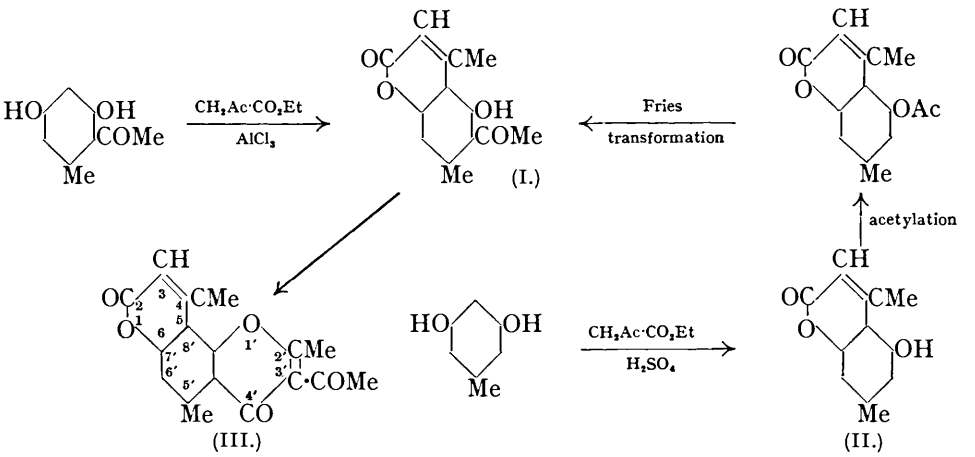
269. *Aluminium Chloride, a New Reagent for the Condensation of β-Ketonic Esters with Phenols. Part III. The Condensation of Phenolic Ketones with Ethyl Acetoacetate.*

By N. M. Shah and R. C. Shah.

In continuation of previous work (Part I; this vol., p. 228), di- and tri-hydroxyphenyl ketones have been condensed with ethyl acetoacetate in the presence of aluminium chloride to give hydroxyacylcoumarins. Orcacetophenone and 2 : 4-dihydroxybenzophenone afford 5-hydroxy-6-acylcoumarins, similarly to resacetophenone. The probable mechanism of the formation of 5-hydroxycoumarin derivatives in such cases is discussed; it is suggested that the chelation between the acyl and the *o*-hydroxyl groups fixes the double bonds in the nucleus, the condensation then taking place at the 3-position with subsequent ring closure to a 5-hydroxycoumarin.

In Part I, with Sethna (this vol., p. 228), we showed that methyl β-resorcylate, β-resorcylic acid, and resacetophenone smoothly condense with ethyl acetoacetate in the presence of aluminium chloride, giving otherwise difficultly accessible 5-hydroxycoumarin derivatives, and the study has now been extended to the condensation of ethyl acetoacetate with a number of phenolic ketones, *viz.*, orcacetophenone, 2 : 4-dihydroxybenzophenone, 2-acetylresorcinol, and phloracetophenone.

Condensation of Orcacetophenone.—Orcacetophenone on condensation with ethyl acetoacetate in presence of aluminium chloride similarly to resacetophenone (Part I, *loc. cit.*) gave a mixture of *5-hydroxy-6-acetyl-4 : 7-dimethylcoumarin* (I) and 5-hydroxy-4 : 7-dimethylcoumarin (II); the latter was identical with the product obtained by the condensation of orcinol with ethyl acetoacetate in presence of sulphuric acid (Pechmann and Cohen,

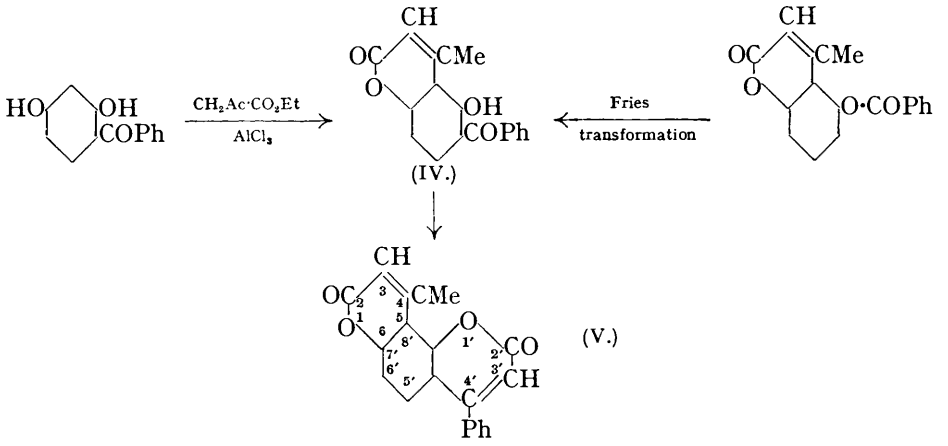


Ber., 1884, **17**, 2188), and its formation is probably due to the elimination of the acetyl group from (I) during the reaction. When sulphuric acid was used as condensing agent,

