ON THE REDUCTION OF *vic*-DIOXO-PYRROLO[2,3-*b*]INDOLES WITH LITHIUM ALUMINUM HYDRIDE *

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Abstract - Dioxopyrrol[2,3-*b*]indoles and their structural analogues, diaza[n,3,3]propellanediones were reduced by lithium aluminum hydride affording their hydrogenated derivatives (**1**) and (**2**), each of them representing a mixture of diastereomers. Under equal reaction conditions an open-chain compound (**3**) was obtained by reduction of 2,3-dioxo-8,8a-diphenyl-1,2,8,8a-tetrahydropyrrolo[2,3-*b*]indole. **3** cyclizes with oxalyl chloride affording **4**. Under acidic conditions **1** and **2** could be decomposed to the indole derivatives (**5**) and (**6**), respectively.

The basic structural skeleton (**I**) of the alkaloid physostigmine, which has found an interest in the treatment of Alzheimer disease,[1] is also found in pyrrolo[2,3-*b*]indole derivatives, synthesized by Kollenz *et al.* through a

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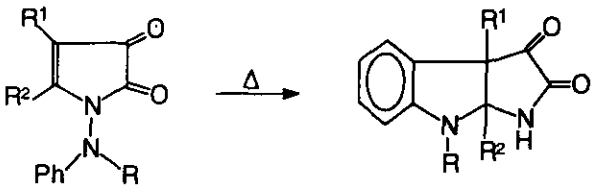
* dedicated to Prof.A.Katritzky on the occasion of his 65th birthday.

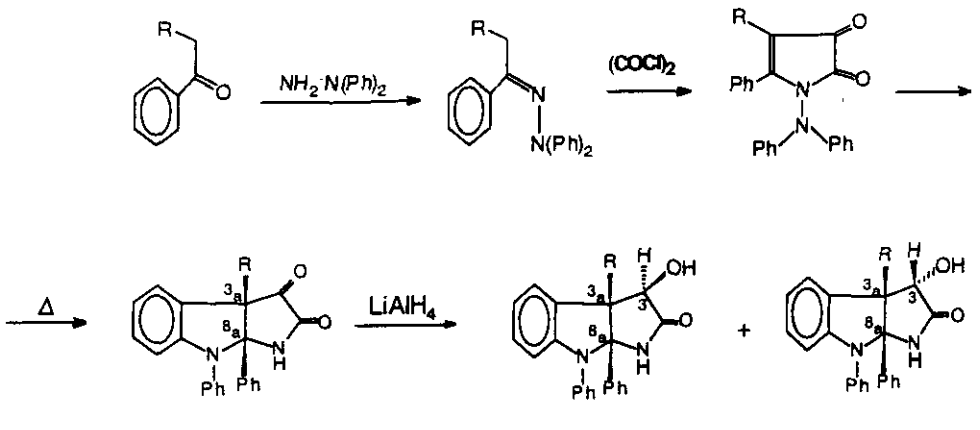
thermical Fischer-indole rearrangement of 4,5-disubstituted 1-diphenylaminopyrrole-2,3-diones, resulting from cyclocondensation reactions of *N,N*-diphenylhydrazones and oxalyl chloride:[2]



(I)

In structure (**I**) two parts could be modified - the benzene ring and the pyrroldione moiety. Chemical modifications of the benzene ring, in particular at C-5 position, have been done by Hutter.[3] The modification of pyrroldione moiety we tried was to reduce one (or both)carbonyl groups by lithium aluminum hydride into the *CH-OH* (or CH_2) *moieties . Recently, it was reported that from a-* diketones a stereoselective reduction to OH - groups can be achieved by using a carbonyl reductase.[4] In all our experiments only one carbonyl group was reduced. This can be explained reasonably from the reduction mechanism. $LiAlH_4$ prefers to attack that carbonyl carbon in *a*-diketo compounds which exhibits higher reactivity within that reduction process due to a lower electron density.[5] The experimental findings are in agreement with the behaviour of $LiAlH_4$. As shown in the Scheme, the primary Fischer-indolization process of the pyrrol-2,3-diones into the pyrrolo[2,3-*b*]indoles leads to an equimolar mixture of two enantiomeric molecules since from sterical reasons the "*cis*"-configuration of the substituents at C-3a and C-8a, respectively, is only possible. An extraordinary high ring strain would prevent the corresponding "*trans*"-products to be formed.

