

A. Šačkus, S. Krikštolaitytė, V. Martynaitis

 ANNELETION OF LACTAM RINGS
 TO 2,3,4,4a-TETRAHYDRO-1H-CARBAZOLE DERIVATIVES

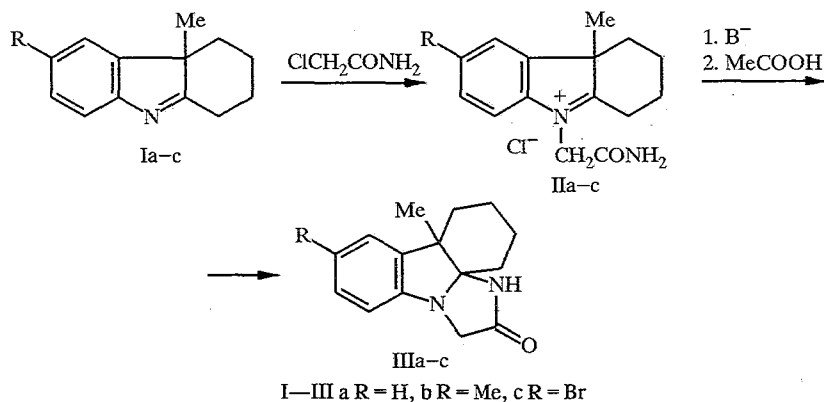
In the reaction of 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole and its 6-methyl- and 6-bromosubstituted derivatives with 2-chloroacetamide respective 9-carbamoylmethyl-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazolium chlorides are formed, which can be cyclized into 5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-one derivatives. Reaction of 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole hydrochloride with acrylamide gives 8a-methyl-1,2,6,7,8,8a-hexahydro-5H-pyrimido[2,1-*k*]carbazol-3(4H)-one. 7a,12-Dimethyl-3,4,4a,5,6,7,7a,12-octahydropyrido[3,2-*j*]carbazol-2(1H)-one was synthesized by the reaction of 4a,9-dimethyl-2,3,4,4a-tetrahydro-9H-carbazole with acrylamide.

It has been reported previously [1, 2] that reaction of 2,3,3-trimethyl-3H-indole with α -chloroacetamides and subsequent treatment of the reaction product with bases yields derivatives of 1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one. Reaction of 2,3,3-trimethyl-3H-indolium salts with acrylamide in acetic acid gives 1-(2-carbamoylethyl)-2,3,3-trimethyl-3H-indolium salts, which under the action of potassium hydroxide undergoes cyclization into derivatives of pyrimido[1,2-*a*]indol-2-one [3, 4]. During heating of 2-methylene-2,3-dihydro-1H-indole with acrylamide in proton-containing solvents 1,3-dihydrospiro[2H-indolo-2,2'-piperidine] derivative is formed [5].

In the present work, we studied the annelation of lactam rings to 2,3,4,4a-tetrahydro-1H-carbazole derivatives. The tetrahydrocarbazole is a part of a ring system of such indole-derived alkaloids as strychnine and aspido-spermidine [6—8].

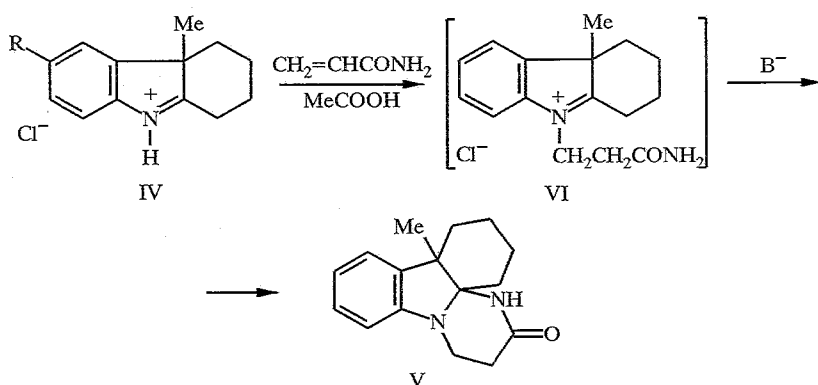
The starting 4a-methylcarbazolenine Ia was prepared from phenylhydrazine and 2-methylcyclohexanone by employing the literature procedure [9]. A similar method has been used for the synthesis of 4a,6-dimethyl- and 6-bromo-4a-methylcarbazolenines Ib,c from *p*-tolyl- and 4-bromophenylhydrazines.