the only product was (II), probably derived from orcinol, produced from orcacetophenone by elimination of the acetyl group by the action of sulphuric acid.

The constitution of (I) was established by analysis, by analogy with the resacetophenone condensation product (Part I, *loc. cit.*), and by the facts that (i) it was identical with the product of the Fries transformation of 5-acetoxy-4 : 7-dimethylcoumarin (Pechmann and Cohen, *loc. cit.*); (ii) it gave a strong ferric chloride colour reaction; and (iii) on acetylation with sodium acetate and acetic anhydride, it gave 3′-*acetyl*-4 : 2′ : 5′-*trimethylchromono*-(7′ : 8′ : 6 : 5)-α-*pyrone* (III).

Condensation of 2 : 4-*Dihydroxybenzophenone.*—The condensation product from 2 : 4-dihydroxybenzophenone and ethyl acetoacetate in the presence of aluminium chloride has been assigned the constitution 5-hydroxy-6-benzoyl-4-methylcoumarin (IV) by analogy with previous condensations and on the following grounds: (*a*) it was identical with the Fries transformation product of 5-benzoyloxy-4-methylcoumarin (Part I, *loc. cit.*); (*b*) it gave a strong ferric chloride reaction; (*c*) on heating with acetic anhydride and sodium acetate, it afforded 4′-*phenyl*-4-*methylcoumarino*-(7′ : 8′ : 6 : 5)-α-*pyrone* (V) (cf. Canter, Martin, and Robertson, J., 1931, 1881).



Condensation of 2-*Acetylresorcinol.*—2-Acetylresorcinol on condensation with ethyl acetoacetate in presence of aluminium chloride gave 7-hydroxy-8-acetyl-4-methylcoumarin (VI), obtained by Limaye by the Fries transformation of 7-acetoxy-4-methylcoumarin (*Ber.*, 1932, **65**, 375). In presence of sulphuric acid (cf. Limaye, *Rasayanam*, 1936, **1**, 65) the same product is obtained, but in poorer yield. 2-Acetylresorcinol is therefore more reactive than resacetophenone, which does not condense in presence of sulphuric acid. This is analogous to the greater reactivity of 2-nitro- than of 4-nitro-resorcinol (Chakravarti and Banerji, *J. Indian Chem. Soc.*, 1937, **14**, 37). Clemmensen reduction of the methoxy-derivative of (VI) afforded 7-*methoxy*-4-*methyl*-8-*ethylcoumarin* (VII).

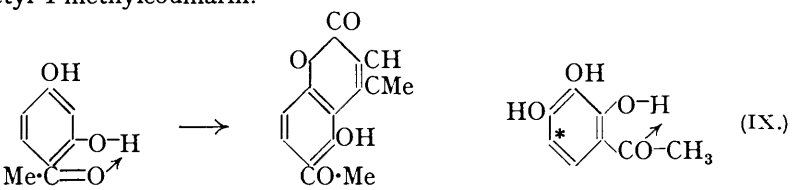
Condensation of Phloracetophenone.—Phloracetophenone on condensation with ethyl acetoacetate gave the same product in presence of aluminium chloride or of sulphuric acid. Of the two possible constitutions, 5 : 7-*dihydroxy*-6(or 8)-*acetyl*-4-*methylcoumarin*, the latter is the more likely, as the compound can be readily and completely methylated by methyl iodide in acetone solution in the presence of potassium carbonate.

Gallacetophenone, quinacetophenone, and *o*-hydroxyacetophenone did not condense in presence of either aluminium chloride or sulphuric acid, the ketones being recovered

unchanged, or tarry products being obtained from which no definite product could be isolated.

