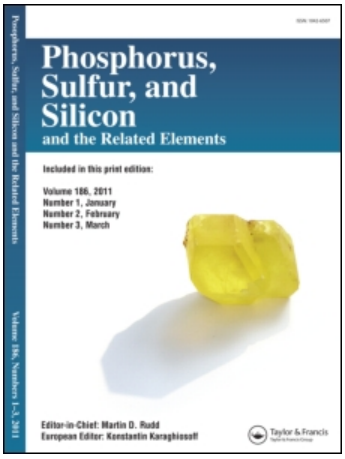

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Synthesis and NMR Properties of Pentacyclic Heterocycles Containing Sulfur, Nitrogen And Oxygen Or Selenium

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SYNTHESIS AND NMR PROPERTIES OF PENTACYCLIC HETEROCYCLES CONTAINING SULFUR, NITROGEN AND OXYGEN OR SELENIUM*

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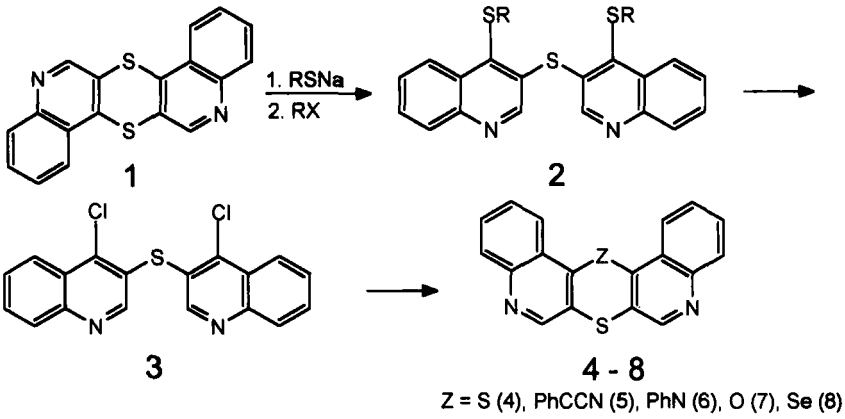
4,4'-Dichloro-3,3'-diquinolinyl sulfide **3** underwent ring closure reactions with divalent nucleophiles to pentacyclic heterocycles: dithiin **4**, thiopyran **5**, thiazine **6**, oxathiin **7** and thiaselenin **8** in good yield (76–100%). The chemical shift of the H-1 and H-13 protons in ^{1}H NMR spectra is a result of the interaction between these atoms and the Z-atom.

Key words: Ring opening, ring closure, cyclization, thiopyran, 1,4-dithiin, 1,4-thiazine, 1,4-oxathiin, 1,4-thiaselenin.

INTRODUCTION

Quinolines condensed with various heterocycles have recently become important compounds because of their affinity to the benzodiazepine receptors,[1,2] interesting ^{1}H and ^{13}C NMR spectral properties[3–6] or isolation from marine organisms.[7] The pentacyclic heterocycle-thio-quinanthrene **1** (1,4-dithiino[2,3-c; 5,6-c']diquinoline—easy to obtain in 60–64% yield from the products of exhaustive sulfurization of quinoline with elemental sulfur[8]) is an excellent substrate for synthesis of various 3,4-disubstituted quinolines in the reactions of the 1,4-dithiin ring opening with O-, S-, N and C-centered nucleophiles.[9–15] The reactions of dithiin **1** with sodium alkanethiolates or with S-alkylisothiouronium salts (in the presence of alkali) in DMSO or DMF at 70°C led unexpectedly after S-alkylation to symmetrical 4,4'-dialkylthio-3,3'-diquinolinyl sulfides **2** being the result of the Smiles rearrangement of primary products.[13,14] Easy transformation some of sulfides **2** (an alkyl group was methyl or benzyl) into 4,4'-dichloro-3,3'-diquinolinyl sulfide **3**[16,17] offers possibility to use the latter compound as a very useful and universal substrate to obtain pentacyclic heterocycles **4–8**, possessing different central 6-membered ring (i.e. a dithiin, a thiopyran, a thiazine, an oxathiin and a thiaselenin ring).

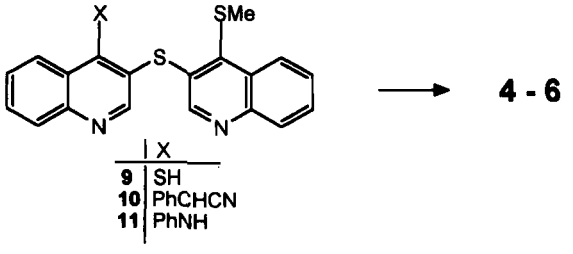
*Part XXXIII in the series of Azinyl Sulfides. Part XXXII: A Maślankiewicz and A. Zięba, Polish J. Chem. (submitted).



