STUDIES IN THE FRIEDEL-CRAFTS REACTION.

Part IV. The Action of Acetyl Chloride and Acetic Anhydride on Resorcinol and its Derivatives. An Evidence for γ-Substitution in the Resorcinol Nucleus.

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Phenolic ethers have been condensed with acetyl chloride and acetic anhydride in the presence of anhydrous aluminium chloride with the formation of methoxy-acetophenones which, on demethylation, give their hydroxy-derivatives. The literature is very scanty with regard to the use of free phenols in such condensations. As we required O-hydroxy-acetophenones and their substitutuion products for the coumarin as well as the chromone synthesis, we thought that the best method would be the application of the Friedel-Crafts Reaction to the free phenols themselves. The Nencki Reaction[1] which usually gives this type of ketones does not give a good yield when higher fatty acids or aromatic acids are used.

An additional point of interest attaches itself to the use of resorcinol and its derivatives in this type of condensation from the view-point of substitution. Resorcinol (or 1 : 3-dihydroxy-benzene) undergoes monosubstitution at position 4 (B-substitution) and not at position 2 (Y-substitution) because the former position receives a greater amount of electron-accession from the two hydroxyl groups than the latter. The second substituent takes up again position 6 (β-position) and not position 2, which is attacked only when positions 4 and 6 are occupied. Baker and co-workers[2] have brought forward some evidence of γ-substituion in the case of certain derivatives of resacetophenone, and our object has been to see whether γ-substitution would take place in the case of resorcinol or its monosubstitution derivatives. With this object in view, we have condensed resorcinol, 4-ethylresorcinol, β-methylresorcylate, resacetophenone (4-acetylresorcinol) and orcinol with either acetyl chloride or acetic anhydride with the following results :—

Resorcinol and acetyl chloride gave 4-acetyl resorcinol unaccompanied by any trace of 2-acetylresorcin. Similarly 4-ethylresorcinol yielded 2 : 4-dihydroxy-5-ethylacetophenone, not a trace of the isomeric 2 : 6-dihydroxy-3-ethylacetophenone being formed. An authentic specimen of the latter ketone

was synthesised from methyl 2 : 4-dihyrdoxy-5-ethylbenzoate and acetyl chloride in the presence of anhydrous aluminium chloride, hydrolysing the resulting ester, and decarboxylating the corresponding acid. The same ketone was also obtained from Shah and Samant's[3] 7-hydroxy-6-ethyl-4-methyl coumarin by Limaye's process.[4] Incidentally we have studied some of the properties of 8-acetyl-7-hydroxy-6-ethyl-4-methyl coumarin, *e.g.*, the preparation of functional derivatives, bromination and hydrolysis of the bromocoumarin.

β-Methylresorcylate did not condense with acetyl chloride at the ordinary temperature, but acetic anhydride at 100° gave methyl 2 : 4-dihydroxy-5-acetyl benzoate unaccompanied by any detectable trace of the isomeric methyl 2 : 4-dihydroxy-3-acetyl benzoate. The constitution of the ester was proved by following the method of Liebermann and Lindemann.[5]

Resacetophenone and acetic anhydride gave an equimolecular mixture of 2 : 4-diacetyl- and 4 : 6-diacetylresorcinols. Orcinol reacted with acetyl chloride giving mainly orsacetophenone (2 : 4-dihydroxy-6-methylacetophenone) to gather with a small amount of 5-hydroxy-4 : 7-dimethyl coumarin which could arise only from the isomeric 2 : 6-dihydroxy-4-methyl-acetophenone, by the acetylation of one of the hydroxyl groups and subsequent ring-closure.

