Synthesis of 3-alkyl-1,4-dihydrocyclopenta[*b*]indoles: unexpected formation of dimeric compounds

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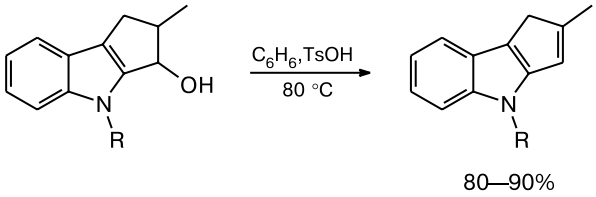
Acid-catalyzed dehydration of 3-alkyl(aryl)-4-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ols gives dimeric derivatives of 3-alkyl(aryl)-4-methyl-1,4-dihydrocyclopenta[*b*]indole.

Key words: 1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ols, dehydration, 1,4-dihydrocyclopenta[*b*]indoles, dimerization.

Earlier,[1] we described a convenient method for the synthesis of 4-alkyl(aryl)-2-methyl-1,4-dihydrocyclopenta[*b*]indoles by dehydration of the corresponding alcohols (Scheme 1).

Scheme 1



R = Me, Ph, *p*-Tol

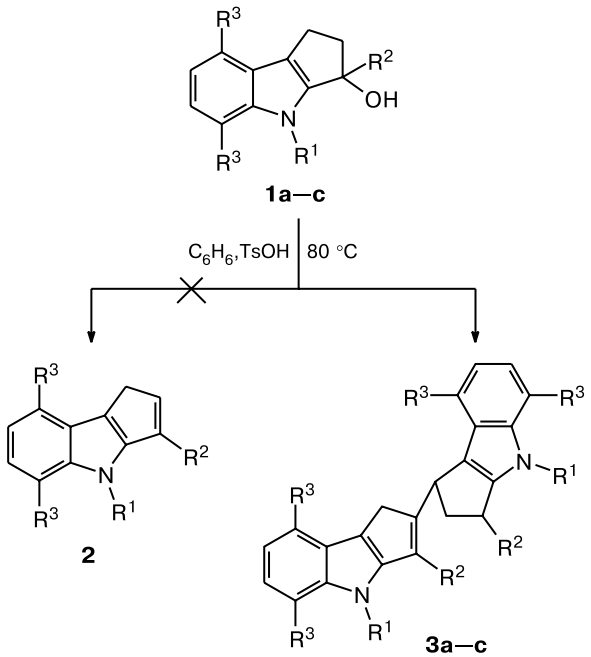
However, the dehydration of 2-unsubstituted alcohols **1** did not afford the expected compounds **2**. According to the ^{1}H and ^{13}C NMR data, the reaction products have a more complex structure **3** (Scheme 2).

The structure of compound **3b** was confirmed by X-ray diffraction data (Fig. 1).

The main bond lengths and angles in structure **3b** are close to the expected values (Table 1). Comparison of the bond lengths in its cyclopentadiene and cyclopentene fragments shows that the ring geometry is virtually unaffected by the presence of the saturated C atoms. The dihedral angle between the tricyclic fragments is 72°.

Structure **3b** contains a shortened contact between the H atom at the C(1) atom and the methyl group at the C(14´) atom (H...H 2.04 Å), which probably leads to elongation of the C(1)—C(2´) bond to 1.496(3) Å. The C(1)—C(5) ring exists in an envelope conformation with the C(2) atom deviating by 0.38 Å. Analysis of the crystal packing revealed that all intermolecular distances correspond to normal van der Waals interactions (except for weak C—H...π-contacts (H...C 2.7 Å, C—H—C 158°)).

Scheme 2



1: $R^1 = R^3 = Me$, $R^2 = Ph$ (**a**); $R^1 = Me$, $R^2 = Me$, $R^3 = H$ (**b**); $R^1 = Me$, $R^2 = Ph$, $R^3 = H$ (**c**)

3: $R^1 = R^3 = Me$, $R^2 = Ph$ (**a**), 47%; $R^1 = Me$, $R^2 = Me$, $R^3 = H$ (**b**), 65%; $R^1 = Me$, $R^2 = Ph$, $R^3 = H$ (**c**), 34%

Apparently, the formation of dimers **3** follows Scheme 3.

