Stereochemistry of 1,3-Dipolar-cycloaddition of 3,4-Dihydro-isoquinoline- and 3,4-Dihydro-carboline-*N*-methoxycarbonyl- and *N*-Phenacyl-methylides with Maleic and Fumaric Nitrile

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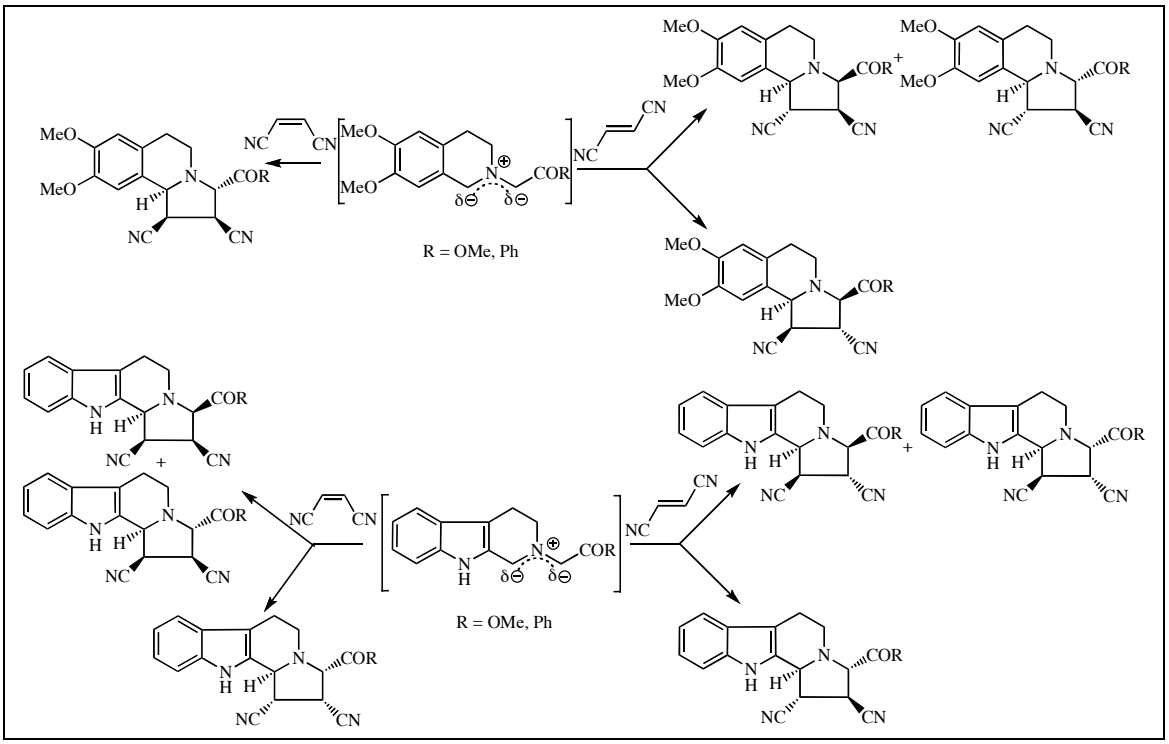
Dedicated to Professor Albert Lévai (University of Debrecen, Hungary) on the ocassion of his 65th birthday



The 1,3-dipolar-cycloadditions of two kind of isoquinolinium and carbolinium ylides with fumaric and maleic nitrile resulted in pyrroloisoquinoline and indolizino[8,7-*b*]indole derivatives, respectively, which are analogues of biologically active alkaloids. The cycloadditions were performed in good yield and proved to be stereoselective. The structure elucidation and complete ^{1}H and ^{13}C assignments have been achieved by a combination of various one- and two-dimensional NMR experiments.

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INTRODUCTION

In the last decade new pyrroloisoquinoline and indolizino[8,7-*b*]indole alkaloids, having cytotoxic and other biologic activity, were isolated from *Carduus crispus* and *Kopsia griffithii*, respectively, by Chinese [1] and Malaysian [2] groups. At the same time Poissonnet *et al.* reported on 1,2-dicyano substituted analogues of the latter alkaloids with considerable anti-leukemic activity [3]. Considering these effects this class of compounds seems to be promising also from biological aspects.

Earlier we reported the 1,3-cycloaddition of azomethine-ylide **3a**, obtained with the deprotonation method [4] from the quaternary isoquinoline salt **2a** in the presence of organic base, with several dipolarophiles and studied the stereochemistry of the cycloadducts [5-15]. In most cases the deprotonation method proved to be the best preparative way to obtain cyclic azomethine ylides, therefore we decided to continue these studies utilising this method. In our present report, the 1,3-dipolar-cycloaddition of ylide **2a** with both stereoisomers of the powerful dipolarophile 1,2-dicyano-ethylene: the maleic

