Synthesis of Benzophenothiazinone Derivatives from 2,3,5-Trisubstituted-1,4-naphthoquinones with 2-Aminothiophenol

Seiko Nan'ya*, Eturô Maekawa, Wen-Bing Kang and Yoshio Ueno

Department of Applied Chemistry, Nagoya Institute of Technology,
Gokiso, Showa-ku, Nagoya-shi 466, Japan

Received August 19, 1985

The 1-substituted-5*H*-benzo[2,3-*a*]phenothiazin-5-one, 4-substituted-5*H*-benzo[6,5-*a*]phenothiazin-5-one and 6-substitutedbenzo[a][1,4] benzothiazino[3,2-*c*]phenothiazine derivatives were prepared by the condensation of 5-substituted-2,3-dichloro-1,4-naphthoquinones with 2-aminothiophenol. Reduction, acetylation and dehalogenation of the resulting compounds were carried out and the structures of the products were inferred from comparison with the authentic compound.

J. Heterocyclic Chem., **23**, 589 (1986).

Phenoxazinone and phenothiazinone derivatives have received remarkable attention because of the considerable biological and pharmaceutical activities of the iminoquinones. Some of these derivatives have been prepared as stable cyclic iminoquinones [1-5]. We have previously reported that 5*H*-pyrido[2,3,-*a*]-and 5*H*-pyrido[3,2-*a*]phenoxazin-5-one derivatives were prepared by the condensation of substituted-2-aminophenols with 6,7-dibromo-5,8-quinolinquinone [6].

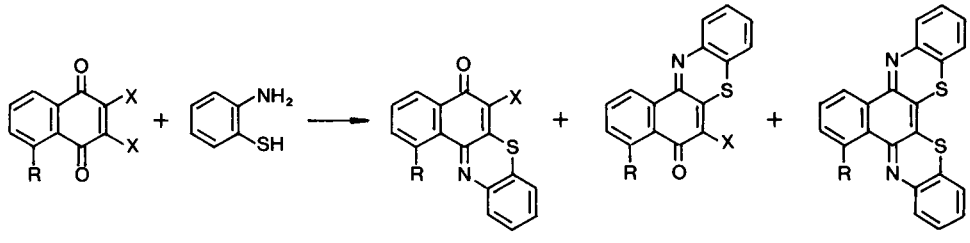
In this work, 1-substituted-5*H*-benzo[2,3-*a*]phenothiazin-5-ones **3**, 4-substituted-5*H*-benzo[6,5-*a*]phenothiazin-5-ones **4** and 6-substitutedbenzo[*a*][1,4]benzothiazino[3,2*c*]-phenothiazines **5** are obtained from 2,3,5-trisubstituted-1,4-naphthoquinones and 2-aminothiophenol (**2**).

The condensation between 5-substituted-2,3-dichloro-1, 4-naphthoquinones **1a**,**b** and **d** and **2** in ethanol in the presence of 15% hydrochloric acid or in pyridine produce **3a**, **b** and **d**, **4a**, **b** and **d** and **5a**, **b** and **d**. In the case of **1b** with **2** the reaction barely occured in ethanol in the presence of 15% hydrochloric acid. The facility in condensation and the ratio of the products **3**/**4** may depend on the properties of the substituents in the 5-position of the compound **1**. The relationships between reactivities and substituents are subject to the further investigation.

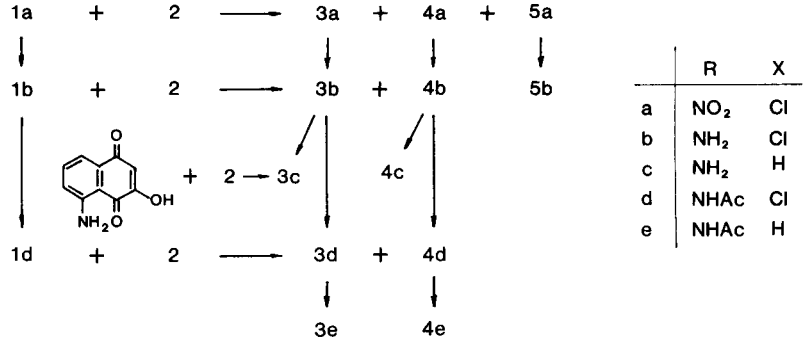
The reduction of the compounds **3a**, **4a** and **5a** in acetic acid in the presence of stannous chloride and hydrochloric acid afforded **3b**, **4b**, and **5b**, in good yield respectively.

