Electrophilic Acetylation and Bromination Reactions of Benzo[*b*]naphtho[2,3-*e*][1,4]dioxin

Adam Piórko*, Michelle Crook and Peter Sampson

Department of Chemistry, Saint Mary's University,
Halifax, Nova Scotia, B3H 3C3 Canada

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The reactivity of benzo[*b*]naphtho[2,3-*e*][1,4]dioxin in the electrophilic aromatic substitution reactions has been studied. Friedel-Crafts acetylation resulted in the formation of three out of the possible five monoacetylated products, with the acetyl group located in positions 8 (major), 7 and 6 (minor) of the heterocycle. In the bromination reaction a higher selectivity was observed with the 6-bromo derivative found as the only monobrominated product and the 6,11-dibromo derivative found as the only polybrominated product. A ratio of unreacted heterocycle:6-bromo:6,11-dibromo derivatives in the bromination reaction has been found to depend strongly on the reaction conditions and on the heterocycle:bromine ratio.

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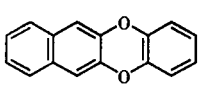
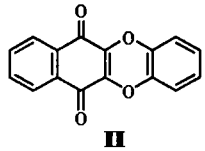
A considerable part of the research effort in the area of heterocyclic chemistry has recently been directed toward the chemistry of unsymmetrical heterocycles. Since many of these heterocycles exhibit biological activity, both the general properties and selective methods of synthesis of heterocyclic derivatives have been studied. Oxygen-containing heterocycles are frequently the subject of investigation and recently Keumi *et al.* [1] presented their results on the study of positional reactivity of benzofuran in electrophilic aromatic substitution reactions.

Benzo[*b*]naphtho[2,3-*e*][1,4]dioxin **I** has been synthesized only recently by Sutherland *et al.* [2] although the 6,11-quinone of this system **II** and its derivatives were reported earlier. The original synthesis of **II** was described by Ullmann and Ettisch [3] and some of its derivatives were shown to exhibit cancerostatic activity against ascites tumor cells [4]. Improved methods of synthesis of **II** have been proposed recently [5,6]; the quinone **II**, its dicyano, tricyanoquinomethane and *N,N'*-dicyanoquinone diimine derivatives have been obtained and studied as potential electron acceptors in charge-transfer complexes and as organic conductors [6]. We have initiated a study of the reactivity of the parent heterocycle **I** and wish to present our results concerning the electrophilic acetylation and bromination of **I**.



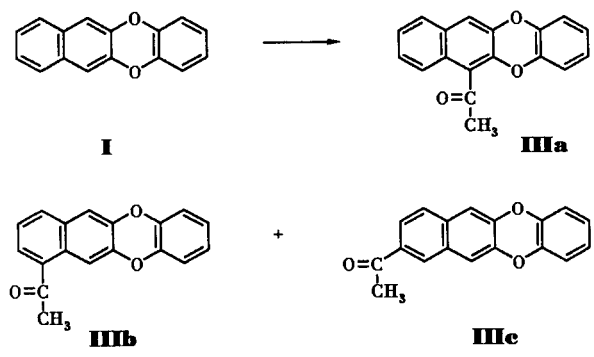
I



II

Benzo[*b*]naphtho[2,3-*e*][1,4]dioxin **I** was prepared following the reported procedure [2]. Attempted acetylation of this compound under mild conditions (acetic anhydride and boron trifluoride-methanol complex) led only to the recovery of over 90% of unreacted **I**. Under typical conditions of the Friedel-Crafts reaction, using acetyl chloride in the presence of aluminum trichloride, a mixture of unreacted **I** and products were obtained (Scheme 1). This mixture has been subjected to plc separation and, in addition to unreacted **I**, three monoacetylated products **IIIa**, **IIIb** and **IIIc** have been isolated. The isomeric acetylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxins **IIIa**, **IIIb** and **IIIc** were characterized and their analytical and spectral data are presented in the experimental part.

