

## The Structure of the Pechmann Condensation Product of *p*-Orsellinic Acid with Ethyl Acetoacetate

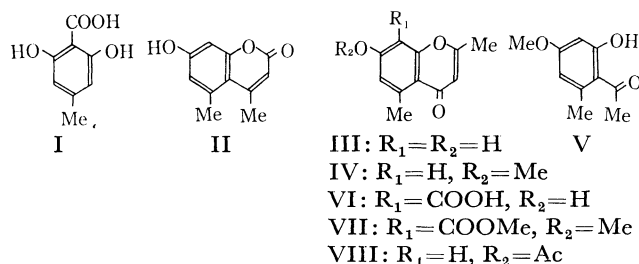
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**Synopsis.** The product obtained by the Pechmann condensation, followed by the decarboxylation, of *p*-orsellinic acid with ethyl acetoacetate has been established not to be such 4,5-dimethyl-7-hydroxycoumarin as previously reported, but to be 2,5-dimethyl-7-hydroxychromone.

In the course of the structural determination of aloenin,<sup>1)</sup> a new bitter glucoside isolated from *Aloe* species, we carried out the Pechmann condensation of *p*-orsellinic acid (I) with ethyl acetoacetate, followed by the decarboxylation, with a view to obtaining 4,5-dimethyl-7-hydroxycoumarin (II) following the method in a literature.<sup>2)</sup> However, all physico-chemical and chemical examinations indicated the product to be 2,5-dimethyl-7-hydroxychromone (III), but not the coumarin. We now wish to describe evidences leading to the chromone structure (III) for the product.

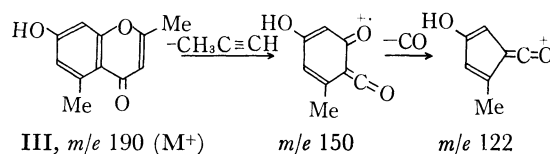


### Results and Discussion

We repeated the treatment of *p*-orsellinic acid (I) with ethyl acetoacetate in the presence of sulfuric acid, followed by the decarboxylation, in accordance with Sethna's report<sup>2)</sup> and obtained an *O*-heterocyclic compound (III),  $\text{C}_{11}\text{H}_{10}\text{O}_3$ , whose properties are identical with those reported by Sethna and Shah. The compound exhibited the IR and UV spectra characteristic of a chromone;<sup>3,4)</sup>  $\nu_{\text{max}}$  (dioxane)  $1663\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ) and  $\lambda_{\text{max}}$  (EtOH)  $291\text{ nm}$  ( $\log \epsilon$  4.08),  $250$  (4.31), and  $241$  (4.22). The alkaline degradation of its monomethyl ether (IV) yielded 2-hydroxy-4-methoxy-6-methylacetophenone (V). As the formation of the acetophenone derivative by such a degradation is also characteristic of a chromone,<sup>5)</sup> the heterocyclic compound (III) appeared to be 2,5-dimethyl-7-hydroxychromone.

The chromone structure was proved by the mass spectrum, which exhibited a base peak of the parent ion at  $m/e$  190 and two significant peaks capable of demonstrating the chromone skeleton at  $m/e$  150 and 122. As shown in Scheme 1, the occurrence of the  $m/e$  150 peak is caused by the retro-Diels-Alder cleavage, which has not been observed for coumarin derivatives

yet,<sup>6,7)</sup> with loss of acetylene and retention of the charge on the fragment. The fragment of mass 122 is formed by the sequential loss of a CO molecule from the  $m/e$  150 ion. These fragments were completely characterized by high-resolution mass spectrum measurements.



Scheme 1.

