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SYNTHESIS OF HEXAHYDRO[1,4]DIAZOCINO[7,8,1-*jk*]CARBAZOLES AND 1-METHOXY-9-(β-VINYLETHYLAMINO)ETHYLCARBAZOLES

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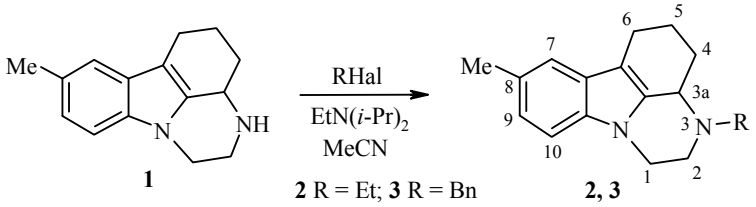
3-Ethylhexahydropyrazino[3,2,1-jk]carbazole is converted into hexahydro[1,4]diazocino[7,8,1-jk]carbazoles by the action of methyl propiolate and acetylacetylene in acetonitrile and into 1-methoxy-9-(β-vinylethylamino)ethylcarbazoles by the action of acetylenedicarboxylic ester and methyl propiolate in methanol. 3-Benzyl-substituted pyrazinocarbazole does not react with alkynes.

Keywords: hexahydrodiazocinocarbazoles, 1-methoxy-9-(β-vinylethylamino)ethylcarbazoles, pyrazine ring cleavage domino reaction, pyrazine ring extension domino reaction,.

Earlier we have found that tetrahydropyrrolo[1,2-*a*]pyrazines are converted into tetrahydropyrrolo[1,2-*d*]-[1,4]diazocines in domino transformations under the action of alkynes activated with electron-withdrawing substituents in acetonitrile [1, 2]. In methanol, mixtures of the corresponding diazocines and the products of cleavage of the tetrahydropyrazine ring involving a molecule of methanol, i.e., 2-methoxyethyl-(methoxybenzyl)-substituted pyrroles, are mostly formed [1]. By means of the investigated reaction it is possible to convert tetrahydropyridines and tetrahydropyrazines, fused with an aromatic and a heteroaromatic ring, into the corresponding fused azocines and diazocines, which allowed to propose this approach as a general method for construction such heterocyclic systems [3].

With the aim of extending the synthesis limits of the reaction we chose a heterocyclic system containing partially hydrogenated pyrazine and carbazole fragments, i.e. 8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (**1**). This compound is used in medical practice as an antidepressant (Pyrazidol) [4]. Alkylation of the pyrazinocarbazole **1** was realized by the action of ethyl iodide and benzyl chloride in acetonitrile in the presence of Hünig's base. The 3-ethyl- and 3-benzyl-substituted hexahydropyrazinocarbazoles **2** and **3** were obtained with yields of 72% and 95% respectively.



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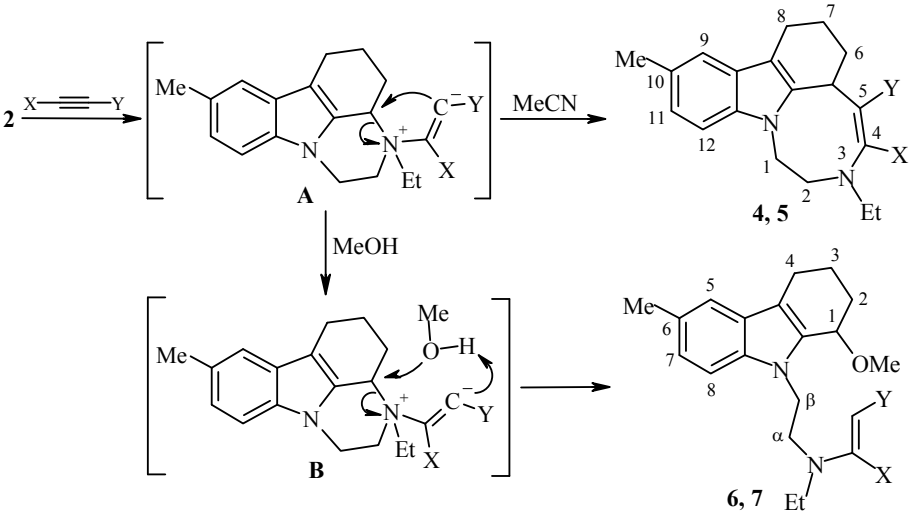
3-Ethyl-substituted pyrazinocarbazole **2** reacts with methyl propiolate, acetylacetylene, and dimethyl acetylene dicarboxylate (DMAD) at 30°C with formation of multicomponent mixtures, which are separated by chromatography on aluminum oxide. From the products of the reaction of compound **2** with methyl propiolate and acetylene in acetonitrile, derivatives of the previously unknown heterocyclic system [1,4]diazocino[7,8,1-*jk*]-carbazole **4** and **5** were isolated chromatographically with yields of 34% and 41% respectively. In methanol, 1-methoxycarbazoles **6** and **7**, i.e., the products of cleavage of the pyrazine fragment of compound **2** involving a molecule of methanol, were obtained.