Reduction of that racemate should now lead to 4 stereoisomers, always two of them representing a pair of diastereomers (**1A,B**). It is interesting to note, that the experimental (=spectroscopic) findings show a remarkable diastereoselectivity with **1a** and even diastereospecifity with **1b**! The reason for that selectivity comes from the fact, that due to sterical hinderance the $LiAlH_4$ attacks predominantly **1a** or even exclusively **1b** the C=O from the side opposite to the substituent at C-3a![6]



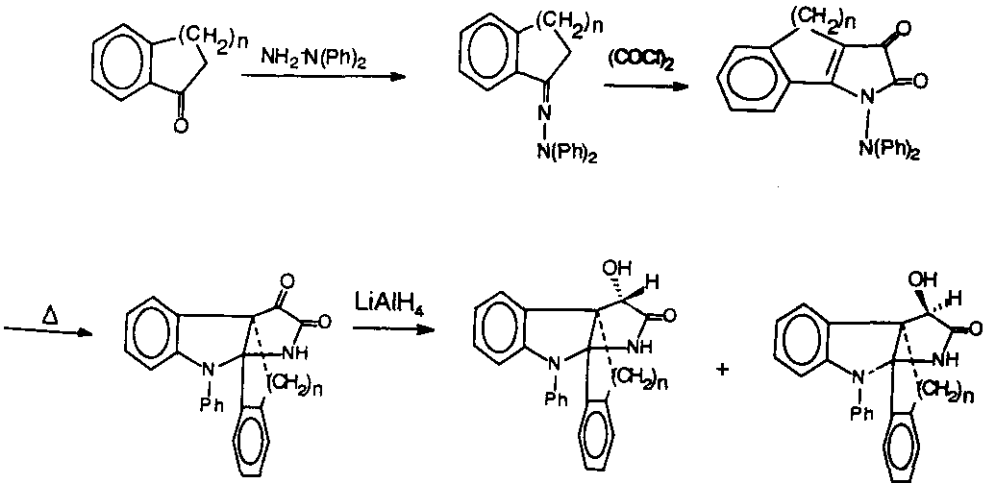
1	R	diastereomers ratio 1A /1B
a	Me	84 /16
b	Bzl	100 /0

The structure of reduction products was confirmed, besides the analytical data, by spectroscopic measurements:

The ir spectrum of **1a** shows characteristic absorption bands of N-H, O-H (2900-3500), and C=O (1695 cm^{-1}). In the ^1H nmr spectrum , the signals of higher intensity at 2.75, 4.30 ppm (d,J=7.8 Hz) were assigned to OH and C-H of **1A**, clarified by a NOE-experiment. Irradiating the proton at 4.30 ppm no resonance of the methyl group (1.12 ppm) was observed thus indicating their " *anti* "-position. In the second diastereomer(**1B**),the position of CH_3/C-H is " *syn* "-, the signal of methyl group slightly shifted upfield (0.93 ppm); the low intense signals at 2.85 and 4.50 ppm (d,J=4.6 Hz) were assigned to the corresponding OH and C-H, respectively. From the integration of signals the ratio of diastereomers (**1A/B**) is found approximately 84/16. The ir spectrum of **1b** is nearly identical with that of **1a**. Surprisingly, in the ^1H nmr spectrum of **1b** only one diastereomer was detected: The corresponding OH/CH-protons are found at 2.46, 4.72 ppm (d, J=4.8 Hz), respectively. The two protons H_a and H_b of the benzyl group are chemically unequivalent (d,^2J = 12.5 Hz); H_a, which is closer to the OH- group, should get a downfield shift (2.75 ppm) compared to H_b (2.2 ppm).

The reason for the absence of the second diastereomer in **1b** could be seen in the more bulky Ph-CH_2- group which allows the $LiAlH_4$ to attack the C=O from the non-hindered side only.

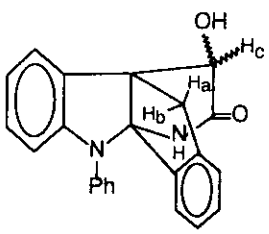
Using C-4, C-5 bridged pyrroldiones the thermal Fischer-indolization affords diaza[n,3,3]propellanes, the pyrroldione moiety of which again can be reduced by $LiAlH_4$ leading to the propellanes (**2**).



