CHEMISTRY OF INDOLES CARRYING BASIC FUNCTIONS. PART II.[1] SYNTHESIS OF 4-SUBSTITUTED CYCLOHEPT[c,d]INDOLES. A NEW ENTRY INTO THE RING SYSTEM

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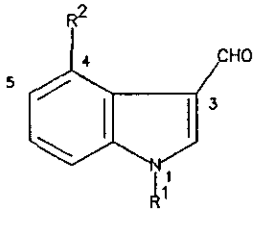
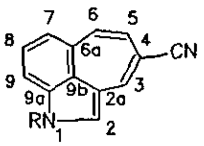
Abstract - *Cyclohept[c,d]indoles* (**7a**), (**7b**), (**12**) *were synthesized starting from 4-iodoindole-3-carboxaldehydes* (**3a**) *and* (**3b**).

Transition metals are widely used in modern organic synthesis.[2] Their application in the field of indole chemistry has been reviewed by Hegedüs.[3] One branch of this method, thallation and thallation-iodination of indole-3-carboxaldehyde (**1a**) was applied by Somei and co-workers[4] to synthesize ergot alkaloids and their precursors[5] *via* (3-formylindol-4-yl)thallium (III) bistrifluoroacetate (**2a**)[4] or 4-iodoindole-3-carboxaldehyde (**3a**).[4] By implementing this method both **2a** and **3a** were allowed to react with several olefins[6,7] in a modified Heck-reaction. The obtained 4-alkenylindole-3-carboxaldehydes proved to be suitable for further transformation.[4]
Based on the results of the above approach we intended to prepare indole-3-carboxaldehydes and their *N*-methyl analogues substituted at C-4 (**4a**, **4b**, **5a**, **5b**), as potential intermediates of lysergic acid. The starting materials (**2b**)[8] and (**3b**)[9] were prepared from *N*-methylindole-3-carboxaldehyde (**1b**)[10] by Somei's procedure. It is noted that while reproducing Somei's method[12] **6**,[11] a structural isomer of **3a**, was also isolated.



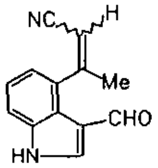
	R^1	R^2		R^1	R^2
1a	H	H	**4a**	H	$CH=CH\text{-}CH_2\text{-}COOH$
1b	Me	H	**4b**	Me	$CH=CH\text{-}CH_2\text{-}COOH$
2a	H	$Tl(TFA)_2$	**5a**	H	$CH=CH\text{-}CH_2\text{-}CN$
2b	Me	$Tl(TFA)_2$	**5b**	Me	$CH=CH\text{-}CH_2\text{-}CN$
3a	H	I			
3b	Me	I			
6	H	H, 5-I			

When the thallium derivatives (**2a**) or (**2b**) were allowed to react with allyl cyanide or vinylacetic acid or its methyl ester [DMF; 120°C; $PdCl_2$ or $Pd(OAc)_2$ catalyst; 3 equivalents of reagent], we were unable to isolate the desired compounds. On the other hand the iodo derivatives (**3a**) and (**3b**) gave unexpected but useful results. Upon reacting **3b** with allyl cyanide the tricyclic compound (**7b**)[13] was isolated in 44% yield. When the *N*-desmethyl analog (**3a**) was allowed to react under analogous reaction conditions, we isolated a further new compound (**8a**)[14] in addition to the tricyclic derivative (**7a**).[14]



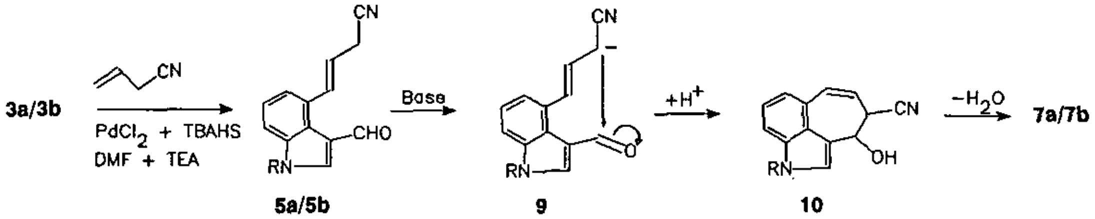
7a R=H

7b R=Me



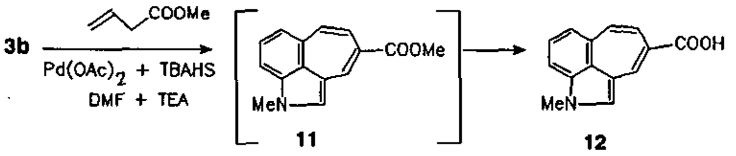
8 (E:Z = 1:2.5)

We can rationalize the formation of compounds (**7a**) and (**7b**) *via* the following sequence (Scheme 1).



