Chemistry of Quinazolines: Reinvestigation of the Action of Hydrazine on Thioxo Derivatives

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The action of hydrazine on 2-mercapto and 2-alkylmercaptoquinazolin-4-ones is reinvestigated. The structure of the isolated products have been revised.

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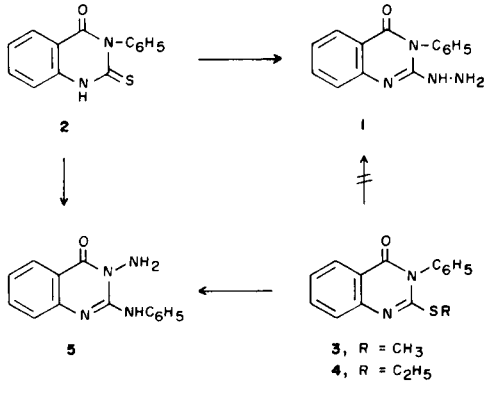
The synthesis of 2-hydrazino-3-phenylquinazolin-4(3*H*)-one (**1**) has been described twice in literature [1,2].

In one publication it was reported that the action of hydrazine in ethanol on 2-thioxo-3-phenylquinazolin-4(1*H*,-3*H*)-one (**2**) gave compound **1**, mp 202-203° [1]. The same product **1**, mp 151° was reported as the product from the action of hydrazine on 2-ethylmercapto-3-phenylquinazolin-4(3*H*)-one (**4**) [2].

Our recent findings on the rearrangement of heterocyclic systems containing an aryl group on a thiourea moiety closely related to compound **2** or alkylisothiourea moieties analogues to **3** and **4** [3-6] anticipates a second isomeric product **5** from the action of hydrazine on compounds **2-4**. Therefore we decided to reinvestigate these reactions. Thus we have found that the action of hydrazine on compound **4** gives a product with mp 151°, however we established that this compound should be assigned structure **5** and not **1** as reported previously. The same compound **5** was also, now, obtained by treatment of compound **3** with hydrazine.

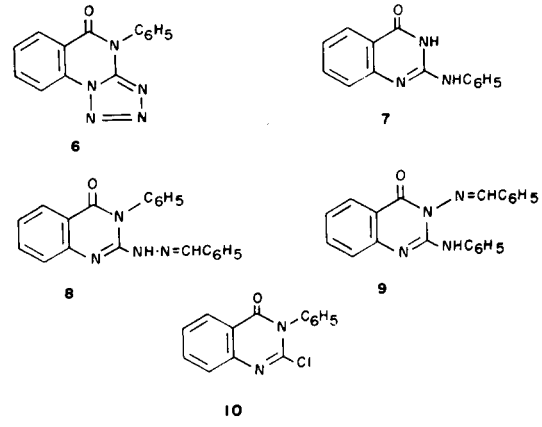


On the other hand, we now have found that the action of hydrazine on 2-thioxo-3-phenylquinazolin-4(1*H*,3*H*)-one (**2**) gave two isomeric products, one has a mp 151° and is identical with compound **5**; obtained from the reaction of hydrazine on compounds **3** and **4**; and the other has mp 203°. The structure of the latter compound was established by chemical reactions to be the 2-hydrazino-3-phenylquinazolin-4(3*H*)-one (**1**) as reported earlier [1].

Structural assignment of compounds **1** and **5** is based on the following facts:

a) Compound **1** reacts with nitrous acid to give 4-phenyl-4,5-dihydrotetrazolo[1,2-*a*]-5-quinazolone (**6**), however treatment of compound **5** with nitrous acid led to deamination and formation of 2-anilinoquinazolin-4(3*H*)-one (**7**) [7].

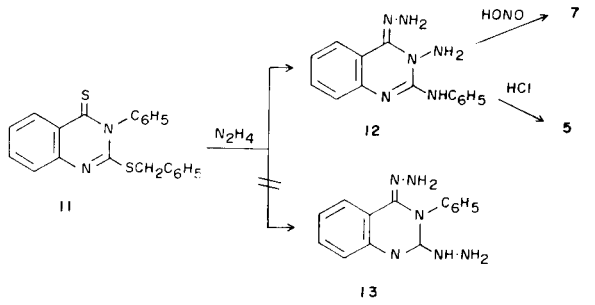
b) Each of compounds **1** and **5** reacts with benzaldehyde to give different condensation products **8** and **9** respectively.



c) Heating compound **9** in an oil bath at 200° for 2 hours yielded compound **7** together with benzonitrile.

d) The 2-hydrazino quinazoline **1** was also obtained by the action of hydrazine on 2-chloro-3-phenylquinazolin-4(3*H*)-one **10** [8] under mild conditions.

We now have also found that the product obtained from the action of hydrazine on 2-benzylthio-3-phenylquinazoline-4(3*H*)-thione (**11**) should be assigned the structure, 2-anilino-3-aminoquinazoline-4(3*H*)-hydrazone (**12**) instead of the reported 2-hydrazino-3-phenylquinazoline-4(3*H*)-hydrazone (**13**) [2].



The structure of compound **12** is assigned based on the following facts:

a) It reacts with nitrous acid to give compound **7**.

b) It reacts with 6 *N* hydrochloric acid to give compound **5**.

EXPERIMENTAL

All melting points are uncorrected. The mass spectra were obtained on a Mass Spectrometer MAT 112. Elemental analyses were carried out by the Microanalytical Center, Cairo University.

