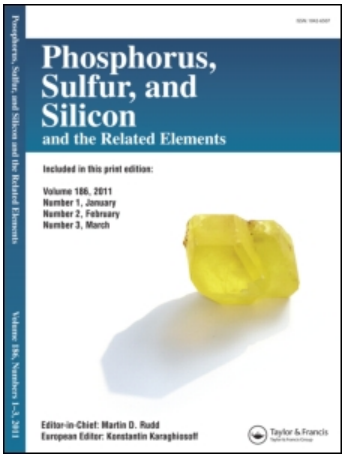

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SYNTHESIS AND PROPERTIES OF 14-SUBSTITUTED 1,4-THIAZINODIQUINOLINES

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SYNTHESIS AND PROPERTIES OF 14-SUBSTITUTED 1,4-THIAZINODIQUINOLINES

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4,4'-Dichloro–3,3'-diquinolinyl sulfide **1** reacted with aryl-, heteroaryl- and alkylamines in MEDG or phenol to 14-substituted thiazino[2,3-c;6,5-c']diquinolines **2**. Reaction with ammonia, ammonium carbonate or benzylamine led to unsubstituted thiazine **2a**. Alkylation of thiazine **2a** with alkyl halides gave 14-alkyl-I,4-thiazinodiquinolines **2b**, **2c** and **2f**. The nature of the 14-substituent has a significant effect on ^{1}H NMR and MS spectral properties.

Keywords: Ring closure; cyclization; 1,4-thiazine; 1,4-thiazinodiquinolines; diquinolinyl sulfides

INTRODUCTION

Azinobenzothiazines i diazinothiazines are analogs of phenothiazines in which annular nitrogen atoms form part of the ring structure. They attract attention because of their pharmacological activity, sometimes higher than phenothiazines.[1–4] Routes to phenothiazines and azaphenothiazines very often involve formation of o-aminoaryl- and o-aminoheteroaryl sulfides, followed by the Smiles rearrangement and cyclization.[3,5]

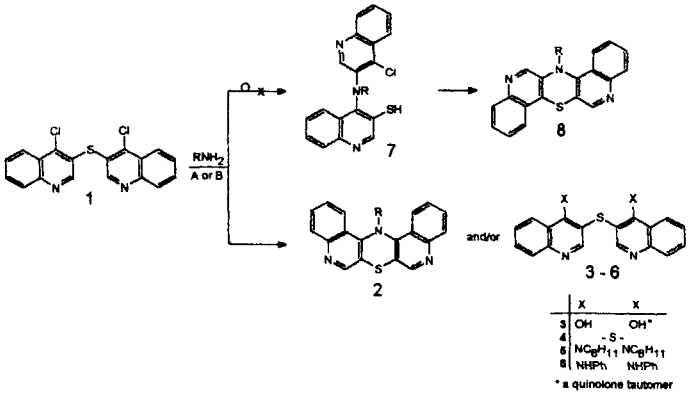
We found thioquinanthrene (1,4-dithiino[2,3-c;5,6-c']diquinoline- easy to obtain by direct sulfurization of quinoline with elemental sulfur[6]) to be an excellent substrate for synthesis of ortho,ortho'-disubstituted 3,3'-, 3,4'- and 4,4'-diquinolinyl sulfides in one or a few steps.[7–18] What is more, we observed the unprecedented S→ S type of the Smiles rearrangement of alkali metal salt of o'-mercapto–3,4'-diquinolinyl sulfides in DMSO or DMF to alkali metal salt of o'-mercapto–3,3'-diquinolinyl sulfides.[10,11,16] In contrast to this the sodium salt of o-anilino,-o'-mercapto–3,4'-diquinolinyl sulfide underwent only the S→ N type of the Smiles rearrangement to sodium salt of o,o'-dimercapto–4,4'-diquinolinylanine.[19]

This all prompted us to examine the reactions of 4,4'-dichloro–3,3'-diquinolinyl sulfide **1** with ammonia, aryl-, heteroaryl- and alkylamines in terms of the Smiles rearrangement of quinolinyl derivatives and as a method for synthesis of 14*H*- and 14-substituted thiazinodiquinolines **2**.

