Acta Chemica Scandinavica, 1994: 48: 530–532
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Short Communication

X-Ray Structure of a Saturated Methylene-bridged Isoindolo[1,2-*b*][1,3]benzoxazine

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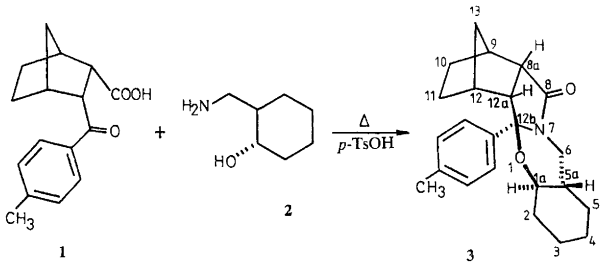
Argay, G., Sillanpää, R., Stájer, G. and Bernáth, G., 1994. X-Ray Structure of a Saturated Methylene-bridged Isoindolo[1,2-*b*][1,3]benzoxazine. – Acta Chem. Scand. 48: 530–532 © Acta Chemica Scandinavica 1994.

In a continuation of earlier X-ray studies of cycloalkane-condensed saturated heterocycles,[1] we recently dealt with tetracyclic and pentacyclic saturated fused-skeleton isoindolone derivatives containing different 1,3-hetero rings as structural moieties.[2–6] These compounds were synthesized with pharmacological and stereochemical aims; some of the aromatic analogues exhibit an anorexic effect.[7–9]

As the structures of these compounds are rather complicated, the NMR assignments are dubious or impossible in some cases because of overlapping and merged signals. In addition, difficulties may arise from the possible isomerization during the reactions. It is well known that the cyclohexane-condensed six-membered heterocycles undergo isomerization on heating or by the action of acids or bases.[10–13] Hence, proof of the structure of **3** is important. Furthermore, **3** is of interest since both of the terminal rings are saturated, and thus the aryl substituent can be situated close to or far from H-1a,5a and H-8a,12a.†

Experimental

For the preparation, di-*endo*-3-(*p*-methylbenzoyl)bicyclo-[2.2.1]heptane-2-carboxylic acid[7] (**1**) and *trans*-2-(aminomethyl)cyclohexanol[14] (**2**) were refluxed in toluene with *p*-toluenesulfonic acid as a catalyst (Scheme 1). After evaporation of the mixture and purification of the residue by column chromatography (Kieselgel), crystallization from ethanol yielded 9,12-methano-12b-(*p*-tolyl)perhydroisoindolo[1,2-*b*][1,3]benzoxazin-8-one (**3**), m.p. 190–192°C.



Scheme 1.

Crystal structure determination

Crystal data on **3** ($C_{23}H_{29}NO_2$, $M_r = 351.49$): orthorhombic, space group $Pna2_1$, $a = 17.229(2)$, $b = 6.410(2)$, $c = 17.161(4)$ Å, $V = 1895(1)$ Å^3, $Z = 4$, and $D_c = 1.232$ g cm^{-3}, μ(Mo Kα) = 0.72 cm^{-1}, $T = 296(1)$ K, crystal dimensions $0.18 \times 0.18 \times 0.26$ mm.

Data collection, analysis and refinement. A Rigaku AFC5S diffractometer was used, with graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å) in the ω–2θ scan mode [ω-scan rate: 8.0° min^{-1}, width: $(0.79 + 0.30 \tan\theta)$°]. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. The data obtained were corrected for Lorentz and polarization effects. 1967 reflections were obtained ($2\theta_{max} = 50°$). Direct methods and difference Fourier syntheses were used. Full-matrix least-squares refinement (for non-hydrogen atoms, anisotropic and hydrogen atoms with fixed isotropic temperature parameters: 1.2 times B_{eq} of the carrying atom). In the final cycles, the 1013 data with $I > 3.0\sigma(I)$ gave an R value of 0.038 [$R_w = 0.041$, $w = 4F_o^2/\sigma^2(F_o^2)$] for 234 parameters, max. shift/error < 0.01, maximum/minimum residual electron density = 0.14/−0.16 e Å^{-3}.

