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1,3-Dipolar Cycloaddition of 3,4-Dihydro-6,7-dimethoxyisoquinoline-*N*-methoxycarbonyl methylide with Schiff bases

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Abstract

1,3-Dipolar cycloaddition of 3,4-dihydro-6,7-dimethoxyisoquinoline-*N*-methoxycarbonyl methylide to Schiff bases results in the imidazo[2,1-*a*]isoquinolines as single racemates. The cycloadducts obtained are *exo* isomers, with one exception. The only compound with *endo* structure isomerized *via* cycloreversion followed by cycloaddition to the thermodynamically stable *exo* isomer. Structural assignment of the products was achieved by comprehensive two-dimensional NMR methods. Both the *exo* and *endo* isomers exist in a *trans* ⟷ *cis-1* ⟷ *cis*-2 conformational equilibrium.

Keywords : cycloadditions; imines; stereochemistry; NMR

Introduction

Previously we reported the 1,3-cycloaddition of azomethine ylide **2** obtained from the quaternary isoquinoline salt **1** (*N*-methoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxy-isoquinolinium bromide) under basic conditions with olefins, where generally *endo* cycloadducts were formed [1-3]. Another study showed that ylide **2** formed with 3,4-dihydro-6,7-dimethoxy-isoquinolines a dimer with *endo* structure [4]. Further reactions of **2** with Schiff bases resulted in imidazo[2,1-*a*]isoquinolines. When the substituent R was methyl, only the pure *exo* isomer could be detected, but when a phenyl group was attached to the nitrogen atom of the Schiff base, an *exo-endo* isomeric mixture was formed [5].

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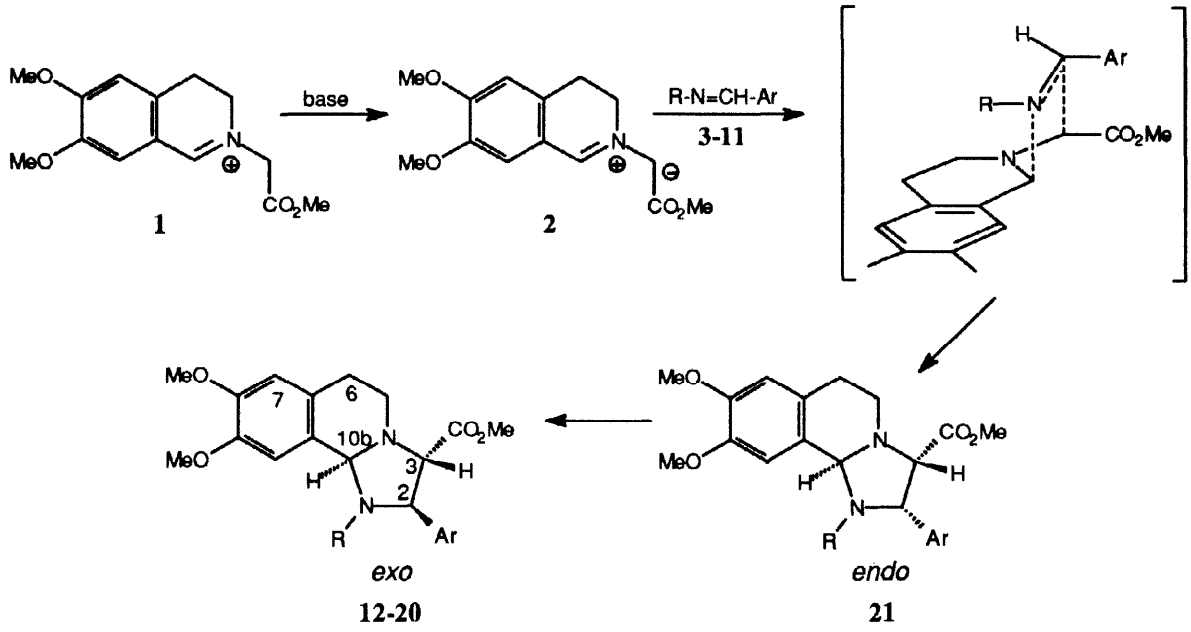
Results and discussion

In order to investigate further the *endo-exo* selectivity, we have employed as dipolarophiles Schiff bases, synthesized from β-aralkylamines or methylamine and various aromatic aldehydes. Considering the low energy barrier of the nitrogen inversion in Schiff bases, the *E* arrangement of the R and Ar groups should be preferred.