RESULTS AND DISCUSSION

Sulfide **1** is an unique compound amidst o,o'-dichlorodiazinyl sulfides because of its relative simplicity of synthesis and synthethic abilities to obtain various compounds, including 4,4'-disubstituted 3,3'-diquinolinyl sulfides[14, 15, 20, 21] and heterocyclodiquinolines[22], among them 14-phenyl–1,4-thiazinodiquinoline **2g**. Although sulfide 1 can be obtained from 4,4'-dimethylthio–3,3'-diquinolinyl sulfide in one step by action of gaseous chlorine[15] or the mixture phosphoryl chloride-ethanol[14], however these reactions needed some care. Therefore a two-step synthesis via formation of hydrochloride of 3,3'-thiobis(4-quinolone) **3·HCl** in reaction with a mixture of hydrochloric acid-ethanol (1:1) followed by reaction with phosphoryl chloride seems more convenient and efficient (with total yield of 87%).

Reactions of sulfide **1** with three-fold or five-fold amounts of selected primary aryl-, heteroaryl- and alkylamines in monomethyl ether of diethylene glycol (MEDG, method A) or in phenol (method B) led mainly to 14-substituted 1,4-thiazino[2,3-c;6,5-c']diquinolines **2** and/or to 4,4'-disubstituted sulfides **3–6**. The yields of these reactions depended mainly on the basicity and structural features of the amines. In no cases did we observe a stage of the S→ N type of the Smiles rearrangement to substituted 3,4'-diquinolinylamines **7** or further to 1,4-thiazino[2,3-c;5,6-c']diquinolines **8**, regardless of the basicity of the amines used (Scheme 1).



SCHEME 1

Reactions of sulfide **1** with amines were carried out in boiling MEDG (194°C) for 4 hours. After cooling thiazinodiquinoline **2** was precipitated most often as crystals. The best yields were achieved for m- and p-substituted anilines (up to 73%, Table I). On the other hand o-chloroaniline gave thiazine **2k** in the lowest yield (9%) which is ascribed to the steric hindrance. The steric hindrance was also the reason for low yields when two-ring arylamines (1- and 2-naphthylamines) were used.

TABLE I Synthesis of 14H- and 14-substituted 1,4-thiazino[2,3-c;6,5-c']diquinolines **2**

No.	*Substrate*	*Method, reagent*	*Product*		*Yield, %*
			2	*R*	
1	**1**	A, $(NH_4)_2CO_3$	**2a**	H	27
2	**1**	B, NH_3	**2a**	H	65
3	**2a**	C, MeI	**2b**	Me	61
4	**1**	B, $MeNH_2$	**2b**	Me	89
5	**2a**	C, C_3H_5Cl	**2c**	allyl	71
6	**1**	B, i-$BuNH_2$	**2d**	i-Bu	76
7	**1**	A, $C_6H_{11}NH_2$	**2e**	C_6H_{11}	10
8	**1**	A, $C_6H_5C_{11}NH_2$	**2f**	$C_6H_5CH_2$	10[a]
9	**2a**	C, $C_6H_5CH_2Cl$	**2f**	$C_6H_5CH_2$	62
10	**1**	B, $C_6H_5CH_2NH_2$	**2a**	H	86
11	1	A, p-$MeC_6H_4NH_2$	**2h**	p-MeC_6H_4	64
12	**1**	A, p-$HOC_6H_4NH_2$	**2i**	p-HOC_6H_4	42[b]
13	**1**	A, p-$MeOC_6H_4NH_2$	**2j**	p-$MeOC_6H_4$	38
14	**1**	A, o-$ClC_6H_4NH_2$	**2k**	o-ClC_6H_4	9
15	**1**	A, m-$ClC_6H_4NH_2$	**2l**	m-ClC_6H_4	68
16	**1**	A, p-$ClC_6H_4NH_2$	**2m**	p-ClC_6H_4	73
17	**1**	A, p-$HOOCC_6H_4NH_2$	**2n**	p-$HOOCC_6H_4$	47[c]
18	**1**	A, p-$O_2NC_6H_4NH_2$	**2o**	p-$O_2NC_6H_4$	64
19	**1**	A, p-$BrC_6H_4NH_2$	**2p**	p-BrC_6H_4	48
20	**1**	A, 1-naphthylamine	**2r**	1-naphthyl	13
21	**1**	A, 2-naphthylamine	**2s**	2-naphthyl	16
22	**1**	A, 2-aminothiazole	**2t**	2-thiazolyl	26[d]
23	**1**	A, 2-aminopyridine	**2u**	2-pyridyl	64

* Methods: A - in MEDG, B - in PhOH, C - in DMF/NaH. [a] Thazine **2a** was also isolated in 27% yield. [b, c] A by-product - sulfid **3** in 19% yield. [d] A by-product - isothioquinanthrene **4** in 17% yield.

