CHAPTER V

STUDIES ON SYNTHESIS OF 7-HYDROXY-6-ACYLCOUMARINS

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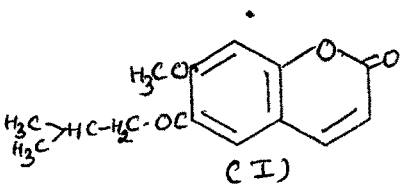
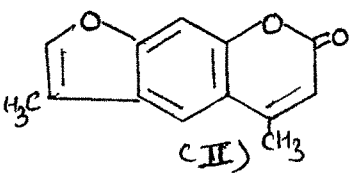
Studies on the synthesis of 7-hydroxy-6-acyl-coumarins

7-Hydroxy-6-acylcoumarins are found in nature. For example, Geijerin (I) isolated from the bark of Geijeria salicifolia is 7-methoxy-6-isovalerylcoumarin (I). Further, 7-hydroxy-6-acylcoumarins are intermediates for the synthesis of furocoumarins of psoralene group. Thus 3',4-dimethylpsoralene (II) is synthesised from 7-hydroxy-6-acetyl-4-methylcoumarin (2).

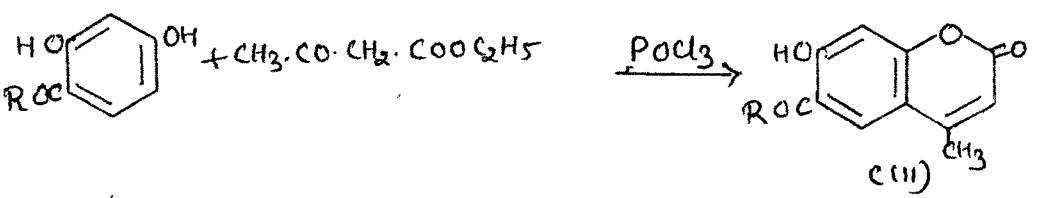


(I)



(II)

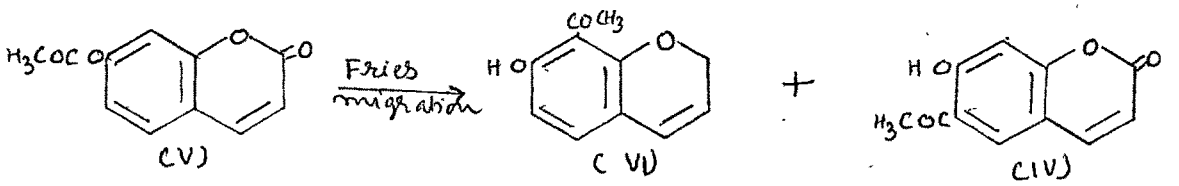
There is however no good general method available for the synthesis of 7-hydroxy-6-acylcoumarins though 7-hydroxy-6-acyl-4-methylcoumarins (III) can be synthesised by the Pechmann condensation of 4-acyl-resorcinols with ethyl acetoacetate in the presence of phosphorus oxychloride as the condensing agent (3).



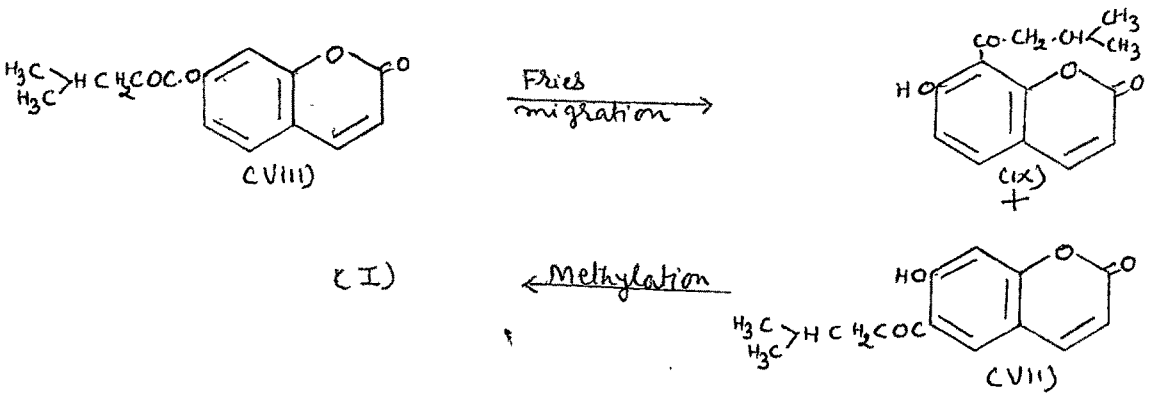
(III)

