## 44. *Aluminium Chloride, a New Reagent for the Condensation of β-Ketonic Esters with Phenols. Part I. The Condensations of Methyl β-Resorcylate, β-Resorcylic Acid, and Resacetophenone with Ethyl Acetoacetate.*

By S. M. Sethna, N. M. Shah, and R. C. Shah.

Ethyl acetoacetate condenses with methyl β-resorcylate in presence of aluminium chloride with the formation of *methyl 5-hydroxy-4-methylcoumarin-6-carboxylate*, and with β-resorcylic acid to give the corresponding coumarin-6-carboxylic acid. The constitution of the coumarin ester has been determined by its degradation to 5-hydroxy-4-methylcoumarin, the coumarin structure of which is established by the formation of the methoxycinnamic acid derivative by Robertson and Canter's method. Resacetophenone, condensed similarly, affords *5-hydroxy-6-acetyl-4-methylcoumarin*, the constitution of which is established by its identity with the product of the Fries transformation of 5-acetoxy-4-methylcoumarin and by the formation of a chromone. The smooth formation, in the above condensations, of 5-hydroxycoumarin derivatives, which are otherwise difficultly accessible, is of interest, as other condensing agents give 7-hydroxycoumarin derivatives.

The condensation of β-ketonic esters with phenols has been extensively studied in recent years, the principal condensing agents being concentrated sulphuric acid (Pechmann reaction) (*Ber.*, 1883, **16**, 2119) and phosphoric oxide (Simonis reaction) (*Ber.*, 1913, **46**, 2015). Zinc chloride, hydrogen chloride, phosphoryl chloride, phosphoric acid, and sodium ethoxide also have been used (Naik, Desai, and Desai, *J. Indian Chem. Soc.*, 1929, **6**, 801; Chakravarti, *ibid.*, 1935, **12**, 536; Appel, J., 1935, 1031), with results of no particular interest; phosphoryl chloride, however, acts in some cases like phosphoric oxide (Goodall and Robertson, J., 1936, 426).

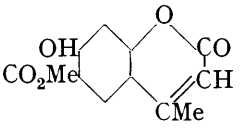
Clayton (J., 1908, **93**, 2016) stated that negative substituents, such as carboxyl and carbethoxyl, in a phenol inhibit Pechmann's coumarin condensation. Two of us (S.M.S. and R.C.S.), however, have condensed methyl β-resorcylate with ethyl acetoacetate in presence of sulphuric acid and obtained methyl 7-hydroxy-4-methylcoumarin-6-carboxylate (I) (under publication), the constitution of which was established by hydrolysis and subsequent decarboxylation to the 7-hydroxy-4-methylcoumarin, m. p. 185°, of Pechmann and Duisberg (*Ber.*, 1883, **16**, 2119). In an examination of other

possible condensing agents, the authors found that anhydrous aluminium chloride acted efficiently, the main product being *methyl 5-hydroxy-4-methylcoumarin-6-carboxylate* (II, R = Me), m. p. 185—186°, accompanied by a small quantity of methyl 7-hydroxy-4-methylcoumarin-6-carboxylate (I), m. p. 212—214°, whose identity with the product obtained by the sulphuric acid method was established by direct comparison. The new ester, m. p. 185—186°, on hydrolysis gave an acid, $C_{11}H_8O_5$, m. p. 244°, which on decarboxylation gave a compound, $C_{10}H_8O_3$, m. p. 263°. The decarboxylated product, which may be a hydroxymethyl-coumarin or -chromone, was definitely shown to be a coumarin derivative by the formation of a methylated cinnamic acid, $C_{12}H_{14}O_4$, by Robertson and Canter's method (J., 1931, 1875). The possibility of the substance being 7-hydroxy-2-methylchromone (m. p. 249—250°; Bloch and Kostanecki, *Ber.*, 1900, **33**, 471) or 5-hydroxy-2-methylchromone (m. p. 92°; Limaye and Kelkar, *Rasāyanam*, 1936, **1**, 28; *Abstr.*, 1937, *A*, ii, 257) is thus excluded. Of the two alternative constitutions, 7-hydroxy-4-methylcoumarin and 5-hydroxy-4-methylcoumarin, the latter (IV) undoubtedly represents the decarboxylated product, as the former compound is known and has m. p. 185° and also because the ester (II), m. p. 185—186°, is different from methyl 7-hydroxy-4-methylcoumarin-6-carboxylate (I), m. p. 212—214°, as previously mentioned. Limaye and Kelkar have recently reported the formation of 5-hydroxy-4-methylcoumarin, m. p. 263°, as a by-product in minute yield in the Kostanecki acetylation of 2-acetylresorcinol (which can only give a 5-hydroxy-compound), the main product being 5-hydroxy-3-acetyl-2-methylchromone, m. p. 122°, from which 5-hydroxy-2-methylchromone, m. p. 92°, was obtained by the action of alkali (*Rasāyanam*, 1936, **1**, 27, 47; *Abstr.*, 1937, *A*, ii, 254, 257). Our melting points for 5-hydroxy-4-methylcoumarin, its acetyl derivative, and its methyl ether agree with those recorded by these authors. The melting point of our 5-hydroxy-4-methylcoumarin was not depressed by a specimen kindly supplied by Prof. Limaye. Our m. p. 148—150° for the methylated *cinnamic acid* (V), however, differs from the m. p. 185° given by Limaye, the difference being probably due to *cis-trans* isomerism.

