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A peculiar selective rearrangement during the NiS-catalysed dehydrogenation of 4,5-dihydro-1*H*-benz[*g*]indole

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The dehydrogenation of 4,5-dihydro-1*H*-benz[*g*]indole on NiS/Al_2O_3 (350 °C) is accompanied by a peculiar rearrangement to give 3*H*-benz[*e*]indole (71%).

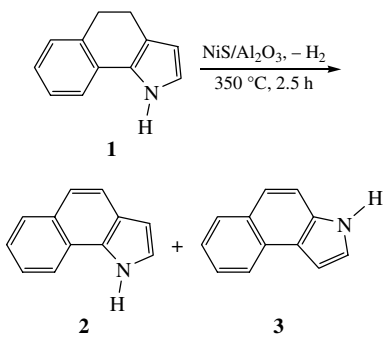
Among indole antibiotics (CC-1065 and duocarmycins), which are strong cytotoxins and potential anticancer drugs,[1] benz[*e*]-indole analogues are more stable and pharmacologically active,[2] though a number of benz[*g*]indoles are also used for the therapeutic purposes.[3] Recently, carbocyanine and 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene dyes with benz[*e*]indole[4] and benz[*g*]indole[5] moieties, showing fluorescence in the near-infrared spectral region, have been synthesised for biomonitoring.

So far the syntheses of unsubstituted benzindoles are of low to moderate yieding multistep procedures based on inaccessible starting materials.[6–9]

In order to elaborate a novel expedient synthesis of 1*H*-benz-[*g*]indole **2**, we studied the dehydrogenation of 4,5-dihydro-1*H*-benz[*g*]indole **1**, which is readily available from 1-tetralone[10] or 1-tetralonoxime[11] and acetylene using the KOH/DMSO catalytic system (the yield of **1** was 72%).[10]

It would be expected that the dehydrogenation of indole **1** proceeds easily. This can be seen, for example, during the aromatizations of tetraline,[12] indolines[13] and a 4,5-dihydro-1*H*-benz[*g*]indole moiety (in BODIPY dyes),[5] which takes place quantitatively. However, under these conditions, indole **1** was inactive.

The successful catalytic dehydrogenation of indole **1** has been achieved in the presence of NiS on granular alumina at 350 °C. Unexpectedly, on the 'fresh' catalyst, 3*H*-benz[*e*]indole **3** was detected as the major product (its concentration in the catalysate reached 71%). As the reaction time was increased, the concentration of indole **3** decreased and that of target indole **2** increased. Finally, after 2.5 h, the overall yield of indoles **2** and **3** in 2.5 h reached 88% (70% **2** + 18% **3**) (Scheme 1).†



Scheme 1

Pure crystalline *g*-isomer **2** can be easily isolated from the catalysate due to its low solubility in cold *n*-hexane, whereas *e*-isomer **3** is soluble in *n*-hexane, benzene and diethyl ether.

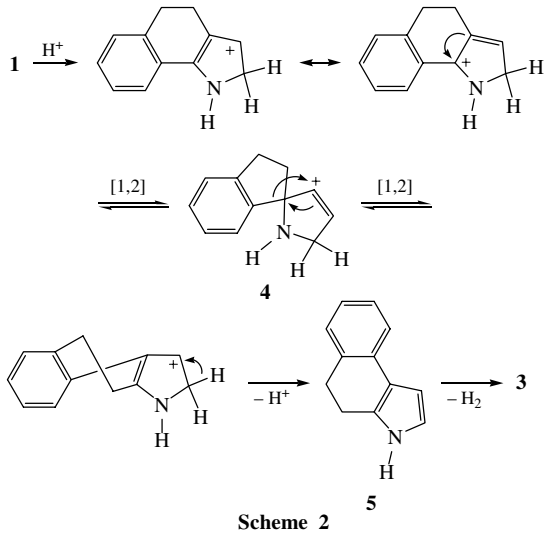
† NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13 MHz for ^{1}H; 101.61 MHz for ^{13}C) with HMDS as an internal standard. The assignments of ^{1}H and ^{13}C NMR spectra were performed by COSY, NOESY, HSQC and HMBC experiments. IR spectra were obtained on a Bruker IFS 25 instrument in KBr pellets. GLC analysis was carried out on Agilent 6890N, HMS – on Shimadzu GCMS-QP5050A.

