SYNTHESIS OF 1H-1,2-DITHIOL-1-THIONES AND THIOAMIDES CONTAINING HYDROQUINOLINE GROUP

G. M. Manahelohe[a]*, K. S. Shikhaliev[a] and A. Y. Potapov[a]

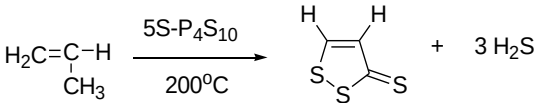
Keywords: 1H-1,2-dithiol-1-thione, Willgerodt-Kindler reaction, thioamides, hydroquinolinecarbaldehyde.

This study is concerned with the synthesis and characterization of derivatives of 1H-1,2-dithiol-1-thiones and thioamides having the hydroquinoline moiety. 5-Alkyl-8-(carbonothioyl)-4,5-dihydro-4,4-dimethyl-1H-[1,2]dithiolo[3,4-*c*]quinoline-1-thiones were synthesized by reacting of N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehydes, cyclic secondary amines and excess elemental sulfur (7.33 equivalents) in refluxing DMF. A series of thioamides derivatives containing hydroquinoline fragment were obtained in 56-84% yields by the three-component reaction of N-alkylhydroquinoline-6-carbaldehydes, cyclic secondary amines and 1.33 equivalent of elemental sulfur by refluxing in DMF.

* Corresponding Authors
Mobile No. : +79601299727
E-Mail: gizachewm75@gmail.com
[a] Voronezh State University, Department of Organic Chemistry, Voronezh, Russian Federation. 394006 Voronezh Universitetskaya pl., 1.

Introduction

1H-1,2-dithiole-3-thiones are pseudo-aromatic heterocyclic compounds which are known for several years.[1-2] They have been synthesized from a wide range of starting materials. In most case sulfur or phosphorus pentasulfide is utilized to dehydrogenate and sulfurize an allylic methyl group[3-5] as shown in scheme 1 for propene. The 3,4-double bond and the 4-methyl group in N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline forms such a system. Thus, 1H-1,2-dithiol-1-thiones can be synthesized in the same way as 3H-1,2-dithiole-3-thiones.[6]



Scheme 1. Synthesis of 1,2-dithiole-3-thione.

Presently, there is an increased interest in the synthesis of 3H-1,2-dithiole-3-thiones due to their wide range of biological activities such as antischistosomal agent,[7] HIV-1 (AIDS) virus replication inhibitor,[8] chemoprotective agent,[9] fungicide[10] and insecticide.[11]

Thioamides are essential building blocks for the synthesis of heterocycles.[12] They have a wide range of biological properties, such as pesticidal,[13] fungicidal,[14] insecticidal,[15] antioxidant,[16] antitubercular,[17] and anthelmintic activity.[18] Furthermore, thioamides have a wide range of applications in the fields of peptide chemistry,[19] polymers[20] and organocatalysis.[21]

Numerous methods[22] are available in the literature for the synthesis of thioamides. Although the Willgerodt-Kindler method of preparation of thioamides using derivatives of benzaldehyde has been reported in the literature,[23] the use of hydroquinolinecarbaldehyde has so far received no attention.

Thus, in this work, we report the synthesis of 1H-1,2-dithiol-1-thiones via the reaction of N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehydes, amines and excess sulfur. We also describe the synthesis of thioamides containing the hydroquinoline moiety by the three-component reaction of N-alkylhydroquinoline-6-carbaldehydes, cyclic secondary amines and sulfur in DMF.

Experimental

General

DMF was purchased from Bekton company. Dry DMF was prepared by drying it overnight over calcium oxide, followed by filteration of the drying agent and vacuum distillation (~20 mmHg). All other commercial reagents were purchased from Bekton, Lancaster, Acros, Aldrich, and Sigma and were used as received. The course of the reactions and purities of the compounds were monitored by thin layer chromatography (TLC) on SILUFOL UV-254 plates, eluent: chloroform, methanol, hexane, ethyl acetate, petroleum ether in different proportions and spots were visualized by exposure to iodine vapors. The ^{1}H-NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 500.13 MHz, using DMSO-d_6 as solvent ($CDCl_3$ for compound **4d**) and TMS as internal standard. Elemental analyses were determined by using a Carlo Erba NA 1500 elemental analysis instrument. Melting points were recorded using *Stuart SMP30* melting point instrument.

General Procedure for the Synthesis of thioamides (3a-f, 3'a-h)

A mixture of the corresponding aldehyde **1** or **1'** (1 mmol), amine **2a-2g** (1.33 mmol), and elemental sulfur (1.33 mmol) in DMF (2 ml) was refluxed until the reaction is completed (monitored by TLC: hexane/ethyl acetate 7:3). On the

completion of the reaction the warm, dark syrup was poured in to 5 ml of vigorously stirred ice water containing 1 ml of 2N HCl. The resulting gum was solidified by triturating in the acid. The pH was maintained at about 4 by addition of more acid as needed. The solid obtained was filtered, washed with water and recrystallized in an appropriate solvent.[24] ^{1}H-NMR spectra of thiocarboxamides (**3a-f**, **3'a-g**) (δ) are given in ppm (J in Hz).

