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Synthesis and Antimicrobial Activity of Some 2-Alkyl-2*H*-1,4-benzothiazin-3(4*H*)-ones and 2-Alkylbenzo[d]imidazolo[2,1-b]-thiazolidin-3-ones

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Summary. Sodium 2-aminothiophenoxide (**1**) reacts with ethyl 2-bromoalkanoates (**2**) under direct cyclization to form 2-alkyl-2*H*-1,4-benzothiazin-3(4*H*)-ones (**3**). Reaction of the sodium salt of 2-mercaptobenzimidazole (**4**) with **2** or 2-bromoalkanoic acids (**5**) affords only S-alkylated products (**6** or **7**, respectively). The cyclization products – 2-alkylbenzo[d]imidazolo[2,1-b]thiazolidin-3-ones (**8**) – can be obtained only from the corresponding 2-(2-benzimidazolylthio)alkanoic acids (**7**) by the action of acetic anhydride. Both compounds **3** and **8** exhibit only moderate antimicrobial activity against some gram-positive bacteria.

Keywords. 4*H*-1,4-Benzothiazines; Benzo[d]imidazolo[2,1-b]thiazolidines; Antimicrobial activity.

Synthese und antimikrobielle Wirkung von einigen 2-Alkyl-2*H*-1,4-benzothiazin-3(4*H*)-onen und 2-Alkylbenzo[d]imidazolo[2,1-b]thiazolidin-3-onen

Zusammenfassung. Bei der Reaktion von Natrium-2-aminothiophenolat mit 2-Bromoalkansäureethylestern (**2**) entstehen als Cyclisierungsprodukte 2-Alkyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**3**). Die Umsetzung von Natriumbenzimidazol-2-thiolat mit **2** oder mit 2-Bromoalkansäuren (**5**) liefert nur S-Alkylierungsprodukte (**6** oder **7**). Die Cyclisierungsprodukte – 2-Alkylbenzo[d]imidazolo[2,1-b]thiazolidin-3-one (**8**) – sind nur durch Umsetzung von entsprechenden 2-(2-Benzimidazolylthio)-alkansäuren (**7**) mit Acetanhydrid erhältlich. Die Verbindungen **3** und **8** weisen nur mäßige antimikrobielle Wirkung gegen einige gram-positive Bakterien aus.

Introduction

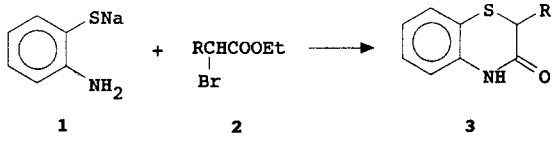
4*H*-1,4-Benzothiazines gained some significance with regard to the studies on ylides [1] as well as to the preparations of pharmacologically effective analogues of phenothiazines [2–4]. On the other hand, benzo[d]imidazolo[2,1-b]thiazolidin-3-ones substituted with a halogen atom in the benzene ring were studied only from structural points of view [5–7].

In our previous papers [7, 8] we have reported that some nitrogen containing heterocycles with a long alkyl chain (hexyl, heptyl, octyl) exhibit remarkable antimicrobial efficiency, especially against gram-positive bacteria. In this paper we have focused our attention on the synthesis of some 2-alkyl-2*H*-1,4-benzothiazin-

3(4*H*)-ones and 2-alkylbenzo[d]imidazolo [2,1-b]-thiazolidin-3-ones and the relation between the length of alkyl chain and antimicrobial activity.

