Chemistry of Heterocyclic Compounds, Vol.35, No. 6, 1999

SYNTHESIS OF [1,3]BENZOXAZINO[2,3-*k*]- AND [2,4]BENZODIAZEPINO[3,2-*k*]- CARBAZOLE DERIVATIVES

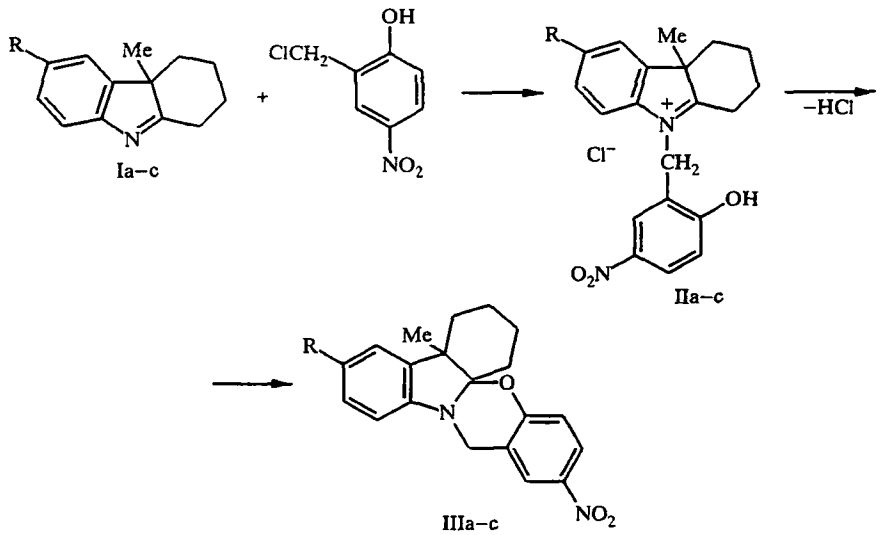
A. Shachkus, S. Krikshtolaitite, and V. Martinaitis

Alkylation of 4a-methyl-, 4a,6-dimethyl- and 6-bromo-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazoles using 2-chloromethyl-4-nitrophenol gives [1,3]benzoxazino[2,3-k]carbazoles. Derivatives of [2,4]benzodiazepino-[3,2-k]carbazole have been synthesized by alkylation of the indicated carbazolenines using 2-bromomethylbenzonitrile followed by hydrolysis of the nitrile group of the 9-(2-cyanobenzyl)-carbazolium salts obtained to amide.

Previously we have studied the alkylation of 2,3,3-trimethyl-3H-indole by benzyl halides which have a hydroxyl or nitrile group in the *ortho* position. It was shown that reaction of the indicated indole with 2-chloromethyl-4-nitrophenol gives indolo[2,1-b][1,3]benzoxazines [1, 2] and, in the case of 2-bromomethyl-benzonitrile, indolo[1,2-*b*][2,4]benzodiazepines [3, 4].

In this work we have studied the annelation of the [1,3]benzoxazine and [2,4]benzodiazepine nucleus to a tetrahydrocarbazole nucleus, which is contained in the structure of a series of indole alkaloids [5, 6] and neuroactive substances [7].

Reaction of 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole (Ia) with 2-chloromethyl-4-nitrophenol in nitromethane at room temperature gave [1,3]benzoxazino[2,3-*k*]carbazole derivative IIIa, the structure of which was confirmed by spectral investigation. It can be assumed that the first stage of the mentioned reaction is the formation of the 9-(2-hydroxybenzyl)carbazolium salt IIa.