Scheme 1

First the desired cyano derivatives (**5a**) or (**5b**) form in the modified Heck-reaction, followed by generation of carbanions (**9**) in the basic medium. An aldol-type reaction and subsequent water-elimination from **10** concludes in the formation of the end-products (**7a**) or (**7b**). When **3b** was allowed to react with vinylacetic acid methyl ester[15] as the olefinic component, once again a tricyclic derivative (**12**)[16] (18 %) was isolated, *i.e.* the carbomethoxy group of **11** had hydrolysed during the work-up of the reaction mixture (Scheme 2).



Scheme 2

So far only tetrahydro analogues of the ring-system represented by **7a**, **7b** and **12** have been reported in the litrerature,[17] and these tetrahydro compounds were constructed by using synthetic approaches different from ours. We are now exploring the scope of other transformations based on this process.

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4. a) M. Somei, Adv. Pharm. Sci., 1985, **1**, 45; b) M. Somei, Yakugaku Zasshi, 1988, **108**, 361.
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7. a) M. Somei and F. Yamada, Chem. Pharm. Bull., 1984, **32**, 5065; b) M. Somei, Y. Makita, and F. Yamada, Chem. Pharm. Bull., 1986, **34**, 948; c) M. Somei, F. Yamada, and H. Ohnishi, Heterocycles, 1987, **26**, 2823.
8. Compound **2b**: **1b** (7.7 g, 48.4 mmol) was dissolved in trifluoroacetic acid (27 ml) and thallium(III) trifluoroacetate [TTFA; 90 ml; prepared from thallium(III) oxide (20 g) + trifluoroacetic acid (80 ml) + water (10 ml); reflux; 24 h] was added and the reaction mixture was stirred for 2 h at 25-30 °C. After removal of the solvents in vacuo, the residue was treated with ether (50 ml) to give crystalline **2b** (27.1 g; 98%). mp: 213-218°C.
9. Compound **3b**: **2b** (27.1 g, 46 mmol) was dissolved in DMF (325 ml) and iodine (42 g, 165 mmol) and copper(I) iodide (20.5 g, 107 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The mixture was diluted with a mixture of methylene chloride and methanol (3000/300 ml) and filtered through silica (80 g). The filtrate was washed with an aqueous solution of $Na_2S_2O_3$ (10%; 2 x 270 ml), with brine (100 ml), then with water (500 ml) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure and the residue was recrytallized from a mixture of acetone and water (60/50 ml) to give **3b** (8.3 g; 63.2 %). mp: 156-159 °C. Ir (Nicolet 205- FT-IR; KBr): 1645 (CHO), 1556, 1519 cm^{-1}. Uv (Shimadzu UV-160; EtOH): 226 (3.83); 252.4 (4.00); 318.8 (3.98). Nmr[18]: ^1H nmr ($CDCl_3$) δ: 3.86 (3H, s, NMe), 7.01 (1H, t, J=8.4 Hz, H-6), 7.38 (1H, dd, J=8.4 and 1.5 Hz, H-7), 7.77 (1H, dd, J=8.4 and 1.5 Hz, H-5), 7.96 (1H, s, H-2), 11.12 (1H, s, CHO).
10. A. H. Jackson and A. E. Smith, J. Chem. Soc., 1964, 5510.
11. Compound **6**: **2a** (1.15 g, 2 mmol) was dissolved in DMF (12 ml) and iodine (2 g, 7.8 mmol) and copper(I) iodide (0.8 g, 4.4 mmol) was added to the reaction mixture. After stirring at room temperature for 1

