3-[(*Z*)-2-*t*-Butoxyethenyl]-4-hydroxy-2(5*H*)-furanone, an Interesting Byproduct Obtained from Reaction of 4-*t*-Butoxy-2-butenoate with the Alkoxide Anion of Methyl Glycolate

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Treatment of methyl 4-*t*-butoxy-2-butenoate (**1**) with the alkoxide anion of methyl glycolate gives, in addition to the previously reported (Fried, *et al.* [2]) 2,3-disubstituted-2,3-dihydro-4-furanone **2**, an equivalent amount of the interestingly substituted 3-[(*Z*)-2-*t*-butoxyethenyl]-4-hydroxy-2(5*H*)-furanone **3**. Isolation, structure proof and possible mechanism of formation are presented

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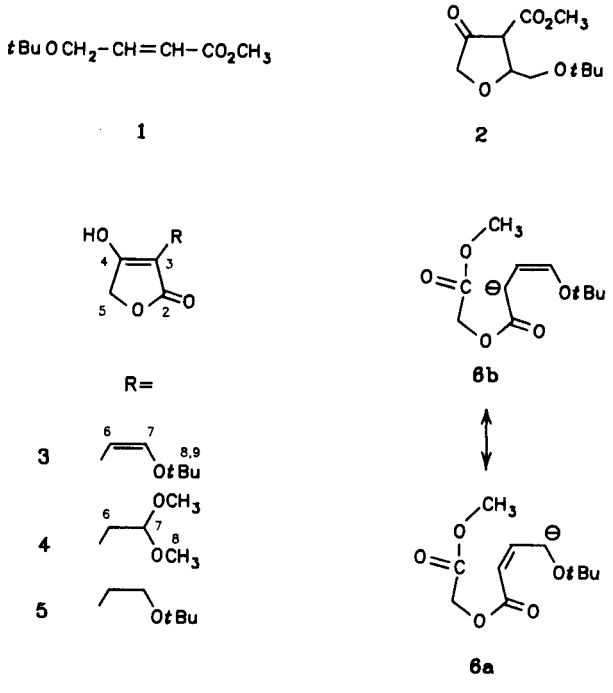
In connection with our preparation of 2,3-substituted furans as potential thromboxane-A_2 antagonists we have been using the Gianturco [1] synthesis of furans as applied by Fried and co-workers [2] to prepare starting material **2**. In this synthesis methyl glycolate alkoxide anion is added in a Michael fashion to the unsaturated ester **1**, [2] which then cyclizes to the 4-furanone **2**. During these syntheses, we repeatedly isolated a second major, strongly uv absorbing product **3**, which was produced in nearly equal amounts along with the desired **2**.

The ^{1}H nmr and ms analysis of the second product **3** showed retention of the *t*-butoxy group and also indicated that it differed from the expected furan **2** by the elements of methanol. The most unusual feature of this molecule was a deuterium oxide exchangeable proton at 10.23 ppm, which suggested the possibility of a free acid or an enolic proton but not an aldehyde (non-exchangeable). A singlet at 4.60 ppm was likely the methylene formerly of the glycolate and a doublet at 6.26 ppm, which was coupled with an unusually high field doublet at 5.19 ppm, suggested olefinic protons of vinyl ether. The coupling constant (J = 6.8 Hz) further suggested a *cis* orientation for the vinyl ether. [3] An ir spectrum of **3** showed only weak absorption in the hydroxyl region, which would be uncommon for a free carboxylic acid, but more likely to occur for a non-hydrogen-bonded enol. There was also a ν C=O stretch at 1769 cm^{-1} which suggested a five membered lactone. Based on these observations we initially assigned structure **3** to the byproduct being produced in this reaction.

Further chemical and spectral analysis was consistent with this structural assignment. The uv spectra indicated extended conjugation as proposed in structure **3**. Conventional APT and heteronuclear correlation nmr spectroscopy was used to assign carbon resonances which were also consistent with structure **3** as the second product being produced in this reaction.