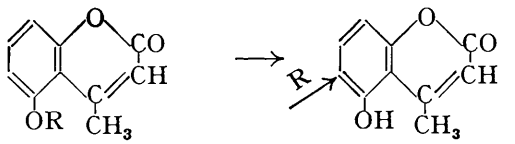
The Mechanism of Formation of 5-Hydroxycoumarin Derivatives.—The formation of 5-hydroxycoumarins in the condensations with resacetophenone, orcacetophenone, and 2 : 4-dihydroxybenzophenone obviously depends upon the reactivity in the 2-position in the resorcinol nucleus. Resorcinol derivatives easily undergo various substitutions and condensations; these generally take place in the 4- in preference to the 2-position, which is usually inaccessible. The reactivity in the 2-position in the present case becomes explicable in the light of the view that in these *o*-hydroxy-acyl ketones, one of the two Kekulé forms becomes stabilised owing to chelation between the hydroxyl and the acyl groups, which requires the fixation of double bonds in the benzene nucleus between the carbon atoms bearing these two groups. Such a view of fixation of double bonds in the benzene nucleus was first put forward by Mills and Nixon for compounds in which another ring is fused on to the benzene ring (J., 1930, 2510), and has been applied by Baker and his collaborators (J., 1934, 1684; 1935, 628, and subsequent papers; also *Ann. Reports*, 1936, **33**, 283) to substitution in resorcinol derivatives.

The formation of 5-hydroxycoumarins in the present investigation, it is suggested, also depends on the stabilisation of one of the Kekulé forms by the fixation of double bonds; *e.g.*, in resacetophenone (VIII), owing to the chelate bond between the hydroxyl and the acetyl group, this takes place, and the point of attack is the carbon atom joined by a double bond to that bearing the other hydroxyl group, with the subsequent ring closure to 5-hydroxy-6-acetyl-4-methylcoumarin.

(VIII.)  (IX.)

The non-condensation of gallacetophenone (IX) can be also satisfactorily explained by application of the above views. It will be seen that the carbon atom marked *, where the condensation might be expected to take place, is not reactive as it is united by a single bond to a carbon atom bearing the hydroxyl group. Baker (J., 1934, 1686) states that aluminium chloride may prevent chelation, but since in the present investigation, 5-hydroxycoumarin derivatives are exclusively formed in good yields, it appears that this reagent may also promote chelation.

The results of the Fries transformation of 5-acetoxy- (Part I, p. 232) and 5-benzoyloxy-4-methylcoumarin (this paper) are also explicable on the same view. The α-pyrone ring stabilises one of the Kekulé forms by the fixation of double bonds, and the 6-acylcoumarin derivatives are produced.

 (R = COMe or COPh.)

Experimental.

Condensation of Orcacetophenone with Ethyl Acetoacetate.—(i) *In presence of anhydrous aluminium chloride.* Orcacetophenone (Hoesch, *Ber.*, 1915, **48**, 1127) (6 g.; 1 mol.), ethyl acetoacetate (5·50 g.; 1 mol.), and anhydrous aluminium chloride (13 g.; 2 mols.), dissolved in dry nitrobenzene (60 c.c.), were heated on an oil-bath at 110—115° with a calcium chloride guard-tube. The reaction was vigorous at 80—100°, and after the evolution of hydrogen chloride had slackened (about 1 hr.), the temperature was finally raised to 150°. The reaction mixture was cooled, ice and concentrated hydrochloric acid (10 c.c.) added, and the nitrobenzene distilled in steam. The remaining brown solid was collected and crystallised from rectified spirit (charcoal), forming needles, m. p. 200—228°. It dissolved completely in alkali with a yellow colour. After two

recrystallisations from alcohol, *5-hydroxy-6-acetyl-4 : 7-dimethylcoumarin* (I) was obtained as needles, m. p. 180° (Found : C, 67·5; H, 5·25. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%), soluble in alkalis with a yellow colour without any fluorescence, and giving a reddish-blue colour with alcoholic ferric chloride. Its *acetyl* derivative crystallised from dilute alcohol in small needles, m. p. 149—150° (Found : C, 65·7; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·0; H, 5·1%).

The mother-liquor from (I) on standing gave a further crop of the same product. The remaining alcoholic solution was then diluted with water, and the solid that separated crystallised from acetic acid in needles, m. p. 252—253° undepressed when mixed with an authentic specimen of 5-hydroxy-4 : 7-dimethylcoumarin (Pechmann and Cohen, *loc. cit.*). This substance did not give any ferric chloride colour, but dissolved in alkali with a yellow colour without any fluorescence.

