SUMMARY

Coumarins have been subjected to various reactions such as bromination, nitration and sulphonation but there was no reference in literature to any studies on the iodination and only one reference to the application of Mannich reaction to coumarins. The present work deals with the iodination of some typical coumarin derivatives and the conversion of the iodo derivatives obtained into cyanocoumarins by the Rosenmund-von Braun reaction, ~~and~~ into bicoumarinyls by the Ullmann reaction and into 8-phenylcoumarins by the Crossed Ullmann reaction. Further, some typical coumarins have been subjected to Mannich reaction with primary and secondary amines. 6,7-Dihydroxy-4-methylcoumarin and its methyl ethers have also been subjected to various reactions and the structures of the products obtained have been established.

Chapter I - General Introduction :

The previous work on the halogenation of coumarins has been reviewed. The results obtained in the application of a few other reactions to coumarins have also been discussed to show the pattern of substitution in the coumarin ring systems.

Chapter II - Iodination of coumarins

The iodination of 7-hydroxycoumarin, 7-hydroxycoumarin-6-carboxylic acid, ethyl-7-hydrocycoumarin-3-

carboxylate, 7-hydroxycoumarin-4-acetic acid, 6-hydroxycoumarin and methyl 5-hydroxycoumarin-6-carboxylate and their methyl ethers and 7,8-dihydroxycoumarin and naptha-1,2-a-pyrone have been studied using (i) iodine and ammonia (ii) iodine and iodic acid and (iii) iodine monochloride.

With equimolecular proportions of all these reagents 7-hydroxycoumarin gave a monoiodo derivative to which the 8-iodo structure has been assigned, as its methyl ether did not give a coumarilic acid derivative on alkaline hydrolysis and it gave a product in good yield on Elbs Persulphate Oxidation. Using higher molar proportions of iodine and iodic acid, and iodine monochloride the 3,6,8-triiodo derivative was obtained. With higher proportions of iodine in presence of ammonia the 6,8-diiodo and the 3,6,8-triiodo derivatives were obtained.

7-Hydroxycoumarin-6-carboxylic acid and 7-hydroxycoumarin-4-acetic acid with equimolecular proportions of the three iodinating agents gave the 8-iodo derivatives. With double the quantity of iodine in presence of ammonia 7-hydrocycoumarin-4-acetic acid gave the 6,8-diiodo derivative. 7-Hydroxycoumarin-6-carboxylic acid when treated with 4 moles of iodine and iodic acid furnished the 3,8-diiodo derivative. 7-Hydrocycoumarin-4-acetic acid yielded the 3,6,8-triiodo derivatives when treated with higher proportions of iodine and iodic acid. Ethyl 7-hydroxycoumarin-3-carboxylate yielded the 8-iodo derivative when treated with equimolecular proportions of these iodinating agents. With double the quantity of iodine and iodic acid it yielded the 6,8-diiodo derivative.

6-Hydroxycoumarin with all these iodinating agents furnished ~~the~~ a mono-iodo derivative the methyl ether of which did not give a coumarilic acid. The mono-iodo derivative was proved to be the 5-iodo derivative as follows:

6-Hydroxycoumarin on nitration gave a mononitro derivative the methyl ether of which remained unchanged on boiling with liquor ammonia indicating that the nitro group had not entered the 3-position. (cf. Clayton J. Chem. Soc., 1910, 97, 1388). The nitro coumarin was reduced to the corresponding aminocoumarin which was converted by heating with dilute hydrochloric acid in a sealed tube as well as through the corresponding diazo compound into a hydroxycoumarin which gave a yellow colour with alkali and was different from 6-methoxy-7-hydroxycoumarin, hence the nitrocoumarin was assigned the 6-hydroxy-5-nitrocoumarin structure and the amine was 6-methoxy-5-aminocoumarin. The latter was diazotized and treated with potassium iodide which yielded 6-methoxy-5-iodocoumarin. This was identical with the methyl ether of the monoiodo derivative obtained on direct iodination of 6-hydroxycoumarin as described above. 7-Methoxycoumarin, methyl-7-methoxycoumarin-6-carboxylate and methyl 5-methoxycoumarin 6-carboxylate could not be iodinated with iodine and ammonia and iodine and iodic acid. With equimolecular proportions of iodine monochloride these yielded the 3-iodo derivatives and methyl 5-methoxycoumarin-6-carboxylate gave the 8-iodo derivative. With higher proportions of iodine monochloride 7-methoxycoumarin gave the 3,6-diiodo derivative but the other two did not yield the higher iodination products. 7-Methylcoumarin, 7,8-dihydroxycoumarin and naphtha 1,2-α-pyrone did not undergo iodination with any of the above iodinating agents.

