ISOQUINOLINIUM *N*-ARYLIMIDES AND *TRANS*-CYCLOOCTENES [1]

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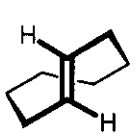
Dedicated with warmest wishes to Wolfgang Steglich, München, on the occasion of his 65th birthday

Abstract - The inertness of isoquinolinium *N*-arylimides (**5a,b**) versus common cycloalkenes is overcome by the highly reactive *(E)*-cyclooctene and *(E,Z)*-1,5-cyclooctadiene. NMR spectra and an X-Ray analysis established the retention of dipolarophile configuration in the cycloadducts (**7a,b**) and (**9a,b**) which were obtained in > 90% yield. Acid-base catalysis effects the opening of the pyrazolidine ring by ß-elimination; the products are 1-[*trans*-2-arylaminocyclooctyl]-isoquinolines (**8,10**).

INTRODUCTION

The dihedral angle at the double bond of a *trans*-alkene (180°) is diminished in *trans*-cyclooctene (138°); the reduction by 42° is composed of a torsion at the C=C bond axis and pyramidal bending at the olefinic C-atoms, as electron diffraction in the gas phase [2] and an X-Ray analysis of a derivative of *(E)*-cyclooctene [3] revealed. The twist conformation (**1**) has C_2 symmetry.



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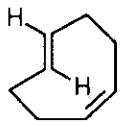

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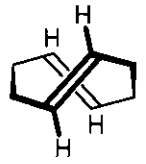

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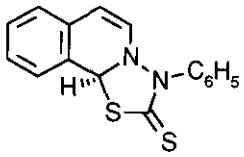
(E,Z)-1,5-Cyclooctadiene (**2**) was first obtained by Willstätter and Veraguth in 1905 by degradation of the alkaloid pseudopelletierine;[4] 50 years later, Ziegler *et al.* studied its chemistry.[5]

The conversion of *cis*- to *trans*-cyclooctenes by a sequence of *cis*-addition and *trans*-elimination offers a rational pathway to the highly strained rings. We found the sequence, developed by Bridges and Witham,[6] efficient and reliable; it consists of epoxidation, ring opening of the oxirane by lithium di-

phenylphosphide, oxidation to the *trans*-ß-hydroxyphosphine oxide, and treatment with sodium hydride. The twofold inversion of *(Z,Z)*-1,5-cyclooctadiene by the mentioned method gave access to the elusive *(E,E)* isomer in the Munich laboratory; the chiral twist form (**3**) was established.[7] The strain energies of **1** and **2** exceed those of the *cis* isomers by 10 and 13 kcal mol^{-1}.[8,9] The rates of cycloadditions onto the *trans* double bond in the 8-membered ring are high. E.g., the following rate constants were measured for the additions of phenyl azide (CCl_4, 25 °C): $10^7 k_2$ ($M^{-1}s^{-1}$) = 1.05 for *(Z)*-cyclooctene, 16 900 for **1**, and 1 140 000 for **2**.[10] However, it would be naive to assume a direct relation between activation energy and strain release; we discussed that recently for additions to norbornene.[11]



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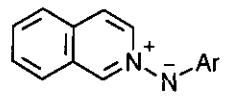
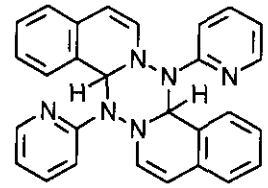


5a Ar = C_6H_5
5b Ar = C_5H_4N-(2)



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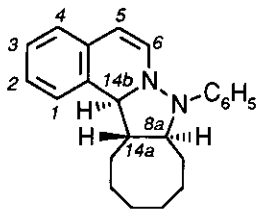
The CS_2 adduct (**4**) is a neutral storage form of the not isolable isoquinolinium *N*-phenylimide (**5a**); a mobile cycloreversion/cycloaddition equilibrium in solution establishes a small stationary concentration of **5a**. The more stable *N*-(2-pyridyl)imide (**5b**) exists in solution in an equilibrium with its storable dimer, the hexahydrotetrazine derivative (**6**).[12]

In preceding papers we described the cycloadditions of **5a** and **5b** to electrophilic CC double and triple bonds.[13,14] The electron-rich C=C bond of enamines likewise accepts **5**.[15] However, the inertness of **5** towards cyclopentene, cyclohexene, or *(Z)*-cyclooctene indicates the rate minimum typical for 1,3-dipoles of Sustmann's class II.[16]

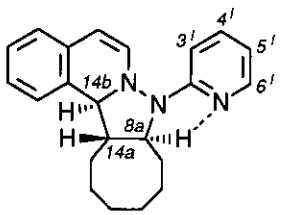
CYCLOADDITIONS AND OPENING OF THE PYRAZOLIDINE RING

The *N*-phenylimide (**5**) is responsible for the red color of a solution of **4** in dichloromethane. After adding 1.4 equiv. of *(E)*-cyclooctene, decolorization took place within 1 h. The oily cycloadduct (**7a**) (96%) was characterized by its ^1H NMR spectrum. The reaction of the *N*-(2-pyridyl)imide (**5b**) at room temperature afforded the colorless crystals of **7b** in 95% yield. The chiral cycloadducts are represented by the configuration with 14b-H on the ß-side.