First, alcohol **1** converts into compound **2** through loss of a water molecule. Compound **2** adds a proton to give a relatively stable carbocation that attacks a second

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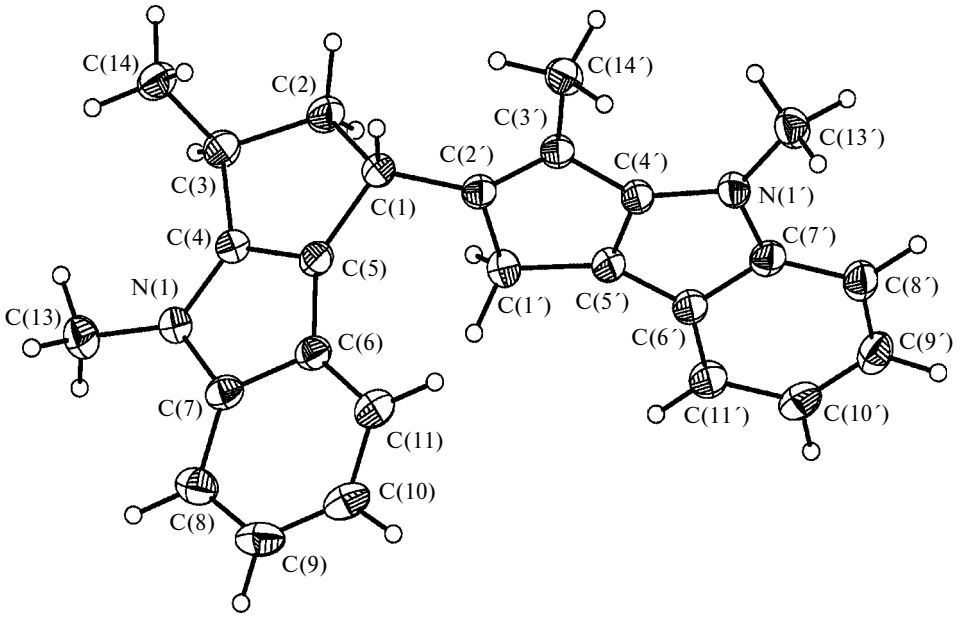


Fig. 1. General view of molecule **3b** with atomic thermal displacement ellipsoids (p = 50%).

molecule of compound **2**. Two generated carbocations **A** and **B** are possible; however, the addition of cation **A** to the C(2)—C(3) bond of compound **2** is sterically hindered. The resulting tertiary carbocation **C** loses H^+ to give compound **3**.

The formation of intermediates of the types **A** and **B** during various transformations of acyl derivatives of indole in acidic media has been reported earlier.[2,3]

Attempts to isolate compounds **2** failed since under mild conditions (ether, 20 °C), the reaction virtually does not occur, while heating mainly leads to products **3**.

Dehydration of 3-unsubstituted alcohols (**1**, R^2 = H) prepared by the reduction of ketones **4** with $LiAlH_4$ in ether gives a mixture of unidentified colored products.

Alcohols **1** are easy to synthesize by reactions of the corresponding ketones **4** with Grignard reagents or organolithium compounds (in the latter case, the yields of alcohols are usually higher).

Earlier, ketones **4** were obtained by cyclization of 3-indolylpropionic acids **5** in the presence of polyphosphoric acid[4] or phosphorus pentoxide in an inert solvent.[5] We found that the best results are attained with a solution of P_2O_5 in methanesulfonic acid as a ring-closing agent (Scheme 4). This reagent was previously used to synthesize some heterocyclic ketones.[6]

The starting compounds **5** can be easily prepared by reactions of the corresponding indoles with acrylic acid.[7]