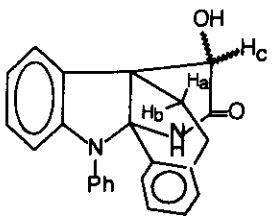
2A 2B

2	n	diastereomers ratio 2A /2B
a	1	60 / 40
b	2	90 / 10

The ir spectra of **2** exhibit characteristical absorption bands at 2900-3500 cm^{-1} (NH, OH, CH) and 1695 cm^{-1} (**2a**)/1690 cm^{-1} (**2b**) (C=O). The ^1H nmr spectrum of **2a** makes evident a ratio of diastereomers (**2A/B**) of about 6:4. One signal of H_c appeared at 4.64 ppm (higher intensity = less hindered attack of $LiAlH_4$ = "*anti*"-position to the -CH_2- bridge) coming from **2A**, H_c of **2B** is found at 4.43 ppm (lower intensity = attack of $LiAlH_4$ slightly unfavoured = "*syn*"-position to the -CH_2- bridge). The corresponding OH-protons absorb at 2.92 and 3.19 ppm (broad, exchangeable by D_2O). The two protons of the -CH_2- bridge (H_a and H_b,d,^2J=16.3 Hz) are unequivalent.In addition, H_a is splitted into two signals (3.61, 3.82 ppm, respectively) coming from interaction through space with the OH- group (**2A**). H_b is detected at 3.34 ppm.



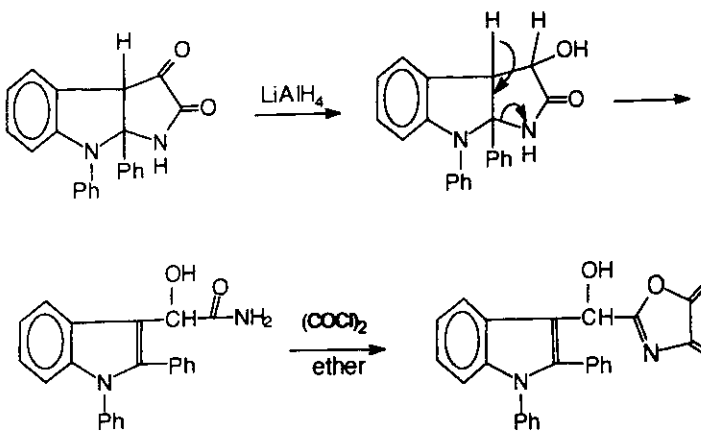
2a



2b

The ^{1}H nmr spectrum of **2b** exhibits H_c of the diastereomers (**2A/B**) at 4.4 ppm (**2A**) and 4.62 ppm (**2B**) as singlets, their relative intensities indicate a ratio of diastereomers of approximately 90:10. In **2A** the chemical shift values of the two protons (H_a, H_b) of that CH_2- group influenced by the -OH group, are found at 2.62 ppm (H_a) and 1.95 ppm (H_b). The shift difference again comes from the "through space" interaction of the -OH group. Both signals are splitted due to geminal- and vicinal (-CH_2 group) coupling (^{2}J=15 Hz, ^{3}J=3 Hz). The lower-intensity signal of H_a of the diastereomer (**2B**) appears at 2.26 ppm. The benzylic CH_2 is observed at 2.7-2.9 ppm (multiplet).

As an additional example the reduction of the 2,3-dioxo-8,8a-diphenyl-1,2,8,8a-tetrahydropyrrolo[2,3-*b*]-indole[2d] with $LiAlH_4$ was investigated. Product (**3**) was further subjected to react with oxalyl chloride affording the indole derivative (**4**):



