Russian Journal of Organic Chemistry, Vol. 40, No. 4, 2004, pp. 502–505. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 4, 2004, pp. 533–536.

Synthetic Approaches to Physiologically Active Polycyclic Compounds: IV.* X-Ray Diffraction Study of Isomeric Amino Acid Derivatives of Adamantane

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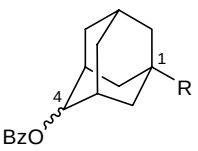
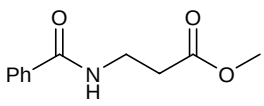
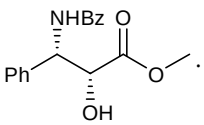
Received August 10, 2003

Abstract—According to the X-ray diffraction data, the major isomer of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane obtained by esterification of β-alanine with 5-hydroxyadamantan-2-one and subsequent benzoylation has *trans* configuration. The *trans–cis* isomer ratio is 2:1. A similar isomer ratio was found for 1-(*N*-benzoylphenylisoseryloxy)-4-benzoyloxyadamantane synthesized by an analogous method.

In the framework of our studies on the design of simplified analogs of taxane antitumor agents, we have synthesized 1-(*N*-benzoyl-β-alanyloxy)- and 1-[(2*R*,3*S*)-*N*-benzoylphenylisoseryloxy]-4-benzoyloxyadamantanes **I** and **II** [1, 2]. Compounds **I** and **II** were obtained by esterification of β-amino acids with 5-hydroxyadamantan-2-one, followed by reduction of the ketone carbonyl and benzoylation of the hydroxy group thus formed. Both final products were isolated as inseparable mixtures of *cis* and *trans* isomers. Compound **I** showed in the ^{13}C NMR spectrum double signals at δ 80.00/79.65 and 75.04/75.53 ppm, while the corresponding signals of compound **II** were observed at 82.36/81.96 and 74.70/75.25 ppm. These signals belong, respectively, to the C^1 and C^4 atoms of the two isomers at a ratio of 1:2.



I, **II**

I, R =  ; **II**, R =  .

The signals were assigned to particular isomers [1] by analogy with the spectra of structurally related compounds [4–6]. More intense signals were assigned to the *cis* isomers (with respect to the R substituent) which, according to calculations, should be thermodynamically more stable. However, the signal assignment by analogy with the spectra of disubstituted adamantanes given in [7, 8], is the reverse. Therefore, we did not assign signals in the spectrum of **II** to particular isomers [2], for unambiguous conclusion could be drawn only on the basis of the results of a special X-ray diffraction study which was the subject of the present work.

The isomers of **I** were separated by high-performance liquid chromatography (HPLC) using columns charged which silica gel which was modified with triethoxysilyl quinine derivative [9]. The chromatogram contained two main peaks with retention times of 17 and 25 min (approximate intensity ratio 1:2). According to the HPLC and ^1H NMR data, the purity of samples thus obtained was more than 95%. Crystals suitable for X-ray analysis were grown for the major isomer of **I**. The results (Fig. 1, see table) showed that this isomer has *trans* configuration with respect to the substituents on C^4 and C^1.** Hence the signals at

* For preceding communications, see [1–3].

** The molecule of *trans* isomer **I** has an extended structure in which the two terminal benzene rings appear at a maximal distance from each other (Fig. 1).

δ_C 79.65 and 75.53 ppm in the ^{13}C NMR spectrum and the triplet at δ 5.18 ppm in the ^1H NMR spectrum [1] should be assigned to the *trans* isomer, and those at δ_C 80.00 and 75.04 ppm and at δ 5.06 ppm [1], to the *cis* isomer. Likewise, the more intense signals at δ_C 81.96 and 75.25 ppm in the ^{13}C NMR spectrum and at δ 5.07 ppm in the ^1H NMR spectrum of compound **II** [2] belong to the *trans* isomer.

Taking into account that the formation of isomers during the synthesis of compounds **I** and **II** occurred at the stage of reduction of the corresponding ketones to alcohols [1, 2], the predominance of the *trans* isomers may be interpreted in terms of increased stability of intermediate products arising from frontal attack by hydride ion at the carbonyl group [8].

Thus in the present work we performed unambiguous assignment of signals in the NMR spectra of compounds **I** and **II** to their respective *cis* and *trans* isomers by determining the configuration of one of these on the basis of the X-ray diffraction data. Analogous assignment can be performed for structurally related compounds, such as 1-(*N*-benzoyl-β-alanyloxy)- and 1-[(2*R*,3*S*)-*N*-benzoylphenylisoseryloxy]-4-hydroxyadamantanes [1, 2].