Scheme 3

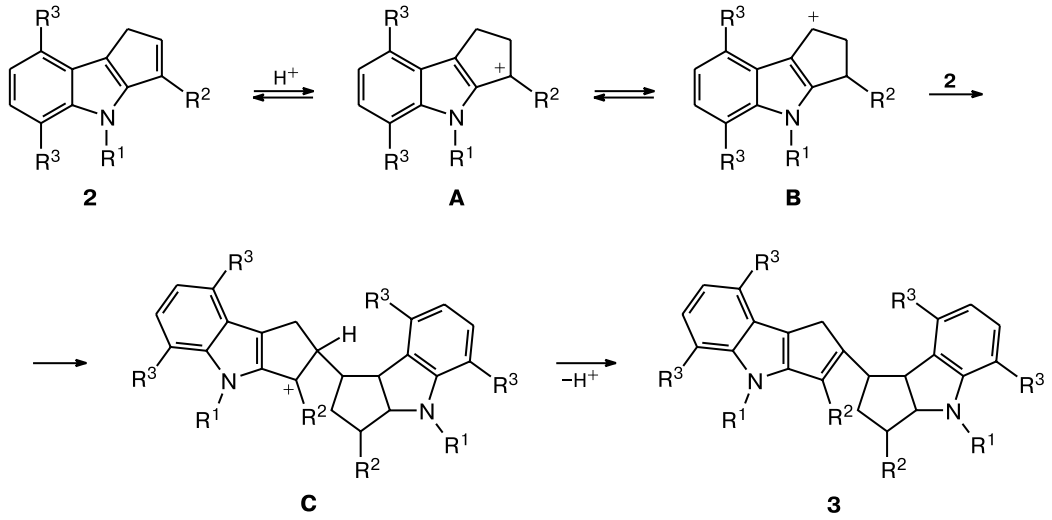
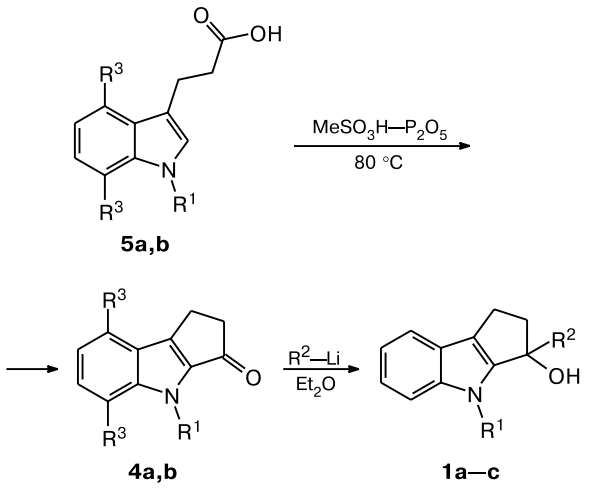


Table 1. Selected bond lengths (*d*) and angles (ω) in structure **3b**

Bond	*d*/Å	Angle	ω/deg
N(1)—C(4)	1.365(3)	C(4′)—N(1′)—C(7′)	106.8(2)
N(1)—C(7)	1.383(3)	C(4′)—N(1′)—C(13′)	128.4(2)
N(1)—C(13)	1.443(3)	C(7′)—N(1′)—C(13′)	124.8(2)
C(5)—C(6)	1.431(3)	C(4)—N(1)—C(7)	106.9(2)
C(6)—C(7)	1.416(3)	C(4)—N(1)—C(13)	127.0(2)
C(2)—C(3)	1.554(3)	C(7)—N(1)—C(13)	126.0(2)
C(1)—C(2′)	1.496(3)		
N(1′)—C(4′)	1.379(2)		
N(1′)—C(7′)	1.391(3)		
N(1′)—C(13′)	1.450(3)		
C(5′)—C(6′)	1.424(3)		
C(6′)—C(7′)	1.426(3)		
C(2′)—C(3′)	1.350(3)		

Scheme 4



1: $R^1 = R^3$ = Me, R^2 = Ph (**a**), 61%; R^1 = Me, R^2 = Me, R^3 = H (**b**), 78%; R^1 = Me, R^2 = Ph, R^3 = H (**c**), 86%
4: $R^1 = R^3$ = Me (**a**), 85%; R^1 = Me, R^3 = H (**b**), 93%
5: $R^1 = R^3$ = Me (**a**); R^1 = Me, R^3 = H (**b**)

Thus, we showed that the dehydration of 1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ols depends on the presence of a substituent in position 2 of the cyclopentene fragment. Elimination of water from 2-alkyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol leads to the expected 2-alkyl-1,4-dihydrocyclopenta[*b*]indole, while the dehydration of a 2-unsubstituted analog affords dimeric product **3**.