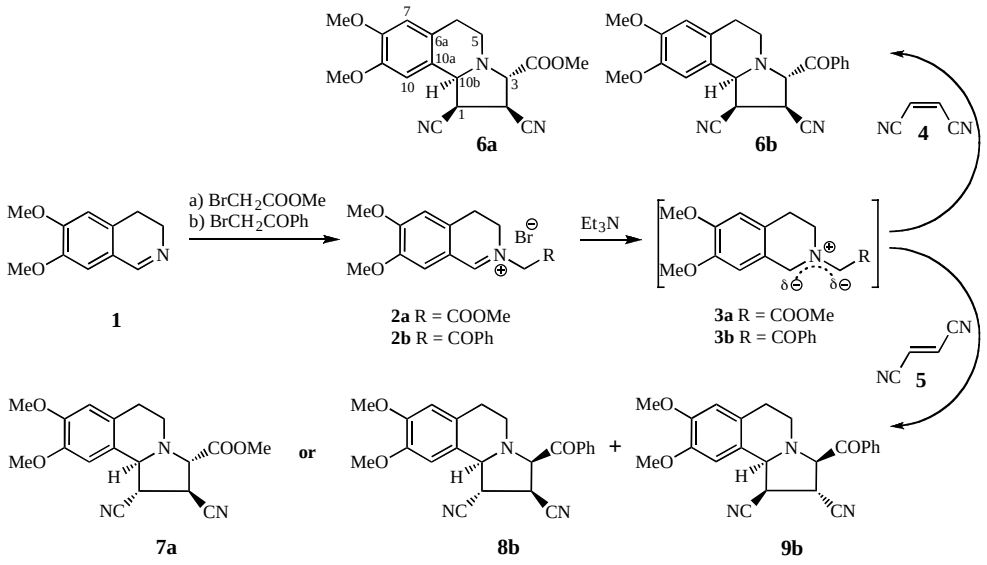
(**4**) and fumaric nitrile (**5**) have been investigated resulting the isomers **6a** and **7a**, and in the frame of our ongoing program to synthesize biologically active alkaloid analogues, we aimed at extending the cycloaddition studies to other quaternization agents and other cyclic azomethines (Scheme 1).

RESULTS AND DISCUSSION

The deprotonation method for the preparation of stabilized cyclic azomethine ylides is one of the most direct routes of generating 1,3-dipoles. At first Huisgen [16] applied this approach in the study of 1,3-dipolar cycloaddition of *N*-phenacyl-3,4-dihydro-isoquinolinium ylides. Despite the considerable advantages of this method in the next years it was relatively sparsely applied: only Tsuge *et al.* used it also for the preparation of isoquinolinium ylides [17], then Potaček [18] and Sliwa [19] applied it for the synthesis of phenantridinium and benzo[*h*]napthyridinium ylides, respectively. It is worth mentioning some other less direct synthetic routes, which were also applied for the preparation of non-stabilized cyclic azomethine ylides by Poissonnet (desylilation route [3]), and Novikov (difluoro-carbene addition route [20]) and for stabilized cyclic ylides by Grigg (dehydrogenation route [21]). The cited authors [3,16-21] studied the 1,3-dipolar cycloaddition reactions of the so prepared cyclic azomethine ylides with activated olefines *e.g.* maleic imides, fumaric and maleic esters and even with fumaric nitrile [18], but none of them examined the cycloadditions of stabilized dihydro-isoquinoline and carboline ylides with maleic and fumaric nitriles and in most cases the investigations were not extended to thorough stereochemical studies applying one- and two dimensional NMR methodes.

As it was outlined in the introduction first we extended our quaternization-deprotonation sequence to a quaternization reagent, the phenacyl bromide, which was not applied by us earlier. Thus, we quaternized 3,4-dihydro-6,7-dimethoxy-isoquinoline (**1**) with phenacyl-bromide to **2b** from which ylide **3b** could be prepared *in situ* with triethylamine and latter was reacted immediately with the desired dipolarophiles **4** and **5**. The obtained cycloadducts were **6b, 8b** and **9b**, respectively. The reactions resulted racemates but for the sake of clarity only one enantiomer with H-10b in 'α' position is shown.

Scheme 1



Synthesis of pyrroloisoquinoline derivatives **6-9** (racemate).

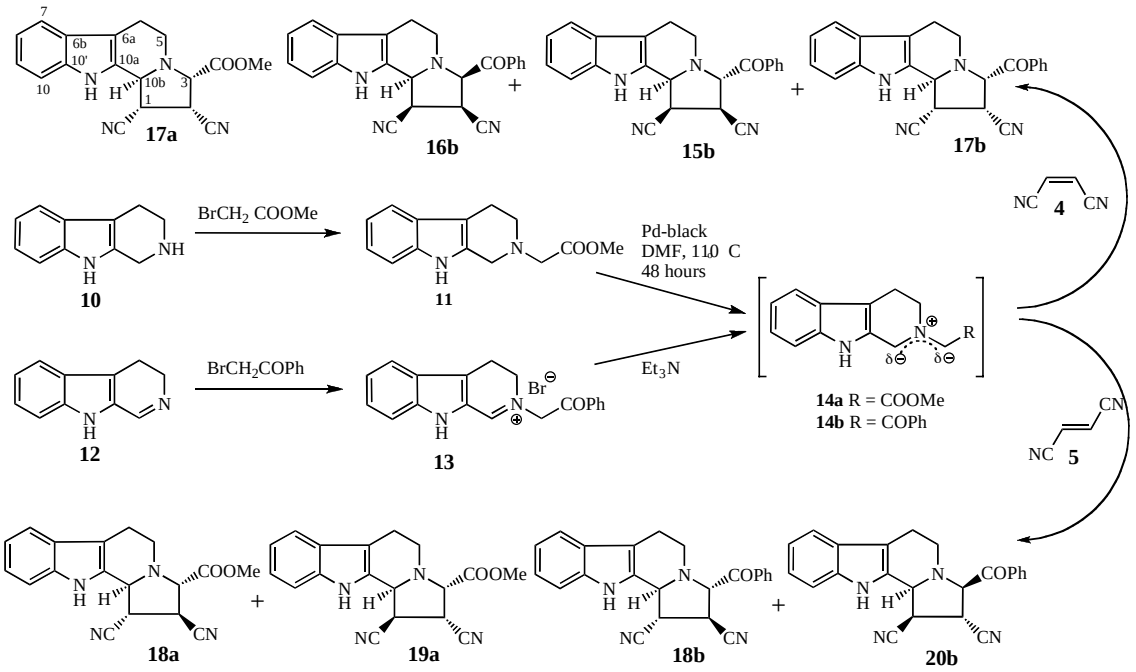
As a further extension of our studies to 3,4-dihydro-carboline ylides, we used the dehydrogenation method [21] for the preparation of the methoxycarbonyl-derivera-tive because in this case the use of the deprotonation method failed. The starting material for the dehydro-genation method, tetrahydro-carboline derivative **11** could be synthesized from tetrahydro-ß-carboline **10** and methyl bromoacetate in dimethyl-formamide. The ylide **14a** could be obtained *in situ* in dimethyl-formamide in the presence of Pd-black at 110 °C. Dipolarophiles **4** and **5** were added at the beginning of the reaction which was continued for 48 hours at 110 °C and the reaction yielded isomers **17a, 18a** and **19a**, respectively (Scheme 2).

