Benzofuran Systems. Regioselective Bromination and some other Reactions of 1-(3-Benzofuranyl)-2-phenylethanones

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1-[3-(2-Alkylbenzofuranyl)]-2-(3,5-dibromo-4-hydroxyphenyl)ethanones **5a,b** and 1-[3-(2-alkylbenzofuranyl)-2-(3-bromo-4-methoxyphenyl)ethanones **3a,b** were readily prepared by selective bromination of hydroxy **1a,b** and methoxy **1c,d** ethanones, respectively. A successful method of *O*-alkylamination of **5a** with *N*-(2-chloroethyl)-*N,N*-diethylammonium chloride to **6a** by a two-phase reaction under phase transfer conditions has been applied. Lithium aluminium hydride reduction of the carbonyl group of **1b** to carbinol **4b** was carried out in good yields.

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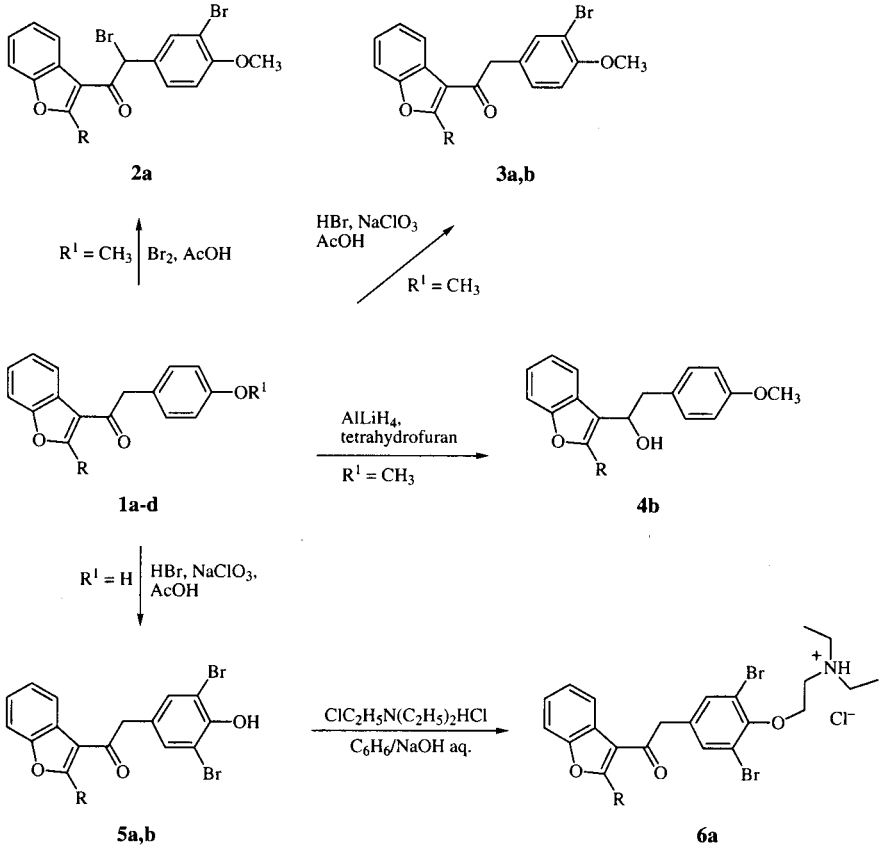
1-(3-Benzofuranyl)-2-(4-hydroxyphenyl)ethanones are potent spasmolytic agents [1-4], and benzofuranyl phenyl ketones and carbinols posses pesticidal properties [5,6]. Various benzofuranyl phenyl ketones have acquired practical importance as convenient intermediates in the preparation of more complicated pharmaco-

Scheme 1



1	R	R^1	2, 3, 4, 5, 6	R
a	C_2H_5	H	a	C_2H_5
b	C_4H_9	H	b	C_4H_9
c	C_2H_5	CH_3		
d	C_4H_9	CH_3		

logically significant and therapeutically valuable compounds [7-13].

