[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

3-PHENYL-4-HYDROXYCOUMARIN

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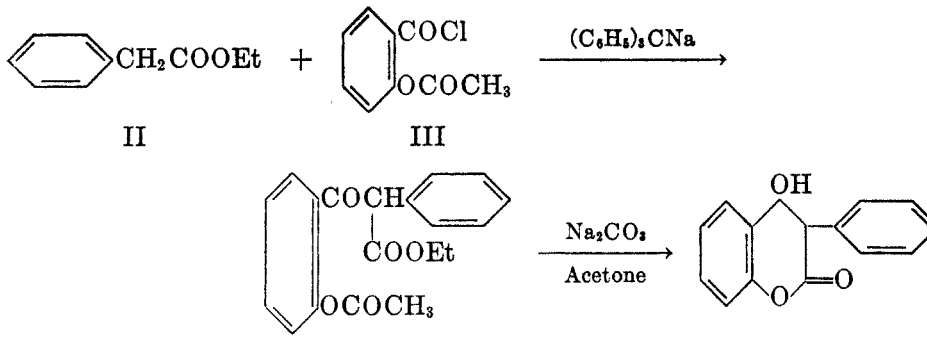
Few data can be found in the literature which describe in detail the chemical and physical properties of 3-phenyl-4-hydroxycoumarin (I) although its synthesis has been recorded several times. Pauly and Lockmann (1) reported the first synthesis by the intramolecular condensation of methyl O-phenylacetylsalicylate with sodium. This method has been reinvestigated and the yields improved by Link and co-workers (2). Urbain and Mentzer (3) prepared 3-phenyl-4-hydroxycoumarin (I) in 43% yield by heating phenol and diethyl α-phenylmalonate at elevated temperatures.

The present work describes another synthesis of I as well as the preparation of its acetate and methyl ether. These substances were desired for study as model compounds for another investigation under study.

The sodium salt of ethyl phenylacetate (II), prepared by the action of sodium-triphenylmethyl on the ester, was condensed with O-acetylsalicyl chloride (III) to give a 56% yield of ethyl 2-(O-acetylsalicyl)phenylacetate (IV). Ester IV was cyclized in 66% yield to 3-phenyl-4-hydroxycoumarin (I), m.p. 237–238°, by being heated with sodium carbonate in acetone. The ester was also cyclized in 26% yield with concentrated sulfuric acid.



The acetate of I was prepared by heating the parent compound with acetic anhydride, while the methyl ether was prepared by the action of diazomethane on the parent compound in the cold. Both the acetate and the methyl ether were insoluble in cold 10% aqueous alkali.

It was expected that alkaline treatment of I would readily cleave the molecule to yield salicylic and phenylacetic acids. Yet treatment of the compound with 10% aqueous potassium hydroxide at 100° for 14 hours resulted in the recovery of 39% of the starting material. The stability of I towards alkali can be explained

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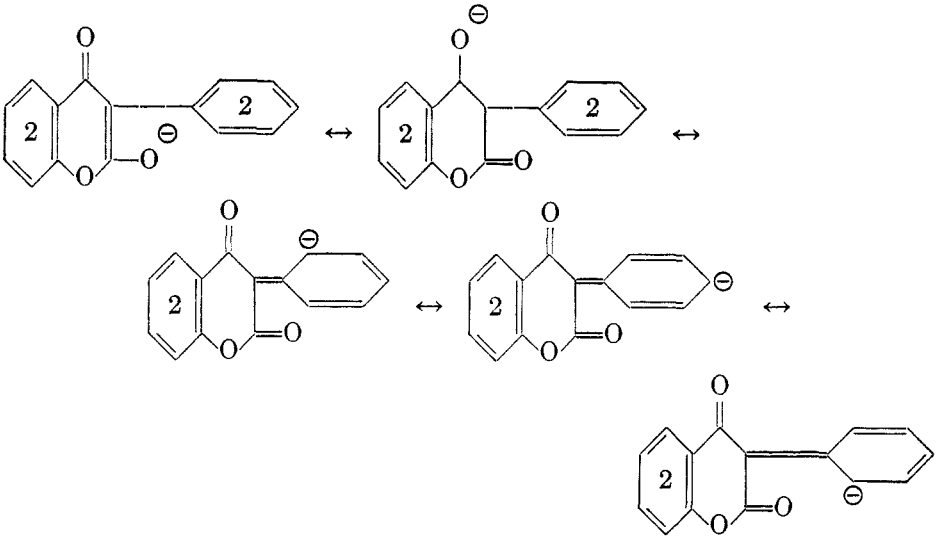
on the basis of resonance in the anion among the fourteen classical forms which may be represented as follows:



