

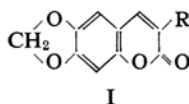
Synthetic Studies of Sesamol Derivatives. I. A New Synthesis of Ayapin

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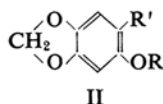
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Ayapin, a coumarin isolated from the leaves of *Eupatorium ayapana* Vent.^{1,2)} is an interesting compound because of its biological activity³⁾. Its chemical structure has been established by Späth, Bose and Schläger²⁾ as Ia, and it is the only known natural methylenedioxy coumarin. It was synthesized by the action of methylene iodide on aesculetin (6,7-dihydroxycoumarin)²⁾.

This paper describes an improved synthesis of Ia by two routes, that is, by the Knoevenagel and by the Perkin reaction from 2-hydroxy-4,5-methylenedioxybenzaldehyde (IIb).



- I
a) R=H
b) R=COOC₂H₅
c) R=COCH₃
d) R=COOH



- II
a) R=R'=H
b) R=H, R'=CHO
c) R=CH₃CO, R'=CHO

2-Hydroxy-4,5-methylenedioxybenzaldehyde (IIb), which was used as the starting material, was readily prepared from seamol (IIa)^{4,5)}, either by formylation by the Gattermann reaction⁵⁾ or by the dimethylformamide method. The aldehyde IIb was acetylated to the 2-acetoxy-4,5-methylenedioxybenzaldehyde (IIc), m.p. 125~126°C, with acetic anhydride in the presence of pyridine or anhydrous sodium acetate.

The condensation of hydroxyaldehyde (IIb) with ethyl malonate by the Knoevenagel reaction gave ethyl 6,7-methylenedioxy coumarin-3-carboxylate (Ib), m.p. 190~191°C. On the other hand, when IIb was treated with ethyl acetoacetate in absolute ethanol, it gave 3-acetyl-6,7-methylenedioxy coumarin (Ic), m.p.

1) P. K. Bose and A. Ch. Roy, *J. Indian Chem. Soc.*, **13**, 586 (1936) (*Chem. Abstr.*, **31**, 1787 (1937)).

2) E. Späth, P. K. Bose and J. Schläger, *Ber.*, **70**, 702 (1937).

3) P. K. Bose and P. B. Sen, *Ann. Biochem. and Exptl. Med.*, **1**, 311 (1941); **5**, 1 (1945) (*Chem. Abstr.*, **37**, 3835 (1943); **40**, 2224 (1946)); D. P. Chakraborty, A. D. Gupta and P. K. Bose, *ibid.*, **17**, 59 (1957) (*Chem. Abstr.*, **52**, 1352 (1959)).

4) J. Boeseken, W. D. Cohen and C. J. Kip, *Rec. Trav. Chem.*, **55**, 815 (1936) (*Chem. Abstr.*, **31**, 1017 (1937)); M. Beroza, *J. Agr. Food Chem.*, **4**, 49 (1956) (*Chem. Abstr.*, **50**, 6737 (1956)).

5) H. Sugimoto, *Tetrahedron Letters*, **1960**, No. 19, 16.

237~238°C. Compound Ib was easily converted by alkaline hydrolysis to acid (Id), m. p. 263~265°C. This acid Id was also obtained by the reaction of Iib with malonic acid, cyanoacetic acid and ethyl cyanoacetate. It was then decarboxylated in quinoline with copper powder to ayapin (6,7-methylenedioxcoumarin) (Ia), m. p. 227~228°C.

In an alternate route, Ia was prepared by the Perkin reaction. This substance exhibited no melting point depression when mixed with the above sample.