The dehalogenation of the compounds **3b** and **4b** in the presence of sodium hydrosulfite dissolved in aqueous pyridine under nitrogen atmosphere gave **3c** and **4c** respectively.

The structure of **3c** is identified by comparing its ir and



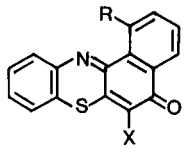
1 2 3 4 5



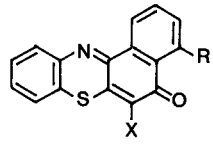
	R	X
a	NO_2	Cl
b	NH_2	Cl
c	NH_2	H
d	NHAc	Cl
e	NHAc	H

Table 1

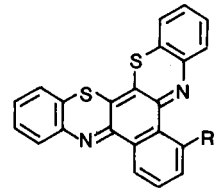
Analytical Data for Compounds **3**, **4** and **5**



3



4



5

Compound	R	X	Mp(°C) (recrystallized)	Molecular Formula	Mass (M^+) [a] (relative intensity %)	Elemental Analyses (%) Found/(Calcd.) C	H	N
3a	NO_2	Cl	305.5-306.0 (Benzene)	$C_{16}H_7ClN_2O_3S$ (342.8)	342/344 (100) (41)	56.22 (56.07)	1.91 (2.06)	8.04 (8.17)
4a	NO_2	Cl	305.0-306.0 (Benzene)	$C_{16}H_7ClN_2O_3S$ (342.8)	342/344 [A] (100) (36)	56.26 (56.07)	1.95 (2.06)	8.05 (8.17)
5a	NO_2	–	343.5-345.0 (Benzene)	$C_{22}H_{11}N_3O_2S_2$ (413.5)	413	63.84 (63.91)	2.56 (2.68)	10.03 (10.16)
3b	NH_2	Cl	254.5-255.5 (Benzene)	$C_{16}H_9ClN_2OS$ (312.8)	312/314 (100) (36)	61.68 (61.44)	3.06 (2.90)	8.68 (8.96)
4b	NH_2	Cl	297.0-298.5 (Benzene)	$C_{16}H_9ClN_2OS$ (312.8)	312/314 (100) (37)	61.66 (61.44)	2.65 (2.90)	9.10 (8.96)
5b	NH_2	–	316.0-318.0 (Benzene)	$C_{22}H_{13}N_3S_2$ (383.5)	383	69.14 (68.90)	3.28 (3.42)	10.59 (10.96)
3c	NH_2	H	259.0-261.0 (Benzene)	$C_{16}H_{10}N_2OS$ (278.3)	278	69.32 (69.05)	3.34 (3.62)	10.21 (10.06)
4c	NH_2	H	234.5-236.5 (Benzene)	$C_{16}H_{10}N_2OS$ (278.3)	278	69.45 (69.05)	3.54 (3.62)	9.69 (10.06)
3d	NHAc	Cl	314.0-316.0 (Acetone)	$C_{18}H_{11}ClN_2O_2S$ (354.8)	354/356 [A] (100) (43)	61.15 (60.93)	2.87 (3.13)	7.80 (7.90)
4d	NHAc	Cl	344.0-346.5 (Acetic acid)	$C_{18}H_{11}ClN_2O_2S$ (354.8)	354/356 [A] (100) (39)	61.35 (60.93)	3.07 (3.13)	7.69 (7.90)
3e	NHAc	H	249.8-251.5 (Benzene)	$C_{18}H_{12}N_2O_2S$ (320.4)	320 [A]	67.50 (67.48)	3.57 (3.78)	8.76 (8.74)
4e	NHAc	H	261.5-263.0 (Benzene)	$C_{18}H_{12}N_2O_2S$ (320.4)	320 [A]	67.82 (67.48)	3.77 (3.78)	8.32 (8.74)

