Synthetic Studies of Sesamol Derivatives. IV.[*1] *Preparation and Reaction of 2-Hydroxy-4,5-methylenedioxyacetophenones*[*2]

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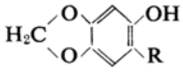
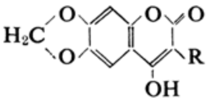
In continuation of a series of studies of sesamol derivatives, the present paper will report on the preparation of 2-hydroxy-4,5-methylenedioxyacetophenones (I) and the reaction of I to give 4-hydroxycoumarins (II).

2-Hydroxy-4,5-methylenedioxyacetophenone (Ia)[1] has been obtained by the Fries rearrangement of sesamol acetate in a poor yield (5%). A better result (35%) was obtained by means of the Hoesch reaction of sesamol (III) with acetonitrile. On the other hand, the acetylation of III with acetic acid and boron trifluoride to obtain the ketone Ia was extremely difficult, and it was unsuccessful with polyphosphoric acid. The failure may be due to an attack on the methylenedioxy system by the reagents which is not encountered in the Hoesch reaction. The Friedel-Crafts reaction of the methyl ether[2] of III also gave Ia (36%). By a similar Hoesch reaction employing methoxyacetonitrile and phenylacetonitrile, III was converted into 2-hydroxy-4,5-methylenedioxy-ω-methoxyacetophenone (Ib)[3] and 2-hydroxy-4,5-methylenedioxyphenyl benzyl ketone (Ic) respectively. 4-Hydroxyayapin (IIa) was obtained from Ia with ethyl carbonate,[4] but not with ethyl chloroformate.[5] The condensation of Ia with ethyl cyanoacetate[6] also gave IIa. On the other hand, either with ethyl carbonate or with ethyl chloroformate, Ib and Ic were converted into 3-methoxy- (IIb) and 3-phenyl-4-hydroxy-6,7-methylenedioxycoumarin (IIc) respectively. 7-Benzyloxy-3-(3′,4′-methylenedioxyphenyl)-4-hydroxycoumarin (IV) was obtained from 4-benzyloxy-2-hydroxyphenyl 3,4-methylenedioxybenzyl ketone[7] with the former reagent.

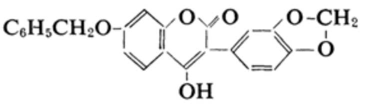
These 4-hydroxycoumarins (II) exhibited fluorescence in alcohol, as did 3-substituted ayapin,[8] and the fluorescence of the acetate and the methyl ether of IIc was especially strong.



Ia $R=COCH_3$
Ib $R=COCH_2OCH_3$
Ic $R=COCH_2C_6H_5$
III $R=H$



IIa $R=H$
IIb $R=OCH_3$
IIc $R=C_6H_5$



IV

Experimental[*3]

2-Hydroxy-4,5-methylenedioxyacetophenone (Ia). —*The Hoesch Reaction.*—A mixture of III (5.0 g.),[9] acetonitrile (2.0 g.) and anhydrous zinc chloride (2.0 g.) in dry ether (30 ml.) was saturated with dried hydrogen chloride for 3 hr. at 0°C and then allowed to stand overnight. The ethereal solution was decanted from the greenish mass of ketimine hydrochloride which had separated. The residue was washed twice with dry ether (20 ml.) and then heated on a steam bath with water (30 ml.) for 0.5 hr. After cooling and standing, the resulting precipitates were collected and recrystallized from ethanol to give Ia in the form of pale yellow needles; m. p., 113∼114°C (reported m. p. 114°C[1]); yield, 2.3 g. (35%). This was identical with an authentic sample[1] and gave a blue color with alcoholic ferric chloride solution. IR: 1634 (C=O); 1023, 918 ($O-CH_2-O$) cm^{-1}.

Found: C, 59.77; H, 4.53. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.33%.

The Boron Trifluoride Method.—With good cooling, a solution of III (5.0 g.) in acetic acid (40 ml.) was saturated with dried boron trifluoride for 3 hr., during which time care was taken to prevent the formation of solids. The resulting solution was heated at 80∼90°C for 1.5 hr. and poured into a

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[*1] Part III: K. Fukui and M. Nakayama, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 606 (1963).

[*2] Presented in part at the Tokushima Meeting of the Chemical Society of Japan, Tokushima, August, 1962.

1) A. Romeo and G. Gargellini, *Ann. chim.* (*Rome*), **42**, 361 (1952); *Chem. Abstr.*, **47**, 10529 (1953).

2) K. Fukui and M. Nakayama, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 606 (1963).

3) K. Fukui and T. Matsumoto, This Bulletin, **35**, 1931 (1962).

4) J. Boyd and A. Robertson, *J. Chem. Soc.*, **1948**, 174.

5) A. H. Gilbert, A. McGookin and A. Robertson, ibid., **1957**, 3740.

6) A. Sonn, *Ber.*, **50**, 1292 (1917).

7) H. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.*, **1934**, 1769.