Agarwal and Dutt's (4) claim that they synthesised 7-hydroxy-6-acetylcoumarin (IV) by the condensation of resacetophenone with malic acid in the presenea of sulphuric acid was later disproved by Gaind Gupta and Ray (5) who found the work unrepeatable and showed that no condensation took place.

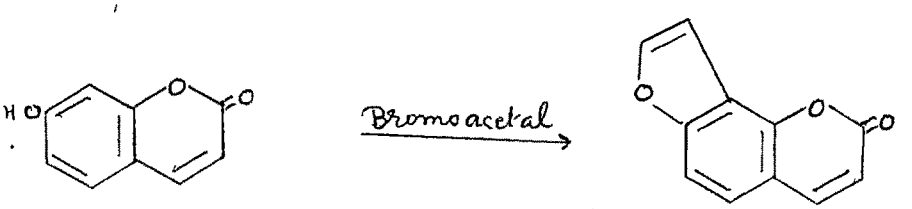
Limaye and Joshi (6) carried out the Fries migration of 7-acetoxycoumarin (V) and obtained 7-hydroxy-6-acetylcoumarin (IV) in very poor yield, the 8-isomer (VI) being obtained in a preponderating yield.



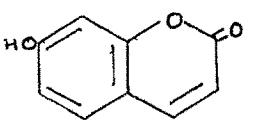
That this method is unsuitable as a general method for the synthesis of 7-hydroxy-6-acylcoumarins which is also illustrated by the work of Shah et al.(7) who found in their synthesis of Geijerin (I) that the yield of 7-hydroxy-6-isovalerylcoumarin(VII) in the Fries migration of 7-isovaleryloxycoumarin(VIII) was only 0.1 g. from 22.5 g. of the ester, whereas the yield of the 8-isomer(IX) was 2 g. for 11 g. of the ester.



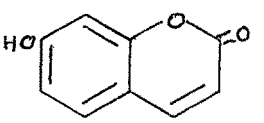
Rangaswami and Seshadri (17) explained the reactivity of 7-hydroxycoumarin derivatives on the theory of the fixation of the double bonds. They state that though in coumarin itself substitution invariably takes place in the 6-position, in the 7-hydroxycoumarins it is exclusively in the 8-position. When attempts are made to build up a fresh ring starting with 7-hydroxycoumarin, it is the 8-position that is involved in the ring formation. Thus employing 7-hydroxycoumarin and bromoacetal Spath and Pailor (18) obtained the angular compound angelicin.



Again attempts to introduce a formyl group into 7-hydroxycoumarin gave the 8-formylcoumarin. All these show that 7-hydroxycoumarins react in the form (A).



(A)



(B)

Further evidence for this structure comes from the work of Baker and Lothian (19) who found that 7-allyloxy-4-methylcoumarin undergoes Claisen transformation to 7-hydroxy-8-allyl-4-methylcoumarin thus proving conclusively that there exists a double bond between the 7 and 8 positions.

