# HECK ANNULATION ON 2-POSITION OF INDOLES OR 1*H*-PYRROLO[2,3-*b*]PYRIDINE

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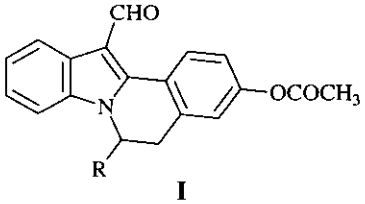
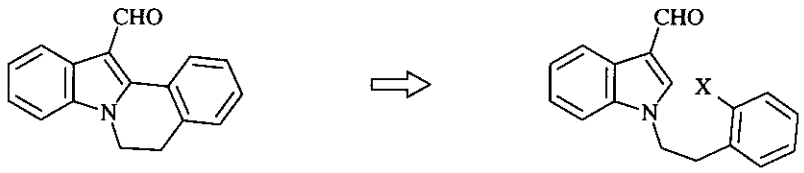
*Abstract* - 1-Substituted 3-formylindoles lead to annulated indolo[2,1-*a*]-isoquinoline or pyrrolophenanthridine *via* palladium coupling. Under the same conditions 1-substituted 7-azaindoles afforded the 7-aza analogues.

Antiestrogens play an important role[1] in the therapy of breast cancer but some patients show no clinical response to treatment with some drugs, like Tamoxifen. So there is a great need for new products with higher efficacy and more prolonged duration of response.

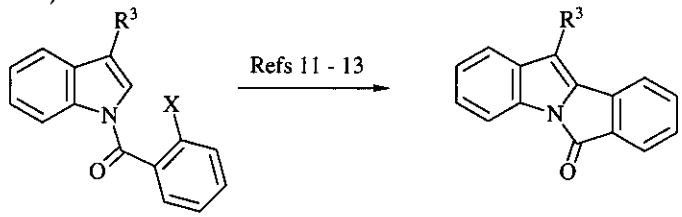
Nonsteroidal heterocyclic compounds like 2-phenylindoles,[2] benzofurans,[3] benzothiophenes[4] and benzocarbazoles[5] have already been investigated by Von Angerer.[6] Ambros reported on the binding affinities of indolo-[2,1-*a*]isoquinoline for steroid hormone receptors[7] and showed that the introduction of a formyl group into 12-position of the tetracycle of type (I) improved cytostatic activity.[8,9] Our aim was to find a straightforward synthesis of type compounds (I) possessing a formyl group and thus to obtain useful synthons for our ongoing research on oxidation of formylindoles.[10] Palladium chemistry is widely used for carbon-carbon bond formation (Heck,[11] Stille,[12] Suzuki[13] reactions); indolo[2,1-*a*]isoquinoline-12-carboxaldehyde, after retrosynthetic analysis, could be the result of the formation of carbon-carbon bond using palladium strategy between the C2 atom of the indole moiety and a Csp2 of the aromatic ring of an *N*-phenylethyl chain.




I




The cyclization of 1-benzoylindole (**1**) into tetracyclic compounds (**2**) has already been reported using different catalytic systems ( $Pd(OAc)_2$ / $PPh_3$,[14] $Pd(CH_3CN)_2Cl_2$[15]) or stoichiometric systems[16,17] (Scheme 1).

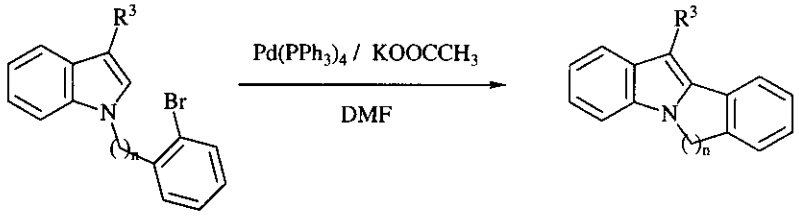



**1** **2**

X = H, I $R^3$ = H, $CH_3$, CHO

Scheme 1

Similarly, 1-alkylaryl substituted indoles (**3**) lead to cyclized compounds (**4**) in 2-position of the initial indolic system (Scheme 2).[18]