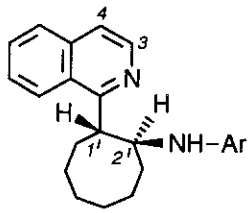
The pairs of sharp doublets at δ_H 5.31 and 6.15 for **7a** and at 5.45 and 6.20 for **7b** belong to 5-H and 6-H of the 1,2-dihydroisoquinoline derivatives; the 5-H in the ß-position of an enehydrazine is shielded. The difference δ is more pronounced in the ^{13}C NMR spectrum, as values of 102.4 ppm for C-5 and 137.5 ppm for C-6 in the case of **7b** indicate. The doublet at δ 3.57 for both **7a** and **7b** is assigned to 14b-H. Its coupling constant, $J_{14a,14b}$ = 10.0 and 10.1 Hz, respectively, suggests a *trans-vic*-relation. The ^1H NMR analyses of three dozen cycloadducts of **5a** and **5b** show $J_{trans} > J_{cis}$, although there is a broad overlap zone.[13] A more convincing structural conclusion is based on δ(8a-H): ~ 3.50 for **7a** and 4.34 for **7b**, the latter being a well-resolved ddd in the 400 MHz spectrum. A δ of that size was established as a criterion for a hydrogen bond of the pyridine nitrogen to the 8a-ßH [13] and



7a



7b



8a Ar = C_6H_5
8b Ar = C_5H_4N-(2)

confirmed by an X-Ray analysis.[17]

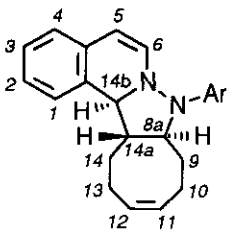
Retention of dipolarophile configuration is suggested by 14a-H on the α-side and 8a-H on the ß-side. An X-Ray analysis of **9a** corroborated the NMR information (next section). 1,3-Dipolar cycloadditions are concerted [18] and the few exceptions to the rule are well-understood.[19]

On attempting to purify the oily **7a** by thick-layer chromatography on silica gel, a partial opening of the pyrazolidine ring was observed. Unchanged **7a** was eluted by dichloromethane, but the extraction of a yellow layer required hot acetone, and the secondary amine (**8a**) (14%) was obtained. In the analogous thick-layer procedure with **7b**, 52% of the starting material was recovered, and 42% of the crystalline **8b** was isolated. Remarkably, column chromatography on another brand of silica gel did not give rise to **8**. Acid-base catalysis is considered, and indeed commercial qualities of silica gels differ in their active centers, as has been experienced in our laboratory for the stereoisomerization of an aliphatic *sec*-nitro compound.[20]

When cycloadduct (**7a**) was treated with acetic acid in chloroform for 1 d at room temperature, 84% of the ring-opened **8a** was isolated. It is noteworthy that this ring cleavage has not been observed for other cycloadducts of **5** to C=C bonds. Most of these are amenable to an acid-catalyzed hydrazo rearrangement related to Fischer's indole synthesis.[21] The *trans*-annellated cyclooctane ring of **7** probably generates steric hindrance in the hydrazo rearrangement, thus raising the energy of the transition state. Furthermore, strain release and aromatization of the isoquinoline ring possibly contribute to the unexpected prototropic ring-opening of a *trans*-cyclooctapyrazolidine.

The NH signals appeared at δ 3.28 (**8a**) and 4.42 (**8b**); the infrared N-H frequency was observed at 3320 and 3325 cm^{-1}. The ^1H NMR doublets of 5-H and 6-H of **7b** (δ 5.45, 6.20, J = 7.6 Hz) are converted on ring-opening to **8b** into doublets at δ 7.41 for 4-H and 8.40 for 3-H with J = 5.5 Hz, in agreement with values of δ 7.50 and 8.45 ($J_{3,4}$ = 6.0 Hz) for isoquinoline itself. A line broadening, observed in the ^{13}C NMR spectrum (100 MHz) of **8b**, especially in the signals of the 8-membered ring, intimates a dynamic process, which is probably the inversion of the cyclooctane ring (enantiomerization). A barrier to inversion of 8.1 kcal mol^{-1} was reported for cyclooctane itself,[22] but the voluminous 1,2-substituents will substantially increase the barrier.

Analogously, **5a** and **5b** were reacted with *(E,Z)*-1,5-cyclooctadiene (**2**) and furnished 93% and 94% of the crystalline adducts (**9a**) and (**9b**). The C5=C6 bond of the enehydrazine gives rise to a strong IR absorption at 1623 cm^{-1}. The ^1H NMR spectra of **9** closely correspond to those of **7**, e.g., δ(14b-H) appears at 3.68 (J = 10.5 Hz) for **9a** and at 3.62 (J = 10.4 Hz) for **9b**. The vinylic 11-H and 12-H form a multiplet at δ ~5.70 in **9a** and two ddd at δ 5.62 and 5.77 for **9b**. The test for the ß-configura-



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a Ar = C_6H_5

b Ar = C_5H_4N-(2)

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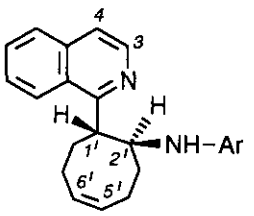


tion of 8a-H is reliable: δ(8a-H) 3.57 for **9a** and 4.29 for **9b** are consistent with an intramolecular hydrogen bond in **9b**.

X-RAY STRUCTURE OF CYCLOADDUCT (**9a**)

X-Ray structures of two cycloadducts of **5a** and **5b** have been reported.[17] The structure of **9a** (Figure 1) resembles those previously established in several features. The bond systems of both N-atoms of **9a** are pyramidalized: N7 (N8) is located above the plane of its three ligands by 0.40 Å (0.44 Å). The n-orbitals of the unshared electron pairs define a torsion angle of 99.0° at N7-N8, not far from the 91° measured for gaseous hydrazine.[23] An angle of 91° between the n-orbital of N7 and the plane of the C5=C6 bond makes the enamine-type resonance efficient. The n-orbital at N8 cuts the phenyl plane at 69.6°, suggesting a somewhat reduced aniline-type resonance.

