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NOTE

Dedicated to Professor Dr. ALEXANDRU T. BALABAN, member of the Roumanian Academy on the occasion of his 75th anniversary

FLOW-VACUUM PYROLYSIS OF POLYCYCLIC COMPOUNDS. 23 [1]

PYROLYSIS OF *t*-BUTYL-TETRAZOLO[1,5-*a*]DIBENZO[*c,g*]AZOCINES AS SYNTHESIS METHOD OF SUBSTITUTED 5H- AND 6H-INDOLO[2,3-*b*]QUINOLINES

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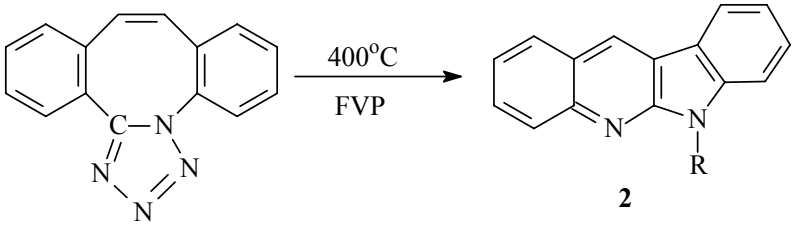
The flow-vacuum pyrolysis (FVP) of 2-*t*-butyl-tetrazolo[1,5-*a*]dibenzo[*c,g*]azocine (**5**) and 10-*t*-butyl-tetrazolo [1,5-*a]*dibenzo[*c,g*]azocine (**6**) in quartz tube, inert atmosphere (argon, flow rate 4mL/min) between 475-500°C at 1mmHg was investigated using GC/MS. The stable reaction products, 2-*t*-butyl-6H-indolo[2,3-*b*]quinoline (**3)** and 2-*t*-butyl-5H-indolo[2,3-*b*]quinoline (**4**) were separated and characterized by IR, ^{1}H-, ^{13}C-NMR and mass spectroscopy. A radical mechanism explaining the formation of above mentioned reaction products is suggested.

Cryptolepsis genus derived compounds are commonly used in therapeutical and industrial purposes. *Cryptolepsis* roots extracts have been used to treat a variety of diseases as malaria[2], infections of the respiratory, urogenital tracts[3] and arthritis[4]. Moreover, the same extracts have been utilized for dyeing leather and textiles[5a].

Cryptolepis sanguinolenta roots contain alkaloids with indoloquinoline skeletons. Specific compounds (as cryptolepine and neocryptolepine) were isolated from the biologically active plant extracts and their structures were determined.[5] Many groups focused on the organic synthesis[6] and testing[7-9] of the derivatives of parent active structures (exemple: methyl-substituted indolo[2,3-*b*]quinolines as novel cytotoxic, DNA topoisomerase II inhibitors[6a]).

In 1999, we obtained 6H-indolo[2,3-*b*]quinoline (**2a**) (*norcryptotackiene)* by flow-vacuum pyrolysis of tetrazolo[1,5-*a*]dibenzo[*c,g*]azocine (**1**).[10] (Scheme 1).



1 **2**

2a : R = H
2b: R = COCH3

Scheme 1

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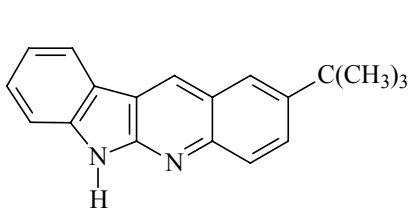
Herein, we aimed to synthesize *t*-butyl-indolo[2,3-*b*]quinolines (**3,4)** by flow vacuum pyrolysis of corresponding tetrazoles (*t*-butyl-tetrazolo[1,5-*a*]dibenzo[*c,g*]azocines, **5**, **6**) in the same reaction conditions as for thermal decomposition of other polycyclic compounds[11-13]:



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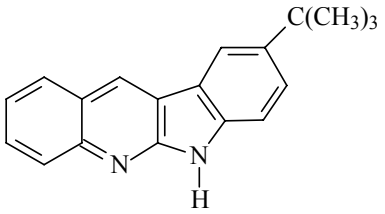

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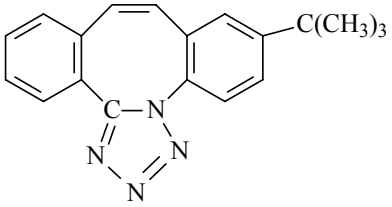

