SUMMARY

Benzo-α-pyrones or coumarins are of interest as many members of this class of compounds are found in nature and a number of natural and synthetic coumarins are found to have therapeutic properties.

The present work consists of studies on the synthesis of 3-hydroxy- and 4-hydroxycoumarin derivatives, coumarino-α-pyrones and furocoumarins, and the use of ion exchange resins as catalysts in the Pechmann, Knoevenagel and Michael reactions. Further, several approaches have ~~also~~ been tried to synthesise 7-hydroxy-6-acylcoumarins.

Chapter I. Studies on 3-hydroxycoumarin

Though 3-hydroxycoumarin was first synthesised as early as 1885, the studies on 3-hydroxycoumarins are relatively few. The present work deals with the synthesis of some substituted 3-hydroxycoumarins and a study of the pattern of substitution in 3-hydroxycoumarin.

5-Bromo-, 3,5-dibromo-, 3-nitro-, and 3,5-dinitrosalicylaldehyde, methyl-2,4-dihydroxy-3-formyl benzoate and 2,4-dihydroxy-3-formylacetophenone were condensed with acetylglycine in the presence of sodium acetate and acetic anhydride and the corresponding 3-acetamidocoumarins were obtained which on hydrolysis with 3 N alcoholic hydrochloric acid gave the corresponding 3-hydroxycoumarins. None of these was found to have any antibacterial properties. Further, 3-hydroxycoumarin has been subjected to various reactions.

3-Hydroxycoumarin gave 4-isonitroso-2,3-diketochroman with nitrous acid indicating that it partly exhibits ketonic character. With bromine in acetic acid it gave the 4-bromoderivative and with iodine and iodic acid the 4-iododerivative both of which gave the original coumarin on reduction with zinc and acetic acid. Further bromination did not succeed but 6-bromo- and 6,8-dibromo-3-hydroxycoumarin could be brominated in the 4-position. 3-Acetoxycoumarin underwent Fries migration to 4-acetyl-3-hydroxycoumarin which was also obtained on Friedel-Crafts acetylation of 3-hydroxycoumarin. The structure of this compound was proved by alkaline permanganate oxidation to salicylic acid. 3-Hydroxycoumarin when treated with formaldehyde gave 4,4'-methylene bis (3-hydroxycoumarin).

Chapter II. Studies on 4-hydroxycoumarins

It has been observed by several workers that 3-alkyl or aralkyl-4-hydroxycoumarin derivatives possess coagulant, anticoagulant and antibacterial properties. The present work deals with the synthesis of 3-alkyl- or 3-aralkyl-4-hydroxycoumarins by the condensation of different phenols with ethyl methyl malonate or ethyl benzyl malonate in refluxing diphenyl ether. In the case of reactive phenols such as resorcinol, phloroglucinol and α-naphthol the yields are over 60 %, but they are poor in the case of less reactive phenols such as phenol and β-naphthol.

Resorcinol, when condensed with ethyl methyl malonate, gave 3-methyl-4,7-dihydroxycoumarin but when condensed with ethyl benzyl malonate, it gave 3-benzyl-

4,5-dihydroxycoumarin. The structure of this compound was proved by its conversion to the known 4,5-dihydroxycoumarin on heating with anhydrous aluminium chloride. Orcinol, when condensed with ethyl methyl malonate and ethyl benzyl malonate gave compounds which developed bluish violet colouration with alcoholic ferric chloride solution and hence were assigned 3,7-dimethyl-4,5-dihydroxycoumarin and 3-benzyl-7-methyl-4,5-dihydroxycoumarin structure respectively. Hydroquinone, pyrogallol, phloroglucinol, α-naphthol and β-naphthol on a similar condensation with ethyl methyl malonate and ethyl benzyl malonate gave the corresponding 3-substituted-4-hydroxycoumarins.

Chapter III. Synthesis of Coumarino-α-pyrones and Furocoumarins

7-Hydroxy-3,4-dimethylcoumarin when condensed with malic acid gave 3,4-dimethylcoumarino-7,8-α-pyrone. The structure was proved by direct comparison with the product obtained on Perkin acetylation of 7-hydroxy-8-formyl-3,4-dimethylcoumarin. The structure of the formyl derivative was proved by converting it to the known 7,8-dihydroxy-3,4-dimethylcoumarin by Dakin Oxidation. 7,8-Dihydroxy-3,4-dimethylcoumarin and 5-hydroxy-3,4,7-trimethylcoumarin on a similar condensation with malic acid gave 8-hydroxy-3,4-dimethylcoumarino-7,6-α-pyrone and 3,4,7-trimethylcoumarino-5,6-α-pyrone respectively. 7-Hydroxy-4,8-dimethylcoumarin and 7-hydroxy-4,6-dimethylcoumarin did not condense with malic acid.

