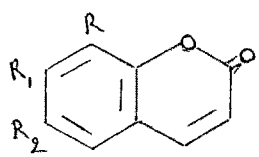
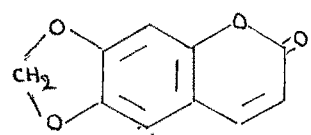
# INTRODUCTION

## General Introduction

Coumarins or benzo-α-pyrones occur in plant kingdom, either in the free or in the combined state. Coumarin, Scopoletin, Aesculetin, Ayapin, Fraxetin and Daphnetin are a few of the simple coumarins found in nature.

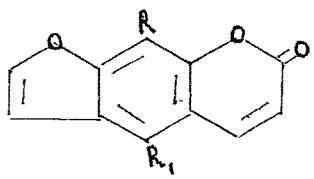


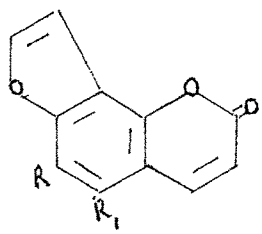




Ayapin

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| Coumarin | H | H | H |
| Scopoletin | H | OH | $OCH_3$ |
| Aesculetin | H | OH | OH |
| Fraxetin | OH | OH | $OCH_3$ |
| Daphnetin | OH | OH | H |

Another group of interesting naturally occuring coumarin derivatives are the furocoumarins. Psoralene, Angelicin, Bergapten, Xanthotoxin, Pimpinellin, isopimpinellin and Oreoselone are a few members of this group.





| | R | $R_1$ | | R | $R_1$ |
|---|---|---|---|---|---|
| Psoralene | H | H | Angelicin | H | H |
| Xanthotoxin | $OCH_3$ | H | Pimpinellin | $OCH_3$ | $OCH_3$ |
| Bergapten | H | $OCH_3$ | | | |
| Isopimpinellin | $OCH_3$ | $OCH_3$ | | | |

Natural coumarins have some interesting biochemical properties (see review by Bose) (1). They possess varied and often remarkable physiological actions. A few of these may be very briefly described here.

Many natural coumarins affect the living cells of plants and animals in various ways. 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 methylene bis-4,4'-dihydroxycoumarin (dicoumarol). 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, Tromexan Cumopyran 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, has been proved to be a coumarin derivative. The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin.

Tuberculostatic activity (13) is exhibited by pimpinellin and isopimpinellin.

Coumarin and some of its derivatives having m.p.s 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 many natural 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).

There are various methods for the synthesis of coumarin derivatives and they have been reviewed by Sethna and Shah (19) and by Wawzonek (20) and need not be enumerated here.

The coumarin derivatives have also been subjected to various substitution reactions such as chlorination (21,22,23,24), bromination (25,26,27,28,29,30,31,32,33), iodination (34,35), chloromethylation (36), nitration (37,38,39,40,41,42), Fries and Friedel-Crafts reactions (43,44,45,46,47,48), formylation (49,50,51,52,53), sulphonation (54,55,56) and other reactions.

The present work forms a part of the systematic study of the chemistry of coumarins which has been going on in this laboratory for the past few years. Three aspects of the chemistry of coumarins have been studied in the

course of the present work.

In the first part of chapter I, the syntheses of several furocoumarins which have been hitherto unknown have been described. In the second part of the same chapter the synthesis of some coumarino-α-and γ-pyrones has been described. The formyl and the acetyl coumarins, which are the intermediates in these syntheses, have been synthesised and their structures established.

In chapter II, the Beckmann transformation of the oximes of some C-acylcoumarins have been described. The structures of the aminocoumarins obtained have been proved by their synthesis by unambiguous methods or by their conversion into known products.

In chapter III, the preparation of Mannich bases from some coumarin derivatives has been described. The oxazino derivatives obtained in some cases have been degraded to the Mannich bases. The Mannich bases have been converted into known products and thus their structures established.

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