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Stereochemical outcome of perhydro hexaazadibenzotetracene formation from *trans*-1,2-diaminocyclohexane

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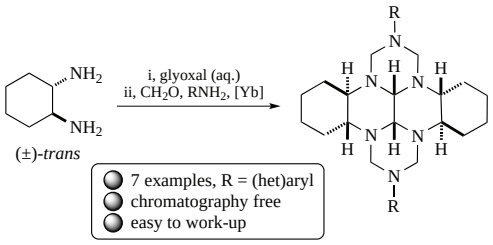
A one-pot reaction between (±)-*trans*-1,2-diaminocyclohexane and glyoxal affords intermediate perhydro-1,6,7,12-tetraazatetracene whose further treatment with formaldehyde and (het)arylamines in the presence of $YbCl_3 \cdot 6H_2O$ gives 2,9-di(het)aryl substituted (3b*R,7a*R**,10b*R**,14a*R**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]-tetracenes with *cis*-junction of the cycles along the C(14c)–C(14d) bond.**



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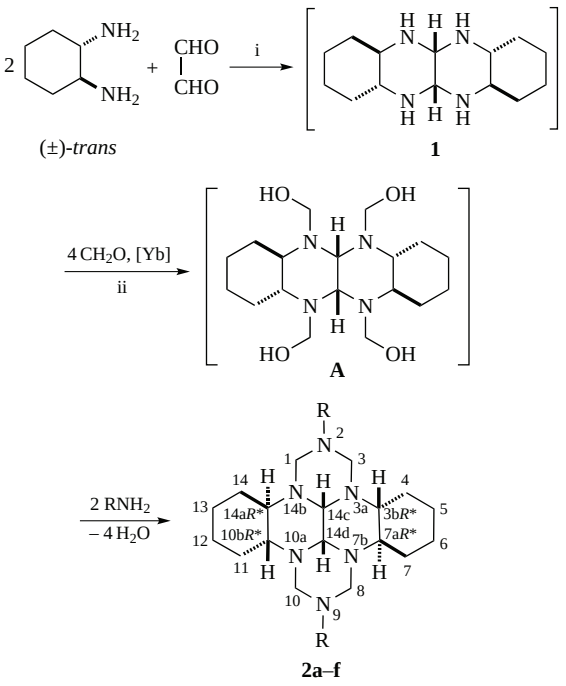
By the time when our studies started, a single example[1] had been described concerning the synthesis of an N,N′-disubstituted hexaazaperhydrodibenzotetracene by cyclocondensation of 4-aminopiperidine, paraformaldehyde and perhydrotetraazatetracene in the presence of strongly acidic Lewatit cation resin, however the stereo configuration of the product was not discussed. Recently,[2] we have reported on a one-pot preparation of 2,9-di(cyclo)alkyl substituted (3b*S**,7a*R**,10b*R**,14a*S**)-perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes based on the catalytic reaction of *cis*-1,6,7,12-tetraazaperhydrotetracene with cycloaminomethylating reagents.

In continuation of ongoing studies on the synthesis of polyazapolycycles with pronounced biological activity,[3,4] we examined the possibility of synthesizing perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracenes on the basis of *trans*-1,6,7,12-tetraazaperhydrotetracene, since the compounds containing a *trans*-1,2-diaminocyclohexane moiety possess antitumor activity[5–8] and antiproliferative effects.[9] Herein, we carried out the cyclocondensation of 1,6,7,12-tetraazaperhydrotetracene **1** obtained *in situ* from (±)-*trans*-1,2-diaminocyclohexane with formaldehyde and primary (het)arylamines (Scheme 1). Analysis of components of the reaction mixture obtained from *p*-aminophenol and formaldehyde using MALDI TOF/TOF mass spectrometry showed exclusively the arylimine[10] responsible for the cycloaminomethylation of the starting amino substrate. Attempts to use *N*,*N*-bis(methoxymethyl)-*N*-(het)arylamines or 1,3,5-tri(het)aryl-1,3,5-triazinanes in the reaction as the cyclomethylating reactants failed. For this reason, we used a different order of reactant mixing when tetraazaperhydrotetracene **1** was first reacted with formaldehyde and then (het)arylamine was added. Preliminary experiments have shown that in the absence of a catalyst, the reaction of compound **1** with formaldehyde and *p*-aminophenol in a molar ratio of 1 : 4 : 2, respectively, in MeOH at 20°C for 3 h selectively gave 2,9-bis(4-hydroxyphenyl)perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene **2a** in yields no higher than 15%. To increase the yield of product **2a**, multicomponent condensation was carried out in the presence of homogeneous catalysts based on salts of transition metals (Cu, Co, Ni, Fe, Pt) and rare-earth elements (Sm, Eu, La, Er, Yb) that were used previously in heterocyclization reactions.[10] It should be noted



a R = 4-HOC_6H_4 (58%)
b R = 4-$HO_2CC_6H_4$ (51%)
c R = 5-methyl-1,2-oxazol-3-yl (56%)
d R = 1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl (52%)
e R = pyridin-2-yl (55%)
f R = pyridin-4-yl (48%)