Experimental *

2 - Hydroxy - 4, 5 - methylenedioxybenzaldehyde (Iib).—a) Dimethylformamide Method.—To a solution of sesamol (IIa) (2.0 g.) in dimethylformamide (3.0 ml.), phosphorous oxychloride (2.0 ml.) was added drop by drop with ice cooling. The reaction mixture was heated on a steam bath for 1 hr. and frequently shaken. After being cooled in an ice bath, the solution was diluted with a saturated sodium acetate solution (ca. 50 ml.) and was heated for 0.5 hr. on a steam bath. Upon cooling of the mixture, the solid which had deposited was collected and recrystallized from ethanol to give Iib in the form of colorless needles, m. p. 125~126°C (reported m. p. 125~126°C)⁶, with a blue violet ferric reaction in ethanol; yield, 1.9 g. (79%).

Found: C, 57.84; H, 3.70. Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.64%.

b) Gattermann Reaction.—This aldehyde Iib was prepared from sesamol (IIa) (2.0 g.) and zinc cyanide (4.0 g.) by the Gattermann reaction⁷; m. p., 124~125°C; yield, 2.0 g. (83%). This substance showed no depression of the melting point on admixture with the specimen derived by the above-mentioned method a).

2 - Acetoxy - 4, 5 - methylenedioxybenzaldehyde (Iic).—a) A mixture of Iib (500 mg.), acetic anhydride (3 ml.) and pyridine (5 ml.) was kept at room temperature for 24 hr. and then poured into dilute hydrochloric acid. The precipitates were collected and recrystallized from ethanol to give Iic in the form of colorless needles, m. p., 125~126°C (reported m. p. 126~7°C)⁷, with a negative ferric reaction; yield, 620 mg. (99%).

Found: C, 57.64; H, 3.88. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.87%.

b) A mixture of Iib (1.0 g.) and anhydrous sodium acetate (1.2 g.) in acetic anhydride (10 ml.) was refluxed for 4 hr. The cooled mixture was poured into water, and the precipitates were collected. This was recrystallized from ethanol to give Iic in the form of colorless needles; m. p. 125~126°C; yield, 1.0 g. (78%). This substance showed no depression of the melting point on admixture with the specimen derived by the above-mentioned method a).

Ethyl 6,7-methylenedioxcoumarin-3-carboxylate (Ib).—To a solution of Iib (2.0 g.) in pyridine (20 ml.), ethyl malonate (3.0 g.) and piperidine (5 drops) were added. The mixture was refluxed for 0.5 hr., kept at 100°C for 2 hr., and then poured into dilute hydrochloric acid (150 ml.). The precipitates were collected and recrystallized from ethanol to give Ib in the form of pale yellow needles, m. p. 190~191°C, with a strong fluorescence in concentrated sulfuric acid (green) and in ethanol (blue) and with a negative ferric reaction; yield, 2.6 g. (81%); IR; 1739 (C=O); 1029, 938 cm^{-1} (O—CH₂—O) (Nujol)⁸.

Found: C, 59.97; H, 4.14. Calcd. for $C_{13}H_{10}O_6$: C, 59.54; H, 3.84%.

3-Acetyl-6,7-methylenedioxcoumarin (Ic).—To a solution of Iib (1.5 g.) in warm absolute ethanol (20 ml.), ethyl acetoacetate (1.5 g.) and piperidine (3 drops) were added. The mixture was refluxed for 5 min. After the mixture had been cooled, the crystalline products were filtered and recrystallized from ethanol to give Ic in the form of pale yellow needles, m. p. 237~238°C (decomp.), with a fluorescence in ethanol (pale blue) and a negative ferric reaction; yield, 2.0 g. (95%); IR; 1725, 1682 (C=O); 1030, 926 cm^{-1} (O—CH₂—O) (Nujol).

Found: C, 61.84; H, 3.43. Calcd. for $C_{12}H_8O_5$: C, 62.07; H, 3.47%.

6, 7 - Methylenedioxcoumarin-3-carboxylic Acid (Id).—a) From Ib.—A suspension of ester Ib (1.0 g.) in a 4% sodium hydroxide solution (50 ml.) was stirred for 10 hr. The resulting mixture was filtered, the filtrate was acidified with dilute hydrochloric acid, and the precipitates were collected and recrystallized from ethanol to give Id in the form of pale yellow needles, m. p. 263~265°C, with a strong fluorescence in concentrated sulfuric acid (green) and in ethanol (blue); yield, 0.7 g. (89%); IR: 1736, 1674 (C=O); 1026, 918 cm^{-1} (O—CH₂—O) (Nujol).