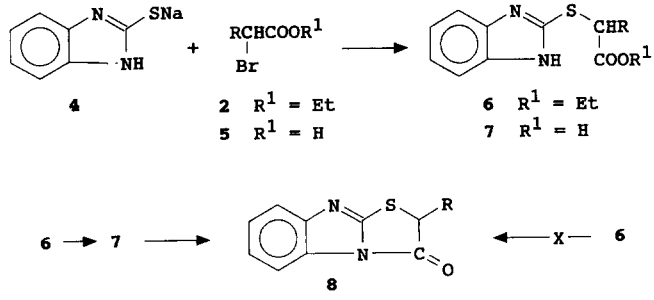
Results and Discussion

Reaction of sodium 2-aminothiophenoxide (**1**) with selected ethyl 2-bromoalkanoates (**2**) in ethanol at room temperature gave cyclization products – 2-alkyl-2*H*-1,4-benzothiazin-3(4*H*)-ones (**3**)-without isolation of the corresponding intermediate ethyl 2-(2-aminophenylthio)alkanoates (Scheme 1). The same results were obtained if this reaction was carried out in water. On the other hand, the sodium salt of 2-mercaptobenzimidazole (**4**), when reacted with **2**, afforded only products of S-alkylation (ethyl 2-(2-benzimidazolylthio)-alkanoates (**6**)). Cyclization of compounds **6** to 2-alkylbenzo[d]imidazolo[2,1-b]thiazolidin-3-ones (**8**) under usual conditions was unsuccessful. However, 2-(2-benzimidazolylthio)alkanoic acids (**7**) underwent cyclization when heated in a mixture of acetic anhydride and pyridine affording **8** in appr. 50% yields (Scheme 2). Compounds **7** can be prepared either by the direct alkylation of **4** with 2-bromoalkanoic acid (**5**) or by the base-catalyzed hydrolysis of an ester group starting from **6**. We have found that the last mentioned approach is more convenient because of higher total yield of **7** (about 90% yields in the alkylation step and almost quantitative hydrolysis of the ester, in contrast to about 55% yields of **7** in the case of direct alkylation of **4** with **5**).



1 2 3

Scheme 1



4 2 R^1 = Et, 5 R^1 = H 6 R^1 = Et, 7 R^1 = H 8

Scheme 2

The cyclic structures were confirmed on the basis of ^{1}H and ^{13}C NMR spectra as well as mass spectral data. In the case of compounds **3**, no signals of methyl and methylene protons of the ester group were observed, but a signal of an amidic proton at $\delta \approx 9.45$ ppm was registered in the ^{1}H NMR spectra. In the ^{13}C NMR spectra, only a signal of one methyl group (terminal methyl group in alkyl chain) at $\delta \approx 14.0$ ppm was found. These evidences as well as the presence of intensive ($I_r \approx 80\%$) peaks corresponding to the molecular ions (M^+) in the mass spectra strongly support the cyclic structure of

Table 1. Characterization of compounds **3** and **8**. All compounds gave satisfactory elemental analyses

Compound	R	Molecular formula	Molecular weight	Yield (%)	m.p. (°C)
3a	Methyl	C_9H_9NOS	179.25	95	106–107
3b	Ethyl	$C_{10}H_{11}NOS$	193.28	93	108–109
3c	Propyl	$C_{11}H_{13}NOS$	207.31	94	111–112
3d	Butyl	$C_{12}H_{15}NOS$	221.34	92	102–103
3e	Hexyl	$C_{14}H_{19}NOS$	249.40	91	93–94
3f	Heptyl	$C_{15}H_{21}NOS$	263.43	92	92–93
3g	Octyl	$C_{16}H_{23}NOS$	277.46	91	90–91
3h	Decyl	$C_{18}H_{27}NOS$	305.52	89	91–93
3i	Dodecyl	$C_{20}H_{31}NOS$	333.58	87	95–97
8a	Methyl	$C_{10}H_8N_2OS$	204.26	51	128–129
8b	Ethyl	$C_{11}H_{10}N_2OS$	218.29	49	131–132
8c	Propyl	$C_{12}H_{12}N_2OS$	232.32	50	133–134
8d	Butyl	$C_{13}H_{14}N_2OS$	246.35	47	126–127
8e	Hexyl	$C_{15}H_{18}N_2OS$	274.41	51	119–120
8f	Heptyl	$C_{16}H_{20}N_2OS$	288.44	48	121–122
8g	Octyl	$C_{17}H_{22}N_2OS$	302.47	49	117–118
8h	Decyl	$C_{19}H_{26}N_2OS$	330.53	46	120–122
8i	Dodecyl	$C_{21}H_{30}N_2OS$	358.59	45	123–125

Table 2. Antimicrobial activity (MIC, $\mu g \cdot cm^{-3}$) of compounds **3** and **8**

Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*Streptococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella typhimurium*
3a	1000	1000	1000	1000	1000	1000
3b	1000	1000	1000	1000	1000	1000
3c	1000	1000	1000	1000	1000	1000
3d	100	100	1000	1000	1000	1000
3e	10	<10	<100	1000	1000	<1000
3f	10	10	100	1000	<1000	100
3g	10	10	100	1000	1000	<1000
3h	100	100	1000	1000	1000	1000
3i	1000	1000	1000	1000	1000	1000
8a	1000	1000	1000	1000	1000	1000
8b	1000	1000	1000	1000	1000	1000
8c	1000	1000	1000	1000	1000	1000
8d	<1000	100	1000	1000	1000	1000
8e	10	10	<1000	1000	1000	<1000
8f	10	10	100	1000	1000	<1000
8g	10	10	<1000	1000	1000	<1000
8h	<1000	<1000	1000	1000	1000	1000
8i	1000	1000	1000	1000	1000	1000

3. The same spectral observations were conclusive for the determination of the uncyclized structures of **6** and **7** and the cyclic structures of **8**. For further data on compounds **3** and **8** and their characterization see Table 1.