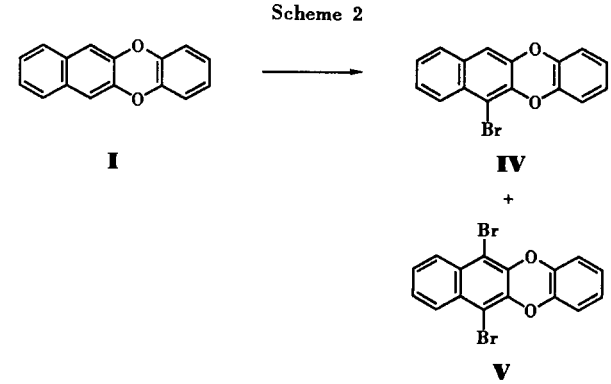
Scheme 1



I **IIIa** **IIIb** **IIIc**

Bromination of **I** was carried out with bromine in an appropriate solvent at an elevated temperature (55-65°). No reaction occured in carbon tetrachloride or methylene chloride solutions, but when acetic acid, methanol-water solution or concentrated sulfuric acid was used as the solvent, a reaction took place to give a mixture of the starting heterocycle **I** and the 6-bromo and 6,11-dibromo derivatives **IV** and **V**, respectively (Scheme 2). The ratio of the

Scheme 2



I **IV** **V**

components of such a mixture **I:IV:V** was found to depend both on the ratio of the reagents and on the solvent used in the reaction. In acetic acid all three components were present up to a bromine:heterocycle **I** ratio of 5:1. For higher ratio the starting heterocycle **I** was absent and the yield of **V** was found to increase. We have found that with a bromine/**I** ratio of 10:1, the **IV:V** ratio was 1:3 while for 20:1 bromine/**I** ratio, the **IV:V** ratio was 8:92. The ratio of products was calculated from the integration of well separated signals in the ^{1}H nmr spectra. A similar pattern of product ratios was observed using water-methanol as the solvent. In concentrated sulfuric acid solution the bromination reaction is exhaustive with **V** being the only product at a ratio bromine/**I** equal to 5:1.

While the synthesis of the 6,11-dibromo derivative **V** may be achieved in a selective manner using concentrated sulfuric acid as solvent, the isolation of the monobromo compound **IV** is rather difficult. Since both **IV** and **V** exhibit very poor solubility in most solvents, a pure sample of **IV** for analysis was obtained by plc separation employing carbon disulfide as the eluent. Attempted selective bromination reactions, aimed at the preparation of pure **IV**, were unsuccessful with extended reaction time and/or at lower temperature because of side reactions leading to products with a high molecular weight. Both the structure of such products and the type of reactions involved in their formation are under investigation.

Reactivity of the heterocycle **I** was expected to reflect its composition, *i.e.* reactions typical for 2,3-disubstituted naphthalenes [7] and *o*-disubstituted benzenes or dibenzo[*b*,*e*][1,4]dioxin [8] should be observed. In this context it is of interest to note that the acetylation reaction, which may be controlled toward the synthesis of monoacetylated products, gave three of the five possible isomeric products. We did not find products with the acetyl group located on the benzene ring of **I** (1- and 2-acetyl-**I**). The bromination reaction is even more selective giving only one of the five monobromo products **IV** (6-bromo-**I**) and, in a subsequent second bromination, only a single dibromo derivative **V** (6,11-dibromo-**I**).

These results indicate a higher reactivity of 2,3-diaryloxynaphthalene than that of the 2,3-diaryloxybenzene fragment in **I** in the electrophilic aromatic substitution reaction which is in agreement with the well recognized reactivity of unsubstituted arenes [7]. Both bromination and acetylation reactions give derivatives with the substituents located on the naphthalene ring of the system. These results of the bromination reactions may lead to the conclusion that the relative positional reactivity at carbons 6 and 11 of **I** is highest among all the carbons in a kinetically controlled and irreversible (in the absence of a Lewis acid catalyst) reaction. Those two positions are equivalent to the 1 and 4 ("α" of a substituted ring) positions of 2-mono- or 2,3-disubstituted naphthalene which were found to be the most reactive in earlier studies [7a]. Additionally, due to the poor solubility, derivative **V** precipitated in each of our experiments and this certainly could prevent its further bromination.

The acetylation reaction has been studied in this work at extended reaction time and it shows an equal ratio of "α" to "β" substitution products, **IIIa** + **IIIb** *versus* **IIIc**. This seems to indicate that under conditions favoring the thermodynamic product **IIIc** the composition of a mixture after reaction may actually result from the Lewis acid catalyzed one-way equlibriation observed earlier in studies on the acylation of naphthalene [8b] and on the acetylation of 2-methoxynaphthalene [7a,9]:

IIIa → IIIb → IIIc

Having characterized compounds **III-V**, we are currently trying to assess and justify the observed positional reactivity of **I** in the electrophilic reactions of this heterocycle.

