1,5-Di(tetrazol-5-yl)-3-oxapentane as a substrate in the synthesis of novel heterocyclic systems

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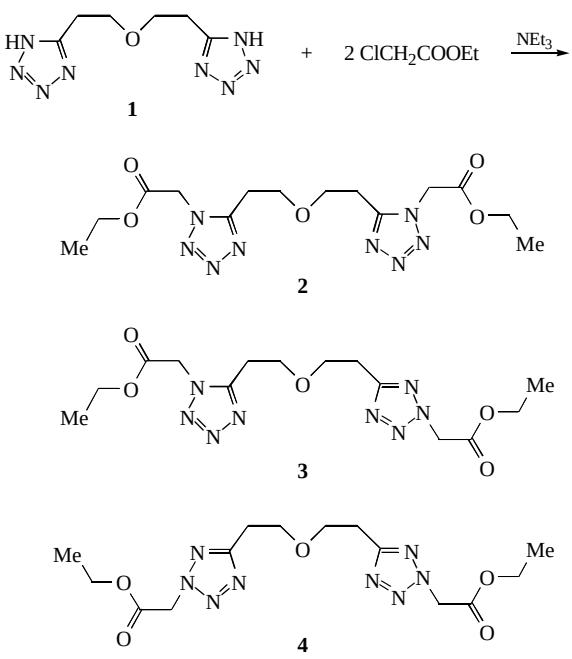
The preparation of novel bifunctional and macroheterocyclic systems by N-alkylation and N-acylation of 1,5-di(tetrazol-5-yl)-3-oxapentane has been developed.

The synthesis of 1,5-di(tetrazol-5-yl)-3-oxapentane **1** was reported previously.[1] Reactions of this compound with electrophilic agents have not yet been examined, although this way may lead to novel heterocyclic derivatives.[2,3] Here we have studied the reactions of substrate **1** with ethyl chloroacetate, 1,5-dichloro-3-oxapentane, *tert*-butanol and acetic anhydride.

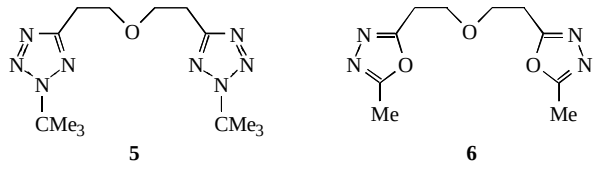
The interaction of substrate **1** with ethyl chloroacetate in acetonitrile at 70 °C leads to three carboethoxymethyl derivatives of the initial tetrazole: 1,5-bis(1-ethoxycarbonylmethyltetrazol-5-yl)-3-oxapentane **2**, 1-(1-ethoxycarbonylmethyltetrazol-5-yl)-5-(2-ethoxycarbonylmethyltetrazol-5-yl)-3-oxapentane **3** and 1,5-bis(2-ethoxycarbonylmethyltetrazol-5-yl)-3-oxapentane **4** (Scheme 1). The isomers of **2**–**4** were separated by column chromatography [Fluka Kieselgel 100 (0.063–0.200), gradient elution of 0–3% MeOH–$CHCl_3$]. The structure of the compounds obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.† According to the ^{1}H NMR spectroscopy data, the ratio between the 1,1′-, 1,2′- and 2,2′- isomers is 0.9:1.3:1.0.

In this study, we have also examined typical selective chemical reactions of 5-substituted tetrazoles.[4,5] Thus, substrate **1** interacts with *tert*-butanol in concentrated sulfuric acid to give 1,5-bis(2-*tert*-butyltetrazol-5-yl)-3-oxapentane **5**.‡ Under the refluxing of the initial tetrazole **1** in acetic anhydride, 1,5-bis(2-methyl-1,3,4-oxadiazol-5-yl)-3-oxapentane **6** was obtained.§

Using α,ω-dihaloderivatives as alkylating agents for substrate **1**, the corresponding tetrazole-containing macrocycles can be obtained. Thus, by the interaction of tetrazole **1** with 1,5-dichloro-3-oxapentane in highly dilute solutions in an aprotic dipolar solvent, the following ditetrazolyl-containing crown-like ethers were obtained: 5,6,8,9,14,15,17,18-octahydrodi[1,2,3,4]tetrazolo-[1,5-*d*:5,1-*k*][1,8,4,12]dioxadiazacyclotetraene **7**, 4,14-dioxa-1,7,8,9,10,18,19,20-octaazatricyclo[15.2.1.0^{7,10}]icosa-8,10,17(20),18-tetraene **8** and 4,13-dioxa-1,7,8,9,17,18,19,20-octaazatricyclo-[14.2.1.1^{7,10}]icosa-8,10(20),16(19),17-tetraene **9** (Scheme 2).¶



Scheme 1



Macrocycles **8** and **9** were separated using column chromatography (chromatography under the conditions described for compounds **2**–**4**). Cyclic ether **7** was not isolated because of its very low concentration in the reaction mixture. Compounds **8** and **9** were identified by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. These macrocycles may be considered as promising complexing agents for coordination chemistry. The spatial structure of compounds **8** and **9** is of paramount importance for the complexation with metal ions. For this reason, we have performed theoretical conformational analysis

† NMR spectra were recorded on a Bruker DPX-300 spectrometer (with TMS as an internal standard) at 300.1 (^{1}H) and 75.5 MHz (^{13}C).

