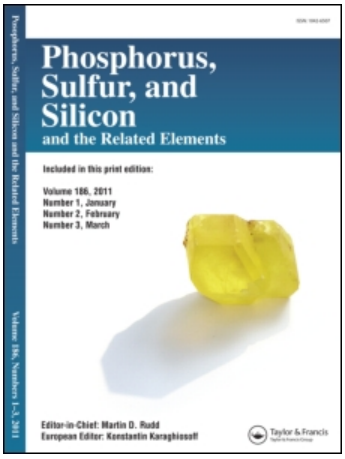

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N,N-DIALKYLAMINOALKYL SUBSTITUTED QUINOBENZO[1,4]THIAZINES AND DIQUINO[1,4]THIAZINES#

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N,N-DIALKYLAMINOALKYL SUBSTITUTED QUINOBENZO[1,4]THIAZINES AND DIQUINO[1,4]THIAZINES#

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12-(*N,N*-Dialkylaminoalkyl)quino[1,4]benzothiazines **2c-2g** were obtained by alkylation of 12*H*-quino[1,4]benzothiazines **2a** and **2b** with *N,N*-dialkylaminoalkyl chlorides in dioxane. 14*H*-Diquino[1,4]thiazine **4a** was unreactive in the same conditions. 14-(*N,N*-Dialkylaminoalkyl)diquino[1,4]thiazines **4b-4d** were synthesized in the annulation of 4,4′-dichloro-3,3′-diquinolinyl sulfide **3** with alkanediamines in hot phenol.

Keywords: Ring closure; diquinolinyl sulfides; quino[1,4]thiazines; 1,4-thiazine

INTRODUCTION

Phenothiazine derivatives attract attention because of their wide chemical properties and pharmaceutical activities.[1–6] Some modification of the phenothiazine structures were directed into azaphenothiazines, where the benzene ring was substituted with the azine ring.[3–5] Our interest in the chemistry of quinolinyl sulfides has brought original syntheses of new four or five ring heterocycles, where quinoline moiety was condensed directly with thiopyran, 1,4-dithiin, 1,4-oxathiin, 1,4-thiaselenin and 1,4-thiazine rings.[7–9] In continuation of our search for pharmacoactive quinolines, we now describe methods of synthesis of quino[3,4-b][1,4]benzothiazines and diquino[3,4-b;4′,3′-e][1,4]thiazines (being benzo- and dibenzoazaphenothiazines) with the *N,N*-dialkylaminoalkyl substituent attached to the thiazine nitrogen.

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We found thioquinanthrene **1** (1,4-dithiino[2,3-c;5,6-c′]diquinoline – easy to obtain by direct sulfurization of quinoline with elemental sulfur[10] to be a very useful substrate for synthesis of 3,4-disubstituted quinolines. For example, fusion of thioquinanthrene **1** with arylamine hydrochlorides at 200°C led to 12*H*-unsubstituted quino[1,4]benzothiazines **2a** and **2b** via ring opening – ring closure reactions.[7] Next reactions of 4,4′-dichloro-3,3′-diquinolinyl sulfide **3** (easy to obtain in two steps from thioquinanthrene **1**[11,12] with ammonia and alkyl-, aryl- and hetarylamines in monomethyl ether of diethylene glycol at 194°C or in hot phenol at 180°C gave 14*H*- and 14-substituted diquino[1,4]thiazines **4a** and **4** (substituent = alkyl, aryl and hetaryl).[9]