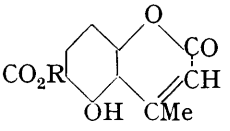
The constitution 5-hydroxy-4-methylcoumarin (IV) for the decarboxylated product leads to the alternative structures, *5-hydroxy-4-methylcoumarin-6-carboxylic acid* (II, R = H) and 5-hydroxy-4-methylcoumarin-8-carboxylic acid (III), for the carboxylic acid, m. p. 244°. The structure (II, R = H) is assigned, as the acid and the ester both give an intense violet coloration with alcoholic ferric chloride. 5-Hydroxy-4-methylcoumarin gives no ferric chloride reaction; only the 6-carboxylic acid, as an *o*-hydroxybenzoic acid, would give it, and not the 8-carboxylic acid, which would correspond to a *p*-hydroxybenzoic acid. This is supported by analogy, as the similar condensation with resacetophenone, described later, yields *5-hydroxy-6-acetyl-4-methylcoumarin* (VI), the structure of which as a 6-acetyl compound has been definitely establised by chromone formation.

β-Resorcylic acid was similarly condensed with ethyl acetoacetate, the product being 5-hydroxy-4-methylcoumarin-6-carboxylic acid (II, R = H), identical with the acid obtained by the hydrolysis of (II, R = Me).

The condensation of methyl β-resorcylate with ethyl acetoacetate in presence of freshly fused zinc chloride gave a mixture consisting mainly of the 7-hydroxy-compound (I) together with a minute quantity of (II, R = Me).



(I.)



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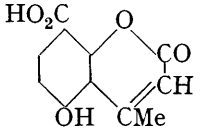
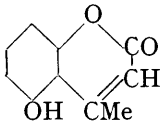
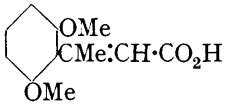


(III.)

(IV.)



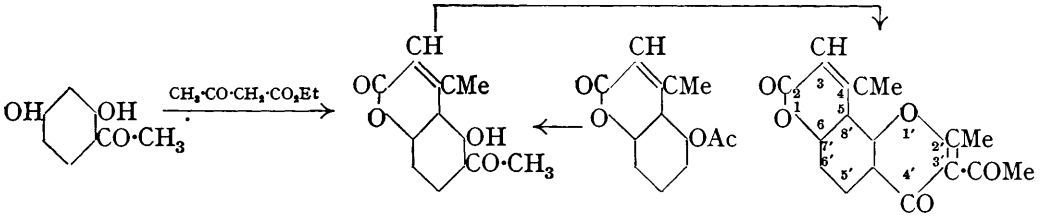



(V.)

With anhydrous aluminium chloride as condensing agent, resacetophenone condensed with ethyl acetoacetate, similarly to methyl β-resorcylate, the product, obtained in high yield, being exclusively 5-hydroxy-6-acetyl-4-methylcoumarin (VI), m. p. 165°.

The observation of Agarwal and Dutt (*J. Indian Chem. Soc.*, 1937, **14**, 109) that resacetophenone condenses with ethyl acetoacetate in the presence of sulphuric acid or sodium ethoxide, giving 7-hydroxy-6-acetyl-4-methylcoumarin, m. p. 147°, could not be confirmed, only unchanged resacetophenone being obtained in both cases. Desai and Hamid have recently carried out the same condensation in the presence of phosphoryl chloride and obtained 7-hydroxy-6-acetyl-4-methylcoumarin, m. p. 210° (*Proc. Indian Acad. Sci.*, 1937, **6**, 185).

