

NEW SYNTHETICAL METHODS IN COUMARIN CHEMISTRY.

By R. C. SHAH.

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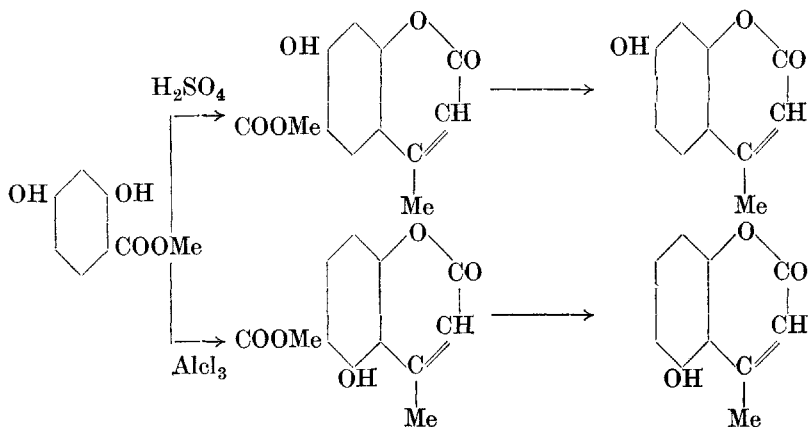
A variety of coumarin derivatives have been synthesized by new methods developed in these laboratories. A number of coumarins, particularly 5-hydroxycoumarins, which are of synthetic importance and have been hitherto inaccessible or accessible only with great difficulty, are thus made readily available.

Of the various synthetic methods available for the synthesis of coumarins that of Pechmann and Duisberg (*Ber.*, 1883, 16, 2119), which consists in the condensation of a B-ketonic ester with a phenol, is one of the more important and has been most widely used. The principal condensing agents which have been hitherto used have been concentrated sulphuric acid (Pechmann Reaction; *Ber.*, 1883, 16, 2119) and phosphoric anhydride (Simonis Reaction; *Ber.*, 1913, 46, 2015), the product being either a coumarin or a chromone or rarely a mixture of both, depending on the nature of the ester, the phenol, and the condensing agent. It is now generally accepted that more reactive phenols give coumarins with both the condensing agents, whereas less reactive phenols, which either do not react at all or give only poor yields of coumarins in presence of sulphuric acid, tend to give chromones with phosphoric anhydride (Chakrawarti, *J. Ind. Chem. Soc.*, 1932, 9, 31). A number of other condensing agents, like zinc chloride, hydrogen chloride, phosphoryl chloride, phosphoric acid, and sodium ethoxide have been also occasionally used, with results of no particular interest, the same products as those with sulphuric acid being obtained in varying yields (Naik, Desai and Desai, *J. Ind. Chem. Soc.*, 1929, 6, 801; Chakravarti, *ibid.*, 1935, 12, 536; Appel, *J.C.S.*, 1935, 1031). Phosphoryl chloride however promises to be of interest as it can replace phosphoric oxide in some cases (Goodall and Robertson, *J.C.S.*, 1936, 426) and has been found to be valuable for the condensation of polyhydroxy-phenolic ketones with B-ketonic esters (Desai and Hamid, *Proc. Ind. Acad. Sci.*, 1937, 6, 185).

The condensation of B-ketonic esters with phenols in the presence of anhydrous aluminium chloride, a new reagent for this purpose, has been studied in these laboratories for some time, and from the results obtained, which are unique in some respects, it promises to be a valuable reagent. The condensation is generally carried out in the presence of a solvent-ether in which aluminium chloride dissolves readily (Shah, *Current Science*, 1934, 157) or in nitrobenzene where elevated temperatures have to be used.

1. *Simple phenols*.—The same products are obtained as with sulphuric acid, in some cases with higher yields. In no case has a chromone been obtained. The reagent is of particular value in the case of the little reactive monohydric phenols. Phenol uniformly gives a yield of 30–40% of 4-methylcoumarin, the recorded yield in literature using sulphuric acid being only 3% (Sethna, Shah and Shah, *Current Science*, 1937, 3, 93). O-cresol, which does not condense using sulphuric acid, readily condenses with ethyl acetoacetate giving 4 : 8-dimethyl-coumarin.

