Chemistry of Heterocyclic Compounds, Vol. 41, No. 3, 2005

SYNTHESIS OF DERIVATIVES OF (4-METHYL-2-QUINOLYLTHIO)ACETIC AND (4-METHYL-2-QUINOLYLTHIO)PROPIONIC ACIDS

A. A. Avetisyan and I. L. Aleksanyan

An efficient synthesis has been developed for derivatives of (4-methyl-2-quinolylthio)acetic and (4-methyl-2-quinolylthio)propionic acids by the reaction of 4-methyl-2-thioxoquinoline with methyl methacrylate, the amide of methacrylic acid, acrylonitrile, ethyl bromoacetate, and ethyl acrylate. The hydrolysis of the resultant intermediates by (quinolylthio)acetic and (quinolylthio)propionic acids gave the corresponding acid products, which are also formed in the reaction of 4-methyl-2-thioxoquinoline with chloroacetic and acrylic acids. The reaction of 4-methyl-2-thioxoquinoline with allyl bromide was studied. The potassium permanganate oxidation of the resultant 2-allylthio-4-methylquinoline led to (4-methyl-2-quinolylthio)acetic acid.

Keywords: derivatives of (quinolylthio)acetic and (quinolylthio)propionic acids, (2-quinolylthio)-propionitrile.

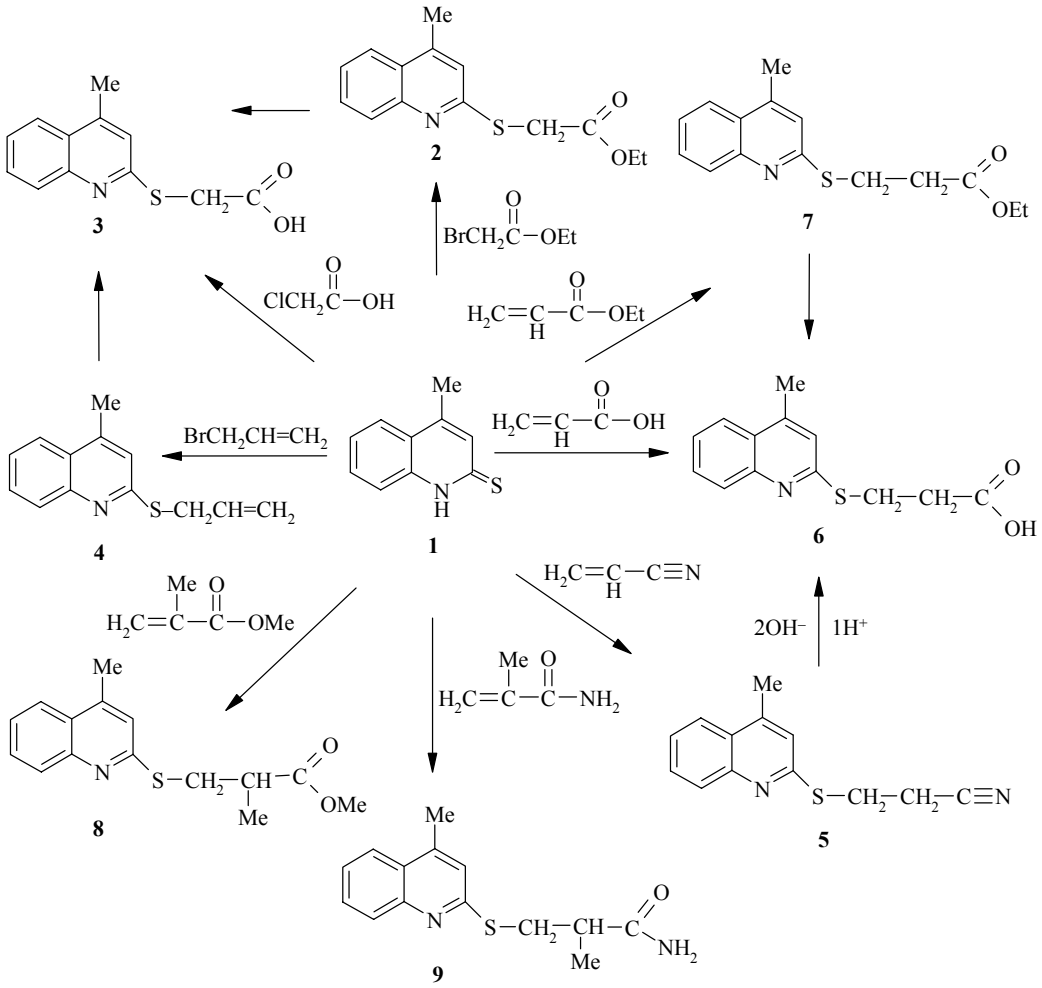
In a continuation of work on the synthesis of 2-hydroxy- and 2-mercapto-4-methylquinolines and a study of the properties of these derivatives [1-3], we synthesized 4-methyl-2-quinolylthio derivatives of acetic and propionic acids.

