Synthesis of Heterocycles, 186. The Reaction of Ethyl β-Aminocrotonate with Orcinol and *p*-Orsellinic Acid

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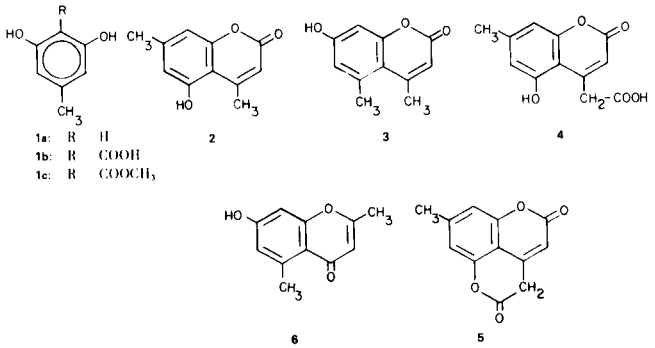
Pechmann and Cohen (3) effected the condensation of orcinol (**1a**, R = H) with ethyl acetoacetate in presence of sulphuric acid and obtained 4,7-dimethyl-5-hydroxycoumarin (**2**). These authors were unable to decide upon the structure of their product and suggested the isomeric 4,5-dimethyl-7-hydroxycoumarin (**3**) but did not prove its constitution. In the course of heating a mixture of ethyl acetoacetate and its sodio-derivative Collie and Chrystoll (4) obtained an orcinol derivative which was degraded to **2**. Later, the positions 4 and 5 assigned to one of the methyl groups and the OH group, respectively, in **2** were established by Bihari Dey (5) upon decarboxylating 4-carboxymethyl-7-methyl-5-hydroxycoumarin (**4**), and by the formation of the lactone **5** therefrom. On the other hand, the compound obtained by Sethna and Shah (6), by condensing *p*-orsellinic acid (**1b**, R = COOH) with ethyl acetoacetate in presence of sulphuric acid at 70° followed by decarboxylation, has been established recently by Hirata and Suga (7) to be 2,5-dimethyl-7-hydroxychromone (**6**) and not the isomeric coumarin **3**. Further, both authors obtained traces of **2** as byproduct due to the decarboxylation of *p*-orsellinic acid (**1b**, R = COOH) prior to the Pechmann condensation.



The aforementioned reaction (7), however, has aroused our interest to study the condensation of ethyl β-aminocrotonate with orcinol (**1a**, R = H) and *p*-orsellinic acid (**1b**, R = COOH) according to the conditions devised by Kappe, Baxevanidis and Ziegler (8) whereby coumarins and α-pyrono derivatives are obtained exclusively. Heating ethyl β-aminocrotonate and orcinol afforded a product whose physical constants are identical with those of the coumarin **2**. However, a tlc showed it to be contaminated with a minor product having a lower Rf. The minor product was found not to be the chromone **6**, as indicated by tlc, but probably 4,5-dimethyl-7-hydroxycoumarin (**3**). Attempts to synthesise 4,5-dimethyl-7-hydroxycoumarin (**3**) by heating *p*-orsellinic acid with ethyl β-aminocrotonate at 170° or refluxing in toluene yielded exclusively 4,7-dimethyl-5-hydroxycoumarin (**2**) subsequent to decarboxylation of *p*-orsellinic acid. However, the reaction did not proceed at lower temperatures designed to avoid decarboxylation. In a trial to effect the condensation in the presence of sodium ethoxide in ethanol only unreacted *p*-orsellinic acid and ethyl acetoacetate were obtained. Similarly, heating sodium *p*-orsellinate with ethyl β-aminocrotonate afforded a low yield of the coumarin **2**. In order to avoid the decarboxylation of *p*-orsellinic acid, its methyl ester (**1c**, R = $COOCH_3$) was heated with ethyl β-aminocrotonate but no reaction took place. The required ester was first synthesised by Herzig (9) using diazomethane and later by Robertson and Robinson (10) by the action of methyl iodide on the silver salt in benzene. In the present investigation, the ester was obtained by refluxing the acid with methanol in presence of sulphuric acid.

EXPERIMENTAL

All melting points are corrected. The ir spectrum was determined on Perkin Elmer 421, using potassium bromide pellets. The nmr spectrum was recorded on Varian A-60A spectrometer using DMSO-d_6 as solvent.