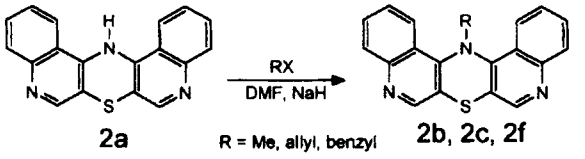
In the case of the substituted anilines with acidic groups (p-aminophenol and p-aminobenzoic acid) thiazines **2i** (42%) and **2n** (47%) were accompanied by the product of hydrolysis - 3,3'-thiobis(4-quinolone) **3** (19%). Not all amines were stable in the reactions in MEDG. 2-Aminothiazole reacted with sulfide **1** with formation of thiazine **2t** and isothioquinanthrene **4** (17%, an isomer of thioquinanthrene), being a by-product formed through decomposition of the thiazole ring.

The 14-unsubstituted thiazine **2a** was formed when sulfide **1** was heated with ammonium carbonate as a source of the amino group.

Although alkylamines are stronger bases than arylamines the yields of 14-alkyl–1,4-thiazinodiquinolines **2** were lower. Unexpectedly, reaction of sulfide **1** with benzylamine led to two products: the expected thiazine **2f** (10%) and additionally 14-unsubstituted thiazine **2a** (27%) as a N-debenzylation product. Even less effective was the reaction with cyclohexylamine producing thiazine **2e** in 10% yield. A significant excess (ten-fold) of amine and prolonged reaction time (18 hours) promoted formation of the disubstituted product - 4,4'-dicyclohexylamino–3,3'-diquinolinyl sulfide **5** (55%).

The unsatisfactory yields of reactions with alkylamines and the presence of some tarry compounds in the products (being neither thiazines nor 4,4'-dialkylamino–3,3'-diquinolinyl sulfides) forced us to change the reaction conditions and employ phenol (at 180°C) instead of MEDG, widely used in synthesis of 2- and 4-amino- and alkylaminoquinolines from chloroquinolines.[23] Using the phenolic procedure we obtained 14H- and 14-alkyl–1,4-thiazinodiquinolines from gaseous ammonia, methylamine and isobutylamine in good yield (**2a**, **2b** and **2d** in 65%, 89% and 76% yield). However, similar to the reaction in MEDG the reaction of sulfide **1** with cyclohexylamine in hot phenol gave 4,4'-dicyclohexylamino–3,3'-diquinolinyl sulfide **5** (77%), which is ascribed to steric congestion in the amine. It is worth noting that reaction of benzylamine led only to the N-debenzylation product – 14*H*-thiazinodiquinoline **2a** in high yield (86%).

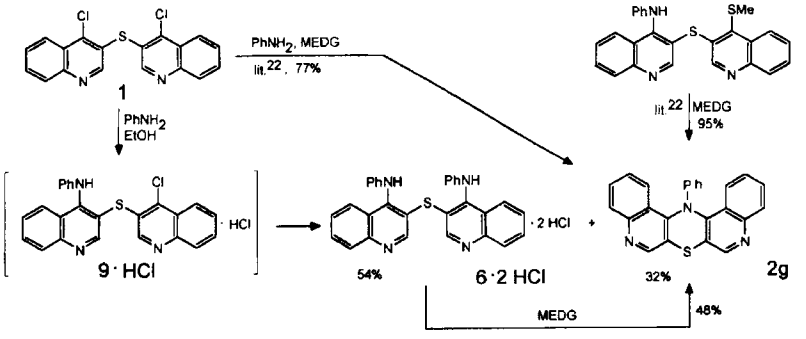
The latter compound was used as a substrate in benzylation with benzyl chloride in DMF in the presence of sodium hydride (method C), giving 14-benzyl–1,4-thiazinodiquinoline **2f** in a 62% yield. Methylation and allylation with methyl iodide and allyl bromide gave 14-alkyl derivatives **2b** and **2c** in 61 and 71% yield (Scheme 2).