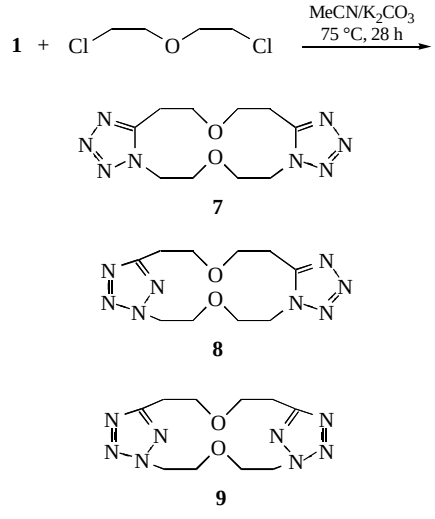
Compound **2**: colourless crystals, yield 22%, mp 166–168 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 6H, 2OCH$_2$*Me*, *J* 4.3 Hz), 3.07 (t, 4H, 2 tetrazole C-5–C*H*$_2$CH$_2$O, *J* 4.3 Hz), 3.89 (t, 4H, 2 tetrazole C-5–CH$_2$C*H*$_2$O, *J* 4.3 Hz), 4.26 (q, 4H, 2OC*H*$_2$Me, *J* 4.3 Hz), 5.13 (s, 4H, 2 tetrazole N-1–CH$_2$CO). ^{13}C NMR ($CDCl_3$) δ: 13.7 (OCH$_2$*Me*), 23.7 (tetrazole C-5–*C*H$_2$CH$_2$O), 47.5 (tetrazole N-1–*C*H$_2$CO), 62.5 (O*C*H$_2$Me), 67.4 (tetrazole C-5–CH$_2$*C*H$_2$O), 153.6 (1,5-tetrazole C-5), 165.1 (COO).

Compound **3**: colourless crystals, yield 26%, mp 75–78 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 6H, 2OCH$_2$*Me*, *J* 4.5 Hz), 2.93 (t, 4H, 2 tetrazole C-5–C*H*$_2$CH$_2$O, *J* 5.0 Hz), 3.61 (tt, 4H, 2 tetrazole C-5–CH$_2$C*H*$_2$O, *J* 4.0 Hz), 4.06 (qq, 4H, 2OC*H*$_2$Me, *J* 4.4 Hz, *J* 7.6 Hz), 5.03 (s, 2H, tetrazole N-1–CH$_2$CO), 5.24 (s, 2H, tetrazole N-2–CH$_2$CO). ^{13}C NMR ($CDCl_3$) δ: 13.5 (OCH$_2$*Me*), 23.6 and 25.6 (tetrazole C-5–*C*H$_2$CH$_2$O), 47.5 (tetrazole N-1–*C*H$_2$CO), 52.7 (tetrazole N-2–*C*H$_2$CO), 62.0 and 62.1 (O*C*H$_2$Me), 67.8 and 67.9 (tetrazole C-5–CH$_2$*C*H$_2$O), 154.1 (1,5-tetrazole C-5), 164.0 (2,5-tetrazole C-5), 165.0, 165.5 (COO).

Compound **4**: viscous oil, yield 17%. ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 6H, 2OCH$_2$*Me*, *J* 4.3 Hz), 3.08 (t, 4H, 2 tetrazole C-5–C*H*$_2$CH$_2$O, *J* 4.3 Hz), 3.80 (t, 4H, 2 tetrazole C-5–CH$_2$C*H*$_2$O, *J* 4.3 Hz), 4.16 (q, 4H, 2OC*H*$_2$Me, *J* 4.3 Hz), 5.29 (s, 4H, tetrazole N-2–CH$_2$CO). ^{13}C NMR ($CDCl_3$) δ: 13.6 (OCH$_2$*Me*), 25.8 (tetrazole C-5–*C*H$_2$CH$_2$O), 52.7 (tetrazole N-2–*C*H$_2$CO), 62.1 (O*C*H$_2$Me), 67.8 (tetrazole C-5–CH$_2$*C*H$_2$O), 164.1 (2,5-tetrazole C-5), 164.9 (COO). Here and elsewhere the identification of the compounds obtained was carried out on the basis of published data.[2,3]

