# *Reactions of Active Methylene Compounds. III. A New Synthesis of 4-Hydroxy-3-phenylcoumarins*

By Yoshiyuki KAWASE

(Received January 13, 1958)

In a previous paper[1], the author reported a preparation of 2-methoxybenzoyl-phenylacetonitriles (I), ethyl 2-methoxybenzoylphenylacetates (II), and 2-hydroxyphenyl benzyl ketones by ester condensation and subsequent ethanolysis and hydrolysis. In connection with it, a new synthesis of 3-aryl-4-hydroxycoumarins has been developed, and the preparation of 4-hydroxy-3-phenyl-coumarin (IVa) and its 7-methoxy-derivative (IVb) is reported in this paper.

4-Hydroxy-3-phenylcoumarins have hitherto been prepared by the following four methods:

(A) The cyclization of *o*-phenylacetoxy-derivatives of the benzoic ester with sodium at a high temperature[2].

(B) The interaction of phenols with diethyl phenylmalonate[3] or the cyclization of phenyl phenylmalonates[4] at a high temperature.

(C) The interaction of *o*-acetoxybenzoyl chloride with ethyl sodio-phenylacetate and subsequent hydrolysis[5].

(D) The cyclization of 2-hydroxyphenyl benzyl ketones by carbethoxylation with ethyl carbonate or ethyl chloroformate[6].

In the present work, the action of anhydrous aluminum chloride on the nitriles I in nitrobenzene caused demethylation and subsequent cyclization to give 4-hydroxy-3-phenylcoumarin-2-imides (III), which were also obtained by ester condensation of methyl 2-hydroxybenzoates with phenylacetonitrile. These imides III were soluble in hydrochloric acid, and seemed to be keto-forms because of their negative ferric reaction in ethanol and of their insolubility in cold aqueous alkali. The imides III

---

[1] Y. Kawase, This Bulletin, **31**, 336 (1958).

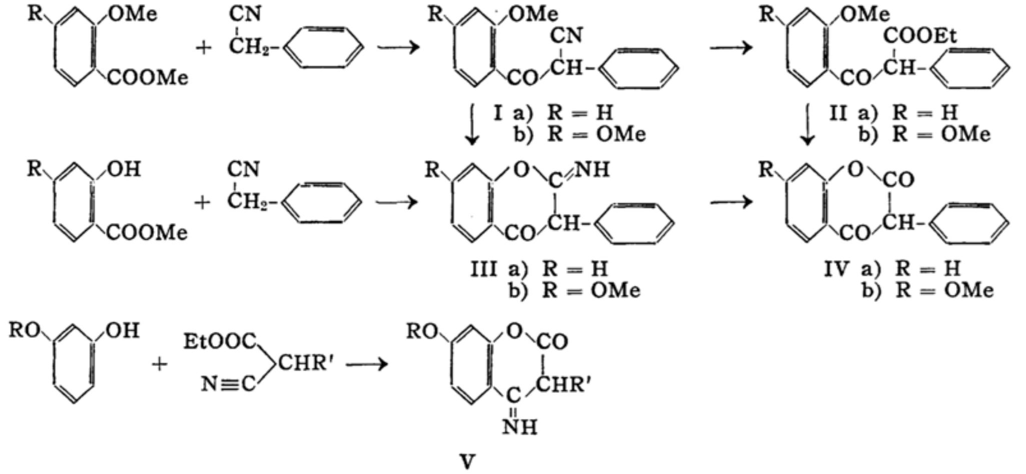
[2] a) H. Pauly and K. Lockemann, *Ber.*, **48**, 32 (1915). b) M. A. Stahmann, I. Wolff and K. L. Link, *J. Am. Chem. Soc.*, **65**, 2285 (1943).

[3] G. Urbain and C. Mentzer, *Bull. soc. chim.*, **11**, 171 (1944); C. Mentzer, D. Molho, and P. Vercier, *Bull. soc. chim. France*, **1949**, 749; P. Vercier, D. Molho and C. Mentzer, ibid., **1950**, 12480.

[4] E. Ziegler and H. Junek, *Monatsh.*, **86**, 29 (1955); **87**, 217, 789 (1956).

[5] B. S. Wildi, *J. Org. Chem.*, **16**, 407 (1951).

[6] J. Boyd and A. Robertson, *J. Chem. Soc.*, **1948**, 174; A. H. Gilbert, A. McGookin and A. Robertson, ibid., **1957**, 3740.



gave 4-hydroxy-3-phenylcoumarins (IV)’ when hydrolyzed with hydrochloric acid, and while salicylic acid and its 4-methoxy-derivative with aqueous sodium hydroxide. These coumarins IV were also obtained from ethyl 2-methoxybenzoyl-phenylacetates II by the action of anhydrous aluminum chloride in nitrobenzene; they were soluble in aqueous sodium carbonate, and supposed to be in keto-forms from their negative ferric reaction in ethanol.

It had been reported that the condensation of ethyl cyanoacetate with phenols according to the method of Hoesch gives 4-hydroxycoumarin-4-imides[7] (V, R=R′=H). So an attempt was made to prepare 4-hydroxy-3-phenylcoumarin-4-imides (V, R′=Ph), isomers of the imides III, from ethyl phenylcyanoacetate and resorcinol or resorcinol monomethyl ether by the Hoesch reaction, but it resulted in a failure, giving only a small amount of phenylmalonmonoamide ethyl ester[8].

