SYNTHESIS OF QUINAZOLINO[3,2-d]-1,4-BENZODIAZEPIN-6,9(5H,7H)-DIONES

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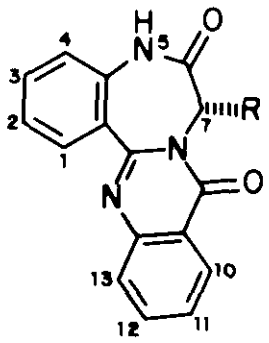
Abstract—2-(2-Nitrophenyl)-3,1-benzoxazin-4-one **3** was elaborated in two ways to afford the title compounds **1** and **2** via novel cyclodehydrations.

In connection with an ongoing synthetic program, we required a method for the preparation of the quinazolinobenzodiazepine **1**. Despite the ubiquity of benzodiazepines in the chemical literature, to our knowledge, the title ring system has not been previously reported. Herein, we describe a practical and efficient entry into this novel class of compounds.

Retrosynthetic analysis of the parent compound **1** revealed that it should be accessible via anthranilic acid annulation to the readily available *1,4-benzodiazepin-2,5-dione (or suitable derivative)*. While this synthetic approach appeared straightforward and has precedence[1,2] its major drawback concerns the regiochemical questions which require attention in the penultimate step[3] and/or which must ultimately be addressed in the annulation reaction. The assembly of **1** via the formation of strategic bonds in the 7-membered ring seemed equally feasible; however, it was our expectation that application of Errede's findings on the reaction of amines with acylanthranils would provide a more expedient solution.[4] Accordingly, the known benzoxazine **3** was prepared and elaborated as outlined in the scheme.

