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Synthesis of 1-iodo-1,2,3,4,4a,9a-hexahydrocarbazole, 2a,3,4,5,5a,10a-hexahydrooxazolocarbazolium iodide and 4-bromo-1,2,3,4,4a,11b-hexahydrodibenzoxazepine from *N*-benzoyl-2-(cyclohex-2-en-1-yl)aniline

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The reaction of *N*-benzoyl-2-(cyclohex-2-en-1-yl)aniline **1** with molecular oxygen in the presence of $NaHCO_3$ results in *N*-benzoyl-1-iodo-1,2,3,4,4a,9a-hexahydrocarbazole, which was isomerised to 1-phenyl-2a,3,4,5,5a,10a-hexahydro[1,3]oxazolo-[5,4,3-*j*,*k*]carbazol-10-ium iodide, whereas the reaction of amide **1** with molecular bromine results in dibromide, but the interaction with NBS leads to 4-bromo-6-phenyl-1,2,3,4,4a,11b-hexahydrodibenzo[*d*,*f*][1,3]oxazepine.

Benzo-condensed heterocyclic systems are used in the synthesis of alkaloids or for medical purposes. Because of this, these systems are of great interest to scientists. The cyclization of *ortho*-alkenyl anilines affected by electrophilic reagents is used for producing benzo-condensed heterocyclic systems.[1] The use of halogens[2] or organoselenium compounds[3] allows one not only to construct a heterocyclic fragment but also to introduce a good living group into a molecule. The cyclization of *ortho*-alkenylanilines with electrophilic reagents is known to give indoline and quinoline compounds. The following transformation of heterocycles to other systems, as well as the formation of a 7-*exo*-cyclization product, is rarely observed.

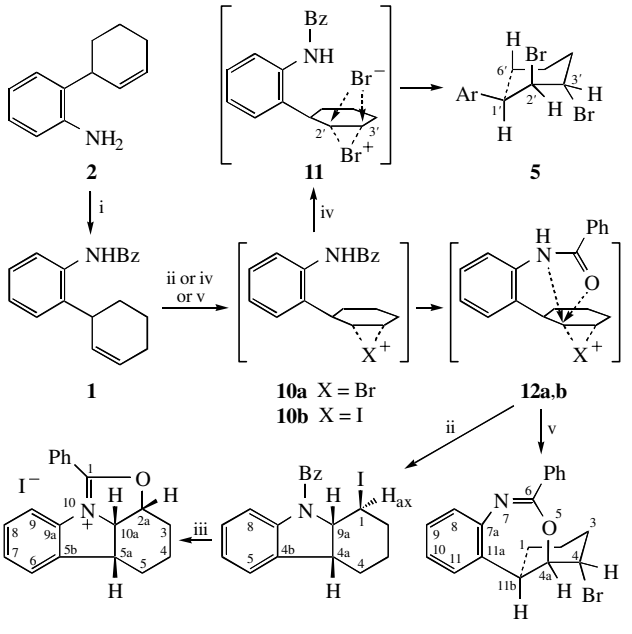
We found that the reaction leads to different compounds depending on the conditions and nature of the halogenating agent.

Thus, benzamide **1** obtained from amine **2**[5] forms hexahydrocarbazole **3** in the reaction with molecular iodine. The cyclization proceeds over a long period of time. Compound **3** is unstable. Being left in a solvent for a long time or boiled in benzene for a short time, it isomerises to tricyclic compound **4** in practically quantitative yield.

The reaction of amide **1** with Br_2 gives a mixture of reaction products, from which dibromide **5** was isolated. The latter is a basic reaction product, which precipitates in a crystalline form from solution after the completion of bromination.

However, the use of *N*-bromosuccinimide in the heterocyclization of benzamide **1** leads to benzoxazepine **6**. The cyclization proceeds rapidly in contrast to that with I_2.

It has been found earlier that 2-hexahydrocarbazole **7**[4] and its analogues[6] undergo isomerization to propane tetrahydroquinoline **8**[4] in solution. To confirm the structure of tetracycle **4**, benzoate **9** was produced from quinoline **8**. Its spectral characteristics were compared with those of compound **4** (Scheme 2).

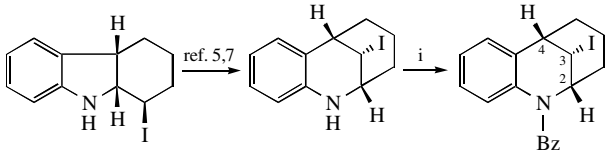


2 **11** **5**

1 **10a** X = Br **10b** X = I **12a,b**

4 **3** **6**

Scheme 1 *Reagents and conditions*: i, BzCl, 10% aqueous NaOH solution; ii, I_2, $NaHCO_3$, CH_2Cl_2, 20° C; iii, > 30 days in CH_2Cl_2, 20 °C or reflux in benzene; iv, Br_2, CH_2Cl_2, 20 °C; v, NBS, CH_2Cl_2, 20 °C.