I–III a R = H, b R = Me, c R = Br

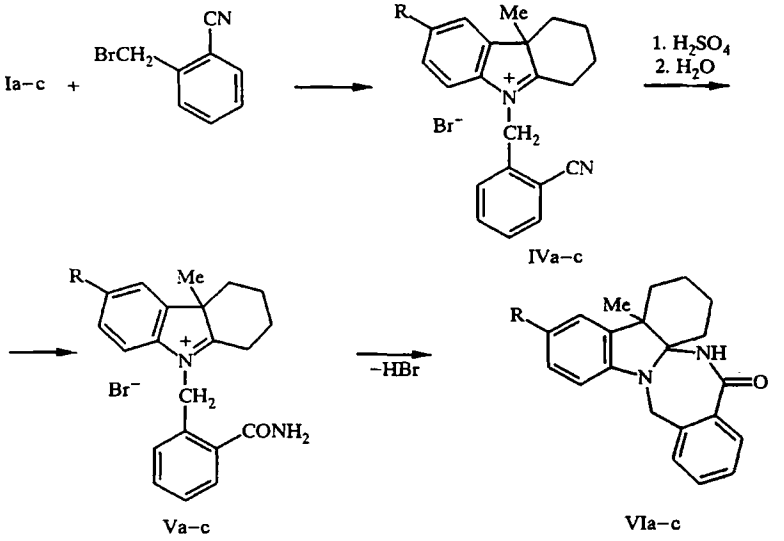
Kaunas Technological University, Kaunas, LT-3028, Lithuania; e-mail: asackus@ctf.ktu.lt. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 818-821, June, 1999. Original article submitted June 5, 1998.

0009-3122/99/3506-0729$22.00©1999 KluwerAcademic/Plenum Publishers

The PMR spectrum of IIIa shows a multiplet for the 8 methylene protons of the tetrahydrocarbazole ring in the region 1.23-2.30 ppm and the signal for the protons of the methylene group of the benzoxazine ring forms an AB-system (J_{AB} = 17.5 Hz) at 4.54-4.69 ppm. The ^{13}C NMR spectrum shows a characteristic signal at 102.7 ppm for the sp^3 hybridized C_{4a} atom covalently bonded to the nitrogen and oxygen atoms. The IR spectra of the obtained compound does not show the absorption band for a hydroxyl group and the characteristic absorption bands for a nitro group are found at 1510 and 1335 cm^{-1}.

In a similar way, 6-methyl- and 6-bromocarbazolenines Ib,c with 2-chloromethyl-4-nitrophenol gave 14-methyl- and 14-bromo[1,3]benzoxazino[2,3-*k*]carbazoles IIIb,c respectively.

Heating of the carbazolenine Ia with 2-bromomethylbenzonitrile in xylene gives 9-(2-cyanobenzyl)-carbazolium bromide IVa. The nitrile group of salt IVa could then be converted to amide function using concentrated sulfuric acid. Treatment of the reaction mixture with bases caused cyclization of the 9-(2-carbamoylbenzyl)carbazolium salt Va to [2,4]benzodiazepino[3,2-*k*]carbazole derivative VIa.



IV–VI a R = H, b R = Me, c R = Br

In the PMR spectrum of compound VIa the signals for the methylene protons of the diazepine ring appear as an AB-quartet (J_{AB} = 16.2 Hz) at 4.46-4.82 ppm and in the ^{13}C NMR spectrum the signal for the C_{4a} atom covalently bonded to two nitrogen atoms appears at 84.3 ppm.

Compounds IIIa-c and VIa-c have two chiral atoms C_{4a} and C_{15b} but the presence in the NMR spectra of a single pair of signals indicates that only one pair of enantiomers is formed.

EXPERIMENTAL

IR Spectra were measured on a Specord M-80 instrument for KBr tablets. PMR spectra were obtained on Hitachi-Perkin Elmer R-22 (90 MHz) and Jeol-270 (270 MHz) spectrometers using TMS as internal standard. ^{13}C NMR spectra were recorded on a Jeol-270 (67.5 MHz) instrument.