The NMR spectrum of the monomethyl ether (IV) in a deuterochloroform solution showed signals of two methyl (at 2.25 and 2.77 ppm), one methoxy, two aromatic, and one ethylenic protons. The signal at 2.77 ppm was assigned to the C(5)-methyl group, because it is strongly deshielded by the adjacent carbonyl group.<sup>8)</sup> This assignment was proved by the benzene-induced downfield shifts<sup>9)</sup> ( $\Delta\delta = -0.16\text{ ppm}$ ) observed only for the C(5)-methyl group. No such chemical shift and solvent effect in the NMR spectrum can be explained for 4,5-dimethyl-7-hydroxycoumarin (II) proposed previously by Sethna and Shah.<sup>2)</sup> Thus, all evidences have established the condensation product (III) to be 2,5-dimethyl-7-hydroxychromone. Such a formation of the chromone is a unique example in the Pechmann condensation in the presence of sulfuric acid, although Simonis and Remmert<sup>10)</sup> have described the formation of chromones in the presence of phosphorus pentoxide.

### Experimental

The NMR spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer. Mass spectral analyses were performed on a Hitachi RMU-7L high-resolution mass spectrometer and a Hitachi RMS-4 mass spectrometer, ionizing at the order of 70 eV.

*The Condensation of p-Orsellinic Acid (I) with Ethyl Acetoacetate.*

Following the method in a literature,<sup>2)</sup> *p*-orsellinic acid (I) (800 mg; mp  $166\text{--}167^\circ\text{C}$ ; prepared<sup>11)</sup> from orcinol) was stirred with ethyl acetoacetate (640 mg) at  $65\text{--}70^\circ\text{C}$  for 4 hr in the presence of sulfuric acid (8.4 ml) and the reaction mixture was poured into water to give a solid product, which then was ground up with a 5% sodium bicarbonate solution. The solution, on acidification, gave 2,5-dimethyl-7-hydroxychromone-8-carboxylic acid (VI) (342 mg; mp  $222\text{--}225^\circ\text{C}$  (effervescence); IR (Nujol):  $3500\text{--}2500$  (OH and COOH),  $1650$  ( $\text{C}=\text{O}$ ) and  $1580\text{ cm}^{-1}$  ( $\text{C}=\text{C}$ ); UV (EtOH):  $304\text{ nm}$  ( $\log \epsilon$  3.94),  $282$  (4.03), and  $248$  (4.41); MS:  $m/e$  (rel. intensity)  $234$  ( $\text{M}^+$ , 64),  $216$  (94),  $190$  (18),  $188$  (18),  $160$  (100), and  $120$  (28).

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Found: C, 61.38; H, 4.51%. Calcd for  $C_{12}H_{10}O_5$ : C, 61.54; H, 4.30%.

*The Dimethyl Derivative (VII).* The treatment of the acid (VI) with diazomethane as usual gave the dimethyl derivative (VII): mp 147–148 °C; IR (Nujol): 1730 (COOMe), 1650 (C=O), and 1600  $cm^{-1}$  (C=C); NMR ( $CDCl_3$ ):  $\delta$  2.30 (s, C(2)–Me), 2.83 (s, C(5)–Me), 3.91 (s, COOMe), 3.94 (s, OMe), 6.01 (s, C(3)–H), and 6.69 ppm (s, C(6)–H); ( $C_6H_6$ )  $\delta$  1.52 (s, C(2)–Me), 2.97 (s, C(5)–Me), 3.18 (s, COOMe), 3.67 (s, OMe), 5.80 (s, C(3)–H), and 6.19 ppm (s, C(6)–H); MS:  $m/e$  (rel. intensity) 262 ( $M^+$ , 94), 230 (100), and 191 (51).

