On the Conformation of 1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones

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Received March 14, 1991

^{1}H- and ^{13}C-NMR spectra of the 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones **2a-l** were examined. It was found that the 1-aryl group assumes a roughly axial position on the boat conformation of the heterocyclic ring in *meta*- and *para*-substituted derivatives only. However, the *ortho*-substituted 1-phenyl group occupies the quasi equatorial position.

Über die Konformation von 1-Aryl-1,4-dihydro-3(2*H*)-isochinolonen

^{1}H- und ^{13}C-NMR Spektren der 1-Aryl-1,4-dihydro-3(2*H*)-isochinolone **2a-l** wurden untersucht. Es wurde festgestellt, daß sich die 1-Arylgruppe nur in *meta*- und *para*-substituierten Derivaten in nahezu axialer Stellung der Wannenform des heterocyclischen Ringes befindet. Die *ortho*-substituierte 1-Phenylgruppe nimmt jedoch die quasi-äquatoriale Stellung ein.

The importance of 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones as synthetic intermediates and biologically active compounds has been reflected in the development of numerous methods for their preparation[1-3]. 1-Phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**2a**) was first prepared by *Deák* et al.[4] by cyclization of benzaldehyde and benzyl cyanide in polyphosphoric acid (PPA). Several 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones, substituted at different positions, have also been synthesized by this method[5-10]. A kinetic study of the reaction led to the conclusion that the corresponding bis-amide **1** is formed as an intermediate, which then undergoes rapid cyclization with elimination of aryl-acetamide[11]. The electron impact induced fragmentation pathways, and conformation of some 3(2*H*)-isoquinolinones was studied as well[12-14].

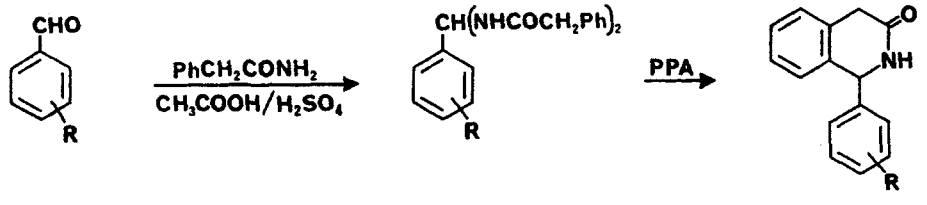
Recently we described our results of a conformational analysis of some cyclic amides incorporated into the ring system containing a β-carboline fragment[15,16]. On the other hand, one of the 1,2,3,4-tetrahydro-β-carbolin-1-one derivatives is a very potent atypical antidepressant agent[17]. We also put forward a hypothesis that the specific nature of the amide bond in such derivatives is important for their CNS activity[18].

In order to pursue our structure-activity relationship studies with CNS agents, in the present paper we have discussed conformations of the 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones **2a-l** in solution.

All the investigated compounds were prepared according to *Deák* et al.[3,8,9], as shown in Scheme 1.

^{1}H- and ^{13}C-NMR chemical shifts of compounds **2a-l** are listed in Tables 1 and 2. The data were assigned by correlation with the spectra of the 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**2a**)[14]. Simple decoupling experiments were carried out for the assignment of some resonance signals in ^{1}H-NMR spectra, and an analysis of the signal multiplicity in ^{13}C-NMR spectra was also helpful for identification of some resonances.