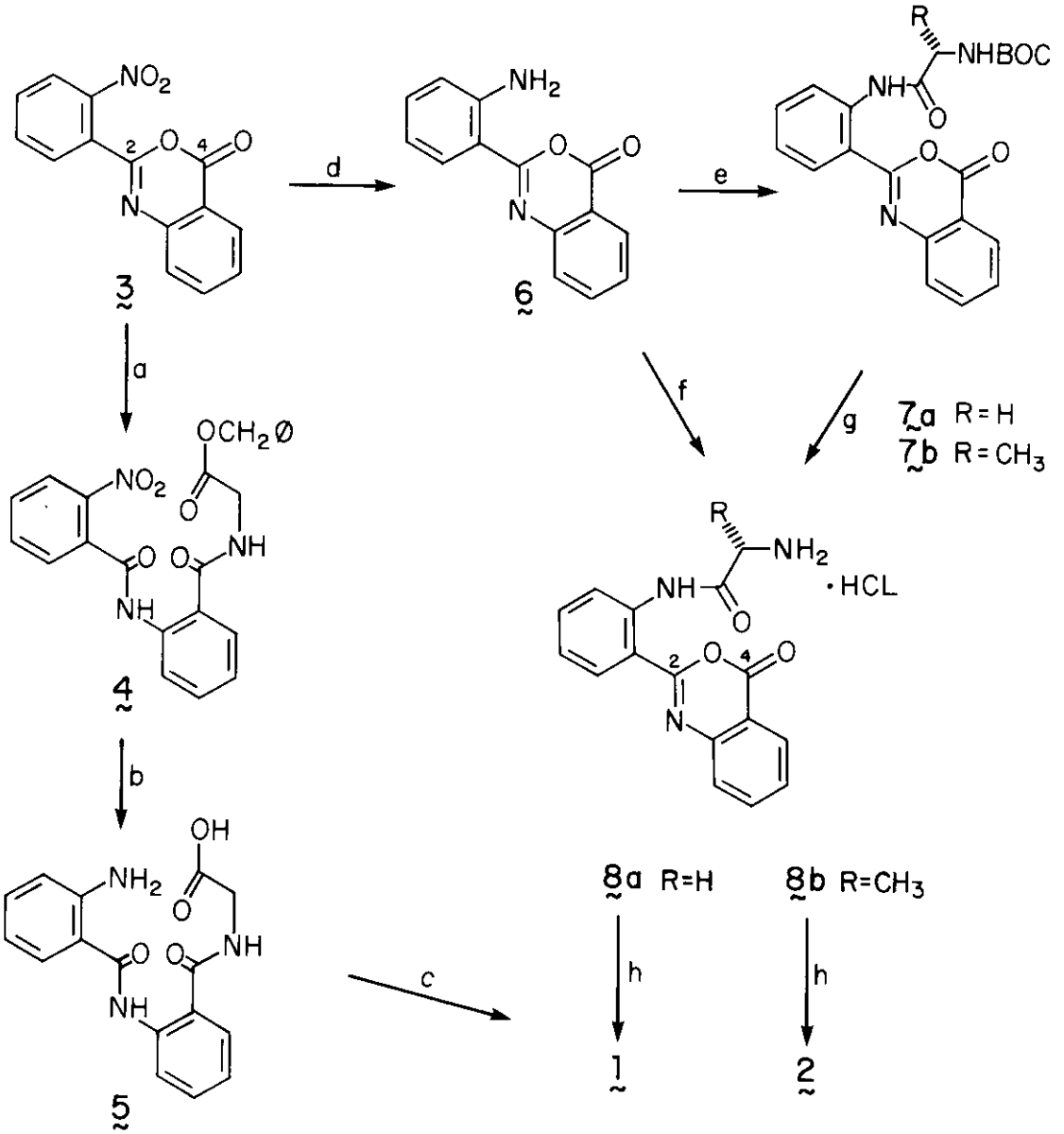


1, R = H
2, R = CH_3

A minor modification[5a] of Schroeter's method[5b] was employed to obtain 2-(2-nitrophenyl)-3,1-benzoxazin-4-one **3** in 90% yield[6] (mp 193.5-194.5°C; lit.[5b] mp 197°C). In the first approach to the quinazolino[3,2-d]-1,4-benzodiazepine **1**, the benzoxazin-4-one **3** was reacted with glycine benzyl ester hydrochloride [dry dimethylformamide, 95°C (bath), 12 h] to afford the amide **4** (70%). Catalytic reduction of **4** (10% Pd/C, 1 atm, 1 h) selectively and quantitatively reduced the nitro group; simultaneous reduction of the benzyl ester and nitro group could be effected with 10% Pd/C at 50 psi (ethyl acetate, 6 h) to afford the amino acid **5** (80%). Cyclodehydration (250°C, neat, 0.5 h) of **5** then afforded **1**[7] as the only isolable product (ca. 30-40%).

In the preferred route to the quinazolino[3,2-d]-1,4-benzodiazepine **1**, the benzoxazin-4-one **3** was reduced

Scheme



a. H-Gly-OBz·HCl, 95°, DMF; b. H_2, Pd/2, 50 psi, EtOAc; c. 250°, neat; d. H_2, PtO_2, 1atm., EtOAc;
e. Boc-Gly-OH or Boc-L-alanine, DCC, CH_2Cl_2; f. H-Gly-Cl·HCl, THF; g. HCl gas, EtOAc, 0°; h. 95°, DMF.

catalytically (PtO_2, 1 atm, ethyl acetate) to give the aminophenyl benzoxazin-4-one **6** (75%, mp 163-165°C; lit.[8] mp 162°C). When **6** was coupled with tert-butyloxycarbonyl-N-glycine there was obtained the acylated product **7a** (60-70% - after recycling starting material, dicyclohexylcarbodiimide (DCC), methylene chloride) which in turn was deprotected (HCl gas, ethyl acetate, 0°C) to yield the key benzoxazin-4-one **8a** (ca. 100%). Alternatively, **8a** was available in 90% yield by direct treatment of **6** with glycinyl chloride hydrochloride[9] in dry tetrahydrofuran. Heating **8a** in dry dimethylformamide at 95°C for 5 h then afforded **1** in 93% yield.[7]