Finally the 3,4-dihydro-ß-carboline (**12**) was easily quaternized with phenacyl-bromide to **13**, which was then deprotonated with triethylamine *in situ* to the ylide **14b** in the presence of the desired dipolarophiles **4** and **5**. These reactions gave the isomers **16b, 15b, 17b** and **18b, 20b**,

respectively. It should be mentioned that for these compounds we applied a special not IUPAC numbering to allow the easy comparison of the NMR data of pyrroloisoquinoline and indolizino[8,7-*b*]indole derivatives.

equilibrium should be taken into account as it is shown on the example of indolizino[8,7-*b*]indole (**15b**-**20b**) derivatives (Figure 1). We accomplished a conformational examination with the help of the program HyperChem 7.0.

Scheme 2



Synthesis of indolizino[8,7-*b*]indole derivatives **15**-**20** (racemate).

When only one isomer was formed during the reaction, it was isolated by extraction with benzene, in other cases column chromatography was used to separate and isolate the products. At any time, when dehydrogenation method was used to perform the cycloaddition, the yields always surpassed that of the deprotonation method, a plausible reason could be that the latter way utilizes milder conditions.

STRUCTURE ELUCIDATION

The structures of products were determined with comprehensive one- and two-dimensional NMR methods using widely accepted strategies [22, 23]. To alleviate the characterization of diastereomers we introduced the abbreviation including the α or β position of the hydrogen atoms H-10b, H-1, H-2, H-3. Characteristic ^{1}H and ^{13}C NMR data were collected in Tables 1-3. The structure elucidation was particularly challenging since the resulting pyrroloisoquinoline (**6a**-**9b**) and indolizino[8,7-*b*]indole (**15b**-**20b**) derivatives besides four stereogenic centres, also incorporate a bridgehead nitrogen in a relatively flexible skeleton. Thus as we discussed previously [7,9,11] due to nitrogen and ring inversions for the junctions of the six-membered and five-membered rings the existence of a triple *trans* ⇆ *cis*-1 ⇆ *cis*-2 type conformational

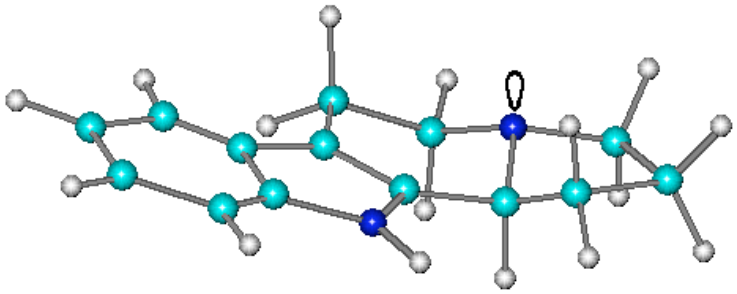
In the *trans* conformation the lone electron pair of the nitrogen atom between the six- and five-membered rings is in an antiperiplanar position to the 10b-hydrogen, whereas its arrangement is gauche in *cis*-1 and *cis*-2. Inversion of the pyramidal nitrogen atom in the *trans* conformer leads to the *cis*-1 conformer in which the C-3 atom is axial with respect to the six-membered ring resulting the characteristic ~5 ppm γ-gauche upfield shift at C-6. Ring inversion of the *cis*-1 conformer results in formation of *cis*-2. The pseudorotation of the five-membered ring renders possible the coexistence of several conformations at this ring. Differentiation of the *trans* and *cis*-2 conformers can be achieved utilizing the H_{α}-10b/H_{α}-5 steric proximity detected by NOE response in conformer *trans*. Detection of H_{β}-5/H_{β}-1 or H_{β}-5/H_{β}-2 NOE cross-peaks prove the *cis*-2 conformation, but it should be mentioned, that in several cases the absence of these cross-peaks can be explained with pseudorotation of the five-membered ring of the *cis*-2 conformer. The H_{α}-5 and H_{β}-6 hydrogen atoms are diaxial in the *trans* and *cis*-1 conformers and the corresponding $^{3}J_{H,H}$ coupling is about 10-11 Hz, whereas these hydrogens are diequatorial arranged in *cis*-2 resulting a ~ 3 Hz coupling. Detection of an averaged $^{3}J_{H,H}$ value of the *trans* arranged H-5 and H-6 atoms indicates a conformation equilibrium with a considerable appearance of

cis-2 conformer, as it was observed in case of compounds **6a**, **7a** and **9b** (Table 1). According to our investigations compounds **6b** and **8b** appeared predominantly in *cis*-2 conformer. It is worth mentioning that the chemical shifts of C-6 in **7a** (26.7 ppm) is *ca*. 1.5 ppm smaller than in compounds **6a, 6b**, **8b** and **9b**, may be indicative of the participation of *cis*-1 in the equilibrium.