7 **8** **9**

Scheme 2

The formation of onium complexes in the reactions of olefins with halogens is a conventional supposition. Halogen onium complexes **10a**,**b**, formed in the reactions with Br_2 or NBS in the presence of Br^- anions lead to dibromide **5** as a result of the attack of this anion on C-2′ or C-3′ carbons (**11**, Scheme 1). In the reaction with NBS, the Br^- anion is absent; probably, by this reason, an oxygen atom of the amide fragment is a nucleophilic particle, and that leads to compound **6**.

The structure of the compounds obtained was determined using spectral methods and elemental analysis.† The assignment of signals in the ^{1}H and ^{13}C NMR spectra of compounds **5** and **6** was made using the CH correlation and the double resonance. Thus, the H-1 proton of hexahydrocarbazole **3** is axial, as confirmed by a high spin–spin coupling constant (12.0 Hz) in the ^{1}H NMR spectrum of this compound. In oxazepine **6**, the H-11b proton is axial; it has a high spin–spin coupling constant with the axial H-1 proton (~12 Hz). The oxygen and bromine atoms are disposed most distant axially, and owing to that H-4 and H-4a protons are equatorial.

Probably, the dihedral angle between H-11b and H-4a protons is close to 90°; in this situation, the spin–spin coupling constant is practically equal to 0 because the H-4a proton doublet signal transforms to a singlet at the suppression of the H-4 proton signal.

Two negative bromine atoms of compound **5** are disposed distinct axial due to the mutual repulsion. Owing to that, the spin–spin coupling constants are low, in the ^{1}H NMR spectrum they are observed as narrow multiplets. The H-1′ proton signal has a high diaxial spin-spin coupling constant with the H-6′ proton (J 12.0 Hz).

In the ^{1}H NMR spectrum, the signals of H-2, H-3 and H-4 protons are observed as narrow multiplets owing to the low spin–spin coupling constant caused by their equatorial disposition in tetrahydroquinoline derivative **9**.

† IR spectra were recorded on a UR-20 instrument. ^{1}H and ^{13}H NMR spectra (internal TMS) were measured on a Bruker AM-300 spectrometer (300.13 and 75.45 MHz for ^{1}H and ^{13}H, respectively). Elemental analysis was performed on a C-H-N Analyzer M-185 B. Column chromatography was performed over silica gel 60 (0.040–0.063 mm; 230–400 mesh, Lancaster). For quantitative TLC, Sorbil UV 254 plates were used (Luminofor, Russia) detecting the compounds with iodine and a UV detector (λ 254 nm). Mass spectra were recorded on an MX 1320 device (70 eV).

N-*Benzoyl-2-(cyclohex-2-en-1-yl)aniline* **1**: 100 ml of a 1% aqueous NaOH solution and a solution of aniline **2** (1.73 g, 10 mmol) in benzene (20 ml) were mixed in a 250 ml flask; benzoyl chloride (1.55 g, 11 mmol) in benzene (10 ml) was added through a dropping funnel. An exothermic reaction was observed. The reaction mixture cooled to 30 °C was stirred for 1 h. After completion of the reaction, the aqueous phase was removed; the organic phase was washed with water (2×20 ml) and dried with Na_2SO_4. The yield of the crude product was 2.7 g. The recrystallization from ethanol alcohol gave 2.5 g (90%), mp 127–130 °C. Found (%): C, 82.19; H, 6.80; N, 4.98. Calc. for $C_{19}H_{19}NO$ (%): C, 82.28; H, 6.90; N, 5.05.

N-*Benzoyl-1-iodo-1,2,3,4,4a,9a-hexahydrocarbazole* **3**: a mixture of amide **1** (0.89 g, 3 mmol), I_2 (1.52 g, 6 mmol) and $NaHCO_3$ (9 g, 30 mmol) in CH_2Cl_2 (30 ml) was stirred for 72 h. The progress of the reaction was monitored by TLC. After the disappearance of the starting compound, the mixture was diluted with CH_2Cl_2 (50 ml). The organic solution was washed with a 10% $Na_2S_2O_3$ solution (2×20 ml) and water (2×20 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel. The yield was 0.63 g (50%); mp 152–155 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30–2.40 (m, 6H, 3CH_2), 3.70 (m, 1H, H-4a), 4.18 (ddd, 1H, H-1, J_1 3.8 Hz, J_2 8.8 Hz, J_3 12.0 Hz), 5.00 (dd, 1H, H-9a, J_1 7.5 Hz, J_2 8.8 Hz), 7.05–7.60 (m, 9H, ArH). IR (ν/cm^{-1}): 1650, 1470, 1390, 1280, 1180, 1120, 770, 730, 430. Found (%): C, 56.38; H, 4.29; I, 31.26; N, 3.28. Calc. for $C_{19}H_{18}INO$ (%): C, 56.59; H, 4.50; I, 31.47; N, 3.47.

