ALUMINIUM CHLORIDE, A NEW REAGENT FOR THE CONденSATION OF β-KETONIC ESTERS WITH PHENOLS

Part V. The Condensation of Substituted Resacetophenones with Ethyl Acetoacetate

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In Part I of this series, one of the present authors (N. M. S.) with Sethna and Shah, R. C.,¹ has shown that resacetophenone condensed with ethyl acetoacetate in presence of anhydrous aluminium chloride with the formation of otherwise difficultly accessible 5-hydroxy-6-acetyl-4-methyl coumarin in good yield. In the subsequent parts, the investigation was extended to the similar condensation of other di-hydroxy- and tri-hydroxy-phenyl-ketones and also to various 4-acyl-resorcinols with ethyl acetoacetate; in all cases, whenever the reaction took place, the product obtained was found to be 5-hydroxy-6-acetyl-coumarin derivative (Shah, N. M., and Shah, R. C.²; Deliwala and Shah, N. M.³).

Recently Desai and Ekhlas⁴ have studied the condensation of some substituted resacetophenones with ethyl acetoacetate in presence of phosphorus oxychloride as the condensing agent.

The work described in this paper was undertaken with a view to ascertain the influence of constitutional factors in resacetophenone molecule on the course of the reaction with ethyl acetoacetate in presence of anhydrous aluminium chloride.

In this communication, the condensation of (1) 5-ethyl-, (2) 5-bromo-, (3) 5-nitro-, (4) 5-benzyl-, (5) ω-methoxy-resacetophenones, (6) methyl β-resacetophenone carboxylate, (7) 2:4-diacetyl-resorcinol, and (8) 4:6-diacetyl-resorcinol with ethyl acetoacetate with aluminium chloride as the condensing agent has been investigated.

5-Ethyl-resacetophenone (2:4-dihydroxy-5-ethyl-acetophenone) condenses with ethyl acetoacetate in presence of aluminium chloride in dry nitro-benzene solution at about 115°, giving 5-hydroxy-6-acetyl-8-ethyl-4-methyl coumarin.
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(I; \( X = C_2H_5 \)). The constitution (I; \( X = C_2H_5 \)) has been assigned to it as 

(a) it gives ferric chloride colour reaction, and dissolves in alkali with non-fluorescent yellow colour, characteristic of a 5-hydroxy-coumarin derivative; 

(b) on Clemmensen reduction, it gives 5-hydroxy-6:8-di-ethyl-4-methylcoumarin (III) identical with that of Mehta and Shah; 

(c) it is identical with 5-hydroxy-6-acetyl-8-ethyl-4-methyl coumarin obtained by Desai and Ekhlas, and 

(d) it gives on Kostanecki acetylation, the coumarino-chromone, 4:2'-di-methyl-3'-acetyl-6'-ethyl-chromono-7':8':6:5-\( \alpha \)-pyrone (II; \( X = C_2H_5 \); \( R = CO \cdot Me \)) identical with that of Desai and Ekhlas. It may be mentioned here that 5-ethyl-resacetophenone does not condense with acetoacetic ester in presence of sulphuric acid.

5-Bromo-resacetophenone on condensation with acetoacetic ester in presence of anhydrous aluminium chloride gave 5-hydroxy-6-acetyl-8-bromo-4-methylcoumarin (I; \( X = Br \)); its constitution rests on the following grounds: 

(i) it gives a positive ferric chloride test and dissolves in alkali giving non-fluorescent yellow colour characteristic of a 5-hydroxy-coumarin derivative, and 

(ii) it gives on Kostanecki acetylation, 4:2'-dimethyl-6'-bromo-chromono-7':8':6:5-\( \alpha \)-pyrone (II; \( X = Br \); \( R = H \)). 5-Bromo-resacetophenone does not condense either in presence of phosphorus oxychloride or sulphuric acid.

5-Benzyl-, 5-nitro-, \( \alpha \)-methoxy-resacetophenones as well as methyl \( \beta \)-resacetophenone carboxylate did not condense in spite of several attempts.

Owing to the close resemblance between \( \alpha \)-naphthol and resorcinol in undergoing the Pechmann reaction, the condensation of 4-acetyl- and 4-propionyl-\( \alpha \)-naphthols was studied in presence of aluminium chloride, but instead of the expected acyl-coumarin derivative, 4-methyl-1:2-\( \alpha \)-napththapyrone was obtained in both the cases, the acyl group being split off during the reaction. Desai and Ekhlas have found that the acyl group is eliminated even in presence of phosphorus oxychloride.