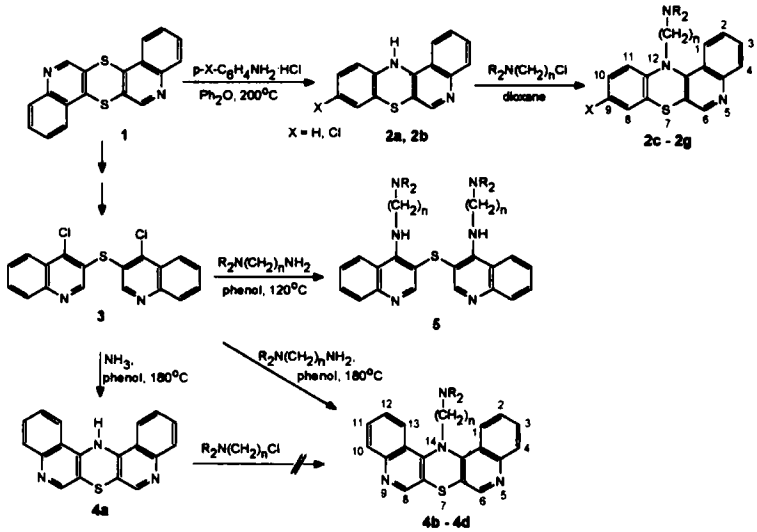
As drugs with the phenothiazine and azaphenothiazine moieties contain an *N,N*-dialkylaminoalkyl substituent attached to the thiazine nitrogen[3–5] we undertook further study to find a procedure to obtain the *N,N*-dialkylaminoalkyl derivatives (**2c-2g** and **4b-4d**) of quino[1,4]benzothiazines **2** and diquino[1,4]thiazines **4**.

RESULTS AND DISCUSSION

Although 12-*N,N*-dialkylaminoalkylquino[1,4]benzothiazines **2c-2g** and 14-*N,N*-dialkylaminoalkyldiquino[1,4]thiazines **4b-4d** are quite similar (being at last quinothiazines and diquinothiazines), we were not able to work out an universal method of synthesis of them.

As the original synthesis of 12*H*-quino[1,4]benzothiazine **2a** was performed in fusion conditions using 2.5 mmoles of thioquinanthrene **1**, we improved the procedure in large scale (80 mmoles) employing diphenyl ether as the reaction solvent, what enabled better stirring of the reagents. This procedure afforded the yield increase of thiazine as free base from 30% to 49%. The same procedure employed in synthesis of 12*H*-9-chloroquino[1,4]benzothiazine **2b** brought the yield increase from 28% to 37%. Unfortunately, the same procedure to obtain *N*-substituted thiazines **2** in the reaction of thioquinanthrene with secondary alkylarylamine (N-methylaniline) failed giving mainly 12*H*-unsubstituted thiazine **2a**. Therefore we worked out a method of synthesis by N-alkylation of *N*-unsubstituted thiazines **2a** and **2b** with *N,N*-dialkylaminoalkyl chlorides in dioxane in the presence of sodium hydroxide and catalytic amounts of triethylbenzylam-

monium chloride. In this way we obtained five 12-(*N,N*-dialkylaminoalkyl)quino[1,4]benzothiazines **2c-2g** with the *N,N*-dimethylethyl-, *N,N*-dimethylpropyl and (1-methyl-2-piperidyl)ethyl substituents in 42–58% yield.



	X	n	NR_2		n	NR_2
2c	H	2	NMe_2	**4b**	2	NH_2
2d	H	3	NMe_2	**4c**	2	NEt_2
2d	H	2	1-Me-2-pyridyl	**4d**	3	NMe_2
2f	Cl	3	NMe_2	**5**	2	NEt_2
2g	Cl	2	1-Me-2-pyridyl			

SCHEME 1

Application of this method in synthesis of 14-(*N,N*-dialkylaminoalkyl)diquino[1,4]thiazines **4b-4g** unexpectedly failed. Even alkylation in DMF in the presence of sodium hydride, which was very effective in a introduction of the methyl, allyl and benzyl group into 14*H*-diquinothiazine **4a**[9], was unsuccessful. It seems to be a result both of weakness of alkylating agent and accessibility of the thiazine nitrogen atom. Only the annulation of 4,4′-dichloro-3,3′-diquinolinyl sulfide **3** with alkanedi-

amines (ethylenediamine, *N,N*-diethylaminoethylamine and *N,N*-dimethylaminopropylamine) in phenol at 180°C was effective. We obtained three 14-(aminoalkyl)diquinothiazines **4b-4d** in relatively good yield (53–55%). Abatement of the reaction temperature from 180°C to 120°C favoured the formation of the disubstitution product, possessing two *N,N*-diethylaminoethylamino groups – 4,4′-di(*N,N*-diethylaminoethylamino)-3,3′-diquinolinyl sulfide **5**(R = Et, n = 2) in 58%.