Piperidin-1-yl(1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)-methanethione (3a)

Yield = 67 %, m.p. 85-87 °**C**. ^{1}H NMR (DMSO-d_6): δ = 1.29 (s, 6H, $(CH_3)_2$-C2), 1.45-1.60 (bro. s., 6H, $3CH_2$-piperidin.), 1.89 (s, 3H, CH_3-C4), 2.76 (s, 3H, N-CH_3) 3.60-4.30 (bro. s., 4H, $2CH_2$-piperidin), 5.39 (s, 1H, CH-DHQ), 6.44 (d, J=8.54, 1H, ArH's), 6.95 (d, J=2.18, 1H, ArH's), 7.05 (dd, J=8.46, J=2.18, 1H, ArH's). Anal. Calcd. for $C_{19}H_{26}N_2S$: C, 72.56, H, 8.33, N, 8.91, S, 10.20 Found: C, 72.57, H, 8.39, N, 8.97, S, 10.22.

4-(1,2,2,4-Tetramethyl-1,2-dihydroquinoline-6-carbonothio-yl)piperazine-1-carbaldehyde (3b)

Yield = 65 %, m.p. >250 °C. ^{1}H NMR (DMSO-d_6): δ = 1.29 (s, 6H, $(CH_3)_2$-C2), 1.90 (s, 3H, CH_3-C4), 2.78 (s, 3H, N-CH_3), 3.50-4.30 (bro. s., 8H, $4CH_2$-piperazin.), 5.39 (s, 1H, CH), 6.45 (d, J=8.64, 1H, ArH's), 7.06 (s, 1H, ArH's), 7.17 (dd, J=8.54, J=1.97, 1H, ArH's), 8.10 (s, 1H, CHO). Anal. Calcd. for $C_{19}H_{25}N_3OS$: C, 66.44, H, 7.34, N, 12.23, S, 9.34 Found: C, 66.46, H, 7.40, N, 12.29, S, 9.35.

(1-Benzyl-2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)(piperidin-1-yl)methanethione (3c)

Yield = 81 %, m.p. 80-82 °C. ^{1}H NMR (DMSO-d_6): δ = 1.35 (s, 6H, $(CH_3)_2$-C2), 1.45-1.70 (bro. s., 6H, $3CH_2$-piperidin.), 1.95 (s, 3H, CH_3-C4), 3.50-4.25 (bro. s., 4H, $2CH_2$-piperidin), 4.56 (s, 2H, CH_2-Bn), 5.48 (s, 1H, CH), 6.13 (d, J=8.61, 1H, ArH's), 6.85 (dd, J=8.53, J=2.17, 1H, arom.), 6.97 (d, J=2.19, 1H, ArH's), 7.15-7.35 (m, 5H, arom.).). Anal. Calcd. for $C_{25}H_{30}N_2S$: C, 76.88, H, 7.74, N, 7.17, S, 8.21 Found: C, 76.90, H, 7.75, N, 7.21, S, 8.24.

Pyrrolidin-1-yl(1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methanethione (3d)

Yield = 58 %, m.p. 113-115°C. ^{1}H NMR (DMSO-d_6): δ = 1.28 (s, 6H, $(CH_3)_2$-C2), 1.87 (p, J=6.73, 2H, CH_2-pyrrolidin), 1.89 (s, 3H, CH_3-C4), 1.97 (p, J=6.94, 2H, CH_2-pyrrolidin), 2.77 (s, 3H, N-CH_3), 3.60 (t, J=6.62, 2H, CH_2-pyrrolidin), 3.77 (t, J=7.02, 2H, CH_2-pyrrolidin), 5.39 (s, 1H, CH), 6.43 (d, J=8.59, 1H, ArH's), 7.12 (d, J=2.20, 1H, arom.), 7.20 (dd, J=8.52, J=2.22, 1H, arom.). Anal. Calcd. for $C_{18}H_{24}N_2S$: C, 71.95, H, 8.05, N, 9.32, S, 10.67 Found: C, 71.97, H, 8.11, N, 9.38, S, 10.69.

(4-Methylpiperazin-1-yl)(1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methanethione hydrochloride (3e)

Yield = 60 %, m.p. 160-162 °C. ^{1}H NMR (DMSO-d_6): δ = 1.30 (s, 6H, $(CH_3)_2$-C2), 1.92 (s, 3H, CH_3-C4), 2.75 (d, J=4.55, 3H, N-CH_3-piperazin), 2.78 (s, 3H, N-CH_3-DHQ), 4.10-4.85 (m, 8H, $4CH_2$-piperazin), 5.41 (s, 1H, CH), 6.51 (d, J=8.56, 1H, ArH's), 7.07 (d, J=2.05, 1H, ArH's), 7.20 (dd, J=8.48, J=2.16, 1H, ArH's), 11.40 (s, 1H, HCl). Anal. Calcd. for $C_{19}H_{28}ClN_3S$: C, 62.36, H, 7.71, N, 11.48, S, 8.76, Cl, 9.69 Found: C, 62.40, H, 7.75, N, 11.50, S, 8.81, Cl, 9.70.

(4-Phenylpiperazin-1-yl)(1,2,2,4-tetramethyl-1,2-dihydroquinolin-6-yl)methanethione (3f)

Yield = 72 %, m.p. 101-103°C. ^{1}H NMR (DMSO-d_6): δ = 1.29 (s, 6H, $(CH_3)_2$-C2), 1.91 (s, 3H, CH_3-C4), 2.78 (s, 3H, N-CH_3), 3.70-4.50 (bro. s., 8H, $4CH_2$-piperazin), 5.41 (s, 1H, CH), 6.46 (d, J=8.59, 1H, ArH's), 6.75-7.30 (m, 7H, ArH's). Anal. Calcd. for $C_{24}H_{29}N_3S$: C, 73.63, H, 7.46, N, 10.73, S, 8.19 Found: C, 73.66, H, 7.51, N, 10.79, S, 8.23.

