SUMMARY

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The present work was undertaken with a view to study some aspects of the chemistry of coumarins and it forms a part of the systematic study of coumarins going on in this laboratory since the past few years. Three aspects have been studied e.g. the synthesis of some hitherto unknown furocoumarins and coumarino-α-and γ-pyrones, Beckmann rearrangement of the oximes of some C-acyl coumarins and the application of Mannich reaction to some coumarin derivatives.

Chapter I : Studies on 8-hydroxycoumarins have been meagre probably because of the difficulty of getting this coumarin. It was therefore thought of interest to study the formylation and acetylation of this coumarin and to utilise the intermediates obtained to build up the furan and α and γ-pyrone rings on this coumarin. The 7-formyl derivative required was obtained by direct formylation of 8-hydroxycoumarin with hexamethylene tetramine and its structure established by its conversion into the known 7,8-dihydroxycoumarin by Dakin oxidation.

The formyl derivative was condensed with ethylbromoacetate and the ester obtained was hydrolysed to acid. This on heating with sodium acetate and acetic anhydride was cyclised to furo-2'-carboxy(4',5'-7,8)-coumarin.

Furo-3'-methyl(4',5'-7,8)-coumarin was similarly synthesised from 8-hydroxy-7-acetylcoumarin. The 7-acetyl derivative was obtained by the Friedel-Crafts acetylation of 8-hydroxycoumarin.

The same was also obtained on Fries-migration of 8-acetoxycoumarin. Its structure has been proved by conversion into the known 7,8-dihydroxycoumarin by Dakin oxidation.

Furo-3',5-dimethyl(5',4'-7,8)coumarin has been synthesised from 7-hydroxy-8-acetyl-5-methylcoumarin through the same sequence of reactions described above. 7-Hydroxy-5-methylcoumarin on Friedel-Crafts acetylation gave the 8-acetyl derivative. Its structure is based on the fact that its methyl ether underwent Elbs persulphate oxidation easily. The same 8-acetyl derivative was obtained on Fries migration of 7-acetoxy-5-methylcoumarin.

Furo-3',8-dimethyl(4',5'-6,7)coumarin was synthesised from 7-hydroxy-6-acetyl-8-methylcoumarin. This acetyl derivative was derived from 7-hydroxy-8-methylcoumarin by Friedel-Crafts acetylation. It gave purple brown colouration with alcoholic ferric chloride and as there is no other position where the acetyl group can migrate, 7-hydroxy-6-acetyl-8-methylcoumarin structure has been assigned. The same 6-acetyl derivative was obtained on Fries-migration of 7-acetoxy-8-methylcoumarin.

Whereas many furocoumarins have been synthesised from coumarins, there does not appear to have been any attempt to synthesise the furan ring on a benzocoumarin probably because of the difficult accessibility of hydroxybenzocoumarin[5].

3'-Methyl benzofurano-(6',7'-8,7)-4-methyl-7,8-benzocoumarin has now been synthesised from 6'-hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin. The 5'-acetyl

derivative was prepared by the Friedel-Crafts acetylation of 6'-hydroxy-4-methyl-7,8-benzocoumarin. The same acetyl derivative was obtained on Fries migration of 6'-acetoxy-4-methyl-7,8-benzocoumarin.

In the second part of this chapter the synthesis of several coumarins, α and γ-pyrones has been described.

8-Hydroxy-7-formylcoumarin on Perkin acetylation gave α-pyrono-(5',6'-7,8)-coumarin. Knoevenagel condensation of 8-hydroxy-7-formylcoumarin and 7-hydroxy-6-formyl-8-methylcoumarin with diethylmalonate gave 3'-carbethoxy-α-pyrono-(5',6'-7,8)-coumarin and 3'-carbethoxy-α-pyrono-(5',6'-6,7)-8-methylcoumarin respectively.

8-Hydroxy-7-acetylcoumarin, 7-hydroxy-6-acetyl-8-methylcoumarin, 7-hydroxy-8-acetyl-5-methylcoumarin and 6'-hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin were subjected to Kostanecki-Robinson benzoylation, when 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-7,8)-coumarin, 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-6,7)-8-methylcoumarin, 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-8,7)-5-methylcoumarin and 4-methyl-3'-benzoyl flavono-(7',8'-8,7)-coumarin were obtained respectively.