The results of antimicrobial activity testing revealed that some of the prepared compounds **3** and **8** exhibit moderate activity against some gram-positive bacteria (Table 2). Similarly to our previous findings [8, 9], the best efficiency (expressed by the integer values of minimum inhibitory concentration – MIC) was exhibited by those derivatives where the alkyl chain R represented hexyl, heptyl or octyl. Derivatives with shorter or longer alkyl chains showed considerably lower activity. As a standard for MIC value determination we have used [1-(ethoxycarbonyl)-pentadecyl]-trimethylammonium bromide (Septonex), an antiseptic agent.

Experimental

Melting points were determined on a Kofler hot-stage and are uncorrected. Electron-impact mass spectra (70 eV) were recorded on a Jeol JMS 100 D spectrometer at an emission current of 300 μA, applying direct sample-introduction technique. NMR spectra were measured on a Bruker AM 300 instrument operating at 300.13 or 75.46 MHz (^{1}H and ^{13}C, resp.) with *TMS* as an internal standard. Elemental analyses were performed on a Perkin Elmer 240 analyzer. The purity and identity of the prepared compounds were routinely checked by TLC on Silufol UV254 plates (Kavalier, Czech Republic) using a mixture of ethyl acetate:n-hexane = 3:2 as eluent. 2-Bromoalkanoic acids and ethyl 2-bromoalkanoates were prepared according to conventional methods [10–13]. All other chemicals were commercially available products (Merck, Darmstadt; Fluka, Buchs). MIC was determined by using the suspension method on solid cultivation media [8].

2-Hexyl-2H-1,4-benzothiazin-3(4H)-one (**3**, R = hexyl)

Method A. To a solution of sodium ethoxide (0.68 g, 10 mmol) in dry ethanol (50 ml), 2-aminothiophenol (1.25 g, 10 mmol) was added. After 30 min of stirring, ethyl 2-bromooctanoate (**2**, R = hexyl, 2.51 g, 10 mmol) was added dropwise at 25 °C and the mixture was then heated under reflux for 3 h. The solvent was evaporated under reduced pressure, the residue dissolved in ethyl acetate (50 ml), washed with water and dried (Na_2SO_4). After evaporation of the solvent, the crude product was crystallized from hot n-hexane (using decolourizing charcoal) affording white crystalls of **3**.

Yield, 2.27 g (91%); m.p., 93–94 °C; EI-MS (m/z, %): 249 (M^+, 80), 178 (18), 164 (100), 136 (20), 96 (22); ^{1}H NMR ($CDCl_3$, δ (ppm)): 7.70–6.92 (4H, m, aromatics), 3.40 (1H, dd, J = 8.6 Hz and 6.1 Hz, H-2), 1.90 (2H, m, first CH_2 in hexyl), 1.60 (2H, m, second CH_2 in hexyl), 1.28 (6H, m, remaining CH_2 in hexyl), 0.89 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$, δ (ppm)): 168.7 (C=O), 136. 2 (C-4a), 128.2 (C-5), 127.0 (C-6), 123.8 (C-7), 118.6 (C-8a), 116.9 (C-8), 42.7 (C-2), 25.3–21.3 (five CH_2), 14.0 (CH_3).

Method B. To a solution of NaOH (0.4 g, 10 mmol) in water (50 ml), 2-aminothiophenol (1.25 g, 10 mmol) was added and the mixture was stirred until the emulsion disappeared. Then, bromide **2** (R = hexyl, 2.51 g, 10 mmol) was added dropwise under stirring at room temperature and the mixture was stirred for an additional hour. The separated oil was extracted with ethyl acetate and worked up as above affording **3**. Yield, 2.05 g (82%).

Procedures A and B are of general applicability for the preparation of compounds **3**.

Ethyl 2-(2-benzimidazolylthio)propionate (**6**, R = methyl)

A solution of the sodium salt of 2-mercaptobenzimidazole (**4**, 10 mmol) (prepared from 10 mmol of 2-mercaptobenzimidazole and 10 mmol of sodium ethoxide in 50 ml of dry ethanol) and ethyl

2-bromopropionate (**2**, R = methyl, 10 mmol) in dry ethanol (50 ml) was heated under reflux for 5 h. After cooling, the reaction mixture was poured onto crushed ice (300 ml), the separated solid filtered off and crystallized from ethanol-ether giving **6**.