As previously described, 1-[3-(2-alkyllbenzofuranyl)]-2-(4-hydroxyphenyl)ethanones **1a,b** were prepared by acylation of 2-alkylbenzofurans with 4-methoxyphenylacetyl chloride followed by demethylation of the methoxy group with pyridine hydrochloride [14]. The aim of this work was to develop an efficient method for the synthesis of 1-[3-(2-alkylbenzofuranyl)]-2-(3,5-dibromo-4-hydroxyphenyl)-ethanones **5a,b**. It was not easy because there are two *ortho*-hydroxyl centers prone to substitution and an active hydrogen in the α position to the carbonyl group in the molecules of **1a,b**. Hence whenever 1-[3-(2-ethylbenzofuranyl)]-2-(4-hydroxyphenyl)ethanone **1a** was treated with bromine in acetic acid, a dark oil resulted from the reaction. Thin-layer chromatography showed it to be a mixture of products impossible to separate. A similar effect was observed when a higher dilution or an insufficient quantity of bromine was used, or the bromination was accomplished with 48% aqueous hydrobromic acid in the presence of sodium chlorate as an oxidising agent. On the other hand, 1-[3-(2-alkylbenzofuranyl)-2-(4-methoxyphenyl)ethanones **1c,d** when brominated in acetic acid solution with bromine, gave a product **2a** with one bromine substituent on the ring and another bromine in the α position to the carbonyl group (Scheme 1). None the less, selective bromination of both positions *ortho* to the hydroxyl group was accomplished when *ca.* 20% aqueous hydrobromic acid was employed in the process. The desired aromatic-ring brominated products **5a,b** were produced in high yields. This method of bromination applied to 1-[3-(2-alkylbenzofuranyl)-2-(4-methoxyphenyl)ethanones gave 3-bromo-4-methoxy derivatives **3a,b** in good yields; the reaction products were precipitated from the reaction mixture. Unfortunately, in spite of excess bromine and higher temperatures, the 3,5-dibromomethoxy derivative was not formed. Next, dibromohydroxy derivatives **5a** were subjected to reaction with *N*-(2-chloroethyl)-*N,N*-diethylammonium chloride. Since no satisfactory results were obtained by the known method of *O*-alkylation of the dry sodium salt of phenols with 2-diethylaminoethyl chloride in dry benzene or toluene, a two-phase reaction aided by a phase transfer catalyst has been applied successfully. The reaction was carried out in benzene and aqueous sodium hydroxide using tetrabutylammonium hydroxide as the phase transfer catalyst. The reaction product was obtained in 70% yield in the form of its hydrochloride and the structure of the compound was established by elemental analysis and and nmr spectroscopy.

Reduction of the methoxy derivative **1b** by sodium borohydride in methanol gave product **4b** in poor yields, whereas treatment of **1b** with lithium aluminium hydride in refluxing tetrahydrofuran gave the product in almost quantitive yield.

Some of the novel compounds of the benzofuran system were tested for their biological activity. Only weak fungicidal activity against *Phytophthora infestans* and *Botritis cinera* and no significant herbicidal or insecticidal effects were observed in testing of compounds **3a,b** and **5a**. Compound **6a** showed some activity on lemna and cell culture in laboratory tests.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and were not corrected. The ir spectra were recorded on a Specord M 80 Carl Zeiss, Jena spectrophotometer. The ^{1}H nmr spectra were taken on a TM Bruker DPX 400 spectrometer, in deuteriochloroform as the solvent. Chemical shifts were reported as δ values (ppm) down field from internal tetramethylsilane.

Synthesis of 1-[3-(2-ethylbenzofuranyl)]-2-bromo-2-(3-bromo-4-methoxyphenyl)ethanones **2a.**

To a solution of **1c** (2.9 g, 10 mmoles) in 45 ml of acetic acid, bromine (2.6 g, 16 mmoles) in 15 ml acetic acid was added dropwise with stirring at ambient temperature. After the addition was completed, the reaction mixture was stirred for an additional 2 hours. The precipitate was filtered, washed and dried. Crystallization from methanol gave **2a** (3.0 g, 67%) mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 7.90-7.89 (d, J = 7.5, 1H, benzofuranyl), 7.79 (d, J = 2.0, 1H, phenyl), 7.54-7.48 (m, 2H, benzofuranyl), 7.39-7.32 (m, 1H, benzofuranyl), 7.35 (d, J = 1.5, 1H, phenyl), 6.89 (d, J = 8.6, 1H, phenyl), 6.07 (s, 1H, CHBr), 3.89 (s, 3H, OCH_3), 3.20 (q, J = 7.5, 2H, CH_2), 1.36 (t, J = 7.5, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{16}Br_2O_3$ (452.14): C, 50.47; H, 3.57; Br, 35.34. Found: C, 50.27; H, 3.30; Br, 35.40.