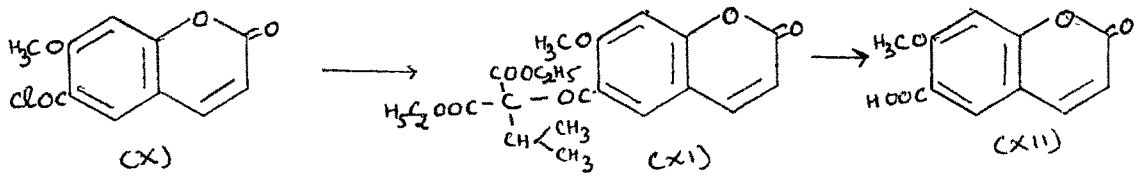
Evidence which does not fall into line with the above was first obtained by Limaye and Gangal (2)) who found that when 7-acetoxy-4-methylcoumarin was subjected to Fries migration, the 8-acetyl derivative was the major product but it was accompanied by a small quantity of the 6-acetyl isomer. The simultaneous formation of the angular coumarino-α-pyrone and the linear isomer from the Pechmann condensation between 7-hydroxycoumarin and malic acid (20) corroborates the above observation and shows the slight but significant reactivity of the 6-position in this compound. These authors applied Fieser's technique to the coumarin ring system and obtained unequivocal evidence on the distribution of the single and double bonds. They (21) found that 7-hydroxy-4,8-dimethylcoumarin coupled with diazotised p-nitraniline and formed with mercuric acetate a mercury derivative which contained two acetoxymercuri groups replacable by bromine atoms. The allyl ether and the acetyl derivative also smoothly underwent the Claisen transformation and Fries migration respectively. In structure (A) the carbon atom

7 which carries the hydroxyl group is attached by means of a double bond to the carbon atom 8. Therefore, the position 8 will be more reactive than the position 6. In structure (B) for the same reason the position 6 will be more reactive than the position 8. All these reactions can be explained only on the assumption of a reactive 6-position which is possible only if the bonds can take up positions as depicted in structure (B). Thus in coumarins while the normal structure corresponds to (A) the other is not precluded. Thus the double bond fixation theory does not satisfactorily account for all the recorded observations, if this fixation is taken to be rigid.

The theory of Resonance as put forward by Pauling and coworkers (22 and 23) seems to eliminate this difficulty. According to this theory, the actual structure of coumarin can neither be (A) nor (B), but some intermediate between the two. If (A) is of materially lower energy than (B), the actual structure will resemble more closely to the structure of the lower energy (A). Since the structure with a double bond common to both the rings possesses lower energy (due to less distortion of valency bonds) the actual structure will resemble more the structure (A) and hence the reactivity will be manifested according to the structure (A) and the 6-position will be less reactive than the 8-position.

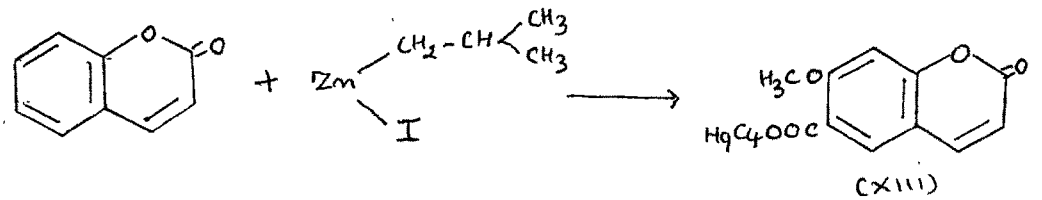
Kumar, Ram and Ray (8) in their attempt to synthesise oreoselone, tried different approaches for the synthesis of 7-hydroxy-6-acylcoumarins. They first carried out the Fries migration of 7-isovaleryloxycoumarin (VIII) and obtained 7-hydroxy-8-isovalerylcoumarin(IX) along with a little of the 6-isomer (VII) but they did not report the melting point of the latter.

They then tried the condensation of acid chloride of 7-methoxy-6-carboxycoumarin (X) with ethyl sodio isopropyl malonate under pressure and obtained a product (XI) which could not be hydrolysed to 7-methoxy-6-isovalerylcoumarin but gave only 7-methoxy-6-carboxycoumarin (XII) under all conditions tried.



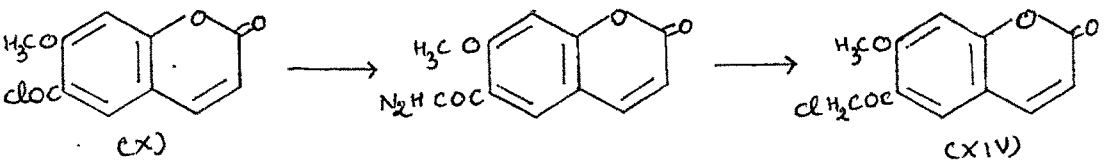
(X) (XI) (XII)

They also tried the condensation of acid chloride of 7-methoxy-6-carboxycoumarin with isobutyl zinc iodide and obtained only an impure sample of isobutyl ester of 7-methoxy-6-carboxycoumarin (XIII).



