Synthetic Studies on the Benzofuran Derivatives. VII.
A New Synthesis of Angelicin and 4-Methylangelicin

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Angelicin, a furocoumarin isolated from *Angelica archangelica*[1-4] and *Psoralea corylifolia*[5], is an interesting compound because of its fluorescence and biological activity. Its chemical structure was established by Späth and Pesta[4] to be represented by the formula Ia. For the synthesis of Ia, several methods were reported by Späth and Pailer[6], Limaye[7], Naik and Thakor[8] and Seshadri et al.[9], and recently the synthesis of 4-methylangelicin (Ib) also has been reported by Antonello[10].

The present paper describes a new synthesis of Ia and Ib accomplished with more ease and furnishing higher yields following Tanaka's method[11] for benzofuran synthesis, as shown in the chart.

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1) L. A. Buchner, *Ann.*, **42**, 226 (1842).

2) C. Brimer, ibid., **180**, 269 (1876).

3) E. Bocker and A. Hahn, *J. prakt. Chem.*, (2) **83**, 243 (1911).

4) E. Späth and O. Pesta, *Ber.*, **67**, 853 (1934).

5) H. S. Jois and B. L. Manjunath, *Proc. Indian Sci. Congress*, **21**, 243 (1934) ; ibid., **22**, 147 (1935) ; *Ber.*, **69B**, 964 (1936).

6) E. Späth and M. Pailer, ibid., **67**, 1212 (1934) ; ibid., **68**, 940 (1935).

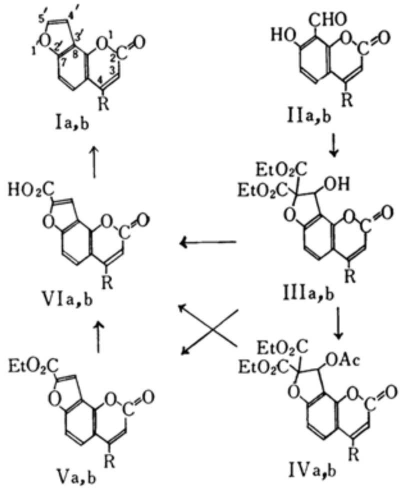
7) D. B. Limaye, *Rasayanam*, **1**, 1 (1936) ; *Chem. Abstr.*, **31**, 2206 (1937).

8) R. M. Naik and V. M. Thakor, *J. Org. Chem.*, **22**, 1696 (1957).

9) T. R. Seshadri et al., *Tetrahedron*, **4**, 256 (1958).

10) C. Antonello, *Gazz. chim. ital.*, **88**, 430 (1958) ; *Chem. Abstr.*, **53**, 20046 (1959).

11) S. Tanaka, *J. Am. Chem. Soc.*, **73**, 872 (1951).



For I—VI; a) R=H, b) R=Me

The starting material is 8-formyl-7-hydroxycoumarin⁶⁾ (IIa) and 8-formyl-7-hydroxy-4-methylcoumarin⁷⁾ (IIb) as in the syntheses of Späth and Pailer, Naik and Thakor and Antonello. As the aldehydes were obtained only in poor yields by the formylation of coumarins following the hexamine method⁶,¹²⁾ attempts were made to improve the formylation by the glyceroboric acid-hexamine method¹³⁾ and by the dimethylformamide method¹⁴⁾, but they resulted only in failure.

The aldehyde, IIa or IIb, was made to react with ethyl bromomalonate and potassium carbonate in ethyl methyl ketone. Procedures of very little difference, namely, refluxing either with or without stirring, gave two different products: a higher melting ester (Va, m. p. 212∼213°C or Vb, m. p. 194∼195°C) with stirring and a lower melting ester (IIIa, m. p. 178∼180°C or IIIb, m. p. 175∼176°C) without stirring. Analysis and infrared spectroscopy proved that the latter is a hydroxy-diester IIIa or IIIb because it showed a sharp OH band (IIIa, 3226 cm^{-1}; IIIb, 3185 cm^{-1}) and ester CO bands (IIIa, 1767, 1727 cm^{-1}; IIIb, 1773, 1730 cm^{-1}), and that the former is an ester Va or Vb without a hydroxy-group because it showed the ester CO band (Va, 1718 cm^{-1}; Vb, 1724 cm^{-1}) and no OH band. As hydroxy-ester IIIa (or IIIb) was converted into ester Va (or Vb) by further action of potassium carbonate in ethyl methyl ketone under reflux with stirring, IIIa (or IIIb) seems to be the intermediate compound to Va (or Vb); the compound of this type has been reported in some cases¹⁵⁾. Ester IIIa (or IIIb) was converted into Va (or Vb) also by the action of phosphoric acid, but was not affected by 10% hydrochloric acid and by *p*-toluenesulfonyl chloride, and was converted only into its acetate IVa or IVb by acetic anhydride with or without sodium acetate.

