure (see Scheme 1) [3]. They exhibit the characteristic diazo stretching vibrations at 2120-2130 cm^{-1} in the ir spectra and diazo carbon absorptions at δ 56 for **5a,b** and δ 59 for **6a,b** in the ^{13}C nmr spectra. As expected [4], the tetrazole C-resonances of **5a,b** (δ 145) are shielded compared with those of **6a,b** (δ 156) and the same phenomenon is observed for the α-carbon and hydrogen resonances of the R-substituents (see Experimental).

Scheme 1



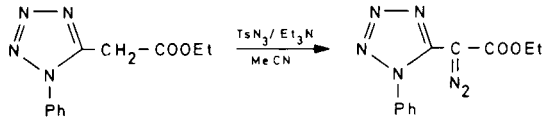
a : R = Me ; b : R = Et

In benzene at 70° the diazo compounds **5a,b** decomposed with evolution of nitrogen to give the norcaradienes **7a,b** as the sole reaction products. Their structures were easily established by the presence of high field resonances for the cyclopropyl CH atoms in the ^1H nmr (δ 3.4) and ^{13}C nmr spectra (δ 39). Furthermore, the tetrazole substituents are located at the endo-7 position, as evidenced by the ^3J-coupling constants between the cyclopropyl hydrogens and the tetrazole C-5 or ester CO carbons: $^3J_{C5\text{-}H}$ = 2 Hz, $^3J_{CO\text{-}H}$ = 4.5 Hz [5].



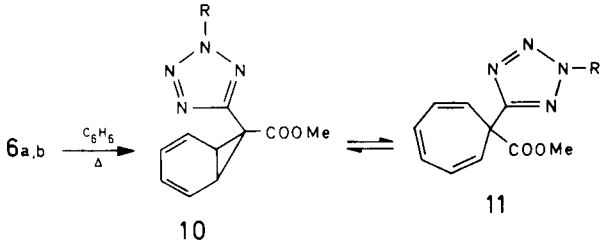
7a : R = Me
7b : R = Et

The rate of decomposition of **5a** in deuterated benzene was measured by integration of the methyl singlets in the nmr spectra at several time intervals, giving a first-order rate constant $k_1 = 0.48\ 10^{-5}\ s^{-1}$ (half-life 40 hours). This value is similar to that found for the decomposition of **9** in benzene ($k_1 = 0.53\ 10^{-5}\ s^{-1}$, half-life 36 hours), indicating that the tetrazole N-1 substituent has no influence on the decomposition rate of the diazo function. Compound **9** was prepared in 87% yield from the known methylene derivative **8** [6] by diazo transfer with tosyl azide in the presence of triethylamine.



8 9

Decomposition of **6a,b** in boiling benzene afforded products which were identified by their ^1H and ^{13}C nmr spectra as fast equilibrating mixtures of the norcaradienes **10a,b** and the cycloheptatrienes **11a,b**. Indeed, the 1,6-H and C-atoms absorb at positions (δ 4.15 and 66 in deuteriochloroform) between those expected for norcaradienes (δ_H ~3.4 and δ_C 36-40) and cycloheptatrienes (δ_H ~5.4 and δ_C ~120) [1,7].



10 11

a : R = Me ; b : R = Et

A detailed analysis of the nmr spectra of **10a/11a** showed that they are strongly temperature and solvent dependent, producing a shift of the 1,6-H resonances from δ 4.69 at 137° (1,2-dideuterio-1,1,2,2-tetrachloroethane) to δ 3.15 at -90° (deuteriomethylene chloride). This is accompanied by C-shifts from δ 85 to δ 36 for the 1,6-C-atoms and from δ 36 to δ 15 for the C-7 atom. Below room temperature the averaged 1,6-hydrogen and carbon peaks broaden but no separation to the individual isomers is observed, so that we can only estimate the isomeric distribution at the different temperatures. The percentage of cyclohaptatriene **11a** was calculated from the observed positions of the 1,6-carbons in the ^{13}C nmr spectra, assuming that the single isomers **10a** and **11a** absorb at δ 36 and δ 120 respectively. The results are summarized in Table 1. Thus, the equilibrium shifts towards the norcaradiene **10a** by lowering the temperature, in agreement with earlier findings on other systems [8]. For the N-1 isomer **7a** we have found that the cycloheptatriene form is present for less than 10% at 100° in DMSO-d_6 solution (δ C-1,6 = 44 ppm).

