

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

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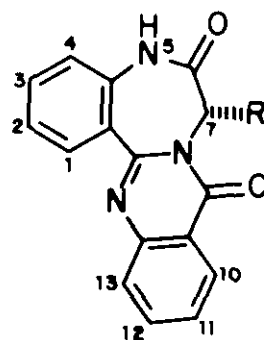
Abstract—2-(2-Nitrophenyl)-3,1-benzoxazin-4-one **3** was elaborated in two ways to afford the title compounds **1** and **2** via novel cyclodehydrations.

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 step³ 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.

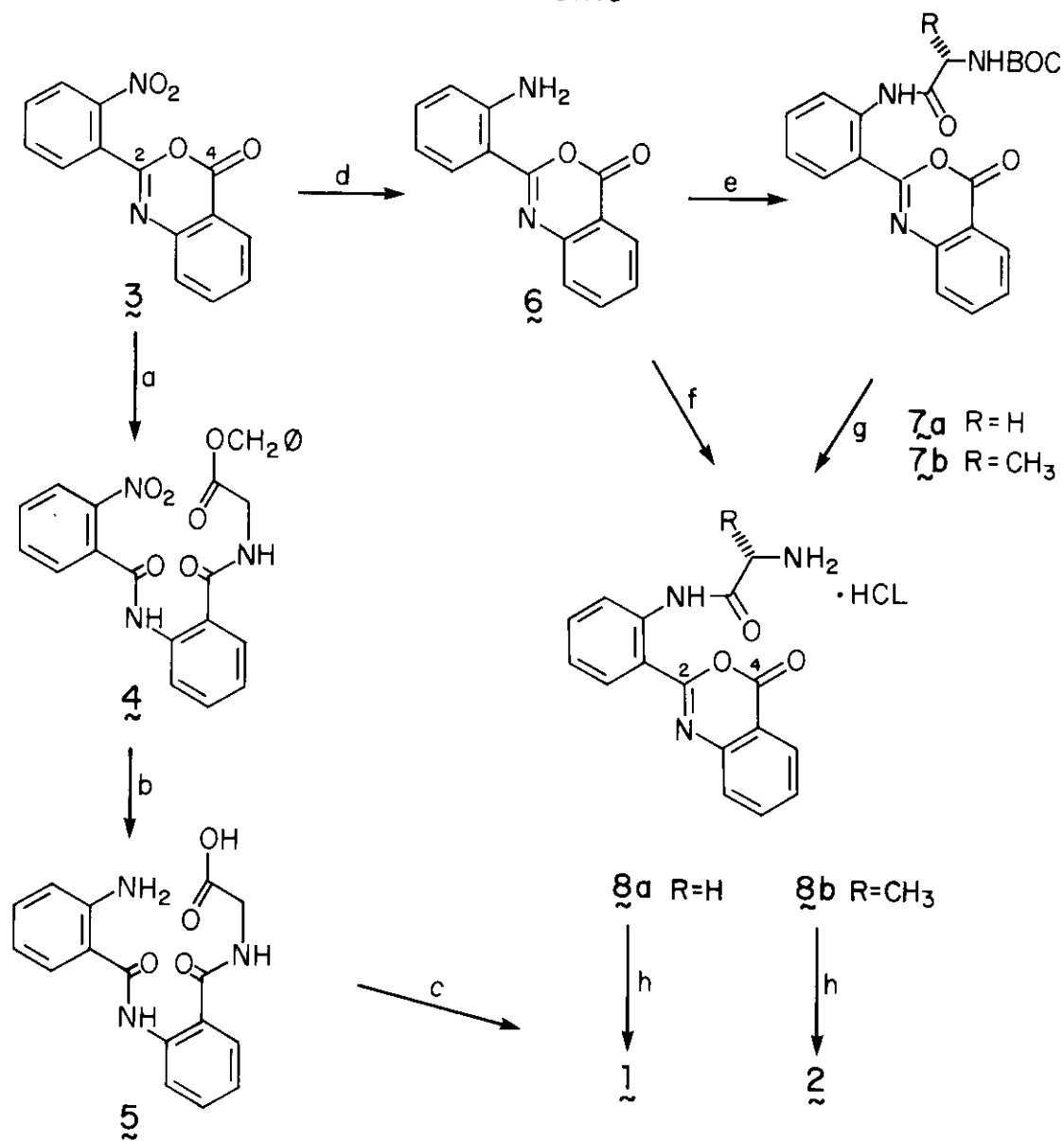
A minor modification^{5a} of Schroeter's method^{5b} was employed to obtain 2-(2-nitrophenyl)-3,1-benzoxazin-4-one **3** in 90% yield⁶ (mp 193.5-194.5°C; lit.^{5b} mp 197°C). In the first approach to the quinazolino[3,2-d]-1,4-benzodiazepine **1**, the benzoxazin-4-one **3** was reacted with glycine 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



1, R = H
2, R = CH₃

Scheme



a. H-Gly-OBz·HCl, 95°, DMF; b. H₂, Pd/2, 50 psi, EtOAc; c. 250°, neat; d. H₂, PtO₂, 1 atm., EtOAc; e. Boc-Gly-OH or Boc-L-alanine, DCC, CH₂Cl₂; 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 glycyl chloride hydrochloride⁹ 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 ($\sim 40-45^\circ$) 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 quinazolin[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.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the assistance of Mr. J. P. Moreau for obtaining elemental analyses. We extend our appreciation to Drs. B. E. Evans, G. D. Hartman, J. R. Huff, S. M. Pitzenberger, and D. F. Veber for useful discussions and thank Mrs. Mary Z. Banker for manuscript preparation.

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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 combustion analyses ($\pm 0.35\%$).
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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9. E. Fischer, Chem. Ber., 1905, 38, 2915.
10. (a) L. A. Errede, H. T. Oien, and D. R. Yarian, J. Org. Chem., 1977, 42, 12; (b) M. F. Ismail, N. A. Shams, M. R. Salem, and S. A. Emora, J. Org. Chem., 1983, 48, 4172.
11. L. A. Errede, J. J. McBrady, and H. T. Oien, J. Org. Chem., 1977, 42, 656.
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.

Received, 22nd October, 1984