*1-Phenyl-2a,3,4,5,5a,10a-hexahydro[1,3]oxazolo[5,4,3-*j,k*]carbazol-10-ium iodide* **4**. Hexahydrocarbazole **3** (1.1 g, 3 mmol) was refluxed in benzene for 5–7 min. The solvent was evaporated *in vacuo*. The residue was washed with benzene (1 ml). The yield of the crude product was 1.09 g. The recrystallization from ethanol gave 0.56 g (51%) of compound **4**, which is insoluble in C_6H_6, CH_2Cl_2 or $CHCl_3$; mp 157–159 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.20–2.00 (m, 6H, 3CH_2), 3.50 (dt, 1H, H-5a, J_1 6.2 Hz, J_2 8.0 Hz), 4.25 (dd, 1H, H-10a, J_1 4.6 Hz, J_2 6.2 Hz), 5.35 (ddd, 1H, H-2a, J_1 4.6 Hz, J_2 4.9 Hz, J_3 9.2 Hz), 7.05–7.12 (m, 2H, ArH), 7.22 (t, 1H, ArH, J 7.3 Hz), 7.32 (d, 1H, ArH, J 7.2 Hz), 7.51 (t, 2H, ArH, J 7.4 Hz), 7.67 (t, 1H, ArH, J 7.4 Hz), 7.90 (d, 1H, ArH, J 7.2 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 19.6 (C-4), 25.6 (C-3), 27.4 (C-5), 40.3 (C-5a), 60.8 (C-10a), 70.1 (C-2a), 118.2 (C-8), 124.2 (C-6), 127.7 (C-9), 128.1 (C-7), 128.5 (C-3′), 129.2 (C-5b), 129.4 (C-2′), 133.5 (C-4′), 137.8 (C-9a), 139.1 (C-1′), 164.5 (N$^+$=C–O). IR (ν/cm^{-1}): 1725, 1475, 1375, 1270, 1115, 1035, 775, 725. UV (MeCN): λ_{max} 365 nm, λ_{min} 330 nm. Found (%): C, 56.41; H, 4.32; Anionic iodine, 31.00; N, 3.26. Calc. for $C_{19}H_{18}INO$ (%): C, 56.59; H, 4.50; Anionic iodine, 31.47; N, 3.47.

4-Bromo-1,2,3,4,4a,11b-hexahydrodibenzoxazepine **6**: a solution of compound **1** (0.2 g, 0.7 mmol) and NBS (0.125 g, 0.7 mmol) was stirred in CH_2Cl_2 (5 ml). The progress of the reaction was monitored by TLC. After the disappearance of the starting amide, the mixture was diluted with 50 ml of CH_2Cl_2 and washed with a 10% $Na_2S_2O_3$ solution (2×20 ml) and water (2×50 ml). The organic phase was dried over Na_2SO_4; the solvent was evaporated *in vacuo*. The yield of the crude product was 0.25 g (97%). R_f 0.84 (C_6H_6–EtOAc, 85:15). The product was subjected to chromatography on silica gel. The yield of an amorphous white powder was 0.2 g. An attempt to recrystallise it from hot 95% ethanol lead to hydrolysis. ^{1}H NMR ($CDCl_3$) δ: 1.70–1.80 (m, 2H, H_{eq}-1, H_{eq}-2), 1.88 (dk, 1H, H_{ax}-1, J_1 2.0 Hz, J_2 12.0 Hz, J_{gem} 12.0 Hz), 2.05 (m, 2H, H_{eq}-3, H_{ax}-2), 2.45 (m, 1H, H_{ax}-3), 3.73 (dd, 1H, H-11b, J_1 3.4 Hz, J_2 12.0 Hz), 4.59 (ddd, 1H, H-4, J_1 1.7 Hz, J_2 2.0 Hz, J_3 3.2 Hz), 4.80 (d, 1H, H-4a, J 3.2 Hz), 7.01–7.22 (m, 3H, ArH), 7.31–7.39 (m, 2H, ArH), 8.05 (dd, 2H, J_1 2.0 Hz, J_2 8.1 Hz). MS, *m/z*: 355 [M]$^+$, 105 [PhC≡O]$^+$, 276 [M – Br]$^+$, 234 [M – C_3H_6Br]$^+$, 250 [M – PhC=O]$^+$. Found (%): C, 63.94; H, 5.00; Br, 22.35; N, 3.84. Calc. for $C_{19}H_{18}BrNO$ (%): C, 64.06; H, 5.09; Br, 22.43; N, 3.93.

