Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2009, **19**, 81–83

Mendeleev Communications

Reaction of diaziridine-3,3-dicarboxylic acid dihydrazide with acetone

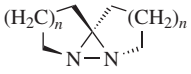
Boriss Strumfs,[a] Edvards Liepin'sh,[a] Sergey Belyakov,[a] Peteris Trapencieris*[a] and Remir G. Kostyanovsky*[b]

[a] *Latvian Institute of Organic Synthesis, LV-1006 Riga, Latvia. Fax: +371 6755 0338; e-mail: peteris@osi.lv*
[b] *N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 651 2191; e-mail: kost@center.chph.ras.ru*

DOI: 10.1016/j.mencom.2009.03.009

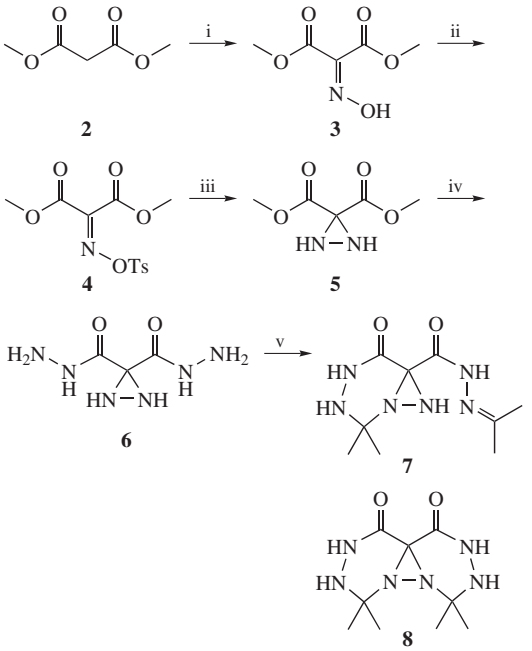
Using the reaction of diaziridine-3,3-dicarboxylic acid dihydrazide with acetone, new bicyclic diaziridines 7a,b have been obtained instead of expected tricyclic heterocycle 8.

Diaziridines are known to display anticancer[1–5] and psychotropic[6] activity. In this aspect, the chiral diaziridines are of special interest, in particular, tricyclic 'butterfly' **1a**,**b** (liquids) of C_2 symmetry.[7–10]

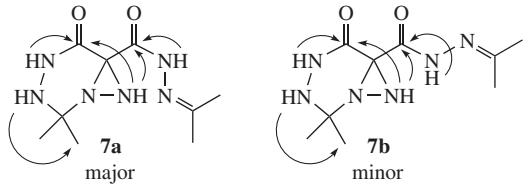


1a $n = 1$
1b $n = 2$

This work aimed to obtain crystalline functionalized tricyclic diaziridines capable of resolving into enantiomers and thus potentially useful for structural and biological studies. As we reported earlier, aziridine-2-carboxylic acid hydrazide reacted with aldehydes and ketones to give bicyclic aziridines,[11] and with acetone it formed a crystalline conglomerate, which underwent spontaneous resolution.[12]



Scheme 1 Synthesis of diaziridine **7**. *Reagents and conditions*: i, AcOH–H_2O, $NaNO_2$, –5 °C to room temperature, 6 h; ii, NEt_3, Et_2O, TsCl, 5 °C to room temperature, 4 h; iii, NH_3 (2 equiv.) in MeCN, –40 °C, 1.5 h; iv, 1 mol dm^{-3} hydrazine in THF, room temperature, 12 h; v, Me_2CO (excess), reflux, 1.5 h.



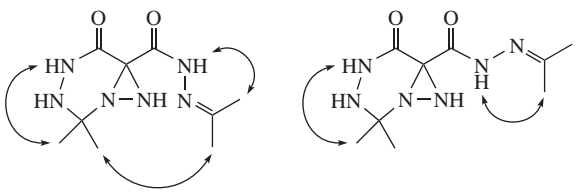
7a major **7b** minor

Figure 1 Important $^1H \rightarrow {}^{13}C$ connectivities observed in HMBC spectra.