2. *Phenolic esters*.—Methyl B-resorcyrate condenses with ethyl acetoacetate in the presence of sulphuric acid giving methyl 7-hydroxy-4-methyl-coumarin-6-carboxylate (Shah *et al.*, *J. Ind. Chem. Soc.*, 1937, 12, 717). The same condensation in the presence of aluminium chloride affords mainly methyl 5-hydroxy-4-methyl-coumarin-6-carboxylate, from which by hydrolysis and subsequent decarboxylation, 4-methyl-5-hydroxy-coumarin is readily obtained (Sethna, Shah and Shah, *J.C.S.*, 1938, 228). Limaye previously obtained 4-methyl-5-hydroxy coumarin in a minute yield as a bye-product in the Kostanecki acetylation of 2-acetylresorcinol, the main product being 5-hydroxy-2-methyl-chromone (Limaye and Kelkar, *Rasayanam*, 1936, 45). Methyl 2 : 4-dihydroxy-5-ethyl-benzoate similarly gives methyl 5-hydroxy-4-methyl-8-ethyl-coumarin-6-carboxylate from which 5-hydroxy-4-methyl-8-ethyl coumarin has been obtained (Sethna and Shah, *J.C.S.*, 1938, 1066). The work is being extended to α -chloro, and α -alkyl-, acetoacetic esters, and benzoylactic and acetone dicarboxylic esters on the one hand, and other phenolic esters on the other.

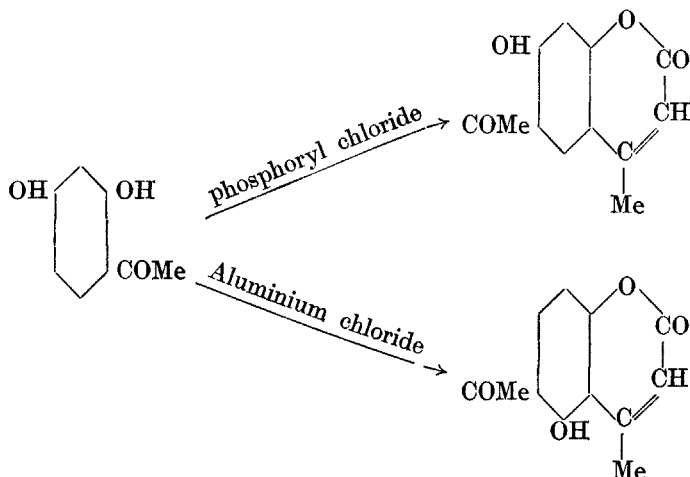


3. *Phenolic ketones*.—Resacetophenone does not condense with ethyl acetoacetate in the presence of sulphuric acid or sodium ethoxide contrary to the statement of Aggrawal and Dutt (*J. Ind. Chem. Soc.*, 1937, 14, 109). The condensation takes place readily in the presence of aluminium chloride, the product obtained in high yield being proved to have the constitution of

5-hydroxy-4-methyl-6-acetyl coumarin (Sethna, Shah and Shah, *loc. cit.*). Orsacetophenone and 2:4-dihydroxy-benzophenone react similarly giving the corresponding 5-hydroxy-coumarin derivatives, 5-hydroxy-6-acetyl-4:7-dimethyl-coumarin and 5-hydroxy-6-benzoyl-4-methyl-coumarin respectively. Phloracetophenone gives an acetyl coumarin, which may have the constitution of 5:7-dihydroxy-4-methyl-6-acetyl-coumarin or 5:7-dihydroxy-4-methyl-8-acetyl-coumarin; the latter constitution is more likely as it can be completely methylated easily. 2-Acetyl resorcinol gives 7-hydroxy-8-acetyl-coumarin in better yield than with sulphuric acid. O-hydroxy-acetophenone, quinacetophenone and gallacetophenone do not react (N. M. Shah and R. C. Shah, *J.C.S.* 1939, 1424.)

In this connection it is worthy of note that although resacetophenone does not condense with B-ketonic esters in the presence of sulphuric acid, Desai and Hamid (*loc. cit.*) find that the condensation takes place readily in the presence of phosphoryl chloride, the products being 7-hydroxy-6-acetyl-coumarins.