Arylthioacetic acids, used in the synthesis of thioindigoid dyes [4], were obtained by the reaction of thiolates with salts or esters of chloroacetic acids.

In the present work, we studied the reaction of 4-methyl-2-thioxoquinoline (**1**) with ethyl bromoacetate. This reaction proceeds smoothly in absolute ethanol in the presence of sodium alcoholate to give the ethyl ester of (4-methyl-2-quinolylthio)acetic acid (**2**). The hydrolysis of **2** gives (4-methyl-2-quinolylthio)acetic acid (**3**), also obtained by convergent synthesis using the reaction of 4-methyl-2-thioxoquinoline with chloroacetic acid in an alkaline medium and by the potassium permanganate oxidation of 2-allylthio-4-methylquinoline (**4**). The synthesis of quinoline **4** was readily accomplished by the reaction of 4-methyl-2-thioxoquinoline with allyl bromide in 1:1.2 ratio in anhydrous acetone at room temperature, which makes the latter method valuable.

Quinolylthiopropionic acid derivatives were synthesized by the Michael reaction involving the nucleophilic addition of 2-thioxoquinoline **1** to α,β-unsaturated carbonyl compounds. Depending of the structure of the α,β-unsaturated compounds, this reaction can also proceed without catalysis as a consequence of the strong nucleophilicity of sulfur. The effect of various factors on the course of these reactions was studied and optimal conditions were established.

Yerevan State University, 375025 Yerevan, Republic of Armenia, e-mail: Panahit1@yandex.ru; organkim@sun.ysu.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 403-406, April, 2005. Original article submitted October 7, 2002; revision submitted November 1, 2004.



The reaction of quinoline **1** with acrylonitrile, acrylic acid, and ethyl acrylate gave β-(4-methyl-2-quinolylthio)propionitrile (**5**), 3-(4-methyl-2-quinolylthio)propionic acid (**6**), and the ethyl ester of 3-(4-methyl-2-quinolylthio)propionic acid (**7**) in 80-95% yield. Products **5** and **7** were converted to the corresponding acid **6** by hydrolysis.

The reactions of 2-thioxoquinoline **1** with methyl methacrylate and the amide of methacrylic acid were also studied. Optimal conditions were found for these reactions. The reaction was found to proceed readily in pyridine in the presence of alkali and leads to desired products **8** and **9** in 81-89% yield.

EXPERIMENTAL

The ^{1}H NMR spectra were taken for DMSO solutions on a Varian Mercury 300 spectrometer at 300 MHz with TMS as the internal standard. The IR spectra were taken on a UR-20 spectrometer in vaseline mull. The purity of the products was determined by thin-layer chromatography on Silufol UV-254 plates with iodine vapor as the developer.

Ethyl Ester of (4-Methyl-2-quinolylthio)acetic Acid (2). 4-Methyl-2-thioxo-1H-quinoline **1** (3.5 g, 20 mmol) [5] was added to the alcoholate obtained from absolute ethanol (50 ml) and metallic sodium (0.46 g, 20 mmol) and heated on a water bath for 0.5 h. Then, ethyl bromoacetate (5.01 g, 30 mmol) was added with stirring and heated at reflux on a water bath for 8 h until the solution was weakly basic. Then, ethanol was

distilled off and water (100 ml) was added to the residue. The precipitate obtained was filtered off, washed with water, and recrystallized from 50% aq. ethanol to give 4.28 g (82%) of compound **2**; mp 85-86°C, R_f 0.52 (1:3 chloroform–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.3 (3H, t, *J* = 6.6, CH_3); 2.7 (3H, s, CH_3); 4.3 (2H, q, *J* = 7.1, OCH_2); 4.85 (2H, s, SCH_2); 6.5 (1H, s, CH arom); 7.32-8.32 (4H, m, arom). Found, %: N 4.97; S 12.49. $C_{14}H_{15}NO_2S$. Calculated, %: N 5.36; S 12.26.

(4-Methyl-2-quinolylthio)acetic Acid (3). A. A mixture of NaOH (0.8 g, 20 mmol) in water (4 ml), quinoline **1** (0.875 g, 5 mmol), and chloroacetic acid (0.59 g, 6.25 mmol) was heated on a water bath for 2 h. The mixture was then cooled and water (20 ml) was added. The mixture was filtered and acidified by adding hydrochloric acid to pH 4-5. The residue was filtered off and washed with water to give 1.13 g (97%) of compound **3**; mp 105-106°C. IR spectrum, ν, cm^{-1}: 1730 (>C=O acid), 2700-3300 (OH, acid). ^{1}H NMR spectrum, δ, ppm: 2.80 (3H, s, CH_3); 5.0 (2H, s, CH_2); 6.5 (1H, s, CH arom); 7.4-8.3 (4H, m, arom). Found, %: N 6.14; S 13.59. $C_{12}H_{11}NO_2S$. Calculated, %: N 6.00; S 13.73.