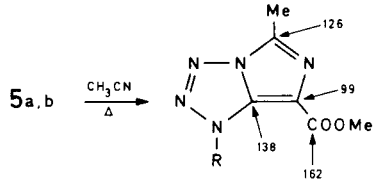
Table 1

Temperature and Solvent Dependence of the Fluxional System **10a/11a**

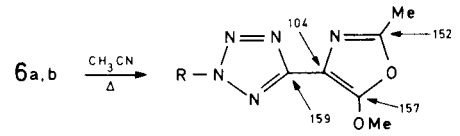
Solvent	T (°C)	δ C-1,6	% **11a**
$CDCl_3$	30	65.9	35
	-55	46	12
CD_2Cl_2	30	73.1	44
	-90	36.4	0
$CDCl_2CDCl_2$	137	85.1	58
Toluene-d_8	100	82.2	55
	30	69.2	39
CD_3CN	77	89.1	63
	30	82.3	55
DMSO-d_6	100	88.6	62
	30	77.7	49

The rate of decomposition of **6a** was determined spectroscopically in deuterated benzene at 70° and found to be $k_1 = 0.22\ 10^{-5}\ s^{-1}$ (half-life 87 hours). This is two times slower than **5a** and in line with the qualitative observation of Moderhack and Goos [2] for thermolysis of the diazomethyltetrazoles.

A more drastic difference between **5a,b** and **6a,b** occurred on thermolysis in acetonitrile. Whereas the 1-alkyl substituted tetrazoles **5a,b** yielded imidazotetrazoles **12a,b** in analogy with the 1-phenyltetrazole **9** [1], the 2-alkyl isomers **6a,b** furnished oxazole derivatives **13a,b**. Apparently, the intermediate carbene is capable of reacting with the participation of either the heterocycle or the ester function, depending on the structure of the tetrazole.



12a : R = Me
12b : R = Et



13a : R = Me
13b : R = Et

A distinction between **12** and **13** is readily made on the basis of the chemical shifts in the ^{13}C nmr spectra. The tetrazole C-5 resonance of **5** (δ 145) is shifted upfield in the fused derivative **12** (δ 138), leaving the ester CO absorption unaltered (δ 162). In **13**, on the contrary, the tetrazole

C-5 resonance (δ 159) is comparable with that in **6** (δ 156), but a new absorption appears at δ 157 at the expense of the original ester CO peak. Note also that the C=N carbon atom of the reacting acetonitrile resonates in the products **12** and **13** at quite different positions (δ 126 and 152 respectively). The δ-values of the oxazole ring are compatible with those reported [9] if the substituent effect of the methoxy group is taken into account. The most pertinent absorptions are indicated on the structures.

EXPERIMENTAL

Synthesis of the Diazoesters **5**, **6** and **9**.

The tetrazolylacetic esters **3**, **4** or **8** [3,6] (10 mmoles) were allowed to react with equimolar amounts of tosyl azide (1.97 g) and triethylamine (1.01 g) in acetonitrile (100 ml) at room temperature for the appropriate reaction time (overnight for **3a,b** and **8**; 3 weeks for **4a,b**). After removal of the solvent *in vacuo* and extraction with an aqueous sodium hydroxide solution, the residue was chromatographed on silica gel with ether-hexane (1:1) as the eluent.

5-(Methoxycarbonyldiazomethyl)-1-methyltetrazole (**5a**).

This compound was obtained in 76% yield, mp 32° (ether); ir (potassium bromide): 2130 (s), 1720 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.9 (s, 3H, OCH_3), 4.1 (s, 3H, NCH_3); ^{13}C nmr (deuteriochloroform): δ 35.7 (NCH_3), 53.0 (OCH_3), 55.6 (CN_2), 145.4 (tetrazole C), 162.5 (CO).

Anal. Calcd. for $C_5H_6N_6O_2$ (mol wt 182): C, 32.97; H, 3.32. Found: C, 33.07; H, 3.21.

1-Ethyl-5-(methoxycarbonyldiazomethyl)tetrazole (**5b**).

This compound was obtained as a yellow oil in 47% yield; ir (neat): 2120 (s), 1720 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.6 (t, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.5 (q, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 14.7 and 44.5 (C_2H_5), 52.9 (OCH_3), 55.6 (CN_2), 144.4 (tetrazole C), 162.5 (CO).

Anal. Calcd. for $C_6H_8N_6O_2$ (mol wt 196): C, 36.74; H, 4.11. Found: C, 36.91; H, 4.24.

5-(Methoxycarbonyldiazomethyl)-2-methyltetrazole (**6a**).

This compound was obtained in 66% yield, mp 41° (ether); ir (potassium bromide): 2120 (s), 1720 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.9 (s, 3H, OCH_3), 4.4 (s, 3H, NCH_3); ^{13}C nmr (deuteriochloroform): δ 39.8 (NCH_3), 52.7 (OCH_3), 59.3 (CN_2), 155.8 (tetrazole C), 162.9 (CO).

