SUMMARY

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Benzo-α-pyrones commonly known as coumarins occur widely in nature. Most of them are isolated from plants and few from animals or microorganisms. Coumarins attracted attention due to their varied physiological and biochemical properties.

Coumarin itself inhibits the germination and root growth of the plants. Coumarins are widely used from ancient times in Tibetan and Chinese medicines. Furocoumarins are used as fish poison. Psoralen incombination with UV light (PUVA) is the best available photochemotherapy for the treatment of skin diseases like psoriasis, vitiligo etc.

In the present work synthesis of linear and as well as angular furocoumarins, aminomethylangelicin and psoralen derivatives and some reactions with 3,4-dihydrocoumarins which leads to the synthesis of some naturally occuring compounds like graveolone, xanthyletin and their derivatives have been carried out.

CHAPTER - II

SYNTHESIS OF FUROBENZOPYRONES

7-Hydroxy-4-methylcoumarin on cinnamylation with cinnamylchloride in the presence of dry acetone, K_2CO_3 gave 7-

cinnamyloxy-4-methylcoumarin, which on Claisen rearrangement in N,N-dimethylaniline gave two alkali soluble products and one alkali insoluble product. The alkali soluble products were separated by preparative TLC and assigned 7-hydroxy-4-methyl-8-(1'-phenylprop-1'-ene) coumarin, 7-hydroxy-4-methyl-6-(1'-phenylprop-2'-ene) coumarin while the alkali insoluble product was assigned trans-3,7-dimethyl-2-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5[H]-one on the basis of PMR. The formation of the compound and its mechanism is discussed. The trans stereochemistry established by nOe difference spectra.

The isomeric cis- 2,7-dimethyl-3-phenyl-2,3-dihydrofuro (2,3-h)benzopyran-[H]-one was obtained when 7-hydroxy-4-methyl-8-(1'-phenylprop-1'-ene)coumarin was triturated with con. H_2SO_4. A linear trans-2,7-dimethyl-3-phenyl-2,3-dihydro-furo(3,2-g)benzopyran-7[H]-one was yielded by triturating 7-hydroxy-4-methyl-6-(1'-phenylprop-2'-ene)coumarin with 75% H_2SO_4. These dihydrofurocoumarins were dehydrogenated either with Pd/c in diphenylether or DDQ in dry benzene to make furobenzopyrononeS.

Similarly, Claisen rearrangements were studied on the following coumarin derivatives, 7-cinnamyloxy-4,8-dimethyl-coumarin, 7-cinnamyloxy-4-phenylcoumarin, 7-cinnamyloxy-8-iodo-4-methylcoumarin and 7-cinnamyloxy-8-iodo coumarin.

Following furocoumarins werre synthesised.

(1) 2,7-Dimethyl-3-phenylfuro(2,3-h)benzopyran-5[H]-one

(2) 3,7-Dimethyl-2-phenylfuro(2,3-h)benzopyran-5[H]-one

(3) 2-Methyl-3-phenylfuro(2,3-h)benzopyran-5[H]-one

(4) 2-Methyl-3,7-diphenylfuro(2,3-h)benzopyran-5[H]-one

(5) 2,5-Dimethyl-3-phenylfuro(3,2-g)benzopyran-7[H]-one

(6) 2-Methyl-3-phenylfuro(3,2-g)benzopyran-7[H]-one

(7) 2,5,9-Trimethyl-3-phenylfuro(3,2-g)benzopyran-7[H]-one

CHAPTER - III

SYNTHESIS OF AMINOMETHYLFUROBENZOPYRONES

4,5'-Dimethylangelicin or psoralen are photodynamically active compounds. In this chapter one of the methyl groups in 4,5'-dimethylangelicin or psoralen was transformed to aminomethyl group to enhance the hydrophilic character of the compounds.

2,7-Dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5[H]-one, 2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7[H]-one on bromination with pyridinehydrobromide perbromide in acetic acid gave 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran 5[H]-one and 6-bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g) benzopyran-7[H]-one respectively, which on condensation with

piperidine using dimethylformamide as solvent yielded two products each, 6-piperidinyl-2,7-dimethyl-2,3-dihydrofuro(2,3-h) benzopyran-5[H]-one, 2-methyl-7-piperidinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5[H]-one and 6-piperidinyl-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7[H]-one, 2-methyl-5-piperidinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7[H]-one, the later one being the unexpected product in both the cases whose formation and mechanism is discussed, while the condensation of the bromo compounds with other secondary cyclic amines morpholine, N-methylpiperizine and N-phenylpiperizine only yielded 2-methyl-7-aminomethyl-2,3-dihydrofuro(2,3-h)benzopyan-5[H]-one and 2-methyl-5-aminomethyl-2,3-dihydrofuro (3,2-g)benzopyran-7[H]-one.

