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 was undertaken with a view to study some aspects of the chemistry of coumarins. It consists of studies in the syntheses of cyclohexenocoumarin derivatives, reactions on 7-hydroxy-3,4-cyclohexenocoumarin, the syntheses of some hitherto unknown psoralene derivatives and coumarino-α-and γ-pyrones, reactions on 4-hydroxy-5,6-benzocoumarin and the syntheses of bi(coumarinoxy)methanes.

Chapter I . Studies in the syntheses of cyclohexeno--coumarins

Cyclohexenocoumarins in which the cyclohexene ring is attached in the 3,4-position are prepared by the condensation of phenols with cyclic-β-ketonic esters. It was therefore thought of interest to synthesise different cyclohexenocoumarin derivatives in which the cyclohexene ring is fused in the 5,6-position of the coumarin ring systems.

Succinoylation of resorcinol afforded β-(2,4-dihydroxybenzoyl) propionic acid which on Clemmensens reduction with zinc amalgam and hydrochloric acid gave γ-(2,4-dihydroxyphenyl)butyric acid. The acid on Pechmann

reaction with ethyl acetoacetate and sulphuric acid gave 7-hydroxy-4-methylcoumarin-6-butyric acid and its ethyl ester. The structure of the latter was proved by esterification of the former with ethanol and sulphuric acid and also by hydrolysis. This ester on methylation afforded ethyl 7-methoxy-4-methylcoumarin-6-butyrate which on treatment with sodium hydroxide and excess of dimethyl sulphate furnished the corresponding cinnamic acid, thus confirming the coumarin structure. 7-Hydroxy-4-methylcoumarin-6-butyric acid on methylation with dimethyl sulphate gave methyl 7-methoxycoumarin-6-butyrate which on hydrolysis with 6% sodium hydroxide solution afforded 7-methoxy-4-methylcoumarin-6-butyric acid. This acid on cyclisation furnished 7-methoxy-4-methyl-4'-ketocyclohexeno(5',6',5,6)coumarin by using either polyphosphoric acid or by Johnson's inverse process of cyclisation with phosphorus pentachloride and anhydrous aluminium chloride.

α-Naphthol condensed with succinic anhydride in the presence of anhydrous aluminium chloride and nitro - benzene and gave (4-hydroxynaphthoyl) propionic acid. This on Clemmensens reduction afforded (4-hydroxynaphthyl) butyric acid. The acid on condensation with ethyl acetoacetate and con. sulphuric acid gave 4-methyl-7,8-benzocoumarin-6-butyric acid which on cyclisation with polyphosphoric acid yielded 4-methyl-4'-ketocyclohexeno (5',6',5,6)benzo(h)coumarin.

α-Naphthol on reduction with sodium and amyl alcohol gave ar-tetrahydro-1-naphthol which on Pechmann reaction with ethyl acetoacetate and ethyl benzoylacetate yielded 4-methylcyclohexeno(h)coumarin and 4-phenyl-cyclohexeno(h) coumarin respectively.

Chapter II . Reactions on 7-hydroxy-3,4-cyclohexeno-coumarin

7-Hydroxy-3,4-cyclohexenocoumarin on acetylation with sodium acetate and acetic anhydride gave 7-acetoxy-3,4-cyclohexenocoumarin which on Fries migration with anhydrous aluminium chloride afforded 7-hydroxy-8-acetyl-3,4-cyclohexenocoumarin and 7-hydroxy-6-acetyl-3,4-cyclohexenocoumarin. These compounds were also prepared by the condensation of 2-acetyl resorcinol and resaceto-phenone with ethyl 2-cyclohexanone-2-carboxylate respectively. 7-Hydroxy-8-acetyl-3,4-cyclohexenocoumarin was condensed with ethyl bromoacetate to ethyl 8-acetyl-3,4-cyclohexeno-7-coumarinyloxyacetate and the ester thus obtained was hydrolysed to the corresponding acid which was cyclised by refluxing it with fused sodium acetate and acetic anhydride to 11-methyl-2H-furo(2,3-h)-3,4-cyclohexeno-benzopyran-2-one. 7-Hydroxy-6-acetyl-3,4-cyclohexeno-coumarin on similar series of reactions afforded 8-methyl-2H-furo(3,2-g)-3,4-cyclohexenobenzopyran-2-one.