Tóth et al.[13] concluded that the 1-phenyl group of the derivative **2a** occupies a quasi axial position on the boat conformation of the heterocyclic ring (Fig. 1, conformer **B**). A more detailed NMR study indicated that this compound has not a homogeneous conformation, and in the **A** ⇄ **B**



1a-l **2a-l**

1, 2	R	1, 2	R
a	H	g	3-Me
b	4-Br	h	4-Me
c	2-Cl	i	4-NMe_2
d	3-Cl	j	2-NO_2
e	4-Cl	k	3-NO_2
f	2-Me	l	4-NO_2

Scheme 1

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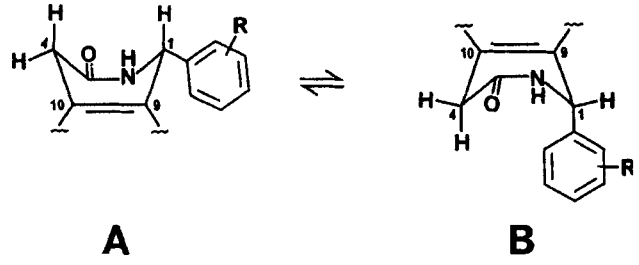
equilibrium a considerable contribution of conformer A must be taken into account[14]. However, in view of our results, this conclusion requires some modifications.



A **B**

Fig. 1: The boat conformations of compounds **2a-l**

There are several characteristic chemical shifts and coupling constants in the ^{1}H-NMR spectra which are diagnostic for conformation determination of the investigated compounds (Table 1).

Signals of the 1-H and 2-H atoms appear as doublets in the spectra of the investigated derivatives **2a-l**; the vicinal coupling constants $^3J(1,2)$ and $^3J(2,1)$ are shown in Table 1. The dihedral angle (φ) between H1-C1-N2-H2 was estimated from the $^3J(2,1)$ coupling constants using a basic *Karplus* equation (1)[19].

$$^3J(2,1) = 4.5\cos 2\varphi - 0.5\cos\varphi + 4.22 \quad (1)$$

The calculated values of the dihedral angle are φ = 46-49° for the 1-phenyl compound **2a** and all the meta and para substituted derivatives **2b**, **2d**, **2e**, **2g-2i**, **2k**, and **2l**. For the *ortho*-substituted derivatives **2c** and **2f** the dihedral angle is *ca.* 115°, and for the 2'-nitro derivative **2j** it is *ca.* 54° (Fig. 2). The above results indicate that the 1-aryl group should assume the quasi axial position (conformer **B**, Fig. 1) in compound **2a** and all the *meta*- and *para*-substituted derivatives of **2**, while in the *ortho*-substituted derivatives **2c**, **2f**, and **2j** this group should occupy a roughly equatorial steric position (conformer **A**).

The position of the 2-NH resonance signal is indicative of a steric arrangement of the amide bond. In the case of the 2'-chloro (**2c**) and 2'-methyl (**2f**) derivatives this signal is shifted upfield by *ca.* 0.2 ppm in relation to the respective *meta*- and *para*-substituted compounds, whereas in the case of the 2'-nitro derivative **2j** the observed upfield shift is

Table 1: δ (^{1}H) Chemical shifts (in ppm) and characteristic coupling constants (in Hz) of compounds **2a-l** in DMSO-d_6

Hydrogen atom	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l
1-H	5.75	5.75	6.18	5.80	5.76	5.98	5.69	5.69	5.60	6.34	5.97	5.95
$^3J(1,2)$	3.5	3.5	1.6[a]	3.6	3.4	1.3[a]	3.5	3.5	3.3	1.7[a]	3.6	3.7
2-NH	8.68	8.68	8.52	8.73	8.68	8.46	8.61	8.63	8.51	8.43	8.82	8.81
$^3J(2,1)$	3.4	3.5	1.7	3.5	3.3	1.6	3.4	3.4	3.3	2.6	3.6	3.7
4-H^{eq}	3.72	3.71	3.86	3.74	3.71	3.78	3.73	3.69	3.66	3.90	3.74	3.76
4-H^{ax}	3.56	3.55	3.70[b]	3.53	3.55	3.68[b]	3.55	3.55	3.53	3.72[b]	3.58	3.59
$^2J(4,4)$	19.7	19.8	20.3	19.8	19.7	20.0	19.7	19.6	19.7	20.4	19.8	19.8
5-H	c)	c)	7.34	c)	c)	7.35	c)	c)	c)	7.36	7.45	7.43
6-H	c)	c)	7.28	c)	c)	c)	c)	c)	c)	7.29	c)	c)
7-H	c)	c)	7.25	c)	c)	c)	7.18	c)	c)	7.26	c)	c)
8-H	c)	c)	7.09	c)	c)	6.90	7.19	7.23	c)	7.14	c)	c)
2'-H	c)	7.62		c)	7.50		c)	c)	7.16		8.26	7.70
3'-H	c)	7.35	7.59[d]		7.40	c)		7.25	6.76	8.07		8.29
4'-H	c)		7.41[e]	c)		c)	c)			7.64	8.23	
5'-H	c)	7.35	7.42[e]	c)	7.40	c)	c)	7.25	6.76	7.77	7.74	8.29
6'-H	c)	7.62	7.60[d]	c)	7.50	7.10	c)	c)	7.16	7.48	7.83	7.70