h, the reaction mixture was diluted with a mixture of methylene chloride and methanol (190/10 ml) and filtered through silica (4 g). The filtrate was washed with a solution of $Na_2S_2O_3$ (10 %; 2 x 20 ml) with brine (2 x 20 ml) and with water (60 ml) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure and the residue was chromatographed on silica (eluent: a mixture of cyclohexane/ethylacetate; 6/4). The faster running fraction contained **3a** (0.31 g, 57.4 %). For the physical data of **3a** see ref. 12.
The further fraction yielded **6** (30 mg, 5.5 %). mp: 228-229 °C (from ether). Ir (KBr): 3500, 1610 cm^{-1}. ^{1}H nmr (DMSO-d_6) δ: 7.38 (1H, d, J=8.5 Hz, H-7), 7.55 (1H, dd, J=8.5 and 1.7 Hz, H-6), 8.44 (1H, d, J=1.7 Hz, H-4), 8.31 (1H, s, H-2), 9.92 (1H, s, CHO), 12.28 (1H, br s, NH).

12. M. Somei, F. Yamada, and N. Kunimoto, Heterocycles, 1984, 22, 797.
13. Compound **7b**: **3b** (0.285 g; 1 mmol) and tetrabutylammonium hydrogen sulfate (TBAHS; 0.34 g, 1 mmol) was dissolved in a mixture of DMF and TEA (1.5/1.5 ml) at 80 °C and $Pd(OAc)_2$ (20 mg) was added. The reaction mixture was heated to 100 °C, then a solution of allyl cyanide (0.2 ml, 3 mmol) in DMF (2 ml) was added and stirred for 2 h at 110-120 °C, then cooled to room temperature. The solvents were removed by evaporation and the residue was dissolved in a mixture of chloroform and water (40/20 ml). The aqueous phase was extracted with chloroform (2 x 10 ml). The combined organic phase was washed with a solution of $Na_2S_2O_3$ (10 ml, 10%) and water (2 x 10 ml) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue was chromatographed on silica (10 g; eluent: chloroform). The faster running fraction contained **7b** (90 mg, 44%). mp: 112-113 °C (from ether; deep violet crystals). Ir (KBr): 2227 (CN), 1728 cm^{-1}. Uv (Hewlett Packard 8452A; EtOH): 252 (4.10); 284 (3.43); 296 (3.56); 328 (3.85); 528 (2.73). Ms (MS-902; m/z, %): 207 (16), 206 (100, M^+), 205 (10), 191 (41, M^+-15), 189 (1.4, M^+-17), 177 (2.7, M^+-29), 165 (5, M^+-41), 164 (9, M^+-42). ^{1}H nmr (DMSO-d_6) δ : 3.45 (3H, s, NMe), 4.94 [1H, dd, J=12.5 and 1.4 Hz ('W' coupling to H-3), H-5], 5.57 (1H, d, J=12.5 Hz, H-6), 6.04 (1H, d, J=7.5 Hz, H-7), 6.58 [1H, s (broadened by long-range couplings), H-3], 6.64 (1H, t, J=7.5 Hz, H-8), 6.70 (1H, d, J=7.5 Hz, H-9), 6.94 (1H, s, H-2). ^{13}C nmr (DMSO-d_6) δ : 32.6 (NMe), 103.7 (C-4), 110.8 (C-9), 116.8 (C-2a), 118.8 (C-7), 121.2 (CN), 125.3 (C-8), 125.5 (C-5), 129.2 (C-2), 132.0 (C-9b), 134.4 (C-6a), 134.7 (C-6), 138.9 (C-9a), 144.1 (C-3).
The starting material was also isolated (**3b**, 60 mg, 21%).
14. Compounds **7a** and **8**: **3a** (135.5 mg, 0.5 mmol) and TBAHS (170 mg, 0.5 mmol) were dissolved in a mixture of DMF (0.75 ml) and TEA (0.75 ml) at 80 °C, and $PdCl_2$ (10 mg) was added. The reaction mixture was heated to 100 °C then allyl cyanide (0.1 ml, 1.5 mmol) in DMF (1 ml) was added and stirred for 2 h at 110-120 °C. The work-up of the reaction mixture was similar to that of **7b**. The crude oil was chromatographed on silica (eluent: cyclohexane). The faster running fraction contained **7a** (32 mg, 17 %). mp: 195-200 °C. Ir (KBr): 2205 cm^{-1}. Uv (ETOH): 251 (3.97), 294 (3.52), 312 (3.67), 322 (3.69), 490 (2.51), 524 (2.51). ^{1}H nmr (DMSO-d_6) δ : 4.90 (1H, dd, J=12.4 and 2.0 Hz, H-5), 5.53 (1H, d, J=12.4 Hz, H-6), 5.99 (1H, d, J=7.1 Hz, H-7), 6.56 (1H, dd, J=8.4 and 7.1 Hz, H-8), 6.58 (1H, s, H-3), 6.66 (1H, d, J=8.4

