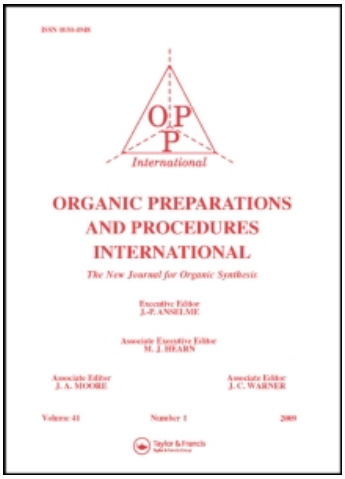

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SYNTHESIS OF (2-BUTYL-3-BENZOFURANYL)[4-[2-(DIETHYLAMINO)ETHOXY]-3,5-DIIODOPHENYL)METHANE DERIVATIVES

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SYNTHESIS OF (2-BUTYL-3-BENZOFURANYL){4-[2-(DIETHYLAMINO)ETHOXY]-3,5-DIIODOPHENYL}METHANE DERIVATIVES

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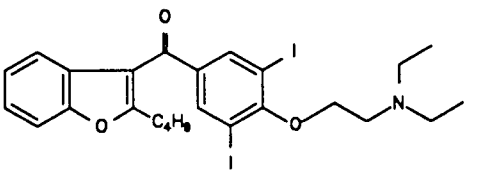
The mechanism of toxicity of synthesis of (2-butyl-3-benzofuranyl){4-[2-(diethylamino) ethoxy]-3,5-diiodophenyl}methane derivatives is unknown. However, certain evidence supports the postulation that the molecule is enzymatically oxidized to free radical intermediates.[1] The extended π conjugation available to the amiodarone molecule could facilitate free-radical reactions by stabilizing the radical intermediates. This conjugation could be interrupted by eliminating the bridging sp^2 hybridized carbonyl carbon and, presumably, reduce the toxicity of the agent. We wish to report the synthesis of a series of benzofuranyl agents in which the bridging carbonyl is replaced by a methylene derivatives of the general structure, 2.

Synthesis of the (2-butyl-3-benzofuranyl){4-[2-diethylamino)ethoxyl]-3,5-diiodophenyl} methane derivatives involved the conversion of the alcohol (2a) to the corresponding ester (2b), ether (2c) and hydrocarbon (2d) of amiodarone. Formation of the pivalate (2b) was achieved by treatment of the alcohol (2a) with excess pivaloyl chloride in pyridine at 65°.[2] The pivalate ester



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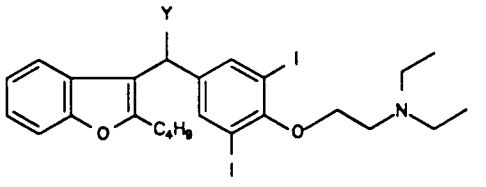

2

a) Y = OH b) Y = $OCCMe_3$ c) Y = OCH_3 d) Y = H_2

was synthesized for steric reasons; it was felt that the bulky t-butyl group would effectively block the reactive benzylic position. Since ether derivatives would be expected to be even more stable

than the corresponding esters, the methyl ether analog 2c, was prepared by treating alcohol 2a sequentially with lithium diisopropylamide and methyl iodide.[3] The preparation of the hydrocarbon analog 2d would provide the most effective means of stabilizing the molecule. The analog 2d, was synthesized by a direct reduction of the alcohol 2a with sodium borohydride in trifluoroacetic acid.[4]

Preliminary toxicity studies were carried out using ventilated and perfused rabbit lungs. In parallel experiments, the new hydrocarbon analog, 2d, exhibited no toxicity whereas amiodarone 1 caused acute lung injury. The compounds are currently undergoing more extensive biological testing.

EXPERIMENTAL SECTION

Mps. were determined on glass slides using a Fishner Johns apparatus and are uncorrected. Thin layer chromatographic analysis (TLC) were performed with 250 R)Lm thick (layers of silica gel coated on glass plates (Analtech, Inc.). The NMR spectra were obtained at 90 MHz with a JEOL-FX900 spectrometer samples were dissolved in deuteriochloroform and the resonances are recorded downfield (δ) from the internal tetramethylsilane standard. MS spectrum was measured by ZAB-EQ. Elemental analyses were performed by Galbraith Laboratories, INC., Knoxville, Tn. All chemicals and solvents were analytical grade and were used without further purification. The (2-butyl-3-benzofuranyl){4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl}methanone was prepared according to literature procedures.[5]