2a R = Me, allyl, benzyl **2b, 2c, 2f**

SCHEME 2

In order to understand the mechanism of the cyclization, the reaction of sulfide **1** with aniline was carried out in boiling ethanol. After 30 minutes thiazine **2g** was filtered off from hot solution (in 32% yield) and after cooling dihydrochloride of 4,4'-dianilino–3,3'-diquinolinyl sulfide **6·2HCl**(in 54% yield). When the latter compound was heated in MEDG, thiazine **2g** was isolated in 48% yield. This lower yield (vs. 77% yield of the direct reaction of sulfide **1** with aniline in MEDG[22]) and the fact that the precipitation of thiazine from cold solution needed a few hours, induced us to conclude that the ring closure proceeded mainly through the cyclization stage of hydrochloride of 4-anilino–4'-chloro–3,3'-diquinolinyl sulfide **9·HCl** rather than dihydrochloride of 4,4'-dianilino–3,3'-diquinolinyl sulfide **6·2HCl** (Scheme 3). Unsuccessful attempts at isolation of the monosubstitution product **9 . HCl** and easiness of cyclization of other monoaminocompound - 4-anilino-4'-methylthio-3,3'-diquinolinyl sulfide (in 95% yield[22]) seem to support the supposition.



SCHEME 3

PROPERTIES

All thiazinodiquinolines **2a–2u** showed interesting TLC properties. The coloured spots, mainly yellow, orange or orange red, changed upon irradiation with the UV lamp (λ = 360 nm) into green or blue-green, what facilitated the detection of thiazines **2** among other reaction products.

The ^{1}H NMR spectra of thiazines **2** were recorded at 300 MHz, enabling the benzene proton signals in nearly all compounds to be obtained as separated multiplets. The H–6 and H–8 proton signals were recorded as singlets (Table II). Only five signals of the quinoline protons were observed, what indicates the symmetrical structure of thiazines (both of the quinoline moieties were identical) excluding the stage of the Smiles rearrangement.

TABLE II Physical and spectroscopical data of 14*H*- and 14-substituted-1,4-thiazino[2,3-c;6,5-c'] -diquinolines **2**

No.	*Thiazine*	*R*	*M. p.* (°C)	*^{1}H NMR, δ ($CDCl_3$, ppm)*	*MS (15 eV), m/e (rel. intensity)*
1	**2a**	H	200–201	7.51 (br, 1H, NH) 7.63 (m, 2H, H-2, H-12) 7.70 (m, 2H, H-3, H-11) 7.80 (dd, 2H, H-4, H-10) 8.03 (dd, 2H, H-1, H-13) 8.39 (s, 2H, H-6, H-8)	301 (M^+, 100) 269 (M-S, 4.5)
2	**2b**	Me	156–157	3.55 (s, 3H, NM_e) 7.68 (m, 2H, H-2, H-12) 7.73 (m, 2H, H-3, H-11) 8.11 (dd, 2H, H-4, H-10) 8.36 (dd, 2H, H-1, H-13) 8.68 (s, 2H, H-6, H-8)	315 (M^+, 100) 300 (M-Me, 98.4)
3	**2c**	allyl	155–156	4.55 (d, 2H, CH_2, J = 1.1 Hz) 4.76 (d, 1H, trans CH_2=, J = 17 Hz) 4.91 (d, 1H, cis CH_2=, J = 10 Hz) 6.04 (d, 1H, CH=, J = 7 Hz) 7.61 (m, 2H, H-2, H-12) 7.70 (m, 2H, H-3, H-11) 8.10 (dd, 2H, H-4, H-10) 8.33 (dd, 2H, H-1, H-13) 8.65 (s, 2H, H-6, H-8)	341 (M^+, 96.5) 301 (M-C_3H_4, 100) 300 (M-C_3H_5, 99.2)
4	**2d**	i-Bu	188–189	0.85 (d, 6H, $2CH_3$, J = 6.6 Hz) 1.72 (m, 1H, CH, J = 6.6 Hz) 4.09 (d, 2H, CH_2, J = 6.6 Hz) 7.63 (m, 2H, H-2, H-12) 7.70 (m, 2H, H-3, H-11) 8.10 (dd, 2H, H-4, H-10) 8.23 (dd, 2H, H-1, H-13) 8.61 (s, 2H, H-6, H-8)	357 (M^+, 62.1) 314 (M-C_3H_7, 10.8) 300 (M-C_4H_9, 100)
5	**2e**	C_6H_{11}	264–265	0.85–1.50 (m, 8H, $4CH_2$) 2.06–2.10 (d, 2H, CH_2) 3.76–3.86 (m, 1H, CH) 7.65 (m, 2H, H-2, H-12) 7.72 (m, 2H, H-3, H-11) 8.10 (dd, 2H, H-4, H-10) 8.60 (dd, 2H, H-1, H-13) 8.80 (s, 2H, H-6, H-8)	383 (M^+, 32.7) 301 (M-C_6H_{10}, 100)
5	**2f**	CH_2Ph	220–221	5.01 (s, 2H, CH_2) 6.62 (m, 2H, o-C_6H_4) 7.06 (m, 2H, m-C_6H_4) 7.19 (m, 1H, p-C_6H_4) 7.71 (m, 2H, H-2, H-12) 7.75 (m, 2H, H-3, H-11) 8.13 (dd, 2H, H-4, H-10) 8.46 (dd, 2H, H-1, H-13) 8.50 (s, 2H, H-6, H-8)	391 (M^+, 27.5) 300 (M-CH_2Ph, 100)

