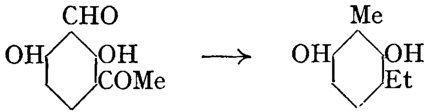
31. *γ-Substitution in the Resorcinol Nucleus. Part II. The Gattermann Reaction with Resacetophenone.*

By H. A. Shah and R. C. Shah.

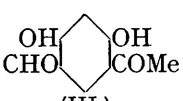
Resacetophenone has been formylated by the modified Gattermann reaction of Shah and Laiwalla (Part I; J., 1938, 1828) to give 2 : *4-dihydroxy-3-formylacetophenone*. The 3-substitution is explained as being due to the fixation of one of the Kekulé forms of resacetophenone on account of chelation between the hydroxyl and the acetyl group.

In view of the preparation of methyl 2 : 4-dihydroxy-3-formylbenzoate from methyl β-resorcylate by Shah and Laiwalla's modification (*loc. cit.*) of the Gattermann process, the formyl group entering the usually inaccessible γ-position, it became of interest to study the formylation of polyhydric phenolic ketones.

Resacetophenone did not undergo the Gattermann reaction under the usual conditions, but its formylation was readily achieved by the modified method of Shah and Laiwalla. The product may have the constitution (I) or (III). On condensation with ethyl malonate by the Knoevenagel method (*Ber.*, 1904, **37**, 4461), it furnished a *coumarin* derivative which gave a yellow coloration without fluorescence in alkaline and in sulphuric acid



(I.) (II.)

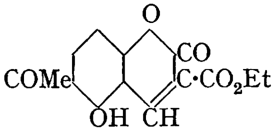


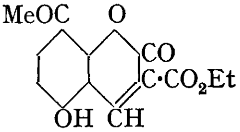
(III.)

solution—a characteristic property of 5-hydroxycoumarins (Collie and Chrystall, J., 1907, **91**, 1804; Dey, J., 1915, **107**, 1614, 1621). These results suggested that it is 2 : 4-*dihydroxy*-3-*formylacetophenone* (I), and this view was confirmed by its reduction by the Clemmensen method to 2-methyl-4-ethylresorcinol (II) (Robinson and Shah, J., 1934, 1494), now characterised by the preparation of 7-*hydroxy*-4 : 8-*dimethyl*-6-*ethylcoumarin* by condensation with ethyl acetoacetate by the Pechmann method.

2 : 4-Dihydroxy-3-formylacetophenone forms a 2 : 4-*dinitrophenylhydrazone*, a *semicarbazone*, and a *dioxime*. The coumarin derivative produced by its condensation with ethyl malonate may have the constitution (IV) or (V) : the former is assigned to it, as it gave an intense coloration with alcoholic ferric chloride. This is supported by analogy, since, in the condensation of resacetophenone with ethyl acetoacetate in presence of aluminium chloride to give 5-hydroxy-6-acetyl-4-methylcoumarin (Sethna, Shah, and Shah, J., 1938, 228), the 4-hydroxyl group is involved in coumarin ring closure. Similarly, 2 : 4-dihydroxy-3-formylacetophenone condensed with ethyl acetoacetate and with cyanoacetic acid to give 5-*hydroxy*-3 : 6-*diacetylcoumarin* and 5-*hydroxy*-6-*acetylcoumarin*-3-*carboxylic acid* respectively.

(IV.)





(V.)

The Gattermann reaction with resacetophenone is therefore analogous to that of methyl β-resorcylate (Shah and Laiwalla, *loc. cit.*), substitution taking place exclusively in the γ-position.

The 3-substitution in the present case is explicable on the assumption of the stabilisation of one of the Kekulé forms of resacetophenone. Fixation of the double bonds in the nucleus takes place on account of chelation between hydroxyl and the acetyl group, for which a double bond between these groups is essential (Mills and Nixon, J., 1930, 2510; Baker, J., 1934, 1684). Substitution then takes place at the 3-carbon atom, which is joined by a double bond to the carbon atom bearing the 4-hydroxyl group (cf. the formation of 5-hydroxy-6-acetyl-4-methylcoumarin from resacetophenone and ethyl acetoacetate mentioned above).

EXPERIMENTAL.

2 : 4-*Dihydroxy*-3-*formylacetophenone*.—To a solution of resacetophenone (15 g.; 1 mol.) in dry ether (250 c.c.) cooled in a freezing mixture, zinc cyanide (23 g.; 2 mols.) was added followed by aluminium chloride (26 g.; 2 mols.) dissolved in dry ether (100 c.c.). Dry hydrogen chloride was rapidly passed for 4½ hours into the stirred mixture. After 24 hours in the ice-chest the ether was decanted, the aldimine hydrochloride washed thrice with dry ether (30 c.c. each time) and dissolved in water (100 c.c.), and the solution heated on the steam-bath for 20 minutes. 2 : 4-*Dihydroxy*-3-*formylacetophenone*, which separated as an orange solid, crystallised from alcohol (charcoal) in stout colourless needles (8 g.), m. p. 112—114° (Found : C, 59·8; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·4%), sparingly soluble in cold alcohol but easily soluble in hot alcohol, benzene, chloroform, and light petroleum. The substance was easily volatile in steam and gave a bright yellow colour in alkaline solution and a brownish-red coloration with alcoholic ferric chloride.

