Monatshefte für Chemie 118, 381—385 (1987)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Some 5*H*-Benzo[a]phenothiazin-5-one Derivatives

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(Received 22 December 1985. Accepted 10 February 1986)

Several substituted 6-anilino-5*H*-benzo[a]phenothiazin-5-one derivatives were prepared by condensation of substituted 1,4-naphthoquinones with 2-aminobenzenethiol in pyridine. The reduction and acetylation of the resulting compounds were also investigated.

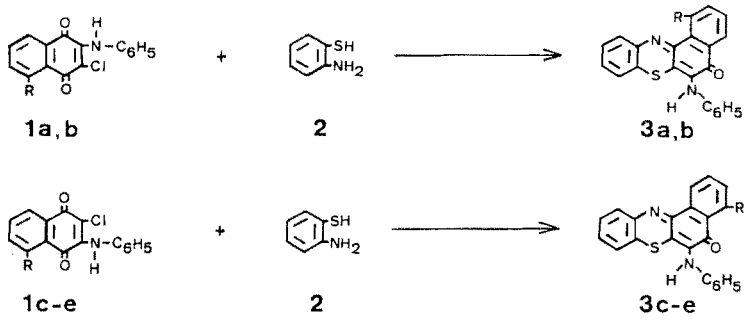
(Keywords: 6-Anilino-4-nitro-5H-benzo[a]phenothiazin-5-one; 4-Amino-6-anilino-5H-benzo[a]phenothiazin-5-one; 1-Acetylamino-6-anilino-5H-benzo[a]-phenothiazin-5-one)

Synthese einiger 5H-Benzo[a]phenothiazin-5-on-Derivate

Es wurden mittels Kondensation substituierter 1,4-Naphthochinone mit 2-Aminothiophenol in Pyridin einige substituierte 6-Anilino-5*H*-benzo[a]-phenothiazin-5-one dargestellt. Die Reduktion und Acetylierung der resultierenden Verbindungen wurde ebenfalls untersucht.

Phenothiazones have been extensively used as enzyme inhibitors, antioxidants, dyestuffs, and indicators in titrimetry [1–7]. As part of a study concerning the synthesis, structure and chemical reactivity of quinone imines [8–11], we now report the preparation of 5*H*-benzo[a]phenothiazin-5-one derivatives.

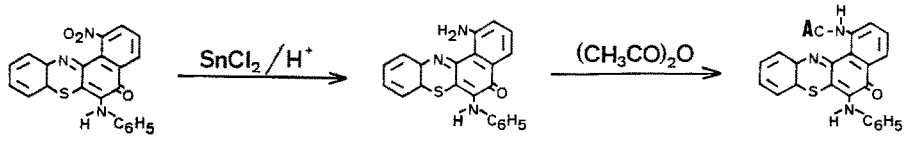
In this work, 1- and 4-substituted-6-anilino-5*H*-benzo[a]-phenothiazin-5-ones (**3**) were prepared by condensation of substituted 1,4-naphthoquinones (**1**) with 2-aminobenzenethiol (**2**) in pyridine. The structure of the resulting compounds were determined on the basis of the spectroscopic data. The condensation of **1 a** with **2** readily proceeeded at room temperature, giving **3 a** in quantitative yield. On the other hand, **1 b**

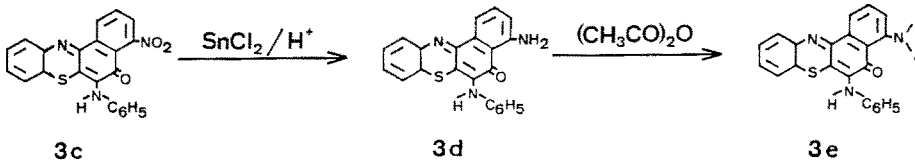


1a, **3a**, R = NO_2
1b, **3b**, R = AcNH
1c, **3c**, R = NO_2
1d, **3d**, R = NH_2
1e, **3e**, R = AcNH

did not react with **2** under the same condition. The difference in the reactivity may be attributed to the intramolecular hydrogen bonding between the acetylamino hydrogen and the carbonyl oxygen atom in the original 1,4-naphthoquinones.

