CHAPTER – I

INTRODUCTION

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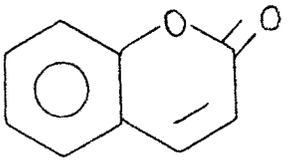
Benzo-α-pyrones, generally known as coumarins, are found to be widely distributed in nature,[1,2] either in the free state or in the combined state. They are found in plants with four major families, the Umbelliferae (e.g. Parsley, Parsnip, Celery, Ammi majus, Angelica archangelica), Rutaceae (e.g. Bergamol fruit, lime, gas plant, cloves, common rue), Leguminosae (Psoralea Corylifolia, Xanthoxylum) and Moraceae (e.g. Ficus Caria).[3] They are found in entire plant from roots to leaves, fruits and flowers.

Coumarins have been reported neither in algae nor in mosses however there are a few reports of coumarins in bacteria and fungi.

Coumarin was first isolated by Vogel[4] in Munich in 1820 from tonka bean. The word coumarin originates[5] from a Carribbean word " Coumarou" for the tonka bean tree, which was known botanically as coumarouna odorata . Aubl. Coumarin is now the accepted trivial name for the compound (1) and the parent name for the group of naturally occuring lactones. Some of the important naturally occuring coumarins are Umbelliferon (2), Aesculetin (3), Ayapin (4), Daphnetin (5), Scopoletin (6) and Fraxetin (7).



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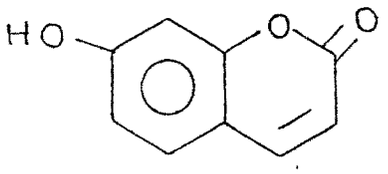

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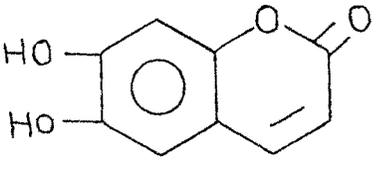

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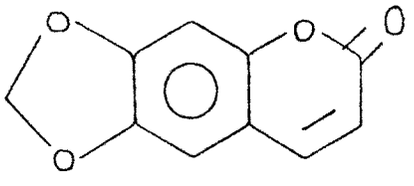

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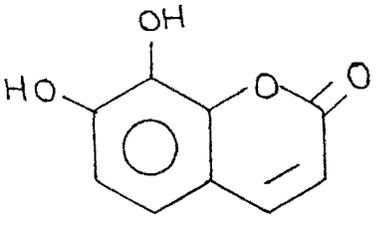

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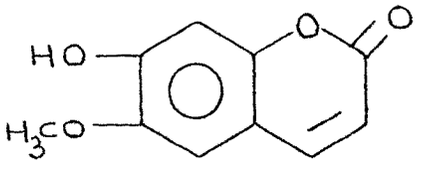

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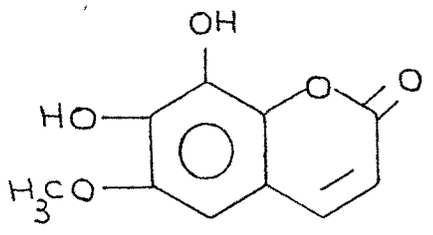
Another group of interesting naturally occuring coumarin derivatives are the furocoumarins. Psoralene (8), Angelicin (9), Bergapten (10), Xanthotoxin (11), Pimpinellin (12), and isopimpinellin (13) are a few members of this group.

Among so many heterocycles, coumarin and its derivatives have attracted considerable interest because of their various physiological and biochemical properties.

Many naturally occuring coumarins affect the living cell of plants and animals in various ways. Bose[6] has reviewed the biochemical properties of natural coumarins. Our knowledge of the biological activities of the simple coumarins dates back for several decades reflecting the long period for which the existence of these compounds has been recognized. In fact, the toxicity of coumarin to green algae was noted by Kelbs[7] before the end of the nineteenth century.