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† See the numbering in Scheme 1.

Atomic scattering and dispersion factors were taken from *International Tables for Crystallography*.[15] All calculations were performed with TEXSAN-89 software[16] on a VAXSTATION 3520 computer. Lists of anisotropic thermal parameters and observed and calculated structure factors are available from the authors on request.

Results and discussion

Fig. 1 shows a perspective view of compound **3**, computed from the final fractional coordinates of non-hydrogen atoms listed in Tables 1 and 2.

Compound **3** exhibits di-*endo*-fused norbornane and pyrrolidine rings (Fig. 1). On the methylene-bridged isoindolone moiety, the *p*-tolyl substituent and the di-*exo*-hydrogens are in a *trans* disposition. For comparison, in the compound which contains the cyclohexane and norbornene terminal rings in the reversed position, the aryl group and the di-*exo*-norbornene annellation hydrogens are either *cis*[2] or *trans*[3] to the oxazine ring. These diastereomers are formed as a result of the cyclization. In compound **3**, the cyclohexane and the 1,3-oxazine rings are *trans*-fused, with *trans*-diaxial annellation hydrogens H-1a,5a. The 12b-aryl substituent and H-1a (the annellation hydrogen adjacent to the oxygen in the oxazine) are *cis* disposed.

The *trans*-2-(aminomethyl)cyclohexanol (**2**) underwent no isomerization during the reaction. With *cis*-2-(*p*-methylbenzoyl)cyclohexanecarboxylic acid and di-*endo*-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ylamine as starting materials, the analogous compound formed exhibited *trans* cyclohexane–pyrrolidine fusion, i.e., *cis*→*trans* isomerization took place during the ring-closure reaction.[2,3] In the present case, the retention of configuration is due to the *trans* ring fusion, because the

Table 1. Fractional atomic coordinates ($\times 10^4$) and temperature factors U_{eq} (Å^2, $\times 10^3$) for non-hydrogen atoms of **3**, with e.s.d.s in parentheses.

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
O(1)	2661(2)	1122(5)	−224(0)	37(1)
O(14)	4287(2)	−2644(7)	726(3)	64(1)
N(7)	3323(2)	−2101(5)	−177(0)	35(1)
C(1A)	2005(3)	212(8)	178(3)	37(1)
C(2)	1588(3)	1945(8)	600(4)	44(1)
C(3)	886(3)	1096(10)	1037(4)	56(2)
C(4)	1098(3)	−670(10)	1574(4)	56(2)
C(5)	1538(3)	−2375(9)	1159(3)	47(1)
C(5A)	2252(3)	−1497(8)	734(4)	38(1)
C(6)	2718(3)	−3131(8)	285(3)	37(1)
C(8)	4031(3)	−1708(9)	161(4)	42(1)
C(8A)	4434(3)	11(8)	−269(4)	44(1)
C(9)	5179(3)	−520(10)	−732(4)	52(2)
C(10)	5071(3)	−2643(10)	−1100(4)	64(2)
C(11)	4460(3)	−2216(10)	−1732(4)	65(2)
C(12)	4289(3)	137(10)	−1659(4)	58(2)
C(12A)	3843(3)	692(8)	−905(4)	40(1)
C(12B)	3084(3)	−402(7)	−686(3)	33(1)
C(13)	5109(3)	950(10)	−1422(4)	63(2)
C(15)	2584(3)	−1032(8)	−1368(4)	33(1)
C(16)	2217(3)	507(8)	−1795(4)	48(2)
C(17)	1764(3)	37(9)	−2440(4)	46(2)
C(18)	1668(3)	−1999(9)	−2687(3)	37(1)
C(19)	2038(3)	−3544(8)	−2259(4)	40(1)
C(20)	2485(3)	−3077(8)	−1616(3)	37(1)
C(21)	1168(3)	−2520(10)	−3382(4)	51(1)