The reduction of **3a** and **3c** with stannous chloride easily proceeded in acetic acid at room temperature, giving **3d** and **3f**, respectively, in good





yield. The structures of the latter compounds were also determined spectroscopically. Compound **3d** was further identified by direct comparison with a sample prepared by an alternate route involving the condensation of **1d** with **2** in pyridine. The acetylation of **3d** and **3f** proceeded in a mixture of acetic acid and acetic anhydride to give **3b** and **3e**, respectively. The same compounds, **3b** and **3e**, could also be obtained by the condensation of compounds **1b** and **1e** with **2** in pyridine, respectively.

We believe that the proposed methods provide new synthetic routes to quinone imine derivatives.

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. The infrared spectra were recorded on a Jasco A-102 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian XL-200 spectrometer using tetramethylsilane as an internal reference. Mass spectra were determined on a Hitachi M-80 spectrometer.

6-Anilino-1-nitro-5H-benzo[a]phenothiazin-5-one (**3a**)

A solution of 2-aminobenzenethiol (**2**) (50 mg, 0.4 mmol) in pyridine (5 ml) was gradually added with stirring to a solution of 2-anilino-3-chloro-5-nitro-1,4-naphthoquinone (**1a**) (100 mg, 0.3 mmol) in pyridine (15 ml) at 80 °C and the mixture was stirred and heated for a further 1 h. After the removal of the solvent under reduced pressure, the residue was chromatographed on an aluminium oxide column using benzene as an eluent.

Compound **3a** gave violet crystals; m.p. 240 °C. Yield 83%.

IR (KBr): 1621 cm^{-1} (C=O).

^{1}H-NMR (*DMSO-d_6*): 6.76–6.96 (m, 3H, arom.), 7.25 (t, 2H, arom.), 7.52–7.63 (m, 3H, arom.), 7.72 (m, 1H, arom.), 8.05 (t, 1H, arom.), 8.22 (d, 1H, arom.), 8.47 (s, 1H, NH), 8.50 (d, 1H, arom.).

MS calcd. for $C_{22}H_{13}N_3O_3S$ = 399.0679, found *m/e* = 399.0681 (M^+).

1-Acetylamino-6-anilino-5H-benzo[a]phenothiazin-5-one (**3b**)

Method (A)

A solution of **2** (80 mg, 0.64 mmol) in pyridine (5 ml) was gradually added with stirring to a solution of 5-acetylamino-2-anilino-3-chloro-1,4-naphthoquinone (**1b**) (170 mg, 0.5 mmol) in pyridine (16 ml) at room temperature and the mixture was refluxed for 6 h. After the removal of the solvent under reduced pressure, the residue was chromatographed on an aluminium oxide column using benzene as an eluent. The solid obtained on concentration of the eluate was recrystallized from dimethyl sulfoxide.

Compound **3b** gave violet crystals; m.p. > 300 °C. Yield 56%.

IR (KBr): 1614, 1685 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): 2.44 (s, 3H, CH_3), 6.77 (d, 2H, arom.), 7.08 (t, 1H, arom.), 7.30–7.54 (m, 5H, arom., 1H, NH), 7.76 (m, 2H, arom.), 8.24 (d, 1H, arom.), 9.22 (d, 1H, arom.), 14.10 (s, 1H, CONH).

MS calcd. for $C_{24}H_{17}N_3O_2S$ = 411.1043, found *m/e* = 411.1045 (M^+).

Method (B)

A mixture of 1-amino-6-anilino-5*H*-benzo[a]phenothiazin-5-one (**3f**) (56 mg, 0.15 mmol), acetic acid (6 ml), and acetic anhydride (6 ml) was refluxed for 10 min. After the removal of the solvent under reduced pressure, the residue was purified and analyzed by the same way as above. Yield 33%.

6-Anilino-4-nitro-5H-benzo[a]phenothiazin-5-one (**3c**)

The compound **3c** was prepared by the reaction of 2-anilino-3-chloro-8-nitro-1,4-naphthoquinone (**1c**) with **2** in a similar way as **3a**.

Compound **3c** gave violet crystals; m.p. 285 °C. Yield 89%.

IR (KBr): 1618 cm^{-1} (C=O).

^{1}H-NMR (*DMSO-d_6*): 6.77–6.90 (m, 3H, arom.), 7.25 (t, 2H, arom.), 7.61–7.80 (m, 4H, arom.), 8.05–8.23 (m, 2H, arom.), 8.47 (s, 1H, NH), 9.18 (d, 1H, arom.).