The reaction of the Schiff bases **3-10** with ylide **2** gave cycloadducts **12-19** (Scheme 1), each as a single racemate. When *N*-furfurylidenetryptamine (**11**) was used as dipolarophile, also a single product (**21**) was obtained, but with different relative configuration in the imidazole ring. Taking into account the concerted mechanism of the cycloaddition (see the transition state in Scheme 1), the appearance of two types of products is unexpected and needs detailed explanation. The structures of products were elucidated with comprehensive one- and two-dimensional NMR methods. Characteristic ^{1}H and ^{13}C NMR data are collected in Table 1.



Schiff base	Cyclo-adduct	R	Ar
3	**12**	Me	2-furyl
4	**13**	3,4-$(MeO)_2C_6H_3$-CH_2CH_2	Ph
5	**14**	3,4-$(MeO)_2C_6H_3$-CH_2CH_2	2-furyl
6	**15**	3-indolyl- CH_2CH_2	Ph
7	**16**	3-indolyl- CH_2CH_2	3,4-$(OCH_2O)C_6H_3$
8	**17**	3-indolyl- CH_2CH_2	3,4,5-$(MeO)_3C_6H_2$
9	**18**	3-indolyl- CH_2CH_2	2-thienyl
10	**19**	3-indolyl- CH_2CH_2	*N*-methyl-2-pyrrolyl-
11	**20,21**	3-indolyl- CH_2CH_2	2-furyl

Scheme 1

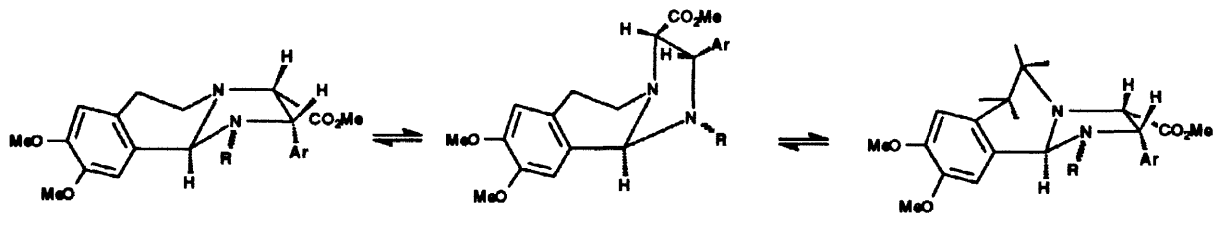
For sake of clarity only one enantiomer with H-10b in the α position is shown. Considering the transition state, *endo*-type products can be anticipated in which H-10b is located on the side of the imidazoline ring opposite to H-2, so that the product should have H-10b α, H-2β, H-3β configuration, and similarly, the *exo*-type cycloadduct should have α,α,β configuration.

Table 1.

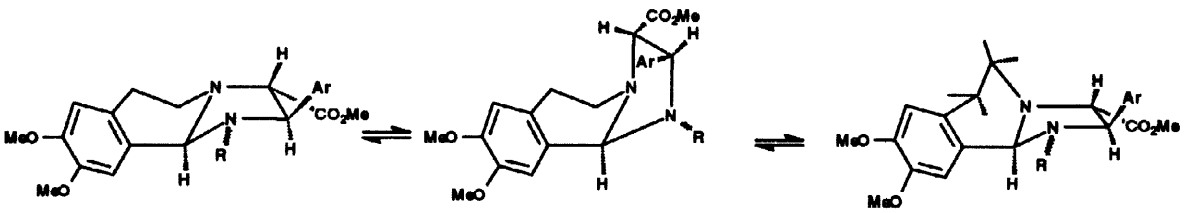
Characteristic chemical shifts [ppm] and coupling constants [Hz] for compounds **12-21**

Compound	δH-2	δH-3	δH-10b	$J_{2\text{-}H,3\text{-}H}$	δC-2	δC-3	δC-6	δC-10b
12	3.80	3.90	4.34	7.2	64.9	69.5	27.4	81.7
13	4.13	3.56	4.94	7.5	71.4	71.8	24.8	80.2
14	4.24	3.70	4.82	7.4	64.0	68.5	25.3	80.0
15	4.20	3.60	5.00	8.0	71.6	71.6	24.5	80.0
16	4.11	3.53	4.96	7.9	71.2	71.8	24.8	79.8
17	4.18	3.70	5.06	7.8	71.0	72.4	24.7	80.8
18	4.53	3.65	4.98	7.5	66.7	72.0	24.2	80.1
19	4.36	3.70	4.95	8.0	64.5	69.2	25.1	79.6
20	4.34	3.86	4.92	7.2	63.8	68.5	25.3	79.6
21	4.90	4.30	5.04	6.8	58.5	66.4	24.4	78.7