Hz, H-9), 6.92 (1H, d, J=2.7 Hz, H-2), 11.15 (1H, br s, NH). ^{13}C nmr (DMSO-d_6) δ : 103.8 (C-4), 112.6 (C-9), 117.7 (C-2a), 118.8 (C-7), 121.1 (CN), 125.1 (C-8), 125.2 (C-5), 125.8 (C-2), 131.8 (C-9b), 134.2 (C-6a), 134.9 (C-6), 138.5 (C-9a), 144.6 (C-3).

The lower running fraction contained **8** (37 mg, 18%).

^{1}H nmr (DMSO-d_6) (the Z and E isomer were distinguished via ^{1}H{^{1}H} NOE difference experiments) δ (Z isomer): 2.23 (3H, d, J=1.5 Hz, Me), 5.84 (1H, q, J=1.5 Hz, =CH), 7.07 (1H, dd, J=7.5 and 1.5 Hz, H-5), 7.34 (1H, t, J=7.5 Hz, H-6), 7.58 (1H, dd, J=7.5 and 1.5 Hz, H-7), 8.39 (1H, s, H-2), 9.86 (1H, s, CHO), 12.45 (1H, br s, NH). (E isomer): 2.33 (3H, d, J=1.1 Hz, Me), 5.51 (1H, q, J=1.1 Hz, =CH), 7.06 (1H, dd, J=7.5 and 1.5 Hz, H-5), 7.30 (1H, t, J=7.5 Hz, H-6), 7.57 (1H, dd, J=7.5 and 1.5 Hz, H-7), 8.40 (1H, s, H-2), 9.84 (1H, s, CHO), 12.45 (1H, br s, NH).

15. It was prepared from vinylacetic acid using diazomethane.
^{1}H nmr (60 MHz): 3.72 (s, 3H, COOMe).

16. Compound **12**: **3b** (0.285 g, 1 mmol) and TBAHS (0.34 g, 1 mmol) was dissolved in a mixture of DMF and TEA (1.5 / 1.5 ml) at 80 °C and Pd(OAc)$_2$ was added. The reaction mixture was heated to 100 °C and a solution of vinylacetic acid methyl ester (0.2 ml, 3 mmol) in DMF (2 ml) was added; the mixture was then stirred for 2 h at 110-120 °C. The usual work-up and chromatography (eluent: chloroform) gave **12** (oil, 40 mg, 17.7 %). ^{1}H nmr (DMSO-d_6) δ : 3.48 (3H, s, NMe), 5.60 (1H, d, J=12.8 Hz, H-6), 5.71 (1H, dd, J=12.8 and 1.5 Hz, H-5), 6.05 (1H, dd, J=6.5 and 1.5 Hz, H-7), 6.62-6.71 (2H, m, H-8 and H-9), 6.99 (1H, s, H-3), 7.04 (1H, s, H-2), 12.10 (1H, s, COOH). ^{13}C nmr (DMSO-d_6) δ : 32.5 (NMe), 109.8 (C-9), 116.7 (C-2a), 117.7 (C-7), 122.2 (C-4), 125.0 (C-8), 126.7 (C-5), 129.0 (C-2), 131.7 (C-6), 131.9 (C-9b), 135.4 (C-6a), 138.8 (C-9a), 139.2 (C-3), 167.9 (COOH). Ms: 225 (100, M$^+$), 210 (20, M$^+$-15), 206 (3, M$^+$-19), 180 (6, M$^+$-45), 164 (6, M$^+$-61), 149 (6, M$^+$-76).

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18. All nmr measurements were carried out on a Varian VXR-300 instrument (300 MHz for ^{1}H and 75 MHz ^{13}C) at 28°C. Chemical shifts are given relative to $\delta_{TMS}=0.00$ ppm. The structures and assignments for **7b** and **12** were further verified with the aid of detailed ^{1}H{^{1}H} and selective ^{13}C{^{1}H} NOE difference experiments and 2D ^{13}C/^{1}H heterocorrelated spectra.

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