SUMMARY

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Benzo-α-pyrones or coumarins are substances of interest because of their occurrence in nature, their varied biochemical properties, industrial uses and analytical applications.

The present work consists of (i) some studies on alkyl coumarins viz. 4,6-dimethyl-, 4,7-dimethyl-, 7-methyl- and 6-methylcoumarin ; (ii) synthesis of some coumarino-α-pyrones and furocoumarins and (iii) studies on 3-(4'-hydroxyphenyl)coumarin.

Chapter I. General Introduction :

The previous work on substitution in various coumarins is reviewed briefly to show the pattern of substitution in the coumarin ring system.

Chapter II. Some studies on alkyl coumarins :

The studies on alkyl coumarins are fewer compared to the studies on hydroxycoumarins. It was therefore thought of interest to study some reactions on alkyl coumarins.

Chloromethylation of 4,6-dimethyl- and 4,7-dimethylcoumarin has been studied. 4,6-Dimethylcoumarin on chloromethylation with paraformaldehyde in acetic acid using zinc chloride as the catalyst at 70° gave the 3-chloromethyl derivative which on reduction with zinc and hydrochloric acid gave the known 3,4,6-trimethylcoumarin.

This 3-chloromethylcoumarin on condensation with morpholine and dimethyl amine gave the 3-morpholinomethyl- and the 3-dimethylaminomethylcoumarin. On Sommelet reaction, the chloromethyl derivative did not give the desired 3-formyl derivative. 4,6-Dimethyl-3-chloromethylcoumarin on condensation with alcoholic potassium cyanide gave 4,6-dimethyl-3-cyanomethylcoumarin which on hydrolysis with 70 % sulphuric acid gave 4,6-dimethylcoumarin-3-acetic acid. Attempt was then made to condense the ethyl ester of this acid with salicylaldehyde in the presence of piperidine, to synthesise 4,6-dimethyl-3,3'-bicoumariryl but the condensation did not take place.

4,7-Dimethylcoumarin on chloromethylation with paraformaldehyde in acetic acid using zinc chloride as catalyst gave the 3-chloromethylcoumarin which on reduction afforded the known 3,4,7-trimethylcoumarin. On condensation with morpholine and dimethyl amine the chloromethylcoumarin gave the 3-morpholinomethyl and 3-dimethylaminomethylcoumarin. In this case also the formyl derivative was not obtained on reacting the chloromethylcoumarin with hexamine.

The 3-chloromethylcoumarin on condensation with alcoholic potassium cyanide gave the 3-cyanomethylcoumarin which was hydrolysed to the corresponding acid with 70 % sulphuric acid. The synthesis of 4,7-dimethyl-3,3'-bicoumariryl by the condensation of the ethyl ester of this acid with salicylaldehyde was attempted but no condensation took place and the original coumarin was obtained back.

This study was further extended to some bromo methylcoumarins, viz. 4-methyl-6-bromomethyl-, 4-methyl-7-bromomethyl-, 7-bromomethyl- and 6-bromomethylcoumarin prepared by the action of N-bromo succinimide on 4,6-dimethyl-, 4,7-dimethyl-, 7-methyl- and 6-methylcoumarin respectively.

These bromomethylcoumarins were converted into the corresponding acetoxymethylcoumarins by heating with acetic anhydride and fused sodium acetate. Mannich bases have been prepared from 4-methyl-6-bromomethyl- and 4-methyl-7-bromomethylcoumarin by the condensation with morpholine and dimethyl amine.

On Sommelet reaction with hexamine in acetic acid, 4-methyl-6-bromomethyl-, 4-methyl-7-bromomethyl-, 7-bromomethyl- and 6-bromomethylcoumarin gave 4-methyl-6-formyl-, 4-methyl-7-formyl-, 7-formyl- and 6-formyl coumarin respectively. These formyl coumarins on Perkin acetylation with fused sodium acetate and acetic anhydride gave the corresponding β-coumarinyl acrylic acids.