Due to pyramidal inversion at *N*-4 bridgehead junction of the B/C rings analogously to the pyrrolo[2,1-*a*]isoquinolines discussed previously [3], the existence of a *trans* ⟷ *cis-1* ⟷ *cis-2* type conformational equilibrium should also be expected in solution (*cf.* Scheme 2a and 2b). It emerges from the Schemes that only in the *exo* isomers are H-10b and H-2 in proximity. In fact on irradiation of the H-2 signal of **15** and **16**, an intensity enhancement could be observed on the H-10b signal indicating the steric proximity of the respective protons. Irradiating on the H-10b signal corroborated this arrangement. Thus from the NOE data it can be concluded that the H-2 and H-10b protons are situated on the same side of the imidazole ring, *i.e.* the cycloaddition results in products with an *exo* configuration.



Scheme 2a. Conformational equilibrium of the *exo* compounds



trans *cis-1* *cis-2*

Scheme 2b. Conformational equilibrium of the *endo* compounds

When *N*-furfurylidenetryptamine (**11**) was applied as dipolarophile, the NMR spectra of the cycloadduct **21** showed significant differences from those of compounds **12-19**. H-2 and H-3 signals were shifted downfield, while C(2) and N(1)-CH_2 signals had an upfield shift compared to the adducts with *exo* configuration. In the case of compound **21** the 1D NOE experiment detected the steric proximity of the H-2 and H-3 protons, while the intensity enhancement was negligible at the H-10b signal irradiating the H-2 signal. However, the NOE contact between H-10b and H-3′ of the furyl moiety unambigously proves the α,β,β configuration and hence the *endo* structure of compound **21**. This means that a small modification of the structure of the Schiff base resulted in different configuration of cycloadducts.

An interesting time dependence of the NMR spectra of **21** in $CDCl_3$ solution was observed, with slow appearance of a set of new signals which could be assigned to an isomeric compound (**20**) of the *exo* series. After a week, transformation to **20** was complete at room temperature. Compound **20** was also prepared from **21** by boiling in chloroform-*d* for 24 hours. The **20-21** isomeric pair was the subject of a detailed NMR study, where the 1D NOE results were compared with 2D NOESY experiments. For the sake of an unambiguous signal assignment, the COSY, HMQC and HMBC spectra of these compounds were recorded. The results of these experiments are summarized in Table 2. The 2D NOESY spectrum also corroborated the *exo* configuration of compound **20**.

Comparing the NMR data of the *exo* compounds (**12-20**) with those of compound **21**, it emerges that the $J_{H\text{-}2,H\text{-}3}$ coupling constants differ significantly. In the case of the compounds with an *exo* configuration (**12-20**) these values are 7.2-8.0 Hz (which correspond to 0-20° dihedral angle according to the modified Karplus equation [7]), while in the case of compound **21** it is only 6.8 Hz (dihedral angle ca 25° or 125°).

It is known that the orientation of the lone pair of the nitrogen atom has a specific influence on the $^1J_{C,H}$ coupling constants and this can be exploited for the determination of the relative configuration of the NC-H hydrogens and of the lone pair [7]. For the analogous pyrrolo[2,1-*a*]isoquinoline derivatives it was found that in the case of an antiperiplanar arrangement the $^1J_{C\text{-}3,H}$ coupling constant is 141 Hz, whereas for the synclinal arrangement the value is 149 Hz [1]. The

measured $^1J_{C\text{-}3,H}$ data for compounds **20** and **21** being 141 Hz and 139 Hz, respectively, are in good agreement with the preference of the *cis-1* conformation for both compounds. The slightly smaller coupling observed for compound **21** reflects the higher population of *cis-1* conformation in the conformational equilibrium (*cf.* Table 2). Characteristically different values of $^1J_{C\text{-}2,H}$ were measured for this pair of isomers, namely 136 Hz (**20**) and 147 Hz (**21**). This phenomenon reflects the *trans* and *cis* arrangements of H-2 and the *N*-1 lone pair.