(XIII)

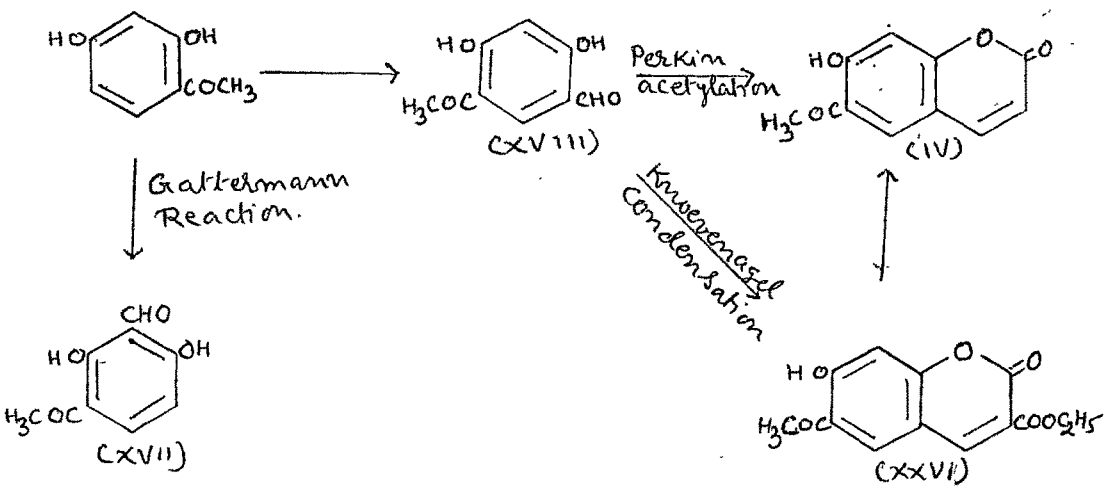
Bruchhausen and Hoffmann (9) in their synthesis of oreoselone, prepared 7-methoxy-6-chloroacetylcoumarin (XIV) by condensing the acid chloride of 7-methoxy-6-carboxycoumarin with diazomethane followed by boiling with fuming hydrochloric acid in acetic acid.



Parekh and Thakor (10) carried out the Friedel-Crafts acetylation of 7-hydroxy-4-methylcoumarin (XV) and obtained 7-hydroxy-8-acetyl-4-methylcoumarin (XVI), the 6-isomer was not obtained .

The present work deals with three approaches to the synthesis of 7-hydroxy-6-acylcoumarins, none of which has however yielded the desired products.

(1) Attempt was made to see if 7-hydroxy-6-acetylcoumarin could be synthesised according to the following scheme:

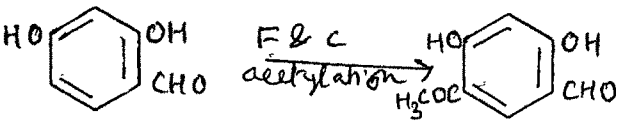


It was observed by Shah and Shah (11) that resacetophenone on Gattermann formylation gives 2,4-dihydroxy-3-formylacetophenone (XVII). Attempts were made to see if the isomeric product 2,4-dihydroxy-5-formylacetophenone (XVIII) could be synthesised by the other formylation methods.

Resacetophenone when subjected to Reimer-Tiemann reaction gave a polymeric product under various conditions, which did not melt upto 360°. When resacetophenone was subjected to the action of hexamine a yellow nitrogenous product was obtained which did not melt upto 360° and which could not be hydrolysed with acids. In the formylation of resacetophenone with N-methylformanilide and phosphorus oxychloride only resacetophenone was obtained back.

Attempts were then made to see if the product (XVIII) could be obtained by the Friedel-Crafts

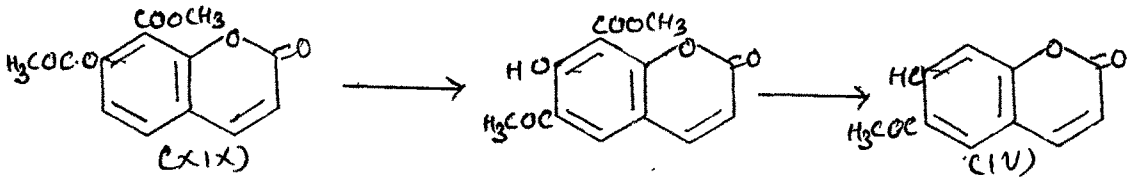
acetylation of β-resorcylaldehyde.