(2-Butyl-3-benzofuranyl){4-[2-(diethylamino)ethoxyl-3,5-diiodophenyl}methanol) 2a.- Sodium borohydride (45 mg, 1.2 mmole) was added in portions to a solution of (2-butyl-3-benzofuranyl) {4-[2-diethyl-amino)ethoxy]-3,5-diiodophenyl}methanone, 1, (645 mg, 1 mmole) in 30 ml of THF:MeOH (10:1, v/v) at O°. After stirring for 15 min, the excess borohydride was decomposed via the dropwise addition of water (0.5 mL). The solvent was evaporated in vacuo, the residue treated with water (10 mL) and the product extracted into methylene chloride (50 mL). The methylene chloride layer was separated, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue chromatographed (2% methanol in methylene chloride, silica gel) to yield 595 mg (92%) of alcohol 2a as a white solid mp. 106-107°. ^1H NMR ($CDCl_3$): δ 7.83 (s, 2H, ArH); 7.10-7.34 (m, 4H, Ar-H); 5.93 (s, 1H, Ar-CH-Ar); 3.99 (t, 2H, OCH_2); 2.81 (t, 2H, Ar-CH_2-); 2.57-2.65 (m, 6H, CH_2-N[CH_2]); 0.94-1.83 (m, 14H, OH, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$): δ 156.8, 165.3, 154.3, 142.5, 137.4, 126.9, 123.7, 122.6, 120.2, 116.1, 110.9 (Ar carbons); 90.7 (= C-I); 70.8 (CH_2); 66.3 (CHOH); 52.0 (CH_2N); 47.6 (N[CH_2]$_2$); 30.6, 26.7, 22.6, (CH_2); 13.9, 11.7 (CH_3). Hydrochloride, mp. 143-145°.

Anal. Calcd for $C_{25}H_{32}ClI_2NO_3$: C, 43.91; H, 4.72; N, 2.05. Found: C, 43.87; H, 4.93; N, 1.93

(2-Butyl-3-benzofuranyl){4-[2-diethylamino)ethoxyl-3,5-diiodophenyl}methyl Pivalate (2b).- Pivaloyl chloride (605 mg, 5 mmoles) was added to a solution of alcohol 2a (647 mg, 1 mmole) in dry pyridine (5 ml). The reaction mixture was heated to 65° and the solution stirred under nitrogen atmosphere for 12 hrs. After removal of the volatile solvents in vacuo, the residue was dissolved in methylene chloride (50 mL), washed with 5% aqueous sodium hydroxide (2 x 25

ml) and water (25 ml), and dried (Na_2SO_4). After removal of solvent under reduced pressure the residue was chromatographed (1% methanol in methylene chloride, basic alumina) to yield 683 mg (89%) of the pivalate 2b as a pale yellow visous oil. ^1H NMR ($CDCl_3$): δ 7.72 (s, 2H, Ar-H); 7.15-7.40 (m, 4H, Ar-H); 6.95 (s, 1H, Ar-CH-Ar); 4.05 (t, 3H, OCH_2); 3.02 (t, 3H, $ArCH_2$-); 2.52-2.85 (m, 6H, CH_2 $N[CH_2]_2$); 0.94-1.75 (m, 22 H, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$): 177.6 (-C-O); 158.0, 157.9, 154.6, 139.4, 137.9, 127.2, 124.1, 123.1, 120.4, 112.9, 111.4, (Ar carbons; 91.2 (+ C-I); 71.5 (OCH_2); 67.7 (CH-O); 52.4 (CH_2N); 48.1 (-$N[CH_2]_2$); 39.5 (C-CMe_3); 30.8 (CH_2); 27.6 (Me_3); 27.0, 22.9 (-CH_2-); 14.3, 12.4 (CH_3). High resolution MS: calcd for $C_{30}H_{40}NO_4I_2$ 732.1048 $(M + H)^+$.

Found 732.0953 $(M + H)^+$; hydrochloride, mp. 108-110°.

