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Preparation and Structure of Saturated 1-Oxopyrrolo[2,1-*b*]quinazoline and 1-Oxopyrrolo[1,2-*a*]quinazoline†

Angela E. Szabó,[a] Géza Stájer,*[,a] Pál Sohár,[b] Reijo Sillanpää[c] and Gábor Bernáth[a]

[a]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, P.O.B. 121, H-6701 Szeged, Hungary, [b]Department of General and Inorganic Chemistry, Loránd Eötvös University, P.O.B. 32, H-1518 Budapest-112, Hungary and [c]Department of Chemistry, University of Turku, SF-20500 Turku, Finland

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The reaction of 3-(*p*-chlorobenzoyl)propionic acid (**1**) with *cis*-2-aminocyclohexylmethanamine (**2**) yielded two structural isomers: the saturated linearly condensed 3a-(*p*-chlorophenyl)perhydropyrrolo[2,1-*b*]quinazolin-1-one (**3**) and the angularly fused 3a-(*p*-chlorophenyl)perhydropyrrolo[2,1-*a*]quinazolin-1-one (**4**), containing the cyclohexane ring fused next to the NH group (**3**) or in the vicinity of the lactam nitrogen (**4**), respectively. The *cis*-2-aminocyclohexylmethanamine (**2**) did not undergo isomerization during the reaction, but the relative positions of the aryl group and the annelational hydrogens are *cis* in **3** and *trans* in **4**. Formation of the differently annulated saturated pyrrolidinone–quinazoline ring systems can be rationalized by the similar nucleophilicities of the two nitrogens in **2**. The steric structures were established by ^{1}H and ^{13}C NMR spectroscopy and X-ray analysis.

In a continuation of earlier studies to convert aroylcyclohexane- and aroylnorbornane-carboxylic acids to new, saturated or partly saturated heterocycles containing four or five condensed rings,[1,2] in this work an aliphatic β-aroylcarboxylic acid, the 3-(*p*-chlorobenzoyl)propionic acid[3] (**1**) was used. **1** was reacted with *cis*-2-aminocyclohexylmethanamine[4] (**2**) which was obtained from *cis*-2-aminocyclohexanecarboxamide[5] on reduction with lithium aluminium hydride (LAH). This diamine (**2**), whose platinum derivatives have antitumour effects,[6] differs from the bifunctional compounds applied previously[1,2] in that the ring closures involve two amino groups, one of them being attached to a secondary cyclohexane-carbon and the other nitrogen function being an aminomethyl; their nucleophilicities are very similar.

The interesting feature of this reaction is that structural isomers can be formed, depending on which of the nitrogens of **2** cyclizes with the carbonyl groups of **1**. Furthermore, isomers are to be expected, differing in the mutual positions of the aryl ring and the annelational hydrogens. The annelation of the cycloalkane rings too has to be determined, because isomerization of *cis* or *trans* starting compounds often occurs during the formation of highly condensed ring systems having an aroyl substituent at one of the ring fusions.[1]

Experimental

The NMR spectra were recorded for samples in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 (^{1}H) and 63 (^{13}C) MHz, with the ^{2}H-signal of the solvent as the lock, and with the following parameters: spectral width 5 and 18.5 kHz, pulse width 1.0 (^{1}H) and 7.0 (^{13}C) μs (ca. 20° and ca. 90° flip angle, respectively), acquisition time 1.64 and 0.40 s, number of scans 16 (^{1}H) and 256–3.5 K (^{13}C), computer memory 16 K, Lorentzian exponential multiplication for signal-to-noise enhancement (linewidth 0.7 or 1.0 Hz), and complete proton noise decoupling (ca. 0.5 W) for the ^{13}C NMR spectrum. The standard Bruker microprogram DNOEMULT.AU was used to generate NOE (nuclear Overhauser effect[7c,8]) with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of ca. 3–40 mW. The 2D-HSC (two-dimensional heteronuclear shift correlation[9]) spectra were obtained by using the standard Bruker pulse program XHCORRD.AU. Data points: 4 K (^{13}C domain), increments: 64–256, digital