a) This coupling constant may be also assigned to $^5J(1,4^{ax})$

b) $^5J(4^{ax},1)$ = 1.5 Hz

c) Strongly coupled, overlapping signals between: 7.45-7.29 for **2a**, 7.35-7.27 for **2b**, 7.49-7.29 for **2d**, 7.37-7.28 for **2e**, 7.36-7.21 for **2f**, 7.37-7.25 for **2g**, 7.33-7.25 for **2h**, 7.31-7.25 for **2i**, 7.39-7.30 for **2k**, and 7.40-7.30 for **2l**.

d,e) Assignments for particular pairs of signals in column may be interchanged

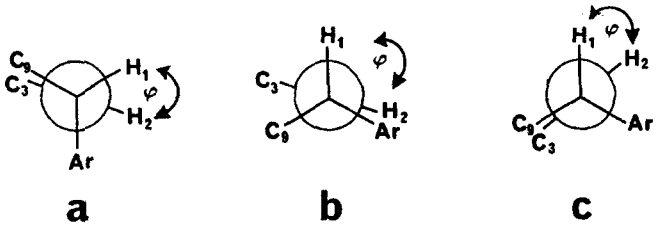


Fig. 2: The dihedral angles H_1-C_1-N_2-H_2 calculated from eq. (1):
a - φ = 46-49° for **2a, 2b, 2d, 2e, 2g-2i, 2k,** and **2l**:
b - φ ≈ 115° for **2c** and **2f**;
c - φ ≈ 54° for **2j**.

even greater and reaches *ca.* 0.4 ppm (Table 1). The observed effect permits us to conclude that the amide bond in **2c, 2f,** and **2j** is significantly twisted as a result of steric hindrance of both the bulky *ortho*-substituted phenyl group and the 1-H and 4-H diaxial interaction in conformer A. The 4-H_2 signals of *ortho*-derivatives are shifted downfield by *ca.* 0.1 - 0.15 ppm in relation to the *meta* and *para* analogues. The observed downfield shift of the signals may be due to a deshielding effect of the neighbouring aromatic ring. The deshielding effect can be observed only in the case of the flattening of a C-3 - C-4 - C-10 fragment of the boat conformer **A**. Further evidence for the flattening of this fragment is backed up by the value of geminal coupling constants $^2J(4,4)$ for **2c, 2f,** and **2j**, which is slightly higher (by 0.3 - 0.6 Hz) in comparison with the respective meta and para derivatives. The value of the geminal coupling constant depends on the angle between the π orbital of the aromatic ring or the carbonyl group and the C-H bond[20,21]. This angle in the flattened conformation of the heterocyclic ring is ca. 30°, where $^2J(4,4)$ reaches the maximum.