[a] Molecular ion peaks were base peaks except [A] marked data.

mass spectrum and mixed melting point with authentic sample which was prepared by the reaction of 8-amino-2-hydroxy-1,4-naphthoquinone with **2** in acetic acid at 100° for 1 hour. From this identification and the spectroscopic data as well as elemental analyses, the structures of **3**, **4** and **5** are inferred as Scheme 1.

The compounds **3d**, **4d** and **5d** were also obtained by the acetylation of **3b**, **4b** and **5b** respectively. The compounds **3d** and **4d** gave **3e** and **4e** by the dehalogenation under the same conditions with **3b** and **4b**.

The nmr spectra of **3c,e** and **4c,e** exhibited a characteristic singlet at 6.68-6.98 ppm due to an olefinic proton which is substituted for the chlorine atom of **3b,d** and **4b,d**. The signal at 13.64, 13.82 or 12.58, 12.68 are assigned to the amino proton of acetylamino group of **3d,e** and **4d,e**.

The absorption maxima of **4b,c,d,e** in uv spectra show a red shift to that of the coresponding **3b,c,d,e** compounds. This fact suggests the greater participation of the 4-amino or the 4-acetylamino group of **4b,c,d,e** on hydrogen bonding than that of the 1-amino or the 1-acetylamino group of **3b,c,d,e**.

The analytical data for the compounds obtained in these reactions are listed in Table 1.

EXPERIMENTAL

Melting points were determined on a Yanaco micro-melting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer for potassium bromide disk and the ultraviolet spectra were recorded with a JASCO UVIDEC-505. The nuclear magnetic resonance spectra were measured on a Varian XL-200 spectrometer, using tetramethylsilane as the internal standard. Some of the

compounds were recorded for 0.5% w/v solutions operating in an FT mode. Mass spectra were obtained with a Hitachi M-52 spectrometer. For column chromatography, aluminium oxide 90 (Merck, 70-230 mesh ASTM) and Kieselgel 60 (Merck, 70-230 mesh ASTM) were used. One of the starting materials, 2-aminothiophenol was purchased from Tokyo Kasei Kogyo Co., Ltd.

Condensation of 2,3-Dichloro-5-nitro-1,4-naphthoquinone (**1a**) with 2-Aminothiophenol (**2**).

To a stirred suspension of 816 mg (3 mmoles) of **1a** [7] in 60 ml of ethanol was added dropwise a solution of 338 mg (2.7 mmoles) of **2** in 20 ml of 15% hydrochloric acid over 25 minutes. After stirring at room temperature for an additional 30 minutes, the mixture was filtered. The residue was column chromatographed on aluminium oxide using benzene as the eluent. From the first blue fraction 20 mg of 6-nitrobenzo [*a*][1,4]benzothiazino[3,2-*c*]phenothiazine (**5a**) was obtained, then from the second red fraction 712 mg of 6-chloro-1-nitro-5*H*-benzo[2,3-*a*]phenothiazin-5-one (**3a**) and from the third red fraction 107 mg of 6-chloro-4-nitro-5*H*-benzo[6,5-*a*]phenothiazin-5-one (**4a**) were obtained. The overall yield of the products based on **2** was 92% in the ratio of 6.7:1.0:0.2 (**3a**:**4a**:**5a**).

Compound **3a**.