Assuming that an analogous double cyclization could be feasible, we have studied the reaction of diaziridine-3,3-dicarboxylic acid dihydrazide **6** with acetone in an attempt to obtain the target tricyclic diaziridine similar to **1b**. However, instead of tricycle **8**, a mixture of bicyclic diaziridines **7a** and **7b** was obtained (Scheme 1).† The initially formed precipitate consists of two isomers **7a** and **7b**, but after recrystallization from acetone, only bicycle **7b** was isolated.

Several attempts to convert the mixture of hydrazones **7a**,**b** into tricyclic **8** were unsuccessful. Thus, heating a solution of **7a**,**b** in boiling [$^2H_6$]acetone at 60 °C for 10 or 48 h in pure boiling CD_3OD (and with 10 mol% DABCO) produced no changes in ^1H NMR spectra.

The structure of the bicyclic hydrazones was investigated using NMR spectroscopy. When recrystallised isomer **7b** was dissolved in [$^2H_6$]DMSO, signals corresponding to two isomeric monohydrazones **7a** and **7b** were observed in an equilibrium ratio of 3:2. Both structures were confirmed by important $^1H \rightarrow {}^{13}C$ connectivities observed in HMBC spectra (Figure 1) and observed NOEs (Figure 2). According to this evidence, the isomers may differ in the *E*/*Z* geometry of the *N*-acylhydrazone or in stereochemistry at the diaziridine nitrogen. Stereochemistry at the diaziridine NH nitrogen seems to be well defined due to a much higher inversion barrier in diaziridines as compared to



7a major **7b** minor

Figure 2 Observed NOEs.

simple aziridines. According to X-ray structure of **7b** (Figure 3), diaziridine NH proton is pointed towards uncyclised substituent due to electronic repulsions of N(1) and N(2) lone electron pairs. One more possibility to generate isomers is the planar inversion of hydrazone nitrogen. However, this is very high energy process and cannot count for observed exchange cross peaks on NOESY/ROESY spectra between **7a** and **7b**. Thus, we conclude that interconversion of **7a** to **7b** is restricted rotation around amide bond as it was observed in the case of other acylhydrazones.[13,14] At the same time, the geometry of the preferred solid state isomer is confirmed, as shown for bicyclic diaziridine **7b** according to the X-ray diffraction study (Figure 3).‡

In summary, bicyclic diaziridines **7** (semi butterfly) have been synthesised for the first time from diaziridine-3,3-dicarboxylic acid dihydrazide and acetone. No tricyclic structure **8** (butterfly) was detected in these studies.

This work was supported by the Russian Academy of Sciences and the Russian Foundation for Basic Research (grant no. 06-03-32840).

† NMR spectra were recorded on a Varian UNITY INOVA 600 MHz spectrometer equipped with a cryoprobe, in [$^2H_6$]DMSO solution at 25 °C, and on a 200 MHz NMR Spectrometer Varian 200 Mercury. Chemical shifts are reported in ppm relative to residual solvent signal [δ (^{1}H) 2.50 ppm, δ (^{13}C) 39.5 ppm] (for 600 MHz spectrometer) or TMS as an internal reference (for 200 MHz spectrometer). Two-dimensional spectra recorded included DQF-COSY, ROESY, TOCSY, sensitivity-enhanced ^{13}C-HSQC and ^{13}C–^{1}H HMBC. Pulsed-field gradients were used for all ^{13}C correlation spectra. The ROESY mixing time was 200 ms, and the TOCSY mixing time was 70 ms. ^{13}C-HMBC spectra were recorded with coupling evolution delay for the generation of multiple-bond correlations set to 62.5 ms. All 2D spectra were run with 4096×1024 points data matrix, giving $\tau_{2\,max}$ = 250 ms for ^{1}H in the acquisition dimension and τ_{1max} = 100 ms for ^{1}H or τ_{1max} = 50 ms for ^{13}C for the indirect dimension. Prior to Fourier transform the data matrix was zero-filled twice and multiplication by shifted sine-bell window function was applied. For ^{1}H–^{13}C HMBC the magnitude spectra were calculated.

