# Synthesis of 1-iodo-1,2,3,4,4a,9a-hexahydrocarbazoles and their isomerization into 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinolines

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The reactions of 2-(cyclohex-2-enyl)-4,5-difluoroaniline or *N*-methyl-2-(cyclohex-2-enyl)aniline with $I_2$ in $CCl_4$ in the presence of $NaHCO_3$ give 1-iodo-1,2,3,4,4a,9a-hexahydrocarbazoles, which isomerize in MeCN into the corresponding 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinolines in quantitative yields.

**Key words:** cyclohexenylanilines, iodocyclization, hexahydrocarbazoles, 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinolines.

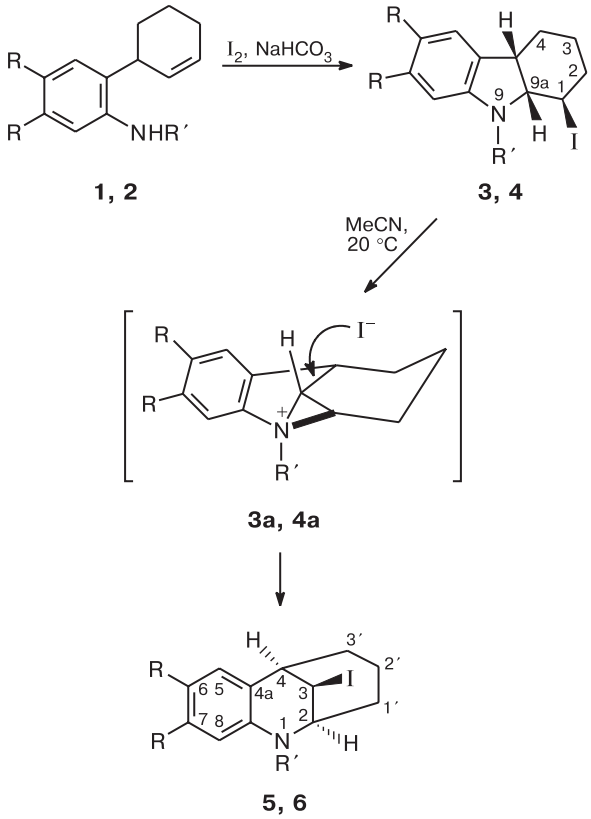
Carbazole derivatives are used as intermediates in the synthesis of some biologically active preparations.[1,2] Tetra- or hexahydrocarbazoles are obtained by the reactions of 2-chlorocyclohexanones with anilines in the presence of alkali metal carbonates.[3] Alternatively, they can be prepared by treating 2-(cyclohex-2-enyl)anilines with polyphosphoric acid[2] or organoselenium compounds[4] or by exposing them to UV radiation.[5]

In continuation of the study on heterocyclization of *ortho*-alkenylanilines,[6,7] we investigated the reactions of 2-(cyclohex-2-enyl)-4,5-difluoroaniline (**1**)[8] and *N*-methyl-2-(cyclohex-2-enyl)aniline (**2**)[5] with $I_2$ in the presence of $NaHCO_3$.

Amines **1** and **2** react with $I_2$ in $CCl_4$ to exclusively give 1-iodo-1,2,3,4,4a,9a-hexahydrocarbazoles **3** or **4**, respectively, in 90% yields. Being insoluble in $CCl_4$, heterocycles **3** and **4** precipitated from the reaction mixture as they formed. When dissolved in $CDCl_3$, hexahydrocarbazole **4** irreversibly isomerizes into the corresponding 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinoline (**5**); after five days, the ratio of compound **4** to **5** becomes ~1 : 1 ($^1$H NMR data). Unlike this, difluoro derivative **3** in $CDCl_3$ undergoes no isomerization.

Cyclization of compound **2** in MeCN exclusively yields heterocycle **5**. Iodide **4** isomerizes in MeCN into compound **5** within two days. In contrast, carbazole **3** containing two fluorine atoms in the aromatic ring undergoes slow isomerization into a tetrahydroquinoline derivative **6** (under analogous conditions, its nearly complete isomerization takes ~140 days). The reaction of amine **1** with $I_2$ in MeCN affords carbazole **3** and tetrahydroquinoline **6** in the 50 : 1 ratio ($^1$H NMR data).

**Scheme 1**




**1**, **3**, **3a**, **6:** R = F, R′ = H
**2**, **4**, **4a**, **5:** R = H, R′ = Me

6-*endo*-Cyclization products **5** and **6** obtained in MeCN are probably due to subsequent transformations

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1227—1229, July, 2002.