From the above results and those of Chakravarty, Desai, Limaye and their co-workers and Sethna, Shah, N. M., and Shah, R. C., and Deliwala
and Shah, it can be safely concluded that the condensing agents so far found efficient for effecting the condensation of 4-substituted resorcinol and derivatives are phosphorus oxychloride and aluminium chloride. Both are characteristic in their behaviour as condensing agents. Phosphorus oxychloride, if the reaction takes place, produces mainly 7-hydroxy-6-acyl-coumarins. It is a good substitute for sulphuric acid in cases where the acid fails. Aluminium chloride entirely changes the course of the condensation with the production of 5-hydroxy-6-acyl-coumarin derivatives, difficultly accessible by the hitherto-known methods.

It has been already pointed out by Shah, N. M., and Shah, R. C., that the above reactivity in 2-position of the resorcinol nucleus is explicable on the view of the fixation of double bonds of the benzene nucleus, the chelation between —OH and —CO. R (R = Me, Et, etc.) in 4-acyl-resorcinols bringing about that state in the presence of aluminium chloride. On the same view, the reactivity of the substituted resacetophenones studied here can also be explained.

The presence of negative groups like —NO₂, —CO—Me, —COOMe in the resacetophenone molecule has de-activating effect and therefore hinder the condensation; moreover, they introduce an additional chelating factor, which may also be responsible for the de-activation of the molecule:

But the introduction of the positive groups like —CH₃, —C₂H₅ has no such effect; hence the condensation in case of 5-ethyl-resacetophenone easily takes place. The introduction of ethyl group in 5-position of the resacetophenone molecule excludes the possibility of the 7-hydroxy-coumarin-formation. This also explains the formation of 5-hydroxy-coumarin even in presence of phosphorus oxychloride (Desai and Ekhlas).

5-Bromo-resacetophenone does not condense in presence of phosphorus oxychloride (Desai and Ekhlas) or sulphuric acid; while in presence of aluminium chloride, 5-hydroxy-6-acyl-coumarin derivative was obtained.
Phosphorus oxychloride has a little or no tendency to promote chelation; the possibility of 7-hydroxy-coumarin-formation is excluded as both 4- and 6-positions (considered as resorcinol molecule) are already substituted. In presence of aluminium chloride, the chelation between —OH and —COMe stabilises one of the Kekule forms by the fixation of double bonds. 4-Halo-geno-resorcinols are feebly chelated (Sidgwick\textsuperscript{10}) but such chelation cannot be dependent upon the electromeric transfer as halogen cannot increase number of its electrons, hence the reactivity in 2-position of the resorcinol molecule brings about the condensation with the subsequent 5-hydroxy-coumarin ring-formation.

Experimental

Condensation of 5-ethyl-resacetophenone with ethyl acetoacetate in presence of aluminium chloride: Formation of 5-hydroxy-6-acetyl-8-ethyl-4-methylcoumarin.—5-Ethyl-resacetophenone (3.8 g.: 1 mol.) prepared according to Shah, R. C., and Mehta (J. Univ. Bom., 1935, 4, 110) and ethyl acetoacetate (2.6 g.: 1 mol.) were added to the solution of aluminium chloride (5.6 g.: 2 mols.) dissolved in dry nitro-benzene (25 c.c.) and heated for one hour at 110–15\textdegree, keeping the temperature at 90\textdegree in the beginning. (Calcium chloride guard-tube.) HCl fumes were evolved. After HCl evolution was negligible, the reaction-mixture was cooled, ice and conc. HCl (10 c.c.) added and nitro-benzene steam-distilled off. The brown residue on crystallisation from alcohol gave needles, m.p. 168–69\textdegree (yield, 2 g.). Desai and Ekhlas also give the same melting point, which was not depressed on mixture with the above sample.

5-Hydroxy-6-acetyl-8-ethyl-4-methylcoumarin was reduced according to Clemmensen: the reduction product, 5-hydroxy-6:8-di-ethyl-4-methyl-coumarin obtained melted at 171\textdegree, after crystallisation from alcohol. It did not give any colour with alcoholic ferric chloride; it dissolved in alkali with deep yellow colour. It was identical in all respects with an authentic sample prepared by the Pechmann condensation of 4:6-di-ethyl-resorcinol with ethyl acetoacetate in presence of sulphuric acid, according to the method of Shah and Mehta.\textsuperscript{6}
5-Hydroxy-6-acetyl-8-ethyl-4-methylcoumarin (1 g.) was subjected to the Kostanecki reaction with acetic anhydride (8 c.c.) and fused sodium acetate (2 g.) by heating the mixture at 170-80° for ten hours. The chromono-coumarin obtained on working up the reaction-mixture in the usual manner crystallised from alcohol, needles, m.p. 173°, identical with the sample of Desai and Ekhas.4