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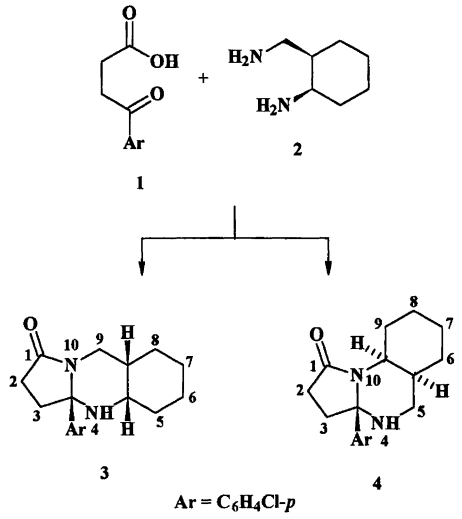
* To whom correspondence should be addressed.

resolution (^{1}H domain): better than 5 Hz/point, transients: 256, relaxation delay: 3 s. All C–H correlations were found by using J(C, H) = 135 Hz for calculation of the delay. DEPT (distortionless enhancement by polarization transfer[10]) spectra were run in the standard way,[11] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively.

IR spectra were run for KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer.

For the preparation, *cis*-2-aminocyclohexylmethanamine (**2**), obtained from *cis*-2-aminocyclohexanecarboxamide by reduction with LAH, was refluxed with 3-(*p*-chlorobenzoyl)propionic acid (**1**) in toluene in the presence of *p*-toluenesulphonic acid as catalyst (Scheme 1). After evaporation of the mixture, the residue was separated by column chromatography (basic Al_2O_3, activated, 50–200 μm, Janssen): elution with ethyl acetate, monitoring by TLC [Polygram SIL G, solvent: benzene–ethanol–petroleum ether (b.p. 40–70°C) 3:1:4, development in iodine vapour]. The early eluate fractions contained **4** (higher R_f) and the later ones **3** (lower R_f). Crystallization from ethyl acetate yielded 3a-(*p*-chlorophenyl)perhydropyrrolo[2,1-*b*]quinazolin-1-one (**3**), m.p. 151–154°C, (35%) and 3a-(*p*-chlorophenyl)perhydropyrrolo[2,1-*a*]quinazolin-1-one (**4**), m.p. 205–208°C (30%). As the nucleophilicities of the two nitrogens in **2** are very similar, **3** and **4** are formed in almost equal yields. Analytical data: found (for **3**): C 66.73; H 6.85; N 9.10 and found (for **4**): C 66.65; H 6.72; N 9.07. Calc. for $C_{17}H_{21}N_2ClO$ C 66.99; H 6.94; N 9.19%.

Crystal data for **3**. $C_{17}H_{21}ClN_2O$, $M_r = 304.82$, orthorhombic, space group $P2_12_12_1$, $a = 12.756(7)$, $b = 18.748(2)$, $c = 6.621(2)$ Å, $Z = 4$, $V = 1583(1)$ Å^3, $D_c = 1.278$ g cm^{-3}, μ(Mo K_α) = 2.39 cm^{-1}, $F(000) = 648$, $T = 295(1)$ K, colourless prisms, crystal dimensions 0.20 × 0.22 × 0.22 mm.



Scheme 1.

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 θ scan rate of 8.0° min^{-1} and a scan width of $(1.10 + 0.30 \tan \theta)$. The weak reflections [$F < 10\sigma(F)$] were rescanned up to two times; 1650 unique reflections were measured ($2\theta_{max} = 50°$). The data were corrected for Lorentz and polarization effects. The lattice parameters were calculated by least-squares refinements of 25 reflections. The structure was solved by direct methods and refined by full-matrix least-squares techniques to an R value of 0.042 ($R_w = 0.041$). The enantiomer depicted in Fig. 2 gave a slightly better R_w value and was therefore chosen. The final cycle was based on 1053 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). Neutral atomic scattering and dispersion factors were taken from *International Tables for X-Ray Crystallography*.[12] All calculations were performed with TEXSAN[13] crystallographic software. The figure was drawn with ORTEP.[14]