(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)(piperidin-1-yl)methanethione (3'a)

Yield = 76 %, m.p. 115-117°C. ^{1}H NMR (DMSO-d_6): δ = 1.24 (s, 3H, $(CH_3)_{2A}$-C4), 1.25 (s, 3H, $(CH_3)_{2B}$-C4), 1.32 (d, J=6.59, 3H, CH_3-C4), 1.40-1.75 (m., 7H, CH_{2A}+$3CH_2$-piperidin), 1.90 (dd, J=13.03, J=4.67, 1H, CH_{2B}), 1.96 (m., 1H, CH), 3.50-4.15 (m, 4H, $2CH_2$-piperidin), 4.26 (d, J=18.06, 1H, CH_{2A}-Bn), 4.77 (d, J=18.09, 1H, CH_{2B}-Bn), 6.12 (d, J=8.65, 1H, ArH's), 6.85 (dd, J=8.60, J=2.13, 1H, ArH's), 7.10-7.35 (m, 6H, ArH's). Anal. Calcd. for $C_{25}H_{32}N_2S$: C, 76.48, H, 8.22, N, 7.14, S, 8.17 Found: C, 76.50, H, 8.25, N, 7.20, S, 8.21.

4-(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinoline-6-carbonothioyl)piperazine-1-carbaldehyde (3'b)

Yield = 56 %, m.p. 160-162°C. ^{1}H NMR (DMSO-d_6): δ = 1.24 (s, 3H, $(CH_3)_{2A}$-C2), 1.26 (s, 3H, $(CH_3)_{2B}$-C2), 1.32 (d, J=6.36, 3H, CH_3-C4), 1.64 (t, J=12.77, 1H, CH_{2A}), 1.91 (dd, J=12.92, J=4.50, 1H, CH_{2B}), 2.96 (m, 1H, CH), 3.60-4.20 (m., 8H, $4CH_2$-piperazin), 4.27 (d, J=17.75, 1H, CH_{2A}-Bn), 4.78 (d, J=18.25, 1H, CH_{2B}-Bn), 6.14 (d, J=8.69, 1H, ArH's), 6.90-7.40 (m, 7H, ArH's), 8.07 (s, 1H, CHO). Anal. Calcd. for $C_{25}H_{31}N_3OS$: C, 71.22, H, 7.41, N, 9.97, S, 7.61 Found: C, 71.23, H, 7.43, N, 10.03, S, 7.65.

4-(1,2,2,4-Tetramethyl-1,2,3,4-tetrahydroquinoline-6-carbonothioyl)piperazine-1-carbaldehyde (3'c)

Yield = 58 %, m.p. 199-201°C. ^{1}H NMR (DMSO-d_6): δ = 1.17 (s, 3H, $(CH_3)_{2A}$-C2), 1.27 (s, 3H, $(CH_3)_{2B}$-C2), 1.28 (d, J=7.36, 3H, CH_3-C_4), 1.40 (t, J=12.81, 1H, CH_{2A}), 1.83 (dd,

J=12.98, J=4.24, 1H, CH_{2B}), 2.77 (m, 1H, CH), 2.79 (s, 3H, N-CH_3), 3.60-4.40 (bro. m, 8H, 4CH_2-piperazine), 6.49 (d, J=9.17, 1H, ArH's), 7.17 (d, J=6.60, 1H, ArH's), 7.18 9 (s, 1H, ArH's), 8.10 (s, 1H, CHO). Anal. Calcd. for $C_{19}H_{27}N_3OS$: C, 66.05, H, 7.88, N, 12.16, S, 9.28 Found: : C, 66.07, H, 7.90, N, 12.22, S, 9.30.

Piperidin-1-yl(1,2,2,4-tetramethyl-1,2,3,4-tetrahydro-quinolin-6-yl)methanethione (3'd)

Yield = 79 %, m.p. 115-117ºC. ^{1}H NMR (DMSO-d_6): δ =1.17 (3H, s, $(CH_3)_{2A}$-C2), 1.26 (3H, s, $(CH_3)_{2B}$-C2), 1.27 (3H, d, J=6.59, CH_3-C4), 1.40 (1H, t, J=12.85, CH_{2A}), 1.44-1.65 (6H, bro. m., 3CH_2-piperidin.), 1.83 (1H, dd, J=13.04, J=4.44, CH_{2B}), 2.76 (1H, m, CH), 2.78 (3H, s, N-CH_3), 3.50-4.30 (4H, bro. m., 2CH_2-piperidin), 6.47 (1H, d, J=9.18, ArH's), 7.03 (1H, dd, J=6.79, J=2.16, ArH's), 7.04 (1H, s, ArH's). Anal. Calcd. for $C_{19}H_{28}N_2S$: C, 72.10, H, 8.92, N, 8.85, S, 10.13 Found: C, 72.13, H, 8.95, N, 8.91, S, 10.15.