Treatment of **3** with methanol and a catalytic amount of *p*-toluenesulfonic acid (1 hour, 50°) gave a single major new product **4**. However, upon standing overnight, the isolated acetal **4** turned yellow and could not be completely redissolved in ether, suggesting that polymerization/decomposition had occurred.



Catalytic hydrogenation of **3** over Pd/C gave **5** as the only product detected, as evidenced by loss of the alkenyl protons in the parent molecule. Based on these observations we conclude that the byproduct possesses the 3,4-disustituted 2-furanone structure **3**, in which, apparently, the enol ether is in the thermodynamically least favorable *cis* configuration.

We recognized that *beta*-alkoxy elimination (*beta* to both the ester and ketone) by the anion of **2**, followed by intramolecular attack of the alkoxide ion on the ester would result in a five-membered lactone which, after tautomerization to **3**, would produce a molecule consistent

with the observed spectral information of the second product. That such a reaction does not occur, was shown by the fact that treatment of purified **2** with one equivalent of sodium hydride, under the reaction conditions used for the original furan formation, resulted in no detectable conversion to the second product **3** (tlc, ^{1}H nmr) in 14 hours. Consequently, the beta-alkoxy elimination route does not appear to be a major contributing route to formation of the 3,4-disustituted-2-furanone **3** in the original reaction.

A reasonable mechanism for the formation of **3** would be *via* initial attack of the glycolate anion on ester **1** to form a *trans* esterified intermediate with the loss of methanol. Under the basic conditions employed, a proton adjacent to the *t*-butoxy group could be abstracted generating anion **6a**. The resonance hybrid of this anion, **6b**, could then ultimately cyclize to give **3**. Alternatively, the reverse reaction, in which attack of the anion of **1** on the ester of the glycolate is the first step, would also appear possible. Even though the proposed anion **6** is delocalized, there was some question in our minds that the protons adjacent to the *t*-butoxy group would be acidic enough to be abstracted under the conditions employed. However, that it is possible to form such a delocalized anion **6** is suggested by the fact that when **1** is treated with one equivalent of sodium hydride in dimethyl sulfoxide it turns dark green, suggesting delocalized charge. Subsequent neutralization of the green reaction mixture returns **1** in greater than 80% yield upon workup. It is noteworthy that a similar color is observed in the complete reaction mixture generating these two products.

EXPERIMENTAL

Infrared spectra (ir) were obtained on a Nicolet MX-1 FT Infrared Spectrometer as solutions (carbon tetrachloride) in potassium bromide cells. Low resolution electron impact mass spectra (ms) were obtained on a Varian MAT 112-S mass spectrometer (70 eV). All nmr were obtained using either a Nicolet NT-200 or NT-360 sectrometer equipped with 1280/293C data system and are reported in ppm δ downfield from tetramethylsilane.

Gas-Liquid Chromatography (glc) analyses were carried out on a Perkin-Elmer Model Sigma 2000 gas chromatograph (fid). All column chromatography was preformed over silica gel (Sigma type H, 10-40 μ) using a low pressure pump. Thin layer chromatography (tlc) was performed on Merk Silica Gel 60 F_{254} (0.2 mm, precoated on tlc aluminum sheet) and spots were visualized by uv light or iodine vapor.

3-[(*Z*)-2-*t*-Butoxyethenyl]-4-hydroxy-2(5*H*)-furanone (**3**).

