

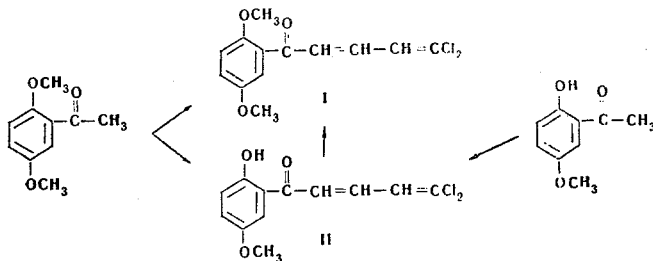
PHENOLIC DERIVATIVES OF 2-PYRONE. III\*. EXAMINATION  
OF THE REACTIONS OF 1, 1-DICHLORO-5-(2', 5'-DIMETHOXYPHENYL)-1,3-  
PENTADIENE-5-ONE AND ITS CONVERSION PRODUCTS

Yu. V. Maevskii, S. V. Sokolovskaya,  
and I. P. Komkov

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The synthesis and reactions of the mono- and dimethyl ethers of 1, 1-dichloro-5-(2', 5'-dihydroxyphenyl)-1, 3-pentadiene-5-one have been examined. The interesting capability of the fully etherified compound to dimerize under the influence of light is noted. The mono-ether with a hydroxyl group in the o-position to the side chain does not show this capability, but cyclizes to give two heterocycles, the pyrone and the chromanone. Demethylation of 6-(2', 5'-dimethoxyphenyl)-2-pyrone followed by oxidation affords the corresponding quinone. Replacement of the heteroatom of the pyrone ring by nitrogen gives 6-(2', 5'-dimethoxyphenyl)-2-pyridone.

In continuation of the search [1, 2] for physiologically active 6-substituted 2-pyrones, the preparation and dimerization of 1, 1-dichloro-5-(2', 5'-dimethoxyphenyl)-1, 3-pentadiene-5-one (I) has been examined. In the condensation of 2, 5-dimethoxyacetophenone with 1, 1, 1, 3-tetrachloro-3-ethoxypropane (TCEP), 1, 1, 1, 3-tetrachloro-3-butoxypropane (TCBP), or  $\beta$ ,  $\beta$ -dichloroacrolein (DCA), in addition to the formation of the main reaction product I, partial demethylation of one of the methoxy-groups occurs.



Fission of the ether group occurs to an even greater extent in the reaction of TCEP with 2, 5-diethoxyacetophenone.

The position of the free hydroxyl group was established by the independent synthesis of 1, 1-dichloro-5-(2'-hydroxy-5'-methoxyphenyl)-1, 3-diene-5-one (II) from 2-hydroxy-5-methoxyacetophenone, and confirmed by the conversion of I into II by treatment with dimethyl sulfate, and also by comparison of the UV and IR spectra of I and II. (Figs. 1 and 2). The absence of the phenolic hydroxyl stretching band at 3610  $\text{cm}^{-1}$ , and the reduction in the intensity of the carbonyl absorption band at 1653  $\text{cm}^{-1}$ , are to be explained by the presence of intramolecular hydrogen bonding between the o-hydroxy-group and the carbonyl oxygen atom.

\* For Part II, see [1].