2-Anilino-3-aminoquinazolin-4(3*H*)-one (**5**). Method A. From 2-Thioxo-3-phenylquinazolin-4(1*H*,3*H*)-one.

A mixture of 2-thioxo-3-phenylquinazolin-4(1*H*,3*H*)-one (**2**) (2.5 g) and hydrazine (99%, 2 ml) in ethanol (25 ml) was refluxed for 10 hours whereby a precipitate began to separate. After cooling the precipitate was collected and recrystallized from butanol to give compound **1** (1 g), mp 202-203°; ms: m/e = 252 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.80; N, 22.21. Found: C, 66.80; H, 5.00; N, 22.30.

Concentration of the mother liquor from the reaction mixture gave a colorless precipitate, which was collected, and recrystallized from ethanol to give compound **5** (0.6 g), mp 151°; ms: m/e = 252 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.80; N, 22.21. Found: C, 66.90; H, 5.00; N, 22.10.

Method B. From 2-Alkylmercapto-3-phenylquinazolin-4(3*H*)-one. General Procedure.

The following exemplifies the procedure. A mixture of 2-methylmercapto-3-phenylquinazolin-4(3*H*)-one (**3**) (2.7 g) and hydrazine (99%, 3 ml) in isopropyl alcohol (7 ml) was refluxed for 10 hours, cooled and the precipitate which formed upon dilution with water was collected and recrystallized from ethanol to give compound **5** (1.5 g), mp 151°. This compound was identical with compound **5** obtained from the previous reaction (mp and mixed mp).

Action of Nitrous Acid on Compound **1**.

To a suspension of compound **1** (0.5 g) in hydrochloric acid (6 *N*, 10 ml) was added dropwise with cooling and stirring a solution of sodium nitrite (0.5 g in 5 ml of water) over a period of 15 minutes. The mixture was further stirred at room temperature for 30 minutes. The precipitate was collected and crystallized from butanol to give compound **6**, (0.3 g), mp 192-193° [1]; ms: m/e = 263 (M^+).

Anal. Calcd. for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.60. Found: C, 63.50; H, 3.50; N, 26.90.

Action of Nitrous Acid on Compound **5**.

To a suspension of compound **5** (0.5 g) in hydrochloric acid (6 *N*, 10 ml) was added a solution of sodium nitrite (0.5 g in 5 ml of water) dropwise with cooling and stirring over a period of 15 minutes. The mixture was further stirred at room temperature for 30 minutes. The precipitate was collected and then was heated under reflux for 2 hours in aqueous sodium hydroxide solution (5%, 6 ml). After cooling it was acidified with hydrochloric acid to give colorless crystals. The crystals were washed with cold water and crystallized from ethanol to give compound **7**, mp 256°; ms: m/e = 237 (M^+). Compound was identical with an authentic sample [7] (mp and mixed mp).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.50; H, 5.00; N, 18.00.

Action of Benzaldehyde on Compounds **1** and **5**.

Each of compounds **1** and **5** (1.3 g) was heated under reflux in ethanol (35 ml) with benzaldehyde (0.6 ml) for 6 hours, whereby, a precipitate was formed. This was collected and crystallized from butanol into compounds **8** and **9** respectively.

Compound **8** (1.7 g) had mp 218°; ms: m/e = 340 (M^+).

Anal. Calcd. for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.50; H, 5.00; N, 16.20.

Compound **9** (1.5 g) had mp 153-155°; ms: m/e = 340 (M^+).

Anal. Calcd. for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.10; H, 4.80; N, 16.00.

Action of Hydrazine on 2-Chloro-3-phenylquinazolin-4(3*H*)-one (**10**).

A mixture of compound **10** (0.6 g) [8] in hydrazine (99%, 1 ml) in ethanol (6 ml) was heated under reflux for 3 minutes. After cooling, the precipitate was collected and recrystallized from butanol to give compound **1** (0.5 g). This compound was identical with compound **1** obtained in the previous procedure (mp and mixed mp).

Thermolysis of Compound **9**.

Compound **9** (1 g) was heated in an oil bath at 200° for 2 hours. After cooling, ethanol (7 ml) was added. The precipitate was collected and recrystallized from ethanol into colorless crystals of **7** (0.4 g), mp 256°. This compound is identical with authentic sample (mp and mixed mp).

Action of Hydrazine on Compound **11**.

A mixture of compound **11** [9] (2 g) and hydrazine (99%, 5 ml) in isopropyl alcohol (25 ml) was refluxed for 5 hours and then cooled. The precipitate was collected and crystallized from DMF to give compound **12** (1.2 g), mp 186°; ms: m/e = 266 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.55. Found: C, 62.90; H, 5.50; N, 31.30.

Action of Nitrous Acid on Compound **12**.

To a suspension of compound **12** (0.5 g) in hydrochloric acid (10 *N*, 10 ml) was added a solution of sodium nitrite (0.5 g in 5 ml of water) dropwise with cooling and stirring over a period of 10 minutes. The mixture was then further stirred at room temperature for 1 hour. The precipitate which formed was collected and crystallized from ethanol to give compound **7** (0.2 g), mp 256°, identical with an authentic sample [7] (mp and mixed mp).

Acid Hydrolysis of Compound **12**.

A suspension of compound **12** (0.5 g) in 6 *N* hydrochloric acid (15 ml) was refluxed for 1½ hours, cooled, filtered and the filtrate basified with sodium hydroxide solution. The solid precipitate was crystallized from ethanol to give compound **5**, mp 151° (0.3 g). This compound was identical with the same compound obtained previously (mp and mixed mp).

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