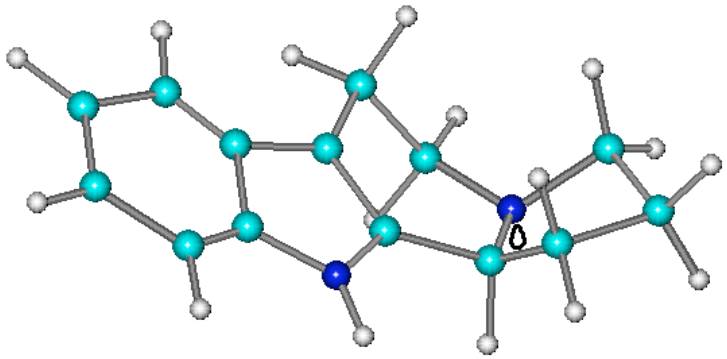
It was found that the characteristic ^{13}C chemical shift of C-6 in the indolizino[8,7-*b*]indole derivatives is 21.5 ppm (Table 2) for the *trans* and *cis*-2 conformers (**15b**, **16b**), whereas in case of *cis*-1 it is only 16.5 ppm (**19a**). These chemical shifts are in good agreement with the data obtained for indolo[2,3-*a*]quinolizine derivatives [24]. The δC-6: 19.5 ppm in compound **18a** proves the existence of *cis*-1 in the conformational equilibrium with *cis*-2 and *trans*. Compound **17a** should exist in an equilibrium of *cis-1*/*trans*, in accordance with the value of δC-6: 18.2 ppm and with the strong NOE response of H_{α}-5/Hα-10b. We were prompted to investigate the temperature dependence of this equilibrium.

Lowering the temperature from 300K till 215K we didn't observed a coalescence, but the equilibrium shifted strongly to the site of *cis*-1 as it follows from the value of δC-6: 16.4 ppm, which is in good agreement with the value measured for **19a**.

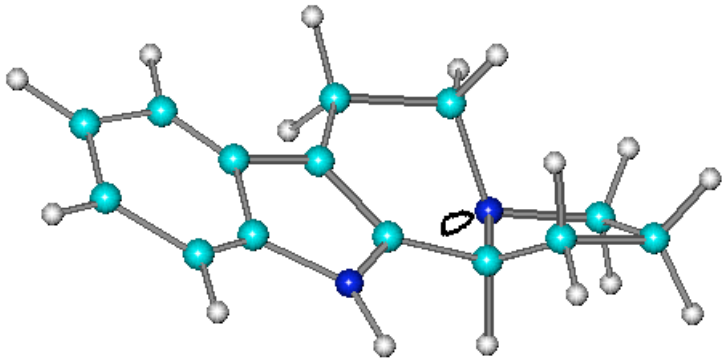
The characteristic NMR data of the indolizino[8,7-*b*]-indole derivatives with R = COPh substituent are summarized in Table 3.



trans



cis-1



cis-2

Figure 1. Conformational equilibrium of the indolizino[8,7-*b*]indole skeleton.

Table 1

Chemical shifts and coupling constants of cycloadducts **6-9** in DMSO-d_6.