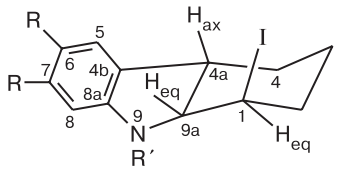
1066-5285/02/5107-1329 $27.00 

of 1-iodocarbazoles **3** and **4**; their rates depend on the nature of substituents in the aromatic ring or at the nitrogen atom.

Presumably,[9] the isomerization proceeds through an intramolecular attack of the N atom on the C(1) atom to give aziridinium salts **3a** and **4a**. The latter are in turn attacked by a nucleophilic $I^-$ anion with the formation of tricyclic compounds **6** and **5**.

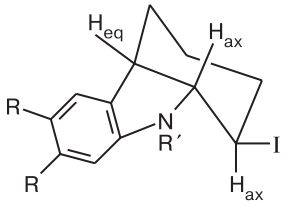
An analysis of the $^1H$ NMR spectra of carbazoles **3** and **4** showed that dominant conformations of their cyclohexane fragments are different. Thus the H(9a) and H(1) protons in carbazole **3** are nearly axial, as evident from their high coupling constant (9.1 Hz), whereas a signal for the equatorial H(4a) proton appears as an ill-resolved multiplet since $J$ = 1—2 Hz (Scheme 2, conformer **B**).

**Scheme 2**




**A**

For **3** For **4**




**B**

In solution, the cyclohexane fragment of hexahydrocarbazole **4** predominantly exists in a chair conformation (conformer **A**) with the equatorial H(1) and H(9a) protons ($J$ = 2.4 Hz).[10] A high coupling constant (6.4 Hz) for the H(9a) and H(4a) protons suggests the *cis*-fusion of the rings. Apparently, the equilibrium is shifted from conformer **B** to **A** in the presence of the *N*-methyl substituent.

Earlier,[7] we have synthesized a propanoquinoline structurally close to compounds **5** and **6**. Its structure was determined from spectroscopic data consistent with those for **5** and **6**.[7]

Thus, the reactions of *ortho*-(cyclohex-2-enyl)anilines with $I_2$ in $CCl_4$ afford 1-iodohexahydrocarbazoles in good yields. In $CDCl_3$ and $CH_3CN$, the latter undergo rearrangement into 3-iodo-2,4-propano-1,2,3,4-tetrahydroquinolines at different rates depending on the substituent at the aromatic ring and at the N atom.

## Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM 300 instrument (300.13 and 75.47 MHz, respectively) in $CDCl_3$ with $Me_4Si$ as the internal standard. IR spectra were recorded on a UR-20 instrument. The course of the reaction was monitored using Silufol UV 254 plates with benzene as an eluent.

**Synthesis of hexahydrocarbazoles (3, 4).** Sodium bicarbonate (10 mmol) and $I_2$ (2 mmol) were added to a solution of amine **1**[8] or **2**[5] (1 mmol) in 20 mL of $CCl_4$. After the starting amine was completely consumed (monitoring by TLC in benzene), $CCl_4$ was decanted. The precipitate, to which $CH_2Cl_2$ (30 mL) was added, was treated with a 10% aqueous solution of $Na_2S_2O_3$ (2×20 mL). The organic phase was washed with water (2×10 mL) and dried over $MgSO_4$. The solvent was evaporated.

**6,7-Difluoro-(1*R**,4a*S**,9a*R**)-1-iodo-1,2,3,4,4a,9a-hexahydrocarbazole (3)**, yield 90%. Amorphous substance gradually becoming darker in air, $R_f$ 0.6 ($C_6H_6$). Found (%): C, 42.69; H, 3.47; F, 11.05; I, 37.48; N, 3.89 $C_{12}H_{12}F_2IN$. Calculated (%): C, 43.01; H, 3.62; F, 11.34; I, 37.87; N, 4.18. IR (ν/cm$^{-1}$): 3352 (NH). $^1H$ NMR ($CDCl_3$), δ: 1.10—2.20 (m, 6 H, 3 $CH_2$); 3.20 (m, 1 H, H(4a)); 3.90 (dd, 1 H, H(9a), $J_{H(9a),H(1)}$ = 9.1 Hz, $J_{H(9a),H(4a)}$ = 7.2 Hz); 4.00 (dt, 1 H, H(1), $J_1$ = 3.9 Hz, $J_2$ = 9.1 Hz); 4.20 (br.s, 1 H, NH); 6.50—7.20 (m, 2 H, Ar). $^{13}C$ NMR ($CDCl_3$), δ: 35.80 (C(1)); 37.50 (C(2)); 23.60 (C(3)); 23.8 (C(4)); 42.0 (C(4a)); 69.70 (C(9a)); 99.60 (d, C(8), $J$ = 21.8 Hz); 115.40 (d, C(4b), $J$ = 18.3 Hz); 111.60 (d, C(5), $J$ = 19.5 Hz); 144.10 (dd, C(6), $J_1$ = 13.6 Hz, $J_2$ = 237.7 Hz); 145.0 (dd, C(7), $J_1$ = 14.5 Hz, $J_2$ = 143.6 Hz); 145.50 (d, C(8a), $J$ = 9.2 Hz).

