264. *Aluminium Chloride, a New Reagent for the Condensation of β-Ketonic Esters with Phenols. Part IV. The Condensation of 4-Acylresorcinols with Ethyl Acetoacetate.*

By C. V. Deliwala and N. M. Shah.

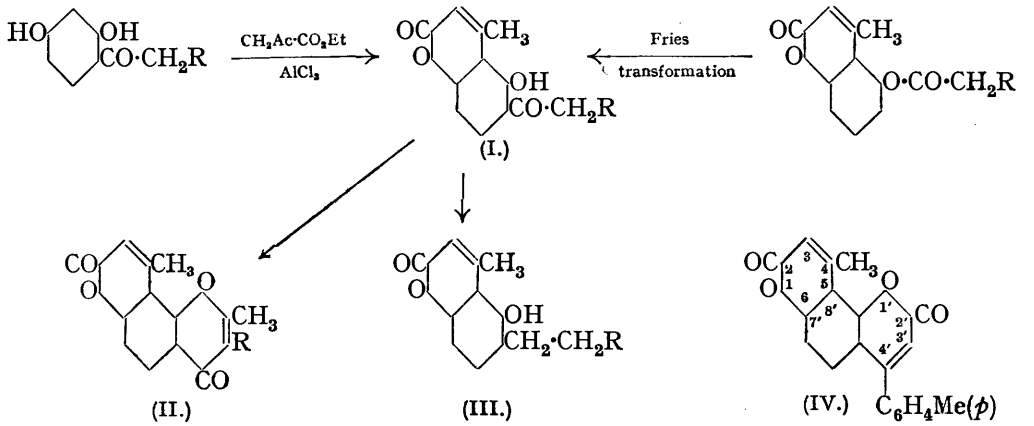
In continuation of Parts I, II, and III (J., 1938, 228, 1066, 1424), 4-acylresorcinols have been condensed with ethyl acetoacetate in presence of aluminium chloride. In all cases, 5-hydroxy-6-acylcoumarin derivatives have been obtained, the reaction proceeding similarly to that of resacetophenone (see Part I).

The work described in Parts I and III (*locc. cit.*) has been extended to the condensation of ethyl acetoacetate with various 4-acylresorcinols, *viz.*, respropiophenone, resbutyrophenone, 2 : 4-dihydroxyphenyl benzyl ketone, and 4-*p*-toluoylresorcinol.

Condensation of Respropiophenone.—Anhydrous respropiophenone on condensation with ethyl acetoacetate in presence of aluminium chloride similarly to resacetophenone (Part I, *loc. cit.*) gave 5-*hydroxy*-6-*propionyl*-4-*methylcoumarin* (I; R = Me), m. p. 164—165°. Its constitution is established by the facts that (i) it was identical with the product of the Fries transformation of 5-*propionoxy*-4-*methylcoumarin* prepared from 5-hydroxy-4-methylcoumarin (Part I), and (ii) on acetylation with sodium acetate and acetic anhydride, it gave 2′ : 3′ : 4-*trimethylchromono*-7′ : 8′ : 6 : 5-α-*pyrone* (II; R = Me). Clemmensen reduction of (I) gave 5-*hydroxy*-4-*methyl*-6-*propylcoumarin* (III; R = Me).

Condensation of Resbutyrophenone.—This condensation proceeded readily; the product is proved to be 5-*hydroxy*-6-*butyryl*-4-*methylcoumarin* (I; R = Et) by analogy with

previous condensations and on the following grounds: (i) it is identical with the Fries transformation product of 5-*butyroxy*-4-*methylcoumarin* prepared from 5-hydroxy-4-methylcoumarin (*loc. cit.*), and (ii) on Kostanecki acetylation, it afforded 4 : 2′-*dimethyl*-3′-*ethylchromono*-7′ : 8′ : 6 : 5-α-*pyrone* (II; R = Et). On Clemmensen reduction it gave 5-*hydroxy*-4-*methyl*-6-*butylcoumarin* (III; R = Et).