Ethyl 1-(1,2,2,4-tetramethyl-1,2,3,4-tetrahydro-quinoline-6-carbonothioyl)piperidine-4-carboxylate (3'e)

Yield = 74 %, m.p. 110-112ºC. ^{1}H NMR (DMSO-d_6): δ = 1.10-2.10 (m, 19H, 4CH_3+CH_2-THQ+2CH_2-piperidin.), 2.72-2.80 (m, 8H, N-CH_3+2CH_2-piperidin.+CH-THQ), 4.08 (q, J=7.08, 2H, -O$\underline{CH_2}CH_3$), 6.47 (d, J=8.56, 1H, arom.), 7.05 (dd, J=8.14, J=2.00, 1H, ArH's), 7.07 (s, 1H, ArH's). Anal. Calcd. for $C_{22}H_{32}N_2O_2S$: C, 68.00, H, 8.30, N, 7.21, S, 8.25 Found: C, 68.01, H, 8.34, N, 7.25, S, 8.29.

(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)(morpholino)-methanethione (3'f)

Yield = 84 %, m.p. 140-142ºC. ^{1}H NMR (DMSO-d_6): δ = 1.24 (s, 3H, $(CH_3)_{2A}$-C2), 1.26 (s, 3H, $(CH_3)_{2B}$-C2), 1.32 (d, J=6.59, 3H, CH_3-C4), 1.64 (t, J=12.98, 1H, CH_{2A}), 1.90 (dd, J=13.03, J=4.72, 1H, CH_{2B}), 2.96 (m, 1H, CH), 3.50-4.20 (bro. m, 8H, 4CH_2-morph.), 4.26 (d, J=18, 1H, CH_{2A}-Bn), 4.78 (d, J=18.07, 1H, CH_{2B}-Bn), 6.13 (d, J=8.65, 1H, ArH's), 6.90 (dd, J=8.63, J=2.13, 1H, ArH's), 7.15-7.35 (m, 6H, ArH's).). Anal. Calcd. for $C_{24}H_{30}N_2OS$: C, 73.06, H, 7.66, N, 7.10, S, 8.13 Found: : C, 73.09, H, 7.70, N, 7.14, S, 8.14.

(4-Methylpiperazin-1-yl)(1,2,2,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)methanethione hydrochloride (3'g)

Yield = 66 %, m.p. 180-182 ºC. ^{1}H NMR (DMSO-d_6): δ = 1.19 (3H, s, $(CH_3)_{2A}$-C2), 1.28 (3H, s, $(CH_3)_{2B}$-C2), 1.30 (3H, d, J=7.31, CH_3-C4), 1.42 (1H, t, J=12.45, CH_{2A}), 1.85 (1H, dd, J=13.08, J=4.52, CH_{2B}), 2.75 (3H, d, J=4.55, N-CH_3-piperazin.), 2.81 (3H, s, N-CH_3-THQ), 3.08 (1H, m, CH), 4.10-4.70 (8H, bro. m., 4CH_2-piperazin), 6.50-7.35 (3H, m, ArH's), 11.25 (1H, s, HCl). Anal. Calcd. for $C_{19}H_{30}ClN_3S$: C, 62.02, H, 8.22, N, 11.42, S, 8.71, Cl, 9.63 Found: C, 62.06, H, 8.26, N, 11.46, S, 8.75, Cl, 9.67.

(1-Benzyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolin-6-yl)(4-methylpiperazin-1-yl)methanethione hydrochloride (3'h)

Yield = 70 %, m.p. 170-172 ºC. ^{1}H NMR (DMSO-d_6): δ = 1.26 (3H, s, $(CH_3)_{2A}$-C2), 1.27 (3H, s, $(CH_3)_{2B}$-C2), 1.34 (3H, d, J=6.59, CH_3-C4), 1.65 (1H, t, J=12.68, CH_{2A}), 1.92 (1H, dd, J=13.00, J=4.63, CH_{2B}), 2.73 (3H, d, J=4.56, N-CH_3), 2.99 (1H, m, CH), 4.26 (1H, d, J=18.19, CH_{2A}-Bn), 4.50-4.76 (8H, m, 4xCH_2-piperazin.), 4.80 (1H, d, J=18.23, CH_{2B}-Bn), 6.13-7.40 (8H, m, ArH's), 11.20 (1H, s, HCl). Anal. Calcd. for $C_{25}H_{34}ClN_3S$: C, 67.62, H, 7.22, N, 9.46, S, 7.22, Cl, 7.98 Found: C, 67.68, H, 7.77, N, 9.51, S, 7.27, Cl, 8.01.

General procedure for the synthesis of 5-alkyl-8-(carbonothioyl)-4,5-dihydro-4,4-dimethyl-1H-[1,2]dithiolo[3,4-*c*]quinoline-1-thiones (4a-d)

A mixture of N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehyde **1** (1 mmol), the corresponding amine (1.33 mmol), and elemental sulfur (7.33 mmol) in DMF (2 ml) was refluxed until the reaction is completed (monitoring using TLC: hexane/ethyl acetate 7:3). Up on the completion of the reaction the reaction mixture was allowed to cool overnight and 5 ml of isopropyl alcohol was added to ensure complete precipitation of the product. The solid obtained was filtered, washed with cold isopropyl alcohol followed by cold water.