Thus we conclude from our experiments that resacetophenone and orcinol are the only two resorcinol derivatives which undergo γ-substitution side by side with the normal reaction (B-substitution). Baker (*loc. cit.*), while studying the intramolecular rearrangements of certain resacetophenone derivatives, has made similar observations. Instances of γ-substitution in the case of orcinol exist in literature. Thus it undergoes the Pechmann Reaction with open-chain as well as cyclic B-ketonic esters giving 5-hydroxy-coumarins as observed by Dey[6], and Ahmad and Desai,[7] though malic acid gives the 7-hydroxy-coumarin. By condensing orcinol with glacial acetic acid in the presence of phosphorus oxychloride, Rasinski[8] obtained a ketone which was proved to be 2 : 6-dihydroxy-4-methyl-acetophenone by Ludwinowsky and Tambor[9]. Recently Shah and his co-workers[10] have brought forward the evidence of γ-substitution in resorcinol derivatives, in course of studying Pechmann and Gattermann Reactions. We are busy extending these observations to β-resorcylaldehyde, 4-nitroresorcinol, 4-cyanoresorcinol and orcinol derivatives.

Experimental.

Condensation of acetyl chloride with resorcinol.—

A mixture of resorcinol (5·9 g.), acetyl chloride (3·3 c.c.), anhydrous aluminium chloride (6·9 g.) and nitrobenzene (50 c.c.) was kept at the ordinary

temperature for 24 hours. After decomposing aluminium chloride with dilute ice-cold hydrochloric acid, the nitrobenzene was removed in steam and the precipitate obtained on cooling was collected, dried and crystallised from benzene, when colourless needles melting at 146° were obtained. This was identified as resacetophenone by mixed m.p. with an authentic specimen prepared by Nancki's method (yield 65 per cent.). The aqueous mother-liquor was saturated with salt, and extracted with ether. The gummy residue, on purification through the alkali treatment gave only resacetophenone, and no detectable trace of 2-acetylresorcinol. 4-Ethylresorcinol, on similar condensation with acetyl chloride, gave 2 : 4-dihydroxy-5-ethylacetophenone,[11] and not a trace of the isomeric 2 : 6-dihydroxy-3-ethylacetophenone, which was synthesised as follows :

Synthesis of 2 : 6-*dihydroxy*-3-*ethylacetophenone*.—

(*A*) A solution of methyl 2 : 4-dihydroxy-5-ethylbenzoate (2 g.) and acetic anhydride (1·2 c.c.) in dry nitrobenzene (10 c.c.) was added to the solution of anhydrous aluminium chloride (3·6 g.) in nitrobenzene (30 c.c.) with cautious cooling, and the mixture heated in an oil-bath at 110° for two hours. Excess of aluminium chloride was decomposed by dilute, ice-cold hydrochloric acid, and the nitrobenzene steam distilled off. The solid obtained on cooling crystallised from dilute alcohol in colourless needles melting at 76°. (Found C, 60·4 ; H, 6·1 ; $C_{12}H_{14}O_5$ requires C, 60·5 ; H, 5·9 per cent.)

Methyl 2 : 4-*dihydroxy*-3-*acetyl*-5-*ethylbenzoate* is volatile in steam, and is slightly soluble in petrol and hexane, but very easily soluble in benzene, acetic acid, acetone, and alcohol. Its alcoholic solution gave a dark-violet colouration with aqueous ferric chloride.

Hydrolysis of the above ester with caustic soda to 2 : 6-*dihydroxy*-3-*ethylacetophenone*.—A solution of the ester (1 g.) in 10 per cent. caustic soda (10 c.c.) was heated on sand-bath, for two hours, and acidified with dilute hydrochloric acid on cooling. The precipitated solid was treated with cold sodium bicarbonate solution and the residue cyrstallised from dilute alcohol when yellowish needles melting at 135° were obtained (found C, 66·4 ; H, 6·8 ; $C_{10}H_{12}O_3$ requires C, 66·6 ; H, 6·6per cent.) More of the same ketone was obtained on extracting with ether, the acid mother-liquor saturated with sodium chloride. The alcoholic solution of the ketone gave green colouration with ferric chloride, while it dissolved in concentrated sulphuric acid with a yellow colour.

The semicarbazone, prepared in the usual manner, crystallised from alcohol in needles melting at 252°. (Found C, 55·3 ; H, 6·4.$C_{11}H_{15}O_3N_3$ requires C, 55·7 ; H, 6·3 per cent.) On condensing this ketone with acetic

anhydride in the usual manner, 2 : 6-*diacetyl*-4-*ethylresorcinol* was easily obtained, and this crystallised from dilute alcohol in fine, colourless needles melting at 76°. This was appreciably volatile in steam, and was fairly soluble in petrol, and hexane. Its alcoholic solution gave dark reddish-brown colouration with aqueous ferric chloride. (Found C, 64·6 ; H, 6·2 ; $C_{12}H_{14}O_4$ requires C, 64·9 ; H, 6·3 per cent.)