RESULTS AND DISCUSSION

Synthesis

A substituent in position 4 in quinoline ring is most often introduced in the nucleophilic substitution of chlorine atom in 4-chloroquinolines.[18] This fact prompted us to use dichlorocompound **3** and divalent nucleophiles to build fused heterocyclic compounds. The solvents for these syntheses were found in preliminary experiments using dichlorocompound **3** and thiourea (the best results were found in 2-(2-methoxyethoxy)ethanol—100%, in DMSO and DMF—80–85%) or using modified standard conditions[19,20] (DMSO and anhydrous potassium carbonate for the carbanion reaction; pyridine-acetic acid-acetic anhydride for the oxathiin synthesis). All the described heterocycles **4–8** were obtained in good yield (77–100%). A tendency of dichlorocompound **3** to undergo the ring closure reactions was much greater than the disubstitution reactions (giving 4,4′-disubstituted-3,3′-diquinolinyl sulfides). The confirmation of the easiness of cyclization is a behaviour of S-methyl group during heating 4-substituted 4′-methylthio-3,3′-diquinolinyl sulfides **9–11** (the products of the 1,4-dithiin ring opening reactions in dithiin **4**[13]) in the same conditions as for dichlorocompound **3**. Although there are only a few reports[21–23] involving nucleophilic substitution of a S-methyl or a S-ethyl group in 2- and 4-alkylthiopyridines and quinolines however the S-methyl group in sulfides **9–11** turned to be as good leaving group as chlorine giving heterocycles **4–6** in 78–96% yield. Inconvenience of these syntheses is unpleasant odour of methanethiol liberated.



Attempts to use dichlorocompound **3** in the building of larger central heterocyclic rings (8-, 9- and 12-membered ones) in the reactions with alkanedithiols and their disodium salts were unsuccessful. Dithiin **4** was isolated as the main product from the reaction mixture as a result of a degradation process. The idea of synthesis of quinolinophane crown thioethers possessing 3,3'-thiobis(4-quinolinyl) units has been realized on a separate way.[24]

^{1}H NMR Study

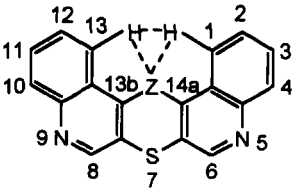
4,4'-Disubstituted 3,3'-diquinolinyl sulfides similar to 4-substituted 3,4'-diquinolinyl sulfides[12,25,26] exhibit non-typical ^{1}H NMR properties.[27–29] The signals of the H-$5_{quinolinyl}$ protons in deuteuriochloroform are shifted downfield due to through-space interaction with the 4- and 4'-heteroatoms in comparison with the signal of the H-$5_{quinolinyl}$ proton in quinoline (7.68 ppm[30]). This "peri" effect causes that the signal of the H-$5_{quinolinyl}$ proton is found even more downfield than the signal of the H-$8_{quinolinyl}$ proton (8.05 ppm in quinoline[30]). On the other hand the conformations of 3,3'- and 3,4'-diquinolinyl sulfides have an effect on the signal of the H-$2_{quinolinyl}$ protons, which are sometimes shifted upfield in the region of 7.85–8.30 ppm[27,31] (8.85 ppm in quinoline[30]). The conformations of diquinolinyl sulfides are connected with a rotation around the central sulfide bond. In the case of heterocyclodiquinolines **4–8** the rotation is restricted by the presence of the Z group linking the carbons C_{13b} and C_{14a}.

The ^{1}H NMR spectra of the pentacyclic heterocycles, recorded in deuteriochloroform at 300 MHz, showed multiplets of ABCD system of the benzene ring protons and a singlet of the H-$2_{quinolinyl}$ (i.e. the H-6 and H-8) protons. The assignment of the ABCD system was accomplished by the ^{1}H-^{1}H correlation (COSY) and the LAOCOON-3 calculation.

All the ^{1}H NMR spectra showed symmetrical structure of the heterocycles **4–8** (the "left" side is equal to the "right" side) what means that the 3-quinolinyl bond was not cleaved in the course of the synthesis as was observed during synthesis of sulfide **2** from dithiin **1**.[13,14] The ^{1}H NMR spectra of dithiin **4** and oxathiin **7** (published separately[16,32] showed interesting properties in comparison with the open ring compound—4-methoxy-4'-methylthio-3,3'-diquinolinyl sulfide.[27] Whereas the "peri" effect caused by the influence of the sulfur atom on the H-1 and H-13 (the H-$5_{quinolinyl}$) protons is close to the effect of the methylthio group ($\Delta\delta$ = 0.80 vs 0.85 ppm), the effect of the oxygen atom is greater than the methoxy group ($\Delta\delta$ = 0.62 vs 0.50 ppm). In thiopyran **5**, thiazine **6** and thiaselenin **8** the deshielding effect is even greater ($\Delta\delta$ = 1.01, 0.71 and 0.66 ppm respectively) than found in oxathiin **7**.