Table 2.

^{1}H, ^{13}C chemical shifts, characteristic NOESY and HMBC responses of compounds **20** and **21**.

	20				**21**			
Atom	^{1}H	NOESY	^{13}C	HMBC (^{1}H partners)	^{1}H	NOESY	^{13}C	HMBC (^{1}H partners)
2	4.34	3; 10b;NCH_2	63.8	3; 10b; NCH_2	4.90	3; 3'; NCH_2	58.5	3; NCH_2
3	3.86	2; 5α; 5β; 6β	68.5	2; 5β; 10b	4.30	2; 5β	66.4	2; 5α
5α	3.16		47.3	3; 6α; 6β; 10b	3.10		48.0	6α; 6β; 10b
5β	3.32				3.02			
6α	2.64	5α; 5β; 7	25.3	5α; 5β; 7	2.43	6β; 7	24.4	5α; 5β; 7
6β	2.92	3; 5b; 7			2.98			
6a			127.1	7; 10			126.9	7; 10
7	6.59	6α; 6β; MeO-8	111.0	6α	6.70	6α; MeO-8	111.5	6α; 10
8			148.1	10; MeO-8			148.1	10; MeO-8
9			146.9	7; MeO-9			146.9	7; MeO-9
10	6.73	10b; MeO-9; NCH_2	111.4	7; 10b	6.61	10b; MeO-9; NCH_2	111.5	7; 10b
10a			128.0	6α; 7; 10; 10b			130.8	7; 10; 10b
10b	4.92	2; 10; NCH_2	79.6	2; 5α; 10; NCH_2	5.04	10; 3'; NCH_2	78.7	2; 5α; 10; NCH_2
C=O			172.7	2; 3; MeO			171.6	3; MeO
MeO	3.77		52.2		3.55		51.9	
MeO-8	3.84	7	55.7		3.88	7	56.0	
MeO-9	3.51	10	55.5		3.68	10	55.8	
2'			153.7	2; 3; 3'; 4', 5'			151.1	2; 3; 4', 5'
3'	6.17	2; 3	107.6	2; 4'; 5'	6.41	2; 10b; 4';	110.0	2; 4'; 5'
4'	6.27	5'	110.2	3'; 5'	6.38	3'; 5'	110.1	3'
5'	7.34	4'	142.0	3'; 4'	7.47	4'	142.6	3'; 4'
NCH_2	3.13	10; 10b	52.8	2; 10b	2.52	10; 10b	49.1	2; 3; 10b
	3.28				2.94			

In our previous works [1,3] we reported that in solution imidazo[2,1-*a*]isoquinolines show a *trans* ⟷ *cis-1* ⟷ *cis-2* conformational equilibrium. On the basis of NMR parameters this conformational equilibrium could be evaluated semiquantitatively. In this respect the value of the $J_{5\text{-}H\alpha,6\text{-}H\beta}$ is informative, because these protons are antiperiplanar in the *trans* and *cis-1* conformer, while they occupy *gauche* position in the *cis-2* conformer. On the other hand, the chemical shift of

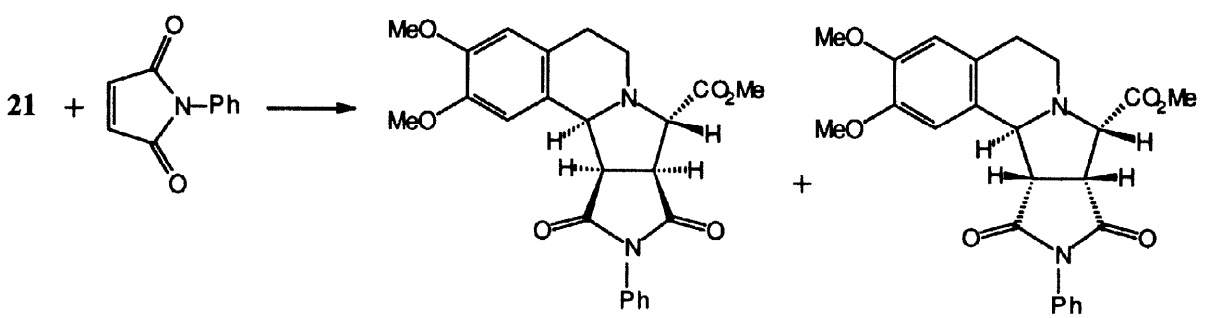
C-6 reflects the relative weight of the *cis-1* conformer, because in this conformer a *γ-gauche* steric effect is present and C-6 is shifted upfield. The chemical shift of C-6 without this *γ-gauche* effect is 29.0 ppm in our model compound [3]. The chemical shifts of the C-6 signals (24-25 ppm) indicates that in each case, but with compound **12** the conformer *cis-1* predominates.