4, 6 X = H, Y = CO_2Me; **5** X = H, Y = COMe; **7** X = Y = CO_2Me

The domino transformations of pyrazinocarbazole **2** evidently begin with formation of a zwitterion of the ammonium type **A**. In acetonitrile the extension of the pyrazine ring to diazocine then occurs as a result of attack by the anionic center on the C-3a atom. The reaction in methanol probably takes place through the transition state **B**, leading to the cleavage of the pyrazine ring with participation of a solvent molecule and formation of products **6** and **7**.

The 3-benzyl-substituted pyrazinocarbazole **3** does not enter into reaction with DMAD, methyl propiolate, and acetylacetylene in acetonitrile or in methanol even in the presence of an excess of the reagents or on refluxing. This may be due to screening of the lone pair of the nitrogen atom by the sterically bulky benzyl radical, thereby impeding its attack by the alkyne.

Structure of the obtained compounds was confirmed by a number of spectral methods. In the IR spectra of compounds **4**, **6**, and **7** in the region of 1685-1744 cm^{-1} there are bands for the stretching vibrations of C=O in ester groups, and the stretching vibrations of the keto group in compound **5** appear at 1632 cm^{-1}. The ^{1}H-NMR spectra are characterized by the presence of a signal in the region of 7.20-7.25 ppm, corresponding to the H-4 atom of the enamino fragment in compounds **4** and **5**. The *trans* substitution of the enamine fragment in compound **6** is confirmed by the spin-spin coupling constant J = 13.1 Hz. The proton of the vinyl group of compound **7** is observed in the form of a broad singlet at 4.72 ppm. In the spectra of 1-methoxycarbazoles **6** and **7** there are signals for the 1-MeO group in the form of a singlet at 3.47 ppm.

Thus, it has been shown for the first time that the tetrahydropyrazine fragment in pyrazino[3,2,1-*jk*]-carbazoles can undergo extension to diazocine under the action of alkynes in acetonitrile, and cleavage with the formation of 1-methoxycarbazoles in methanol. A benzyl substituent at the nitrogen atom of the pyrazine ring prevents the tandem transformation reactions under the action of alkynes activated with electron-withdrawing substituents.

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded in pellets with KBr on an Infralum FT Fourier spectrometer. The ^{1}H NMR spectra were recorded on Bruker-400 and JEOL JNM-ECA600 spectrometers (400 and 600 MHz respectively). The ^{13}C spectra were recorded on a Bruker-400 spectrometer (100 MHz). The residual signals of the solvent or TMS were used as internal standard. The mass spectra were recorded on a Thermo Scientific MAT 95 XL chromato-mass spectrometer with direct injection into the ion source at 70 eV (EI ionization). The LC/MS spectra were recorded on a system including an Agilent 100 Series liquid chromatograph, an Agilent Technologies LC/MSD VL mass spectrometer (electrospray, CI at atmospheric pressure), and a Sedex 75 ELSD detector. Elemental analysis was performed on a Carlo Erba 1106 instrument. The melting points of the synthesized compounds were determined on an SMP instrument. For thin-layer chromatography, we used Sorbfil and Alufol plates (development with iodine vapor), and for column chromatography we used neutral Fluka-507C Al_2O_3 (0.05-0.15 mm) and Acros silica gel (0.04-0.06 mm), 60 Å.

All the solvents used in the study were purified by distillation. The methyl propiolate, acetylacetylene, and DMAD from Acros Organics were used without further purification.

