An Anomalous By-Product in the von Pechmann Reaction

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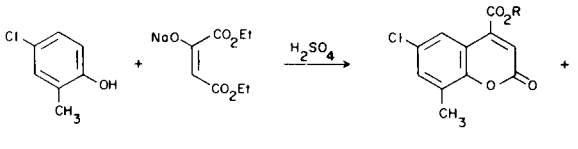
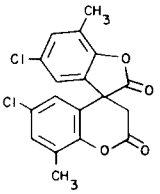
During condensation of 4-chloro-2-methylphenol with diethyloxalacetate in sulfuric acid the spirodilactone **3** was observed as well as the desired coumarin **1**. Further reaction of **1** under the reaction conditions with 4-chloro-2-methylphenol did not produce **3** readily. These observations imply the formation of the intermediate **10** prior to production of the novel spirodilactone **3**.

J. Heterocyclic Chem., **16**, 803 (1979).

The condensation of phenols with β-ketonic esters in the presence of dehydrating agents such as concentrated sulfuric acid, known as the von Pechmann reaction (1), has proved to be of great utility in the preparation of coumarins (2). During the synthesis of the coumarin ester **1** by the reaction of 4-chloro-2-methylphenol with the sodium salt of diethyl oxalacetate, we observed the formation of appreciable amounts of an unexpected by-product, the spirodilactone **3**, in addition to the production of **1** and a trace of acid **2**.



1 R = Et
2 R = H



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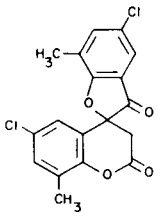

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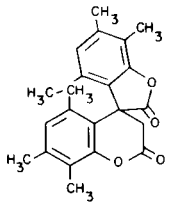

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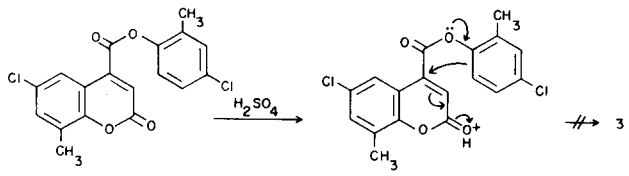
The analytical data for these three products are entirely consistent with the postulated structures. Both the ^{13}C-nmr chemical shift of the quaternary carbon atom and the ir carbonyl stretching frequencies exclude the alternative structure **4**. We have observed the similar formation of a spirodilactone by-product **5** in the reaction of 2,3,5-trimethylphenol with the sodium salt of diethyl oxalacetate. This implies that the spirolactonization reaction has some generality.

Some preliminary experiments were performed to explore the mechanism of formation of **3** and **5**. When the phenolic ester **6** (3) (this plausible transesterification product of **1** is readily prepared) (4) (from the acid **2**) was added to concentrated sulfuric acid and maintained under varying conditions of time (1-18 hours) and temperature (25-35°), only the starting material **6** could be isolated. These experiments exclude a mechanism involving cation **7**. When coumarin ester **1** and additional 4-chloro-2-methylphenol were combined in concentrated sulfuric acid, again under varying conditions of time and temperature, a trace of the spirodilactone formed. However, this reaction appears far less facile than the combination of the oxalacetate salt and the phenol. This result does not support a mechanism in which the 4-chloro-2-methylphenol undergoes a Michael type *C*-alkylation on the 4-position of the carboethoxy coumarin **1** followed by spirolactonization.



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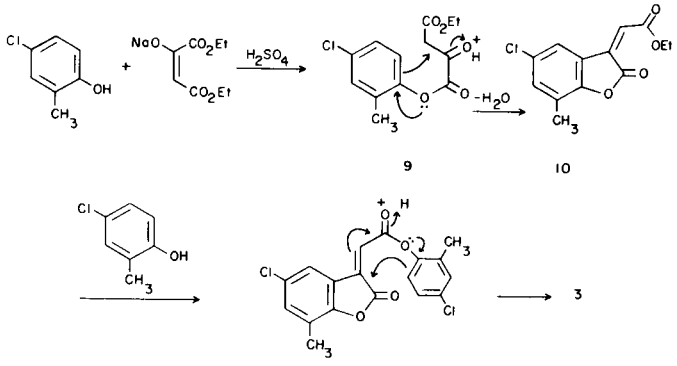
A plausible mechanism involves transesterification of the oxalacetate ester and 4-chloro-2-methylphenol to form the ketoester **9**. The intermediate **9** may undergo an intramolecular condensation/dehydration to form **10**, which could, upon transesterification, protonation and cyclization, proceed to the spirolactone **3**.