This compound had ir: (cm^{-1}) 1643 (C=O), 1510 and 1368 (NO_2); uv (chloroform): λ max, nm (log ε), 495 (4.08), 387 (3.96), 368 (sh, 399), 323 (4.27), 261 (4.37), 240 (4.37); ^1H nmr (deuteriochloroform): δ 8.65 (d, 1H), 7.96-7.77 (m, 3H), 7.63 (m, 3H).

Compound **4a**.

This compound had ir: (cm^{-1}) 1635 (C=O), 1507 and 1372 (NO_2); uv (chloroform): λ max, nm (log ε), 497 (4.09), 387 (3.99), 371 (4.01), 352 (4.03), 322 (4.16), 260 (4.36), 242 (4.37); ^1H nmr (deuteriochloroform): δ 9.20 (d, 1H), 8.14-8.08 (m, 1H), 7.93 (t, 1H). 7.82-7.60 (m, 4H).

Compound **5a**.

This compound had ir: (cm^{-1}) 1530 and 1375 (NO_2); uv (chloroform): λ max, nm (log ε), 590 (sh, 4.21), 557 (4.26), 375 (4.23), 351 (4.27), 277 (4.68; ^1H nmr (deuteriochloroform): δ 8.02-7.56 (m, 4H), 7.50-7.33 (m,7H).

Condensation of 5-Amino-2,3-dichloro-1,4-naphthoquinone (**1b**) with **2**.

To a stirred solution of 242 mg (1 mmole) of **1b** [7] in 20 ml of pyridine was added a solution of 138 mg (1.1 mmoles) of **2** in 7 ml of pyridine over 5 minutes. After stirring for 1 hour the mixture was evaporated *in vacuo*. The residue was chromatographed on aluminium oxide column using benzene-ethyl acetate (20:1) as eluent. The resulting red fraction was chromatographed on Silica gel using benzene as eluent. From the first red fraction 191 mg of 1-amino-6-chloro-5*H*-benzo[2,3-*a*]phenothiazin-5-one (**3b**) and from the second red fraction 49 mg of 4-amino-6-chloro-5*H*-benzo[6,5*a*]phenothiazin-5-one (**4b**) were obtained. The over all yield of **3b** and **4b** was 77% in the ratio of 3.9:1.

Compound **3b**.

This compound had ir: (cm^{-1}) 3380 (NH), 1620 (C=O); uv (chloroform): λ max, nm (log ε), 515 (sh, 4.12), 484 (4.14), 379 (3.92), 363 (3.96), 335 (3.96), 305 (4.23), 246 (4.57); ^1H nmr (dimethylsulfoxide-d_6): δ 8.62 (br, 1H), 8.09 (d, 1H), 7.89 (d, 1H), 7.66-7.46 (m, 3H), 7.40 (s, 2H), 7.32 (m, 1H).

Compound **4b**.

This compound had ir: (cm^{-1}) 3390 and 3280 (NH), 1600 (C=O); uv (chloroform): λ max, nm (log ε), 542 (4.05), 470 (sh, 3.73), 442 (sh, 3.61), 380 (3.90), 360 (3.99), 343 (sh, 4.03), 327 (4.03), 281 (4.13), 250 (4.56); ^1H nmr (dimethylsulfoxided$_6$): δ 8.07 (d, 1H), 7.95-7.71 (m, 4H), 7.65-7.48 (m, 3H), 7.12 (d, 1H).

Reduction of **3a**, **4a** and **5a**.

To a stirred suspension of 171 mg (0.5 mmole) of **3a** in 8ml of acetic acid was added a solution of 580 mg (2.5 mmoles) of stannous chloride in 4 ml of hydrochloric acid at room temperature over 5 minutes. After stirring for 30 minutes, the mixture was filtered. To a suspension of resulting solid in 30 ml of water, a solution of ferric chloride in water (5 ml) was added dropwise under stirring. After stirring for 1 hour, the product was filtered and washed with water. The yield of the dark blue crystals was 85%. This is identical with **3b** which was prepared above from **1b** and **2**.