It was found that 4a-methylcarbazolenine Ia reacts with α -chloroacetamide to give the 9-carbamoylmethyl-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazolium chloride (IIa). Treatment of the latter salt with base and subsequent heating of the liberated substance in a mixture of ethanol and acetic acid afforded 7a-methyl-5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-one (IIIa). 7a,9-Dimethyl- and 9-bromo-7a-methyl-5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-ones (IIIb,c) were synthesized by a similar method.



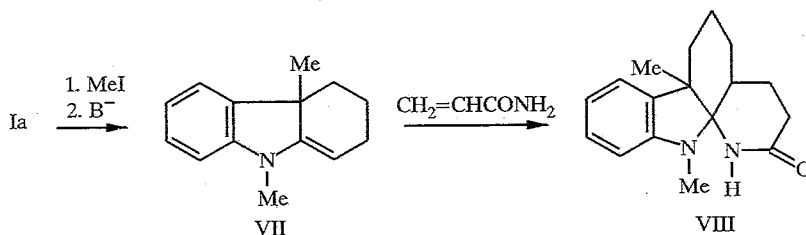
Absorption bands characteristic of five-membered lactams are observed in the IR spectrum of IIIa at 3150 (N—H) and 1695 cm^{-1} (C=O). The PMR spectrum of IIIa showed a multiplet of 8 methylene protons of tetrahydrocarbazole ring system in the 1.32...2.16 ppm region, together with a singlet of the 4a-CH₃ group at 1.42 ppm. The methylene protons of the imidazolidine ring resonate in the form of an AB-quadruplet with a geminal SSCC of 16.5 Hz in the 3.73...3.93 ppm region. In the ¹³C NMR spectrum, the signal of the C_(3a) atom is at 91.4 ppm, and that of the carbon atom of carbonyl group is at 175.0 ppm. Imidazo[2,1-*k*]carbazolones IIIa—c have two chiral centers at C_(3a) and C_(12a), however each of the compounds gives only one set of signals in their NMR spectra. This fact points that only one of two possible diastereomers has been obtained.

The addition of acrylamide to 4a-methylcarbazolenine hydrochloride IV proceeds smoothly in acetic acid. We found that 8a-methyl-1,2,6,7,8,8a-hexahydro-5H-pyrimido[2,1-*k*]carbazol-3(4H)-one (V) is formed, when adduct VI is treated with a base.



In the ¹³C NMR spectrum of compound V the signal of *sp*³-hybridized C_(4a) atom appears at 84.3 ppm, while the signal for the carbon atom of the carbonyl group appears at 170.1 ppm.

Further, we have examined annelation of six-membered lactam ring to *j*-edge of tetrahydrocarbazole. The starting enamine VII has been prepared by alkylation of carbazolenine Ia with methyl iodide followed by workup of resulted salt with base. Heating of enamine VII with acrylamide in ethylene glycol lead to the formation of the 3,4,4a,5,6,7,7a,12-octahydropyrido[3,2-*j*]carbazol-2(1H)-one derivative VIII, which was obtained as a single diastereomer.



The IR spectrum of octahydrohydropyrido[3,2-*j*]carbazol-2-one VIII contains absorption bands at 3370 (N—H) and 1650 (C=O) characteristic of δ -lactam. The ¹³C NMR spectrum of VIII showed the signal of the C_(12a) atom at 86.3 ppm.

EXPERIMENTAL

PMR and ^{13}C spectra were recorded on a Bruker DPX 300 instrument (300 MHz for ^1H , 75 MHz for ^{13}C), internal reference TMS. IR spectra were recorded on an IR-75 spectrometer (KBr pellets). Mass-spectra were obtained on a Hitachi M-80A instrument at ionizing voltage 20 eV. The course of the reactions was observed using TLC on Silufol plates, eluent acetone-hexane, 1 : 3.