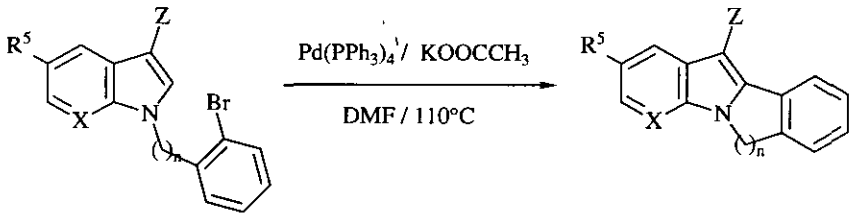



**3** n = 1 or 3 $R_3$ = H, $CH_2CON(n\text{-}C_3H_7)_2$ **4**

Scheme 2

These results show the 5-exo trig cyclization preference versus endo trig of the intermediate vinylpalladium in the reactions affording five and six membered rings. It also proves that the five membered ring is kinetically favored over the six membered one.[14] The synthesis of six membered rings to obtain pyrrolophenanthridine alkaloids has only been described in 7-position[17,19,20] but not yet in 2-position of indole. The required polycyclic compounds (**6**) were obtained in good yields (except (**6c** and **6g**)) by palladium cyclization from indole or 7-azaindole substituted with withdrawing groups (CHO, CN) in 3-position and substituted in 1-position with 2-halogenophenylalkyl groups (Scheme 3). The cyclization in 2-position occurred in

dimethylformamide (DMF) at 110°C in presence of $KOOCCH_3$ and 5% mol. of $Pd(PPh_3)_4$[18] (Scheme 3). The starting materials (**5**) were obtained by alkylation of 3-formylindole, 3-formyl-7-azaindole or indole-3-carbonitrile with α-bromobenzyl bromide (compounds (**5a,c,e**)) or 2-(2-bromophenyl)ethyl tosylate (compounds (**5b,d,f,g**)) in $CH_3CN$ in the presence of $K_2CO_3$




**5a-g** **6a-g**

| 5 - 6 | n | X | Z | $R^5$ | Reaction time | Yield of **6** (%) |
|---|---|---|---|---|---|---|
| **a** | 1 | CH | CHO | H | 2.5 h | 87 |
| **b** | 2 | CH | CHO | H | 3 h | 85 |
| **c** | 1 | N | CHO | H | 10 h | 25 |
| **d** | 2 | N | CHO | H | 3 h | 90 |
| **e** | 1 | CH | CN | H | 1.5 h | 87 |
| **f** | 2 | CH | CHO | $CH_3O$ | 2 h | 76 |
| **g** | 2 | CH | CHO | Br | 4 h | 34 |

Scheme 3

It is noteworthy that in the 7-azaindole series, the six membered ring compound (**6d**) is obtained in good yield compared to the five membered compound (**6c**). During the cyclization of 1-(2-bromobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (**5c**), 1-benzyl-1*H*-pyrrolo-[2,3-*b*]pyridine-3-carboxaldehyde (**7**) (15% yield) and unreacted **5c** (15% yield) were obtained. Similarly to a palladium intermediate postulated by Grigg,[14] the formation of a palladium complex (**8**) with the 7-nitrogen atom can explain the low yield of cyclic compound (**6c**) and the presence of dehalogenated compound (**7**). Attempts to increase the yield of compound (**6g**) (34%) were unfruitful and we observed in each case unreacted compound (**5g**) (33%). If compound (**5a**) is treated using Kraus conditions ($Pd(CH_3CN)_2Cl_2$ / $Bn(C_2H_5)_3N^+Cl^-$ /

$HCOONH_4$)[15] only 1-benzyl-3-formylindole (**9**) is obtained resulting from a dehalogenation process.

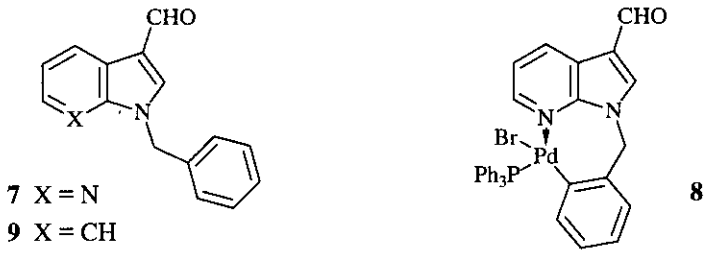
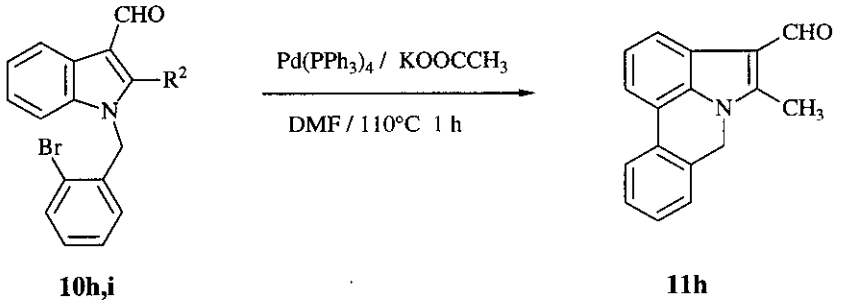



Figure 1

When the 2-position of indole was substituted with a methyl group (compound (**10h**), $R^2$ = $CH_3$), cyclization occurred in 7-position to give **11h** in 97% yield. Compound (**10i**) ($R^2$ = $COOCH_3$) gave degradation products (Scheme 4).