To conclude, an interesting feature of crystal packing of molecules of *trans* isomer **I** (Fig. 2) should be noted. Usually, an amide hydrogen atom is involved in fairly strong intermolecular hydrogen bond with the amide carbonyl oxygen atom of the neighboring molecule. However, in crystal of *trans*-**I** the amide hydrogen atom H^N is characterized by only one slightly shortened contact with the amide oxygen atom O^3 of the neighboring molecule: $N–H^N\cdots O^3(i)$. The distance $H^N\cdots O^3(i)$ is 2.45(2) Å [symmetry transformation (*i*) $-1/2 - x$, $1/2 + y$, $1/2 - z$]. On the other hand, there exists a more strongly shortened intermolecular contact with $O^3(i)$: $C^{20}–H^{20}\cdots O^3(i)$ with the $H^{20}\cdots O^3(i)$ distance equal to 2.32(2) Å. All other shortened intermolecular contacts in the crystalline structure of the *trans* isomer of **I** are either similar or slightly shorter than the sum of the corresponding van der Waals radii.

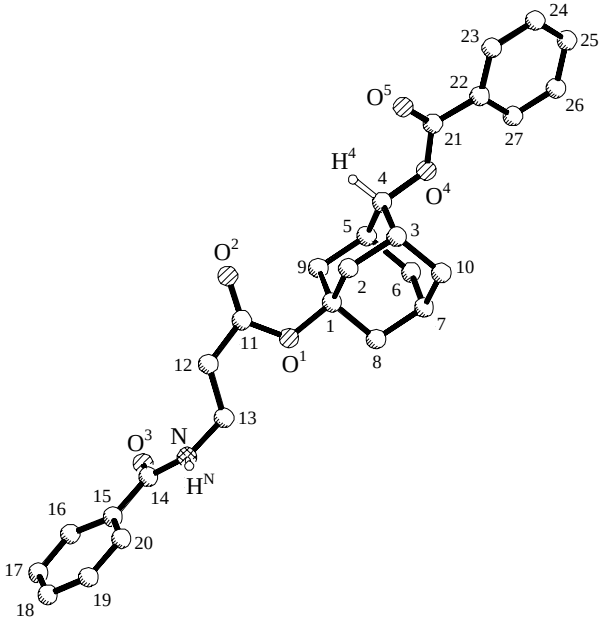


Fig. 1. Molecular structure of the *trans* isomer of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**I**) in crystal (most hydrogen atoms and low-populated positions of the disordered N' and $C^{13'}$ atoms are not shown).

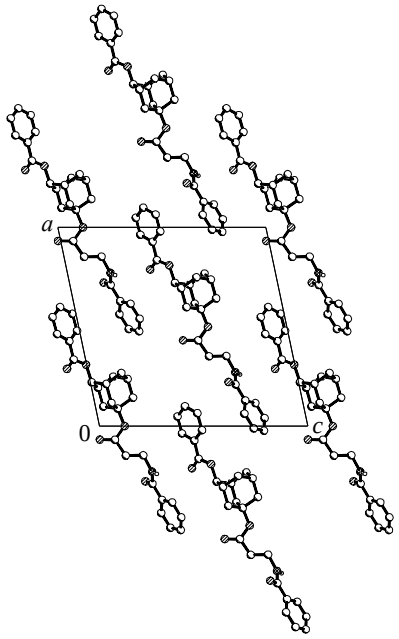


Fig. 2. Fragment of crystal packing of molecules of the *trans* isomer of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**I**) (projection along the *b* axis is shown).

EXPERIMENTAL

The *cis* and *trans* isomers of **I** were separated on a liquid chromatograph equipped with a Beckman 114-M high-pressure pump, a Micro U-Vis 20 spectrophotometric detector, and a Rheodyne 7125 250-ml loop sampler. Chromatographic separation was performed using two consecutive 250×4-mm Diasorb–Khinin columns (7-μm silica gel modified with triethoxysilyl quinine derivative); eluent hexane–methylene chloride–2-propanol (66:33:1), flow rate 1 ml/min. The chromatograms were recorded (detec-

Table 1. Relative coordinates ($\times 10^4$) of atoms in the crystalline structure of the *trans* isomer of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**I**)[a]