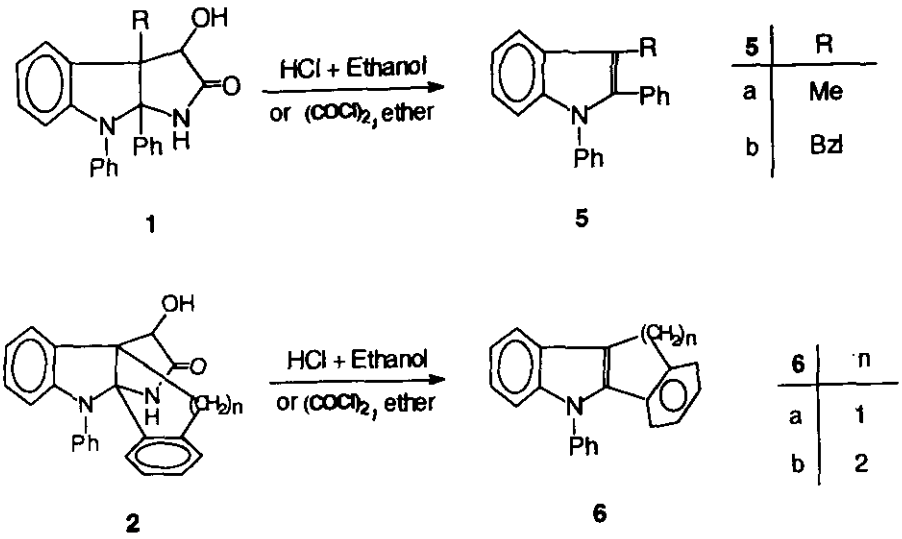
3 **4**

In contrary to the results discussed above, the primary formed reduced product is not stable but undergoes an elimination reaction to afford the racemic ring-opened indole derivative (**3**). This elimination process has been observed with the educt itself[2d] and corresponds to the last step of the Fischer-indolization, the elimination of NH_3.[7] In the ir spectrum of **3** the NH_2 group absorbs at 3350, 3470 cm^{-1}, the absorption bands at 2900-3300, 1680 cm^{-1} were assigned to OH and C=O respectively. In the ^1H nmr spectrum, the signals of OH and C-H appeared at 3.55 and 5.32 ppm (d, J=2.8 Hz) respectively. The two protons of the amide-group are chemical nonequivalent (5.55, 6.12 ppm, respectively), demonstrated by a D_2O-exchange experiment. The open-ring structure of **3** was further confirmed by ^{13}C nmr measurements: Only one sp^3 carbon was detected at 67 ppm (d, J=137.5 Hz). the signal at 176 ppm was assigned to the amide-carbonyl.

The ir spectrum of **4** shows the characteristic absorption bands of O-H (3000-3300), O-C=O (1770) and N-C=O (1725 cm^{-1}). In the ^1H nmr spectrum the signals at 6.42 and 12.55 ppm were assigned to the C-H and OH protons respectively. The element analytical data as well as the ^1H nmr spectrum (s, 2.36ppm, $PhCH_3$) indicated the product crystallizing with one half mole of solvent (toluene). From the ^{13}C nmr spectrum of **4** the assignment of signals is easy : 75.5 (d,J= 135 Hz, chiral carbon), 168.6 (s, O-C=O), 154.0 (s, N-C=O), 141,7 ppm (s, ring-C=N).

Indole derivatives (**5**) and (**6**), respectively, were obtained in yields of 76-93%, when compounds (**1**) and (**2**) were treated with acidic ethanol. Using oxalyl chloride instead of acidic ethanol gave the same results:

It is interesting to note, that the indoles (**5a**, **6a** and **6b**) were also obtained from the corresponding non-reduced pyrrol[2,3-*b*]indolediones or diaza[n,3,3]propellanediones by hydrolysis with alkaline H_2O_2 or heating.[2a,2f,2g] In contrast, hydrolysis in acidic medium leads to quite different products.[2a] The structure of the indoles were determined and confirmed by spectroscopic and analytical data or compared with the corresponding data from the literature.[2a,2f,2g]



EXPERIMENTAL

Melting points were determined on a Tottoli Apparatus and are *uncorrected*. Elemental Analyses were performed with a Carlo Erba Elemental Analyzer. Ir spectra were recorded on a Perkin-Elmer 421. ^{1}H and ^{13}C-nmr spectra were obtained on a Varian 200 Gemini spectrometer with TMS as internal standard.

General Procedure of Reduction: To a stirred suspension of the educt (pyrrolo[2,3-*b*]indoles or diazapropellanes) *(0.6 mmol) in 50 ml of dry ether,* 0.8 mmol(30.4 mg) of lithium aluminum hydride (1 M solution in ether) were added dropwise. Then the mixture was stirred at room temperature for about 4 h. The complex formed was decomposed by adding water. After filtration , the ether layer was washed with water twice, dried over anhydrous magnesium sulfate. Ether was removed and the crude products were recrystallized from ethanol (**1a**, **2a**, **2b**) or benzene (**1b**, **3**).