Methoxy (2-butyl-3-benzofuranyl){4-[2-(diethylamino)-ethoxyl-3,5-diiodophenyl}methane (2c).- A solution of lithium diisopropylamide in cyclohexane (0.73 mL of a 1.5 M solution, 1.1 mmole) was added slowly to a solution of alcohol 2a (647 mg, 1 mmole) in 10 mL of THF at -78°. Methyliodide (0.17 g, 1.2 mmole) was then added and the reaction mixture allowed to warm slowly to room temperature. The volatile components were removed under reduced pressure and the residue dissolved in methylene chloride (50 mL). The organic layer was washed with brine (2 x 25 mL), dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on a column of silica gel (30 g) using, intially, CH_2Cl_2 and then 1% MeOH in CH_2Cl_2 as the eluents, to give 450 mg (68%) of ether 2c as a viscous oil. ^1H NMR ($CDCl_3$); 7.82-7.85 (m, 2H, Ar-H); 7.02-7.38 (m, 4H, Ar-H); 6.02 (s, 1H, Ar-CH-Ar); 3.78 (t, 2H, OCH_2); 3.56-3.91 (m, 6H, $CH_2N[CH_2]_2$); 3.44 (s, 3H, -OCH_3); 2.85 (t, 2H, Ar-CH_2); 0.82-1.94 (m, 13H, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$); 157.3, 156.2, 154.2, 143.0, 138.0, 128.0, 123.6, 122.6, 120.8, 120.3, 116.4, 110.9 (Ar-carbons); 90.6 (= C-I); 71.2 (OCH_3); 54.1 (OCH_3); 52.2 (CH_2N); 47.8 ($N[CH_2]_2$), 30.6, 26.7, 22.6, (CH_2); 13.9, 12.0 (CH_3). Hydrochloride, mp. 103-104°.

Anal. Calcd for $C_{26}H_{34}ClI_2NO_3$: C, 44.75; H, 4.91; N, 2.00

Found : C, 44.36; H, 4.87; N, 1.98

(2-Butyl-3-benzofuranyl) {4-[2-diethylamino)ethoxyl-3, 5-diiodophenyl}methane, 2d.- Sodium borohydride (380 mg, 10 mmoles) was added to trifluoroacetic acid (25 mL) at 0-5° under nitrogen over a 10 min. period. A solution of alcohol 2a (647 mg, 1 mmole) in dry methylene chloride (20 mL) was then added dropwise to this mixture over 15 min. A brilliant red-orange coloration developed (carbocation) and the rapidly disappeared as the substrate contacted the reaction mixture. The mixture was stirred under nitrogen at 25-30°C for 2 hrs and then diluted with water, made alkaline with sodium hydroxide (pellets) and the product extracted into methylene chloride. The methylene chloride solution was washed with water, brine, and then dried over Na_2SO_4. Evaporation of solvent in vacuo followed by column chromatography (1% methanol in methylene chloride, basic alumina) of the residue provided 540 mg (86%) of hydrocarbon 2d as a white solid mp. 80-81°. ^1H NMR ($CDCl_3$): δ 7.58 (s, 2H, Ar-H);

7.19-7.21 (m, 4H, Ar-H); 4.01 (t, 2H, OCH_2); 3.85 (s, 2H, $ArCH_2$-); 3.01 (t, 2H, $ArCH_2$); 2.56-2.70 (m, 6H, $CH_2N[CH_2]_2$); 0.85-2.16 (m, 13H, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$): 156.5, 156.0, 154.1, 139.7, 139.5, 129.1, 123.5, 122.4, 119.0, 111.7, 110.9 (Ar carbons); 90.9 (= C-I); 71.2 (-OCH_2-); 52.1 (CH_2N); 47.8 ($N[CH_2]_2$); 30.5, 28.0, 26.3, 22.5 (-CH_2-); 13.9, 12.1 (CH_3). hydrochloride, mp. 119-121°.

Anal. Calcd for $C_{25}H_{31}NO_2I_2$: C, 47.56; H, 5.06; N, 2.22 Found: C, 47.54; H, 4.94; N, 2.52

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L-DOPA-3-O-SULFATE BY THE PERSULFATE OXIDATION OF L-TYROSINE

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The Elbs persulfate oxidation of p-substituted phenols proceeds with poor yields of the catechol sulfates for unknown reasons;[1] the oxidation of L-tyrosine is no exception. A dark, polymeric melanin-like material is the major product.[2] Oxidation of the amino group does not appear to be responsible for the poor yields of the sulfate ester as this reaction is slow.[3] We have studied various factors which might influence the yield of the sulfate ester.[3] The best yields, as measured by the Folin-Denis phosphotungstic acid reagent,[4] were around 25% with a persulfate-tyrosine ratio between two and three;[3,5] the yield decreased with increasing concentration of alkali. Despite these relatively poor yields, we have carried out the isolation and