Although the selenium atom possesses the greatest van de Waals' radius (2.0 or 2.15 Å[33,34]) the effect found in thiaselenin **8** is quite small. It is obvious that the value of the "peri" effect depends on the H-1 . . . Z and H-13 . . . Z distance. This distance is relative to the length of the C(13b)—Z and C(14a)—Z bonds, which is the greatest for the C—Se bond (1.91–1.93 Å in perphenylselenobenzene and naphthalene,[35,36] which is about 0.16–0.17 Å greater than the $C_{4\text{-quinolinyl}}$—S bond length in dihydrochloride of dithiin **1**[37]). For thiopyran **5** and thiazine **6** the deshielding effect is greater than expected from the open ring compounds **10** and

11.[38] In our opinion the deshielding effect in thiopyran **5** and thiazine **6** is consistent of the "peri" effect (the interaction between the H-1 . . . Z and H-13 . . . Z atoms) and the additional interaction between the H-1 . . . H-13 atoms. The interaction between the H-1 and H-13 atoms and the ortho-phenyl hydrogen atoms was observed using homonuclear NOE (Nuclear Overhauser Enhancement) difference spectroscopy. Upon irradiation of ortho-phenyl protons in thiopyran **5** and thiazine **6** (7.89 and 6.46 ppm, respectively) the significant enhancement of the H-1 and H-13 protons signals was observed (8.69 ppm–18.4% and 8.39 ppm–10.2%). The influence of the sulfur atom at position 7 on the chemical shift of the H-6 and H-8 protons ("ortho" effect) seems to be different. This signal is shifted upfield in heterocycles **5** and **7** (8.82 and 8.52[16] ppm) and the downfield in heterocycles **4**, **6** and **8** (8.90,[32] 9.04 and 8.95 ppm). Although the influence of the Z atom can not be underestimated ("meta" effect) however such an effect is considered as small.[39] In our opinion the chemical shift of the H-6 and H-8 protons is influenced by the conformation of the central heterocyclic ring which is considered as nonplanar.[40]



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CONCLUDING REMARKS

In conclusion we can state the transformation of dithiin **1** into sulfide **3** by ring opening reactions and followed by ring closure reactions of the latter compound offers very useful and universal way to prepare pentacyclic heterocycles from quinoline.

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 spectrometer at 300 MHz in deuteriochloroform. The NOE difference measurements were performed at 300 MHz on the same sample used to determine the ^{1}H NMR spectra. The sample was not degassed. Acquisition parameters: spectral width −400 Hz, pulse width −3 μs (90°), irradiation time −4 s, irradiation power −22 L, relaxation time −40 s. Mass spectra were run on a LKB 9000S spectrometer using the electron impact method. Thin layer chromatography was performed on aluminum 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.

4,4'-Dichloro-3,3'-diquinolinyl sulfide **3** was obtained from sulfide **2** as described previously.[16,17] 1,4-Dihydro-4-thioxo-4'-methylthio-3,3'-diquinolinyl sulfide[17] **9**, 4-(1-cyanobenzyl)-4'-methylthio-3,3'-diquinolinyl sulfide[13] **10** and 4-anilino-4'-methyl-3,3'-diquinolinyl sulfide[13] **11** were obtained according to the literature.

1,4-Dithiino[2,3-c;6,5-c']diquinoline **4**. A solution of sulfide 3 (0.36 g, 1 mmol) and thiourea (0.15 g, 2 mmols) in 20 ml of 2-(2-methoxyethoxy)ethanol was stirred for 30 minutes at ambient temperature and then refluxed for 1 hour. After cooling long pale yellow needles were precipitated which were filtered off to give dithiin **4** (0.32 g, 100%); mp 270–271°C, lit[13] mp 270–271°C.

14-Cyano-14-phenyl-thiopyrano[2,3-c;6,5-c']diquinoline **5**. A mixture of sulfide **3** (0.36 g, 1 mmol), phenylacetonitrile (0.23 g, 2 mmols), anhydride potassium carbonate (0.28 g, 2 mmols) and anhydrous DMSO (10 ml) was stirred at 80°C for 1 hour. After cooling the reaction mixture was poured into water (40 ml). A resulting solid was filtered off and crystallized from 2-(2-methoxyethoxy)ethanol to give thiopyran **5** (0.32 g, 80%); mp > 300°C, lit[13] mp > 300°C. ^{1}H NMR ($CDCl_3$): δ, ppm, 7.14 (m, 1H, p-C_6H_5), 7.31 (m, 2H, m-C_6H_5), 7.58 (m, 2H, H-2, H-12), 7.64 (m, 2H, H-3, H-11), 7.89 (m, 2H, o-C_6H_5), 8.08 (ddd, 2H, H-4, H-10), 8.69 (ddd, 2H, H-1, H-13), 8.82 (s, 2H, H-6, H-8), the values of aromatic coupling constants [Hz] are: $J_{1,2}$ = 8.8, $J_{1,3}$ = 1.1, $J_{1,4}$ = 0.6, $J_{2,3}$ = 6.8, $J_{2,4}$ = 1.3, $J_{3,4}$ = 8.5.

