

Resolution and racemization of nonbenzenoid atropenantiomers

Pavel V. Novikov,^a Oleg R. Malyshev,^b Konstantin A. Lyssenko^c and Remir G. Kostyanovsky^{*a}

^a N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation.

Fax: +7 095 651 2191; e-mail: kost@chph.ras.ru

^b N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation.

Fax: +7 095 135 5328; e-mail: enantiomer@land.ru

^c A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation.

Fax: +7 095 135 5085; e-mail: kostya@xrlab.ineos.ac.ru

DOI: 10.1070/MC2004v014n06ABEH002049

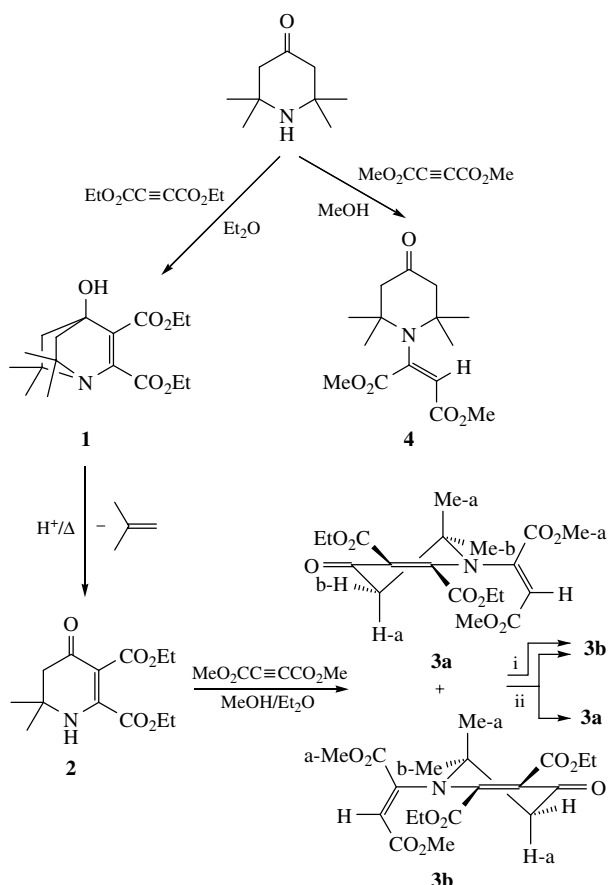
The three-step synthesis of adduct **3** has been reinvestigated; enantiomers **3a** and **3b** have been separated by enantioselective chromatography and the racemization barrier of **3a** was determined as $\Delta G^\ddagger = 24.4 \text{ kcal mol}^{-1}$ (16 °C).

Atropisomerism is one of the extensively developing fields of stereochemistry.^{1,2} Its main objects are axially chiral biaryls and aryl-X systems with hindered rotation around the chiral axis.^{3–17} Some cases of the spontaneous resolution of aryl-X systems were reported.^{13,15,17} Natural atropenantiomers are also known,^{15,18} for example, ‘the most unusual of all, the isoquinoline alkaloids’, (–)-aneistrocladine, which is configurationally stable to above 200 °C.^{18(b)} Earlier, a one-step synthesis of quinuclidine **1**^{19(a)} was carried out, its fragmentation to give piperidienone **2**^{19(b)} was found, and reaction of **2** with dimethyl acetylenedicarboxylate to form adduct **3**^{19(c)} was studied. Its crystal structure was investigated (space group $P\bar{1}$, $Z = 2$), the enantiomers were detected by ¹H NMR using the chiral shift reagent Eu(tfc)₃ with splitting the signals of α -Me and α -MeO₂C. The low limit of the enantiomerization barrier was evaluated on the basis of the fact that the non-equivalency of α -Me and β -Me protons remains up to 200 °C in Ph₂O (60 MHz): $\Delta\nu = 12.3 \text{ Hz}$, $\Delta G^\ddagger > 25 \text{ kcal mol}^{-1}$.