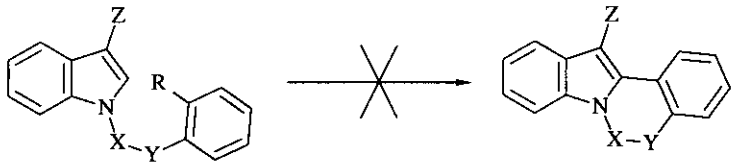



**10h,i** **11h**

Scheme 4

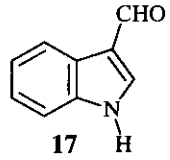
Cyclization in 7-position has been reported by Black[17] for C-7 activated dimethoxyindole derivative and by Sakamoto[20] for 7-bromoindole derivative. Our convenient procedure gave rapid access to substituted phenanthridine.

A synthesis of indoloisoquinolines (**14**), (**15**) from indolic precursors (**12a,b**) and (**13**) was designed using the same procedure (Scheme 5). Surprisingly, Itahara conditions[16] (1/2 eq. $Pd(OAc)_2$ in AcOH) used to cyclize **12a** gave the deformylated product (**16**) in 65% yield (Scheme 5). Compound (**16**) was also obtained after 3 days in 40% yield if the reaction was performed under catalytic palladium conditions (5% $Pd(OAc)_2$ / AcOH). Few examples of direct deformylation procedures have been described in the literature; palladium on charcoal at high temperature (t > 160°C) [21,22] or rhodium complexes at room temperature[23] were the most often used.



**12a** X = $CH_2$ Y = CO R = H Z = CHO
**16** X = $CH_2$ Y = CO R = H Z = H
**12b** X = $CH_2$ Y = CO R = Br Z = CHO
**13** X = CO Y = $CH_2$ R = Br Z = CHO

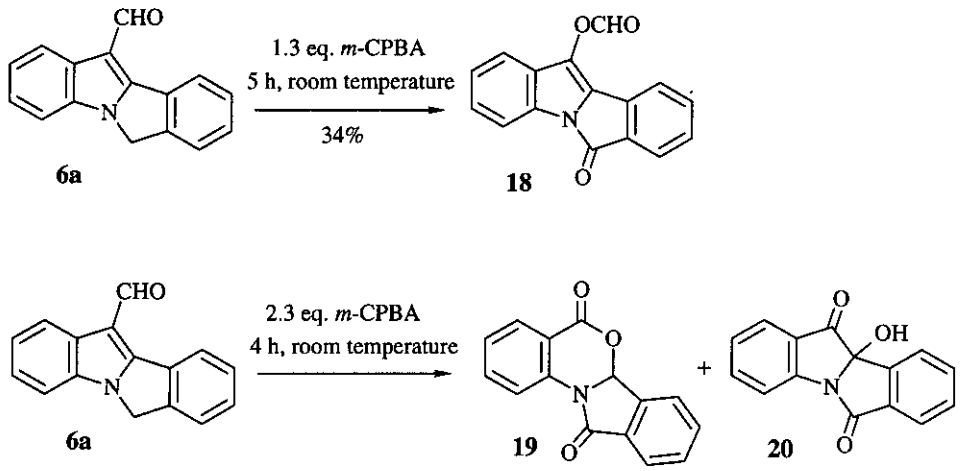
**14** X = $CH_2$ Y = CO Z = CHO
**15** X = CO Y = $CH_2$ Z = CHO
**21** X = NH Y = CO Z = H

| | Conditions | Product | Yield (%) |
|---|---|---|---|
| **12a** | A | **16** | 65 |
| **12b** | B |  **17** | 95 |
| | C | Degradation | - |
| | D | Degradation | - |
| **13** | B | **17** | 83 |
| | C | **17** | 85 |

Conditions A: 1/2 eq. $Pd(OAc)_2$, AcOH; conditions B: $Pd(PPh_3)_4$ (10%), KOAc, DMF; conditions C: $Pd(CH_3CN)_2Cl_2$ (10%), $Bn(C_2H_5)_3N^+Cl^-$, $HCO_2NH_4$, DMF; conditions D: $Pd(OAc)_2$ (10%), $PPh_3$, $Bn(C_2H_5)_3N^+Cl^-$, $K_2CO_3$, DMF.