Analysis of changes in chemical shifts of the H-1 protons in thiazines **2a** and **4a** (7.95 and 8.03 ppm[9]) in comparison with the adequate proton in quinoline (7.78 ppm[13]) being a result of the peri effect of the *N*-substituent and the plane of symmetry in thiazines **2** and **4** indicate lack of a stage of the S-N type of the Smiles rearrangement of the appropriate quinolinyl sulfides during formation of thiazines **2** and **4**. The *N*-substituent has also an influence on the chemical shift of the H-6 proton causing downfield shift by 0.18–0.27 ppm in comparison with the signals in *N*-unsubstituted thiazines (8.48–8.51 ppm in **2c-2g** *vs* 8.30 ppm in **2a**, and 8.61–8.66 ppm in **4b-4d** *vs* 8.39 ppm in **4a**[9]).

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 and a UNITYplus-300 spectrometers at 300 MHz in deuteriochloroform with tetramethylsilane as the internal standard. EIMS spectra were run on a LKB 9000S spectrometer at 15 eV. FAB MS spectrum was recorded on a Finnigan MAT 95 spetrometer in FAB mode (Cs^+, 13 keV, nitrobenzyl alcohol).

Thioquinanthrene **1**[10], 4,4′-dichloro-3,3′-diquinolinyl sulfide **3**[11,12] and thiazine **4a**[9] were obtained according to the references.

Synthesis of 12H-quino[1,4]benzothiazine 2a

To a suspension of thioquinanthrene **1** (25.6 g; 80 mmoles) in diphenyl ether (250 ml) at 200°C aniline hydrochloride (41.6 g; 320 mmoles) was added portionally. The reaction mixture was stirred at this temperature for 9 hours. After cooling down to 80°C the resulting solid was filtered off,

washed with toluene and air-dried to give a crude product. The solid was triturated with hot water (2000 ml) and resulting red solution was alkalized at room temterature with 30% aqueous sodium hydroxide to pH = 8. A yellow precipitate was filtered off, washed with water, air-dried and recrystallized from 96% ethanol to give 12*H*-quino[1,4]benzothiazine **2a** (19.4 g; 49%), mp 220–221°C, lit.[7] mp 225–226°C. ^{1}H NMR ($CDCl_3$): δ, ppm, 6.68 (m, 1H, H_{arom}), 6.75 (broad, 1H, NH), 6.91 (m, 1H, H_{arom}), 6.99 (m, 1H, H_{arom}), 7.03 (m, 1H, H_{arom}), 7.49 (m, 1H, H-2), 7.60 (m, 1H, H-3), 7.66 (m, 1H, H-4), 7.95 (m, 2H, H-1), 8.30 (s, 1H, H-6).

Synthesis of 12H-9-chloroquino[1,4]benzothiazine 2b

The reaction was carried out as described above using 4-chloroaniline hydrochloride (52.2 g; 320 mmoles). Recrystallization from ethanol gave 12*H*-9-chloroquino[1,4]benzothiazine **2b** (13.0 g; 37%), mp 195–196°C, lit.[9] mp 199–200°C.