7-Hydroxy-3,4-cyclohexenocoumarin on allylation gave 7-allyloxy derivative which on Claisen rearrangement

with dimethyl aniline yielded 7-hydroxy-8-allyl-3,4-cyclohexenocoumarin, the structure of which was proved by its n.m.r.spectra. This on triturating with concentrated sulphuric acid cyclised to 10-methyl-2H-10,11-dihydro-furo(2,3-h) 3,4-cyclohexenobenzopyran-2-one in good yield. This was dehydrogenated by refluxing it with diphenyl ether in the presence of palladised charcoal to 10-methyl-2H-furo (2,3-h) 3,4-benzo-benzopyran-2-one. Dehydrogenation of cyclohexene ring also took place simultaneously.

Bromination of 7-hydroxy-3,4-cyclohexenocoumarin with one mole of bromine gave 8-bromo derivative, the structure of which was proved by the preparation of 7-hydroxy-8-bromo-3,4-cyclohexenocoumarin from 2-bromo resorcinol and ethylcyclohexenone-2-carboxylate. With two moles of bromine it gave 7-hydroxy-6,8-dibromo-3,4-cyclohexenocoumarin which was also obtained by further bromination of 7-hydroxy-8-bromo-3,4-cyclohexenocoumarin.

7-Hydroxy-3,4-cyclohexenocoumarin when treated with hexamethylenetetramine gave 7-hydroxy-8-formyl-3,4-cyclohexenocoumarin the structure of which was confirmed by n.m.r.spectra. Mannich reaction on 7-hydroxy-3,4-cyclohexenocoumarin with formalin and piperidine afforded 7-hydroxy-8-piperidinemethyl-3,4-cyclohexenocoumarin which on treatment with hexamethylenetetramine gave 7-hydroxy-8-formyl-3,4-cyclohexenocoumarin. Similarly with morpholine and formalin 7-hydroxy-3,4-cyclohexenocoumarin gave 8-morpholinomethyl derivative which on Sommelet reaction

with hexamine and acetic acid gave 7-hydroxy-8-formyl-3,4-cyclohexenocoumarin.

Pechmann reaction of 7-hydroxy-3,4-cyclohexenocoumarin with malic acid furnished 2H,10H-pyrano(2,3-h) 3,4-cyclohexenobenzopyran-2,10-dione. 7-Hydroxy-8-acetyl-3,4-cyclohexenocoumarin on Kostanecki-Robinson acetylation with sodium acetate and acetic anhydride gave 10-methyl-11-acetyl-2H,12H-pyrano(2,3-h)3,4-cyclohexenobenzopyran-2,12-dione.

7-Hydroxy-8-acetyl-3,4-cyclohexenocoumarin on condensation with ethylchloroformate gave ethyl-8-acetyl-3,4-cyclohexeno-7-coumarinyloxycarboxylate, which on prolonged refluxion with potassium carbonate in toluene gave the mixture of 7-hydroxy-8-acetyl-3,4-cyclohexenocoumarin and 8-acetyl-3,4-cyclohexeno-7-coumarinyloxy carboxylic acid.

7-Hydroxy-3,4-cyclohexenocoumarin on dehydrogenation with palladised charcoal and diphenyl ether gave 7-hydroxy-3,4-benzocoumarin.