4a,6-Dimethyl-2,3,4,4a-tetrahydro-1H-carbazole (Ib). A mixture of 2-methylcyclohexanone (6.73 g, 60 mmol) and *p*-tolylhydrazine (7.33 g, 60 mmol) was kept for 1 h at room temperature and then was heated for 1 h at 120 °C. The obtained hydrazone was dissolved in acetic acid (80 ml), and heated for 4 h at 100 °C. The reaction mixture was poured into 300 ml of water, treated with 10% KOH, and extracted with ether (2 × 30 ml). The combined organic extract was washed with solution of 5% H_2SO_4 (3 × 30 ml), the organic layer was separated and the acidic solution was treated with sodium carbonate. The compound separated out was extracted with ether (2 × 30 ml), the solvent was removed, and the residue was crystallized from hexane. The yield of compound Ib was 5.20 g (43%), m. p. 75...76 °C. PMR spectrum (CDCl_3): 1.13...2.83 (8H, m, 4 × CH_2); 1.27 (3H, s, 4a- CH_3); 2.37 (3H, s, 6- CH_3); 7.07...7.46 ppm (3H, m, ArH). ^{13}C -NMR spectrum (CDCl_3): 20.23 (k, 4a- CH_3); 21.79 (k, 6- CH_3); 21.81 (t, CH_2); 29.41 (t, CH_2); 30.08 (t, CH_2); 39.04 (t, CH_2); 53.99 (s, $\text{C}_{(4a)}$); 120.09 (d, CH); 122.53 (d, CH); 128.43 (d, CH); 134.85 (s, C); 147.36 (s, C); 152.51 (s, C); 189.52 ppm (s, N=C). Found, %: C 84.44; H 8.42; N 6.90. $\text{C}_{14}\text{H}_{17}\text{N}$. Calculated, %: C 84.37; H 8.60; N 7.03.

6-Bromo-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole (Ic) was obtained from 2-methylcyclohexanone (6.73 g, 60 mmol) and *p*-bromophenylhydrazine (11.22 g, 60 mmol) similarly to compound Ib. The yield was 6.65 g (42%), m. p. 77...78 °C (from hexane). PMR spectrum (CDCl_3): 1.12...2.88 (8H, m, 4 × CH_2); 1.31 (3H, s, CH_3); 7.40...7.45 ppm (3H, m, ArH). ^{13}C -NMR spectrum (CDCl_3): 20.05 (k, 4a- CH_3); 21.65 (t, CH_2); 29.30 (t, CH_2); 30.10 (t, CH_2); 38.91 (t, CH_2); 54.72 (s, $\text{C}_{(4a)}$); 118.99 (s, C); 121.93 (d, CH); 125.26 (d, CH); 130.92 (d, CH); 149.31 (s, C); 153.69 (s, C); 191.00 ppm (s, N=C). Found, %: C 59.31; H 5.39; Br 30.16. $\text{C}_{13}\text{H}_{14}\text{BrN}$. Calculated, %: C 59.11; H 5.34; Br 30.25.

9-Carbamoylmethyl-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazolium chloride (IIa). A mixture of 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole Ia (3.71 g, 20 mmol), α -chloroacetamide (2.43 g, 26 mmol), and xylene (8 ml) was heated at 140 °C for 3 h. The mixture was cooled, the crystalline compound was filtered, washed with acetone (10 ml), and crystallized from ethanol. Yield 2.34 g (42%) of chloride IIa, m. p. 258...260 °C. IR spectrum: 3300 (N—H), 3130 (N—H), 1695 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 1.26...3.17 (8H, m, 4 × CH_2); 1.42 (3H, s, CH_3); 5.24 (2H, s, CH_2CO); 7.36...7.56 ppm (4H, m, ArH). Found, %: C 64.56; H 7.11; Cl 12.48. $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}$. Calculated, %: C 64.63; H 6.87; Cl 12.72.