Scheme 1 *Reagents and conditions*: i, MeOH, 70 °C, 3 h; ii, CH_2O (aq., 4 equiv.), $YbCl_3 \cdot 6H_2O$ (cat.), then RNH_2 (2 equiv.), MeOH, room temperature, 3 h.

that the use of the above catalysts did not change the reaction chemoselectivity but affected the yields. Of the catalysts tested, 5 mol% $YbCl_3 \cdot 6H_2O$ exhibited the greatest activity. If the reaction was performed in the presence of more than 7 mol% of $YbCl_3 \cdot 6H_2O$, the yield was not improved significantly, while with the application of less than 3 mol% of this catalyst the yield dropped, apparently, due to decrease in the number of catalytically active sites. In the presence of 5 mol% $YbCl_3 \cdot 6H_2O$, the heterocyclization of *trans*-1,6,7,12-tetraazaperhydrotetracene with formaldehyde and *p*-aminophenol resulted in compound **2a** having (3b*R**,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-configuration with *cis*-junction of the cycles along C(14c)–C(14d) bond in 58% yield. The reaction with *p*-aminobenzoic acid proceeds similarly to afford compound **2b** in 51% yield (see Scheme 1).

The cyclocondensation of *trans*-1,6,7,12-tetraazaperhydrotetracene **1** with formaldehyde and some hetarylamines in the presence of 5 mol% $YbCl_3 \cdot 6H_2O$ in MeOH at 20 °C for 3 h leads to the corresponding 2,9-bis(hetaryl) derivatives **2c–f** in 48–56% yields (see Scheme 1). According to the suggested mechanism, the condensation of *trans*-1,6,7,12-tetraazaperhydrotetracene **1** with formaldehyde in the presence of $YbCl_3 \cdot 6H_2O$ involves the stage of formation of tetrakis(hydroxymethyl) derivative **A**.[10,11] Probably, $YbCl_3 \cdot 6H_2O$ as a hard Lewis acid is coordinated to the oxygen atom of intermediate **A** to give a carbocation. The subsequent nucleophilic addition of the primary (het)arylamine to the carbocation results in *N*,*N*′-di(het)aryl-substituted perhydro-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]-tetracenes **2a–f**.

It should be clarified that (±)-*cis*-diaminocyclohexane in the similar transformation was converted into (3b*S**,7a*R**,10b*R**,14a*S**)-perhydrohexaazadibenzotetracene compounds[2] with the rings having a *trans*-junction along the C(14c)–C(14d) bond. A distinct feature of the present work is provision of a synthetic pathway based on (±)-*trans*-diaminocyclohexane that allows one to obtain 2,3a,7b,9,10a,14b-hexazadibenzotetracenes having chiral centers at the carbon atoms C(3b), C(7a), C(10b), C(14a) in *R**,*R**,*R**,*R**-relative configuration and a *cis*-junction of the piperazine rings. We note hereby that the data on configurations of compounds in reactions of 1,2-diaminocyclohexane isomers with glyoxal is completely absent in the literature. Still, a data has been retrieved that the reactions of *trans*-diaminocyclohexane[12,13] with 2,3-dihydro-5,6-dimethylpyrazine give tetraazapolycyclane compounds with *cis*-junction of piperazine rings. The products obtained in the reactions of triethylenetetraamine[14] with glyoxal are characterized by similar stereochemistry. It is noteworthy that polyazapolycycles of perhydropyrene series are also characterized by both *trans*-[3] and *cis*-junction[4] of piperazine rings.

