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The synthesis of new pyrazolo[4,3-*c*]β-carbolines (**8a,b**) is achieved by condensation of the appropriate aldehyde with 3-(4-amino-1,3-dimethylpyrazol-5-yl)indole (**4**) under Pictet- Spengler reaction conditions. Regioselective cyclization occurred at the usual indole C-2 position as evidenced from the ^{1}H- and ^{13}C nmr spectra of **8a,b** which lack the pyrrolic H-2 signal, present in **4** (δ 7.26, 1H, d, J_{CH-NH} = 2.5 Hz).

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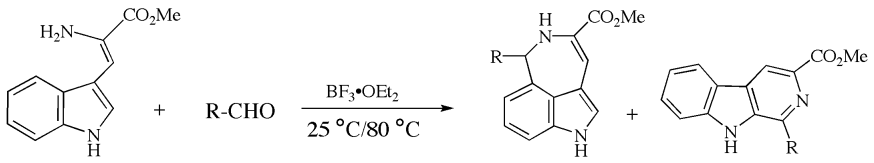
Introduction.

Condensation of dehydrotryptophan methyl ester (**1**) with alkanals, in the presence of boron trifluoride etherate, was reported to give the respective 5,6-dihydroazepino-[5,4,3-*cd*]indoles (**2**) as the major cyclization products together with small amounts of the isomeric β-carbolines (**3**) (Scheme 1) [1]. The minor products (**3a-c**) were produced by Pictet-Spengler type cyclization at position-2 of the indole nucleus, followed by further oxidation of the resultant 2,3–dihydro-β-carbolines that were, however, not detected on silica gel TLC of the reaction mixture [1]. Comparative reaction of **1** with arenecarboxaldehydes was, nonetheless, not investigated therein [1].

Scheme 1

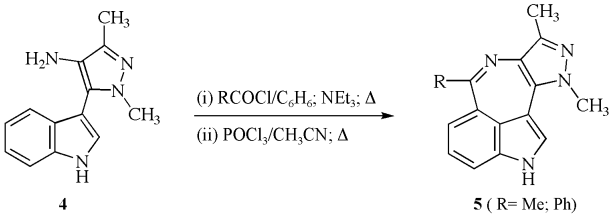


Entry	a	b	c
R	Me	*i*-Pr	*i*-Bu

Quite recently, we have utilized 3-(4-amino-1,3-dimethylpyrazol-5-yl) indole (**4**) as a synthon in the course of our work on the synthesis of some new pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]indoles (**5**) [2] under Bischler - Napieralski reaction conditions (Scheme 2).

Having the 3-(aminopyrazolyl)indole **4** in hand [2], we have investigated its condensation with 2-methylpropanal in presence of BF_3•OEt_2 (Scheme 3). After usual work-up, the expected 6,7-dihydropyrazolo[3',4':6,7]azepino[5,4,3-*cd*]-indole (**6a**) was not detected, and the main isolable crystalline product was identified as the pyrazolo[4,3-*c*]β-carboline **8a** on the basis of its spectroscopic data (*vide infra*). Under similar conditions, the reaction of **4** with 4-chlorobenzaldehyde took the same course with ultimate production of the respective β-carboline derivative **8b** (Scheme 3).