Similarly **4a** and **5a** were reduced to **4b** and **5b** in 80% and 92% yield respectively.

Compound **5b**.

This compound had ir: (cm^{-1}) 3445 (NH); uv (chloroform): λ max, nm (log ε), 575 (sh, 4.20), 530 (4.33), 377 (4.10), 323 (4.10), 266 (4.73); ^1H nmr (dimethylsulfoxide-d_6): δ 8.35 (br, 2H), 8.07 (d, 1H), 7.77-7.58 (m, 4H), 7.43 (m, 5H), 7.33 (d, 1H).

Condensation of 5-Acetylamino-2,3-dichloro-1,4-naphthoquinone (**1d**) with **2**.

After the treatment of **1d** [7] with **2** in the similar manner as the condensation of **1a** with **2**, the residue was chromatographed on Silica gel column using benzene-ethyl acetate (4:1) as eluent. From the first fraction **1d** was recovered. Then from the second fraction 4-acetylamino-6-chloro-5*H*-benzo[6,5-*a*]phenothiazin-5-one (**4d**) and from the third fraction 1-acetylamino-6-chloro-5*H*-benzo[2,3-*a*]phenothiazin-5-one (**3d**) were obtained. The total yield of **3d** and **4d** based on used **1d** was 82% in the ratio of 0.7:1.

Compound **3d**.

This compound had ir: (cm^{-1}) 1685 and 1630 (C=O); uv (chloroform): λ max, nm (log ε), 486 (4.14), 379 (3.96), 363 (3.95), 323 (4.19), 297 (4.15), 276 (4.14), 244 (4.58); ^1H nmr (dimethylsulfoxide-d_6): δ 13.64 (s, 1H, N*H*CO), 9.05 (d, 1H), 8.00 (m, 3H), 7.82 (t, 1H), 7.70 (m, 2H), 2,39 (s, 3H, COCH_3).

Compound **4d**.

This compound had ir: (cm^{-1}) 1690 and 1612 (C=O); uv (chloroform): λ max, nm (log ε), 512 (4.33), 379 (4.04), 363 (sh), 330 (4.27), 247 (4.78); ^1H nmr (deuteriochloroform): δ 12.58 (s, 1H, N*H*CO), 9.15 (d, 1H), 8.78 (d, 1H), 8.32 (s, 1H), 8.07 (m, 1H), 7.81 (m, 1H), 7.61 (m, 2H), 2.32 (s, 3H, COCH_3).

Acetylation of **3b** and **4b**.

The mixture of 0.1 mmole of **3b**, 3 ml of acetic acid and 3 ml of acetic anhydride was refluxed for 5 minutes to give reddish brown crystals in the yield of 80%. This is identical with **3d** which was prepared above from **1d** and **2**. Compound **4b** was similarly acetylated to **4d** with 73% yield.

Dehalogenation of **3b**, **4b**, **3d** and **4d**.

To a suspension of **3b** (0.5 mmole) in the mixture of benzene (7 ml), dioxane (13 ml) and water (12 ml) was added sodium hydrosulfite (5 mmoles) at room temperature under nitrogen atmosphere. After addition of pyridine (21 ml) the mixture was refluxed for 40 minutes. The product was extracted with benzene from the mixture and the organic layer was evaporated *in vacuo*. The residue was washed with water to afford 1-amino-5*H*-benzo[2,3-*a*]phenothiazin-5-one (**3c**) in the yield of 79%.

Compound **3c**.

This compound had ir: (cm^{-1}) 3325 (NH), 1620 (C=O); uv (chloroform): λ max, nm (log ε), 490 (4.16), 378 (3.96), 363 (3.99), 325 (4.00), 303 (4.25), 277 (4.14), 246 (4.60); ^1H nmr (dimethylsulfoxide-d_6): δ 8.01 (m, 1H), 7.89 (m, 1H), 7.60-7.42 (m, 4H), 7.28 (m, 1H), 6.98 (s, 1H), 3.74 (br, 2H, NH_2).