The semicarbozone crystallised from alcohol in pale-yellow needles melting at 267°.

(*B*) *Preparation of* 6-*ethyl*-7-*hydroxy*-4-*methyl coumarin*.—A mixture of ethylresorcinol (10 g.), acetoacetic ester (10 g.) and 73 per cent. sulphuric acid (50 c.c.) was left for 24 hours at the ordinary temperature, and poured over ice. The crude solid melted at 208°, but on crystallising it from alcohol, white needles melting at 213° were obtained (yield 80–85 per cent.) This coumarin has been prepared by Shah and Samant, and also Chakravarty (*loc. cit.*). The *methyl ether*, prepared by the usual method, crystallised from dilute alcohol in colourless needles melting at 160°. (Found : C, 71·2 ; H, 6·6 ; $C_{13}H_{14}O_3$ requires C, 71·6 ; H, 6·4 per cent.) *The carboethoxy* derivative was obtained by gradually treating the solution of the coumarin (0·2 g.) in 10%, caustic soda (5 c.c.) with ethyl chlorocarbonate (2 c.c.). The precipitated solid, after trituration with alkali, crystallised from dilute alcohol in colourless needles melting at 144°. (Found : C, 64·9 ; H, 6·0 ; $C_{15}H_{16}O_5$ requires C, 65·2 ; H, 5·8 per cent.)

Attempts to bring about the Fries Transformation of the carboethoxy derivative by using either anhydrous aluminium chloride or zinc chloride were not successful.

The acetyl derivative crystallised from dilute alcohol in prismatic needles melting at 143°. (Found : C, 68·1 ; H, 5·9 ; $C_{14}H_{14}O_4$ requires C, 68·3 ; H, 5·7 per cent.)

Synthesis of 8-*acetyl*-7-*hydroxy*-6-*ethyl*-4-*methylcoumarin*.—An intimate mixture of 7-acetoxy-6-ethyl-4-methylcoumarin (10 g.) and finely powdered anhydrous aluminium chloride (25 g.) was heated in an oil-bath at 140–50 for one hour. After decomposing the aluminium chloride with ice-cold hydrochloric acid, the solid was dissolved in sodium carbonate solution, and acidified with concentrated hydrochloric acid. The *coumarin* crystallised from dilute alcohol in straw-coloured needles melting at 139°. The alcoholic mother-liquor on evaporation left a residue (m.p. 105–10°), which was treated with benzene to dissolve the coumarin m.p. 139°. The benzene-insoluble portion proved to be the original 7-hydroxy-6-ethyl-4-methyl-coumarin (yield 90 per cent.). (Found : C, 68·4 ; H, 6·0 ; $C_{14}H_{14}O_4$ requires

C, 68·3 ; H, 5·7 per cent.) It dissolved in alkali with a yellow colour, and its alcoholic solution gave blackish-violet colour with ferric chloride. It did not give the acetyl, methyl and carboethoxy derivatives by the usual methods.

The *semicarbazone* did not melt upto 290°.

The Kostanecki Reaction with 4-methyl-6-ethyl-7-hydroxy-8-acetyl coumarin and synthesis of 4 : 2'-dimethyl-6'-ethyl-3-acetyl-coumarino (7 : 8)-γ-pyrone.—The mixture of the coumarin (1 g.), acetic anhydride (7 c.c.) and anhydrous sodium acetate (2·5 g.) was heated in an oil-bath at 175–80° for ten hours. The solid obtained by decomposing the mixture with water was filtered off and treated with 5 per cent. NaOH solution to remove the unchanged coumarin. The *coumarino-γ-pyrone* crystallised from benzene in colourless needles melting at 192°. Its alcoholic solution did not give any colour with $FeCl_3$ solution. It dissolved in sodium hydroxide solution on warming, while its solution in concentrated sulphuric acid was yellow. (Found : C, 69·0 ; H, 5·0; $C_{18}H_{16}O_5$ requires C, 69·2 ; H, 5·1 per cent.)