The dichotomy in the mode of addition of the glycine amino moiety to the 2- and 4-positions in the benzoxazin-4-ones **3** and **8a**, respectively, is of special interest. Earlier studies indicated that electronic and steric effects associated with the substituent at the 2-position in benzoxazin-4-ones are significant factors in governing the selectivity of the nucleophilic attack.[10] Further, steric hindrance on the part of the coreactant amine was also postulated to play a role in determining regioselectivity.[11] In this context, it appears consistent that steric factors overcome electronic effects in causing glycine benzyl ester to react at the 4-position in **3**. On the other hand, the precise course of the intramolecular variant of this reaction remains undefined. Careful analysis of the reaction mixtures as a function of solvent, temperature, and pH revealed no intermediates derived from attack at either C-2 or C-4. Nevertheless, we infer that the reaction occurs via the alternate pathway (i.e. attack at the imine carbon C-2 in **8a**) based on the following reasoning. Both the 2- and 4-positions in **8a** are accessible by the glycine primary amino group. However, molecular models indicate that attack at C-2 allows the glycine amide bond to assume a cis configuration and remain planar, whereas attack at C-4 requires an out-of-plane twist (~40-45°) of the amide bond. This element would appear sufficient to direct addition to the 2-position. Finally, an increase in steric bulk α to the amino group also had no influence on the course of the reaction. For example, **8b**, prepared from **6** and L-alanine using standard conditions (vide supra) was cyclized to **2** in the expected manner (86%).[12,13] Efforts to rigorously establish the mechanism of this cyclodehydration reaction are now in progress.

In sum, we have developed methodology making previously unknown quinazolino[3,2-d]-1,4-benzodiazepin-6,9-diones readily accessible. Reports on the application of our findings to more complex systems will be forthcoming.

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2. R. Gompper and W. Breitschaft, Angew. Chem., 1983, **95** (9), 727; Angew. Chem. Int. Ed., 1983, **22** (9), 717.

3. We were unable to "selectively" activate either of the two amide carbonyl groups.

4. L. A. Errede and J. J. McBrady, J. Org. Chem., 1978, **43**, 1884, and references cited therein.

5. (a) o-Nitrobenzoyl chloride was added to a solution of anthranilic acid and triethylamine in dry tetrahydrofuran at 0°C; (b) G. Schroeter and O. Eisleb, Liebigs Ann., 1909, **367**, 101.

6. Yields refer to isolated, chromatographically homogeneous compounds; all compounds were completely characterized spectroscopically (ir, pmr, MS) and displayed satisfactory combusion analyses (±0.35%).

7. mp 318-319°C (ethyl acetate); ir (KBr, partial) 1695, 1590, 1485, 770 cm^{-1}; MS (20 ev) 277 (M^+), 265, 234, 146; pmr (360 MHz, DMSO-d_6) 4.2 (H_7, br s), 5.4 (H_7, br s), 7.23 (H_4, d, J = 8.3), 7.37 (H_2, t, J = 7.5), 7.58 (H_{11}, t, J = 7.7), 7.63 (H_3, t, J = 8.3), 7.76 (H_{13}, d, J = 8.2), 7.89 (H_{12}, t, J = 8.2), 8.08 (H_1, d, J = 8.0), 8.21 (H_{10}, d, J = 8.1), 10.70 (NH, br s).

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12. mp 290-291°C (ethyl acetate); ir (KBr, partial) 1680, 1605, 1595, 1150, 780, 770 cm^{-1}; MS (20 ev) 291 (M^+), 248, 247, 194; pmr (360 MHz, DMSO-d_6) 1.20 (CH_3, d, J = 7.6), 6.24 (H_7, q, J = 7.6), 7.22 (H_4, d, J = 8.3), 7.35 (H_2, t, J = 7.4), 7.59 (H_{11}, t, J = 7.8), 7.62 (H_3, t, J = 8.3), 7.76 (H_{13}, d, J = 8.3), 7.89 (H_{12}, t, J = 8.3), 8.08 (H_1, d, J = 8.1), 8.21 (H_{10}, d, J = 8.1), 10.77 (NH, br s).

13. Cyclodehydration was accompanied by ca. 10% racemization. The enantiomeric purity of **2** was determined by digesting **2** in 6 N HCl solution at 110°C for 20 h and derivatizing the released alanine with 5-dimethylaminophthalene-1-sulfonyl chloride at pH 9.5. The resulting "dansyl" derivative was analyzed by hplc according to the method of S. K. Lam and F. K. Chow, J. Liquid Chrom., 1980, **3**, 1575.

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