The *N*- and *C*-Substituted Benzonaphthyridines

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Five *N*-substituted benzo[*c*][1,5]-, benzo[*h*][1,6]-, and benzo[*f*][1,7]-naphthyridines have been synthesized by quaternization reactions, and two *C*-substituted benzonaphthyridines by condensation of corresponding methyl derivatives with formaldehyde. Their ^{1}H NMR and MS values are presented.

The *N*- and *C*-substituted benzonaphthyridines (bn) are interesting in view of their reactivity and biological activities; they are useful synthons in a number of reactions [1—4].

It is worth noting that quaternary azaaromatics are promising for their applications and chemical properties [5, 6]. These species may be used, for example, in the construction of electronic devices [7, 8] as NLO materials [9—11], dyes [12], and synthons of numerous compounds [13]; they show biological activities [14, 15] and serve as models of biochemical processes [16]. Some quaternary azaaromatics are components of supramolecular chemistry systems [17, 18].

The aim of our work involves the investigation of the reactivity of benzonaphthyridines and methylbenzonaphthyridines as well as the potential use of obtained products as pharmaceuticals. Some species of this class show antibacterial, fungicidal, and antineoplastic activities [19—21], or influence the enzymic activity in plants [22].

The present paper deals with derivatives of benzo[*c*][1,5]-, benzo[*h*][1,6]-, and benzo[*f*][1,7]-naphthyridines *I*—*III*, *i.e.* *N*-substituted bns *IV*—*VIII* synthesized by quaternization of bns with 2-bromoethanol and 1,6-dibromohexane, and *C*-substituted bns, *i.e.* hydroxyethylbns *IX* and *X* obtained by condensation of methylbns *XI* and *XII* with formaldehyde (Formula 1).

In order to obtain quaternary salts *IV* and *V*, the corresponding bns *I* and *III* have been subjected to reaction with 2-bromoethanol in acetonitrile medium, the mole ratio of reagents being 1:1. In the case of *I*, as expected, only N-5 undergoes quaternization, due to steric reasons. This result is in accordance with our earlier experiments concerning reactions of *I* with diiodomethane [23], 1,2-dibromoethane [24] as well as those with phenacyl bromide [3] and ethyl bromoacetate [25]. In the case of *III* both nitrogen atoms are similarly accessible, however, N-6 is more reactive than N-4. The same behaviour of *III* was observed in its quaternization reactions, given above. The quaternization of *I*—*III* with 1,6-dibromohexane, performed in benzene medium using 1:10 mole ratio of reagents leads to 5- and 6-*N*-substituted products *VI*—*VIII*.

In order to obtain *C*-substituted bns *IX* and *X*, the methylbns *XI* and *XII*, respectively, have been condensed with formaldehyde. The reaction involves deprotonation of methyl group and proton shift to oxygen atom of formaldehyde. In spite of various conditions used in quaternization of bns and condensation of methylbenzonaphthyridines (temperature, reaction time, and mole ratio of reagents), their yields could not be improved. The structures of the obtained products *IV*—*X* have been confirmed by elemental and MS analysis as well as by NMR spectrometry results.

Comparison of ^{1}H NMR spectra of quaternary salts *IV*—*VIII* with those of corresponding unsubstituted bns *I*—*III* [19] shows a deshielding of protons situated at *ortho* position to quaternized *N*-atoms, *i.e.* H-6 in the case of *IV* and *VI*, and H-5 in the case of *V*, *VII,* and *VIII*, resulting from the presence of hydroxyethyl or bromohexyl *N*-substituents.

Comparing ^{13}C NMR spectrum of *IX* with that of parent bn *I* [19], the deshielding of C-2 and C-6 atoms due to the influence of hydroxyethyl group at 2-position has been observed.

EXPERIMENTAL

As chemicals 2-bromoethanol ($\geq$ 95 %, Fluka, Switzerland), 1,6-dibromohexane (97 %, Lancaster, England), and formaldehyde (36—38 %, anal. grade, POCh, Gliwice, Poland) have been used.

Benzonaphthyridines *I*—*III* were obtained from aminoazanaphthalenes in the Skraup reaction [26].