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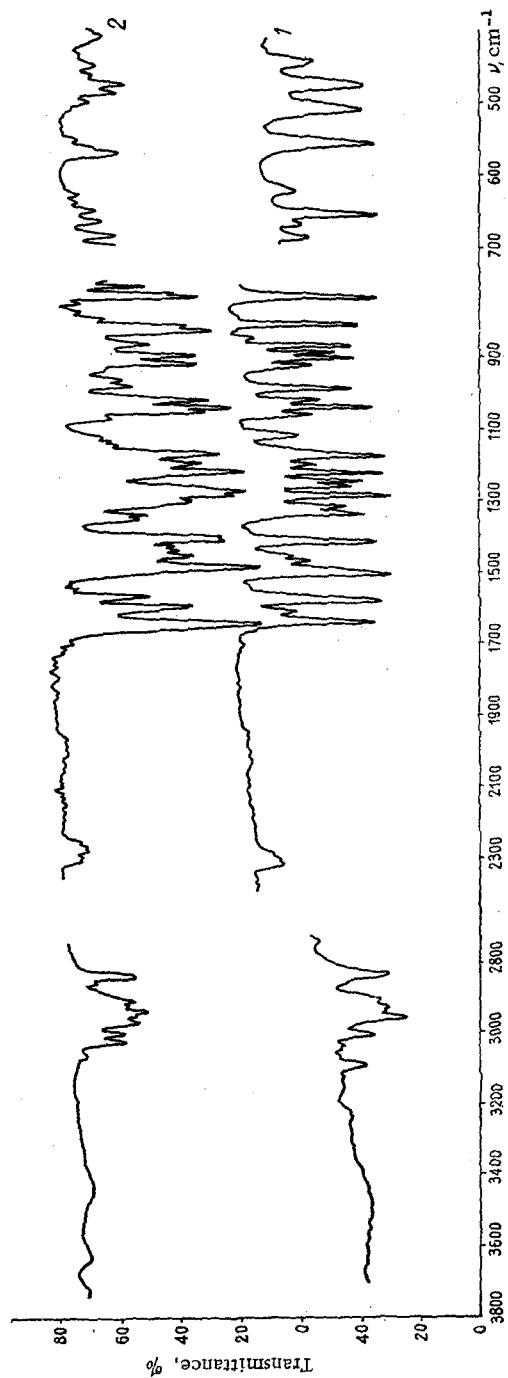


Fig. 1. IR Spectra. 1) 1, 1-Dichloro-5-(2', 5'-dimethoxyphenyl)-1, 3-pentadiene-5-one (I); 2) its dimer (II); KBr disks, UR-10 spectrophotometer.

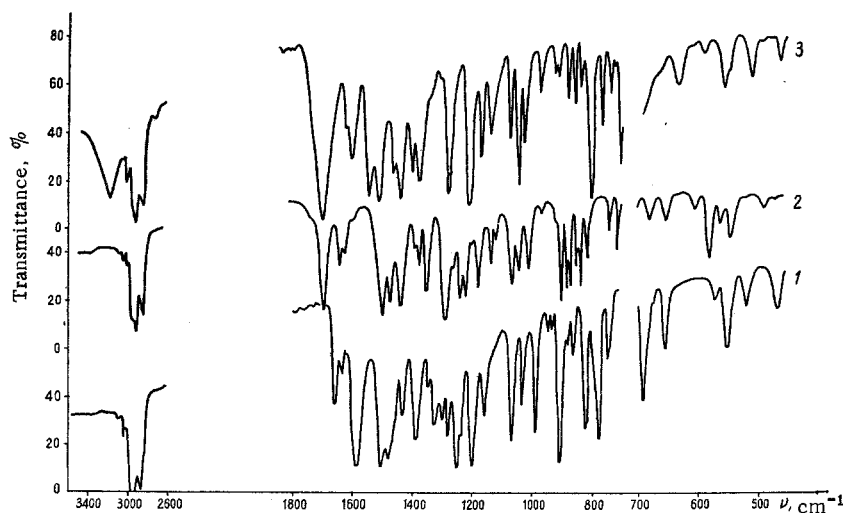
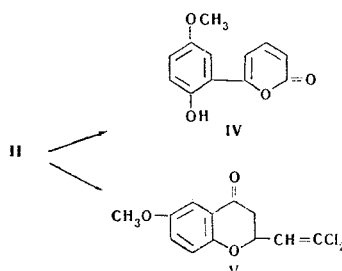


Fig. 2. IR Spectra. 1) 1, 1-Dichloro-5-(2'-hydroxy-5'-methoxyphenyl)-1, 3-pentadiene-5-one (II); 2) 6-methoxy-2-( $\beta$ ,  $\beta$ -dichlorovinyl)-4-chromanone (V); 3) 6-(2'-hydroxy-5'-methoxyphenyl)-2-pyrone (VI); pastes in vaseline oil, UR-10 spectrophotometer.

