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ALKYLBENZONAPHTHYRIDINONES AND BENZONAPHTHYRIDINIUM QUATERNARY SALTS

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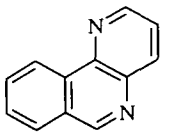
Four methyl and ethylbenzonaphthyridinones, along with two ethylbenzonaphthyridinium iodides, 2,5-dimethyl-1,5-benzo[c]naphthyridinium iodide, as well as three isomeric N-3'-bromopropylbenzonaphthyridinium bromides have been synthesized and their structures confirmed by ^{1}H NMR spectroscopy. Biological data (minimal inhibitory concentrations) for two of the obtained compounds are presented.

Keywords: alkylbenzonaphthyridinones, benzonaphthyridinium quaternary salts, antibacterial activity.

Quaternary salts of azaaromatics [1] are of interest for their chemical reactivity [2, 3] and applications, e.g., as NLO materials [4], biomimetic models [5], biological agents [6, 7], as well as components of supramolecular systems [8, 9].

The present work is a continuation of our research concerning benzonaphthyridines (BNs) **1-3**.



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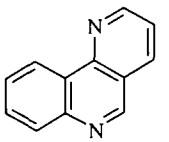

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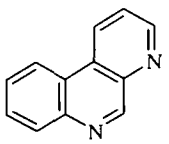

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These compounds and their derivatives show antibacterial, antifungal, and in some cases antineoplastic activities [10-13]. Due to the presence of two nitrogen atoms in the molecule, BNs form N-oxides [14, 15] and complexes with metal ions [16]. The quaternary salts of BNs **1-3** are precursors of ylides serving as 1,3-dipoles in cycloaddition reactions [17, 18].

RESULTS AND DISCUSSION

In the present investigation the synthesis of four methyl and ethylbenzonaphthyridinones, and that of six benzonaphthyridinium quaternary salts, has been performed. Their structures have been confirmed by ^{1}H NMR spectroscopy and are consistent with elemental analysis data.

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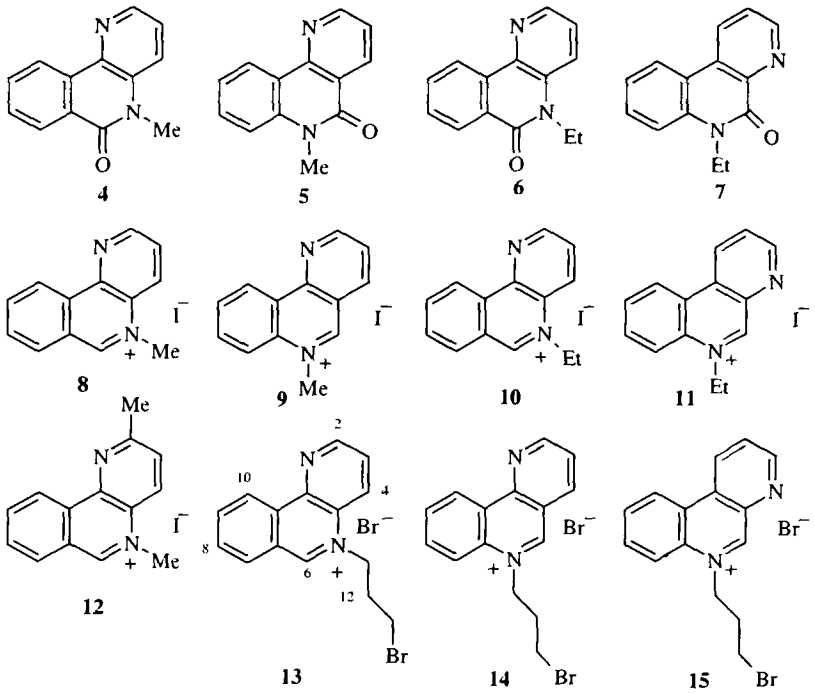
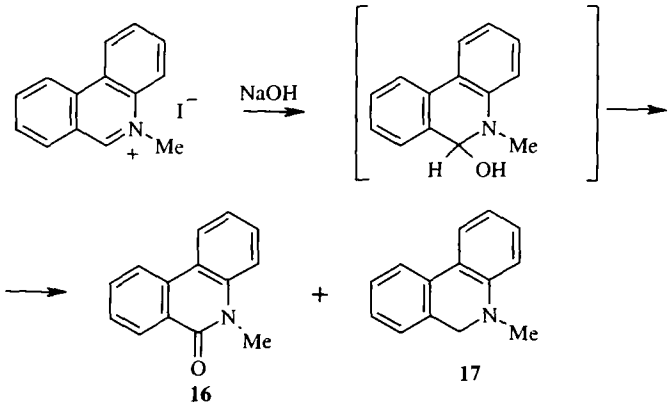


Methyl- and ethylbenzonaphthyridinones **4-7** have been synthesized by treatment of N-methyl- and N-ethylbenzonaphthyridinium iodides **8-11** with aqueous potassium hydroxide analogously to transformation of N-methylphenanthyridinium iodide, which resulted in two products, 5-methyl-6-phenanthridinone **16** and 5,6-dihydro-5-methylphenanthridine **17** [19].