B. Ester **2** (1.3 g, 5 mmol) was dissolved in ethanol (30 ml). Then, NaOH (0.5 g, 12.5 mmol) in water (5 ml) was added and the mixture was heated at reflux for 3 h. Ethanol was then distilled off and water (20 ml) was added to the residue. The mixture was filtered and acidified by adding hydrochloric acid to pH 4-5. The residue was filtered off and washed with water to give 1.07 g (92%) of compound **3**; mp 105-106°C.

C. Potassium permanganate (1.58 g, 10 mmol) was added slowly in small portions to a mixture of **4** (1.08 g, 5 mmol), acetone (30 ml), and potassium carbonate (0.69 g, 5 mmol) with stirring and ice cooling over 2 h. The mixture was stirred for an additional 2 h and left overnight. The precipitate was then filtered off and treated with water. The aqueous layer was acidified by adding hydrochloric acid. The precipitate was filtered off and washed with water to give 0.73 g (63%) of compound **3**; mp 105-106°C. The samples of acid **3** obtained by methods A, B, and C did not give depressed mixed melting points.

2-Allylthio-4-methylquinoline (4). A mixture of quinoline **1** (0.875 g, 5 mmol) and allyl bromide (0.726 g, 6 mmol) in anhydrous acetone (30 ml) was stirred at room temperature for 24 h. Then, acetone was distilled off and water (25 ml) was added to the residue. The precipitate was filtered off, washed again with water, and recrystallized from 1:2 ethanol–water to give 0.89 g (82%) of compound **4**; mp 45-46°C, R_f 0.57 (1:1 chloroform–hexane). IR spectrum, ν, cm^{-1}: 1640 (CH=CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 4.75 (2H, d, *J* = 7, S–CH_2); 5.10 (1H, d, J_{cis} = 10, =CH_2); 5.38 (1H, d, J_{trans} = 17, =CH_2); 6.0 (1H, m, CH=); 6.7 (1H, s, CH arom); 7.5-8.0 (4H, m, arom). Found, %: N 6.67; S 15.02. $C_{13}H_{13}NS$. Calculated, %: N 6.51; S 14.88.

β-**(4-Methyl-2-quinolylthio)propionitrile (5).** A mixture of 2-thioxoquinoline **1** (0.875 g, 5 mmol) and acrylonitrile (0.318 g, 6 mmol) in dioxane (20 ml) and 4-5 drops 10% aq. NaOH was vigorously stirred and left overnight at room temperature. Then, the mixture was heated on a water bath for 2 h. Dioxane was distilled off and water (25 ml) was added to the residue. The residue obtained was filtered off, washed with water, and recrystallized from 50% aq. ethanol to give 1.08 g (95%) of compound **5**; mp 75-76°C, R_f 0.58 (1:3 chloroform–hexane). IR spectrum, ν, cm^{-1}: 2250-2210 (–C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 2.75 (2H, t, *J* = 10, CH_2); 4.1 (2H, t, *J* = 10, CH_2S); 6.75 (1H, s, CH arom); 7.8-8.2 (4H, m, arom). Found, %: N 12.75; S 13.90. $C_{13}H_{12}N_2S$. Calculated, %: N 12.28; S 14.04.

3-(4-Methyl-2-quinolylthio)propionic Acid (6). A. A sample of acrylic acid (0.432 g, 6 mmol) and 2-3 drops of hydrochloric acid were added with stirring to a solution of quinoline **1** (0.875 g, 5 mmol) in dioxane (20 ml) and left for 2 h at room temperature. The reaction mixture was then heated on a water bath for 2 h and dioxane was distilled off. Then, water (30 ml) was added to the residue. The precipitate was dissolved in dilute alkali. The alkaline solution was filtered and acidified by adding hydrochloric acid. The precipitate formed was filtered off and washed with water to give 1 g (81%) of compound **6**; mp 124-125°C. IR spectrum, ν, cm^{-1}: 1730 (>C=O acid), 2700-3300 (OH, acid). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.8 (3H, s, CH_3); 3.3 (2H, t, *J* = 8, CH_2); 4.0 (2H, t, *J* = 8, CH_2S); 6.7 (1H, s, CH arom); 7.7-8.1 (4H, m, arom). Found, %: N 5.38; S 13.21. $C_{13}H_{13}NO_2S$. Calculated, %: N 5.67; S 12.96.