On heating in acetic acid (either in the presence or absence of  $\text{H}_3\text{PO}_4$ ), I and II cyclize to the corresponding 2-pyrones, III and IV. In addition, II gives about 20% of 6-methoxy-2-( $\beta$ ,  $\beta$ -dichlorovinyl)-4-chromanone (V) under the same conditions, by migration of the hydrogen of the free hydroxyl group, as in the case of 1, 1-dichloro-5-(2'-hydroxyphenyl)-1, 3-pentadiene-5-one [2].



The yield of the chromanone is increased to 30-35% when cyclization of II is carried out in the presence of sodium acetate (IV is hardly formed at all under these conditions). The use of phosphoric acid prevents the formation of the chromanone.

The structures of IV and V were confirmed spectroscopically. The UV spectrum of V [ $\lambda_{\text{max}}$ , nm, ( $\epsilon$ ): 225.5 (24360), 256 (8100), 350 (3870)], as compared with that of II [220 (12700), 310 (27600), 407 (5000)] and IV [221 (21300), 243.3 (6690), 325 (7290), 375 (12600)] shows a shift of the bands towards shorter wave lengths together with some reduction in intensity, indicating a reduction in the length of the system of conjugated bonds in V. The IR spectrum of V does not show the characteristic OH group absorption, whereas the wide band at  $3210\text{ cm}^{-1}$  in the spectrum of the pyrone IV corresponds the stretching of the intramolecularly hydrogen-bonded phenolic hydroxyl group (Fig. 2).

The NMR spectra of V in  $\text{CCl}_4$  and  $\text{C}_6\text{D}_6$  are similar to the spectrum of 2-( $\beta$ ,  $\beta$ -dichlorovinyl)-4-chromanone (X) (Fig. 3). The two protons of the  $\text{CH}_2$  group in the 3-position of the heterocyclic ring interact with the proton at  $\text{C}_2$ , and appear as a quartet with a chemical shift ( $\delta$ ) of 2.70 ppm (for X, the value is 2.77 ppm). The octet with  $\delta$  5.17 ppm (for X, 5.28 ppm) corresponds to the proton at  $\text{C}_2$ , interacting with the proton at  $\text{C}_3$  and the proton of the side chain (this octet is more clearly seen if the spectrum is recorded in deuterated benzene, Fig. 3). Also, a doublet occurs at  $\delta$  6.20 ppm (for X, 6.23 ppm), which is attributed to the proton of the  $-\text{CH}=\text{CCl}_2$  group interacting with the proton at  $\text{C}_2$ . A group of signals, corresponding to the protons of the benzene ring fused at the 9, 10-position with the heterocycle, occurs at lower field. The spectrum of V displays a signal due to the protons of the  $\text{CH}_3\text{O}$  group at  $\delta$  3.79 ppm.

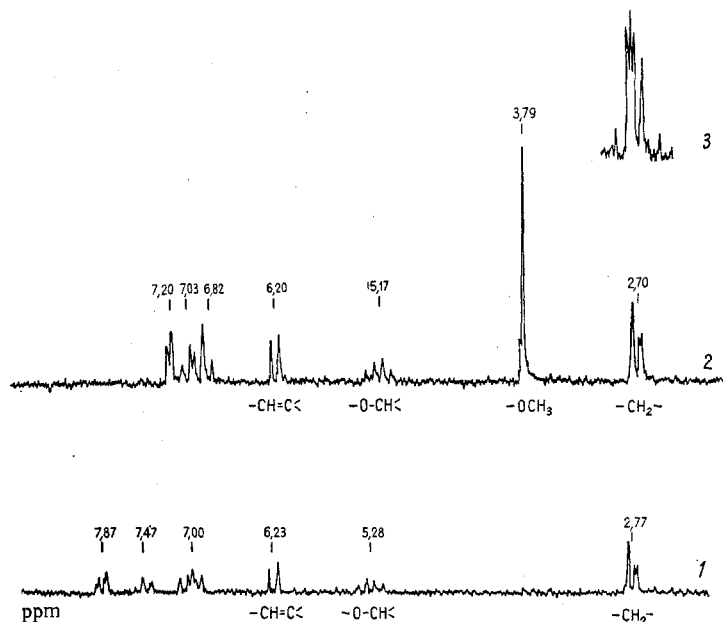
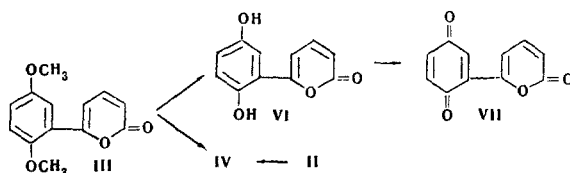