The ^{1}H NMR spectra of compounds **2a–f** contain four doublet signals of the AB spin system at δ 3.00–5.75 corresponding to methylene protons of the carbon atoms located between the nitrogen atoms at positions H-1,8 and H-3,10. The junction pattern between the piperazine rings exerts a prominent effect on chemical shifts for the 14c/14d-positioned protons. In case of *cis*-junction, their chemical shifts are observed in a lower field compared to the case of the *trans*-junction, which correlates with our previous results.[2,3,10] In the ^{13}C NMR spectra, the formation of the hexaazaperhydrodibenzotetracene frame of compounds **2a–f** confirms the presence of signals in the region of δ 62.1–67.3 and 66.2–71.5 belonging to carbon atoms at positions 3,10 and 1,8, respectively. In general, the perhydrohexaazadibenzotetracene frame is described by nine pairwise resonating carbon signals due to the presence of a center of symmetry between the C(14c) and C(14d) atoms. The assignment of signals was carried out on the basis of two-dimensional homo- (COSY) and heteronuclear (HSQC, HMBC) NMR experiments. The suggested structures are confirmed by the presence of molecular peaks recorded in the MALDI TOF/TOF mass spectra with matrix-induced laser desorption of positive ions.

Note that our procedure provides precipitation of products **2a–f** from the reaction mixture as powders thus allowing one to avoid the need of chromatographic purification. Other components of the reaction mixture remain in the mother liquor.

In order to obtain single crystal sample suitable for X-ray diffraction study, tosylation[15] of compound **2a** was carried out to provide new ditosyl derivative **2′a**. Recrystallization of compound **2′a** from chloroform gave transparent plate-shaped single crystals. X-Ray diffraction analysis† (Figure 1) revealed the presence of a second-order local axis passing through the middle of the C(14c)–C(14d) bond in the polyazapolycyclic molecule frame, which is in agreement with NMR spectroscopy data. The hydrogen atoms, with the exception for those at carbon atoms C(3b), C(7a), C(10b), C(14a), C(14c), and C(14d) used to determine the type of ring junction, were removed to clarify the structure. The six-membered carbo- and azacycles in perhydro hexaazadibenzotetracene moiety of compound **2′a** assume the *chair* conformation. Similarly to difurazanohexahydrohexaazapyrenes reported previously,[4] the piperazine rings in compound **2′a** have a *cis*-junction, which is confirmed by the value of the H(14c)–C(14c)–C(14d)–H(14d) torsion angle that is 55.3(2)°.

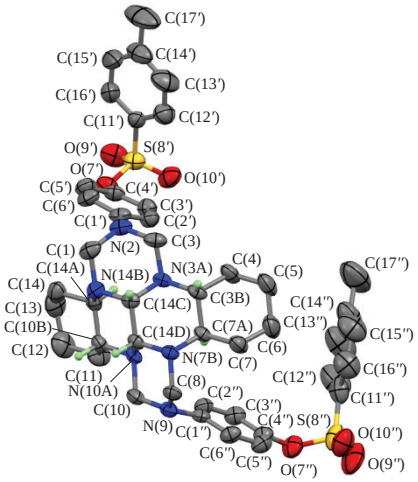


Figure 1 The molecular structure of compound **2′a** with the atoms presented as thermal vibration ellipsoids with 30% probability.

† *Crystal data for* **2′a**. $C_{44}H_{52}N_6O_6S_2$ (M = 825.04), monoclinic, space group $P2_1/c$: a = 9.6826(4), b = 23.7412(9) and c = 17.9380(5) Å, β = 98.760(3)°, V = 4075.4(3) Å^3, Z = 4, d_{calc} = 1.345 g cm^{-3}, μ(MoKα) = 0.188 mm^{-1}, F(000) = 1752.0. Total of 19531 were collected (9426 independent reflections, R_{int} = 0.0248) and used in the refinement, which converged to wR_2 = 0.1294, GOOF 1.028 for all independent reflections [R_1 = 0.0542 was calculated for 9426 reflections with $I > 2\sigma(I)$].

The X-ray diffraction measurements were performed on an Agilent XCalibur (Gemini, Eos) diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). Collected data were processed using the program CrysAlisPro.[16] Structures determinations were carried out with the OLEX2 program.[17] The structure was solved with the ShelXT[18] structure solution program using Intrinsic Phasing and refined with the ShelXL[19] refinement package using Least Squares minimisation. All hydrogen atoms were generated using the proper HFIX command and refined isotropically using the riding model.

CCDC 1957459 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

The piperazine and cyclohexane rings are *trans*-bound, and the H(3b)–C(3b)–C(7a)–H(7a) and H(10b)–C(10b)–C(14a)–H(14a) torsion angles are 175.71(17) and 176.14(19)°, respectively. The aryl substituents are *syn*-oriented and occupy an axial position relative to the polyazapolycyclic frame. The nitrogen atoms have a pyramidal conformation where the sum of the angles at the nitrogen atoms varies from 327 to 349.4°. The dihedral angles between the middle planes C(1′)–C(2')–C(3′)–C(4′)–C(5′)–C(6′)/C(11′)–C(12′)–C(13′)–C(14′)–C(15′)–C(16′) and C(1′′)–C(2′′)–C(3′′)–C(4′′)–C(5′′)–C(6′′)/C(11′′)–C(12′′)–C(13′′)–C(14′′)–C(15′′)–C(16′′) of the phenyl and tosyl rings are 67.49(8) and 76.92(10)°, respectively.