Alkaline hydrolysis of the esters IIIa, IVa, and Va or IIIb, IVb, and Vb furnished the same corresponding acid VIa or VIb, which was decarboxylated in quinoline into compound Ia, m. p. 137∼138°C, or Ib, m. p. 190∼192°C, in a good yield.

Experimental¹⁶⁾

5′, 5′-Diethoxycarbonyl-4′-hydroxy-4′, 5′-dihydroangelicin (IIIa).—To a solution of 8-formyl-7-hydroxycoumarin⁶⁾ (IIa, m. p. 184∼185°C, 0.5 g.) and ethyl bromomalonate (1 g.) in anhydrous ethyl methyl ketone (60 ml.) was added anhydrous potassium carbonate (1.5 g.); the mixture was refluxed for 8 hr. in a steam bath. The resulting mixture was freed from precipitates, and the solvent was distilled off. The residual product was recrystallized from ethanol to give IIIa in the form of colorless microcrystals, m. p. 178∼180°C, giving a negative ferric reaction; yield 0.5 g. (54.9%).

Found: C, 58.83; H, 4.67. Calcd. for $C_{17}H_{16}O_8$: C, 58.62; H, 4.63%.

Acetate IVa was prepared quantitatively by refluxing IIIa (0.1 g.) and acetic anhydride (10 ml.) with or without anhydrous sodium acetate (0.1 g.), m. p. 140∼141°C (from ethanol).

Found: C, 58.62; H, 4.65. Calcd. for $C_{19}H_{18}O_9$: C, 58.46; H, 4.69%.

5′, 5′-Diethoxycarbonyl-4′-hydroxy-4′, 5′-dihydro-4-methylangelicin (IIIb).—By a method similar to that described for IIIa, IIIb was obtained from 8-formyl-7-hydroxy-4-methylcoumarin⁷⁾ (IIb, m. p. 176∼177°C, 2 g.), ethyl bromomalonate (2.3 g.), anhydrous potassium carbonate (4.8 g.) and anhydrous ethyl methyl ketone (150 ml.); colorless microcrystals, m. p. 175∼176°C (from ethanol), giving a negative ferric reaction; yield 2 g. (56.5%).

Found: C, 59.84; H, 5.14. Calcd. for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01%.

Acetate IVb: M. p. 189∼190°C (from ethanol).

Found: C, 59.57; H, 4.97. Calcd. for $C_{20}H_{20}O_9$: C, 59.40; H, 4.99%.

5′-Ethoxycarbonyl-angelicin (Va).—*From Aldehyde IIa.*—A mixture of IIa (0.3 g.), ethyl bromomalonate (0.6 g.), potassium carbonate (0.8 g.) and ethyl methyl ketone (60 ml.) was refluxed with stirring for 8 hr. in a steam bath. The resulting mixture was treated similarly to IIIa; colorless needles, m. p. 212∼213°C (from ethanol); yield 0.2 g. (50%).

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12) T. R. Seshadri et al., *Proc. Indian Acad. Sci.*, **6A**, 112 (1937); *Chem. Abstr.*, 32, 559 (1938); A. N. Nesmeyanov et al., *J. Gen. Chem.* (*U. S. S. R.*), **7**, 2767 (1937); *Chem. Abstr.*, 32, 2915 (1938).

13) J. C. Duff, *J. Chem. Soc.*, **1941**, 547.

14) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, **75**, 989 (1953).

15) T. Matsumoto and K. Fukui, This Bulletin., **30**, 3 (1957).

16) Melting points are uncorrected, and IR spectra were taken by the Nujol method.

Found: C, 65.06; H, 4.07. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90%.