MS calcd. for $C_{22}H_{13}N_3O_3S$ = 399.0679, found *m*/e = 399.0659 (M^+).

4-Amino-6-anilino-5H-benzo[a]phenothiazin-5-one (**3d**)

Method (A)

The same procedure as in the preparation of **3b** was applied, except for the use of **1d** as a starting material in place of **1b**.

Compound **3d** gave violet crystals; m.p. 303 °C Yield 57%.

IR (KBr): 1610 cm^{-1} (C=O).

^{1}H-NMR (*DMSO-d_6*): 6.73 (d, 2H, arom.), 6.86 (t, 1H, arom.), 7.10 (d, 1H, arom.), 7.23 (t, 2H, arom.), 7.36–7.61 (m, 4H, arom.), 7.60–7.78 (br, 2H, NH_2), 7.82 (d, 1H, arom.), 8.11 (d, 1H, arom.), 8.19 (s, 1H, arom.).

MS calcd. for $C_{22}H_{15}N_3OS$ = 369.0937, found *m*/e = 369.098 (M^+).

Method (B)

A solution of stannous chloride dihydrate (280 mg) in hydrochloric acid (2 ml) was added with stirring to a solution of **3c** (100 mg, 0.25 mmol) in acetic acid (5 ml) and the mixture was stirred for 1 h at room temperature. The precipitate was collected by filtration and suspended in water (20 ml), following by the gradual addition of ferric chloride solution (1.2%, 5 ml). The mixture was stirred for 0.5 h at room temperature. The precipitate was collected and chromatographed on an aluminium oxide column using benzene as an eluent. The solid obtained on concentration of the eluate was recrystallized from benzene and identified (IR, ^{1}H-NMR, and MS) as **3d**. Yield 87%.

4-Acetylamino-6-anilino-5H-benzo[a]phenothiazin-5-one (**3e**)

Method (A)

A solution of **2** (80 mg, 0.64 mmol) in pyridine (5 ml) was gradually added with stirring to a solution of 5-acetylamino-3-anilino-2-chloro-1,4-naphthoquinone (**1e**) (170 mg, 0.5 mmol) in pyridine and the mixture was stirred for 4.5 h. The precipitate was collected and recrystallized from dimethyl sulfoxide.

Compound **3e** gave violet crystals; m.p. 257 °C. Yield 92%.

IR (KBr): 1597, 1688 (C=O).

^{1}H-NMR ($CDCl_3$): 2.50 (s, 3H, CH_3), 6.75 (d, 2H, arom.), 7.16 (s, 1H, NH), 7.32–7.58 (m, 5H, arom.), 7.98 (d, 1H, arom.), 8.80 (d, 1H, arom.), 9.09 (d, 1H, arom.), 12.51 (s, 1H, CONH).

MS calcd. for $C_{24}H_{17}N_3O_2S$ = 411.1043, found *m*/e = 411.1057 (M^+).

Method (B)

A mixture of **3d** (41 mg, 0.11 mmol), acetic acid (5 ml), and acetic anhydride (5 ml) was stirred for 1.5 h at room temperature and then poured into cold water (300 ml). The resulting solid was collected, washed with water, dried, and chromatographed on an aluminium oxide column using benzene as an eluent. The residue obtained on concentration of the eluate was recrystallized from dimethyl sulfoxide and identified (m.p., IR, ^{1}H-NMR, and MS) as **3e**. Yield 70%.

1-Amino-6-anilino-5H-benzo[a]phenothiazin-5-one (**3f**)

The compound **3f** was prepared by the reduction of **3a** in a similar way as **3d**. Compound **3f** gave violet crystals; m.p. 287 °C. Yield 91%.

IR (KBr): 1619 (C=O).

^{1}H-NMR (*DMSO-d_6*): 6.71 (d, 2H, arom.), 6.83 (t, 1H, arom.), 7.15–7.32 (m, 3H, arom.), 7.40–7.60 (m, 3H, arom.), 7.65 (d, 1H, arom.), 7.99 (d, 1H, arom.), 8.12 (s, 1H, arom.), 8.35–8.68 (br, 2H, NH_2).

MS calcd. for $C_{22}H_{15}N_3OS$ = 369.0937, found *m/e* = 369.0895 (M^+).

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