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

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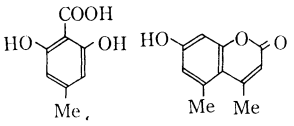
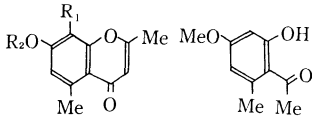
Synopsis. The product obtained by the Pechmann condensation, followed by the decarboxylation, of *p*-orsellinic acid with ethyl acetoacetate has been established not to be such 4,5-dimethyl-7-hydroxycoumarin as previously reported, but to be 2,5-dimethyl-7-hydroxychromone.

In the course of the structural determination of aloenin,[1] 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.[2] 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.



I

II



III: $R_1=R_2=H$ V

IV: $R_1=H$, $R_2=Me$

VI: $R_1=COOH$, $R_2=H$

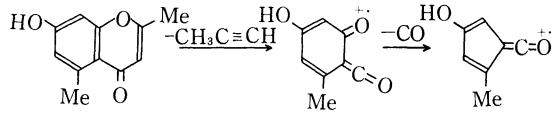
VII: $R_1=COOMe$, $R_2=Me$

VIII: $R_1=H$, $R_2=Ac$

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[2] and obtained an *O*-heterocyclic compound (III), $C_{11}H_{10}O_3$, whose properties are identical with those reported by Sethna and Shah. The compound exhibited the IR and UV spectra characteristic of a chromone;[3,4] ν_{max} (dioxane) 1663 cm^{-1} (C=O) and λ_{max} (EtOH) 291 nm (log ε 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,[5] 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,[6,7] 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.



III, *m/e* 190 (M^+) *m/e* 150 *m/e* 122

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.[8] This assignment was proved by the benzene-induced downfield shifts[9] ($\Delta\delta=-0.16$ 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.[2] 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[10] 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,[2] *p*-orsellinic acid (I) (800 mg; mp 166—167 °C; prepared[11] from orcinol) was stirred with ethyl acetoacetate (640 mg) at 65—70 °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—225 °C (effervescence); IR (Nujol): 3500—2500 (OH and COOH), 1650 (C=O) and 1580 cm^{-1} (C=C); UV (EtOH): 304 nm (log ε 3.94), 282 (4.03), and 248 (4.41); MS: *m/e* (rel. intensity) 234 (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 ($CDCl_3$): δ 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) δ 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): δ 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 ($C_{10}H_9O_2$: 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 ($CDCl_3$): δ 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 ($CDCl_3$): δ 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) δ 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,[12] mp 79 °C); IR ($CHCl_3$): 1610 and 1585 cm^{-1}; UV (EtOH): 279 nm (log ε 4.13) and 231 (4.05); NMR ($CDCl_3$): δ 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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