Found: C, 56.43; H, 2.58. Calcd. for $C_{11}H_6O_6$: C, 56.42; H, 2.58%.

b) From Iib.—To a solution of Iib (1.0 g.) and malonic acid (1.3 g.) in pyridine (10 ml.), aniline (5 drops) was added. The mixture was heated on an oil-bath at 55°C for 4 hr. and then poured into dilute hydrochloric acid (150 ml.). The precipitates were collected and recrystallized from ethanol to give Id, m. p. 263~265°C, with a negative ferric reaction; yield, 1.0 g. (71%). This was found to be identical with the specimen obtained by method a).

c) From Iib.—A mixture of Iib (1.0 g.), a 20% sodium hydroxide solution (30 ml.) and cyanoacetic acid (1.0 g.) was stirred at room temperature for 24 hr. The resulting mixture was acidified with dilute hydrochloric acid, and the precipitates were collected and recrystallized from ethanol to give Id, m. p. 260~262°C, with a negative ferric reaction; yield, 1.1 g. (78%). This was found to be identical with the specimen obtained by method a).

d) From Iib.—By a method similar to that described for Ic, the products were obtained from Iib (1.0 g.), ethyl cyanoacetate (1.0 g.), piperidine

* All melting points are uncorrected.

6) K. N. Campbell, P. F. Hopper and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).

7) R. T. Arnold and F. Bordwell, *J. Am. Chem. Soc.*, **64**, 2983 (1942).

8) L. H. Briggs, L. D. Colebrook, H. M. Fales and W. C. Wiemann, *Anal. Chem.*, **29**, 904 (1957).

(3 drops) and absolute ethanol (20 ml.). Then, a mixture of the products and a 5% sodium hydroxide solution was heated on a steam bath for 8 hr. and kept at room temperature for 12 hr. The resulting mixture was filtered, and the filtrate was acidified with dilute hydrochloric acid. The precipitates were collected and recrystallized from ethanol to give Id, m.p. 263~264°C, with a negative ferric reaction; yield, 400 mg. (38%). This was found to be identical with the specimen obtained by method a).

Ayapin (6,7-Methylenedioxcoumarin) (Ia)—a)

From Id.—A mixture of the acid (Id) (500 mg.), copper powder (500 mg.) and quinoline (20ml.) was heated while being stirred in an atmosphere of nitrogen for 20 min. at 200~220°C until the evolution of carbon dioxide ceased. The cooled mixture was diluted with ether (100 ml.), filtered and extracted with 8% hydrochloric acid. After being washed with aqueous sodium bicarbonate and then with water, the ethereal solution was dried and evaporated. The residue was recrystallized from ethanol to give Ia in the form of colorless crystals; m.p. 227~228°C (reported 231~232°C in sealed tube)²⁾; yield, 350 mg. (86%); IR: 1712 (C=O); 1036, 938 cm^{-1} (O—CH₂—O)⁹⁾ (Nujol).

Found: C, 63.36; H, 3.39. Calcd. for C₁₀H₈O₄: C, 63.16; H, 3.18%,

9) IR spectrum of ayapin: H. Bickel and H. Schmid, *Helv. Chem. Acta*, **36**, 670 (1953).

b) From IIb.—A mixture of IIb (1.0 g.), anhydrous sodium acetate (1.5 g.) and acetic anhydride (15 ml.) was vigorously refluxed for 10 hr. The cooled mixture was poured into water, and the precipitates were collected. These recrystallized from ethanol to give Ia in the form of colorless crystals, m.p., 226~227°C, with a negative ferric reaction; yield, 700 mg. (61%). This substance showed no depression of its melting point on admixture with the specimen derived by the above-mentioned method a).

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