

Short Communication

Saturated Heterocycles. Part 243.† Preparation and Steric Structure of Dodecahydroindolo-[1,7a-a]benzoxazin-12-one Isomers

Reijo Sillanpää,^{a,*} Miklós Virág,^b Géza Stájer^b and Gábor Bernáth^b

^aDepartment of Chemistry, University of Turku, FIN-20014 Turku, Finland and ^bInstitute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, POB 121, H-6701 Szeged, Hungary

Sillanpää, R., Virág, M., Stájer, G. and Bernáth, G., 1997. Saturated Heterocycles. Part 243. Preparation and Steric Structure of Dodecahydroindolo[1,7a-a]benzoxazin-12-one Isomers. – Acta Chem. Scand. 51: 810–812. © Acta Chemica Scandinavica 1997.

2-Aroyl-1-cyclohexanecarboxylic acids have often been used to prepare saturated fused-skeleton tetra- or pentacyclic compounds containing two heterorings and one or two terminal cycloalkane rings.^{2–4} Oxocycloalkanecarboxylates were applied for the preparation of bicyclic lactams,⁵ condensed thiophenes,⁶ pyrones,⁷ dibenzo[b,f]thiepienes⁸ or pyrrolidines.⁹ As the reactions of saturated γ -oxocarboxylic acids and bifunctional reagents such as 1,3-amino alcohols, α,ω -diamines, resulted in compounds with rather complex stereostructures, the establishment of their structures has also posed a challenging task.

In this paper we extend these methods to the reactions of 2-ethoxycarbonylmethylcyclohexanone (**1**) with *cis*- and *trans*-6-hydroxymethylcyclohex-3-en-1-amines (**2a** and **2b**). While the earlier reactions with 2-aroyl-1-cyclohexanecarboxylic acid led to ring systems in which the isoindolone moiety was the central structural unit,^{2–4} in the experiments described here **1** furnished a different type of saturated indolone in which the indole moiety is fused at the nitrogen-annulated carbon bond with a partly saturated 3,1-benzoxazine.

Because of the significant overlap of the signals of the numerous almost equivalent aliphatic protons in the NMR spectra, the structure elucidation was difficult. Depending on the conditions, the configurations of the starting compounds often changed during the course of similar reactions.^{3,4} In addition, a new chirality center is formed on the carbon of the oxo group in the cyclohexane ring, hence, establishment of the stereostructure is of basic importance. As both **3a** and **3b** provided suitable

crystals, the structures were determined by X-ray analysis.

Results and discussion

Perspective views of the molecules **3a** and **3b** are shown in Figs. 1 and 2 and selected bond parameters in Table 1. The bond lengths of two compounds are the same, to within experimental error. The bond angles of the compounds are also almost the same, the greatest deviations being around atom N(13). The basic feature of these structures is the fused indolooxazine moiety, where the O6–C6a and C10a–H10a bonds are in the same steric orientation. In **3a** the cyclohexene is *cis*, while in **3b** it is *trans* to the 1,3-oxazine ring, which proves that the amino alcohols **2a** and **2b** did not undergo isomerization

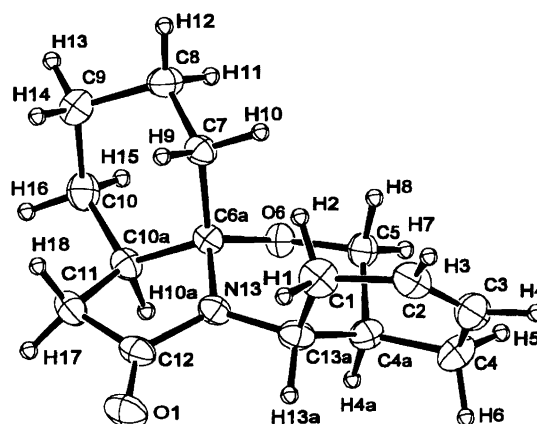


Fig. 1. ORTEP perspective view of **3a** showing the labelling system. Thermal ellipsoids are drawn at the 30% probability level.

† Part 242, see Ref. 1.

* To whom correspondence should be addressed.