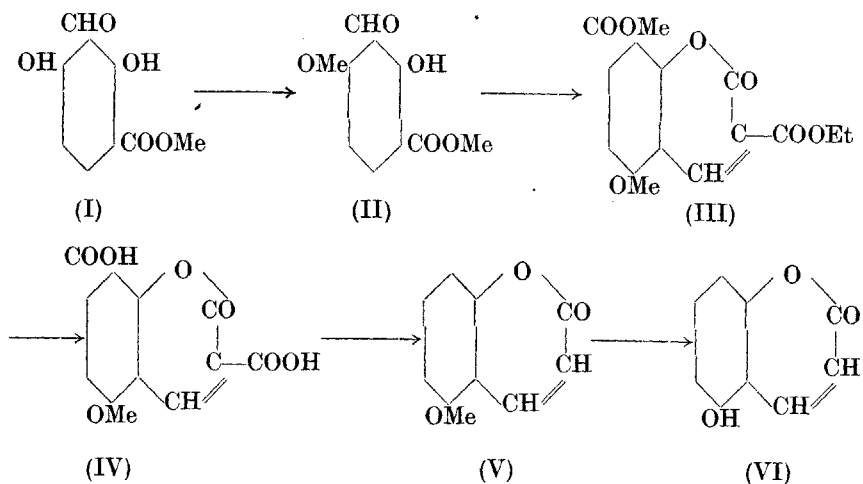
Thus the main points of interest with regard to the use of the new reagent are: (1) With less reactive phenols like monohydric phenols, aluminium chloride is a much more efficient condensing agent than sulphuric acid. (2) With phenolic esters and phenolic ketones, 5-hydroxy coumarin derivatives, which are otherwise difficultly accessible, are easily obtained, the other condensing agents like sulphuric acid or phosphoryl chloride giving 7-hydroxy-coumarin derivatives.



The Gattermann reaction on phenolic esters has provided another route to interesting coumarin derivatives. Methyl B-resorcyloate does not undergo the Gattermann reaction under the usual conditions, but under the modified conditions of Shah and Laiwalla (in the presence of aluminium chloride dissolved in dry ether), formylation smoothly takes place with the formation of the Y-resorcyloaldehyde derivative, methyl 2:4-dihydroxy-3-formyl benzoate (I),

the aldehyde group entering the usually inaccessible Y-position in the resorcinol nucleus (Shah and Laiwalla, *Current Science*, 1936, 5, 197; *J.C.S.*, 1939, 1828). The aldehyde ester (I) has been found to be a suitable intermediate for synthesis of several coumarin derivatives, through the Knoevenagel condensation with ethyl malonate, ethyl-aceto-acetate and cyanacetic acid.

The most interesting application of this method is the synthesis of the hitherto unknown 5-hydroxy coumarin. 5-hydroxy-4-methyl coumarins are now readily obtained by the aluminium chloride method of Sethna, Shah and Shah (*loc. cit.*) but this method is obviously inapplicable for the synthesis of 5-hydroxy coumarin. This has been synthesized from methyl-2 : 4-dihydroxy-3-formyl-benzoate (I) through the stages methyl 4-methoxy-2-hydroxy-3-formyl benzoate (II) *malonic ester* ethyl-5-methoxy-8-carbmethoxy-coumarin-3-carboxylate (III) \longrightarrow 5-methoxy-coumarin-3 : 8-dicarboxylic acid (IV) \longrightarrow 5-methoxy-coumarin (V) \longrightarrow 5-hydroxy coumarin (VI) (H. A. Shah and R. C. Shah, *Current Science*, 1938, 7, 107; *J.C.S.*, 1939, 1832).