LC-MS analysis was performed on a Waters Acquity ultra performance liquid chromatography (UPLC) system (Waters Corp., Milford, USA) (column Acquity UPLC BEH C18 1.7 μm, 2.1×50 mm) coupled to a Micromass Q-Tof micro API Time Of Flight (TOF) mass spectrometer (Waters Corp., Milford, USA) equipped with an electrospray source operating in positive ion mode. The source temperature was set at 120 °C with a cone gas flow of 30 dm^3 h^{-1}. A desolvation gas temperature of 300 °C and a gas flow of 400 dm^3 h^{-1} were employed. The capillary voltage was set at 3.0 kV and the cone voltage was 45 V.

Diester **4** was obtained according to the reported method,[15] yield 5.22 g (73%). ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 2.47 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 7.33–7.44 (m, 2H), 7.83–7.94 (m, 2H).

Diaziridine **5** was prepared according to the known procedure[16] and purified by sublimation. Dihydrazide **6** is extremely hygroscopic and, therefore, was used without purification.

Bicyclic diaziridine **7**: 170 mg (1.06 mmol) of diaziridine **5** was dissolved in 10 ml of dry THF (from Na/benzophenone), and 2.2 ml of 1 mol dm^{-3} hydrazine solution in THF was added. The mixture was stirred for 12 h under argon. A white precipitate was filtered under argon, dissolved in dry acetone, and the solution was heated under reflux for 1.5 h. The precipitate was filtered, dried *in vacuo* and recrystallized from acetone to give **7b**, yield 50 mg (20%). LC-MS, *m*/*z*: 263 [M + Na]$^+$. Major isomer **7a** (in solution): ^{1}H NMR (600 MHz, [$^2H_6$]DMSO) δ: 1.12 (s, 3H, Me), 1.32 (s, 3H, Me), 1.80 (s, 3H, Me), 1.83 (s, 3H, Me), 3.76 (s, 1H, HN), 4.85 (s, 1H, HN), 8.90 (s, 1H, HN), 10.62 (s, 1H, HN). ^{13}C NMR (150 MHz, [$^2H_6$]DMSO) δ: 17.7, 21.8, 24.9, 25.27, 52.5, 71.3, 159.1, 161.0, 167.9. Minor isomer **7b** (in solution): ^{1}H NMR (600 MHz, [$^2H_6$]DMSO) δ: 1.16 (s, 3H, Me) 1.17 (s, 3H, Me), 1.87 (s, 3H, Me), 1.94 (s, 3H, Me), 4.10 (s, 1H, HN), 5.16 (s, 1H, HN), 9.42 (s, 1H, HN), 11.32 (s, 1H, HN). ^{13}C NMR (150 MHz, [$^2H_6$]DMSO) δ: 18.0, 21.5, 24.9, 25.33, 57.7, 71.8, 151.1, 165.2, 167.7.

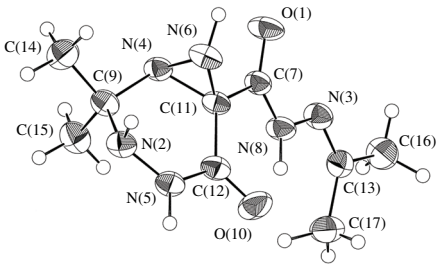


Figure 3 X-ray structure for **7b** in representation of atoms as thermal ellipsoids drawn at 50% probability level.