Chapter III . Syntheses of coumarino-α-pyrones and furocoumarins

Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate afforded 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran which on bromination gave 3-bromo derivative. This on hydrolysis with sodium carbonate solution gave 2-(o-hydroxy-α-naphthyl)4-methylfuran-3-carboxylic acid. The cyclisation

of the above acid with hydrochloric acid yielded 3-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran. Similarly 4-hydroxy-5,6-benzocoumarin on condensation with malic acid resulted in the formation of 2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran, the 3-bromo derivative of which was hydrolysed to 4-oxo-4H-furo(3,2-c)benzo(f)benzopyran-2-carboxylic acid. The acid on decarboxylation with copper-quinoline gave 4-oxo-4H-furo(3,2-c)benzo(f)benzopyran.

The Kostanecki-Robinson acetylation and benzoylation of 7-hydroxy-6-acyl-8-methyl derivatives was carried out to synthesise coumarino-α-and γ-pyrones, the structures of which were established by their i.r.spectra.

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin on K.R.acetylation with acetic anhydride and sodium acetate gave 7-acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g) benzopyran-2,6-dione. K.R.benzoylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin with benzoic anhydride and sodium benzoate afforded 4,10-dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione.

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin on condensation with benzaldehyde in alcoholic potassium hydroxide afforded 4,10-dimethyl-8-phenyl-7,8-dihydro-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione. This product on dehydrogenation with selenium dioxide in amyl alcohol gave 4,10-dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione,which was identical with the product obtained from the K.R.benzoylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin.

7-Hydroxy-6-propionyl-4,8-dimethylcoumarin on K.R. acetylation gave 4,7,8,10-tetramethyl-2H,6H-pyrano (3,2-g)benzopyran-2,6-dione.

7-Hydroxy-6-benzoyl-4,8-dimethylcoumarin on refluxion with acetic anhydride and sodium acetate afforded the mixture of 4,10-dimethyl-6-phenyl-2H,8H-pyrano(3,2-g) benzopyran-2,8-dione and 7-acetoxy-6-benzoyl-4,8-dimethyl-coumarin.

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin on condensation with ethyl bromoacetate in the presence of potassium carbonate in acetone yielded ethyl-4,8-dimethyl-6-acetyl-7-coumarinyloxyacetate which on hydrolysis with alkali solution gave 6-acetyl-4,8-dimethyl-7-coumarinyloxy-acetic acid. The cyclisation of this acid was affected by refluxing it with acetic anhydride and freshly fused sodium acetate. Simultaneous decarboxylation and ring closure took place and 4',4,8-trimethylpsoralene was obtained.

Similarly 4'-ethyl-4,8-dimethylpsoralene and 4'-phenyl dimethylpsoralene were synthesised from 7-hydroxy-6-propionyl and 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin respectively.

4,5',8-Trimethylpsoralene is a naturally occuring furocoumarin and was synthesised by Kaufmann. The present work deals with the synthesis of this compound by an another route with the improved yield. 7-Hydroxy-6-allyl-4,8-dimethylcoumarin was cyclised with concentrated sulphuric acid to 4,5',8-trimethyl-4',5'-dihydropsoralene

which was dehydrogenated by refluxing it with diphenyl ether in the presence of palladised charcoal (10 %) to 4,5',8-trimethylpsoralene.

The study of the photodynamic activity of these psoralene derivatives by FMN method is in progress.

Chapter IV. Reactions on 4-hydroxy-5,6-benzocoumarin

It has been observed by several workers that 3-alkyl-or 3-aralkyl-4-hydroxycoumarin derivatives possess coagulant, anticoagulant and antibacterial properties. The present work deals with the study of some reactions on 4-hydroxy-5,6-benzocoumarin and its pattern of substitution towards different reagents.

4-Hydroxycoumarin on Pechmann condensation with ethyl acetoacetate in the presence of trifluoroacetic acid furnished 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 reported by Woods. Similarly 4-hydroxy-5,6-benzocoumarin on condensation with ethyl acetoacetate gave 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran. The structures were confirmed by their i.r.spectra and comparing the products with the authentic samples prepared by using either concentrated sulphuric acid or anhydrous aluminium chloride as condensing agents. The same products were also prepared by refluxing 4-hydroxycoumarin and 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate in the presence of diphenyl ether.