Table 3.

Conformational ratios and selected NMR data for compounds **16**, **20** and **21**

Compound	δC-6	$J_{5\text{-}H\alpha,6\text{-}H\beta}$	*trans* %	*cis-1* %	*cis-2* %
16	24.8	10.4	8	76	16
20	25.3	8.2	~0	62	38
21	24.4	10.9	12	76	12

The phenomenon of the **20** ⟶ **21** (*endo* ⟶ *exo*) isomerism shows that the reaction of ylide **2** with the Schiff bases results in the kinetically favoured *endo* cycloadduct. When the reaction of **2** with **5** and **6** was monitored by ^{1}H NMR spectroscopy, initially the signals of the *endo* cycloadduct occurred, but later these signals disappeared. This means that the primary product of the cycloaddition is the *endo* isomer in every case, altough only compound **21** is stable enough to be isolated.



22 **23** **24**

In a further experiment *N*-phenylmaleimide (**22**) was added to the solution of compound **21**. The analysis of the reaction mixture revealed that, besides the Schiff base **11**, **23** and **24**, pyrrolo[2,1-*a*]isoquinolines were also formed, which were previously synthesized by us, reacting **2** with **22** [8]. From the facts mentioned above it can be concluded, that ylide **2** and Schiff base **11** are formed by the cycloreversion of the kinetically controlled adduct **21** and a further cycloaddition led to thermodynamically more stable *exo* isomer **20**. Our experiment also proves that the pyrrolo[2,1-*a*]isoquinolines are more stable than the analogous imidazo[2,1-*a*]isoquinolines. Literature data also show that cycloadducts synthesized from dipolarophiles

containing carbon-hetero double bonds have greater ability for cycloreversion, than those obtained from C=C bond dipolarophiles [9-12].

Adding maleimide **22** to the solution of the more stable **14** *exo* cycloadduct, compounds **23** and **24** could both be detected by NMR spectroscopy. We found that the cycloreversion in this case was much slower, than in the reaction of **21** *endo* cycloadduct.

Heating the ethanolic solution of compound **15** with 70% perchloric acid, the yellow quaternary perchlorate salt of **1** was obtained, whereas in a control experiment without acid, the unchanged **15** was isolated. These findings also prove that an acid-catalyzed cycloreversion occurs. The *endo-exo* isomerization **21**→ **20** also takes place *via* cycloreversion, because it is also catalyzed by traces of acid. The solution of **21** is quite stable in acid-free chloroform and its isomerization can be avoided in the presence of bases, *e.g.* triethylamine.

Experimental

General. Melting points were determined in a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were taken in KBr pellets with a SPECORD 75 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker DRX-500 and AC-250 spectrometers. For the two-dimensional experiments the Bruker software package was applied.

The known Schiff bases **3** [13], **4** [14], **5** [15], **6** [16] and **11** [17] were prepared according to literature procedures. Schiff bases **7-10** were synthesized with the following general method. Tryptamine (8.0 g, 5 mmol) and aromatic aldehyde (5 mmol) in ethanol (20 ml) were boiled for 30 min. After cooling the reaction mixture, the Schiff bases formed slowly crystallized out. The crude products were filtered, dried and recrystallized from ethanol.

Piperonylidene tryptamine (**7**): yield 1.28 g (87.7 %) pale yellow crystals, mp 129-130°C. IR (KBr): 1640 cm^{-1} (C=N); 3310 cm^{-1} (NH), NMR 5.92 (s, 2H, OCH_2O); 7.91 (s, 1H, N=CH); 8.30 (broad, 1H, NH). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C 73.95 H 5.52 N 9.58, found: C 73.83 H 5.89 N 9.50%.