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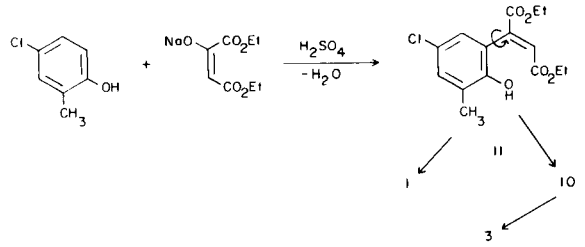
Alternatively, condensation to afford carbon-carbon bond formation may occur prior to transesterification producing the intermediate **11**, which could intramolecularly lactonize to **1** or **10**.



EXPERIMENTAL

A.

During the addition in six portions (causing a moderate exotherm) over 5 minutes of a mixture of 4-chloro-2-methylphenol (Aldrich, technical grade, 28.0 g., 0.196 mole) and the sodium salt of oxalacetic acid diethyl ester (Sigma, practical grade, 42.2 g., 0.199 mole) to a vigorously stirred, precooled (0°), 150 ml. portion of concentrated sulfuric acid, a yellowish orange solution formed. After stirring at room temperature for eighteen hours the reaction mixture was poured over crushed ice, stirred to effect granulation, and filtered. The solid was taken up in ethyl acetate (800 ml.), washed successively with water, saturated sodium bicarbonate (solution A) and saturated brine. After drying over magnesium sulfate, filtering, and removing volatiles, a yellow solid (37.9 g.) remained. Analytical thin layer chromatography (EM Reagents, 0.25 ml., silica gel F-254 plates, developed with benzene) revealed 2 spots (RF, 0.1, 0.2). Trituration of the yellow solid first with ethanol and then with benzene afforded an insoluble fraction (18 g.), which was recrystallized from benzene to afford the pure dilactone **3** (14.9 g., RF, 0.2). The supernatant from the trituration was passed down a column (500 ml.) of silica gel. Elution with benzene afforded several additional grams of crude **3** and the second major product, the ester **1** (RF, 0.1). Recrystallization from ethanol gave analytically pure **1** (15.5 g.). Upon acidification of the initial bicarbonate extract (solution A), 1.0 g. of acid **2** was obtained, after recrystallization from ethanol-water.

B.

In a similar manner, from the sodium salt of diethyl oxalacetic ester (42 g., 0.20 mole) and 2,3,5-trimethylphenol (Aldrich, 27.2 g., 0.02 mole), the novel spirolactone **5** (14.6 g.) was obtained after chromatography. Kugelrohr distillation (T < 200°, 0.3 mm) afforded analytically pure material.

Compound **1**.

This compound had m.p. 104-106°; ms: m/e 266, 268 (indicating 1 Cl); ir (potassium bromide): 5.74, 5.80, 11.44, 12.74, 13.50 μ; nmr (deuteriochloroform): δ 8.03 (d, J = 2 Hz, ArH, 1H), 7.29 (d, J = 2 Hz, ArH, 1H), 6.89 (s, Olef. H, 1H), 4.44 (q, J = 7 Hz, CH_2, 2H), 2.40 (s, $ArCH_3$, 3H), 1.45 (t, J = 7 Hz, CH_3, 3H).

Anal. Calcd. for $C_{13}H_{11}O_4Cl$: C, 58.55; H, 4.16; Cl, 13.29. Found: C, 58.34; H, 4.13; Cl, 13.43.

Compound **2**.

This compound had m.p. 228-230°; ms: m/e 238, 240 (indicating 1 Cl); ir (potassium bromide): 5.74, 5.87, 11.14, 11.32, 13.44 μ; nmr (deuteriochloroform): δ 8.15 (d, J = 2.5 Hz, ArH, 1H), 7.88 (brs, COOH, 1H), 7.25 (d, J = 2.5 Hz, ArH, 1H), 2.40 (s, $ArCH_3$, 3H).