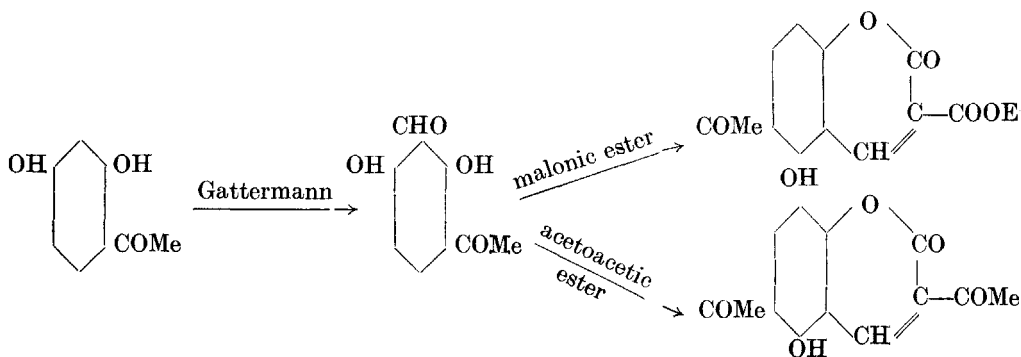


The modified Gattermann reaction above described is applicable also to polyhydroxy-phenolic ketones. In the case of resacetophenone, orsacetophenone and 2 : 4-dihydroxybenzophenone, in which the 3, i.e., the Y-position is free, formylation occurs in the 3-position (Shah and Shah, *Nature*, 1938, 142, 163). 5-Hydroxy-coumarin derivatives are obtainable from these 3-formyl-hydroxy-phenyl-ketones. Thus 2 : 4-dihydroxy-3-formyl-acetophenone by Knoevenagel condensation with malonic and aceto acetic esters affords ethyl 5-hydroxy-6-acetyl-coumarin-3-carboxylate and 5-hydroxy-3 : 6-diacetyl coumarin respectively. 7-Hydroxy-coumarin derivatives of the same type have been previously obtained by Weiss and Mercksammer (*Monatsch.*, 1928, 50, 115) and Weiss and Kratz (*ibid*, 1929, 51, 386) who prepared 7-hydroxy-3:

6-diacetyl coumarin and 7-hydroxy-6-acetyl-coumarin-3-carboxylic acid by condensing resacetophenone with ethyl ethoxy-methylene-acetoacetate and ethyl ethoxy-methylene-malonate respectively in the presence of sodium ethoxide.

2-Acetyl resorcinol by the Gattermann reaction gives 2 : 4-dihydroxy-3-acetyl-benzaldehyde from which 7-hydroxy-3 : 8-diacetyl coumarin and 7-hydroxy-8-acetyl-coumarin-3-carboxylic acid have been prepared through the Knoevenagel reaction.

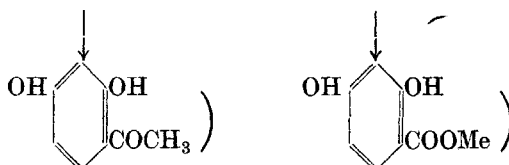
The synthesis of these hydroxy-formyl-phenyl-ketones, a class of compounds hitherto unknown, opens up various possibilities for the synthesis of heterocyclic compounds like furo-chromones, coumarino-chromones, etc., which are being explored.



The two apparently unconnected types of reactions referred to above, viz. the condensation of phenolic esters and ketones with β -ketonic esters in the presence of aluminium chloride to give 5-hydroxy-coumarin derivatives and the modified Gattermann reaction on phenolic esters and ketones to give 3-formyl derivatives, which have been serviceable for synthesis of some 5-hydroxy-coumarins, have a common theoretical basis. Both the phenomena, condensation in the first case and substitution in the second case at the 3- or Y-position, are due ultimately to the reactivity in the 3-, i.e. the Y-position in the resorcinol nucleus. This can be satisfactorily explained on the view that this is due to the stabilization of one of the Kekulé forms on account of chelation between the carbomethoxy or the acetyl group and the ortho-hydroxyl group.

The fixation of one of the Kekulé forms in the benzene nucleus was first suggested by Mills and Nixon (*J.C.S.*, 1930, 2510) in the case of compounds in which another ring is fused on to the benzene nucleus. Baker (*J.*, 1934, 1684) has explained the formation of 2 : 4-diacetyl-resorcinol from 4-O-acetyl resorcinol by assuming the stabilization of one of the Kekulé forms by chelation between the acetyl and the hydroxyl groups. It may be noted that Baker

suggests that aluminium chloride may prevent chelation, but the present experiments definitely show that aluminium chloride does not prevent chelation, and may even promote it. Further, as no case of 3-substitution in B-resorcylic acid or its ester was previously known, it has hitherto appeared that the chelation between the carbomethoxy group and the ortho-hydroxyl group in methyl B-resorcylate does not lead to a stabilization of one of the kekule forms (Baker, *loc. cit.*). The work on methyl B-resorcylate above referred to definitely points to the stabilization of one of the kekule forms under the experimental conditions.



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