Reactions and Rearrangement of 2,4-Quinazolinediones. An Efficient Simple Synthesis of 3-Amino-1*H*,3*H*-quinazolinedione

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An efficient synthesis of 3-amino-1*H*,3*H*-quinazolinedione by the action of hydrazine on the readily accessible 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione and 2-anilino-4*H*-3,1-benzoxazin-4-one are described.

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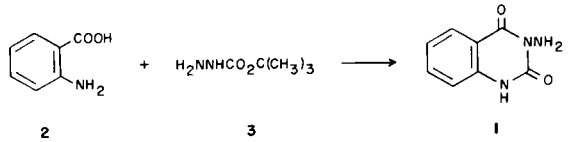
In a recent publication Lalezari and Stein [2] reviewed seven reported procedures [3-7] for the synthesis of 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**1**). They described also an additional simple new synthetic approach of **1** in 55% yield by reacting anthranilic acid (**2**) with *t*-butyl carbazate (**3**) in refluxing quinoline (Scheme I).

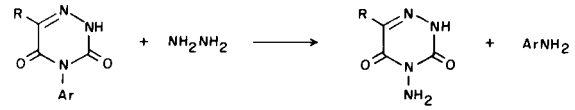
Scheme I



2 **3** **1**

While we are currently engaged in a study of the chemistry of quinazoline derivatives, the report of Lalezari and Stein [2] prompted us to publish some of our results dealing with efficient syntheses of compound **1**. This synthesis depends upon our recent findings that hydrazine readily attacks the C=O group of some nitrogen heterocyclic compounds which contain the CONAr moiety, and with compounds containing a suitable *N*-arylimidic group, *N*-aminoimidic heterocyclic compounds may be formed in good yield [8-11] (*e.g.* **4** to **5**, Scheme II).

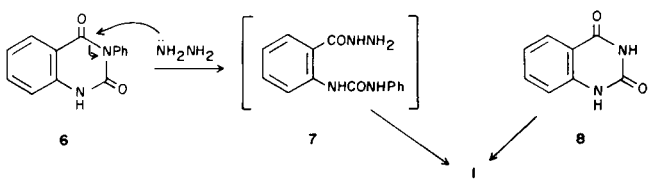
Scheme II



4 **5**

Thus, we now have found that 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (**6**) reacts with hydrazine in refluxing propyl alcohol to give 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**1**) in 90% yield together with aniline (Scheme III).

Scheme III

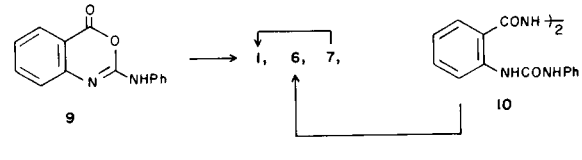


6 **7** **8** **1**

The reaction most probably proceeds by the attack of hydrazine on the amidic carbonyl at position 4 with ring opening to give intermediate **7** which then cyclizes by loss of aniline which was indeed separated from the reaction mixture. The relatively low temperature reaction in this case is undoubtedly due to the increased electrophilicity of the carbonyl group in position 4 caused by the electron withdrawing effect of the phenyl group on the adjacent nitrogen atom. In the case of unsubstituted 2,4-(1*H*,3*H*)-quinazolinedione (**8**) the action of hydrazine yields compound **1** only under drastic conditions [5] (Scheme III).

Since we were unable to isolate the intermediate **7** from the above reaction, we investigated other possible routes for the synthesis of this proposed intermediate in order to study its cyclization products. Thus, when 2-anilino-4*H*-3,1-benzoxazin-4-one (**9**) was treated with hydrazine in boiling ethanol, the intermediate **7** was isolated as a minor product along with compounds **1** and **7**. However, portionwise addition of **9** to excess hydrazine gave only compound **7**. On the other hand, dropwise addition of hydrazine to compound **9** yielded the dibenzoyl derivative **10** (Scheme IV).

Scheme IV



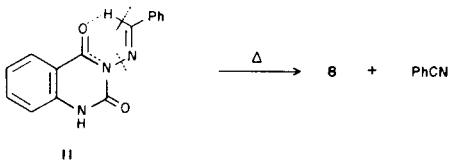
9 **10**

Cyclization of compound **7** into the 3-aminoquinazolinedione **1** was readily achieved by refluxing in ethanol. On the other hand compound **10** was only cyclized by the action of cold concentrated sulfuric acid into the 3-phenylquinazolinedione **6** (Scheme IV).

We were able to deaminate compound **1** into the quinazolinedione **8** by two methods: a) by the action of nitrous acid in hydrochloric acid suspension (Lalezari and Stein [2] reported similar deamination but in acetic acid followed by a somewhat tedious workup), b) by converting **1** first

into the benzalamino derivative **11** followed by thermolysis into **8** and benzonitrile in high yield (Scheme V). The conversion of **1** into **8** *via* the benzalamino derivative **11** could also be accomplished in one step by heating **1** and benzaldehyde at high temperature.

