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The Synthesis of Benzophenothiazine Derivatives

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Summary. The reaction of substituted 1,4-naphthoquinones with 2-aminothiophenol and *o*-aminoheterocyclic thiones in acidic condition afforded benzophenothiazin-5-one and azabenzophenothiazin-5-one derivatives, respectively.

Keywords. Azabenzophenothiazin-5-one; Benzo[a]phenothiazin-5-one; Benzothiazinophenothiazine.

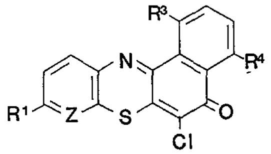
Die Synthese von Benzophenothiazin-Derivaten

Zusammenfassung. Die Reaktion von substituierten 1,4-Naphthochinonen mit 2-Aminophenol bzw. *o*-aminoheterocyclischen Thionen führte unter sauren Bedingungen zu Benzophenothiazin-5-onen bzw. Azabenzophenothiazin-5-onen.

The scope of interest in phenothiazine derivatives covers a wide assortment of areas. Many of phenothiazines have been used as dyes, indicators, antioxidants, and in medical practice [1–4]. Some of substituted 5*H*-benzophenothiazin-5-ones **1** were synthesized for i.r. dyes [5]. Our interest in the chemistry and the pharmaceutical usage of these compounds has allowed us to prepare some of phenothiazines [6, 7].

In this work we synthesized **1** by condensation of 2-aminothiophenol or substituted 3-aminopyridine-2[1*H*]-thiones **2** with substituted 1,4-naphthoquinones **3** in alcoholic solution in the presence of acid. The structures of the resulting compounds were assigned by comparing their analytical and spectral data with that of related known benzophenothiazines [6]. The condensation of 2-aminothiophenol (**2a**) with 5,8-diamino-2,3-dichloro-1,4-naphthoquinone (**3a**) gave a mixture from which 6,9-diaminobenzo[a][1,4]benzothiazino[3,2-c]-phenothiazine (**4**) and 1,4-diamino-6-chloro-5*H*-benzo[2,3-a]phenothiazin-5-one (**1a**) were isolated. Only 8-aza-1,4-diamino-6,9-dichloro-5*H*-benzo[2,3-a]-phenothiazin-5-one (**1b**) was produced by the reaction of **3a** and 3-amino-6-chloropyridine-2[1*H*]-thione (**2b**). The same result was obtained in the case of **3a** and **2c**.

The reaction of 5-amino-2,3-dichloro-8-nitro-1,4-naphthoquinone (**3b**) and 3-amino-6-chloropyridine-2[1*H*]-thione (**2b**) gave two expected compounds **1d** and **1e**. However in the condensation of **3b** and 3-amino-6-methoxypyridine-2[1*H*]-thione (**2c**), besides the expected products **1f** and **1g**, 8-aza-1,4-diamino-6-methoxy-5*H*-benzo[2,3-a]phenothiazin-5-one (**1a**) was also obtained. The ratio of the products depended on the reaction conditions.



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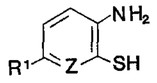

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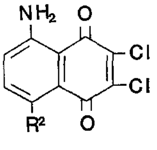

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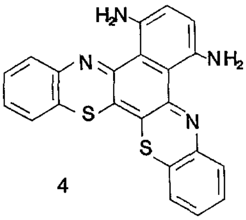

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1a: $R^1 = H, Z = CH, R^3 = R^4 = NH_2$
1b: $R^1 = Cl, Z = N, R^3 = R^4 = NH_2$
1c: $R^1 = OCH_3, Z = N, R^3 = R^4 = NH_2$
1d: $R^1 = Cl, Z = N, R^3 = NH_2, R^4 = NO_2$
1e: $R^1 = Cl, Z = N, R^3 = NO_2, R^4 = NH_2$
1f: $R^1 = OCH_3, Z = N, R^3 = NH_2, R^4 = NO_2$
1g: $R^1 = OCH_3, Z = N, R^3 = NO_2, R^4 = NH_2$

2a: $R^1 = H, Z = CH$
2b: $R^1 = Cl, Z = N$
2c: $R^1 = OCH_3, Z = N$

3a: $R = NH_2$
3b: $R = NO_2$

On the UV spectra of the products **1a–1g**, the λ_{max} of the diamino compounds **1a–1c** (λ_{max} = ca. 700 nm) were shifted to longer wavelengths than that of the monoamino compounds **1d–1g** (λ_{max} = ca. 540 nm) showing the effect of the introduction of electron-donating amino group.

Experimental

Melting points were determined on a Yanaco micromelting point apparatus and uncorrected. The IR spectra were recorded with a JASCO A-102 spectrometer and the UV spectra with a JASCO UVIDEC-505 instrument. The ^{1}H-nmr spectra were measured on a Varian XL-200 spectrometer operating in an FT mode using tetramethylsilane as internal reference. Mass spectra were obtained with a JEOL 01SG-2 (photographic dry plate) spectrometer. For column chromatography, silica gel (Merck, 70–230 mesh) was used.