Scheme 5

Attemps to cyclize **12b** and **13** into compounds (**14**) and (**15**) were unfruitful whatever palladium catalyst system was used. The presence of a bromine substituent on the phenyl ring did not help the cyclizations. We obtained either in high yield the 3-formylindole (**17**) or degradation products (Scheme 5). No reaction occurred when compound (**12a**) was heated with $Pd(PPh_3)_4$ in presence of KOAc in DMF at 110°C (compound (**21**) struturally related to **14** has been described by Thal[28]). Compounds (**12b**) or (**13**) on heating in DMF at 100°C, without palladium catalyst, afforded compound (**17**). Baeyer-Villiger oxidation of compounds (**6**) is still in progress in order to obtain indirectly compounds (**14**) or (**15**) since we have observed the oxidation of compound (**6a**) into lactam (**18**) accompanied by the Baeyer-Villiger oxidation of the formyl group (Scheme 6). Excess of *m*-CPBA leads to compound (**19**) (identified with an authentic sample)[27] (34% yield) and compound (**20**) (33% yield) (Scheme 6).




Scheme 6

Isoindolo[2,1-*a*]indole (**6a**) or pyrrolo[3,2,1-*de*]phenanthridine (**11h**) are obtained in good yield but unexpectedly, the corresponding six membered ketones (**14**) or (**15**) cannot be prepared by palladium annulation.

## EXPERIMENTAL SECTION

Melting points were measured using a Kofler apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 1320 spectrophotometer, $^1$H-nmr on a Bruker AM 300 spectrometer and ms on a Nermag R-10-10C spectrometer (ionization with ammonia). Chromatography was carried out with Merk silica gel (230-400 mesh) and tlc with Merk silica gel 60 $F_{254}$ tlc plates (200 μ). 1*H*-Indole-3-carbonitrile,[24] 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde[25] and 2-methyl-1*H*-indole-3-carboxaldehyde[26] were prepared according to reported procedure.

**Preparation of compounds (5a,c,e): General procedure.**

A solution of 20 ml of $CH_3CN$ containing 5 mmol of indoles or 1*H*-pyrrolo[2,3-*b*]pyridine derivatives, 1.50 g (6 mmol) of 2-bromobenzyl bromide and 1.59 g (11.5 mmol) of $K_2CO_3$ was stirred at reflux until completion (1.5 h to 3 h, tlc controlled). The solution was poured into a solution of ice and water (40 ml) and the precipitate was filtered to give compounds (**5a,c,e**).

**1-(2-Bromobenzyl)-1*H*-indole-3-carboxaldehyde (5a):** Yield: 93% , mp 142-144°C (MeOH); ir (KBr) ν: 1630 cm$^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.45 (s, 2H, $CH_2$), 6.79 (m, 1H, $H_{arom}$), 7.19 - 7.22 (m, 2H, $H_{arom}$), 7.30 - 7.35 (m, 3H, $H_{arom}$), 7.65 (m, 1H, $H_{arom}$), 7.71 (s, 1H, $H_2$), 8.35 (m, 1H, $H_{arom}$),

10.02 (s, 1H, CHO). *Anal.* Calcd for $C_{16}H_{12}NOBr$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.34; H, 3.80; N, 4.40.

**1-(2-Bromobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (5c):** Yield: 74%, mp 124-126°C (MeOH); ir (KBr) ν: 1645 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.65 (s, 2H, $CH_2$), 7.10 - 7.35 (m, 4H, $H_{arom}$), 7.64 (m, 1H, $H_{arom}$), 7.86 (s, 1H, $H_2$), 8.46 (dd, 1H, $H_6$, J = 1.5, 4.4 Hz), 8.59 (dd, 1H, $H_4$, J = 1.5, 7.4 Hz), 9.96 (s, 1H, CHO). *Anal.* Calcd for $C_{15}H_{11}N_2OBr$: C, 57.16; H, 3.52; N, 8.89. Found: C, 56.99; H, 3.50; N, 8.99.

**1-(2-Bromobenzyl)-1*H*-indole-3-carbonitrile (5e):** Yield: 86%, mp 116-118°C (MeOH); ir (KBr) ν: 2200 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.43 (s, 2H, $CH_2$), 6.72 (m, 1H, $H_{arom}$), 7.15 - 7.40 (m, 5H, $H_{arom}$), 7.62 (s, 1H, $H_2$), 7.63 (m, 1H, $H_{arom}$), 7.81 (m, 1H, $H_{arom}$). *Anal.* Calcd for $C_{16}H_{11}N_2Br$: C, 61.76; H, 3.56; N, 9.00. Found: C, 61.59; H, 3.62; N, 8.85.