Experimental

Ether was distilled over sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 instrument. Merck Kieselgel 60 silica gel (0.06—0.2 mm) was used as a sorbent for column chromatography. Thin-layer chromatography was carried out on Merck Silica Gel 60 F_{256} plates. 1,4,7-Trimethylindole was prepared according to a known procedure.[8]

X-ray diffraction analysis of compound 3b. Suitable crystals of compound **3b** for X-ray diffraction analysis were obtained by slow cooling of its saturated solution in DMF—MeCN. Measurements were performed at 110 K on a Smart CCD automatic three-circle diffractometer (Mo-Kα radiation, graphite monochromator, ω scan mode, $2\theta_{max} = 54°$). Crystals at 110 K are monoclinic: $a = 15.361(2)$ Å, $b = 14.717(2)$ Å, $c = 8.821(2)$ Å, $\beta = 101.006(4)°$, $V = 1957.4(5)$ Å^3; $d_{calc} = 1.244$ g cm^{-3}, empirical formula $C_{26}H_{26}N_2$, $M = 366.49$, $F(000) = 784$, $\mu = 0.72$ cm^{-1}, $Z = 4$, space group $P2_1/c$. The total number of measured reflections was 9685, out of which 4142 independent reflections ($R_{int} = 0.0763$) were used in further calculations and refinement. The structure was solved by the direct method and refined on F^2_{hkl} by the least-squares method in the anisotropic full-matrix approximation. Hydrogen atoms were located from the electron density difference maps and refined in the "rider" model. Final residuals are $wR_2 = 0.1384$ and GOOF = 0.966 for all reflections ($R = 0.0581$ was calculated on F for 2402 reflections with $I > 2\sigma(I)$). All calculations were performed with the SHELXTL PLUS program package. Atomic coordinates have been deposited with the Cambridge Crystallographic Database.

3-(1-Methyl-1*H*-indol-3-yl)propionic acid[7] (5b). A mixture of 1-methylindole (26.2 g, 0.2 mol) and acrylic acid (39 mL, 0.56 mol) in acetic anhydride (35 mL) and glacial AcOH (100 mL) was refluxed for 3 h. On cooling, the excess of AcOH was removed *in vacuo* (15 Torr) and the viscous residue was treated with a solution of NaOH (30 g, 0.75 mol) in 150 mL of water. The product was extracted with ether (3×50 mL) and carefully acidified with 10% HCl to pH 1. The precipitate that formed was filtered off, washed with water, and dried *in vacuo*. The yield of acid **5b** was 33 g (86%), m.p. 124—125 °C (*cf.* Ref. 7: m.p. 125—126 °C). ^{1}H NMR ($CDCl_3$), δ: 12.2 (br.s, 1 H); 7.60 (d, 1 H, $J = 9.1$ Hz); 7.30 (m, 1 H); 7.24 (d, 4 H, $J = 9.1$ Hz); 7.11 (m, 1 H); 6.94 (s, 1 H); 3.75 (s, 3 H); 3.12 (t, 2 H, $J = 8$ Hz); 2.78 (t, 2 H, $J = 7$ Hz).