Hydrolysis of 4-methyl-6-ethyl-7-hydroxy-8-acetyl coumarin with 2N-NaOH.—A solution of the coumarin (1 g.) in 2N-caustic soda (15 c.c.) was heated on sand-bath under reflux for three hours ; and the cooled solution was acidified with dilute hydrochloric acid. The filtered solid was shaken up with 2 per cent. sodium bicarbonate solution, and the residue crystallised from alcohol, when yellowish needles melting at 135° were obtained. This hydroxy ketone was identical with the one prepared by hydrolysing the condensation product of methyl 2 : 4-dihydroxy-5-ethylbenzoate with acetic anhydride. On condensing it with acetoacetic ester in the presence of conc. H_2SO_4, the coumarin (m.p. 139°) was obtained.

Bromination of 4-methyl-6-ethyl-7-hydroxy-8-acetyl-coumarin to 3-bromo-4-methyl-6-ethyl-7-hydroxy-8-acetyl-coumarin.—The solution of the coumarin (2 g.) in glacial acetic acid (25 c.c.) was gradually treated with a solution of bromine (2·5 c.c.) in glacial acetic acid (10 c.c.). The mixture which became warm immediately, was exposed to bright sunlight for one hour, and the crystalline solid that had separated out was filtered off. The crude solid (m.p. 176°) crystallised from dilute acetic acid in colourless needles melting at 180°. The glacial acetic acid mother-liquor, on dilution with water, gave a further amount of the bromo-compound contaminated with the original product. (Found : Br, 24·8 ; $C_{14}H_{13}O_4Br$ requires Br, 24·6 per cent.)

Hydrolysis of the bromo-coumarin by sodium carbonate solution.—A solution of the bromo-coumarin (2 g.) in 5 per cent. sodium carbonate solution (35 c.c.) was heated on sand-bath under reflux for two hours, cooled and extracted with ether. The ethereal solution gave, on the removal of the

solvent, a solid which crystallised from methyl alcohol in yellowish needles melting at 66°. This was *3-methyl-5-ethyl-6-hydroxy-7-acetyl-coumarone*, because it was also obtained by the decarboxylation of the *coumarilic acid* described below. (Found : C, 71·4 ; H, 6·5 ; $C_{13}H_{14}O_3$ requires C, 71·6 ; H, 6·4 per cent.)

The coumarone was soluble in hot caustic soda. Its alcoholic solution gave green colouration with $FeCl_3$. It could not be methylated, acetylated or carboethoxylated by the usual methods.

The *semicarbazone* crystallised from alcohol in small plates unmelted below 290°. (Found : C, 60·7 ; H, 6·3 ; $C_{14}H_{17}O_3N_3$ requires C, 61·1 ; H, 6·2 per cent.)

The sodium carbonate solution, on acidification with concentrated hydrochloric acid, gave a solid which dissolved almost completely in the cold 2 per cent. sodium bicarbonate solution. On acidification of the filtered solution, 3-methyl-5-ethyl-6-hydroxy-7-acetyl-coumarilic acid melting at 204–06° (decomp.) was obtained. The acid could not be satisfactorily crystallised from any solvent. (Found : C, 63·8 ; H, 5·4 ; $C_{14}H_{14}O_5$ requires C, 64·1 ; H, 5·3 per cent.)

Condensation of methyl-β-resorcylate with acetic anhydride.—The condensation of methyl-β-resorcylate with acetyl chloride at the ordinary temperature did not take place appreciably. The following method using the acetic anhydride was found to give the best yield of methyl 2 : 4-dihydroxy-5-acetyl benzoate after a number of trial experiments.