3,4,5- Trimethoxybenzylidene tryptamine (**8**): yield 1.35 g (79.9 %) pale yellow crystals, mp 180-181°C. IR (KBr): 1635 cm^{-1} (C=N); 3320 cm^{-1} (NH), NMR 3.81 (s, 9H, OCH_3); 8.02 (s, 1H, N=CH); 8.30 (broad, 1H, NH). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C 70.99 H 6.55 N 8.28, found: C 70.76 H 6.36 N 8.0 3%.

2-Thienylmethylene tryptamine (**9**): yield 0.30 g (23.6 %) pale yellow crystals, mp 133-134°C. (Lit. mp 98-102° [18]) IR (KBr): 1640 cm^{-1} (C=N); 3320 cm^{-1} (NH), NMR 8.10 (s, 1H, N=CH); 8.40 (broad, 1H, NH). Anal. Calcd for $C_{15}H_{14}N_2S$: C 70.83 H 5.55 N 11.01, found: C 70.54 H 5.31 N 10.92%.

(N-Methyl-2-pyrrolyl)methylene tryptamine (**10**): yield 0.26 g (20.6 %) pale yellow crystals, mp 77-78°C; IR (KBr): 1640 cm^{-1} (C=N); 3315 cm^{-1} (NH), NMR 3.43 (s, 3H, NCH_3); 8.03 (s,

1H, N=CH); 8.30 (broad, 1H, NH). Anal. Calcd for $C_{16}H_{17}N_3$: C 76.46 H 6.82 N 16.72, found: C 76.32 H 6.61 N 16.48%.

exo Methyl 1-methyl-2-(2-furyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**12**): *N*-Methoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide (**1**, 1.0 g, 2.9 mmol), *N*-furfurylidene methylamine (**3**, 0.33 g, 3 mmol) and triethylamine (0.33 g, 3 mmol) were dissolved in $CHCl_3$ (10 ml) and stirred for one day. After evaporation of the solvent, the solid material was recrystallized from methanol/water. Yield 0.50 g (46.1 %) colourless crystals, mp 114-115°C. IR (KBr): 1735 cm^{-1} (C=O). NMR: for chemical shifts see Table 1. 1D NOE experiments: irradiating at H-2 results in NOE enhancement at H-10b (5.6%), NMe (4.3%) and H-3 (3.5%) signals; irradiating at H-3 results in NOE enhancement at H-2 (3%), H-5α (2.3%) and H-5β (3.1%) signals; irradiating at H-10b results in NOE enhancement at H-2 (6.1%), H-10 (7.9%) and NMe (3.0%) signals; irradiating at the NMe signal results in NOE enhancement at H-2 (13.7%), H-10 (10.9%), H-10b (9.8%) and H-3′ (2.7%) signals. Anal. Calcd for $C_{20}H_{24}N_2O_5$: C 64.50 H 6.50 N 7.52, found: C 64.43 H 6.42 N 7.44%.

General procedure for the preparation of cycloadducts **13-19** *and* **21**:
N-Methoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide (**1**, 1.0 g, 2.9 mmol), dipolarophile (Schiff bases **4-11**, 3.0 mmol) and triethylamine (0.3 g, 3 mmol) were dissolved in methanol (10 ml) with stirring. The slowly crystallized cycloadducts were filtered, washed with methanol and dried.

exo Methyl 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**13**): yield 0.95 g (61.7 %) pale yellow crystals, mp 84-85°C. IR (KBr): 1735 cm^{-1} (C=O). NMR: see Table 1. Anal. Calcd for $C_{31}H_{36}N_2O_6$: C 69.91 H 6.81 N 5.26, found: C 69.75 H 6.70 N 5.07%.

exo Methyl 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-(2-furyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**14**): yield 0.90 g (59.2 %) colourless cryst. powder mp 77-78°C. IR (KBr) 1735 cm^{-1} (C=O). NMR: see Table 1. Anal. Calcd for $C_{29}H_{34}N_2O_7$: C 66.65 H 6.56 N 5.36, found: C 66.42 H 6.48 N 5.18%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-phenyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**15**): yield 0.99 g (66.9 %) white powder, mp 136-137°C. IR (KBr) 1735 cm^{-1} (C=O); 3325 cm^{-1} (NH). NMR: for chemical shifts see Table 1. 1D NOE experiments: irradiating at H-2 results in NOE enhancement at H-3 (1%), H-10b (2.9%) and H-2′,6′ (Ph *ortho*) (10.5%) signals; irradiating at H-3 results in NOE enhancement at H-2 (2.3%) and H-5 (4.4%) signals; irradiating at H-10b results in NOE enhancement at H-2 (3.6%), H-10 (6.0%) and NCH_2 (6.0%) signals. Anal. Calcd for $C_{31}H_{33}N_3O_4$: C 72.78 H 6.50 N 8.21, found: C 72.58 H 6.29 N 8.09%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-(3,4-methylenedioxyphenyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**16**): yield 1.00 g (62.1 %) white powder, mp 172-173°C. IR (KBr) 1735 cm^{-1} (C=O); 3325 cm^{-1} (NH). NMR: for chemical shifts see Table 1. 1D NOE

