

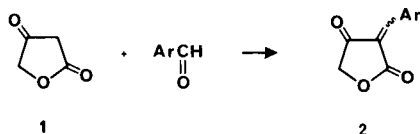
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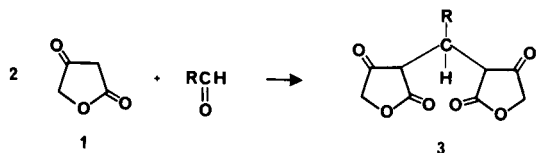
2,4(3*H*,5*H*)-Furandione, **1**, condenses with heteroaromatic aldehydes in the presence of concentrated hydrochloric acid to yield 3-(heteroarylmethylene)-2,4(3*H*,5*H*)-furandiones, **4**. The condensation of **1** with acid sensitive aldehydes, including 2-furanacrolein and *N*-methylpyrrole-2-carboxaldehyde proceeded well with **1** as the sole proton source. The *E/Z* ratio of type **4** compounds was determined by <sup>1</sup>H-nmr spectroscopy.

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3-(Phenylmethylene)-2,4(3*H*,5*H*)-furandiones, **2**, appeared to us to be useful as synthons for the preparation of lignans of the  $\alpha,\beta$ -dibenzyl- $\gamma$ -butyrolactone class. These compounds should be readily available through an aldol condensation between 2,4(3*H*,5*H*)-furandione, commonly known as  $\beta$ -tetronic acid **1**, and aromatic aldehydes.



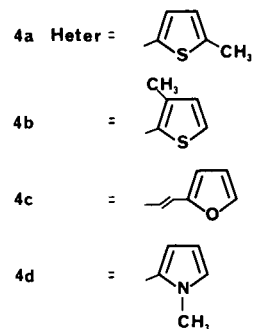
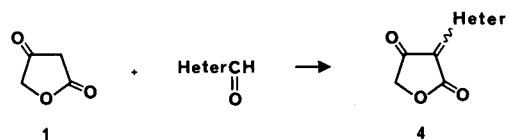
A Wittig reaction of **2** with an appropriately substituted aromatic aldehyde should give an  $\alpha,\beta$ -diarylidene- $\gamma$ -butyrolactone which upon hydrogenation would give the desired lignans. However, according to earlier reports (3,4) the aldol condensation of **1** with aldehydes did not produce the 1:1 adduct, **2**, but rather gave only compounds of the general structure **3**.



Since there appears to be no theoretical reason why the 1:1 aldol condensation product should not form, we re-investigated this reaction (5). It was found that the 1:1 products could be obtained if the condensation was run as a melt with gaseous or concentrated hydrochloric acid as catalyst. Under these conditions a wide variety of type **2** compounds could be prepared. A condensation between **1** and heterocyclic aromatic aldehydes should lead to 3-(heteroarylmethylene)-2,4(3*H*,5*H*)-furandiones, **4**, which represents a potential synthetic pathway toward the synthesis of heteroaryl analogs of lignans.

When **1** and heteroaromatic aldehydes were combined, their reaction proceeded well under the mentioned conditions. The 5-methylthiophene-2-carboxaldehyde condensed smoothly with **1** to give product **4a** in high yield. In contrast, the isomeric-3-methylthiophene-2-carboxaldehyde afforded a much diminished yield of **4b**. Analogously

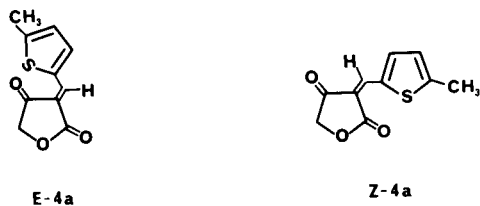
ortho-substituted benzaldehydes in this condensation also gave rise to mediocre yields (**5**). The reason for this observed behavior is most probably steric hindrance. The acid sensitivity of the other two aldehydes used in this study, 2-furanacrolein and *N*-methylpyrrole-2-carboxaldehyde, precluded the use of concentrated or gaseous mineral acid as catalyst in the condensation with **1**. Attempts to achieve the condensation under strongly acidic conditions resulted in excessive tar formation. Reactions of these two aldehydes proceeded as desired with **1** as the sole acidic proton source in ethanol as solvent.