Anal. Calcd. for $C_5H_6N_6O_2$ (mol wt 182): C, 32.97; H, 3.32. Found: C, 33.11; H, 3.24.

2-Ethyl-5-(methoxycarbonyldiazomethyl)tetrazole (**6b**).

This compound was obtained in 55% yield, mp 40° (ether); ir (potassium bromide): 2120 (s), 1730 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.7 (t, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.7 (q, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 14.4 and 48.7 (C_2H_5), 52.5 (OCH_3), 59.2 (CN_2), 155.5 (tetrazole C), 163.0 (CO).

Anal. Calcd. for $C_6H_8N_6O_2$ (mol wt 196): C, 36.74; H, 4.11. Found: C, 36.88; H, 4.02.

5-(Ethoxycarbonyldiazomethyl)-1-phenyltetrazole (**9**).

This compound was obtained as yellow crystals in 87% yield, mp 70° (hexane); ir (potassium bromide): 2120 (s), 1720 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.0 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 7.6 (s, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 13.9 and 62.3 (C_2H_5), 123.8, 129.6, 130.2 and 134.9 (phenyl C-atoms), 144.4 (tetrazole C), 161.4 (CO), the CN_2 resonance was not observed.

Anal. Calcd. for $C_{11}H_{10}N_6O_2$ (mol wt 258): C, 51.16; H, 3.90. Found: C, 50.97; H, 3.91.

Thermolysis of the Diazoesters **5** and **6**.

Solutions of the diazoesters in benzene or acetonitrile (~0.03 *M*) were heated for the appropriate reaction times (*vide infra*) at 70-80° and then worked up by column chromatography on silica gel with ether or ether-hexane as the eluent (except for **12a** and **13a** which were isolated by crystallization from chloroform-ether and acetone respectively).

7-Methoxycarbonyl-7-(1-methyltetrazol-5-yl)norcaradiene (**7a**).

This compound was obtained in 47% yield (reaction time 3 weeks at 70°), mp 126° (chloroform-ether); ir (potassium bromide): 1730 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 3.45 (t, 2H, H-1 and H-6), 3.70 (s, 3H, OCH_3), 3.94 (s, 3H, NCH_3), 5.95 and 6.3 (two m, 4 vinyl H); ^{13}C nmr (deuteriochloroform): δ 14.5 (C-7), 33.9 (N-CH_3), 39.4 (C-1 and C6, $^1J_{CH}$ = 170 Hz), 53.5 (OCH_3), 122.7 and 126.2 (vinyl C), 148.6 (tetrazole C), 172.4 (CO).

Anal. Calcd. for $C_{11}H_{12}N_4O_2$ (mol wt 232): C, 56.89; H, 5.21. Found: C, 57.05; H, 5.21.

7-(1-Ethyltetrazol-5-yl)-7-methoxycarbonylnorcaradiene (**7b**).

This compound was obtained in 68% yield (reaction time 2 weeks at 70°), mp 107° (ether); ir (potassium bromide): 1730 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.55 (t, 3H, CH_3), 3.45 (t, 2H, H-1 and H-6), 3.70 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 5.9 and 6.3 (two m, 4 vinyl H); ^{13}C nmr (deuteriochloroform): δ 14.4 (C-7), 14.2 and 42.8 (C_2H_5), 39.1 (C-1 and C-6, $^1J_{CH}$ = 171.2 Hz), 53.4 (OCH_3), 123.0 and 126.0 (vinyl C), 147.9 (tetrazole C), 172.6 (CO).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$ (mol wt 246): C, 58.53; H, 5.73. Found: C, 58.42; H, 5.63.

7-Methoxycarbonyl-7-(2-methyltetrazol-5-yl)norcaradiene/cycloheptatriene (**10a** ⇌ **11a**).

This mixture was obtained in 47% yield (reaction time 5 weeks at 70°), mp 90° (ether); ir (potassium bromide): 1725 cm^{-1} (br s); ^1H nmr (deuteriochloroform) room temperature, δ 3.65 (s, 3H, OCH_3), 4.15 (m, 2H, H-1 and H-6), 4.27 (s, 3H, NCH_3), 6.05 and 6.35 (two m, 4 vinyl H); ^{13}C nmr (deuteriochloroform): room temperature, δ 27.8 (C-7), 39.3 (NCH_3), 53.0 (OCH_3), 65.9 (br, C-1 and C-6), 125.0 and 126.7 (vinyl C), 161.4 (tetrazole C), 173.0 (CO).

Anal. Calcd. for $C_{11}H_{12}N_4O_2$ (mol wt 232): C, 56.89; H, 5.21. Found: C, 57.00; H, 5.19.

7-(2-Ethyltetrazol-5-yl)-7-methoxycarbonylnorcaradiene/cycloheptatriene (**10b** ⇌ **11b**).