4,4,5-Trimethyl-8-(morpholine-4-carbonothioyl)-4,5-dihydro-1H-[1,2]dithiolo[3,4-c]quinoline-1-thione (4a)

Light orange solid, Yield = 68 %, m.p. 105-107 ºC. ^{1}H NMR (DMSO-d_6): δ =1.55 (s, 6H, C4-C$(CH_3)_2$), 2.90 (s, 3H, N-CH_3), 3.60-3.90 (6H, bro. s, 6H, morph.), 4.20-4.40 (2H, bro. s, 2H, morph.), 6.94 (d, J = 8.65, 1H, H-6), 7.39 (dd, J = 6.34 and J = 2.26, H-7), 9.24 (d, J=8.65, 1H, H-8). Anal. Calcd. for $C_{18}H_{28}N_2OS_4$: C, 52.91, H, 4.93, N, 6.86, S, 31.39 Found: C, 52.93, H, 4.90, N, 6.89, S, 31.41.

5-Benzyl-4,4-dimethyl-8-(piperidine-1-carbonothioyl)-4,5-dihydro-1H-[1,2]dithiolo[3,4-c]quinoline-1-thione (4b)

Yellow solid, Yield = 86 %, m.p. 97-99 ºC. ^{1}H NMR (DMSO-d_6): δ =1.50 (bro. s, 6H, piper.), 1.67 (s, 6H, C4-C(CH3)2), 3.60 (bro. s, 2H, piper.), 4.25 (bro. s, 2H, piper.), 4.70 (s, 2H, Bn), 6.75 (d, J=8.71, 1H, H-6), 7.17 (dd, J = 8.64 and J = 2.19, 1H, H-7), 7.20-7.33 (m, 5H, Ph), 9.27 (d, J = 2.19, 1H, H-8). Anal. Calcd. for $C_{25}H_{26}N_2S_4$: C, 62.20, H, 5.43, N, 5.80, S, 26.57 Found: C, 62.23, H, 5.40, N, 5.84, S, 26.60.

5-Benzyl-4,4-dimethyl-8-(morpholine-4-carbonothioyl) -4,5-dihydro-1H-[1,2]dithiolo[3,4-c]quinoline-1-thione (4c)

Orange solid, Yield = 69 %, m.p. 110-112 ºC. ^{1}H NMR (DMSO-d_6): δ =1.70 (s, 6H, C4-C$(CH_3)_2$), 3.55-3.85 (bro. s, 6H, morph.), 4.20-4.40 (bro. s, 2H, morph.), 4.71 (s, 2H, Bn), 6.76 (d, J = 8.73, 1H, H-6), 7.23 (dd, J = 8.72 and

J=2.09, 1H, H-7), 7.30-7.40 (m, 5H, Ph), 9.31 (d, J = 2.23, 1H, H-8). Anal. Calcd. for $C_{24}H_{24}N_2OS_4$: C, 59.47, H, 4.99, N, 5.78, S, 26.46 Found: C, 59.50, H, 5.02, N, 5.81, S, 26.49.

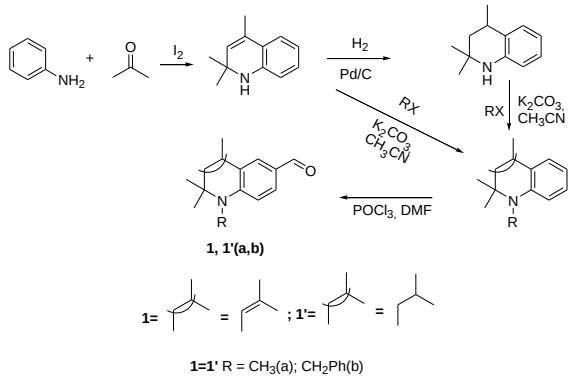
4,4,5-Trimethyl-8-(4-phenylpiperazine-1-carbono-thioyl)-4,5-dihydro-1H-[1,2]dithiolo[3,4-c]quinoline-1-thione (4d)

Light orange solid. Yield = 80 %, m.p. 90-92 °C. . ^{1}H NMR ($CDCl_3$): δ =1.25 (s, 6H, C4-C(CH_3)$_2$), 2.97 (s, 3H, N-CH3), 3.50-4.50 (m, 8H, piperazine), 6.95(d, J=8.59, 1H, H-6), 7.50-7.70 (m, 5H, Ph), 8.00 (dd, J = 8.50 and J = 2.19, 1H, H-7), 9.50 (d, J = 2.09, 1H, H-8). Anal. Calcd. for $C_{24}H_{25}N_2S_4$: C, 59.59, H, 5.21, N, 8.69, S, 26.51. Found: C, 59.63, H, 5.23, N, 8.67, S, 26.55.

RESULTS AND DISCUSSIONS

The purpose of this study is to investigate the regioselectivity in the three-component reaction of hydroquinoline-6-carbaldehydes, cyclic secondary amines and sulfur by taking 1.33 equivalent and excess of elemental sulfur.

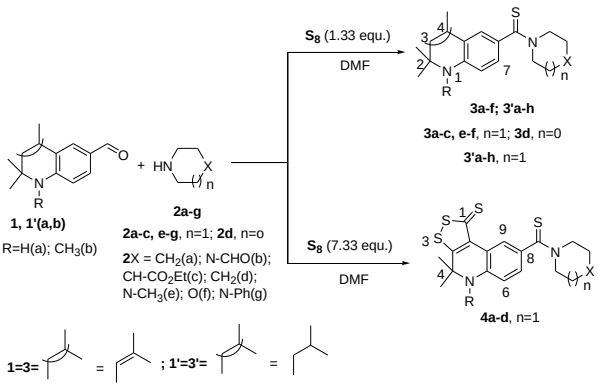
The multi-step synthesis of the starting materials 1-alkylhydroquinoline-6-carbaldehydes **1a**, **1b**, **1'a** and **1'b** were carried out by the know methods[25-26] as represented in Scheme 2.