3-Ethyl-8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (2). Hünig's base (0.94 g, 7.3 mmol) and EtI (0.84 g, 5.4 mmol) were added to a solution of pyrazinocarbazole **1** (1.10 g, 4.9 mmol) in MeCN (20 ml) with constant stirring. The reaction was monitored by TLC (Sorbfil, EtOAc). The reaction was finished after stirring for four days at room temperature. The precipitate was then filtered off and recrystallized from a mixture of EtOAc and hexane. Yield 0.89 g (72%). Colorless crystals; mp 104-106°C (105-106°C (MeOH) [5]); R_f 0.46 (Sorbfil, EtOAc–hexane, 1:1). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 1.47-1.54 (1H, m) and 1.81-1.89 (1H, m, 5-CH_2); 2.17-2.22 (1H, m) and 2.30-2.34 (1H, m, 4-CH_2); 2.41-2.47 (1H, m) and 3.06 (1H, dq, *J* = 7.2, *J* = 13.1, $NC\underline{H}_2CH_3$); 2.46 (3H, s, 8-CH_3); 2.64-2.68 (1H, m) and 2.74-2.78 (1H, m, 6-CH_2); 2.71-2.75 (1H, m) and 3.33 (1H, ddd, *J* = 1.1, *J* = 5.0, *J* = 12.1, 2-CH_2); 3.42-3.44 (1H, m, H-3a); 3.77-3.82 (1H, m) and 4.15 (1H, ddd, *J* = 1.1, *J* = 4.4, *J* = 11.0, 1-CH_2); 6.97 (1H, dd, *J* = 1.5, *J* = 8.2, H-9); 7.13 (1H, d, *J* = 8.2, H-10); 7.25 (1H, br. s, H-7). Mass spectrum, *m*/*z* (I_{rel}, %): 254 $[M]^+$ (37), 253 (14), 227 (16), 226 (100), 197 (28), 182 (9), 167 (5), 127 (7), 115 (5), 105 (13), 91 (3), 42 (4). Found, %: C 80.11; H 8.58; N 10.94. $C_{17}H_{22}N_2$. Calculated, %: C 80.27; H 8.72; N 11.01.

3-Benzyl-8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (3). Hünig's base (0.73 g, 5.4 mmol) and benzyl chloride (0.52 g, 4.1 mmol) were added with constant stirring to a solution of pyrazinocarbazole **1** (0.85 g, 3.8 mmol) in MeCN (20 ml). The reaction was monitored by TLC (Alufol, EtOAc). The reaction was finished after stirring at room temperature for seven days. The precipitate was then filtered off and recrystallized from a mixture of EtOAc and hexane. Yield 1.13 g (95%). Colorless crystals; mp 173-175°C (EtOAc–hexane); R_f 0.89 (Alufol, EtOAc). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.53-1.67 (1H, m) and 1.83-1.96 (1H, m, 5-CH_2); 2.18-2.22 (1H, m) and 2.37-2.44 (1H, m, 4-CH_2); 2.44 (3H, s, 8-CH_3); 2.60-2.66 (1H, m) and 3.13 (1H, dd, *J* = 4.3, *J* = 12.3, 2-CH_2); 2.64-2.72 (1H, m) and 2.79 (1H, dd, *J* = 6.2, *J* = 15.6, 6-CH_2); 3.20 (1H, d, AB-system, *J* = 13.2) and 4.29 (1H, d, AB-system, *J* = 13.2, $C\underline{H}_2Ph$); 3.48-3.54 (1H, m, H-3a); 3.69 (1H, dt, *J* = 4.6, *J* = 11.7) and 4.03 (1H, dd, *J* = 3.1, *J* = 10.8, 1-CH_2); 6.96 (1H, *J* = 8.1, H-9); 7.10 (1H, d, *J* = 8.1, H-10); 7.25-7.39 (6H, m, H-7, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 316 $[M]^+$ (47), 315 (17), 289 (15), 288 (82), 225 (12), 223 (10), 198 (13), 197 (100), 196 (22), 195 (12), 182 (20), 181 (15), 180 (9), 178 (7), 177 (7), 154 (7), 141 (4), 115 (4), 91 (53), 65 (9). Found, %: C 83.34; H 7.52; N 8.74. $C_{22}H_{24}N_2$. Calculated, %: C 83.50; H 7.64; N 8.85.