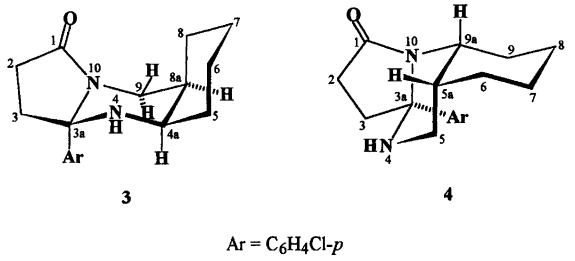
Structure

The structural isomeric nature of the two products follows from the downfield separated signals in the range characteristic for the saturated CH groups in the ^{1}H NMR spectra. Because of the $-I$ effect of the vicinal amide group and the additional anisotropic effect of the coplanar carbonyl,[7a] the separated signal appears with a relatively very high paramagnetic shift (3.88 ppm for **3** and 4.37 ppm for **4**) (the spectral data on **3** and **4** are given in Table 1). As for **3**, this signal is a doublet and the splitting is characteristic of geminal couplings of ^2J(H, H) type[7b] (13.4 Hz), and thus the methylene group in the hetero ring is vicinal to the lactam group. For **4**, the two small (4.7 Hz) and one large (12.3 Hz) couplings cause triple doublet multiplicity, which points to three vicinal (one *diaxial* and two *axial–equatorial*) interactions; hence, the methine group (and not the methylene) is next to the lactam nitrogen (there is no geminal coupling). The results of 2D-HSC measurements support this structure: the 50.6 ppm carbon line relates to the 4.37 ppm signal and corresponds to the methine group in **4** according to the DEPT spectrum. For **4**, however, as part of a methylene group, the hydrogen gives the separate 3.88 ppm signal, and the corresponding lines at 42.3 ppm point to a secondary carbon (DEPT). On 2D-HSC, the signal of the other methylene hydrogen appears at 2.95 ppm and indicates geminal coupling. Thus, for **3**, the vicinal couplings of the two hydrogens of the NCH_2 group with the neighbouring 8a-methine hydrogen are 3.3 and < 1 Hz; for **4**, the analogous couplings of the NCH (9a) hydrogen to the 9-methylene protons are 12.3 and 4.7 Hz. The conformations of **3** and **4** follow from this and the vicinal 12.7 Hz and 3.5 Hz couplings of the 5-methylene hydrogens in **4**.

Table 1. Characteristic IR, ^1H and ^{13}C NMR data on **3** and **4**[a]

	^1H NMR/IR						^{13}C NMR	
Group	**3**			**4**			**3**	**4**
CH_2 (Posn. 8/9)	~1.3[b]		~1.75[c, d]	~0.9[b]		~1.5[c]	25.1	27.5
CH_2 (7/8)		~1.5[e]		1.15[f]		~1.5[c]	24.0	25.1
CH_2 (6/7)	~1.3[b]		~1.5[e]	~0.9[b]		1.32	19.7	20.6
CH_2 (5/6)	~1.5[e]		~1.75[c]		~1.5[c]		30.9	28.5
CH (8a/5a)		~1.5[e]			~1.85[e]		33.8	36.7
NCH_2	2.95[g]		3.88[h]	2.65[g]		2.88[g]	42.3	41.6
NCH		2.89[i]			4.37[j]		47.9	50.6
CH_2CO (2)		2.45[k]		2.40[k]		2.55[k]	28.6	28.8
CH_2C_q (3)		~2.1[k]		~1.85[e]		2.05[k]	37.3	39.3
C_q (3a)		–		–			78.5	76.4
$C_{Ar}H$ (2′, 6′)		~7.35[l]			~7.45[m]		127.3	127.4
$C_{Ar}H$ (3′, 5′)		~7.35[l]			7.30[d]		129.0	128.5
$C_{Ar}Cl$ (4′)		–			–		133.4	133.4
$C_{Ar}C_q$ (1′)		–			–		140.6	144.3
C=O	1690		(1675)[n]	1689		(1665)[n]	173.4	173.1
νNH IR-band		3305			3313		–	–

[a] IR in KBr discs (cm^{-1}), NMR in $CDCl_3$ solution ($\delta_{TMS}=0$ ppm) at 250 (^1H) and 63 MHz (^{13}C). The NMR assignments were supported by DNOE, DEPT and 2D-HSC measurements. [b, c, e, l] Overlapping signals. [d] Doublet-like signal. [f] Double quartet signals. [g] Double doublet, split by 13.4 and 3.3 Hz (**3**), 14.0 and 3.5 Hz (**4**, upfield signal), or 14.0 and 12.7 Hz (**4**, downfield signal). [h] Doublet, split by 13.4 Hz. [i] Unresolved multiplet, half-band-width ca. 10Hz. [j] Triple doublet, split by 12.3, 4.7 and 4.7 Hz. [k] Complex multiplet.