Scheme 2. Synthesis of starting materials 1-alkylhydroquinoline-6-carbaldehydes **1** and **1'**.

Brown[6] has reported the synthesis of 4,5-dihydro-4,4-dimethyl-1H-1,2-dithiolo-[3,4-c]quinoline-1-thiones from 2,2,4-trimethyl-1,2-dihydroquinoline (and its 1-methyl and 6-ethoxy-derivatives) and 4.0 equivalents of sulfur in refluxing DMF. We have extended this reaction to N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehydes (**1a, b**) and N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes (**1'a, b**). In the case of **1a** and **1b** there is a competition between the Willgerodt-Kindler reaction of formyl group in the presence of amine and formation of 1H-1,2-dithiol-1-thione cycle from the 3, 4-double bond and the 4-methyl-group.

When 1.33 equivalents of elemental sulfur is used the Willgerodt-Kindler reaction takes place exclusively for both di- and tetrahydroquinolinecarbaldehydes (**1a**, **1b**, **1'a** and **1b**) resulting in thioamides **3a-f** and **3'a-h** as shown in Scheme 3. As one would expect this regioselectivity is due to the more reactivity of formyl group as compared to the double bond 4-CH_3-C4 = C3.



(**3a**) R=CH_3, X=CH_2; (**3b**) R=CH_3, X=N-CHO; (**3c**) R=CH_2Ph, X=CH_2; (**3d**) R=CH_3, X=CH_2; (**3e**) R=CH_3, X=NCH_3; (**3f**) R=CH_3, X=NPh; (**3'a**) R=CH_2Ph, X=CH_2, (**3'b**) R=CH_2Ph, X=N-CHO; (**3'c**) R=CH_3, X=N-CHO; (**3'd**) R=CH_3, X=CH_2; (**3'e**) R=CH_3, X=CH-COOEt; (**3'f**) R=CH_2Ph, X=O; (**3'g**) R=CH_3, X=NCH_3; (**3'h**) R=CH_2Ph, X=NCH_3; (**4a**) R=CH_3, X=O); (**4b**) R=CH_2Ph, X=CH_2; (**4c**) R=CH_2Ph, X=O; (**4d**) R=CH_3, X=NPh.

Scheme 3. Synthesis of thioamides **3a-f**, **3'a-g** and 1H-1,2-dithiol-1-thiones **4a-d**.

The ^{1}H-NMR spectra of compound **3a-f** indicated that there are singlet 4-methyl protons signals in the range of δ 1.89-1.95 ppm and singlet 3-CH-methine protons signals in the range δ 5.39-5.48 ppm. As compared to the starting materials **1a,b**, there is no formyl proton signal instead there are broad singlet signals in the range δ 1.45-1.70 ppm and δ 3.50-4.30 ppm for compounds **3a** and **3c** which are assignable for ten piperidine methylene protons.

For compounds **3b, 3e** and **3f** the eight piperazine methylene protons appeared as broad signals in the range δ 3.50-4.85 ppm. The pyrolidine methylene protons of compound **4d** are clearly seen as a pair of pentat signals at δ 1.87 ppm, J=6.73 Hz and δ 1.97 ppm, J=6.94 Hz, and two triplet signals at δ 3.60 ppm, J=6.62 Hz and δ 3.77 ppm, J= 7.02 Hz.

The 4-methyl doublet protons, 4-CH methine multiplet proton and the two diastreotropic 3-CH_{2A} (triplet) and 3-CH_{2B} (doublets of doublet) methylene protons signals of compound **3'a-h** appeared in the range δ 1.27-1.34, 1.96-3.08, 1.40-1.65 and 1.80-1.92 ppm, respectively.

In the ^{1}H NMR spectra of compounds **3e, 3'g, 3h**, isolated in hydrochloride form, the proton signals are broadened in the range of 11.20 -11.40 ppm.

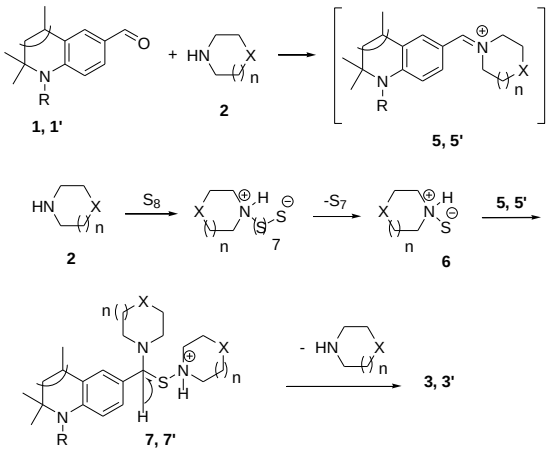
Compounds **3a-f, 3'a-h** is obtained in 56-84% yields. Their colors vary from light yellow to red. They are soluble in most polar solvents (chloroform, DMF, DMSO, ethanol).