General Procedure for the Synthesis 1-[3-(2-Alkylbenzofuranyl)-2-(3-bromo-4-methoxyphenyl)ethanones **3a,b** and 1-[3-(2-Alkylbenzofuranyl)-2-(3,5-dibromo-4-hydroxy-phenyl)-ethanones **5a,b**.

To a solution of **1a-d** (10 mmoles) in 70-85 ml of acetic acid and 15 ml of 20% aqueous hydrobromic acid, sodium chlorate (3.8 g, 36 mmoles) in 15 ml of water was added dropwise with stirring at ambient temperature. After the addition was completed, the reaction mixture was stirred for an additional 2 hours. The precipitate was filtered, washed and dried. Crystallization from methanol gave **3a,b** and **5a,b**.

1-[3-(2-Ethylbenzofuranyl)-2-(3-bromo-4-methoxyphenyl)-ethanone (**3a**).

This compound was obtained as white crystals (2.8 g, 75%) mp 121-122°; ir, ν 1670-1680 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.93-7.91 (m, 1H, benzofuranyl), 7.50-7.48 (m, 1H, benzofuranyl), 7.43 (d, J = 1.8, 1H, phenyl), 7.35-7.30 (m, 2H, benzofuranyl), 7.16 (dd, J = 6.6, 1.6, 1H, phenyl), 6.88 (d, J = 8.4, 1H, phenyl), 4.22 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.18 (q, J = 7.5, 2H, CH_2), 1.35 (t, J = 7.5, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{17}O_3Br$ (373.25): C, 61.14; H, 4.52; Br, 21.41. Found: C, 60.20; H, 4.74; Br, 21.08.

1-[3-(2-Butylbenzofuranyl)-2-(3-bromo-4-methoxyphenyl)-ethanone (**3b**).

This compound was obtained as white crystals (3.2 g, 80%) mp 94-96°; ^{1}H nmr (deuteriochloroform): δ 7.93-7.91 (m, 1H, benzofuranyl), 7.49-7.46 (m, 1H, benzofuranyl), 7.44 (d, J = 1.8, 1H, phenyl), 7.35-7.30 (m, 2H, benzofuranyl), 7.16 (dd, J = 1.8, 6.5, 1H, phenyl), 6.88 (d, J = 8.3, 1H, phenyl), 4.22 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.15 (t, J = 7.6, 2H, CH_2), 1.75 (pentet, J = 7.6, 2H, CH_2), 1.41 (sextet, J = 8.4; 7.5; 2H, CH_2), 0.94 (t, J = 7.4, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{21}O_3Br$ (401.30): C, 62.85; H, 5.27; Br, 19.91. Found: C, 62.58; H, 5.49; Br, 19.69.

1-[3-(2-Ethylbenzofuranyl)-2-(3,5-dibromo-4-hydroxyphenyl)-ethanone (**5a**).

This compound was obtained as white crystals (3.8 g, 86%); mp 172-173°; ir (potassium bromide): ν 1670 (C=O), 3300-3450 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.91-7.88 (m, 1H, benzofuranyl), 7.51-7.49 (m, 1H, benzofuranyl), 7.36 (s, 2H, phenyl), 7.35-7.33 (m, 2H, benzofuranyl), 5.88 (s, 1H, OH), 4.20 (s, 2H, CH_2), 3.19 (q, J = 7.5, 2H, CH_2), 1.36 (t, J = 7.5, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{14}O_3Br_2$ (438.12): C, 49.35; H, 3.22; Br, 36.48. Found: C, 49.30; H, 3.31; Br, 36.25.

1-[3-(2-Butylbenzofuranyl)-2-(3,5-dibromo-4-hydroxyphenyl)-ethanone (**5b**).