With the aim of the separation of atropenantiomers **3a** and **3b**, the synthesis of compounds **1–3**[†] was reproduced in this work (Scheme 1). It was shown that **2** forms a solvate with C₆H₆ (it makes easier isolation and purification); the solvate composition (**2**·0.5C₆H₆) was determined by ¹H NMR[†] and XRD analysis.[‡] Atropenantiomers **3a** and **3b** were resolved by enantioselective chromatography (Figure 1)[§] and characterised by CD spectra (Figure 2). Racemization was carried out in the mixture of PrⁱOH/*n*-hexane (30/70 vol.%, *c* 0.1 mg cm^{–3}) at 16 °C. The rate constant $k_{\text{rac}} = 9.2 \times 10^{-7} \text{ s}^{-1}$ and $\Delta G_{\text{rac}}^\ddagger = 24.4 \text{ kcal mol}^{-1}$ were calculated under assumption of the first order of the reaction.

The molecular and crystal structures of **2**·0.5C₆H₆ were studied by XRD analysis.[‡] The ring of **2** is in the chair conformation with deviation of the atoms N(1) and C(6) by 0.31 and 0.77 Å, respectively. The orientation of ester groups in reference to the ring is considerably different; the values of the torsion angles O(2)C(10)C(3)C(4) and O(4)C(7)C(2)C(3) are 16.8 and 64°, respectively (Figure 3). In the crystal, the molecules of **2** are combined into chains by non-symmetrical forked N–H···O bonds. The solvate molecules of benzene are located between the chains and fixed by C–H··· π contacts with the methyl groups of ester substituents (Figure 4).

The structure of adduct **4** was established on the basis of the NMR data, according to which ‘no hindered rotation or conversion of the ring were observed’ in **4**.^{19(c)} In this work, the struc-



Scheme 1 The synthesis of **1–4** (see ref. 19). Reagents and conditions: i, solution of (±)-**3** maintained in (2*R*,3*R*)-(+)-diethyl tartrate solution for nine months at 20–22 °C; ii, enantioselective chromatography.[§]

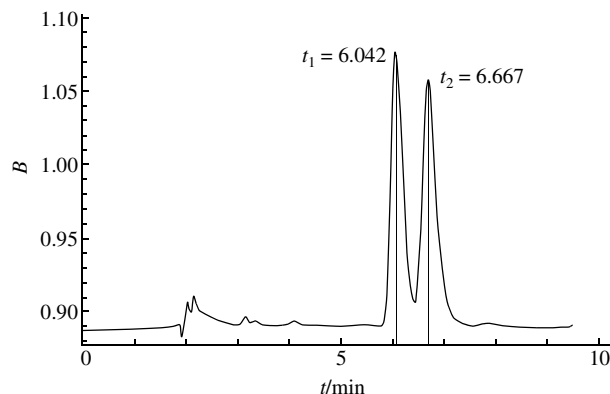


Figure 1 Chromatographic separation of the enantiomers of racemate **3**. Retention times: t_1 for (+)-**3** and t_2 for (–)-**3**.

[†] NMR spectra were recorded on a WM-400 spectrometer (¹H, 400.13 MHz; ¹³C, 100.62 MHz), UV spectra were measured on a Specord instrument. Melting points were measured on a Stuart SMP3 table, the heating rate was 3 K min^{–1}. NMR spectra of **1–4** are identical to those described earlier.¹⁹

Solvate **2**·0.5C₆H₆ was obtained by crystallisation of **2** (1.6 g) from a mixture of EtOAc (16 ml) and C₆H₆ (15 ml), yield 52%, mp 82–83 °C. ¹H NMR (CDCl₃) δ : 1.29 and 1.34 (t, 2×3H, MeCH₂O, ³J 7.0 Hz), 1.36 (s, 2×3H, Me₂C), 2.47 (s, 2H, CH₂), 4.23 and 4.31 (q, 2×2H, MeCH₂O, ³J 7.0 Hz), 5.76 (br. s, 1H, NH), 7.36 (s, C₆H₆). The ratio of the peak intensities of C₆H₆ and Me₂C was 1:2.

(±)-**3**, mp 93–94 °C, UV [25% PrⁱOH in *n*-hexane, λ_{max} /nm (ϵ): 312 (15520).