Reaction of 5,8-diamino-2,3-dichloro-1,4-naphthoquinone (**3a**) *and 2-Aminothiophenol* (**2a**)

A solution of 2-aminothiophenol (100 mg, 0.8 mmol) in ethanol (3 ml) was added with stirring to a solution of 5,8-diamino-2,3-dichloro-1,4-naphthoquinone (100 mg, 0.39 mmol) in ethanol (50 ml) in the presence of 2 ml of 15% hydrochloric acid. The mixture was refluxed for 1 hour, poured into 150 ml of water, and extracted with benzene. After removal of the solvent, the residue was passed down a column of silica gel using benzene then benzene-ethyl acetate as the eluents. From the first fraction a reddish violet compound was obtained and confirmed as 6,9-diaminobenzo[a][1,4]benzothiazino[3,2-c]phenothiazine (**4**) (13 mg, 8.5%). The major green band yielded 1,4-diamino-6-chloro-5*H*-benzo[2,3-a]phenothiazin-5-one (**1a**) (42 mg, 33%).

Compound **1a** had m.p. 256–258°C; IR (KBr): 3 360, 3 250 (NH_2), 1 632 (C=O) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 60°C, δ 8.93 (b, 2 H, NH_2), 8.18 (b, 2 H, NH_2), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.41–7.31 (m, 2 H), 7.24 (d, 1 H), 7.10 (d, 1 H); UV (chloroform): λ_{max}, 693, 647, 595 (sh), 480, 454, 380 (sh), 348 nm; MS calcd. for $C_{16}H_{10}ClN_3OS$ = 327.0235, found *m*/e = 327.0224.

Compound **4** had m.p. 219°C (decomp.); IR (KBr): 3 425 (NH_2), 1 618 (C=N) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 60°C, δ 8.36 (b, 4 H, NH_2), 7.52–7.26 (m, 8 H), 7.11 (s, 2 H); UV (chloroform): λ_{max}, 624 (sh), 535 nm; MS calcd. for $C_{22}H_{14}N_4S_2$ = 398.0662, found *m*/e = 398.0632.

8-Aza-1,4-diamino-6,9-dichloro-5H-benzo[2,3-a]phenothiazin-5-one (**1b**)

To a suspension of **3a** (48.4 mg, 0.2 mmol) and 3-amino-6-chloropyridine-2[1*H*]-thione (**2b**, 48.2 mg, 0.3 mmol) in 80 ml of ethanol was added 4 ml of 15% hydrochloric acid and stirred at 50–60°C for 20 h. After usual workup 44.3 mg of **1b** was obtained. Yield 64%.

Compound **1b** had m.p. 258°C; IR (KBr): 3 380, 3 260 (NH_2), 1 639 (C=O) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 60°C, δ 9.14 (b, 2 H, NH_2), 8.44 (b, 2 H, NH_2), 7.98 (d, 1 H), 7.39 (d, 1 H), 7.28 (d, 1 H), 7.15 (d, 1 H); UV (chloroform): 700, 642, 598, 483 (sh), 455, 432 (sh), 350 nm; MS calcd. for $C_{15}H_8Cl_2N_4OS$ = 361.9798, found *m*/e = 361.9786.

8-Aza-1,4-diamino-6-chloro-9-methoxy-5H-benzo[2,3-a]phenothiazin-5-one (**1c**)

The suspension of **3a** (25 mg, 0.1 mmol) and **2c** (23 mg, 0.15 mmol) in ethanol (20 ml) and 15% hydrochloric acid (3 ml) was refluxed for 7 h with stirring. Then additional 8 mg of **2c** was added and the mixture was refluxed for 5 h until the starting quinone (**3a**) had disappeared. After column chromatography 38 mg of **1c** was isolated from the green band. Yield 97%.

Compound **1c** had m.p. 260°C; IR (KBr): 3350, 3260 (NH_2), 1632, 1589 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 70°C, δ 8.68 (b, 2 H, NH_2), 8.13 (b, 2 H, NH_2), 7.98 (d, 1 H), 7.27 (d, 1 H), 7.11 (d, 1 H), 6.85 (d, 1 H), 3.95 (s, 3 H, OCH_3); UV (chloroform): λ_{max}, 698, 642, 605 (sh), 479, 451, 430 (sh) nm; MS calcd. for $C_{16}H_{11}ClN_4O_2S$ = 358.0293, found *m*/e = 358.0343.