Attempts to prepare derivatives characteristic of the ketonic group in (I) were unsuccessful, no doubt owing to the steric hindrance of the *o*-methyl group.

Fries transformation of 5-acetoxy-4 : 7-dimethylcoumarin. A mixture of the coumarin (Pechmann and Cohen, *loc. cit.*) (4·5 g.) and powdered aluminium chloride (10·5 g.) was heated for 2½ hours at 170—180°. After cooling, the mixture was treated with dilute hydrochloric acid and crushed ice, and the separated solid repeatedly crystallised from hot rectified spirit, being obtained as tiny needles, m. p. 178—180°, identical (mixed m. p., and properties) with (I).

The compound (I) (0·5 g.), acetic anhydride (10 c.c.), and sodium acetate (2 g.) were heated in an oil-bath at 160—170° for 8—9 hours, the mixture cooled and poured into cold water, and the separated *3′-acetyl-4 : 2′ : 5′-trimethylchromono-(7′ : 8′ : 6 : 5)-α-pyrone* (III) washed with water and dilute sodium hydroxide solution, and crystallised from acetic acid; small reddish needles, m. p. 275—276° (Found : C, 68·2; H, 4·85. $C_{17}H_{14}O_5$ requires C, 68·45; H, 4·7%).

(ii) *In presence of sulphuric acid.* Orcacetophenone (3 g.) was condensed with ethyl acetoacetate (2·5 g.) in presence of concentrated sulphuric acid (15 c.c.), and the reaction mixture poured into ice-water after 24 hours. The solid obtained crystallised from acetic acid in needles, m. p. 252°, alone or mixed with an authentic sample of 4 : 7-dimethyl-5-hydroxycoumarin. A separate experiment on the action of concentrated sulphuric acid on orcacetophenone gave indications of the formation of orcinol by the elimination of the acetyl group.

Condensation of 2 : 4-Dihydroxybenzophenone with Ethyl Acetoacetate in Presence of Anhydrous Aluminium Chloride.—To 2 : 4-dihydroxybenzophenone (Hoesch, *Ber.*, 1915, **48**, 1130; 2 g., 1 mol.) and ethyl acetoacetate (2 g.; 1 mol.), dissolved in nitrobenzene, aluminium chloride (4 g.; 2 mols.) dissolved in nitrobenzene (total, 25 c.c.) was added, and the mixture heated to 130° for about 1½ hours; when the evolution of hydrogen chloride had slackened, the temperature was raised to 150—160°, and the mixture was then treated as described on p. 1426. The brown solid left after steam-distillation of nitrobenzene crystallised from acetic acid in small yellowish needles, m. p. 184—185° (Found : C, 72·1; H, 4·2. $C_{17}H_{12}O_4$ requires C, 72·8; H, 4·3%). In some experiments, a fairly pure product was obtained by merely washing the brown residue with alcohol. *5-Hydroxy-6-benzoyl-4-methylcoumarin* (IV) is soluble in hot acetic acid or benzene, and sparingly so in alcohols. It dissolves in alkalis with a deep yellow colour, and gives a deep greenish-red colour with alcoholic ferric chloride solution.

The *acetyl* derivative crystallised from dilute acetic acid and then from alcohol in hexagonal plates, m. p. 150° (Found : C, 70·6; H, 4·3. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·35%), and the *benzoyl* derivative from alcohol in rectangular needles, m. p. 199—200° (Found : C, 74·6; H, 4·2. $C_{24}H_{16}O_5$ requires C, 75·0; H, 4·2%).

Attempts to prepare derivatives characteristic of the ketonic group were unsuccessful.

Fries Transformation of 5-Benzoyloxy-4-methylcoumarin.—This coumarin (this vol., p. 229; 0·5 g.) mixed with anhydrous aluminium chloride (4 g.) was heated at 160—170° for 2—2½ hours, cooled, and ice-water and some hydrochloric acid added. The solid obtained was crystallised from acetic acid and then from alcohol, forming small needles, m. p. 176—177°, not raised by repeated recrystallisation. The mixed m. p. with the condensation product (IV) was 182—183°, and the mixed m. p. of the two acetyl derivatives also showed identity.