2-Oxo-3-hydroxy-8,8a-diphenyl-1,2,3,3a,8,8a-hexahydro-3a-methylpyrrolo[2,3-*b*]indole (**1a**): Yield 0.15 g (70%), mp 234°C. Ir(KBr): 3320 (NH), 2900-3500 (OH), 1695 cm^{-1} (C=O). ^{1}H Nmr ($CDCl_3$): *0.93* (*s*, CH_3 of 1B), 1.12 (s, CH_3 of 1A), 2.75 (d, J= 7.8 Hz, OH of 1A), 2.85 (d, J= 4.6 Hz,OH of 1B), 4.30 (d, J=7.8

Hz, C-H of 1A), 4.50 (d, J= 4.6 Hz, C-H of 1B), 6.28 (s, 1H, NH), 6.6-7.6 (m, 14H , Ph-H). Anal. Calcd for $C_{23}H_{20}N_2O_2$: C,77.51; H, 5.66; N, 7.86. Found: C, 77.47; H, 5.51; N, 7.80.

2-Oxo-3-hydroxy-8,8a-diphenyl-1,2,3,3a,8,8a-hexahydro-3a-benzylpyrrolo[2,3-*b*]indole (**1b**): Yield 0.15 g (59%), mp 228°C. Ir(KBr): 3330 (NH), 2900-3500 (OH), 1685 cm^{-1} (C=O). ^1H Nmr ($CDCl_3$): 2.29 (d, J=12.5 Hz, 1H, CH_b), 2.46 (d, J=4.8 Hz, 1H, OH), 2.75 (d, J=12.5 Hz, 1H, CH_a), 4.72 (d, J=4.8 Hz, 1H, C-H), 6.32 (s, 1H, NH), 6.6-7.7 (m, 14H, Ph-H). Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found : C, 80.50; H, 5.26; N, 5.97.

12-Oxo-13-hydroxy-5-phenyl-5H,10H-9b,4b-iminoethanoindeno[1,2-*b*]indole (**2a**): Yield 72 mg (34%), mp 244°C. Ir(KBr): 3300 (NH), 2900-3500 (OH), 1690 cm^{-1} (C=O). ^1H Nmr($CDCl_3$): 2.92 (s, OH of 2B), 3.19 (s, OH of 2A), 3.34 (d, J=16.3 Hz, 1H, H_b), 3.61 (d, J=16.3 Hz, H_a of 2B), 3.82 (d, J=16.3 Hz, H_a of 2A), 4.43 (s, H_c of 2B), 4.64 (s, H_c of 2A), 6.2-7.6 (m, 14H, Ph-H and NH). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.94; H, 5.12; N, 7.91. Found: C, 78.09; H, 5.15; N, 7.83.

13-Oxo-14-hydroxy-11-phenyl-5,6-dihydro-6a,11a-iminoethanobenzo[a]carbazol (**2b**): Yield 66mg (30%), mp 216°C. Ir(KBr): 3360 (NH), 2900-3500 (OH), 1690 cm^{-1} (C=O). ^1H Nmr($CDCl_3$): 1.95 (td, ^2J=15 Hz, ^3J=3 Hz, H_b), 2.26 (dd, ^2J=12.5 Hz, ^3J=3 Hz, H_a of 2B), 2.62 (dt, ^2J=15 Hz, ^3J=3 Hz, H_a of 2A), 2.70-2.90 (m, 2H, CH_2), 4.40 (s, H_c of 2A), 4.62 (s, H_c of 2B), 6.3-7.7 (m, 13H, Ph-H). Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.61. Found: C, 78.38; H, 5.24; N, 7.82.

2-Hydroxy-2-(1,2-diphenyl-indol-3-yl)acetylamide (**3**): Yield 115 mg (56%), mp 210°C. Ir(KBr): 3350, 3470 (NH_2), 2900-3500 (OH), 1680 cm^{-1} (C=O). ^1H Nmr ($CDCl_3$): 3.55 (d, J=2.8 Hz, 1H, OH), 5.32 (d, J=2.8 Hz, 1H, H), 5.55, 6.12 (2s, 2H, NH_2), 7.0-7.8 (m, 14H, Ph-H). ^{13}C Nmr ($CDCl_3$): 176 (C=O), 141, 138, 132.6, 131, 129.8, 127.8, 126.8, 125.8, 124.8, 122.9, 121.5, 119.8, 118.3, 112.6, 111.9, 109.4, 67 (d, ^1J=137.5 Hz,

C-H). Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found : C, 77.17; H, 5.32; N, 8.07.