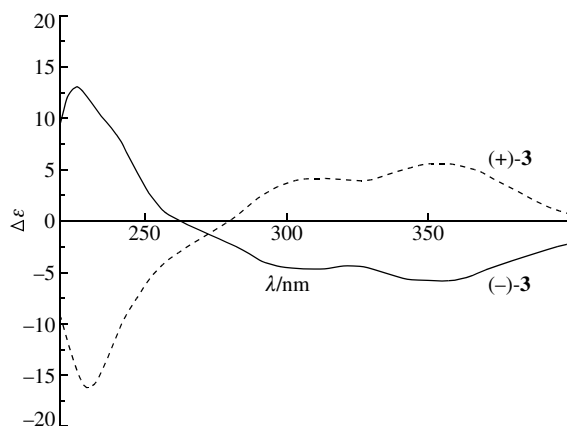


Figure 2 CD spectra of (+)-**3** and (-)-**3**; the solvent is 20% (v/v) propan-2-ol in hexane.

ture of **4** was unambiguously confirmed by XRD data (Figure 5). The ^1H NMR spectrum of **4** remained unchanged even at -70°C (in CD_2Cl_2), i.e., the rotation around the N–substituent bond is not restricted sterically. The XRD revealed that ester groups are in the *cis* configuration (Figure 5). In spite of possible conjugation between the nitrogen electron lone pair and the C(10)–C(11) double bond the dihedral angle between the N(1)C(3)C(4)C(10) and C(12)C(11)C(10)C(14) planes is equal to 27.6° . At the same time, the nitrogen atom N(1) is slightly pyramidal [the deviation of N(1) from the C(3), C(4) C(10) plane is equal to $0.0804(7)\text{ \AA}$]. Note that the C(10)–C(11) double bond is twisted

‡ At 120 K, the crystals of $2 \cdot 0.5\text{C}_6\text{H}_6$ ($\text{C}_{16}\text{H}_{22}\text{NO}_5$) are monoclinic, space group $C2/c$, $a = 16.784(2)$, $b = 16.711(2)$ and $c = 13.025(1)\text{ \AA}$, $\beta = 114.784(2)^\circ$, $V = 3316.9(6)\text{ \AA}^3$, $Z = 8$, $M = 308.35$, $d_{\text{calc}} = 1.235\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 0.92\text{ cm}^{-1}$, $F(000) = 1320$.

At 120 K, the crystals of **4** ($\text{C}_{15}\text{H}_{23}\text{NO}_5$) are triclinic, space group $P\bar{1}$, $a = 6.7421(9)$, $b = 8.1017(12)$, $c = 14.881(2)\text{ \AA}$, $\alpha = 90.746(7)^\circ$, $\beta = 94.234(7)^\circ$, $\gamma = 110.268(6)^\circ$, $V = 759.77(18)\text{ \AA}^3$, $Z = 2$, $M = 297.34$, $d_{\text{calc}} = 1.300\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 0.97\text{ cm}^{-1}$, $F(000) = 320$.

Intensities of 11022 ($2 \cdot 0.5\text{C}_6\text{H}_6$) and 20677 (**4**) reflections were measured with a Smart 1000 CCD diffractometer at 120 K [$\mu(\text{MoK}\alpha) = 0.71072\text{ \AA}$, $2\theta < 60^\circ$ ($2 \cdot 0.5\text{C}_6\text{H}_6$) 90° (**4**)] and 4799 ($2 \cdot 0.5\text{C}_6\text{H}_6$) and 9891 (**4**) independent reflections [$R_{\text{int}} = 0.0151$ ($2 \cdot 0.5\text{C}_6\text{H}_6$), 0.0190 (**4**)] were used in the further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The analysis of the Fourier synthesis have revealed that the benzene molecule and one of Et groups in ($2 \cdot 0.5\text{C}_6\text{H}_6$) are disordered by two positions. The hydrogen atoms for an ordered part were located from the Fourier density synthesis. The positions of the remaining hydrogen atoms were calculated from a geometrical point of view. The refinement converged to $wR_2 = 0.1072$ and $\text{GOF} = 1.042$ for all independent reflections [$R_1 = 0.0434$ was calculated against F for 3716 observed reflections with $I > 2\sigma(I)$] for $2 \cdot 0.5\text{C}_6\text{H}_6$; to $wR_2 = 0.0978$ and $\text{GOF} = 0.992$ for all independent reflections [$R_1 = 0.0492$ was calculated against F for 7098 observed reflections with $I > 2\sigma(I)$] for **4**. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 257661 and 257662. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

§ Chromatographic separation was performed using a Laboratory pristroje Praha chromatograph with an injector with a 20- μl sample loop.

Conditions: Chiralpak AD stationary phase (250 \times 4.6 mm i.d.) available from Diacel Chemical Industries (Japan); mobile phase, 20% (v/v) propan-2-ol in hexane; flow rate of 2 ml min $^{-1}$; temperature, ambient; detection UV 254 nm.