	6a			**7a**			**6b**				**8b**			**9b**			
		aaaβ			*αβαβ*			*aaaβ*				*αβαα*			*aaβα*		
		cis2/trans			**cis2/trans**			**cis2**				**cis-2**			**cis2/trans**		
	^{1}**H**	$^3J_{H,H}$	^{13}**C**	$^1J_{C,H}$	^{1}**H**	$^3J_{H,H}$	^{13}**C**	$^1J_{C,H}$	^{1}**H**	$^3J_{H,H}$	^{13}**C**	$^1J_{C,H}$	^{1}**H**	$^3J_{H,H}$	^{13}**C**	$^1J_{C,H}$	^{1}**H**	$^3J_{H,H}$	^{13}**C**	$^1J_{C,H}$
1	4.48 (α)	dd; 8.1, 5.5	39.05		3.91 (β)	dd; 8.5, 8.1	38.0	146	4.48 (α)	dd; 9.5, 6.5	39.7	152	4.02 (β)	dd; 9.4, 7.4	38.7	145	4.47 (α)	dd; 8.0, 7.0	38.9	147
2	4.19 (α)	dd; 8.1, 5.8	34.1		4.17 (α)	dd; 8.1, 5.4	34.2	145	4.44 (α)	dd; 9.5, 3.0	32.4	150	4.32 (α)	dd; 7.4, 2.8	32.1	143	4.38 (β)	t; 7.0	32.4	141
3	4.33 (β)	d; 5.8	67.7		4.22 (β)	d; 5.4	68.05	145	5.49 (β)	d; 3.0	72.5	146	5.40 (α)	d; 2.8	72.9	147	5.54 (α)	d; 7.0	70.1	147
5	2.97 (α)	ddd; 11.4, 6.4, 4.8	45.8		3.00	m	46.1		3.23 (β)	ddd; 11.3, 9.9, 4.5	46.6		3.01 (β)	ddd; 11.3, 10.7, 4.6	46.4		2.87 (β)	dt; 11.4, 6.5	46.6	
	3.14 (β)	ddd; 11.4, 6.7, 4.8			3.01	m			3.38 (α)	ddd; 11.3, 4.6, 3.7			3.44 (α)	ddd; 11.3, 4.7, 2.6			3.21 (α)	dt; 11.4, 4.3		
6	2.72	ddd; 15.8, 6.7, 4.8	28.25		2.67	ddd; 16.4, 6.9, 6.0	26.7		2.74	m	28.8		2.72	m	28.5		2.74	m	28.5	
	2.795	ddd; 15.8, 6.4, 4.8			2.78	dt; 16.4, 5.2			2.77	m			2.76	m			2.74	m		
6a	-		127.0		-		126.6		-		126.4		-		125.6				126.5	
7	6.77	s	111.6		6.77	s	111.9		6.73	s	111.4		6.75	s	111.8		6.72	s	111.3	
8	-		148.0		-		148.4		-		148.2		-		148.4		-		148.1	
9	-		147.35		-		147.2		-		147.4		-		147.1		-		147.4	
10	6.85	s	110.2		6.86	s	109.6		6.89	s	110.8		6.82	s	109.8		6.95		111.3	
10a	-		123.7		-		123.8		-		123.2		-		123.1		-		123.2	
10b	4.30 (α)	d; 5.5	61.5	149	4.365 (α)	d; 8.5	63.7	148	4.09 (α)	d; 6.5	62.3	147	3.98 (α)	d; 9.4	63.8	148	4.42 (α)	d; 8.0	62.0	148
1-CN	-		118.0		-		119.2		-		118.9		-		119.7		-		119.6	
2-CN	-		118.5		-		118.9		-		120.0		-		120.2		-		118.4	
3-COOMe	-		170.1		-		170.0													
3-COOMe	3.717	s	52.4		3.72	s	52.6													
8-OMe	3.745	s	55.3		3.74	s	55.5		3.72	s	55.4		3.72	s	55.5		3.72	s	55.7	
9-OMe	3.724	s	55.7		3.72	s	55.5		3.70	s	55.7		3.70	s	55.4		3.70	s	55.4	
Ph-C=O									-		194.5		-		193.5		-		194.4	
Ph-ipso									-		134.9		-		134.6		-		134.7	
Ph-orto									8.08	d; 7.5	129.3		8.10	d; 7.5	129.2		8.07	d;	129.0	
Ph-meta									7.55	t; 7.7	128.8		7.55	t; 7.8	128.6		7.57	t;	129.0	
Ph-para									7.66	t; 7.4	133.8		7.67	t; 7.3	133.6		7.69	t;	134.2	

Table 2

Chemical shifts and coupling constants of cycloadducts **17a-19a** in $CDCl_3$.

	17a **300K** αβββ **cis1/trans**				**17a** **215K**		**18a** αβαβ **cis2/cis1/trans**				**19a** αααββ **cis1**			
	^{1}H	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**^{13}C**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**
1	3.49 (β)	dd; 7.8, 5.8	37.0		3.76	36.8	3.37 (β)	d; 8.1, 7.5	37.6	145	3.97 (α)	dd; 10.8, 6.4	35.5	145
2	3.69 (β)	dd; 8.2, 7.8	34.7		3.60	34.0	3.91 (α)	d; 8.1, 5.6	35.4	144	3.41 (β)	dd; 10.8, 9.3	34.1	144
3	4.09 (β)	d; 8.2	64.4	144	4.03	52.8	4.11 (β)	d; 5.6	67.6	145	4.10 (β)	d; 9.3	58.8	145
5	3.21		45.6		3.23	44.6	3.22		46.8		3.15 (α)	ddd; 14.1, 11.2, 4.6	45.0	
	3.21				3.26		3.22				3.35 (β)	ddd; 14.1, 5.2, 1.5		
6	2.75 (α)		18.2		2.71	16.4	2.83 (α)		19.5		2.72 (α)	dddd; 16.4, 4.6, 1.8, 1.5	16.5	
	2.85 (β)				2.89		2.86 (β)				3.00 (β)	dddd; 16.4, 11.2, 5.2, 1.8		
6a	-		110.2		-	110.0	-		128.8		-		112.7	
6b	-		126.3		-	126.0	-		126.1		-		126.6	
7	7.49		118.5		7.49	118.4	7.50		118.6		7.53		118.5	
8	7.13		120.1		7.11	119.8	7.14		120.0		7.16		120.2	
9	7.21		123.0		7.17	122.8	7.22		122.9		7.26		123.5	
10	7.38		111.5		7.36	111.5	7.37		111.4		7.40		111.6	
10’	-		136.6		-	136.0	-		136.6		-		136.6	
10a	-		128.8		-	128.0	-		128.2		-		126.3	
10b	5.07 (α)	d; 5.8	60.8	152	5.16	61.0	4.71 (α)	d; 7.5	61.5	149	5.02 (α)	dt; 6.4, 1.8	61.7	152
1-CN	-		117.2		-		-		117.4		-		116.8	
2-CN	-		115.4		-		-		117.7		-		115.3	
NH	8.34	s	-		8.69	-	8.36	s	-		8.35	s	-	
3-**C**OOMe	-		169.0		-		-		169.6		-		169.9	
3-COO**Me**	3.89	s	53.0		3.87	53.4	3.88	s	53.3		3.89	s	53.0	

Table 3s

Chemical shifts and coupling constants of cycloadducts **15-20** in DMSO-d_6.