Catalyst Preparation. Granulated Al_2O_3 (50 g) in 110 ml of an aqueous solution of $Ni(OAc)_2$ (21.18 g) was stirred for 1 h and then kept overnight. Afterwards, H_2S (100 ml min^{-1}) was passed through the mixture for 30 min. The catalyst was filtered off, washed with a 3% aqueous solution of NaOH (200 ml) and then washed with distilled water to pH 7 and dried in air at 100 °C for 5 h.

*Dehydrogenation of 4,5-dihydro-1*H*-benz[*g*]indole* **1**. *Method A*: 4,5-Dihydro-1*H*-benz[*g*]indole **1** (0.50 g, 3 mmol) in 10 ml of benzene was passed in N_2 flow (3 dm^3 h^{-1}) dropwise through the quartz reactor (a 10 mm diameter tube filled with a catalyst: NiS/Al_2O_3, 0.44% Ni, alumina particles, 2×3 mm; catalyst layer, 8.5 cm) at 350 °C for 2.5 h. Afterwards, another portion of neat benzene (10 ml) was passed through the reactor at the same temperature for 1.5 h. Benzene was evaporated from the reaction mixture to give 0.45 g of a solid (mixture of indoles **2** and **3**). The mixture was dissolved in boiling *n*-hexane and after cooling to ambient temperature, kept at 6–8 °C overnight. The crystals precipitated were washed with cold *n*-hexane to give 0.35 g (70% yield) of *g*-isomer **2** as light-gray crystals with metallic luster, mp 181 °C (lit.,[6] mp 177–178 °C). After the evaporation of *n*-hexane, 0.10 g of 3*H*-benz[*e*]indole **3** (90% purity, 18% yield) was isolated as viscous yellow oil (lit.,[6] mp 34–35 °C; yellow oil[7]). ^{1}H and ^{13}C NMR spectral data of **2** and **3** are in a good accordance with literature data.[9]

Method B: 4,5-Dihydro-1*H*-benz[*g*]indole **1** (1.50 g, 9 mmol) in 30 ml of benzene was passed in N_2 flow (3 dm^3 h^{-1}) dropwise through the same reactor with the fresh catalyst at 350 °C for 8.5 h. Afterwards, the reactor was washed with 10 ml of neat benzene at the same temperature for 1.5 h. After evaporation of benzene, 1.01 g of a mixture of indoles **2** and **3** was obtained (the indole **3** content of the mixture was 41%, yield 28%).

Method C: 4,5-Dihydro-1*H*-benz[*g*]indole **1** (1.50 g, 9 mmol) in 30 ml of benzene was passed in N_2 flow (3 dm^3 h^{-1}) dropwise through the reactor with granulated Al_2O_3 (catalyst layer of 8.5 cm) at 350 °C for 8.5 h. After the evaporation of benzene, 0.22 g of a mixture of indoles **1** (recovered 9.8%), **2** (yield 0.9%), **3** (yield 3.6%) and, possibly, deprotonated **4** and dihydro derivative **5** (yields of 0.3 + 0.4%) was obtained. MS (EI) for benzindoles **2** and **3**: *m*/*z* (%), 167 ([M$^+$], 100), 139 (32), 84 (30). MS (EI) for isomers **1**, **5** and deprotonated **4**: *m*/*z* (%), 168 ([(M – H)$^+$], 100), 139 (13), 115 (10), 83 (55).



Scheme 2

The rearrangement of **1** to **3** is likely to involve *spiro*-intermediate **4**, which undergoes further substituent migration over the pyrrolenine ring to give 4,5-dihydro-3*H*-benz[*e*]indole **5**, which is dehydrogenated to indole **3** (Scheme 2). These substituent migrations are presumed to be of a carbocationic nature due to the remaining acidic centres of $Al_2O_3(H_2O)_n$, which are gradually quenched by the basic products of pyrrole ring oligomerization.

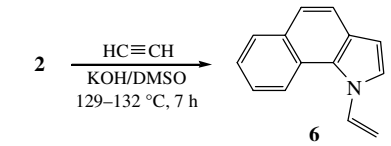
The proposed mechanism is confirmed by an experiment on the pure carrier Al_2O_3 performed under the same conditions as with NiS/Al_2O_3. In this case, in the catalysate, apart from starting indole **1** (the main component, recovery is 9.8%) among the reaction products (over 10) isomers **2** and **3** (in 0.9 and 3.6% yields, respectively) were identified using MS and GLC techniques. Obviously, the dehydrogenation in the absence of NiS occurs owing to the energy gain due to the aromatization of tricyclic ensembles. However, the process becomes less selective and 85% of the products remain on alumina because of the pyrrole ring oligomerization in the presence of acids.[14] Upon GLC and MS analysis of the product mixture, two other isomers of the starting material were detected, which may correspond to dihydro derivative **5** and deprotonated *spiro*-intermediate **4**. Thus, the NiS deposition on Al_2O_3 secures the selective dehydrogenation **1** → **2** suppressing isomerization processes.