The constitution (VI) for our condensation product, m. p. 165°, which dissolves in alkali with a deep yellow colour without fluorescence indicative of a 5-hydroxycoumarin, rests on the following grounds : (i) the Fries transformation of 5-acetoxy-4-methylcoumarin (VII) gave a compound, m. p. 164—165°, identical in all respects with the condensation product; (ii) it gives a strong ferric chloride reaction; (iii) acetylation with sodium acetate and acetic anhydride gives an acetylchromone, *3′-acetyl-4 : 2′-dimethylchromono-7′ : 8′ : 6 : 5-α-pyrone* (VIII); benzoylation gave the flavone, *3′-benzoyl-2′-phenyl-4-methylchromono-7′ : 8′ : 6 : 5-α-pyrone*. Clemmensen reduction of (VI) gave *5-hydroxy-4-methyl-6-ethylcoumarin*.




(VI.) (VII.) (VIII.)

## Experimental.

*Condensation of Methyl β-Resorcylate with Ethyl Acetoacetate in Presence of Anhydrous Aluminium Chloride : Formation of Methyl 5-Hydroxy-4-methylcoumarin-6-carboxylate* (II, R = Me).—Anhydrous methyl β-resorcylate (Robinson and Shah, J., 1934, 1496) (20 g.; 1 mol.) and ethyl acetoacetate (17 g.; 1·1 mols.) were dissolved in hot dry nitrobenzene (20 c.c.), and a solution of anhydrous aluminium chloride [32 g.; 2 mols. (less or more than 2 mols. diminished the yield)] in 120 c.c. of hot dry nitrobenzene added. The mixture, protected from moisture, was heated at 125—130° for about an hour until the evolution of hydrogen chloride was negligible; it was then cooled, ice and concentrated hydrochloric acid (10 c.c.) added, and the nitrobenzene distilled in steam. The brown solid left was collected and refluxed with sufficient rectified spirit to dissolve about half of it.

The insoluble portion crystallised from rectified spirit in needles (5 g.), m. p. 185—186°, of *methyl 5-hydroxy-4-methylcoumarin-6-carboxylate* (Found : C, 61·4; H, 4·4. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). The m. p. was depressed 20° by the 7-hydroxy-isomer (I). The substance was sparingly soluble in alcohols, benzene, light petroleum, and 10% sodium hydroxide solution, more soluble in acetone, chloroform, and glacial acetic acid. It gave with alkali a deep yellow colour without fluorescence, characteristic of 5-hydroxycoumarins (Collie and Chrystall, J., 1907, **91**, 1804; Dey, J., 1915, **107**, 1614, 1621).

The substance obtained from the initial solution in rectified spirit was a mixture (about 5 g.). It was ground with 10% sodium hydroxide solution (35 c.c.). The insoluble portion crystallised from rectified spirit in needles (about 3 g.), m. p. and mixed m. p. with methyl 5-hydroxy-4-methylcoumarin-6-carboxylate 175—186°. Total yield of (II, R = Me), 8 g. The alkaline filtrate on acidification gave a product which crystallised from rectified spirit in needles (0·5 g.), m. p. and mixed m. p. with (I) 212—214°. It gave with alkali the blue fluorescence characteristic of 7-hydroxycoumarin derivatives, and a violet coloration with ferric chloride.

The *acetyl* derivative of (II, R = Me), prepared by refluxing the substance (0·5 g.) with acetic anhydride (4 c.c.) and pyridine (1 c.c.) for 2 hours, crystallised from dilute alcohol in

needles, m. p. 153—155° (Found : C, 60·7; H, 4·3. $C_{14}H_{12}O_6$ requires C, 60·9; H, 4·3%). The *benzoyl* derivative crystallised from alcohol in needles, m. p. 164—166° (Found : C, 67·4; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·45; H, 4·1%). The *methyl* ether, prepared by refluxing a solution of the ester (0·5 g.) in acetone (50 c.c.) for 20 hours with potassium carbonate (1 g.) and methyl iodide (3 c.c.), crystallised from rectified spirit in long needles (0·4 g.), m. p. 106—107° (Found : C, 62·8; H, 5·0. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%); it was insoluble in alkali and did not give a ferric chloride reaction.

*5-Hydroxy-4-methylcoumarin-6-carboxylic Acid* (II, R = H).—(A) The ester (II, R = Me) (2 g.) was heated in a sealed tube with glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (15 c.c.) for 3 hours at 130—140°. The separated product crystallised from rectified spirit in needles (1·5 g.), m. p. 244° (efferv.) (Found : C, 58·5; H, 3·8. $C_{11}H_8O_5,0{\cdot}25H_2O$ requires C, 58·7; H, 3·8%). (B) The above ester (0·5 g.) was shaken with 10% sodium hydroxide solution (20 c.c.) and kept for 60 hours; the substance obtained on acidification crystallised from alcohol in needles (0·25 g.), m. p. and mixed m. p. with the product from (A) 244° (efferv.).