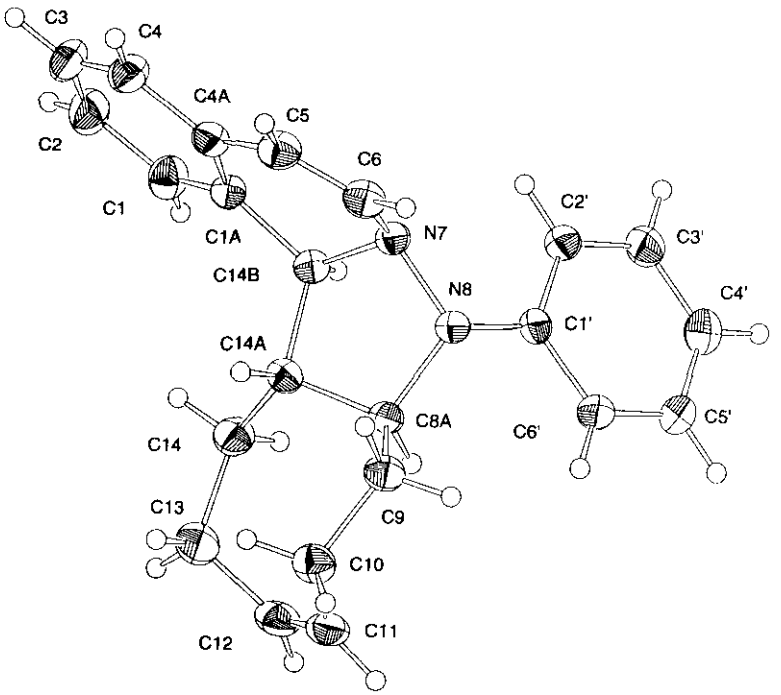


Figure 1. X-Ray structure of cycloadduct (**9a**); ZORTEP plot (thermal ellipsoids represent 30% probability)

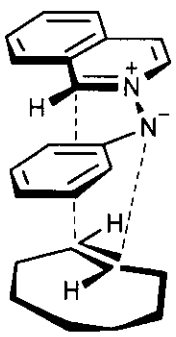
Table 1. X-Ray Structure of (rel-14bß,8aß,14aα)-(±)-8,8a,9,10,13,14,14a,14b-Octahydro-8-phenylcycloocta[3,4]pyrazolo[5,1-*a*]isoquinoline (**9a**); Selected Bond Lengths and Angles (in parentheses standard deviations on the last decimal)

Bond Lengths (Å)					
N7-N8	1.426(3)	N7-C14b	1.462(4)	C9-C10	1.528(4)
N7-C6	1.404(4)	N8-C1'	1.421(4)	C10-C11	1.493(5)
C6-C5	1.321(5)	C8a-C9	1.526(4)	C11-C12	1.316(5)
Bond Angles (°)					
C14a-C8a-C9	114.8(3)	C10-C11-C12	123.7(3)	C6-N7-C14b	115.1(3)
C8a-C9-C10	113.2(3)	C11-C12-C13	125.9(4)	N8-N7-C14b	105.2(2)
C9-C10-C11	112.0(3)	C6-N7-N8	113.1(3)		

Dihedral Angles (°); Force-field calculation of *(Z)*-Cyclooctene [26]				
C10-C11-C12-C13	-1.9(6)	2.3 [26]	N7-N8-C8a-C14a	11.4(3)
C11-C12-C13-C14	80.4(5)	83	N8-C8a-C14a-C14b	12.8(3)
C12-C13-C14-C14a	-68.8(4)	-73	C8a-C14a-C14b-N7	-32.1(3)
C13-C14-C14a-C8a	67.5(4)	71.4	C14a-C14b-N7-N8	40.6(3)
C14-C14a-C8a-C9	-103.7(3)	-103.0	C14b-N7-N8-C8a	-32.9(3)
C14a-C8a-C9-C10	58.4(4)	55.5	C1a-C4a-C5-C6	9.1(5)
C8a-C9-C10-C11	48.1(4)	48.6	C1a-C14b-N7-C6	41.2(4)
C9-C10-C11-C12	-91.9(4)	-90.8		

The torsion angles in the pyrazolidine ring of **9b** (Table 1) notably differ from those of the previous model, the adduct of **5a** to methyl α-chloroacrylate.[17] No longer is the aniline-type N8 the flap of an envelope; the conformation is a cross-breed between twist and envelope (with N7 as the flap). Supposedly, the *trans*-annellation of the cyclooctene ring generates some steric constraints.

X-Ray analyses of cyclooctane derivatives [24] reveal a strong preference for the *boat-chair* conformation. According to force-field calculations of cyclooctane itself, the *boat-chair* has the lowest energy level among various conformations.[25] *(Z)*-Cyclooctene has been calculated on the basis of two different force-fields;[25,26] the favored structure is derived from the cyclooctane *boat-chair* by placing the double bond at the position of the smallest torsion angle; the structure has no symmetry.



