HETEROCYCLIC COMPOUNDS

Part XVIII. Condensation of Cyclic-β-Ketonic Esters with Methyl-β-Resorcylate and Resacetophenone in Presence of Anhydrous Aluminium Chloride

BY R. D. DESAI, M. M. GAITONDE, S. MEHDI HASAN AND R. C. SHAH

(From the Department of Chemical Technology, Bombay University, and the Chemistry Departments of St. Xavier's College and Royal Institute of Science, Bombay)

Received September 30, 1946

7-HYDROXY-COUMARINS from various open-chain as well as cyclic β-ketonic esters and resacetophenone have been prepared by Desai and co-workers[1] using phosphorous oxychloride as the condensing agent, while 5-hydroxy coumarins have been prepared by Shah and co-workers[2] from open-chain β-ketonic esters and methyl β-resorcylate as well as resacetophenone using anhydrous aluminium chloride as the condensing agent. As the condensation of cyclic β-ketonic esters with methyl β-resorcylate has not been studied, we have studied this reaction in presence of various condensing agents. We have also studied the coumarin condensation between the cyclic β-ketonic esters and resacetophenone in presence of anhydrous aluminium chloride.

Methyl β-resorcylate condensed with ethyl cyclohexanone-2-carboxylate in presence of sulphuric acid, phosphorous oxychloride or aluminium chloride giving only one product which was found to be 7-hydroxy-6-carbomethoxy-3:4-cyclohexeno-coumarin. This result was quite surprising, as Shah and co-workers (*loc. cit.*) had invariably obtained the 5-hydroxy-coumarins from open-chain β-ketonic esters and methyl β-resorcylate in presence of anhydrous aluminium chloride.

Resacetophenone, on the other hand, condensed with ethyl cyclohexanone-2-carboxylate in the presence of anhydrous aluminium chloride giving 5-hydroxy-6-acetyl-3:4-cyclohexeno-coumarin, thus simulating the behaviour of open-chain β-ketonic esters.

Identical results were obtained from ethyl cyclopentanone-2-carboxylate and ethyl 4-methylcyclopentanone-2-carboxylate. 7-Hydroxy-6-acetyl-3:4-cyclohexeno-and cyclopenteno-coumarin have been already described by Chowdhry and Desai (*loc. cit.*) while 5-hydroxy-6-acetyl-3: 4-cyclo hexeno- and -cyclopenteno-coumarins are described in the body of this paper. In order to complete our observation and compare their properties, the

isomeric 7-hydroxy-8-acetyl-3:4-cyclohexeno- and cyclopenteno-coumarins have been synthesised by the Fries migration of 7-acetoxy-3:4-cyclohexeno- and cyclopenteno-coumarins.

Shah and co-workers (*loc. cit.*) have suggested the stabilisation of one of the kekule forms of the benzene ring in resacetophenone ard methyl β-resorcylate in virtue of the chelation between hydroxyl and acetyl as well as carbo-methoxy groups in order to explain the formation of 5-hydroxy coumarins. That the chelation does take place is amply borne out, not only by the work of Shah and co-workers[3] on coumarin condensations, and formylation of resorcinol derivatives, but also by the work of W. Baker and his co-workers[4] on distribution in resorcinol nucleus. The discrepancy noticed in this work regarding the inability of methyl β-resorcylate to give 5-hydroxy coumarins in presence of aluminium chloride leads us to the conclusion that the stabilisation of one of the kekule forms of the benzene ring due to chelation is of a transient or labile nature, in the case of this ester.

Experimental

(*A*) *Coumarins from ethyl cyclohexanone-2-carboxylate-7-hydroxy-6-carbomethoxy-3 : 4-cyclohexeno-coumarin.*—

(1) A solution of methyl β-resorcylate (2 g.) and the keto-ester (2 g.) in 73 per cent. sulphuric acid was kept in the refrigerator for two days, and poured into ice-cold water. The resulting solid was treated with dilute sodium bicarbonate solution to remove the acidic impurities, and the insoluble residue was crystallised from alcohol when colourless needles, m.p. 226°, were obtained (yield, 2·0 gm.).

(2) A mixture of the phenol ester (2 g.), keto-ester (2 g.) and phosphorous oxychloride (3·5 g.) was warmed on the water-bath for two hours. The residue was thrice extracted with benzene (25 c.c.) to remove the coumarin, and the solvent was removed from the combined extracts. The residue crystallised from alcohol in colourless needles, m.p. 226° (yield, 2·5 g.).

