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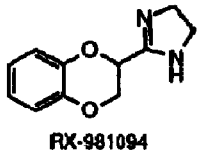
Novel Dibenzo[d,f][1,3]dioxepines

Robert E. Johnson* and Edward R. Bacon

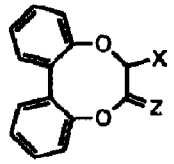
Sterling Winthrop Pharmaceuticals Research Division, 1250 S. Collegeville Road, P.O.Box 5000, Collegeville, PA 19426

Abstract: Two novel syntheses of dibenzo[d,f][1,3]dioxepines starting with biphenol are described. Treatment of biphenol **11a** with 2-chloroacrylonitrile gave a 47% yield of dibenzo[d,f][1,3]dioxepin-6-acetonitrile **4**, and treatment of **11a** with two equivalents of diethyl bromomalonate gave a 95% yield of diethyl dibenzo[d,f][1,3]dioxepin-6,6-dicarboxylate **5a**.

As part of a program to synthesize compounds for evaluation as potential alpha-2 antagonists, we proposed to prepare the 6,7-dihydrodibenzo[e,g][1,4]dioxocin analog **1** of the potent alpha-2 antagonist RX-981094.[1] We felt that compounds **2** or **3** would be reasonable intermediates for the preparation of **1**. Unfortunately, neither of these compounds could be prepared under a wide variety of conditions. During the course of these investigations we did discover two novel syntheses* of the related dibenzo[d,f][1,3]dioxepines **4** and **5a**.[2,3]



RX-981094



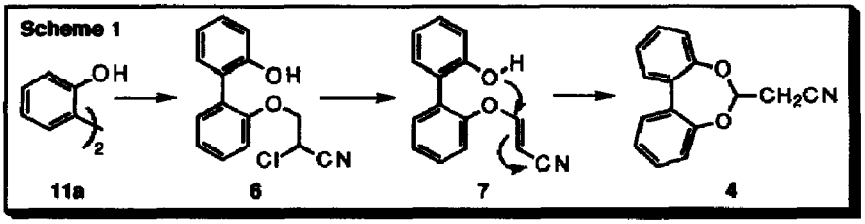
1 X =  Z = H_2

2 X = CN Z = H_2

3 X = $CO_2C_2H_5$ Z = O

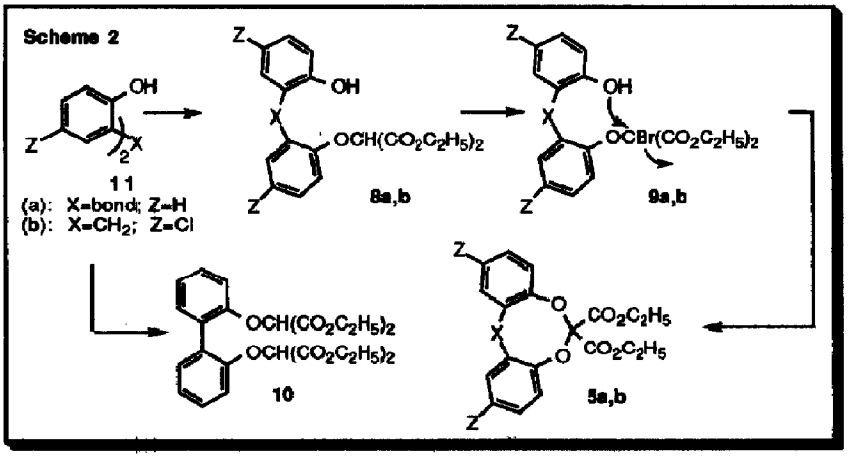
Our proposed pathway (Scheme 1) leading to the formation of compound **4** involves initial Michael addition of a phenolate anion to 2-chloroacrylonitrile to give **6**, followed by elimination of HCl to give intermediate acrylonitrile **7**, which undergoes an intramolecular Michael addition to give **4**. Although the formation of a seven-membered ring is favored over an eight-membered ring (i.e. **4** vs. **2**) from an energetics standpoint, to our surprise we obtained **4** as the sole product, despite having successfully prepared the unsubstituted eight-membered ring parent dihydrodibenzo[e,g][1,4]dioxocin[4] from 2,2'-biphenol **11a** and 1,2-dibromoethane with relative facility. The apparent mode of addition observed (**11a** → **4**) appears to be unprecedented and in contrast to the pathway reported for the analogous reaction of catechol with similar α-halo Michael acceptors, producing exclusively, six-membered ring 1,4-benzodioxins[5] and not the five-membered ring benzodioxoles, which would be generated via our observed pathway.

Scheme 1



11a **6** **7** **4**

The proposed mechanism for formation of **5a** (Scheme 2) involves a rapid bromination of intermediate **8a** with a second equivalent of diethyl bromomalonate to give **9a**, followed by ring closure to give **5a**. The use of a stoichiometric quantity (1 eq) of the bromomalonate gives a 50:50 mixture of **5a** and unreacted 2,2'-biphenol **11a**. Phenol has been reported to react with diethyl bromomalonate in a similar manner, in what was initially described as a "disproportionation" reaction.[6,7] Predictably,[7] substitution of diethyl chloromalonate (2 eq) for the bromomalonate gave compound **10**, thus supporting the premise that diethyl bromomalonate serves as an effective brominating agent under these conditions. Using the method described here,[4] **5b** was prepared in 66% yield (mp 115-116.5°C; lit.[8] mp 117-118°C). Compound **5b** has originally been prepared in very poor yield by the reaction of phenolate **11b** with diethyl dibromomalonate.[8]



REFERENCES AND NOTES

* All new compounds prepared displayed satisfactory ^{1}H-NMR, IR, MS (EI), and elemental analyses (± 0.45% of theoretical values).

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2. Compound **4**: A mixture of **11a** (93.5 g, 502 mmol) and potassium carbonate (158 g, 1110 mmol) in 500 mL of dry DMF was heated to 110°C under N_2. To this mixture was added dropwise with stirring, a solution of 2-chloroacrylonitrile in DMF (50 mL) in 1 h. After heating 2 h, the mixture was cooled and poured into a mixture of 1.2 N NaOH (1 L) and ice (1 Kg). The resulting solution was cooled in an ice bath overnight. The precipitated crystalline product was collected by filtration, washed with water and hexane, and then dried to give 55.7 g (47%) of **4**. Recrystallization from cyclohexane gave analytically pure material mp 113-115.5° C.
3. Compound **5a**: Diethyl bromomalonate (118 g, 630 mmol) was added dropwise to a rapidly stirred mixture of **11a** (302 g, 1265 mmol) and potassium carbonate (209 g, 1510 mmol) in 700 mL of dry DMF under N_2. After stirring for 4 h at ambient temperature, the reaction was poured into a biphasic mixture of water (2 L) and pentane (1 L). The solid which crystallized at the water/pentane interface was collected, washed with water (3 L), pentane (2 L) and dried at 70°C/0.05 Torr to give 224 (95%) of analytically pure **5a**, mp 129.5-131° C.
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