## Experimental[9]

**4-Hydroxy-3-phenylcoumarin-2-imide(IIIa).** (*a*) *From nitrile I a.* — A mixture of 0.7 g. of nitrile I a[1] and 1.5 g. of anhydrous aluminum chloride in 5 cc. of nitrobenzene was heated for two hours on a steam bath. The cooled solution was treated with water, and nitrobenzene was driven off by steam distillation. The residual aqueous mixture was extracted with ether, and the ethereal solution was then extracted with dilute hydrochloric acid. The acid aqueous solution was made alkaline with sodium bicarbonate, and the solid product which separated was recrystallized from ethanol. Colorless microcrystals, m. p. 219.5~220.5°. Yield 0.2 g., identical with the other sample from (b).

(*b*) *By ester condensation.* — To a suspension of dry sodium ethoxide (from 2 g. of sodium) in 50 cc. of absolute benzene, a mixture of 6.5 g. of methyl 2-hydroxybenzoate and 5 g. of phenylacetonitrile was added, and the mixture was heated at about 100° on an oil bath for four hours while most of benzene was driven off with the ethanol produced. Dilute hydrochloric acid was added to the well-cooled resulting mixture, which was extracted with ether. Ether and the unchanged starting materials were driven off by steam distillation. The residual aqueous mixture was treated as before to give the product, colorless microcrystals, m. p. 223~4°, yield 1.5 g.

*Anal.* Found: C, 76.03; H, 4.97; N, 5.40. Calcd. for $C_{15}H_{11}O_2N$: C, 75.93; H, 4.67; N, 5.90%.

When 2 g. of sodium hydride was used instead of dry sodium ethoxide, the yield was 1.3 g., m. p. 219~220°, from 5 g. of methyl salicylate and 4 g. of phenylacetonitrile.

**4-Hydroxy-3-phenylcoumarin (IVa).** (*a*) *From imide III a*—A solution of 0.5 g. of imide III a in 10 cc. of dilute hydrochloric acid (1 : 1) was heated for three hours on a steam bath. A crystalline product separated from the warm solution was collected and recrystallized from ethanol to give the product in colorless needles, m. p. 231~2°, yield 0.25 g. The reported melting point is 230°[4], 234~5°[2b], 236°[2a], 237~8°[5], and 240°C[3].

*Anal.* Found: C, 75.41; H, 4.43. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23%.

(*b*) *From ester II a.*—A mixture of 0.9 g. of ester II a[1] and 2 g. of anhydrous aluminum chloride in 5 cc. of nitrobenzene was heated for one and a half hours on a steam bath. Water was added to the cooled solution, and nitrobenzene was driven off by steam distillation. The residual aqueous mixture was extracted with ether, and the ethereal solution was then extracted with aqueous sodium hydroxide. The soild product separated from the alkaline solution by acidification was purified from ethanol. Colorless needles,

---

[7] A. Sonn, *Ber.*, **50**, 1292 (1917); K. H. Bauer and F. Schoder, *Arch. Pharm.*, **259**, 53 (1921); cf. E. Ziegler, G. Wildtgrube and M. Junek, *Monatsh.*, **88**, 164 (1957).

[8] W. Wislicenus and K. Goldstein, *Ber.*, **29**, 2602 (1896).

[9] All melting points are uncorrected.

m. p. 229∼230°, yield 0.5g., identical with the other sample from (a).

**4-Hydroxy-7-methoxy-3-phenylcoumarin-2-imide (III b).** (*a*) *From nitrile I b.*—From 1 g. of nitrile I b1) and 1.9 g. of anhydrous aluminum chloride in 5 cc. of nitrobenzene, 0.2 g. of the compound was obtained by the same operation described before, colorless microcrystals, m. p. 232∼232.5° (from ethanol).

*Anal.* Found: C, 71.52; H, 5.04; N, 5.42. Calcd. for $C_{16}H_{13}O_3N$: C, 71.90; H, 4.90; N, 5.24%.

(*b*) *By ester condensation.*—To a suspension of dry sodium ethoxide (from 0.6 g. of sodium) in 50 cc. of absolute benzene, a mixture of 2 g. of methyl 2-hydroxy-4-methoxybenzoate and 1.4 g. of phenylacetonitrile was added, and the mixture was treated as before to give 0.2 g. of the product, m. p. 230∼1°, identical with the other sample from (a). When 0.3 g. of sodium hydride was used instead of dry sodium ethoxide, the yield was 0.1 g., m. p. 229∼230°, from 1.2 g. of ester and 0.8 g. of nitrile.

**4-Hydroxy-7-methoxy-3-phenylcoumarin (IV b).** (*a*) *From imide III b.*—From 0.1 g. of imide III b, 40mg. of the compound was obtained by the same operation described before, colorless microcrystals, m. p. 196∼7° (form dilute ethanol), identical with the other sample from (b).

(*b*) *From ester II b.*—From 0.4 g. of ester II b1) and 0.9 g. of anhydrous aluminum chloride, 50 mg. of the compound was obtained by the same operation described before, m. p. 196∼7°. The reported melting point is 202°3) and 204°6).

*Anal.* Found: C, 71.33; H, 4.62. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%.

The author wishes to express his hearty thanks to Professor K. Fukui for his helpful advice and encouragement, and to the members of the Agricultural Department of Kyoto University for microanalyses.

*Faculty of Literature and Science*
*Toyama University, Toyama*