Condensation of 2 : 4-*Dihydroxyphenyl Benzyl Ketone.*—The condensation product of this ketone and ethyl acetoacetate in presence of aluminium chloride, on grounds similar to those of previous cases, is assigned the constitution 5-*hydroxy*-6-*phenylacetyl*-4-*methylcoumarin* (I; R = Ph); on Kostanecki acetylation it gave 3′-*phenyl*-4 : 2′-*dimethylchromono*-7′ : 8′ : 6 : 5-α-*pyrone* (II; R = Ph), but acetylation by means of acetic anhydride in pyridine solution gave only a diacetyl derivative, possibly by the enolisation of the $-CO\cdot CH_2Ph$ group.

Condensation of 4-p-*Toluoylresorcinol.*—The product in this case was 5-*hydroxy*-6-(p-*toluoyl*)-4-*methylcoumarin* (I; $CH_2R = p\text{-}C_6H_4Me$), which on Kostanecki acetylation gave 4′-(p-*tolyl*)-4-*methylcoumarino*-7′ : 8′ : 6 : 5-α-*pyrone* (IV).

It was pointed out in Part I (*loc. cit.*) that resacetophenone does not condense with ethyl acetoacetate in presence of sulphuric acid, and the same applies to the 4-acylresorcinols now described. The corresponding 2-acylresorcinols, however, condense with ethyl acetoacetate even in presence of sulphuric acid (Shah and Shah, J., 1938, 1425; Limaye and Shenolikar, *Rasayanam*, 1937, p. 99), and the greater reactivity of 2- than of 4-nitroresorcinol has been noticed by Chakravarti (*J. Indian Chem. Soc.*, 1937, **14**, 37). The reactivity of 4-acylresorcinols is thus brought out only in presence of aluminium chloride which has therefore a specific action in effecting condensation in the otherwise very inaccessible 2-position of the resorcinol molecule. Desai and Ekhlas (*Proc. Indian Acad. Sci.*, 1938, **8**, *A*, 567) have recently condensed certain 4-acylresorcinols with ethyl acetoacetate in presence of phosphorus oxychloride, obtaining 7-hydroxy-6-acylcoumarin derivatives.

During attempts to benzoylate 5-hydroxy-6-acylcoumarin derivatives by means of benzoyl chloride in pyridine solution, the expected products were not obtained, and this matter is being investigated.

Experimental.

Condensation of Respropiophenone with Ethyl Acetoacetate.—Anhydrous respropiophenone (4·2 g.; 1 mol.) and ethyl acetoacetate (3·25 g.; 1 mol.) were dissolved in dry nitrobenzene and added to a solution of anhydrous aluminium chloride (6·7 g.; 2 mols.: more or less than 2 mols. decreased the yield) in dry nitrobenzene (35 c.c.). The mixture (protected from moisture by a calcium chloride guard-tube) was heated at 120—130° until evolution of hydrogen chloride was negligible (*ca.* 1 hour); it was then cooled, ice and concentrated hydrochloric acid (15 c.c.) added, and the nitrobenzene steam-distilled off. The brown residue solidified on cooling; it was collected, and decolorised by washing with a small quantity of alcohol. Crystallisation from alcohol gave fine silky needles (2 g.), m. p. 164—165° (Found: C, 67·1; H, 5·2. $C_{13}H_{12}O_4$

requires C, 67·2; H, 5·2%). *5-Hydroxy-6-propionyl-4-methylcoumarin* (I; R = Me) is soluble in chloroform, sparingly so in benzene, alcohol, and acetic acid, and insoluble in light petroleum. It dissolves in alkali with a deep yellow non-fluorescent colour characteristic of a 5-hydroxycoumarin derivative (Collie and Chrystall, J., 1907, **91**, 1804; Dey, J., 1915, **107**, 1614, 1621), and gives a deep reddish-brown coloration with alcoholic ferric chloride.

The *acetyl* derivative, prepared by means of acetic anhydride in pyridine, crystallised from alcohol in needles, m. p. 167—168° (Found: C, 65·65; H, 5·35. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%). The *oxime* crystallised from acetic acid in needles, m. p. 257—258° (Found: N, 5·7. $C_{13}H_{13}O_4N$ requires N, 5·7%).

