Synthesis of 2,4-(1*H*,3*H*)-Quinazolinediones

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Improved procedures for syntheses of kilogram quantities of quinazolinedione **5** and its intermediates **2**, **3** and **4** are described. The mechanism of formation of **5** is discussed as well as a side reaction resulting in **7**.

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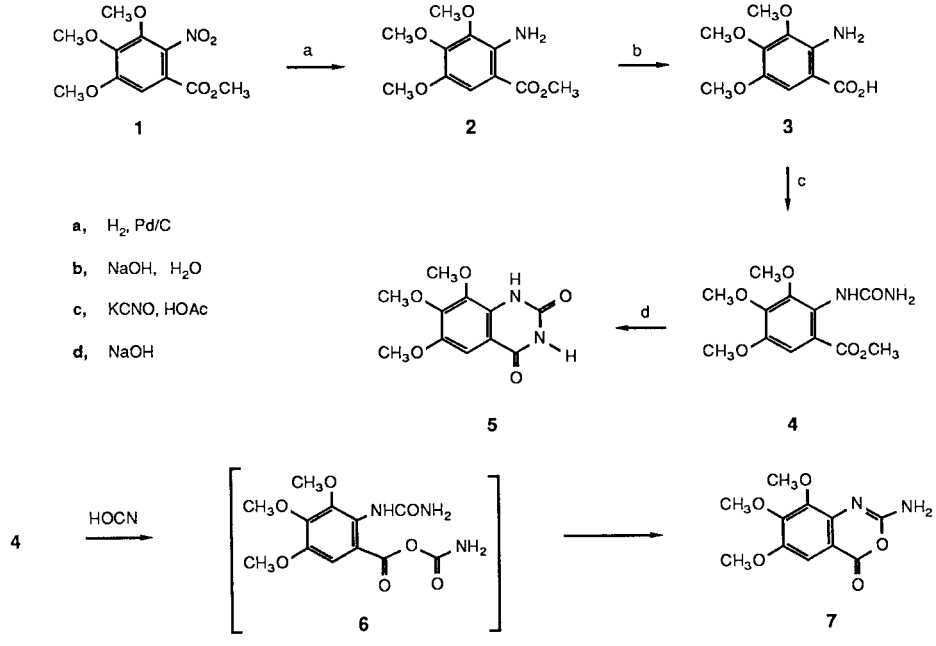
As part of our commercial interest [1,2] in the synthesis of quinazoline antihypertensive agents such as prazosin [3] and trimazosin [4], we sought to obtain the highest possible yield of quinazolinedione **5** from inexpensive, readily available starting materials. The preparation of the unsubstituted analog of **5** from anthranilic acid is described in *Organic Synthesis* [5]; the method gives 82-87% yield but is operationally awkward on a large scale. More recently, analogs of **5** have been prepared either by the fusion of an *o*-aminobenzamide with urea in 78% yield [6] or sodium hydroxide catalyzed condensation of an *o*-ureidobenzamide in 95% [7] yield. The actual preparation of **5** in 86% yield by the latter route has been described [8]. Since the anthranilic acid route appeared more attractive from the standpoint of raw material availability, we chose to optimize that process. The procedure described in this note has given analytically pure **5** in the four described chemical steps from **1** in 99.5% overall yield at more than 100 kg scale. A similar set of conditions, run more dilute to compensate for solubility differences, has been used to prepare the 7,8-dimethoxy analog of **5**.

The Pd/C catalyzed reduction of commercially available nitro ester **1** to amino ester **2** and its subsequent hydrolysis to substituted anthranilic acid **3** are straight forward reactions which occur in quantitative yields. Reaction products were not isolated in order to eliminate losses, and hplc was used to monitor the reactions to insure 99.9% completion for both steps. On the other hand, the conversions of **3** to ureido acid **4** and then to desired quinazolinedione **5** are sensitive reactions which require careful control of conditions and monitoring by hplc for optimum results.