TABLE II Physical and spectroscopical data of 14*H*- and 14-substituted–1,4-thiazino[2,3-c;6,5-c'] -diquinolines **2** (continued)

No.	*Thiazine*	*R*	*M. p. (°C)*	*^1H NMR, δ ($CDCl_3$, ppm)*	*MS (15 eV), m/e (rel. intensity)*
6	**2h**	p-MeC_6H_4	> 300	2.20 (s, 3H, Me) 6.37 (dd, 2H, o-C_6H_4) 6.85 (dd, 2H, m-C_6H_4) 7.67 (m, 2H, H–2, H–12) 7.78 (m, 2H, H–3, H–11) 8.22 (dd, 2H, H–4, H–10) 8.39 (dd, 2H, H–1, H–13) 9.03 (s, 2H, H–6, H–8)	391 (M^+, 100) 359 (M-S, 3.3) 300 (M-MeC_6H_4, 2.2)
7	**2i**	p-HOC_6H_4	> 300	6.35[a] (dd, 2H, o-C_6H_4) 7.50 (dd, 2H, m-C_6H_4) 7.78 (m, 2H, H–2, H–12) 7.85 (m, 2H, H–3, H–11) 8.15 (dd, 2H, H–4, H–10) 8.51 (dd, 2H, H–1, H–13) 9.08 (s, 1H, OH) 9.13 (s, 2H, H–6, H–8)	393 (M^+, 100) 361 (M-S, 9.9) 301 (M-OC_6H_4, 10.1) 300 (M-HOC_6H_4, 9.2)
8	**2j**	p-$MeOC_6H_4$	> 300	3.67 (s, 3H, OMe) 6.44 (dd, 2H, o-C_6H_4) 6.61 (dd, 2H, m-C_6H_4) 7.68 (m, 2H, H–2, H–12) 7.79 (m, 2H, H–3, H–11) 8.21 (dd, 2H, H–4, H–10) 8.42 (dd, 2H, H–1, H–13) 9.01 (s, 2H, H–6, H–8)	407 (M^+, 100) 392 (M-Me, 7.7) 375 (M-S, 9.5) 300 (M-$MeOC_6H_4$, 6.5)
9	**2k**	o-ClC_6H_4	> 300	6. 82–7.17 (m, 4H, C_6H_4) 7.68 (m, 2H, H–2, H–12) 7.76 (m, 2H, H–3, H–11) 8.19 (dd, 2H, H–4, H–10) 8.52 (dd, 2H, H–1, H–13) 9.02 (br, 2H, H–6, H–8)	411 (M^+, 100) 413 (M+2, 44.7) 379 (M-S, 2.2) 300 (M-ClC_6H_4, 3.8)
10	**2l**	m-ClC_6H_4	> 300	6.30–6.45 (m, 2H, C_6H_4) 6.86–7.00 (m, 2H, C_6H_4) 7.71 (m, 2H, H–2, H–12) 7.81 (m, 2H, H–3, H–11) 8.23 (dd, 2H, H–4, H–10) 8.34 (dd, 2H, H–1, H–13) 9.06 (s, 2H, H–6, H–8)	411 (M^+, 100) 413 (M^+2, 45.9) 379 (M-S, 3.3) 300 (M-ClC_6H_4, 6.1)
11	**2m**	p-ClC_6H_4	> 300	6.38 (dd, 2H, o-C_6H_4) 7.00 (dd, 2H, m-C_6H_4) 7.70 (m, 2H, H–2, H–12) 7.80 (m, 2H, H–3, H–11) 8.23 (dd, 2H, H–4, H–10) 8.33 (dd, 2H, H–1, H–13) 9.04 (s, 2H, H–6, H–8)	411 (M^+, 100) 413 (M+2, 30.4) 379 (M-S, 3.4) 300 (M-ClC_6H_4, 4.0)
12	**2n**	p-$HOOCC_6H_4$	> 300	6.41[a] (dd, 2H, o-C_6H_4 7.67 (dd, 2H, m-C_6H_4)	421 (M^+, 100) 389 (M-S, 10.7)

