

NUCLEAR METHYLATION OF RESACETOPHENONE.

Preparation of 3-Methylresacetophenone and Its Derivatives.

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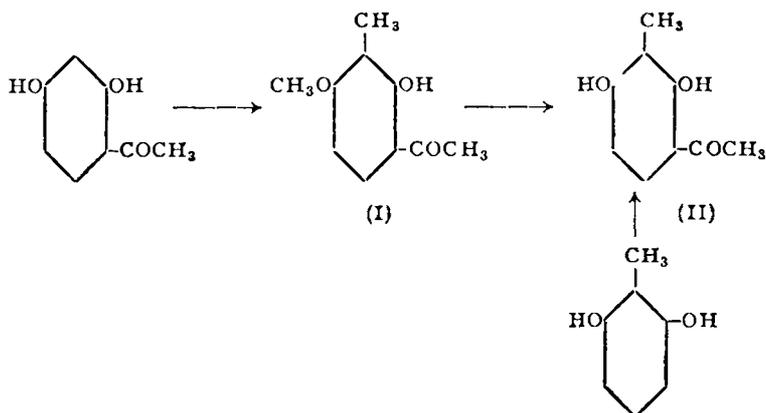
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THE reactions of resacetophenone are controlled by the existence of chelation as a consequence of which the aromatic double bonds have a tendency to get fixed. Baker and Lothian¹ have shown that 2-hydroxy-4-allyloxyacetophenone on heating gives 3-allylresacetophenone thereby indicating that the 3-position is the reactive one. A similar result has been obtained by Shah and others in the condensation of resacetophenone with ethyl acetate in the presence of aluminium chloride in ether solution, the formation of the coumarin ring involving the 3-position.² Under the same conditions hydrogen cyanide introduces an aldehyde group in the 3-position in resacetophenone and its analogues.³

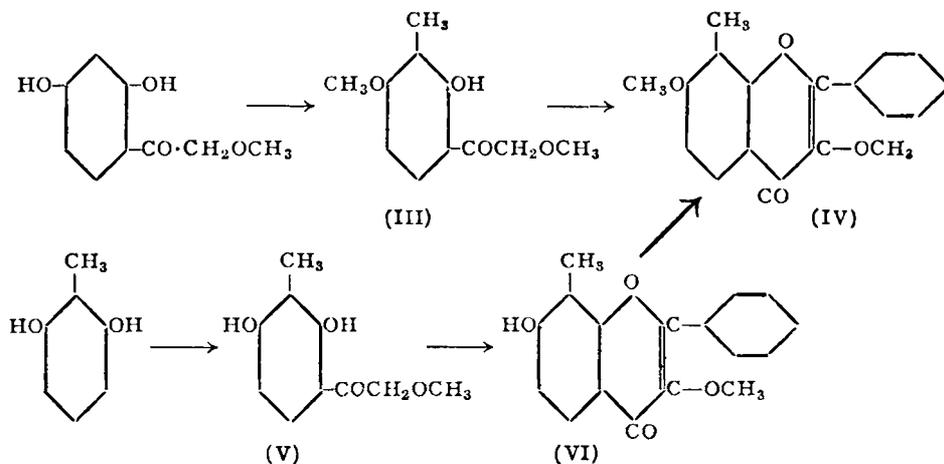
Since 3-methylresacetophenone and its derivatives were required as reference compounds and starting materials in connection with other work in progress in these laboratories and their preparation *via* 2-methyl-resorcinol is rather round about the nuclear methylation of resacetophenone and ω -methoxy-resacetophenone has now been studied.

Resacetophenone formed 2-hydroxy-3-methyl-4-methoxy-acetophenone (I) on treatment with methyl iodide and methyl alcoholic potash. This underwent demethylation to give 3-methyl-resacetophenone (II). The constitution of this compound was established by its synthesis from 2-methylresorcinol (Perkin⁴; Rangaswami and Seshadri⁵) by condensation with acetonitrile. With regard to the progress of this methylation resacetophenone resembles the esters of β -resorcylic acid, the same factors obviously being involved in both cases.

The work has been repeated with ω -methoxyresacetophenone⁶ and in this connection the assumption that the hydroxy group which undergoes etherification is the one present in the 4th position and not the one in the 2nd position has been substantiated. The product of nuclear methylation (III) easily undergoes condensation with sodium benzoate and benzoic anhydride according to the procedure developed by Allan and Robinson⁷



and yields a flavone which has been found to be 3 : 7-dimethoxy-8-methyl-flavone (IV). The production of a flavone is itself sufficient proof that the 2-hydroxy group has not been affected by the process of methylation. The identity of (IV) has however been established by its synthesis starting from 2-methylresorcinol. By condensation with methoxyacetonitrile ω -methoxy-3-methyl-resacetophenone (V) was obtained which with sodium benzoate and benzoic anhydride gave rise to 3-methoxy-7-hydroxy-8-methyl-flavone (VI) which subsequently underwent methylation easily to give (IV).



