SUMMARY

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Coumarins have been subjected to various reactions such as, bromination, nitration, sulphonation etc., but the iodination and chloromethylation of coumarins has not been studied at all. Both, the iodocoumarins and chloromethylcoumarins, are compounds of synthetical importance. The present work deals with the iodination and chloromethylation of some typical coumarin derivatives and the conversion of the iodo and the chloromethyl derivatives into various substituted coumarin derivatives.

Chapter I - General Introduction : A review of the work described in the literature on substitution in the coumarin ring system.

Chapter II - Iodination of coumarins

The iodination of 7- and 5-hydroxy-4-methylcoumarin and their methyl ethers, 7-hydroxy-4-methylcoumarin-6-carboxylic acid, its methyl ester and methoxymethylester ; methyl-5-hydroxy-4-methylcoumarin-6-carboxylate and its methyl ether has been studied using (i) iodine monochloride (ii) iodine and iodic acid and (iii) iodine and ammonia and the structures of all the compounds have been established.

With equimolecular proportions of all these reagents, 7-hydroxy-4-methylcoumarin 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 hydrolysis and it gave a product in good yield on Elbs Persulphate Oxidation. With higher molar proportions of iodine monochloride the 3,6-diiodo-, the 3,8-diiodo- as well as the 3,6,8-triiodocoumarin derivatives were obtained. With double the molar proportions of iodine and iodic acid the 3,6,8-triiodo derivative was directly obtained. With higher proportions of iodine ~~in~~ and ammonia the 6,8-diiodo derivative, not obtained by the other two methods, was obtained.

5-Hydroxy-4-methylcoumarin with equimolar proportion of iodine monochloride gave the 8-iodo derivative while with iodine and ammonia it gave the 6-iodo derivative. With equimolar proportions of iodine and iodic acid as well as with higher proportions of iodine monochloride and iodine and ammonia it yielded the 6,8-diiodo derivative. No triiodo derivative could be obtained by any of these methods.

7-Methoxy- and 5-methoxy-4-methylcoumarin could not be iodinated with iodine and ammonia and with iodine and iodic acid but with equimolar proportions of iodine monochloride 7-methoxy-4-methylcoumarin yielded the 3-iodo derivative and the 5-methoxy-4-methylcoumarin gave the 8-iodo derivative. 7-Methoxy-4-methylcoumarin gave the 3,6-diiodo derivative when excess of iodine monochloride was used but the 5-methoxy-4-methylcoumarin did not give the higher iodination product.

Methyl-7-hydroxy- and methyl-5-hydroxy-4-

methylcoumarin-6-carboxylate gave the 8-iodo derivatives with iodine and ammonia and with iodine and iodic acid. Further iodination did not take place even with excess of iodinating agents. Methyl-7-methoxy- and methyl-5-methoxy-4-methylcoumarin-6-carboxylate could not be iodinated with iodine and ammonia and with iodine and iodic acid but with equimolar proportions of iodine monochloride methyl-7-methoxy-4-methylcoumarin-6-carboxylate gave the 3-iodo derivative while methyl-5-methoxy-4-methylcoumarin-6-carboxylate gave the 8-iodo derivative.

~~In the iodination of 7-hydroxy-4-methylcoumarin-8-carboxylic acid with iodine and ammonia the carboxyl group was replaced by iodine.~~

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

Dey and Row (J. Indian Chem. Soc., 1924, 1, 107) prepared 4,3'-dicoumarinyls by 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 Ullmann reaction. No other work on the synthesis of bicoumarinyls has been reported. Further, 8-phenylcoumarins have not hitherto been prepared except for some 8-phenylsulphonylcoumarins prepared by Aleykutty and Baliah(J. Indian Chem. Soc., 1955, 32, 773) by the Fries migration of 7-coumarinylbenzenesulphonates. In this part the syntheses of several bicoumarinyl derivatives and 8-phenylcoumarin derivatives by the Ullmann reaction on the iodocoumarins has been described.

7-Methoxy-8-iodo-4-methylcoumarin when subjected to Ullmann reaction using copper bronze in boiling diphenyl ether gave 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl. Methyl-7-methoxy-8-iodo-4-methylcoumarin-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-4,4'-dimethyl-8,8'-bicoumarinyl described above. Attempts to resolve the acid into its optically active forms using (-) brucine failed owing to the insolubility of the acid in organic solvents. Crossed Ullmann reaction between iodobenzene and 7-methoxy-8-iodo-4-methylcoumarin gave 7-methoxy-8-phenyl-4-methylcoumarin. Methyl-7-methoxy-8-phenyl-4-methylcoumarin-6-carboxylate was similarly prepared. It was hydrolysed and the acid obtained decarboxylated to 7-methoxy-8-phenyl-4-methylcoumarin which on demethylation gave 7-hydroxy-8-phenyl-4-methylcoumarin.

7-Methoxy-3-iodo-4-methylcoumarin, methyl-7-methoxy-3-iodo-4-methylcoumarin-6-carboxylate, 5-methoxy-8-iodo-4-methylcoumarin and methyl-5-methoxy-8-iodo-4-methylcoumarin-6-carboxylate have been subjected to Ullmann reaction and the corresponding bicoumarinyl derivatives synthesised.