Compound **3c** was also prepared from **3a** with the same method above from **3b** in the yield of 81%.

Compound **4b**, **3d** and **4d** were dehalogenated in the similar manner to give 4-amino-5*H*-benzo[6,5-*a*]phenothiazin-5-one (**4c**) 1-acetylamino-5*H*-benzo[2,3-*a*]phenothiazin-5-one (**3e**) and 4-acetylamino-5*H*-benzo-[6,-5-*a*]phenothiazin-5-one (**4e**) in the yield of 78%, 77% and 93% respectively.

Compound **4c**.

This compound had ir: (cm^{-1}) 3390 and 3285 (NH), 1600 (C = O); uv (chloroform): λ max, nm (log ε), 533 (4.08), 378 (3.95), 359 (4.02), 322 (4.12), 278 (4.21), 248 (4.61); ^1H nmr (deuteriochloroform): δ 8.24 (d, 1H), 7.84 (m, 1H), 7.56-7.36 (m, 4H), 7.02-6.95 (m, 1H) 6.68 (s, 1H), 2.17 (br, 2H, NH_2).

Compound **3e**.

This compound had ir: (cm^{-1}) 1685 and 1625 (C = O); uv (chloroform): λ max, nm (log ε), 479 (4.22), 377 (4.06), 361 (4.05), 317 (4.30), 294 (4.27), 274 (4.30), 242 (4.52); ^1H nmr (deuteriochloroform): δ 13.82 (s, 1H, CONH), 9.16 (d, 1H), 8.10 (d, 1H), 7.73 (m, 2H), 7.62-7.44 (m, 3H), 6.86 (s, 1H), 2.40 (s, 3H, $COCH_3$).

Compound **4e**.

This compound had ir: (cm^{-1}): 1687 and 1610 (C = O); uv (chloroform): λ max, nm (log ε), 503 (4.33), 378 (4.05), 362 (4.05), 322 (4.34), 246 (4.76); ^1H nmr (deuteriochloroform): δ 12.68 (s, 1H, CONH), 9.10 (d, 1H), 8.69 (d, 1H), 7.98 (m, 1H), 7.76 (t, 1H), 7.60-7.45 (m, 3H), 6.77 (s, 1H), 2.31 (s, 3H, $COCH_3$).

Synthesis of 1-Amino-5*H*-benzo[2,3-*a*]phenothiazin-5-one.

A mixture of 8-amino-2-hydroxy-1,4-naphthoquinone [8], **2** and acetic acid was heated at 100° under stirring. To the resulting mixture was added water and extracted with benzene. After the benzene layer was evaporated *in vacuo* the residue was chromatogaphed on aluminium oxide column using benzene and benzene-ethyl acetate (20:1) as eluent. From benzene-ethyl acetate fraction dark violet crystals was obtained which is identical with **3c** prepared above from **3b**.

REFERENCES AND NOTES

[1] H. Beecken and H. Musso, *Chem. Ber.*, **94** 601 (1961).

[2] N. L. Agarwal and W. Schäfer, *J. Org. Chem.*, **45**, 2155 (1980).

[3] C. W. Bird and M. Latif, *Tetrahedron*, **36**, 529 (1980).

[4] M. Terdic, *Ann. Chem.*, **746**, 200 (1971).

[5] M. Akatsuka and S. Yoshinaga, *Yakugaku Zasshi*, **90**, 154 (1970); *Chem. Abstr.*, **72**, 100625 (1970).

[6] S. Nan'ya, E. Maekawa, H. Hayakawa, Y. Kitaguchi and Y. Ueno, *J. Heterocyclic Chem.*, **22**, (1985) in press.

[7] T. Kasai, T. Nakamori and K. Sekiguchi, *Nippon Kagaku Kaishi*, 1862 (1980).

[8] W. A. Remers, P. N. James and M. J. Weiss, *J. Org. Chem.*, **28**,1169 (1963).