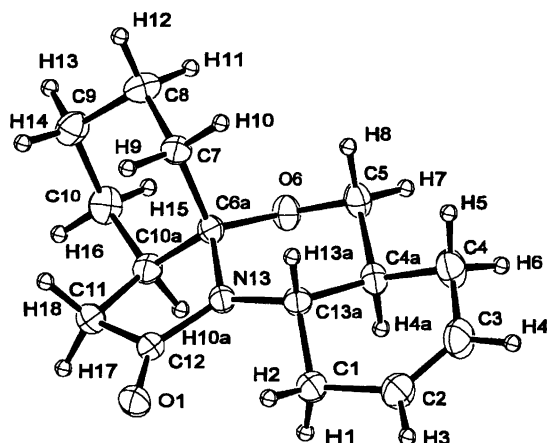


Fig. 2. ORTEP perspective view of **3b** showing the labelling system. Thermal ellipsoids are drawn at the 30% probability level.

Table 1. Selected bond distances (in Å) and angles (in °)^a

	3a	3b
O(1)–C(12)	1.227(2)	1.224(2)
O(6)–C(5)	1.442(2)	1.440(2)
O(6)–C(6a)	1.426(2)	1.417(2)
N(13)–C(6a)	1.471(2)	1.485(2)
N(13)–C(12)	1.359(2)	1.362(2)
N(13)–C(13a)	1.468(3)	1.475(2)
C(1)–C(2)	1.494(3)	1.506(3)
C(2)–C(3)	1.309(3)	1.308(3)
C(3)–C(4)	1.500(4)	1.498(3)
C(4a)–C(5)	1.510(3)	1.512(3)
C(4a)–C(13a)	1.530(3)	1.533(2)
C(6a)–C(10a)	1.535(3)	1.530(2)
C(5)–O(6)–C(6a)	113.7(2)	113.0(1)
C(6a)–N(13)–C(12)	113.2(2)	111.0(1)
C(6a)–N(13)–C(13a)	122.5(2)	119.9(1)
C(12)–N(13)–C(13a)	124.2(2)	128.2(1)
C(2)–C(1)–C(13a)	113.6(2)	110.7(2)
C(1)–C(2)–C(3)	123.9(3)	124.6(2)
C(2)–C(3)–C(4)	123.9(3)	123.0(2)
C(3)–C(4)–C(4a)	113.8(2)	111.9(2)
C(4)–C(4a)–C(5)	112.6(2)	111.1(2)
C(4)–C(4a)–C(13a)	112.4(2)	110.0(2)
C(5)–C(4a)–C(13a)	109.8(2)	110.9(2)
O(6)–C(5)–C(4a)	110.8(2)	110.1(2)
O(6)–C(6a)–N(13)	110.7(2)	111.5(1)
O(6)–C(6a)–C(7)	110.5(2)	111.6(1)
O(6)–C(6a)–C(10a)	108.2(2)	108.3(1)
N(13)–C(6a)–C(7)	112.9(2)	111.5(1)
N(13)–C(6a)–C(10a)	101.5(2)	101.5(1)
C(7)–C(6a)–C(10a)	112.7(2)	112.1(1)
C(6a)–C(10a)–C(10)	116.0(2)	114.2(2)
C(6a)–C(10a)–C(11)	102.4(2)	101.3(1)
C(10)–C(10a)–C(11)	116.7(2)	118.2(2)
C(10a)–C(11)–C(12)	103.3(2)	104.0(2)
O(1)–C(12)–N(13)	125.1(2)	127.7(2)
O(1)–C(12)–C(11)	127.5(2)	124.8(2)
N(13)–C(12)–C(11)	107.4(2)	107.5(2)
N(13)–C(13a)–C(1)	112.2(2)	113.4(2)
N(13)–C(13a)–C(4a)	107.7(2)	108.0(1)
C(1)–C(13a)–C(4a)	113.3(2)	109.6(2)

^aEsds are given in parentheses.

during the reaction. Otherwise, in **3a**, the indole ring-junction hydrogen (H10a) and the two cyclohexene ring-junction hydrogens (H4a and H13a) are in the all-*cis* (α,α,α) position, while in the *trans* compound **3b**, the ring-junction hydrogen of the saturated indole moiety (H10a) and that on the bridgehead carbon next to the nitrogen (H13a) lie on the opposite side of the molecular skeleton, i.e., H10a, H13a and H4a are in the α,β,α position.

Selected torsion angles values are presented in Table 2. These indicate that in both compounds, rings A and C have a distorted chair conformation. Ring B of **3a** adopts an envelope and the same ring of **3b** a half chair conformation. Ring D (in both compounds) is in the half chair conformation. The torsion angles of ring B clearly show that the five-membered ring B has been slightly modified due to the differences between the amino alcohol moieties and the condensed molecules.