Scheme 2

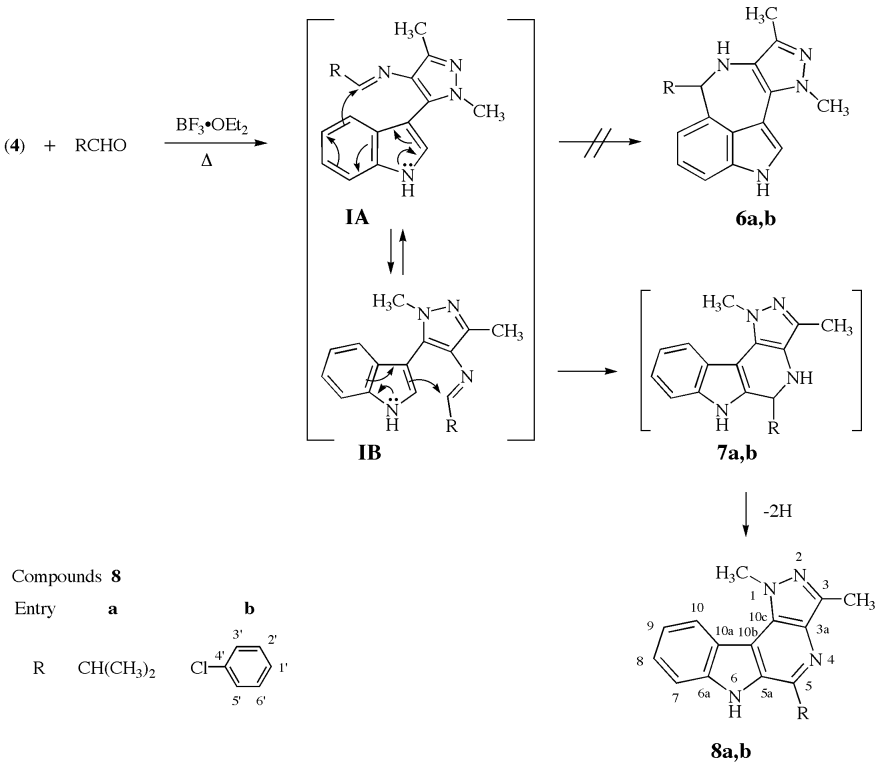


Results and Discussion.

In the present study, direct condensation of **4** with aldehydes, exemplified by 2-methylpropanal and *p*-chlorobenzaldehyde, would yield the corresponding imines (**IA** ⇌ **IB**, Scheme 3) which, in solution, underwent BF_3-catalyzed cyclization. The main recrystallized cyclized products were indentified as the pyrazolo-[4,3-*c*]β-carbolines **8a,b**. Their dihydro-β-carboline precursors **7a,b** were, however, not detected in this one-pot reaction, carried out in 1,2-dichloroethane under reflux. The formation of **8a,b** might be attributed, at least in part, to the predominance of the cisoid form **IB** of the intermediate imine which is more stable than the transoid form **IA**. The latter form suffers the burden of repulsive interaction between the N1-CH_3 and the nearby C2-*H*, whereas in **IB** such repulsion, involving N1-CH_3 and the distant C4-*H*, is virtually absent.

The ms and nmr spectral data, and microanalyses of the new compounds (**8a,b**) conform with the suggested structures, and are included in the experimental part. Thus, their ms spectra display the correct M^+ for which the measured high resolution data are in good agreement with the calculated values. ^{1}H-signal assignments are straightforward,

Scheme 3



and carbon-13 assignments are based on DEPTand 2D (COSY, HMQC, HMBC) experiments. The pyrrolic *H*-2 proton in **4** is coupled to the vicinal N1-*H* proton and thus appears as a doublet (δ 7.26, J = 2.5 Hz) that collapses to a singlet upon addition of D_2O. In accordance with this , the ^1H nmr spectra of several related 3-substituted indoles display such a doublet (δ 7.1 - 7.8, J = 2.0 - 3.1 Hz) that was assigned to the pyrrolic proton at C-2 [3]. The disappearance of this *H*-2 doublet in the ^1H nmr spectra of the cyclized products **8a,b**, provides supporting evidence that intramoecular cylization has taken place regioselectively at C-2 of the indole nucleus. Furthermore, *C*-5a in the ^{13}C nmr spectra of the cyclized products **8a,b** is a quaternary carbon compared to the pyrrolic *C*H-2 in **4**.

In conclusion, compounds **1** and **4** display different affinities in their regioselective annulation with alkanals. Currently, we are exploring the reaction of **4** with a variety of carboxyaldehydes in order to unravel the main criteria that govern regioselective cyclization at position-2 *versus* position-4 (if any) of the indole nucleus.

EXPERIMENTAL

The required synthon, 3-(4-amino-1,3-dimethylpyrazolyl)-indole (**4**), is prepared according to a reported procedure [2]. Melting points (uncorrected) were determined on an electrothermal Mel-Temp. apparatus. ^1H- and ^{13}C nmr spectra were measured on a Bruker DPX-300 instrument with TMS as internal reference. Electron impact (EI) mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. Microanalysis was performed at the microanalytical Laboratory-Inorganic Chemistry Department, Tübingen Universität, Germany.

1,3-Dimethyl-5-*iso*propyl-1*H*,6*H*-pyrazolo[3',4':5,6]pyrido-[3,4-*b*]indole (**8a**).