Synthesis of 12-(N,N-dialkylaminoalkyl)quino[1,4]benzothiazines 2c-2g. General procedure

A mixture of 12*H*-quino[1,4]benzothiazine **2a** (2.0 g; 8 mmoles) or 12*H*-9-chloroquino[1,4]-benzothiazine **2b** (2.0 g; 7 mmoles), powdered sodium hydroxide (3.2 g; 80 mmoles) and triethylbenzylammonium chloride (0.286 g; 1 mmole) in dry dioxane (50 ml) was stirred and heated to 90°C. *N,N*-Dialkylaminoalkyl (*N,N*-dimethylaminoethyl, *N,N*-dimethylaminopropyl or (1-methyl-2-piperidyl)ethyl) chloride (15 mmoles) was added portionally and the mixture was stirred for 4 hours. After cooling down to room temperature the mixture was poured into water (200 ml) and extracted with toluene (5 × 40 ml). The extract was dried with anhydrous calcium chloride and the solvent was evaporated in vacuo to give crude product. The product was purified by column chromatography (silica gel 60, chloroform) to give 2-(*N,N*-dialkylaminoalkyl)quino[1,4]benzothiazines **2c-2g**

2c: yellow oil, yield 58%. ^{1}H NMR ($CDCl_3$,): δ 2.11 (s, 6H, 2Me), 2.57 (t, J = 7.4 Hz, 2H, CH_2), 4.21 (t, J = 7.4 Hz, 2H, CH_2), 7.02 (m, 1H, H_{arom}), 7.13 (m, 1H, H_{arom}), 7.19 (m, 1H, H_{arom}), 7.20 (m, 1H, H_{arom}), 7.48 (m, 1H, H-2), 7.59 (m, 1H, H-3), 8.00 (m, 2H, H-1, H-4), 8.49 (s, 1H, H-6). MS (15 eV), m/z (%) = 321 (M^+, 100), 290 (M-CH_3NH_2, 20), 263

(M-C_3H_8N, 15), 250 (M-C_4H_9N, 72). Anal. Calcd. for $C_{19}H_{19}N_3S$ (321.43) C, 71.00; H, 5.96; N, 13.07; S, 9.97. Found C, 70.91; H, 6.16; N, 13.01; S, 9.79.

2d: yellow oil, yield 49%. ^1H NMR ($CDCl_3$,): δ 2.02 (m, J = 7.0 and 7.3 Hz, 2H, CH_2), 2.33 (s, 6H, 2Me), 2.70 (t, J = 7.3 Hz, 2H, CH_2), 4.27 (t, J = 7.0 Hz, 2H, CH_2), 7.04 (m, 1H, H_{arom}), 7.15 (m, 1H, H_{arom}), 7.17 (m, 1H, H_{arom}), 7.24 (m, 1H, H_{arom}), 7.50 (m, 1H, H-2), 7.62 (m, 1H, H-3), 7.95 (m, 1H, H-4), 8.02 (m, 1H, H-1), 8.50 (s, 1H, H-6). MS (15 eV), m/z (%) = 335 (M^+, 31), 263 (M-$C_4H_{10}N$, 13), 250 (M-$C_5H_{11}N$, 100). Anal. Calcd. for $C_{20}H_{21}N_3S$ (335.46) C, 71.61; H, 6.31; N, 12.53; S, 9.56. Found C, 71.39; H, 6.49; N, 12.41; S, 9.35.

2e: yellow oil, yield 49%. ^1H NMR ($CDCl_3$,): δ 1.16–2.11 (m, 8H,), 1.97–2.09 (m, 2H, CH_2), 2.05 (s, 3H, NMe), 2.80 (m, 1H, NCH), 4.08–4.29 (m, 1H, NCH_2), 4.29 (m, 2H, CH_2), 7.02 (m, 1H, H_{arom}), 7.14 (m, 1H, H_{arom}), 7.17 (m, 1H, H_{arom}), 7.22 (m, 1H, H_{arom}), 7.49 (m, 1H, H-2), 7.60 (m, 1H, H-3), 8.00 (m, 1H, H-4), 8.01 (m, 1H, H-1), 8.49 (s, 1H, H-6). MS (15 eV), m/z (%) = 375 (M^+, 7), 264 (M-$C_7H_{13}N$, 1), 250 (M-$C_8H_{15}N$, 2), 98 ($C_6H_{12}N^+$, 100). Anal. Calcd. for $C_{23}H_{25}N_3S$ (375.53) C, 73.56; H, 6.71; N, 11.19; S, 8.54. Found C, 73.32; H, 6.88; N, 11.10; S, 8.43.