Experimental.

Nuclear methylation of resacetophenone :—2-hydroxy-3-methyl-4-methoxy-acetophenone.—A solution of resacetophenone (2 g.) in methyl alcoholic potash containing 15 c.c. of anhydrous methyl alcohol and 2.6 g. of caustic potash was cooled in freezing-mixture and treated with ice-cold methyl

iodide (4.2 c.c.) all at once. The mixture was well shaken to render it homogeneous and the container left well stoppered in the ice-bath to assume laboratory temperature slowly. After standing overnight the mixture which had deposited a little solid was gently boiled under reflux in a water-bath for 7 hours and then poured into excess of ice-water (150 c.c.). The slightly pasty mass that separated overnight was filtered, washed with water and then macerated with cold dilute alkali when nearly half of it went into solution leaving the remainder as a clean solid. This insoluble portion when filtered and washed with water melted indefinitely in the neighbourhood of 80° and on crystallisation from alcohol gave 2-hydroxy-3-methyl-4-methoxy-acetophenone in the form of stout needles and micacious plates melting at $82-3^{\circ}$. (Found: C, 66.5; H, 7.0; OCH_3 , 17.3; $\text{C}_{10}\text{H}_{12}\text{O}_3$ requires C, 66.7; H, 6.7; OCH_3 , 17.2 per cent.). Yield 0.6 g. The compound was easily soluble in the common organic solvents and gave a greenish blue colour with alcoholic ferric chloride.

Demethylation of above to produce 3-methylresacetophenone.—The above compound (0.5 g.) was dissolved in a mixture of phenol (0.5 g.) and acetic anhydride (0.5 c.c.) and gently boiled for half an hour with hydriodic acid (sp. gr. 1.70; 8 c.c.). The resulting liquid was diluted with water (20 c.c.) and repeatedly ether-extracted. The combined ether-extract was shaken with sodium bicarbonate solution to remove the acetic acid and then washed with a little water. On evaporation of the solvent a dark-coloured oil was left behind. This was stirred thrice with small quantities of water which was then thrown away, so as to remove most of the phenol used. The residual oil was then dissolved in alcohol and allowed to crystallise whereby a compound melting from 141 to 146° was obtained. This on two further crystallisations from benzene gave 3-methylresacetophenone in the form of plates and needles melting at $154-5^{\circ}$ and was found to be identical with the specimen prepared from 2-methylresorcinol (see below).

3-Methylresacetophenone from 2-methylresorcinol.—A solution of 2-methylresorcinol (1 g.) in absolute ether (25 c.c.) was treated with pure acetonitrile (0.8 g.) and anhydrous zinc chloride (0.5 g.) and saturated with dry hydrogen chloride. The current of the gas was stopped at the end of two hours and the mixture left overnight. The clear solution that was obtained on the addition of water (25 c.c.) was shaken with ether to remove unchanged reactants. The pale yellow aqueous solution containing the ketimine-hydrochloride was heated for one hour in a boiling water-bath and then cooled when the ketone separated in the form of a crystalline powder. On recrystallising from methyl alcohol it was obtained as colourless needles and rectangular plates melting at $156-7^{\circ}$. (Found: C, 64.6; H, 6.1; $\text{C}_9\text{H}_{10}\text{O}_3$

requires C, 65.1; H 6.0 per cent.). It gave a violet colour with alcoholic ferric chloride. A mixed melting point with the sample obtained starting from resacetophenone showed no depression.

2-Hydroxy-3-methyl- ω :4-dimethoxyacetophenone.—The nuclear methylation of ω -methoxyresacetophenone was carried out according to the same procedure as was adopted in the case of resacetophenone. The reaction was more easy and the product was obtained pure more readily. The solution of the ω -methoxy ketone in alcoholic potash which set to a thick cake at the temperature of the freezing-bath was diluted with enough anhydrous methyl alcohol to enable uniform mixing and shaking, before methyl iodide was added. As the methylation proceeded big crystals of potassium iodide separated from the solution. When after refluxing for 7 hours the mixture was poured into water and left overnight the precipitated solid was found to be only slightly sticky and to melt rather sharply at 96–8°. After crystallisation from alcohol in which it was easily soluble the 3-methyl-4-methoxy ketone came down as long woolly fibres melting at 109°. (Found: C, 62.4; H, 6.5; $-\text{OCH}_3$, 29.2; $\text{C}_{11}\text{H}_{14}\text{O}_4$ requires C, 62.9; H, 6.7; $-\text{OCH}_3$, 29.5 per cent.).