4-Methyl-6-formyl-, 4-methyl-7-formyl- and 7-formylcoumarin have been condensed with hippuric acid in the presence of acetic anhydride and sodium acetate and 4-(4'-methyl-6'-coumarinal)-2-phenyl-5-oxazolone, 4-(4'-methyl-7'-coumarinal)-2-phenyl-5-oxazolone and 4-(7'-coumarinal)-2-phenyl-5-oxazolone obtained. These oxazolones were converted into β-(4-methyl-6-coumarinyl) alanine, β-(4-methyl-7-coumarinyl)alanine and β-(7-coumarinyl)alanine, by the action of red phosphorus

and hydriodic acid.

The condensation of 4-methyl-6-formyl-. 4-methyl-7-formyl-. 7-formyl- and 6-formylcoumarin with o-hydroxy acetophenone in the presence of alcoholic potassium hydroxide gave β-(4-methyl-6-coumarinyl)vinyl-o-hydroxy-phenyl ketone, β-(4-methyl-7-coumarinyl)vinyl-o-hydroxy-phenyl ketone, β-(7-coumarinyl)vinyl-o-hydroxy phenyl ketone and β-(6-coumarinyl)vinyl-o-hydroxy phenyl ketone respectively.

These ketones afforded the corresponding acetoxy derivatives indicating that the hydroxy group was free. The hydroxy ketones on refluxing with selenium dioxide in iso-amyl alcohol gave 4-methyl-6-(2'-chromonyl)coumarin, 4-methyl-7-(2'-chromonyl)coumarin ,7-(2'-chromonyl)coumarin and 6-(2'-chromonyl)coumarin.

Chapter III . Synthesis of some coumarino-α-pyrones and furocoumarins :

It was thought of interest to further exploit the synthetic possibilities of 7-formylcoumarins.

7-Formylcoumarin on Elbs persulphate oxidation gave 6-hydroxy-7-formylcoumarin. This was subjected to Perkin acetylation with a view to synthesise coumarino (6',5'; 6,7)α-pyrone but this was unsuccessful. Only a polymeric product was obtained.

Attempt was then made to synthesise the above mentioned coumarino-α-pyrone by Knoevenagel reaction on 6-hydroxy-7-formylcoumarin. This hydroxy formylcoumarin

with diethyl malonate in the presence of piperidine gave 3'-carbethoxycoumarino(6',5':6,7)α-pyrone. Since the yield of 6-hydroxy-7-formylcoumarin was very poor, the hydrolysis and decarboxylation could not be attempted.

Attempt was then made to synthesise 4-methyl-coumarino-(6',5':6,7)α-pyrone from 4-methyl-7-formyl-coumarin. This formyl coumarin on Elbs persulphate oxidation gave 6-hydroxy-4-methyl-7-formylcoumarin which was then condensed with diethylmalonate in the presence of piperidine. 3'-Carbethoxy-4-methylcoumarino(6',5':6,7) α-pyrone thus obtained was hydrolysed with 5 % sodium hydroxide solution to 3'-carboxy-4-methylcoumarino(6',5':6,7) α-pyrone. Decarboxylation of this acid could not be attempted because of the low yield of the hydroxy formyl coumarin.

The synthesis of furo(5',4':6,7)coumarin was then tried from 6-hydroxy-7-formylcoumarin. This hydroxy formyl coumarin on condensation with ethyl bromomalonate afforded 3'-carbethoxy furo(5',4':6,7)coumarin. The hydrolysis and decarboxylation could not be achieved because of the low yield of 6-hydroxy-7-formylcoumarin. However, the synthesis of 4-methylfuro(5',4':6,7)coumarin was achieved from 6-hydroxy-4-methyl-7-formylcoumarin. This on condensation with ethyl bromoacetate gave 6-carbethoxymethoxy-7-formyl-coumarin which was then hydrolysed with 5% sodium hydroxide solution to the corresponding acid. This acid was cyclised by refluxing with acetic anhydride and fused sodium acetate

and obtained 2'-carboxy-4-methylfuro(5',4':6,7)coumarin obtained which on decarboxylation with copper bronze and quinoline gave 4-methylfuro(5',4':6,7)coumarin.