When β-resorcylaldehyde was subjected to Friedel-Craft acetylation, only a complex product which did not melt till 360° was obtained, even on keeping the reaction mixture at room temperature.

(2) Fries migration of 7-acetoxy-8-carbomethoxy-4-methylcoumarin : Attempted synthesis of 7-hydroxy-6-acetyl-8-carbomethoxy-4-methylcoumarin

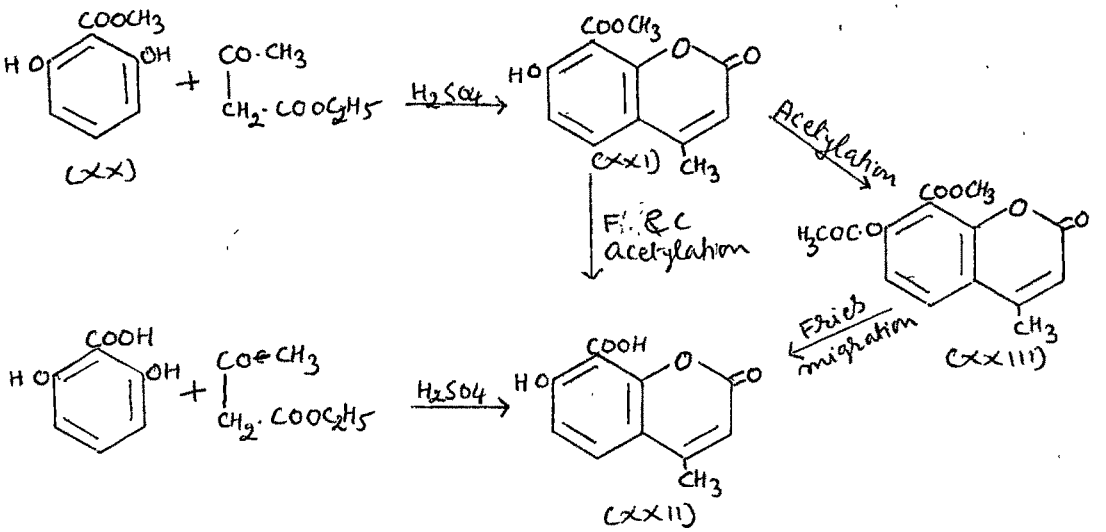
Limaye and Joshi (6) as stated before carried out the Fries migration of 7-acetoxycoumarin and obtained 7-hydroxy-8-acetyl-and 7-hydroxy-6-acetylcoumarin. It was thought of interest to see if the migration could take place in the 6-position when the 8-position was blocked with a carbomethoxy group (XIX). The required 7-hydroxy-6-acetyl-coumarin (IV) could then be obtained after hydrolysis and decarboxylation as shown below in case the migration took place.



As 7-hydroxy-8-carbomethoxycoumarin is difficult to obtain the reaction was studied with the more readily available 7-hydroxy-8-carbomethoxy-4-methylcoumarin.

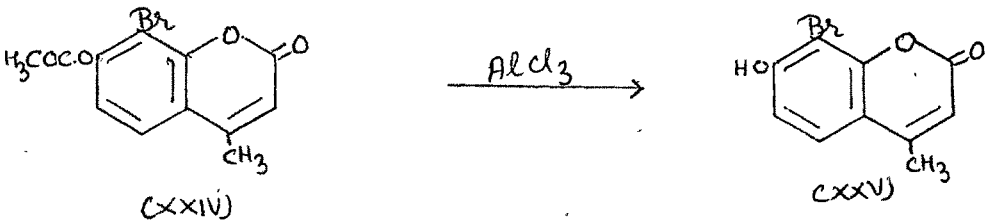
Methyl-γ-resorcylate (XX) on Pechmann condensation with ethyl acetoacetate gave 7-hydroxy-8-carbomethoxy-4-methylcoumarin (XXI) and 7-hydroxy-4-methylcoumarin-8-carboxylic acid (XXII). The former was converted into 7-acetoxy-8-carbomethoxy-4-methylcoumarin (XXIII). On Fries rearrangement under different experimental conditions it gave 7-hydroxy-4-methylcoumarin-8-carboxylic acid (XXII).