In conclusion, we have demonstrated that the multicomponent condensation of *trans*-1,6,7,12-tetraazaperhydrotetracene with formaldehyde and (het)arylamines catalyzed by $YbCl_3 \cdot 6H_2O$ represents the first example of new *N*,*N*′-di(het)aryl substituted (3b*R**,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexazadibenzo[*fg*,*op*]tetracenes. Synthesis of hybrids comprising structures with pronounced biological activity and polycyclic ones for producing up-to-date pharmaceuticals is of undoubted interest. Our future strategy includes expanding the range of amino substrates and gaining further insights into the antitumor activity of synthesized N,N′-disubstituted perhydro hexaazadibenzotetracene compounds *in vitro*. Computational calculations to rationalize the phenomena observed herein are also underway.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.015.

References

1 P. Neumann, A. Aumueller and H. Trauth, *US Patent 4,904,779*, 1990.
2 E. B. Rakhimova, V. Yu. Kirsanov, E. S. Mescheryakova, L. M. Khalilov, A. G. Ibragimov and U. M. Dzhemilev, *Synlett*, 2018, **29**, 1861.
3 E. B. Rakhimova, V. Yu. Kirsanov, E. S. Meshcheryakova, L. M. Khalilov, B. I. Kutepov, A. G. Ibragimov and U. M. Dzhemilev, *Tetrahedron*, 2017, **73**, 6880.
4 E. B. Rakhimova, V. Yu. Kirsanov, E. S. Mescheryakova, L. M. Khalilov, A. G. Ibragimov, L. U. Dzhemileva, V. A. D’yakonov and U. M. Dzhemilev, *ACS Med. Chem. Lett*., 2019, **10**, 378.
5 M. Dragoun, T. Günther, C. Frias, A. Berkessel and A. Prokop, *J. Cancer Res. Clinic. Oncol*., 2018, **144**, 685.
6 A. R. Khokhar, S. Al-Baker, S. Shamsuddin and Z. H. Siddik, *J. Med. Chem*., 1997, **40**, 112.
7 F. Morales, A. Ramírez, C. Morata-Tarifa, S. A. Navarro, J. A. Marchal, J. M. Campos and A. Conejo-García, *Future Med. Chem.*, 2017, **9**, 293.
8 K. H. Omer, A. A. Seliman, M. Altaf, N. Casagrande, D. Aldinucci, S. Altuwaijri and A. A. Isab, *Polyhedron*, 2015, **102**, 773.
9 J. Iwanejko, E. Wojaczyńska, J. Trynda, M. Maciejewska, J. Wietrzyk, A. Kochel and J. Wojaczyński, *Tetrahedron*, 2017, **73**, 2276.
10 E. B. Rakhimova, V. Yu. Kirsanov, A. G. Ibragimov and U. M. Dzhemilev, *Russ. J. Org. Chem*., 2018, **54**, 1085 (*Zh. Org. Khim*., 2018, **54**, 1078).
11 Y. A. Barsegyan, V. V. Baranov, A. N. Kravchenko, Y. A. Strelenko, L. V. Anikina, V. A. Karnoukhova and N. G. Kolotyrkina, *Synthesis*, 2018, **50**, 2099.
12 T. Yamaguchi, S. Ito, Y. Iwase, K. Watanabe and K. Harano, *Heterocycles*, 1999, **51**, 2305.
13 T. Yamaguchi, S. Ito, Y. Iwase, K. Watanabe and K. Harano, *Heterocycles*, 2000, **53**, 1677.
14 P. Désogère, C. Bernhard, C. Goze, M.-J. Penouilh, Y. Rousselin and F. Denat, *Eur. J. Org. Chem.*, 2013, 1538.
15 X. Lei, A. Jalla, M. A. A. Shama, J. M. Stafford and B. Cao, *Synthesis*, 2015, **47**, 2578.
16 *CrysAlis PRO*, Agilent Technologies, Yarnton, Oxfordshire, England, 2012.
17 O. V. Dolomanov, L. J. Bourhis, R. J Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr*., 2009, **42**, 339.
18 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3.
19 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3.

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