experiments: irradiating at H-2 results in NOE enhancement at H-10b (2.7%) H-2′ (4.0%) and H-6′ (6.2%) signals; irradiating at H-10b results in NOE enhancement at H-2 (3.7%), H-10 (6.8%) and NCH_2 (5.8%) signals. Anal. Calcd for $C_{32}H_{33}N_3O_6$: C 69.17 H 5.99 N 7.56, found: C 69.02 H 5.79 N 7.36%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-(3,4,5-trimethoxyphenyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**17**): yield 1.48 g (85.1 %) white powder, mp 97-98°C. IR (KBr) 1730 cm^{-1} (C=O); 3325 cm^{-1} (NH), NMR: see Table 1. Anal. Calcd for $C_{34}H_{39}N_3O_7$: C 67.87 H 6.53 N 6.98, found: C 67.69 H 6.41 N 6.81%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-thienyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**18**): yield 0.40 g (26.6 %) pale yellow powder, mp 160-161°C. IR (KBr) 1735 cm^{-1} (C=O); 3330 cm^{-1} (NH), NMR: see Table 1. Anal. Calcd for $C_{29}H_{31}N_3SO_4$: C 67.29 H 6.03 N 8.12, found: C 67.21 H 5.88 N 7.95%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-(N-methyl-2-pyrrolyl)-1,2,3,5,6,10b-hexahydroimidazo-[2,1-a]isoquinoline-3-carboxylate (**19**): yield 0.94 g (63.1 %) pale yellow powder, mp 156-157°C. IR (KBr) 1735 cm^{-1} (C=O); 3345 cm^{-1} (NH), NMR: see Table 1. Anal. Calcd for $C_{30}H_{34}N_4O_4$: C 70.02 H 6.66 N 10.89, found: C 69.85 H 6.48 N 10.65%.

endo Methyl 1-[2-(3-indolyl)ethyl]-2-(2-furyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**21**): yield 1.40 g (55.8 %) pale yellow powder, mp 183-184°C. IR (KBr) 1745 cm^{-1} (C=O); 3420 cm^{-1} (NH), NMR: see Table 1 and 2, assignment of the 3-indoyl-CH_2 moiety : ^{1}H-NMR : 6.75 (s, 1H, H-2); 7.28 (d, 1H, H-4); 7.00 (t, 1H, H-5); 7.11 (t, 1H, H-6); 7.26 (d, 1H, H-7), 2.73 (m, 1H,) + 2.96 (m, 1H) CH_2 :^{13}C-NMR : 121.7 (C-2); 114.0 (C-3); 118.7 (C-4); 118.9 (C-5); 121.5 (C-6); 111.0 (C-7); 136.1 (C-8); 127.4 (C-9); 24.1 (CH_2). Anal. Calcd for $C_{29}H_{31}N_3O_5$ (501.58), calcd: C 69.44 H 6.23 N 8.38, found: C 69.31 H 6.10 N 8.23%.

exo Methyl 1-[2-(3-indolyl)ethyl]-2-(2-furyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**20**): **21** (0.50 g, 1 mmol) dissolved in chloroform-*d* (0.6 ml) was boiled for 24 h. After evaporation of the solvent, pure **20** was obtained. Yield 1.39 g (99.2 %) pale yellow powder, mp 126-127°C. IR (KBr): 1735 cm^{-1} (C=O); 3380 cm^{-1} (NH), NMR: see Table 1 and 2, assignment of the 3-indoyl-CH_2 moiety : ^{1}H-NMR : 6.82 (s, 1H, H-2); 7.30 (d, 1H, H-4); 7.03 (t, 1H, H-5); 7.12 (t, 1H, H-6); 7.45 (d, 1H, H-7), 2.83 (m, 2H, CH_2); ^{13}C-NMR : 121.5 (C-2+C-6); 113.6 (C-3); 118.5 (C-4); 118.8 (C-5); 110.8 (C-7); 136.1 (C-8); 127.2 (C-9); 23.5 (CH_2). Anal. Calcd for $C_{29}H_{31}N_3O_5$: C 69.44 H 6.23 N 8.38, found: C 69.25 H 6.07 N 8.15%.