Chapter III - Ullmann reaction reaction on some iodocoumarins : Synthesis of some bicoumarinyls and 8-phenylcoumarin derivatives

Dey and Row (J. Indian Chem. Soc., 1924, 1, 107) prepared 4,3'-dicoumarinyls by the condensation of various phenolic aldehydes with 4-coumarinyl acetic acids. Huebner and Link (J. Am. Chem. Soc., 1945, 67, 99) reported the formation of the bicoumarinyl derivative from 3-bromo-4-methoxycoumarin by the Ullmann reaction. No other work on the synthesis of bicoumarinyls was reported when this work was undertaken. Further, 8-phenylcoumarins have not hitherto been prepared except for some 8-phenyl sulphonylcoumarins prepared by Aleykutty and Baliah (J. Indian Chem. Soc., 1955, 32, 773) by the Fries migration of 7-coumarinyl benzene sulphonates. This chapter deals with the synthesis of several bicoumarinyl and 8-phenylcoumarin derivatives by the Ullmann reaction on the iodocoumarins described earlier.

7-Methoxy-8-iodocoumarin when subjected to Ullmann reaction with copper bronze in boiling diphenyl ether gave 7,7'-dimethoxy-8,8'-bicoumarinyl. Methyl 7-methoxy-8-iodo coumarin-6-carboxylate on similar Ullmann reaction gave the corresponding bicoumarinyl derivative. This was hydrolysed to the corresponding acid and the acid decarboxylated to 7,7'-dimethoxy-8,8'-bicoumarinyl. Attempts to resolve the acid into active forms using (-) brucine failed owing to the insolubility of the acid in organic solvents.

7-Methoxy-3-iodocoumarin, 6-methoxy-5-iodocoumarin, methyl 7-methoxy-3-iodocoumarin-6-carboxylate and methyl 5-methoxy-8-iodocoumarin-6-carboxylate on Ullmann reaction gave the corresponding bicoumarinyl derivatives. The esters have been hydrolysed to the corresponding acids and the acids decarboxylated.

Crossed Ullmann reaction between iodobenzene and 7-methoxy-8-iodocoumarin and methyl 7-methoxy-8-iodocoumarin-6-carboxylate gave the corresponding 8-phenyl derivatives. The ester was hydrolysed to the corresponding acid and the acid was decarboxylated to 7-methoxy-8-phenylcoumarin.

As 7,8-dihydroxycoumarin and naphtha 1,2,α-pyrone did not undergo iodination it was thought of interest to see if the bicoumarinyl derivatives of these could be prepared from the bromo derivatives of these coumarins. Both these coumarins underwent bromination to give the 3-bromo derivatives as seen by their conversion into coumarilic acid derivatives. These on Ullmann reaction gave the debrominated coumarin and the unchanged bromo coumarin respectively. In order to see if other bromo coumarins would undergo the Ullmann reaction or not. 7-Methoxy-8-bromo-4-methylcoumarin was tried it underwent Ullmann reaction and crossed Ullmann reaction with iodobenzene to give

7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl and 7-methoxy-8-phenyl-4-methylcoumarin but in poor yields.

