SUMMARY

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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 in the synthesis of coumarino-α-pyrones and furocoumarins, benzofurocoumarins and coumarino-γ-pyrones.

CHAPTER I : Studies in the synthesis of coumarino-α-pyrones and furocoumarins.

Coumarino-α-pyrones in which α-pyrone ring is built on 3,4-position of coumarin ring system, are synthesised by the Pechmann condensation of 4-hydroxycoumarin with malic acid and ethyl acetoacetate in the presence of sulphuric acid and anhydrous aluminium chloride.

4-Hydroxycoumarin on Pechmann condensation with malic acid in the presence of 80 % sulphuric acid gave 2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran which on bromination gave the 3-bromo derivative. This bromo derivative on hydrolysis with 10 % sodium carbonate solution afforded 4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid which on decarboxylation gave 4-oxo-4H-furo(3,2-c)benzopyran.

4-Hydroxycoumarin was condensed with ethyl acetoacetate in the presence of 80 % sulphuric acid

to give 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran. When 4-hydroxycoumarin was condensed with ethyl acetoacetate in the presence of trifluoroacetic acid it gave the same 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran and not 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran as claimed by Woods. The structure was confirmed by I.R.Spectra and by comparing the product with the authentic sample prepared by using anhydrous aluminium chloride as condensing agent. The same coumarino-α-pyrone was also prepared by refluxing 4-hydroxycoumarin with ethyl acetoacetate in diphenyl ether.

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran on bromination gave 3-bromo derivative. This bromo derivative when hydrolysed by refluxing with 10 % sodium carbonate solution it gave 2-(o-hydroxyphenyl)-4-methyl-furan-3-carboxylic acid and not the corresponding 3-methyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid. This acid on cyclisation by refluxing it with con.hydrochloric acid gave 3-methyl-4-oxo-4H-furo(3,2-c)benzopyran.

Similarly 4-hydroxy-6-methylcoumarin and 4-hydroxy-7-methoxycoumarin on Pechmann condensation with ethyl acetoacetate in the presence of trifluoroacetic acid or diphenyl ether or sulphuric acid or anhydrous aluminium chloride gave 4,9-dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran and 8-methoxy-4-methyl-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran respectively. These coumarino-α-pyrones

on bromination gave corresponding 3-bromo derivatives which were hydrolysed by refluxing with 10 % sodium carbonate solution to 2-(2'-hydroxy-5'-methylphenyl) -4-methylfuran-3-carboxylic acid and 2-(2'-hydroxy-4'-methoxyphenyl)-4-methylfuran-3-carboxylic acid respectively. These acids were then cyclised to corresponding 3,8-dimethyl-4-oxo-4H-furo(3,2-c) benzopyran and 3-methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran.

4-Hydroxy-7-methoxy-8-methylcoumarin on Pechmann condensation with ethyl acetoacetate in the presence of anhydrous aluminium chloride gave 4,7-dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran which on bromination followed by hydrolysis and subsequent cyclisation gave 3,6-dimethyl-7-methoxy-4-oxo-4H-furo (3,2-c)benzopyran.

4-Hydroxy-3-benzoylcoumarin was condensed with ethyl bromoacetate in dry acetone to give ethyl- 3-phenyl 4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate which was hydrolysed and subsequently decarboxylated to 3-phenyl-4-oxo-4H-furo(3,2-c)benzopyran. 4-Hydroxy-6-methyl-coumarin was benzoylated with benzoyl chloride in the presence of pyridine and piperidine to give 4-benzoyloxy-6-methylcoumarin which on Fries migration gave 4-hydroxy-3-benzoyl-6-methylcoumarin. This on condensation with ethyl bromoacetate, followed by hydrolysis and decarboxylation yielded 3-phenyl-8-methyl-4-oxo-4H-furo (3,2-c)benzopyran.