(3) A solution of the phenol ester (2 g.), keto-ester (2 g.) and anhydrous aluminium chloride (3·5 g.) in nitro-benzene (20 c.c.) was heated in oil-bath at 110–15° for two hours, and worked up as usual. The solid crystallised from alcohol in needles, m.p. 226°, undepressed by the sample prepared by methods (1) and (2) (yield, 2·5 gm.). Its alcoholic solution gave reddish violet coloration with ferric chloride, while its alkaline solution gave an intense blue fluorescence. (Found: C, 65·4; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·0%.)

The acetyl derivative prepared in the usual manner crystallised from alcohol in white needles, m.p. 185°. (Found: C, 64·7; H, 5·2. $C_{17}H_{16}O$ requires C, 64·6; H, 5·1%.)

7-Hydroxy-6-carboxy-3: 4-cyclohexeno-coumarin obtained by the cold alkaline hydrolysis of the above coumarin crystallised from alcohol in minute needles, m.p. 263° (Decomp.). The same coumarin could be obtained by condensing β-resorcylic acid with ethyl cyclo-bexanone-2-carboxylate in presence of 73 per cent. sulphuric acid. Its alcoholic solution gave brown-red coloration with ferric chloride. When heated above its m.p. (250–60°) for one hour, the acid decomposed giving 7-hydroxy-3: 4-cyclohexeno-coumarin, identified by comparison with an authentic specimen. (Found: C, 64·3; H, 4·6. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%.)

7-Hydroxy-8-acetyl-3: 4-cyclohexeno-coumarin was obtained by heating an intimate mixture of 7-acetoxy-3: 4-cyclohexene-coumarin (1 g.), anhydrous aluminium chloride (2 g.) at 140°–50° for one hour. It crystallised from alcohol in fine needles, m.p. 172°, and its alcoholic solution gave reddish violet coloration with ferric chloride. (Found: C, 69·6; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%.)

The *acetyl* derivative crystallised from alcohol in lustrous needles, m.p. 224°. (Found: C, 67·8; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%.)

5-Hydroxy-6-acetyl-3: 4-cyclohexeno-coumarin was prepared by heating the solution of resacetophenone (1·8 g.), the keto-ester (2 g.) and aluminium chloride (3·5 g.) in nitrobenzene (30 c.c.) at 110–15° for 1½ hours, and worked up as usual. The brown solid crystallised from alcohol in pale-yellow needles, m.p. 202° (yield, 2·5 g.). Its alkaline solution was yellow and non-fluorescent, while its alcoholic solution gave reddish-violet coloration with ferric chloride. (Found: C, 69·5; H, 5·2. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%.)

The *acetyl* derivative crystallised from alcohol in small needles, m.p. 124–25°. (Found: C, 68·1; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H., 5·3%.)

(*B*) *Coumarins from ethyl cyclopentanone-2-carboxylate 7-hydroxy-6-carbomethoxy-3 : 4-cyclo-penteno-coumarin* was obtained from methyl β-resorcylate (2 g.), ethylcyclopentanone carboxylate (2 g.) and 73 per cent. sulphuric acid (20 c.c.) (yield, 1·3 g.). It crystallised from alcohol in needles m.p. 223. The use of aluminium chloride or phosphorous oxychloride as a condensing agent gave the same coumarin. Its alcoholic solution gave faint violet coloration with ferric chloride. (Found : C, 64·2; H, 4·2. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%.)

The *acetyl* derivative crystallised from alcohol in lustrous needles, m.p. 182–83°. (Found: C, 63·4; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%.)

7-Hydroxy-6-carboxy-3: 4-cyclo-penteno-coumarin crystallised from alcohol in tiny needles, m.p. 261° (decomp.). Its alcoholic solution gave deep reddish violet coloration with ferric chloride. (Found: C, 63·2; H, 4·2. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%.)

On decarboxylation, the acid gave 7-hydroxy-3: 4-cyclo-penteno-coumarin, m.p. 242°, undepressed by comparison with an authentic specimen.

The *phenyl ester* was obtained by heating the coumarin acid (0·1 g.), phenol (2 g.) and acetic anhydride on sand-bath for three hours, and crystallised from alcohol in needles, m.p. 160–61°. (Found: C, 71·0; H, 4·5. $C_{19}H_{14}O_5$ requires C, 70·8, ; H, 4·3%.)

7-Hydroxy-8-acetyl-3: 4-cyclopenteno-coumarin was obtained by heating an intimate mixture of 7-acetoxy-3: 4-cyclopenteno-coumarin (1 g.), and aluminium chloride (2 g.) as usual, and crystallised from alcohol in needles, m.p. 154°. (Found: C, 68·6; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%.)

The *acetyl* derivative crystallised from alcohol in needles, m.p. 219–20°. (Found: C, 67·0; H, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%.)