Condensation of 5-Amino-2,3-dichloro-8-nitro-1,4-naphthoquinone (**3b**) *and* **2b**

Method A. To a solution of **3b** (58 mg, 0.2 mmol) and **2b** (32 mg, 0.2 mmol) in 60 ml of ethanol was added 8 ml of 15% hydrochloric acid. The resulting mixture was stirred at 40°C and an additional 16 mg of **2b** was added at each 8 h. After stirring for 40 h the reaction completed. Then the mixture was extracted and chromatographed on a silica gel column eluting with benzene-ethyl acetate. From the first reddish violet band 22 mg of 4-amino-8-aza-6,9-dichloro-1-nitro-5*H*-benzo[3,2-a]phenothiazin-5-one (**1e**) (yield 28%) and from the second reddish brown band 56 mg of 1-amino-8-aza-6,9-dichloro-4-nitro-5*H*-benzo-[2,3-a]phenothiazin-5-one (**1d**) (71%) were separated.

Method B. Compound **3b** (86 mg, 0.3 mmol) and 96 mg (0.3 mmol) of **2b** were dissoloved in 7 ml of N,N-dimethylformamide and then 98 mg of sodium acetate was added. After stirring for 1 h at room temperature the reaction mixture was poured to 100 ml of water and extracted with benzene. Removal of the solvent and column chromatography on silica gel gave 16 mg of **1e** (14%) and 31 mg of **1d** (27%) together with some of unidentified products.

Compound **1d** had m.p. > 270°C; IR (KBr): 3 425 (NH_2), 1 605 (C=O) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 60°C, δ 8.92–8.84 (m, 2 H, NH_2), 8.62 (d, 1 H), 7.76–7.71 (m, 2 H), 7.37 (d, 1 H); UV (chloroform): λ_{max}, 504, 485 nm; MS calcd. for $C_{15}H_6Cl_2N_4O_3S$ = 391.9540, found *m*/e = 391.9594.

Compound **1e** had m.p. 349–350°C; IR (KBr): 3 480, 3 340 (NH_2), 1 618 (C=O) cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 60°C, δ 8.21 (b, 2 H, NH_2), 7.82 (d, 1 H), 7.73 (d, 1 H), 7.66 (d, 1 H), 7.21 (d, 1 H); UV (chloroform): λ_{max}, 540, 464, 437 nm; MS calcd. for $C_{15}H_6Cl_2N_4O_3S$ = 391.9540, found *m*/e = 391.9506.

Reaction of **3b** *and* **2c**

(a) A solution of 5-amino-2,3-dichloro-8-nitro-1,4-naphthoquinone (**3b**, 29 mg, 0.1 mmol) and **2c** (32 mg, 0.2 mmol) in 20 ml of ethanol and 15% hydrochloric acid (4 ml) was refluxed for 12 h with stirring under argon. Then the reaction mixture was extracted with benzene and the solvent was removed under reduced pressure and the residue was chromatographed to give **1c** (18 mg, 50%) identical to that obtained above.

(b) The solution of **3b** (50 mg, 0.17 mmol) and **2c** (55 mg, 0.34 mmol) in 20 ml of ethanol and 15% hydrochloric acid (8 ml) was stirred at refluxing temperature under argon for 2.5 h. Then an additional 10 mg of **2c** was added and the mixture was refluxed for another 5 h. After workup 4-amino-8-aza-6-chloro-9-methoxy-5*H*-benzo[3,2-a]phenothiazin-5-one (**1g**, 18 mg, 26%), 1-amino-8-aza-6-chloro-9-methoxy-5*H*-benzo[2,3-a]phenothiazin-5-one (**1f**, 41 mg, 60%), and **1c** (8 mg, 13%) were obtained.

(c) Quinone **3b** (50 mg, 0.17 mmol) and **2c** (27 mg, 0.17 mmol) were dissolved in 20 ml of ethanol in the presence of 4 ml of 15% hydrochloric acid. The resulting mixture was stirred at 55–60°C for 2.5 h. An additional 28 mg of **2c** and after 4 h another 23 mg of **2c** were added and the stirring was continued for 2.5 h. After column chromatography 16 mg of **1g** (23%) and 51 mg of **1f** (70%) were collected together with only a trace amount of **1c**.

Compound **1f** had m.p. 356°C; IR (KBr): 3450 (NH_2), 1637 (C=O), 1600 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 70°C, δ 8.78 (b, 2 H, NH_2), 8.48 (d, 1 H), 7.70 (d, 1 H), 7.34 (d, 1 H), 7.11 (d, 1 H), 4.04 (s, 3 H, OCH_3); UV (chloroform): λ_{max}, 528, 507, 361 (sh), 346 nm; MS calcd. for $C_{16}H_9ClN_3OS$ = 388.0035, found *m*/e = 388.0039.

Compound **1g** had m.p. 343°C; IR (KBr): 3380 and 3275 (NH_2), 1602, 1588 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): 90°C, δ 8.11 (b, 2 H, NH_2), 7.77 (d, 1 H), 7.69 (d, 1 H), 7.15 (d, 1 H), 7.03 (d, 1 H), 4.02 (s, 3 H, OCH_3); UV (chloroform): λ_{max}, 544, 462, 437, 414 (sh), 370 (sh), 348 nm; MS calcd. for $C_{16}H_9ClN_3OS$ = 388.0035, found *m*/e = 388.0047.

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