The anion of methyl glycolate was generated by dropwise addition of methyl glycolate (6.30 g, 70 mmoles) to oil-free sodium hydride (2.8 g, 60% in oil, 70 mmoles, washed with dry hexane) in dry ether (75 ml) at ice bath temperature. The ether was removed *in vacuo* and the white solid was dissolved in dimethyl sulfoxide (75 ml). Methyl 4-*t*-butoxy-2-butenoate [2] (**1**, 11.4 g, 66 mmoles) was added in one portion to the reaction and the mixture stirred 30 minutes in an ice bath and then 1 hour at room temperature. After neutralization with aqueous sulfuric acid (5%, 200 ml), the reaction mixture was extracted with ether (3 x 200 ml), washed with ice-cold sodium bicarbonate (5%, 2 x 20 ml), the extracts dried (magnesium sulfate) and solvents removed *in vacuo*. The tlc (silica gel, hexane:ether, 10:4) of this residue showed two major (**2**, R_f 0.33; **3**, R_f 0.26) and several minor products. Column [4] chromatography of the residue (silica gel, hexane:ether, 10:2) gave, after removal of solvent, the pure target furan **2** (20%), a mixture of **2** and **3** (11%) and the more polar, crystalline **3** (18%). Two recrystallizations from hexane gave the analytical sample **3**, 98% recovery: mp 110-111°; tlc (silica gel, hexane: ether 10:4), R_f 0.26; glc (10 m, cap, methylsilicone, He at 1.5 ml/minute, 100° for 5 minutes, 15°/minutes to 250°) retention 8.57 minutes; ^{1}H nmr (deuteriochloroform): 1.42 (s, 9H, *t*-butyl), 4.60 (s, 2H, C_5-*H*'s), 5.19 and 6.26 (2 x d, 2 x 1H, olefinic *H*'s), 10.23 (s, 1H, deuterium oxide exchangeable enol *H*); ms: (EI) 124 (100), 142 (92); ir (carbon tetrachloride): 1769 cm^{-1}, ν C=O; uv (methanol): λ max (ϵ) 279.7 (8,601), 269.7 (6,800); ^{13}C nmr (deuteriochloroform): (numbering as shown in **3**) C_2 (C_4) 173.3, C_3 97.9, C_4 (C_2) 170.4, C_5 66.6, C_8 80.8, C_9 27.6.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.23. Found: C, 60.59; H, 7.12.

3-(2-*t*-Butoxyethyl)-4-hydroxy-2(5*H*)-furanone (**4**).

The olefin **3** (1.98 g, 10 mmoles) was hydrogenated in methanol (100 ml) over Pd/C (10%, 100 mg) using a Parr-hydrogenator at 35 psi for 8 hours. The reaction mixture was filtered through celite and the solvent removed with a rotary evaporator. The light brown solid so obtained was recrystallized from ether to give the saturated derivative **4** as white crystalline needles (1.8 g, 90%), mp 80-81°, tlc (ether:hexane 45:55) R_f 0.25; ^{1}H nmr (deuteriochloroform): 4.57 (s, 2H, C_5-*H*'s), 3.67 and 2.50 (2 x t, 2 x 2H, ethylene *H*'s), 1.32 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.92; H, 8.05. Found: C, 59.94; H, 8.10.

Acid Catalyzed Methanolysis of **3**.

Treatment of **3** (0.65 g, 3.3 mmoles) under nitrogen in methanol (10 ml) with a catalytic amount of *p*-toluenesulfonic acid gave a single major new product **4** over a period of one hour at 50° (tlc, silica gel, ether, R_f 0.1; starting material **3**, R_f 0.5). The methanol was removed *in vacuo* (this must be done rapidly to avoid decomposition), and the residue dissolved in ether containing solid sodium bicarbonate to remove the acid catalyst. Filtration and removal of the ether gave the acetal **4** (84%, ^{1}H nmr, tlc); ^{1}H nmr (deuteriochloroform): (numbering as indicated on **4**) 2.63 (d, 2H, C_6-H_2), 3.49 (s, 6H, OCH_3), 4.60 (s, 2H, C_5-H_2), 4.62 (t overlapping CH_2 resonance, 1, C_7-H). Upon standing overnight, the product **4** turned yellow and could not be completely redissolved in ether, suggesting that decomposition had occurred.

Acknowledgement.

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REFERENCES AND NOTES

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[4] All column chromatography was performed using tlc silica gel G (Sigma) at low pressure.