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Short Communication

X-Ray Structure of a Second Epimer of a Partially Saturated Methylene-bridged Isoindolo[2,1-*a*][3,1]benzoxazinone

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Within a program aimed at the synthesis of new anorexic agents, aroylcyclohexanecarboxylic acids were allowed to react with 1,2- and 1,3-difunctional reagents.[1–3] The structures of the condensed tetra- and penta-cyclic compounds formed were established by means of ^1H and ^{13}C NMR spectral methods, which sometimes turned out to be difficult owing to severe signal overlap. However, the knowledge of the structure is essential, since especially reactions involving 1,3-bifunctional reagents, e.g., amino alcohols containing a cycloalkane ring, may give products that are epimeric about the aryl group and the terminal rings. For this reason, and because of the possible changes in the annulation, which can take place in a manner dependent on the reaction conditions,[2,4–6] elucidation of the steric structure of these compounds is very important. We have used X-ray methods to establish the steric structure of the former group of compounds.[7,8]

The present work deals with the stereostructure of 6a-*p*-tolyl-1,4,4a,5,6a,6b,7,8,9,10,10a,12a-dodecahydro-1,4-methanoisoindolo[2,1-*a*][3,1]benzoxazin-11-one (**3a**). The structure of the epimeric counterpart, labelled here as (**3b**), has already been published.[8] Since an NMR spectral study in $CDCl_3$ solution proved that **3b** epimerizes to **3a**,[3] the epimer **3a** was successfully separated from a freshly prepared sample of **3**.

Experimental

Preparation of the compounds. Compound **3a** was prepared[3] from *cis*-2-(*p*-methylbenzoyl)cyclohexane-1-carboxylic acid[9,10] (**1**) and 3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-en-2-*endo*-ylamine[11] (**2**), which were refluxed in toluene with *p*-toluenesulphonic acid as a catalyst. After evaporation of the mixture, purification by column chromatography (Kieselgel) and crystallization from ethanol yielded **3a**, (m.p. 218–220°C; yield 66%) whereas only the other epimer **3b**[8] (m.p. 210–212°C; yield 15%) was originally isolated from the mother liquor by fractional crystallization from ethanol.

Crystal data for **3a**. $C_{23}H_{27}NO_2$, $M_r = 349.47$, monoclinic, space group $P2_1/n$, $a = 9.612(2)$, $b = 16.801(4)$, $c = 11.549(2)$ Å, $\beta = 94.06(1)$, $Z = 4$, $V = 1860(1)$ Å^3, $D_c = 1.247$ g cm^{-3}, μ(Mo K_α) = 0.73 cm^{-1}, $F(000) = 752$, $T = 296(1)$ K, colourless prisms, crystal dimensions 0.15 × 0.17 × 0.20 mm.

Data Collection, Analysis and Refinement. A Rigaku AFC5S diffractometer was used, with graphite-monochromated Mo K_α radiation ($\lambda = 0.71069$ Å), in the ω–2θ scan mode with an ω scan rate 4.0 deg min^{-1} and a scan width of $(1.42 + 0.30 \tan\theta)$. The weak reflections $[F < 10\sigma(F)]$ were rescanned up to two times and 3412 unique reflections were measured ($2\theta_{max} = 50°$). The data were corrected for Lorentz and polarisation effects. Absorption (DIFABS[12]) and decay (−1.2%) corrections were also taken into account.

The lattice parameters were calculated by least-squares refinements of 20 reflections for **3a**. The structure was solved by direct methods and refined by full-matrix least-squares techniques to an *R*-value of 0.061 ($R_W = 0.056$). The final cycle was based on 1524 independent, observed reflections $[I > 2\sigma(I)]$. The heavy atoms were refined anisotropically and the hydrogen atoms were included in calculated positions with fixed isotropic temperature factors (1.2 times B_{eq} of the carrying atom). Neutral atomic scattering and dispersion factors were taken from Ref. 13. All calculations were performed using the TEXSAN[14] crystallographic software. Figures were drawn with PLUTO.[15] The final atomic positional coordinates and equivalent isotropic temperature factors are listed in Table 2.