From Hydroxy-ester IIIa.—1) By the Action of Potassium Carbonate.—A solution of IIIa (0.1 g.) in ethyl methyl ketone (20 ml.) was refluxed for 8 hr. while anhydrous potassium carbonate (0.5 g.) was stirred in and then treated as before to give Va, m. p. 210∼211°C. *2) By the Action of Phosphoric Acid.*—A mixture of IIIa (0.1 g.) and phosphoric acid (40 ml.) was heated for 30 min. in a steam bath. The cooled mixture was poured into water, and the solid product was recrystallized from ethanol to give Va, m. p. 210∼212°C.

5′-Ethoxycarbonyl-4-methylangelicin (Vb).—*From Aldehyde IIb.*—By a method similar to that described for Va, Vb was obtained from IIb (1 g.), ethyl bromomalonate (1.2 g.), potassium carbonate (2.4 g.) and ethyl methyl ketone (70 ml.); colorless needles, m. p. 194∼195°C (from ethanol); yield 0.65 g. (48.9%). Reported m. p. is 192°C[10].

Found: C, 65.86; H, 4.48. Calcd. for $C_{15}H_{12}O_5$: C, 66.15; H, 4.45%.

From Hydroxy-ester IIIb.—1) By the Action of Potassium Carbonate.—Vb was obtained similarly to Va; m. p. 193∼194°C. *2) By the Action of Phosphoric Acid.*— Vb was obtained similarly to Va; m. p. 193∼194°C.

5′-Carboxy-angelicin (VIa).—*a) From Ester Va.*—A mixture of Va (0.4 g.) and a 5% potassium hydroxide solution in 50% aqueous methanol (20 ml.) was refluxed for 30 min. in a steam bath. The resulting mixture was filtered and acidified with dilute hydrochloric acid, and the precipitates were collected and recrystallized from ethanol to give VIa in the form of colorless needles, m. p. 320∼325°C (decomp.); yield 0.35 g. (98.3%). Reported m. p. is 315°C[8].

Found: C, 62.30; H, 2.73. Calcd. for $C_{12}H_6O_5$: C, 62.66; H, 2.63%.

b) From Hydroxy-ester IIIa.—By a treatment similar to a), VIa was obtained from IIIa (0.1 g.); m. p. 315∼320°C (decomp.).

c) From Acetoxy-ester IVa.—By a similar treatment, VIa was obtained from IVa (0.1 g.); m. p. 320°C (decomp.).

5′-Carboxy-4-methylangelicin (VIb).—*From Ester Vb.*—By a method similar to that described for VIa, VIb was obtained from Vb (0.6 g.) and a 5% potassium hydroxide solution in 50% aqueous methanol (25 ml.); colorless needles, m. p. 295∼299°C (decomp.) (from ethanol); yield 0.5 g. (92.6%).

Found: C, 63.85; H, 3.45. Calcd. for $C_{13}H_8O_5$: C, 63.94; H, 3.30%.

From Hydroxy-ester IIIb.—VIb was obtained similarly; m. p. 290∼295°C (decomp.).

From Acetoxy-ester IVb.—VIb was obtained similarly; m. p. 290∼295°C (decomp.).

Angelicin (Ia).—A mixture of acid Va (0.3 g.), copper powder (0.5 g.) and quinoline (40 ml.) was heated while being stirred in an atmosphere of nitrogen at 200∼220° until evolution of carbon dioxide ceased. The quinoline was distilled off by steam-distillation from the resulting mixture, the copper was filtered off while hot, and the precipitates obtained on cooling were collected and recrystallized from dilute ethanol to give Ia in the form of colorless needles, m. p. 137∼138°C; this was not depressed on admixture with a natural specimen; yield 0.1 g. (41.7%).

Found: C, 70.84; H, 3.33. Calcd. for $C_{11}H_6O_3$: C, 70.95; H, 3.25%.

4-Methylangelicin (Ib).—By a method similar to that described for Ia, Ib was obtained from Vb (0.5 g.), copper powder (0.8 g.) and quinoline (40 ml.); colorless needles, m. p. 190∼192°C (from petroleum benzine or methanol); yield 0.2 g. (50%). Reported m. p. is 194°C[10].

Found: C, 71.88; H, 4.08. Calcd. for $C_{12}H_8O_3$: C, 71.99; H, 4.03%.

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