Chapter IV - Synthesis of cyanocoumarins from the iodocoumarins by the Rosenmund-von Braun reactions

The mono iodocoumarins described in chapter II have been subjected to the Rosenmund-von Braun reaction by heating them above their melting point with anhydrous cuprous cyanide and various cyanocoumarins have been synthesised. The action of sulphuric acid and alkali on the cyanocoumarins has also been studied.

7-Methoxy-8-cyano- and 6-methoxy-5-cyanocoumarins remained unchanged on boiling with 10 % alkali. 7-Methoxy-8-cyanocoumarin when heated with 90 % sulphuric acid gave the corresponding 8-carbamoyl derivative in excellent yield. On further hydrolysis with 50 % sulphuric acid the carbamoyl derivative gave 7-methoxycoumarin. Stephen aldehyde reaction on 7-methoxy-8-cyanocoumarin and 6-methoxy-5-cyanocoumarin failed, the original cyano derivatives were recovered unchanged. Methyl 7-methoxy-8-cyanocoumarin-6-carboxylate, methyl 7-methoxy-8-cyanocoumarin-3-carboxylate and methyl 7-methoxy-8-cyanocoumarin-4-acetate on heating with 10 % alkali hydrolysed to the corresponding acids but the cyano group remained unaffected. However, on heating with 90 % sulphuric acid the cyano group was partially hydrolysed and the carbamoyl derivatives were obtained.

Chapter V - Mannich reaction on some hydroxycoumarins

No work on the application of the Mannich reaction to coumarins appears to have been reported except the one by Robertson and Link (J. Am. Chem. Soc., 1953, 75, 1883) in which they reported the Mannich reaction on 4-hydroxycoumarin. Several coumarin derivatives have now been subjected to Mannich reaction with paraformaldehyde and dimethylamine, aniline and benzylamine and the structures of the products obtained have been established. 7-Hydroxycoumarin with paraformaldehyde and dimethylamine gave 7-hydroxy-8-dimethylaminomethylcoumarin. This on Sommelet reaction gave the known 7-hydroxy-8-formylcoumarin in good yield. 7-Hydroxy-8-dimethylaminomethylcoumarin when treated with acetic anhydride and sodium acetate gave 7-acetoxy-8-acetoxymethylcoumarin. With equimolecular proportions of benzylamine and paraformaldehyde 7-hydroxycoumarin gave 7-hydroxy-8-benzylaminomethylcoumarin which gave 7-hydroxy-8-formylcoumarin on Sommelet reaction. When the proportions of paraformaldehyde was doubled 7-hydroxycoumarin gave with benzylamine 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6',8,7-coumarin. With aniline 7-hydroxycoumarin gave 2'-H-3'-phenyl 3',4'-dihydro-1',3'-oxazino-5',6',8,7-coumarin.

Ethyl 7-hydroxycoumarin-3-carboxylate with formaldehyde and dimethylamine gave the 8-dimethylamino methylcoumarin which on bromination gave 7-hydroxy-8-dimethylaminomethyl-6-bromocoumarin-3-carboxylate identical with the product obtained from the Mannich reaction on ethyl

7-hydroxy-6-bromocoumarin-3-carboxylate with formalin and dimethylamine. With double the quantity of formalin ethyl 7-hydroxycoumarin-3-carboxylate and benzylamine gave 2'H-3'-benzyl-3',4'-dihydro-3-carboethoxy-1',3'-oxazino-5',6',8,7-coumarin, which on bromination gave the corresponding 6-bromo derivative identical with the Mannich reaction product from ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate with benzylamine and 2 moles of formaldehyde.