Coumarin itself inhibits the germination and subsequent root growth of plants. Sigmund[8] 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 supress the germination at the low concentration on seeds[9] as well as on animals.[10]



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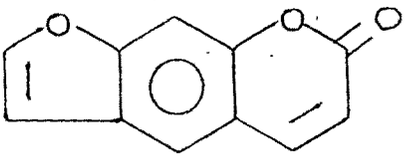

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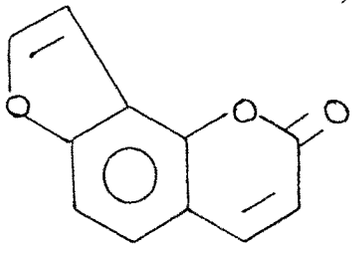

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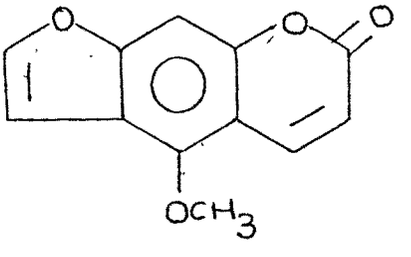

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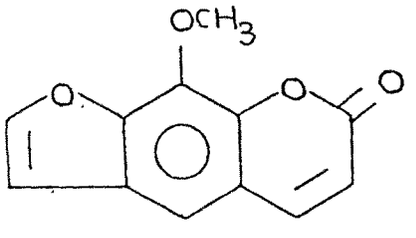

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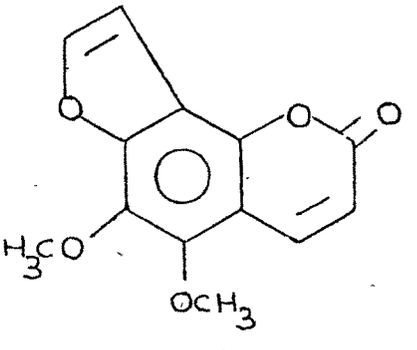

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There is also a good probability that coumarins act as growth regulators in a number of plants.[11]

Coumarins have interesting cytogenetic properties.[12] Cytohistological and macroscopical effects of coumarin and its derivatives have been studied by Quercioli.[13]

Coumarin acts as a narcotic for some animals and as a sedative and hypnotic for mice.[14] Fraxin causes paralysis of the central nervous system of frogs and mice on intravenous injections[15] and it has been found to be superior to atophan in the treatment of gout.[16] Dicoumarol (14) is an effective rodenticide. Antimicrobial action has also been reported for dicoumarol (14) against a variety of bacteria.[17-21]

Link et al.[22] discovered that the haemorrhagic principle of the spoiled sweet clover was 3,3'-methylene-bis-(4-hydroxy-coumarin), also known as dicoumarol (14). This has led to the preparation and testing of several 4-hydroxycoumarin derivatives as anticoagulant drugs and a number of very effective drugs of this group, such as Warfarin, Tromaxan, Coumachlor and Marcoumar are on the market. Later Arora & Mathur[23] found that weak anticoagulant activity was shown by 3- and 4-phenylcoumarins and marked activity by one of the latter. They suggestedthat molecular shape, 8-substitution, ionizing ability and presence of methoxyl function all probably govern anticoagulant activity.

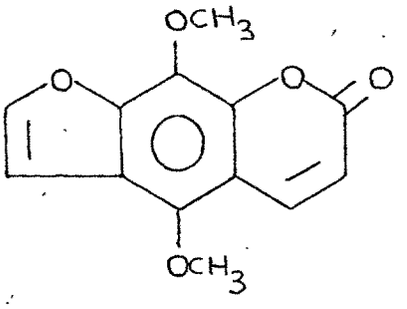
It is interesting to note that some simple coumarins have the opposite effect. Mavingrin and Ayapin (4) have been found to possess remarkable haemostatic property and are active both in vitro and vivo.[24]

Novobiocin[25] (15) an antibiotic, isolated from streptomyces sp., has been found to be a coumarin derivative. The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin, but in vitro is less potent than penicillin and erythromycin.

In the investigation of the mode of novobiocin (15) action, a number of publications suggested that it might exert an effect on nucleic acid metabolism. Smith et al.[26] who first described this antibiotic, noted that it inhibited cell division. Brock[27] observed a decrease in DNA synthesis in partially inhibited cultures of E.Coli and S.aureus.

The inhibition of nucleic acid synthesis in E.Coli was also recently confirmed by Smith and Daris[28,29] in S.aureus by Winshow et al.[30] Higgins et al.[31,32] have found that novobiocin (15) and coumarmycin A, (16) inhibit DNA gyrase by preventing the binding of ATP to the enzyme, interacting competitively in both the supercoiling and ATPase reactions.