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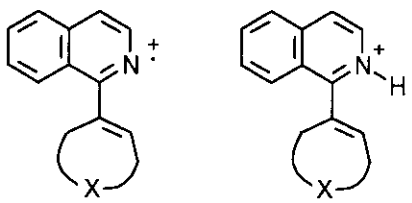
The *cis*-cyclooctene unit in structure (**9a**) has such a distorted *boat-chair conformation without symmetry*. The eight torsion angles show a amazing resemblance to those of the force-field calculation; the data of Ermer and Lifson [26] on *(Z)*-cyclooctene are included in Table 1 for comparison. Possibly, structure (**9a**) provides the first verification of the calculated structure, since we are not aware of previous structure analyses of *cis*-cyclooctene derivatives. The natural product *laurencine* contains an oxacyclooct-4-ene

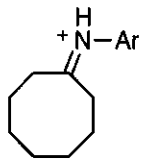
ring; its X-Ray structure [27] - a *boat-chair*, too - resembles **9a** less closely.
The *trans* relation of 14a-H and 14b-H suggests an approach of the reactants *via* an orientation complex (**11**) which might be the sterically favorable pathway. Admittedly, the bending of the *N*-phenyl towards C1 of isoquinoline is a speculative assumption.

MASS SPECTRA

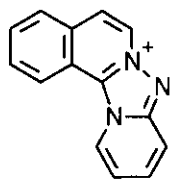
The four cycloadducts and the open-chain derivatives contain probes which reveal the provenance of the fragments: the mass difference between phenyl vs. pyridyl, and cyclooctane vs. cyclooctene ring. The molecular peak is more populous for the *N*-phenyl series than for the *N*-(2-pyridyl) compounds (Table 2).
The peaks at *m/z* 235-238 point to the loss of the arylamine; the pairs correspond to the radical cations (**12,13**) and the cations (**14,15**) as possible structures. These peaks are stronger for the pyridyl series **b** than for phenyl series **a**, and stronger for the ring-opened products (**8**) and (**10**) than for **7** and **9**. The formulae here and in the following represent a kind of bookkeeping with respect to the constituents, rather than the (unknown) structures; the principle of minimal structural change has been applied.



12 X =  **14**
13 X =  **15**



16a Ar = C_6H_5
16b Ar = C_5H_4N-(2)



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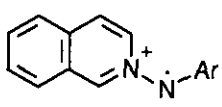
The loss of isoquinoline (fragments with *m/z* 201 - 202) was observed only for the compounds with cyclooctane ring, preferentially the ß-elimination products (**8a,b**); **16** would be the "least change" structure. Isoquinoline$^{+\cdot}$ (*m/z* 129) and isoquinolinium^{+} (*m/z* 130) were regularly observed.
The fragment *m/z* 220 occured three times as the base peak, and its missing in the MS of **8** and **10** allows two conclusions: The precursors harbor the N-N bond, and the fragmentation pathways are separate for **7**, **9** and **8**, **10**. The *m/z* 220 does not contain the former dipolarophile and, remarkably, does not reflect the difference of *N*-phenyl and *N*-(2-pyridyl) residue. $M^{+\cdot}$ undergoes a cycloreversion, and a wealth of cycloadducts of **5a** and **5b** shows *m/z* 220 in their MS.[13] High resolution established that *m/z* 220 in the cycloadducts of **5a** is $C_{15}H_{12}N_2^{+\cdot}$, whereas the *N*-(2-pyridyl) cycloadducts give rise to $C_{14}H_{10}N_3^{+}$. The latter formula signals the loss of 1 H, and the attractive triazolium ion (**17**) was proposed.[13] $C_{15}H_{12}N_2^{+\cdot}$ has the same molecular formula as **5a**; besides **18**, many rearranged structures are conceivable. Among these, the diazepine (**19**) has been considered,[13] in accordance with the photochemical conversion of type (**5**) zwitterions into diazepines.
The cycloadducts of **5a** with electron-deficient ethylenes or enamines undergo an acid-catalyzed hydrazo rearrangement,[15,21] which can be viewed as a Fischer indole synthesis that stops one step short

Table 2. Selected Data from the Mass Spectra of **7- 10** (Intensities in % of Base Peak)

		Ar = C_6H_5			Ar = C_5H_4N-(2)			
m/z	Formula	**7a**	**8a**	**9a**	**7b**	**8b**	**9b**	**10b**
331	M^+				17	13		
330	M^+	47	41					
329	M^+						19	6
328	M^+			89				
238	M^+- $ArNH_2$	2	33		22	72		
237	"				15	65		
236	"			3			13	19
235	"						8	15
220	**17 - 19**	100		100	100	5	79	
219	(**21**)		4	10				
202	M^+- C_9H_7N				7	45		
201	"	5	69					
157			37			55	15	14
156	$C_{10}H_8N_2^+$	8	100	15	29	100	100	100
130	$C_9H_8N^+$	14	34	24	9	14	11	4
129	$C_9H_7N^+$	22	9	37	13	8	18	3

of the indole. Structure (**20**) was established for the rearranged cycloadduct of **5a** to dimethyl fumarate.[21] The radical cation (**20**$^{+\cdot}$) eliminates fumaric ester, and *m/z* 220 appears here, too; species with N-N bond like **14-16** can be dismissed here. However, the MS of **20**$^{+\cdot}$ and many related radical cations regularly show a duet of two peaks, *m/z* 220 and 219, in nearly equal intensity, often as base peaks and sometimes accompanied by a middle-sized peak *m/z* 218. The fragment *m/z* 219 (Table 2) hardly appears in the MS of **7-10**. The indolo[2,3-*c*]isoquinolinium ion (**21**) was discussed as a possible structure of *m/z* 219.[15]



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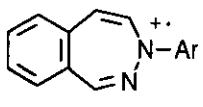

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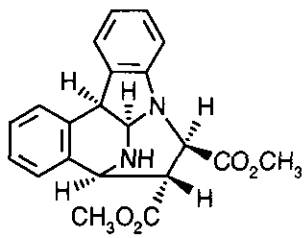

