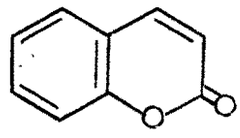
INTRODUCTION

GENERAL INTRODUCTION

Benzo-α-pyrones, generally known as coumarins, are found to be widely distributed in the plant kingdom, either in the free or in the combined state. Coumarin(1), scopoletin (2), aesculetin (3), ayapin (4), fraxetin (5) and daphnetin (6) are a few of the simple coumarins occuring in nature.



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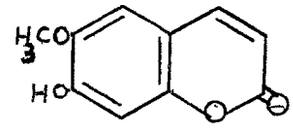

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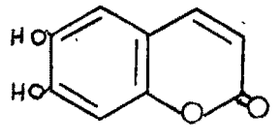

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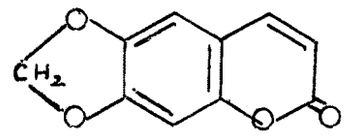

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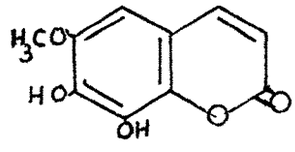

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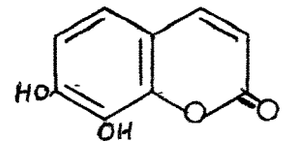
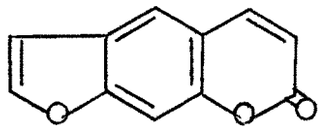


(6)

Another group of the interesting naturally occuring coumarin derivatives are the furocoumarins. Psoralene (7), angelicin (8), bergapten (9), xanthotoxin (10), pimpinellin (11), isopimpinellin (12) and oreoselone (13) are a few members of this group.



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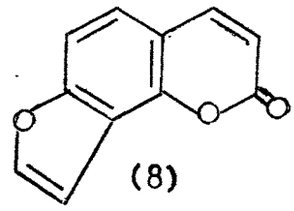

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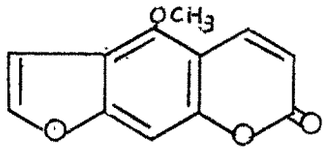

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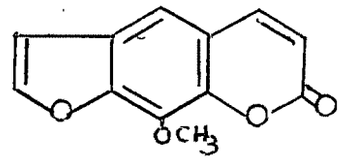

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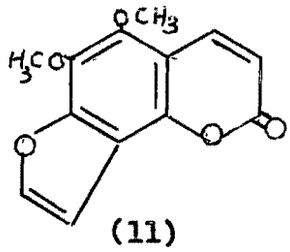

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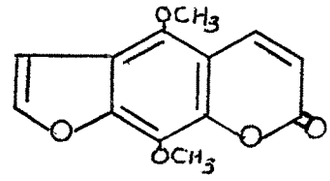

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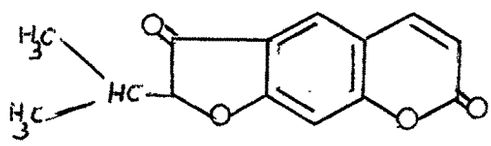


(13)

The interest in coumarin derivatives has increased considerably in recent years because of the discovery of their varied biochemical properties, industrial uses and analytical applications ; a few of these may be briefly described here.

Many natural coumarins affect the living cells of plants and animals in various ways. Bose[1] has reviewed the biochemical properties of natural coumarins. Coumarin itself, inhibits the germination and subsequent root growth of plants. Kelbs[2] observed its toxic action on algae. Sigmund[3] noted the effects of both daphnetin and its isomer aesculetin, on seed germination. It has since been shown that a number of unsaturated lactones, including coumarin possess, what is called the blastocholine effect i.e. the property to suppress the germination of seeds at low concentrations.

There is also a good probability that coumarins act as growth regulators in a number of plants[4].

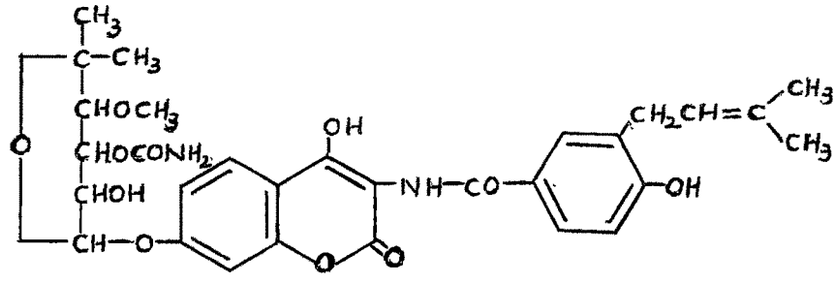
Coumarins have interesting cytogenetic properties.[5] Cytohistological and macroscopical effects of coumarin and its derivatives have been studied by Quercioli[6].

Coumarin acts as a narcotic for some animals and as a sedative and hypnotic for mice[7].