EXPERIMENTAL

Melting points are uncorrected. All the chemicals used were of reagent grade quality and were purified according to the standard procedures. Merck plates were used for tlc analysis (aluminum backed, 0.2 mm layer of Kieselgel 60 F_{254}) and for plc separations (glass plates, 20 x 20 cm, 0.5 mm layer of Kieselgel 60 F_{254}) without prior activation. The nmr spectra were recorded with Bruker MSL300 (300 MHz, ^{1}H; 75 MHz, ^{13}C; MBI NRC) and Nicolet 360 NB (360 MHz, ^{1}H; ARMRC) spectrometers using (acetone-d_6) solutions of compounds; chemical shifts are reported in δ, ppm scale (internal TMS for proton, calculated from the solvent shift for carbon-13 nmr) where δ_{TMS} = 0 ppm. Due to the poor solubility of compounds **IIIb** and **IIIc** carbon-13 data are not presented since only non-quaternary carbon atom signals were distinguishable in the spectra. The ir spectra have been recorded with a Perkin Elmer 1600 FT IR instrument using chloroform solutions of compounds and the stretching C=O frequency region (cm^{-1}) is reported. Mass spectra were obtained using electron impact ionization at 70 eV. Picture of M^+ region for the 6-bromo **IVb** and 6,11-dibromo **Vc** derivatives in their ms spectra is typical for the bromo and dibromo derivatives due to the presence of isotopic peaks. Purity of the compounds **III-V** has been confirmed by the elemental analysis results (courtesy of University of Saskatchewan) and a tlc analysis using two solvent systems of different polarity.

General Procedure for Acetylation.

To a stirred solution of benzo[*b*]naphtho[2,3-*e*][1,4]dioxin **I** (0.234 g, 1 mmole) in dichloromethane (10 ml), acetyl chloride (0.079 g, 71 μl, 1 mmole) and anhydrous aluminum trichloride (0.133 g, 1 mmole), were added. The reaction mixture was stirred for 16 hours and gently refluxed for 2 hours. After cooling the mixture was carefully poured onto 50 ml of ice containing 5 ml of concentrated hydrochloric acid. The solution was extracted with dichloromethane and the extracts were dried and evaporated giving 0.183 g of a mixture of products. The individual isomeric acetyl derivatives **III** and unreacted **I** were recovered from the

mixture using ten preparative plates (hexane-acetone 9:1). Both the reaction and the separation have been repeated several times to obtain the isomeric products in quantities sufficient for the analytical purpose.

6-Acetylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxin (**IIIa**).

The 6-acetyl derivative was obtained as white powder, mp 124-126° yield 0.022 g (8%); ^{1}H nmr (acetone-d_6): δ 2.89 (s, CH_3), 7.03-7.16 (m, H1, 2, 3, 4), 7.41-7.45 (m, H8, 9), 7.51 (s, H11), 7.65-7.70 (m, H10), 7.79-7.85 (m, H7); ^{13}C nmr (acetone-d_6): δ 26.40 (*C*H_3), 113.79, 116.54, 116.58, 123.95, 123.99, 124.40, 124.50 (quaternary), 125.79, 126.41, 127.28, 131.24 (quaternary), 135.74 (quaternary); 140.92 (quaternary), 142.19 (quaternary), 144.69 (quaternary), 146.05 (quaternary), 199.44 (C=O); ir: 1697, 1602; ms: m/z 276 (M^+, 62), 261 (100).

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.55; H, 4.56.

7-Acetylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxin (**IIIb**).

The 7-acetyl derivative was obtained as white solid, mp 161-162°, yield 0.033 g (12%); ^{1}H nmr (acetone-d_6): δ 2.89 (s, CH_3), 7.03-7.06 (bs, H1, 2, 3, 4), 7.47 (s, H11), 7.49 (d, 8.2, d, 7.5, H9), 7.98 (d, 8.2, d, 1.0, H8), 8.11 (d, 7.5, d, 1.0, H10), 8.46 (s, H6); ^{13}C nmr (acetone-d_6): δ 29.50 (*C*H_3), 111.53, 112.30, 116.39, 116.68, 123.81, 123.81, 123.95, 128.78, 131.92 (quaternary), 132.05, 132.88 (quaternary), 133.71 (quaternary), 140.07 (quaternary), 141.44 (quaternary), 142.08 (quaternary), 143.71 (quaternary), 198.33 (C=O); ir: 1674, 1602; ms: m/z 276 (M^+, 87), 261 (100).