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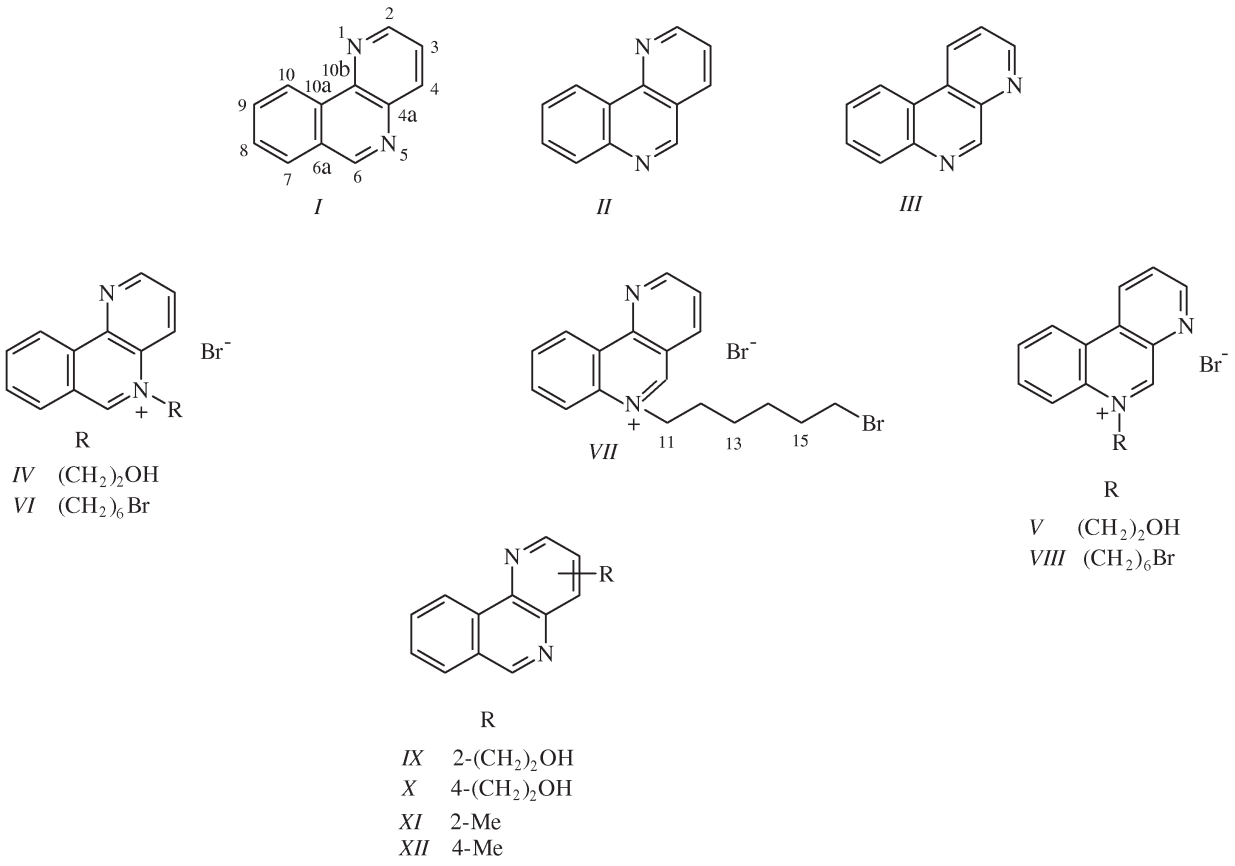

Formula 1

Methylbenzonaphthyridines *XI* and *XII* have been synthesized from 4-aminoisoquinoline by the modified Skraup procedure using crotonaldehyde and methyl vinyl ketone instead of glycerol [20].

Melting points of the obtained compounds were determined on a Boëtius apparatus. The NMR spectra were recorded on a 200 MHz Bruker spectrometer in $(CD_3)_2SO$ with $SiMe_4$ as internal standard, and mass spectra on an AMD-604 mass spectrometer at 70 eV.

5-(2-Hydroxyethyl)benzo[*c*]-1,5-naphthyridinium Bromide *IV* and 6-(2-Hydroxyethyl)benzo[*f*]-1,7-naphthyridinium Bromide *V*

The solution of *I* or *III* (1.8 g; 10 mmol) in acetonitrile (54 cm^3) was treated with 2-bromoethanol (1.25 g; 10 mmol) and refluxed during 30 h. The obtained precipitate was filtered off as the first portion, and the solution was refluxed for additional 5 h. The formed solid was filtered, combined with the first portion and recrystallized from absolute ethanol. Compounds *IV* and *V* were obtained as small yellow crystals.

