SUMMARY

SUMMARY

Coumarins or benzo-α-pyrones form an important group of oxygen heterocycles. In recent years coumarin derivatives have received considerable attention on account of their abundant occurrence in nature, their varied biochemical properties, industrial uses and analytical applications. Extensive studies have been made on substitution in the coumarin ring system and on building up of other heterocyclic rings on coumarins.

The present work consists of : (i) bromination of some ~~of~~ alkyl coumarins with N-bromosuccinimide, establishment of the structures of the bromo compounds and the utilisation of these bromo compounds for further synthetic work; (ii) chloromethylation of some alkylcoumarins and some further reactions on the chloromethyl derivatives; (iii) synthesis of some furocoumarins and coumarino-α- and γ-pyrones and (iv) cyanoethylation of some xylenols with a view to synthesise some alkylchromones.

Chapter I deals with the action of N-bromosuccinimide on 5,7-dimethyl-, 4,5,7-trimethyl- and 4,6,7-trimethylcoumarin and further reactions of the bromomethylcoumarins obtained.

The bromination of 5,7-dimethyl-, 4,5,7-trimethyl- and 4,6,7-trimethylcoumarin was carried out with one mole of N-bromosuccinimide in the presence of benzoyl peroxide. In each case, it resulted in a monobromomethyl derivative. The structures of these monobromomethyl derivatives have been

established, by converting them into coumarins of known structures. Thus, the monobromomethyl derivatives so obtained were converted into the corresponding monoformyl derivatives by Sommelet reaction. In the case of the monobromomethyl derivative from 5,7-dimethylcoumarin, the monoformyl derivative on oxidation with ammonical silver nitrate gave an acid, the decarboxylation of which under different conditions did not succeed, so the monoformyl derivative was subjected to the Elbs persulphate oxidation to introduce a hydroxyl group at 6-position. This product was found to be different on direct comparison with the 7-methyl-6-hydroxy-5-formylcoumarin. This proved that the 7-methyl group had undergone bromination and was converted into the formyl group on Sommelet reaction. 5-Methyl-7-bromomethyl-coumarin structure is, therefore, assigned to the monobromo-methyl derivative.

In the case of 4,6,7-trimethylcoumarin, the mono-formyl derivative could not be oxidised to the corresponding acid. Therefore, it was converted into the oxime which gave the corresponding cyano derivative on dehydration. This, on hydrolysis with polyphosphoric acid gave a carboxylic acid which on decarboxylation gave the known 4,7-dimethyl-coumarin indicating that the bromination had taken place at 6-position and the bromo derivative was the 6-bromomethyl derivative.

Attempts to oxidise the monoformyl derivative

obtained from 4,5,7-trimethylcoumarin met with failure. On the basis of the NMR spectral data, the monobromomethyl derivative is tentatively assigned the 5-bromomethyl-4,7-dimethylcoumarin structure.

These bromomethylcoumarins were converted into the corresponding acetoxymethylcoumarins by heating with acetic anhydride and fused sodium acetate. Mannich bases have been prepared by the condensation of the monobromomethylcoumarins with morpholine and dimethylamine. The monoformylcoumarins obtained by the Sommelet reaction on bromomethylcoumarins described above, on Perkin acetylation with fused sodium acetate and acetic anhydride gave the corresponding β-coumarinyl acrylic acids. 5-Methyl-7-formyl- and 4,7-dimethyl-6-formylcoumarin on condensation with hippuric acid in the presence of acetic anhydride and fused sodium acetate gave 4-(5'-methyl-7'-coumarinal)-2-phenyl-5-oxazolone and 4-(4',7'-dimethyl-6'-coumarinal)-2-phenyl-5-oxazolone respectively. These oxazolones were converted into β-(5-methyl-7-coumarinyl)-alanine and β-(4,7-dimethyl-6-coumarinyl)alanine respectively, by heating with red phosphorus and hydriodic acid. The isolation of the latter, however, did not succeed.

