Chapter I

Introduction

The plants belonging to *Uncaria* genus of family Rubiaceae are widely distributed throughout Thailand. Variety of specific names of *Uncaria* in Thailand have been reported in different localities (Craib, 1932; Thailand. Royal Forest Department, 1948; Backer and Bakhuizen van den Brink Jr., 1965; Ridsdale, 1978). Recently, a world wide revision of this genus has been undertaken by Ridsdale and 34 species are now recognized. Several species of *Uncaria* are employed for making astringent preparations for application to wounds, for gargles and for treating intestinal complaints and other ills. The leaves of *U. acida* (Hunt.) Roxb. are used to relieve pain by rubbing on the body (Burkill, 1870). *U. africana* G. Don has reportedly been used for the treatment of stomach pains and syphillis. Specifically, the bark of this specie has been used in common cold, and the leaves for chest complaints. *U. gambir* (Hunt.) Roxb. is well known as the source of the astringent substance gambir (Burkill, 1870). The leaves are also used locally by the Malays for chewing betel (Willis, 1960). Alternatively, *U. bernaysii* F.V. Muell. is mentioned as a possible source of gambir, while *U. callophylla* Korth. has the same uses as, but has been proved to be inferior to, *U. gambir* (Hunt.) Roxb. for gambir production. Additionally, *U. elliptica* R. Br. ex G. Don has also been used as a source of gambir in Sri Lanka (Phillipson, Hemmingway and Ridsdale, 1978). The Malays use a decoction of the leaves of *U. ferrea* Dc. for cleaning wounds and ulcers, and an infusion

of the uninjured roots as a drink for inflammation of the intestine. Decoction of the leaves of *U. guianensis* (Aubl.) Gmel. is used for dysentery (Uphof, 1968). Young shoots of *U. horsfieldiana* Miq. have been reported as a source of a dye. More specifically, the Malays are said to use a decoction of the leaves and also an infusion of the uninjured roots of the plant as they use those of *U. ferrea* DC. The leaves of *U. longiflora* (Poir.) Merr. are said to be used against rheumatism and are rubbed into the body for the relief of pain. Extracts of *U. perrottetii* (A. Rich) Merr. containing alkaloids had slight antitumour activity when tested by The Medical Research Center, National Institute of Science and Technology, Manila, The Philippines. *U. rhynchophylla* Miq. has been used in the treatment of children's disease, including infantile fevers and nervous diseases and also in adults for dizziness and for vision and bilious disorders. Antispasmodic activity and sedative action is attributed to the hooked thorns. *U. Sinensis* (Oliv.) Havil. has been reported to be replaced by *U. rynchophylla* Mig. for the treatment of children's disease in Japan. The hooks are reportedly an important drug in traditional Chinese medicine for the treatment of fevers and various nervous disorders. In an analysis of prescriptions, the suggestion has been made that the hooks may be employed for their sedative action (Phillipson, Hemmingway and Ridsdale, 1978).

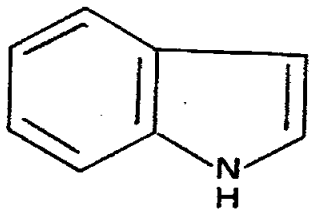
In Thailand, leaves of some species of *Uncaria* are chewed and used as a substitute for the leaves of *Mitragyna speciosa* Korth., known as "Kratom" (Ponglux, Tantivatana and Pummangura, 1977) which are chewed as a mild narcotic (Henry, 1949).

Uncaria is a large genus and several species, but not all have been subjected to chemical and pharmacological investigations, although chemotaxonomy reveals that major constituents commonly isolated from this genus are indole compounds. Recently, phytochemical investigations of *Uncaria salaccensis* bakh. f. nom provis, a specie commonly found in Thailand, have been undertaken.