Yield, 2.23 g (89%); m.p., 146–147 °C; $C_{12}H_{14}N_2O_2S$ (250.34); calcd. C 57.57, H 5.65, N 11.19; found C 57.51, H 5.68, N 11.23; EI-MS (m/z, %): 250 (M^+, 100), 235 (64), 205 (42), 177 (66), 163 (51), 150 (82), 134 (18), 101 (23), 91 (33); ^{1}H NMR ($CDCl_3$, δ (ppm)): 7.56 (2H, bs, H-4 and H-7), 7.26–7.19 (2H, m, H-5 and H-6), 4.28 (1H, q, J = 7.3 Hz, CH), 4.23 (2H, q, J = 7.1 Hz, CH_2), 1.62 (3H, d, J = 7.3 Hz, CH_3), 1.25 (3H, t, J = 7.1 Hz, ethyl-CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm)): 173.5 (C=O), 147.1 (C-2), 122.5 (C-5 and C-6), 62.2 (CH_2), 43.8 (CH), 17.7 (CH_3), 13.9 (ethyl-CH_3); the signals of C-3a, C-4, C-7, and C-7a are missing in the spectrum.

This procedure is of general applicability for the preparation of compounds **6**.

2-(2-Benzimidazolylthio)butyric acid (**7**, R = ethyl)

Method A. To a mixture of powdered NaOH (1.2 g, 30 mmol) in ethanol (60 ml), 2-mercaptobenzimidazole (4.5 g, 30 mmol) was added and the mixture was heated at 60 °C for 15 min. Then, 2-bromobutyric acid (5.01 g, 30 mmol) was added and the mixture was heated under reflux for 6 h. After evaporation of the solvent under reduced pressure, cold water (200 ml), acidified with acetic acid (3 ml), was added to the residue. The separated solid was filtered off, washed with water and acetone and crystallized from ethanol giving **7**.

Yield, 3.9 g (55%), m.p. 173–174 °C; $C_{11}H_{12}N_2O_2S$ (236.31); calcd. C 55.91, H 5.13, N 11.86; found C 55.87, H 5.15, N 11.83; EI-MS (m/z, %): 236 (M^+, 17), 219 (36), 192 (100), 163 (63), 150 (82), 134 (22), 101 (25), 91 (40); ^{1}H NMR ($CDCl_3$, δ (ppm)): 7.52 (2H, bs, H-4 and H-7), 7.24–7.20 (2H, m, H-5 and H-6), 4.21 (1H, t, J = 7.5 Hz, CH),1.90 (2H, dq, J = 7.5 Hz and 7.0 Hz, CH_2), 1.16 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ (ppm)): 175.6 (C=O), 146.9 (C-2), 122.6 (C-5 and C-6), 44.1 (CH), 32.7 (CH_2), 14.3 (CH_3); the signals of C-3a, C-4, C-7, and C-7a are missing in the spectrum.

Method B. A mixture of ester **6** (R = ethyl, 1.30 g, 5 mmol) and NaOH (2.00 g, 50 mmol) in water (60 ml) was heated under reflux for 3 h. After cooling, it was neutralized with 3*N*-HCl. The separated product was filtered off, washed with acetone and recrystallized from ethanol giving **7**. Yield, 1.11 g (94%).

Procedures A and B are of general applicability for the preparation of compound **7**.

2-Methylbenzo[d]imidazolo[2,1-b]thiazolidin-3-one (**8**, R = methyl)

A mixture of acid **7** (**R** = methyl, 1.11 g, 5 mmol), acetic anhydride (2 ml) and pyridine (5 ml) was heated under reflux for 1 h. After cooling, methanol (5 ml) was carefully added and the solvents were evaporated under reduced pressure. Cold water (25 ml) was added to the residue and the product was filtered off and recrystallized from ethanol affording **8**.

Yield, 0.52 g (51%); m.p., 128–129 °C; EI-MS (m/z, %): 204 (M^+, 100), 189 (76), 176 (69), 161 (26), 101 (18), 91 (27); ^{1}H NMR ($CDCl_3$, δ (ppm)): 7.59–7.23 (4H, m, aromatics), 4.56 (1H, q, J = 7.9 Hz, H-2), 1.68 (3H, d, J = 7.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ (ppm)): 174.4 (C=O), 152.7 (C-9a), 148.3 (C-4a), 132.1 (C-8a), 124.5 (C-6), 121.9 (C-7), 119.2 (C-5), 112.4 (C-8), 44.2 (C-2), 18.1 (CH_3).

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