Fig. 3. NMR Spectra. 1) 2-( $\beta, \beta$ -dichlorovinyl)-4-chromanone (XI); 2, 3) 6-methoxy-2-( $\beta, \beta$ -dichlorovinyl)-4-chromanone (V): solutions in  $\text{CCl}_4$  (1 and 2) and in  $\text{C}_6\text{D}_6$  (3). Apparatus JNM-IN-100 (working frequency 100 MHz), internal standard TMS.

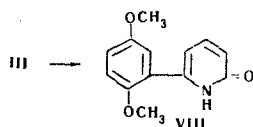
6-(2', 5'-Dimethoxyphenyl)-2-pyrone was readily demethylated by anhydrous aluminum chloride in toluene to give VI. A reduction in the temperature of the reaction (in boiling benzene) gave IV.

The dihydroxyphenylpyrone (VI) was oxidized with freshly prepared silver oxide. The reaction proceeded very smoothly without affecting the pyrone ring to give 6-(*p*-quinonyl)-2-pyrone (VII) in yields of about 90%.

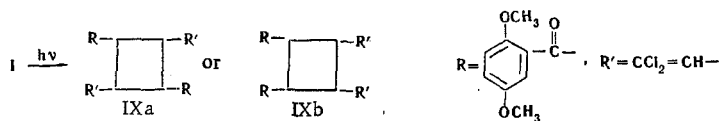


The quinone VII may be readily reconverted into VI by treatment with sodium hydrosulfite.

Prolonged heating of III with ammonium acetate afforded 6-(2', 5'-dimethoxyphenyl)-2-pyridone (VIII), showing the possibility of preparing 2-pyridones from the corresponding substituted 6-phenyl-2-pyrones.



We have observed the interesting ability of I to photodimerize to the cyclobutane structure IX (a or b)



Similar behavior is known in photochemistry [3, 4], but has not previously been observed in dichlorodiene ketones. The presence of powerful terminal electron-acceptor groups (the benzoyl and dichlorovinyl groupings) increases the lability of the C<sub>3</sub>-C<sub>4</sub> double bond, and facilitates its rupture under the influence of light. Only I dimerizes rapidly and smoothly (dimers are also obtained from 1, 1-dichloro-5-(4'-methoxyphenyl)-, 1, 1-dichloro-5-(p-tolyl)- [2], and 1, 1-dichloro-5-(2', 5'-diethoxyphenyl)-1, 3-pentadiene-5-one, but by the more prolonged action of light); diene ketones with hydroxyl groups in the phenyl radical (e. g., I) do not afford dimers under similar conditions. This may be explained by a reduction in the electrophilic properties of the carbonyl group by intramolecular hydrogen bonding with the o-hydroxy group. The change in the length of the conjugated double bond system in I and IX influences their UV and IR spectra. The UV spectrum of I shows absorption maxima at  $\lambda$  223 ( $\epsilon$  4260), 298.5 ( $\epsilon$  26400), and 373 ( $\epsilon$  14640), and IX absorbs at  $\lambda_{\max}$  about 210 ( $\epsilon$  about 46800) and at  $\lambda_{\max}$  337.5 nm ( $\epsilon$  7860). In the IR spectrum of the latter, the loss of the conjugation of the carbonyl group with the double bonds of the aliphatic chain affects mainly the absorption of the C=O group (1666 cm<sup>-1</sup>), the stretching frequency of which in IX is shifted in comparison with that of I by 20 cm<sup>-1</sup> towards higher frequencies, and becomes more intense. (Fig. 2).