As attempts to carry out the Fries migration of 7-acetoxy-8-carbomethoxy-4-methylcoumarin were unsuccessful, Friedel-Crafts acetylation of 7-hydroxy-8-carbomethoxy-4-methylcoumarin was next tried. But once again 7-hydroxy-4-methylcoumarin-8-carboxylic acid was the only isolable product under different experimental conditions.



Fries migration of 7-acetoxy-8-bromo-4-methylcoumarin

Fries migration of 7-acetoxy-8-bromo-4-methylcoumarin (XXIV) was then tried. In this case also deacetylated product (XXV) was obtained.

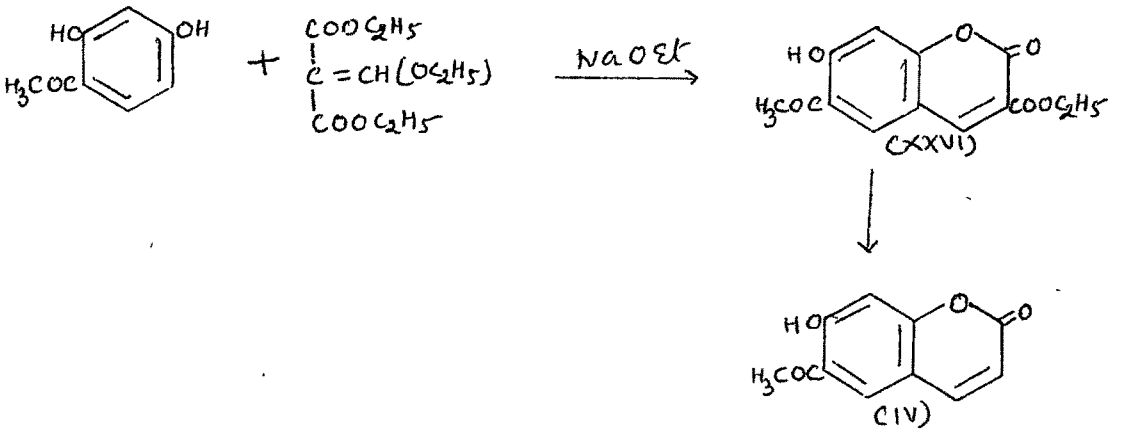


(XXIV) (XXV)

Friedel-Crafts acetylation of 7-hydroxy-8-bromo-4-methylcoumarin also failed.

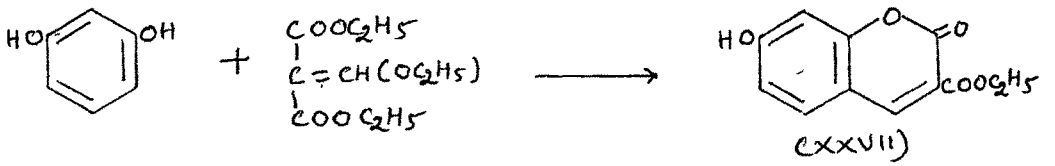
(3) Attempted condensation of resacetophenone with diethyl ethoxymethylenemalonate in the presence of sodium ethoxide

Weiss and Woldich (12) condensed resacetophenone with ethyl ethoxymethylene acetoacetate in the presence of sodium ethoxide and obtained a product which later on was found to be 7-hydroxy-3,6-diacetylcoumarin by Weiss and Merksammer (13). It was thought of interest to condense resacetophenone with diethyl ethoxymethylene-malonate in the presence of sodium ethoxide to obtain 7-hydroxy-6-acetyl-3-carboethoxycoumarin (XXVI) which when hydrolysed and decarboxylated would furnish the desired 7-hydroxy-6-acetylcoumarin. Resacetophenone however did not condense with diethyl ethoxymethylene malonate and only unreacted resacetophenone was obtained.