Equimolecular quantities of 6-hydroxycoumarin, paraformaldehyde and dimethylamine gave the corresponding 5-dimethylaminomethylcoumarin which on treatment with hexamethylene tetramine gave the known 6-hydroxy-5-formylcoumarin. 6-Hydroxycoumarin with two moles of formalin and benzylamine gave 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6'-5,6-coumarin and with aniline and double the quantity of paraformaldehyde 2'H-3'-phenyl-3',6'-dihydro-1',3'-oxazino-5',6'-5,6-coumarin. All the 1',3'-oxazino derivatives were hydrolysed with concentrated hydrochloric acid in alcohol to the corresponding alkyl & arylamino methyl coumarin derivatives which on treatment with hexamethylene tetramine gave the known formyl derivatives.

Chapter VI - Studies on 6,7-dihydroxy-4-methylcoumarin and its methyl ethers

The pattern of substitution in 6,7-dihydroxy-4-methylcoumarin is of interest as both the 5-and 8-positions are capable of substitution and it would be of interest to see which one is more reactive.

6,7-Dihydroxy-4-methylcoumarin, 6-hydroxy-7-methoxy-

4-methylcoumarin and 6,7-dimethoxy-4-methylcoumarin with one mole of bromine gave the 3-bromo derivative. The dimethyl ether of the above bromocoumarin gave a coumarilic acid on alkaline hydrolysis. 6,7-Dihydroxy-4-methylcoumarin and its dimethyl ether with two moles of bromine gave dibromo derivatives which on alkaline hydrolysis gave a bromo-coumarilic acid derivative which fixed the position of one of the bromine atoms. That the other bromine atom had entered the 8-position was shown by the following synthesis.

2-Bromo resorcinol on Pechmann condensation with ethyl acetoacetate gave 7-hydroxy-8-bromo-4-methylcoumarin which was methylated and subjected to Elbs Persulphate Oxidation when 6-hydroxy-7-methoxy-8-bromo-4-methylcoumarin was obtained. With one molecule of bromine it gave a dibromo derivative the methyl ether of which gave a bromo coumarilic acid. The dibromo derivative was identical with the 3:8-dibromo product obtained on direct bromination of 6,7-dimethoxy-4-methylcoumarin. 6-Hydroxy-7-methoxy-4-methylcoumarin furnished the 3,5-dibromo derivative with two moles of bromine. The methyl ether of this gave a bromo coumarilic acid on boiling with alkali which was different from the bromo coumarilic acid obtained from 6,7-dimethoxy-3,8-dibromo-4-methylcoumarin.

6,7-Dihydroxy-4-methylcoumarin on nitration gave an unworkable mass but 6,7-dimethoxy-4-methylcoumarin gave a mononitro derivative which could be hydrolysed with liquor ammonia to the known 2-hydroxy-4,5-dimethoxyacetophenone which indicated that the nitro group had entered the 3 position. The nitro derivative was reduced to the corresponding 3-aminocoumarin which was hydrolysed to the 3-hydroxy derivative. Similarly 6-hydroxy-7-methoxy-4-methylcoumarin on nitration gave the 5-nitro derivative . It was different from an authentic specimen of 6-hydroxy-7-methoxy-8-nitro-4-methylcoumarin synthesised by the Elbs Persulphate Oxidation of 7-methoxy-8-nitro-4-methylcoumarin and did not give any hydroxy ketone on treatment with liquor ammonia.

Iodination, Friedel-Crafts acetylation and Fries migration of 6,7-dihydroxy and 6-hydroxy-7-methoxy-4-methylcoumarin were carried out under varying conditions without any success. Only original coumarin was obtained. Chloromethylation of 6,7-dihydroxy-4-methylcoumarin gave a polymeric product while that of 6-hydroxy-7-methoxy-4-methylcoumarin gave a pasty product. 6,7-Dimethoxy-4-methylcoumarin on chloromethylation yielded a ? ?-methylene-bis- (6,7-dimethoxy-4-methylcoumarin). ~~The~~ 6-Hydroxy-7-methoxy-4-methylcoumarin on treatment with hexamine yielded the 5-formyl derivative, but ~~The~~ 6,7-dimethoxy-4-methylcoumarin on treatment with hexamine yielded the above methylene bis coumarin.