A Simple One-Step Synthesis of 3-Amino-2,4(1*H*,3*H*)quinazolinediones

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Anthranilic acids and alkyl carbazates in refluxing quinoline give high yields of 3-amino-2,4(1*H*,3*H*)-quinazolinediones.

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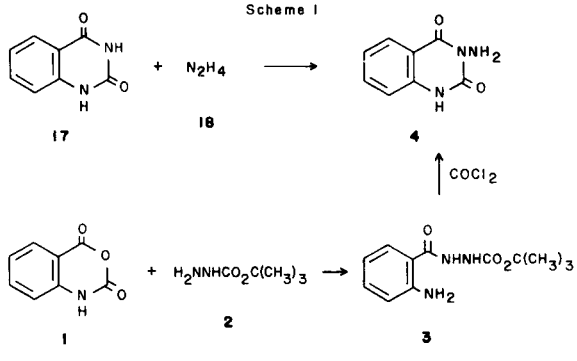
3-Amino-2,4(1*H*,3*H*)-quinazolinedione (**4**) was first synthesized by Kunckell [1] reacting hydrazine hydrate (**18**) and 2,4(1*H*,3*H*)-quinazolinedione (**17**) under drastic conditions. Jacobs [2] prepared **4** by a multi-step reaction starting with isatoic anhydride (**1**). *o*-Amino-*N*-(*t*-butoxycarbonyl)aminobenzamide (**3**) which was obtained by the reaction of *t*-butyl carbazate (**2**) with isatoic anhydride, was heated with phosgene to give **4**.

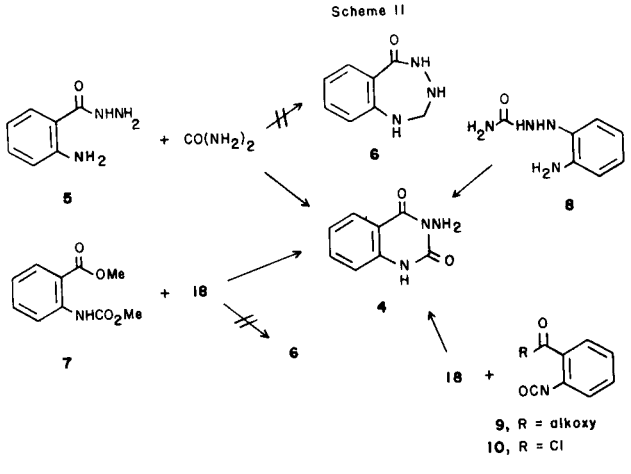
Scheme I



Peet and Sunder [3] have shown that contrary to previous reports [4], treatment of 2-aminobenzoylhydrazine (**5**) with urea in decalin at reflux gave **4** rather than 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (**6**).

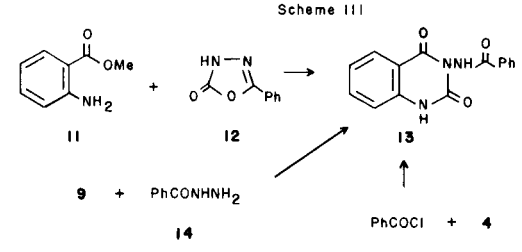
Another reported synthesis of compound **6** [5], the reaction of methyl *N*-carbomethoxyanthranilate (**7**) with hydrazine, gave exclusively **4** rather than **6** [3]. In addition, two independent methods for the synthesis of quinazoline derivative **4** were reported [3]. Thermal cyclization of 1-(2-aminobenzoyl)semicarbazide (**8**) in boiling decalin as well as the interaction of 2-carboalkoxyphenyl isocyanate (**9**) and/or 2-isocyanatobenzoyl chloride (**10**) with hydrazine hydrate gave **4** (Scheme II).

Scheme II



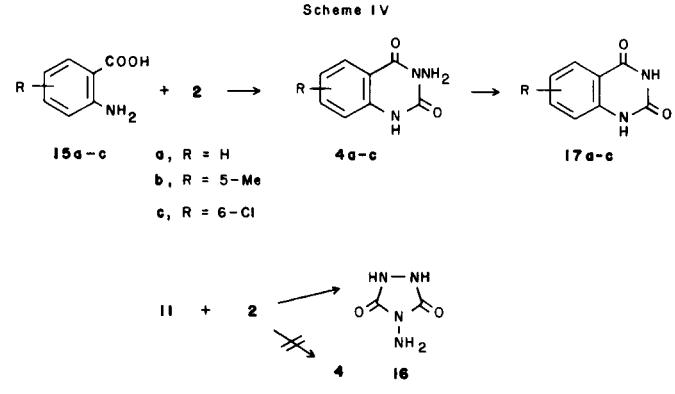
Chau *et al.* [6] have prepared *N*-(2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**13**) by the reaction of methyl anthranilate (**11**) with 2-aryl-1,3,4-oxazolin-5-ones (**12**) in refluxing *m*-cresol or by heating benzoylhydrazide (**14**) with 2-carbomethoxyphenylisocyanate (**9**, R = OMe). The structure of compound **13** has been confirmed by its independent synthesis through the condensation of compound **4** with benzoyl chloride (See Scheme III).

Scheme III



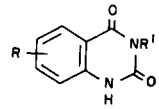
In the present work, we describe a simple one-step synthesis of 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**4**) and its derivatives by treating anthranilic acids (**15**) with *t*-butyl carbazate (**2**) in refluxing quinoline (See Scheme IV).