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Results and discussion

X-Ray analysis of **3a** gave the solid-state structure (Fig. 1), computed from the final fractional coordinates of the non-hydrogen and hydrogen atoms listed in Table 1. The relevant bond lengths and bond angles are given in Table 2 and selected torsion angles in Table 3. There exists a close resemblance, to within experimental error, to the corresponding values for the majority of the bond angles and distances of the other epimer **3b**.[8]

Table 1. Atomic positional parameters and equivalent isotropic temperature factors for **3a** with their standard deviations in parentheses.[a]

Atom	x	y	z	$B_{eq}/Å^2$
O(1)	0.7937(3)	−0.1847(2)	0.3530(2)	3.1(2)
O(2)	0.8766(4)	−0.2015(2)	−0.0219(3)	4.7(2)
N	0.7716(4)	−0.1797(2)	0.1471(3)	2.7(2)
C(1)	0.6630(5)	−0.2258(3)	0.3557(4)	3.4(2)
C(1A)	0.6433(5)	−0.2848(3)	0.2561(4)	3.0(2)
C(3)	0.4889(5)	−0.3082(3)	0.2230(4)	3.2(2)
C(4)	0.4104(5)	−0.2312(3)	0.2031(5)	4.3(3)
C(5)	0.4511(5)	−0.1989(3)	0.1056(5)	4.2(3)
C(6)	0.5549(5)	−0.2548(3)	0.0574(4)	3.5(2)
C(6A)	0.6908(5)	−0.2542(3)	0.1384(4)	2.8(2)
C(8)	0.8676(5)	−0.1647(3)	0.0688(4)	3.4(2)
C(8A)	0.9607(5)	−0.0980(3)	0.1167(4)	3.0(2)
C(9)	1.1104(5)	−0.0946(3)	0.0855(4)	4.1(3)
C(10)	1.1821(5)	−0.0262(3)	0.1542(5)	4.7(3)
C(11)	1.1661(6)	−0.0312(3)	0.2842(5)	4.6(3)
C(12)	1.0132(5)	−0.0383(3)	0.3124(4)	3.5(2)
C(12A)	0.9499(5)	−0.1086(3)	0.2462(4)	2.9(2)
C(12B)	0.7982(4)	−0.1334(3)	0.2561(4)	2.6(2)
C(13)	0.4975(5)	−0.3346(3)	0.0963(4)	4.1(3)
C(14)	0.7007(5)	−0.0625(3)	0.2634(4)	2.7(2)
C(15)	0.6780(5)	−0.0286(3)	0.3709(4)	3.6(2)
C(16)	0.5980(6)	0.0391(3)	0.3792(4)	4.3(3)
C(17)	0.5372(5)	0.0756(3)	0.2811(5)	3.8(3)
C(18)	0.5589(5)	0.0429(3)	0.1747(4)	3.9(3)
C(19)	0.6393(5)	−0.0248(3)	0.1662(4)	3.2(2)
C(20)	0.4482(6)	0.1498(3)	0.2903(5)	6.1(3)
H(1)	0.5893	−0.1881	0.3496	4.1
H(2)	0.6613	−0.2537	0.4271	4.1
H(3)	0.6942	−0.3318	0.2768	3.6
H(4)	0.4488	−0.3454	0.2729	3.9
H(5)	0.3439	−0.2096	0.2513	5.2
H(6)	0.4202	−0.1496	0.0726	5.1
H(7)	0.5667	−0.2498	−0.0232	4.2
H(8)	0.7504	−0.2938	0.1101	3.4
H(9)	0.9174	−0.0489	0.0945	3.6
H(10)	1.1559	−0.1434	0.1052	5.0
H(11)	1.1137	−0.0852	0.0045	5.0
H(12)	1.1429	0.0225	0.1261	5.6
H(13)	1.2789	−0.0273	0.1418	5.6
H(14)	1.2154	−0.0765	0.3144	5.5
H(15)	1.2046	0.0155	0.3201	5.5
H(16)	0.9643	0.0090	0.2896	4.3
H(17)	1.0080	−0.0463	0.3935	4.3
H(18)	1.0056	−0.1535	0.2685	3.6
H(19)	0.5600	−0.3777	0.0880	4.9
H(20)	0.4091	−0.3474	0.0587	4.9
H(21)	0.7185	−0.0528	0.4399	4.4
H(22)	0.5845	0.0609	0.4535	5.1
H(23)	0.5179	0.0671	0.1061	4.8
H(24)	0.6529	−0.0460	0.0916	3.9
H(25)	0.3562	0.1396	0.2578	7.3
H(26)	0.4875	0.1923	0.2493	7.3
H(27)	0.4446	0.1642	0.3696	7.3

[a]The equivalent isotropic temperature factors for non-hydrogen atoms are of the form $B_{eq} = 4/3\Sigma_i\Sigma_j\beta_{ij}a_i \cdot a_j$.