Methyl 3-Ethyl-10-methyl-2,3,5a,6,7,8-hexahydro-1*H*-[1,4]diazocino[7,8,1-*jk*]carbazole-5-carboxylate (4). Methyl propiolate (0.20 g, 2.4 mmol) was added to a solution of pyrazinocarbazole **2** (0.40 g, 1.6 mmol) in MeCN (20 ml). The reaction was finished after five days at 30°C. It was monitored by TLC (Sorbfil, EtOAc–hexane, 1:1). The solvent was evaporated under vacuum, and the residue was separated by column chromatography (SiO_2) with 1:15 EtOAc–hexane as eluent. Yield 0.18 g (34%). Yellow oil, solidifying on standing; R_f 0.75 (Sorbfil, EtOAc–hexane, 1:1). IR spectrum, ν, cm^{-1}: 1686 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (*J*, Hz): 1.03 (3H, t, *J* = 7.2, $NCH_2C\underline{H}_3$); 1.71-1.80 (1H, m), 2.02-2.10 (2H, m) and 2.28-2.36 (1H,

m, 6,7-CH_2); 2.46 (3H, s, 10-CH_3); 2.71-2.74 (2H, m, 8-CH_2); 2.91-2.97 (2H, m, NC$\underline{H}_2CH_3$); 3.28-3.34 (1H, m) and 3.46 (1H, ddd, J = 2.6, J = 4.7, J = 13.9, 2-CH_2); 3.71 (3H, s, CO_2CH_3); 4.04-4.05 (1H, m, H-5a); 4.10-4.15 (1H, m) and 4.41 (1H, ddd, J = 2.6, J = 9.9, J = 14.9, 1-CH_2); 6.96 (1H, dd, J = 1.5, J = 8.3, H-11); 7.10 (1H, d, J = 8.3, H-12); 7.20 (1H, s, H-4); 7.28 (1H, br. s, H-9). ^{13}C NMR spectrum, δ, ppm: 14.6; 21.3; 21.4; 23.2; 29.3; 33.5; 43.4; 50.9; 52.6; 52.7; 107.8; 109.6; 112.4; 117.9; 121.9; 127.8; 128.1; 134.7; 138.2; 148.7; 168.6. Mass spectrum, m/z (I_{rel}, %): 338 $[M]^+$ (100), 309 (8), 293 (13), 280 (23), 279 (97), 278 (15), 251 (15), 249 (11), 244 (12), 243 (15), 220 (10), 209 (19), 208 (23), 194 (18), 181 (10), 168 (10), 59 (39), 56 (21), 42 (15), 41 (10). Found, %: C 74.34; H 7.61; N 8.20. $C_{21}H_{26}N_2O_2$. Calculated, %: C 74.53; H 7.74; N 8.28.

1-(3-Ethyl-10-methyl-2,3,5a,6,7,8-hexahydro-1*H*-[1,4]diazocino[7,8,1-*jk*]carbazol-5-yl)ethanone (5). Acetylacetylene (0.10 g, 1.5 mmol) was added to a solution of pyrazinocarbazole **2** (0.30 g, 1.2 mmol) in MeCN (15 ml). The reaction was finished after four days at 30°C. The reaction was monitored by TLC (Sorbfil, EtOAc–hexane, 1:1). The solvent was evaporated under vacuum, and the residue was separated by column chromatography (SiO_2) with 1:5 EtOAc–hexane as eluent. Yield 0.16 g (41%). Yellow oil, solidifying on standing; R_f 0.37 (Alufol, EtOAc–heptane, 1:4). IR spectrum, ν, cm^{-1}: 1632 (C=O). ^{1}H NMR spectrum (600 MHz), δ, ppm (J, Hz): 1.05 (3H, t, J = 7.2, $NCH_2C\underline{H}_3$); 1.69-1.76 (1H, m), 1.91-2.01 (2H, m), and 2.21-2.27 (1H, m, 6,7-CH_2); 2.27 (3H, s, $COCH_3$); 2.44 (3H, s, 10-$C\underline{H}_3$); 2.69-2.72 (2H, m, 8-CH_2); 2.90-2.96 (2H, m, $NC\underline{H}_2CH_3$); 3.27-3.34 (1H, m) and 3.40 (1H, ddd, J = 3.0, J = 4.5, J = 13.7, 2-CH_2); 4.09-4.14 (2H, m) and 4.15 (1H, ddd, J = 3.0, J = 9.7, J = 14.9, H-5a, 1-CH_2); 6.94 (1H, dd, J = 1.2, J = 8.3, H-11); 6.99 (1H, s, H-4); 7.07 (1H, d, J = 8.3, H-12); 7.25 (1H, br. s, H-9). Mass spectrum, m/z (I_{rel}, %): 322 $[M]^+$ (31), 280 (5), 279 (23), 251 (3), 234 (9), 194 (5), 181 (4), 150 (3), 56 (5), 43 (100). Found, %: C 78.04; H 8.00; N 8.62. $C_{21}H_{26}N_2O$. Calculated, %: C 78.22; H 8.13; N 8.69.