It is well-known that the homoallylic coupling constants $^5J(1,4)$ depend on the relative orientation of the coupled protons. The following order J(ax,ax) > J(ax,eq) >> J(eq,eq)

Table 2: ^{13}C Chemical shift of the 1-C and 3-CO atoms, and ranges of the skeleton carbon atoms 4 - 10

No.	δ (ppm)[a]		Carbon atom	δ (ppm)[a]
	1-C	3-CO		
2a	58.6	169.8	4	36.3 - 35.5
	(60.0)	(171.1)		(36.5 - 35.9)
2b	57.9	169.8	5	128.1 - 127.3
	(59.4)	(171.3)		(128.4 - 127.7)
2c	55.9	169.2	6	127.9 - 126.9
	(56.6)	(170.4)		(128.3 - 127.4)
2d	58.0	169.8	7	127.4 - 126.5
	(59.5)	(171.2)		(127.2 - 126.6)
2e	57.9	169.4	8	126.7 - 126.3
	(59.3)	(171.1)		(127.2 - 126.5)
2f	56.0	169.3	9	136.2 - 133.6
	(57.5)	(170.6)		(135.6 - 135.0)
2g	58.7	169.8	10	132.1 - 131.7
	(60.1)	(171.0)		(132.8 - 131.2)
2h	58.4	169.8		
	(59.8)	(171.1)		
2i	58.2	169.8		
	(59.6)	(170.9)		
2j	53.7	169.0		
	(55.1)	(169.9)		
2k	57.7	169.9		
	(59.4)	(171.1)		
2l	58.0	169.9		
	(59.4)	(171.2)		

[a] Downfield from TMS, in DMSO-d_6 solution; data in parentheses for solutions in $CDCl_3$.

was established for systems with aromatic bonds, with typical values of 2.5, 1.5, and 0.5 Hz, respectively[21-23]. *Tóth* et al. quoted a value of *cis* $^5J(1,4)$ = 1.9 Hz, obtained for compound **2a**[14]. On the other hand, we observed a homoallylic coupling constant $^5J(1,4)$ = 1.5 Hz, yet only in the *ortho*-substituted derivatives **2c**, **2f**, and **2j** (Table 1). This finding supports our conclusion that compounds **2c**, **2f**, and **2j** exist predominantly in conformation **A** with a flattened C-3 - C-4 - C-10 fragment where the 4-H_{ax} atom is deviated from the axial position. Nevertheless, the other investigated derivatives would rather exist in conformation **B**, since the *cis* ^5J(1eq,4eq) and *trans* ^5J(1eq,4ax) coupling constants are not observed, thus it can be assumed that their values are lower than 1 Hz.

The value of the 8-H atom chemical shift is also indicative of the steric arrangement of the 1-aryl group. The 8-H resonance signal in the ortho substituted derivatives is shifted upfield by at least 0.2 ppm in relation to their *meta* and *para* analogues. It means that the 8-H atom in **2c**, **2f**, and **2j** is shielded by the quasi equatorial 1-aryl group, since the planes of the two aromatic rings are nearly perpendicular[14].

The ^{13}C-NMR spectra of the investigated compounds **2a-l**, recorded for both $CDCl_3$ and DMSO-d_6 solution, are very similar (Table 2). The signals of the 1,4-dihydro-3(2*H*)-isoquinolinone skeleton carbon atoms 4-10 (Table 2) and the 1-aryl substituent were found at their typical values and within a narrow range from those values expected[14,24]. The C-1 resonance signal is almost insensitive to the electronic nature of the 1-phenyl group substitents. However, this signal is shifted upfield by 2.0 - 4.3 ppm in compounds **2c**, **2f**, and **2j** (Table 2), owing to a steric hindrance of the *ortho*-substituted 1-phenyl group. The 3-CO chemical shifts support the conclusion drawn from the ^{1}H-NMR spectra that the amide bond in the derivatives **2c**, **2g**, and **2j** is not planar. The conjugation within the amide bond decreases for a non-planar conformation, since the 3-CO signal shifts upfield by 0.5 - 0.9 ppm in DMSO-d_6 solution, and by 0.4 - 1.3 ppm for solution in $CDCl_3$ (Table 2).