3-(1,4,7-Trimethyl-1*H*-indol-3-yl)propionic acid (5a). A mixture of 1,4,7-trimethylindole (31.8 g, 0.2 mol) and acrylic acid (39 mL, 0.56 mol) in acetic anhydride (35 mL) and glacial AcOH (100 mL) was refluxed for 5 h. The product was isolated as described for **5b**. The yield of acid **5a** was 25.9 g (56%), m.p. 174—175 °C (decomp.). Found (%): C, 72.71; H, 7.43; N, 6.03. $C_{14}H_{17}NO_2$. Calculated (%): C, 72.70; H, 7.41; N, 6.06. ^{1}H NMR (DMSO-d_6), δ: 6.90 (s, 1 H); 6.65 (d, 1 H, $J = 7.1$ Hz); 6.58 (d, 1 H, $J = 7.2$ Hz); 3.90 (s, 3 H); 3.07 (t, 2 H, $J = 7.1$ Hz); 2.64 (s, 3 H); 2.57 (m, 2 H); 2.50 (s, 3 H).

Synthesis of 4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-ones 4 (general procedure). A suspension of a corresponding propionic acid (160 mmol) in 50 mL of methanesulfonic acid was added at 80 °C to a solution of P_2O_5 (17 g, 120 mmol) in 70 mL of $MeSO_3H$. The reaction mixture was stirred at this temperature for 10 to 15 min and poured into vigorously stirred ice water (500 mL). After 30 min, the precipitate that formed was filtered off, washed to a neutral reaction, and dried *in vacuo*.

4,5,8-Trimethyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (4a). Yield 29 g (85%), m.p. 161—162 °C (decomp.). Found (%): C, 78.87; H, 7.05; N, 6.59. $C_{14}H_{15}NO$. Calculated (%): C, 78.84; H, 7.09; N, 6.57. ^{1}H NMR ($CDCl_3$), δ: 6.95 (d, 1 H, $J = 7.2$ Hz); 6.78 (d, 1 H, $J = 7.2$ Hz); 4.15 (s, 3 H); 3.10, 2.90 (both m, 2 H each); 2.70, 2.57 (both s, 3 H each).

4-Methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (4b). Yield 28 g (93%), m.p. 134—135 °C (*cf.* Ref. 9: m.p. 135—136 °C).

^{1}H NMR ($CDCl_3$), δ: 7.68 (d, 1 H, J = 7.4 Hz); 7.41, 7.34, 7.16 (all m, 1 H each); 3.90 (s, 3 H); 3.05, 3.12, 2.97 (all m, 2 H each).

4,5,8-Trimethyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (1a). A suspension of ketone **4a** (4.3 g, 20 mmol) in 20 mL of ether was treated with 1.2 *M* phenyllithium (25.2 mmol, 21 mL) in ether. The target alcohol was isolated as a viscous oil in a conventional way. The yield of product **1a** was 3.6 g (61%). An analytical sample was purified by chromatography in benzene and recrystallized from ether—pentane, m.p. 117—118 °C. Found (%): C, 82.46; H, 7.22; N, 4.83. $C_{10}H_{21}NO$. Calculated (%): C, 82.44; H, 7.26; N, 4.81. ^{1}H NMR (C_6D_6), δ: 7.75 (m, 1 H); 7.20 (m, 5 H); 6.90 (dd, 1 H, J = 7.3 Hz); 3.30 (s, 3 H); 2.90 (m, 2 H); 2.75 (m, 1 H); 2.62 (s, 3 H); 2.52 (m, 1 H); 2.35 (s, 3 H); 1.80 (br.s, 1 H).

3,4-Dimethyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (1b). A solution of MeLi in ether was prepared as follows. A solution of MeI (2.5 mL, 40 mmol) in 15 mL of ether was added dropwise under argon to a stirred suspension of finely divided lithium (0.56 g, 80 mmol) in 30 mL of ether. The addition rate was such as to provide uniform boiling of the reaction mixture. After the reaction was completed, the mixture was refluxed for an additional 2 h. Then the solution was cooled with ice, ketone **4b** (5.6 g, 30 mmol) was carefully added, and the resulting suspension was refluxed for 3 h. The mixture was cooled to 0 °C and 10% NH_4Cl (30 mL) was added dropwise. The organic phase was separated, washed with water, dried with $MgSO_4$, and concentrated *in vacuo* to 1/4 of the initial volume. The solid product was filtered off and dried *in vacuo* to give a fine crystalline yellowish substance (4.8 g, 78%), m.p. 124—126 °C. Found (%): C, 77.60; H, 7.53; N, 6.93. $C_{13}H_{15}NO$. Calculated (%): C, 77.58; H, 7.51; N, 6.96. ^{1}H NMR (C_6D_6), δ: 7.65 (m, 1 H); 7.30 (m, 2 H); 7.15 (m, 1 H); 3.30 (s, 3 H); 2.80, 2.65, 2.45, 2.30 (all m, 1 H each); 1.95 (br.s, 1 H); 1.50 (s, 3 H).