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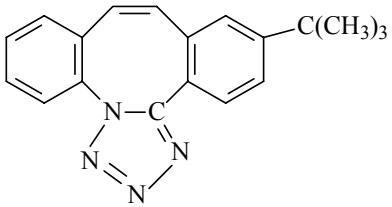
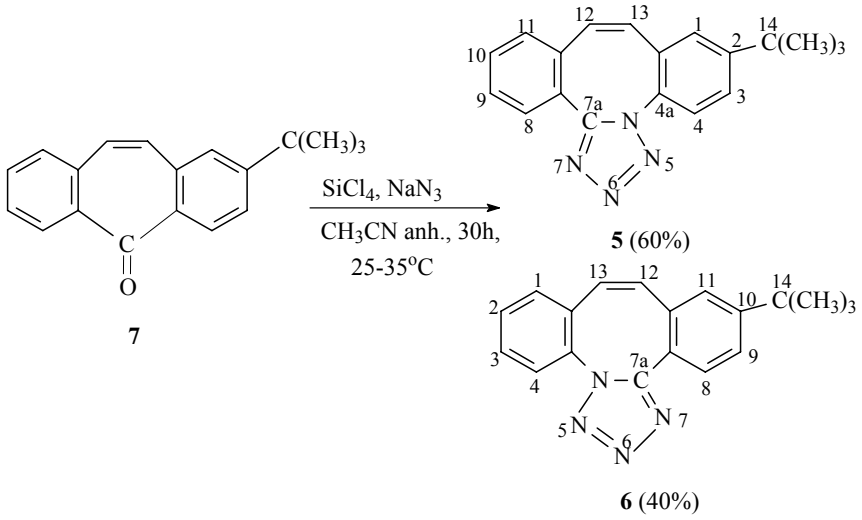


6

RESULTS

t-Butyl-tetrazolo[1,5-*a*]dibenzo[*c,g*]azocines **5** and **6** were initially obtained in 1998[14] by reaction of 2-*t*-butyl-dibenzosuberenone (**7**) with triazidochlorosilane generated *in situ* from silicon tetrachloride and sodium azide, at 25-35°C in anhydrous acetonitrile (Scheme 2).

The mixture of **5** and **6** (white crystals, m.p. = 201-203°C after recristalization from methanol) could not be preparative separated by thin liquid chromatography (TLC).



7

5 (60%)

6 (40%)

Scheme 2

Thus, their spectral characterization was performed using enriched TLC fractions.

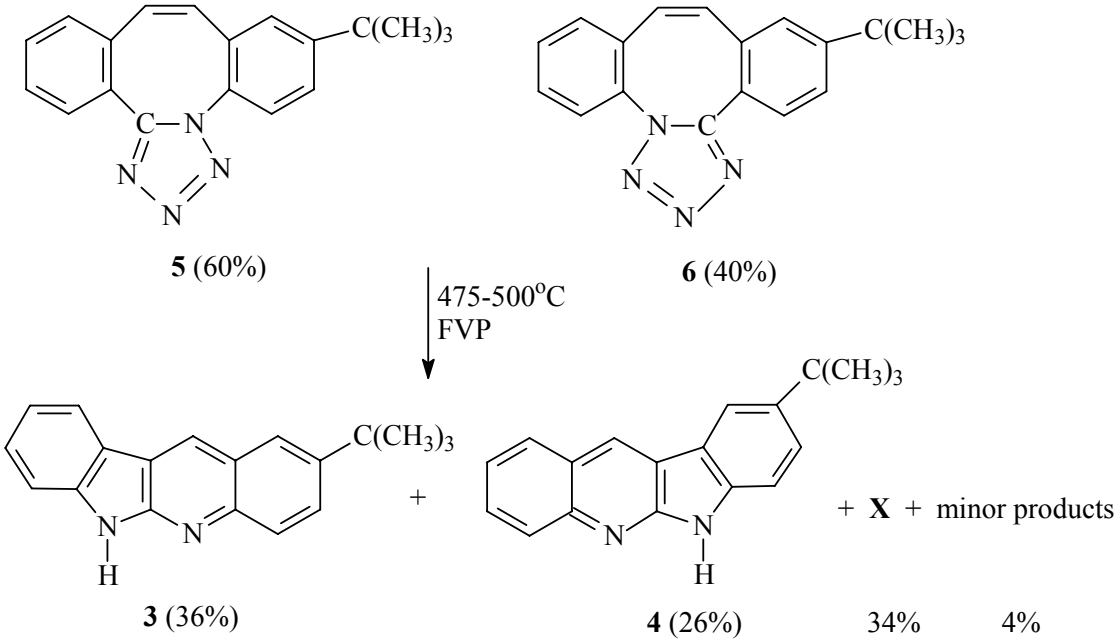
IR spectrum[1] (CH_2Cl_2, cm^{-1}) mixture: 836 m, 1000 w, 1101 m, 1365 w, 1380 m, 1470 m, 1500 s, 1598 m, 2870 m, 2905 m, 2968 s, 3070 w.