**Preparation of compounds (5b,d,f,g): General procedure.**

A solution of 10 ml of $CH_3CN$ containing 2.5 mmol of indoles or 1*H*-pyrrolo[2,3-*b*]pyridine derivatives, 0.887 g (2.5 mmol) of toluene-4-sulfonic acid 2-(2-bromophenyl)ethyl ester and 0.690 g (5 mmol) of $K_2CO_3$ was stirred at reflux until all starting material had disappeared (tlc controlled). The solution was poured into a solution of ice and water (20 ml) then the precipitate was filtered to give compounds (**5b,d**). Column chromatography was performed to give **5d** (eluent: $CH_2Cl_2$).

**1-[2-(2-Bromophenyl)ethyl]-1*H*-indole-3-carboxaldehyde (5b):** Yield: 68%, mp 98-100°C (MeOH); ir (KBr) ν: 1630 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.30 (t, 2H, $CH_2Ø$, J = 7.4 Hz), 4.46 (t, 2H, $CH_2N$, J = 7.4 Hz), 6.87 (m, 1H, $H_{arom}$), 7.08 - 7.15 (m, 2H, $H_{arom}$), 7.30 - 7.38 (m, 2H, $H_{arom}$), 7.43 (m, 1H, $H_{arom}$), 7.49 (s, 1H, $H_2$), 7.59 (m, 1H, $H_{arom}$), 8.31 (m, 1H, $H_{arom}$), 9.92 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{14}NOBr$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.25; H, 4.25; N, 4.13.

**1-[2-(2-Bromophenyl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde (5d):** Yield: 61%, mp 99-101°C (MeOH); ir (KBr), ν: 1640 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.36 (t, 2H, $CH_2Ø$, J = 6.6 Hz), 4.64 (t, 2H, $CH_2N$, J = 6.6 Hz), 6.88 (m, 1H, $H_{arom}$), 7.05 - 7.15 (m, 2H, $H_{arom}$), 7.28 (dd, 1H, $H_5$, J = 5.1, 8.1 Hz), 7.50 (s, 1H, $H_2$), 7.58 (m, 1H, $H_{arom}$), 8.45 (dd, 1H, $H_6$, J = 1.5, 5.1 Hz), 8.55 (dd, 1H, $H_4$, J = 1.5, 8.1), 9.85 (s, 1H, CHO). *Anal.* Calcd for $C_{16}H_{13}N_2OBr$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.49; H, 3.89; N, 8.40.

**1-[2-(2-Bromophenyl)ethyl]-5-methoxy-1*H*-indole-3-carboxaldehyde (5f):** Yield: 62%, mp 96-98°C (MeOH); ir (KBr) ν: 1650 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.26 (t, 2H, $CH_2Ø$, J = 7.4 Hz), 3.88 (s, 3H, $OCH_3$), 4.39 (t, 2H, $CH_2N$, J = 7.4 Hz), 6.83 (m, 1H, $H_{arom}$), 6.95 (dd, 1H, $H_6$, J = 2.2, 8.8 Hz), 7.10 (m, 2H, $H_{arom}$), 7.28 (d, 1H, $H_7$, J = 8.8 Hz), 7.40 (s, 1H, $H_2$), 7.57 (m, 1H, $H_{arom}$), 7.77 (d, 1H, $H_4$, J = 2.2 Hz), 9.85 (s, 1H, CHO). *Anal.* Calcd for $C_{18}H_{16}NO_2Br$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.17; H, 4.25; N, 4.03.

**5-Bromo-1-[2-(2-bromophenyl)ethyl]-1*H*-indole-3-carboxaldehyde (5g):** Yield: 70%, mp 135-137°C (MeOH); ir (KBr) ν: 1650 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.26 (t, 2H, $CH_2Ø$, J = 6.2 Hz), 4.41 (t, 2H, $CH_2N$, J = 6.2 Hz), 6.81 (m, 1H, $H_{arom}$), 7.10 (m, 2H, $H_{arom}$), 7.24 (m, 1H, $H_{arom}$), 7.38 (d, 1H, $H_6$, J = 8.8 Hz), 7.43 (s, 1H, $H_2$), 7.56 (m, 1H, $H_{arom}$), 8.44 (d, 1H, $H_4$, J = 2.2 Hz), 9.85 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{13}NOBr_2$: C, 50.15; H, 3.22; N, 3.44. Found: C, 50.37; H, 3.37; N, 3.29.

**1-(2-Bromobenzyl)-2-methyl-1*H*-indole-3-carboxaldehyde (10h):** Similarly obtained as for compound (**5a**) starting from 2-methyl-3-formyl-1*H*-indole; Yield: 66%, mp 152-154°C (MeOH); ir (KBr), ν: 1640 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 2.64 (s, 3H, $CH_3$), 5.42 (s, 2H, $CH_2$), 6.30 (m, 1H, $H_{arom}$), 7.00 - 7.40 (m, 5H, $H_{arom}$), 7.63 (m, 1H, $H_{arom}$), 8.32 (m, 1H, $H_{arom}$), 10.27 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{14}NOBr$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.07; H, 4.20; N, 4.15.