However, in our experiments alkylbenzonaphthyridinones **4-7** were the sole products.

N-Methylbenzonaphthyridinium iodides **8** and **9** were obtained earlier [11]; for comparison a sample of 2,5-dimethyl-1,5-benzo[*c*]naphthyridinium iodide (**12**) was also prepared.

Salts **10**, **11**, and **13-15** have been obtained using quaternization reactions of appropriate BNs with ethyl iodide and 1,3-dibromopropane, respectively, in benzene medium.

Due to steric reasons, the nitrogen atoms in positions 5 and 6 of compounds **1** and **2** but not those in position 1 undergo quaternization, the products being salts **10**, **13** and **14**; the quaternization of 2-methyl-1,5-benzonaphthyridine proceeds in the same way affording quaternary salt **12**. In BN **3** the localization of both nitrogen atoms is sterically similar. However, the reactions with ethyl iodide and 1,3-dibromopropane occur only at N(7) atom to give salts **11** and **15**. The same behavior has been observed on quaternization of compound **3** [17, 18, 20].

Comparing the ^{1}H NMR spectra of salts **4-7** with those of parent BNs **1-3** [10, 18, 21] the upfield shift of signals of all ring protons is observed. In the case of salts **10**, **11**, and **13-15** the downfield shift of all ring protons due to the presence of positively charged nitrogen atoms occurs; a similar observation was made for quaternary salts of BNs **1-3** with 1,2-dibromoethane [20].

For salt **12**, however, the signals of all ring protons are shifted upfield, this fact being influenced by the presence of the methyl group. This observation is in accordance with a comparison of ^{1}H NMR signals of ring protons of methylated BNBs relatively to their parent BNs [13].

For methylbenzonaphthyridinone **4** and salt **12** chosen as examples among the synthesized compounds, the activities against Gram-negative and Gram-positive bacteria were investigated. The MIC (minimal inhibitory concentration) was determined by the method of serial dilutions on Grove Randall bacterial media (Table 1). Turbidity indicated the growth of a strain, while clarity showed its decrease. The lowest concentration of the investigated compound when no growth of strains could be observed was taken as the MIC [22].

For both compounds under consideration, a higher activity was observed against Gram-positive than against Gram-negative strains, similarly as for other BN derivatives [10]; among these compounds, **12** shows higher activity.

TABLE 1. MIC Values (mg/ml) against Gram-negative and Gram-positive Bacteria for Compounds **4** and **12**

Strains	**4**	**12**
Gram-negative		
Escherichia coli	0.9	0.3
Salmonella paratyphi B	1.0	0.4
Gram-positive		
Staphylococcus aureus	0.5	0.1
Listeria monocytogenes	0.5	0.1

TABLE 2. Characteristics of Alkylbenzonaphthyridinones **4-7** and Benzonaphthyridinium Salts **10-15**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
4	$C_{13}H_{10}N_2O$	74.2 / 74.3	4.8 / 4.8	13.4 / 13.3	189-190	84
5	$C_{13}H_{10}N_2O$	74.1 / 74.3	4.7 / 4.8	13.3 / 13.3	174-175	34.5
6	$C_{14}H_{12}N_2O$	75.2 / 75.0	5.3 / 5.4	12.2 / 12.5	144-145	36
7	$C_{14}H_{12}N_2O$	75.2 / 75.0	5.2 / 5.4	12.3 / 12.5	142	18
10	$C_{14}H_{13}IN_2$	50.2 / 50.0	3.7 / 3.9	8.2 / 8.3	218-219	49
11	$C_{14}H_{13}IN_2$	50.2 / 50.0	3.7 / 3.9	8.3 / 8.3	241-242	46
12	$C_{15}H_{15}IN_2$	50.6 / 50.0	3.9 / 3.9	8.4 / 8.3	249-250	42
13	$C_{15}H_{14}Br_2N_2$	46.9 / 47.1	4.1 / 3.7	7.5 / 7.3	214-215	57.5
14	$C_{15}H_{14}Br_2N_2$	47.2 / 47.1	3.6 / 3.7	7.3 / 7.3	215-216	38
15	$C_{15}H_{14}Br_2N_2$	47.1 / 47.1	3.6 / 3.7	7.2 / 7.3	199-200	35