[1] IR spectrum was registered on a C. Zeiss Jena UR-20 double beam spectrometer.

[1]H-NMR spectrum[(2)] ($CDCl_3$, δ, ppm, J Hz, TMS internal standard): For compound **5**: 1.32 (s; 9H; $3CH_3$); 6.71 (d; 12.2; $1H^{12}$); 6.83 (d; 12.2; $1H^{13}$), 7.20- 7.61 (m; 7H; H [3, 4, 8, 9, 11, 12]). For compound **6**: 1.31 (s; 9H; $3CH_3$); 6.70 (d; 12.2; $1H^{12}$); 6.85 (d; 12.2; $1H^{13}$), 7.20- 7.61 (m; 7H; H [3, 4, 8, 9, 11, 12]).

[13]C-NMR spectrum[(2)] ($CDCl_3$, δ, ppm): 31.08 (CH_3 from **6**); 31.15 (CH_3 from **5**); 34.90 (C^{14} from **5**); 34.93 (C^{14} from **6**); 120.05 (Cq); 123.24 (Cq); 125.64 (CH); 126.25 (CH); 126.32 (CH); 126.41 (CH); 126.85 (CH); 126.92 (CH), 128.17 (CH); 128.73 (CH); 128.76 (CH); 129.50 (CH); 129.63 (CH); 129.89 (CH); 130.19 (CH); 130.82 (CH); 131.08 (CH); 131.16 (CH); 132.38 (Cq); 132.66 (Cq); 133.21 (CH); 134.12 (CH); 136.61 (Cq); 137.25 (Cq); 153.72 (Cq); 154.72 (C^{7a} from **6**); 156.18 (C^{7a} from **5**).

The flow-vacuum pyrolysis of **5** and **6** was performed with the same devices and reaction conditions as for **1**[6]: the quartz tube (60 cm length, 10 mm internal diameter, filled with quartz chips on 30 cm length); temperature (475-500°C) and pressure (1 mmHg) were monitored by a thermocouple and a McLeod manometer under inert atmosphere (argon, flow rate: 4 mL/min), respectively. The reaction products were dissolved in methylene chloride, the solvent was evaporated *in vacuo* and the residue was analyzed by a gas chromatograph coupled with a mass spectrometer (GC/MS) (Scheme 3).



Scheme 3

The 2-*t*-butyl-6H-indolo[2,3-*b*]quinoline (**3**) and 2-*t*-butyl-5H-indolo[2,3-*b*]quinoline (**4**) could not be separated by thin liquid chromatography and the full characterisation by ^{1}H- and ^{13}C-NMR was realized using enriched TLC fractions (**3**/**4**: 66.4% / 33.6%).

IR spectrum[(1)] (KBr, cm^{-1}): 726 vs, 824 vs, 911 m, 1263 m, 1361 s, 1408 s, 1464 vs, 1611 vs, 2861 m, 2956 vs, 3117 m.

[1]H-RMN spectrum[(3)] ($CDCl_3$, δ, ppm, J Hz) for **3**: 1.46 (9H,s); 7.30 (1H, ddd, 7.2, 7.6 1.0); 7.54 (1H, ddd, 7.2, 8.0, 1.0); 7.59 (1H, d, 8.0); 7.89 (1H, dd, 8.9, 2.2); 7.99 (1H, d, 2.2); 8.12 (1H, d, 8.9); 8.18 (1H, d, 7.6); 8.79 (1H, s); 10.83 (1H, NH, bs).

[2] ^{1}H-NMR and ^{13}C-NMR spectra were registered on a VARIAN GEMINI spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C using TMS as internal standard.