It would be expected that the stabilized anion would resist further attack by the hydroxyl ion.

The ultraviolet absorption spectra of 3-phenyl-4-hydroxycoumarin, its acetate, and its methyl ether are given in Figure 1 and show that each of the three compounds possesses two bands of practically the same intensity ($\log \epsilon = 4$) in the regions of 270–290 and 310–320 mμ. For comparison the absorption spectra of isoflavone is also given in Figure 1, which shows the presence of two bands of unequal intensities at 245 mμ. ($\log \epsilon = 4.3$) and 305 mμ. ($\log \epsilon = 3.7$).

The infrared absorption spectra of 3-phenyl-4-hydroxycoumarin, its methyl ether, and ethyl 2-(O-acetylsalicyl)phenylacetate (IV) is given in Figure 2. The spectrum of 3-phenyl-4-hydroxycoumarin shows the presence of bands at 2.87 and 5.90 μ corresponding to absorptions of the hydroxyl and lactone carbonyl groups respectively, while the spectrum of the methyl ether shows no absorption in the hydroxyl region but does have the lactone carbonyl absorption at 5.85 μ. The spectrum of 2-(O-acetylsalicyl)phenylacetate (IV) shows no absorption in the hydroxyl region but does show a broad carbonyl band at 5.75 μ. This demonstrates that the keto carbonyl of the ester IV does not enolize until the ring has been closed to the lactone, I.

EXPERIMENTAL

The *ethyl phenylacetate* (II) used in these experiments was prepared in 72% yield according to the directions of Volhard (4). The substance was distilled just before use; b.p. 61.5°/1–2 mm.

O-Acetylsalicyl chloride (III) was prepared in 94% yield by the reaction of O-acetylsalicylic acid with phosphorus pentachloride according to the procedure of Anspach, Fresenius, and Claus (5). The acid chloride, b.p. 100°/1–2 mm., was distilled just before use.

Ethyl 2-(O-acetylsalicyl)phenylacetate (IV). An ether solution of sodiumtriphenylmethyl (1.20 l. of 0.1275 *N*) (6) was placed in a 2-liter three-necked flask fitted with a stirrer, dropping-funnel, guarded condenser, and gas-inlet tube. A slow stream of nitrogen was swept through the apparatus during the reaction. Ethyl phenylacetate (25 g.), dissolved in 100 ml. of dry ether, was introduced into the flask. As soon as the solution had changed color