Attempted thermal condensation of resacetophenone with diethyl ethoxymethylene malonate in diphenyl ether

Mentzer and his coworkers (14) observed that reactive phenols such as resorcinol and pholoroglucinol when condensed with diethyl ethoxymethylene malonate at 190-210° for 3.5 hr. gave the corresponding 3-carboethoxy-coumarin (XXVII) in good yield.



When resacetophenone was refluxed with diethyl ethoxymethylene malonate for 8 hr. in diphenyl ether only unchanged resacetophenone was obtained.

EXPERIMENTAL

Attempted formylation of resacetophenone by Reimer-Tiemann method

Resacetophenone (10 g.) dissolved in sodium hydroxide solution (100 ml.; 10 %) was refluxed with chloroform (30 ml.) on a steam bath for 8 hr. Excess of chloroform was distilled off. The product obtained on acidification with hydrochloric acid melted above 360°.

Attempted formylation of resacetophenone with hexamine

Resacetophenone (10 g.) hexamine (20 g.) and acetic acid were heated on a sand bath for 10 hr. Dilute hydrochloric acid (100 ml ; 1:1) was then added and the reaction mixture was heated on a steam bath for another 5 hr. On cooling, a yellow product separated which did not melt on spatula. The filtrate was extracted with ether. The product obtained on removal of ether did not crystallise from any solvent. It did not melt till 360°.

Attempted formylation of resacetophenone with N-methylformanilide and phosphorus oxychloride

To resacetophenone (5 g.) dissolved in chlorobenzene (20 ml.) N-methylformanilide (12 ml.) and phosphorus oxychloride (5 ml.) were added and the reaction mixture was heated on a steam bath for 1 hr. with intermittant shaking. Water was then added and the reaction mixture was steam distilled to remove chlorobenzene. The product obtained gave m.p.140° and was found to be

resacetophenone.

Attempted Friedel-Crafts acetylation of β-resorcylaldehyde

β-Resorcylaldehyde (2.75 g. ; 0.02 mole) and acetic anhydride (2.04 g. ; 0.02 mole) in nitrobenzene (20 ml.) were heated with anhydrous aluminium chloride (2.6 g. ; 0.02 mole) in nitrobenzene (15 ml.) on a steam bath for 3 to 4 hr. On working up as usual a product was obtained which was difficult to crystallise from any solvent and did not melt on spatula. The same amorphus product was obtained when the reaction mixture was kept at room temperature for 24 hr.

Attempted condensation of resacetophenone with diethyl ethoxy methylene malonate in the presence of sodium ethoxide

Resacetophenone (3.04 g. ; 0.02 mole) sodium (0.46 g. ; 0.02 mole) dissolved in absolute alcohol (30 ml.) and diethyl ethoxymethylene malonate (4.5 g. ; 0.02 mole) were heated on a steam bath for 3 hr. On acidification with hydrochloric acid, only unchanged resacetophenone was obtained.

Attempted thermal condensation of resacetophenone with diethyl ethoxymethylene malonate in diphenyl ether

Resacetophenone (3.04 g. ; 0.02 mole) diethyl ethoxy methylene malonate (4.5 g. ; 0.02 mole) and diphenyl ether (25 ml.) were heated under reflux for 8 hr. in a flask fitted with a short air condenser which allowed alcohol to escape. On cooling, no product separated so the diphenyl

ether was steam distilled. The product which separated after steam distillation was found to be resacetophenone.

Condensation of methyl-γ-resorcylate with ethyl acetoacetate in the presence of sulphuric acid

Methyl-γ-resorcylate (5 g. ; 0.03 mole) ethyl acetoacetate (3.9 g. ; 0.03 mole) and concentrated sulphuric acid (25 ml.) were mixed with external cooling and left over night. Next day the mixture was added to crushed ice and filtered. The product obtained was treated with sodium hydrogen carbonate solution and filtered. The residue crystallised from alcohol in colourless needles, m.p. 231-32°. Yield 3.0 g.

Analysis :

4.726 mg. of the substance gave 10.6 mg. of carbon dioxide and 1.94 mg. of water.

Found : C = 61.21 % ; H = 4.60 %.