2f: yellow oil, yield 46%. ^1H NMR ($CDCl_3$,): δ 1.81 (m, J = 6.9 and 7.0 Hz, 2H, CH_2), 2.06 (s, 6H, 2Me), 2.29 (t, J = 7.0 Hz, 2H, CH_2), 4.15 (t, J = 6.9 Hz, 2H, CH_2), 7.07 (m, 1H, H_{arom}), 7.12 (m, 1H, H_{arom}), 7.17 (m, 1H, H_{arom}), 7.50 (m, 1H, H-2), 7.62 (m, 1H, H-3), 8.00 (m, 1H, H-4), 8.02 (m, 1H, H-1), 8.48 (s, 1H, H-6). MS (15 eV), m/z (%) = 369 (M^+, 7), 371 (M^++2, 3), 283 (M-$C_5H_{12}N$, 3), 58 ($CH_2NMe_2^+$, 100). Anal. Calcd. for $C_{20}H_{20}ClN_3S$ (369.91) C, 64.94; H, 5.45; N, 11.36; S, 8.67. Found C, 64.71; H, 5.66; N, 11.15; S, 8.42.

2g: yellow oil, yield 42%. ^1H NMR ($CDCl_3$,): δ 1.18–2.31 (m, 10H), 2.35 (s, 3H, NMe), 2.55–3.24 (m, 3H, NCH_2 and NCH), 4.17–4.51 (m, 2H, NCH_2), 7.16 (m, 2H, H_{arom}), 7.23 (m, 1H, H_{arom}), 7.55 (m, 1H, H-2), 7.66 (m, 1H, H-3), 7.97 (m, 1H, H-4), 8.04 (m, 1H, H-1,) 8.51 (s, 1H, H-6). MS (15 eV), m/z (%) = 409 (M^+, 8), 411 (M^++2, 3), 283 (M-$C_8H_{16}N$, 39), 98 ($C_6H_{12}N^+$, 100). Anal. Calcd. for $C_{23}H_{24}ClN_3S$ (409.97) C, 67.38; H, 5.90; N, 10.25; S, 7.82. Found C, 67.07; H, 6.14; N, 10.02; S, 7.49

Synthesis of 14-aminoalkyl- and 14-(N,N-dialkylaminoalkyl)diquino [1,4]thiazines 4b-4d. General procedure

A solution of 4,4′-dichloro-3,3′-diquinolinyl sulfide **3** (0.36 g; 1 mmole) in phenol (2g) at 180°C alkanediamines (*N,N*-diethylaminoethylamine, *N,N*-dimethylaminopropylamine or ethylenediamine; 5 mmoles) was added portionally during 1 hour. After cooling down water was added and phenol was distilled off. The crude product was filtered off, washed with water, air-dried and purified by column chromatography (silica gel 60, chloroform) to give 4-aminoalkyl- and 14-(*N,N*-dialkylaminoalkyl)diquino[1,4]thiazines **4b-4d**.

4b: yellow crystals, yield 55%, m.p. 65–66°C. ^{1}H NMR ($CDCl_3$,): δ 1.87 (broad, NH_2), 2.85 (t, J = 6.7 Hz, 2H, CH_2), 4.24 (t, J = 6.7 Hz, 2H, CH_2), 7.64 (m, 2H, H-2, H-12), 7.71 (m, 2H, H-3, H-11), 8.12 (m, 2H, H-4, H-10), 8.31 (m, 2H, H-1, H-13), 8.66 (s, 2H, H-6, H-8). MS (15 eV), m/z (%) = 344 (M^+, 39), 314 (M-CH_2NH_2, 42), 301 (M-$C_2H_3NH_2$, 100). Anal. Calcd. for $C_{20}H_{16}N_4S$ (344.43) C, 69.74; H, 4.68; N, 16.27; S, 9.31. Found C, 69.67; H, 4.81; N, 16.09; S, 9.22.