References

1 S. Takase, M. Watanabe, O. Shiratori and Y. Hata, *Biochem. Biophys. Res. Commun*., 1982, **104**, 746.
2 Y. Kobayashi, C. Sridar, U. M. Kent, S. G. Puppali, J. M. Rimoldi, H. Zhang, L. Waskell and P. F. Hollenberg, *Drug. Metab. Dispos*., 2006, **34**, 2102.
3 Y. Hata and M. Watanabe, *Biochem. Biophys. Res. Commun*., 1982, **106**, 526.
4 G. Sosnovsky and J. Lukszo, *Z. Naturforsch*., 1983, **B38**, 884.
5 G. Sosnovsky and J. Lukszo, *J. Cancer Res. Clin. Oncol*., 1984, **107**, 217.
6 R. G. Kostyanovsky, G. V. Shustov, O. G. Nabiev, S. N. Denisenko, S. A. Sukhanova and E. F. Lavretskaya, *Khim.-Farm. Zh*., 1986, **20**, 671 (in Russian) (*Chem. Abstr*., 1987, **106**, 27665q).
7 S. N. Denisenko, E. Pasch and G. Kaupp, *Angew. Chem., Int. Ed. Engl*., 1989, **28**, 1381.
8 S. N. Denisenko, G. Kaupp, A. J. Bittner and P. Rademacher, *J. Mol. Struct*., 1990, **240**, 305.
9 G. Kaupp, S. N. Denisenko, G. V. Shustov and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1991, 2496 (*Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1991, **40**, 2173).
10 G. Kaupp and S. N. Denisenko, *Magn. Res. Chem*., 1992, **30**, 637.
11 P. T. Trapentsier, I. Ya. Kalvin'sh, E. E. Liepin'sh, E. Ya. Lukevits, G. A. Bremanis and A. V. Eremeev, *Khim. Geterotsikl. Soedin*., 1985, 774 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 1985, **21**, 646].
12 R. G. Kostyanovsky, P. E. Dormov, P. Trapencieris, B. Strumfs, G. K. Kadorkina, I. I. Chervin and I. Ya. Kalvin's, *Mendeleev Commun*., 1999, 26.
13 O. V. Hordiyenko, A. V. Biitseva, M. Yu. Kornilov, N. Brosse, A. Hocquet, B. Jamart-Grégoire, O. V. Shishkin and R. I. Zubatyuk, *Eur. J. Org. Chem*., 2006, 2833.
14 P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias and E. Mikros, *J. Mol. Struct*., 2003, **650**, 213.
15 A. J. Zambito and E. E. Howe, *Org. Synth., Coll. Vol*., 1973, **5**, 373.
16 R. G. Kostyanovskii, G. V. Shustov and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1974, 2823 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1974, **23**, 2725).

‡ X-Ray quality crystals of **7b** ($C_9H_{16}N_6O_2$, M = 240.267) were obtained by slow evaporation of acetone solution of equilibrium mixture of **7a** and **7b**. Crystals are triclinic, space group $P\bar{1}$, colourless prisms, size 0.07×0.12×0.19 mm, at room temperature (20±2 °C): a = 7.4559(4), b = 7.7749(4) and c = 11.5958(7) Å, V = 592.94(6) Å^3, Z = 2, d_{calc} = = 1.346 g cm^{-3}, μ = 0.10 mm^{-1}, F(000) = 256, final R-factor 0.0675. The data were collected on a Nonius KappaCCD diffractometer at room temperature (20±2 °C) using MoKα radiation (λ = 0.71073 Å) by the φ and ω scan method. Accurate lattice parameters were determined from 1569 reflections. Crystallographic computations were carried out with the Denzo-SMN program[17] of Bruker-Nonius. The structures were solved by an application of the direct method using the programs DETMAX.[18,19] The crystal structures were refined by full-matrix least-squares method using the SHELXL97.[20] Minimized functional was $\sum w[|F_o|^2 - (1/k)|F_c|^2]$. The final round of refinement was performed with anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms were refined using a riding model. The molecular graphics were performed with the help of the program ORTEP.[21]

CCDC 689085 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

17 Z. Otwinowski and W. Minor, in *Methods in Enzymology*, eds. C. W. Carter Jr. and R. M. Sweet, Academic Press, New York, 1997, vol. 276, p. 307.
18 A. F. Mishnev and S. V. Belyakov, *Kristallografiya*, 1988, **33**, 835 (in Russian).
19 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
20 G. M. Sheldrick, *SHELXL97. Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
21 C. K. Johnson, *ORTEP-II. A Fortran Thermal-Ellipsoid Plot Program. Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA, 1976.

Received: 29th August 2008; Com. 08/3205