Atom	*x*	*y*	*z*
O^1	3.6(9)	2291(2)	1207.1(9)
O^2	–677(1)	2832(2)	–123(1)
O^3	–2774(1)	151(2)	1645(1)
O^4	3096.6(8)	2482(2)	–28.1(8)
O^5	2886.6(9)	4304(2)	–986(1)
N	–2287(1)	2393(2)	2067(2)
H^N	–2397(17)	3231(23)	2268(16)
N'	–2750(10)	2728(18)	1418(10)
C^1	889(1)	2238(2)	1047(1)
C^2	1170(1)	3766(2)	804(2)
C^3	2123(1)	3689(2)	743(1)
C^4	2207(1)	2579(2)	65(1)
H^4	1840	2878	–472
C^5	1940(1)	1057(2)	310(1)
C^6	2492(1)	589(2)	1152(2)
C^7	2380(1)	1696(2)	1824(1)
C^8	1433(1)	1778(3)	1889(1)
C^9	990(1)	1116(2)	377(1)
C^{10}	2677(1)	3213(2)	1583(1)
C^{11}	–685(1)	2665(2)	600(2)
C^{12}	–1479(2)	2853(3)	963(2)
C^{13}	–1464(1)	2210(3)	1800(2)
$C^{13'}$	–2082(19)	2741(30)	902(17)
C^{14}	–2898(1)	1343(2)	1955(1)
C^{15}	–3711(1)	1627(2)	2257(1)
C^{16}	–4365(1)	593(3)	2083(2)
C^{17}	–5112(2)	768(3)	2383(2)
C^{18}	–5222(1)	1988(3)	2853(2)
C^{19}	–4592(1)	3045(3)	3007(1)
C^{20}	–3838(1)	2868(2)	2718(1)
H^{20}	–3391	3618	2839
C^{21}	3356(1)	3413(2)	–573(1)
C^{22}	4278(1)	3219(2)	–597(1)
C^{23}	4635(1)	4153(3)	–1114(1)
C^{24}	5490(2)	4005(3)	–1159(2)
C^{25}	5996(2)	2959(3)	–698(2)
C^{26}	5656(1)	2038(3)	–173(2)
C^{27}	4802(1)	2167(2)	–122(1)

[a] Given are the coordinates of only three structurally significant hydrogen atoms. Two neighboring non-hydrogen atoms in the molecule of *trans*-**I** in crystal are statistically disordered by two positions, N/N' and C^{13} and $C^{13'}$. The populations of these positions are 0.908(4) (N, H^N, C^{13}) and 0.092(4) (N', $C^{13'}$).

tion at λ 254 nm) and processed using Mul'tikhrom 1.52 software.

Colorless transparent crystals of *trans*-**I** were obtained by crystallization from petroleum ether (40–70°C)–ethyl acetate (1:8). The unit cell parameters and reflection intensities (a three-dimensional set) were determined on an Enraf–Nonius CAD-4 automatic diffractometer (CuK_α radiation, graphite monochromator). Monoclinic crystals. $C_{27}H_{29}NO_5$. *M* 447.51. Unit cell parameters: a = 15.835(2), b = 9.050(1), c = 16.192(3) Å; β = 101.83(1)°; V = 2271.1(6)Å^3; Z = 4; d_{calc} = 1.309 g/cm^3; μ(CuK_α) = 7.29 cm^{-1}; space group $P2_1/n$. Crystal habit 0.07×0.27×0.80 mm. Intensities of 3766 reflections were measured in the reciprocal space quadrant ($2\theta \le 120°$) by ω/2θ scanning. The structure was solved by the direct method using SHELXS-97 program [10] and was refined by the full-matrix least-squares procedure with respect to F^2 using SHELXL-97 program [10]. The positions of non-hydrogen atoms were refined in anisotropic approximation (except for N' and $C^{13'}$ which are characterized by very small populations and were refined in isotropic approximation). Almost all reflections, including very weak [$I < 2\sigma(I)$], were involved in the refinement; several reflections were excluded because of poor consistency between the measured and calculated values of F^2.