[3] ^{1}H-NMR spectra were registreted on a Bruker AVANCE DRX 500 spectrometer at 500.132 MHz using TMS as internal standard. The instrument was equipped with a 5-mm multinuclear, inverse-detection probe with a z-gradient. The three-bond ^{1}H,^{1}H correlation experiment was acquired using the gradient COSY *cosygpqf* pulse program with 2K data points and 2 transients in *t2* per 512 increments in *t1*. The one-bond ^{1}H, ^{13}C correlation experiments were acquires using the gradient HMQC *inv4gpqf* sequence with an evolution delay of 3.45 ms for an average $^1J_{(C,H)}$ of 160 Hz. The experiments resulted in a 1K data points and 4 transients in *t2* per 256 increments in *t1*. The long-range ^{1}H-^{13}C correlation experiments were recorded using the gradient HMBC *inv4gplplrndqf* pulse program with 1K data points and 2 transients in *t2* per 512 increments in *t1*.

[1] H-NMR shfts for compound **4**: 1.49 (9H, s); 7.50 (1H, ddd, 8.0, 6.8, 1.0); 7.52 (1H, d, 8.4); 7.63 (1H, dd, 8.4, 1.8); 7.76 (1H, ddd, 8.2, 6.8, 1.4); 8.07 (1H, d, 8.0); 8.15 (1H, d, 8.2); 8.22 (1H, d, 1.8); 8.82 (1H, s), 10.66 (1H, NH, bs).(Fig. 1).

[13]C-RMN spectrum[(4)] ($CDCl_3$, δ, ppm) for compound **3**: 31.54 (C^{19}); 35.08 (Cq^{18}); 111.30 (C^{10}); 119.03 (Cq^{15}); 120.46 (C^{12}); 121.55 (Cq^{14}); 121.89 (C^{13}); 124.11 (C^{1}); 124.35 (Cq^{14}); 126.64 (C^{4}); 128.17 (C^{16}); 128.51 ($C^{3,11}$); 141.63 (Cq^{9}); 145.33 (Cq^{5}); 146.3 (Cq^{2}); 153.81 (Cq^{7}). For compound **4**: 32.05 (C^{19}); 35.07 (Cq^{18}); 110.82 (C^{4}); 118.4 (C^{1}); 119.56 (Cq^{16}); 121.12 (Cq^{17}); 123.38 (C^{12}); 124.66 (Cq^{14}); 126.56 (C^{3}); 127.09 (C^{10}); 127.81 (C^{15}); 129.09 (C^{11}); 129.25 (C^{13}); 139.62 (Cq^{5}); 143.87 (Cq^{2}); 146.80 (Cq^{9}); 153.78 (Cq^{7}). (Fig.2).