Table 2. Selected torsion angles (in °)^a

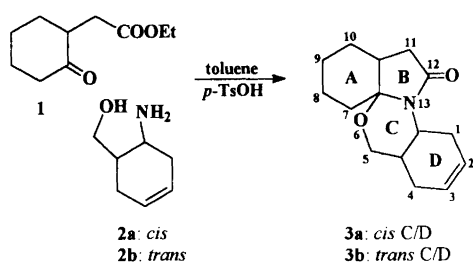
	3a	3b
<i>Ring A</i>		
C(6a)–C(7)–C(8)–C(9)	59.2(3)	59.0(2)
C(7)–C(8)–C(9)–C(10)	–61.9(3)	–59.6(2)
C(8)–C(9)–C(10)–C(10a)	53.9(3)	54.2(2)
C(9)–C(10)–C(10a)–C(6a)	–44.0(3)	–48.2(2)
C(10)–C(10a)–C(6a)–C(7)	40.1(3)	46.4(2)
C(10a)–C(6a)–C(7)–C(8)	–47.1(3)	–51.7(2)
<i>Ring B</i>		
N(13)–C(6a)–C(10a)–C(11)	32.9(2)	37.3(2)
C(6a)–C(10a)–C(11)–C(12)	–32.6(2)	–32.5(2)
C(10a)–C(11)–C(12)–N(13)	20.0(2)	15.3(2)
C(11)–C(12)–N(13)–C(6a)	1.7(2)	9.6(2)
C(12)–N(13)–C(6a)–C(10a)	–22.4(2)	–30.3(2)
<i>Ring C</i>		
C(13a)–C(4a)–C(5)–O(6)	–61.2(2)	–60.2(2)
C(4a)–C(5)–O(6)–C(6a)	60.9(2)	61.7(2)
C(5)–O(6)–C(6a)–N(13)	–47.7(2)	–51.7(2)
O(6)–C(6a)–N(13)–C(13a)	41.2(2)	44.5(2)
C(6a)–N(13)–C(13a)–C(4a)	–42.5(3)	–43.0(2)
N(13)–C(13a)–C(4a)–C(5)	49.4(2)	49.1(2)
<i>Ring D</i>		
C(1)–C(2)–C(3)–C(4)	–2.5(4)	–1.9(4)
C(2)–C(3)–C(4)–C(4a)	15.6(4)	–13.7(3)
C(3)–C(4)–C(4a)–C(13a)	–39.0(3)	45.6(2)
C(4)–C(4a)–C(13a)–C(1)	50.8(3)	–63.5(2)
C(4a)–C(13a)–C(1)–C(2)	–37.5(3)	47.0(2)
C(13a)–C(1)–C(2)–C(3)	13.6(4)	–15.5(3)
<i>Joint C/D</i>		
C(4)–C(4a)–C(5)–O(6)	172.8(2)	177.1(2)
C(4)–C(4a)–C(13a)–N(13)	175.5(2)	172.4(2)
C(1)–C(13a)–N(13)–C(6a)	82.8(2)	–164.8(2)
C(1)–C(13a)–C(4a)–C(5)	–75.4(2)	173.1(2)
H(4a)–C(4a)–C(13a)–H(13a)	48(2)	173(1)

^aEsds are given in parentheses.

Experimental

Syntheses. Compound **1** (1.84 g, 0.01 mol), prepared by a standard method,¹⁰ was refluxed in toluene (40 ml) for 8 h with *cis*- or *trans*-6-hydroxymethylcyclohex-3-enamines¹¹ (**2a** and **2b**) (1.27 g, 0.01 mol) in the presence of a catalytic amount (0.05 g) of *p*-toluenesulfonic acid, with the application of a water separator (Scheme 1). After evaporation to dryness, the residue was purified on a silica gel column (Acros 24.165.12) by elution with *n*-hexane–EtOAc (3:1). On crystallization from diethyl ether, the product gave colourless crystals, m.p. 116–118 °C (**3a**), yield 1.61 g (65%), and m.p. 91–93 °C (**3b**), yield 1.66 g (67%). Analysis: C₁₅H₂₁NO₂, Calc. C 72.84, H 8.56, N 5.66%; Found: (**3a**) C 72.96, H 8.66, N 5.84%; (**3b**) C 72.89, H 8.51, N 5.73%.