Methyl (2*E*)-3-{Ethyl[2-(1-methoxy-6-methyl-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)ethyl]amino}-acrylate (6). Methyl propiolate (0.12 g, 1.4 mmol) was added to a solution of pyrazinocarbazole **2** (0.30 g, 1.2 mmol) in MeOH (15 ml). The reaction was finished after three days at 30°C. The reaction was monitored by TLC (Alufol, EtOAc–heptane, 1:2). The solvent was evaporated under vacuum, and the residue was separated by column chromatography (Al_2O_3) with 1:10 EtOAc–hexane as eluent. Yield 0.10 g (23%). Colorless crystals; mp 92-93°C (EtOAc–hexane); R_f 0.71 (Alufol, EtOAc–heptane, 1:2). IR spectrum, ν, cm^{-1}: 1693 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (J, Hz): 1.01 (3H, t, J = 7.0, $NCH_2C\underline{H}_3$); 1.77-1.97 (3H, m) and 2.20-2.29 (1H, m, 2,3-CH_2); 2.44 (3H, s, 6-CH_3); 2.50-2.61 (1H, m) and 2.76-3.01 (3H, m, 4-CH_2, $NC\underline{H}_2CH_3$); 3.47 (3H, s, 1-OCH3); 3.47-3.51 (2H, m, α-CH_2); 3.69 (3H, s, CO_2CH_3); 4.07-4.13 (1H, m) and 4.29-4.40 (1H, m, β-CH_2); 4.44 (1H, t, J = 3.4, H-1); 4.73 (1H, m, CH=C$\underline{H}CO_2$Me); 7.04 (1H, d, J = 8.3, H-7); 7.15 (1H, d, J = 8.3, H-8); 7.30 (1H, s, H-5); 7.45 (H, d, J = 13.1, CH=$CHCO_2$Me). Mass spectrum, m/z (I_{rel}, %): 371 $[M+H]^+$. Found, %: C 71.14; H 8.01; N 7.44. $C_{22}H_{30}N_2O_3$. Calculated, %: C 71.32; H 8.16; N 7.56.

Dimethyl 2-{Ethyl[2-(1-methoxy-6-methyl-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)ethyl]amino}but-2-enedioate (7). DMAD (0.19 g, 1.3 mmol) was added to a solution of pyrazinocarbazole **2** (0.28 g, 1.1 mmol) in MeOH (15 ml). The reaction was finished after seven days at 30°C. The reaction was monitored by TLC (Alufol, EtOAc–heptane, 1:2). The solvent was evaporated under vacuum, and the residue was separated by column chromatography (Al_2O_3) with 1:10 EtOAc–heptane as eluent. Yield 0.18 g (38%). Yellow crystals; mp 95-97°C (EtOAc–hexane); R_f 0.75 (Alufol, EtOAc–heptane, 1:2). IR spectrum, ν, cm^{-1}: 1744 (C=O), 1697 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (J, Hz): 1.00 (3H, t, J = 7.0, $NCH_2C\underline{H}_3$); 1.79-1.96 (3H, m) and 2.21-2.31 (1H, m, 2,3-CH_2); 2.44 (3H, s, 6-CH_3); 2.51-2.62 (1H, m), 2.68-2.82 (2H, m), and 2.92-3.00 (1H, m, 4-CH_2, $NC\underline{H}_2CH_3$); 3.44-3.52 (2H, m, α-CH_2); 3.47 (3H, s, 1-OCH_3); 3.67 (3H, s, CO_2CH_3); 3.95 (3H, s, CO_2CH_3); 4.12 (1H, dt, J = 5.2, J = 11.1) and 4.39-4.50 (1H, m, β-CH_2); 4.49 (1H, t, J = 3.6, H-1); 4.72 (1H, s, CH=); 7.05 (1H, d, J = 8.2, H-7); 7.21 (1H, d, J = 8.2, H-8); 7.29 (H, s, H-5). GC/MS (ESI) spectrum, m/z: 429 $[M+H]^+$. Found, %: C 67.13; H 7.40; N 6.44. $C_{24}H_{32}N_2O_5$. Calculated, %: C 67.27; H 7.53; N 6.54.

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