Fries Transformation of 5-Propionoxy-4-methylcoumarin.—5-Hydroxy-4-methylcoumarin (Part I, *loc. cit.*) was heated with propionyl chloride for about 10 hours, the temperature being slowly raised after some hours to 120°. The cooled mixture was poured into water, the solid collected, washed with dilute sodium carbonate solution and then with water, and crystallised from alcohol; m. p. 100—101° (Found: C, 67·2; H, 5·2. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). This *propionyl* derivative (0·5 g.) and aluminium chloride (2·5 g.) were intimately mixed and heated at 120—130° for about 2 hours; the solid that separated on cooling, and addition of ice-water and concentrated hydrochloric acid was collected, and twice crystallised from alcohol; m. p. 164°, alone or mixed with the condensation product (I; R = Me), with which it was identical in all respects.

2′ : 3′ : 4-Trimethylchromono-7′ : 8′ : 6 : 5-α-pyrone (II; R = Me).—5-Hydroxy-6-propionyl-4-methylcoumarin (1 g.), acetic anhydride (20 c.c.), and anhydrous sodium acetate (3 g.) were heated at 160—170° for 10—11 hours; the mixture was cooled, poured into cold water, and the separated solid washed with dilute sodium hydroxide solution and finally with water. On crystallisation from alcohol, it gave needles, m. p. 241—242°, of the *chromono-pyrone* (II; R = Me), which does not give a ferric chloride test and is insoluble in alkali (Found: C, 70·2; H, 4·7. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

5-Hydroxy-4-methyl-6-propylcoumarin (II; R = Me).—The coumarin (I; R = Me), dissolved in alcohol, was added to a mixture of zinc amalgam (prepared from 12 g. of zinc dust; Robinson and Shah, J., 1934, 1497) and hydrochloric acid (30 c.c.) and heated on the water-bath for 2 hours, 5 c.c. more of acid being added after one hour. The filtrate from the unchanged amalgam on cooling deposited fine needles, which crystallised from acetic acid in clusters of long needles, m. p. 152° (Found: C, 70·9; H, 6·6. $C_{13}H_{14}O_3$ requires C, 71·55; H, 6·4%). It did not give a ferric chloride colour, but dissolved in alkali with a deep yellow colour without fluorescence.

Condensation of Resbutyrophenone with Ethyl Acetoacetate.—Resbutyrophenone (3 g.; 1 mol.) and ethyl acetoacetate (2·5 g.; 1 mol.) were added to a solution of aluminium chloride (5·0 g.; 2 mols.) in dry nitrobenzene (25 c.c.) and the mixture treated as in the first condensation. The decolorised product crystallised from alcohol in prismatic needles (1·5 g.), m. p. 141—142° (Found: C, 68·4; H, 5·7. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). *5-Hydroxy-6-butyryl-4-methylcoumarin* (I; R = Et) is soluble in chloroform, hot acetic acid, and benzene, sparingly so in alcohols, and insoluble in light petroleum. It gives with alkali a deep yellow colour without fluorescence and with alcoholic ferric chloride develops a deep red colour. The *acetyl* derivative crystallised from alcohol in white needles, m. p. 167° (Found: C, 66·4; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). The *methyl ether*, prepared by the methyl iodide–acetone–potassium carbonate method (24 hours' refluxing), crystallised from dilute alcohol in prismatic plates, m. p. 83—84° (Found: C, 69·4; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·15%). The *oxime*, crystallised from acetic acid, had m. p. 210° (Found: N, 4·75. $C_{14}H_{15}O_4N$ requires N, 5·4%).

Fries Transformation of 5-Butyroxy-4-methylcoumarin.—This *compound* was prepared by refluxing 5-hydroxy-4-methylcoumarin (0·5 g.) with butyric anhydride (4 c.c.) and pyridine (2 c.c.) for 3 hours. The solid obtained on pouring the cooled mass into water was collected and crystallised from dilute alcohol, forming long needles, m. p. 100—101° (Found: C, 68·4; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). This derivative was isomerised by means of aluminium chloride as above; the product crystallised from alcohol in prismatic needles, m. p. 140°, alone or mixed with the condensation product (I; R = Et).

4 : 2′-Dimethyl-3′-ethylchromono-7′ : 8′ : 6 : 5-α-pyrone (II; R = Et).—5-Hydroxy-6-butyryl-4-methylcoumarin was treated with acetic anhydride, etc., as described above. The *chromonopyrone* crystallised from alcohol as fine, light, silky needles, m. p. 201—202° (Found: C, 71·5; H, 5·4. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), insoluble in alkali and giving no ferric chloride colour.