The substance appeared as long rectangular rods under the microscope, gave a pinkish brown colour with alcoholic ferric chloride and was insoluble in cold dilute alkali. During combustion it melted smoothly to a brown liquid, after which it decomposed to give a dark oily product which proved very refractory. Yield of the twice-crystallised product was 0.6 g. from 2 g. of ω -methoxyresacetophenone.

3:7-Dimethoxy-8-methylflavone from the above ketone.—An intimate mixture of the ketone (1 g.), sodium benzoate (1.5 g.) and benzoic anhydride (4 g.) was heated in an oil-bath at 200° for 4 hours under a pressure of about 40 mm. of mercury. The residue was treated with a large excess of water containing a little sodium carbonate and left for some hours in order to remove the excess of benzoic anhydride. The aqueous portion was decanted off and the solid left behind treated again in the same fashion with excess of water and carbonate. A dark coloured oil remained which when dissolved in alcohol and left for some days deposited needles with a glistening yellow colour and melting at 143–45°. When recrystallised from alcohol the flavone melted at 145–46° and had the appearance of stout rectangular prisms under the microscope. (Found: C, 72.9; H, 5.3; $\text{C}_{18}\text{H}_{16}\text{O}_4$ requires C, 73.0; H, 5.4 per cent.). A mixed melting point showed it to be identical with the specimen prepared from 2-methylresorcinol as described below.

3-Methyl- ω -methoxyresacetophenone.—The preparation of this compound from 2-methylresorcinol was very similar to that of 3-methylresaceto-

phenone. Methoxyacetonitrile (b.p. 119–23°) was used instead of acetonitrile and the condensation took place even without the addition of anhydrous zinc chloride, the ketimine hydrochloride separating in a crystalline form in about 4 hours from the commencement of the reaction. When the mixture was treated with water the next day and the aqueous solution after shaking with ether was heated in a boiling water-bath the required ketone separated in the form of a crystalline powder. After recrystallisation from alcohol it came out as rectangular and hexagonal prisms melting at 203–5°. (Found : C, 60.8 ; H, 6.4 ; $C_{10}H_{12}O_4$ requires C, 61.2 ; H, 6.1 per cent.). The compound was fairly soluble in hot water and easily in the common organic solvents and gave a dark violet colour with alcoholic ferric chloride.

3-Methoxy-7-hydroxy-8-methylflavone from the above ketone.—An intimate mixture of the ketone (0.4 g.), sodium benzoate (1 g.) and benzoic anhydride (4 g.) was heated under reduced pressure for 4 hours in an oil-bath at 190°. The product was then refluxed for half an hour with 10 per cent. alcoholic potash (30 c.c.) to hydrolyse the 7-benzoyloxy compound first formed. Most of the alcohol was then distilled off, the residue diluted with water and the clear solution saturated with carbon dioxide. The required 7-hydroxy flavone was thus precipitated and when crystallised from alcohol was obtained in the form of rectangular plates melting at 252–3°. (Found : C, 71.9 ; H, 5.4 ; $C_{17}H_{14}O_4$ requires C, 72.3 ; H, 5.0 per cent.). It did not give any colour with alcoholic ferric chloride.

3 : 7-Dimethoxy-8-methylflavone from the above.—The 7-hydroxy-flavone (0.2 g.) was dissolved in dry acetone (15–20 c.c.) and heated under reflux on a water-bath for 16 hours with a large excess of methyl iodide (2 c.c.) and anhydrous potassium carbonate (0.4 g.). The residue after evaporation of the solvent was treated with acidulated water and the water-insoluble portion filtered. The precipitate was dissolved in a slight excess of alcohol and the solution filtered from insoluble matter and allowed to stand. Beautiful crystals separated in the course of a few days which after filtering and washing with a few drops of cold alcohol melted at 135–6°. After another crystallisation from aqueous alcohol the methyl ether was obtained as pale yellow needles which melted at 141–2° and appeared as rectangular rods under the microscope. (Found : C, 72.8 ; H, 5.6 ; $C_{18}H_{16}O_4$ requires C, 73.0 ; H, 5.4 per cent.). It was identical in all respects with the one prepared from 2-hydroxy-3-methyl- ω : 4-dimethoxyacetophenone.

Summary.

The methylation of resacetophenone and its ω -methoxy derivative using methyl iodide and methyl alcoholic potash has been studied. The former

gave 2-hydroxy-3-methyl-4-methoxyacetophenone the constitution of which was established by demethylation to 3-methylresacetophenone and comparison with a specimen prepared from 2-methylresorcinol. In the same way ω -methoxyresacetophenone gave 2-hydroxy-3-methyl- ω :4-dimethoxyacetophenone which was subsequently converted to 3:7-dimethoxy-8-methylflavone. The identity of this flavone was proved by its synthesis from 2-methyl-resorcinol.

It is concluded that under the above conditions resacetophenone undergoes nuclear methylation in the 3-position and that the hydroxyl group in the 4th position gets etherified.

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