15b-Methyl-8-nitro-1,3,4,15b-tetrahydro-2H,10H-[1,3]benzoxazino[2,3-*k*]carbazole (IIIa). A mixture of 4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole (Ia, 1.85 g, 10 mmol), 2-chloromethyl-4-nitrophenol (2.06 g, 11 mmol), and nitromethane (5 ml) was held at room temperature for 6 h and then at 5°C for 18 h. The crystalline product was filtered off and recrystallized from acetone to give IIIa (1.42 g, 42%); mp 178-179°C. PMR spectrum ($CDCl_3$): 1.32-2.30 (8H, m, $4CH_2$); 1.59 (3H, s, 15b-CH_3); 4.54-4.69 (2H, AB quadruplet, J_{AB} = 17.5 Hz, NCH_2); 6.64-8.07 ppm (7H, m, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$): 15.4 (CH_3); 21.3 (CH_2); 22.5 (CH_2); 27.8 (CH_2); 39.7 (CH_2); 39.9 (CH_2); 47.4 (C_{15b}); 102.7 (C_{4a}); 109.1 (CH); 117.9 (CH); 118.7 (C); 120.4 (CH); 121.6 (CH); 123.2 (CH); 123.9 (CH); 127.3 (CH); 139.0 (C); 140.2 (C); 146.4 (C); 159.4 ppm (C). Found, %: C 71.75; H 6.24. $C_{20}H_{20}N_2O_3$. Calculated, %: C 71.41; H 5.99.

14,15b-Dimethyl-8-nitro-1,3,4,15b-tetrahydro-2H,10H-[1,3]benzoxazino[2,3-*k*]carbazole (IIIb) was obtained similarly to compound IIIa from 4a,6-dimethyl-2,3,4,4a-tetrahydro-1H-carbazole (Ib, 1.00 g, 5 mmol) and 2-chloromethyl-4-nitrophenol (1.03 g, 5.5 mmol). Yield 0.54 g (31%); mp 149-150°C (acetone). IR spectrum: 1510, 1335 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 1.31-2.27 (8H, m, 4 CH_2); 1.55 (3H, s, 15b-CH_3); 2.25 (3H, s, 14-CH_3); 4.52-4.64 (2H, AB-quadruplet, J_{AB} = 17.5 Hz, NCH_2); 6.50-8.03 ppm (6H, m, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$): 15.3 (CH_3); 21.0 (CH_3); 21.3 (CH_2); 22.6 (CH_2); 27.9 (CH_2); 39.8 (CH_2); 39.9 (CH_2); 47.5 (C_{15b}); 102.9 (C_{4a}); 108.9 (CH); 117.9 (CH); 118.8 (C); 122.5 (CH); 123.2 (CH); 123.9 (CH); 127.6 (CH); 129.7 (C); 139.1 (C); 140.2 (C); 144.1 (C); 159.5 ppm (C). Found, %: C 72.21; H 6.50. $C_{21}H_{22}N_2O_3$. Calculated, %; C 71.98; H 6.33.

14-Bromo-15b-methyl-8-nitro-1,3,4,15b-tetrahydro-2H,10H-[1,3]benzoxazino[2,3-*k*]carbazole (IIIc) was prepared similarly to compound IIIa from 6-bromo-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazole (Ic, 1.06 g, 4.4 mmol) and 2-chloromethyl-4-nitrophenol (0.83 g, 4.4 mmol). Yield 0.70 g (42%); mp 193-194°C (acetone). IR spectrum: 1510, 1335 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$); 1.29-2.26 (8H, m, 4CH_2); 1.54 (3H, s, 15b-CH_3); 4.56 (2H, s, NCH_2); 6.49-8.04 ppm (6H, m, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$): 15.3 (CH_3); 21.1 (CH_2); 22.4 (CH_2); 27.7 (CH_2); 39.7 (CH_2); 39.8 (CH_2); 47.6 (C_{15b}); 102.6 (C_{4a}); 110.7 (CH); 112.4 (C); 118.0 (CH); 118.4 (C); 123.2 (CH); 124.1 (CH); 125.0 (CH); 130.0 (CH); 140.4 (C); 141.3 (C); 145.6 (C); 159.1 ppm (C). Found, %: C 58.01; H 4.34; Br 19.49. $C_{20}H_{19}BrN_2O_3$. Calculated, %: C 57.84; H 4.61; Br 19.24.