**(1*R**,4a*S**,9a*R**)-1-Iodo-9-methyl-1,2,3,4,4a,9a-hexahydrocarbazole (4)**, yield 90%. Amorphous dark brown substance, $R_f$ 0.8 ($C_6H_6$). Found (%): C, 49.39; H, 4.74; I, 40.26; N, 4.14. $C_{13}H_{16}IN$. Calculated (%): C, 49.86; H, 5.15; I, 40.52; N, 4.74. IR (ν/cm$^{-1}$): 550 (C—I). $^1H$ NMR ($CDCl_3$), δ: 1.10—2.30 (m, 6 H, 3 $CH_2$); 2.60 (s, 3 H, Me); 3.20 (ddd, 1 H, H(4a), $J_{H(4a),H_{ax}(4)}$ = 11.2 Hz, $J_{H(4a),H_{eq}(4)}$ = 6.2 Hz, $J_{H(4a),H(9a)}$ = 6.4 Hz); 3.50 (dd, 1 H, H(9a), $J_{H(1),H(9a)}$ = 2.4 Hz, $J_{H(9a),H(4a)}$ = 6.4 Hz); 4.80 (ddd, 1 H, H(1), $J_{H(1),H_{ax}(2)}$ = 6.3 Hz, $J_{H(1),H_{eq}(2)}$ = 2.0 Hz, $J_{H(1),H(9a)}$ = 2.4 Hz); 6.60 (d, 1 H, H(8), $J$ = 7.8 Hz); 6.80 (t, 1 H, H(7), $J$ = 7.8 Hz); 7.10—7.20 (m, 2 H, H(5), H(6)). $^{13}C$ NMR ($CDCl_3$), δ: 20.90 (C(3)); 29.80 (C(2)); 30.90 (C(4)); 31.60 ($CH_3$); 34.80 (C(1)); 37.90 (C(4a)); 73.80 (C(9a)); 108.80 (C(8)); 119.10 (C(6)); 122.80 (C(5)); 127.40 (C(7)); 134.30 (C(4b)); 151.90 (C(8a)).

**Synthesis of compounds 5 and 6 by isomerization of hexahydrocarbazoles 3 and 4 in MeCN.** A solution of carbazole **3** or **4** (1 mmol) in 5 mL of MeCN was kept at 20 °C for 140 and two days, respectively. After the starting reagent was completely consumed (monitoring by TLC in benzene), the solvent was evaporated. The residue was chromatographed on silica gel (1 g) in a short column with $CCl_4$ as the eluent. The yields of heterocycles **6** and **5** were 98 and 90%, respectively.

**Synthesis of compound 5 by cyclization of amine 2 in MeCN.** Sodium bicarbonate (10 mmol) and $I_2$ (2 mmol) were added to

a solution of amine **2** (1 mmol) in 20 mL of MeCN. The reaction mixture was stirred at 20 °C for 48 h while shaking it periodically. After the starting amine **2** was completely consumed (monitoring by TLC in benzene), the solvent was evaporated, and $CH_2Cl_2$ (30 mL) was added. The resulting mixture was treated with a 10% aqueous solution of $Na_2S_2O_3$ (2×20 mL). The organic phase was washed with water (2×10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (1 g) in a short column with $CCl_4$ as the eluent to give compound **5** in 88% yield.