A solution of anhydrous aluminium chloride (7 g.) in nitrobenzene (60 c.c.) was added to the solution of methyl-β-resorcylate (4 g.) and acetic anhydride (2·5 g.) in nitrobenzene (20 c.c.) and the mixture was heated on water-bath for four hours. After decomposing the aluminium chloride with ice-cold dilute hydrochloric acid, the nitrobenzene was steam-distilled off, and the residue filtered off. On purification through alkali treatment, the crude solid melted at 108–12°. On refluxing with hexane, the hexane-soluble portion crystallised in colourless needles melting at 124° mixed. melting point with anhydrous methyl-β-resorcylate m.p. 124° was 98–100°. (Found : C, 56·8 ; H, 4·8 ; Calc. for $C_{10}H_{10}O_5$: C, 57·1 ; H, 4·9 per cent.)

The hexane-insoluble portion was treated with warm benzene which dissolved a portion of the residue. The solid obtained on the removal of benzene melted at 256°, and was identical with 2 : 4-dihydroxy-5-acetyl-benzoic acid described below.

Hydrolysis of the ester to the acid.—A solution of the ester (1 g.) in normal sodium hydroxide (10 c.c.) was heated on sand-bath under reflux for three

hours. On acidification, the free acid which was identified as 2 : 4-dihydroxy-5-acetyl-benzoic acid crystallised from dilute alcohol in small needles melting at 256°. On heating the acid in an oil-bath at 250°, much of the product sublimed ; and the sublimate (m.p. 146°) was identified as resacetophenone by a mixed melting point (Liebermann and Lindemann (*loc. cit.*).

Condensation of resacetophenone with acetic anhydride.—Resacetophenone did not condense with acetyl chloride at ordinary temperature. The following conditions gave the best result with acetic anhydride.

A solution of anhydrous aluminium chloride (16 g.) in nitrobenzene (100 c.c.) was added to a mixture of resacetophenone (8 g.), acetic anhydride (6 g.) and nitrobenzene (35 c.c.), and the resulting mixture was heated in an oil-bath at 105–10° for two hours. After decomposing the aluminium chloride, nitrobenzene was cautiously steam-distilled off. (Care was taken to see that 2 : 4-diacetyl resorcinol does not volatilise away.) The solid obtained on cooling was filtered off, and the mother-liquor was extracted with ether after saturating it with salt. The solid residue was first boiled with 10 per cent. NaOH, as it was sticky, and the solid recovered after acidification with concentrated hydrochloric acid. The dry solid was first extracted with benzene in which most of it dissolved. The benzene solution, on cooling, deposited 4 : 6-diacetylresorcinol melting at 185° (1·5 g.). The benzene was removed from the mother-liquor, and the residue extracted with hexane. The hexane solution, on cooling, deposited 2 : 4-diacetyl-resorcinol melting at 85–86° (1·5 g.). Authentic specimens of 4 : 6-acetyl-resorcinol and 2 : 4-diacetyl resorcinol were prepared for comparison by following Baker's directions (*loc. cit.*).

Condensation of orcinol with acetyl chloride.—Orcinol (6 g.) dissolved in nitrobenzene (25 c.c.) was added to the solution of aluminium chloride (6·5 g.) in nitrobenzene (50 c.c.) and finally acetyl chloride (5 g.) was cautiously added. After keeping the mixture for 24 hours, and decomposing the aluminium chloride with ice-cold hydrochloric acid, the nitrobenzene was steam-distilled off, and the solid filtered and dried. A considerable portion went in solution in benzene leaving a small residue (0·5 g.) melting at 230–35°. On recrystallisation from dilute alcohol, it melted at 258° and was identified as 4 : 7-dimethyl-5-hydroxy-coumarin by comparison with an authentic specimen.

The benzene solution, on concentration and cooling, deposited glistening plates melting at 159–60°, and was identified as orsacetophenone, by its properties (4 g.). A small amount of orsacetophenone (0·5 g.) was also recovered by extracting with ether the original mother-liquor.

Summary.

Acetyl chloride and acetic anhydride have been condensed with resorcinol 4-ethylresorcinol, methyl β-resorcylate, resacetophenone and orcinol in the presence of anhydrous aluminium chloride and it is found that resacetophenone and orcinol show evidence of γ-substitution side by side with usual β-substitution. Two independent methods of synthesising 2 : 6-dihydroxy-3-ethyl-acetophenone have been worked out, as this unknown ketone was required during the course of the work.

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