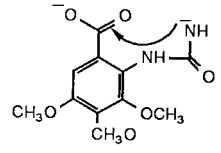
We found that the conversion to **4** occurred best at *p*H 6.8-7.3. If the *p*H was lower than 6.5, yield loss occurred by two routes: 1) precipitation of the anthranilic acid **3**, making it less available for reaction; 2) formation of a by-product, the corresponding 2-aminobenzoxazin-4-one **7**. Compound **7** was thought to come from the intermediate carboxylic carbamic anhydride, **6**, which presumably could be formed by reaction of **4** with cyanic acid. We were able to prepare **7** in reasonable yield from **4** by using a large excess of cyanate and maintaining the reaction at *p*H 5.6-6.0. If the conversion to **4** was run at higher than



optimum *p*H, the desired reaction still proceeded, but at a much lower rate. For example at *p*H 8.0, the reaction took at least 50% longer to run.

The base induced conversion of **4** to dione **5** is mechanistically noteworthy. Bruice [9] has shown kinetic evidence to support formation of a dianion **8** as the key intermediate. He found the reaction to be second order in ureido acid and hydroxide. Correspondingly the pseudo 1st order constant for disappearance of ureido acid was 50X greater at *p*H 13.0 than *p*H 11.3. In our case *p*H > 13 was essential for optimum rate and a rapid adjustment to that point was critical for yield. Otherwise some hydrolysis of **4** back to **3** occurred, particularly in the *p*H 10-11 region where formation of **5** was not competitive. Our observation provides additional support for the dianion intermediate proposed by Bruice. At *p*H values below which ionization of the NH_2 can occur, attack by hydroxyl at the urea carbonyl becomes the important reaction.

The fate of compound **7** under the high *p*H conditions was of interest because it could conceivably convert to **5** after ring opening by hydroxyl. Comparative experiments were run by separately heating dilute solutions of **4** and **7** at 50-55° in 1*N* sodium hydroxide. Whereas **4** was cleanly converted to **5** within 1 hour, **7** contained only 20% **5** in 3 hours. Clearly any formation of **7** which occurs during the preparation of **5** will result in overall yield loss.



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EXPERIMENTAL

All melting points were taken in glass capillary tubes on a Thomas Hoover melting point apparatus and are uncorrected. All reactions were monitored by hplc using a Laboratory Data Control Spheresorb ODS column (25 cm x 4.6 mm ID). The mobil phase consisted of a solution containing 650 parts 0.05 *M* dibasic potassium phosphate: 400 parts methanol: 45 parts THF, v/v.

Methyl 2-Amino-3,4,5-trimethoxybenzoate (**2**) from **1**.

To a slurry of 271 g (1.00 mole) of **1** in 1.0 liter of 2-propanol under nitrogen was charged 6.78 g of 5% Pd/C (50% water wet). The mixture was purged with hydrogen and hydrogenated at 40 psig and 68-75° until uptake ceased (*ca* 8 hours). A sample of the reduction mixture was checked by hplc for completion of reaction at this point. The slurry was cooled to ambient temperature, purged with nitrogen and filtered to remove the catalyst. The catalyst was washed with 100 ml of 2-propanol. The combined filtrate and wash, containing pure **2**, was used directly as a solution for the preparation of **3**. If desired, **2** as its hydrochloride salt can be obtained by passing hydrogen chloride gas into the solution until it is strongly acidic. The product is isolated by displacing the 2-propanol with heptane to give a white solid, mp 175-176° (reported mp 170-171° [10]).

2-Amino-3,4,5-trimethoxybenzoic Acid (**3**) from **2**.