7-Hydroxy-6-acetyl-3: 4-cyclopenteno-coumarin was obtained by heating a solution of resacetophenone (2 g.), the keto-ester (2 g.), and phosphorous oxychloride (2 c.c.) in dry benzene (20 c.c.), on water-bath for two hours. The benzene extract left a solid which crystallised from alcohol in clusters of needles, m.p. 247 (yield, 25 per cent.). Its alcoholic solution gave reddish violet coloration with ferric chloride. Its alkaline solution gave blue fluorescence. (Found: C, 68·5; H, 5·1. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%.)

The *acetyl derivative* crystallised from alcohol in needles, m.p. 162°. (Found: C, 66·8; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9.)

5-Hydroxy-6-acetyl-3: 4-cyclopenteno-coumarin was obtained from resacetophenone (2 g.), the keto-ester (2 g.), aluminium chloride (3·5 g.) and nitrobenzene (30 c.c.) in the usual manner and crystallised from benzene in pale-yellow needles, m.p. 192°. Its yellow alkaline solution was devoid of fluorescence. (Found: C, 68·5; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%.)

The *acetyl* derivative crystallised from alcohol in needles, m.p. 116–17°. (Found: C, 66·9; H, 5·2. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%.)

(*C*). *Coumarins from ethyl-4-methyl-cyclopentanone-2-carboxylate, 7-Hydroxy-6-carbo-methoxy-3 : 4-(4′-methyl-cyclopenteno-coumarin* obtained as usual from methyl β-resorcylate (2 g.). the keto-ester (2 g.) and 73 per cent. sulphuric acid (20 c.c.) crystallised from alcohol in needles, m.p. 168° (yield, 1·5 g.). (Found: C, 65·5; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·0%.)

The *acetyl* derivative crystallised from alcohol in needles, m.p. 132°. (Found: C, 64·5; H, 5·1. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%.)

7-Hydroxy-6-carboxy-3 : 4-(4-methyl-cyclopenteno)-coumarin prepared from β-resorcylic acid crystallised from alcohol in needles, m.p. 243–44° (decomp.). On decarboxylation, it gave 7-hydroxy-3 : 4-(4′-methyl cyclopenteno-coumarin, m.p. 176°. The alkaline solutions of the coumarin ester as well as the acid gave blue fluorescence, and their alcoholic solutions gave reddish violet coloration with ferric chloride. (Found: C, 64·4; H, 4·7. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%.)

8-Acetyl-7-hydroxy-3 : 4-(4′-methyl-cyclopenteno)-coumarin was obtained by heating the intimate mixture of 7-acetoxy-coumarin (1 gm.) and aluminium chloride (2 g.) as usual, and crystallised from alcohol in needles, m.p. 118° Its alcoholic solution gave reddish violet, coloration. (Found: C, 69·6; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%.)

The *acetyl* derivative crystallised from alcohol in needles, m.p. 182°. (Found: C, 67·9; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%.)

5-Hydroxy-8-acetyl-3 : 4-(4′-methyl-cyclopenteno)-coumarin was obtained from the keto-ester (2 g.), resacetophenone (2 g.), aluminium chloride (3·5) and nitrobenzene (30 c.c.) as usual, and crystallised from benzene in small needles, m.p. 154–55° (depressed to 123° by resacetophenone). Its yellow alkaline solution was non-fluorescent, while its alcoholic solution gave reddish violet coloration with ferric chloride. (Found : C, 69·5; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%.)

The *acetyl* derivative crystallised from dilute alcohol in needles, m.p. 69–70°. (Found: C, 68·1; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%.)

Summary

Coumarins have been prepared from ethyl-β-resorcylate and resacetophenone by condensing them with cylic β-ketonic esters like ethyl cyclohexanone-2-carboxylate, ethyl cyclo-pentanone-2-carboxylate and ethyl-4-methyl-cyclopentanone-2-carboxylate in presence of 73 per cent. sulphuric

acid, phosphorous oxychloride and anhydrous aluminium chloride as condensing agents. Only 7-hydroxy coumarins were obtained in the case of methyl β-resorcylate, while resacetophenone gave 7-hydroxy-coumarins in presence of phosphorous oxychloride, but 5-hydroxy coumarins with aluminium chloride.

References

1. Desai and co-workers .. *Proc. Ind. Acad. Sci.* (A), 1937, **5**, 277; **6**, 187; 1938, **8**, 1, 12.
2. Shah and co-workers .. *J. C. S.*, 1938, 228, 1066, 1414, 1939, 1250.
3. ———— .. *Ibid.*, 1938, 1828, 1939, 132, 949.
4. W. Baker and co-workers .. *Ibid.*, 1934, 1684, 1935, 479, 628, 1937.