The *acid* formed sparingly soluble sodium and potassium salts. It readily dissolved in caustic alkali with a yellow colour without fluorescence and, like its methyl ester, gave an intense violet coloration with alcoholic ferric chloride. Acetyl and benzoyl derivatives could not be prepared by the usual methods.

*5-Hydroxy-4-methylcoumarin* (IV).—The ester (II, R = Me) (2 g.) was heated with water (15 c.c.), glacial acetic acid (15 c.c.), and concentrated hydrochloric acid (10 c.c.) in a sealed tube for 6—7 hours at 180—185°. The product crystallised from dilute alcohol in needles (1 g.), m. p. 263° (Found : C, 67·9; H, 4·5. Calc. for $C_{10}H_8O_3$ : C, 68·2; H, 4·55%).

The acid (II, R = H) can be decarboxylated quantitatively by heating it until it melts. 5-Hydroxy-4-methylcoumarin is soluble in alcohols, acetic acid, and acetone and sparingly soluble in chloroform, benzene, and light petroleum. It gives an intense yellow colour with alkali.

The acetyl derivative crystallised from benzene in needles, m. p. 112—114° (Found : C, 66·0; H, 4·75. Calc. for $C_{12}H_{10}O_4$ : C, 66·1; H, 4·6%). The *benzoyl* derivative crystallised from alcohol in needles, m. p. 175—177° (Found : C, 72·6; H, 4·4. $C_{17}H_{12}O_4$ requires C, 72·85; H, 4·3%). The methyl ether, prepared by means of methyl sulphate and cold sodium hydroxide solution and crystallised first from alcohol and then from benzene, had m. p. 140—142°. Limaye and Kelkar (*loc. cit.*) give m. p. 143° (Found : C, 69·4; H, 5·2. Calc. for $C_{11}H_{10}O_3$ : C, 69·5; H, 5·3%).

*2 : 6-Dimethoxy-β-methylcinnamic Acid* (V).—The substance (IV) (0·7 g.) was refluxed for 15 minutes with 4% sodium hydroxide solution (15 c.c.), and methyl sulphate (2 c.c.) added. More of these two reagents were added and the mixture was heated on the water-bath for a few minutes and left overnight. The *product* obtained on acidification with hydrochloric acid was crystallised from 20% acetic acid and then from benzene–light petroleum; m. p. 148—150°. It decolourised bromine water and dilute permanganate solution and gave no coloration with ferric chloride (Found : C, 64·8; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

*Condensation of β-Resorcylic Acid with Ethyl Acetoacetate in Presence of Aluminium Chloride.*—β-Resorcylic acid (10 g.), ethyl acetoacetate (10 g.), and aluminium chloride (17 g.) in dry nitrobenzene (70 c.c.) were heated at 115—120° for 1½ hours, and the mixture worked up as in the case of methyl β-resorcylate. The solid obtained, twice crystallised from rectified spirit, formed needles (2 g.), m. p. 244°, identical with the acid obtained by the hydrolysis of (II, R = Me). The mother-liquor gave a faint blue fluorescence with alkali, but no 7-hydroxycoumarin derivative could be isolated.

*Condensation of Methyl β-Resorcylate in Presence of Zinc Chloride.*—Methyl β-resorcylate (5 g.; 1 mol.), ethyl acetoacetate (5 g.; 1 mol.), and freshly fused zinc chloride (10 g.) were mixed, and heated for 1½ hours at 135—140°; after cooling, water and a few c.c. of hydrochloric acid were added. The product was collected and crystallised from rectified spirit; it was a mixture (m. p. 172—187°). On recrystallisation from benzene, crystals separated, m. p. and mixed m. p. with (I) 212—214°. The mother-liquor on evaporation gave a product which after two recrystallisations from benzene had m. p. and mixed m. p. with (II, R = Me) 184—185°.