The role of a proton catalyst and the difficulty encountered by earlier investigators (3) in obtaining a mono-condensation product between **1** and an aldehyde may be more clearly understood in terms of a proposed reaction mechanism (Scheme 1). The aldehydic carbonyl group is protonated either by **1** ( $pK_a = 3.76$ )(6) or an added mineral acid to generate the carbocation **5**. Attack at the positive center by **1** results in the formation of the aldol product **6**. Subsequent tautomerization of **6** to **7** followed by protonation and loss of water gives the carbocation **8**. Attack by **1** (Path A) results in the formation of the bis-product **9**. Loss of a proton from **8** affords the dehydrated aldol product **10**. The electrophilic character of the carbon-carbon double bond in **10**, however, makes this

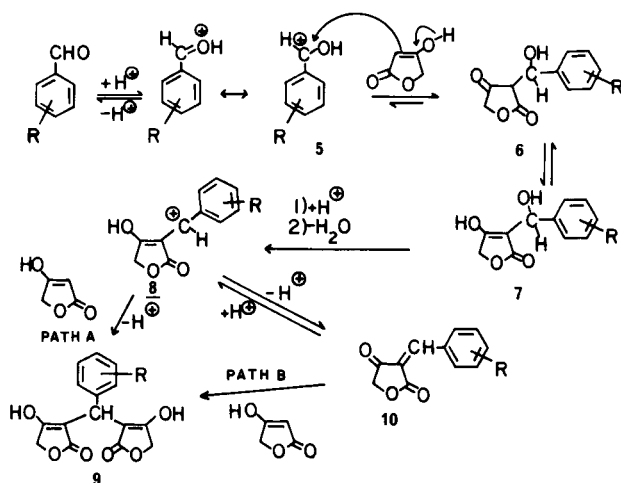
linkage highly susceptible to attack by another molecule of **1** to form **9** (Path B). Thus, only in the presence of large excesses of aldehyde **6** and in the absence of solvent is the formation of bis-condensation product **9** suppressed. Conducting the condensation in solution and at high concentrations of protons and **1**, as was done by the earlier investigators (3), seems to strongly favor formation of **9**, which is in agreement with this proposed mechanism.

Compounds **4a-4d** are formed as a mixture of *E/Z* isomers. The  $^1\text{H}$ -nmr spectrum of **4a-4d** exhibited two characteristic singlets in the  $\delta$  4.5-4.7 region for the



lactone methylene protons which are considered to be indicative of the *E* and *Z* geometric isomers. An nmr study of **4a** demonstrated the presence of *E* and *Z* isomers, and permitted estimation of their relative amounts. The addition of  $\text{Eu}(\text{fod})_3$  (**7**) shift reagent separates the *E* and *Z* methylene signals further and shifts the *E* and *Z* vinyl proton signals out from under the envelop of the signals arising from the thiophene ring protons (Figure 1,2). The *E/Z* ratio for **4a**, as determined by integration, is about 1:2. Attempts to separate and isolate the *E* and *Z* isomers *via* chromatography have thus far been unsuccessful.

#### SCHEME 1



In conclusion, we have synthesized 3-(heteroaryl-methylene)-2,4(3*H*,5*H*)-furandiones **4**. They represent potential synthetic intermediates for a synthesis directed towards heteroaryl analogs of antineoplastic lignans. A

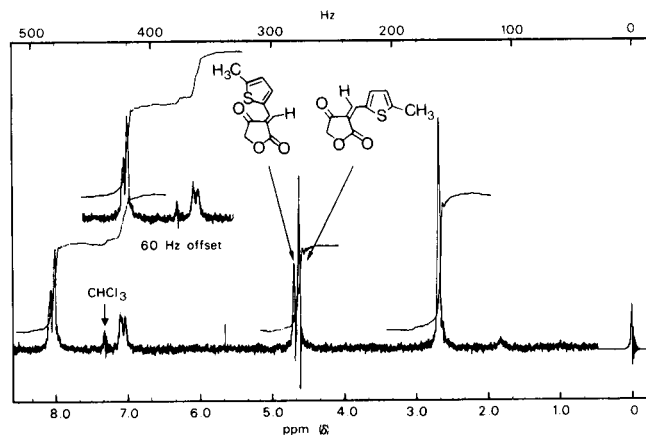


Figure 1. The  $^1\text{H}$  nmr spectrum of (*E/Z*)-3-[(5-methyl-2-thienyl)methylene]-2,4(3*H*,5*H*)-furandione in deuteriochloroform.