Condensation of 5-bromo-resacetophenone with ethyl acetoacetate in presence of aluminium chloride: Formation of 5-hydroxy-6-acetyl-8-bromo-4-methyl coumarin.—5-Bromo-resacetophenone (5 g.: 1 mol.) prepared according to Desai and Ekhas,4 and ethyl acetoacetate (3 g.: 1 mol.) were added to aluminium chloride (5–5 g.: 2 mols.) in nitrobenzene (30 c.c.). The mixture protected from moisture (CaCl₂ guard-tube) was heated on oil-bath at 115-20° for one hour and finally to 130° till the evolution of HCl gas was negligible. After removal of nitro-benzene as before, the residue on crystallisation from alcohol gave needles, m.p. 208-10°; yield 1 g. (Found: Br, 27.17; C₁₂H₉O₄Br requires Br, 26.9 per cent.) The coumarin dissolves in alkali with deep yellow colour without any fluorescence and gives with ferric chloride deep cherry-red colour in alcoholic solution.

The acetyl derivative prepared by acetic anhydride in pyridine solution by heating for about 6 hours on water-bath crystallised from dilute alcohol, m.p. 150°. (Found: Br, 23.32; C₁₄H₁₁O₄Br requires Br, 23.6 per cent.)

The oxime crystallised from nitro-benzene in needles unmelted below 250°.

Kostanecki acetylation of 5-hydroxy-6-acetyl-8-bromo-4-methyl-coumarin: Formation of 4: 2'-dimethyl-6'-bromo-chromono-7': 8': 6: 5-α-pyrone.—The coumarin (1 g.), acetic anhydride (20 c.c.) and sodium acetate (2 g.) were reflexed at 170-80° for 10 hours. The cooled reaction-mixture was poured into water; the solid that separated was treated with Na₂CO₃ (5%) solution, washed with water and collected, and crystallised from dil. alcohol, granular crystals, m.p. 240-41° after shrinking. (Found: Br, 25.3; C₁₄H₉O₄Br requires Br, 24.92 per cent.) The chromono-α-pyrene did not give colouration with ferric chloride in alcoholic solution. It is sparingly soluble in dilute alkali solution.

Attempted condensation of 4-acyl-α-naphthol and other substituted resacetophenone derivatives.—We are thankful to Dr. R. D. Desai for the detailed information regarding the preparation of 4-acetyl-α-naphthol, recently published in these Proceedings.11
4-Acetyl-a-naphthol (3.5 g.) and ethyl acetoacetate (2.5 g.) were added to aluminium chloride (5.5 g.) in dry nitro-benzene (30 c.c.) and the mixture protected from moisture was heated at 100° for an hour. On working it up as in previous cases, the purified product obtained melted at 172°, the mixed melting point with an authentic sample of 4-methyl-1:2-a-naphtha-pyrone being undepressed. 4-Propionyl-a-naphthol on similar condensation also gave 4-methyl-1:2-a-naphtha-pyrone, the propionyl group being eliminated.

5-Nitro-resacetophenone, 5-benzyl-resacetophenone, ω-methoxy-resacetophenone, methyl-β-resacetophenone-carboxylate, 4:6-diacetyl-resorcinol and 2:4-diacetyl-resorcinol were tried but the condensation could not be affected, either the original ketone being recovered or tarry material being formed.

The work on the effect of α-substituent in acetoacetic ester on the course of the reaction is in progress.

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Summary

The condensation of acetoacetic ester with substituted resacetophenones in the presence of aluminium chloride has been investigated. 5-Ethyl-resacetophenone, 5-bromo-resacetophenone underwent the condensation giving the expected 5-hydroxy-6-acetyl-coumarin derivatives. 4-Acetyl-a-naphthol and 4-propionyl-a-naphthol underwent the condensation but the product obtained was found to be 4-methyl-1:2-a-naphtha-pyrone, the acyl group being split off during the condensation. Negative results were obtained with 5-nitro-resacetophenone, 5-benzyl-resacetophenone, ω-methoxy-resacetophenone, methyl-β-resacetophenone carboxylate, 4:6-diacetyl-resorcinol and 2:4-diacetyl-resorcinol. The results obtained have been explained; negative groups like —NO₂, —CO.Me, etc., hinder the reaction, while positive groups like —C₂H₅ have no de-activating effect on the course of the reaction.
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