The yield was improved by the addition of potassium chloride (0·33 mol.) (Arnold and Sprung, *J. Amer. Chem. Soc.*, 1938, **60**, 1699) along with the zinc cyanide. For dissolving the resacetophenone, ethyl acetate, in which it is more soluble, can be used instead of ether. The 2 : 4-*dinitrophenylhydrazone*, prepared from alcoholic solutions of 2 : 4-dinitrophenylhydrazine hydrochloride (1·2 mols.) and the ketone-aldehyde, crystallised from glacial acetic acid in tiny yellow needles, m. p. 283—285° (decomp.) (Found : N, 14·9. $C_{15}H_{12}O_7N_4$ requires N, 15·6%). The *semicarbazone*, prepared by mixing a solution of semicarbazide hydrochloride (1·2 mols.) in aqueous sodium acetate with an alcoholic solution of the ketone-aldehyde, crystallised from glacial acetic acid in tiny colourless needles, m. p. 230—231° (decomp.) (Found : N, 17·7. $C_{10}H_{11}O_4N_3$ requires N, 17·7%). The *dioxime*, prepared by refluxing an alcoholic solution of the ketone-aldehyde (0·2 g.) with an aqueous solution of hydroxylamine hydrochloride (0·3 g.) and 2 c.c. of 30% potassium hydroxide solution for 3 hours, crystallised from dilute alcohol in tiny slender needles, m. p. 218—219° (decomp.) (Found : N, 13·0. $C_9H_{10}O_4N_2$ requires N, 13·3%).

Ethyl 5-*Hydroxy*-6-*acetylcoumarin*-3-*carboxylate* (IV).—To a cooled mixture of ethyl malonate (1 g.) and the ketone-aldehyde (1 g.), 4 drops of piperidine were added; the mixture was then left for 24 hours at room temperature. The dark red solid obtained crystallised from dilute alcohol in lustrous yellow plates (0·75 g.), m. p. 155—156° (Found : C, 60·6; H, 4·5. $C_{14}H_{12}O_6$ requires C, 60·9; H, 4·4%). It gave a brownish-red coloration with alcoholic ferric chloride.

5-*Hydroxy*-6-*acetylcoumarin*-3-*carboxylic Acid*.—A solution of 2 : 4-dihydroxy-3-formylacetophenone (1 g.) in 20% aqueous sodium hydroxide (15 c.c.) and an aqueous solution of cyanoacetic acid (1 g.) (Heyes and Robertson, J., 1936, 1832) were shaken together for 3 hours, kept at room temperature for 24 hours, and acidified with dilute hydrochloric acid (Congo-red). The yellow solid obtained was collected and boiled with 4% hydrochloric acid (50 c.c.) for 15 minutes. The insoluble *acid* crystallised from dilute alcohol in stout straw-coloured needles (1 g.), m. p. 202—204° (efferv.) (Found : C, 57·9; H, 3·1. $C_{12}H_8O_6$ requires C, 58·1; H, 3·2%). It gave a brownish-red coloration with alcoholic ferric chloride.

5-*Hydroxy*-3 : 6-*diacetylcoumarin*, prepared from a cooled mixture of ethyl acetoacetate (1 g.), the ketone aldehyde (1 g.), and 4 drops of piperidine, crystallised from dilute alcohol in tiny yellow needles (0·5 g.), m. p. 170—171° (Found : C, 63·3; H, 4·4. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%). It gave a brownish-red coloration with alcoholic ferric chloride.

2-*Methyl*-4-*ethylresorcinol* (II).—To zinc amalgam prepared from zinc dust (30 g.) according to Robinson and Shah (J., 1934, 1491), dilute (1 : 1) hydrochloric acid (50 c.c.) and glacial acetic acid (10 c.c.) were added, the mixture heated on a steam-bath, a solution of (I) (5 g.) in acetic acid added in small quantities, and heating continued till an ethereal extract of a sample did not give a coloration with alcoholic ferric chloride. The solution was filtered hot, and extracted with ether after cooling. The residual amalgam also was extracted with ether. The oily residue left after evaporation of the ether from the combined extracts gave a colourless crystalline solid on distillation (180°/25 mm.). Recrystallised from light petroleum, this formed pearly lustrous prisms (1·5—2 g.), m. p. 88—90°, not depressed by authentic 2-methyl-4-ethylresorcinol (Robinson and Shah, *loc. cit.*). Reduction of 2 : 4-dihydroxy-3-formylacetophenone in alcoholic solution by the Clemmensen method gave an inferior yield and an impure product.

7-*Hydroxy*-4 : 8-*dimethyl*-6-*ethylcoumarin*.—2-Methyl-4-ethylresorcinol (0·5 g.) and ethyl acetoacetate (0·5 g.) were mixed together, and sulphuric acid (80%; 2 c.c.) added. Next day the brownish solid which separated on treatment with water was crystallised from light petroleum and then from 10% aqueous alcohol; it formed colourless slender needles, m. p. 187—188° (Found : C, 71·7; H, 6·6. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

All the analyses recorded are micro-analyses.

ROYAL INSTITUTE OF SCIENCE, BOMBAY. [*Received, November* 28*th*, 1938.]