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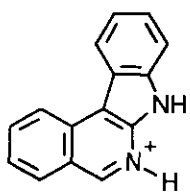

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The radical cations $M^{+\cdot}$ of the ring-opened **8** and **10** give rise to *m/z* 156 as the base peak, and $C_{10}H_8N_2^{+\cdot}$ was confirmed by high resolution. The ring-closed species furnished this peak to a smaller

extent, except for **9b** (100%). The *N*-aryl and seven C-atoms of the 8-membered ring are getting lost on the pathway to *m/z* 156. This peak was absent in the MS of the adducts of **5** to electron-poor ethylenes. Formally, $C_{10}H_8N_2^{+\cdot}$ is isoquinoline$^{+\cdot}$ plus HCN. One C-atom of the somewhat mysterious structure must come from the 8-membered ring.

EXPERIMENTAL

General Methods. IR spectra were recorded with a Perkin-Elmer 125 instrument. The NMR spectra were originally taken with a Varian A60 or a Bruker WP80 spectrometer; several spectra were repeated with a Varian XR400S instrument, 400 MHz for ^1H and 100 MHz for ^{13}C. Acid-free $CDCl_3$, stored over dry K_2CO_3, was used as solvent and TMS as internal standard. The MS are EI spectra with 70 eV, recorded on an AEI instrument MS902; isotope effects are given in the mode ^{13}C % calcd./% found, and HR is high resolution. Silica gel Merck 60 PF was used for the thick-layer (2 mm) chromatography (PLC); silica gel Woelm was the adsorbent for column chromatography (CC). Melting points are uncorrected.

(rel-14bß,8aß,14aα)-(±)-8,8a,9,10,11,12,13,14,14a,14b-Decahydro-8-phenylcycloocta[3,4]pyrazolo[5,1-*a*]isoquinoline (7a). *(E)*-Cyclooctene [6] (**1**, 286 mg, 2.60 mmol) was added to the deep-red solution of 592 mg (2.00 mmol) of the CS_2 adduct (**4**) [12] in 4 mL of CH_2Cl_2; decolorization took place within 1 h. Removal of the solvent and CC furnished 635 mg (96%) of a yellow oil; the ^1H NMR spectrum fits structure (**7a**), although the specimen was not obtained in an analytically pure state. - IR ($CHCl_3$): $\tilde{\nu}$ 1495 cm^{-1}, 1571, 1600 (arom. ring vibr.), 1629 st (C=C of enehydrazine). - ^1H NMR (60 MHz): δ 0.8 - 2.5 (br m, 6 CH_2), 2.71 (br m, 14a-H), - 3.50 (m, 8a-H), superimposed by 3.57 (d, $J_{14a,14b}$ = 10.0 Hz, 14b-H), 5.31, 6.15 (AB, $J_{5,6}$ = 7.8 Hz, 5-H and 6-H), 6.6 - 7.4 (m, 9 arom. H). - MS (90 °C); *m/z* (%): 330 (47) [M^+, ^{13}C 12.0/12.5, **7a**$^+$], 220 (100) [$C_{15}H_{12}N_2^+$, **18**, HR 220.0998/.1004], 156 (8) [$C_{10}H_8N_2^+$], 130 (14) [$C_9H_8N^+$, isoquinolinium], 129 (22) [$C_9H_7N^+$, isoquinoline], 91 (13), 77 (15) [$C_6H_5^+$].

1-(*trans*-2-Anilinocyclooctyl)isoquinoline (8a). (a) The purification of the oily **7a** (2.0 mmol experiment) was attempted by PLC; development with benzene and elution with CH_2Cl_2 afforded 510 mg (77%) of an oil (R_f 0.65), ^1H NMR-identical with **7a**. A yellow layer was eluted with hot acetone and gave 90 mg (14%) of pale-yellow crystals, mp 139-140 °C (CH_2Cl_2/hexane 1:3). - IR (KBr): $\tilde{\nu}$ 692 cm^{-1}, 730, 820 (arom. and *cis*-olefinic CH out-of-plane deform.), 1502, 1603 (arom. ring vibr.), 3320 (N-H). - ^1H NMR (80 MHz): δ 1.3 - 2.2 (2 br m, 6 CH_2), 3.28 (br s, NH, disappeared with D_2O), 3.81 (m, 2'-H), 4.58 (m, 1'-H), 6.3 - 7.2 (2 m, 5 arom. H), 7.33, 8.37 (AX, $J_{3,4}$ = 5.6 Hz, 4-H and 3-H), 7.4 - 7.8 (m, 3 arom. H), 8.2 (m, 8-H). - ^{13}C NMR (20 MHz, H-decoupled and off-resonance): δ 24.7, 25.8, 26.7, 28.0, 29.1, 31.1 (6 t, 6 CH_2), 46.9 (br d, C-2'), 56.7 (d, C-1'), 113.7 (d, C-2/6 of C_6H_5), 116.7, 118.9, 124.3, 126.8, 127.7, 129.4 (6 d, 6 arom. CH), 128.8 (d, C-3/5 of C_6H_5), 136.5 (s, C-4a), 141.9 (d, C-3), 147.5 (s, C-1 of C_6H_5), 165.1 (s, C-1). - MS (120 °C); *m/z* (%): 330 (41) [M^+, ^{13}C 10/11], 238 (33) [M^+ - C_6H_5NH, **14**, ^{13}C 6.2/5.2], 220 (4), 212 (57), 201 (69) [M^+ - isoquinoline, $C_{14}H_{19}N^+$, **16a**], 156 (100) [$C_{10}H_8N_2^+$, HR 156.0687/.0691], 143 (92) [$C_{10}H_9N^+$,

1-methylisoquinoline$^+$?], 130 (34) [isoquinolinium$^+$], 129 (9) [isoquinoline$^+$], 119 (30), 93 (22) [$C_6H_5NH_2^+$], 77 (27) [$C_6H_5^+$]. - Anal. Calcd for $C_{23}H_{26}N_2$: C 83.59, H 7.93, N 8.48. Found C 83.63, H 8.02, N 8.29.