The ring cleavage of methyl 1-[2-(3-indolyl)ethyl]-2-phenyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-a]isoquinoline-3-carboxylate (**15**) *with 70% perchloric acid: preparation of N-methoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinolinium perchlorate:* Methyl 1-[2-(3-indolyl)ethyl]-2-phenyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**15**, 0.20 g, 0.4 mmol) was suspended in ethanol (5 ml), 70% perchloric acid (2 ml) was added and the reaction mixture cautiously was boiled during stirring. After some minutes a yellow precipitate

was formed, which was filtered off after cooling, washed with ethanol and dried. Yield 0.10 g (68.7 %) yellow crystals, mp 185-186°C; IR (KBr): 1735 cm^{-1}(C=O); 1640 cm^{-1} (C=N). Anal. Calcd for $C_{14}H_{18}NO_8Cl$: C 46.22.46 H 4.99 N 3.86, found: C 46.11 H 4.83 N 3.77%.

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References

[1] Tóth, G.; Janke, F; Bende, Z.; Bende, Z.; Simon, K., *J. Chem. Soc., Perkin Trans. 2*, **1983**, 1961
[2] Bende, Z.; Tőke,.L.; Weber, L.; Tóth, G.; Janke, F; Csonka, G., *Tetrahedron*, **1984**, *40*, 369
[3] Janke, F., Himmelreich, U.; Tóth, G.; Tischer, T.; Kádas, I.; Bende, Z.; Tőke, L., *J. Heterocycl. Chem.*, **1991**, *28*, 867
[4] Bende, Z.; Bitter, I.; Tőke,.L.; Weber, L.; Tóth, G., *Liebigs Ann. Chem.*, **1982**, 924
[5] Bende, Z.; Simon, K.; Tóth, G.; I.; Tőke,.L., *Liebigs Ann. Chem.*, **1982**, 2146
[6] Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; Altona, C., *Org. Magn. Reson.*, **1981**, *11*, 43
[7] Gil, V.M.S.; von Philipsborn, W., *Magn. Reson. Chem.*, **1989**, *27*, 409
[8] Tóth, G.; Tischer, T.; Bende, Z.; Szejtli, G.; Tőke,L., *Monatsch. Chem.*, **1990**, *121*, 529
[9] Bianchi, G.; Gandolfi, R., In : Padwa, A. editor. 1,3-Dipolar Cycloaddition Chemistry Vol *2*., New York; J. Wiley and Sons, **1984**, 451
[10] Bianchi, G.; De Micheli, C.; Gandolfi, R., *Angew. Chem.*, **1979**, *91*, 781
[11] Black, D.S.C.; Watson, K. G., *Aust. J. Chem.*, **1973**, *26*, 2491
[12] Huisgen, R.; Wulff, J., *Chem. Ber.*, **1969**, *102*, 746
[13] Schwabbauer, G., *Ber. Deutsch. Chem. Ges.*, **1902**, *35*, 410 ; Emling, B.L.; Beatty J.E.; Stevens, J.R., *J. Am. Chem. Soc.*, **1949**, *71*, 703
[14] Buck, J.S., *J. Am. Chem.Soc.*, **1930**, *52*, 4119; Viel, C., *Ann. Chim. (Paris)[13]* **1963**, *8*, 515
[15] Takano, S.; Oshima, Y.; Ito F.; Ogasawara, K., *Yakugaku Zasshi*, **1980**, *100*, 1194 ; *C.A.* **1981**, *95*, 24871x
[16] Jackson, A.H.; Smith, AE., *Tetrahedron*, **1968**, *24*, 403-413
[17] Severin, T.; Heidenhain, B., *Z. Lebensm. Unters. Forsch.*, **1966**, *132*, 65-69 ; Severin, T.; Bräutigam, K.H., *Chem. Ber.*, **1973**, *106*, 2943
[18] Imperial Chemical Industries Ltd, *BP.*, 1 055 203, 1964; *Neth. Pat.*, 6 512 087 , 1966 ; *C.A.* **1966**, *65*, P3844