1,2-Diphenyl-3-[hydroxy-(4,5-dioxo-4,5-dihydro-1,3-oxazol-2-yl)methyl]indole (**4**): To 0.12 g (0.35 mmol) of **3**, mixed with 20 ml of ether, diluted oxalyl chloride (0.08 ml (0.92 mmol) + 2 ml ether) was added dropwise. The mixture was stirred at room temperature for 40 min. Then the solvent was removed in vacuo and the residue was triturated with ether and petroleum ether. After suction the crude product was recrystallized from toluene. Yield 87 mg (63%), mp 170°C (decomp.). Ir(KBr): 3000-3300 (OH), 1770 (O-C=O), 1725 cm^{-1} (N-C=O). ^1H Nmr (DMSO-d_6): 6.42 (s, 1H, CH), 7.1-7.85 (m, 14H, Ar-H), 12.55 (s, 1H, OH). ^{13}C Nmr(DMSO-d_6): 168.6 (O-C=O), 154.0 (N-C=O), 141.7 (C=N-), 137.3, 136.7, 131.2, 130.4, 129.4, 128.6, 127.6, 126.9, 125.1, 124.1, 122.1, 120.5, 118.9, 111.4, 109.7, 107.4, 75.5 (d, C-H). Anal. Calcd for $C_{24}H_{16}N_2O_4$ + 1/2 Toluene : C, 74.64; H, 4.56; N, 6.33. Found : C, 74.84; H, 4.58; N, 6.36.

3-Methyl-1.2-diphenylindole (**5a**): a) The solution (2 ml) of concentrated HCl and ethanol (1:1) was added to the ethanol solution (3 ml) of **1a** (30 mg, 0.08 mmol) until the mixture gets turbid. Keep stirring at room temperature for 1 h, then a white solid is obtained by suction and recrystallized from ethanol. Yield 21 mg (93%), mp 116°C (lit.,[2a,8] 115°C).

b) To 0.2 g (0.56 mmol) of **1a**, suspended in 20 ml ether, diluted oxalyl chlorid (0.08 ml (0.92 mmol) in 5 ml ether) was added dropwise with stirring at room temperature for half an hour. After removing part of the ether a solid precipitated and was recrystallized from ethanol. Yield 0.14 g (88%), mp 114°C (lit.,[2a,8] 115°C). Anal. Calcd for $C_{21}H_{17}N$: C, 88.99; H, 6.05; N, 4.94. Found : C, 88.93; H, 5.90; N, 4.92.

1,2-Diphenyl-3-benzylindole (**5b**): A solution (2ml) of conc. HCl and ethanol (1:1) was added to 0.1 g (0.23 mmol) of **1b**, dissolved in 10 ml of ethanol, and stirred at room temperature for 2 h. Then the solvent was removed and the residue treated with ether and water. The ether layer was separated and washed with water twice, dried over anhydrous magnesium sulfate. After evaporation, the residue was recrystallized from ethanol

to give colorless crystals. Yield 63 mg (76%), mp 104°C. Anal. Calcd for $C_{27}H_{21}N$: C, 90.23; H, 5.89; N, 3.90. Found : C, 90.16; H, 5.89; N, 3.84.

General Procedure for the Synthesis of **6a**, **6b** :

To 0.1 g of **2a** (0.28 mmol) or **2b** (0.27 mmol), suspended in 3 ml of ethanol, 5 ml of a mixture of concentrated HCl and ethanol (1:1) was added and stirred at room temperature for 2 h. After suction, the crude product was recrystallized from ethanol.

5-Phenyl-5,10-dihydroindeno[1,2-*b*]indole (**6a**):

Yield 42 mg (54%), mp 102°C (lit.,[2f] 103-104°C).

11-Phenyl-5,6-dihydrobenzo[a]carbazole (**6b**):

Yield 64 mg (80%), mp 138°C (lit.,[2f,9] 140°C).

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