	15b	αααβ cis2			**16b**	αααα trans			**17b**	αββββ cis2			**18b**	αβαβ cis2			**20b**	αaβα cis2		
	^{1}H	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**	**^{1}H**	**$^3J_{H,H}$**	**^{13}C**	**$^1J_{C,H}$**
1	4.31 (α)	dd; 9.3, 7.0	38.5		4.32 (α)	dd; 8.6, 5.3	36.2		4.16 (β)	dd; 7.7, 6.7	37.2		4.16 (β)	dd; 7.8, 6.6	37.3		4.13 (α)	dd; 8.3, 7.3	37.7	146.4
2	4.50 (α)	dd; 9.3, 3.2	33.5		4.64 (α)	dd; 9.4, 8.6	34.5		4.31 (β)	dd; 6.7; 3.1	33.4		4.41 (α)	dd; 6.6, 2.9	33.4		4.506 (β)	dd; 7.3, 7.0	32.75	142.0
3	5.57 (β)	d; 3.2	71.3	146	4.725 (α)	d; 9.4	66.8	43	5.35 (β)	d; 3.1	70.7	145	5.40 (β)	d; 2.9	70.8	145	5.63 (α)	d; 7.0	69.2	146.4
5	3.34	ddd; 11.3, 9.7, 4.1	47.5		2.52 (α)	td; 11.1, 4.2	46.46		3.10	ddd; 11.9, 9.1, 4.1	46.9		3.17	ddd; 11.5, 9.2, 4.1	47.0		3.02 (β)		47.6	
	3.51	dd; 11.3; 5.2; 3.6			3.25 (β)	ddd; 11.1, 6.1, 1.0			3.48	ddd; 11.9; 5.5, 4.1			3.52	ddd; 11.5, 5.4, 4.8			3.37 (α)			
6	2.69	ddd; 15.4; 9.7, 5.2	21.4		2.72 (α)	dd; 15.1, 4.2	21.5		2.65	ddd; 15.9, 9.1, 5.5	20.2		2.71	ddd; 15.8, 9.2, 5.4	20.2		2.71 (α)		20.9	
	2.86	ddd; 15.4; 4.1, 3.6			2.91 (β)	dddd; 15.1, 11.1, 6.1, 2.0			2.87	dt; 15.9, 4.1			2.89	ddd; 15.8, 4.8, 4.1			2.85 (β)			
6a	-		108.6		-		108.8		-		108.0		-		107.9		-		108.65	
6b	-		125.8		-		126.3		-		125.9		-		125.9		-		125.7	
7	7.45	d; 7.8	118.2		7.46	d; 7.8	118.1		7.42	d; 7.8	118.2		7.45		118.2		7.445	d; 7.8	118.16	
8	7.00	t; 7.8	118.7		7.02	dd; 7.8, 7.0	118.7		6.98	dd; 7.8, 7.2	118.9		7.03	t; 7.6	118.9		6.99	ddd; 7.8, 7.0, 0.9	118.6	
9	7.10	dd; 8.1, 7.8	121.5		7.11	dd; 8.2, 7.0	121.2		7.08	dd; 8.1, 7.2	121.7		7.14	t; 7.6	121.6		7.09	ddd; 8.1, 7.0, 1.1	121.45	
10	7.38	d; 8.1	111.4		7.41	d; 8.2	111.3		7.37	d; 8.1	111.8		7.45		111.8		7.39	dt; 8.1, 0.9	111.4	
10’	-		136.4		-		136.0		-		136.8				136.8		-		136.4	
10a	-		129.2		-		130.1		-		129.4		-		129.4		-		129.0	
10b	4.26 (α)	d; 7.0	59.0	148	3.96 (α)	d; 5.3	60.4	38	4.29 (α)	d; 7.7	61.2	149	4.38 (α)	d; 7.8	61.3	148	4.58 (α)	d; 8.3	58.8	149.3
1-CN	-		118.3		-		117.6		-		118.9		-		118.8		-		118.8	
2-CN	-		119.8		-		117.3		-		120.0		-		119.9		-		118.1	
NH	10.91		-		11.16		-		10.9		-		10.94	s	-		10.82	s	-	
Ph-C=O	-		194.5		-		194.0		-		194.1		-		193.9		-		194.35	
Ph-ipso	-		134.8		-		135.5		-		134.9		-		134.9		-		134.5	
Ph-orto	8.11	d; 7.5	129.2		8.115	d; 7.6	128.4		8.10	d; 7.7	129.2		8.14	d; 8.0	129.2		8.11	dd; 8.5, 1.2	129.1	
Ph-meta	7.57	t; 7.7	128.7		7.61	t; 7.7	129.0		7.57	t; 7.7	128.8		7.57	t; 7.7	128.7		7.59	t; 7.8	128.9	
Ph-para	7.68	t; 7.4	133.7		7.73	t; 7.4	134.1		7.68	t; 7.4	133.8		7.67	t; 7.3	133.7		7.71	tt; 7.5, 1.2	134.1	

The only derivative with the relative configuration at C-10b/C-1/C-2/C-3 atoms, containing the hydrogen atoms in αααα positions is **16b**, and it exhibits *trans* conformation most probably due to sterical reason. In the case of the cycloadducts **15b, 16b**, and **17b** the following statements can be settled: the *cis*-1 conformer can be excluded because of the value of the chemical shift of the C-6 atom; the characteristic shift of the C-6 atom in case of the *cis*-1 conformer is between 15-16 ppm, but in contrast, the chemical shifts for the cycloadducts are about 21 ppm. The missing spatial proximity between the H-10b and H_{ax}-5 nuclei and the steric proximity between the H-1 and H_{ax}-5 nuclei – which is characteristic for *cis*-2 – prove the fact that the compounds **15b** and **17b** are mainly in the *cis*-2 conformer.