Drlica and Snyder[33] found reduced superhelical densities in folded chromosomes from E.Coli strains treated in Vivo



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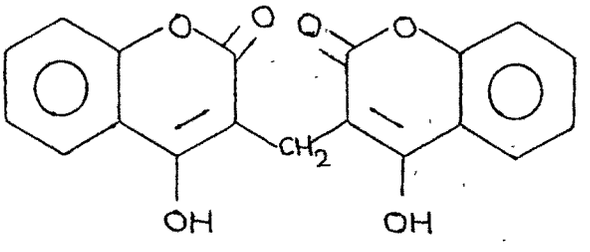

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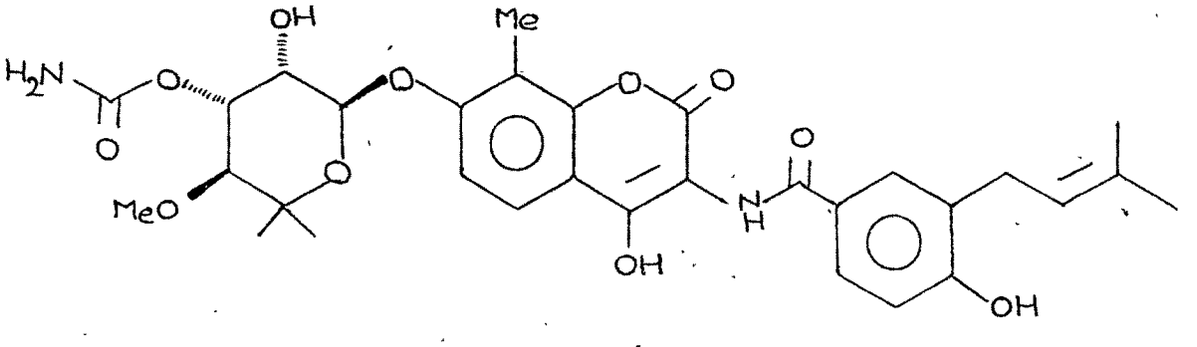

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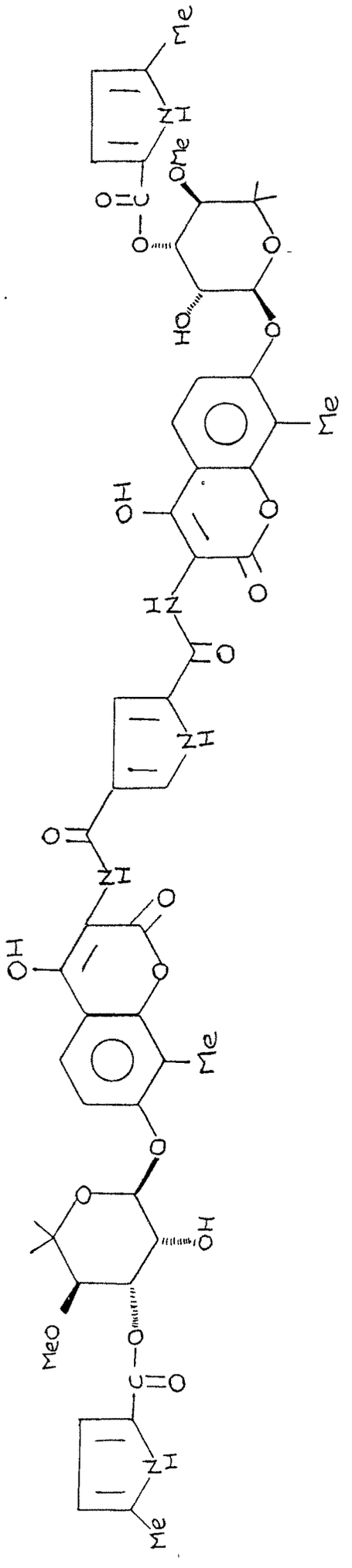