*Condensation of Resacetophenone with Ethyl Acetoacetate in Presence of Anhydrous Aluminium Chloride : Formation of 5-Hydroxy-6-acetyl-4-methylcoumarin* (VI).—Resacetophenone (Robinson and Shah, J., 1934, 1494) (7·6 g.; 1 mol.) and ethyl acetoacetate (6·5 g.; 1 mol.) were added

to a solution of aluminium chloride (13·5 g.; 2 mols.) in dry nitrobenzene (80 c.c.) and the mixture treated as described on p. 230. The brown solid left after steam-distillation of the nitrobenzene crystallised from glacial acetic acid in needles; recrystallisation from boiling alcohol gave colourless needles (4—4·5 g.), m. p. 165° (Found: C, 65·7; H, 4·6. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·7%). *5-Hydroxy-6-acetyl-4-methylcoumarin* was easily soluble in chloroform and benzene, sparingly soluble in water and alcohol, and insoluble in light petroleum. It gave with alkali a deep yellow colour without fluorescence, and with alcoholic ferric chloride a deep cherry-red coloration.

The *acetyl* derivative, prepared by refluxing the substance (0·5 g.) with acetic anhydride (5 c.c.) and pyridine (1—2 c.c.) for 3 hours, crystallised from absolute alcohol in clusters of needles, m. p. 152° (Found: C, 64·0; H, 4·7. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%). The *phenylhydrazone*, crystallised from glacial acetic acid and then from alcohol, formed long, yellow, rectangular needles, m. p. 236—237° (Found: * N, 9·2. $C_{18}H_{16}O_3N_2$ requires N, 9·1%). The *oxime* crystallised from nitrobenzene in thin lustrous plates, m. p. 260° (decomp.) (Found: * N, 6·2. $C_{12}H_{11}O_4N$ requires N, 6·0%). The semicarbazone was sparingly soluble in the common organic solvents and separated from nitrobenzene in granular crystals, m. p. about 290° (decomp.).

*Fries Transformation of 5-Acetoxy-4-methylcoumarin.*—A mixture of the coumarin derivative (VII) (0·5 g.) and aluminium chloride (2·5 g.) was heated for 2 hours at 170—180° and cooled, and ice-water and a few drops of hydrochloric acid added. The solid that separated was crystallised from acetic acid and recrystallised from alcohol; it had m. p. 163—164°, alone or mixed with the condensation product (VI).

*3′-Acetyl-4 : 2′-dimethylchromono-7′ : 8′ : 6 : 5-α-pyrone* (VIII).—5-Hydroxy-6-acetyl-4-methylcoumarin (1 g.), acetic anhydride (20 c.c.), and anhydrous sodium acetate (3 g.) were heated together at 150—160° for 6—7 hours, the mixture cooled and poured into cold water, and the separated solid washed with water and with dilute sodium hydroxide solution. On crystallisation from alcohol it gave yellowish needles, m. p. 204°, of the *chromonopyrone* (VIII). It did not give a coloration with ferric chloride and was insoluble in cold aqueous sodium hydroxide, but formed a yellow solution on heating (Found: C, 67·6; H, 4·4. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%).

*3′-Benzoyl-2′-phenyl-4-methylchromono-7′ : 8′ : 6 : 5-α-pyrone.*—The coumarin (VI) (1 g.), benzoic anhydride (8 g.), and sodium benzoate (3 g.) were heated together at 180—190° for 9 hours. After the usual treatment with alcohol (25 c.c.) and potassium hydroxide (5 g.) and gentle heating, the solid *compound* obtained separated from pyridine or glacial acetic acid in tiny yellow crystals, m. p. 301° after shrinking (Found: C, 76·2; H, 4·0. $C_{26}H_{16}O_5$ requires C, 76·5; H, 3·9%).

*5-Hydroxy-4-methyl-6-ethylcoumarin.*—5-Hydroxy-6-acetyl-4-methylcoumarin (1 g.) was dissolved in alcohol, added to a mixture of zinc amalgam (prepared from 12 g. of zinc dust; Robinson and Shah, J., 1934, 1497) and concentrated hydrochloric acid (30 c.c.), and heated on a boiling water-bath for about an hour; concentrated hydrochloric acid (5 c.c.) was then added, and heating continued for another hour. The filtrate from the unchanged amalgam, on cooling, deposited needles, m. p. 172°, which were recrystallised from aqueous methyl alcohol; m. p. 174—175° (Found: C, 67·8; H, 6·1; loss at 100°, 4·0. $C_{12}H_{12}O_3,\frac{1}{2}H_2O$ requires C, 67·6; H, 6·1; $H_2O$, 4·2%). The *compound* did not give a ferric chloride reaction and dissolved in alkali with a deep yellow colour.

All the analyses recorded are microanalyses; those marked with an asterisk were done by Dr. J. N. Ray of Lahore, to whom our thanks are due, and the others by Dr. Schoeller.

A discussion of the mechanism of the formation of 5-hydroxycoumarin derivatives in these reactions is postponed pending further work on similar lines which is being carried out in view of the remarkable results described above.

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