Table 2. Bond distances (Å) and angles (°) in the molecule **3a**.[a]

O1–C1	1.436(5)	C8A–C9	1.509(6)
O1–C12B	1.416(5)	C8A–C12A	1.517(6)
O2–C8	1.226(5)	C9–C10	1.532(6)
N–C6A	1.474(5)	C10–C11	1.523(7)
N–C8	1.360(5)	C11–C12	1.532(7)
N–C12B	1.486(5)	C12–C12A	1.512(6)
C1–C1A	1.519(6)	C12A–C12B	1.529(6)
C1A–C3	1.557(6)	C12B–C14	1.522(6)
C1A–C6A	1.553(5)	C14–C15	1.398(6)
C3–C4	1.506(7)	C14–C19	1.383(6)
C3–C13	1.537(6)	C15–C16	1.380(6)
C4–C5	1.333(6)	C16–C17	1.382(7)
C5–C6	1.505(7)	C17–C18	1.375(6)
C6–C6A	1.552(6)	C17–C20	1.520(7)
C6–C13	1.530(6)	C18–C19	1.382(6)
C1–O1–C12B	112.7(3)	C8A–C9–C10	107.8(4)
C6A–N–C8	119.4(4)	C9–C10–C11	113.3(4)
C6A–N–C12B	124.1(4)	C10–C11–C12	112.3(4)
C8–N–C12B	112.5(4)	C11–C12–C12A	108.1(4)
O1–C1–C1A	111.1(4)	C8A–C12A–C12	110.8(4)
C1–C1A–C3	114.6(4)	C8A–C12A–C12B	103.8(4)
C1–C1A–C6A	114.8(4)	C12–C12A–C12B	121.8(4)
C3–C1A–C6A	101.7(3)	O1–C12B–N	109.7(3)
C1A–C3–C4	106.2(4)	O1–C12B–C12A	107.9(3)
C1A–C3–C13	101.1(4)	O1–C12B–C14	112.3(4)
C4–C3–C13	99.4(4)	N–C12B–C12A	100.8(3)
C3–C4–C5	107.8(4)	N–C12B–C14	112.8(3)
C4–C5–C6	107.5(4)	C12A–C12B–C14	112.6(4)
C5–C6–C6A	109.0(4)	C3–C13–C6	94.1(4)
C5–C6–C13	100.1(4)	C12B–C14–C15	120.2(4)
C6A–C6–C13	97.7(4)	C12B–C14–C19	122.9(4)
N–C6A–C1A	114.0(4)	C15–C14–C19	116.8(4)
N–C6A–C6	117.6(4)	C14–C15–C16	121.3(5)
C1A–C6A–C6	103.8(4)	C15–C16–C17	120.9(5)
O2–C8–N	124.5(5)	C16–C17–C18	118.3(5)
O2–C8–C8A	127.6(4)	C16–C17–C20	120.9(5)
N–C8–C8A	107.8(4)	C18–C17–C20	120.8(5)
C8–C8A–C9	119.3(4)	C17–C18–C19	120.9(5)
C8–C8A–C12A	101.1(4)	C14–C19–C18	121.9(4)
C9–C8A–C12A	111.9(4)		

[a]Esds are given in parentheses.

However, there are quite large differences in some bond distances and angles between the isomers in the C1–C1A–C6A–N bond chain. For instance, the C1A–C6A and N–C6A bond lengths in **3a** are 1.553(5) and 1.474(5) Å, but 1.576(3) and 1.1448(3) Å in **3b**, respectively. The bond angle C6A–N–C8 is 119.4(4) in **3a** and 124.4(2)° in **3b**. These values may explain why the isomer **3a** is formed more easily than **3b**.

The conformation of the cyclohexane ring (C12A, ..., C12) is a chair ($^4C_1$) with the puckering parameters[16] $Q = 0.582(1)$ Å, $\phi = 196(1)°$ and $\theta = 175.0(1)°$. The torsion angles of the ring vary from 62.9(5) to 53.2(5)° (see Table 3). These values are very similar to the relevant values for **3b**. The puckering parameters for the oxazine