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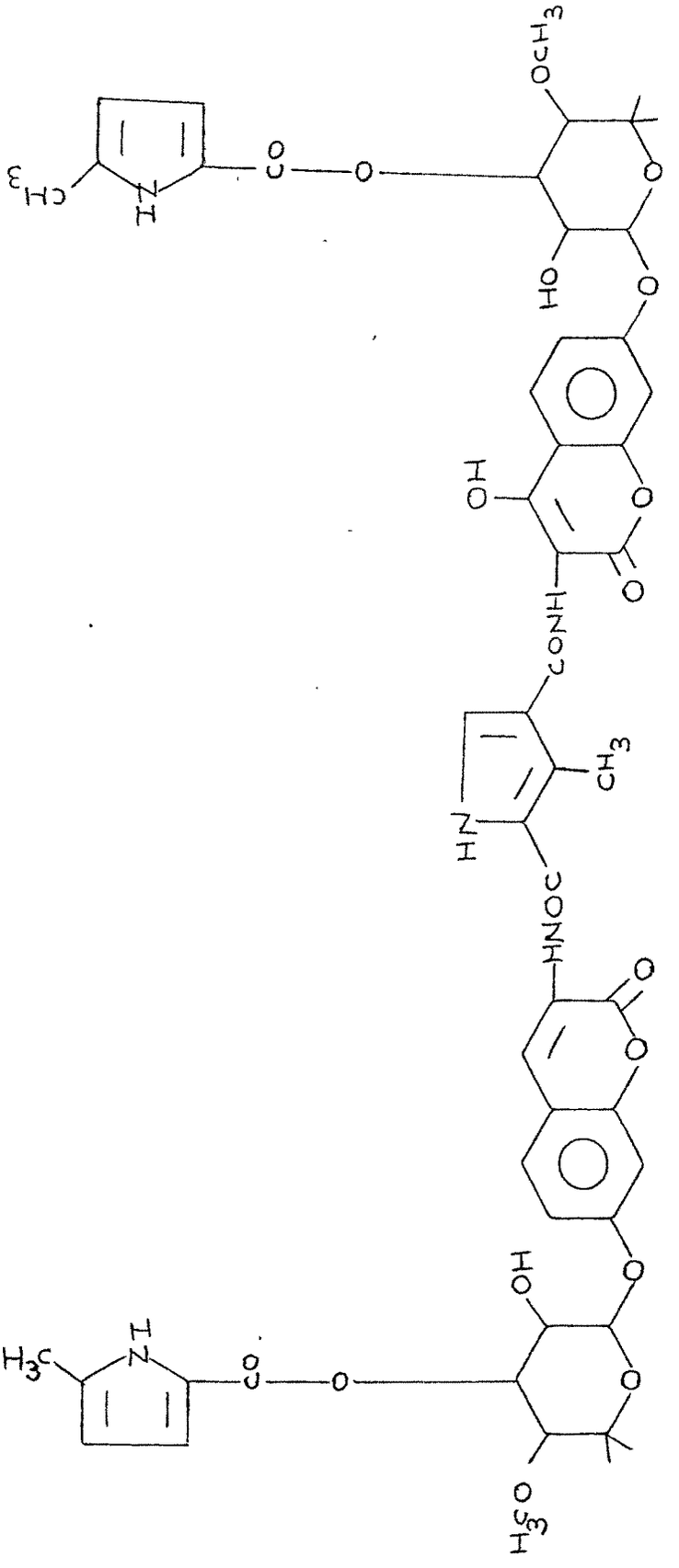
with coumarmycin A_1 (16) and the loss of DNA supercoiling paralleled the inhibition of DNA synthesis. Their results indicated that the observed relaxation of supercoiling is due to the inhibition of DNA gyrase.

Tuberculostatic activity[34] is exhibited by pimpinellin (12) and isopimpinellin (13).

Kawaguchi and coworkers[35] have obtained a new coumarin derivatives, an antibiotic coumarmycin A_1 (16), from filtrate (pH-5) residue of the fermentation beers of Streptomyces resshiviensis (17). It inhibits the growth of gram positive, gram negative and acid fast bacteria and against Staphylcocai. It is about 30 times more potent than novobiocin (15).

Recently some coumarin derivatives are found to have important pharmacological activities, (18) is active against mylobacterium tuberculosis, (19), a fungicidal agent, (20) an insecticidal agent, (21) an active vasodilating agent and (22) inhibits aggregation of thrombocytes.

Buu-Hoi and coworkers[36] prepared a series of hydroxylated-3-aryl coumarins as potential carcinostatic and virusytatic agents. Lednicer et al.[37] also suggested that 3,4-diaryl derivatives are more active than 3-aryl coumarins. Elderfield and Ray[38] have synthesised nitrogen mustards from 6-substituted coumarins as potential anticancer agents.