X-Ray diffraction studies. All data were collected on a Rigaku AFC5S diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71069 \text{ \AA}$) in the ω - 2θ scan mode. The lattice parameters were calculated by least-squares refinements of 25 reflections. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. For **3a** 2303 and for **3b** 2446 unique reflections were obtained ($2\theta_{\max} = 50^\circ$). The data were corrected for Lorentz and polarization effects. The data of compound **3a** were also corrected for secondary extinction. The structures were solved by direct methods and refined by full-matrix least-squares techniques to an *R* value of 0.040 ($R_w = 0.033$) for **3a** and $R = 0.039$ ($R_w = 0.031$) for **3b**. The final cycle was based on 1621 (**3a**) or 1684 (**3b**) independently observed reflections [$I > 2\sigma(I)$]. The heavy atoms were refined anisotropically, and the hydrogen atoms with fixed isotropic temperature factors (1.2 times B_{eq} of the carrying atom). All calculations were performed with TEXSAN¹²



Scheme 1.

crystallographic software. The figures were drawn with ORTEP.¹³ The final atomic coordinates and full lists of bond lengths and angles for **3a** and **3b** have been deposited with the Cambridge Crystallographic Data Centre (CCDC).

Crystal data for 3a. C₁₅H₂₁NO₂, $M_r = 247.34$, triclinic, space group $P\bar{1}$ (No. 2), lattice parameters: $a = 8.8370(6)$, $b = 12.191(1)$, $c = 6.4202(4) \text{ \AA}$, $\alpha = 99.746(6)$, $\beta = 103.555(5)$, $\gamma = 98.464(7)^\circ$, $Z = 2$, $V = 649.94(9) \text{ \AA}^3$, $D_c = 1.264 \text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 0.78 \text{ cm}^{-1}$, $F(000) = 268$, $T = 294 \text{ K}$; colourless prisms, crystal dimensions $0.22 \times 0.26 \times 0.32 \text{ mm}$.

Crystal data for 3b. C₁₅H₂₁NO₂, $M_r = 247.34$, monoclinic, space group $P2_1/n$ (No. 14), lattice parameters: $a = 5.467(1)$, $b = 11.742(1)$, $c = 20.560(1) \text{ \AA}$, $\beta = 96.24(1)^\circ$, $Z = 4$, $V = 1312.0(4) \text{ \AA}^3$, $D_c = 1.252 \text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 0.77 \text{ cm}^{-1}$, $F(000) = 536$, $T = 294 \text{ K}$; colourless plates, crystal dimensions $0.22 \times 0.34 \times 0.38 \text{ mm}$.

Acknowledgements. The authors' thanks are due to Mrs. E. Csiszár-Makra for valuable technical assistance. The authors also thank the Hungarian Research Foundation (OTKA No. 2693) and the Ministry of Welfare (ETT T-121) for financial support.

References

- Bernáth, G., Kóbor, J., Lázár, J. and Fülöp, F. *J. Heterocycl. Chem. In press.*
- Bernáth, G. *Bull. Soc. Chim. Belg.* 103 (1994) 509.
- Stájer, G., Csende, F., Bernáth, G. and Sohár, P. *Heterocycles* 37 (1994) 883.
- Sohár, P., Nagy, K., Bernáth, G. and Stájer, G. *Magn. Reson. Chem.* 33 (1995) 329.
- Omar, F. and Frahm, A. W. *Archiv. Pharm. (Weinheim)* 323 (1994) 923.
- Noe, C. R., Knollmüller, M. and Wagner, E. *Monatsh. Chem.* 117 (1986) 621.
- Maeng, J. C. and Bensovssan, D. *Synlett* (1990) 223.
- Kratz, V. *Synthesis* (1984) 267.
- Ragan, J. A. and Claffey, M. C. *Heterocycles* 41 (1995) 57.
- Mondon, A. *Chem. Ber.* 92 (1959) 1461.
- Bernáth, G., Stájer, G., Szabó, A. E., Fülöp, F. and Sohár, P. *Tetrahedron* 41 (1985) 1353.
- TEXSAN-TEXRAY: *Single Crystal Structure Analysis Software*, Version 5.0, Molecular Structure Corporation, the Woodlands, Texas 1989.
- Johnson, C. K. ORTEP-II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN 1976.

Received October 24, 1996.