7a-Methyl-5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-one (IIIa). A solution of chloride IIa (2.23 g, 8 mmol) in water (25 ml) was treated with sodium carbonate and extracted with ether (2 × 20 ml). The extract was dried with sodium sulfate, the solvent was removed. The residue dissolved in a mixture of ethanol (7 ml) and acetic acid (4.5 ml) was refluxed for 15 min. The solution was then cooled, poured into water (40 ml), and the substance separated out was filtered off and recrystallized from ethanol. The yield of compound IIIa was 1.20 g (62%), m. p. 212...213 °C. PMR spectrum (CDCl_3): 1.32...2.18 (8H, m, 4 × CH_2); 1.42 (3H, s, CH_3); 3.73...3.93 (2H, AB-system, $J_{\text{AB}} = 16.5$ Hz, NCH_2); 6.77...7.26 ppm (5H, m, ArH, NH). ^{13}C -NMR spectrum (CDCl_3): 18.7 (CH_3); 20.4 (CH_2); 22.8 (CH_2); 31.0 (CH_2); 40.1 (CH_2); 46.1 (CH_2); 55.2 ($\text{C}_{(7a)}$); 91.4 ($\text{C}_{(3a)}$); 113.0 (CH); 121.7 (CH); 122.3 (CH); 127.5 (CH); 139.9 (C); 150.7 (C); 175.0 ppm (C=O). Mass spectrum, m/z (rel. intensity, %): 242 (M^+ , 100), 227 (11), 199 (51), 186 (62), 185 (50), 171 (6), 158 (23), 144 (12), 143 (19), 130 (17), 117 (6), 77 (11). Found, %: C 74.08; H 7.70. $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$. Calculated, %: C 74.34; H 7.49.

7a,9-Dimethyl-5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-one (IIIb). A mixture of 4a,6-dimethylcarbazolenine Ib (1.99 g, 10 mmol), α -chloroacetamide (1.22 g, 13 mmol), and xylene (3 ml) was heated at 140 °C for 3 h. The reaction products were dissolved in 5 ml of acetone, the solution was poured into 50 ml of 5% HCl, and the excess amide was extracted with ether (2 × 15 ml). The organic layer was separated, and the acidic solution was treated with sodium carbonate. The compound separated out was extracted with ether (2 × 20 ml), the extract was washed with water (20 ml), the solvent was removed, and the residue dissolved in a mixture of ethanol (8 ml) and acetic acid (4 ml) was refluxed for 15 min. The solution was then cooled, poured into water and extracted with ether (2 × 30 ml). The solvent was distilled off, and the residue crystallized from acetone. The yield of compound IIIb was 0.55 g (21%), m. p. 181...182 °C. PMR spectrum (CDCl_3): 1.32...2.18 (8H, m, 4 × CH_2); 1.40 (3H, s, 7a- CH_3); 2.29 (3H, s, 9- CH_3); 3.70...3.88 (2H, AB-system, $^2J_{\text{AB}} = 16.5$ Hz, NCH_2); 6.68 (1H, d, $^3J = 7.92$ Hz,

10-H); 6.82 (1H, d, $^4J = 0.99$ Hz, 8-H); 6.96 (1H, dd, $^4J = 0.99$ Hz, $^3J = 7.92$ Hz); 7.03 ppm (1H, broad s, NH). ^{13}C NMR spectrum (CDCl_3): 18.6 (CH_3); 20.5 (CH_2); 21.0 (CH_3); 22.9 (CH_2); 31.6 (CH_2); 40.1 (CH_2); 46.1 (CH_2); 55.1 ($\text{C}_{(7a)}$); 91.3 ($\text{C}_{(3a)}$); 113.0 (CH); 122.4 (CH); 128.1 (CH); 131.8 (C); 139.9 (C); 148.3 (C); 174.5 ppm ($\text{C}=\text{O}$). Found, %: C 75.25; H 7.88; N 10.78. $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$. Calculated, %: C 74.97; H 7.86; N 10.93.

9-Bromo-7a-methyl-5,6,7,7a-tetrahydro-1H,4H-imidazo[2,1-*k*]carbazol-2(3H)-one (IIIc) was obtained from 6-bromo-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole Ic (1.32 g, 5 mmol) and α -chloroacetamide (0.61 g, 6.5 mmol) similarly to compound IIIb. The yield of compound IIIc was 0.50 g (31%), m. p. 186...187 °C. PMR spectrum (CDCl_3): 1.31...2.19 (8H, 4 \times CH_2); 1.38 (3H, s, 7a- CH_3); 3.74...3.96 (2H, AB-system, $^2J_{\text{AB}} = 16.5$ Hz, NCH_2); 6.69...7.18 ppm (4H, m, ArH, NH). Found, %: C 55.84; H 5.66; N 8.97. $\text{C}_{15}\text{H}_{17}\text{BrN}_2\text{O}$. Calculated, %: C 56.09; H 5.33; N 8.72.