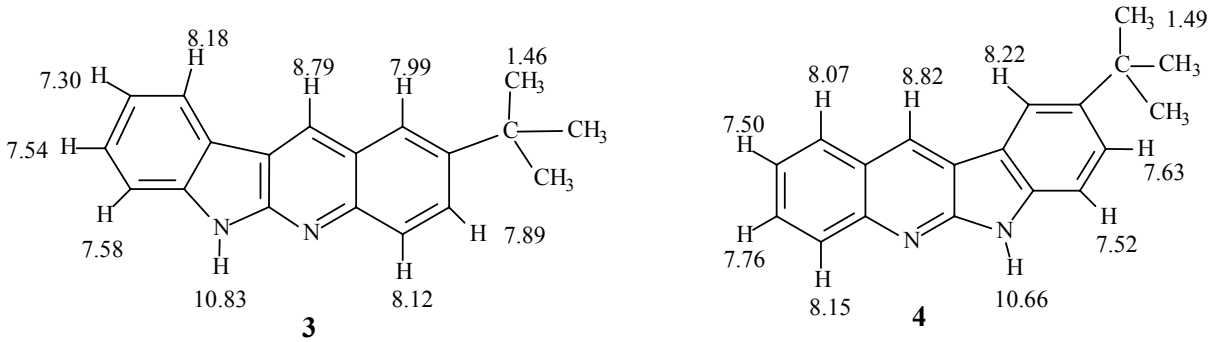


Fig. 1 – [1] H-NMR chemical shifts of compounds **3** and **4.**

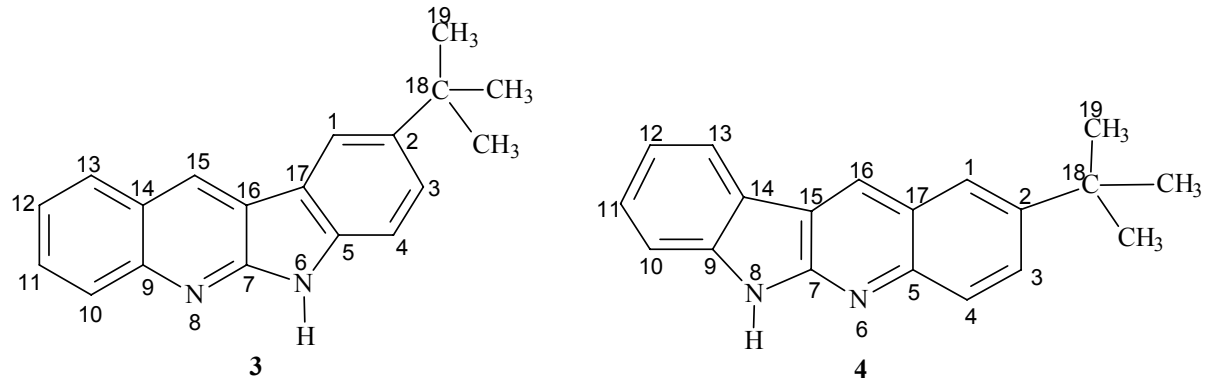


Fig. 2 – Carbon numbering of compounds **3** and **4** in the [13]C-NMR spectra.

Mass spectrum [(5)] (m/z, relative abundance %): For compound **3**: 51 (2); 63 (2); 75 (2); 89 (2); 102 (4); 115 (46); 129 (9); 137 (4); 190 (4); 218 (20); 231 (11); 243 (11); 259 (B.P., 100); 274 (M, 30).

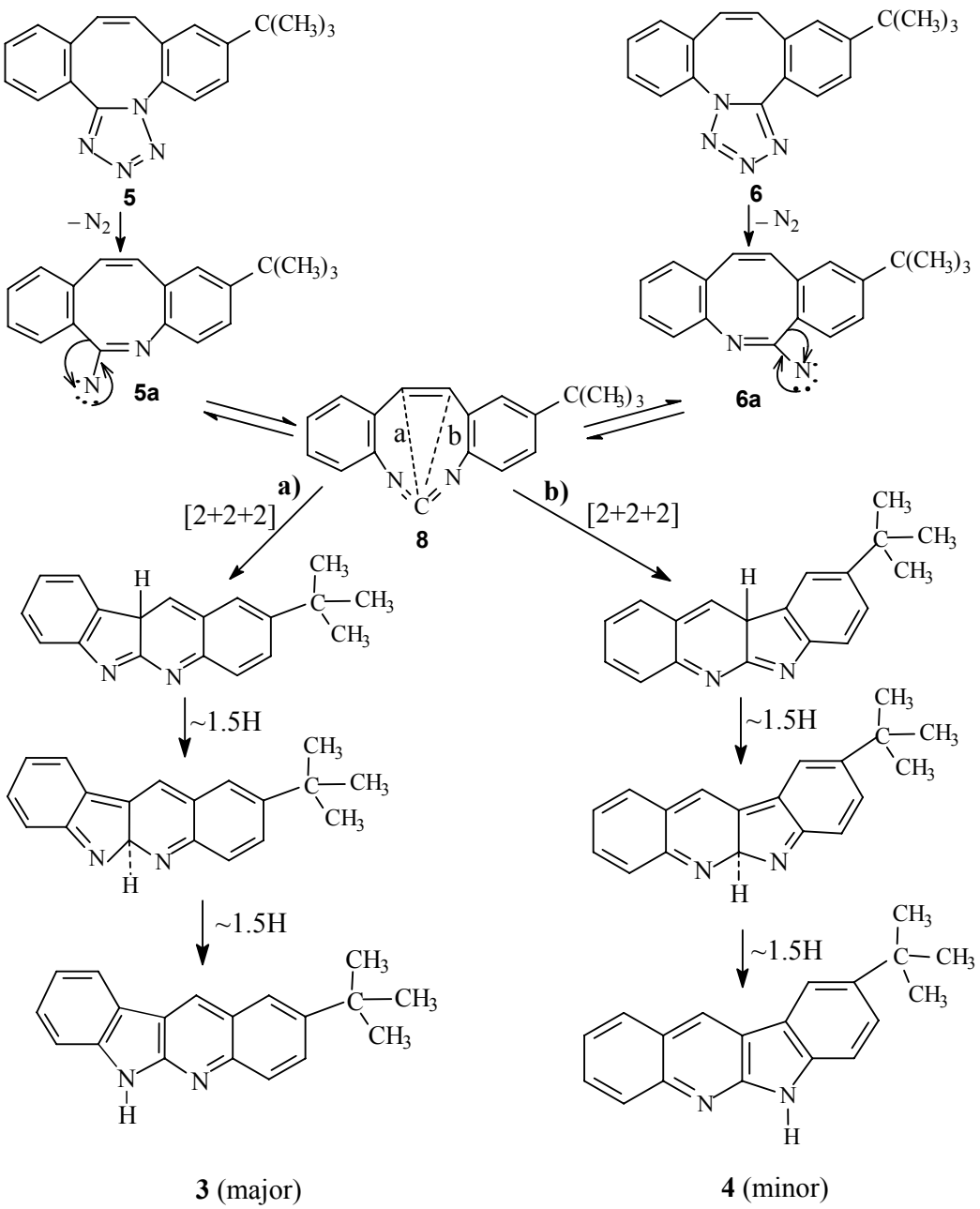
For compound **4**: 51 (2); 63 (2); 75 (2); 89 (3); 102 (11); 115 (37); 129 (7); 190 (4); 218 (17); 231 (9); 243 (15); 259 (B.P., 100); 274 (M, 33).

