Synthesis of New Dihydrooxathiino[2,3-*b*]quinoline

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Received January 25, 1996

A synthesis of new dihydrooxathiinoquinoline **4** is described. The key compound **6** was prepared by known methods from acetoacetanilide **1**. A condensation of β-chlorosulfide **6** in 75% aqueous sulfuric acid gave quinolone **5**. Conversion of **5** to **4** was achieved by treatment with potassium hydroxide in ethanol solution.

J. Heterocyclic Chem., **33**, 2055 (1996).

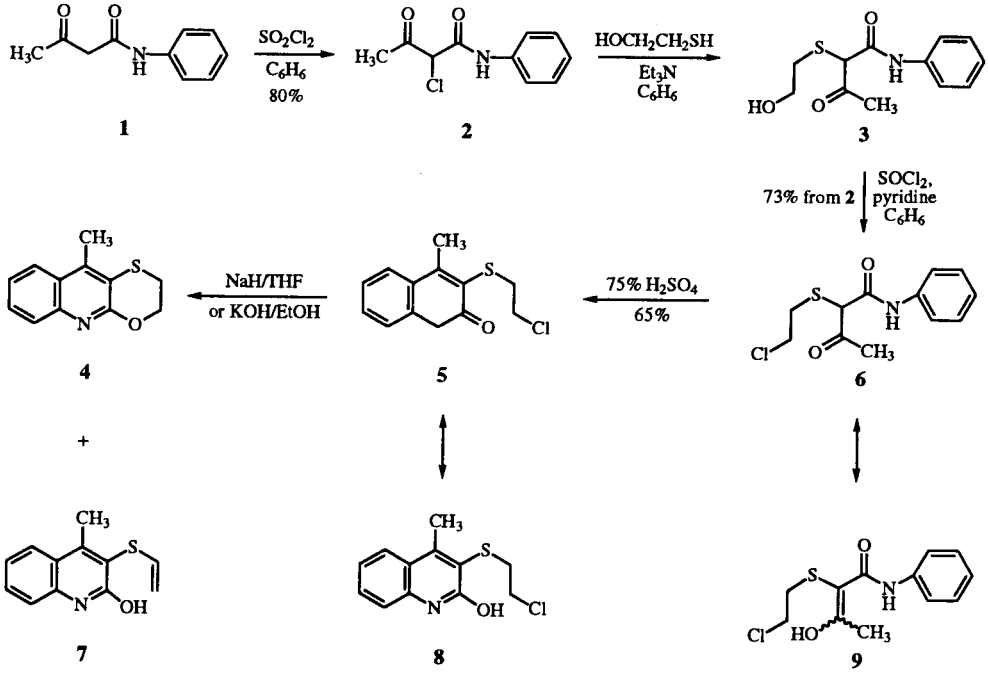
Introduction.

Synthetic methods available for the construction of heterocyclic molecules can be used to effect a number of valuable synthetic transformations. Carboxin, which is a well-known systemic fungicide used for seed treatment has a sulfur and an oxygen atom in a dihydro-1,4-oxathiin skeleton [2]. In our previous paper, we reported the syntheses of 1,4-oxathiin, and benzoxathiin [3]. As an extension of our studies on the synthesis of new heterocycles including the 1,4-oxathiin group, we report herein the synthesis of a new dihydrooxathiinoquinoline derivative.

Results and Discussion.

A new dihydrooxathiinoquinoline **4** was prepared according to Scheme 1 as shown below. β-Hydroxysulfide **3** was obtained from a reaction of α-chloroacetoacetanilide **2**, which was prepared by chlorination of acetoacetanilide **1**, with 2-mercaptoethanol by a previously reported method [4]. Treatment of **3** with thionyl chloride in the presence of pyridine gave the previously unknown β-chlorosulfide **6** in high yield (88%). This product is the enol form **9** and not the keto form **6** as has been demonstrated by its ir and ^{1}H nmr spectrum. Thus, the ketone carbonyl band is absent in the ir spectrum and the singlet at δ 15.6 ppm in the ^{1}H nmr is indicative of an enolic proton. The enolization appears to be aided by the sulfur atom since unsubstituted β-ketoamides are largely the keto tautomer [5]. The β-cholorosulfide **6** was converted to a new quinoline derivative **5** by heating it at 80° in 75% aqueous sulfuric acid. A similar condensation of the **1** to 4-methylcarbostyril in concentrated sulfuric acid has been reported [6]. When the reaction of **6** to **5** was allowed to proceed in concentrated sulfuric acid at 80°, we obtained a mixture of **5** and a small amount of decomposed product **1**. The yield of **5** was 45% in this case. On the other hand, the reaction did not proceed in 50% aqueous sulfuric acid at the same temperature. The identity of **5** was established by comparison of its ir and ^{1}H nmr spectra with those of the 4-methylcarbostyril. A broad

Scheme 1



singlet at δ 11.7 ppm in the ^{1}H nmr spectrum was assigned to the hydroxy proton of **8** rather than amide proton of **5** (tautomer). Although the molecular ion (M^+) was not found in mass spectrum **5** gave fragmentations at m/z 217 resulting from ring closure to **4**.