In conclusion, the results of our present investigation clearly indicate that 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**2a**) and its *meta*- and *para*-substituted derivatives in the phenyl ring (**2b**, **2d**, **2e**, **2g-2i**, **2k**, **2l**) exist predominantly in conformation **B** (Fig. 1). However, the *ortho*-substituted derivatives **2c**, **2f**, and **2j** assume the conformation shown in Fig. 3. In this conformation the 1-aryl group is

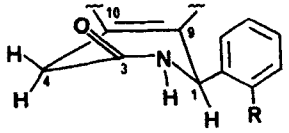


Fig. 3: Observed conformation of the compounds **2c**, **2f**, and **2j**.

nearly perpendicular to the fused aromatic ring and is placed on the quasiequatorial position of the flattened (at the C-3 - C-4 - C-10 fragment) boat conformation of the heterocyclic ring with a twisted amide bond.

Experimental Part

Materials and apparatus: syntheses of the investigated compounds are described: **1a**[7], **1c-e**, **1h-l**[5], **1f,g,j**, **2f,g,j,l**[8], and **2a**, **c-e,h,k**[6].- Uncorrected m.p.s: Boetius apparatus (Analytic, Dresden).- Elemental analyses: Institute of Organic Chemistry, PAS, Warsaw.- ^{13}C-NMR spectra: Bruker 300; 75.47 MHz, DMSO-d_6, and Tesla BS 55672; 25 MHz, $CDCl_3$.- ^{1}H-NMR spectra: Bruker 300, 300 MHz, $CDCl_3$, TMS as internal standard.- Mass spectra: LKB 9005.

Preparation of bis[phenylacetamides] (**1**)

To a mixture of glacial acetic acid (10 ml) and 1 ml of conc. H_2SO_4 were added 0.05 mol of the appropriate aldehyde under stirring; then the mixture was left at a room temp. for 10 min and then phenylacetamide (13.5 g, 0.1 mol) was added. The mixture was left for 24 h at a room temp. and was then diluted with water (50 ml). The precipitate was filtered off and washed with water and acetone. The crude product was recrystallized from ethanol.

N,N'-(4'-Bromophenyl)-bis[phenylacetamide] (**1b**)

Colourless crystals, 18.5 g (84%), m.p. 248-250°C.- $C_{23}H_{21}BrN_2O_2$ (437.3) Calcd. C 63.2 H 4.8 N 6.4 Found C 63.2 H 4.7 N 6.5.

N,N'-[4'-(Dimethylamino)phenyl]-bis[phenylacetamide] (**1i**)

Pale yellow crystals, m.p. 209-212°C (decomp.).- $C_{25}H_{27}N_3O_2$ (401.5) Calcd. C 74.8 H 6.8 N 10.5 Found C 74.6 H 6.8 N 10.5.

Preparation of derivatives **2**

A suspension of **1** (0.015 mol) in PPA[6] (110 g) was stirred for 5 h at a room temp. and was then left overnight. The mixture was poured into water (400 ml), adjusted to pH 8 with 25% ammonia, heated to boiling, and the precipitate was filtered off. The crude product was washed with hot water and recrystallized from ethanol.

1-(4'-Bromophenyl)-1,4-dihydro-3(2H)-isoquinolinone(**2b**)

Colourless crystals, 2.5 g (55%), m.p. 191-193°C.- $C_{15}H_{12}BrNO$ (302.2) Calcd. C 59.6 H 4.0 N 4.6 Found C 59.7 H 3.8 N 4.7.- MS (70 eV): m/z = 301 (27, M^+; ^{79}Br), 300 (12), 272 (3), 146 (100), 118 (24).

1-[4'-(N,N'-Dimethylamino)phenyl]-1,4-dihydro-3(2H)-isoquinolinone(**2i**)

Pale yellow crystals, 3.1 g (78%), m.p. 178-180°C.- $C_{17}H_{18}N_2O$ (266.3) Calcd. C 76.7 H 6.8 N 10.5 Found C 76.8 H 6.8 N 10.6.- MS (70 eV): m/z = 266 (100, M^+), 265 (44), 237 (3), 146 (12), 118 (6).

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