(b) Oily **7a** (1.00 g, 3.02 mmol) in 10 mL of $CHCl_3$ was mixed with 3.0 mL of acetic acid. After 1 d at rt, the acid was extracted with aqueous 2N sodium carbonate. Washing with water and evaporation of $CHCl_3$ left a light-brown mass which crystallized from $CHCl_3$/hexane (1:1): 834 mg (84%) of **8a** was obtained as pale-brown needles, mp 139-140 °C (IR and ^{1}H NMR spectra).

8,8a,9,10,11,12,13,14,14a,14b-Decahydro-8-(2-pyridyl)cycloocta[3,4]pyrazolo[5,1-*a*]isoquinoline (7b). Dimer (**6**) [12] (442 mg, 1.00 mmol) and 275 mg (2.50 mmol) of **1** were reacted in 4 mL of $CHCl_3$; the deep-red color faded in 2 h. Evaporation of the solvent and CC on silica gel with ether gave 651 mg (98%) of an orange-yellow oil; dissolved in little acetone, 631 mg (95%) of **7b** crystallized in colorless needles within a month at -25 °C, mp 113-114 °C (hexane). - IR (KBr): $\tilde{\nu}$ 670 cm^{-1}, 750, 768; 1436, 1468 (pair of pyridyl bands),[13] 1559, 1565, 1595 (arom. ring vibr.); 1625 (C=C-N). - ^{1}H NMR (400 MHz): δ 1.19 - 1.86 (3 m in integral ratio of 1:3:7, 11 H), 2.37 (m, 1 H), 2.71 (dddd, 14 lines resolved, 14a-H), 3.57 (d, $J_{14a,14b}$ = 10.1 Hz, 14b-H), 4.34 (ddd, J = 12.2, 7.5, 4.7 Hz, 8a-H), 5.45, 6.20 (AX, $J_{5,6}$ = 7.6 Hz, 5-H and 6-H), 6.59 (ddd, 5'-H), 6.95 (dq, 4-H), 7.01 (ddd, 1-H), 7.05 (td, 2-H), 7.08 (dt, 3'-H), 7.20 (td, 3-H), 7.44 (ddd, 4'-H), 8.23 (ddd, 6'-H). - ^{13}C NMR (100 MHz, DEPT): δ 22.4, 24.0, 26.7, 26.8, 30.8, 35.9 (6 CH_2), 50.9 (C-14a), 63.9 (C-14b), 67.9 (C-8a), 102.4 (C-5), 107.9 (C-3'), 114.8 (C-5'), 124.6, 125.3, 126.9, 128.1 (C-1 to C-4), 130.7, 131.9 (C-4a, C-14c), 137.5 (C-6), 140.7 (C-4'), 148.0 (C-6'), 161.5 (C-2'); the assignments of δ_H and δ_C are based on two-dimensional NMR analyses of related cycloadducts.[17] - MS (80 °C); *m/z* (%): 331 (17) [M$^+$, ^{13}C 3.5/4.5], 238 (22) [M$^+$ - C_5H_4N-NH, **14**], 237 (15) [M$^+$ - C_5H_4N-NH_2, **12**], 220 (100) [$C_{14}H_{10}N_3^+$, HR 220.0873/.0854, **18**], 202 (7) [$C_{13}H_{18}N_2^+$, **16b**], 156 (29) [$C_{10}H_8N_2^+$, confirmed by HR], 143 (11), 130 (9) [isoquinolinium$^+$], 129 (13) [$C_9H_7N^+$], 119 (14) [$C_7H_7N_2^+$?], 78 (8) [pyridyl$^+$]. - Anal. Calcd for $C_{22}H_{25}N_3$: C 79.72, H 7.60, N 12.68. Found C 79.48, H 7.33, N 12.58.

1-[*trans*-2-(2-Pyridyl)aminocyclooctyl]isoquinoline (8b). PLC on silica gel with ether/CCl_4 (1:1) converted **7b** partially to **8b**. Unchanged **7b** was eluted with CH_2Cl_2; 52% crystallized from hexane, mp 113-114 °C. Refluxing of the still yellow adsorbent with acetone and evaporation led to yellow crystals of **8b**, mp 137-138 °C (CH_2Cl_2/hexane 1:3) in 42% yield. - IR (KBr): $\tilde{\nu}$ 735 cm^{-1}, 749, 768, 822 (arom. CH out-of-plane deform.), 1444, 1488, 1511, 1605 (arom. ring vibr.), 3325 (N-H). - ^{1}H NMR (400 MHz): δ 1.5 - 2.2 (m, 6 CH_2), 3.91 (br s, 2'-H), 4.42 (d, J = 7.1 Hz, disappeared with D_2O, NH), 4.76 (ddd, 1'-H), 6.30 (br s, 3-H of pyridyl), 6.36 (t, 5-H of pyridyl), 7.25 (t, 7-H), 7.41 (d, $J_{3,4}$ = 5.5 Hz, 4-H), 7.58 (t, 4-H of pyridyl), 7.62 (td, 6-H), 7.75 (dd, 5-H), 7.81 (br d, 8-H), 8.21 (d, 6-H of pyridyl), 8.40 (d, $J_{3,4}$ = 5.5 Hz, 3-H); the ^{1}H and ^{13}C of isoquinolyl were assigned by comparison with those of isoquinoline itself. - ^{13}C NMR (100 MHz, DEPT): δ 24.7, 25.7, 26.8, 28.1, 29.5, 31.3 (6 CH_2, 4 signals broadened), 46.0 (br, C-2'), 55.3 (C-1'), 106,3 (br, Py C-3), 112.2 (Py C-5), 119.0 (br, C-4), 124.1 (C-8a), 124.4, 127.0 (C-5, C-8), 127.6, 129.5 (C-6, C-7), 136.5 (C-4a), 137.1 (br, Py C-4), 141.9 (br, C-3), 147.9 (Py C-6), 158.2 (br, Py C-2), 164.8 (C-1); the line broade-