Chapter II : Beckmann transformation of the oximes of the formyl and acyl derivatives of coumarins has been studied. ~~No~~ only one reference is found in literature to the Beckmann transformation of the formyl and acyl derivatives of coumarins.

The oxime of 7-hydroxy-6-acetyl-4-methylcoumarin on treatment with polyphosphoric acid gave an acetamido derivative which on hydrolysis gave 7-hydroxy-6-amino-

4-methylcoumarin. Its structure was proved by the synthesis of an authentic specimen of the amine by the reduction of the known 7-hydroxy-6-nitro-4-methylcoumarin.

The oxime of 7-hydroxy-8-acetyl-4-methylcoumarin rearranged to an acetamido derivative with polyphosphoric acid, which on hydrolysis gave 7-hydroxy-8-amino-4-methylcoumarin. Its structure was established by conversion into the known 7,8-dihydroxy-4-methylcoumarin by heating with hydrochloric acid in a sealed tube at 150°.

The oxime of 5-hydroxy-6-acetyl-4-methylcoumarin on Beckmann rearrangement gave an acetamido derivative which on hydrolysis gave 5-hydroxy-6-amino-4-methylcoumarin. It afforded the known 5,6-dihydroxy-4-methylcoumarin on heating with dilute hydrochloric acid in a sealed tube.

The oxime of 8-hydroxy-7-acetylcoumarin gave 8-hydroxy-7-acetamido derivative on rearrangement. On hydrolysis it afforded 8-hydroxy-7-aminocoumarin, identical with the authentic specimen prepared by the reduction of 8-hydroxy-7-nitrocoumarin.

The isolation of the aminocoumarin in each case leads to the conclusion that oximes have a syn-methyl structure.

Chapter III : The Mannich bases of the coumarins have been found to stimulate the central nervous system. Further, the Mannich bases are of synthetic importance. Some of the coumarin derivatives have been subjected to the Mannich reaction with primary and secondary amines.

7,8-Dihydroxy-4-methylcoumarin, when subjected to Mannich reaction with formalin and dimethylamine, morpholine and piperidine gave corresponding aminomethyl derivatives. The structures of these derivatives have been established by their conversion into the known 7,8-dihydroxy-6-formyl-4-methylcoumarin when heated with hexamethylenetetramine.

5-Hydroxy-4-methylcoumarin, formalin and benzylamine gave the oxazino derivative which on hydrolysis gave the 6-benzylaminomethyl derivative. This when heated with hexamine gave the formyl derivative. On Dakin oxidation it afforded the known 5,6-dihydroxy-4-methylcoumarin.

Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate when reacted with dimethyl amine and formalin gave a product to which methyl-5-hydroxy-8-dimethylaminomethyl-4-methylcoumarin-6-carboxylate structure has been assigned. The aminomethyl derivative was converted into acetoxymethyl derivative by heating with acetic anhydride and sodium acetate. The same acetoxymethyl derivative was prepared by chloromethylation of methyl-5-hydroxy-4-methyl-coumarin-6-carboxylate and subsequent treatment with the acetic anhydride and sodium acetate.

8-Hydroxycoumarin, formalin and benzylamine gave an oxazino derivative which on hydrolysis afforded 8-hydroxy-7-benzylaminomethylcoumarin. This was subjected to Sommelet reaction when 8-hydroxy-7-formylcoumarin described earlier was obtained.

8-Hydroxycoumarin, formalin and piperidine gave the 7-piperidino methylcoumarin which on treatment with hexamine gave the 8-hydroxy-7-formylcoumarin.

The 6'-hydroxy-4-methyl-7,8-benzocoumarin with formalin and benzylamine gave an oxazino derivative which on hydrolysis gave 6'-hydroxy-5'-benzylaminomethyl-4-methyl-7,8-benzocoumarin. This on Sommelet reaction afforded 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin. With aniline also it afforded the oxazinoderivative which could not be hydrolysed further and gave polymeric product.

6'-Hydroxy-4-methyl-7,8-benzocoumarin, formalin and morpholine gave 6'-hydroxy-5'-morpholinomethyl-4-methyl-7,8-benzocoumarin. On Sommelet reaction it gave 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin.

5,7-Dihydroxy-4-methylcoumarin, formalin and dimethylamine on Mannich reaction gave a polymeric product.