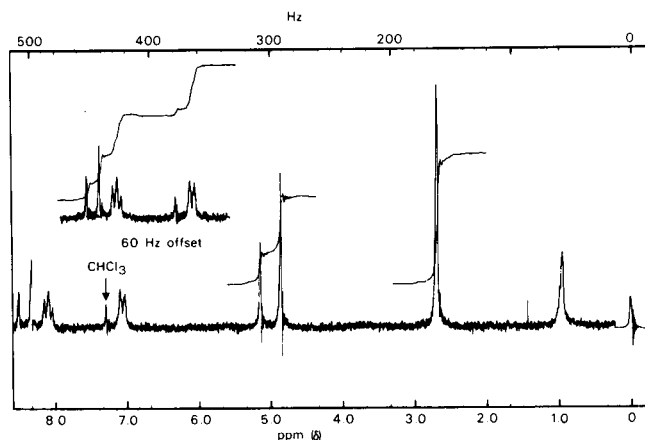


Figure 2. The  $^1\text{H}$  nmr spectrum of (*E/Z*)-3-[(5-methyl-2-thienyl)methylene]-2,4(3*H*,5*H*)-furandione in deuteriochloroform with  $\text{Eu}(\text{fod})_3$ ; reagent/substrate  $\sim 0.02$ .

mechanistic rationale for the results of earlier workers, who obtained only 2:1 condensation products between **1** and aldehydes, has been presented. Further, an nmr shift reagent study demonstrated the presence of *E/Z* geometric isomers of **4** and permitted estimation of their relative amounts, 1:2.

#### EXPERIMENTAL

Infrared spectra (ir) were obtained on a Perkin-Elmer Model 599 spectrometer and were calibrated against the  $1601\text{ cm}^{-1}$  band of polystyrene. Proton nuclear magnetic resonance spectra ( $^1\text{H}$ -nmr) were recorded using a Varian T-60 spectrometer. Chemical shifts are reported on the  $\delta$  scale in parts per million downfield from internal tetramethylsilane (TMS), and apparent coupling constants (J) are given in hertz (Hz). A Perkin-Elmer RMU-7 mass spectrometer was used to record mass spectral data at 70eV. Melting points were determined using a Mel-Temp melting point apparatus and are uncorrected. Analytical thin-layer chromatography (tlc) was performed using the ascending technique with EM silica gel 60 F<sub>254</sub> precoated glass plates. Iodine or uv visualization

was employed. Column chromatography was done with EM silica gel (less than 0.08 mm). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee or by MHW Laboratories, Phoenix, Arizona.

#### 2,4-(3*H*,5*H*)-Furandione (**1**, $\beta$ -Tetronic Acid).

This lactone was conveniently prepared in preparative quantities by a recently published procedure from our laboratory (8).

#### 3-[(5-Methyl-2-thienyl)methylene]-2,4(3*H*,5*H*)-furandione, **4a**.

To a stirred mixture of **1** (500 mg, 5 mmoles) and 5-methylthiophene-2-carboxaldehyde (0.85 ml, 15 mmoles) was added concentrated hydrochloric acid (0.5 ml). Within 10 minutes the reaction solidified. The mass was broken up with a glass rod then washed on a Buchner funnel with water and ether. After drying *in vacuo* over phosphorus pentoxide the dark yellow residue weighed 650 mg. An additional 253 mg was isolated upon concentration of the washings for a total crude yield of 903 mg (87% of theory). The tlc data were: (10% methanol in chloroform) crude product,  $R_f$  0.0, 0.07 and 0.77; starting aldehyde  $R_f$  0.77; (chloroform) crude product  $R_f$  0.0, 0.24 (yellow) and 0.44; starting aldehyde,  $R_f$  0.44. Column chromatography on silica gel with chloroform elution gave 864 mg (83% of theory, mp 173-174°) of yellow-orange product. Recrystallization from hexanes (170 mg/400 ml hexanes with 80% recovery) improved the mp to 175-175.5°. Physical data for **4a** are:  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  2.67 (s, 3H), 4.62 and 4.7 (s, and s, 2H), 7.06 (d, 1H,  $J = 4$  Hz), 8.05 (d, 2H,  $J = 4$  Hz); ir (potassium bromide): 2985, 1745, 1695, 1565, 1440, 1385, 1305, 1155, 1035, 820, 690  $\text{cm}^{-1}$ ; ms:  $m/e$  (relative intensity) 208  $M^+$  (63), 209  $M+1$  (8), 210  $M+2$  (4), 150 (100).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_8\text{O}_3\text{S}$ : C, 57.68; H, 3.87; S, 15.4. Found: C, 57.44; H, 3.81; S, 15.41.