*The Decarboxylation of the Acid (VI).* The acid (VI) (100 mg) was maintained at 230 °C for 10 min, melting with the effervescence. The crystalline mass obtained after cooling was crystallized from ethanol to give the heterocyclic compound, 2,5-dimethyl-7-hydroxychromone (III) (48 mg): mp 245 °C (decomp.); IR (Dioxane): 1663 (C=O), 1615 and 1585 (C=C); UV (EtOH), described above; NMR ( $C_5H_5N$ ):  $\delta$  2.06 (s, C(2)–Me) and 2.97 ppm (s, C(5)–Me); MS:  $m/e$  (rel. intensity) 190 ( $M^+$ , 100), 175 (3), 162 (33), 161 (43), 150 (18), and 122 (23); High-resolution MS:  $m/e$  190.0636 (calcd for  $C_{11}H_{10}O_3$ : 190.0630), 162.0654 ( $C_{10}H_{10}O_2$ : 162.0680), 161.0594 ( $C_{10}H_8O_2$ : 161.0601), 150.0299 ( $C_8H_6O_3$ : 150.0316), and 122.0361 ( $C_7H_6O_2$ : 122.0366).

*The Acetyl Derivative (VIII).* Mp 117–118 °C; IR (Nujol): 1765, 1659, 1630, and 1615  $cm^{-1}$ ; ( $CHCl_3$ ) 1769, 1654, and 1611  $cm^{-1}$ ; NMR ( $CDCl_3$ ):  $\delta$  2.30 (s, C(2)–Me and OAc), 2.83 (s, C(5)–Me), 6.07 (s, C(3)–H), 6.83 (d,  $J=2.0$  Hz, C(6)–H), and 7.06 ppm (d,  $J=2.0$  Hz, C(8)–H).

*The Monomethyl Ether (IV).* The treatment of the chromone (III) with diazomethane gave the ether (IV): mp 116–117 °C (recrystallized from ethyl acetate); IR (KBr): 3050, 1655, 1628, 1610, and 1569  $cm^{-1}$ ; ( $CHCl_3$ ) 1657, 1612, and 1570  $cm^{-1}$ ; NMR ( $CDCl_3$ ):  $\delta$  2.25 (s, C(2)–Me), 2.77 (s, C(5)–Me), 3.81 (s, OMe), 5.95 (s, C(3)–H), 6.60 (s, C(6)– and C(8)–H); ( $C_6H_6$ )  $\delta$  1.64 (s, C(2)–Me), 2.93 (s, C(5)–Me), 3.24 (s, OMe), 5.84 (s, C(3)–H), 6.40 (d,  $J=2.5$  Hz, C(8)–H), and 6.51 ppm (d,  $J=2.5$  Hz, C(6)–H); MS:  $m/e$  (rel. intensity) 204 ( $M^+$ , 100), 189 (2), 176 (9), 175 (10), 164 (7), and 161 (31).

#### *The Alkaline Degradation of the Monomethyl Ether (IV).*

The monomethyl ether (IV) (36 mg) was refluxed in a mixture of 50% potassium hydroxide (4 ml) and ethanol (2 ml) for 2 hr in a current of nitrogen. The reaction mixture, after acidification, was extracted with ether and the ether extract was washed with a 5% sodium bicarbonate solution. Removal of the solvent afforded 2-hydroxy-4-methoxy-6-methylacetophenone (V) (25 mg): mp 78.0–78.5 °C (lit.<sup>12</sup> mp 79 °C); IR ( $CHCl_3$ ): 1610 and 1585  $cm^{-1}$ ; UV (EtOH): 279 nm ( $\log \epsilon$  4.13) and 231 (4.05); NMR ( $CDCl_3$ ):  $\delta$  2.53 (s, C(6)–Me), 2.58 (s,  $COCH_3$ ), 3.77 (s, OMe), 6.25 (s, aromatic 2H), and 13.48 ppm (s, phenolic OH); MS:  $m/e$  (rel. intensity) 180 ( $M^+$ , 28) and 165 (100); High-resolution MS:  $m/e$  180.0779 (calcd for  $C_{10}H_{12}O_3$ : 180.0785) and 165.0532 ( $C_9H_9O_3$ : 165.0550).

Found: C, 66.53; H, 6.58%. Calcd for  $C_{10}H_{12}O_3$ : C, 66.65; H, 6.71%.

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