This compound was obtained as white crystals (3.6 g, 77%) mp 107-108°; ^{1}H nmr (deuteriochloroform): δ 7.90-7.88 (m, 1H, benzofuranyl), 7.51-7.48 (m, 1H, benzofuranyl), 7.36 (s, 2H, phenyl), 7.35-7.32 (m, 2H, benzofuranyl), 5.85 (s, 1H, OH), 4.20 (s, 2H, CH_2), 3.16 (t, J = 7.6, 2H, CH_2), 1.75 (pentet, J = 7.6, 2H, CH_2), 1.43 (sextet, J = 7.6, 7.4, 2H, CH_2), 0.95 (t, J = 7.4, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{18}O_3Br_2$ (466.17): C, 51.53; H, 3.89; Br, 34.28. Found: C, 51.39; H, 4.06; Br, 34.10.

Synthesis of 1-[3-(2-Butylbenzofuranyl)]-2-(4-methoxyphenyl)-ethanol **4b**.

To a mixture of lithium aluminium hydride (0.26 g, 7 mmoles) and 20 ml of dry ether a solution of 2.5 g (8 mmoles) of 1-[3-(2-butylbenzofuranyl)]-2-(4-methoxyphenyl)ethanone **1d** dissolved in 25 ml of dry ether was added dropwise with stirring. After the addition was completed, the reaction mixture was refluxed and stirred for 2.5 hours. The mixture was then cooled, 3 ml of water was added dropwise and then 10% aqueous hydrochloride solution. The mixture was stirred for 30 minutes. The ether layer was separated, dried (sodium sulfate) and evaporated to give **4b** (2.9 g, 90%) as a pale yellow oil; ir (potassium bromide): δ 3500-3300 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.80-7.78 (m, 1H, benzofuranyl)), 7.41-7.74 (m, 1H, benzofuranyl), 7.25-7.72 (m, 2H, benzofuranyl), 7.01 (d, J = 8.5, 2H, phenyl), 6.78 (d, J = 8.5, 2H, phenyl), 4.99 (t, J = 7.2, 1H, CH), 3.76 (s, 3 H, OCH_3), 3.25 (dd, J = 7.2, 6.1, 1H, CH_2), 3.11 (dd, J = 7.0, 6.3, 1H, CH_2), 2.57-2.43 (m, 2H, CH_2), 1.72 (broad band, 1H, OH), 1.51-1.47 (m, 1H, CH_2), 1.35-1.31 (m, 1H, CH_2), 1.30-1.21 (m, 2H, CH_2), 0.86 (t, J = 7.3, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{24}O_3$ (324.42): C, 77.75; H, 7.46. Found: C, 77.34, H, 7.24.

Synthesis of 1-[3-(2-Ethylbenzofuranyl)]-2-[3,5-dibromo-4-(*N*,*N*-diethyl-*N*-ethyloxy)phenyl]ethanone **6a**.

To a suspension of 1-1-[3-(2-ethylbenzofuranyl)]-2-[3,5-dibromo-4-hydroxy)ethanone (2.6 g, 6 mmoles) in 38 ml of benzene and 14.5 ml of aqueous 5% sodium hydroxide were added *N*-(2-chloroethyl-*N*,*N*-diethylammonium chloride (1.1 g, 6.3 mmoles) and 50 mg of tetrabutylammonium hydroxide. The mixture was stirred for 3 hours at 50°. After the mixture was cooled to ambient temperature the separated organic phase was washed with water. The benzene layer was mixed with charcoal, filtered and finally evaporated to give **6a** (1.8 g) as a viscous pale brown oil. The hydrochloride salt of **6a** was prepared from a solution of hydrogen chloride in methanol as a colorless solid, mp 179-181°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.83 (br s 1H, HCl), 8.06-8.04 (m, 1H, benzofuranyl), 7.67 (s, 2H, phenyl), 7.66-7.65 (m, 1H, benzofuranyl), 7.40-7.36 (m, 2H, benzofuranyl), 4.48 (s, 2H, CH_2CO), 4.36 (t, J = 4.9, 2H, OCH_2), 3.61 (q, J = 4.5, 2H, CH_2N, 3.34-3.31 (m, 4H, CH_2), 3.21 (q, J = 7.5, 2H, CH_2), 1.34-1.27 (m, 9H, CH_3).

Anal. Calcd. for $C_{24}H_{28}Br_2NO_3Cl$ (573.75): C, 50.24; H, 4.92; N, 2.44; Br, 27.85. Found: C, H, N, Br.

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