The condensation of 5-methyl-7-formyl- and 4,7-dimethyl-6-formylcoumarin with o-hydroxyacetophenone in the presence of alcoholic potassium hydroxide gave β-(5-methyl-7-coumarinyl)vinyl-o-hydroxyphenyl ketone and β-(4,7-dimethyl-6-coumarinyl)vinyl-o-hydroxyphenyl ketone

respectively.

β-(5-Methyl-7-coumarinyl)vinyl-o-hydroxyphenyl ketone on cyclisation by refluxing in the presence of iso-amyl alcohol and selenium dioxide gave 5-methyl-7-(2'-chromonyl)coumarin. Attempts to cyclise β-(4,7-dimethyl-6-coumarinyl)vinyl-o-hydroxyphenyl ketone to 4,7-dimethyl-6--(2'-chromonyl)coumarin, however, met with failure.

4,7-Dimethyl-6-bromomethylcoumarin on condensation with alcoholic potassium cyanide gave the 6-cyanomethyl derivative which was hydrolysed to the corresponding acid with 70 % sulphuric acid. The ethyl ester of this acid was condensed with salicylaldehyde to get 4,7-dimethyl-6,3'-bicoumarinyl. 7-Bromomethyl-5-methylcoumarin on condensation with alcoholic potassium cyanide gave a sticky product which was directly hydrolysed into the corresponding acid. This acid was obtained in such a poor yield that further work was not possible.

Chapter II deals with the work on the chloro-methylation of some alkyl coumarins.

During the survey of literature, it was noticed that the chloromethylation of coumarins proceeds smoothly to give 3-chloromethyl derivatives when there is a methyl group in the 4-position of the α-pyrone ring. So it was thought of interest to do a comparative study of the chloro-methylation of some coumarins with and without the methyl group in the 4-position of the α-pyrone ring.

4,6,7-Trimethyl-, 6,7-dimethyl-, 4,5,7-trimethyl-, 5,7-dimethyl-, 5-hydroxy-4,7-dimethyl-, 7-hydroxy-5-methyl-coumarin and 4'-methylnaphtha(1,2 : 6',5')-α-pyrone were chloromethylated and it was found that in all the cases where methyl group was present in the α-pyrone ring, the chloromethylation proceeded smoothly to give the corresponding 3-chloromethyl derivative. The structures of these chloro-methyl derivatives were proved by reducing them to the methylcoumarins of known structures. In the case of the coumarins without the 4-methyl group, however, the reaction either did not proceed at all or resulted in an unworkable polymeric product.

The above 3-chloromethylcoumarins on condensation with morpholine and dimethylamine gave the corresponding 3-morpholinomethyl- and 3-dimethylaminomethylcoumarin. On Sommelet reaction with hexamine and acetic acid the chloro-methyl derivative did not give the desired 3-formyl derivatives. On heating with acetic anhydride and sodium acetate, the corresponding acetoxy derivatives were obtained.

4,6,7-Trimethyl-3-chloromethylcoumarin and 3'-chloro-methyl-4'-methyl-naphtha(1,2 : 6',5')-α-pyrone on condensation with alcoholic potassium cyanide gave the corresponding 3- and 3'-cyanomethyl derivatives which on hydrolysis with 70 % sulphuric acid gave 4,6,7-trimethyl-3-acetic acid and 4'-methyl-naphtha(1,2 : 6',5')-α-pyrone-3'-acetic acid respectively. Attempt was then made to condense the ethyl esters of these acids

with salicylaldehyde in the presence of piperidine but in each case the original ester was recovered.

Chapter III deals with the synthesis of some (a) furocoumarins and (b) coumarino-α- and γ-pyrones.

With a view to build up further oxygen heterocyclic rings on 5-hydroxy-4,7-dimethyl-, 7-methyl-6-hydroxy-, and 5-methyl-6-hydroxy-7-formylcoumarin they were subjected to Friedel-Crafts reaction and formylation with hexamine and acetic acid to obtain o-hydroxy-acetyl and o-hydroxy-formyl derivatives which would serve as intermediates for such synthesis.