A comparison of the quantum-chemical calculations (the B3LYP hybrid functional[15] with 6-31G* basis set, **2**:**3** = 44:56 at 625 K; MP2/6-311G**, **2**:**3** = 42:58 at equilibrium) with the experimental results confirms that the reaction mixture does not reach an equilibrium and the indole ratio **2**:**3** is controlled by kinetic factors such as the concentration of protogenic centres of a catalyst and their evolution during the reaction.

A synthetic advantage of the catalytic method developed is that it allows parent benz[*e*]- and benz[*g*]indoles, so far practically inaccessible, to be synthesised from readily available 1-tetralone oxime in only two simple steps.

So far these heterocycles have been a challenge to synthesise, but functionalizations on the ring are a matter of appropriate experimental technique. For example, indole **2** is readily vinylated with acetylene under atmospheric pressure in the superbase catalytic system KOH/DMSO (129–132 °C, 7 h) to afford 1-vinyl-1*H*-benz[*g*]indole **6** in 78% yield (85% conversion of **2**) (Scheme 3).‡

New vinyl derivative **6**, is a structural isomer of *N*-vinylcarbazole, which is a widely used monomer and precursor of active materials in the manufacture of light emitting diodes and lasers.[16] Thus, **6** may be expected to find similar application in optoelectronics, as well as a useful intermediate in drug design. The rearrangement described, apart from its synthetic utility, unveils novel facets of basic benzindoles chemistry under heterogeneous catalysis conditions.



Scheme 3

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‡ *Vinylation of benz[g]indole* **2**. 1*H*-benz[*g*]indole **2** (1.90 g, 11.3 mmol), $KOH \cdot 0.5H_2O$ (2.50 g, 38.5 mmol) and DMSO (20 ml) were placed in a 50 ml flask furnished with a magnetic stirrer, a thermometer and a tube for acetylene introduction. The mixture was heated (129–132 °C) and acetylene was fed for 7 h with stirring. GLC was used for the reaction control. The cooled reaction mixture (20 °C) was extracted by *n*-hexane (6×20 ml); the combined extracts were washed with water (3×20 ml) and dried over K_2CO_3. Hexane was removed, and the crude product was column chromatographed (basic Al_2O_3; eluent, *n*-hexane) to give 1.71 g (8.8 mmol, 78% yield) of 1-vinyl-1*H*-benz[*g*]indole **6**, yellowish viscous oil, soluble in organic solvents.

1-Vinyl-1H-benz[g]indole **6**. ^{1}H NMR ($CDCl_3$) δ: 8.36 (d, 1H, H-9, *J* 8.5 Hz), 7.91 (d, 1H, H-6, *J* 8.1 Hz), 7.74 (dd, 1H, H_X, J_{B-X} 15.6 Hz, J_{A-X} 9.0 Hz), 7.61 (d, 1H, H-4, *J* 8.5 Hz), 7.52 (d, 1H, H-5, *J* 8.1 Hz), 7.50 (t, 1H, H-8, *J* 8.1 Hz, *J* 1.2 Hz), 7.40 (t, 1H, H-7, *J* 8.5 Hz, *J* 1.2 Hz), 7.31 (d, 1H, H-2, *J* 3.1 Hz), 6.68 (d, 1H, H-3, *J* 3.1 Hz), 5.43 (d, 1H, H_B, J_{B-X} 15.6 Hz), 5.11 (d, 1H, H_A, J_{A-X} 9.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 134.73, 131.79, 129.41, 129.28, 126.27, 125.91, 125.62, 123.45, 123.12, 122.02, 121.38, 120.91, 105.12, 104.61. IR (KBr, ν/cm^{-1}): 3097, 3056, 3017, 2957, 2922, 2851, 1639, 1587, 1563, 1527, 1503, 1457, 1419, 1403, 1355, 1343, 1321, 1298, 1273, 1231, 1203, 1073, 1046, 980, 967, 942, 880, 868, 810, 783, 766, 745, 727, 693, 680, 589, 561, 422. Found (%): C, 86.99; H, 6.01; N, 7.15. Calc. for $C_{14}H_{11}N$ (%): C, 87.01; H, 5.74; N 7.25.

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