Fraxin causes paralysis of the central nervous system of frogs and mice on intravenous injections[8]. Fraxin has been found to be superior to atophan in the treatment of gout[9].

Link et al.[10] discovered that the haemorrhagic principle of the spoiled sweet clover was 3,3'-methylene bis-(4-hydroxycoumarin) also known as Dicoumarol. This has led to the preparation and testing of several 4-hydroxy-coumarin derivatives as anticoagulant drugs and a number of very effective drugs of this group such as warfarin, tromexan, coumachlor and marcoumar are on the market. It is interesting to note that some simple coumarins have the opposite effect. Herniarin and ayapin have been found to possess a remarkable haemostatic property and are active both in vitro and in vivo[11].

Novobiocin[12], an antibiotic, isolated from Streptomyces Sp., has been proved to be a coumarin derivative having the structure (14). The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin, but, in vitro it is less potent than penicillin and erythromycin.



(14)

Tuberculostatic activity[13] is exhibited by pimpinellin and isopimpinellin.

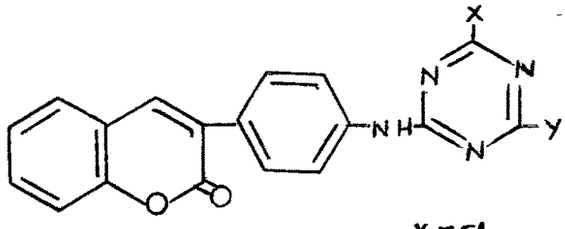
Coumarins and some of its derivatives having m.ps. lower than 70-100^{0} have been generally found to have strong anthelmintic action[14]. An examination of a number of simple coumarin derivatives employing fish, and the turning time as a measure of toxicity has now established, that they have weak toxic properties[15,16]. While coumarins particularly those with furan ring system are toxic to fish[17].

In recent years the discovery of photodynamic action of some of the furocoumarins has led to considerable work in this field[18].

The photodimerization of coumarins is being increasingly studied. The photodimerization product of 7-methoxycoumarin was formulated as a head to head dimer.[19] Simple coumarin however, was found to give both, the head to head and the head to tail dimers[20]. Hammond et al.[21] investigated the mechanism of photodimerization of coumarin. The solvent effects on the photodimerization of coumarin have also been studied.[22]

A number of substituted coumarin derivatives are found to have optical brightening properties for cellulose, polyacrylo nitrile, polyamides and polyester fibers and the literature has been growing in this field.[23,24,25] More complex coumarin derivatives such as (15) obtained by reacting cyanuric chloride with 3(p-aminophenyl)coumarin and treating the compound formed with N-ethyl cyclohexyl-amine ; 7-(1,2,3-triazol-2-yl)-3-phenyl-2-coumarin[26] and

substituted 7-(s-triazinyl amino)-3-arylcoumarin[27,28] are a few of the coumarin derivatives which have good optical brightening properties.



(15)

X = Cl
Y = N-ethylcyclohexylamine

Buu-Hoi and coworkers[29] prepared a series of hydroxylated-3-arylcoumarins as potential carcinostatic and virustatic agents and Elderfield and Roy[30] have very recently synthesised nitrogen mustards from 6-substituted coumarins as potential anticancer agents.

The therapeutic properties of furocoumarins and those of 3,3'-methylene bis-(4-hydroxycoumarin) derivatives are described in chapters III and IV respectively.

There are a number of methods available for the syntheses of coumarin derivatives. These have been reviewed by Sethna and Shah[31] and Wawzonek[32] and need not be enumerated here.

The coumarin derivatives have also been subjected to various substitution reactions such as chlorination,[33,34,35,36] bromination,[37,38,39,40,41,42,43,44,45] iodination,[46,47] chloromethylation,[48] nitration,[49,50,51,52,53,54] Fries and Friedel-Crafts reaction,[55,56,57,58,59,60] formylation,[61,62,63,64,65] sulphonation[66,67,68] and other reactions.

The present work deals with some aspects of the chemistry of coumarins.

In chapter I, the syntheses of some substituted cyclohexenocoumarins from phenols such as resorcinol, α-naphthol and ar-tetrahydro-1-naphthol are described.

In chapter II, several reactions are studied on 7-hydroxy-3,4-cyclohexenocoumarin and the structure of the intermediate compounds obtained, have been proved by their independent syntheses, by their conversion into known compounds and by studying their IR and NMR spectra.

In chapter III, the syntheses of some psoralene derivatives have been described. The same chapter also deals with the study of the Kostanecki-Robinson reaction on 7-hydroxy-6-acyl-4,8-dimethylcoumarin derivatives. The structures of the coumarino-α-and γ-pyrones are established by IR spectra.

In chapter IV, the reactions on 4-hydroxy-5,6-benzocoumarin are described.

In chapter V, o-methylenation study of some hydroxycoumarins is described and different bi(coumarinoxy)methane derivatives have been prepared.

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