Chapter 1

Introduction

A large number of local plants belonging to *Uncaria* genus are used in Thailand as therapeutic agents for various undesirable symptoms. Extracts of the root, leaves and bark of the tropical and subtropical trees of this genus are used in traditional remedies for treating intestinal complaints and other ills. The genus, belongs to family Rubiaceae, is widely distributed throughout Thailand. Varieties of specific name of *Uncaria* in Thailand have been reported in different localities (Craib,1932; Backer and Bakhuizen,1965; Ridsdale.1978; Thailand Royal Forestry Department,1980). Recently, a worldwide revision of the genus has been undertaken by Ridsdale (1978) and 34 species are now recognized.

Several species of *Uncaria* are employed in making astringent preparation for application to wounds, and used as gargles. The leaves of *U. acida* are used to relieve pain by rubbing on the body (Burkill, 1870). *U. africana* has reportedly been used for the treatment of stomach pains and syphillis. Specifically, the bark of this species has been used in common cold, and the leaves in chest complaints. The bark of *U.sessilifructus* is used by chewing as a substitute for betel. *U.gambir* is well known as the source of the famous astringent substance gambir (Burkill, 1870). *U. bernaysii* is mentioned as a possible alternative source of gambir. So are *U. lanosa, U.callophylla* which have also been documented as other sources of gambir, although the quality may

be inferior to *U. gambir* for gambir production. Another source of gambir reported in Sri Lanka is *U. elliptica* (Phillipson, Hemingway and Ridsdale, 1978). The Malaysian use a decoction of the leaves of *U. ferrea* for cleaning wounds, ulcers and an infusion of the uninjured roots is used as a drink for inflammation of the intestine. Decoction of the leaves of *U. guianensis* is used in dysentery (Uphol, 1968). The leaves of *U. longiflora* are used against rheumatism and are rubbed into the body for the relief of pain. Extracts of *U. perrottetii* containing alkaloids had slight antitumour activity, as reported by the Medical Research Center, National Institute of Science and Technology, Manila, Philippines (Phillipson, Hemingway and Ridsdale, 1978). *U. rhynchophylla* has been used in pediatric diseases, including infantile fevers and nervous diseases and also in adults for dizziness and for vision and bilious disorders. This species has antispasmodic activity and sedative action, which are attributed to the hooked thorns. Poultices prepared from the roots have been reported to be used in skin ulcers. *U. sinensis* has been stated to be replaced by *U. rhynchophylla* for the treatment of children's diseases in Japan. The hooks are reportedly an important drugs in traditional Chinese medicine for the treatment of fevers and various nervous disorders. In an analysis of prescription, the suggestion has been made that the hooks may be employed for their sedative action (Phillipson, Hemingway and Ridsdale, 1978).

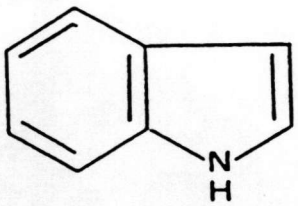
In Thailand, leaves of some species of *Uncaria* are chewed and used as a substitute for the leaves of *Mitragyna speciosa* known as "Kratom" (Ponglux, Tantivatana and Pummangura, 1977) which are chewed as a mild narcotic (Henry, 1949).

Uncaria is a large genus with 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 species commonly found in Thailand, have been undertaken. This species is found in Khao-Yai National park, Nakorn Rachasima,Thailand, having a climbing habit, globose flowering heads and peduncles converted into recurved hooks as outstanding characters.

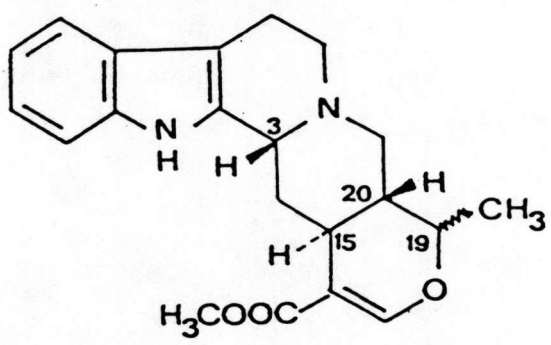
By means of column chromatography, pentacyclic heteroyohimbines 3-isoajmalicine and 19-epi-3-isoajmalicine, and pentacyclic oxindoles mitraphylline and uncarine B were isolated from the leaves of this species (Wongseripipatana, 1978). These alkaloids have indole nucleus (Fig. 1A). Two of the four major alkaloids isolated are pentacyclic heteroyohimbines. The compound tentatively designated in the isolation process as I-1 has been identified as 19-epi-3-isoajmalicine, while another indole 1-2 as 3-isoajmalicine. Both have the same basic structure, the configuration of which are as follow : (Fig : 1B).

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

The melting points of I-1, I-2, O-1 and O-2 are 107^{o}C, 150^{o}C, 197^{o}C and 270^{o}C respectively; the molecular weights determined by mass spectrometry are 352, 352, 368 and 368 respectively.

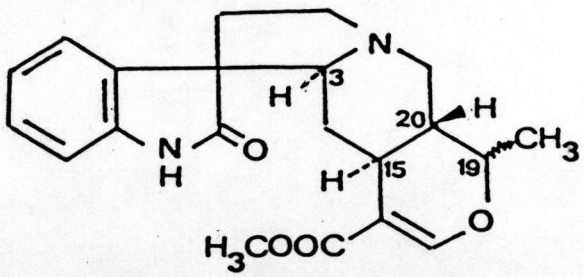


A. Indole nucleus



B. Pentacyclic heteroyohimbines

I-1	19-epi-3-isoajmalicine	C(19)-CH_3 = β
I-2	3-isoajmalicine	C(19)-CH_3 = α



C. Pentacyclic oxindoles

O-1	Uncarine B	C(19)-CH_3 = β
O-2	Mitraphylline	C(19)-CH_3 = α

Figure 1. Structures 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. Hirsutine 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 alkaloids has also been shown to paralyse parasympathetic nerve endings (Henry, 1949). Mitraphylline has been reported to have hypotensive activity and to exert general depressant effect on smooth muscle (Saxton, 1965). Studying of the effects of indole alkaloids from *Uncaria salaccensis* on isolated atria of rats suggests that these alkaloids have negative effects on chronotropic, inotropic and dromotropic responses. These effects were resistant to atropine. In addition positive chronotropic responses of 5-hydroxytryptamine are antagonized by these alkaloids while the responses to adrenaline and isoproterenol are unaffected. (Archongka, 1983).

The present thesis describes physiological pharmacology of the four indoles isolated from *Uncaria salaccensis*, with special emphasis on their effects on smooth muscle of isolated intestine of rabbit , isolated intestine of quinea-pig and isolated aortic strip of rabbit. The results suggest that I-1 and I-2 have antiserotonergic properties.