Treatment of the **5** with sodium hydride in tetrahydrofuran gave a 6:4 mixture of dihydrooxathiinoquinoline **4** and the vinyl sulfide **7** accompanied by a trace amount of disulfide [7] in 86% yields. Deprotonation of the hydroxy and displacement of the chloride by the alkoxide undoubtly results in the formation of **4**. When the quinolone **5** refluxed in ethanol solution in the presence of excess (1.2 equivalents) potassium hydroxide **4** was obtained in moderate yield (55%) without competing formation of **7**. Potassium hydroxide is not basic enough to abstract a proton α to sulfur but is basic enough to facilitate displacement of chloride by the amide oxygen. While it was known that intramolecular *O*-alkylation products are rarely formed in comparison to *N*-alkylation products under alkaline conditions [8], this regiospecific cyclization can be explained by the proximity of the oxygen atom to the carbon atom bearing the chloride. Disappearance of the signal for the OH proton of **8** was accompanied by the appearance of the two multiplets at δ 3.17-3.33 ppm and δ 4.60-4.76 ppm in the ^{1}H nmr spectrum of **4**.

EXPERIMENTAL

Melting points were determined on a Electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded on a Analect FX 6160 spectrophotometer using the potassium bromide technique. All ^{1}H nmr spectra were acquired on either a Varian EM 360 at 60 MHz, or Varian Gemini 300 spectrometer at 300 MHz in deuteriochloroform, with tetramethylsilane as an internal standard and are reported in δ units. Mass spectra (ms) were recorded on a JEOL JMS-DA 303 mass spectrometer, equipped with JMA-DA 5000 data system. Elemental analyses of new compounds were performed by a FISON 1108 analyzer. All chromatographic isolation were accomplished by Kieselgel GF 254 (230-400 mesh) silica gel.

Preparation of 2-(2-Chloroethylthio)-3-oxo-*N*-phenylbutanamide (**6**).

To a suspended solution of α-chloroacetoacetanilide **2** [4] (150 g, 0.71 mole) in benzene (600 ml) was added a solution of 2-mercaptoethanol (51 ml, 0.717 mole) and triethylamine (100 ml, 0.717 mole) dropwise over 30 minutes at below 30°. The reaction mixture was stirred for 2 hours at room temperature. Without isolation of the β-hydroxysulfide **3**, the reaction mixture was treated sequentially with pyridine (59 ml, 0.78 mole), and then added thionyl chloride (57 ml, 0.78 mole) dropwise over an hour at below 10°. The reaction mixture was stirred for 2 hours at room temperature. The cold water (500 ml) poured into the reaction mixture and then organic layer was separated, washed with 1*N* hydrochloric acid, saturated sodium bicarbonate solution, water and then dried (magnesium sulfate). The solvent was evaporated to give yellow oily residue. Crystallized form ethanol (500 ml) gave β-chlorosulfide **6** as a pale yellow crystals (140 g, 73%), mp 81-82°; ^{1}H nmr (60 MHz): 2.40 (s, 3H, CH_3), 2.87 (t, 2H, J = 7 Hz, SCH_2), 3.67 (t, 2H, J = 7 Hz, CH_2Cl), 7.07-7.70 (m, 5H, ArH), 9.05 (br s, 1H, NH), 15.6 (s, 1H, OH); ir: 1620 (C=O), 1600 (C=C), 3332 (OH), 3440 (NH) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}NO_2SCl$: C, 53.0; H, 5.19; N, 5.15; S, 11.8. Found: C, 53.3; H, 5.24; N, 5.12; S, 11.8.

Preparation of 3-(2-Chloroethylthio)-4-methyl-2-quinolone (**5**).

To 75% aqueous sulfuric acid (700 ml) at 80° in an oil bath was added a solution of β-chlorosulfide **6** (100 g, 0.368 mole) in methylene chloride (150 ml) dropwise over 30 minutes. The reaction mixture stirred for 1 hour 45 minutes at the same temperature and cooled to room temperature. This solution poured into ice-water (4.5 l) dropwise over an hour. The brown precipitate was filtered, washed with water and then dried in air. The brown solid was triturated with ethanol (100 ml), and then dried in air to give quinolone **5** as a brown solid (60.2 g, 65%), mp 184-187°; ^{1}H nmr (300 M Hz): 2.85 (s, 3H, CH_3), 3.44 (t, J = 7.5 Hz, 2H, SCH_2), 3.67 (t, J = 7.5 Hz, 2H, CH_2Cl), 7.29-7.78 (m, 4H, ArH), 11.6 (br.s, 1H, OH); ir: 1598 (C=C), 1650 (C=C), 3435 (OH) cm^{-1}; ms: m/z (relative intensity) 217 (100), 161 (11), 117 (25).