ning suggests that the rate constant of cyclooctane ring inversion is approaching the NMR time scale; several ^{1}H signals likewise are broadened. - MS (120 °C); *m/z* (%): 331 (13) [M^+], 260 (11), 238 (72) [$C_{17}H_{20}N^+$, **14**], 237 (65) [M^+ - C_5H_4N-NH_2, **12**], 220 (5%) **[17]**, 212 (41), 202 (45) [$C_{13}H_{18}N_2^+$, **16b**], 168 (18), 157 (55), 156 (100) [$C_{10}H_8N_2^+$], 143 (36), 133 (21), 130 (14) [isoquinolinium$^+$], 129 (8) [isoquinoline$^+$], 120 (23), 119 (45), 94 (20) [$C_5H_6N_2^+$, pyridylamino$^+$], 88 (25), 78 (27) [pyridyl$^+$]. - Anal. Calcd for $C_{22}H_{25}N_3$: C 79.72, H 7.60, N 12.68. Found C 79.77, H 7.62, N 12.65.

8,8a,9,10,13,14,14a,14b-Octahydro-8-phenylcycloocta[3,4]pyrazolo[5,1-*a*]isoquinoline (9a). The solution of **4** (592 mg, 2.00 mmol) in 4 mL of CH_2Cl_2 at 0 °C was mixed with 280 mg (2.59 mmol) of *(E,Z)*-1,5-cyclooctadiene [6] (**2**); the redbrown solution faded in 20 min. The solvent was removed, and the residue subjected to CC on silica gel with ether. The oil crystallized from a small volume of ether in 14 d at 5 °C, and 614 mg (93%) of **9a** was obtained in colorless crystals, mp 117-118 °C (hexane). - IR (KBr): $\tilde{\nu}$ 695 cm^{-1}, 736, 750, 757 (arom. CH out-of-plane deform.), 1456, 1493, 1600 (arom. ring vibr.), 1623 st (C=C-N). - ^{1}H NMR (400 MHz): δ 1.14 - 1.25 (m, 1 H), 1.74 - 1.83 (m, 2 H), 2.09 - 2.37 (m, 5 H), 2.63 (dddd, 14 lines visible, 14a-H), 3.57 (ddd, 8a-H), 3.68 (d, $J_{14a,14b}$ = 10.5 Hz, 14b-H); 5.42, 6.20 (AX, $J_{5,6}$ = 7.6 Hz, 5-H and 6-H), 5.62 - 5.77 (m, 15 lines, 11-H and 12-H), 6.83 (tt, 4'-H), 6.95 (dd, 4-H), 6.98 (ddd, 2'/6'-H), 7.01 (dd, 1-H), 7.05 (td, 2-H), 7.21 (td, 3-H), 7.23 (dd, 3'-/5'-H). - ^{13}C NMR (100 MHz, DEPT): δ 23.2, 25.4 (C-9, C-14), 28.4, 33.9 (C-10, C-13), 53.0 (C-14a), 66.1 (C-8a), 69.1 (C-14b), 101.7 (C-5), 112.9 (C-2'/6'), 119.5 (C-4'), 124.5, 125.1, 127.1, 128.1 (C-1 to C-4), 129.1 (C-3'/5'), 129.6, 130.1 (C-11, C-12), 131.0, 131.6 (C-4a, C-14c), 141.0 (C-6), 151.4 (C-1'). - MS (90 °C); *m/z* (%): 328 (89) [M^+, ^{13}C 23/24], 236 (3) **[15]**, 220 (100) [$C_{15}H_{12}N_2^+$, ^{13}C 17/17], 219 (10), 205 (16), 188 (15), 156 (15) [$C_{10}H_8N_2^+$], 145 (10), 143 (10), 130 (24) [$C_9H_8N^+$], 129 (37) [$C_9H_7N^+$], 119 (20), 93 (24) [$C_6H_5NH_2^+$], 91 (32), 79 (40), 77 (45) [$C_6H_5^+$]. - Anal. Calcd for $C_{23}H_{24}N_2$: C 84.10, H 7.37, N 8.53. Found C 84.29, H 7.31, N 8.83.