In the ^{1}H-NMR spectra of compounds **4a-d** there are no 3-CH-methine, 4-methyl- and formyl protons signals as compared to the starting materials **1a,b**. This is due the

formation of the pseudoaromatic heterocyclic ring via the 3,4-double bond and 4-methyl of N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehydes and sulfur in addition to the formation of thioamides.

An attempt that was made to synthesis 5-R-8-(carbonothioyl)-4,5-dihydro-4,4-dimethyl-1H-[1,2]dithiolo [3,4-c]quinolin-1-thione from the reaction of N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines **1'a,b**, secondary cyclic amine and excess sulfur was not successful. This might be due the reason that the amine catalyst is unable to facilitate the dehydrogenation reaction of C3-C4 bond to form the allylic methyl form to undergo sulfurization.

A plausible reaction mechanism for the Willgerodt-Kindler reaction of hydroquinolinecarbaldehydes with amines and elemental sulphur is shown in Scheme 4 and we propose that the reaction mechanism is analogous with the work reported in reference[27] for phenyl glyoxals. The condensation of hydroquinolinecarbaldehydes **1, 1'** with amine **2a-g** gave the iminium salt **5, 5'**. Subsequent nucleophilic addition of amine to sulphur, followed by elimination of S7, ammonium sulfide leads to **6**. Intermediate **7, 7'** is then produced by nucleophilic addition of **6** to iminium salt **5, 5'** which is finally converted into the desired thioamides **3, 3'** by the elimination of a molecule of amine.



Scheme 4. Plausible Reaction mechanism for the synthesis of **3, 3'**.

Conclusions

When 1.33 equivalent of elemental sulfur is used exclusively the Willgerodt-Kindler reaction takes place both for the N-alkyl-2,2,4-trimethyl-1,2-dihydro-quinoline-6-carbaldehydes and N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-6-carbaldehydes which results in the formation of thioamides. The use of excess sulfur leads to the formation of both 5-R-8-(carbonothioyl)-4,5-dihydro-4,4-dimethyl-1H-[1,2]dithiolo [3,4-*c*]quinolin-1-thione cycle and thioamide for N-alkyl-2,2,4-trimethyl-1,2-dihydroquinoline-6-carbaldehydes. In the case of N-alkyl-2,2,4-trimethyl-1,2,3,4-tetrahydro-quinoline-6-carbaldehydes the use of excess sulfur gave only the Willgerodt-Kindler thioamide product and there is no formation of 1H-1,2-dithiol-1-thione.

Acknowledgments

This work was supported by the Ministry of Education and Science of Russian Federation within the frame work of contract No. 218.N 02.G25.31.000.