These aminomethyl dihydrofurobenzopyrones were subjected to dehydrogenation with DDQ in dry benzene, DDQ in dioxan and Pd/c in diphenylether. Dehydrogenation had not taken place with DDQ while with Pd/c in diphenylether hydrogenolysis had occurred giving known compounds 2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5[H]-one and 2,5-dimethyl-2,3-dihydrofuro (3,2-g)benzopyran-7[H]-one.

Synthesis of aminomethylangelicin or psoralen derivatives was achieved first by brominating 4,5'-dimethyl angelicin and 4,5'-dimethylpsoralen with N-bromosucciimide in CCl_4 using benzoylperoxide as reaction initiator to give 2-bromo-

methyl-7-methylfuro(2,3-h)benzopyran-5[H]-one and 2-bromomethyl-5-methylfuro (3,2-g)benzopyran-7[H]-one respectively, bromination on 2-methyl group was confirmed by ^{13}C NMR which on condensation with piperidineusing dimethylformamide as solvent afforded

2-piperidinomethyl-7-methylfuro(2,3-h)benzopyran-5[H]-one,
2-piperidinomethyl-5-methylfuro(3,2-g)benzopyran-7[H]-one.

Alongwith 2-piperidinomethyl derivatives small amount of 4,5'-dimethylangelicin or psoralen was also isolated.

Similar condensation of 2-bromomethyl angelicin with other cyclic secondaryamines morpholine, N-methylpiperizine, N-phenylpiperizine and secondary amines diethanolamine and diethylamine yielded respective 2-aminomethylangelicin derivatives and 2-bromomethylpsoralen with other cyclic secondary amines morpholine, N-methylpiperizine and N-phenylpiperizine afforded corresponding 2-aminomethylpsoralen derivatives.

CHAPTER - IV

SOME REACTIONS OF 3,4-DIHYDROCOUMARINS

It is well established that majority of natually occuring coumarins are C-6 substituted while the substitution and migration on 7-hydroxycoumarin ring system is regiospecifically directed to C-8 position with traces of C-6 isomer. This regiospecificity is shifted to C-6 position in the

case of 7-hydroxy-3,4-dihydrocoumarin ring system. In this chapter C-6 substituted coumarins and some naturally occuring coumarins were synthesised using Friedel-Crafts method.

7-Hydroxy-3,4-dihydrocoumarin on Fridel-Crafts acetylation using nitrobenzene and $AlCl_3$ gave 2,4-dihydroxy-5-acetyl-phenylpropionic acid whichgets cyclised by heating above its melting point furnished 6-acetyl-7-hydroxy-3,4-dihydro-benzopyran-2[H]-one. Dehydrogenation of the compound with Pd/c in diphenyl ether resulted 6-aetyl-7-hydroxybenzopyran-2[H]-one a naturally occuring compound.

Similarly 6-propionyl-7-hydroxy-benzopyran-2[H]-one, 6-acetyl-7-hydroxy-4-phenylbenzopyran-2[H]-one, 6-propionyl-7-hydroxy-4-phenylbenzopyran-2[H]-one and 8,8-dimethylpyano (3,2-g)benzopyran (2H, 6H)-dione (graveolone) were also synthesised.

Xanthyletin and 4-phenylxanthyletin were attempted to synthesise first by condensing 7-hydroxy-3,4-dihydrocoumarin 7-hydroxy-4-phenyl-3,4-dihydrocoumarin with 2-methyl-3-butene-2-ol in the presence of BF_3 etherate in dioxan afforded corresponding phenyl propionic acid derivatives which on cyclisation followed by dehydrogenation with Pd/c in diphenyl ether furnished 8,8-dimethyl-6,7-dihydropyrano(3,2-g)benzo-pyran-2[H]-one and 8,8-dimethyl-4-phenyl-6,7-dihydropyrano

(3,2-g)benzopyran-2[H]-one respectively. Further dehydrogenation at 6,7 position failed.

In all the above reactions of 3,4-dihydrocoumarins the regiospecificity of the ring system was maintained. Hence it was thought of interest to synthesise a linear furocoumarin using the same dihydrocoumarin ring system. Surprisingly the Claisen rearrangement of 7-allyloxy-4-phenyl-3,4-dihydrocoumarin yielded 8-allyl-4-phenyl-3,4-dihydrocoumarin instead of 6-allyl isomer.