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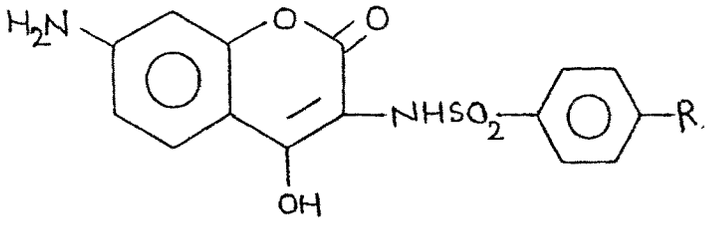

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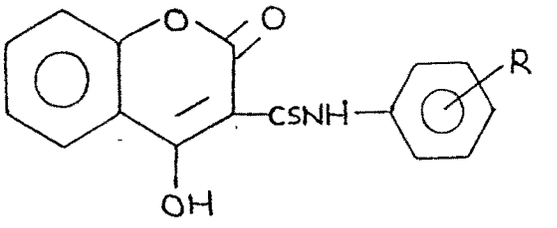

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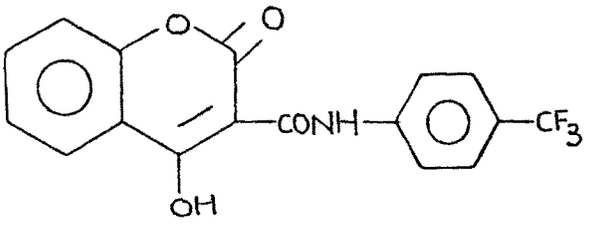

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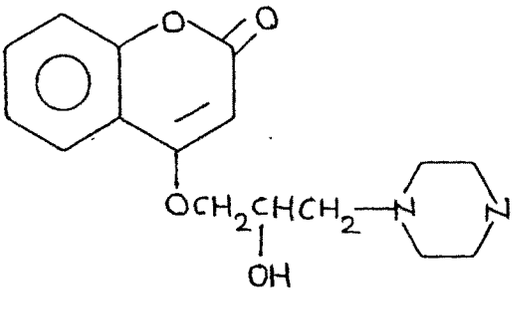

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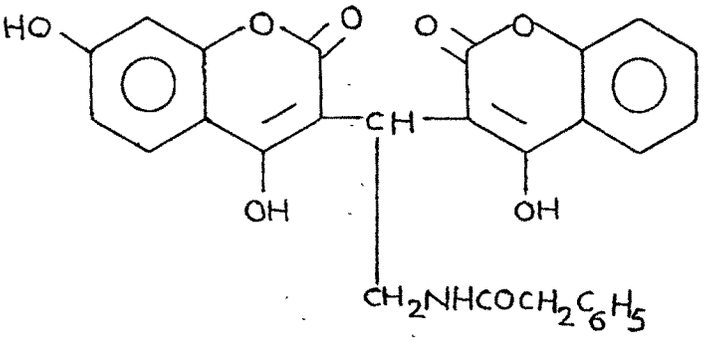


(22)

Coumarin and some of its derivatives having m.p.s. lower than 70-100°C have been generally found to possess strong anthelmintic action.[39] An examination of a number of simple coumarin derivatives employing fish and the turning times as a measure of toxicity has now established that they have weak toxic properties.[40,41] While many natural coumarins particularly those with furan ring system are toxic to fish.[42]

In recent yearsthe discovery of photodynamic action of some of the furocoumarins has led to considerable work in this field.[43]

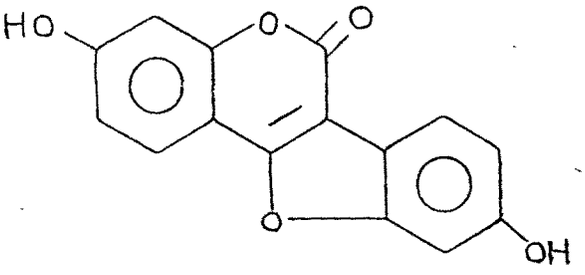
Perhaps of the greatest fundamental biochemical interest is the photosensitizing effect on cells, of certain linear furocoumarins, which is intimately associated with their cross-linking of the strands of DNA.