5-Methoxy-8-phenyl-4-methylcoumarin was synthesised by crossed Ullmann reaction between iodobenzene and 5-methoxy-8-iodo-4-methylcoumarin.

Chapter IV - Synthesis of cyanocoumarins from iodocoumarins

Monoiodocoumarins described in Chapter II have been subjected to Rosenmund-von Braun nitrile synthesis. Iodo derivatives were heated above their melting points with cuprous cyanide and various cyanocoumarins synthesised.

7-Methoxy- and 5-methoxy-8-cyano-4-methylcoumarin remained unchanged on boiling with alkali (10 %) but when heated with sulphuric acid (90 %) gave the corresponding 8-amido derivatives in excellent yield. On further hydrolysis with sulphuric acid (50 %) or with alkali (10 %) 7-methoxy-8-amido-4-methylcoumarin gave the known coumarin-8-carboxylic acid derivative while 5-methoxy-8-amido-4-methylcoumarin gave the unknown 5-methoxy-4-methylcoumarin-8-carboxylic acid. Stephen aldehyde reaction on both the cyano derivatives failed, the original cyano derivatives were recovered unchanged. Methyl-7-methoxy- and methyl-5-methoxy-8-cyano-4-methylcoumarin-6-carboxylate when heated with alkali (10 %) gave the corresponding 6-carboxylic acids the cyano group remaining unaffected. However, when heated with sulphuric acid (90 %) they gave the corresponding 8-amido-6-carboxylic acid derivatives. On further hydrolysis 7-methoxy-8-amido-4-methylcoumarin-6-carboxylic acid gave the known 7-methoxy-4-methylcoumarin-6-carboxylic acid while 5-methoxy-8-amido derivative gave the unknown 5-methoxy-4-methylcoumarin-6,8-dicarboxylic acid. 7-Methoxy-3-cyano-4-methylcoumarin on hydrolysis either with alkali (10 %) or with sulphuric acid (90 %) gave the known 7-methoxy-4-

methylcoumarin-3-carboxylic acid. Methyl-7-methoxy-3-cyano-4-methylcoumarin-6-carboxylate gave with cold alkali the corresponding cyano acid which on further hydrolysis with alkali (10 %) gave 7-methoxy-4-methylcoumarin-3,6-dicarboxylic acid.

Chapter V- Chloromethylation of coumarins

No work on the chloromethylation of coumarins was found reported in literature. It was therefore thought of interest to study the chloromethylation of some typical coumarin derivatives as the chloromethyl derivatives are substances of synthetical importance.

Coumarin could not be chloromethylated with paraformaldehyde using aqueous solutions. In glacial acetic acid using anhydrous zinc chloride as catalyst it gave the 3-chloromethyl derivative, even with excess of paraformaldehyde. 4-Methylcoumarin was similarly chloromethylated to yield 3-chloromethyl-4-methylcoumarin. 7-Methoxy-4-methylcoumarin on chloromethylation with one mole of paraformaldehyde using acetic acid (80 %) gave a mixture of different products from which only the 6-chloromethyl derivative was obtained in a pure state. It was reduced to the known 7-methoxy-4,6-dimethylcoumarin and was converted to the hitherto unknown 6-formyl derivative through the Sommelet reaction. The action of potassium cyanide, acetic acid and fused sodium acetate, and methyl alcohol on this chloromethyl derivative has also been studied. The 3,6-dichloromethyl-, the 3,8-dichloromethyl- and the 3,6,8-trichloromethyl derivatives have been obtained using larger quantities of paraformaldehyde and their structures proved by reduction to the corresponding methyl derivatives which have been synthesised by unambiguous methods.

7-Hydroxy-4-methylcoumarin-6-carboxylic acid and its methyl ester on chloromethylation gave directly the 3,8-dichloromethyl derivatives which on reduction gave the corresponding methyl derivatives. Monochloromethyl derivatives could not be isolated. The methyl derivatives have been degraded to 7-hydroxy-3,4,8-trimethylcoumarin. Methyl-7-methoxy-4-methylcoumarin-6-carboxylate on chloromethylation gave 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid.

Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate on chloromethylation gave the 8-chloromethyl derivative. On reduction it gave the corresponding methyl derivative which was also synthesised from methyl-2,4-dihydroxy-5-methylbenzoate by Pechmann condensation with ethyl acetoacetate. The proof of its structure has been given. With excess of paraformaldehyde methyl-5-hydroxy-4-methylcoumarin-6-carboxylate gave the 3,8-dichloromethyl derivative. It was reduced to the corresponding methyl derivative. The methyl derivative was degraded to 5-hydroxy-3,4,8-trimethylcoumarin. 5-Methoxy-4-methylcoumarin on chloromethylation with one mole of paraformaldehyde gave a chlorine free compound. With excess of paraformaldehyde, however, it gave the 3,8-dichloromethyl derivative. Its reduction product on demethylation yielded 5-hydroxy-3,4,8-trimethylcoumarin mentioned above.

N.B. - All the micro and the semi-micro analyses of the compounds mentioned in this thesis, were carried out by the author himself.