9-(2-Cyanobenzyl)-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazolium Bromide (IVa). A mixture of the tetrahydro-1H-carbazole Ia (2.78 g, 15 mmol), 2-bromomethylbenzonitrile (3.33 g, 17 mmol), and xylene (4 ml) was held at 100°C for 3 h. The crystalline product was filtered off and recrystallized from alcohol to give bromide IVa (3.03 g, 53%); mp 190-191°C°. IR spectrum: 2220 cm^{-1} (CN). PMR spectrum (CF_3COOD): 0.94-3.34 (8H, m, 4CH_2); 1.47 (3H, s, 4a-CH_3); 5.54-5.96 (2H, AB-quadruplet, J_{AB} = 17.0 Hz, NCH_2); 6.81-7.79 ppm (8H, m, H_{Ar}). Found, %: C 66.00; H 5.72; Br 20.76. $C_{21}H_{21}BrN_2$. Calculated, %: C 66.15; H 5.55; Br 20.95.

9-(2-Cyanobenzyl)-4a,6-dimethyl-2,3,4,4a-tetrahydro-1H-carbazolium Bromide (IVb) was obtained similarly to compound IVa from the tetrahydro-1H-carbazole Ib (1.00 g, 5 mmol) and 2-bromomethylbenzonitrile (1.08 g, 5.5 mmol). Yield 1.01 g (53%); mp 134-135°C. PMR spectrum (CF_3COOD): 0.98-3.31 (8H, m, 4CH_2); 1.42 (3H, s, 4a-CH_3); 2.16 (3H, s, 6-CH_3); 5.57-5.87 (2H, AB-quadruplet, J_{AB} = 17.0 Hz, NCH_2); 6.88-7.66 ppm (7H, m, H_{Ar}). Found, %: C 66.53; H 6.09. $C_{22}H_{23}BrN_2$. Calculated, %: C 66.84; H 5.86.

6-Bromo-9-(2-cyanobenzyl)-4a-methyl-2,3,4,4a-tetrahydro-1H-carbazolium Bromide (IVc) was obtained similarly to compound IVa from the tetrahydro-1H-carbazole Ic (1.06 g, 4 mmol) and 2-bromomethyl-benzonitrile (0.86 g, 4.4 mmol). Yield 1.09 g (59%); mp 182-183°C. IR spectrum: 2220 cm^{-1} (CN). PMR spectrum (CF_3COOD): 0.96-3.38 (8H, m, 4CH_2); 1.43 (3H, s, 4a-CH_3); 5.52-5.92 (2H, AB-quadruplet, J_{AB} = 17.0 Hz, NCH_2); 6.92-7.63 ppm (7H, m, H_{Ar}). Found, %: C 54.77, H 4.21. $C_{21}H_{20}Br_2N_2$. Calculated, %: C 54.81; H 4.38.

16b-Methyl-1,3,4,16b-tetrahydro-2H,5H-[2,4]benzodiazepino[3,2-*k*]carbazol-6(11H)-one (VIa). A solution of bromide IVa (1.14 g, 3 mmol) in concentrated sulfuric acid (5 ml) was held for 4 h at 50°C. The reaction mixture was poured onto ice, treated with sodium carbonate, and the product was separated by filtration and recrystallized from alcohol. Yield 0.46g (48%); mp 165-166°C. IR spectrum: 3150 (N–H); 1630 cm^{-1} (C=O). PMR spectrum ($CDCl_3$); 1.34-2.16 (8H, m, 4CH_2); 1.42 (3H, s, 16b-CH_3); 4.46-4.82 (2H, AB-quadruplet, J_{AB} = 16.2 Hz, NCH_2); 6.26-8.08 ppm (9H, m, H_{Ar}, NH). ^{13}C NMR spectrum ($CDCl_3$): 19.6 (CH_3); 20.4 (CH_2); 21.3 (CH_2); 33.1 (CH_2); 38.9 (CH_2); 47.3 (CH_2); 49.2 (C_{16b}); 84.3 (C_{4a}); 109.0 (CH); 119.0 (CH); 121.3 (CH); 127.2 (CH); 127.4 (CH); 128.8 (CH); 131.4 (CH); 132.3 (CH); 132.9 (CH); 137.0 (C); 138.6 (C); 146.7 (C); 168.7 ppm (C=O). Found, %: C 79.37; H 7.33; N 8.66. $C_{21}H_{22}N_2O$. Calculated, %: C 79.21; H 6.96; N 8.80.