The effect of the oestrogenically active 3-phenylcoumarin, coumestrol (a coumestan) (23), has been studied in the uterus of the ovariectomized rat.[44] This coumarin as its diacetate, stimulated the incorporation of (2 - ^{14}C) glycin into protein and of (^{32}p) orthophosphate into RNA, more than two fold in vitro. They have pointed out that coumestrol (23) contains phenolic groups which may satisfy the configurational and electrostatic requirements for an oestrogenic molecule.

In plants, coumestrol (23) inhibited ATP formation in cucumber hypocotyls.[45,46] The photochemical interaction between xanthyletin (24) and DNA was recently examined by Dall' Acqua et al.[47] A weak molecular complex was formed in the dark and a covalent complex was formed at a low value when irradiation at 365 nm. ensued. Xanthyletin (24) was moderately active in inhibiting nucleic acid synthesis in Ehrlich ascites tumor cells, inactivating phage T_2, and killing Escherichia coli cells. Steric hindrance from the methyl groups evidently impedes intercalation with DNA.

In lettuce[48] and Cucumber[46] mitochonchria oxidative phosphorylation is inhibited by coumarin with a reduction in the P:O ratio. It has been found that compounds with oxypropanolamide side chain are β-blocking agents and known to have antihypertensive activity.[49-51]

Recent studies have provided some indication of antitumour activity by simple coumarins. Coumarin itself has been reported to be a moderately potent inhibitor of chemical carcinogen induced neoplasia[52] and micromelin (25), mammein (26) and several related coumarins have antitumour activity.[53,54] Notable among the physiological effects exerted by coumarins are the acute hepatotoxicity and carcinogenicity of certain aflatoxin and anticoagulant action of dicoumarol (14) and the antibiotic activity of novobiocin (15) and coumermyein (16).



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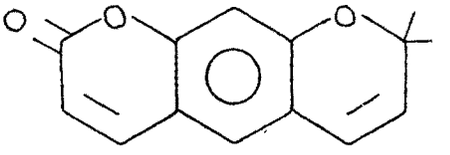

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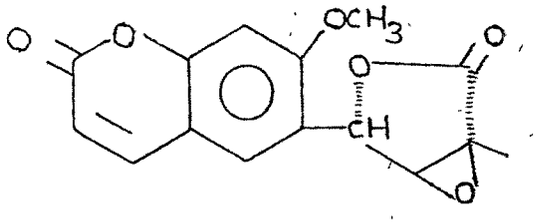

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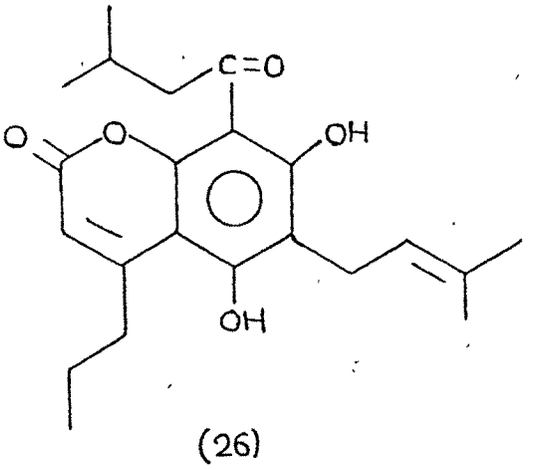

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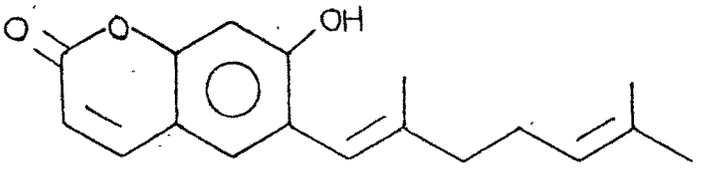

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A few studies have been published on the effect of coumarins on necleic acid metabolism in higher plants.[55-57] It appears therefore that coumarins can intervene in plant metabolism at the level of RNA synthesis.

Many enzymes reported to have been affected by coumarins. For example, the inhibition of tryptophan 5-hydroxylase by aesculetin (3) appears largely due to the presence of the vicinal hydroxyl groups, which may complex as essential metal ion cofactor.[58] In a number of other cases, attention has been devoted to elucidation of the structural features responsible for the observed effects, most notably by a czechoslovakian group. Ostrathin (6-geranyl-7-hydroxy coumarin)(27) inhibited, succinate oxidase.[59] Here the isoprenoid side chain is apparently necessary as umbelliferone (2) was without inhibition, 4-hydroxycoumarin did inhibit. Dihydroxy derivatives were more effective than monohydroxy ones, especially when occupying vicinal position. Zboril et al.[60] suggested that a reductive as well as chelating effect of this grouping could form the basis of the dihydroxycoumarin inhibitory effects.