Anal. Calcd. for $C_{11}H_7O_4Cl$: C, 55.37; H, 2.96; Cl, 14.85. Found: C, 55.22; H, 3.04; Cl, 14.85.

Compound **3**.

This compound had m.p. 235-237°; ms: m/e (low resolution) 362, 364, 366 (indicating 2 Cl); ms: m/e (high resolution) 362.0070 (Th $^{35}Cl_2$ = 362.0113), 364.0040 (Th $^{35,37}Cl_2$ = 364.0083), 366.0052 ITh $^{37}Cl_2$ = 366.0054); ir (potassium bromide): 5.5/5.6 (only partially resolved), 11.60, 13.10, 13.44, 13.83, 14.32 μ; ^{1}H-nmr (deuteriochloroform/DMSO-d_6): δ 7.42 (brs, ArH, 3H), 6.54 (d, J = 2 Hz, ArH, 1H), 3.73, 3.21 (AB quartet, J = 17 Hz, CH_2 2H), 2.33 (s, $ArCH_3$, 6H); ^{13}C-nmr (DMSO-d_6) (5): δ (chemical shifts (ppm) relative to TMS (6) 174.675, 164.113, 150.488, 148.559, 131.490, 129.036, 128.769, 128.016, 127.931, 123.311, 122.759, 121.911, 48.960, 34.899, 15.407, 14.704.

Anal. Calcd. for $C_{16}H_{12}O_4Cl_2$: C, 59.53; H, 3.33; Cl, 19.52. Found: C, 59.67; H, 3.35; Cl, 19.44.

Compound **5**.

This compound had m.p. 223-226°; ms: m/e 350; ir (potassium bromide): 5.51, 5.65, 10.48, 11.70, 13.35, 13.75 μ; nmr (deuteriochloroform): δ 6.75 (brs, ArH, 2H), 3.20, 2.87 (AB quartet, J = 16 Hz, CH_2, 2H), 2.30 (s, $ArCH_3$, 12H), 1.95 (s, $ArCH_3$ 3H), 1.88 (s, $ArCH_3$, 3H).

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.76; H, 6.38.

REFERENCES AND NOTES

(1) For a review see, S. Sethna and R. Rhadke, *Org. React.*, **7**, 1 (1953).

(2) For a review see, S. Wawzonek, in "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1951, pp. 173-216.

(3) M.p. (from ethyl acetate/hexane) 198-199°; ir (potassium bromide): 5.70 μ; nmr (deuteriochloroform): δ 8.12 (d, J = 2.5 Hz, ArH, 1H), 7.4-6.9 (m, Olef. H, ArH, 5H), 2.45 (s, $ArCH_3$, 3H), 2.22 (s, $ArCH_3$, 3H); ms: m/e 362, 364, 366 (indicating 2 Cl).

Anal. Calcd. for $C_{16}H_{12}O_4Cl_2$: C, 59.53; H, 3.33. Found: C, 59.57; H, 3.48.

(4) J. H. Brewster and C. J. Ciotti, *J. Am. Chem. Soc.*, **77**, 6214 (1955).

(5) The ^{13}C-nmr spectra were obtained in the FFT mode on a Varian XL-100A-15 (25.2 MHz) spectrometer equipped with a Nicolet technology 1080 data system. Complete proton decoupling was provided by square wave modulation of the Varian gyrocode heteronuclear decoupler (J. B. Grutzner and R. E. Santani, *J. Magn. Reson.*, **19**, 173 (1975). The spectra were obtained with a tip angle of approximately 30° and an aquisition time of 1.4 seconds using quadrature phase detection. The field-frequency lock was maintained by the solvent deuterium resonance in a 5 mm sample tube (O.D.) and the deuterated solvent resonance (DMSO-d_6) used as an internal standard adjusted to 39.6 ppm to provide chemical shift values relative to tetramethylsilane.

(6) G. C. Ivy and G. L. Nelson, "^{13}C-Nuclear Magnetic Resonance for Organic Chemists", Wiley, New York, N. Y., 1972.

(7) The authors would like to acknowledge helpful discussions with Prof. E. J. Corey and Drs. T. H. Cronin, G. Chmurny and E. Whipple.