The component **X**, formed with 34% yield, could not be preparative separated by TLC as pure compound due to its instability. Its mass spectrum indicated a molecular mass of 262.

Mass spectrum[(5)] (m/z, relative abundance %) for compound **X**: 63(1); 89 (1); 102 (1); 115 (1); 126 (1); 139 (1); 150 (1); 165 (2); 178 (5); 190 (9); 203 (10); 218 (17); 219 (17); 249 (3); 262 (B.P., M, 100,); 263 (M+1, 59).

[4] [13]C-NMR spectra were registreted on a Bruker AVANCE DRX 500 spectrometer at 125.758 MHz. See n. 3.

[5] VARIAN 3400 gas-chromatograph with split/splitless injector coupled with a VARIAN SATURN II mass spectrometer provided with ion trap. Analysis conditions: capillary DB-5 column (30 m length; 0.25 mm internal diameter); injector temperature: 250°C; split rate: 1:5; temperature program: 60-280°C at 10°C/min; carrier gas: helium (flow-rate 1mL/min); temperature of transfer line: 250°C; electron ionization: 70 eV.



Scheme 4

t-Butyl-indolo[2,3-*b*]quinolines **3** and **4** formation could be explained by common mechanisms encountered in the flow vacuum pyrolyses of tetrazoles.[10, 15-18] Formation of nitrenes **5a** and **6a**, generated in the first step by nitrogen thermal elimination, is generally accepted and their ring enlargement affords the same substituted carbodiimide **8** (Scheme 4).

The formation of carbodiimides in pyrolyses of tetrazoles is proved by isolation of such intermediates and their dimmers at low temperatures.[19,20] Transformation of *t*-butyl-carbodiimide **8** in the stable reaction products **3** and **4** is explained by a sequence of thermally allowed[21] concerted processes: [2+2+2] electrocyclization[10] [routes a) and b)] followed by successive [1.5H] migrations, *t*-butyl being used as marker group. The route a) is preferred because 2-*t*-butyl-6H-indolo[2,3-*b*]quinoline (**3**) is more stable than its isomer **4** as proven by energy calculation (0.5 Kcal/mol difference)**.**

In conclusion, in this work we have presented the similar thermal behavior in flow-vacuum pyrolysis conditions of *t*-butyl-tetrazolo[1,5-*a*]dibenzo[*c,g*]azocines **5** and **6** with unsubstituted derivative **1**.

The synthesis of 2-*t*-butyl-6H-indolo[2,3-*b*]quinoline and 2-*t*-butyl-5H-indolo[2,3-*b*]quinoline certifies flow vacuum pyrolysis as a fast procedure obtaining substituted quinolines with potential biological activity.

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