References

[1]Landis, P. S. *Chem. Rev.* **1965**, 65, 237.
[2]Pedersen, C. *Th. Adv. Heterocyclic Chem.* **1982**, 31, 63 and *Sulfur Rep.* **1995**, 16, 173.
[3]Bottcher, B., and Bauer, F., *Ann*., **1950**, 227, 568, *Ber*., **1951**, 84, 458, *Ann*., 1951, 218, 574.
[4]Mollier, Y., and Lozach, N., *Bull. Soc. Chim. France*, **1958**, 651, **1960**, 700.
[5]Spindt, R. S., Stevens, D. R., and Baldwin, W. E., *J. Am. Chem. Soc*., **1951**, 73,3693.
[6]Brown, J. P., *J. Chem. Soc. (C)*, **1968**, 1074.
[7]Barreau, M., Cotrel, C., Jeanmart, C., *Chem. Abst*. **1977**, 86, 121373.
[8]Prochaska, H. J., Rubinson, L., Yeh, Y., Baron, P., Polsky, B. *Molecular Pharmacology*, **1991**, 45, 916.
[9]Kensler, T. W., Groopman, J. D., Eaton, D. L., Curphey, T. J., Roebuck, B. D. *Carcinogenesis* **1992**, 13, 95.
[10](a) Hagen, H., Fleig, H. Ger. Offen. Patent 2, 460,783, *Chem. Abst.* **1976**, 85, 123899. (b) Bader, J., Gaetzi, K. Ger. Offen. Patent 1, 278,701, *Chem. Abst*. **1969**, 70, 115147.
[11]Misra, P., Misra, S., Mohapatra, R., Mittra, A. J. *Indian Chem. Soc*. **1979**, 61, 404.
[12](a) Suzuki, Y., Yazaki, R., Kumagai, N., Shibasaki, M. *Chem. Eur. J*. **2011**, 17, 11998. (b) Suzuki, Y., Yazaki, R., Kumagai, N., Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, 48, 5026. (c) Sureshkumar, D., Kawato, Y., Iwata, M., Kumagai, N., Shibasaki, M. *Org. Lett*. **2012**, 14, 3108. (d) Koduri, N. D., Scott, H., Hileman, B., Cox, J. D., Coffin, M., Glicksberg, L., Hussaini, S. R. *Org. Lett.* **2012**, 14, 440. (e) Ogawa, T., Mouri, S., Yazaki, R., Kumagai, N., Shibasaki, M. *Org. Lett.* **2012**, 14, 110. (f) Yazaki, R., Kumagai, N., Shibasaki, M. *Org. Lett.* **2011**, 13, 952. (g) Murai, T., Ui, K., Narengerile *J. Org. Chem.* **2009**, 74, 5703. (h) Arshad, N., Hashim, J., Kappe, C. O. *J. Org. Chem.* **2009**, 74, 5118.
[13](a) Hanzlie, R. P., Vyas, K. P., Traiger, G. J. *Toxicol. Appl. Pharmacol*. **1980**, 46, 685. (b) Walter, H., Zambach, W. *Chem. Abstr*. **1996**, 125, 55871.
[14](a) Wingert, H., Sauter, H., Bayer, H., Oberdorf, K., Lorenz, G., Ammermann, E. EP 35, **1994**, *Chem. Abstr*. **1994**, 121, 533719. (b) Wei, Q.-L., Zhang, S.-S., Gao, J., Li, W.-H., Xu, L.-Z., Yu, Z.-G. *Bioorg. Med. Chem.* **2006**, 14, 7146.
[15](a) Thioamide pesticides Searle, R. J. G., Boyce, C. B. C., Bay, H. US 4,096,275, **1978**. (b) Insecticides, nematocides Fauss, R., Findeisen, K., Becker, B., Hamman, I., Homeyer, B. US 4,581,375, **1986**.
[16](a) Bandgar, B. P., Gawande, S. S., Warangkar, S. C., Totre, J. V. *Bioorg. Med. Chem.* **2010**, 18, 3618. (b) Harrowven, D. C., Lucas, M. C., Howes, P. D. *Tetrahedron Lett*. **1999**, 40, 4443.
[17]Reynard, P., Moreau, R. C., Samama, J. P. *Bull. Soc. Chim. Fr*. **1965**, 12, 3623.
[18]Jeschke, P., Harder, A., Etzel, W., Gau, W., Thielking, G., Bonse, G., Iinuma, K. *Pest Manage. Sci.* **2001**, 57, 1000, *Chem. Abstr*. **2001**, 136, 839295.
[19](a) Batjargal, S., Wang, Y. J., Goldberg, J. M., Wissner, R. F., Petersson, E. J. *J. Am. Chem. Soc.* **2012**, 134, 9172. (b) Xie, J., Okano, A., Pierce, J. G., James, R. C., Stamm, S., Crane, C. M., Boger, D. L. *J. Am. Chem. Soc.* **2012**, 134, 1284. (c) Sharma, I., Crich, D. *J. Org. Chem.* **2011**, 76, 6518. (d) Wang, L., Xu, Z., Ye, T. *Org. Lett.* **2011**, 13, 2506.
[20](a) Mason, C. R., Maynard-Atem, L., Al-Harbi, N. M., Budd, P. M., Bernardo, P., Bazzarelli, F., Clarizia, G., Jansen, J. C. *Macromolecules* **2011**, 44, 6471. (b) Deletre, M., Levesque, G. *Macromolecules* **1990**, 23, 4876. (c) Kanbara, T., Kawai, Y., Hasegawa, K., Morita, H., Yamamoto, T. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, 39, 3739.
[21](a) Cao, J.-L., Qu, J. *J. Org. Chem.* **2010**, *75*, 3663. (b) Geng, X.-L., Wang, J., Li, G.-X., Chen, P., Tian, S.-F., Qu, J. *J. Org. Chem.* **2008**, *73*, 8558. (c) Chen, P., Qu, J. *J. Org. Chem.* **2011**, *76*, 2994. (d) Hernández, J. G., García- López, V., Juaristi, E. *Tetrahedron* **2012**, *68*, 92. (e) Ganesh, M., Seidel, D. *J. Am. Chem. Soc.* **2008**, 130, 16464.

[22](a) Raucher, S., Klein, P. *J. Org. Chem.* **1981**, *46*, 3558. (b) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461. (c) Cho, D., Ahn, J., De Castro, K. A., Ahn, H., Rhee, H. *Tetrahedron* **2010**, *66*, 5583. (d) Bergman, J., Pettersson, B., Hasimbegovic, V., Svensson, P. H. *J. Org. Chem.* **2011**, *76*,1546. (e) Smith, D. C., Lee, S. W., Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348. (f) Pathak, U., Pandey, L. K., Tank, R. *J. Org. Chem.* **2008**, *73*, 2890. (g) Shibahara, F., Sugiura, R., Murai, T. *Org. Lett.* 2009, *11*, 3064. (h) Kaboudin, B., Malekzadeh, L. *Synlett* 2011, 2807. (i) Coats, S. J., Link, J. S., Hlasta, D. J. *Org. Lett.* **2003**, *5*, 721. (j) Kaleta, Z., Makowski, B. T., Soós, T., Dembinski, R. *Org. Lett.* **2006**, *8*, 1625.
[23]Brown, E. V. *Synthesis* **1975**, 358, and references cited therein.
[24]Webel, L. M., McNamara, D. J., Colbry, N. L., Johnson, J. L., Degnan, M. J., Whitney, B., *J. Heterocycl. Chem.*, **1979**, 16(5), 881.
[25]Krysin, M. Yu., Shikhaliev, Kh. S., Anokhina, I. K., Shmyreva, Zh. V.,*Chem. Heterocycl. Compd*., **2001**, 37, 227.
[26]Kaijun, T. H., Dehui, H. R., Shuangqing, W., Shayu, L. Y. L., Guoqiang, Y.,*Chem. Commun*., 2011, 47, 10052.
[27]Bagher, E., Saleh, V. K., Orhan, B., *Synlett* **2013**, 24, 977.

Received: 09.06.2015.
Accepted: 30.07.2015.