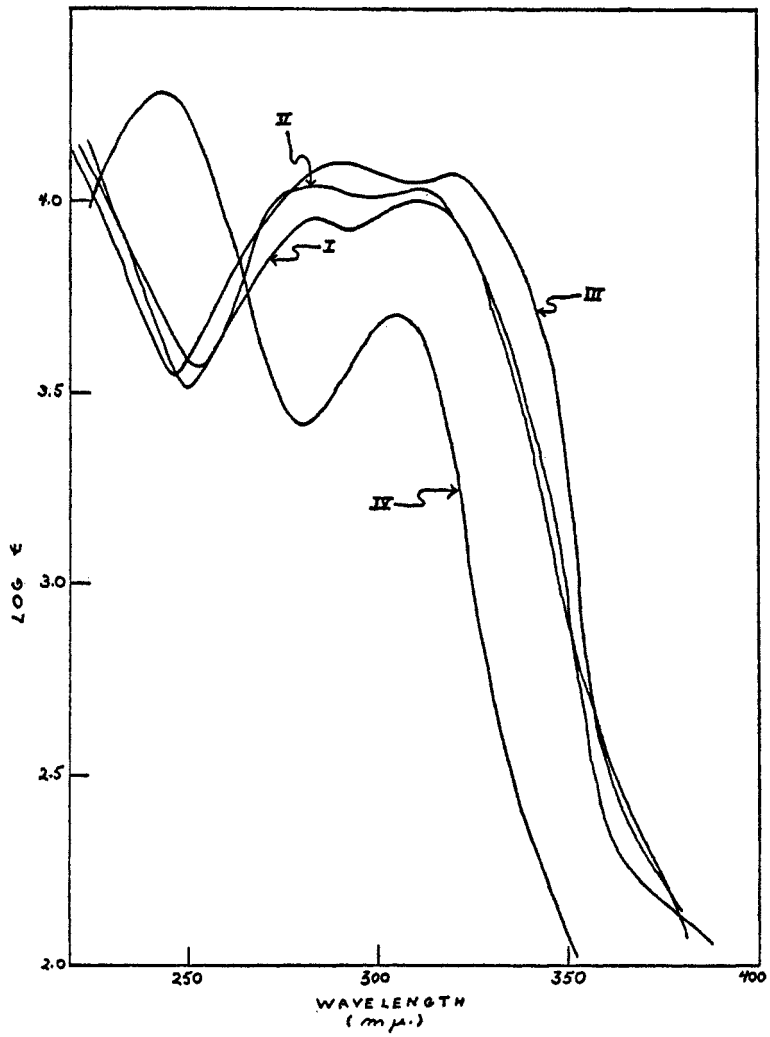


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in 95% ethanol solution) of 3-phenyl-4-hydroxycoumarin (I), 3-phenyl-4-methoxycoumarin (II), 3-phenyl-4-acetoxycoumarin (III), and isoflavone (IV).

from a deep red to an orange, 30.2 g. of O-acetylsalicyl chloride dissolved in 200 ml. of ether was added rapidly. After the ether solution had ceased boiling and had reached room temperature it was washed with 100 ml. of water to remove sodium chloride, followed by three 200-ml. portions of aqueous 10% sodium carbonate. The ether was dried with sodium sulfate, removed, and the residue which remained was dissolved in dry benzene. Successive

concentrations and filtrations of the benzene to 50 ml. yielded 20.5 g. of triphenylmethane, m.p. 90°. Complete removal of the benzene gave 28.0 g. (56% yield) of ethyl 2-(O-acetylsalicyl)phenylacetate as a viscous, orange oil which was used directly in the following experiment.

3-Phenyl-4-hydroxycoumarin (I). Ethyl 2-(O-acetylsalicyl)phenylacetate (5.00 g.) was refluxed for seven hours with 10 g. of anhydrous sodium carbonate in 150 ml. of absolute alcohol. The mixture was cooled with ice, acidified with 6 *N* hydrochloric acid, filtered and the colorless residue washed well with water, dried, and crystallized from benzene.