4-Hydroxycoumarin was allylated with allyl bromide in dry acetone to give 4-allyloxycoumarin which on Claisen rearrangement gave 2-methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran. This dihydrofurocoumarin on dehydrogenation with 10 % palladised charcoal gave 2-methyl-4-oxo-4H-furo(3,2-c)benzopyran. Similarly 4-hydroxy-6-methylcoumarin, 4-hydroxy-7-methoxycoumarin, 4-hydroxy-7-methoxy-8-methylcoumarin and 4-hydroxy-7,8-dimethoxycoumarin were allylated with allyl bromide and the allyloxycoumarin derivatives on Claisen rearrangement gave respective dihydrofurocoumarins which were then dehydrogenated to 2,8-dimethyl-4-oxo-4H-furo(3,2-c) benzopyran, 2-methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran, 2,6-dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran and 2-methyl-6,7-dimethoxy-4-oxo-4H-furo (3,2-c)benzopyran respectively.

A few furocoumarins in which a furan ring is built up on a benzenoid part of 4-hydroxycoumarin ring systems were also synthesised.

2,5-Dihydroxyacetophenone was allylated with allyl bromide to 2-hydroxy-5-allyloxyacetophenone which was converted to 4-hydroxy-6-allyloxycoumarin by sodium and diethyl carbonate. It was then methylated and the methyl ether on Claisen rearrangement in dimethyl aniline afforded 4-methoxy-6-hydroxy-5-allylcoumarin. The structure was proved by NMR spectra. This allylcoumarin was then cyclised by triturating it with con.sulphuric acid to 4-methoxy-2-methyl-2,3-dihydro-6-oxo-6H-furo

(3,2-f)benzopyran which was subsequently dehydrogenated and then demethylated to 4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran. When this furocoumarin was refluxed with formaldehyde solution it gave 5,5'-methylene bis [4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran].

Similarly a linear and an angular furocoumarins were synthesised.

2,4-Dihydroxy-3-methylacetophenone was allylated and then converted into 4-hydroxy-7-allyloxy-8-methyl-coumarin by sodium and diethyl carbonate. It was then methylated and the methyl ether on Claisen rearrangement in diethyl aniline afforded 4-methoxy-6-allyl-7-hydroxy-8-methylcoumarin which was cyclised by triturating it with con.sulphuric acid to 4-methoxy-5',8-dimethyl-4',5'-dihydropsoralene. This dihydropsoralene was then dehydrogenated with 10 % palladised charcoal to 4-methoxy-5',8-dimethylpsoralene. It was then demethylated to 4-hydroxy-5',8-dimethylpsoralene and treated with formaldehyde to give 3,3'-methylene bis(4-hydroxy-5',8-dimethylpsoralene).

Resacetophenone was allylated and then converted to 4-hydroxy-7-allyloxycoumarin. It was then methylated and the methyl ether on Claisen rearrangement in dimethyl aniline afforded 4-methoxy-7-hydroxy-8-allyl-coumarin which was cyclised by triturating it with con. sulphuric acid to 7-methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran.

The same dihydrofurocoumarin was prepared by another route. 4-Allyloxyresacetophenone on Claisen rearrangement gave 3-allylresacetophenone according to Baker and Lothian. This 3-allylresacetophenone was cyclised by triturating it with con.sulphuric acid to 2-methyl-4-hydroxy-5-acetylcoumaran. It was then converted to 7-hydroxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran which was methylated to 7-methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran.

This dihydrofurocoumarin was then dehydrogenated with palladised charcoal and subsequently demethylated to 7-hydroxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran. It was treated with formaldehyde solution to give 6,6'-methylene bis[7-hydroxy-2-methyl-5-oxo-5H-furo (2,3-h)benzopyran].

CHAPTER II : Studies in the synthesis of benzofuro-coumarins :

A few benzofurocoumarin derivatives were prepared by oxidative condensation of catechol with 4-hydroxy-coumarin derivatives.

4-Hydroxy-6-methylcoumarin on oxidative condensation with catechol in the presence of potassium iodate and sodium acetate gave 2-methyl-8,9-dihydroxy-6-oxo-6H-benzofuro(3,2-c)benzopyran which was methylated to 2-methyl-8,9-dimethoxy-6-oxo-6H-benzofuro(3,2-c) benzopyran.