3 **4**

Ar = C_6H_4Cl-*p*

Fig. 1. Stereostructures of **3** and **4**.

For both isomers, the six-membered rings are *cis* annelated and have chair conformation. For the linearly condensed **3**, the 9-methylene group is *equatorial*, and the NH(4) group is *axial*. For the angularly condensed **4**, however, the 5-CH_2 is *axial* and the amide-nitrogen is *equatorial*,† in agreement with earlier findings[15–17] (Fig. 1).

The structures deduced above were supported by DNOE measurements. For **3**, on saturation of the aromatic *ortho*-hydrogens the close 1,3-*diaxial* H-4a and H-9*ax* respond. (The reverse experiment is also positive: saturation of the signals of the latter atoms increases the intensity of the aromatic multiplet.) For **3**, the small H-9*eq*,8a coupling (<1 Hz, see above and Table 1) can be explained by the structure in Fig. 1; H-8a is *equatorial* to the saturated pyrimidine ring, and the electron-withdrawing neighbouring amide-nitrogen *ab ovo* decreases the small *diequatorial* H-9*eq*,8a coupling.[7d]

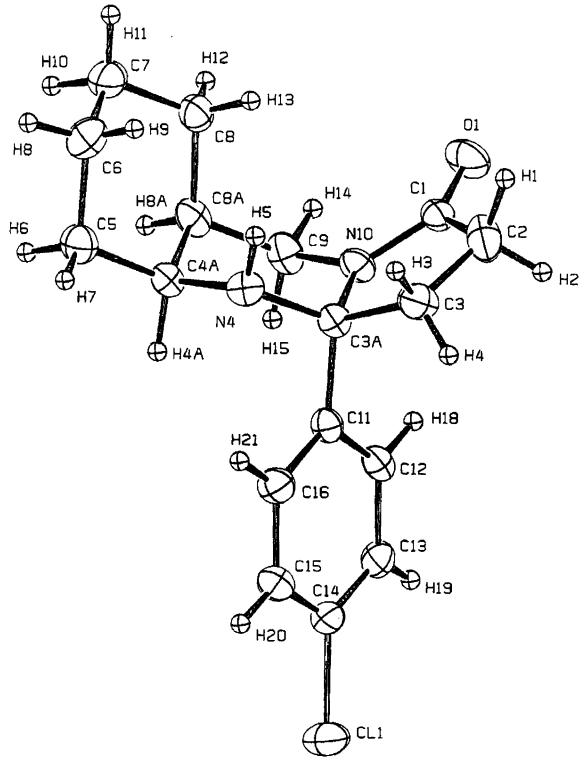


Fig. 2. ORTEP perspective view of molecule **3**, including the atomic labelling scheme. The thermal ellipsoids are drawn at the 30% level.

† For the *cis*-condensed saturated heterobicyclic compounds containing two heteroatoms in the 1,3-positions, that relatively stable conformer containing both six-membered rings in the chair form is stable in which the *O* or unsubstituted *N* (i.e., *N*H) hetero atom is attached *axially* to the annulated carbon, or *equatorially* if the *N* is substituted (*N*R). For the thio analogues, the two conformers are in equilibrium.[18]

For **4**, the other details of the normal ^{1}H NMR spectrum support the postulated structure. In consequence of the steric hindrance between the *endo* H-9*ax* and H-7*ax* and the aromatic ring, the *ortho*-hydrogens give a broadened signal, and the former give signals shifted upfield (by ca. 0.4 ppm) in comparison with the isomer **3**, because of the anisotropic shielding effect of the benzene ring.[7e] In accordance with the stereostructure in Fig. 1, the H-5a and H-9a signals give no response on irradiation of the aromatic *ortho*-hydrogens in the DNOE experiment, but there is a strong increase in intensity of the coincident H-9*ax* and H-7*ax* signals, in addition to the trivial intensity enhancements of the H-5*ax*,*eq*, and H-3,3′ multiplets.