a in DMSO-d_6.

TABLE II Physical and spectroscopical data of 14*H*- and 14-substituted-1,4-thiazino[2,3-c;6,5-c']-diquinolines **2** (continued)

No.	*Thiazine*	*R*	*M. p. (°C)*	*^1H NMR, δ ($CDCl_3$, ppm)*	*MS (15 eV), m/e(rel. intensity)*
				7.81 (m, 2H, H-2, H-12) 7.90 (m, 2H, H-3, H-11) 8.22 (dd, 2H, H-4, H-10) 8.44 (dd, 2H, H-1, H-13) 9.23 (s, 2H, H-6, H-8) 10.9 (s, 1H, COOH)	377 (M-CO_2, 5.3) 300 (M-$HOOCC_6H_4$, 4.3)
13	**2o**	p-$O_2NC_6H_4$	> 300	6.51 (dd, 2H, o-C_6H_4) 7.74 (dd, 2H, m-C_6H_4) 7.84 (m, 2H, H-2, H-12) 7.96 (m, 2H, H-3, H-11) 8.25 (dd, 2H, H-4, H-10) 8.28 (dd, 2H, H-1, H-13) 9.10 (s, 2H, H-6, H-8)	422 (M^+, 100) 392 (M-NO, 2.3) 390 (M-S, 2.5) 376 (M-NO_2, 3.0) 300 (M-$O_2NC_6H_4$, 4.5)
14	**2p**	p-BrC_6H_4	> 300	6.33 (dd, 2H, o-C_6H_4) 7.14 (dd, 2H, m-C_6H_4) 7.70 (m, 2H, H-2, H-12) 7.80 (m, 2H, H-3, H-11) 8.23 (dd, 2H, H-4, H-10) 8.33 (dd, 2H, H-1, H-13) 9.05 (s, 2H, H-6, H-8)	456 (M^+, 93.8) 458 (M+2, 100) 424 (M-S, 3.0) 426 (M+2-S, 3.0) 300 (M-BrC_6H_4, 5.9)
15	**2r**	1-naphthyl	> 300	6.88–7.67[a] (m, 7H, $C_{10}H_7$) 7.35 (m, 2H, H-2, H-12) 7.47 (m, 2H, H-3, H-11) 7.78 (dd, 2H, H-4, H-10) 8.08 (dd, 2H, H-1, H-13) 8.79 (s, 2H, H-6, H-8)	428 (M^+, 100) 396 (M-S, 3.8) 300 (M-$C_{10}H_7$, 6.0)
16	**2s**	2-naphthyl	> 300	6.86–7.66[a] (m, 7H, $C_{10}H_7$) 7.35 (m, 2H, H-2, H-12) 7.48 (m, 2H, H-3, H-11) 7.79 (dd, 2H, H-4, H-10) 8.09 (dd, 2H, H-1, H-13) 8.78 (s, 2H, H-6, H-8)	428 (M^+, 100) 396 (M-S, 4.2) 300 (M-$C_{10}H_7$, 6.9)
17	**2t**	2-thiazolyl	> 300	6.64 (d, 1H, H-5', J = 3.6 Hz) 7.17 (d, 1H, H-4', J = 3.6 Hz) 7.75 (m, 2H, H-2, H-12) 7.80 (m, 2H, H-3, H-11) 8.21 (dd, 2H, H-4, H-10) 8.44 (dd, 2H, H-1, H-13) 9.03 (s, 2H, H-6, H-8)	384 (M^+, 100) 352 (M-S, 2.8) 300 (M-C_3H_2NS, 4.9)
18	**2u**	2-pyridyl	> 300	6.29 (d, 1H, H-3') 6.83 (dd, 1H, H-5') 7.37 (dd, 1H, H-4') 7.65 (m, 2H, H-2, H-12) 7.77 (m, 2H, H-3, H-11) 8.01 (dd, 1H, H-6') 8.20 (dd, 2H, H-4, H-10) 8.32 (dd, 2H, H-1, H-13) 9.03 (s, 2H, H-6, H-8)	378 (M^+, 100) 346 (M-S, 12.1) 300 (M-C_5H_4N, 17.9)