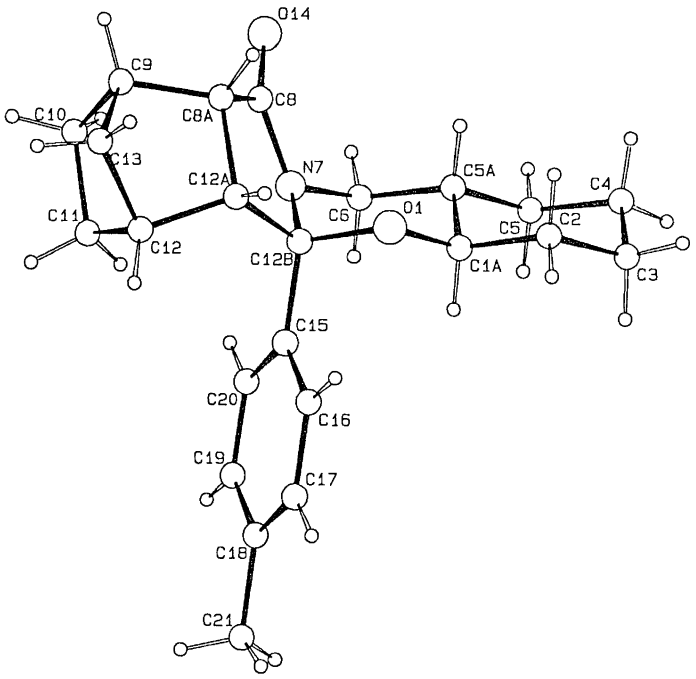

Fig. 1. A perspective view of compound **3**. Hydrogen atoms are shown but not labelled.

Table 2. Fractional atomic coordinates ($\times 10^4$) and temperature factors U_{iso} (Å^2, $\times 10^3$) for hydrogen atoms.

Atom	*x/a*	*y/b*	*z/c*	U_{iso}
H(1)	1663	−369	−199	44
H(2)	1421	2956	231	52
H(3)	1934	2578	960	52
H(4)	516	609	668	67
H(5)	664	2191	1336	67
H(6)	636	−1247	1785	68
H(7)	1412	−142	1983	68
H(8)	1205	−3018	789	57
H(9)	1704	−3379	1530	57
H(10)	2586	−894	1112	45
H(11)	2953	−4071	642	45
H(12)	2381	−3881	−53	45
H(13)	4533	1142	74	53
H(14)	5646	−375	−443	63
H(15)	4887	−3629	−731	76
H(16)	5542	−3135	−1322	76
H(17)	4005	−3015	−1642	78
H(18)	4661	−2537	−2235	78
H(19)	4084	756	−2119	69
H(20)	3770	2160	−880	48
H(21)	5492	716	−1811	76
H(22)	5111	2379	−1277	76
H(23)	2274	1922	−1642	58
H(24)	1518	1136	−2719	55
H(25)	1981	−4960	−2413	48
H(26)	2730	−4174	−1338	45
H(27)	967	−1270	−3600	61
H(28)	752	−3392	−3223	61
H(29)	1473	−3225	−3761	61

cyclohexane-*trans*-condensed six-membered hetero rings containing two hetero atoms are more stable than the corresponding *cis* isomers.[11]

During the reaction, no inversion took place at the di-*endo*-norbornane–pyrrolidine annellation, i.e., the di-*endo* structure of the starting **1** is unchanged in the condensed pentacyclic system. A similar retention of the configuration was found in both compounds containing the norbornene moiety and cyclohexane ring reversed at the terminals[2,3] and during the intramolecular transacylation of norbornane-condensed azetidinones.[13] The stability of the di-*endo* fusion is also enhanced by the anchoring effect of the methylene bridge.

The 1,3-oxazine ring and the cyclohexane moiety have a chair form, and the condensed pyrrolidone ring has an envelope conformation (where the 12b-carbon atom is out of the plane).

Acknowledgements. The authors thank the Hungarian Research Foundation (OTKA No. 2693) and Ministry of Welfare (ETT T-121) for financial support.

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Received November 24, 1993.