Friedel-Crafts acetylation of 4-hydroxy-5,6-benzocoumarin with acetic acid in the presence of phosphorus oxychloride afforded 3-acetyl-4-hydroxy-5,6-benzocoumarin which on Claisen condensation with ethyl acetate gave 3-acetoacetyl-4-hydroxy-5,6-benzocoumarin. The above β-diketone was cyclised with 25 % sulphuric acid to 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran. Similar Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl oxalate yielded 3-aceto-oxalyl-4-hydroxy-5,6-benzocoumarin which on cyclisation gave 2-carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran.

3-Acetyl-4-hydroxy-5,6-benzocoumarin on Kostanecki-Robinson reaction with acetic anhydride and sodium acetate gave 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzo(f)benzopyran.

Friedel-Crafts propionylation of 4-hydroxy-5,6-benzocoumarin with propionic acid afforded 3-propionyl-4-hydroxy-5,6-benzocoumarin.

Fries migration of 4-benzoyloxy-5,6-benzocoumarin yielded 3-benzoyl-4-hydroxy-5,6-benzocoumarin which on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate resulted in the formation of 4-phenyl-2,5-dioxo-2H,5H-pyrano-(3,2-c)benzo(f)benzopyran.

4-Hydroxy-5,6-benzocoumarin on allylation with allyl bromide gave 4-allyloxy-5,6-benzocoumarin. This on Claisen rearrangement by heating at 200° afforded 2-methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran and not

4-hydroxy-3-allyl-5,6-benzocoumarin. The rearranged product on dehydrogenation by refluxing it with diphenyl ether in the presence of palladised charcoal yielded 2-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran.

3-Acetyl-4-hydroxy-5,6-benzocoumarin on condensation with benzaldehyde gave the chalkone,3-cinnamoyl-4-hydroxy-5,6-benzocoumarin.

It was reported that bridge substituted dicoumarols possess anticoagulant activity. 4-Hydroxy-5,6-benzocoumarin on condensation with salicylaldehyde gave 3,3'-alkylidene bis(4-hydroxycoumarin) derivative. 4-Hydroxy-5,6-benzocoumarin on condensation with catechol in the presence of sodium acetate and potassium iodate gave the angular coumaronocoumarin which on methylation afforded the dimethoxy coumaronocoumarin derivative.

Nitration of 4-hydroxy-5,6-benzocoumarin ~~resulted~~ gave 3-nitro-4-hydroxy-5,6-benzocoumarin which on reduction afforded 3-amino-4-hydroxy-5,6-benzocoumarin.

Chapter V . Syntheses of bi(coumarinoxy)methanes

The present work was carried out with a view to study the methylenation of different hydroxycoumarins. Methylenation was carried out by refluxing the mixture of hydroxycoumarin, anhydrous potassium carbonate, dry acetone and methylene iodide ~~where~~ and a bimolecular compound linked by a methylenedioxy group was obtained. Thus

bi-(4-methyl-7-coumarinoxy) methane, bi(3-coumarinoxy), bi(4-coumarinoxy), bi(4-methyl-5-coumarinoxy), bi(4,7-dimethyl-5-coumarinoxy), bi(4-methyl-6-coumarinoxy), bi(7-coumarinoxy) and bi(4-phenyl-7-coumarinoxy) methane were synthesised from 7-hydroxy-4-methyl-, 3-hydroxy-, 4-hydroxy-, 5-hydroxy-4-methyl-, 5-hydroxy-4,7-dimethyl-, 6-hydroxy-4-methyl-, 7-hydroxy-, and 7-hydroxy-4-phenyl-coumarin respectively.