4-Methyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (1c) was obtained by analogy with compound **1b**. Ketone **4b** (5.6 g, 30 mmol) was treated with a solution of phenyllithium prepared from lithium (0.56 g, 80 mmol) and bromobenzene (4.2 mL, 40 mmol) in 45 mL of ether. The yield of compound **1c** was 6.8 g (86%), m.p. 117—119 °C. Found (%): C, 82.12; H, 6.55; N, 5.30. $C_{18}H_{17}NO$. Calculated (%): C, 82.10; H, 6.51; N, 5.32. ^{1}H NMR (C_6D_6), δ: 7.75 (m, 1 H); 7.45, 7.33, 7.20 (all m, 2 H each); 7.15, 7.10 (both m, 1 H each); 3.05 (s, 3 H); 2.85 (m, 3 H); 2.60 (m, 1 H); 1.80 (br.s, 1 H).

4,5,8-Trimethyl-3-phenyl-2-(4,5,8-trimethyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-1-yl)-1,4-dihydrocyclopenta[*b*]indole (3a). Alcohol **1a** (3.56 g, 12.2 mmol) was dehydrated in 150 mL of benzene containing trace amounts of TsOH. After routine workup, the product was purified by chromatography in benzene. The solution in benzene was concentrated *in vacuo* to 50 mL and then hexane (30 mL) was added. The precipitate that formed was filtered off and dried *in vacuo* to give a fine crystalline light yellow powder (1.56 g, 47%), m.p. 218—219 °C (decomp.). Found (%): C, 87.84; H, 7.05; N, 5.11. $C_{40}H_{38}N_2$. Calculated (%): C, 87.87; H, 7.01; N, 5.12. ^{1}H NMR ($CDCl_3$), δ: 7.45, 7.30 (both m, 5 H each); 7.15, 6.70, 4.70 (all m, 2 H each); 3.72, 3.66 (both s, 3 H each); 3.46, 3.32 (both d, 1 H each, J = 23 Hz); 3.10 (m, 1 H); 2.80 (m, 1 H); 2.72 (s, 6 H); 2.50 (s, 3 H); 2.31 (s, 3 H). ^{13}C NMR ($CDCl_3$), δ: 153.7, 148.5, 147.0, 144.6, 140.2, 138.9, 135.5, 131.7, 129.3, 127.8, 127.1, 124.9, 124.4, 121.1, 119.1, 118.8, 116.4 (>C<); 128.6, 127.7, 127.3, 126.4, 123.7, 122.9, 119.7 (=CH—); 119.6, 44.7 (>CH—); 50.3, 32.3 (—CH_2); 38.5, 34.1, 34.05, 19.8, 19.4, 19.05 (—CH_3).