Compound $C_{14}H_{13}N_2OBr$ *IV*: M.p. = 219—220 °C, yield 33 %, w_i(found): 55.4 % C, 4.2 % H, 9.2 % N; w_i(calc.): 55.1 % C, 4.3 % H, 9.2 % N. ^{1}H NMR spectrum, δ: 10.41 (s, 1H, H-6), 9.39 (dd, $J_{2,3}$ = 3.9 Hz, $J_{2,4}$ = 1.5 Hz, 1H, H-2), 9.31 (dd, $J_{10,9}$ = 8.2 Hz, $J_{10,8}$ = 1.4 Hz, 1H, H-10), 9.19 (dd, $J_{4,3}$ = 8.0 Hz, $J_{4,2}$ = 1.5 Hz, 1H, H-4), 8.75 (dd, $J_{7,8}$ = 8.2 Hz, $J_{7,9}$ = 1.2 Hz, 1H, H-7), 8.50 (ddd, $J_{9,10}$ = 8.2 Hz, $J_{9,8}$ = 6.8 Hz, $J_{9,7}$ = 1.2 Hz, 1H, H-9), 8.25 (ddd, $J_{8,7}$ = 8.2 Hz, $J_{8,9}$ = 6.8 Hz, $J_{8,10}$ = 1.4 Hz, 1H, H-8), 8.20 (dd, $J_{3,4}$ = 8.0 Hz, $J_{3,2}$ = 3.9 Hz, 1H, H-3), 5.23 (t, 2H, H-11a,b), 5.19 (t, 1H, —OH), 3.99 (m, 2H, H-12a,b). Mass spectrum: m/z (I_r /%): 225 (M^+ − Br, 100 %), 194 (bn^+ + CH_2, 3 %), 181 (bn^+ + H, 9 %).

Compound $C_{14}H_{13}N_2OBr$ *V*: M.p. = 241—242 °C, yield 36 %, w_i(found): 54.9 % C, 4.3 % H, 9.0 % N; w_i(calc.): 55.1 % C, 4.3 % H, 9.2 % N. ^{1}H NMR spectrum, δ: 10.31 (s, 1H, H-5), 9.61 (dd, $J_{1,2}$ = 8.5 Hz, $J_{1,3}$ = 1.8 Hz, 1H, H-1), 9.43 (dd, $J_{3,2}$ = 4.5 Hz, $J_{3,1}$ = 1.8 Hz, 1H, H-3), 9.27 (dd, $J_{10,9}$ = 7.6 Hz, $J_{10,8}$ = 1.2 Hz,1H, H-10), 8.77 (dd, $J_{7,8}$ = 8.9 Hz, $J_{7,9}$ = 1.5 Hz, 1H, H-7), 8.38 (dd, $J_{2,1}$ = 8.5 Hz, $J_{2,3}$ = 4.5 Hz, 1H, H-2), 8.20—8.26 (m, 2H, H-8, H-9), 5.36 (t, 2H, H-11a,b), 5.20 (t, 1H, —OH), 4.02 (m, 2H, H-12a,b). Mass spectrum: m/z (I_r/%): 225 (M^+ − Br, 100 %), 207 (bn^+ + C_2H_3, 3 %), 195 (bn^+ + CH_3, 2 %), 181 (bn^+ + H, 10 %).

5-(6-Bromohexyl)benzo[*c*]-1,5-naphthyridinium Bromide *VI*, 6-(6-Bromohexyl)benzo[*h*]-1,6-naphthyridinium Bromide *VII*, and 6-(6-Bromohexyl)benzo[*f*]-1,7-naphthyridinium Bromide *VIII*

The mixture of *I*—*III*, respectively, (1.8 g; 10 mmol) and 1,6-dibromohexane (24 g; 100 mmol) in benzene (25 cm^3) was refluxed for 20 h. For compound *VI*, the formed solid was recrystallized from ethanol to give small pale-yellow crystals. For compound *VII*, the resulting solid was recrystallized from benzene to give small colourless crystals. For compound *VIII*, the initially formed negligible amount of oily precipitate was filtered off. The solution was treated once more with 1,6-dibromohexane (24 g; 100 mmol) and refluxed for 1 h. The resulting solid was filtered and recrystallized from a mixture of benzene and ethanol (96 %) (φ_r = 6:1) to give small brown crystals.