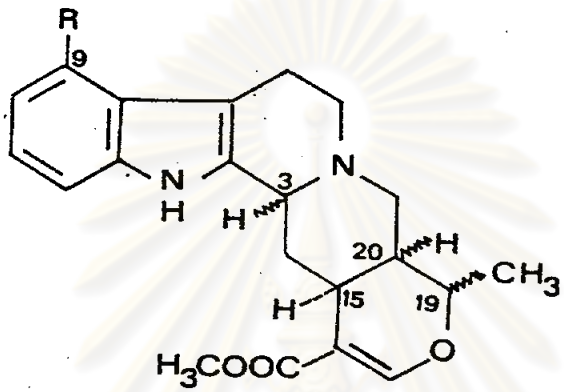
This species is found in the area of Khao-Yai National park, Nakorn Rachasima, Thailand; having a climbing habit, globose flowering heads and peduncles converted into recurved hooks as outstanding characters. By means of column chromatography pentacyclic heteroyohimbines 3-isoajmalicine and 19-epi-3-isoajmalicine, and pentacyclic oxindoles mitraphylline and uncarine B were isolated from the leaves of this species (Wongseripipatana, 1978).

According to Wongseripipatana, 1978, alkaloids obtained from *Uncaria salaccensis* have indole nucleus (Fig. 1A) as their basic structure. Two of the four major alkaloids isolated are pentacyclic heteroyohimbine (closed E ring). The compound tentatively designated in the chemical process as I-1 has been identified as 19-epi-3-isoajmalicine, while another indole I-2 as 3-isoajmalicine. Both have the same basic structure, the configurations of which are as follow: (Fig. 1B).

The other alkaloids belongs to oxindole group, and are indentified as uncarine B (O-1) and mitraphylline (O-2). They are pentacyclic oxindoles with the following configurations. (Fig. 1C).



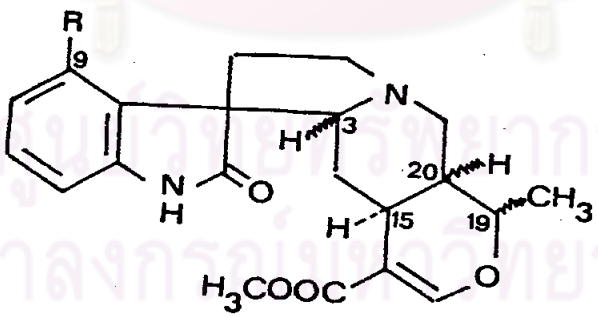
A. Indole nucleus



B. Pentacyclic heteroyohimbine indole alkaloids

I-1 19-epi-3-isoajmalicine R = H C(19)-CH_3 = β

I-2 3-isoajmalicine R = H C(19)-CH_3 = α



C. Pentacyclic oxindoles

O-1 Uncarine B R = H C(19)-CH_3 = β

O-2 Mitraphylline R = H C(19)-CH_3 = α

Figure 1. Structure of indole alkaloids

Indole compounds have been reported to possess a wide range of pharmacological properties. Studies indicate that, when administered intraarterially, indole compounds exert transmission blocking effect in the rat superior cervical ganglion. Hersutine shows a relatively strong inhibitory effect while isorhynchophylline is less potent (Harada, Ozaki and Sato, 1974). In large doses, the indoles also show neuromuscular transmission blocking effects. However, effect of indole compounds on neuromuscular transmission are not consistent (Harada, et al., 1976). Rhynchophylline exhibits a significant antipyretic action and a hypotensive property (Saxton, 1965). This alkaloid has also been shown to paralyse parasympathetic nerve endings (Henry, 1949). The physiological pharmacology of indole alkaloids isolated from *Uncaria salaccensis* is also an interesting issue which merits an investigation. A report is available for mitraphylline (Saxton, 1965), which indicates that the alkaloid exhibits hypotensive and smooth muscle depressant properties. However, pharmacological actions of the other alkaloids from this species are remained to be investigated.

The present thesis described physiological pharmacology of the four indoles isolated from *Uncaria salaccensis*, with special emphasis on their effects on blood pressure and cardiac contractility in experimental animals. The four indoles are found to have hypotensive properties, with cardiac depressant action being the most likely underlying mechanism. An attempt to investigate the molecular mechanism of the observed actions has also been undertaken.