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## EXPERIMENTAL

1,1-Dichloro-5-(2',5'-dimethoxyphenyl)-1,3-pentadiene-5-one (I). Five grams (28 mmole) of 2,5-dimethoxyacetophenone, 6.5 g (29 mmole) of TCEP and 25 ml of acetic acid were kept for 65 hr at 20°. The crystals of I were separated, and the mother liquors poured into water. There was obtained in all 7.17 g (90%) (yields throughout are given for unpurified compounds) of a mixture of I and II. The mixture was separated by chromatography of a chloroform solution on alumina, or by washing out the monoether with 1 N sodium hydroxide. The diester I had mp 106-107° (from alcohol), IR spectrum, cm<sup>-1</sup>: 1641 (C=O); 2840 (OCH<sub>3</sub>); UV spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 223 (14640), 298.5 (26400), 372 (4260). Found C 54.69; H 4.00; Cl 24.33%. C<sub>13</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>. Calculated: C 54.37; H 4.21; Cl 24.70%.

2, 4-Dinitrophenylhydrazone of I, mp 192-193° (purified by chromatography followed by crystallization from benzene-heptane). Found: N 11.96%. C<sub>19</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>. Calculated: N 11.99%. Monoether II, mp 108-109° (from alcohol). Found: C 52.84; H 3.47; Cl 26.35%. C<sub>13</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>3</sub>. Calculated: C 52.77; H 3.69. Cl 25.96%. It gave no depression of mp on admixture with a sample of II obtained by an independent synthesis. Reaction of 2, 5-dimethoxyacetophenone with TCBP for 25 hr gave I in 73% yield. The use of DCA in this reaction gave an improved yield of II.

Photodimerization of I. The compound was kept in a sealed flask in the light. The powder was stirred as it was illuminated. The yield of the dimer IX was quantitative, mp 142-142.5° (from methanol). IR Spectrum, cm<sup>-1</sup>: 1666 (C=O), 2842 (OCH<sub>3</sub>); UV spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 252 (13500), 338 (7860). Found: C 54.70; H 4.20; Cl 24.72%; M 570 (cryoscopic). C<sub>26</sub>H<sub>24</sub>Cl<sub>4</sub>O<sub>6</sub>. Calculated: C 54.37; H 4.21; Cl 24.70%; M 574.

1, 1-Dichloro-5-(2', 5'-diethoxyphenyl)-1, 3-pentadiene-5-one (XI). Obtained together with 1, 1-dichloro-5-(2'-hydroxy-5'-ethoxyphenyl)-1, 3-pentadiene-5-one (XII) by the reaction of 2, 5-diethoxyacetophenone with TCEP, as for I. Overall yield 64%. The separation of the diether from the monoether could only be effected by chromatography of a benzene solution on alumina. XI was obtained in 25% yield, mp 71-72° (from heptane). IR spectrum: 1660 cm<sup>-1</sup> (C=O). Found: C 57.35; H 5.29; Cl 22.30%. C<sub>15</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>3</sub>. Calculated: C 57.15; H 5.12; Cl 22.50%.

Compound XII was isolated in 33% yield, mp 129.5-130.5° (from heptane). IR spectrum: 1650 cm<sup>-1</sup> (C=O). Found: C 54.39 H 4.13; Cl 24.63. C<sub>13</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>. Calculated: C 54.37; H 4.21; Cl 24.70%.