‡ Compound **5**: colourless crystals, yield 87%, mp 58–60 °C (Pr^{i}OH). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.65 (s, 18H, 2CMe$_3$), 3.03 (br. s, 4H, 2 tetrazole C-5–C*H*$_2$CH$_2$O), 3.79 (br. s, 4H, 2 tetrazole C-5–CH$_2$C*H*$_2$O). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 25.9 (tetrazole C-5–*C*H$_2$CH$_2$O), 28.9 (C*Me*$_3$), 63.3 (*C*Me$_3$), 67.9 (tetrazole C-5–CH$_2$*C*H$_2$O), 163.1 (2,5-tetrazole C-5).

§ Compound **6**: viscous oil, yield 75%. ^{1}H NMR ([^{2}H$_6$]DMSO, 200 MHz) δ: 2.45 (s, 6H, 2 1,3,4-oxadiazole C-2–Me), 3.00 (t, 4H, 2 1,3,4-oxadiazole C-5–C*H*$_2$CH$_2$O, *J* 2.3 Hz), 3.75 (t, 4H, 2 1,3,4-oxadiazole C-5–CH$_2$C*H*$_2$O, *J* 2.3 Hz). ^{13}C NMR ([^{2}H$_6$]DMSO, 50 MHz) δ: 10.5 (1,3,4-oxadiazole C-2–*Me*), 25.6 (1,3,4-oxadiazole C-5–*C*H$_2$CH$_2$O), 66.4 (1,3,4-oxadiazole C-5–CH$_2$*C*H$_2$O), 163.6 and 164.6 (C-2 and C-5 in 1,3,4-oxadiazole).



Scheme 2

¶ Compound **8**: colourless crystals, yield 3.5%, mp 137.0–137.5 °C (MeOH). Molecular mass: found 283 (acetone); calc. for $C_{10}H_{16}N_8O_2$ 280.29. ^{1}H NMR ($CDCl_3$) δ: 2.87 (t, 2H, 1,5-tetrazole C-5–CH_2CH$_2$O, J 5.7 Hz), 3.10 (t, 2H, 1,5-tetrazole C-5–CH_2CH$_2$O, J 5.7 Hz), 3.84 (tt, 4H, CH$_2$CH_2OCH_2CH$_2$, J 5.7 Hz, J 4.4 Hz), 3.92 (t, 2H, CH$_2$CH_2O-CH_2CH$_2$, J 5.7 Hz), 4.03 (t, 2H, CH$_2$CH_2OCH_2CH$_2$, J 4.8 Hz), 4.20 (t, 2H, 1,5-tetrazole N-1–CH_2CH$_2$O, J 5.7 Hz), 4.72 (t, 2H, 2,5-tetrazole N-2–CH_2CH$_2$O, J 4.8 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 24.0 (2,5-tetrazole C-5–*C*H$_2$CH$_2$O), 26.1 (1,5-tetrazole C-5–*C*H$_2$CH$_2$O), 46.4 (1,5-tetrazole N-1–*C*H$_2$CH$_2$O), 52.3 (2,5-tetrazole N-2–*C*H$_2$CH$_2$O), 67.4, 68.3, 68.4 and 68.5 (2CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 153.3 (1,5-tetrazole C-5), 163.9 (2,5-tetrazole C-5).

Compound **9**: colourless crystals, yield 8%, mp 194.5–195.5 °C (MeOH). Molecular mass: found 282 (acetone), calc. for $C_{10}H_{16}N_8O_2$ 280.29. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.93 (t, 4H, 2 2,5-tetrazole C-5–CH_2CH$_2$O, J 5.3 Hz), 3.74 (t, 8H, 2 2,5-tetrazole C-5–CH$_2$CH_2O, J 5.3 Hz), 3.90 (t, 4H, 2 2,5-tetrazole N-2–CH_2CH$_2$O, J 4.8 Hz), 4.68 (t, 4H, 2 2,5-tetrazole N-2–CH_2CH$_2$O, J 4.8 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 25.7 (2,5-tetrazole C-5–*C*H$_2$CH$_2$O), 52.1 (2,5-tetrazole N-2–*C*H$_2$CH$_2$O), 67.5 and 67.7 (CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 163.9 (2,5-tetrazole C-5).

of macrocycle **9** using the AM1 method, which showed that this ether can exist in 31 conformations. In this case, the rotation of tetrazole fragments in the molecule is highly hindered.

In summary, the polytetrazol-5-yl substrates react with electrophilic agents analogously to mononuclear 5-substituted tetrazoles. As a result of these transformations, novel polynuclear tetrazole and oxadiazole derivatives of practical importance can be prepared.

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