It is known that the *trans* orientation of the lone pair of the nitrogen atom has a specific influence on the $^1J_{C,H}$ coupling constants and this can be utilized for the determination of the relative configuration of the NC-H hydrogens and of the lone pair [25]. For the analogous pyrroloisoquinolines we detected values of $^1J_{C,H}$ = 135-138 Hz in the *trans*, whereas 147-149 Hz couplings appeared for *cis*-1 and *cis*-2 conformers [10,11]. We measured $^1J_{C\text{-}10b,H\text{-}10b}$ = 138 Hz, which gives further support to the *trans* conformation of compound **16b**.

EXPERIMENTAL

We have reacted two kinds of isoquinolinium and carbolinium ylides with fumaric and maleic nitrile. The reactions were performed in a good (*ca*. 75-80 %) yield, which makes this method a competent way to synthesize such compounds in mild conditions. The cycloadditions were proved to be stereoselective according to the Woodward-Hoffmann rules. The product ratios of the reaction **14b** with **4** were determined by HPLC and also by ^{1}H NMR methods resulting in good agreement 4:1:1 for compounds **16b**, **15b**, **17b**. The product ratios of the other cycloadditions were evaluated by ^{1}H NMR method. Melting points were determined with a Büchi 510-apparatus and are uncorrected. The IR spectra were measured on a Perkin Elmer 1600 FT-IR. The tlc performed on Kieselgel 60 F_{254} (Merck) layer using 1:1 mixture of hexane and ethyl acetate.

The NMR spectra were recorded on BRUKER Avance DRX-500 and Bruker Avance 500 MHz spectrometers. Chemical shifts were determined on δ-scale. For structure elucidation and ^{1}H/^{13}C NMR signal assignment one-dimensional ^{1}H, ^{13}C, APT, DEPT-135, selective 1D-NOESY, selective 1D-ROESY and two-dimensional gradient selected ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMQC, ^{1}H,^{13}C-HMBC, ^{1}H,^{1}H-NOESY and ^{1}H,^{1}H-ROESY spectra were run. The $^1J_{C,H}$ couplings were obtained from the ^{1}H coupled HSQC or HMQC experiments. In case of some selective 1D-NOESY and -ROESY measurements a few drops of benzene-d_6 were added to achieve an appropriate signal dispersion of the hydrogen signals of the five membered ring.

3,4-dihydro-6,7-dimetoxy-*N*-(benzoylmethyl)-isoquinolinium bromide (2b). 3,4-Dihydro-6,7-dimethoxy-isoquinoline (**1**) (1.00 g, 5.23 mmol) was dissolved in acetonitrile (5 mL), and phenacyl-bromide (1.04 g, 5.23 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 6 hours, and the precipitated material was collected by filtration. Yield: 1.05 g (51 %), yellow solid, mp.: 191-198 °C. *Anal*. Calcd. for $C_{19}H_{20}BrNO_3$: C, 58.47; H, 5.17; N, 3.59; found: C, 58.53; H, 5.20; N, 3.52.

Preparation of cycloadducts 6a and 7a. A mixture of 3,4-dihydro-6,7-dimethoxy-*N*-(carbomethoxymethyl)-isoquinolinium bromide (**2a**) (0.3000 g, 0.872 mmol) and maleic nitrile (**4**) or fumaric nitrile (**5**) (0.0681 g, 0.872 mmol) were dissolved in chloroform (10 mL), and triethylamine (0.25 mL, 1.83 mmol) was added to the mixture, which was stirred then for 24 hours at room temperature, the solvents were removed *in vacuo*. In case of both reactions only one isomer was formed, which was isolated then by extracting the reaction mixture residue with benzene. The yield was 77 % in case of maleic nitrile and 79 % in case of fumaric nitrile.

6a: pale yellow solid, mp.: 160-162 °C. *Anal*. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31; found: C, 63.22; H, 5.71; N, 12.36.

7a: yellow solid mp.: 140-142 °C. *Anal*. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31; found: C, 63.23; H, 5.65; N, 12.33.

Preparation of cycloadducts 6b and 8b, 9b: A mixture of 3,4-dihydro-6,7-dimethoxy-*N*-(benzoylmethyl)-isoquinolinium bromide (**2b**) (0.3000 g, 0.872 mmol) and maleic nitrile (**4**) or fumaric nitrile (**5**) (0.0681 g, 0.872 mmol) were dissolved in chloroform (10 mL), and triethylamine (0.25 mL, 1.83 mmol) was added to the mixture, which was stirred then for 24 hours at room temperature, the solvents were removed *in vacuo*. In case of the reaction between **2a** and **4**, only one isomer was formed, which was isolated then by extracting the reaction mixture residue with benzene. When fumaric nitrile (**5**) was used as a dipolarophile, the products were separated by column chromatography on silica eluting with the 1:1 mixture of hexane and ethyl acetate. The combined yield was 76 % in case of maleic nitrile and 82 % in case of fumaric nitrile.

6b: pale yellow solid, mp.: 198-200 °C. *Anal*. Calcd. for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; found: C, 71.31; H, 5.31; N, 10.99.

8b (major compound): yellow solid mp.: 92-94 °C. *Anal*. Calcd. for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; found: C, 71.31; H, 5.31; N, 10.99.