2-[(1R,2S,3S)-2,3-Dibromocyclohexyl]-1-phenylcarboxamidobenzene **5**: to a solution of compound **1** (0.3 g, 1.1 mmol) in 10 ml of CH_2Cl_2 a solution of Br_2 (0.176 g, 1.1 mmol) in 1 ml of CH_2Cl_2 was added dropwise with stirring. After 72 h, crystals were precipitated. The precipitate was filtered off, the yield of the resulting compound was 0.02 g; mp 180–183 °C (CH_2Cl_2). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.55–2.45 (m, 6H, 3CH_2), 3.92 (dt, 1H, H-1′, J_1 2.4 Hz, J_2 12.0 Hz), 4.91 (m, 1H, H-2′), 4.99 (m, 1H, H-3′), 7.20-7.60 (m, 7H, ArH), 8.00 (dd, 2H, ArH, J_1 1.6 Hz, J_2 8.4 Hz), 10.00 (s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 20.5 (C-5′), 24.6 (C-4′), 27.5 (C-6′), 35.6 (C-1′), 54.8 (C-3′), 60.6 (C-2′), 126.6 (C-3), 127.1 (C-5), 128.2 (C-4), 128.7 (C-6), 131.4 (C-4″), 127.7 (C-2″), 128.1 (C-3″), 134.0 (C-2), 135.8 (C-1), 139.5 (C-1″), 166.1 (C=O). Found (%): C, 52.06; H, 4.28; Br, 36.47; N, 3.11. Calc. for $C_{19}H_{19}Br_2NO$ (%): C, 52.20; H, 4.38; Br, 36.55; N, 3.20. The residue was diluted in 50 ml of CH_2Cl_2 and washed with a 10% Na_2SO_3 solution and water (2×50 ml). The organic phase was dried over Na_2SO_4. The solvent was removed *in vacuo*. The yield of the crude mixture was 0.4 g. Dissolving the mixture in benzene yielded dibromide **5** (0.09 g). ^{1}H and ^{13}C NMR spectra confirm the presence of compound **5** (40%) in a master batch (0.31 g).

N-*Benzoyl-3-iodo-2,4-propano-1,2,3,4-tetrahydroquinoline* **9**: 100 ml of a 10% aqueous NaOH solution and compound **8** (0.4 g, 1.33 mmol) in benzene (20 ml) was mixed in a 250 ml flask. A solution of benzoyl chloride (0.2 g, 1.46 mmol) in benzene (10 ml) was added with intense stirring. An exothermic reaction was observed. The mixture was cooled to 30 °C and stirred for 1 h. After completion of the reaction, the organic phase was separated, washed with water (2×20 ml) and dried with Na_2SO_4. The solvent was removed *in vacuo*; the residue was subjected to silica gel chromatography on a short column to produce product **9** as amorphous white powder in 92% yield (0.5 g). ^{1}H NMR ($CDCl_3$) δ: 1.30 (m, 1H, H_{ax}-2′), 1.50 (d, 1H, H_{eq}-2′, J_{gem} 14.3 Hz), 1.7 (d, 1H, H_{eq}-1′, J_{gem} 12.8 Hz), 2.05 (d, 1H, H_{eq}-3′, J_{gem} 13.7 Hz), 2.45 (m, 1H, H_{ax}-1′, H_{ax}-3′), 3.24–3.28 (m, 1H, H-4), 4.77–4.81 (m, 1H, H-2), 4.87–4.91 (m, 1H, H-3), 6.88–7.07 (m, 4H, ArH), 7.35–7.50 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.0, 26.1, 29.9 (3CH_2), 30.1 (C-4), 42.2 (C-3), 55.8 (C-2), 123.0 (C-8), 123.5 (C-6), 126.2 (C-7), 128.1 (C-2″, C-6″), 128.5 (C-3″, C-5″), 129.4 (C-4a), 130.7 (C-5, C-4″), 136.4 (C-8a), 138.7 (C-1″), 171.1 (C=O). Found (%): C, 56.47; H, 4.39; I, 31.38; N, 3.37. Calc. for $C_{19}H_{18}INO$ (%): C, 56.59; H, 4.50; I, 31.47; N, 3.47.

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