***N*-Methyl-(2*R**,3*R**,4*R**)-3-iodo-2,4-propano-1,2,3,4-tetrahydroquinoline (5).** Amorphous substance, $R_f$ 0.8 ($C_6H_6$). Found (%): C, 49.51; H, 4.72; I, 40.11; N, 4.23. $C_{13}H_{16}IN$. Calculated (%): C, 49.86; H, 5.15; I, 40.52; N, 4.47. IR (ν/cm$^{-1}$): 550 (C—I). $^1$H NMR ($CDCl_3$), δ: 1.30—2.80 (m, 6 H, 3 $CH_2$); 2.90 (s, 3 H, Me); 3.00 (ddd, 1 H, H(4), $J_1$ = 1.5 Hz, $J_2$ = 1.7 Hz, $J_3$ = 4.2 Hz); 3.40 (m, 1 H, H(2)); 4.70 (ddd, 1 H, H(3), $J_1$ = 1.7 Hz, $J_2$ = 2.9 Hz, $J_3$ = 3.2 Hz); 6.50 (d, 1 H, H(8), $J$ = 7.8 Hz); 6.60 (t, 1 H, H(6), $J$ = 7.3 Hz); 6.80 (dd, 1 H, H(5), $J_1$ = 1.4 Hz, $J_2$ = 7.3 Hz); 7.10 (m, 1 H, H(7)). $^{13}$C NMR ($CDCl_3$), δ: 16.90 (C(2′); 25.50 (C(3′)); 30.80 (C(1′)); 32.60 (C(4)); 37.00 (N—Me); 42.40 (C(3)); 60.40 (C(2)); 109.00 (C(8)); 118.40 (C(6)); 120.70 (C(7)); 123.90 (C(5)); 128.10 (C(4a)); 146.30 (C(8a)).

**6,7-Difluoro-(2*R**,3*R**,4*R**)-3-iodo-2,4-propano-1,2,3,4-tetrahydroquinoline (6)**, yield 98%. Amorphous substance, $R_f$ 0.4 ($C_6H_6$). Found (%): C, 42.89; H, 3.57; F, 10.95; I, 37.41; N, 3.96. $C_{12}H_{12}F_2IN$. Calculated (%): C, 43.01; H, 3.62; F, 11.34; I, 37.87; N, 4.18. IR (ν/cm$^{-1}$): 3360 (NH). $^1$H NMR ($CDCl_3$), δ: 1.30—2.80 (m, 6 H, 3 $CH_2$); 3.20 (m, 1 H, H(4)); 3.70 (m, 1 H, H(3)); 4.30 (s, 1 H, NH); 4.80 (ddd, 1 H, H(2), $J_1$ = 1.7 Hz, $J_2$ = 2.0 Hz, $J_3$ = 4.1 Hz); 6.60—7.10 (m, 2 H, ArH). $^{13}$C NMR ($CDCl_3$), δ: 16.60 (C(2′); 29.80 (C(3′)); 30.00 (C(1′)); 31.00 (C(4)); 40.90 (C(3)); 51.70 (C(2)); 101.30 (d, C(8), $J$ = 20.3 Hz); 115.30 (d, C(4a), $J$ = 18.2 Hz); 115.90 (d, C(5), $J$ = 17.4 Hz); 145.00—152.00 (m, C(6), C(7), C(8a)).

## References


1. N. I. Andreeva, G. A. Bogdanova, A. I. Bokanov, P. Yu. Ivanov, M. D. Mashkovskii, and V. I. Shvedov, *Khim.-Farm. Zh.*, 1992, **26**, 4 [*Pharm. Chem. J.*, 1992, No. 1 (Engl. Transl.)].
2. A. G. Mustafin, I. N. Khalilov, I. B. Abdrakhmanov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 1989, 816 [*Chem. Nat. Compd.*, 1989, No. 6 (Engl. Transl.)].
3. Ger. Pat. 374.098; *Chem. Abstrs.*, 1924, **18**, 2175.
4. D. L. J. Clive, C. K. Wong, W. A. Kiet, and S. Menchen, *J. C. S. Chem. Commun.*, 1978, 379.
5. S. Jolidon and H.-J. Hansen, *Helv. Chim. Acta*, 1979, **62**, 2581.
6. R. R. Gataullin, T. V. Kazhanova, F. F. Minnigulov, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1789 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1767].
7. R. R. Gataullin, F. F. Minnigulov, T. V. Khakimova, T. V. Kazhanova A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 437 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 456].
8. A. G. Mustafin, D. Sc. (Chem.) Thesis, Inst. of Organic Chemistry, Ufa, 2000, 325 pp.
9. D. R. Williams, M. H. Osterhout, and J. M. McGill, *Tetrahedron Lett.*, 1989, **30**, 1331.
10. E. Pretsch, T. Clerk, J. Seible, and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds*, Springer Verlag, Berlin—Heidelberg—New York—Tokyo, 1983, 730 p.


*Received July 1, 2001;*
*in revised form November 20, 2001*