**Methyl 1-(2-Bromobenzyl)-3-formyl-1*H*-indole-2-carboxylate (10i):** Similarly obtained as for compound (**5a**) starting from methyl 3-formyl-1*H*-indole-2-carboxylate; Yield: 65%, mp 172-174°C (MeOH); ir (KBr), ν: 1640, 1700 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.97 (s, 3H, $CH_3$), 5.85 (s, 2H, $CH_2$), 6.33 (m, 1H, $H_{arom}$), 7.05 - 7.20 (m, 2H, $H_{arom}$), 7.31 (m, 1H, $H_{arom}$), 7.35 - 7.43 (m, 2H, $H_{arom}$), 7.63 (m, 1H, $H_{arom}$), 8.32 (m, 1H, $H_{arom}$), 10.68 (s, 1H, CHO). *Anal.* Calcd for $C_{18}H_{14}NO_3Br$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.97; H, 3.70; N, 3.82.

**General procedure for cyclization:**

0.5 mmol of compounds (**5a-g**) or (**10h**), 0.049 g (0.5 mmol) of KOAc and 0.030 g (0.025 mmol) of $Pd(Ph_3)_4$ were stirred at 110°C in 7 ml of DMF. Reaction times are reported in Schemes 3 and 4. The DMF was evaporated and the crude mixture was chromatographied to give **6a-g** or **11h**.

**1*H*-Isoindolo[2,1-*a*]indole-11-carboxaldehyde (6a):** Yield: 87%, mp 183-185°C (MeOH); ir (KBr), ν: 1640 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.10 (s, 2H, $CH_2$), 7.26 - 7.60 (m, 6H, $H_{arom}$), 8.22 (m, 1H,

$\mathbf{H_{arom}}$), 8.35 (m, 1H, $\mathbf{H_{arom}}$), 10.49 (s, 1H, CHO); ms (m/z, $NH_3$): 234 ($M^+$+1). *Anal.* Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.25; H, 4.81; N, 5.83.

**5,6-Dihydroindolo[2,1-*a*]isoquinoline-12-carboxaldehyde (6b):** Yield: 85%, mp 124-126°C (MeOH); ir (KBr), ν: 1630 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.19 (t, 2H, $\mathbf{CH_2}$∅, J = 6.6 Hz), 4.27 (t, 2H, $\mathbf{CH_2}$N, J = 6.6 Hz), 7.28 - 7.47 (m, 6H, $\mathbf{H_{arom}}$), 7.99 (m, 1H, $\mathbf{H_{arom}}$), 8.46 (m, 1H, $\mathbf{H_{arom}}$), 10.53 (s, 1H, CHO); ms (m/z, $NH_3$): 248 ($M^+$+1). *Anal.* Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.50; H, 5.15; N, 5.41.

**10*H*-Pyrido[3',2':4,5]pyrrolo[2,1-*a*]isoindole-5-carboxaldehyde (6c):** Yield: 25%, mp 236-238°C (MeOH); ir (KBr) ν: 1635 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.31 (s, 2H, $\mathbf{CH_2}$), 7.27 (dd, 1H, $\mathbf{H_3}$, J = 4.4, 7.4 Hz), 7.52 - 7.56 (m, 2H, $\mathbf{H_{arom}}$), 7.82 (m, 1H, $\mathbf{H_{arom}}$), 8.33 (m, 1H, $\mathbf{H_{arom}}$), 8.37 (dd, 1H, $\mathbf{H_2}$, J = 1.5, 4.4 Hz), 8.51 (dd, 1H, $\mathbf{H_4}$, J = 1.5, 7.4 Hz), 10.52 (s, 1H, CHO); ms (m/z, $NH_3$): 235 ($M^+$+1). *Anal.* Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.80; H, 4.22; N, 11.82.

**10,11-Dihydropyrido[3',2':4,5]pyrrolo[2,1-*a*]isoquinoline-5-carboxaldehyde (6d):** Yield: 90%, mp 176-178°C (MeOH); ir (KBr) ν: 1640 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.19 (t, 2H, $\mathbf{CH_2}$∅, J = 6.6 Hz), 4.49 (t, 2H, $\mathbf{CH_2}$N, J = 6.6 Hz), 7.25 (m, 1H, $\mathbf{H_3}$), 7.35 - 7.55 (m, 3H, $\mathbf{H_{arom}}$), 7.98 (m, 1H, $\mathbf{H_{arom}}$), 8.40 (dd, 1H, $\mathbf{H_2}$, J = 1.5, 5.7 Hz), 8.55 (dd, 1H, $\mathbf{H_4}$, J = 1.5, 8.1 Hz), 10.52 (s, 1H, CHO); ms (m/z, $NH_3$): 248 ($M^+$+1). *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.21; H, 4.82; N, 11.39.