[a] in DMSO-d_6.

In a previous paper[22] we showed that the ^{1}H NMR spectra of heterocyclodiquinolines depended mainly on the nature of the heteroatom in position 14. This time the nature of the 14-substituent attached to the nitrogen atom in thiazines **2** exerts an influence on the chemical shift of the H–6/H–8 and H–1/H–13 protons. Whereas the H–6/H–8 protons in 14-aryl- and heteroaryl–1,4-thiazinodiquinolines were deshielded (δ = 9.01–9.10 ppm in deuteriochloroform), the same protons in the alkylthiazines **2b–2f** were significantly shielded (δ = 8.50–8.80 ppm) in comparison with the appropriate signal in quinoline (δ = 8.92 ppm[24]). The most shielded H–6/H–8 protons were found for 14-unsubstituted thiazinodiquinoline **2a** (δ = 8.39 ppm).

The H–1 and H–13 protons were strongly deshielded (δ = 8.23–8.60 ppm) in comparison with the signal in quinoline (δ = 7.78 ppm[24]) as the result of through-space interactions of the NR group with the H–1 and H–13 atoms despite the character of the alkyl, aryl and heteroaryl group. This peri effect causes that the signals of the H–1 and H–13 protons were found even more downfield than the signals of the H–4 and H–10 protons (δ = 8.10–8.25 ppm). For 14-unsubstituted thiazinodiquinoline **2a** (R = H) the peri effect is relatively small (δ = 8.03 ppm). The greatest peri effect was observed for 14-cyclohexyl thiazinodiquinoline **2e** (δ = 8.60 ppm), confirming the steric congestion in this substituent.

Mass spectrometry of phenothiazines is characterized by high stability of their molecular ions.[25] Electron impact mass spectra of 14-aryl- and heteroaryl–1,4-thiazinodiquinolines **2h - 2u** showed the molecular ion to be the base peak. Although the same result was observed in the spectrum of 14-methylthiazinodiquinoline **2b**, in other 14-alkyl derivatives **2c - 2f** the base peak was the $[M-R]^+$ ion. Elimination of sulfur radical was observed for 14-aryl- and 14-heteroaryl thiazines **2h - 2u** giving the $[M-S]^+$ ions of low intensity (2.2–12.1%). The $C_\alpha - C_\beta$ cleavage of the alkyl substituent, characteristic for N-alkylphenothiazines[25], was found only in the spectrum of 14-i-butyl–1,4-thiazinodiquinoline **2d**.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus were uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz in deuteriochloroform or DMSO-d_6. Mass spectra were run on a LKB 9000S spectrometer using the electron impact method. Thin layer chromatography was performed on aluminium oxide (type E) and silica gel 60 254F plates (Merck) using methylene chloride and benzene - ethyl acetate (1:1) solutions as eluents. Elemental analysis of the new compounds were in good agreement with the theoretical values.

Hydrochloride of 3,3'-thiobis(4-quinolone) **3 . HCl** was obtained from thioquinanthrene in two steps according to the procedure[15].

Synthesis of 4,4'-dichloro–3,3'-diquinolinyl sulfide 1

Hydrochloride of 3,3'-thiobis(4-quinolone) **3 . HCl** (dihydrate, 7.85 g, 20 mmols) was refluxed in 30 ml phosphoryl chloride for 1 hour. After cooling the reaction mixture was carefully poured on ice (300 g) and alkalized with concentrated ammonia to pH ~ 10. The resulting solid was filtered off, washed with water and crystallized from ethanol to give sulfide **1** (6.64 g, 93%) as white crystals; mp 129–130°C (lit[15] mp 129–130°C).