Anal. Calcd. for $C_{12}H_{12}NOSCl$: C, 56.8; H, 4.77; N, 5.52. Found: C, 56.8; H, 4.86; N, 5.39.

Preparation of 2,3-Dihydro-5-methyl-1,4-oxathlino[2,3-*b*]quinoline (**4**).

A suspended solution of quinolone **5** (25.3 g, 0.1 mole) and potassium hydroxide (7.9 g, 0.12 mole) in ethanol (800 ml) was refluxed for 20 hours. The reaction mixture cooled to room temperature and the precipitates filtered off. The solvent was removed to afford an oily residue, which was dissolved in methylene chloride (300 ml). The organic layer washed with water, and then dried (magnesium sulfate). The reaction mixture was concentrated until the volume of the remaining solution was about 50 ml. This solution was acidified with concentrated hydrochloric acid (about 20 ml) and the reaction mixture washed with methylene chloride. The aqueous layer was basified with 10*N* sodium hydroxide solution and then extracted with methylene chloride. The organic layer washed with water, saturated sodium bicarbonate solution and then dried (magnesium sulfate). The solvent was removed to give pale gray solid (12.0 g, 55%). Crystallization from ethyl acetate and petroleum ether gave oxathiinoqunoline **4** as an yellow crystals (5.12 g), mp 89-91°; ^{1}H nmr (300 MHz): 2.58 (s, 3H, CH_3), 3.21-3.24 (m, 2H, SCH_2), 4.66-4.69 (m, 2H, OCH_2), 7.38-7.86 (m, 4H, ArH); ir: 1636 (C=C) cm^{-1}; ms: m/z (relative intensity) 217 (100), 161 (11), 117 (32).

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.3; H, 5.10; N, 6.45; S, 14.8. Found: C, 66.0; H, 5.13; N, 6.41; S, 15.1.

Reaction of Quinolone **5** with Sodium Hydride in Tetrahydrofuran (THF).

To a suspended solution of quinolone **5** (10.0 g, 0.039 mole) in THF (150 ml) was added 60% sodium hydride in oil (6.3 g, 0.157 mole) portionwise over 10 minutes at room temperature under nitrogen atmosphere. Stirring was continued for 24 hours at the same temperature. The precipitate was filtered off. The solvent was removed under reduced pressure to give brown oily residue. This was dissolved in methylene chloride (300 ml), washed with water and then dried (magnesium sulfate). The solvent was evaporated to

obtain brown semi solid residue (9.0 g). The solids were treated in ethyl acetate (20 ml) at reflux for a half hour. The reaction mixture cooled to room temperature, the precipitated filtered off (0.33 g). The filtrate was concentrated under reduced pressure to give a brown oily residue (7.3 g, 86%). This mixture was separated by flash chromatography. A mixture of ethyl acetate/*n*-hexane (4/1), ethyl acetate, and methylene chloride were used sequentially as eluents. The first eluate was disulfide [7] (150 mg), the second eluate was 3-vinylthio-4-methyl-2-quinolone **7** (1.55 g), and the third eluate was dihydrooxathiinoquinoline **4** (2.47 g).

Compound **7** had mp 164-167°; ^{1}H nmr (300 MHz): 2.79 (s, 3H, CH_3), 5.13 (d, J = 16.8 Hz, 1H, CH), 5.25 (d, J = 9.7 Hz, 1H, CH), 6.51 (2d, 1H, CH), 7.23-7.77 (m, 4H, ArH), 11.42 (br s, 1H, OH); ir: 1598 (aromatic C=C), 3455 (OH) cm^{-1}; ms: m/z (relative intensity) 217 (100), 202 (9), 184 (91), 117 (14).

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.3; H, 5.10; N, 6.45; S, 14.8. Found: C, 66.0; H, 5.19; N, 6.31; S, 14.9.

REFERENCES AND NOTES

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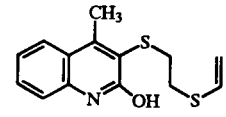
[7] The following structure was proposed of this compound by ^{1}H nmr spectrum and elemental analysis.



This compound had mp 120-124°; ^{1}H nmr (300 MHz): 2.85 (s, 3H, CH_3), 2.89-2.94 and 3.33-3.39 (m, 4H, SCH_2CH_2S), 5.11 (d, J = 16.7 Hz, 1H, exomethylene CH_{trans}), 5.15 (d, J = 10.1 Hz, 1H, exomethylene CH_{cis}), 6.29 (2d, 1H, vinyl CH), 7.24-7.74 (m, 4H, ArH), 11.56 (br s, 1H, OH); ir: 3300, 1650, 1596 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NOS_2$: C, 60.6; H, 5.45; N, 5.05; S, 23.1. Found: C, 60.3; H, 5.49; N, 5.01; S, 23.7.

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