To the 2-propanol solution of **2** described above was charged 80.6 g (1.01 moles) of 50% aqueous sodium hydroxide and 535 ml of water. The mixture was stirred at reflux for 3 hours and checked by hplc for completion. If incomplete, 5% more sodium hydroxide was added and the reaction resumed. Once the reaction was complete, the 2-propanol was removed by distillation. The remaining aqueous solution of pure **3** was used directly in the preparation of **4**. If desired pure **3** may be obtained by adjusting the *p*H to 4.5 with sulfuric acid and filtering the white solid, mp 138-140° (reported mp 137° [11]).

2-[(Aminocarbonyl)amino]-3,4,5-trimethoxybenzoic Acid (**4**) from **3**.

The volume of the above aqueous solution of **3** was diluted to 1.1 liters with water. The *p*H was adjusted to 6.8-7.3 with acetic acid and the solution cooled to 0-5°. Potassium cyanate (88.4 g, 1.09 moles) was added and the *p*H immediately adjusted to 6.8-7.3 with acetic acid and maintained there at 0-5° with acetic additions (total acetic acid added was usually 55.3 g) until the reaction was complete by hplc (7 hours typical). If desired, compound **4** could be isolated by adjusting the *p*H to 4.2 with acetic acid and filtering the product, mp 179-180°.

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.89; H, 4.97; N, 10.28.

6,7,8-Trimethoxy-2,4-(1*H*,3*H*)-quinazolinedione (**5**) from **4**.

While the temperature was maintained at 0-10°, 69.4 g (0.87 mole) of 50% aqueous sodium hydroxide was added as rapidly as possible (preferably 5 minutes or less) to the above described reaction mixture containing **4** to give *p*H > 13 [12]. The mixture was heated at 55-57° until the reaction was complete by hplc (3 hours typical). It was then cooled to 25-30° and the *p*H of the slurry adjusted to 7.0-8.5 with acetic acid. The *p*H was maintained in this range until no more than 0.1 *p*H unit drop occurred in 3-4 hours [13]. The final slurry was filtered, generously washed with water and dried [14] to give 251 g, 99.5% yield, mp 266-269° (also reported mp 271° [8]), of an off-white, analytically pure solid; nmr (DMSO-d_6): 3.80 (s, 3H, OMe) 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 7.15 (s, 1H, AR-H), 10.6 (s [broad], NH), 11.2 (s [broad], CONHCO); ^{13}C-nmr (DMSO-d_6): 55.90, 60.61, 61.23 (COMe), 103.22, 109.27 (CO), 129.84, 139.66, 147.26, 148.59, 150.08, 162.17 (AR).

2-Amino-6,7,8-trimethoxy-4*H*-3,1-benzoxazine-4-one (**7**) from **3**.

A mixture of 22.7 g (0.1 mole) **3**, 122 g (1.5 moles) potassium cyanate and 500 ml of water was treated with acetic acid to maintain *p*H 5.6-6.0 at ambient temperature until the *p*H stabilized (3 hours). The reaction could be monitored by hplc which showed initial formation of compound **4**. The *p*H was adjusted to 8.1 with dilute sodium hydroxide and the resultant solids filtered, washed with water and dried to give 38.5 g of **7** contaminated with inorganic salts. This crude product was recrystallized from DMF-methanol to give several crops totalling 15.5 g (62%), mp 233-234° of **7** as a white solid; ^{1}H nmr (DMSO-d_6): 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 7.10 (s, 1H, AR-H), 7.48 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): 55.85, 60.70, 61.00 (OMe), 103.72, 107.30 (CO), 140.82, 144.82, 144.98, 148.90, 149.39, 154.26, 159.28 (AR-H); ir (potassium bromide): 1730 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.25; H, 4.72; N, 11.05.

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[12] Most *p*H meters can't measure such a high *p*H. We recommend use of *p*H indicator papers. If the *p*H is not in range, additional sodium hydroxide should be added.

[13] The resultant neutralization of the sodium salt of **5** is very slow because of its extreme insolubility. On numerous occasions yield was lost because the product was filtered early and losses in the mother liquor occurred.

[14] If the product does not dry readily, it is contaminated with sodium acetate which is removed by water reslurry.