Below are listed the bond lengths (Å) and principal bond angles (deg) in the molecule of *trans*-**I**: O^1–C^1 1.477(2), O^1–C^{11} 1.354(3), O^2=C^{11} 1.182(3), O^3=C^{14} 1.223(3), O^4–C^4 1.450(2), O^4–C^{21} 1.344(2), O^5=C^{21} 1.202(2), N–C^{13} 1.464(3), N–C^{14} 1.341(3), N–H^N 0.86(2), C^1–C^2 1.529(3), C^1–C^8 1.514(3), C^1–C^9 1.519(3), C^2–C^3 1.534(3), C^3–C^4 1.514(3), C^3–C^{10} 1.521(3), C^4–C^5 1.517(3), C^5–C^6 1.521(3), C^5–C^9 1.530(2), C^6–C^7 1.516(3), C^7–C^8 1.526(3), C^7–C^{10} 1.528(3), C^{11}–C^{12} 1.502(3), C^{12}–C^{13} 1.471(3), C^{14}–C^{15} 1.491(3), C^{15}–C^{16} 1.381(3), C^{15}–C^{20} 1.386(3), C^{16}–C^{17} 1.376(3), C^{17}–C^{18} 1.372(4), C^{18}–C^{19} 1.368(3), C^{19}–C^{20} 1.379(3), C^{21}–C^{22} 1.479(3), C^{22}–C^{23} 1.388(3), C^{22}–C^{27} 1.388(3), C^{23}–C^{24} 1.379(3), C^{24}–C^{25} 1.360(4), C^{25}–C^{26} 1.377(3), C^{26}–C^{27} 1.375(3); $C^1O^1C^{11}$ 122.2(2), $C^4O^4C^{21}$ 117.7(2), $C^{13}NC^{14}$ 122.7(2), $C^{13}NH^N$ 118(2), $C^{14}NH^N$ 119(2), $O^1C^1C^2$ 110.7(1), $O^1C^1C^8$ 103.7(1), $O^1C^1C^9$ 113.0(2), $C^2C^1C^8$ 109.8(2), $C^2C^1C^9$ 109.9(2), $C^8C^1C^9$ 109.6(2), $O^4C^4C^3$ 110.3(2), $O^4C^4C^5$ 107.5(2), $C^3C^4C^5$ 110.0(2), $O^1C^{11}O^2$ 125.4(2), $O^1C^{11}C^{12}$ 111.0(2), $O^2C^{11}C^{12}$ 123.5(2), $C^{11}C^{12}C^{13}$ 117.3(2), $NC^{13}C^{12}$ 112.3(2), $O^3C^{14}N$ 120.6(2), $O^3C^{14}C^{15}$ 120.6(2), $NC^{14}C^{15}$ 118.8(2), $C^{14}C^{15}C^{16}$ 118.6(2), $C^{14}C^{15}C^{20}$

123.1(2), $C^{16}C^{15}C^{20}$ 118.2(2), $O^{4}C^{21}O^{5}$ 123.3(2), $O^{4}C^{21}C^{22}$ 112.2(2), $O^{5}C^{21}C^{22}$ 124.5(2), $C^{21}C^{22}C^{23}$ 118.0(2), $C^{21}C^{22}C^{27}$ 123.3(2), $C^{23}C^{22}C^{27}$ 118.7(2), $O^{1}C^{11}C^{12}$ 111.0(2).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 02-03-32790).

REFERENCES

1. Zefirova, O.N., Selyunina, E.V., Averina, N.V., Zyk, N.V., and Zefirov, N.S., *Russ. J. Org. Chem*., 2002, vol. 38, p. 1125.
2. Zefirova, O.N., Selyunina, E.V., Nuriev, V.N., Zyk, N.V., and Zefirov, N.S., *Russ. J. Org. Chem*., 2003, vol. 39, p. 831.
3. Averina, N.V., Borisova, G.S., Zefirova, O.N., Selyunina, E.V., Zyk, N.V., and Zefirov, N.S., *Russ. J. Org. Chem*., 2004, vol. 40, p. 497.
4. Faulkner, D. and McKervey, M.A., *J. Chem. Soc. C*, 1971, p. 3906.
5. Duddeck, H., *Org. Magn. Reson*., 1975, vol. 7, p. 151.
6. Henkel, J.G. and Spektor, J.H., *J. Org. Chem*., 1983, vol. 48, p. 3657.
7. Srivastava, S., Cheung, S.K., and Le Noble, W., *Org. Magn. Reson*., 1985, vol. 23, p. 232.
8. Chung, W-Sh., Liu, Y-D., and Wang, N-J., *J. Chem. Soc., Perkin Trans. 2*, 1995, p. 581.
9. Nesterenko, P.N., Krotov, V.V., and Staroverov, S.M., *Zh. Fiz. Khim*., 1991, vol. 65, p. 2671.
10. Sheldrick, G.M., *The SHELX-97 Manual*. Göttingen: Univ. Göttingen, 1997.