A solution of 3 mg of compound **3** in 50 μl of propan-2-ol was injected into the chromatograph in four portions.

Retention times of enantiomers are $t_1 = 6.042\text{ min}$ and $t_2 = 6.667\text{ min}$; the void time is $t_0 = 1.56\text{ min}$, as determined by the injection of tri-*tert*-butylbenzene. Separation factor $\alpha = (t_2 - t_0)/(t_1 - t_0) = 1.39$.

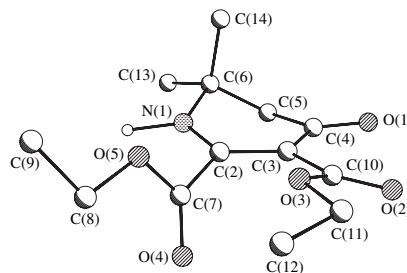


Figure 3 The general view of **2**.

with the torsion angles C(14)C(10)C(11)C(12) and N(1)C(10)–C(11)C(12) equal to 12.4° and 160.3° , respectively. Thus, the presence of the methyl groups at C(3) and C(4) atoms leads to significant weakening of the N–C=C conjugation. The six-membered ring is characterised by a twist conformation. The mutual disposition of the ester groups in **4** is different with the torsion angles C(10)C(11)C(12)O(2) and O(4)C(14)C(10)C(11) equal to 7.9 and 117.2° , respectively, which probably lead to a shortening of the C(11)–C(12) bond [$1.4654(9)\text{ \AA}$] in comparison with the C(10)–C(14) one [$1.5168(9)\text{ \AA}$].

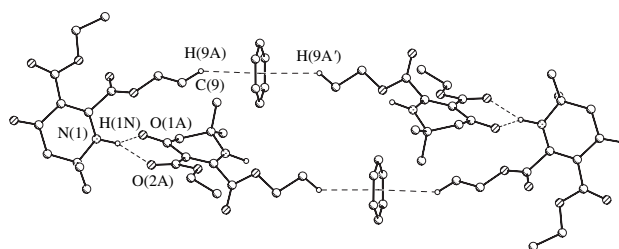


Figure 4 Fragment of the crystal structure of $2 \cdot 0.5\text{C}_6\text{H}_6$ illustrating the formation of bifurcated N–H...O bonds [N(1)–H(1N)...O(1) ($x, -y, z + 1/2$): N(1)...O(1) $2.807(3)\text{ \AA}$, H(1N)...O(1) 2.03 \AA , N(1)–H(1N)O(1) 146° ; N(1)–H(1N)...O(2) ($x, -y, z + 1/2$): N(1)...O(2) $2.936(3)\text{ \AA}$, H(1N)...O(1) 2.28 \AA , N(1)–H(1N)O(1) 132°] and C–H... π contacts [C(9)H(9A)... X_{Bz} (centroid of benzene): C(9)... X_{Bz} $3.707(3)\text{ \AA}$, H(9A)... X_{Bz} 2.83 \AA , C(9)–H(9A) X_{Bz} 139°].

This work was supported by the Russian Academy of Sciences and the Russian Foundation for Basic Research (grant nos. 03-03-32019 and DFG-RFBR 03-03-04010).

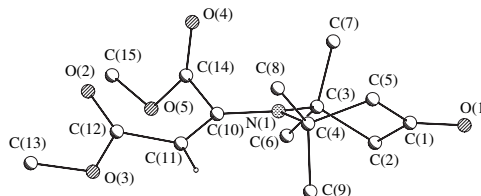


Figure 5 The general view of **4**. Selected bond lengths (\AA): O(1)–C(1) $1.2198(9)$, O(2)–C(12) $1.2173(8)$, O(3)–C(12) $1.3525(9)$, O(3)–C(13) $1.4415(9)$, O(4)–C(14) $1.2053(9)$, O(5)–C(14) $1.3388(9)$, O(5)–C(15) $1.4485(9)$, N(1)–C(10) $1.3790(8)$, N(1)–C(4) $1.5049(9)$, N(1)–C(3) $1.5121(9)$, C(10)–C(11) $1.3618(9)$, C(10)–C(14) $1.5168(9)$, C(11)–C(12) $1.4654(9)$; selected bond angles ($^\circ$): C(10)–N(1)–C(4) $118.72(5)$, C(10)–N(1)–C(3) $121.24(5)$, C(4)–N(1)–C(3) $119.15(5)$, O(1)–C(1)–C(5) $122.81(8)$, O(1)–C(1)–C(2) $122.77(8)$, C(5)–C(1)–C(2) $114.41(6)$, C(11)–C(10)–N(1) $125.14(6)$, C(11)–C(10)–C(14) $116.31(6)$, N(1)–C(10)–C(14) $118.16(6)$, C(10)–C(11)–C(12) $123.98(6)$.