$C_{12}H_{10}O_5$ requires : C = 61.5 % ; H = 4.3 %.

The filtrate on acidification gave a product which crystallised from acetic acid m.p. 261-62°. Yield 0.8 g. Mixed m.p. with an authentic specimen of 7-hydroxy-4-methylcoumarin-8-carboxylic acid prepared according to Limaye and Kulkarni (15) was not depressed.

7-Acetoxy-8-carbomethoxy-4-methylcoumarin

A mixture of 7-hydroxy-8-carbomethoxy-4-methyl coumarin (1 g.) acetic anhydride (1 ml.) and pyridine (0.5 ml.) were heated on a steam bath for 4 hr. The reaction mixture was then added to dilute hydrochloric acid and

filtered. The product crystallised from alcohol in colourless needles, m.p. 150°. Yield 0.8 g.

Analysis :

5.08 mg. of the substance gave 11.27 mg. of carbon dioxide and 1.99 mg. of water.

Found : C = 60.56 % ; H = 4.39 %.

$C_{14}H_{12}O_6$ requires : C = 60.90 % ; H = 4.30 %.

Fries migration of 7-acetoxy-8-carbomethoxy-4-methylcoumarin

7-Acetoxy-8-carbomethoxy-4-methylcoumarin (2.7 g. ; 0.01 mole) and anhydrous aluminium chloride (1.32 g. ; 0.01 mole) were thoroughly mixed and the mixture was heated in an oil bath at 150-55° for 3 hr. The product obtained on working up as usual crystallised from acetic acid, m.p. 261-62°. Mixed m.p. with an authentic specimen of 7-hydroxy-4-methylcoumarin-8-carboxylic acid prepared as above was not depressed.

Friedel-Crafts acetylation of 7-hydroxy-8-carbomethoxy-4-methylcoumarin

7-Hydroxy-8-carbomethoxy-4-methylcoumarin (2.34 g. ; 0.01 mole) acetic anhydride (1.02 g. ; 0.01 mole) and anhydrous aluminium chloride (1.32 g.; 0.01 mole) were heated in an oil bath at 120° for 3 hr. The product obtained on working up as usual crystallised from acetic acid, m.p. 261-62°. Mixed m.p. with an authentic specimen prepared as above was not depressed.

7-Acetoxy-8-bromo-4-methylcoumarin

A mixture of 7-hydroxy-8-bromo-4-methylcoumarin (1 g.) (16), acetic anhydride (1 ml.) and pyridine (0.5 ml.) was heated on a steam bath for 4 hr. The reaction mixture was then added to dilute hydrochloric acid. The product crystallised from acetic acid in long needles, m.p. 185°. Yield 0.7 g.

Analysis :

4.018 mg. of the substance gave 7.09 mg. of carbon dioxide and 1.078 mg. of water.

14.132 mg. of the same substance gave 8.292 mg. of silver bromide.

Found : C = 48.17 % ; H = 3.00% ; Br = 27.98 %.

$C_{12}H_9O_4Br$ requires : C = 48.48 % ; H = 3.03% ; Br = 27.84 %.

Fries migration of 7-acetoxy-8-bromo-4-methyl coumarin

7-Acetoxy-8-bromo-4-methylcoumarin (2.97 g.; 0.01 mole) and anhydrous aluminium chloride (1.32 g. ; 0.01 mole) were thoroughly mixed and the mixture was then heated in an oil bath at 140° for 2 hr. The product obtained on working up as usual crystallised from acetic acid, m.p.255°. Mixed m.p. with an authentic specimen of 7-hydroxy-8-bromo-4-methylcoumarin was not depressed.

Friedel-Crafts acetylation of 7-hydroxy-8-bromo-4-methylcoumarin

7-Hydroxy-8-bromo-4-methylcoumarin (2.55 g.; 0.01 mole), acetic anhydride (1.02 g. ; 0.01 mole) and

anhydrous aluminium chloride (1.32 g. ; 0.01 mole) were heated in an oil bath at 160° for 3 hr. The product obtained on working up as usual crystallised from acetic acid m.p. 255°. Mixed m.p. with an authentic sample of 7-hydroxy-8-bromo-4-methylcoumarin was not depressed.

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