**1*H*-Isoindolo[2,1-*a*]indole-11-carbonitrile (6e):** Yield: 87%, mp 226-228°C (MeOH); ir (KBr) ν: 2200 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.14 (s, 2H, $\mathbf{CH_2}$), 7.26 - 7.36 (m, 2H, $\mathbf{H_{arom}}$), 7.40 - 7.60 (m, 4H, $\mathbf{H_{arom}}$), 7.79 (m, 1H, $\mathbf{H_{arom}}$), 8.08 (m, 1H, $\mathbf{H_{arom}}$); ms (m/z, $NH_3$): 231 ($M^+$+1). *Anal.* Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.23; H, 4.49; N, 12.26.

**5,6-Dihydro-2-methoxyindolo[2,1-*a*]isoquinoline-12-carboxaldehyde (6f):** Yield: 76%, mp 135-137°C (MeOH); ir (KBr), ν: 1630 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.16 (t, 2H, $\mathbf{CH_2}$∅, J = 6.6 Hz), 3.91 (s, 3H, $OCH_3$), 4.21 (t, 2H, $\mathbf{CH_2}$N, J = 6.6 Hz), 6.96 (dd, 1H, $\mathbf{H_6}$, J = 2.9, 8.8 Hz) 7.27 (d, 1H, $\mathbf{H_7}$, J = 8.8 Hz), 7.35 - 7.45 (m, 3H, $\mathbf{H_{arom}}$), 7.91 (m, 1H, $\mathbf{H_{arom}}$), 7.96 (d, 1H, $\mathbf{H_4}$, J = 2.9 Hz), 10.49 (s, 1H, CHO); ms (m/z, $NH_3$): 278 ($M^+$+1). *Anal.* Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.14; H, 5.26; N, 4.89.

**2-Bromo-5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carboxaldehyde (6g):** Yield: 34%, mp 192-194°C (MeOH); ir (KBr), ν: 1640 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 3.18 (t, 2H, $CH_2$Ø, J = 6.6 Hz), 4.22 (t, 2H, $CH_2$N, J = 6.6 Hz), 7.24 (m, 1H, $H_{arom}$), 7.35 - 7.50 (m, 4H, $H_{arom}$), 7.93 (m, 1H, $H_{arom}$), 8.61 (d, 1H, $H_4$, J = 2.2 Hz), 10.47 (s, 1H, CHO); ms (m/z, $NH_3$): 326 ($M^+$+1), 328 ($M^+$+3). *Anal.* Calcd for $C_{17}H_{12}NOBr$: C, 62.60; H, 3.71; N, 4.29. Found: C, 62.83; H, 3.80; N, 4.10.

**5-Methyl-7*H*-pyrrolo[3,2,1-*de*]phenanthridine-4-carboxaldehyde (11h):** Yield: 97%, mp 162-164°C (MeOH); ir (KBr) ν: 1630 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 2.68 (s, 3H, $CH_3$), 5.37 (s, 2H, $CH_2$), 7.15 - 7.40 (m, 4H, $H_{arom}$), 7.54 (m, 1H, $H_{arom}$), 7.90 (m, 1H, $H_{arom}$), 8.00 (m, 1H, $H_{arom}$), 10.17 (s, 1H, CHO); ms (m/z, $NH_3$): 248 ($M^+$+1). *Anal.* Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.35; H, 5.25; N, 5.75.

Compounds (**12a,b**) were obtained according to the preparation of compound (**5b**) using 2-chloroacetophenone for compound (**12a**) and 2,2'-dibromoacetophenone for compound (**12b**).

**1-(2-Oxo-2-phenylethyl)-1*H*-indole-3-carboxaldehyde (12a):** Yield: 87%, mp 186-188°C (MeOH); ir (KBr) ν: 1645, 1685 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.60 (s, 2H, $CH_2$), 7.19 (m, 1H, $H_{arom}$), 7.27 - 7.37 (m, 2H, $H_{arom}$), 7.53 - 7.61 (m, 2H, $H_{arom}$), 7.71 (m, 1H, $H_{arom}$), 7.76 (s, 1H, $H_2$), 8.03 (m, 2H, $H_{arom}$), 8.36 (m, 1H, $H_{arom}$), 10.07 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.38; H, 5.06; N, 5.24.

