BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48 (11), 3421—3422 (1975)

The Synthesis of the Benzofuro[2,3-*b*]benzofuran Derivative

Mutsumu NANBU, Kaishû MOMONOI, Susumu OGURO, and Yoshiyuki KAWASE

Department of Chemistry, Faculty of Literature and Science, Toyama University, Gofuku, Toyama 930

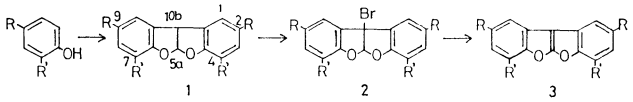
(Received May 15, 1975)

Synopsis. The synthesis of 2,9-dimethoxybenzofuro-[2,3-*b*]benzofuran from its 5a,10b-dihydro-compound was carried out by bromination with *N*-bromosuccinimide, followed by dehydrobromination. The attempted preparation of 2,9-dimethyl-, 2,9-dichloro-, and 2,4,7,9-tetrachloro-derivatives was unsuccessful.

The synthesis of the halo-derivatives of benzofuro-[2,3-*b*]benzofuran (**3**) has been carried out by Riemschneider and his co-workers[1-3] through the condensation of halo-phenols or their methyl ethers with chloral, followed by the cyclization of the products. On the other hand, the halo-[2,3] and methyl-derivatives[5] of 5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (**1**) have been prepared by the condensation of substituted-phenols or -anisoles with dichloroacetal, followed by the cyclization of the products. Also, the **1** compounds have been prepared in one step by the condensation of substituted-phenols with glyoxal.[4,5]

Now, in the present experiments, we have attempted the preparation of several derivatives of **3** from the corresponding dihydro-compounds (**1**) in order to investigate the electrophilic substitution of **3**.

The starting compounds (**1a**—**d**), among which the 2,9-dimethoxy-derivative (**1a**) was newly synthesized, were brominated with *N*-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide. The dehydrobromination of the brominated compounds was attempted by heating them with potassium acetate in ethanol to give the **3** compounds. The attempts succeeded only in the case of **1a**, and the structure of the product was determined to be **3a** from its elemental analysis and spectral data; the shape of the UV absorption curve was different from that of **1a** and was analogous to that of **3d**.[1] Moreover, the peaks due to 5a- and 10b-hydrogen of **1a** disappeared in the NMR spectrum in the case of **3a**. The intermediate brominated compound seems to be the 10b-bromo-compound (**2a**) by analogy to the case of **1c**. In the case of the 2,9-dimethyl-derivative (**1b**), the product was proved to be the 2-ethoxymethyl-9-methyl-derivative of **1** by its elemental analysis and by NMR spectroscopy; the formation of the compound seems to be due to bromination at the methyl group, followed by a reaction with ethanol. In the case of the 2,9-dichloro-derivative (**1c**), the brominated compound was obtained in a pure state and was considered to be the 10b-bromo-derivative (**2c**) from the absence of the doublet peaks due to the 10b-hydrogen in the NMR spectrum. However, the dehydrobromination of **2c** with potassium acetate was difficult. The brominated compound (**2d**) was also obtained from the 2,4,7,8-tetrachloro-derivative (**1d**), but the dehydrobromination was unsuccessful. Some attempts at the direct dehydrogenation as well as the hydroxylation of **2** were fruitless.



1 2 3

a) R=OMe, R'=H b) R=Me, R'=H c) R=Cl, R'=H d) R=R'=Cl

Experimental

The melting points are uncorrected. IR spectra; Hitachi Model EPI-S, UV spectra; Hitachi Model 124, NMR spectra; JEOL Model JNM-C-60H (60 MHz), Mass spectra; JEOL Model JMS-OIS.

*The Preparation of the 5a,10b-Dihydrobenzofuro[2,3-*b*]benzofurans (1).* 2,9-Dimethyl-[4,5] (**1b**), 2,9-dichloro-[3,5] (**1c**), and the 2,4,7,9-tetrachloro-derivative[2,3] (**1d**) of **1** were prepared by the reported methods. The 2,9-dimethoxy-derivative (**1a**) was prepared by an analogous method, which will be described below.