8a-Methyl-1,2,6,7,8,8a-hexahydro-8a-methyl-5H-pyrimido[2,1-*k*]carbazol-3(4H)-one (V). A solution of hydrochloride IV (1.11 g, 5 mmol) and acrylamide (0.39 g, 5.5 mmol) in acetic acid (5 ml) was heated for 3 h at 100 °C. The mixture was poured into water (30 ml), basified with a 5% solution of potassium hydroxide and extracted with ether (2 \times 15 ml). The extract was washed with water (2 \times 15 ml), dried with magnesium sulfate, the solvent removed, and the residue crystallized from ethanol to give 0.43 g (34%) of compound V with m. p. 152...153 °C. PMR spectrum (CDCl_3): 1.32...2.62 (8H, m, 4 \times CH_2); 1.35 (3H, m, CH_3); 3.40...3.82 (4H, m, $\text{NCH}_2\text{CH}_2\text{CO}$); 6.62 (1H, broad s, NH); 6.70...7.16 ppm (4H, m, ArH). ^{13}C -NMR spectrum (CDCl_3): 16.3 (CH_3); 20.8 (CH_2); 22.7 (CH_2); 27.2 (CH_2); 32.4 (CH_2); 36.5 (CH_2); 39.9 (CH_2); 47.5 ($\text{C}_{(8a)}$); 84.3 ($\text{C}_{(4a)}$); 109.8 (CH); 120.4 (CH); 121.7 (CH); 127.3 (CH); 139.4 (C); 146.8 (C); 170.1 ppm ($\text{C}=\text{O}$). Mass spectrum, *m/z* (rel. intensity, %): 256 (M^+ , 83), 241 (7), 213 (87), 200 (100), 185 (11), 180 (7), 170 (8), 158 (7), 146 (23), 143 (14), 130 (10), 115 (7), 77 (9). Found, %: C 74.91; H 8.12; N 11.76. $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$. Calculated, %: C 74.97; H 7.86; N 10.93.

7a,12-Dimethyl-3,4,4a,5,6,7,7a,12-octahydropyrido[3,2-*j*]carbazol-2(1H)-one (VIII). A mixture of carbazolenine Ia (2.50 g, 13.5 mmol) and methyl iodide (5.68 g, 2.49 ml, 40 mmol) was refluxed for 3 h. The crystalline salt (4.10 g) was filtered off, washed with acetone and dissolved in water (100 ml). To the solution 5% sodium hydroxide was added until the mixture was alkaline, and the enamine VII thus formed was extracted with ether (2 \times 25 ml). The dried ethereal solution was evaporated to give the enamine VII as an oil, which was used without further purification. The obtained enamine VII (2.09 g, 10.5 mmol) was heated with acrylamide (1.13 g, 16 mmol) in ethylene glycol (6 ml) for 4 h at 110 °C. The mixture was poured into 75 ml of water and extracted with ether (3 \times 20 ml). The extract was washed with 20 ml of water, dried with magnesium sulfate, the solvent removed, and the residue was crystallized from a mixture of acetone and hexane, 1 : 1. Yield of compound VIII 1.15 g, (41%), m. p. 156...157 °C. PMR spectrum (CDCl_3): 1.38 (3H, s, 7a- CH_3); 1.38...2.46 (11H, m, 5 \times CH_2 , 4a-H); 2.70 (3H, s, NCH_3); 5.71 (1H, broad s, NH); 6.47...7.13 ppm (4H, m, ArH). ^{13}C -NMR spectrum (CDCl_3): 17.1 (7a- CH_3); 19.7, 24.3, 27.7, 28.1, 30.7, 32.6, 38.2 (NCH_3 , 5 \times CH_2 , CH); 47.7 ($\text{C}_{(7a)}$), 86.3 ($\text{C}_{(12a)}$), 108.12 (CH), 118.9 (CH), 121.2 (CH), 127.9 (CH), 136.4 (C), 147.3 (C), 173.1 ppm ($\text{C}=\text{O}$). Found, %: C 75.40; H 8.26; N 10.40. $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$. Calculated, %: C 75.52; H 8.20; N 10.36.

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