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.06; H, 4.33.

8-Acetylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxin (**IIIc**).

The 8-acetyl derivative was obtained as white microcrystals, mp 196-198°, yield 0.055 g (20%); ^{1}H nmr (acetone-d_6): δ 2.88 (s, CH_3), 7.06 (s, H1, 2, 3, 4), 7.48 (s, H11), 7.61 (s, H6), 7.85 (d, 8.6, H10), 7.91 (d, 8.6, d, 1.6, H9), 8.50 (d, 1.6, H7); ^{13}C nmr (acetone-d_6): δ 26.57 (*C*H_3), 112.01, 113.52, 116.52, 116.52, 123.56, 123.96, 124.08, 127.13, 128.79, 129.86 (quaternary), 133.31 (quaternary), 133.98 (quaternary), 141.25 (quaternary), 141.36 (quaternary), 142.25 (quaternary), 143.81 (quaternary), 197.72 (C=O); ir: 1677, 1606; ms: m/z 276 (M^+, 91), 261 (100).

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.61; H, 4.31.

General Procedure for Bromination.

To a stirred solution of benzo[*b*]naphtho[2,3-*e*][1,4]dioxin **I** (0.234 g, 1 mmole) in 10 ml of the chosen solvent an appropriate volume of 0.01*M* solution of bromine (in acetic acid or methanol) was added. The reaction mixture was stirred and heated for 4 hours at 55-65°. After cooling the mixture, a solid that precipitated was filtered off using a sintered glass filter and washed several times with water. Combined filtrate and washings were carefully neutralized with a concentrated alkali solution and this final solution was extracted with chloroform (5 x 40 ml). Combined extracts were dried and evaporated giving a small amount of the product which has been added to a solid. The 6-bromo derivative **IV** was recovered from the mixture after reaction completed in acetic acid and/or 9:1 methanol-water (bromine:**I** ratio 5:1) using ten preparative plates (carbon disulfide) while the pure 6,11-dibromo derivative **V** has been the only product in the reaction completed in sulfuric acid.

The ratio of unreacted starting material to monobromo derivative to dibromo derivative has been calculated from the integration of well separated signals in ^{1}H nmr spectra of the crude reaction products. For the different solvents used in the reactions and a different bromine to substrate ratio the following results have been found, respectively: carbon tetrachloride and dichloromethane; any bromine:**I** ratio; **I:IV:V** ratio 100:0:0 (overall yield >90%); acetic acid or methanol-water (9:1); bromine:**I** ratio 1:1; **I:IV:V** ratio 73:27:0 (55%); bromine:**I** ratio 2:1; **I:IV:V** ratio 41:34:25 (52%); bromine:**I** ratio 5:1; **I:IV:V** ratio 16:45:39 (58%); bromine:**I** ratio 10:1; **I:IV:V** ratio 0:25:75 (72%); bromine:**I** ratio 20:1; **I:IV:V** ratio 0:8:92 (76%); concentrated sulfuric acid; bromine:**I** ratio 5:1; **I:IV:V** ratio 0:traces:99 (75%).

6-Bromobenzo[*b*]naphtho[2,3-*e*][1,4]dioxin (**IV**).

The 6-bromo derivative was obtained as white solid, mp 127-128°, yield 0.119 g (38%); ^{1}H nmr (acetone-d_6): δ 7.03-7.20 (m's, H1, 2, 3, 4), 7.47 (d, 8.5, d, 7.8, H9), 7.48 (s, H11), 7.54 (d, 8.5 d, 7.8, H8), 7.82 (d, 8.5, H10), 8.07 (d, 8.5, H7); ms: m/z 312 (M^+, 41), 234 (100).

Anal. Calcd. for $C_{16}H_9BrO_2$: C, 61.39; H, 2.90. Found: C, 61.78; H, 2.77.

6,11-Dibromobenzo[*b*]naphtho[2,3-*e*][1,4]dioxin (**V**).

The 6,11-dibromo derivative was obtained as white microcrystals, mp 247-248°, yield 0.310 g (79%); ^{1}H nmr (acetone-d_6): δ 7.09-7.18 (m, H1, 2, 3, 4), 7.51-7.61 (A_2B_2 m, H8, 9), 8.14-8.18 (A_2B_2 m, H7, 10); ms: m/z 392 (M^+, 100).

Anal. Calcd. for $C_{16}H_8Br_2O_2$: C, 49.03; H, 2.06. Found: C, 48.70; H, 1.86.

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