14-Phenyl-1,4-thiazino[2,3-c;6,5-c']diquinoline **6**. A solution of sulfide **3** (1.07 g, 3 mmols) and aniline (0.56 g, 6 mmols) in 15 ml of 2-(2-methoxyethoxy)ethanol was refluxed for 4 hours. After cooling yellow crystals were precipitated which were filtered off to give thiazine **6** (0.87 g, 77%); mp > 300°C. ^{1}H NMR ($CDCl_3$): δ, ppm 6.46 (m, 2H, o-C_6H_5), 6.91 (m, 1H, p-C_6H_5), 7.06 (m, 2H, m-C_6H_5), 7.69 (m, 2H, H-2, H-12), 7.79 (m, 2H, H-3, H-11), 8.23 (ddd, 2H, H-4, H-10), 8.39 (ddd, 2H, H-1, H-13), 9.04 (s, 2H, H-6, H-8), the values of aromatic coupling constants [Hz] are: $J_{1,2}$ = 8.4, $J_{1,3}$ = 1.3, $J_{1,4}$ = 0.5, $J_{2,3}$ = 6.9, $J_{2,4}$ = 0.9, $J_{3,4}$ = 8.5. MS (15 eV): m/z (%) 377 (M^+, 100%); 345 (M-S, 6.1); 300 (M-C_6H_5, 5.5).

1,4-Oxathiino[3,2-c;5,6-c']diquinoline **7**. A solution of sulfide **3** (0.36 g, 1 mmol) in the mixture of solvents: pyridine (16 ml), acetic anhydride (14 ml) and acetic acid (2 ml) was refluxed for 3 hours. After cooling the solution was diluted with cold water (40 ml). A resulting solid was filtered off and crystallized from 2-(2-methoxyethoxy)ethanol to give oxathiin **7** (0.23 g, 76%); mp 207–208°C, lit[20] mp 207°C.

1,4-Thiaselenino[2,3-c;6,5-c']diquinoline **8**. A solution of sulfide **3** (0.36 g, 1 mmol) and selenourea (0.25 g, 2 mmols) in 20 ml of 2-(2-methoxyethoxy)ethanol was stirred for 30 minutes at ambient temperature and then refluxed for 1 hour. After cooling long yellow needles were filtered off to give thiaselenin **8** (0.35 g, 96%); mp 271–272°C. ^{1}H NMR ($CDCl_3$): δ ppm, 7.67 (m, 2H, H-2, H-12), 7.76 (m, 2H, H-3, H-11), 8.13 (ddd, 2H, H-4, H-10), 8.34 (ddd, 2H, H-1, H-13), 8.95 (s, 2H, H-6, H-8), the values of aromatic coupling constants [Hz] are: $J_{1,2}$ = 8.4, $J_{1,3}$ = 1.3, $J_{1,4}$ = 0.5, $J_{2,3}$ = 6.9, $J_{2,4}$ = 1.0, $J_{3,4}$ = 8.4. MS (15 eV): m/z (%) 365 (M^+, 100); 333 (M-S, 1.8); 286 (M-Se, 18.1); 285 (M-SeH, 91.0).

Cyclization of sulfide **9**. A solution of sulfide **9** (0.37 g, 1 mmol) in 20 ml of 2-(2-methoxyethoxy)ethanol was refluxed for 30 minutes. After cooling long pale yellow needles were precipitated which were filtered off to give dithiin **4** (0.31 g, 97%), mp 270–271°C, lit[13] mp 270–271°C.

Cyclization of sulfide **10**. A solution of sulfide **10** (0.45 g, 1 mmol) in anhydride DMSO (10 ml) was stirred at 80°C for 2 hours. After cooling the reaction mixture was poured into water (40 ml). A resulting solid was filtered off and crystallized from 2-(2-methoxyethoxy)ethanol to give thiopyran **5** (0.31 g, 78%), mp > 300°C, lit[13] mp > 300°C.

Cyclization of sulfide **11**. A solution of sulfide **11** (0.43 g, 1 mmol) in 5 ml of 2-(2-methoxyethoxy)ethanol was refluxed for 30 minutes. After cooling yellow crystals were precipitated which were filtered off to give thiazine **6** (0.36 g, 95%), mp > 300°C.

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