2-(3,4-Dimethyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-1-yl)-3,4-dimethyl-1,4-dihydrocyclopenta[*b*]indole (3b). A solution of alcohol **1b** (4 g, 20 mmol) in 100 mL of benzene containing trace amounts of TsOH was refluxed in a flask fitted with a Dean—Stark trap until the starting alcohol disappeared (TLC, benzene—ethyl acetate (4 : 1)). After the reaction was completed, the mixture was cooled, washed with a solution of $KHCO_3$, and dried with $MgSO_4$. The solution in benzene was filtered through a short column filled with silica gel, concentrated to half the initial volume, and mixed with hexane (50 mL). The precipitate that formed was filtered off and dried *in vacuo* to give a light yellow crystalline substance (2.2 g, 65%), m.p. 215—216 °C. Found (%): C, 85.19; H, 7.14; N, 7.62. $C_{26}H_{26}N_2$. Calculated (%): C, 85.21; H, 7.15; N, 7.64. ^{1}H NMR (C_6D_6), δ: 7.65 (m, 2 H); 7.35—7.15 (set of m, 6 H); 4.56 (m, 1 H); 3.34 (m, 2 H); 3.30 (s, 3 H); 3.25 (m, 1 H); 3.16 (s, 3 H); 2.65 (m, 1 H); 2.40 (m, 1 H); 2.17 (s, 3 H); 1.21 (d, 3 H). ^{13}C NMR (C_6D_6), δ: 149.8, 149.7, 149.4, 149.1, 149.0, 142.3,142.1, 141.4, 129.3, 128.5 (>C<); 120.7, 119.9, 119.8, 119.7, 119.5, 118.9, 118.2, 116.9 (=CH—); 109.6, 36.0 (>CH—); 45.7, 31.3 (—CH_2); 32.7, 29.8, 20.3, 11.6 (—CH_3).

4-Methyl-2-(4-methyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-1-yl)-3-phenyl-1,4-dihydrocyclopenta[*b*]indole (3c). A solution of alcohol **1c** (0.8 g, 3 mmol) in 15 mL of benzene containing trace amounts of TsOH was refluxed in a flask fitted with a Dean—Stark trap until the starting alcohol disappeared (TLC, benzene—ethyl acetate (4 : 1)). After the reaction was completed, the mixture was cooled, washed with a solution of $KHCO_3$, and dried with $MgSO_4$. The residue was chromatographed on silica gel in benzene and recrystallized from ether. The yield of compound **3c** was 0.25 g (34%), m.p. 207—209 °C. Found (%): C, 88.15; H, 6.18; N, 5.69. $C_{36}H_{30}N_2$. Calculated (%): C, 88.13; H, 6.16; N, 5.71. ^{1}H NMR ($CDCl_3$), δ: 7.75 (m, 2 H); 7.40—7.10 (set of m, 14 H); 6.90 (m, 2 H); 4.80, 4.35 (both m, 1 H each); 3.41 (s, 2 H); 3.14 (s, 3 H); 3.05 (s, 1 H); 2.96 (s, 3 H); 2.70 (s, 1 H). ^{13}C NMR (C_6D_6), δ: 152.0, 151.8, 148.7, 146.8, 144.7, 142.5, 141.6, 135.9, 133.0, 126.7, 124.9, 124.4 (>C<); 129.8, 129.7, 129.0, 128.7, 127.5, 127.4, 126.7,125.7, 125.2, 122.0, 121.2, 120.0, 119.7, 119.1, 118.7, 117.2, 110.0, 109.9 (=CH—); 120.0, 44.7 (>CH—); 50.5, 31.4 (—CH_2); 30.4, 30.0(—CH_3).

References

1. J. F. van Baar, A. D. Horton, K. P. de Kloe, I. V. Taidakov, I. E. Nifant´ev, E. Kragtwijk, S. G. Mkoyan, and P. A. Schut, *Organometallics*, 2003, **22**, 2711.
2. J. Bergman and J. E. Backvall, *Tetrahedron*, 1975, **31**, 2063.
3. J. Bergman, P.-O. Norrby, U. Tilstam, and L. Venemalm, *Tetrahedron*, 1989, **45**, 5549.
4. A. G. M. Barret, D. Dauzonne, I. O´Neil, and A. Renaud, *J. Org. Chem.*, 1984, **49**, 4409.
5. J. Jennings, *J. Chem. Soc.*, 1957, 497.
6. H. Cho and S. Matsuki, *Heterocycles*, 1996, **43**, 127.
7. S. Harts and J. P. Pots, *J. Org. Chem.*, 1962, **27**, 2940.
8. M. L. Baron, L. L. Martin, D. Rae, P. M. Simmonds, and M. L. Woolcock, *Aust. J. Chem.*, 1990, **43**, 741.
9. N. Ishizumi, *Chem. Pharm. Bull.*, 1967, **15**, 863.

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