Similarly 4-hydroxy-6-methoxycoumarin,

4-hydroxy-7-methoxy-8-methylcoumarin, 4-hydroxy-5-methoxycoumarin, 4-hydroxy-7,8-dimethoxycoumarin on oxidative condensation with catechol gave corresponding 2-methoxy-8,9-dihydroxy-6-oxo-6H-benzofuro(3,2-c) benzopyran, 4-methyl-3-methoxy-8,9-dihydroxy-6-oxo-6H-benzofuro(3,2-c)benzopyran, 1-methoxy-8,9-dihydroxy-6-oxo-6H-benzofuro(3,2-c)benzopyran and 3,4-dimethoxy-8,9-dihydroxy-6-oxo-6H-benzofuro(3,2-c)benzopyran. As these benzofurocoumarins were insoluble in many of the common organic solvents, they could not be crystallised and hence were methylated directly to 2,8,9-trimethoxy-6-oxo-6H-benzofuro(3,2-c)benzopyran, 4-methyl-3,8,9-trimethoxy-6-oxo-6H-benzofuro(3,2-c)benzopyran, 1,8,9-trimethoxy-6-oxo-6H-benzofuro(3,2-c)benzopyran and 3,4,8,9-tetramethoxy-6-oxo-6H-benzofuro(3,2-c) benzopyran respectively.

CHAPTER III : Studies in the synthesis of coumarino-γ-pyrones :

3-Acetyl-4-hydroxy-6-methylcoumarin on Claisen condensation with ethyl acetate in the presence of sodium gave 3-acetoacetyl-4-hydroxy-6-methylcoumarin which was subsequently cyclised by 25 % sulphuric acid to 2,9-dimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran. The structure was confirmed on the basis of I.R.spectra.

Similarly 3-acetyl-4-hydroxy-7-methoxycoumarin on Claisen condensation with ethyl acetate gave 3-acetoacetyl-4-hydroxy-7-methoxycoumarin. This

β-dicarbonyl compound on cyclisation with 25 % sulphuric acid gave corresponding coumarino-γ-pyrone but at the same time it was demethylated to give 2-methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran. The structure of this compound was proved by I.R.spectra.

3-Acetyl-4-hydroxy-6-methylcoumarin was condensed with ethyl benzoate in the presence of sodium to give β-diketonic compound, 3-benzoylacetyl-4-hydroxy-6-methylcoumarin which was cyclised with 50 % sulphuric acid to 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran.

3-Acetyl-4-hydroxycoumarin and 3-acetyl-4-hydroxy-6-methylcoumarin on Claisen condensation with ethyl oxalate gave corresponding 3-oxalylacetyl-4-hydroxy-coumarin and 3-oxalylacetyl-4-hydroxy-6-methylcoumarin which were cyclised by refluxing with 50 % sulphuric acid to 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid and 9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran-2-carboxylic acid respectively. These acids when heated with copper and quinoline or heated above their melting points only unworkable products were obtained.

3-Propionyl-4-hydroxy-6-methylcoumarin on Kostanecki-Robinson acetylation gave 2,3,9-trimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran.

4-Hydroxy-7-methoxycoumarin on Friedel-Crafts propionylation gave 3-propionyl-4-hydroxy-7-methoxycoumarin which on Kostanecki-Robinson acetylation gave 2,3-dimethyl-

8-methoxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran.

3-Acetyl-4-hydroxy-6-methylcoumarin and 3-acetyl-4-hydroxy-7-methoxycoumarin on condensation with benzaldehyde in the presence of potassium hydroxide gave corresponding chalkone derivatives, 3-cinnamoyl-4-hydroxy-6-methylcoumarin and 3-cinnamoyl-4-hydroxy-7-methoxycoumarin. Attempts to cyclise these chalkone derivatives to corresponding coumarino-γ-pyrone derivatives by refluxing with selenium dioxide in isoamyl alcohol were unsuccessful.

Similarly 3-acetyl-4-hydroxy-6-methylcoumarin and 3-acetyl-4-hydroxy-7-methoxycoumarin were condensed with anisaldehyde in the presence of potassium hydroxide to give 3-(p-methoxy)-cinnamoyl-4-hydroxy-6-methyl-coumarin and 3-(p-methoxy)-cinnamoyl-4-hydroxy-7-methoxy-coumarin. When these chalkone derivatives were refluxed with selenium dioxide in isoamyl alcohol, they could not be cyclised and only original chalkone derivatives were recovered.