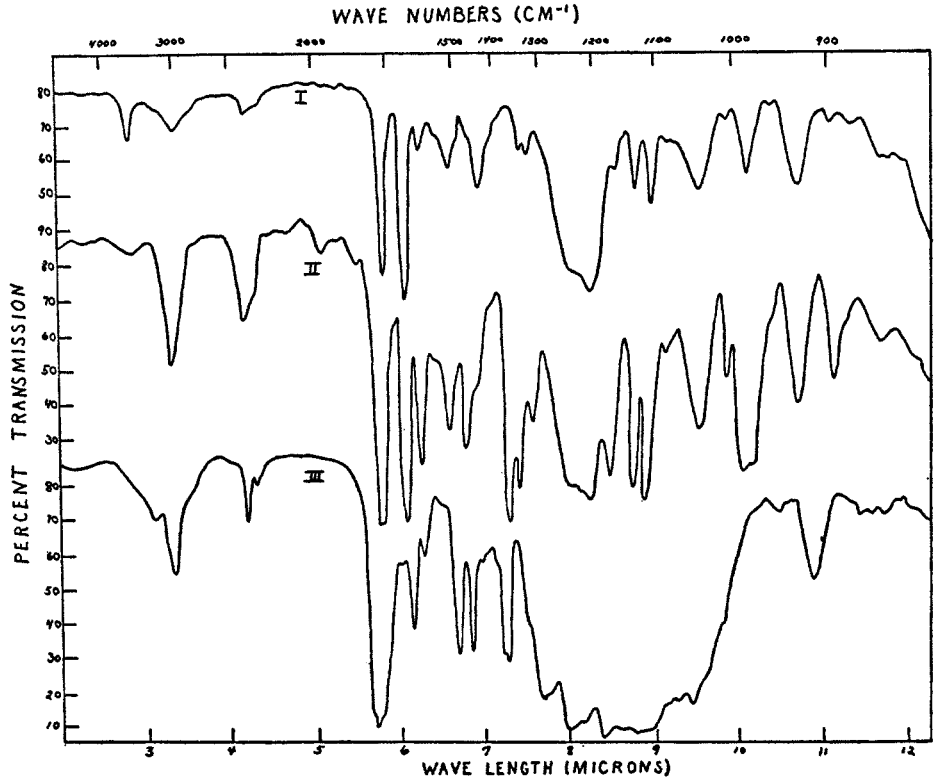


FIG. 2. INFRARED ABSORPTION SPECTRA: I is 3-phenyl-4-hydroxycoumarin; II is 3-phenyl-4-methoxycoumarin; III is ethyl 2-(O-acetylsalicyl)phenylacetate. The data were obtained in chloroform solutions on a Baird recording spectrophotometer.

There was obtained 2.42 g. (yield 66%) of colorless crystals, m.p. 235–236.5°. Further recrystallizations from benzene gave pure material, m.p. 237–238°.

Anal. Calc'd for $C_{15}H_{10}O_3$: C, 75.65; H, 4.23.

Found: C, 75.72; H, 4.14.

3-Phenyl-4-hydroxycoumarin was soluble in aqueous alkali from which it was quantitatively recovered unchanged on acidification. The material gave a negative alcoholic ferric chloride test and could not be hydrogenated in glacial acetic acid solution with platinum oxide at room temperature and at pressures slightly in excess of atmospheric. After 0.20 g. of the compound had been refluxed with 10 ml. of 10% aqueous sodium hydroxide for 2½ hours, 0.16 g. was recovered unchanged. After 0.130 g. had been refluxed with 14 ml. of 10% aqueous potassium hydroxide for 14 hours, 0.050 g. was recovered unchanged. Nothing

crystalline in sufficient quantity for identification was isolated from the reaction products, although the small quantity of oil obtained gave a strong wine-red alcoholic ferric chloride test.

3-Phenyl-4-acetoxycoumarin. 3-Phenyl-4-hydroxycoumarin (0.20 g.) was refluxed for 9 hours with 5.0 ml. of acetic anhydride. The solution was cooled and poured into 100 ml. of an ice-water mixture. After standing overnight in the cold room the solution was filtered and the residue was crystallized from acetone to yield 160 mg. (68%) of colorless crystals, m.p. 179–180°. Further recrystallizations from acetone did not alter the melting point.

Anal. Calc'd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32.

Found: C, 72.54; H, 4.38.

The acetate was insoluble in cold 10% aqueous sodium hydroxide and gave a negative alcoholic ferric chloride test.

3-Phenyl-4-methoxycoumarin. 3-Phenyl-4-hydroxycoumarin (75 mg.) was treated in ether solution with an excess of diazomethane. After standing at room temperature for an hour the nitrogen evolution had ceased and the ether solution was evaporated to dryness on a steam-bath. The colorless oily residue was recrystallized from aqueous acetone to yield 50 mg. (79%) of colorless needles, m.p. 112.5–113.5°. Further recrystallizations from aqueous acetone yielded pure material, m.p. 115–116°.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79.

Found: C, 76.43; H, 4.86.

The methyl ether was insoluble in 10% aqueous potassium hydroxide even on warming to 60° and gave a negative alcoholic ferric chloride test.

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SUMMARY

3-Phenyl-4-hydroxycoumarin, its methyl ether and acetate have been synthesized and the chemical and physical properties elucidated.

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