*2,9-Dimethoxy-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (1a).* (a) Concentrated sulfuric acid (40 ml) was stirred, over a 1.5 h period and at 20—25 °C, into a mixture of *p*-methoxyphenol (24.8 g, 0.2 ml), a 40% aqueous glyoxal solution (28 g, 0.15 mol), and acetic acid (100 ml). After stirring for 40 min at that temperature, the mixture was poured into ice water; the precipitate thus formed was collected, washed with a dilute aqueous sodium hydroxide solution, and dried. Extraction by cyclohexane using a percolater and the recrystallization of the extract from ethanol gave 3 g (11% yield) of **1a**; mp 177—177.5 °C. UV: λ_{max}^{EtOH} nm (log ε) 210 (4.18), 220sh (4.12), 303 (3.93). NMR: $\delta(CDCl_3)$ 3.77 (6H, s, $-OCH_3$), 4.92 (1H, d, J=6 Hz, 10b-H), 6.75—6.95 (7H, m, arom-H and 5a-H). Mass: M^+ (*m/e*) 270. Anal. Found: C, 71.13; H, 5.26%. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22%. (b) Concentrated sulfuric acid (25 ml) was added, at 5—10 °C over a 2 h period, to a solution of *p*-methoxyphenol (12.4 g, 0.1 mol) and dichloroacetal (9 g, 0.05 mol) in acetic acid (25 ml); the mixture was stirred at room temperature for 20 h, and then concentrated sulfuric acid (25 ml) was added once more in a similar manner. The mixture was poured into ice water, extracted with ethyl acetate, and the crude 2,2-dichloro-1,1-bis(5-methoxy-2-hydroxyphenyl)-ethane obtained from the extract was refluxed for 2 h with methanol (100 ml) saturated with ammonia. The solvent was then distilled off, and the residue was crystallized from ethanol to give 0.4 g (6.5% yield) of **1a** (mp 177—177.5 °C, identical with that of the other sample).

*The Bromination of 1 and the Dehydrobromination of the Product to Give Benzofuro[2,3-*b*]benzofuran (3). In the Case of 1a*: A solution of **1a** (1.4 g ,0.005 mol) and *N*-bromosuccinimide (NBS) (1.8 g, 0.01 mol) in carbon tetrachloride (350 ml) was refluxed for 30 h with the addition of benzoyl peroxide (0.05 g). Most of the solvent was then distilled off, the residue was dissolved in chloroform, and the solution was washed with an aqueous sodium bicarbonate solution. The crude product obtained from the chloroform solution was dissolved in ethanol, and the solution was refluxed for 5 h with the addition of potassium acetate (2 g, 0.02 mol). The reaction mixture was then poured into ice water, extracted

with ether, and the ethereal solution was washed with the aqueous sodium bicarbonate solution. The residual product obtained from the ethereal solution was distilled (bp 150—250 °C/2 mmHg (bath-temperature)) and then crystallized from ethanol to give 0.7 g (50% yield) of 2,9-dimethoxybenzofuro[2,3-*b*]benzofuran (**3a**); mp 124.5—125 °C. UV: λ_{max}^{EtOH} nm (log ε) 204sh (4.37), 226 (4.57), 276 (4.28), 283 (4.27), 290 (4.26), 298 (4.14). NMR: δ (CCl_4) 3.84 (6H, s, $-OCH_3$), 6.70 (2H, dd, J=3 and 9 Hz, 3,8-H), 7.07 (2H, d, J=3 Hz, 1,10-H), 7.32 (2H, d, J=9 Hz, 4,7-H). Mass: M^+ (*m/e*) 268.

In the Case of ***1b***: The crude product obtained from **1b** (2.4 g, 0.01 mol) by a procedure similar to that described above was purified by chromatography, with alumina and benzene as the solvents. A fairly large amount of the **1b** was obtained at first, and then a small amount (*ca.* 50 mg) of 2-ethoxymethyl-9-methyl-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (mp 95—96 °C (from ethanol)) was obtained. NMR: δ ($CDCl_3$) 1.24 (3H, t, J=7 Hz, $-CH_2-C\underline{H}_3$), 2.30 (3H, s, $-CH_3$), 3.53 (2H, q, J=7 Hz, $-C\underline{H}_2-CH_3$), 4.45 (2H, s, $-O-CH_2$–arom.), 4.96 (1H, d, J=6 Hz, 10b-H), 6.70—7.45 (7H, m, arom.-H and 5a-H). Found: C, 76.40; H, 6.29%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%.

In the Case of ***1c***: The bromination of **1c** (1.4 g, 0.005 mol) by the procedure described above gave a crude brominated compound which was easily purified by crystallization from acetic acid and then from ethanol to give 10b-bromo-2,9-dichloro-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (**2c**); mp 188—188.5 °C; 0.8 g (45% yield). NMR: δ (CCl_4) 6.81 (2H, d, J=9 Hz, 4,7-H), 6.90 (1H, s, 5a-H), 7.15 (2H, dd, J=2 and 9 Hz, 3,8-H), 7.46 (2H, d, J=2 Hz, 1,10-H). Found: C, 46.82; H, 1.80%. Calcd for $C_{14}H_7BrCl_2O_2$: C, 46.94; H, 1.97%. The dehydrobromination of **2c** by the method described before was unsuccessful.

In the Case of ***1d***: A brominated compound, 10b-bromo-2,4,7,9-tetrachloro-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (**2d**), was obtained by the crystallization of the crude brominated compound from **1d** (2.1 g, 0.006 mol); mp 195—195.5 °C (from acetone); 1.3 g (51% yield). The structure was determined on the basis of the results of the elemental analysis and by analogy to the case of **2c** (the NMR spectrum could not be measured, as it was insoluble in the apropriate solvent). Found: C, 39.22; H, 1.06%. Calcd for $C_{14}H_5BrCl_4O_2$: C, 39.38; H, 1.18%. The dehydrobromination of **2d** was also unsuccessful.

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