Scheme V



11

The last conversion of **11** into **8** and benzonitrile probably proceeds *via* a concerted cyclic six electron aromatic transition state. Compound **1** is among the good candidates investigated so far in our laboratory for the thermal conversion of aldehydes into nitriles [12-15].

EXPERIMENTAL

3-Amino-2,4(1*H*,3*H*)-quinazolinedione (**1**).

Method A. From 3-Phenyl-2,4(1*H*,3*H*)-quinazolinedione.

A mixture of 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (**6**) [16] (1.2 g) and hydrazine hydrate (99%, 2 ml) in propanol (10 ml) was heated under reflux for 12 hours. After cooling the precipitate was collected and recrystallized from water to give compound **1** (0.8 g, *ca.* 90%), mp 290-292°. This compound is identical with an authentic sample [3] (mp and mixed mp).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.71. Found: C, 54.30; H, 4.10; N, 23.80.

Method B. From 2-Anilino-4*H*-3,1-benzoxazin-4-one.

i) A mixture of 2-anilino-4*H*-3,1-benzoxazin-4-one (**9**) [16] (4 g) and hydrazine hydrate (99%, 1.4 ml) in ethanol (25 ml) was refluxed for 16 hours. After cooling the precipitate was collected and crystallized from water to give 35% of compound **1**. Concentration of the mother liquor from the reaction mixture gave a colorless precipitate which was found identical with compound **6**, 15%. Further concentration of the mother liquor gave after dilution with water a colorless precipitate of **7** which was crystallized from ethanol/water, mp 256-258°.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.72. Found: C, 62.40; H, 5.10; N, 20.60.

ii) To a cold solution of hydrazine hydrate (99%, 2.5 ml) in aqueous alcohol (1:1, 25 ml) was added compound **9** (2.4 g) portionwise with stirring over a period of 15 minutes. The mixture was refluxed for 2 minutes and then cooled. The precipitate was collected and recrystallized from dilute ethanol into colorless crystals of **7** (2.0 g, *ca.* 74%), mp 256° which was identical with compound **7** obtained in the previous experiment.

A solution of compound **7** (0.5 g) in ethanol (5 ml) was refluxed for 1 hour and then cooled to precipitate compound **1** (0.25 g, 78%).

2,2'-(Di-3-phenylureido)-*N,N'*-dibenzoylhydrazine (**10**).

To a solution of **9** (2 g) in ethanol (20 ml) was added hydrazine hydrate (99%, 2 ml) dropwise with stirring and cooling over a period of 30 minutes. The reaction mixture was then heated to boiling and filtered. After cooling colorless pure crystals of **10** crystallized out of the solution (1.2 g, *ca.* 56%). This compound was recrystallized from ethanol, mp 236-238°.

Anal. Calcd. for $C_{28}H_{24}N_6O_4$: C, 66.13; H, 4.76; N, 16.52. Found: C, 66.20; H, 4.60; N, 16.40.

Action of Sulfuric Acid on Compound **10**.

Compound **10** (0.5 g) was dissolved in concentrated sulfuric acid (2 ml) at room temperature and left for 24 hours. This was diluted with cold water and filtered to give compound **6**, almost in a pure state, mp 276-279° (reported mp 280-282° [16]), yield 0.4 g; *ca.* 86%.

3-Benzalamino-(1*H*,3*H*)-quinazolin-2,4-dione (**11**).

Compound **1** (1 g) and benzaldehyde (2 ml) were fused together on an oil bath at 180° for 3 minutes. After cooling ethanol (10 ml) was added and the fine needles formed were collected, washed with ethanol to give pure **11**, mp 243-245°, 1.4 g (*ca.* 94%). The product was recrystallized for analysis from 1-butanol.

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.10; H, 4.20; N, 16.00.

Thermolysis of Compound **11**.

Compound **11** (1 g) was heated in an oil bath at 220° for 3 hours. After cooling ethanol (10 ml) was added and left overnight in the refrigerator. The precipitate was collected and recrystallized from ethanol into colorless crystals of **8**, mp >300° [17].

Direct Deamination of **1** into **8**.

(a) By Thermolysis with Benzaldehyde.

A mixture of compound **1** (0.2 g) and benzaldehyde (0.2 ml) was heated at 220-230° (oil bath) for 3 hours. After cooling ethanol (3 ml) was added and the mixture was left in the refrigerator overnight, whereby crystals of **8** precipitated (0.15 g, *ca.* 81%), identical with authentic sample [17].

(b) By the Action of Nitrous Acid.

To a suspension of compound **1** (0,2 g) in concentrated hydrochloric acid (1 ml) was added a solution of sodium nitrite (0.3 g in 1 ml of water) with shaking and cooling. After 15 minutes at room temperature the precipitate was collected, washed with water and dried to give 0.16 g (*ca.* 86%) of **8**.

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