Scheme IV



To elucidate the mechanism of this new reaction, the following experiments were performed: When methyl anthranilate was substituted for anthranilic acid under identical conditions 4-amino-1*H*-1,2,4-triazole-3,5(2*H*,4*H*)-dione (**16**) and a black tar were obtained. The production of

Table I



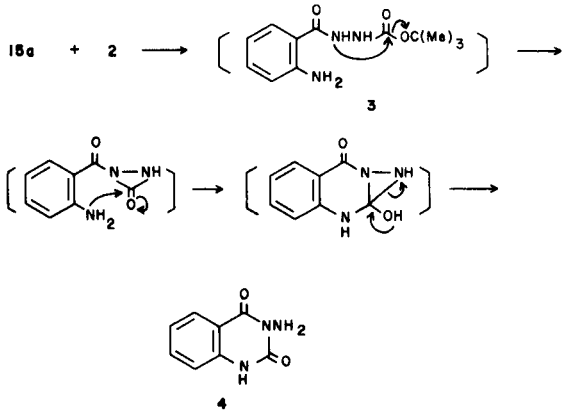
Compound	R	R'	Mp °C	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
4a	H	NH_2	291-293 [a]	55	$C_8H_7N_3O_2$	54.23	54.41	3.98	4.01	23.71	23.66
4b	6-Me	NH_2	266-268	60	$C_9H_9N_3O_2$	56.54	56.70	4.74	4.80	21.97	21.69
4c	7-Cl	NH_2	285-286	64	$C_8H_6ClN_3O_2$	45.40	45.32	2.85	2.77	19.85	19.88
17a	H	H	>300 [b]	98	$C_8H_6N_2O_2$	59.25	59.50	3.72	3.70	17.27	17.41
17b	6-Me	H	314-316 [c]	89	$C_9H_8N_2O_2$	61.30	61.41	4.57	4.55	15.90	15.86
17c	7-Cl	H	>330	95	$C_8H_5ClN_2O_2$	48.87	48.90	2.56	2.49	14.24	14.33

[a] Ref [1] mp 290-291°, ref [2] 291.5-293°. [b] Ref [7] mp 300°. [c] Ref [8] mp 316°.

compound **16** is independent of methyl anthranilate as shown by its formation through the refluxing of **2** in quinoline. Refluxing methyl anthranilate or anthranilic acid with quinoline led to decomposition of both compounds. However, decomposition of the esters was found to be 15 to 20 times faster than that of the free acid.

o-Amino-*N*-(*t*-butoxycarbonyl)aminobenzamide (**3**), a possible intermediate in this reaction was refluxed in quinoline and gave high yields of **4** (Scheme V).

Scheme V



To determine the role of solvent in this reaction, benzyl alcohol, undecane (bp 194-196°), pyridine and ethanol were used in place of quinoline. In all cases the yields of compound **4** obtained ranged between 0 and 15 percent except for compound **4b** where the yield was 39 percent by 18 hours refluxing the reagents in undecane. When ethyl carbazate was used in place of *t*-butyl carbazate, a decrease of 40 to 50 percent of yield was observed.

On the basis of the above information, we propose a mechanism for this reaction as outlined in the Scheme V.

The compounds **4** prepared were identical with samples prepared by other methods [2].

Compounds **4** were successfully deaminated by nitrous acid to afford their corresponding quinazolinediones **17** in theoretical yields. These were identical with samples prepared according to the literature [7,8] (See Scheme IV). The physical properties of the compounds prepared are reported in Table I.

EXPERIMENTAL

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

Method A. From Anthranilic Acid.

A mixture of 1.37 g (0.01 mole) of anthranilic acid (**15a**) and 2 g (0.015 mole) of *t*-butyl carbazate in 15 ml of quinoline was refluxed for 8 hours. A crystalline precipitate was gradually formed. Refrigeration of the reaction mixture gave 825 mg of white crystals which were washed with ether and dried. A subsequent crop of 160 mg was obtained by concentration of the mother liquor. A total yield of 55 percent of recrystallized compound (from water) was obtained, mp 291-293°.

6-Methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (**4b**) and 7-chloro-3-amino-2,4(1*H*,3*H*)-quinazolinedione (**4c**) were prepared similarly starting from 2-amino-5-methylbenzoic acid (**15b**) and 2-amino-4-chlorobenzoic acid (**15c**), respectively (See Table I).

Method B. From *o*-Amino-*N*-(*t*-butoxycarbonyl)aminobenzamide (**3**).

A solution of 1 g (5 mmoles) of *o*-amino-(*t*-butoxycarbonyl)aminobenzamide (**3**) [2] in 10 ml of quinoline was refluxed for 8 hours and worked up as described in method A, giving 425 mg (60 percent) of **4a**.

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

To a suspenion of 100 mg of 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**4a**) in 2 ml of acetic acid and 10 ml of water, a solution of 25 mg of sodium nitrite in 1 ml of water was added. After 15 minutes stirring at room temperature, 5 ml of a 40 percent sodium hydroxide solution was added and warmed to obtain a clear solution. After cooling it was acidified with a 50 percent solution of sulfuric acid to give colorless needles. The crystals were washed with cold water and dried at 100° to give 90 mg (98% percent) of pure 2,4(1*H*,3*H*)-quinazolinedione (**17a**) identical with an authentic sample prepared by the reaction of urea with anthranilic acid [9].

Compounds **17b** and **17c** were prepared similarly (See Table I).

Acknowledgement.

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