#### 3-[(3-Methyl-2-thienyl)methylene]-2,4(3*H*,5*H*)-furandione, **4b**.

To a stirred mixture of **1** (1.00 g, 10 mmoles) and 3-methylthiophene-2-carboxaldehyde (3.791 g, 3.24 ml, 30 mmoles) was added concentrated hydrochloric acid (1.00 ml). The reaction slowly thickened and became dark in color. After 40 minutes, the black mass was triturated with water and hexanes. The tlc data were: (10% methanol in chloroform) crude product  $R_f$  0.0, 0.77 (yellow); starting aldehyde  $R_f$  0.77; (chloroform) crude product  $R_f$  0.0, 0.24 (yellow), 0.48; starting aldehyde 0.48. The crude product was chromatographed on a silica gel column packed and eluted with chloroform. The product was isolated as a bright yellow solid (791 mg, 38% of theory). An analytical sample was recrystallized from hexanes (100 mg, 600 ml, 85% recovery) and melted at 164-165°. Physical data for **4b** are:  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  2.62 (s, 3H), 4.63 and 4.7 (s and s, 2H), 6.83 (poor d, 1H,  $J = 5$  Hz) 7.87-8.13 (m, 1H,  $J = 2, 5$  Hz), 8.2 and 8.28 (d and d,  $J = 2$  Hz); ir (potassium bromide): 3095, 1755, 1695, 1585, 1325, 1185, 745  $\text{cm}^{-1}$ ; ms:  $m/e$  (relative intensity) 208  $M^+$  (100).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_8\text{O}_3\text{S}$ : C, 57.68; H, 3.87; S, 15.4. Found: C, 57.81; H, 3.82; S, 15.19.

#### 3-(2-Furanyl-2-propenylidene)-2,4(3*H*,5*H*)-furandione, **4c**.

A solution of **1** (500 mg, 5 mmoles) and 2-furanacrolein (1.832 g, 15 mmoles) in 5 ml of absolute ethanol was stirred at room temperature for 4 hours. During this time a rust-colored precipitate formed. Isolation of the precipitate by filtration followed by washing with cold ethanol then drying *in vacuo* gave 615 mg (60% of theory). An analytical sample that was recrystallized from hexanes (50 mg/400 ml, sintered at 177° with decomposition). Physical data for **4c** are:  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  4.65 and 4.7 (s and s, 2H), 6.78 (d of d, 1H,  $J = 2, 4$  Hz), 7.18 (d, 1H,  $J = 4$  Hz), 7.64-8.0 (m, 3H), 8.05 (d, 1H,  $J = 2$  Hz); ir (potassium bromide): 2920, 1765, 1690, 1570, 1450, 1155  $\text{cm}^{-1}$ ; mass spectrum,  $m/e$  (relative intensity) 204  $M^+$  (100).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_8\text{O}_4$ : C, 64.70; H, 3.95. Found: C, 64.60; H, 4.04.

#### 3-[(1-Methyl-1*H*-pyrrol-2-yl)methylene]-2,4(3*H*,5*H*)-furandione **4d**.

A solution of **1** (500 mg, 5 mmoles) and *N*-methylpyrrole-2-carboxaldehyde (1.673 g, 15 mmoles) in absolute ethanol (5 ml) was stirred at room temperature for 1.3 hours. As the reaction proceeded, a solid began to precipitate. The product was isolated by filtration, washed with cold ethanol, then dried *in vacuo* to a constant weight of 544 mg (57% of theory). An analytical sample, that was recrystallized from hexanes, darkened and began slowly decomposing at 120°. Physical data for **4d** are:  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  3.57 (s, 3H), 4.53 and 4.63 (s and s, 2H), 6.48 (m, 1H,  $J = 2, 4$ Hz), 7.3 (m, 1H), 7.75 (d, 1H,  $J = 5$  Hz), 8.3 and 8.47 (d of d and d of d,  $J = 2, 4$ Hz); ir (potassium bromide): 2925, 1735, 1625, 1570, 1495, 1380, 1345, 1305, 1195, 1060, 1035, 680  $\text{cm}^{-1}$ ; ms:  $m/e$  (relative intensity) 191  $M^+$  (100).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{NO}_3$ ; N, 7.33. Found: N, 7.12.

## REFERENCES AND NOTES

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