U/V SPECTROSCOPY

UV absorption spectra are useful for distinguishing coumarins from chromones. Chromones have a strong absorption at 240-250 nm (log ε 3.8) whereas coumarins have a minimum at this wavelength. Coumarin shows absorption bands at 274

and 311 nm(log ε 4.03 and 3.72) which are due to the benzene and pyrone rings respectively.[61] Substitution of methyl group at C-3 leads to a small hypsochromic shift in the 311 nm maximum, leaving the other maximum unchanged. Methyl substitution at C-5, C-7 or C-8 leads to a bathochromic shift of the 274 nm maximum but leaves the 311 nm maximum practically unchanged.

The introduction of a hydroxyl group into the coumarin nucleus causes a bathochromicshift of the principle absorption band. The position of new maximum depends on the ability of the hydroxyl group to conjugate with the chromophoric system.

UV spectroscopy and the spectral changes induced by the addition of acid and alkali are particularly useful in deducing the orientation of the acyl groups in mammea-type 4,6,8-trisubstituted 5,7-dihydroxycoumarins.[62-64] The acyl groups may be at C-6 or C-8 lead to different UV base shifts. In the 4-alkyl series, for example the long-wavelength band at ~ 325 nm in the spectrum of a 6-acyl coumarin undergoes a large bathochromic shift to ~ 400 nm on addition of alkali. In contrast the spectrum of a an 8-acyl coumarin shows only a small bathochromic shift and replacement of the absorption near 290 nm with a weaker absorption near 260 nm. Related 4-phenyl coumarins behave in the same fashion.[65]

IR SPECTROSCOPY

The pyrone - carbonyl stretching frequency of a coumarin is usually found in the region 1700-1750 cm^{-1}.[66,67] The exact value depends to a large extent on the conditions used for recording the spectrum. There are normally three strong absorption bands in the region 1600-1660 cm^{-1}, due to C=C skeletal vibration in the IR spectra of coumarins which differentiates it from isomeric chromones, the absorption of which is generally much simpler.[68] Compounds with methoxyl groups show bands in the region 1237-1272 cm^{-1}.

NMR SPECTROSCOPY

^1H NMR technique has been applied to the structural elucidation of naturally occuring coumarins. The important ^1H NMR spectra-structure correlation studied by steck and Hazurek[69] and others which is relevant to present work has been briefly described here.

RING PROTON ANALYSIS

Observation of a pair of doublets, J=9.5Hz centered at δ 6.1-6.4 and 7.5-8.3 in the ^1H NMR spectrum of a natural product strongly indicates a coumarin unsubstituted in the pyrone ring. These characteristic signals arise from the C-3, H and C-4, H protons respectively of coumarin ring.

Oxygen function at C-7 which by electron release leads to an increase in the electron density at C-3 compared to unsubstituted coumarin, there by causing the resonance of C-3, H, to move higher field.[70-72] Oxygen function at C-5 has a similar, though smaller, effect since this involves a less favourable orthoquinonoid electronic distribution.[70] The C-4, H resonance is found in the region δ 7.5-7.9 in coumarin lacking a C-5 oxygen function.[69] An oxygen or alkyl substitution at C-5, however, characteristically shifts the resonance of C-4, H downfield (the peri effect).[73-75] C-4, H now being found at δ 7.9-8.2.

When either C-3 or C-4 is substituted the ^{1}H NMR spectrum can still provide a useful method for establishing the positions of substitution from the chemical shift of the remaining singlet. C-3, H resonates at $\delta \sim 6.15$ with a methyl group at C-4,[76] at $\delta \sim$ 6.0 for a 4-aryl coumarin.[77] On the other hand C-4, H appears at $\delta \sim 7.65$ when there is an alkyl group at C-3 and C-5 is unsubstituted,[78] but at $\delta \sim 7.95$ when there is an oxygen substituent at C-5.[79] In ethers of 7-hydroxycoumarins, the doublets, J=9.5Hz, arising from C-3 H and C-4 H are found centered at δ 6.23 and δ 7.64.