Synthesis of thiazinodiquinolines 2

Method A

To a solution of sulfide 1 (0.36 g, 1 mmol) in 5 ml of MEDG amine (3 mmols) was added and the mixture was refluxed for 4 hours. After cooling the resulting precipitate (as crystals in the case of pure thiazines or as an amorphous solid in the case of contaminated thiazines) was filtered off, washed with water and air-dried. In a few cases a crude thiazine was separated only when a cool reaction mixture was poured into 15 ml of water. A crude thiazine was purified by column chromatography on silica gel 60, using chloroform as eluent.

In the case of synthesis of thiazine **2a** ammonium carbonate (0.48 g, 5 mmols) was added portionally during the reaction time.

When the reaction was carried out with an excess of cyclohexylamine (10 mmols) for 18 hours 4,4'-dicyclohexylamino–3,3'-diquinolinyl sulfide was isolated **5** (0.265 g, 55%); mp 142–143°C. ^{1}H NMR ($CDCl_3$): δ, ppm, 1.13–2.16 (m, 20H, $2C_6H_{10}$), 3.82–3.91 (m, 2H, 2CH), 5.17 (d, 2H, 2NH), 7.42 (m, 2H, 2H–6), 7.61 (m, 2H, 2H–7), 7.93 (dd, 2H, 2H–8), 7.95 (m, 2H, 2H–5), 8.60 (s, 2H, 2H–2). MS (15 eV): m/z (%) 482 (M^+, 100), 399 ($M-C_6H_{11}$, 27.2).

Method B

To a solution of sulfide **1** (0.36 g, 1 mmol) in phenol (2 g) at 180°C gaseous ammonia or alkylamine (5 mmols) was added portionally during 60 minutes. After cooling 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 thiazine **2a**, **2b** and **2d**.

In the case of cyclohexylamine only 4,4'-dicyclohexylamino–3,3'-diquinolinyl sulfide **5** was isolated (0.37 g, 77%).

Method C

To a solution of thiazine **2a** (0.30 g, 1 mmol) in 10 ml of dry DMF sodium hydride (obtained from 50% suspension in mineral oil by washing with hexane, 0.048 g, 2 mmols) was added The mixture was stirred at room temperature for 60 minutes (until hydrogen evolution was ceased). Then alkyl halide (3 mmols) was added and the mixture was stirred for 24 hours. Next 20 ml of water was added to the reaction mixture and the resulting precipitate was filtered off, washed with water, air-dried and purified by column chromatography (silica gel 60, chloroform) to give thiazine **2b**, **2c** and **2f**.

Synthesis of thiazine 2g in ethanol

A solution of sulfide **1** (0.36 g, 1 mmol) and aniline (0.28 g, 3 mmols) in 10 ml of dry ethanol was refluxed for 30 minutes. The resulting precipitate was hot filtered off to give thiazine **2g** (0.12 g, 32%); mp > 300°C (lit[22] mp > 300°C). The filtrate was cooled down and the precipitate was filtered off to give dihydrochloride of 4,4'-dianilino–3,3'-diquinolinyl sulfide **6 . 2HCl** (1.5 dihydrate, 0.31 g, 54%); mp 199–200°C. ^{1}H NMR (DMSO-d_6): δ, ppm, 6.83–7.48 (m, 12H, $2C_6H_5NH$), 7.68 (m, 2H, 2H–6), 7.95 (m, 2H, 2H–7), 8.16 (dd, 2H, 2H–8), 8.35 (dd, 2H, 2H–5), 8.64 (s, 2H, 2H–2), 10.19 (br, 2H, $2NH^+$). MS (15 eV): m/z (%) 470 (M–2HCl, 100), 220 ($C_9H_6NNHC_6H_5^+$, 59.3).

Cyclization of dihydrochloride of 4,4'-dianilino–3,3'-diquinolinyl sulfide **6·2HCl** to thiazine **2g**.

A solution of dihydrochloride of 4,4'-dianilino–3,3'-diquinolinyl sulfide **6 . 2HCl** (1.5 dihydrate, 0.25 g, 0.44 mmols) in 5 ml of MEDG was refluxed for 4 hours. After cooling the resulting crystals of thiazine **2g** was filtered off(0.08 g, 48%), mp > 300°C.

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