Chapter IV. Studies on 3-(4'-hydroxyphenyl)coumarin :

Several studies have been reported on the substitution and building up of heterocyclic rings on hydroxy coumarins in which the hydroxyl group is in the benzenoid part of the α-pyrone ring, but the studies on 3-(4'-hydroxyphenyl)coumarin in which the hydroxyl group is in the side phenyl unit are comparatively fewer. So it was thought of interest to carry out some studies on this molecule.

3-(4'-Hydroxyphenyl)coumarin, on formylation with hexamine in acetic acid gave 3-(4'-hydroxy-3'-formylphenyl) coumarin. This was then subjected to Perkin acetylation with acetic anhydride and fused sodium acetate and 3,6'-bicoumarinyl obtained. This is an unsymmetrical bicoumarinyl in which the heterocyclic unit of one coumarin is linked to the benzenoid part of another coumarin unit. The interest in unsymmetrical bicoumarinyls has increased in recent years due to the isolation of some unsymmetrical bicoumarinyls from plants and there are only a couple of references to the synthesis of such unsymmetrical bi-coumarinyls.

3-(4'-Hydroxy-3'-formylphenyl)coumarin was condensed with ethyl bromoacetate in acetone in the presence of anhydrous potassium carbonate when 3-(4'-carbethoxy-

methoxy-3'-formyl phenyl)coumarin was obtained . This was then hydrolysed with sodium hydroxide to 3-(4'-carboxy-methoxy-3'-formyl phenyl)coumarin which was then cyclised by refluxing with acetic anhydride and fused sodium acetate to 3-(5'-benzofuranyl)coumarin.

3-(4'-Acetoxyphenyl)coumarin, on Fries rearrangement with anhydrous aluminium chloride, yielded 3-(4'-hydroxy-3'-acetyl phenyl)coumarin. This was also condensed with ethyl bromoacetate and the ester thus obtained was hydrolysed to 3-(4'-carboxymethoxy-3'-acetyl phenyl)coumarin. The cyclisation of this acid was carried out by refluxing it with acetic anhydride and fused sodium acetate and 3-(3'-methyl-5'-benzofuranyl)coumarin was obtained.

3-(4'-Hydroxy-3'-acetyl phenyl)coumarin was condensed with benzaldehyde in the presence of alcoholic potassium hydroxide when 3-(3'-cinnamoyl-4'-hydroxy phenyl) coumarin was obtained which gave an acetoxy derivative on heating with acetic anhydride and fused sodium acetate. The above hydroxy ketone on refluxing with selenium dioxide in iso-amyl alcohol underwent cyclisation to 3-(6'-flavonyl) coumarin.

Similar condensation was carried out with anisaldehyde in the presence of alcoholic potassium hydroxide and 3-(4''-methoxy-6'-flavonyl)coumarin synthesised.

3-(6'-Flavonyl)coumarin was also synthesised from 3-(4'-hydroxy-3'-acetyl phenyl)coumarin through the following sequence of reactions. 3-(4'-Hydroxy-3'-acetyl phenyl) coumarin was benzoylated to 3-(4'-benzoyloxy-3'-acetyl phenyl)-

coumarin. This was subjected to Baker-Venkataraman transformation with solid potassium hydroxide in pyridine and the β-diketone obtained was then cyclised by keeping it with concentrated sulphuric acid and 3-(6'-flavonyl) coumarin was obtained.

Kostanecki-Robinson benzoylation of 3-(4'-hydroxy-3'-acetyl phenyl)coumarin gave 3-(3'-benzoyl-6'-flavonyl) coumarin. The debenzoylation of this benzoyl flavone was unsuccessful.

Attempts to condense 3-(4'-hydroxy phenyl)coumarin with (i) malic acid in presence of sulphuric acid (ii) ethyl acetoacetate in presence of sulphuric acid or phosphorus pentoxide or in boiling diphenyl ether without any condensing agent did not succeed and the original 3-(4'-hydroxy phenyl)coumarin was recovered back.