8) K. Fukui and M. Nakayama, This Bulletin, **35**, 1321 (1962).

[*3] All melting points are uncorrected; the infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in an ethanol solution.

9) K. Fukui and M. Nakayama, *J. Sci. Hiroshima Univ.*, Series A-II, **26**, 131 (1963).

saturated sodium acetate solution (100 ml.). After the solution had been extracted with ether, the ethereal solution was washed with a saturated sodium bicarbonate solution and water. The product was recrystallized from ethanol to give Ia; m. p. 112~113°C; yield, 0.3 g. (5%). It was identical with the above sample.

The Friedel-Crafts Reaction.—To a solution of anhydrous aluminum chloride (5.0 g.) in dry ether (50 ml.), sesamol methyl ether (b.p. 110~114°C/18 mmHg)[2] (3.0 g.) was added. Acetyl chloride (2.0 g.) was well stirred drop by drop into the solution for 0.5 hr., the stirring was continued another 5 hr. at room temperature, and the mixture was allowed to stand overnight. The ethereal solution was decanted from the dark-colored mass. Ice water containing dilute hydrochloric acid was cautiously added to the residue in order to dissolve the aluminum compounds. The crystalline product was collected and recrystallized from ethanol to give Ia (m.p. 112~113°C; 0.9 g.). The aqueous layer was extracted with ethyl acetate. After the extracted solution had been washed with water and saturated sodium bicarbonate solution, the solution was extracted with a 2 N sodium hydroxide solution. The aqueous layer was acidified with 2 N hydrochloric acid. The product was collected and recrystallized from ethanol to give Ia (m. p. 112~113°C; 0.4 g.). Total yield; 1.3 g. (36%). It was identical with the above sample.

The acetate was prepared by the pyridine-acetic anhydride method; m.p. 88~89°C (colorless prisms from ethanol), IR: 1731 (acetate); 1662 (C=O); 1027, 918 (O-CH$_2$-O) cm^{-1}.

Found: C, 59.35; H, 4.53. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54%.

2-Hydroxy-4, 5-methylenedioxyphenyl Benzyl Ketone (Ic).—By a similar Hoesch reaction, Ic was obtained from III (5.0 g.), phenylacetonitrile (5.0 g.) and anhydrous zinc chloride (3.0 g.) in dry ether (120 ml.); m. p. 130~131°C (pale yellow prisms from ethanol); yield, 2.6 g. (28%). It gave a green color with an alcoholic ferric chloride solution. IR: 1649 (C=O); 1031, 923 (O-CH$_2$-O) cm^{-1}.

Found: C, 70.30; H, 4.87. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72%.

The acetate; m.p. 124~125°C (colorless needles from methanol). IR: 1768 (acetate); 1692 (C=O); 1031, 923 (O-CH$_2$-O) cm^{-1}.

Found: C, 68.58; H, 4.97. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

4-Hydroxyayapin (IIa).—*The Ethyl Carbonate Method.*—A mixture of Ia (1.0 g.), ethyl carbonate (35 ml.) and pulverized sodium (1.5 g.) was warmed on a steam bath for 20 min. After the vigorous reaction had ceased, sufficient methanol was added to the cooled mixture to destroy the excess of sodium, and then the residue was added to ether (100 ml.). The extraction of the sodium salt of the product with water (100 ml.) and acidification of it with 2 N hydrochloric acid gave IIa, which formed colorless tiny needles from methanol; m.p. 274~275°C (decomp.); yield, 0.9 g. (79%). This dissolved in a sodium bicarbonate solution with effervescence. It did not give any color with an alcoholic ferric chloride solution. IR: 1706 (C=O); 1043, 934 (O-CH$_2$-O) cm^{-1}. UV: λ_{max}^{EtOH} mμ (log ε); 230.5(4.40), 254_i(3.80), 275(3.81), 285(3.88), 328(4.15).

Found: C, 58.15; H, 3.18. Calcd. for $C_{10}H_6O_5$: C, 58.26; H, 2.93%.

The Ethyl Cyanoacetate Method.—A mixture of III (10.0 g.), ethyl cyanoacetate (4.0 g.) and anhydrous zinc chloride (10.0 g.) in dry ether (120 ml.) was saturated with dried hydrogen chloride for 3 hr. at 0°C and then allowed to stand overnight. The ethereal solution was decanted from the dark-colored oil which had separated. The residue was washed twice with dry ether (20 ml.) and then treated with water (150 ml.). Upon being stirred, the ketimine hydrochloride separated as a dark violet mass (m. p.>300°C). It was hydrolyzed with 50% sulfuric acid (80 ml.) by heating it on a steam bath for 2 hr. The reaction mixture was added to a large quantity of water. The resulting precipitates were collected and recrystallized from methanol to give IIa; m.p. 270~272°C (decomp.); yield, 1.6 g. (11%). This was identical with the above sample.

The methyl ether was prepared by the methyl iodide-potassium carbonate method; m.p. 183~184°C (colorless needles from methanol). IR: 1728 (C=O); 1031, 921 (O-CH$_2$-O) cm^{-1}.