(a) 5-Hydroxy-4,7-dimethylcoumarin on Friedel-Crafts reaction with acetyl chloride and aluminium chloride gave 6-acetyl-5-hydroxy-4,7-dimethylcoumarin. This on condensation with ethyl bromoacetate in dry acetone in the presence of potassium carbonate gave the 5-carbethoxymethoxy-coumarin. This on hydrolysis with sodium hydroxide gave the corresponding acid which on cyclisation with sodium acetate and acetic anhydride gave 4,7,3'-trimethyl-furo(5',4' : 5,6)-coumarin.

7-Methyl-6-hydroxycoumarin on formylation with hexamine and acetic acid gave 7-methyl-6-hydroxy-5-formyl-coumarin. This was condensed with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate. Removal of acetone and dilution of the residue, afforded 7-methyl-6-carbethoxymethoxy-5-formylcoumarin, which on hydrolysis gave the 6-carboxymethoxy derivative which on

cyclisation with sodium acetate and acetic anhydride gave 7-methylfuro(5',4' : 6,5)coumarin.

5-Methyl-6-hydroxy-7-formylcoumarin prepared as described in Chapter I was condensed with ethyl bromo-acetate in acetone in the presence of anhydrous potassium carbonate. 5-Methyl-6-carbethoxymethoxy-7-formylcoumarin thus obtained was hydrolysed with 5 % sodium hydroxide solution to the corresponding acid. This acid on cyclisation with sodium acetate and acetic anhydride gave a product which was insoluble in sodium bicarbonate solution, but could not be purified because of its very poor yield.

(b) With a view to synthesise some coumarino-α-pyrones, 7-methyl-6-hydroxy-5-formylcoumarin was subjected to Perkin acetylation with acetic anhydride and fused sodium acetate to give 7-methylcoumarino(6,5 : 6',5')-α-pyrone. By a similar method 5-methyl-6-hydroxy-7-formylcoumarin gave 5-methylcoumarino(6,7 : 6',5')-α-pyrone.

The synthesis of some coumarino-γ-pyrones has also been carried out. 6-Acetyl-5-hydroxy-4,7-dimethylcoumarin was benzoylated and the benzoyl derivative was subjected to Baker-Venkataraman transformation with solid potassium hydroxide in pyridine and the β-diketone obtained was then cyclised by keeping it with conc.sulphuric acid to get 2'-phenyl--4,7-dimethylcoumarino(5,6 : 6',5')-γ-pyrone.

Further 6-acetyl-5-hydroxy-4,7-dimethylcoumarin on Kostanecki-Robinson acetylation with acetic anhydride

and sodium acetate gave 3'-acetyl-2',4,7-trimethylcoumarino--(5,6 : 6',5')-γ-pyrone. The deacetylation of this product did not succeed.

Attempts to synthesise 2',4,7-trimethylcoumarino--(5,6 : 6',5')-γ-pyrone by the Pechman condensation of 5-hydroxy-4,7-dimethylcoumarin and ethylacetoacetate in boiling diphenyl ether did not succeed.

Appendix I deals with the cyanoethylation of 3,4- and 3,5-xylenols with a view to synthesise some alkyl chromones. Cyanoethylation of phenols can give chromones without any substituent in the γ-pyrone ring. Alkyl chromones have not been prepared so far hence the cyanoethylation of 3,4- and 3,5-xylenols with acrylonitrile in the presence of cuprix oxide was carried out. The β-cyanoethoxy derivatives so obtained were hydrolysed with hydrochloric acid and acetic acid to the corresponding acids. The cyclisation of these acids was carried out with sulphuric acid and acetic anhydride to get 6,7-dimethyl-chromanone and 5,7-dimethyl chromanone. The dehydrogenation of these chromanones with palladium and charcoal however met with failure.