7-Hydroxy-3-bromo-4-methylcoumarin when condensed with malic acid gave 3-bromo-4-methylcoumarino-7,8-α-pyrone. It was also obtained by the bromination of 4-methylcoumarino-7,8-α-pyrone. The bromo derivative on hydrolysis with alcoholic potassium hydroxide solution, gave furo-3'-methyl-4',5',5,6-coumarin-2'-carboxylic acid which afforded furo-3'-methyl-4',5',5,6-coumarin on decarboxylation with copper and quinoline. This is a new approach to the synthesis of furocoumarins. 7,8-Dihydroxy-3-bromo-4-methylcoumarin on a similar condensation with malic acid gave 8-hydroxy-3-bromo-4-methylcoumarino-7,6-α-pyrone. Attempts to synthesise 3-methylxanthotoxol and 3-methylxanthotoxin by hydrolysing the bromo compound by alcoholic potassium hydroxide solution, or sodium carbonate solution met with failure. 7-Hydroxy-3,8-dibromo-4-methylcoumarin and 7-hydroxy-3,6-dibromo-4-methylcoumarin did not condense with malic acid.

Attempt was made to synthesise 4-methyl-furo-4',5'-6,5-coumarin by condensing 6-hydroxy-5-formyl-4-methylcoumarin with ethyl bromoacetate followed by hydrolysis and subsequent cyclisation. But it met with failure as no definite product could be isolated in the second step.

4-Methylcoumarino-7,8-α-pyrone was subjected to different reactions such as iodination, chloromethylation and Friedel-Crafts acetylation but only the original coumarin was obtained back in all the reactions.

Chapter IV. Ion exchange resins as catalysts in the synthesis of coumarin derivatives and Michael addition to some coumarin derivatives

The use of cation exchange resins such as Amberlite IR-120 or Duolite C-20 as catalysts in the Pechmann reaction has been investigated. A mixture of resorcinol, ethyl acetoacetate and Duolite C-20 gave 7-hydroxy-4-methylcoumarin in over 40 % yield when the reaction was carried out on a stem bath and in over 60 % yield when the reaction was carried out at 150° for 1 hr. The reactive phenols such as phloroglucinol, pyrogallol and α-naphthol gave the corresponding coumarin derivatives in over 50 % yield but the less reactive phenols such as phenol, β -naphthol and methyl-β-resorcylate did not give any coumarin derivative under the above conditions. The cation exchange resins therefore appear to be mild condensing agents as far as the Pechmann reaction is concerned.

The use of anion exchange resins such as Amberlite IRA-400 in the Knoevenagel reaction has been investigated. Salicylaldehyde on condensation with diethyl malonate and ethyl acetoacetate in the presence of Amberlite IRA-400 gave 3-carboethoxy- and 3-acetylcoumarin respectively. When it was condensed with ethyl cyanoacetate in the presence of Amberlite IRA-400 it gave ethyl salicylidin bis cyanoacetate. 2-Hydroxy-1-naphthaldehyde, on a similar condensation with diethyl malonate, ethyl acetoacetate and ethyl cyanoacetate in the presence of Amberlite IRA-400 gave the corresponding 3-substituted-5,6-benzocoumarin.

The use of anion exchange resins in Michael reaction has also been investigated. Simple coumarin was condensed with cyano acetamide and diethyl malonate in the presence of Amberlite IRA-400 and the corresponding 3,4-dihydrocoumarin-4-cyanoacetamide and diethyl-3,4-

dihydrocoumarin-4-malonate were obtained. 3-Benzoylcoumarin on a similar condensation with cyanoacetamide gave 3-benzoyl-3,4-dihydro-4-cyanoacetamide. 3-Cyanocoumarin similarly condensed with cyanoacetamide and ethyl cyanoacetate to give 3-cyano-3,4-dihydrocoumarin-4-cyanoacetamide and ethyl-3-cyano-3,4-dihydrocoumarin-4-cyanoacetate respectively.

Chapter V. Studies on the synthesis of 7-hydroxy-6-acylcoumarins

7-Hydroxy-6-acylcoumarins are of interest as such compounds are found in nature and further they could be used in the synthesis of psoralene type of furocoumarins. Three approaches to the synthesis of 7-hydroxy-6-acylcoumarins have been tried.

Gattermann formylation of resacetophenone gives 2,4-dihydroxy-3-formylacetophenone, attempt was therefore made to synthesise 2,4-dihydroxy-5-formylacetophenone, an intermediate for the synthesis of 7-hydroxy-6-acylcoumarins, by formylating resacetophenone by other methods such as Reimer-Tiemann reaction, Duff and Bill reaction, etc. Attempt was also made to synthesise it by carrying out Friedel-Crafts acetylation of β-resorcylaldehyde but these attempts did not succeed.

The Fries migration of 7-acyloxy-8-carbomethoxy-4-methylcoumarin was next studied. It gave 7-hydroxy-8-carboxy-4-methylcoumarin. Friedel-Crafts acetylation of 7-hydroxy-8-carbomethoxy-4-methylcoumarin also did not succeed. Fries migration of 7-acetoxy-8-bromo-4-methylcoumarin was then tried. In this case also deacetylated product was obtained.

Friedel-Crafts acetylation of 7-hydroxy-8-bromo-4-methylcoumarin also failed.

Attempt to synthesise 7-hydroxy-6-acyl-3-carboethoxycoumarin by the condensation of resacetophenone with ethoxy methylene malonic ester in the presence of sodium ethoxide and also by refluxing the reaction mixture in boiling diphenyl ether did not succeed.