In accordance with these conformations, the hindered *endo* methylene atoms C-9 and C-7 are more shielded, i.e., their signals are upfield shifted relative to those of their counterparts C-6 and C-8 (by 4.3, 4.5 and 6.8, 1.0 ppm; steric compression shift[19]) for both isomers.

The X-ray analysis of **3** lends support to the NMR results and shows that the *cis*-2-aminocyclohexylmethanamine (**2**) underwent no isomerization during the reaction. The measurements gave the solid-state structure (Fig. 2), computed from the final fractional coordinates of the non-hydrogen and hydrogen atoms. The relevant bond lengths and bond angles are given in Table 2. There are no unusual values for the bonding parameters. The analysis indicates that **3** crystallizes as a single enantiomer. The two six-membered rings have nearly the ideal chair conformation. There is a very weak hydrogen-bond between H(5) and O(1) [N(4)...O(1^i) = 3.591(6) Å, H(5)...O(1^i) = 2.82(4) Å, <N(4)–H(5)...O(1^i) = 152°(4); $i = {}^1/_2 - x, \; -y, \; {}^1/_2 + z$].

Table 2. Bond distances (Å) and bond angles (°) for **3**.[a]

Cl(1)–C(14)	1.746(5)	C(4A)–C(8A)	1.551(8)
O(1)–C(1)	1.224(6)	C(5)–C(6)	1.541(9)
N(4)–C(3A)	1.460(6)	C(6)–C(7)	1.52(1)
N(4)–C(4A)	1.473(6)	C(7)–C(8)	1.52(1)
N(10)–C(1)	1.349(6)	C(8)–C(8A)	1.526(8)
N(10)–C(3A)	1.466(6)	C(8A)–C(9)	1.526(8)
N(10)–C(9)	1.459(6)	C(11)–C(12)	1.394(7)
C(1)–C(2)	1.488(9)	C(11)–C(16)	1.374(7)
C(2)–C(3)	1.496(9)	C(12)–C(13)	1.378(8)
C(3)–C(3A)	1.543(7)	C(13)–C(14)	1.362(8)
C(3A)–C(11)	1.524(6)	C(14)–C(15)	1.381(8)
C(4A)–C(5)	1.525(8)	C(15)–C(16)	1.403(7)
C(3A)–N(4)–C(4A)	113.5(4)	C(4A)–C(5)–C(6)	112.0(5)
C(1)–N(10)–C(3A)	114.6(4)	C(5)–C(6)–C(7)	110.2(6)
C(1)–N(10)–C(9)	125.3(4)	C(6)–C(7)–C(8)	110.6(6)
C(3A)–N(10)–C(9)	118.8(4)	C(7)–C(8)–C(8A)	113.2(5)
O(1)–C(1)–N(10)	125.9(5)	C(4A)–C(8A)–C(8)	111.0(5)
O(1)–C(1)–C(2)	125.7(5)	C(4A)–C(8A)–C(9)	109.7(5)
N(10)–C(1)–C(2)	108.4(5)	C(8)–C(8A)–C(9)	113.2(5)
C(1)–C(2)–C(3)	107.1(5)	N(10)–C(9)–C(8A)	110.1(5)
C(2)–C(3)–C(3A)	106.3(5)	C(3A)–C(11)–C(12)	120.5(5)
N(4)–C(3A)–N(10)	110.9(4)	C(3A)–C(11)–C(16)	121.2(5)
N(4)–C(3A)–C(3)	111.0(4)	C(12)–C(11)–C(16)	118.1(5)
N(4)–C(3A)–C(11)	109.6(4)	C(11)–C(12)–C(13)	121.3(6)
N(10)–C(3A)–C(3)	103.4(4)	C(12)–C(13)–C(14)	119.7(6)
N(10)–C(3A)–C(11)	111.0(4)	Cl(1)–C(14)–C(13)	120.1(5)
C(3)–C(3A)–C(11)	110.8(4)	Cl(1)–C(14)–C(15)	118.8(5)
N(4)–C(4A)–C(5)	110.5(5)	C(13)–C(14)–C(15)	121.1(5)
N(4)–C(4A)–C(8A)	113.0(4)	C(14)–C(15)–C(16)	118.6(5)
C(5)–C(4A)–C(8A)	111.3(5)	C(11)–C(16)–C(15)	121.2(6)

[a] Esds are given in parentheses.

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