X-Ray Diffraction Analysis of 9a (Table 1, Figure 1). $C_{23}H_{24}N_2$, mol. mass 328.4, monoclinic. Space group $P2_1/c$, No. 14. Unit cell dimensions: a = 17.467(3), b = 6.0978(8), c = 17.355(6) Å, ß = 103.09(2)°, volume 1800.5(7) Å^3, Z = 4, D_c = 1.212 mg/ml; $F(000)$ = 704, T = 294(2) K, μ (Mo-K_α) = 0.071 mm^{-1}. Data collection: CAD4 Diffractometer, transparent plate (.13 x .33 x .53 mm), mounted in a glass capillary, cell constants from 25 centered reflections. Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, ω-2Θ-scan, scan width (0.71 + 0.66 tan Θ)°, maximum measuring time 60 sec, intensity of three standard reflections checked every two hours, Θ range 2.39 - 23.97° for all $-h$, $+k$, $\pm l$ reflections, 2902 reflections measured, 2799 unique and 1872 with $I > 2\sigma(I)$. Structure solution by SHELXS-86 and refinement by SHELXL-93,[28] non-hydrogen atoms refined anisotropically, hydrogens with U_i = 1.2 x U_{eq} of the adjacent carbon atom. Full-matrix refinement against F^2. Final $R1$ = 0.0640 and w$R2$ = 0.1525 for 1872 reflections with $I > 2\sigma(I)$ and 226 variables. $R1$ = 0.1010 and w$R2$ = 0.1707 for all data. Weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis 0.193 and -0.207 e Å^{-3}. ZORTEP plot.[29] The data have been deposited with the Cambridge Crystallographic Data Centre (no. 101763).

8,8a,9,10,13,14,14a,14b-Octahydro-8-(2-pyridyl)cycloocta[3,4]pyrazolo[5,1-*a*]isoquinoline(9b). *(E,Z)*-1,5-cyclooctadiene (**2**, 280 mg, 2.59 mmol) was added to 442 mg (1.00 mmol) of **6** in 5 mL of $CHCl_3$; the redbrown solution turned yellow in 1.5 h. After CC of the residue on silica gel with ether, 651 mg (99%) of a yellow oil was obtained. Keeping it in little hexane for 8 d at -25 °C, 617 mg (94%) of **9b** precipitated as colorless needles, mp 137-138 °C. - IR (KBr): $\tilde{\nu}$ 674 cm^{-1}, 732, 753, 770 (arom. CH out-of-plane deform.), 1433, 1466 vst (pyridyl bands),[13] 1488, 1565, 1588 (arom. ring vibr.), 1623 st (C=C-N vibr.). - ^1H NMR (400 MHz): δ 1.24 (m, 1 H), 1.61 -1.77 (m, 2 H), 2.12 (m, 1 H), 2.22 - 2.39 (m, 4 H, 10-H_2, 13-H_2), 2.67 (dddd, 12 lines visible, 14a-H), 3.62 (d, $J_{14a,14b}$ = 10.4 Hz, 14b-H), 4.29 (ddd, 7 lines, 8a-H), 5.46 and 6.19 (AX, $J_{5,6}$ = 7.6 Hz, 5-H and 6-H), 5.62 and 5.77 (2 ddd, vinylic 11-H/12-H), 6.69 (ddd, 5'-H), 6.94 (dq, 4-H), 7.01 (dq, 1-H), 7.05 (td, 2-H), 7.07 (dt, 3'-H), 7.20 (td, 3-H), 7.44 (ddd, 4'-H), 8.23 (ddd, 6'-H). - MS (95 °C); *m/z* (%): 329 (19) [M^+, ^{13}C 4.6/4.8], 236 (13) [$C_{17}H_{18}N^+$, **15**, ^{13}C 2.5/2.7], 235 (8), 220 (79) [$C_{14}H_{10}N_3^+$, **17**], 205 (6), 169 (12), 156 (100) [$C_{10}H_8N_2^+$], 143 (13), 130 (11) [$C_9H_8N^+$], 129 (18) [$C_9H_7N^+$], 120 (13), 119 (14), 95 (9), 79 (19) [$C_5H_5N^+$], 78 (21) [$C_5H_4N^+$]. - Anal. Calcd for $C_{22}H_{23}N_3$: C 80.21, H 7.04, N 12.76. Found C 80.39, H 6.91, N 12.93.

1-[*trans*-2-(2-Pyridyl)aminocyclooct-5-enyl]isoquinoline (10b). PLC of **9b** on silica gel with CH_2Cl_2 rendered back 52% of **9b**, mp 137-138 °C. The *sec*-amine (**10b**) was extracted from the yellow layer with hot acetone; pale-yellow crystals, mp 152-153 °C (hexane/CH_2Cl_2), were obtained in 40% yield. - IR (KBr): $\tilde{\nu}$ 680 cm^{-1}, 713, 739, 750, 772, 824, 1335; 1444, 1456 st (pair of pyridyl bands); 1501 w, 1596 m, 1603 st (arom. ring vibr.), 3232 st (N-H). - ^1H NMR (60 MHz): δ 0.7 - 2.9 (m br, 4 CH_2), 4.20 (dt, 2'-H), superimposed by 4.3 (br s, NH, disappeared with D_2O), 4.70 (br s, 1'-H), 5.80 (m, vinylic 5'-H, 6'-H), 6.1 - 6.5 (m, 2 arom. H), 7.0 - 7.9 (m, 6 arom. H), 8.10 (d, 6-H of pyridyl), 8.29 (d, $J_{3,4}$ = 6 Hz, 3-H). - MS (130 °); *m/z* (%): 329 (6) [M^+, ^{13}C 1.4/1.6], 236 (19) [M^+ - C_5H_4N-NH, **15**], 235 (15) [$C_{17}H_{17}N^+$, **13**], 169 (11), 168 (8), 156 (100) [$C_{10}H_8N_2^+$], 143 (9), 130 (4), 129 (3), 128 (5), 120 (9), 119 (17), 78 (7) [pyridyl$^+$]. - Anal. Calcd for $C_{22}H_{23}N_3$: C 80.21, H 7.04, N 12.76. Found C 80.31, H 6.93, N 12.82.

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