References

- 1 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 1142.
- 2 M. Oki, in *Topics in Stereochemistry*, eds. N. L. Allinger, E. L. Eliel and S. H. Wilen, Scientific Publishers, New York, 1983, vol. 14.
- 3 X. Mei and Ch. Wolf, *Chem. Commun.*, 2004, 2078.
- 4 J. Claiden, A. Lund, L. Vallvezdú and M. Helliwell, *Nature*, 2004, **431**, 966.
- 5 F. Andreoli, N. Vanthuyne and C. Roussel, *Final Program of 16th International Symposium on Chirality*, July 11–14, 2004, New York, **P-261**, p. 115.

- doi> 6 D. A. Lenev, K. A. Lyssenko, O. Weingart, V. Buß and R. G. Kostyanovsky, *Tetrahedron Asymmetry*, 2004, **15**, 537.
- doi> 7 M. Sakamoto, N. Utsumi, M. Ando, M. Saeki, T. Mino, T. Fujita, A. Katoh, T. Nishio and C. Kashima, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 4360.
- doi> 8 A. I. Roschin and R. G. Kostyanovsky, *Mendeleev Commun.*, 2003, **6**, 275.
- 9 P. Skowronek and D. A. Lightner, *Monatsh. Chem.*, 2003, **134**, 889.
- doi> 10 (a) J. Gawroński and K. Kacprzak, *Chirality*, 2002, **14**, 689; (b) J. Gawroński, P. Grycz, M. Kwit and U. Rychlewska, *Chem. Eur. J.*, 2002, **8**, 4210; (c) M. Kwit, U. Rychlewska and J. Gawroński, *New J. Chem.*, 2002, **26**, 1714.
- doi> 11 O. Tissot, M. Gouygou, F. Dallemer, J.-C. Daran and G. G. A. Balavoine, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 1076.
- doi> 12 M. Kondo, T. Iida, H. Fujita, T. Suzuki, K. Yamaguchi and Y. Murakami, *Tetrahedron*, 2000, **56**, 8883.
- doi> 13 M. Tichý, L. Ridvan, P. Holý, J. Závada, I. Cízařová and J. Podlaha, *Tetrahedron Asymmetry*, 1998, **9**, 227.
- 14 W.-C. Shieh and J. A. Carlson, *J. Org. Chem.*, 1994, **59**, 5463.
- 15 G. Sartori, R. Maggi, F. Biggi and M. Grandi, *J. Org. Chem.*, 1993, **58**, 7271.
- 16 L. A. M. Bastiaansen, J. A. Kanters, F. H. Van der Steen, J. A. C. De Graaf and H. M. Buck, *J. Chem. Soc., Chem. Commun.*, 1986, 536.
- doi> 17 (a) K.-H. Rimböck, F. Kastner and A. Mannschreck, *J. Chromatogr.*, 1986, **351**, 346; (b) H. Koller, K.-H. Rimböck and A. Mannschreck, *J. Chromatogr.*, 1983, **282**, 89.
- 18 (a) G. Bringmann and D. Menche, *Acc. Chem. Res.*, 2001, **34**, 615; (b) G. Bringmann, J. R. Jansen and H.-P. Rink, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 913.
- doi> 19 (a) R. G. Kostyanovsky, Yu. I. El'natanov, I. I. Chervin, S. V. Konovalikhin, A. B. Zolotoi and L. O. Atovmyan, *Mendeleev Commun.*, 1996, 143; (b) R. G. Kostyanovsky, Yu. I. El'natanov, I. I. Chervin, S. V. Konovalikhin, A. B. Zolotoi and A. Rauk, *Mendeleev Commun.*, 1996, 108; (c) R. G. Kostyanovsky, Yu. I. El'natanov, I. I. Chervin, S. V. Konovalikhin, A. B. Zolotoi and L. O. Atovmyan, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1796 (*Russ. Chem. Bull.*, 1996, **45**, 1707).

Received: 29th September 2004; Com. 04/2374