4′-Phenyl-4-methylcoumarino-(7′ : 8′ : 6 : 5)-α-pyrone (V).—The product (IV; 1 g.), acetic anhydride (25 c.c.), and sodium acetate (3 g.) were refluxed for 11 hrs. at 170—180°, the mixture cooled, and poured into water; the brown solid that separated was crystallised from acetic acid; m. p. 220—221° (Found : C, 73·75; H, 4·2. $C_{19}H_{12}O_4,0·25H_2O$ requires C, 73·9; H, 4·05%).

Condensation of 2-Acetylresorcinol with Ethyl Acetoacetate.—(*a*) *In presence of anhydrous aluminium chloride.* A mixture of 2-acetylresorcinol (Baker, J., 1934, 1954; 3·8 g., 1 mol.) and ethyl acetoacetate (3·25 g.; 1 mol.) was added to a solution of anhydrous aluminium chloride (7 g.; 2 mols.) in nitrobenzene (35 c.c.) and heated (under a guard-tube) to 125—135° till hydrogen

chloride evolution was negligible (about 1 hr.); the mixture, when worked up as before, afforded 7-hydroxy-8-acetyl-4-methylcoumarin (VI), which crystallised from acetic acid and then from alcohol in needles, m. p. 168° (4·g.) (Found: C, 65·9; H, 4·7. Calc. for $C_{12}H_{10}O_4$: C, 66·1; H, 4·6%), which dissolved in alkalis with a yellowish colour and gave a violet colour with alcoholic ferric chloride. Limaye (*loc. cit.*) gives m. p. 168°.

(*b*) *In presence of sulphuric acid.* By using 78% acid (20 c.c.), 2·5 g. of the above product (mixed m. p.) were obtained. The *O*-methyl derivative, crystallised from water, melted at 136°. Limaye and Sathe (*Rasayanam*, **1936**, **1**, 35) give m. p. 137°.

7-*Methoxy*-4-*methyl*-8-*ethylcoumarin* (VII).—The foregoing *O*-methyl derivative (1 g.), dissolved in alcohol, was added to a mixture of zinc amalgam (prepared from 25 g. of zinc dust; Robinson and Shah, J., **1934**, 1497) and diluted hydrochloric acid (1 : 1; 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 the *coumarin* (VII), which crystallised from dilute methyl alcohol in fine rhombic crystals, m. p. 133—134° [mixed m. p. with (VI), 100°] (Found: C, 71·3; H, 6·6. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%).

Condensation of Phloracetophenone with Ethyl Acetoacetate.—(*a*) *In presence of anhydrous aluminium chloride.* Phloracetophenone (Hoesch, *loc. cit.*) (2 g.; 1 mol.) and ethyl acetoacetate (2 g.; 1 mol.) were added to aluminium chloride (4 g.; 2 mols.) dissolved in nitrobenzene (25 c.c.), and the mixture heated on an oil-bath at 115—120° (guard-tube) till evolution of acid fumes had slackened (about 1 hr.), and then worked up as before. The brown residue was washed with a little alcohol, which dissolved the coloured impurities, leaving a crystalline product, m. p. 278—280°. Recrystallisation from alcohol afforded clusters of silky needles, m. p. 286—287° (0·5 g.) (Found: C, 61·45; H, 4·3. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). 5 : 7-*Dihydroxy*-6(or 8)-*acetyl*-4-*methylcoumarin* gives a bluish-red colour with alcoholic ferric chloride and dissolves in alkali with a yellow colour without any fluorescence.

(*b*) *In presence of concentrated sulphuric acid.* The above reaction was repeated with 20 c.c. of the ice-cold acid as condensing agent, and the mixture kept in ice overnight. It was then poured into ice-water, and the yellowish solid which separated was repeatedly washed with hot water, and then crystallised from rectified spirit in a mossy growth of yellowish needles (0·5 g.), m. p. 298°; mixed m. p. with product obtained in (*a*), 294—295°.

The *dimethyl ether*, obtained by the acetone–methyl iodide method (24 hours' refluxing), crystallised from dilute methyl alcohol in fine needles, m. p. 165—166°, insoluble in cold alkali and giving no ferric chloride reaction (Found: C, 64·2; H, 5·5. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%).

Attempts to prepare derivatives characteristic of the hydroxyl or the ketonic group were unsuccessful.

All the analyses recorded are microanalyses by either Dr. A. Schoeller or Dr. Hoppe (München).

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