4c: yellow crystals, yield 53%, m.p. 82–83°C. ^{1}H NMR ($CDCl_3$,): δ 0.68 (t, J = 7.1 Hz, 6H, 2Me), 2.28 (q, J = 7.1 Hz, 4H, $2CH_2$), 2.67 (t, J = 7.6 Hz, 2H, CH_2), 4.21 (t, J = 7.6 Hz, 2H, CH_2), 7.65 (m, 2H, H-2, H-12), 7.71 (m, 2H, H-3, H-11), 8.10 (m, 2H, H-4, H-10), 8.32 (m, 2H, H-1, H-13), 8.64 (s, 2H, H-6, H-8). MS (15 eV), m/z (%) = 400 (M^+, 50), 327 (M-$NHEt_2$, 1), 314 (M-CH_2NEt_2, 27), 300 (M-$C_2H_4NEt_2$, 5), 86 ($CH_2NEt_2^+$, 100). Anal. Calcd. for $C_{24}H_{24}N_4S$ (400.54) C, 71.97; H, 6.04; N, 13.99; S, 8.00. Found C, 71.79; H, 6.20; N, 13.89; S, 7.95.

4d: yellow oil, yield 54%, ^{1}H NMR ($CDCl_3$,): δ 1.85 (m, J = 7.5 and 7.8 Hz, 2H, CH_2), 2.06 (s, 6H, 2Me), 2.20 (t, J = 7.5 Hz, 2H, CH_2), 4.14 (t, J = 7.8 Hz, 2H, CH_2), 7.63 (m, 2H, H-2, H-12), 7.70 (m, 2H, H-3, H-11), 8.10 (m, 2H, H-4, H-10), 8.28 (m, 2H, H-1, H-13), 8.61 (s, 2H, H-6, H-8). MS (15 eV), m/z (%) = 386 (M^+, 30), 301 (M-$C_3H_5NMe_2$, 27), 86 ($CH_2NEt_2^+$, 100). Anal. Calcd. for $C_{23}H_{22}N_4S$ (386.51) C, 71.47; H, 5.74; N, 14.50; S, 8.29. Found C, 71.35; H, 5.81; N, 14.42; S, 8.21.

Synthesis of 4,4′-di(N,N-diethylaminoethylamino)-3,3′-diquinolinyl sulfide 5

The reaction was carried out at 120°C in the way described above. The crude product was purified by column chromatography (silica gel 60, chloroform) to give 4,4′-di(*N,N*-diethylaminoethylamino)-3,3′-diquinolinyl sulfide **5** (0.25 g; 58.1 %); mp 136–137°C. ^{1}H NMR ($CDCl_3$): δ, ppm, 1.06 (t, J = 7.1 Hz, 12H, 4Me), 2.63 (q, J = 7.1 Hz, 8H, $4CH_2$), 2.71 (t, J = 5.8 Hz, 4H, $2CH_2$), 3.78 (m, J = 5.8 Hz, 4H, $2CH_2$), 6.69 (s, 2H, 2NH), 7.38 (m, 2H, 2H-6), 7.57 (m, 2H, 2H-7), 7.90 (m, 2H, 2H-8), 8.06 (m, 2H, 2H-5), 8.62 (s, 2H, 2H-2). EI MS (15 eV) m/z (%) = 430 ($M-CH_3NEt_2$, 14), 86 ($CH_2NEt_2^+$, 100). FAB MS: 517 (M^++1, 100), 430 ($M-CH_3NEt_2$, 22). Anal. Calcd. for $C_{30}H_{40}N_6S$ (516.74) C, 69.73; H, 7.80; N, 16.26; S, 6.20. Found C, 69.70; H, 7.87; N, 16.21; S, 6.12.

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