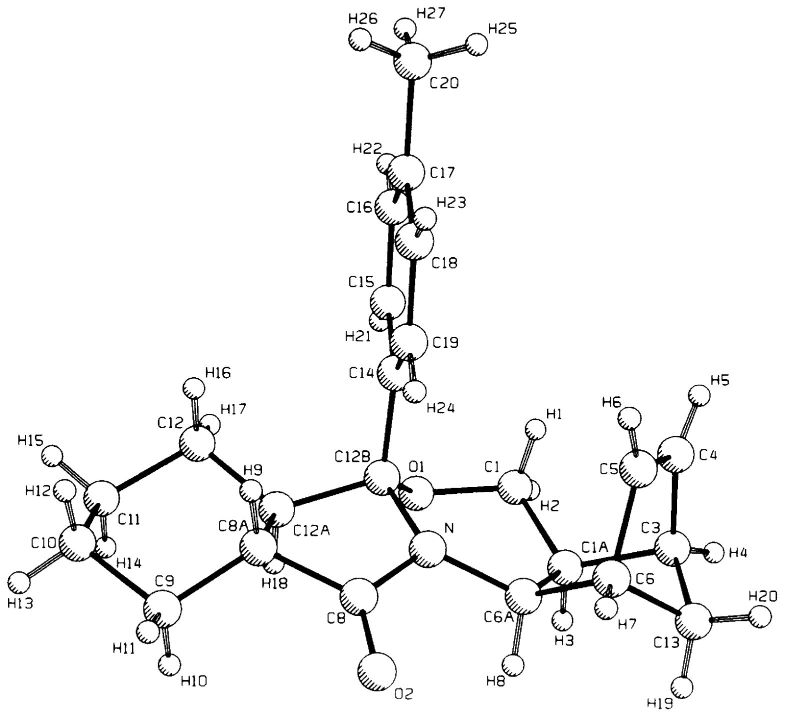

Fig. 1. The PLUTO perspective view of molecule **3a**, including the atomic labelling scheme.

Table 3. Selected torsion angles (deg) for **3a** and **3b**.[a]

	3a	3b
Cyclohexane ring		
C12–C12A–C8A–C9	62.8(5)	62.9(3)
C12A–C8A–C9–C10	−57.3(5)	−58.5(3)
C8A–C9–C10–C11	53.2(5)	53.9(4)
C9–C10–C11–C12	−53.9(6)	−54.0(4)
C10–C11–C12–C12A	54.6(5)	53.8(4)
C11–C12–C12A–C8A	−58.7(5)	−57.2(3)
Oxazine ring		
C12B–O1–C1–C1A	67.4(5)	55.5(3)
O1–C1–C1A–C6A	−40.9(5)	−26.4(2)
C1–C1A–C6A–N	11.2(5)	8.4(3)
C1A–C6A–N–C12B	−4.3(6)	−18.4(3)
C6A–N–C12B–O1	26.3(5)	45.5(3)
N–C12B–O1–C1	−57.9(5)	−62.6(2)
Pyrrolidine ring		
C12A–C12B–N–C8	−17.2(5)	−24.6(2)
C12B–N–C8–C8A	−6.1(5)	2.4(3)
N1–C8–C8A–C12A	26.9(5)	21.2(3)
C8–C8A–C12A–C12B	−36.8(4)	−34.4(2)
C8A–C12A–C12B–N	33.2(4)	36.0(2)
Other torsion angles		
O2–C8–N–C6A	13.5(7)	−0.6(4)
O2–C8–N–C12B	171.9(5)	−176.5(2)
O2–C8–C8A–C9	−27.9(8)	−35.6(4)
O2–C8–C8A–C12A	−151.0(5)	−160.0(3)
C14–C12B–O1–C1	68.4(4)	61.4(3)
C14–C12B–N–C6A	−99.7(5)	−78.6(3)
C14–C12B–N–C8	103.1(4)	97.3(2)
C14–C12B–C12A–C8A	−87.2(4)	−83.9(2)
C14–C12B–C12A–C12	38.3(5)	62.9(3)

[a] Esds are given in parentheses.

ring (O1, ..., C12B) are as follows: $Q = 0.488(1)$ Å, $\phi = 194.5(1)^\circ$ and $\theta = 131.5(1)^\circ$. These values indicate that the conformation of the ring is midway between E_1 and $^2H_1$. The puckering parameters for the pyrrolidine ring are $Q = 0.369(1)$ and $\phi = 315.3(1)$ which indicates a distorted envelope conformation.

Corresponding to the structure of **3b**, the cyclohexane and pyrrolidone rings are annulated in a *trans*-diequatorial manner, i.e., the configuration of the starting *cis* compound **1** has been changed. A similar *cis* → *trans* epimerisation has been detected for cyclohexane-condensed dihydrouracils[4] and very often in the reactions of starting *cis*-aroylcyclohexanecarboxylic acids.[1,2] We earlier observed that the *trans*-annulation of six-membered hetero rings condensed with cyclohexane, and also often that of five-membered hetero rings, is more stable than the *cis*-annulation.[1] At the same time, it is noteworthy that *diendo*-annulation takes place on norbornene–oxazine fusion in both epimers. A similar retention of configuration was experienced during the ring-transformation via *trans*-acylation of the norbornane-condensed azetidones.[17] The stability of this part of the molecule is a consequence of the rigidity of the methylene bridge.

The X-ray results indicate that the *p*-tolyl substituent of **3a** and the axial annulation hydrogen adjacent to the carbonyl group (H-9) are *cis* to the pyrrolidine ring. At the other end, the *trans*-position of the *diexo* H-3 and H-8 atoms in relation to the aryl group, and consequently the nearness of the tolyl group and the olefin bond, are obvious. In the other isomer **3b**,[8] the tolyl group and the H-9 annulation hydrogen were *cis* as well as the tolyl group and the *diexo*-norbornene annulation hydrogens. Thus the two isomers differ only in the mutual positions of the aryl group and the *diexo* H-3 and H-8 atoms.

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