B. Analogously to procedure B for **3**, 1.19 g (96%) of acid **6** was obtained from ester **7** (1.375 g, 5 mmol) and NaOH (0.5 g, 12.5 mmol); mp 124-125°C,.

C. A mixture of **5** (1.14 g, 5 mmol) and 20% hydrochloric acid (20 ml) was heated at reflux for 4 h and, then, cooled. The precipitate formed was filtered off, washed with water and purified as in procedure A to give 1.0 g (82%) of compound **6**; mp 124-125°C.

D. Compound **5** (1.14 g, 5 mmol) was added to a solution of NaOH (0.8 g, 20 mmol) in water (30 ml) and heated at reflux for 1 h. Then, the alkaline solution was filtered and acidified by adding hydrochloric acid. The precipitate was filtered off and washed with water to give 0.98 g (80%) of compound **6**; mp 124-125°C. Samples of acid **6** obtained by methods A-D do not give a depressed mixed melting point.

Ethyl Ester of 3-(4-Methyl-2-quinolylthio)propionic Acid (7). Ethyl acrylate (2 g, 20 mmol) was added with stirring to a solution of quinoline **1** (1.75 g, 10 mmol) in pyridine (5 ml) and left at room temperature overnight. Then, the reaction solution was heated on a water bath for 2-3 h. Pyridine was then distilled off and water (30 ml) was added to the residue. The precipitate formed was filtered off, washed with water, and recrystallized from 1:2 ethanol–water to give 2.2 g (80%) **7**; mp 80-81°C, R_f 0.49 (1:1 ethanol–water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.3 (3H, t, *J* = 6.7, CH_3); 2.7 (3H, s, CH_3); 3.4 (2H, t, *J* = 6.5, CH_2); 4.3 (2H, q, *J* = 7.2, CH_2); 4.5 (2H, t, *J* = 7.0, CH_2); 6.85 (1H, s, CH arom); 7.8-8.1 (4H, m, arom). Found, %: N 4.88; S 11.89. $C_{15}H_{17}NO_2S$. Calculated, %: N 5.09; S 11.64.

Methyl Ester of 2-Methyl-3-(4-methyl-2-quinolylthio)propionic Acid (8). Methyl methacrylate (2 g, 20 mmol) was added with stirring to a solution of methylquinoline **1** (1.75 g, 10 mmol) in pyridine (5 ml) containing NaOH (0.4 g, 10 mmol) and left at room temperature overnight. Then, the reaction mixture was heated on a water bath for 4-5 h. Pyridine was distilled off. The residue was filtered off, washed with water, and recrystallized from 50% aq. ethanol to give 2.23 g (81%) of compound **8**; mp 99-100°C, R_f 0.55 (1:3 chloroform–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, d, *J* = 6.5, CH_3); 2.7 (3H, s, CH_3); 3.2 (3H, s, OCH_3); 3.52 (2H, d, *J* = 8.5, CH_2S); 4.61 (1H, m, CH); 6.5 (1H, s, CH arom); 7.6-7.92 (4H, m, arom). Found, %: N 5.00; S 11.69. $C_{15}H_{17}NO_2S$. Calculated, %: N 5.09; S 11.64.

Amide of 2-Methyl-3-(4-methyl-2-quinolylthio)propionic Acid (9). Analogously to the procedure for compound **8**, 2.30 g (89%) of amide **9** was obtained from methylquinoline **1** (1.75 g, 10 mmol), NaOH (0.4 g, 10 mmol), and amide (0.85 g, 10 mmol) of methacrylic acid in pyridine (5 ml); mp 149-150°C (50% aq. ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, *J* = 6.0, CH_3); 2.75 (3H, s, CH_3); 3.82 (2H, d, *J* = 8.0, CH_2S); 4.18 (1H, m, CH); 6.75 (H, s, CH arom); 7.8-8.2 (4H, m, arom). Found, %: N 10.82; S 12.26. $C_{14}H_{16}N_2OS$. Calculated, %: N 10.77; S 12.31.

REFERENCES

1. L. V. Gyul'budagyan and I. L. Aleksanyan, *Arm. Khim. Zh.*, **36**, 540 (1983).
2. L. V. Gyul'budagyan, I. L. Aleksanyan, and A. Avetisyan, *Arm. Khim. Zh.*, **42**, 636 (1989).
3. L. V. Gyul'budagyan and I. L. Aleksanyan, *Arm. Khim. Zh.*, **42**, 470 (1989).
4. B. I. Stepanov, *Introduction to the Chemistry and Technology of Organic Dyes* [in Russian], Khimiya, Moscow (1984).
5. *Syntheses of Heterocyclic Compounds* [in Russian], Vol. 7, Izd. Akad. Nauk ArmSSR, Yerevan (1966), p. 41.