A solution of **4** (0.5 g, 2.2 mmoles) and 2-methylpropanal (0.17 g, 2.2 mmoles) in 1,2-dichloroethane (30 ml) was stirred at room temperature for 20 minutes. Thereafter, boron trifluoride etherate was added (2.0 ml), and the solution acquired an immediate orange color that was changed to deep red. The resulting mixture was refluxed for 1 hour, and 1,2-dichloroethane was evaporated *in vaccuo.* The solid residue was washed with aqueous sodium hydroxide (5 %), and water (20 ml), collected by suction filtration, dried and recrystallized from methanol/diethyl ether. Yield of pure product 0.34 g (55 %); mp > 270 °C (decomp); ms: m/z (% rel. int.): 278 (M^+, 78), 263(100), 250(97), 219(5), 193(8), 179(10), 139(5), 131(19), 125(8), 117(4), 111(3); hrms: Calcd for $C_{17}H_{18}N_4$: 278.153147. Found: 278.154751; ^1H nmr (300 MHz, DMSO-d_6): δ 1.50 [d, J = 6.9 Hz, 6H, $CH(CH_3)_2$], 2.60 (s, 3H, C3-CH_3), 3.9 [m, 1H, $CH(CH_3)_2$], 4.60 (s, 3H, N1-CH_3), 7.40 (dd, J = 7.6 Hz, 8.3 Hz, 1H, C9-*H*), 7.67 (dd, J = 7.6 Hz, 8.2 Hz, 1H, C8-*H*), 7.80 (d, J = 8.2 Hz, 1H, C7-*H*), 8.60 (d, J = 8.3 Hz, 1H, C10-*H*), 12.70 (br s, 1H, N6-*H*); ^{13}C nmr (75 MHz, DMSO-d_6): δ 12.0 (C3-CH_3), 21.7 [$CH(CH_3)_2$], 30.9 [$CH(CH_3)_2$], 40.0 (N1-CH_3), 113.5 (C-7), 114.0 (C-10b), 118.0 (C-10a), 121.7 (C-9), 124.2 (C-10), 129.2 (C-8), 130.1 (C-5a), 133.1 (C-3), 133.9 (C-10c), 138.3 (C-3a), 141.6 (C-6a), 147.6 (C-5).

Anal. Calcd. for $C_{17}H_{18}N_4$ (278.36): C, 73.35; H, 6.52; N, 20.13. Found: C, 73.18; H, 6.44; N, 20.06.

5-(4-Chlorophenyl)-1,3-dimethyl-1*H*,6*H*-pyrazolo[3',4':5,6]-pyrido[3,4-*b*]indole (**8b**).

This compound was prepared from **4** (0.5 g, 2.2 mmoles) and *p*-chlorobenzaldehyde (0.31 g, 2.2 mmoles) by following the same procedure described above for **8a**. The crude product was recrystallized from methanol/diethyl ether. Yield of pure product 0.34 g (45 %), mp > 320 °C (decomp); ms: m/z (% rel. int.): 346 (M^+, 100), 331(3), 311(4), 290(6), 263(7), 254(11), 228(7), 201(2), 173(15), 156(37), 135(7), 121(10), 114(9); hrms: Calcd for $C_{20}H_{15}ClN_4$: 346.098504. Found: 346.101445; ^{1}H nmr (300 MHz, DMSO-d_6): δ 2.57 (s, 3H, C3-C*H*$_3$), 4.59 (s, 3H, N1-C*H*$_3$), 7.34 (dd, J = 7.6 Hz, 8.2 Hz, 1H, C8-*H*), 7.56 (dd, J = 7.6 Hz, 8.2 Hz, 1H, C9-*H*), 7.69 (d, J = 8.6 Hz, 2H, C2'-*H* / C6'-*H*), 7.74 (d, J = 8.2 Hz, 1H, C7-*H*), 7.96 (d, J = 8.6 Hz, 2H, C3'-*H* / C5'-*H*), 8.57 (d, J = 8.2 Hz, 1H, C10-*H*), 11.89 (s, 1H, N6-*H*); ^{13}C nmr (75 MHz, DMSO-d_6): δ 11.4 (C3-*C*H$_3$), 39.99 (N-*C*H$_3$), 113.5 (C-7), 119.4 (C-10a), 120.9 (C-9), 123.3 (C-10), 127.4 (C-8), 129.1(C2'/6'), 129.4(C-10b), 131.2 (C3'/5'), 132.0 (C-3), 132.1(C-4'), 133.3(C-5a), 134.0 (C-10c), 137.0 (C-1'), 139.7 (C-6a), 140.6 (C-5), 141.7 (C-3a).

Anal. Calcd. For $C_{20}H_{15}ClN_4$ (346.82): C, 69.26; H, 4.36; Cl, 10.22; N, 16.15. Found: C, 69.38; H, 4.31; Cl, 10.13; N, 15.96.

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REFERENCES AND NOTES

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