4,7-Dimethyl-5-hydroxycoumarin (**2**).

Method A.

An intimate mixture of orcinol (**1a**, R = H) (1.24 g., 0.01 mole) and ethyl β-aminocrotonate (1.31 g., 0.01 mole) was heated at 160-165° under nitrogen for 1.45 hours. Ethanol and ammonia were first liberated and then the reaction product solidified. After cooling, the product was crystallised from ethanol, yield 1.5 g. (79.8%). Tlc of the product showed **2** as a major component fluorescing at 350 nm and at 254 nm together with a minor product having a slight lower Rf and fluorescing at 254 nm using 1:9 acetone:benzene as eluant. The minor product is probably the

isomeric 4,5-dimethyl-7-hydroxycoumarin (**3**) and not the chromone (**6**) which has a different Rf. Compound **2** was then obtained in a pure state upon repeated crystallizations from ethanol, m.p. 255-258° dec. Its ir spectrum is characterized by a broad band between 3460 and 2700 cm^{-1} due to the free and associated OH followed by a strong broad band at 1680 cm^{-1} shouldered at 1660 cm^{-1} due to the C=O. The broad band of medium intensity was split at 1630 and at 1605 cm^{-1} is attributed to the C=C and aromatics; nmr (δ ppm): 2.21 (s, CH_3), 2.48 (s, CH_3), 5.85 (s, H at C-3), 6.4 (s, 2H at C-6 and C-8), 10.18 (s, OH).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: 69.22; H, 5.38.

Method B.

The coumarin was obtained exclusively by heating *p*-orsellinic acid (**1b**, R = COOH)(**10**)(1.68 g., 0.01 mole) and ethyl β-aminocrotonate (1.31 g., 0.01 mole) at 170° for 1 hour, yield 1 g. (52.6%). At lower temperatures no reaction took place. When sodium *p*-orsellinate (1.9 g., 0.01 mole) was heated with ethyl β-aminocrotonate (1.31 g., 0.01 mole) at 175° for 20 minutes and the product was subsequently extracted with water and filtered, the insoluble portion contained the coumarin **2** (0.2 g., 10.5%). Acidification of the aqueous filtrate yielded *p*-orsellinic acid (1 g., 59.5%).

Method C.

A low yield of the coumarin (0.2 g., 17.7%) was obtained when *p*-orsellinic acid (1 g., 0.0059 mole) and ethyl β-aminocrotonate (0.8 g., 0.0059 mole) were refluxed in toluene (30 ml.) for 8 hours during which the initially formed salt dissolved. The toluene was then evaporated under reduced pressure and the residue was recrystallized from ethanol.

Methyl *p*-Orsellinate (**1c**, R = $COOCH_3$).

A solution of *p*-orsellinic acid (1 g., 0.0059 mole) in methanol (20 ml.) was refluxed overnight in presence of sulphuric acid (0.5 ml.). The ester was recovered after removal of the solvent under reduced pressure and treatment with a saturated aqueous sodium hydrogen carbonate. It was then crystallized from aqueous methanol as colourless needles, m.p. 94° (lit. 98-99° (**9**), 93-94° (**10**)), yield 0.4 g. (37%). It failed to condense with ethyl β-aminocrotonate when an equimolar mixture was heated at 180-185° for 40 minutes.

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REFERENCES AND NOTES

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(3) H. v. Pechmann and J. B. Cohen, *Ber.*, **17**, 2187 (1884).

(4) J. N. Collie and E. R. Chrystoll, *J. Chem. Soc.*, 1802 (1907).

(5) B. Bihari Dey, *ibid.*, **107**, 1606 (1915).

(6) S. M. Sethna and R. C. Shah, *J. Indian Chem. Soc.*, **17**, 211 (1940).

(7) T. Hirata and T. Suga, *Bull. Chem. Soc. Jap.*, **47**, 244 (1974).

(8) Th. Kappe, G. Baxevanidis and E. Ziegler, *Monatsh. Chem.*, **102**, 1392 (1971).

(9) F. Herzig, *ibid.*, **24**, 894 (1903).

(10) A. Robertson and R. Robinson, *J. Chem. Soc.*, 2196 (1927).