1, 1-Dichloro-5-(2'-hydroxy-5'-methoxyphenyl)-1, 3-pentadiene-5-one (II). 3 g (18 mmole) of 2-hydroxy-5-methoxyacetophenone, 2.67 g (21 mmole) of DCA, and 30 ml of acetic acid were saturated with dry hydrogen chloride, the temperature of the mixture falling after 1 hr from 15-18° to 7-8°. The reaction mixture was kept at room temperature for a further 4 hr, to give 3.96 g (80.3%) of II, mp 108-109° (from alcohol). IR spectrum: 1653 cm<sup>-1</sup> (C=O); UV spectrum,  $\lambda_{\max}$ , nm ( $\epsilon$ ): 220 (12700), 310 (27600), 407 (5000). Found: C 52.56; H 3.76; Cl 26.27%. C<sub>12</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>3</sub>. Calculated: C 52.77; H 3.69; Cl 25.96%.

Methylation of II. A mixture of 1 g (3.7 mmole), 8.6 g of potassium carbonate, 3.2 g of dimethyl sulfate, and 25 ml of dry acetone was boiled for 1 hr. There was isolated 1.04 g (99%) of material, mp 106-107°, which gave no depression of mp on admixture with a sample of I.

6-(2', 5'-Dimethoxyphenyl)-2-pyrone (III). 3 g (10.5 mmole) of I, 45 ml of acetic acid, and 2 ml of 83%  $\text{H}_3\text{PO}_4$  were boiled for 35 h. There was obtained 2.32 g (96%) of III, mp 98-99° (from alcohol). IR spectrum: 1725, 1622, 1540  $\text{cm}^{-1}$  ( $\alpha$ -pyrone ring). Found: C 67.03; H 5.09%.  $\text{C}_{13}\text{H}_{12}\text{O}_4$ . Calculated: C 67.23; H 5.21%.

Demethylation of III. To a solution of 3 g (13 mmole) of III in 100 ml of toluene was added, with vigorous stirring, 6 g (45 mmole) of anhydrous aluminum chloride. After 45 min, the mixture was brought to the boil, and boiled for a further 50 min. The yield of VI was 2.45 g (93%), mp 230-231° (from acetic acid). IR spectrum,  $\text{cm}^{-1}$ : 1698, 1615, 1535 ( $\alpha$ -pyrone ring), 3225, 3357 (OH). Found: C 64.70; H 4.14%.  $\text{C}_{11}\text{H}_8\text{O}_4$ . Calculated: C 64.70; H 3.95%.

Acetate of VI, mp 121-122° (from alcohol). Found: C 62.23; H 4.22%.  $\text{C}_{15}\text{H}_{12}\text{O}_6$ . Calculated: C 62.50; H 4.20%. Demethylation in benzene (boiled for 40 min) gave 84% of IV. A sample of IV thus obtained gave no depression of mp with the pyrone obtained by cyclization of II.

6-(p-Quinonyl)-2-pyrone (VII). An aqueous solution of 2.6 g of  $\text{AgNO}_3$  was basified, with vigorous stirring, with dilute sodium hydroxide. The precipitate was washed 12 times with water, 7 times with acetone, and 7 times with dry dioxane. There was then added 20 ml of dry dioxane, 2.5 g of freshly ignited, powdered magnesium sulfate, and dropwise during 35 min, a solution of 0.5 g (2.45 mmole) of VI in 80 ml of dry dioxane. After stirring for an hour, the temperature was raised to 70° during 1 h 30 min, and maintained at this value for a further 30 min. Removal of the dioxane *in vacuo* gave 0.44 g (89%) of bright orange crystals, mp 198.5-199.5° (from dioxane). IR spectrum: 1720, 1630, 1546  $\text{cm}^{-1}$  ( $\alpha$ -pyrone ring). UV spectrum,  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ): 220 (15160), 244 (6250), 325 (7500), 376.5 (8500). Found: C 65.17; H 2.99%.  $\text{C}_{11}\text{H}_6\text{O}_4$ . Calculated: C 65.35; H 2.99%.