Many 7-oxygenated coumarins are known with alkyl or alkoxy groups at C-8, the signal from C-5, H is found at $\delta \sim 7.3$, downfield from the C-6, H resonance at $\delta \sim 6.8$.

Ring Substituents

Aromatic methoxyl groups normally resonate in the range δ 3.8-4.4 and aromatic methyl groups at δ 2.45-2.75.[76,80,81]

^{13}C NMR SPECTROSCOPY

With the availability of Fourier - transform methods and computer development, ^{13}C spectroscopy has become a sensitive and powerful tool in the structural elucidation of natural products. A number of publications have appeared in which complete assignment of ^{13}C chemical shifts have been presented for hydroxy and methoxycoumarins,[82-84] and also for furanocoumarins.[85]

ELECTRON-IMPACT MASS SPECTROSCOPY

Considerable interest has been shown in the mass spectrometry of natural products. Fragmentation patterns resulting from electron impact of many natural coumarins have been determined and rationalized and have proved to be of great assistance in structural studies.[86-89] High resolution mass spectrometry in particularly has become increasingly used for the determination of molecular formula by accurate measurement of the molecular ion.

INDUSTRIAL APPLICATIONS

Although simple coumarin has a very low fluorescence quantum yield, many natural coumarins and synthetic derivatives

are highly fluorescent and have high quantum yields. Synthetic coumarins have been used extensively as fluorescent brightening agents in detergents, paper and textiles to mask yellowing in white materials. 7-(2'-benzoxazolyl)-3-phenylcoumarin[90] and 2-(3'-coumarinyl)-benzoxazoles[91] have been reported to be optical brighteners for polyesters, polyamides and polyvinylchloride. 2-(3'-coumarinyl)-naphthoxazole with a dialkylamino substituent in 7-position of coumarin ring exhibit brilliant fluorescence with absorption in the visible range and are useful for the dyeing of organic fibers.[92] A recent application of coumarin fluorescence is in the field of tunable dye lasers.[93] More recently Reddy[94] and others have reported synthesis of 3-heterarylcoumarins as optical brighteners.

There are various methods for the synthesis of coumarin derivatives and they have been reviewed by Sethna and Shah[95] and by Wawzonek[96] and need not be enumerated here.

The coumarin derivatives have also been subjected to various substitution reactions such as chlorination[97-100] bromination,[101-109] iodination[110,111] chloromethylation,[112] nitration,[113-118] Fries and Friedel-Crafts reactions,[119-124] formylation,[125-129] Sulfonation[130-132] and other reactions.

The present work was undertaken with a veiw to study three aspects of coumarins, namely synthesis, characterisation

and screening of coumarin derivatives in search of potent biologicaly active compounds.

The first Chapter, which is the general introduction, deals with historical account of coumarins. It includes a brief survey of their various biological activities, spectroscopic methods for elucidation of structure of coumarins, methods of synthesis and chemical reactions.

In the first part of Chapter-II some hydroxy and acyl coumarins have beend subjected to Mannich reaction, involving glycine and other DL-amino acids a basic component instead of usual amines. Structures of Mannich bases thus obtained have been established on the bases of satisfactory elemental analysis, IR, NMR and Mass spectra.

In the second part of the same chapter, the synthesis of Mannich bases by condensing chloromethyl derivative of coumarin with various simple and substituted primary and secondary aromatic, alicyclic and heterocyclic amines have been described. Structures of the aminomethyl derivatives thus synthesised have been established by spectral methods as usual.

In Chapter III, the Schiff bases, which have been hitherto unknown, of some formyl, acyl and aminocoumarins have been

described. Their structures have been proved by IR, NMR and Mass spectra. In Part-II of this chapter, the synthesis of acid hydrazides of coumarins from acid, acid chloride and chloromethyl derivatives and in cases were structures permit their conversioninto oxadiazoles have also been described. The same coumarin oxadiazoles have been synthesised by other route. Their structures established by spectral and other standard methods.

In the first part of Chapter IV, the preparation of anilides, amides and sulfonamides of coumarin derivatives have been discussed. Their structures have been established by spectral methods as usual. In the second Part of the fourth Chapter, screening data for biological activity of representative compounds of each class synthesised as shown in early chapters, has been exhibited and described.

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