5-Hydroxy-4-methyl-6-butylcoumarin (III; R = Et).—The coumarin (I; R = Et) (1 g.) in alcoholic solution was reduced with zinc amalgam and diluted hydrochloric acid (30 c.c.; 1 : 1) and heated on the water-bath for an hour. The filtrate from the unchanged amalgam was cooled, and the resulting fine needles were crystallised from dilute acetic acid; m. p. 145—146° (Found : C, 72·25; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). The *coumarin* dissolves in alkali with a deep yellow colour and gives no ferric chloride colour.

Condensation of 2 : 4-*Dihydroxyphenyl Benzyl Ketone with Ethyl Acetoacetate.*—The ketone (Chapman and Stephen, J., 1923, **123**, 404) (2·3 g.; 1 mol.) and ethyl acetoacetate (1·3 g.; 1 mol.) were added to a solution of aluminium chloride (2·7 g.; 2 mols.) in dry nitrobenzene (35 c.c.), heated at 130—140° for an hour, and worked up as before. The decolorised product crystallised from alcohol as fine slim needles (1·25 g.), m. p. 172—173° (Found : C, 73·4; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%). *5-Hydroxy-6-phenylacetyl-4-methylcoumarin* is soluble in benzene, sparingly so in acetic acid and alcohols, and insoluble in light petroleum. It gives a strong ferric chloride colour reaction and turns deep yellow in alkalis, in which it is sparingly soluble. The *acetyl* derivative, crystallised from alcohol, had m. p. 142° (Found : C, 69·75; H, 4·9. $C_{22}H_{18}O_6$ requires C, 69·8; H, 4·8%). The *methyl ether* melted at 78—79° (Found : C, 73·7; H, 5·5. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%), and the *oxime* at 257° (Found : N, 4·6. $C_{18}H_{15}O_4N$ requires N, 4·5%).

3′-Phenyl-4 : 2′-dimethylchromono-7′ : 8′ : 6 : 5-α-pyrone (II; R = Ph).—The condensation product (I; R = Ph) (0·5 g.), anhydrous sodium acetate (1·5 g.), and acetic anhydride (10 g.) were heated at 170—175° for nearly 30 hours, more acetic anhydride (2 c.c.) being added every eight hours. When the cooled mixture was poured into water, an oil separated which soon solidified. It was collected, washed, and crystallised from alcohol; white needles, m. p. 237—238° (Found : C, 75·4; H, 4·6. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

Condensation of 4-p-*Toluoylresorcinol with Ethyl Acetoacetate.*—The resorcinol (Limaye and Shenolikar, *Rasayanam*, 1937, p. 98; 1·15 g.; 1 mol.) and ethyl acetoacetate (0·6; 1 mol.) were added to a solution of aluminium chloride (1·35 g.) in dry nitrobenzene (15 c.c.) and the mixture heated at 115—120°; after treatment as before, it afforded yellowish lustrous needles (0·8 g.) from alcohol, m. p. 204—205° (after shrinking) (Found : C, 73·6; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%). The *coumarin* is soluble in hot acetic acid, sparingly so in alcohols, and insoluble in light petroleum. It gives a reddish-brown colour with alcoholic ferric chloride, and turns yellow with alkali, in which it is very sparingly soluble. The *acetyl* derivative crystallised from alcohol in needles, m. p. 192—193° (Found : C, 71·4; H, 4·6. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

4′-p-Tolyl-4-methylcoumarino-7′ : 8′ : 6 : 5-α-pyrone (IV).—The condensation product (0·5 g.), anhydrous sodium acetate (1·5 g.), and acetic anhydride (10 c.c.) were refluxed for more than 38 hours at 200°. After being worked up as before, the product was crystallised from alcohol; m. p. 238—239° (Found : C, 74·8; H, 4·5. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

All the analyses recorded are microanalyses by Dr. A. Schoeller.

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THE MADHAVLAL RANCHHODLAL SCIENCE INSTITUTE,
GUJARAT COLLEGE, AHMEDABAD (INDIA).

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