This mixture was obtained in 72% yield (reaction time 5 weeks at 70°), mp 38° (ether-hexane); ir (potassium bromide): 1720 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.57 (t, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.15 (m, 2H, H-1 and H-6), 4.6 (q, 2H, CH_2), 6.05 and 6.3 (two m, 4 vinyl H); ^{13}C nmr (deuteriochloroform): δ 14.3 and 48.2 (C_2H_5), 27.8 (C-7), 53.0 (OCH_3), 65.5 (br, C-1 and C-6), 125.0 and 126.6 (vinyl C), 161.1 (tetrazole C), 173.0 (CO).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$ (mol wt 246): C, 58.53; H, 5.73. Found: C, 58.55; H, 5.60.

1,5-Dimethyl-7-methoxycarbonylimidazo[1,5-*d*]tetrazole (**12a**).

This compound was obtained in 56% yield (reaction time 2 weeks at 70°), mp 199° (chloroform-ether); ir (potassium bromide): 1690 (s), 1620 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 2.68 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.37 (s, 3H, NCH_3); ^{13}C nmr (deuteriochloroform): δ 12.3 (CH_3), 36.2 (NCH_3), 51.6 (OCH_3), 99.4 (C-7), 126.3 (C-5), 138.4 (C-7a), 162.4 (CO).

Anal. Calcd. for $C_7H_9N_5O_2$ (mol wt 195): C, 43.08; H, 4.65. Found: C, 43.22; H, 4.58.

1-Ethyl-7-methoxycarbonyl-5-methylimidazo[1,5-*d*]tetrazole (**12b**).

This compound was obtained in 55% yield (67% before crystallization)

(reaction time 2 days at 80°), mp 107° (ether); ir (potassium bromide): 1680 (s), 1610 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.6 (t, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.8 (q, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 12.3 (CH_3), 15.4 and 45.4 (C_2H_5), 51.5 (OCH_3), 99.4 (C-7), 126.4 (C-5), 137.8 (C-7a), 162.4 (CO).

Anal. Calcd. for $C_8H_{11}N_5O_2$ (mol wt 209): C, 45.93; H, 5.30. Found: C, 45.72; H, 5.12.

5-(5-Methoxy-2-methyloxazol-4-yl)-2-methyltetrazole (**13a**).

This compound was obtained in 75% yield (reaction time 5 days at 80°), mp 138° (acetone); ir (potassium bromide): 1665 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 4.17 (s, 3H, OCH_3), 4.38 (s, 3H, NCH_3); ^{13}C nmr (deuteriochloroform): δ 13.8 (CH_3), 39.2 (NCH_3), 60.2 (OCH_3), 103.9 (oxazole C-4), 152.4 (oxazole C-2), 156.9 (oxazole C-5), 158.9 (tetrazole C).

Anal. Calcd. for $C_7H_9N_5O_2$ (mol wt 195): C, 43.08; H, 4.65. Found: C, 43.21; H, 4.52.

2-Ethyl-5-(5-methoxy-2-methyloxazol-4-yl)tetrazole (**13b**).

This compound was obtained in 28% yield (reaction time 5 days at 80°), mp 63° (ether); ir (potassium bromide): 1670 cm^{-1} (s); ^1H nmr (deuteriochloroform): δ 1.67 (t, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.17 (s, 3H, OCH_3), 4.69 (q, 2H, CH_2); ^{13}C nmr (deuteriochloroform): δ 13.95 (CH_3), 14.5 and 48.3 (C_2H_5), 60.3 (OCH_3), 104.3 (oxazole C-4), 152.5 (oxazole C-2), 157.0 (oxazole C-5), 158.8 (tetrazole C).

Anal. Calcd. for $C_8H_{11}N_5O_2$ (mol wt 209): C, 45.93; H, 5.30. Found: C, 46.01; H, 5.20.

Kinetic Measurements.

Solutions of the diazoesters **5a**, **6a** and **9** in deuterated benzene (10 mg in 1 ml) were placed in nmr tubes at 70° (± 0.1°) for decomposition. At several time intervals, the nmr tubes were cooled to 0° and analyzed by ^1H nmr spectroscopy. The rates of decomposition were followed by integration of the methyl resonances in the spectra. By plotting log (% diazo) *vs* time, linear plots were obtained up to a high degree of conversion (two half-lives), all having a correlation coefficient of at least 0.99. The first-order rate constants were determined from the slopes of the linear plots; **5a**, $k_1 = 0.48\ 10^{-5}\ s^{-1}$; **6a**, $k_1 = 0.22\ 10^{-5}\ s^{-1}$; **9**, $k_1 = 0.53\ 10^{-5}\ s^{-1}$.

Acknowledgement.

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