9b (minor compound): yellow solid, mp.: becomes black at 196-200 °C, and does not melt till 240 °C. *Anal*. Calcd. for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; found: C, 71.31; H, 5.31; N, 10.99.

Methyl 1,2,3,4-tetrahydrocarboline-2-ylacetate (11). Tetrahydro-ß-carboline (**10**) (1.72 g, 10 mmol) was dissolved in dry dimethyl formamide (30 mL), freshly dried potassium-carbonate (0.83 g, 6 mmol) was added and the mixture was heated to 80 °C. Then methyl bromoacetate (1.03 mL, 11 mmol) in dry dimethyl formamide (10 mL) was added to the reaction mixture within 30 minutes. The reaction mixture was kept at 80 °C for 4 hours, cooled and poured on ice. After 10 minutes precipitation began to appear, which was then filtered, washed with water and dried in desiccator. Yield: 1.73 g (71 %), yellow solid. mp.: 141-4 °C. mp (recrystallized from methanol): 142-4 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.82 (m, 2H), 3.00 (m, 2H), 3.45 (s, 2H), 3.75 (s, 3H), 7.06-7.13 (m, 2H), 7.24 (m, 1H), 7.45 (d, 1H), 7.87 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 21.1, 49.9, 50.9, 52.0, 58.1, 108.2, 111.0, 118.1, 119.5, 121.6, 127.4, 131.3, 136.3, 171.4 ppm. *Anal*. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; found: C, 68.84; H, 6.52; N, 11.52.

Preparation of the 3,4-dihydro-2-(benzoylmethyl)-ß-carbolinium bromide (13). 3,4-Dihydro-ß-carboline (**12**) (0.5 g, 0.294 mmol) was dissolved in acetonitrile (10 mL), and phenacyl bromide (0,6 g, 0.300 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 2 hours, and the precipitated material was filtered off. Yield: 0.6 g (55 %), yellow solid, mp.: 228-232 °C. ^{1}H-NMR (DMSO-d_6, 500 MHz, δ): 3.16 (t, 2H), 4.15 (t, 2H), 5.88 (s, 2H), 7.21-8.06 (m, 9H), 9.13 (s, 1H), 12.50 (s, 1H) ppm. ^{13}C-NMR (DMSO-d_6, 125 MHz): 19.3, 50.7, 64.7, 113.7, 121.8, 122.2, 123.7, 124.5, 125.7, 128.3, 129.1, 129.4, 133.9, 134.6, 141.9, 157.4, 191.8 ppm. IR (KBr): ν_{NH}: 3408; ν_{CH}: 2833, 2924 and 3050; ν_{CO}: 1702 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{17}BrNO_2$: C, 61.80; H, 4.64; N, 7.59; found: C, 61.83; H, 4.56; N, 7.65.

Preparation of cycloadducts 17a, 18a and 19a. A mixture of methyl 1,2,3,4-tetrahydrocarbolin-2-yl acetate (**11**) (0.30 g, 1.23 mmol), maleic nitrile (**4**) or fumaric nitrile (**5**) (0.10 g, 1.28 mmol) and palladium black (24.6 mg, 0.246 mmol) in dry dimethyl formamide (10 mL) was stirred and heated at 110 °C for 48 hours. The reaction mixture was cooled, diluted with chloroform (10 mL), and filtered. The solvent was removed under reduced pressure to leave a dark brown viscous oil. The products were purified then by column chromatography on silica eluting with the 1:1 mixture of hexane and ethyl acetate. The combined yield was 55 % in case of maleic nitrile and 49 % in case of fumaric nitrile.

17a: yellow solid, mp.: 192-195 °C. *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; found: C, 67.55; H, 5.06; N, 17.45.

18a: yellow solid, mp.: 156-158 °C. *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; found: C, 67.52; H, 5.07; N, 17.52.

19a: yellow solid, mp.: 125-127 °C. *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; found: C, 67.52; H, 5.12; N, 17.54.

Preparation of cycloadducts 16b, 15b, 17b and 18b, 20b: A mixture of 3,4-dihydro-2-(benzoylmethyl)-ß-carbolinium bromide (**13**) (0.3379 g, 0.916 mmol) and maleic nitrile (**4**) or fumaric nitrile (**5**) (0.0715 g, 0.916 mmol) were dissolved in chloroform (15 mL), and triethylamine (0.25 mL, 1.83 mmol) was added to the mixture, which was stirred then for 24 hours at room temperature. During that time, in case of maleic nitrile, **16b** began to precipitate. After filtering it, chloroform was removed from the reaction mixture in *vacuo* leaving a dark viscous oil. The products were separated then by column chromatography on silica eluting with the 1:1 mixture of hexane and ethyl acetate. The combined yield was 80 % in case of maleic nitrile and 85 % in case of fumaric nitrile.

16b (precipitated compound): pale yellow solid, mp.: 222-225 °C. *Anal.* Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29; found: C, 75.35; H, 4.87; N, 15.35.

15b (major compound): yellow oil (can be crystallized with chloroform), mp.: 80-83 °C. *Anal.* Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29; found: C, 75.45; H, 4.89; N, 15.31.

17b (minor compound): yellow solid, mp.: 207-209 °C. *Anal.* Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29; found: C, 75.49; H, 5.05; N, 15.34.

18b (major compound): yellow solid mp.: 124-127 °C. *Anal.* Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29; found: C, 75.25; H, 4.99; N, 15.39.

20b (minor compound): yellow solid, mp.: 162-164 °C. *Anal.* Calcd. for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29; found: C, 75.52; H, 4.93; N, 15.26.

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