TABLE 3. ^{1}H NMR Spectra of Alkylbenzonaphthyridinones **4-7** and Benzonaphthyridinium Salts **10-15**

Compound	Chemical shifts, ppm											Coupling constants, Hz
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	other signals	
1	2	3	4	5	6	7	8	9	10	11	12	13
4	—	8.59 dd	7.68 dd	8.34 d	—	—	7.99 dd	7.77 ddd	7.93 ddd	8.76 d	3.66 s, CH_3	$J_{2,3}$ = 4.2, $J_{2,4}$ = 2.0, $J_{3,4}$ = 8.2, $J_{7,8}$ = 7.5, $J_{7,9}$ = 1.1, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.4, $J_{9,10}$ = 7.2
5	—	9.05 dd	*	8.63 dd	—	—	*	7.42 ddd	*	8.76 dd	3.73 s, CH_3	$J_{2,3}$ = 4.6, $J_{2,4}$ = 2.0, $J_{4,3}$ = 8.0, $J_{8,7}$ = 8.0, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.2, $J_{10,9}$ = 8.0
6	—	9.59 dd	7.67 dd	8.34 dd	—	—	8.05 dd	7.92 ddd	7.76 ddd	8.78 dd	1.30 t, CH_3, 4.35 q, CH_2	$J_{2,3}$ = 4.5, $J_{2,4}$ = 1.2, $J_{3,4}$ = 7.9, $J_{7,8}$ = 7.4, $J_{7,9}$ = 1.3, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.4, $J_{9,10}$ = 8.0, J_{MeCH_2} = 7.1
7	9.10 d	7.37 dd	8.51 d	—	—	—	*[2]	*[2]	*[2]	*[2]	1.30 t, CH_3 4.40 q, CH_2	$J_{1,2}$ = 8.6, $J_{2,3}$ = 4.5, J_{MeCH_2} = 7.2
10	—	9.36 dd	8.26-8.16 m	9.10 dd	—	10.46 s	8.65 d	8.48 ddd	8.26-8.16 m	9.26 dd	1.71 t, CH_3 5.12 q, CH_2	$J_{2,3}$ = 4.3, $J_{2,4}$ = 1.3, $J_{4,3}$ = 8.6, $J_{7,8}$ = 8.1, $J_{9,7}$ = 1.3, $J_{8,9}$ = 6.8, $J_{8,10}$ = 1.4, $J_{9,10}$ = 8.3, J_{MeCH_2} = 7.2

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
11	9.56 d	*[1]	9.41 dd	—	10.47 s	—	8.71 dd	*[1]	*[1]	9.23 dd	1.70 t, CH_3 5.29 q, CH_2	$J_{1,2}$ = 8.1, $J_{3,2}$ = 4.3, $J_{3,1}$ = 1.4, $J_{7,8}$ = 7.7, $J_{7,9}$ = 1.2, $J_{10,9}$ = 7.3, $J_{10,8}$ = 1.5, J_{Me,CH_2} = 7.2
12	—	—	7.25 d	8.23 d	–	9.03 s	7.72 dd	7.94 ddd	8.08 ddd	8.41 d	4.33 s N–CH_3 3.33 s C–CH_3	$J_{3,4}$ = 7.9, $J_{7,8}$ = 8.4, $J_{7,9}$ = 1.2, $J_{8,9}$ = 6.8, $J_{8,10}$ = 1.3, $J_{9,10}$ = 8.4
13		9.29 d	8.22 dd	9.15 dd		10.55 s	8.68 d	8.50 ddd	8.25 ddd	9.39 dd	5.23 t, CH_2N 3.78 t, CH_2Br 2.64 qn, CH_2	$J_{10,9}$ = 8.4, $J_{10,8}$ = 1.4, $J_{2,3}$ = 3.9, $J_{3,4}$ = 8.9, $J_{4,2}$ = 2.0, $J_{7,8}$ = 8.4, $J_{8,9}$ = 6.9, $J_{8,10}$ = 1.4, $J_{9,7}$ = 1.3, $J_{9,10}$ = 8.4, $J_{11,12}$ = 6.8, $J_{12,13}$ = 7.3
14	—	9.37 dd	8.16 dd	9.03 dd	10.58 s	—	8.73 dd	8.20 ddd	8.29 ddd	9.59 dd	5.26 t, CH_2N 3.80 t, CH_2Br 2.66 qn, CH_2	$J_{2,3}$ = 4.4, $J_{2,4}$ = 1.8, $J_{3,4}$ = 8.2, $J_{7,8}$ = 8.0, $J_{7,9}$ = 1.0, $J_{8,9}$ = 6.6, $J_{8,10}$ = 1.4, $J_{11,12}$ = 6.8, $J_{12,13}$ = 7.3
15	9.61 dd	8.36 dd	9.43 dd	—	10.49 s	—	8.74 dd	8.26 ddd	8.21 ddd	9.26 dd	5.33 t, CH_2N 3.78 t, CH_2Br 2.66 qn, CH_2	$J_{1,2}$ = 8.5, $J_{1,3}$ = 2.0, $J_{2,3}$ = 4.5, $J_{7,8}$ = 8.0, $J_{7,9}$ = 1.1, $J_{8,9}$ = 6.7, $J_{8,10}$ = 1.2, $J_{9,10}$ = 7.8, $J_{11,12}$ = 6.8, $J_{12,13}$ = 7.3