15,16b-Dimethyl-1,3,4,16b-tetrahydro-2H,5H-[2,4]benzodiazepino[3,2-*k*]carbazol-6-(11H)-one (VIb) was prepared similarly to compound VIa from bromide IVb (0.79 g, 2 mmol). Yield 0.27 g (41%); mp 178-179°C (ethanol). PMR spectrum ($CDCl_3$): 1.34-2.18 (8H, m, 4CH_2); 1.43 (3H, s, 16b-CH_3); 2.18 (3H, s, 15-CH_3); 4.45-4.80 (2H, AB-quadruplet, J_{AB} = 16.2 Hz, NCH_2); 6.16-8.06 ppm (8H, m, H_{Ar}, NH). ^{13}C NMR spectrum ($CDCl_3$): 19.2 (CH_3), 20.6 (CH_2); 20.9 (CH_3); 21.5 (CH_2); 33.2 (CH_2); 39.41 (CH_2); 47.7 (CH_2); 49.1 (C_{16b}); 84.6 (C_{4a}); 109.1 (CH); 122.2 (CH); 127.4 (CH); 127.5 (CH); 128.4 (C); 128.9 (CH); 131.4 (CH); 132.3 (C); 132.8 (CH); 137.2 (C); 138.6 (C); 144.5 (C); 168.7 ppm (C=O). Found, %: C 79.51; H 7.08; N 8.27. $C_{22}H_{24}N_2O$. Calculated, %: C 79.48; H 7.28; N 8.43.

15-Bromo-16b-methyl-1,3,4,16b-tetrahydro-2H,5H-[2,4]benzodiazepino[3,2-*k*]carbazol-6(11H)-one (VIc) was prepared similarly to compound VIa from bromide IVc (0.92 g, 2 mmol). Yield 0.28 g (35%); mp 184-185°C (ethanol). PMR spectrum ($CDCl_3$): 1.32-2.17 (8 H, m, $4CH_2$); 1.39 (3H, s, 16b-CH_3); 4.41-4.81 (2H, AB-quadruplet, J_{AB} = 16.5 Hz, NCH_2); 6.09-8.10 ppm (8H, m, H_{Ar}, NH). ^{13}C NMR spectrum ($CDCl_3$): 19.4 (CH_3); 20.2 (CH_2); 21.1 (CH_2); 32.9 (CH_2); 38.8 (CH_2); 46.9 (CH_2); 49.5 (C_{16b}); 84.6 (C_{4a}); 110.4 (CH); 110.8 (C); 124.6 (CH); 127.5 (CH); 128.8 (CH); 129.7 (CH); 131.4 (CH); 132.0 (C); 133.1 (CH); 138.2 (C); 139.4 (C); 145.7 (C); 168.5 ppm (C=O). Found, %: C 63.69; H 5.35; N 7.07. $C_{21}H_{21}BrN_2O$. Calculated, %: C 63.48; H 5.32; N 7.05.

REFERENCES

1. A. A. Shachkus, Yu. A. Degutis, and A. G. Urbonavichyus, *Khim. Geterotsikl. Soedin.*, No. 5, 672 (1989).
2. A. Šačkus, J. Degutis, and A. Jezerskaite, *Studies in Organic Chemistry. 35. Chemistry of Heterocyclic Compounds*, J. Kovač and P. Zalupsky (eds.), Elsevier, Amsterdam (1988), p. 518.
3. A. A. Shachkus, Yu. A. Degutis, and G. S. Myadyakshene, *Khim. Geterotsikl. Soedin.*, No. 6, 815 (1990).
4. A. Šačkus, V. Martynaitis, H. Medekšienė, and J. Degutis, *Chemija (Vilnius)*, No. 1, 93 (1998).
5. C. McCarty and K. Jones, *J. Chem. Soc., Chem. Commun.*, 1717 (1989).
6. T. Oishi, M. Nagai, and Y. Ban, *Tetrahedron Lett.*, No. 4, 491 (1968).
7. J. G. Rodriguez and A. Urrutia. *J. Chem. Soc., Perkin Trans. I*, No. 6, 665 (1995).