Compound $C_{18}H_{20}N_2Br_2$ *VI*: M.p. = 273—274 °C, yield 23 %, w_i(found): 51.1 % C, 4.7 % H, 6.8 % N; w_i(calc.): 51.0 % C, 4.8 % H, 6.6 % N. ^{1}H NMR spectrum, δ: 9.61 (s, 1H, H-6), 9.37 (dd, $J_{2,3}$ = 3.2 Hz, $J_{2,4}$ = 1.5 Hz, 1H, H-2), 9.28 (d, $J_{10,9}$ = 7.9 Hz, 1H, H-10), 8.66 (d, $J_{7,8}$ = 8.0 Hz, 1H, H-7), 8.56 (dd, $J_{4,3}$ = 6.9 Hz, $J_{4,2}$ = 1.5 Hz, 1H, H-4), 8.12—8.28 (m, 2H, H-8, H-9), 7.92 (dd, $J_{3,4}$ = 6.9 Hz, $J_{3,2}$ = 3.2 Hz, 1H, H-3), 5.14 (t, 2H, H-11a,b), 3.51 (t, 2H, H-16a,b), 1.95—2.15 (m, 4H, H-12a,b, H-15a,b), 1.30—1.65 (m, 4H, H-13a,b, H-14a,b). Mass spectrum: m/z (I_r/%): 343 (M^+ − Br, 8 %), 263 (M^+ − 2Br, 7 %), 221 (bn^+ + C_3H_5, 4 %), 207 (bn^+ + C_2H_3, 5 %), 195 (bn^+ + CH_3, 14 %), 180 (bn^+, 100 %).

Compound $C_{18}H_{20}N_2Br_2$ *VII*: M.p. = 153—154 °C, yield 41 %, w_i(found): 50.8 % C, 4.9 % H, 6.9 % N; w_i(calc.): 51.0 % C, 4.8 % H, 6.6 % N. ^{1}H NMR spectrum, δ: 10.55 (s, 1H, H-5), 9.60 (dd, $J_{2,3}$ = 4.5 Hz, $J_{2,4}$ = 1.7 Hz, 1H, H-2), 9.37 (dd, $J_{10,9}$ = 8.1 Hz, $J_{10,8}$ = 1.6 Hz, 1H, H-10), 9.01 (dd, $J_{7,8}$ = 8.0 Hz, $J_{7,9}$ = 1.8 Hz, 1H, H-7), 8.72 (dd, $J_{4,3}$ = 7.9 Hz, $J_{4,2}$ = 1.7 Hz, 1H, H-4), 8.09—8.35 (m, 3H, H-8, H-9, H-3), 5.15 (t, 2H, H-11a,b), 3.54 (t, 2H, H-16a,b), 2.00—2.20 (m, 2H, H-12a,b), 1.75—1.90 (m, 2H, H-15a,b), 1.40—1.60 (m, 4H, H-13a,b, H-14a,b). Mass spectrum: m/z (I_r/%): 343 (M^+ − Br, 100 %), 263 (M^+ − 2Br, 9 %), 222 (bn^+ + C_3H_6, 2 %), 181 (bn^+ + H, 8 %).

Compound $C_{18}H_{20}N_2Br_2$ *VIII*: M.p. = 241—242 °C, yield 24 %, w_i(found): 50.7 % C, 5.0 % H, 6.5 % N; w_i(calc.): 51.0 % C, 4.8 % H, 6.6 % N. ^{1}H NMR spectrum, δ: 9.77 (s, 1H, H-5), 9.48 (d, $J_{10,9}$ = 8.6 Hz, 1H, H-10), 9.30 (d, $J_{3,2}$ = 3.2 Hz, 1H, H-3), 9.00 (dd, $J_{7,8}$ = 9.5 Hz, $J_{7,9}$ = 4.5 Hz, 1H, H-7), 7.99—8.37 (m, 4H, H-1, H-2, H-8, H-9), 5.10—5.25 (m, 2H, H-11a,b), 3.40—3.65 (m, 2H, H-16a,b), 1.90—2.17 (m, 2H, H-12a,b), 1.65—1.85 (m, 2H, H-15a,b), 1.40—1.60 (m, 4H, H-13a,b, H-14a,b). Mass spectrum: m/z (I_r/%): 343 (M^+ − Br, 100 %), 223 (bn^+ + C_3H_7, 16 %), 182 (bn^+ + 2H, 15 %), 121 (BrC_3H_6, 18 %).