* Signals of 3-H, 7-H, and 9-H overlap and appear as a multiplet 7.61-7.72.

*[2] Signals of 7-H, 8-H, 9-H, and 10-H overlap and appear as a multiplet 7.61-7.92.

*[3] Signals of 2-H, 8-H, and 9-H overlap and appear as a multiplet 8.38-8.91.

The same regularity, i.e. higher activity against Gram-positive than against Gram-negative bacteria, has been observed for unsubstituted BNs and their derivatives, methyl- and formyl-BNs [13], BN N-oxides, and nitro derivatives [23], as well as for quaternary salts of BNs with methyl iodide, allyl iodide, benzyl chloride, 2,4-dinitrochlorobenzene, bromoacetophenone, and ethyl bromoacetate [10].

EXPERIMENTAL

Melting points, determined on a Boetius apparatus, are uncorrected. Thin layer chromatography was performed on 60 F 251 silica gel (Merck) precoated DC aluminum sheets. ^{1}H NMR spectra were recorded on a 500-MHz Bruker spectrometer in $(CD_3)_2SO$ with $SiMe_4$ as internal standard.

The biological tests were performed in the Microbiology Department at the Agricultural Academy in Wroclaw.

The characteristics of the newly synthesized compounds are presented in Tables 2 and 3.

5-Methylbenzo[*c*]-1,5-naphthyridin-6-one (4), 6-Methylbenzo[*c*]-1,6-naphthyridin-5-one (5), 5-Ethylbenzo[*c*]-1,5-naphthyridin-6-one (6), and 7-Ethylbenzo[*f*]-1,7-naphthyridin-8-one (7). To a solution of methylbenzonaphthyridinium iodides **8**, **9** or ethylbenzonaphthyridinium iodides **10**, **11** (1.61 g or 1.68 g, respectively, 5 mmol) in H_2O (16 ml), heated on a steam bath at ca. 60°C, was added saturated aq. KOH (ca 10 ml) until turbidity appeared. The reaction mixture was extracted with ether at room temperature, the ethereal solution dried over Na_2SO_4, the solvent removed, and the residue recrystallized from cyclohexane.

5-Ethylbenzo[*c*]-1,5-naphthyridinium Iodide (10) and 7-Ethylbenzo[*f*]-1,7-naphthyridinium Iodide (11). A solution of BN **1** or **3** (1.8 g, 10 mmol) and ethyl iodide (34.79 g, 223 mmol) in benzene (72 ml) was refluxed for 10 h. The product formed was filtered off and recrystallized from benzene.

2,5-Dimethylbenzo[*c*]-1,5-naphthyridinium Iodide (12). A solution of 2-methylbenzo[*c*]-1,5-naphthyridine (1.94 g, 10 mmol) and methyl iodide (44.23 g, 311.5 mmol) in benzene (86 ml) was refluxed and worked up as in the cases of **10** and **11**.

5-(3'-Bromopropyl)benzo[*c*]-1,5-naphthyridinium Bromide (13), 6-(3'-Bromopropyl)benzo[*c*]-1,6-naphthyridinium Bromide (14), and 7-(3'-Bromopropyl)benzo[*f*]-1,7-naphthyridinium Bromide (15). A solution of BN **1**, **2**, or **3** (1.8 g, 10 mmol) and 1,3-dibromopropane (26.76 g, 132.6 mmol) in benzene (25 ml) was refluxed under dry conditions for 24 h. The addition of benzene (10 ml) to the hot reaction mixture resulted in the formation of a product that was filtered off (portion I). The solution was treated with 1,3-dibromopropane (1 ml) and refluxed for 10 h. Cold benzene (ca. 5 ml) was added to produce the portion II. Joint portions were recrystallized from ethanol.

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