Reduction of VII. To a solution of 0.1 g (0.5 mmole) of VII in 25 ml of dry dioxane was added with stirring 0.21 g of sodium hydrosulfite, and, dropwise, 15 ml of water. The mixture was gradually brought to the boil, and the dioxane distilled off. There was obtained 0.09 g (90%) of the pyrone, mp 230-231°, which gave no depression of mp with a sample of VI.

6-(2'-Hydroxy-5'-methoxyphenyl)-2-pyrone (IV). A portion of compound II 1.8 g (6.6 mmole), 54 ml of acetic acid, and 2 ml of water were boiled for 38 h. Water (30 ml) was then added to the hot solution, and most of the II crystallized on cooling. The filtrate was poured into water, and the crystals which separated were washed with water, dried, and extracted with hot light petroleum to extract the chromanone V. The residue was washed with cold benzene and recrystallized from alcohol. The yield of the pyrone IV was 0.46 g (32%), mp 161.5-162.5°. IR spectrum,  $\text{cm}^{-1}$ : 1703, 1622, 1545 ( $\alpha$ -pyrone ring), 3210 (OH). UV spectrum,  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ): 221 (21300), 243.3 (6690), 325 (72900), 375 (12600). Found: C 65.84; H 4.55%.  $\text{C}_{12}\text{H}_{10}\text{O}_4$ . Calculated: C 66.05; H 4.62%. The extracts were evaporated *in vacuo*, and the residue was washed with 1 N alkali and recrystallized from heptane. The yield of the chromanone V was 0.39 g (22%), mp 86-86.5°.

Methylation of IV. A portion of compound IV [1.34 g (6.15 mmole)] was dissolved in 50 ml of 0.5% sodium hydroxide, and 3 ml of dimethyl sulfate was added with stirring. The mixture was heated for 20 min on the water bath to give 1.22 g (86%) of III, mp 98-99°. The material gave no depression of mp on admixture with a sample obtained by the cyclization of I.

6-Methoxy-2-( $\beta$ ,  $\beta$ -dichlorovinyl)-4-chromanone (V). A portion of compound II [0.5 g (1.83 mmole)], 0.3 g of sodium acetate, and 15 ml of glacial acetic acid were boiled for 27 h. The mixture was poured into water, the precipitate (0.44 g) was isolated, and the solid washed repeatedly with 1% NaOH. The residue of V amounted to 0.16 g (32%), and it was crystallized from heptane, mp 86-86.5°. IR spectrum: 1693  $\text{cm}^{-1}$  (C=O); UV spectrum,  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ): 225.5 (24360), 256 (8100), 350 (3870). NMR spectrum,  $\delta$ , ppm: 2.70 ( $-\text{CH}_2-$ ); 3.79 ( $-\text{OCH}_3$ ); 5.17 ( $-\text{O}-\text{CH}$ ); 6.82; 7.03; 7.20 (benzene ring). Found: C 52.61; H 3.80; Cl 25.86%.  $\text{C}_{12}\text{H}_{10}\text{Cl}_2\text{O}_3$ . Calculated: C 52.77; H 3.69; Cl 25.96%.

p-Nitrophenylhydrazone of V, mp 234-234.5° (from alcohol-acetone). Found: N 10.18%.  $\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_4$ . Calculated: N 10.29%.

6-(2', 5'-Dimethoxyphenyl)-2-pyridone (VIII). A portion of compound V [0.8 g (3.45 mmole)], 1.6 g of ammonium acetate, and 2.5 ml of glacial acetic acid were boiled for 43 h. The mixture was poured into water and extracted with chloroform. The extract was evaporated, and the residue was washed with hot heptane to remove V. There was obtained 0.39 g (49%) of VIII, mp 170-170.5° (from benzene). IR spectrum,  $\text{cm}^{-1}$ : 3145, 3063 (NH), 1670 (C=O). Found: C 67.74; H 5.61; N 6.17%.  $\text{C}_{13}\text{H}_{13}\text{NO}_3$ . Calculated: C 67.52; H 5.66; N 6.06%.

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