Found: C, 60.26; H, 3.83. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66%.

3-Methoxy-4-hydroxy-6, 7-methylenedioxycoumarin (IIb).—*The Ethyl Carbonate Method.*—By a similar reaction, IIb was obtained from Ib (m.p. 136~138°C[3]) (0.5 g.), ethyl carbonate (20 ml.) and sodium (0.5 g.); m.p. 261~262°C (decomp.) (colorless needless from methanol); yield, 0.5 g. (89%). It dissolved in a sodium bicarbonate solution with effervescence. It did not give any color with an alcoholic ferric chloride solution. IR: 1699 (C=O); 1031, 937 (O-CH$_2$-O) cm^{-1}. UV: λ_{max}^{EtOH} mμ (log ε); 231(4.52), 256_i(3.90), 280(4.03), 289(4.11), 330(4.52).

Found: C, 55.72; H, 3.52. Calcd. for $C_{11}H_8O_6$: C, 55.94; H, 3.41%.

The Ethyl Chloroformate Method.—A mixture of Ib (1.0 g.), ethyl chloroformate (2 ml.), anhydrous potassium carbonate (5.0 g.) and acetone (50 ml.) was heated under reflux for 5 hr., poured into water, and acidified with concentrated hydrochloric acid. The resulting precipitates were collected and recrystallized from methanol to give IIb, m.p. 261~262°C (decomp.); yield 0.7 g. (62%). This was identical with the above sample.

The methyl ether; m.p. 161~162°C (colorless needles from methanol). IR: 1706 (C=O); 1031, 933 (O-CH$_2$-O) cm^{-1}.

Found: C, 57.66; H, 4.16. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03%.

The acetate: m.p. 136~137°C (colorless needles from methanol). It gave a blue fluorescence in alcohol. IR: 1783 (acetate); 1721 (C=O); 1037, 931 (O-CH$_2$-O) cm^{-1}.

Found: C, 56.16; H, 3.75. Calcd. for $C_{13}H_{10}O_7$: C, 56.12; H, 3.62%.

3-Phenyl-4-hydroxy-6, 7-methylenedioxycoumarin (IIc).—By similar reactions, IIc was obtained from Ic; m. p. 267~268°C (decomp.) (colorless needles from methanol) ; yield, 91% (the ethyl carbonate method) and 69% (the ethyl chloroformate method). It dissolved in a sodium bicarbonate solution with effervescence. It did not give any color with an alcoholic ferric chloride solution. IR ; 1660 (C=O) ; 1040, 941 (O-CH$_2$-O) cm^{-1}. UV : λ_{max}^{EtOH} mμ(log ε) ; 225(4.41), 288(3.87), 336(4.30).

Found : C, 67.98 ; H, 3.78. Calcd. for $C_{16}H_{10}O_5$: C, 68.08 ; H, 3.57%.

The methyl ether ; m.p. 189~190°C (colorless needles from methanol). It gave a blue fluorescence in alcohol. IR : 1703 (C=O) ; 1029, 926 (O-CH$_2$-O) cm^{-1}.

Found : C, 68.96 ; H, 4.19. Calcd. for $C_{17}H_{12}O_5$: C, 68.91 ; H, 4.08%.

The acetate ; m.p. 214°C (colorless plates from methanol). It gave a blue fluorescence in alcohol. IR : 1771 (acetate) ; 1708 (C=O) ; 1041, 941 (O-CH$_2$-O) cm^{-1}.

Found : C, 66.53 ; H, 3.83. Calcd. for $C_{18}H_{12}O_6$: C, 66.67 ; H, 3.73%.

7-Benzyloxy-3-(3′, 4′-methylenedioxyphenyl)-4-hydroxycoumarin (IV). — By the ethyl carbonate method, 2-hydroxy-4-benzyloxyphenyl 3, 4-methylenedioxybenzyl ketone (m.p. 94°C[8]) gave IV ; m.p. 204~205°C (colorless needles from ethanol) ; yield, 85%. IR : 1656 (C=O) ; 1038, 930 (O-CH$_2$-O) cm^{-1}.

Found : C, 71.12 ; H, 4.30. Calcd. for $C_{23}H_{18}O_6$: C, 71.63 ; H, 4.51%.

The methyl ether ; m.p. 134~135°C (colorless needles from ethanol). IR : 1708 (C=O) ; 1038, 921 (O-CH$_2$-O) cm^{-1}.

Found : C, 71.66 ; H, 4.58. Calcd. for $C_{24}H_{18}O_6$; C, 71.63 ; H, 4.51%.

The acetate ; m.p. 184~185°C (colorless needles from ethanol). IR : 1778 (acetate) ; 1721 (C=O) : 1038, 921 (O-CH$_2$-O) cm^{-1}.

Found : C, 69.77 ; H, 4.31. Calcd. for $C_{25}H_{18}O_7$: C, 69.76 ; H, 4.22%.

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