**1-[2-(2-Bromophenyl)-2-oxoethyl]-1*H*-indole-3-carboxaldehyde (12b):** Yield: 30%, mp 140-142°C (MeOH); ir (KBr) ν: 1645, 1685 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.52 (s, 2H, $CH_2$), 7.24 - 7.45 (m, 6H, $H_{arom}$), 7.69 (m, 1H, $H_{arom}$), 7.77 (s, 1H, $H_2$), 8.33 (m, 1H, $H_{arom}$), 10.04 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{12}NO_2Br$: C, 59.67; H, 3.53; N, 4.09. Found: C, 59.85; H, 3.40; N, 4.01.

**1-[2-(2-Bromophenyl)-1-oxoethyl]-1*H*-indole-3-carboxaldehyde (13)** was obtained according to the preparation described by Kraus[14] using 2-bromophenylacetic acid: Yield: 65%, mp 220-222°C (MeOH); ir (KBr) ν: 1660, 1710 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 4.49 (s, 2H, $CH_2$), 7.17 - 7.55 (m, 5H, $H_{arom}$), 7.67 (d, 1H, $H_{arom}$, J = 7.9 Hz), 8.22 (s, 1H, $H_2$), 8.30 (m, 1H, $H_{arom}$), 8.45 (m, 1H, $H_{arom}$), 10.15 (s, 1H, CHO). *Anal.* Calcd for $C_{17}H_{12}NO_2Br$: C, 59.67; H, 3.53; N, 4.09. Found: C, 59.60; H, 3.48; N, 3.99.

**1-(2-Oxophenylethyl)-1*H*-indole (16):** In 20 ml of AcOH, compound (**12**) (0.132 g, 0.50 mmol) and $Pd(OAc)_2$ (0.056 g, 0.25 mmol) were refluxed during 4 h. After evaporation *in vacuo*, the

residue was chromatographied (eluent: $CH_2Cl_2$) to give compound (**16**) (0.076 g, 65%), mp 128-130°C (MeOH); ir (KBr) ν: 1685 $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 5.52 (s, 2H, $CH_2$), 6.61 (d, 1H, $H_3$, J = 3.0 Hz), 7.05 - 7.20 (m, 4H, $H_{arom}$), 7.51 (m, 2H, $H_{arom}$), 7.64 (m, 2H, $H_{arom}$), 8.02 (m, 2H, $H_{arom}$); ms (m/z, $NH_3$): 236 ($M^+$+1). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.87; H, 5.42; N, 6.03.

**6-Oxo-6*H*-isoindolo[2,1-*a*]indol-11-yl formate (18):** In 2 ml of $CH_2Cl_2$, compound (**6a**) (0.050 g, 0.21 mmol) and *meta*-chloroperbenzoic acid (0.049 g, 0.28 mmol) were stirred at room temperature during 5 h. An aqueous solution of 5% $Na_2SO_3$ (3 ml) were added and the organic layer was separated, washed with water (2 ml), dried under $MgSO_4$ and evaporated in reduced pressure. The residue was chromatographied (eluent: $CH_2Cl_2$ / MeOH, 99 / 1, v / v) to give compound (**18**) (19 mg, 34%), mp 208-210°C (MeOH); ir (KBr) ν: 1710 (large) $cm^{-1}$; $^1$H-nmr ($CDCl_3$) δ: 7.87 (m, 2H, $H_{arom}$), 8.04 (m, 1H, $H_{arom}$), 8.20 (m, 1H, $H_{arom}$), 8.71 (m, 2H, $H_{arom}$), 8.84 (m, 2H, $H_{arom}$), 9.33 (s, 1H, OCHO); ms (m/z, $NH_3$): 264 ($M^+$+1). *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 76.82; H, 3.53; N, 5.22.

**6a*H*-Benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11-dione (19)** and **10b-Hydroxy-10b*H*-isoindolo-[2,1-*a*]indole-6,11-dione (20):** Compound (**6a**) was oxidized with 2.3 eq. of *meta*-chloroperbenzoic acid during 4 h and was worked up as compound (**18**) to give after silica gel chromatography ($CH_2Cl_2$) compound (**19**), mp 208-210°C (lit.,[27] 214-215°C) and compound (**20**), mp 178-180°C (MeOH); ir (KBr) ν: 3200, 1735, 1675 (large) $cm^{-1}$; $^1$H-nmr ($CDCl_3$+$D_2O$) δ: 7.29 (t, 1H, $H_{arom}$, J = 7.4 Hz), 7.60 (t, 1H, $H_{arom}$, J = 7.4 Hz), 7.70 - 7.90 (m, 5H, $H_{arom}$), 7.96 (m, 1H, $H_{arom}$); ms (m/z, $NH_3$): 252 ($M^+$+1), 234 ($M^+$-17). *Anal.* Calcd for $C_{15}H_9NO_3$: C, 71.71; H, 3.61; N, 5.57. Found: C, 71.52; H, 3.54; N, 5.39.

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