2-(2-Hydroxyethyl)benzo[*c*]-1,5-naphthyridine *IX* and 4-(2-Hydroxyethyl)benzo[*f*]-1,7-naphthyridine *X*

The mixture of *XI* or *XII* (1.94 g; 10 mmol) and 37 % formaldehyde (26.8 g; 330 mmol) was refluxed for 6 h. The second amount of formaldehyde (26.8 g; 330 mmol) was added to the refluxing reaction mixture in three portions during 18 h, in 6 h periods. The reaction mixture was steam-distilled to remove the excess of *XI* or *XII*. The residue was extracted with ether, the ethereal solution dried over $MgSO_4$ and concentrated at diminished pressure. The obtained solid was recrystallized from toluene, and next from hexane to give small yellow crystals.

Compound $C_{14}H_{12}N_2O$ *IX*: M.p. = 102—103 °C, yield 21 %, w_i(found): 74.7 % C, 5.3 % H, 12.7 % N; w_i(calc.): 75.0 % C, 5.4 % H, 12.5 % N. ^{1}H NMR spectrum, δ: 9.43 (s, 1H, H-6), 9.06 (dd, $J_{10,9}$ = 8.2 Hz, $J_{10,8}$ = 1.3 Hz, 1H, H-10), 8.40 (d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 8.28 (dd, $J_{7,8}$ = 7.9 Hz, $J_{7,9}$ = 1.4 Hz, 1H, H-7), 8.03 (ddd, $J_{9,10}$ = 8.2 Hz, $J_{9,8}$ = 7.2 Hz, $J_{9,7}$ = 1.4 Hz, 1H, H-9), 7.91 (ddd, $J_{8,7}$ = 7.9 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.3 Hz, 1H, H-8), 7.74 (d, $J_{3,4}$ = 8.4 Hz, 1H, H-3), 4.66 (t, J = 5.2 Hz, 2H, H-12a,b), 3.91 (t, J = 5.2 Hz, 2H, H-11a,b), 2.30 (s, 1H, —OH). ^{13}C NMR spectrum, δ: 163.0 (C-2), 154.3 (C-6), 140.2 (C-10b), 138.6 (C-4a), 137.5 (C-4), 133.3 (C-10a), 132.4 (C-9), 130.1 (C-7), 129.1 (C-8), 128.8 (C-6a), 125.7 (C-10), 123.6 (C-3), 63.1 (C-12), 54.2 (C-11). Mass spectrum: m/z (I_r/%): 224 (M^+, 34 %), 223 (M^+ − H, 100 %), 207 (bn^+ + C_2H_4, 32 %), 194 (bn^+ + CH_3, 52 %), 179 (bn^+ − H, 16 %).

Compound $C_{14}H_{12}N_2O$ *X*: M.p. = 105—106 °C, yield 24 %, w_i(found): 75.1 % C, 5.6 % H, 12.8 % N; w_i(calc.): 75.0 % C, 5.4 % H, 12.5 % N. ^{1}H NMR spectrum, δ: 9.49 (s, 1H, H-6), 9.11 (dd, $J_{10,9}$ = 8.1 Hz, $J_{10,8}$ = 1.3 Hz, 1H, H-10), 8.95 (d, $J_{2,3}$ = 4.7 Hz, 1H, H-2), 8.30 (dd, $J_{7,8}$ = 7.7 Hz, $J_{7,9}$ = 1.4 Hz, 1H, H-7), 8.03 (ddd, $J_{9,10}$ = 8.1 Hz, $J_{9,8}$ = 7.1 Hz, $J_{9,7}$ = 1.4 Hz, 1H, H-9), 7.91 (ddd, $J_{8,7}$ = 7.7 Hz, $J_{8,9}$ = 7.1 Hz, $J_{8,10}$ = 1.3 Hz, 1H, H-8), 7.72 (d, $J_{3,2}$ = 4.7 Hz, 1H, H-3), 4.68 (t, J = 5.4 Hz, 2H, H-12a,b), 3.85 (t, J = 5.4 Hz, 2H, H-11a,b), 2.30 (s, 1H, —OH). Mass spectrum: m/z (I_r/%): 224 (M^+, 30 %), 223 (M^+ − H, 100 %), 207 (bn^+ + C_2H_4, 34 %), 205 (M^+ − H_3O^+, 61 %), 194 (bn^+ + CH_3, 52 %).

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